CURRICULUM VITAE OF PROFESSOR (DR.) GOUTAM BRAHMACHARI

Executive Profile: Prof. Goutam Brahmachari

Dr. Goutam Brahmachari, *M.Sc. (1st Class 1st, Ph.D., D.Sc., FRSC, FAScT*, is a Full Professor of Organic Chemistry at Visva-Bharati (a Central University), Santiniketan, India. With nearly three decades of academic excellence, he bridges breakthrough molecular research with national sustainability goals.

Core Scientific Contributions

- **Green & Sustainable Chemistry:** Pioneered effective, eco-friendly synthetic methods for carbon-carbon and carbon-heteroatom bond formations, constructing medicinally vital organic scaffolds via C-H functionalization and cascade approaches.
- **Natural Product Chemistry:** Unearthed the chemical profiles of traditionally used Indian medicinal plants, isolating and mapping novel phytochemicals to elevate indigenous knowledge systems.

***Global Rankings & Research Metrics* (As of June 2026)**

- **ScholarGPS:** Highly Ranked Scholar (Lifetime), positioning in the **top 0.05% of all scholars worldwide**.
- **Stanford/Elsevier World Ranking:** Featured consistently among the **Top 2% Scientists globally** (Organic Chemistry Category; 2020–2025).
- **Research Metrics: 8,150+** citations | h-index: **47** | i10-index: **155** | **300+** global publications.
- **Academic Leadership:** Trained thousands of next-generation chemists; author/editor of 30 foundational books in the domain of green and medicinal chemistry with premier scientific publishers; supervised 20 Ph.D. fellows; Founding Series Editor of the Elsevier Book Series *'Natural Product Drug Discovery'*.

Major National & Global Honors

- **Elected Fellow:** Royal Society of Chemistry (FRSC) & West Bengal Academy of Science & Technology (FAScT).
- **Recent Laurels (2025):** Acharya P. C. Ray Memorial Lecture Award (ISNA, Kolkata) & Dr. Satyajit Chakraborti Memorial Award (Global Contribution to Chemical Science).
- **Research Medals:** CRSI Bronze Medal-2021 (Chemical Research Society of India) & Dr. Basudev Banerjee Memorial Award-2021 (Indian Chemical Society).
- **Teaching Excellence:** INSA Teachers Award-2019 (Indian National Science Academy, New Delhi) & Dr. Kalam Best Teaching Faculty Award-2017 (Dr. Kalam Educational Trust, Chennai).

(ORCID: http://orcid.org/0000-0001-9925-6281); VIDWAN: https://vidwan.inflibnet.ac.in/profile/152899

Detailed CV

Prof. G. Brahmachari
(Acharya P. Ray Memorial Lecture Awardee-2025; CRSI Bronze Medal Awadee-2021; Dr. Basudev Banerjee Memorial Awardee 2021; INSA Teachers Awardee-2019)

1. Name in Full: **BRAHMACHARI** // **GOUTAM**
Surname Forename

2. Designation and Name of the Institution: **Full Professor of Chemistry and Former Head of the Department, Department of Chemistry, Siksha-Bhavana (Institute of Science), VISVA-BHARATI (A Central University), Santiniketan-731235, West Bengal, India.** [University Employee ID No. 1998048]

3. a. Date of Birth: 14th April 1969 (14.04.1969) Age: 57+
b. Citizen: Indian c. Gender: Male

4. Fellow & Life membership
(a) ***Royal Society of Chemistry, London (UK) (FRSC)***
(b) ***West Bengal Academy of Science & Technology (FAScT)***
Life Member: **CRSI** (LM 1914), **ISCA** (L24650), **ICS** (8547),
Indian Photobiology Society (IPS/LM/00394)

5. Address

(a) Official: **Department of Chemistry, Siksha-Bhavana (Institute of Science), Visva-Bharati (A Central University), Santiniketan-731235, Birbhum, West Bengal, India**

(b) Residential: **Dinendrapalli, Simantapalli (North), Santiniketan-731235, Birbhum, WB, India**

(c) Email: brahmg2001@yahoo.co.in; brahmg2001@gmail.com; goutam.brahmachari@visva-bharati.ac.in

(d) Mobile No./Contact No: + **91-9434385744 / +91-8617324394**

6. Subject: CHEMICAL SCIENCES (Organic Chemistry)

7. Educational Qualifications: M.Sc. (1st Class 1st), Ph.D. (Organic Chemistry), D.Sc. (Organic Chemistry)

8. Professional Experience

Teaching and Research (Independent) at the University Level: 28 years

9. Field of Research

Synthetic organic chemistry, Green chemistry, Synthetic methodologies, Natural Products Chemistry

10. Administrative experiences: As shown in the following Table.

Sl. No.	Details of such an experience
1	Successfully executed the responsibilities of the Head of the Department, Department of Chemistry, Siksha-Bhavana, Visva-Bharati, as part of administrative responsibility from 04.03.2020 (afternoon) to 22.12.2023 (afternoon). The Head of the Department is responsible for running the Department both academically and administratively, including planning, execution, finance, budgeting, Department projects, and more.
2	Coordinator of the University's International Collaborations Wing since 21.09.2022
3	Working as a member of the University's "*Students' Grievance Redressal Committee*" since 04.08.2023
4	Working as a member of the University's "Building Committee" since 02.12.2020
5	Member of the Academic Council (since 24.07.2011), Board of Studies of the parent and other Universities
6	Member of the Research Board (Visva-Bharati) 14.12.2017 to 14.12.2020
7	Member of the University Vision-2035 Committee
8	Member of the University Committee for explaining the UGC Regulation-2018
9	Member of the University Committee for exploring the university's multidisciplinary research for the students

11. Master's and Doctoral Dissertations Supervised

Ph. D. students supervised: 20 (*Degrees already awarded*)

Present PhD fellows working with: 04

Master's Dissertations supervised: 70

12. Project Coordinator (Sponsored Research Projects) [Total Grants Amount: INR 210 Lakh]

Successfully completed several research projects sponsored by UGC (New Delhi), CSIR (New Delhi), DST (West Bengal), DBT (New Delhi), and SERB-DST (New Delhi)

I. As PI/Co-PI

- Research Project entitled "*Electrochemical synthesis of functionalized heterocycles of biological relevance*" sponsored by CSIR, New Delhi, No. No. 02/0464/23/EMR-II dated 07.07.2023 (2023-2026) Amount: INR 30 Lakh. [**Ongoing**]
- Research Project entitled "*Electrosynthesis of functionalized heterocycles via C-H functionalization*" sponsored by Science and Engineering Research Board (SERB), Department of Science and Technology (DST), New Delhi, No. No. CRG/2022/000275 dated 08.12.2022 (2022-2025); Amount: INR 50 Lakh. [**Completed**].
- Research Project entitled "Studies on the chemical constituents and biological activities of *Casia sophera* Linn. (Caesalpiniaceae) – an important Indian medicinal plant" sponsored by CSIR, New Delhi, No. 02(0260)/16/EMR-II dt 28.04.16; (1.6.2016 to 31.05.2019) Amount: INR 20 Lakh [**Completed**].
- Research Project entitled "Pharmacokinetics and toxicology of toxins in boiled aqueous extract of *Cleistanthus collinus* leaves" sponsored by Department of Biotechnology, Ministry of Science & Technology, Govt. of India, No.BT/PR12571/TRM/120/25/2014 dt. 15.07.2016 (period 2016-2019), Amount: INR 39.62 Lakh [as *project Joint-investigator*] [**Completed**].
- Research Project entitled "*Design for Energy-Efficient Synthesis of Biologically Relevant Heterocycles*" sponsored by Science and Engineering Research Board (SERB), Department of Science and Technology (DST), New Delhi, No. EMR/2014/001220 dt 08.09.2015 (2015-2018); Amount: INR 35.26 Lakh [**Completed**].
- Research Project entitled "*A sincere drive to develop eco-friendly methodologies for some useful organic transformations in the absence of organic solvents*" sponsored by CSIR, New Delhi, No. 02(0110)/12/EMR-II dt 01.11.2012 (2012-2015); Amount: INR 12.65 Lakh [**Completed**].
- Research Project entitled "*Acaciaside A from Acacia auriculiformis: a novel compound for the control of Bancroftian filariasis*" sponsored by Department of Biotechnology, Ministry of Science & Technology, Govt. of India, No. BT/PR8779/Med/14/1282/2007 dt. 24.09.2008 (period 24.09.2008-23.09.2011), Amount: INR 45.81 Lakh [as *project Joint-investigator*] [**Completed**].
- Research Project entitled "*Naturally Occurring Flavonoids: Isolation, Chemistry and Assessment of Bio-Activity*" sponsored by UGC, New Delhi, No. F.34-357/2008(SR) dt 02.01.2009 (period 01.02.2009 – 31.01.2012). Amount: INR 6,76,800/- [**Completed**].
- Research Project entitled "*Studies on chemical constituents of Limnophila plants available around Santiniketan (Birbhum, West Bengal)*" sponsored by the Department of Science & Technology (West Bengal) [No. 230(Sanc.)/ST/P/S&T/2G-7/2007 dt. 24.07.2008 (2008-2011)]. Amount: INR 7,01,500/- [**Completed**].
- Research Project entitled "*Studies on naturally occurring flavonoids*" sponsored by UGC, New Delhi, No. F.31-152/2005(SR) dt. 31.03.2006 (period 01.05.2006 – 30.04.2008) Amount: INR 55,000/- [**Completed**].

II. Involved in the Institutional research projects

Departmental UGC-SAP Programme, Departmental FIST (DST)-Level 0, 1, 2 programmes, and the University's DST-PURSE programme

13. Academic career and professional attainments:

(a) Academic career (Bachelor's degree onwards)

Degree	Institution	Year	Remarks
Bachelors [B.Sc. (Hons.) in Chemistry]	VISVA-BHARATI	1990	First Class Second
Masters [M.Sc. in Chemistry (Organic Chemistry Specialization)]	VISVA-BHARATI	1992	First Class First
Ph.D.	VISVA-BHARATI	1997	Organic Chemistry
D.Sc.	VISVA-BHARATI	2023	Organic Chemistry

(b) Professional experience

Positions held	Institution	From (year)	To (year)	Experience
Full Professor of Chemistry	Chemistry Department, Visva-Bharati (a Central University), WB, India	24.07.2011	Continuing	15 years so far
Head of the Department	-do-	4.03.2020	22.12.2023	About 4 years
Associate Professor	-do-	24.08.2008	23.07.2011	3 years
Reader (selected and joined afresh in an open post)	-do-	24.07.2005	23.07.2008	3 years
Lecturer (Senior scale)	-do-	08.12.2002	23.07.2005	2 years 8 months
Lecturer in Chemistry	-do-	08.12.1998	07.12.2002	4 years

(c) Recognitions such as Fellowships, awards, prizes, certificates, academic/professional distinctions received, and Editorial Board member of National/International Journals

Type of Recognition	Title of Recognition	Name of Awarding agency	Year of award
Highest academic Degree	Awarded Doctor of Science (D.Sc.) Degree in Chemistry	Visva-Bharati University	2023
Award	Acharya P. C. Ray Memorial Lecture	Indian Science News Association (ISNA), Kolkata	2025
Award	Dr. Satyajit Chakraborti Memorial Award-2025 (global contribution to chemical science)	Institute of Engineering & Management (IEM), Kolkata	2025
Award	CRSI Bronze Medal Award (for the contribution to research in Chemistry)	Chemical Research Society of India (CRSI), Bangalore	2021
Award	Dr. Basudev Banerjee Memorial Award-2021 (contributions in chemical sciences) from the	Indian Chemical Society, Kolkata	2021

Fellowship	Elected Fellow, Royal Society of Chemistry (FRSC)	Royal Society of Chemistry, London, UK	2017
	Elected Fellow, West Bengal Academy of Science & Technology (FAScT)	WB Academy of Science & Technology, Kolkata	2026
Award	INSA Teachers Award -2019	Indian National Science Academy, New Delhi	2019
Award	Dr. Kalam Best Teaching Award	Dr. Kalam Educational Trust, Chennai	2017
Award	Academic Brilliance Award (Award for Excellence in Research)	Prime Time Research Media Private Limited (Education Expo TV (EET) CRS), New Delhi	2015
Recognition	Featured in "the World Ranking of Top 2% Scientists" in the Organic Chemistry category (both whole career and single years)	Stanford University Scientists	2020-2025
Recognition	Featured in the "AD Scientific World Ranking of Scientists"	AD Scientific	2022-2025
Recognition	Featured as the ScholarGPS Highly Ranked Scholar (Lifetime, securing a position in the top 0.05% of all scholars worldwide	ScholarGPS	2022-2025
Recognition	Featured in the "World's Top 5% Scientists" of SciRank Global Registry	SciRank	2025
Reviewer award	Reviewer Excellence Awardee	*Journal of Chemical Sciences*, published by the Indian Academy of Sciences, Bangalore	2019
Reviewer award	Publons 1%Top Reviewer Award-2018 & 2019	Publons (Web of Science)	2018-2019
Recognition	CAS Registry® Innovator-2020	The American Chemical Society	2020
Recognition	Research abstracts in the prestigious *Organic Chemistry Portal*	https://www.organic-chemistry.org/abstracts/lit9/241.shtm; https://www.organic-chemistry.org/abstracts/lit9/738.shtm	2025
Recognition	Highly cited author (2014-15) for the *ACS Sustainable Chemistry & Engineering*	The American Chemical Society	2014-2015
Recognition	Featured in the top 10% of highly cited articles from the Royal Society of Chemistry	The Royal Society of Chemistry, UK	2022
Book series editor	Founder Series Editor of the Elsevier Book series "*Natural Product Drug Discovery*"	Elsevier Science, USA (https://shop.elsevier.com/books/discovery-and-development-of-antidiabetic-agents-from-natural-products/brahmachari/9	2016 onwards

		78-0-12-809450-1)	
Journal editorship	Co-Editor-in-Chief for the *Current Green Chemistry*	Bentham Science (https://www.benthamscience.com/journal/141/editorial-board)	2020 onwards
Journal guest-editorship	*Current Organo-catalysis* (one thematic issue), *Current Green Chemistry* (three thematic issues), Tetrahedron/Tetrahedron Letters (ongoing, Special Hot Issue on Electrocatalysis (https://www.sciencedirect.com/special-issue/328316/tettetl_electrocatalysis)	Bentham Science (links: https://www.benthamdirect.com/content/journals/cocat/3/2 https://www.benthamscience.com/issue/13064 https://www.benthamscience.com/issue/7662 https://www.benthamscience.com/issue/7695	2016, 2022
Journal Editorial Advisory Board Member	*Tetrahedron Green Chemistry, University Journal of Green Chemistry, Current Catalysis, Current Organocatalysis, Current Green Chemistry; Rasayan Journal of Chemistry; Journal of Biochemistry and Molecular Biology Research; Journal of Scientific Research and Advances; Iranian Chemical Communication, and others*	Respective journal administrations	2015 onwards
Session Chairing	Session Chairing in Seminars/Conferences and Invited Talks delivered at several national and international symposia.	-	-
Life-member of Scientific Organizations	Chemical Research Society of India (CRSI) (CRSI, LM 1914), Indian Chemical Society (ICS) of India (Life Member, No. 8547), Indian Photobiology Society (Life Member, No. IPS/LM/00394), Indian Science Congress Association (ISCA) (ISCA, L24650)	-	-

14. Website Pages for Public Viewing

VB Webpage: https://www.visvabharati.ac.in/GautamBrahamachari.html
https://www.visvabharati.ac.in/home/facul_chemistry/

Departmental website: http://vbchem.ac.in/GoutamBrahamachari/

VIDWAN: https://vidwan.inflibnet.ac.in/profile/152899

ORCID ID: http://orcid.org/0000-0001-9925-6281

Google Scholar: https://scholar.google.co.in/citations?hl=en&user=aj7NvGQAAAAJ&view_op=list_works

Research Gate Page: https://www.researchgate.net/profile/Goutam_Brahmachari2/publications

LinkedIn page: https://in.linkedin.com/in/goutam-brahmachari-9308b662

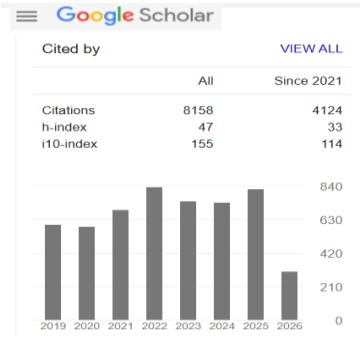
Scopus Page: https://www.scopus.com/authid/detail.uri?authorId=6603056427

Exaly Project Webpage: https://exaly.com/author/2358812/g-brahmachari/rankings

Web of Science: https://www.webofscience.com/wos/author/record/736637
https://www.webofscience.com/wos/author/record/H-9416-2017

15. Citation Indices

Citations: 8,158; h-index: 47; i10-index: 155 (as accessed on 16.06.2026 at the Google Scholar platform)



(https://scholar.google.co.in/citations?user=aj7NvGQAAAAJ&hl=en)

16. (a) Editorship of Book Series

Elsevier Series Editor – Book Series 'Natural Product Drug Discovery'
(https://www.elsevier.com/catalog/all/all/all/natural-product-drug-discovery

(b) Ongoing Journal Guest-Editorship

Tetrahedron/Tetrahedron Letters **(Special Hot Issue on Electrocatalysis)**
(https://www.sciencedirect.com/special-issue/328316/tettetl_electrocatalysis)

17. Other relevant information

Prof. Brahmachari,

a) is involved in the mission of the Royal Society of Chemistry in promoting chemical sciences in India through taking part in the organized sessions and also imparting motivating talks to the students in universities/colleges/schools

b) serves the Scientific Societies (Chemical Research Society of India, Indian Chemical Society, Indian Photobiology Society, Indian Science Congress Association, Indian Association for the Cultivation of Sciences) in India, being their Life Member.

c) serves the Royal Society of Chemistry (London), being an elected Fellow

d) is actively involved in generating a vast number of trained chemical personnel for **about three decades** as a chemical educator at a Central University in India.

e) supervised **twenty (20)** PhD fellows so far.

f) contributed immensely to authoring and editing major reference books in the cutting-edge contemporary areas of chemical sciences from internationally acclaimed publishing houses (Academic Press, Elsevier, Wiley-VCH, CRC Press/Taylor & Francis, World Scientific, Springer, Alpha Science International, Royal Society of Chemistry), which are the giants in imparting knowledge among the chemical communities worldwide.

g) Successfully implemented a significant number of major research projects funded by various national sponsoring bodies (e.g., UGC, CSIR, SERB-DST, DBT), and a couple of such major research projects from the ANRF and CSIR are currently continuing.

18. A list of ten (10) best research publications published in recent times (Please note: All the works were planned, designed, and performed exclusively working in India)

No.	Paper details	Scientific and Societal Impact of the Work
1.	Pintu Karmakar, **Goutam Brahmachari*** (2025). Sono-And Mechanochemistry-Assisted Dual Strategies for Cyanomethylation of Carboxylic Acids: Robust and Practical Synthetic Protocols to a Diverse Series of Cyanomethyl Esters. *Chemistry – a European Journal*, **31**, e01966 (Very Important paper), https://doi.org/10.1002/chem.202501966 [IF 5.02 (2024)] [**Very Important Paper Category**] Article Type: Original	Innovation of a dual synthetic strategy for a practical and general method for the preparation of synthetically important cyanomethyl esters from a diverse range of carboxylic acids (85 examples) by using ultrasound and grinding force at ambient conditions, generating yields up to 96% within 3-5 minutes. The use of no organic solvent or green solvent, large-scale synthetic applicability, reusability of reaction residues, low energy usage, maximum yields, and minimum waste make the method highly attractive to industries.
2.	Debojyoti Mukherjee, Indrajit Karmakar, **Goutam Brahmachari*** (2025). Sono- and mechanochemical dual syntheses of bio-relevant aryldiazenyl-substituted phosphine oxides/phosphonates via P(O)-H functionalisation. *Green Chemistry*, **27**, 2565-2577. https://doi.org/10.1039/D4GC05501B [Print ISSN: 1463-9262; Online ISSN: 1463-9270; IF 9.2 (2024)] Article Type: Original	Innovation of a dual synthetic strategy for an alternative, efficient, and practical method for rarely available and useful (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates by using ultrasound and grinding force at ambient conditions, generating yields up to 95% within 5-7.5 minutes. The use of no organic solvent or green solvent, large-scale synthetic applicability, reusability of reaction residues, low energy usage, maximum yields, low E-factors, high atom economy, and minimum waste make the method highly attractive to industries.
3.	Debojyoti Mukherjee, Indrajit Karmakar, **Goutam Brahmachari*** (2024). Electro- and mechanochemical strategy as a dual synthetic approach for biologically relevant 3-nitro-imidazo-[1,2-*a*]pyridines. *The Journal of Organic Chemistry*, **89**, 12071-12084. https://doi.org/10.1021/acs.joc.4c00881 [Print Edition ISSN: 0022-3263; Web Edition ISSN: 1520-6904; IF 3.6 (2024)] Article Type: Original	Discovery of a dual green methodology for the application-oriented imidazo-[1,2-a]pyridines. Both the electrochemical and mechanochemical strategies are associated with key green metrics, including high yields, gram-scale syntheses, and low waste factors, thereby attracting attention for adoption in commercial synthesis.
4.	Indrajit Karmakar, **Goutam Brahmachari*** (2024). Electro-rearranged di-functionalization of 4-hydroxy-α-benzopyrones. *The*	Innovation of the first laboratory method for a green and useful electrochemical strategy for accessing diversely substituted and biologically promising alkyl 2-hydroxy-3-oxo-2,3-

	Journal of Organic Chemistry, **89**, 10524-10537. https://doi.org/10.1021/acs.joc.4c00734 [Print Edition ISSN: 0022-3263; Web Edition ISSN: 1520-6904; IF 3.6 (2024)] Article Type: Original	dihydrobenzofuran-2-carboxylates through an electrorearranged difunctionalization of 4-hydroxycoumarins, involving the singlet oxygen insertion from molecular oxygen, at ambient temperature. High yields, functional group tolerability, operational simplicity, and scalability make it quite interesting.
5.	Anindita Bhowmick, **Goutam Brahmachari*** (2023). C(sp)–C(sp3) Bond formation through ligand- and additive-free CuO-mediated decarboxylative direct cross-coupling of coumarin-/chromone-3-carboxylic acids and terminal alkynes. *Organic Letters*, **25**, 7095-7099. https://doi.org/10.1021/acs.orglett.3c02369 [ISSN 1523-7060); IF 5.0 (2024)] Article Type: Original	Innovation of a practical and efficient method for the synthesis of functionalized 4-(aryl-/heteroaryl-ethynyl)chroman-2-ones and 2-(aryl-/heteroaryl-ethynyl)chroman-4-ones, leading to the formation of rarely reported C(sp)−C(sp3) bonds, having advantages of avoidance of any ligands and bases, a broad substrate scope, tolerance of diverse functional groups, and good to excellent yields.
6.	Pintu Karmakar, Indrajit Karmakar, Debojyoti Mukherjee, Anindita Bhowmick, **Goutam Brahmachari*** (2023). Mechanochemical solvent-free one-pot synthesis of poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles through a copper(I)-catalyzed click reaction. *Chemistry – a European Journal*, **29**, e202302539. https://doi.org/10.1002/chem.202302539 [Print ISSN:0947-6539; Online ISSN:1521-3765); IF 5.02 (2024)] Article Type: Original	Innovative exploration of a mechanochemistry-driven, practical, and efficient green synthetic alternative protocol for accessing a diverse series of biologically relevant poly-functionalized 5-(arylselanyl)-1*H*-1,2,3-triazoles through copper(I)-catalyzed click reaction, with operational simplicity, avoidance of using solvent and external heating, one-pot synthesis, short reaction time in minutes, good to excellent yields, and gram-scale applications.
7.	Indrajit Karmakar and **Goutam Brahmachari*** (2022), Electrochemical and mechanochemical synthesis of dihydrofuro[3,2-*c*]chromenones via intramolecular C_{sp3}–H cross-dehydrogenative oxygenation within warfarin frameworks: an efficient and straightforward dual approach. *Green Chemistry*, **24**, 2825-2838. https://doi.org/10.1039/D2GC00146B [Print ISSN: 1463-9262; OnlineISSN: 1463-9270; IF 9.2 (2024)]	As a dual approach, we disclosed electrochemical and mechanochemical methods for the efficient and straightforward synthesis of a new series of functionalized dihydrofuro[3,2-c]chromenones using warfarin analogues. The notable features of these newly developed protocols include avoiding the use of transition metal catalysts, short reaction times, good to excellent yields, scalability, and eco-friendliness. These new series of heterocycles will draw the interest of both academia and industry.

	(***Selected as a 2022 HOT Green Chemistry Article***) Article Type: Original	
8.	Goutam Brahmachari*, Indrajit Karmakar, and Pintu Karmakar (2021), Catalyst- and solvent-free C*sp2*−H functionalization of 4-hydroxycoumarins *via* C-3 dehydrogenative aza-coupling under ball-milling. *Green Chemistry*, **23**, 4762-4770. https://doi.org/10.1039/D1GC01341F [Print ISSN: 1463-9262; OnlineISSN: 1463-9270; IF 9.2 (2024)] Article Type: Original	A one-pot procedure for the synthesis of a new series of coumarin hydrazones under ball-milling in the absence of any catalysts/additives and solvents was explored. Catalyst- and solvent-free reaction conditions, no chromatographic purification, high yields of products at short reaction times, a clean reaction profile, and gram-scale synthetic applicability make this procedure green and cost-effective.
9.	**Goutam Brahmachari**,* Indrajit Karmakar Visible light-induced and singlet oxygen-mediated photo-chemical conversion of 4-hydroxy-alpha-benzopyrones to 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides/carboxylates using rose bengal as a photosensitizer. *The Journal of Organic Chemistry*, 2020, **85**, 8851-8864. https://doi.org/10.1021/acs.joc.0c00726 PubMed PMID: 32543197 Impact Factor: 3.6 (2024) Article Type: Original	First-time report on developing a visible light-induced and singlet oxygen-mediated green protocol for skeletal rearrangement of 4-hydroxy-α-benzopyrones to a new series of biorelevant 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxamides and 2-hydroxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylates at ambient temperature.
10.	**Goutam Brahmachari*** (2020). Catalyst- and additive-free decarboxylative C-4 phosphorylation of coumarin-3-carboxylic acids at ambient conditions. *Advanced Synthesis & Catalysis*, **362**, 5411-5421. https://doi.org/10.1002/adsc.202001054 [Print ISSN:1615-4150; Online ISSN:1615-4169; IF 4.0 (2024)] Article Type: Original	Innovative development of a catalyst- and additive-free practical and green synthetic strategy for decarboxylative C-4 phosphorylation of coumarin-3-carboxylic acids, for the first time, to access a series of substituted 4-(diarylphosphoryl)chroman-2-ones at ambient conditions. The developed protocol was successfully applied to large-scale synthesis.

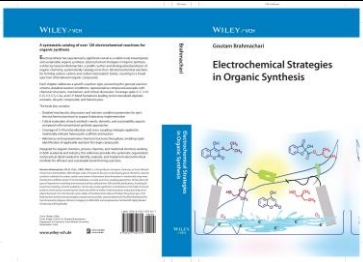
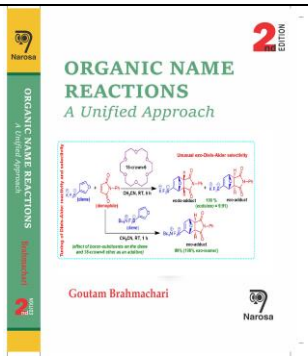
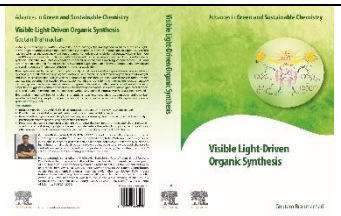
19. Publication Details

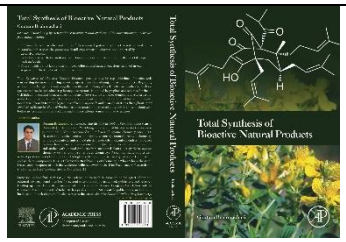
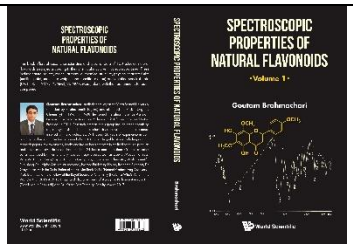
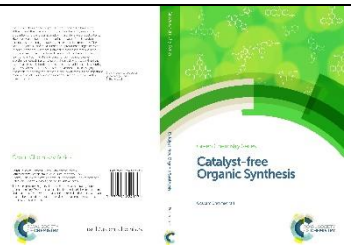
Publication Summary at a glance

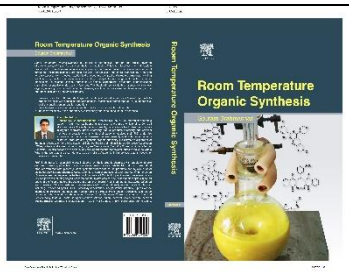
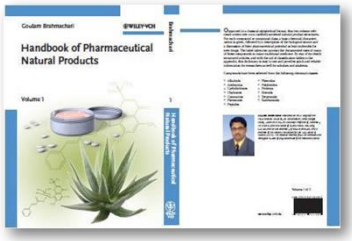
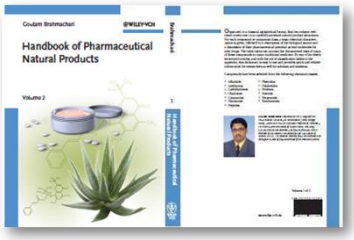
Total publications: 307 (as of 16.06.2026) Books: **30** Research Publications: **213** Educational/popular articles/reports: **03** Editorials in guest-edited journal issues: **04** Invited Book Chapters in edited volumes: **57**	***Others*** **Conference Proceedings: 170** **Invited Talks: 80** **Session chairing: over 50**

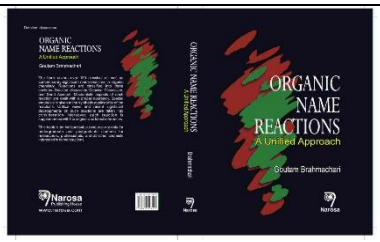
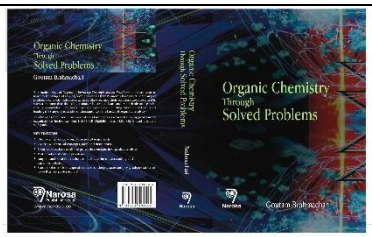
(a) Books Published (authored and edited): [Total 30]

(I) Single-authored books (11)

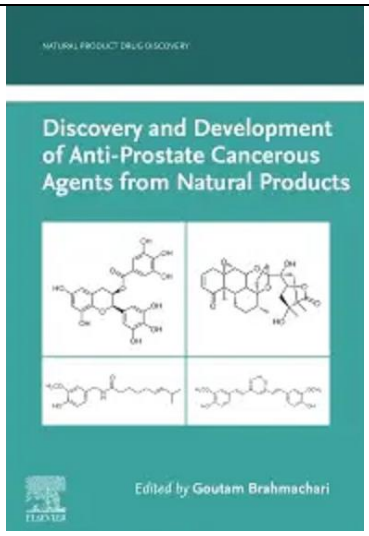
Sl. No.	Book Cover	Book Details
11		**Electrochemical Strategies in Organic Synthesis** *(with a foreword by Prof. Siegfried R. Waldvogel, Director, Max-Planck-Institute for Chemical Energy Conversion; Karlsruhe Institute of Technology, Germany)*, 1st Edn., Wiley-VCH, Weinheim, Germany, 2026, ISBN 978-3-52735576-1 (***forthcoming in 2026***).
10		**Organic Name Reactions: A Unified Approach** *(with a foreword by Prof. Srinivasan Chandrasekaran)*, 2nd Edn., Narosa Publishing House Pvt. Ltd., New Delhi, 2026, ISBN 978-81-8487-812-7 (***forthcoming in 2026***).
9		**Visible Light-Driven Organic Synthesis** (*with a foreword by Prof. Lutz Ackermann*), 1st Edn., Elsevier, Amsterdam, The Netherlands, August 2024; ISBN: 9780323958936.

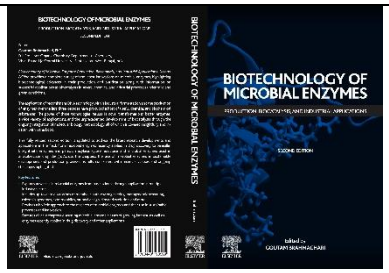
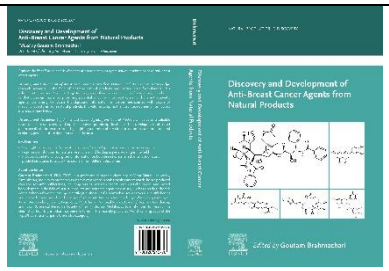
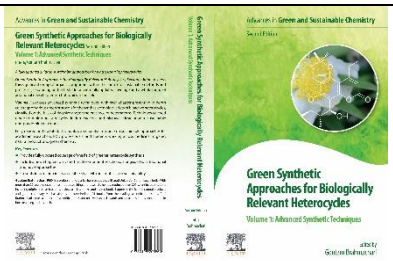
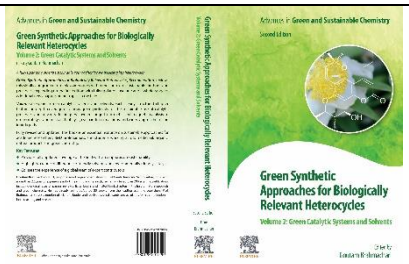
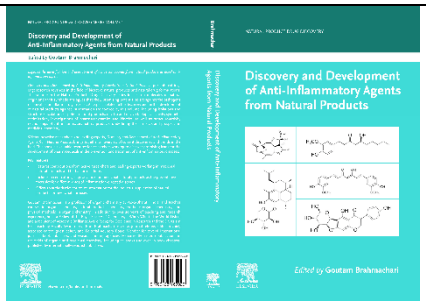
8		**Total Synthesis of Bioactive Natural Products** (*with a foreword by Prof. Srinivasan Chandrasekaran*), Academic Press (Elsevier), Amsterdam, The Netherlands, May 2019; ISBN: 9780081028223
7		**Spectroscopic Properties of Natural Flavonoids** (*with a foreword by Prof. Amit Basak*), World Scientific Publishing Co., Singapore, October 2018; ISBN: 978-981-3275-68-3
6		**Catalyst-Free Organic Synthesis** (under Green Chemistry Series; Book No. 51), The Royal Society of Chemistry, Cambridge, London, November 2017, ISBN: 978-1-78262-412-7. ***Book review:*** "…….This book Catalyst-free organic synthesis, by Goutam Brahmachari, is very comprehensive, and has exhibited the state-of-the-art technology in green chemistry. This book is a great piece of technical literature and unique in regards to being about "Catalyst-free" as there are many books on "catalyst-based organic synthesis". ……The book provides a broad overview of state-of-the-art catalyst-free reactions in organic synthesis. It is strongly recommended for chemical researchers as well as for interested teachers and students, especially those who are involved in catalysis' (*Green Process and Synthesis*, 2018, 7, 180, https://doi.org/10.1515/gps-2017-0184) reviewed by Prof. Can Jin: Zhejiang University of Technology, Hangzhou 310014, P.R. China; and Department of Chemical Engineering and Chemistry, Eindhoven University of Technology, 5612 AP Eindhoven, The Netherlands.

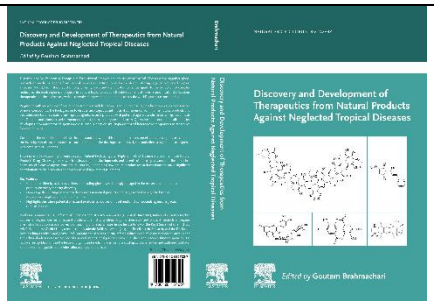
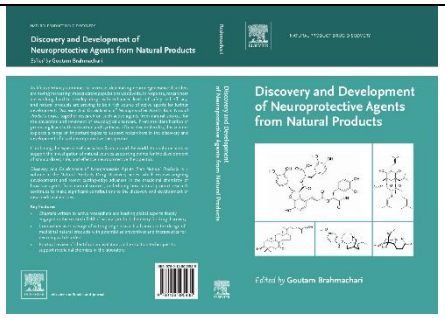
5		**Room Temperature Organic Synthesis** (*with a foreword by Prof. Paul Anastas*), Elsevier, Amsterdam, The Netherlands, March 2015; ISBN: 9780128010259.
4		**Handbook of Pharmaceutical Natural Products - Vol. 1** (Hardcover), 1st Edition, 2010. XX, 926 Pages, ISBN-10: 3-527-32148-9; ISBN-13: 978-3-527-32148-3. Publisher: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.
3		**Handbook of Pharmaceutical Natural Products - Vol. 2** (Hardcover), 1st Edition, 2010. XX, 926 Pages, ISBN-10: 3-527-32148-9; ISBN-13: 978-3-527-32148-3. Publisher: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. ***Book Revew-1.*** "…the author has succeeded in compiling an impressive and highly informative reference text on many pharmaceutically relevant natural products. I would recommend this book to everyone involved in research with biologically active natural products as a convenient and practical source of high quality information….." (*ChemMedChem*, 2010, 5, 10, 1788-1789) reviewed by Prof. Dr. Karl-Heinz Altmann, ETH Zrich (Switzerland). ***Book Review-2.*** "… a useful addition to the bookshelf of every natural material specialist…" – *Pharmazie in unserer Zeit*, 2010, 39(5), 415 (review in German) by Prof. Dr. Thomas Winckler, Jena (Germany). ***Book Review-3.*** "…..This book is clearly for specialists, the natural product chemist and the pharmaceutical chemist… I do not know whether Goutam Brahmachari intends a revised edition in the future but I am sure there will be an ongoing demand for a book

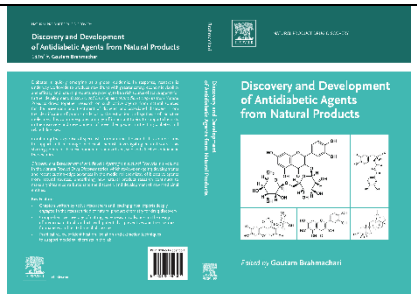
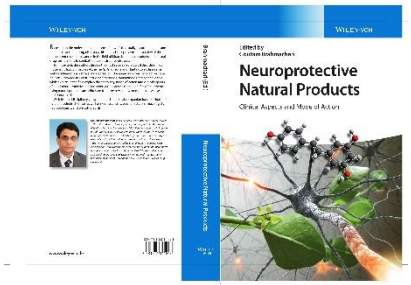
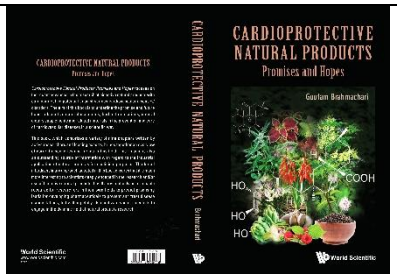
		like this" (*Reference Reviews*, 2011, 25, 3, 42-43) by John Goodier, Consultant, Goldhawk Information, London, UK. Visit: http://www.wiley-vch.de/publish/en/books/ISBN3-527-32148-9/
2		**Organic Name Reactions: A Unified Approach**, (*with a foreword by Prof. S. Chandrasekaran*), Alpha Science International Ltd., Oxford, U.K., 2006 (ISBN: 1-84265-304-0); co-published by Narosa Publishing House Private Ltd., New Delhi, India, 2006 (ISBN: 81-7319-719-2), Reprints 2007, 2009, 2011, 2012, 2014, 2016, 2017, 2021.
1		**Organic Chemistry Through Solved Problems** (*with a foreword by Prof. Swapnadip Thakur*), Narosa Publishing House Private Ltd., New Delhi, India, 2007 (ISBN: 81-7319-816-0), Reprints 2009, 2011, 2012, 2014, 2017.

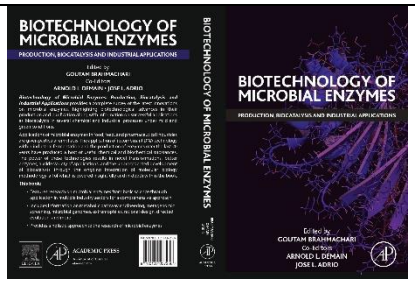
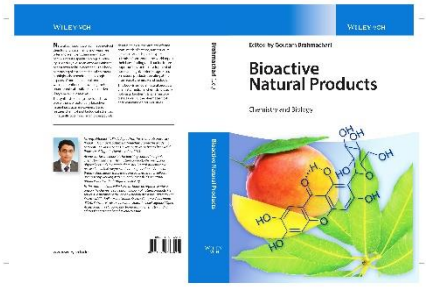
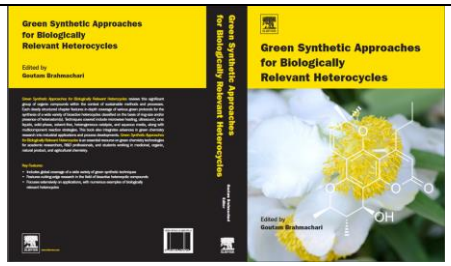
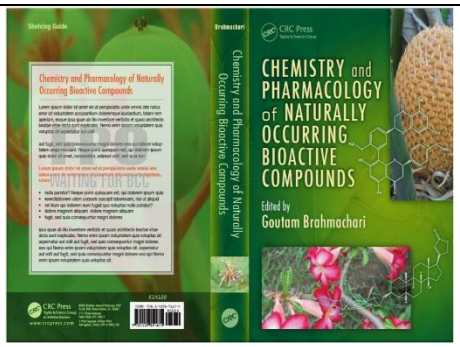
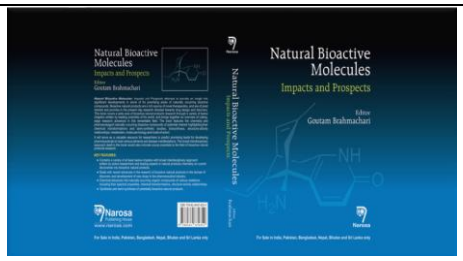
(II) Edited Books (19)

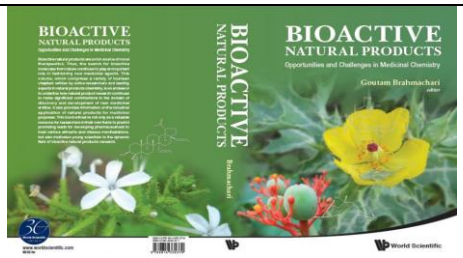
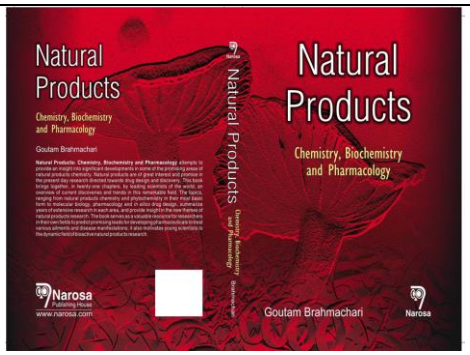
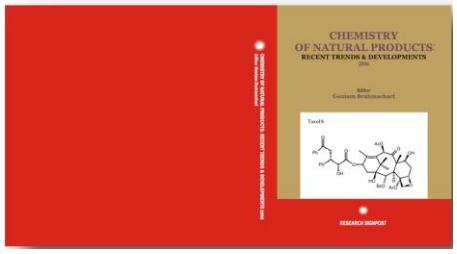
Sl. No.	Book Cover	Book Details
19		**Discovery and Development of Anti-Prostate Cancerous Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 6)**, Elsevier, 2025. ISBN: 9780443218422 (Forthcoming, in production)

18		**Biotechnology of Microbial Enzymes: Production, Biocatalysis and Industrial Applications**, 2nd Edition, Academic Press, London, Elsevier, 2023, ISBN: 9780443190599
17		**Discovery and Development of Anti-Breast Cancer Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 5)** (*with foreword by* Prof. Subrata Ghosh and Prof. Ramapati Tripathi), Elsevier, 2021. ISBN: 9780128212776
16		**Green Synthetic Approaches for Biologically Relevant Heterocycles – Volume 1**, (*with a foreword by Prof. Dr. Peter Licence*), 2nd edition, **Elsevier Inc.**, Waltham, MA, USA, 2021 (ISBN: 978-0-12-820586-0)
15		**Green Synthetic Approaches for Biologically Relevant Heterocycles – Volume 2**, (*with a foreword by Prof. Dr. Vinod K. Singh*), 2nd edition, **Elsevier Inc.**, Waltham, MA, USA, 2021 (ISBN: 978-0-12-820792-5)
14		**Discovery and Development of Anti-Inflammatory Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 4)** (*with a foreword by* Prof. G. Mugesh, IISc, Bangalore), Elsevier, 2019. ISBN: 9780128169926

13		**Discovery and Development of Therapeutics from Natural Products Against Neglected Tropical Diseases (Natural Product Drug Discovery Series – Vol. 3)** (*with a foreword by Prof. Alan Fairlamb, University of Dundee, UK*), Elsevier, April, 2019. ISBN: 978-0-12-815723-7
12		**Discovery and Development of Neuroprotective Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 2)** (*with a foreword by* Dr. Volkan Kisakürek, Zürich, Switzerland), Elsevier, 2017. ISBN: 9780128095935 (June, 2017) **Book Review 1**. (E. A. Abourashed, *Journal of Natural Products*, **2018**, *81*, 1917-1918) "….As health care providers continue to seek new and effective approaches for managing neurodegenerative diseases, Discovery and Development of Neuroprotective Agents from Natural Products attempts to narrow the drug discovery gap through its current and comprehensive coverage of the subject matter. The book provides a well-balanced content that spans major neurodegenerative diseases and potential therapeutic agents that may be obtained from natural sources and/or synthetic routes based on naturally occurring lead compounds…..The book should appeal to a broad audience with diverse backgrounds including chemistry, biology, pharmacy, and medicine. It can also be a valuable resource for researchers, academicians, and graduate students. In addition to enjoying the book's content, its readers will probably be able to identify viable research directions for the discovery and development of new and promising neuroprotective agents." Prof. Ehab A. Abourashed, Medical College of Wisconsin School of Pharmacy, Milwaukee, Wisconsin, United States. **Book Review 2**. (S. Chandrasekhar, *Current*

		Science, **2018**, *115*, 2164-2165) "This book discusses about recent developments in the area of neuroprotective natural products with respect to their isolation, characterization, and their pharmaceutical applications in the area of neurodegenerative diseases……..Overall the book gives a detailed insight into natural products as neuroprotective agents and is recommended for colleges/institutions and industries working in the areas of natural products isolation and/or in the exploration of compounds for their activity on the central nervous system." Prof. Srivari Chandrasekhar, CSIR-Indian Institute of Chemical Technology, Hyderabad, India.
11		**Discovery and Development of Antidiabetic Agents from Natural Products (Natural Product Drug Discovery Series – Vol. 1)** (*with a foreword by Dr. David G. I. Kingston and Dr. Arnold L. Demain*), Elsevier, 2016. ISBN: 9780128094501
10		**Neuroprotective Natural Products: Clinical Aspects and Mode of Action**, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2017 (ISBN: 978-3527341863).
9		**Cardioprotective Natural Products: Promises and Hopes**, (*with a foreword by Dr. Bradley K. McConnell, University of Houston, USA*), World Scientific Publishing Co., Singapore, November 2017 (ISBN: 978-981-3231-15-3)

8		**Biotechnology of Microbial Enzymes: Production, Biocatalysis and Industrial Applications** (ISSBN: 978-0-12-803725-6), **Academic Press**, London, Elsevier, 2016 (co-editors: Dr. Arnold L. Demain and Dr. Jose L. Adrio).
7		**Bioactive Natural Products: Chemistry & Biology** (*with a foreword by Prof. Bimal K Banik*), **Wiley-VCH Verlag GmbH & Co. KGaA**, Weinheim, Germany, 2015 (ISBN: 9783527337941).
6		**Green Synthetic Approaches for Biologically Relevant Heterocycles**, (*with a foreword by Prof. Sciott McN. Sieburth*), **Elsevier Inc**., Waltham, MA, USA, 2014 (ISBN: 978-0-12-800700-0).
5		**Chemistry and Pharmacology of Naturally Occurring Bioactive Compounds**, (*with a foreword by Prof. Raphael Mechoulam and Prof. Takuo Okuda*), **CRC Press/Taylor Francis Group**, LLC, USA, 2013 (ISBN: 978-1-4398-9167-4).
4		**Natural Bioactive Molecules: Impacts & Prospects**, (*with a foreword by Prof. Dr. Arnold Demain*), Alpha Science International Ltd., Oxford, U.K., 2013 (ISBN: 978-1-84265-780-5); co-published by Narosa Publishing House Private Ltd., New Delhi, India, 2013 (ISBN: 978-81-8487-235-4).

3		**Bioactive Natural Products: Opportunities and Challenges in Medicinal Chemistry**, (*with a foreword by Dr. David J. Newman*), World Scientific Publishing Co., Singapore, 2011 (ISBN: 978-981-4335-37-9).
2		**Natural Products: Chemistry, Biochemistry and Pharmacology**, (*with a foreword by Prof. Jorg Heukelbach and Prof. Ricke Speare*), Alpha Science International Ltd., Oxford, U.K., 2009 (ISBN: 978-1-84265-450-7); co-published by Narosa Publishing House Private Ltd., New Delhi, India, 2009 (ISBN: 978-81-7319-886-1).
1		**Chemistry of Natural Products: Recent Trends and Developments**, (*with a foreword by Dr. Manksukh C. Wani*), Research Signpost, Trivandrum, Kerala, India 2006 (ISBN: 81-308-0140-X).

(b) Research Publications [Total 213]

212. Debojyoti Mukherjee, Indrajit Karmakar, Soma Ghosh, Goutam Brahmachari* (2026), Electro- and mechanochemical C(sp2)-H chalcogenations of 4-hydroxycoumarins/4-hydroxy-*N*-methylquinolin-2-one: A dual green synthetic approach. *Chemistry – An Asian Journal*, **21**, e70828. https://doi.org/10.1002/asia.70828

212. Koushik Pal, Pintu Karmakar, Goutam Brahmachari* (2026), Sonochemistry- and mechanochemistry-driven one-pot synthesis of polyfunctionalised 5-iodo-1H-1,2,3-triazoles through a copper(I)-catalysed click chemistry. *RSC Mechanochemistry*, published online on May 20, 2026, https://doi.org/10.1039/D6MR00036C

211. Indrajit Karmakar, Sudipa Chatterjee, Souvik Das, Asanjan Brahmachari, Gourab Kanti Das, Thathagata Choudhuri, **Goutam Brahmachari*** (2026), Functionalized diphenyl (2-oxochroman-4-yl) phosphonates: dual synthetic approaches, mechanistic insights and exploration of a promising anti-lung cancerous molecule. *Synlett*, **37**, 522-530. DOI: 10.1055/a-2725-5792

210. Pintu Karmakar, **Goutam Brahmachari*** (2025). Sono-and mechanochemistry-assisted dual strategies for cyanomethylation of carboxylic acids: robust and practical synthetic protocols to

a diverse series of cyanomethyl esters. *Chemistry – a European Journal*, **31**, e01966 (Very Important paper). https://doi.org/10.1002/chem.202501966

209. Koushik Pal, Pintu Karmakar, **Goutam Brahmachari*** (2025). Mechanochemistry-driven solvent-free synthesis of biologically relevant diversely substituted 2-amino-1,4-naphthoquinones. *RSC Mechanochemistry*, **2**, 833-845. https://doi.org/10.1039/D5MR00068H

208. Pintu Karmakar, Atanu Diger, **Goutam Brahmachari*** (2025). Mechanochemistry-Driven Synthetic Approach for Halogenated Derivatives of 2-Amino-1,4-Naphthoquinones, Indoles, Indazoles and Coumarins. *Asian Journal of Organic Chemistry*, **14**, e202500428. https://doi.org/10.1002/ajoc.202500428

207. Debojyoti Mukherjee, Indrajit Karmakar, **Goutam Brahmachari*** (2025). Sono- and mechanochemical dual syntheses of bio-relevant aryldiazenyl-substituted phosphine oxides/phosphonates via P(O)-H functionalisation. *Green Chemistry*, **27**, 2565-2577. https://doi.org/10.1039/D4GC05501B

206. Anindita Bhowmick, **Goutam Brahmachari*** (2025). Iron(III) triflate-assisted skeletal rearrangement of warfarin framework: A direct synthetic route to a diverse series of biorelevant flavone-coumarin molecular hybrids. *Asian Journal of Organic Chemistry*, **14**, e202400676. https://doi.org/10.1002/ajoc.202400676

205. Indrajit Karmakar, **Goutam Brahmachari***, Chin-Fa Lee (2025), Electrochemistry-driven seleno-functionalization of diverse organic scaffolds: a recent update, *Chemistry – An Asian Journal*, **20**, e00817, https://doi.org/10.1002/asia.202500817

204. Rajib Sarkar, Ayan Bandyopadhyay, **Goutam Brahmachari*** (2025). Residue-specific protein-glycan conjugation strategies for the development of pharmaceutically promising glycoconjugate vaccines: A recent update. *Carbohydrate Research*, **552**, 109446 (invited). https://doi.org/10.1016/j.carres.2025.109476

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20. Scientific Contributions of Professor Goutam Brahmachari

(a) In Brief (50 words)

Professor Goutam Brahmachari has pioneered practical, green synthetic methodologies for carbon-carbon and carbon-heteroatom bond formation, constructing medicinally important scaffolds and functionalized heterocycles via C-H functionalization, cascade reactions, and cross-coupling. He has also made outstanding, globally recognized contributions to natural products chemistry and Indian medicinal plant profiling.

(b) Scientific contribution (250 words)

Professor Goutam Brahmachari, over a distinguished three-decade career, is a globally recognized leader in sustainable organic synthesis and natural product chemistry at Visva-Bharati (a Central University), founded by Gurudev Rabindranath Tagore. His research epitomizes the shift to "*Zero-Waste Molecular Engineering*" by pioneering atom-economical, catalyst-free, and solvent-free transformations for green pharmaceutical manufacturing. Utilizing ultrasound, ball milling, visible light, and electro-synthesis, his methods streamline the

construction of complex heterocyclic scaffolds, significantly reducing the environmental E-factor of chemical production.

Parallel to synthetic innovations, his systematic phytochemical mapping of India's medicinal flora bridges traditional ethnomedicinal knowledge with modern chemical validation. By identifying unique bioactive metabolites with antimicrobial and anticancer potential, his work directly contributes to national bio-resource valuation and the "discovery-to-delivery" drug pipeline.

His scholarly impact is quantified by 300+ publications and 30 foundational books in the domains of green and medicinal chemistry, published with premier global publishers (Elsevier, Wiley-VCH, RSC). Backed by 8,150+ citations (h-index: 47; i10: 155), he is ranked in the World's Top 2% Scientists (Stanford) and the top 0.05% globally (ScholarGPS). An elected FRSC, FAScT, and recipient of the CRSI Bronze Medal and INSA Teachers Award, his legacy includes mentoring 20 PhD scholars and thousands of next-generation chemists. Professor Brahmachari's "Green Chemistry 2030" roadmap positions Indian science at the forefront of global sustainability.

Keywords: Organic Synthesis; Synthetic Methodology; Green Chemistry; Bioactive Natural Products

(c) Scientific contribution in extended form (1000 words)

Professor Goutam Brahmachari: A Legacy of Excellence in Sustainable Chemical Sciences

Dr. Goutam Brahmachari, a Full Professor of Organic Chemistry at Visva-Bharati (a Central University founded by Gurudev Rabindranath Tagore), Santiniketan, is a globally recognized leader in sustainable organic synthesis, green chemistry, and natural product research. Over a distinguished professional career spanning nearly three decades, Professor Brahmachari's work has epitomized the vital fusion of fundamental molecular innovation with the pressing practical demands of global and national sustainability. His scientific contributions are dual-pronged, characterized by the trailblazing development of "green" molecular architectures and the systematic chemical and biological mapping of India's rich medicinal flora. Holding the elite post-doctoral degree of Doctor of Science (D.Sc.), an elected Fellow of the Royal Society of Chemistry (FRSC), London, and consistently ranked among the world's elite scientific minds, Professor Brahmachari's career serves as an outstanding testament to the power of Indian academia in driving global scientific discourse.

Major Scientific Contributions

The central impact of Professor Brahmachari's research lies in orchestrating a paradigm shift in complex organic synthesis, transitioning from traditional, waste-heavy chemical processes to environmentally benign, low-energy protocols. By combining this synthetic agility with the rigorous isolation and characterization of novel bioactive phytochemicals, his laboratory has effectively accelerated the "discovery-to-delivery" pipeline for new drug candidates, directly contributing to national bio-resource valuation and technological self-reliance.

1. Pioneering Green Chemistry and Sustainable Molecular Synthesis

At the heart of Professor Brahmachari's scientific legacy is an unyielding commitment to the twelve principles of Green Chemistry. His research group has pioneered atom-economical, energy-efficient, and waste-minimized synthetic protocols for the construction of complex

heterocyclic scaffolds, which form the structural backbones of modern therapeutics. Backed by competitive research grants from India's top funding bodies—including the Anusandhan National Research Foundation (ANRF), CSIR, DBT, and UGC—his key conceptual and practical innovations include:

- ***Ambient-Temperature, Catalyst-, and Solvent-Free Transformations:*** His group has developed elegant synthetic routes that operate at ambient temperatures and pressures. By eliminating toxic catalysts, hazardous chemical reagents, and volatile organic solvents (VOCs), these protocols drastically reduce the environmental footprint of chemical manufacturing. This work achieves excellent atom economy and minimizes the environmentally detrimental factors.
- ***Advanced Synthetic Methodologies:*** By strategically leveraging C-H functionalization, multi-component cascade transformations, and cross-coupling approaches, his laboratory has streamlined the multi-step construction of medicinally vital molecules into single-pot operations, preventing the loss of materials and energy.
- ***Enabling Green Technologies:*** Embracing the frontier of modern chemical engineering, Professor Brahmachari has integrated sustainable energy inputs—such as ultrasound activation, mechanochemical ball-milling, visible-light photoredox catalysis, and electro-synthesis. These energy-efficient tools enable complex bond-forming reactions that were previously considered difficult or environmentally costly, opening new pathways for clean chemical manufacturing.

  These innovations provide a scalable blueprint for a green pharmaceutical and fine-chemical sector. His work aligns perfectly with India's national priorities, including the *National Mission on Green India*, *Atmanirbhar Bharat*, the transition to a *Circular Economy*, and the United Nations Sustainable Development Goals (SDGs).

2. Unlocking the Phytochemical Potential of Indian Bio-Resources

Parallel to his synthetic breakthroughs, Professor Brahmachari has made outstanding, globally recognized contributions to Natural Product Chemistry. Operating from the bio-culturally rich landscape of Santiniketan, he has conducted systematic phytochemical investigations into several underexplored Indian medicinal plants historically utilized in traditional indigenous medicine.

His targeted extraction, isolation, and spectroscopic structural elucidation have unearthed unique secondary metabolites showcasing potent antimicrobial, antioxidant, and anticancer properties. By bridging ancient ethnomedicinal knowledge with rigorous modern chemical validation, his research preserves India's intangible heritage while providing solid scientific proof of its efficacy. This rigorous value-addition to local botanical resources strengthens India’s sovereign position in the global natural product drug discovery market and safeguards native biodiversity for national health and economic security.

Global Scholarly Impact and Quantitative Excellence

The scale of Professor Brahmachari’s scientific influence is quantified by extraordinary bibliometric indicators that place him at the absolute zenith of his international discipline:

- ***Scholarly Output:*** A prolific author of more than 300 scientific publications (including 211 research publications in high-impact international journals, 57 invited book chapters, and 30

authored/edited books with premier international publishers, such as Elsevier, Wiley-VCH, CRC Press, World Scientific, and the Royal Society of Chemistry).

- ***Global Literature Contribution:*** He has authored/edited 30 foundational reference books in the domains of green and medicinal chemistry, published exclusively by the world's leading scientific houses, including Elsevier, Wiley-VCH, the Royal Society of Chemistry, CRC Press, and World Scientific.
- ***Citation Merit and World Rankings:*** His research has garnered 8,150+ citations from peers globally, establishing a formidable h-index of 47 and an i10-index of 157 (as of June 2026). Consequently, he has been featured continuously in the Stanford University/Elsevier World Ranking of the Top 2% Scientists (2020–2025) across both career-long and single-year metrics. Crucially, the ScholarGPS global analytics platform recognizes him as a *Highly Ranked Scholar (Lifetime)*, placing him in the *top 0.05% of all scholars worldwide.*

Editorial Leadership and International Scientific Governance

As the Founding Series Editor of the prestigious Elsevier Book Series *'Natural Product Drug Discovery'*, Professor Brahmachari has actively shaped the global narrative on the evaluation and translation of natural products into modern medicine. His leadership roles as Co-Editor-in-Chief of Current Green Chemistry, Guest Editor for leading journals such as *Tetrahedron* and *Tetrahedron Letters*, and advisory board member for numerous international publications highlight his status as an international gatekeeper of scientific quality. His unique ability to synthesize complex laboratory data into authoritative reference texts has educated a generation of chemical researchers worldwide.

National Laurels and Institutional Leadership

The highest echelons of the scientific community have consistently validated Professor Brahmachari's contributions. He is an Elected Fellow of the Royal Society of Chemistry (FRSC) and the West Bengal Academy of Science & Technology (FAScT). His major honors include the prestigious CRSI Bronze Medal (2021) from the Chemical Research Society of India and the Dr. Basudev Banerjee Memorial Award (2021) from the Indian Chemical Society.

Reflecting his rare ability to balance elite research with dedicated pedagogy, he was honored with the INSA Teachers Award (2019) by the Indian National Science Academy, New Delhi. His recent accolades in 2025—the Acharya P. C. Ray Memorial Lecture Award (ISNA, Kolkata) and the Dr. Satyajit Chakraborti Memorial Award—celebrate a lifetime of global service to the chemical sciences.

At Visva-Bharati, he has served with distinction as the Head of the Department of Chemistry, Chairman of the Board of Studies, and Coordinator of the International Collaborations Wing, significantly expanding the university's international research partnerships.

Mentorship and National Human Resource Development

Professor Brahmachari's enduring legacy is carried forward by the human capital he has meticulously nurtured. Throughout his tenure, he has inspired thousands of undergraduate and postgraduate students, transforming them into skilled scientists, educators, and molecular inventors serving the nation. He has directly guided 20 Ph.D. scholars to completion and supervised over 70 Master's dissertations, and trained thousands of next-generation chemists.

This formidable cadre of researchers now actively contributes to premier academic institutions and industrial research laboratories globally.

Future Vision: "Green Chemistry 2030"

Looking ahead, Professor Brahmachari's research roadmap focuses on fully realizing **"Zero-Waste Molecular Engineering."** His objective is to build an integrated synthetic platform that couples renewable energy inputs (such as solar and electrochemical power) with renewable feedstocks (such as biomass-derived platform chemicals) to synthesize life-saving pharmaceuticals, completely decoupling drug production from fossil reserves.

Conclusion

A rare synergy of innovation, sustainability, and dedication defines Professor Goutam Brahmachari's scientific and professional career. His work in green chemistry provides the tools for a cleaner future, and his research in natural products preserves and promotes India's botanical heritage. His scholarly impact ensures that Indian science remains at the forefront of global innovation. His multifaceted contributions make him an exemplary candidate for prestigious national/international recognitions, representing the very best of Indian scientific achievement and its service to the global community.

21. Vision of Professor Goutam Brahmachari

Vision Statement: "Green Chemistry 2030" – A Roadmap for Zero-Waste Molecular Engineering

Objective: To establish a transformative paradigm in chemical synthesis that aligns India's pharmaceutical and fine-chemical industries with the global mandates of sustainability, circular economy, and net-zero emissions.

The Core Philosophy

The "**Green Chemistry 2030**" roadmap is predicated on the transition from "Waste Management" to "***Zero-Waste Molecular Engineering***". While traditional green chemistry focused on reducing harm, this roadmap seeks to eliminate the concept of waste entirely by redesigning the fundamental architecture of chemical reactions. It is a commitment to ensuring that the molecules of tomorrow are born from clean energy and renewable matter.

Strategic Pillars of the 2030 Roadmap

1. Energy-Autarkic Synthesis (The Power of Physics) The roadmap prioritizes the replacement of traditional thermal heating with renewable and "clean" energy sources. By leveraging ***electrosynthesis, sonochemistry, mechanochemistry,*** *and* ***visible-light-driven photocatalysis****,* we aim to achieve complex molecular transformations at room temperature. This minimizes the carbon footprint of chemical manufacturing and reduces the energy intensity of industrial processes.

2. Feedstock Sustainability & The Circular Bio-Economy Transitioning away from petroleum-derived precursors is essential for India's resource security. The 2030 vision focuses on the **valorization of biomass-derived feedstocks** and agro-waste. By converting renewable biological resources into high-value platform chemicals and active pharmaceutical ingredients (APIs), this roadmap supports the **National Mission on Sustainable Agriculture** and the **Atmanirbhar Bharat** initiative.

3. Catalyst-Free and Solvent-Free Frameworks A primary goal is the development of "neat" reaction conditions that eliminate the need for hazardous volatile organic compounds (VOCs) and expensive, toxic metal catalysts. Our focus on **water-mediated synthesis** and **catalyst-free**

transformations provides a functional blueprint for a safer, non-toxic industrial environment that protects both workers and the ecosystem.

4. The "Discovery-to-Delivery" Pipeline for Public Health The roadmap integrates the chemical mapping of India's indigenous medicinal flora with green synthetic scaling. By identifying bioactive natural scaffolds and developing green methods to synthesize their derivatives, we ensure that the next generation of life-saving drugs—particularly in oncology and antimicrobial research—is both affordable and environmentally benign.

National Impact and Social Responsibility

"Green Chemistry 2030" is more than a laboratory goal; it is a pedagogical mission. It aims to:

- **Training a "Green Workforce":** Equipping the next generation of PhD scholars and researchers with the skills to lead a sustainable chemical industry.
- **Supporting National Goals:** Directly contributing to India's **2070 Net-Zero target** and the **United Nations Sustainable Development Goals (SDGs)**.
- **Public Science Advocacy:** Using this framework to inspire school and college students through Social Scientific Responsibility (SSR) activities, fostering a culture of "Science for Sustainability."

Conclusion

By 2030, the objective is to move beyond the laboratory bench to provide the Indian chemical industry with a toolkit of "Zero-Waste" protocols. This roadmap ensures that India remains not just a global manufacturing hub, but a global **innovation leader** in the transition toward a cleaner, greener, and more self-reliant future.

22. My Referees: A List of 6 Distinguished Scientists

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Sono-And Mechanochemistry-Assisted Dual Strategies for Cyanomethylation of Carboxylic Acids: Robust and Practical Synthetic Protocols to a Diverse Series of Cyanomethyl Esters

Pintu Karmakar[a] and Goutam Brahmachari*[a]

This paper is dedicated to Prof. Srinivasan Chandrasekaran on the occasion of his forthcoming 80th birthday on 15th November, 2025

We herein disclose a dual synthetic approach involving sonochemical and mechanochemical strategies for a diverse series of cyanomethyl esters of carboxylic acids. Both synthetic protocols offer a straightforward, efficient, and practical alternative to preparing this important class of biologically and synthetically promising organic compounds. Significant advantages of the newly developed methods include mild reaction conditions, avoidance of any metal catalysts and external oxidants, shorter reaction times (in minutes), good to excellent yields, broad substrate scope and tolerance of other various functional groups, gram-scale applicability, and reusability of the solid surface.

1. Introduction

In synthetic organic chemistry, nitrile or cyano compounds are promising building blocks for constructing a diverse array of important complex molecular structures.[1] In addition, these compounds act as valuable synthetic intermediates, providing easy access to versatile groups of organic compounds, including amines, amides, carbonyls, carboxylic acids, esters, and many others.[2,3] Hence, methodologies for introducing the cyano group into an organic compound have been of significant interest to synthetic chemists.

A literature survey reveals that the cyano functionality plays an important role in demonstrating biological potency in bioactive natural compounds and their synthetic analogues. For example, cyanogenic glycosides, such as amygdalin and linamarin, serve as chemical defense agents in the plant kingdom.[4] Another group of compounds containing cyano-substituted alkaloidal architectures, such as cytisine derivatives and cyanocycline A, exhibit potent biological activities.[5] Furthermore, certain marine-derived natural products, such as axisonitrile-3, possess either nitrile or isonitrile functionalities crucial to their antimicrobial and anticancer properties.[6] A few selected examples of bioactive cyano group-containing molecules are shown in Figure 1.[7]

The direct functionalization of carboxylic acids represents a powerful strategy for constructing structurally diverse and value-added molecules from readily available precursors. Directly incorporating a cyanomethyl group into acid frameworks is especially appealing, as the strategy offers a straightforward way to develop targeted cyanomethyl ester derivatives. Over the last few years, with the discovery of the cyanomethylation process, a variety of cyanomethylating reagents like acetonitrile and its derivatives,[8,9] trimethylsilylacetonitrile (TMSAN)[10] have emerged. However, these cyanomethylating agents have certain limitations, particularly requiring harsh reaction conditions and/or nonapplicability toward a wide range of substrates. Recently, bromoacetonitrile has thus successfully emerged as a cost-effective and efficient cyanomethylating agent for organic substrates.[11]

Our comprehensive literature survey disclosed just one synthetic methodology for cyanomethylation of carboxylic acids; in 2015, Wan and co-workers[12] reported a cyanomethylation strategy for carboxylic acids using cyanoacetic acid as the reagent in the presence of *n*-Bu_4NI (TBAI) as a catalyst, *tert*-BuOOH as an external oxidant, and NaOAc as an additive, under heating at 80 °C for 12 hours (Scheme 1a). With the inherent synthetic elegance, this method is still associated with several limitations, particularly using external oxidants and additives to the catalytic system, heating, and prolonged reaction time (12 hours). Hence, the design and development of facile and eco-friendly practical synthetic strategies to functionalize cyanomethyl esters is highly warranted. As part of our green chemistry-driven organic synthesis,[13] we have been successful in exploring a dual approach, both sonochemical and mechanochemical strategies, to access a huge array of diversely substituted cyanomethyl carboxylates, as outlined in Scheme 1b. These newly developed methods offer several notable advantages, including metal-free synthesis, avoidance of any additives, external oxidants, and solvents (in the case of mechanochemistry), short reaction times (in minutes), broad substrate scopes, good to excellent yields (up to 96%), reusability of the solid surface, and gram-scale synthetic applications. The applications of sonochemical[14]

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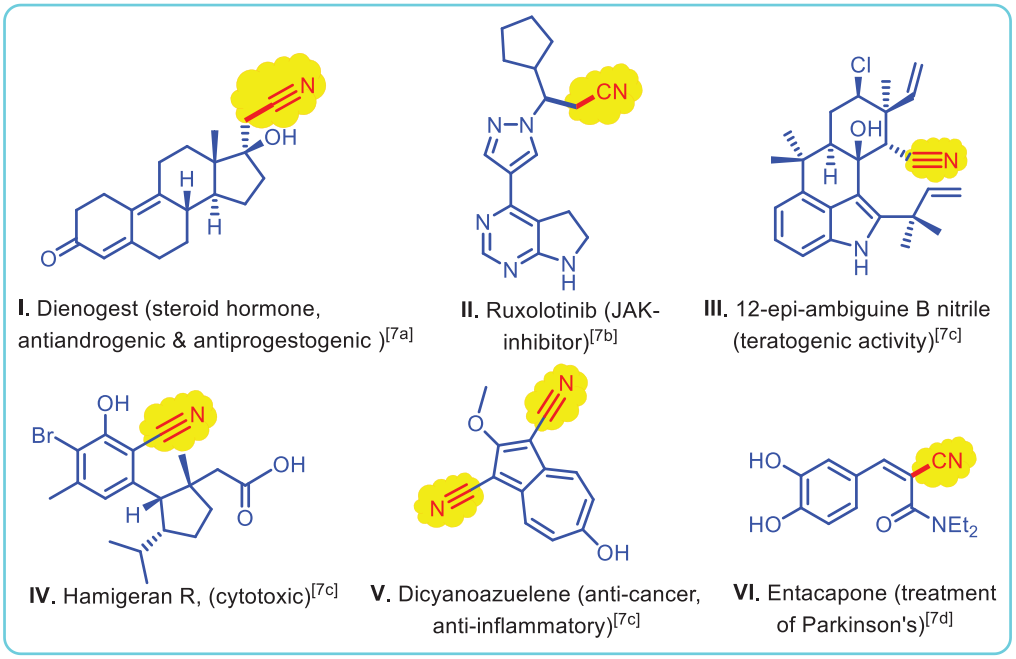
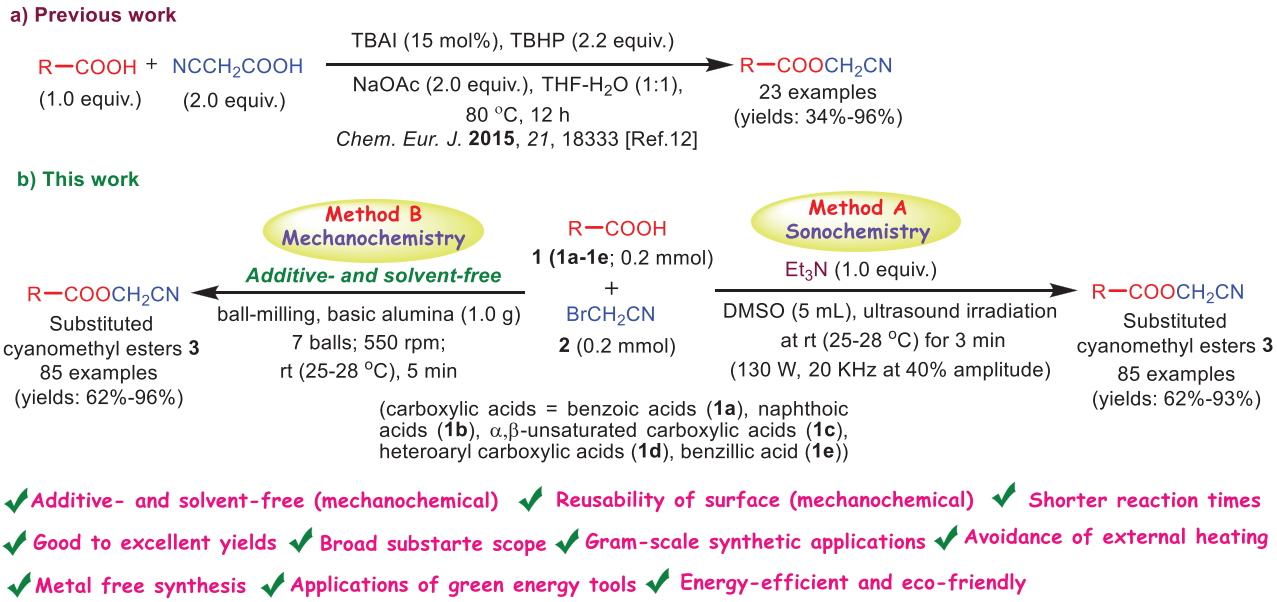


Figure 1. Representative examples of a few bioactive natural and synthetic nitrile drug molecules[7].



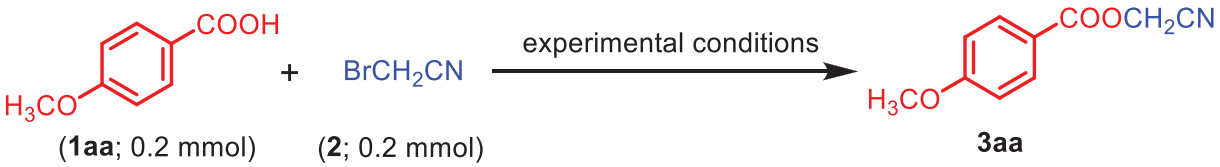
Scheme 1. Dual synthetic approaches (sono- and mechanochemical) for diversely substituted cyanomethyl esters **3**.

and mechanochemical[15] strategies are emerging techniques in synthetic organic chemistry.

2. Results and Discussion

We envisioned that the cyanomethylation reaction between a carboxylic acid and bromoacetonitrile should proceed through a nucleophilic substitution, which might need a base, and accordingly, we performed our model reaction by stirring the mixture of *p*-methoxybenzoic acid (**1aa**; 0.2 mmol), bromoacetonitrile (**2**, 0.2 mmol), and triethylamine (TEA, as a base; 0.2 mmol, 1.0 equiv.) in dimethyl sulfoxide (DMSO; 5 mL) under ambient conditions for 12 hours (720 minutes), when we were successful in isolating the desired product, cyanomethyl 4-methoxybenzoate (**3aa**), in a moderate yield of 42% (Table 1, entry 1). With this somewhat encouraging observation, we then carried out a series of six reactions in six different solvents, such as acetonitrile (CH_3CN), 1,2-dichloromethane (1,2-DCM), *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, ethanol, and water, keeping other reaction parameters unchanged, and found that none of these solvents is superior to dimethyl sulfoxide (DMSO) (Table 1, entries 2–7).

Table 1. Optimization of Reaction Conditions under Ultrasonication[a,b]



(**1aa**; 0.2 mmol) (**2**; 0.2 mmol) **3aa**

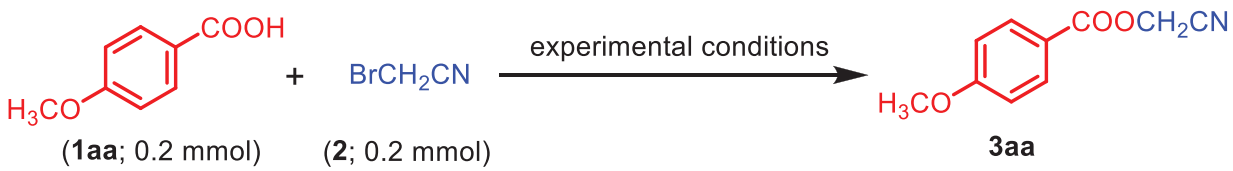
Entry	Cyanomethylating agent [2] [equiv.]	Additive [equiv.]	Solvent [5 mL]	Conditions [amplitude %]	Time [minutes]	Yield [%][a,b]
1	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMSO	stirring at rt	240	42
2	$BrCH_2CN$ (1.0)	Et_3N (1.0)	CH_3CN	stirring at rt	240	21
3	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DCM	stirring at rt	240	13
4	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMF	stirring at rt	240	trace
5	$BrCH_2CN$ (1.0)	Et_3N (1.0)	1,4-dioxane	stirring at rt	240	–
6	$BrCH_2CN$ (1.0)	Et_3N (1.0)	EtOH	stirring at rt	240	trace
7	$BrCH_2CN$ (1.0)	Et_3N (1.0)	H_2O	stirring at rt	240	27
8	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMSO	ultrasound (30%)	5	73
9	**$BrCH_2CN$ (1.0)**	**Et_3N (1.0)**	**DMSO**	**ultrasound (40%)**	**3**	**89**
10	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMSO	ultrasound (50%)	3	68
11	$BrCH_2CN$ (1.0)	–	DMSO	ultrasound (40%)	5	–
12	$BrCH_2CN$ (1.0)	Et_3N (0.5)	DMSO	ultrasound (40%)	3	63
13	$BrCH_2CN$ (1.0)	Et_3N (1.5)	DMSO	ultrasound (40%)	3	84
14	$BrCH_2CN$ (1.0)	*N*, *N*-DIPEA (1.0)	DMSO	ultrasound (40%)	3	73
15	$BrCH_2CN$ (1.0)	DABCO (1.0)	DMSO	ultrasound (40%)	3	47
16	$BrCH_2CN$ (1.0)	DBU (1.0)	DMSO	ultrasound (40%)	3	42
17	$BrCH_2CN$ (1.0)	^tBuOK (1.0)	DMSO	ultrasound (40%)	3	37
18	$BrCH_2CN$ (1.0)	K_2CO_3 (1.0)	DMSO	ultrasound (40%)	3	68
19	$BrCH_2CN$ (1.0)	Cs_2CO_3 (1.0)	DMSO	ultrasound (40%)	3	63
20	$BrCH_2CN$ (0.5)	Et_3N (1.0)	DMSO	ultrasound (40%)	3	68
21	$BrCH_2CN$ (1.5)	Et_3N (1.0)	DMSO	ultrasound (40%)	3	84
22	$BrCH_2CN$ (1.0)	Et_3N (1.0)	CH_3CN	ultrasound (40%)	5	47
23	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DCM	ultrasound (40%)	5	16
24	$BrCH_2CN$ (1.0)	Et_3N (1.0)	DMF	ultrasound (40%)	5	trace
25	$BrCH_2CN$ (1.0)	Et_3N (1.0)	Dioxane	ultrasound (40%)	5	–
26	$BrCH_2CN$ (1.0)	Et_3N (1.0)	EtOH	ultrasound (40%)	5	47
27	$BrCH_2CN$ (1.0)	Et_3N (1.0)	H_2O	ultrasound (40%)	5	52

[a] Reaction conditions: A mixture of *p*-methoxybenzoic acid (**1aa**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was reacted with Et_3N or other bases as additives in 5 mL of varying solvent(s) under either room temperature (rt, 25–28 °C) stirring or ultrasound irradiation (US; 130 W, 20 kHz at 30–50% amplitude).
[b] Isolated yields. *Note*: For the best-suited conditions (entry 9), the isolated yield indicates an average value of three repeated reactions.

Under this purview, we considered applying ultrasound irradiation to expedite the reaction with greater yield. Accordingly, we conducted our model reaction in dimethyl sulfoxide solvent under ultrasonication (130 W, 20 kHz) in three different amplitudes (viz. 30%, 40%, and 50%) and eventually isolated the target compound **3aa** with respective yields of 73%, 89%, and 68% within 3–5 minutes (Table 1, entries 8–10).

With these results at hand, we then performed a set of nine trial reactions with our model entry to elicit the impact of triethylamine by varying its equivalencies (Table 1, entries 11–13) and also replacing it with other bases (*viz*. *N*,*N*-DIPEA, DABCO, DBU, ^tBuOK, K_2CO_3, and Cs_2CO_3) (Table 1, entries 14–19). The experimental outcomes established triethylamine as the most suitable base for this transformation. Afterward, we conducted another set of eight more trial reactions with the model entry by varying the equivalency of bromoacetonitrile (Table 1, entries 20 and 21) and also by varying the solvents (viz. acetonitrile, 1,2-dichloromethane, *N*,*N*-dimethylformamide, 1,4-dioxane, ethanol, and water) (Table 1, entries 22–27), keeping the other reaction parameters intact. The results of these trial reactions suggested the optimum equivalency of bromoacetonitrile as 1.0 and dimethyl sulfoxide (DMSO) as the best-suited solvent for the transformation. Finally, we achieved the optimized reaction conditions for our model reaction in cyanomethylating a carboxylic

Table 2. Optimization of Reaction Conditions under Ball-Milling[a,b]



Entry	Solvent [1.5 mL]	Additive [equiv.]	Cyano-methylating agent [2] [equiv.]	Surface	Condition	No. of balls /rpm	Time [minutes]	Yield [%][a,b]
1	-	-	**$BrCH_2CN$ (1.0)**	**Basic alumina**	**ball milling**	**7/550**	**5**	**94**
2	-	-	$BrCH_2CN$ (0.5)	Basic alumina	ball milling	7/550	5	47
3	-	-	$BrCH_2CN$ (1.5)	Basic alumina	ball milling	7/550	5	89
4	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	7/600	5	84
5	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	7/450	10	68
6	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	8/550	5	89
7	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	6/550	10	58
8	-	-	$BrCH_2CN$ (1.0)	Acidic alumina	ball milling	7/550	5	16
9	-	-	$BrCH_2CN$ (1.0)	Neutral alumina	ball milling	7/550	60	-
10	-	Et_3N (1.0)	$BrCH_2CN$ (1.0)	Neutral alumina	ball milling	7/550	5	73
11	-	Et_3N (1.0)	$BrCH_2CN$ (1.0)	Neutral alumina	ball milling	7/550	10	78
12	CH_3CN	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	13
13	DMSO	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	27
14	EtOH	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	Trace
15	H_2O	-	$BrCH_2CN$ (1.0)	-	stirring at rt	-	240	21
16[c]	-	-	$BrCH_2CN$ (1.0)	Basic alumina	ball milling	7/550	5	94

[a] Reaction conditions: A mixture of *p*-methoxybenzoic acid (**1a**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was reacted in the presence of basic alumina as a surface (1.0 g) for 5 minutes either under ball milling (using a 25 mL stainless-steel jar and balls of 10 mm in diameter, and rotation in an inverted direction with a break of 5 seconds at 2.5-minutes interval) in the absence of any catalysts and solvents without any further additives or by simple stirring at room temperature (25–28 °C);
[b] Isolated yields;
[c] using tungsten carbide jar and balls; pH was measured (1.0 g of acidic/neutral/basic alumina suspended in 5 mL of distilled water, followed by stirring for 10 minutes and then leaving undisturbed for 1 hour) for acidic alumina as 6.08, neutral alumina as 7.07, and basic alumina as 8.14. *Note*: For the best-suited conditions (entry 1), the isolated yield indicates an average value of three repeated reactions.

acid by irradiating the mixture of *p*-methoxybenzoic acid (**1aa**; 0.2 mmol), bromoacetonitrile (**2**; 0.2 mmol) and triethylamine (1.0 equiv.) in dimethyl sulfoxide (5 mL), with ultrasound at 40% amplitude for 3 minutes to isolate the desired compound 3aa in 89% yield (Table 1, entry 9). Compound **3aa** is a new compound characterized by detailed spectral (^{1}H-, ^{13}C-NMR, and HRMS) studies. Table 1 explicitly summarizes all these experimental outcomes in optimizing the reaction conditions.

With the optimized sonochemical conditions at hand, we then envisioned, based on our research experience and understanding, that the same transformation could be attained upon mechanochemical conditions in a high-speed ball mill. With this view, we attempted our model reaction between *p*-methoxybenzoic acid (**1aa**) and bromoacetonitrile (**2**) by grinding the mixture on a basic alumina (1.0 g) surface with seven stainless steel balls at 550 rpm when we successfully isolated our desired product **3aa** in 94% yield at 5 minutes (Table 2, entry 1); the yield and reaction time, both are almost comparable to the sonochemical procedure (Table 1, entry 9). To conclude on the best-suited mechanochemical conditions, we then performed several other trial reactions with this model entry by varying the equivalency of cyanomethylating agent (Table 2, entries 2 and 3), milling parameters, such as the number of balls, frequency (rpm), and milling time (Table 2, entries 4–7), nature of the solid surface and additives (Table 2, entries 8–11); however, we did not observe any marked improvement. The conventional stirrings using varying solvents at ambient conditions were also ineffective (Table 2, entries 12–15). We also carried out a control experiment using a tungsten carbide jar and balls to rule out any catalytic intervention by stainless steel jar and balls (Table 2, entry 16). Finally, we discovered an alternative and efficient protocol for the same transformation to access the desired product **3aa** in an excellent yield of 94% (Table 2, entry 1) under ball-milling using seven stainless steel balls (10 mm in diameter) milled for 5 minutes (rotation in an inverted direction with a 30-second break at 2.5-minute interval) at 550 rpm in the presence of basic alumina (1.0 g) as the surface. Table 2 offers compiled experimental outcomes.

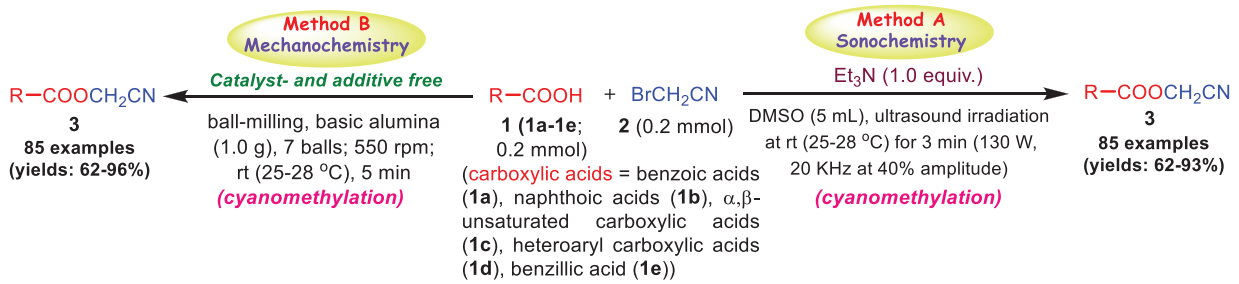
We have thus successfully developed a dual synthetic strategy for the direct cyanomethylation of carboxylic acids, thereby offering eco-friendly and practical synthetic routes to access cyanomethyl ester derivatives by using sonochemical (Method A) and mechanochemical (Method B) approaches (Scheme 1b). At this stage, we turned our attention to exploring the scope of the developed methodologies under the respective optimized reaction conditions, and also comparing the efficacies of both methods, categorically in terms of corresponding yields and reaction times. Accordingly, we screened a set of twenty diversely substituted benzoic acids (**1ab**-**1au**), containing both electron-donating and electron-withdrawing groups (such as methyl, *tert*-butyl, amino, methoxy, ethoxy, chloro, bromo, fluoro, and iodo), and carried out the cyanomethylation reaction by reacting with bromoacetonitrile (**2**) separately under the optimized reaction conditions for sonochemical (Method A) and mechanochemical (Method B) processes. We observed that all the reactions took place very efficiently and smoothly under both processes and isolated the desired cyanomethyl ester derivatives in excellent yields ranging from 75 to 93% in the sonochemical and 82 to 92% in the mechanochemical method, within respective reaction times of 3 and 5 minutes (Table 3, compounds **3ab**-**3au**). We then planned to check the functional group tolerance for both methods, and afterwards performed the cyanomethylation reaction with another set of 10 different benzoic acid derivatives (**1av**-**1az** and **1aa**′-**1ae**′), having other functionalities, such as -$N(CH_3)_2$, -$NHCOCH_3$, -NO_2, -OH, -O-CH_2-O-, CF_3, $COCH_3$, $OCOCH_3$, and CN, under the identical reaction conditions. All the benzoic acid derivatives underwent the reaction very efficiently in both processes, exhibiting excellent functional group tolerance, affording the desired esters **3av**-**3az** and **3aa**′-**3ae**′ with isolated yields ranging from 62 to 88% within 3 minutes under ultrasonication (Method A) and 65 to 94% within 5 minutes under ball milling (Method B) (Table 3, compounds **3av**-**3az** and **3aa**′-**3ae**′).

Encouraged by these results, we then planned to perform the reaction with a series of di-, tri-, or poly-substituted benzoic acids to evaluate the scope and versatility of both strategies, and accordingly, we conducted the cyanomethylation of a diverse range of poly-substituted benzoic acids (**1af"**-**1ap"**) under both the sono- and mechanochemical conditions. To our delight, we isolated the corresponding cyanomethyl esters **3af"**-**3ap"** in all cases (Table 3, compounds **3af"**-**3ap"**) with good to excellent yields ranging from 77–89% under ultrasonication (Method A) within 3 minutes, and 77–90% under ball-milling (Method B) within 5 minutes. In addition, [1,1′-biphenyl]-4-carboxylic acid (**1aq"**), phthalic acid (**1ar"**; required 2.0 equiv. of 2), and its nitro-derivative (**1as'**; required 2.0 equiv. of 2) also took part efficiently under identical conditions, furnishing the corresponding cyanomethyl esters **3aq"**-**3as"** with respective isolated yields of 84%, 74%, and 83% within 3 minutes under sonochemical method and 82%, 70%, and 86% within 5 minutes under mechanochemical method (Table 3, compounds **3aq"**-**3as"**). Furthermore, in another drive, biologically significant carboxylic acid scaffolds, such as chromene-8-carboxylic acid (**1at"**), and 2- and 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acids (**1au"**-**1av"**), were converted to their corresponding cyanomethyl ester derivatives **3at"**-**3av'** with ease using the similar strategy, isolating products in the respective yields of 88%, 66%, and 69% under sono- and 86%, 62%, and 63% under the mechanochemical approach (Table 3, compounds **3at"**-**3av"**).

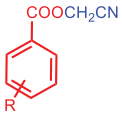
With these successful experimental outcomes, we endeavored to extend the scope of the carboxylic acid substrate once more. Both sonochemical and mechanochemical methods worked efficiently for naphthoic acids, such as 2-(naphthalen-1-yl)acetic acid (**1ba**), 2-(naphthalen-2-yl)acetic acid (**1bb**), and 2-hydroxy-1-naphthoic acid (**1bc**), furnishing the corresponding cyanomethyl ester derivatives **3ba**-**3bc** in excellent yields ranging from 84–89% under ultrasonication (Method A) within 3 minutes, and 80–87% under ball-milling (Method B) within 5 minutes, under the standard reaction conditions (Table 3, compounds **3ba**-**3bc**). Next, we thought about α,β-unsaturated carboxylic acids for this transformation, and carried out a set of five reactions between substituted cinnamic acids (**1ca**-**1ce**) and bromoacetonitrile (**2**) under identical reaction conditions, following both methods separately. All the reactions took place satisfactorily, thereby affording the respective differently substituted cyanomethyl esters **3ca**-**3ce** (Table 3, compounds **3ca**-**3ce**) with good yields ranging from 74–87% under ultrasonication (Method A) within 3 minutes, and 79–85% under ball-milling (Method B) within 5 minutes. Phenyl-3-propiolic acid (**1cf**) also participated in the transformation in both methods to give cyanomethyl 3-phenylpropiolate (**3cf**) with an excellent yield of 86% and 84% under sonication and ball-milling, respectively (Table 3, compound **3cf**).

In a further attempt, we first conducted the transformation with biologically potent nicotinic acid (pyridine-3-carboxylic acid, **1da**) as a heterocyclic carboxylic acid, following both processes under identical reaction conditions. Delightfully, we isolated cyanomethyl nicotinate (**3 da**) in an excellent yield of 86% and 89%, respectively, within the same time frame (Table 3, compound **3 da**). Encouraged by this result, we then carried out a set of thirteen more reactions between a diverse range of bio-relevant heterocyclic acids (**1db**-**1dn**) (viz. nicotinic acid derivatives, 2-amino-isonicotinic acid, pyridine-2,6-dicarboxylic acid, indole-2- and 3-carboxylic acids, furan-2-carboxylic acid, thiophene-2- and 3-carboxylic acids, quinoline-3- and isoquinoline-3-carboxylic acids, and quinoxaline-2-carboxylic acid) and bromoacetonitrile(**2**; used 2.0 equiv. for **1df** as it bears two carboxylic acid groups in its molecule) under the optimized reaction conditions. All these reactions were also found to be implemented smoothly, thereby affording the desired cyanomethyl esters (**3db**-**3dn**) in similar yields ranging from 77–90% for ultrasonication and 73–91% for mechanochemical methodology (Table 3, compounds **3db**-**3dn**). This transformation was also successfully applied to a broad range of another class of bio-relevant heterocyclic carboxylic acids, coumarin-3-carboxylic acids (**1do**-**1dz**, and **1da"**), containing various functional groups containing both electron-donating and withdrawing functionalities (such as methyl, *tert*-butyl, hydroxy, methoxy, fluoro, chloro, bromo, nitro, and naphthyl). All these reactions afforded the desired cyanomethyl coumarin-3-carboxylates (**3do**-**3dz**, and **3da"**) in good yields, ranging from 66–91% for Method

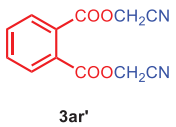
Table 3. Sonochemical and mechanochemical synthesis of diversely functionalized cyanomethyl esters (**3**)[a,b]



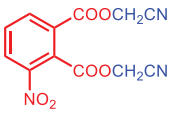
i) Scope of benzoic acids



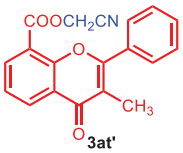
3aa: R = 4-OCH_3,	**Method A:** 89%; **Method B:** 94%	**3aw**: R = 4-$NHCOCH_3$,	**Method A:** 82%; **Method B:** 87%
3ab: R = H,	**Method A:** 93%; **Method B:** 87%	**3ax**: R = 4-NO_2,	**Method A:** 87%; **Method B:** 85%
3ac: R = 2-CH_3,	**Method A:** 86%; **Method B:** 91%	**3ay**: R = 2-OH,	**Method A:** 62%; **Method B:** 65%
3ad: R = 3-CH_3,	**Method A:** 89%; **Method B:** 86%	**3az**: R = 3-OH,	**Method A:** 79%; **Method B:** 85%
3ae: R = 2,4,6-$(CH_3)_3$,	**Method A:** 93%; **Method B:** 89%	**3aa'**: R = 2,3-$(OCH_2O$-),	**Method A:** 83%; **Method B:** 88%
3af: R = 2-$C(CH_3)_3$,	**Method A:** 87%; **Method B:** 92%	**3ab'**: R = 2-CF_3,	**Method A:** 87%; **Method B:** 85%
3ag: R = 3-OCH_3,	**Method A:** 89%; **Method B:** 92%	**3ac'**: R = 4-OCH_3,	**Method A:** 88%; **Method B:** 94%
3ah: R = 3,5-$(OCH_3)_2$,	**Method A:** 90%; **Method B:** 86%	**3ad'**: R = 2-$OCOCH_3$,	**Method A:** 87%; **Method B:** 89%
3ai: R = 4-CH_2CH_3,	**Method A:** 93%; **Method B:** 96%	**3ae'**: R = 4-CN,	**Method A:** 86%; **Method B:** 89%
3aj: R = 2-Cl,	**Method A:** 82%; **Method B:** 87%	**3af'**: R = 2-CH_3-6-NH_2,	**Method A:** 84%; **Method B:** 87%
3ak: R = 3-Cl,	**Method A:** 77%; **Method B:** 82%	**3ag'**: R = 4-NH_2-6-OH,	**Method A:** 83%; **Method B:** 86%
3al: R = 2,4,6-tri-Cl,	**Method A:** 91%; **Method B:** 87%	**3ah'**: R = 2-NH_2-3,4,5-$(OCH_3)_3$,	**Method A:** 79%; **Method B:** 77%
3am: R = 3-Br,	**Method A:** 79%; **Method B:** 83%	**3ai'**: R = 2-NH_2-6-Br,	**Method A:** 82%; **Method B:** 84%
3an: R = 4-Br,	**Method A:** 75%; **Method B:** 79%	**3aj'**: R = 2-NH_2-4-Cl,	**Method A:** 83%; **Method B:** 85%
3ao: R = 3-F,	**Method A:** 81%; **Method B:** 84%	**3ak'**: R = 2-NH_2-6-F,	**Method A:** 88%; **Method B:** 85%
3ap: R = 4-F,	**Method A:** 84%; **Method B:** 78%	**3al'**: R = 2-OCH_3-4-Cl,	**Method A:** 89%; **Method B:** 84%
3aq: R = 2,5-di-F,	**Method A:** 84%; **Method B:** 86%	**3am'**: R = 2-CH_3-5-F,	**Method A:** 85%; **Method B:** 83%
3ar: R = 4-I,	**Method A:** 87%; **Method B:** 91%	**3an'**: R = 2-CH_3-5-I,	**Method A:** 83%; **Method B:** 80%
3as: R = 2-NH_2,	**Method A:** 85%; **Method B:** 88%	**3ao'**: R = 3-OCH_3-4-CH_3,	**Method A:** 88%; **Method B:** 90%
3at: R = 3-NH_2,	**Method A:** 79%; **Method B:** 82%	**3ap'**: R = 3-OCH_3-4-OH,	**Method A:** 77%; **Method B:** 80%
3au: R = 4-NH_2,	**Method A:** 88%; **Method B:** 85%	**3aq'**: R = 4-C_6H_5,	**Method A:** 84%; **Method B:** 82%
3av: R = 4-$N(CH_3)_2$,	**Method A:** 88%; **Method B:** 91%		



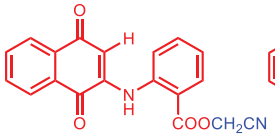
3ar'
Method A: 74%; 3 min
Method B: 70%; 5 min



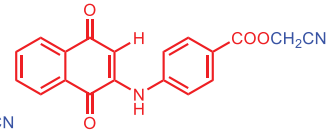
3as'
Method A: 83%; 3 min
Method B: 86%; 5 min



3at'
Method A: 88%; 3 min
Method B: 86%; 5 min

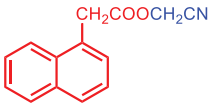


3au'
Method A: 66%; 3 min
Method B: 62%; 5 min

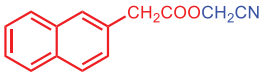


3av'
Method A: 69%; 3 min
Method B: 63%; 5 min

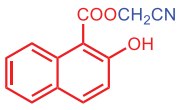
ii) Scope of naphthoic acids



3ba
Method A: 89%; 3 min
Method B: 87%; 5 min

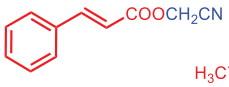


3bb
Method A: 84%; 3 min
Method B: 80%; 5 min

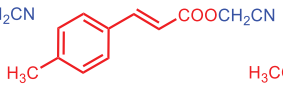


3bc
Method A: 88%; 3 min
Method B: 84%; 5 min

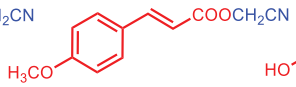
iii) Scope of α,β-Unsaturated carboxylic acids



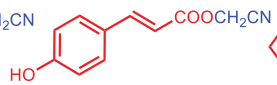
3ca
Method A: 83%; 3 min
Method B: 85%; 5 min



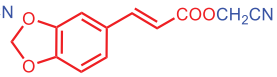
3cb
Method A: 80%; 3 min
Method B: 84%; 5 min



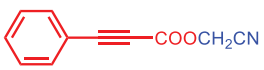
3cc
Method A: 83%; 3 min
Method B: 85%; 5 min



3cd
Method A: 74%; 3 min
Method B: 79%; 5 min



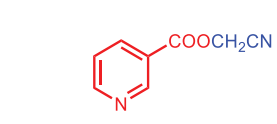
3ce
Method A: 87%; 3 min
Method B: 84%; 5 min



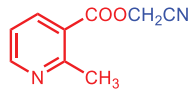
3cf
Method A: 86%; 3 min
Method B: 84%; 5 min

Table 3. (Continued)

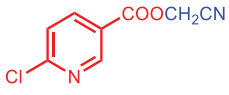
iv) Scope of heterocyclic carboxylic acids



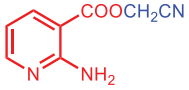
3da
Method A: 86%; 3 min
Method B: 89%; 5 min



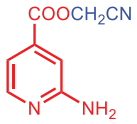
3db
Method A: 88%; 3 min
Method B: 85%; 5 min



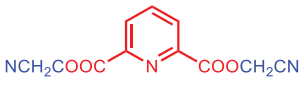
3dc
Method A: 81%; 3 min
Method B: 86%; 5 min



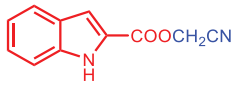
3dd
Method A: 82%; 3 min
Method B: 85%; 5 min



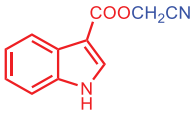
3de
Method A: 79%; 3 min
Method B: 82%; 5 min



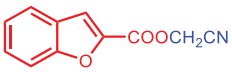
3df
Method A: 77%; 3 min
Method B: 73%; 5 min



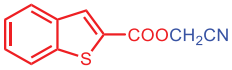
3dg
Method A: 90%; 3 min
Method B: 87%; 5 min



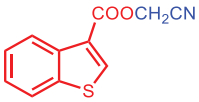
3dh
Method A: 82%; 3 min
Method B: 85%; 5 min



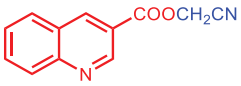
3di
Method A: 87%; 3 min
Method B: 89%; 5 min



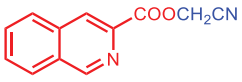
3dj
Method A: 85%; 3 min
Method B: 87%; 5 min



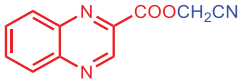
3dk
Method A: 78%; 3 min
Method B: 81%; 5 min



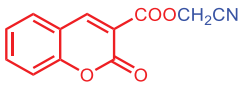
3dl
Method A: 80%; 3 min
Method B: 85%; 5 min



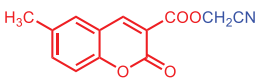
3dm
Method A: 85%; 3 min
Method B: 90%; 5 min



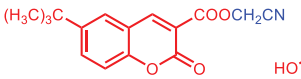
3dn
Method A: 89%; 3 min
Method B: 91%; 5 min



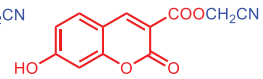
3do
Method A: 83%; 3 min
Method B: 81%; 5 min



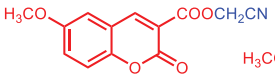
3dp
Method A: 86%; 3 min
Method B: 82%; 5 min



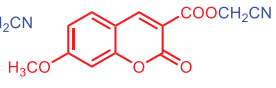
3dq
Method A: 91%; 3 min
Method B: 88%; 5 min



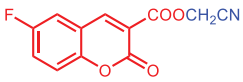
3dr
Method A: 73%; 3 min
Method B: 75%; 5 min



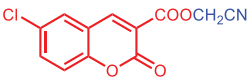
3ds
Method A: 81%; 3 min
Method B: 77%; 5 min



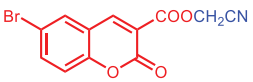
3dt
Method A: 73%; 3 min
Method B: 71%; 5 min



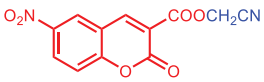
3du
Method A: 73%; 3 min
Method B: 77%; 5 min



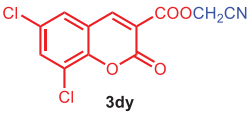
3dv
Method A: 80%; 3 min
Method B: 78%; 5 min



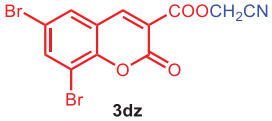
3dw
Method A: 68%; 3 min
Method B: 65%; 5 min



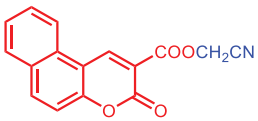
3dx
Method A: 66%; 3 min
Method B: 69%; 5 min



3dy
Method A: 74%; 3 min
Method B: 72%; 5 min

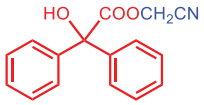


3dz
Method A: 83%; 3 min
Method B: 80%; 5 min

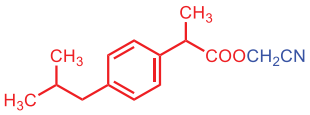


3da'
Method A: 72%; 3 min
Method B: 70%; 5 min

v) Scope of miscellaneous carboxylic acids



3ea
Method A: 86%; 3 min
Method B: 88%; 5 min

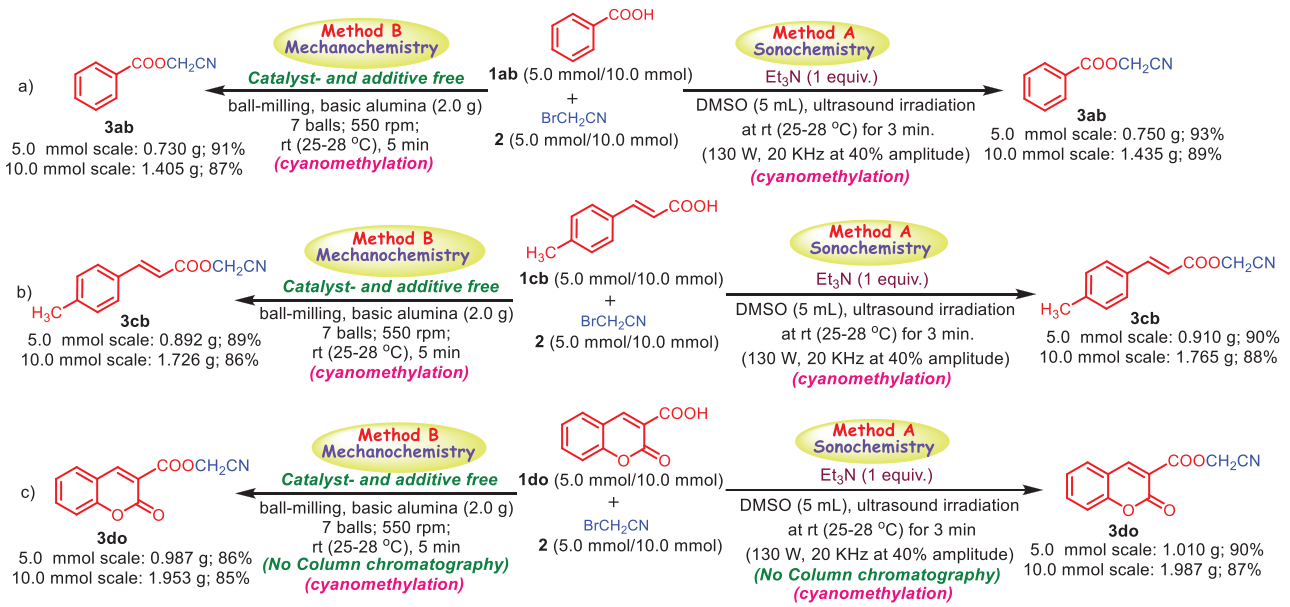


(Ibuprofen cyanomethylester; **3eb**)
Method A: 73%; 3 min
Method B: 78%; 5 min

[a] Reaction conditions: A mixture of carboxylic acids (**1**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was reacted separately under both ultrasonication (Method A) and ball-milling (Method B) reaction conditions.
[b] Isolated yields.

A and 65–88% for Method B within just 3 and 5 minutes of operation, respectively (Table 3, compounds **3do**-**3dz**, and **3da'**). Furthermore, we explored that benzillic acid (**1ea**) and 2-(4-isobutylphenyl)propanoic acid (Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID) molecule; **1eb**) also underwent cyanomethylation reaction, affording the corresponding cyanomethyl esters **3ea** and **3eb** in the corresponding good yields of 88% and 73% under ultrasonication and 86% and 78% under the ball-milling approach within just 3 and 5 minutes, respectively. All the experimental results are shown in Table 3.

However, we observed that simple aliphatic carboxylic acids, such as *n*-propionic acid, *n*-butanoic acid, and betulinic acid, a natural triterpenoic acid, do not undergo the reaction in either method. This is perhaps due to the lower stability of their respective conjugate ions (*i.e.*, carboxylate ions) compared to those from aromatic carboxylic acids and benzylic acids. Again, amino acids (such as alanine, phenylalanine, and tryptophan) were also found to remain unreacted, and we anticipate that their strong zwitterionic structure restricts them from participating in the reaction.



Scheme 2. Gram-scale synthetic applications for representative entries: a) with benzoic acid **1ab**; b) with (*E*)-3-(*p*-tolyl)acrylic acid **1cb**; and c) with coumarin-3-carboxylic acid **1do**.

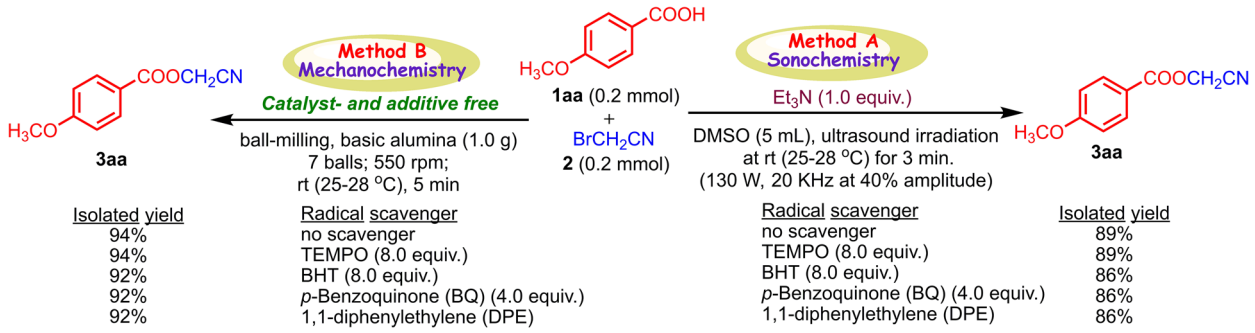
All the isolated products **3** (except **3do**-**3dz**, and **3da′**), synthesized following both Method A (sonochemical) and Method B (mechanochemical), were purified using the column chromatographic technique (*see experimental)*. All are new compounds except **3ab**, **3ac**, **3ad**, **3ak**, **3an**, **3ao**, **3ap**, **3ax**, **3ae′**, **3ba**, and **3ca**. Each synthesized compound was fully characterized based on its detailed spectral studies, including ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR (for **3ao**, **3ap**, **3aq**, **3ab′**, **3ak′**, **3am′** and **3du**), and HRMS (*see experimental*).

To further assess the scalability of both approaches, we carried out gram-scale synthetic applications (5.0 and 10.0 mmol-scales; 25- and 50-fold enhancement; Scheme 2) for three representative entries, *viz*. benzoic acid (**1ab**), (*E*)-3-(*p*-tolyl)acrylic acid (**1cb**), and coumarin-3-carboxylic acid (**1do**). The sonochemical approach (Method A) furnished the products **3ab**, **3cb**, and **3do** with excellent yields of 93%, 90%, and 90% at 5.0 mmol and 89%, 88%, and 87% at 10.0 mmol reactions, respectively, all within just 3 minutes (*see Experimental*). Similarly, the mechanochemical method (Method B) delivered impressive results, affording 91%, 89%, and 86% at 5.0 mmol and 87%, 86%, and 85% at 10.0 mmol reactions within 5 minutes (*see Experimental*). The yields and the reaction times observed in the gram-scale synthesis closely mirrored those obtained for the sub-millimolar-scale reactions.

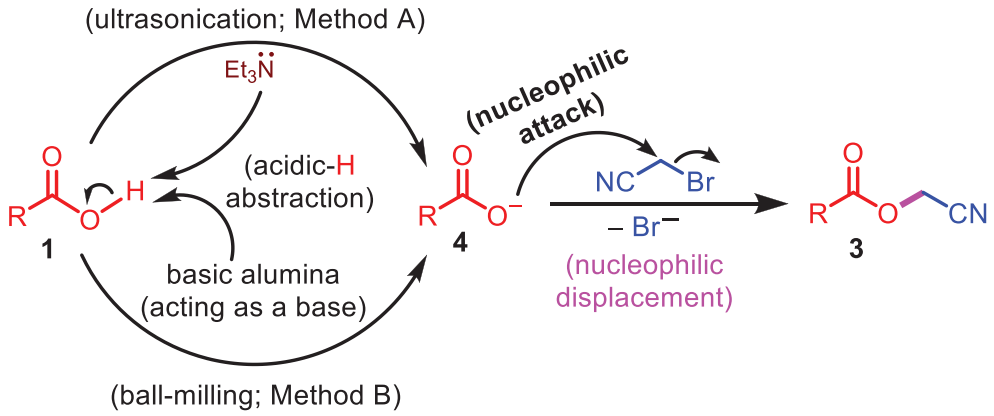
At this point, our efforts were shifted toward uncovering potential mechanistic insights of this sono- and mechanochemically-assisted cyanomethylation strategy applied to a diverse range of carboxylic acids using bromoacetonitrile. With this view, we conducted a set of control experiments with our model reaction in the presence of four different radical scavengers, such as TEMPO, BHT, *p*-benzoquinone (BQ), and 1,1-diphenylethylene (DPE) (Scheme 3). None of the radical scavengers affected the conversion when carried out either sonochemically or mechanochemically, thereby suggesting that the transformation follows an ionic pathway in both cases.

Hence, we propose a plausible reaction mechanism for the sono- and mechanochemical transformation herein proposed, as depicted in Scheme 4. Under ultrasound irradiation, the abstraction of the acidic hydrogen from carboxylic acid **1** by the base, triethylamine (Et_3N), is much facilitated,[16] resulting in the corresponding carboxylate ion intermediate **4**. Once again, we observed (Table 2) that among the three types of alumina (acidic, basic, and neutral) used as the surface,[17] only the basic alumina came out as the most superior surface-cum-catalyst for this chemical conversion. This is because basic alumina (α-alumina), an activated form of aluminum oxide (Al_2O_3), comprising a hexagonal close-packed structure, with aluminum ions surrounded by oxygen anions in a layered arrangement, can act as both an acid and a base, depending upon the circumstances.[18] Hence, when it is subjected to the carboxylic acid **1**, it behaves as a base by abstracting the acidic proton, which is facilitated under high mechanochemical force in a ball mill, to generate the carboxylate ion intermediate **4**. Simultaneously, the amphoteric property of basic alumina is supposed to be responsible for enhancing the electrophilicity of the methylenic carbon of bromoacetonitrile ($BrCH_2CN$; **2**) through electrophilic polarization by coordinating with the unshared electron pairs of the bromine atom by its layered aluminum cations (Al^{3+}).[18] The in situ-generated carboxylate ion **4**, now acting as a nucleophile,[19] undergoes a rapid nucleophilic displacement reaction (preferably via S_N2 pathway) at the methylenic carbon center of the activated bromoacetonitrile electrophile **2**, to afford the desired cyanomethylated product **3** (Scheme 4) through sono-/mechanochemical esterification.[20]

Additionally, the reusability of the solid surface (basic alumina) was examined by conducting the model reaction on a scale of 0.2 mmol to yield cyanomethyl 4-methoxybenzoate (**3aa**), as illustrated in Figure 2. We were pleased to observe that the solid surface demonstrated excellent reusability, maintaining



Scheme 3. Control experiments with radical scavengers.



Scheme 4. Proposed mechanism.

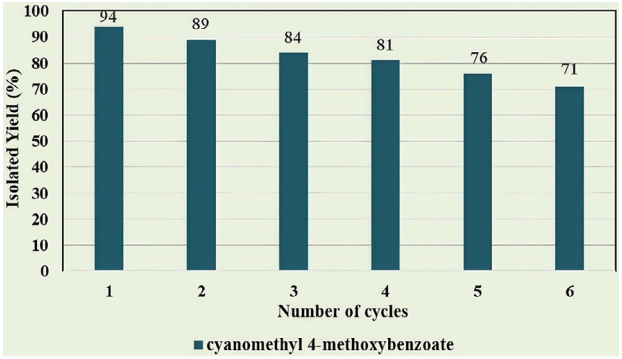


Figure 2. Reusability of the solid surface.

its catalytic efficiency over six consecutive cycles with no significant decrease in activity. Compound **3aa** was isolated in yields of 94%, 89%, 84%, 81%, 76%, and 71% within a uniform reaction time of 5 minutes for each cycle (Figure 2). It is worth noting that after collecting the solid surface during the work-up of each cycle, it was preheated at 70 °C in an oven for subsequent reuse.

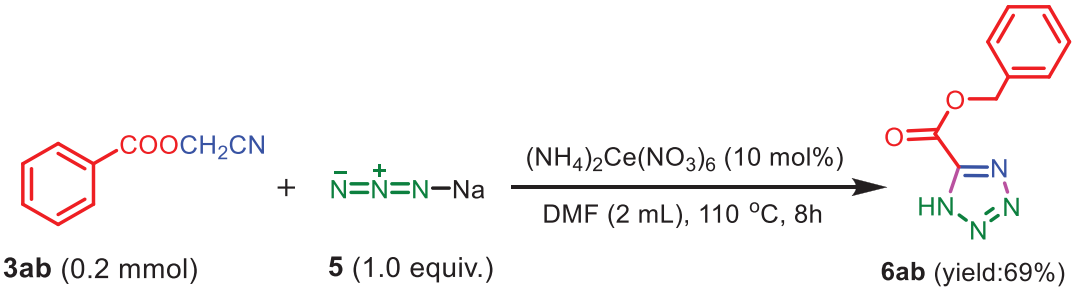
We then planned to extend the synthetic application of the synthesized cyano derivatives by screening a cycloaddition reaction. For this purpose, we tried to synthesize 5-substituted-1*H*-tetrazole (**6ab**) using ceric ammonium nitrate (CAN) via a [3 + 2] cycloaddition of the selected nitrile (**3ab**) with NaN_3 (**5**; 1.0 equiv.) in DMF at 110 °C for 8 hours, following the standard procedure (Scheme 5).[21] We successfully isolated our aimed product **6ab,** in 69% yield.

3. Conclusions

In conclusion, we have unearthed dual synthetic approaches, based on sonochemical and mechanochemical strategies, as efficient and straightforward practical alternative synthetic protocols for diversely functionalized cyanomethyl esters of a vast array of carboxylic acids upon reacting the substrate molecules with bromoacetonitrile as an eco-friendly and cost-effective cyanomethylating agent. Both the ultrasound-assisted sonochemical and the high-speed ball mill-assisted mechanochemical processes are fast (3-5 minutes) and high-yielding (up to 96%). The sonochemical transformation occurs at ambient conditions, while the mechanochemical process avoids using solvents. The key advantages of the newly developed methods are metal-free synthesis, avoidance of any additives and external oxidants, short reaction times (in minutes), broad substrate scope and tolerance of other various functional groups, good to excellent yields, reusability of the solid surface, and gram-scale synthetic applications.

4. Experimental Section

General method: All the chemicals, except 2-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1au"**), 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1av"**), coumarin-3-carboxylic acids (**1do-1dz** and **1da"**), and solvents used in this work were purchased from reputed companies. The substrates 2-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1au"**)[22a]



Scheme 5. [3 + 2] cycloaddition of nitrile **3ab** with sodium azide (**5**) to the corresponding 5-substituted tetrazole **6ab**[a,b].[a]Reaction conditions: A mixture of cyanomethyl ester (**3ab**; 0.2 mmol), NaN_3 (**5**; 1.0 equiv.), and 10 mol% of CAN as a catalyst, dissolved in 2.0 mL of dimethyl formamide (DMF), was stirred for 8 hours at 110 °C, and upon completion of the reaction, the desired product **6ab** was isolated following the standard procedure.[21] [b]Isolated yield.

and 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoic acid (**1av"**)[22b] and coumarin-3-carboxylic acids (**1do-1dz** and **1da"**)[23] were prepared following the reported methods.[22,23] All the synthesized starting compounds are known, and their physical and spectral data are consistent with the previously reported data.[22,23] ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra were collected at 400, 100, and 376 MHz, respectively, on a Bruker DRX spectrometer. Waters (G2-XS Q-TOF) high-resolution mass spectrometer was utilized to collect HRMS spectra. The melting points were recorded on a Chemiline CL-725 melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using silica gel 60 F254 (Merck) plates. Sonics-make ultrasound probe-sonicator (Model: VCX 130) with a frequency of 20 kHz and energy of 130 W was used for sonication. A PM 100, Retsch GmbH, Germany, ball-milling apparatus was used for mechanochemical reactions.

General procedure for the synthesis of functionalized cyanomethyl esters 3 under the sonochemical method (Method A): Carboxylic acid (**1**; 0.2 mmol), bromoacetonitrile (**2**; 0.2 mmol), and triethylamine were added sequentially to an oven-dried glass vessel (20 mL), followed by the addition of 5 mL of dimethyl sulfoxide (DMSO). The mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 3 minutes (monitored by TLC). Upon completion of the reaction, the entire content was transferred into a 25 mL separating funnel, followed by the addition of 20 mL of a 3:1 (v/v) mixture of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the crude mass, which was then subjected to column chromatographic purification (except for compounds **3do-3dz**, and **3da'**) using EtOAc–hexane mixtures as eluents to isolate the desired products, cyanomethyl esters **3** (**3aa-3az**, **3aa"-3av"**, **3ba-3bc**, **3ca-3cf**, **3da-3dz**, **3da'**, **3ea**, and **3eb**). The synthesized compounds were fully characterized by spectroscopic studies, including ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR (for compounds **3ao**, **3ap**, **3aq**, **3ab'**, **3ak'**, **3am',** and **3du**), and HRMS. The physical and spectral data for known compounds (viz. **3ab**, **3ac**, **3ad**, **3ak**, **3an**, **3ao**, **3ap**, **3ax**, **3ae'**, **3ba**, and **3ca**) were consistent with previously reported data[12] (see the Supporting Information).

Gram-scale synthesis of three representative compounds 3ab, 3cb, and 3do, under the sonochemical method (Method A): A mixture of benzoic acid (**1ab**; 5.0 mmol/10.0 mmol)/(*E*)-3-(*p*-tolyl)acrylic acid (**1cb**; 5.0 mmol/10.0 mmol)/coumarin-3-carboxylic acid (**1do**; 5.0 mmol/10.0 mmol) as substrates, and bromoacetonitrile (**2**; 5.0 mmol/10.0 mmol) as cyanomethylating agent was added sequentially to an oven-dried glass vessel (20 mL), followed by adding 5 mL/10 mL of dimethyl sulfoxide. Each reaction mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 3 minutes (monitored by TLC). Upon completion of each reaction, the resultant reaction mixture was worked up (using 250 mL separating funnel and adding 60 mL of ethyl acetate-water (3:1 v/v) mixture for solvent-partitioning) and purified following the same procedure (eluents for flash chromatography: hexane/ethyl acetate 92:8 v/v for **3ab** and 87:13 v/v for **3cb**) as mentioned in the general method (Method A) to obtain pure product **3ab, 3cb, and 3do** in 93% (0.750 g), 90% (0.910 g), and 90% (1.010 g) for 5.0 mmol and 89% (1.435 g), 88% (1.765 g), and 87% (1.987 g) for 10.0 mmol experiments, respectively.

General procedure for the synthesis of functionalized cyanomethyl esters (3) under ball-milling (Method B): A mixture of carboxylic acids (**1**; 0.2 mmol) and bromoacetonitrile (**2**; 0.2 mmol) was subjected to ball-milling in the presence of basic alumina (1.0 g) as the surface at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) made of the same material for 5 minutes. The ball-milling operation was conducted with an inverted rotation direction, with intervals of 2.5 minutes and breaks of 30 seconds. After completion of the reaction (monitored by TLC), the entire content was transferred into a 125 mL separating funnel, followed by adding 30 mL of a mixture (3:1 v/v) of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to obtain a crude mass, which was subjected to column chromatographic purification (except for compounds **3do-3dz**, and **3da'**) using EtOAc–hexane mixtures as eluents to yield pure products of substituted cyanomethyl esters **3** (**3aa-3az**, **3aa"-3av"**, **3ba-3bc**, **3ca-3cf**, **3da-3dz**, **3da'**, **3ea,** and **3eb**).

Gram-scale synthesis of three representative compounds 3ab, 3cb, and 3do under ball-milling (Method B): A mixture of benzoic acid (**1ab**; 5.0 mmol/10.0 mmol)/(*E*)-3-(*p*-tolyl)acrylic acid (**1cb**; 5.0 mmol/10.0 mmol)/coumarin-3-carboxylic acid (**1do**; 5.0 mmol/10.0 mmol) as substrates, and bromoacetonitrile (**2**; 5.0 mmol/10.0 mmol) as a cyanomethylating agent was subjected to ball-milling in the presence of basic alumina (3.0 g for both 5.0 and 10.0 mmol-scale) as the surface at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) made of the same material for 5 minutes (monitored by TLC). The ball-milling operation was conducted with an inverted rotation direction, with intervals of 2.5 minutes and breaks of 30 seconds. Upon completion of each reaction, the resultant reaction mixture was worked up (using 250 mL separating funnel and adding 60 mL of ethyl acetate-water (3:1 v/v) mixture for solvent-partitioning) and purified following the same procedure (eluents for flash chromatography: hexane/ethyl acetate 92:8 v/v for **3ab** and 87:13 v/v for **3cb**) as

mentioned in the general method (Method B) to obtain pure product **3ab, 3cb, and 3do** in 91% (0.730 g), 89% (0.892 g), and 86% (0.987 g) for 5.0 mmol and 87% (1.405 g), 86% (1.726 g), and 85% (1.953 g) for 10.0 mmol experiments, respectively.

The physical and spectral data of the synthesized cyanomethyl esters 3 and 5-substituted tetrazole 6ab are given below:

Cyanomethyl 4-methoxybenzoate (**3aa**). White solid; yield: 89% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 94% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, 2H, J = 8.8 Hz, H-2, H-6), 6.94 (d, 2H, J = 8.8 Hz, H-3, H-5), 4.93 (s, 2H, -OCH_2CN), 3.87 (s, 3H, C_4-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.71 (C_1-COOCH_2CN), 164.36 (C-4), 132.28 (C-2, C-6), 120.19 (C-1), 114.82 (-OCH$_2$CN), 114.07 (C-3, C-5), 55.64 (C_4-OCH_3), 48.69 (-OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_3H$; 192.0661; found: 192.0668.

Cyanomethyl benzoate (**3ab**).[12] Pale brown liquid; yield: 93% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (28 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, 2H, J = 7.2 Hz, H-2, H-6), 7.59–7.57 (m, 1H, H-4), 7.45–7.43 (m, 2H, H-3, H-5), 4.93 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.91 (C_1-COOCH_2CN), 134.05 (C-4), 129.88 (C-2, C-6), 128.61 (C-3, C-5), 128.28 (C-1), 114.62 (-OCH$_2$CN), 48.83 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_2H$; 162.0555; found, 162.0571.

Cyanomethyl 2-methylbenzoate (**3ac**).[12] White solid; yield: 86% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 77–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, 2H, J = 8.4 Hz, H-3, H-6), 7.29 (d, 2H, J = 8.4 Hz, H-4, H-5), 4.96 (s, 2H, -OCH_2CN), 2.45 (s, 3H, C_2-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.11 (C_1-COOCH_2CN), 145.24 (C-2), 130.16 (C-3, C-6), 129.52 (C-4, C-5), 125.23 (C-1), 114.70 (-OCH$_2$CN), 48.79 (-OCH$_2$CN), 21.87 (C_2-CH_3) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_2H$; 176.0712; found: 176.0722.

Cyanomethyl 3-methylbenzoate (**3ad**).[12] White semi-solid; yield: 89% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 93:7. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, 2H, J = 9.2 Hz, H-2, H-6), 7.42 (d, 1H, J = 7.6 Hz, H-5), 7.35 (t, 1H, J = 7.6 Hz, H-4), 4.94 (s, 2H, -OCH_2CN), 2.40 (s, 3H, C_3-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.19 (C_1-COOCH_2CN), 138.67 (C-1), 134.98 (C-2), 130.57 (C-6), 128.65 (C-4), 127.87 (C-3), 127.22 (C-5), 114.63 (-OCH$_2$CN), 48.86 (-OCH$_2$CN), 21.28 (C_3-CH_3) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_2H$; 176.0712; found: 176.0701.

Cyanomethyl 2,4,6-trimethylbenzoate (**3ae**). White semi-solid; yield: 93% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 2H, H-3, H-5), 4.93 (s, 2H, -OCH_2CN), 2.32 (s, 6H, C_2-CH_3, C_6-CH_3), 2.30 (s, 3H, C_4-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 168.33 (C_1-COOCH$_2$CN), 140.74 (C-1), 136.13 (C-2, C-6), 128.84 (C-3, C-5), 128.10 (C-4), 114.46 (-OCH$_2$CN), 48.37 (-OCH$_2$CN), 21.26 (C_2-CH$_3$, C_6-CH$_3$), 20.06 (C_4-CH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_{13}NO_2H$; 204.1025; found: 204.1037.

Cyanomethyl 2-(*tert*-butyl)benzoate (**3af**). White solid; yield: 87% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 92% (40 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, 2H, J = 8.8 Hz, H-5, H-6), 7.59 (d, 2H, J = 8.4 Hz, H-3, H-4), 5.21 (s, 2H, -OCH_2CN), 1.30 (s, 9H, 3 × C_2-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.21 (C_1-COOCH$_2$CN), 158.02 (C-1), 130.05 (C-5, C-6), 126.50 (C-3, C-4), 125.75 (C-2), 116.70 (-OCH$_2$CN), 50.21 (-OCH$_2$CN), 35.57 (C_2-C(CH$_3$)$_3$), 31.32 (3 × C_2-C(CH$_3$)$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_{15}NO_2H$; 218.1181; found: 218.1189.

Cyanomethyl 3-methoxybenzoate (**3ag**). White solid; yield: 89% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 92% (35 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 74–75 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (d, 1H, J = 7.6 Hz, H-2), 8.02–7.98 (m, 2H, H-4, H-6), 7.81–7.79 (m, 1H, H-5), 5.74 (s, 2H, -OCH_2CN), 4.34 (s, 3H, C_3-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.60 (C_1-COOCH$_2$CN), 159.41 (C-3), 130.24 (C-2), 129.23 (C-1), 121.79 (C-6), 120.32 (C-4), 116.03 (-OCH$_2$CN), 114.01 (C-5), 55.41 (C_3-OCH$_3$) 49.86 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_9NO_3H$; 192.0661; found: 192.0650.

Cyanomethyl 3,5-dimethoxybenzoate (**3ah**). White solid; yield: 90% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 87:13, mp = 108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, 2H, J = 2.4 Hz, H-2, H-6), 6.96–6.68 (m, 1H, H-4), 4.94 (s, 2H, -OCH_2CN), 3.82 (s, 6H, C_3-OCH_3, C_5-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.88 (C_1-COOCH$_2$CN), 160.89 (C-3, C-5), 129.66 (C-1), 114.54 (-OCH$_2$CN), 107.61 (C-2, C-6), 106.90 (C-4), 55.73 (C_3-OCH$_3$, C_5-OCH$_3$) 49.04 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{11}NO_4H$; 222.0766; found: 222.0760.

Cyanomethyl 4-ethoxybenzoate (**3ai**). White semi-solid; yield: 93% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 96% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 88:12. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (d, 2H, J = 8.8 Hz, H-2, H-6), 7.05 (d, 2H, J = 8.8 Hz, H-3, H-5), 5.17 (s, 2H, -OCH_2CN), 4.13–4.08 (q, 2H, J = 7.2 & 6.8 Hz, C_4-OCH_2CH$_3$), 3.87 (s, 3H, C_4-OCH$_2$CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.40 (C_1-COOCH$_2$CN), 163.23 (C-4), 131.84 (C-2, C-6), 119.78 (C-1), 116.27 (-OCH$_2$CN), 114.72 (C-3, C-5), 63.75 (C_4-OCH$_2$CH$_3$) 49.50 (-OCH$_2$CN), 14.48 (C_4-OCH$_2$CH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{11}NO_3H$; 206.0817; found: 206.0833.

Cyanomethyl 2-chlorobenzoate (**3aj**). Deep brown liquid; yield: 82% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, 1H, J = 7.6 Hz, H-6), 7.50–7.49 (m, 2H, H-4, H-5), 7.38–7.34 (m, 1H, H-3), 4.97 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.75 (C_1-COOCH$_2$CN), 134.77 (C-2), 133.98 (C-6), 132.09 (C-3), 131.62 (C-4), 127.40 (C-1), 126.94 (C-5), 114.30 (-OCH$_2$CN), 49.10 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6ClNO_2H$; 192.0661; found: 192.0684.

Cyanomethyl 3-chlorobenzoate (**3ak**).[12] Deep brown liquid; yield: 77% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, 1H, J = 8.0 Hz, H-2), 7.51 (d, 2H, J = 8.0 Hz, H-3, H-5), 7.39–7.36 (m, 1H, H-4), 4.98 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.75 (C_1-COOCH$_2$CN), 134.78 (C-3), 133.96 (C-2), 132.08 (C-6), 131.62 (C-4), 126.92 (C-5), 126.71 (C-1), 114.25 (-OCH$_2$CN), 49.08 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6ClNO_2H$; 192.0661; found: 192.0677.

Cyanomethyl 2,4,6-trichlorobenzoate (**3al**). Pale brown solid; yield: 91% (48 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (46 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 93:7, mp = 85–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 2H, H-3, H-5), 4.99 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.71 (C_1-COOCH$_2$CN), 137.53 (C-4), 133.13 (C-2, C-6), 129.92 (C-1), 128.37 (C-3, C-5), 113.45 (-OCH$_2$CN), 49.63 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_4Cl_3NO_2H$; 263.9386; found: 263.9379.

Cyanomethyl 3-bromobenzoate (**3am**). White semi-solid; yield: 79% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 83% (40 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 85:15. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.08 (m, 1H, H-2), 8.00–7.98 (m, 1H, H-6), 7.96–7.93 (m, 1H, H-4), 7.57–7.53 (m, 1H, H-3), 5.23 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.53 (C_1-COOCH$_2$CN), 137.00 (C-2), 131.90 (C-6), 131.36 (C-4), 130.18 (C-1), 128.61 (C-5), 122.06 (C-3), 115.91 (-OCH$_2$CN), 49.08 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6BrNO_2H$; 239.9660; found: 239.9643.

Cyanomethyl 4-bromobenzoate (**3an**).[12] White solid; yield: 75% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 79% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 86:14, mp = 145 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.96 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 7.73 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 5.21 (s, 2H, -OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6BrNO_2H$; 239.9660; found: 239.9680.

Cyanomethyl 3-fluorobenzoate (**3ao**).[12] White semi-solid; yield: 81% (29 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 95:5. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 1H, *J* = 9.2 Hz, H-2), 7.76–7.73 (m, 1H, H-4), 7.67–7.61 (m, 2H, H-3, H-5), 5.24 (s, 2H, -OCH_2CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 111.71 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6FNO_2H$; 180.0461; found: 180.0471.

Cyanomethyl 4-fluorobenzoate (**3ap**).[12] White semi-solid; yield: 84% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 78% (28 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.05 (m, 2H, H-2, H-6), 7.42–7.38 (m, 2H, H-3, H-5), 5.22 (s, 2H, -OCH_2CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 104.28 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6FNO_2H$; 180.0461; found: 180.0455.

Cyanomethyl 2,5-difluorobenzoate (**3aq**). White solid; yield: 84% (33 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 1H, H-6), 7.34–7.28 (m, 1H, H-3), 7.20–7.14 (m, 1H, H-4), 4.98 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.78 (C_1-COOCH$_2$CN), 159.31 (d, $J^4_{C\text{-}F}$ = 2 Hz, C-2), 157.03 (d, $J^2_{C\text{-}F}$ = 23 Hz, C-5), 123.04 (d, $J^3_{C\text{-}F}$ = 9 Hz, C-6), 122.80 (d, $J^3_{C\text{-}F}$ = 9 Hz, C-3), 118.92 (d, $J^2_{C\text{-}F}$ = 26 & 8 Hz, C-3), 118.53 (d, $J^2_{C\text{-}F}$ = 26 Hz, C-4), 117.39 (d, $J^4_{C\text{-}F}$ = 4 Hz, C-1), 114.10 (-OCH$_2$CN), 49.26 (-OCH$_2$CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 113.28 (d) & − 117.03 (d) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_5F_2NO_2H$; 198.0367; found: 198.0363.

Cyanomethyl 4-iodobenzoate (**3ar**). White solid; yield: 87% (50 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (52 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 95:5, mp = 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 7.75 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 4.95 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.67 (C_1-COOCH$_2$CN), 138.25 (C-2, C-6), 131.38 (C-3, C-5), 127.40 (C-1), 114.36 (-OCH$_2$CN), 102.52 (C-4), 49.10 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6INO_2H$; 287.9521; found: 287.9534.

Cyanomethyl 2-aminobenzoate (**3as**). Brown solid; yield: 85% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (31 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 93:7, mp = 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.81 (m, 1H, H-6), 7.34–7.29 (m, 1H, H-3), 6.69–6.64 (m, 2H, H-4, H-5), 4.89 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 166.26 (C_1-COOCH$_2$CN), 151.22 (C-2), 135.44 (C-6), 131.24 (C-3), 116.94 (C-4), 116.63 (C-5), 114.90 (-OCH$_2$CN), 108.28 (C-1), 49.60 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_8N_2O_2H$; 177.0664; found: 177.0652.

Cyanomethyl 3-aminobenzoate (**3at**). Brown solid; yield: 79% (28 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (29 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 1H, H-2), 7.22–7.05 (m, 2H, H-3, H-4), 6.87–6.66 (m, 1H, H-5), 5.48 (br s, 1H, C_3-N*H*), 5.17 (s, 2H, -OCH_2CN), 4.37 (s, 1H,C_3-N*H*) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.03 (C_1-COOCH$_2$CN), 149.29 (C-4), 147.14 (C-1), 129.47 (C-2), 119.28 (C-6), 116.67 (C-3), 114.17 (C-4), 113.50 (-OCH$_2$CN), 49.60 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_8N_2O_2H$; 177.0664; found: 177.0677.

Cyanomethyl 4-aminobenzoate (**3au**). Brown solid; yield: 88% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 124–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, 2H, *J* = 8.8 Hz, H-2, H-6), 6.63 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 4.88 (s, 2H, -OCH_2CN), 4.17 (br s, 2H, C_4-NH_2) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.98 (C_1-COOCH$_2$CN), 152.13 (C-4), 132.32 (C-2, C-6), 116.83 (C-1), 115.10 (-OCH$_2$CN), 113.90 (C-3, C-5), 48.42 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_8N_2O_2H$; 177.0664; found: 177.0669.

Cyanomethyl 4-(dimethylamino)benzoate (**3av**). White solid; yield: 88% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, 2H, *J* = 8.8 Hz, H-2, H-6), 6.64 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 4.90 (s, 2H, -OCH_2CN), 3.06 (s, 6H, 2 × C_4-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.25 (C_1-COOCH$_2$CN), 154.01 (C-4), 131.97 (C-2, C-6), 115.25 (C-1), 114.10 (-OCH$_2$CN), 110.82 (C-3, C-5), 48.34 (-OCH$_2$CN), 40.14 (2 × C_4-CH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{12}N_2O_2H$; 205.0977; found: 205.0991.

Cyanomethyl 4-acetamidobenzoate (**3aw**). White solid; yield: 82% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 50:50, mp = 153 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.38 (s, 1H, C_4-N*H*COCH$_3$), 7.94 (d, 2H, *J* = 8.4 Hz, H-2, C-6), 7.75 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 5.18 (s, 2H, -OCH_2CN), 2.09 (s, 3H, C_4-NHCOCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 169.70 (C_4-NHCOCH$_3$), 164.83 (C_1-COOCH$_2$CN), 145.10 (C-4), 131.40 (C-2, C-6), 122.31 (C-1), 118.97 (C-3, C-5), 116.75 (-OCH$_2$CN), 50.09 (-OCH$_2$CN), 24.79 (C_4-NHCOCH$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{10}N_2O_3H$; 219.0770; found: 219.0785.

Cyanomethyl 4-nitrobenzoate (**3ax**).[12] White solid; yield: 87% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35–8.33 (m, 2H, H-2, H-6), 8.25 (d, 2H, *J* = 8.8 Hz, H-3, H-5), 5.03 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.34 (C_1-COOCH$_2$CN), 151.30 (C-4), 133.26 (C-1), 131.36 (C-2, C-6), 124.00 (C-3, C-5), 113.97 (-OCH$_2$CN), 49.60 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_6N_2O_4H$; 207.0406; found: 207.0417.

Cyanomethyl 2-hydroxybenzoate (**3ay**). White solid; yield: 62% (22 mg, 0.2 mmol scale, Sonochemistry), yield: 65% (23 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 1H, C_2-O*H*), 7.86–7.84 (m, 1H, H-6), 7.56–7.52 (m, 1H, H-3), 7.03 (d, 1H, *J* = 8.0 Hz, H-3), 6.96–6.92 (m, 1H, H-4), 4.99 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.52 (C_1-COOCH$_2$CN), 144.98 (C-2), 137.23 (C-6), 130.14 (C-3), 129.55 (C-1), 119.86 (-OCH$_2$CN), 118.14 (C-5), 117.62 (C-4), 49.04 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_9H_7NO_3H$; 178.0504; found: 178.0495.

Cyanomethyl 3-hydroxybenzoate (**3az**). White solid; yield: 79% (28 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 83:17, mp = 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, 1H, *J* = 7.6 Hz, H-2), 7.51 (s, 1H, H-6), 7.33 (t, 1H, *J* = 8.0 Hz,

H-4), 7.13–7.11 (m, 1H, H-5), 6.43 (br s, 1H, C_3-O*H*), 4.95 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.20 (C_1-*C*OOCH$_2$CN), 156.17 (C-3), 130.19 (C-2), 129.08 (C-1), 122.40 (C-6), 121.73 (C-4), 116.67 (C-5), 114.60 (-OCH$_2$*C*N), 49.11 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7NO_3H$; 178.0504; found: 178.0528.

Cyanomethyl benzo[*d*][1,3]dioxole-4-carboxylate (**3aa′**). White solid; yield: 83% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 91–92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 1H, H-6), 7.43 (d, 1H, *J* = 1.6 Hz, H-4), 6.85 (d, 1H, *J* = 8.0 Hz, H-5), 6.06 (s, 2H, -OCH_2O-), 4.92 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 164.35 (C_1-*C*OOCH$_2$CN), 152.73 (C-2), 148.06 (C-3), 126.37 (C-6), 121.70 (C-1), 114.69 (-OCH$_2$*C*N), 109.70 (C-4), 108.35 (C-5), 102.21 (-OCH_2O-), 48.86 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_7NO_4H$; 206.0453; found: 206.0470.

Cyanomethyl 2-(trifluoromethyl)benzoate (**3ab′**). White solid; yield: 87% (39 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 94:6, mp = 90 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.93–7.90 (m, 2H, H-3, H-6), 7.86–7.83 (m, 2H, H-4, H-5), 5.28 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 164.86 (C_1-*C*OOCH$_2$CN), 132.93 (d, $J^2_{C\text{-}F}$ = 22 Hz, C-6), 130.54 (C-2), 128.51 (C_2-*C*F$_3$), 127.29 (d, $J^3_{C\text{-}F}$ = 6 Hz, C-3), 127.05 (d, $J^4_{C\text{-}F}$ = 4 Hz, C-4), 126.95 (d, $J^3_{C\text{-}F}$ = 4 Hz, C-5), 121.89 (t, $J^1_{C\text{-}F}$ = 272 Hz, C-1), 115.44 (-OCH$_2$*C*N), 50.43 (-OCH$_2$CN) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 58.28 ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_6F_3NO_2H$; 230.0429; found: 230.0438.

Cyanomethyl 4-acetylbenzoate (**3ac′**). White solid; yield: 89% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 94% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 65:35, mp = 91–92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, 2H, *J* = 8.0 Hz, H-2, H-6), 8.03 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 4.99 (s, 2H, -OCH_2CN), 2.65 (s, 3H, C_4-CO*C*H$_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 197.42 (C_4-*C*OCH$_3$), 164.27 (C_1-*C*OOCH$_2$CN), 141.15 (C-4), 131.57 (C-1), 130.42 (C-2), 130.16 (C-6), 128.54 (C-3, C-5), 114.31 (-OCH$_2$*C*N), 49.27 (-OCH$_2$CN), 27.06 (C_4-CO*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_9NO_3H$; 204.0661; found: 204.0650.

Cyanomethyl 2-acetoxybenzoate (**3ad′**). White solid; yield: 87% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 88:12, mp = 86 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 1H, H-6), 7.65–7.60 (m, 1H, H-3), 7.36–7.32 (m, 1H, H-5), 7.15–7.13 (m, 1H, H-4), 4.89 (s, 2H, -OCH_2CN), 2.36 (s, 3H, C_2-OCOCH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 169.61 (C_2-OCOCH$_3$), 162.71 (C_1-*C*OOCH$_2$CN), 151.14 (C-2), 135.20 (C-6), 131.98 (C-3), 126.32 (C-5), 124.21 (C-4), 121.16 (C-1), 114.38 (-OCH$_2$*C*N), 48.96 (-OCH$_2$CN), 20.97 (C_2-OCO*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_9NO_4H$; 220.0610; found: 220.0614.

Cyanomethyl 4-cyanobenzoate (**3ae′**).[12] White solid; yield: 86% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 138–139 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.17 (d, 2H, *J* = 8.4 Hz, H-2, H-6), 7.80 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 5.01 (s, 2H, -OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_6N_2O_2H$; 187.0508; found: 187.0523.

Cyanomethyl 2-amino-6-methylbenzoate (**3af′**). White solid; yield: 84% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 93–95 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15–7.11 (m, 1H, H-3), 6.55–6.52 (m, 2H, H-4, H-5), 5.37 (br s, 2H, C_2-NH_2), 4.92 (s, 2H, -OCH_2CN), 2.47 (s, 3H, C_6-CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 167.60 (C_1-COOCH$_2$CN), 150.84 (C-2), 141.00 (C-3), 133.54 (C-5), 120.70 (C-6), 114.94 (C-4), 114.77 (-OCH$_2$*C*N), 110.29 (C-1), 48.17 (-OCH$_2$CN), 23.86 (C_6-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{10}H_{10}N_2O_2H$; 191.0821; found: 191.0816.

Cyanomethyl 4-amino-2-hydroxybenzoate (**3ag′**). White semi-solid; yield: 83% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.31 (s, 1H, C_2-O*H*), 7.60 (d, 1H, *J* = 8.4 Hz, H-6), 7.26 (s, 1H, H-3), 6.16 (s, 1H, H-5), 4.91 (s, 2H, -OCH_2CN), 4.26 (br s, 2H, C_4-NH_2) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.07 (C_1-*C*OOCH$_2$CN), 164.22 (C-2), 154.59 (C-4), 131.94 (C-6), 114.63 (-OCH$_2$*C*N), 107.45 (C-3), 100.98 (C-1), 100.63 (C-5), 48.46 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_8N_2O_3H$; 193.0613; found: 193.0627.

Cyanomethyl 2-amino-3,4,5-trimethoxybenzoate (**3ah′**). White semi-solid; yield: 79% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 77% (41 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.01 (s, 1H, H-6), 6.21 (br s, 2H, C_2-NH_2), 5.11 (s, 2H, -OCH_2CN), 3.85 (s, 3H, C_3-OCH_3), 3.73 (s, 3H, C_4-OCH_3), 3.71 (s, 3H, C_5-OCH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.19 (C_1-*C*OOCH$_2$CN), 147.80 (C-3), 142.41 (C-4), 141.92 (C-5), 139.50 (C-2), 115.86 (-OCH$_2$*C*N), 107.22 (C-6), 100.63 (C-1), 60.16 (C_3-OCH_3), 59.84 (C_4-OCH_3), 55.78 (C_5-OCH_3), 48.53 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_{14}N_2O_5H$; 267.0981; found: 267.0999.

Cyanomethyl 2-amino-6-bromobenzoate (**3ai′**). White solid; yield: 82% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (43 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 148–149 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, 1H, *J* = 8.8 Hz, H-3), 6.86 (d, 1H, *J* = 1.6 Hz, H-5), 6.78–6.75 (m, 1H, H-4), 5.81 (br s, 2H, C_2-NH_2), 4.89 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.84 (C_1-COOCH$_2$CN), 151.87 (C-2), 132.51 (C-3), 130.33 (C-5), 119.91 (C-5), 119.25 (C-4), 114.73 (-OCH$_2$*C*N), 107.66 (C-1), 48.50 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7BrN_2O_2H$; 211.0274; found: 211.0285.

Cyanomethyl 2-amino-4-chlorobenzoate (**3aj′**). White solid; yield: 83% (35 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 158 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, 1H, *J* = 2.8 Hz, H-4), 7.25–7.23 (m, 1H, H-3), 6.62 (d, 1H, *J* = 8.8 Hz, H-5), 4.89 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.39 (C_1-*C*OOCH$_2$CN), 149.82 (C-4), 135.52 (C-2), 130.28 (C-6), 121.00 (C-3), 118.35 (C-5), 114.60 (-OCH$_2$*C*N), 108.88 (C-1), 48.57 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7ClN_2O_2H$; 211.0274; found: 211.0269.

Cyanomethyl 2-amino-6-fluorobenzoate (**3ak′**). White semi-solid; yield: 88% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.17 (m, 1H, H-6), 6.45 (d, 1H, *J* = 8.4 Hz, H-3), 6.37–6.32 (m, 1H, H-5), 4.91 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.61 (C_1-COOCH$_2$CN), 163.51 (d, $J^1_{C\text{-}F}$ = 257 Hz, C-6), 152.67 (d, $J^4_{C\text{-}F}$ = 5 Hz, C-2), 135.23 (d, $J^3_{C\text{-}F}$ = 12 Hz, C-5), 114.69 (-OCH$_2$*C*N), 112.34 (d, $J^4_{C\text{-}F}$ = 3 Hz, C-3), 103.85 (d, $J^2_{C\text{-}F}$ = 24 Hz, C-4), 99.04 (d, $J^3_{C\text{-}F}$ = 14 Hz, C-1), 48.50 (-OCH$_2$CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = − 104.40 ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_7CFN_2O_2H$; 195.0570; found: 195.0582.

Cyanomethyl 4-chloro-2-methoxybenzoate (**3al′**). White solid; yield: 89% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 82:18, mp = 100 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 1H, *J* = 2.8 Hz, H-6), 7.51–7.48 (m, 1H, H-3), 6.95 (d, 1H, *J* = 9.2 Hz, H-5), 4.92 (s, 2H, -OCH_2CN), 3.91 (s, 3H, C_2-OCH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.02 (C_1-*C*OOCH$_2$CN), 158.68 (C-2), 134.83 (C-6), 131.92 (C-3), 125.42 (C-4), 118.33

(C-1), 114.50 (-OCH$_2$CN), 113.73 (C-5), 56.49 (C$_2$-OCH$_3$), 48.86 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_8ClNO_3H$; 226.0271; found: 226.0286.

Cyanomethyl 5-fluoro-2-methylbenzoate (**3am′**). White solid; yield: 85% (33 mg, 0.2 mmol scale, Sonochemistry), yield: 83% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 96:4, mp = 105 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 7.63 (d, 1H, *J* = 9.2 Hz, H-6), 7.44 (d, 2H, *J* = 6.8 Hz, H-4, H-3), 5.19 (s, 2H, -OC*H*$_2$CN), 3.50 (s, 3H, C$_2$-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 164.42 (C$_1$-*C*OOCH$_2$CN), 159.94 (d, $J^1_{C\text{-}F}$ = 241 Hz, C-5), 136.17 (d, $J^4_{C\text{-}F}$ = 2 Hz, C-2), 133.89 (d, $J^3_{C\text{-}F}$ = 8 Hz, C-6), 128.85 (d, $J^3_{C\text{-}F}$ = 7 Hz, C-1), 120.14 (d, $J^2_{C\text{-}F}$ = 21 Hz, C-3), 123.74 (d, $J^2_{C\text{-}F}$ = 23 Hz, C-4), 115.97 (-OCH$_2$*C*N), 49.83 (-O*C*H$_2$CN), 20.24 (C$_2$-*C*H$_3$) ppm. ^{19}F NMR (376 MHz, DMSO-d$_6$): δ = − 116.43 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_8FNO_2H$; 194.0617; found: 194.0628.

Cyanomethyl 5-iodo-2-methylbenzoate (**3an′**). White solid; yield: 83% (50 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (48 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 94:6, mp = 87–88 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.25 (d, 2H, *J* = 2.0 Hz, H-6, H-3), 7.77–7.75 (m, 1H, H-5), 7.04–6.99 (m, 1H, H-4), 4.93 (s, 2H, -OC*H*$_2$CN), 2.55 (s, 3H, C$_2$-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 164.07 (C$_1$-*C*OOCH$_2$CN), 142.08 (C-6), 141.65 (C-2), 140.09 (C-1), 139.60 (C-3), 133.91 (C-4), 132.82 (C-5), 114.47 (-OCH$_2$*C*N), 48.83 (-O*C*H$_2$CN), 21.58 (C$_2$-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_8INO_2H$; 301.9678; found: 301.9665.

Cyanomethyl 4-methyl-3-methoxybenzoate (**3ao′**). White solid; yield: 88% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 90% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 94:6, mp = 89–90 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.58–7.56 (m, 1H, H-2), 7.45 (d, 1H, *J* = 1.2 Hz, H-6), 7.21 (d, 1H, *J* = 7.6 Hz, H-5), 4.95 (s, 2H, -OC*H*$_2$CN), 3.88 (s, 3H, C$_3$-OC*H*$_3$), 2.27 (s, 3H, C$_4$-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 165.18 (C$_1$-*C*OOCH$_2$CN), 157.86 (C-3), 134.26 (C-4), 130.76 (C-2), 126.56 (C-1), 122.53 (C-6), 114.71 (-OCH$_2$*C*N), 110.70 (C-5), 55.59 (C$_3$-OCH$_3$), 48.86 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{11}H_{11}NO_3H$; 206.0817; found: 206.0801.

Cyanomethyl 4-hydroxy-3-methoxybenzoate (**3ap′**). White semi-solid; yield: 77% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 10.23 (br s, 1H, C$_4$-O*H*), 7.52–7.50 (m, 1H, H-2), 7.45 (s, 1H, H-6), 6.90 (d, 1H, *J* = 8.4 Hz, H-5), 5.15 (s, 2H, -OC*H*$_2$CN), 3.83 (s, 3H, C$_3$-OC*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 164.54 (C$_1$-*C*OOCH$_2$CN), 152.51 (C-4), 147.60 (C-3), 124.17 (C-2), 118.48 (C-1), 116.26 (-OCH$_2$*C*N), 115.44 (C-2), 112.67 (C-5), 55.68 (C$_3$-O*C*H$_3$), 49.36 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{10}H_9NO_4H$; 208.0610; found: 208.0627.

Cyanomethyl [1,1′-biphenyl]-4-carboxylate (**3aq′**). White solid; yield: 84% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 87:13, mp = 132–135 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.13 (d, 2H, *J* = 8.0 Hz, H-2, H-6), 7.70 (d, 2H, *J* = 8.4 Hz, H-3, H-5), 7.63 (d, 2H, *J* = 7.6 Hz, C$_4$-H-2′, H-6′), 7.51–7.47 (m, 2H, C$_4$-H-3′, H-5′), 7.44–7.41 (m, 1H, H-4′), 4.99 (s, 2H, -OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 164.95 (C$_1$-*C*OOCH$_2$CN), 146.96 (C-4), 139.62 (C-4′), 130.67 (C-2, C-6), 129.12 (C-3, C-5), 128.59 (C$_4$-C-1′), 127.43 (C$_4$-C-2′, C-6′), 127.40 (C$_4$-C-3′, C-5′), 126.57 (C-1), 114.65 (-OCH$_2$*C*N), 48.95 (-O*C*H$_2$CN) ppm. HRMS (ESI) *m/z* [M + H]$^+$ calcd. for $C_{15}H_{11}NO_2H$; 238.0868; found, 238.0892.

Bis(cyanomethyl) 3-nitrophthalate (**3ar′**). Pinkish solid; yield: 74% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 70% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30, mp = 271 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 7.88–7.85 (m, 2H, H-3, H-6), 7.82–7.79 (m, 2H, H-4, H-5), 5.21 (s, 4H, C$_1$-OC*H*$_2$CN, C$_2$-OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 165.45 (C$_1$-*C*OOCH$_2$CN, C$_2$-*C*OOCH$_2$CN), 132.82 (C-3, C-6), 129.55 (C-1, C-2), 129.44 (C-4, C-5), 115.55 (C$_1$-OCH$_2$*C*N, C$_2$-OCH$_2$*C*N), 50.31 (C$_1$-OCH$_2$CN, C$_2$-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_8N_2O_4H$; 245.0562; found: 245.0585.

Bis(cyanomethyl) 3-nitrophthalate (**3as′**). White solid; yield: 83% (49 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (50 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 60:40, mp = 134–135 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.62 (d, 1H, *J* = 8.4 Hz, H-4), 8.49–8.47 (m, 1H, H-6), 8.04–7.99 (m, 1H, H-5), 5.33 (s, 2H, C$_2$-OC*H*$_2$CN), 5.28 (s, 2H, C$_1$-OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 163.78 (C$_2$-*C*OOCH$_2$CN), 162.33 (C$_1$-*C*OOCH$_2$CN), 145.83 (C-3), 136.64 (C-6), 132.63 (C-4), 130.17 (C-5), 127.91 (C-2), 127.50 (C-1), 115.44 (C$_2$-OCH$_2$*C*N), 114.99 (C$_1$-OCH$_2$*C*N), 51.02 (C$_2$-O*C*H$_2$CN), 50.65 (C$_1$-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_7N_3O_6H$; 290.0413; found: 290.0402.

3-Methyl-4-oxo-2-phenyl-4*H*-chromene-8-carboxylic acid (**3at′**). White solid; yield: 88% (56 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (55 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 75:25, mp = 213–215 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.54–8.52 (m, 1H, Ar-H), 8.33–8.31 (m, 1H, Ar-H), 7.81–7.79 (m, 2H, Ar-H), 7.57–7.55 (m, 3H, Ar-H), 7.50–7.46 (m, 1H, Ar-H), 4.99 (s, 2H, -C*H*$_2$-), 2.25 (-C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ = 178.08 (*C*O), 162.67 (Ar*C*OO-), 161.17 (*C*), 154.82 (*C*), 136.83 (*C*H), 132.77 (*C*), 132.51 (*C*H), 130.84 (*C*H), 129.41 (2 × *C*H), 128.75 (2 × *C*H), 124.27 (*C*H), 123.51 (*C*), 118.05 (*C*), 117.99 (*C*), 114.32 (-CH$_2$*C*N), 49.27 (-*C*H$_2$-), 11.97 (-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{17}H_{12}O_4H$; 281.0814; found: 281.0820.

Cyanomethyl 2-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoate (**3au′**). Brownish-red semi-solid; yield: 66% (44 mg, 0.2 mmol scale, Sonochemistry), yield: 62% (41 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 97:3. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 10.13 (s, 1H, -N*H*), 8.10–8.04 (m, 2H, Ar-H), 7.98 (d, 1H, *J* = 11.2 Hz, Ar-H), 7.91–7.87 (m, 1H, Ar-H), 7.85–7.81 (m, 1H, Ar-H), 7.80–7.76 (m, 1H, Ar-H), 7.73 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.34–7.31 (m, 1H, Ar-H), 6.43 (s, 1H, Ar-H), 5.24 (s, 2H, -OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 183.23 (*C*O), 181.32 (*C*O), 165.25 (Ar*C*OO-), 144.12 (*C*), 140.07 (*C*), 135.30 (*C*H), 135.15 (*C*H), 133.13 (*C*H), 132.31 (*C*), 131.89 (*C*H), 130.23 (*C*), 126.42 (*C*H), 125.49 (*C*H), 124.16 (*C*H), 122.24 (*C*H), 118.49 (*C*), 115.91 (-OCH$_2$*C*N), 104.94 (*C*H), 50.08 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{19}H_{12}N_2O_4H$; 333.0875; found: 333.0869.

Cyanomethyl 4-((1,4-dioxo-1,4-dihydronaphthalen-2-yl)amino)benzoate (**3av′**). Brownish-red semi-solid; yield: 69% (46 mg, 0.2 mmol scale, Sonochemistry), yield: 63% (42 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 96:4. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 9.52 (s, 1H, -N*H*), 8.08 (d, 1H, *J* = 7.2 Hz, Ar-H), 8.03 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.97 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.90–7.86 (m, 1H, Ar-H), 7.84–7.79 (m, 1H, Ar-H), 7.61 (d, 2H, *J* = 8.4 Hz, Ar-H), 6.43 (s, 1H, Ar-H), 5.21 (s, 2H, -OC*H*$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$): δ = 183.24 (*C*O), 181.33 (*C*O), 164.21 (Ar*C*OO-), 144.81 (*C*), 144.00 (2*C*), 135.00 (*C*H), 133.05 (*C*H), 132.30 (*C*), 131.04 (2 × *C*H), 130.47 (*C*), 126.33 (*C*H), 125.41 (*C*H), 122.99 (*C*), 122.19 (*C*H), 116.18 (-OCH$_2$*C*N), 104.95 (*C*H), 49.73 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{19}H_{12}N_2O_4H$; 333.0875; found: 333.0889.

Cyanomethyl 2-(naphthalen-1-yl)acetate (**3ba**).[12] White solid; yield: 89% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 88:12, mp = 82 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.85–7.81 (m, 3H, H-1, H-4, H-5), 7.74 (s, 1H, H-6), 7.51–7.48 (m, 2H, H-2, H-3), 7.41–7.38 (m, 1H, H-7), 4.74 (s, 2H, -OC*H*$_2$CN), 3.89 (s, 2H, C$_8$-C*H*$_2$-) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{14}H_{11}NO_2H$; 226.0868; found: 226.0853.

Cyanomethyl 2-(naphthalen-2-yl)acetate (**3bb**). White solid; yield: 84% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 84:16, mp = 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.89 (m, 2H, H-1, H-4), 7.84 (d, 1H, J = 8.0 Hz, H-2), 7.59–7.56 (m, 1H, H-3), 7.55–7.51 (m, 1H, H-5), 7.48–7.44 (m, 1H, H-8), 7.55–7.51 (m, 1H, H-6), 7.43–7.41 (m, 1H, H-7), 4.67 (s, 2H, -OCH_2CN), 4.16 (s, 2H, C_8-CH_2-) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 170.02 (C_8-COOCH$_2$CN), 133.91 (C-9), 131.91 (C-10), 128.98 (C-1), 128.71 (C-4), 128.32 (C-2), 127.77 (C-8), 126.80 (C-3), 126.10 (C-5), 125.56 (C-7), 123.41 (C-6), 114.31 (-OCH$_2$CN), 48.73 (-OCH_2CN), 38.26 (C_8-CH_2-) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{14}H_{11}NO_2H$; 226.0868; found: 226.0847.

Cyanomethyl 2-hydroxy-1-naphthoate (**3bc**). White solid; yield: 88% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 92:8, mp = 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.36 (s, 1H, C_7-OH), 8.42 (d, 1H, J = 8.4 Hz, H-6), 7.78 (d, 1H, J = 8.4 Hz, H-5), 7.72 (d, 1H, J = 8.8 Hz, H-4), 7.67–7.63 (m, 1H, H-3), 7.58–7.54 (m, 1H, H-1), 7.31 (d, 1H, J = 8.8 Hz, H-2), 5.03 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 169.32 (C_1-COOCH$_2$CN), 162.00 (C-2), 137.76 (C-9), 130.34 (C-3), 127.71 (C-4), 126.34 (C-8), 124.66 (C-10), 124.20 (C-5), 123.67 (C-6), 119.44 (C-7), 114.24 (-OCH$_2$CN), 103.91 (C-1), 49.03 (-OCH_2CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{13}H_9NO_3H$; 228.0661; found: 228.0674.

Cyanomethyl cinnamate (**3ca**).[12] White solid; yield: 83% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 91:9, mp = 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.78 (m, 1H, C_1-CH = CH-), 7.56–7.54 (m, 2H, H-2, H-6), 7.43–7.41 (m, 3H, H-3, H-4, H-5), 6.47–6.44 (m, 1H, C_1-CH = CH-), 4.85 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.25 (C_1-COOCH$_2$CN), 147.89 (C_1-CH = CH-), 133.37 (C-1), 131.23 (C-4), 129.17 (C-2, C-6), 128.52 (C-3, C-5), 115.36 (C_1-CH = CH-), 114.66 (-OCH$_2$CN), 48.53 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{11}H_9NO_2H$; 188.0712; found: 188.0730.

Cyanomethyl (*E*)-3-(*p*-tolyl)acrylate (**3cb**). White solid; yield: 80% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 87:13, mp = 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, 1H, J = 16 Hz, C_1-CH = CH-), 7.44 (d, 2H, J = 8.0 Hz, H-2, H-6), 7.22 (d, 2H, J = 8.0 Hz, H-3, H-5), 6.40 (d, 1H, J = 16 Hz, C_1-CH = CH-), 4.84 (s, 2H, -OCH_2CN), 2.39 (s, 3H, C_1-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.43 (C_1-COOCH$_2$CN), 147.89 (C_1-CH = CH-), 141.87 (C-1), 131.06 (C-3), 129.88 (C-2, C-6), 128.54 (C-3, C-5), 114.73 (-OCH$_2$CN), 114.17 (C_1-CH = CH-), 48.45 (-OCH$_2$CN), 21.66 (C_4-CH_3) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{12}H_{11}NO_2H$; 202.0868; found: 202.0848.

Cyanomethyl (*E*)-3-(4-methoxyphenyl)acrylate (**3cc**). White solid; yield: 83% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (37 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 86:14, mp = 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, 1H, J = 16 Hz, C_1-CH = CH-), 7.49 (d, 2H, J = 8.8 Hz, H-2, H-6), 6.91 (d, 2H, J = 8.4 Hz, H-3, H-5), 6.30 (d, 1H, J = 16 Hz, C_1–CH = CH-), 4.83 (s, 2H, -OCH_2CN), 3.84 (s, 3H, C_4-OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.55 (C_1-COOCH$_2$CN), 162.11 (C-4), 147.50 (C_1-CH = CH-), 130.30 (C-2, C-6), 126.48 (C-1), 114.82 (-OCH$_2$CN), 114.55 (C-3, C-5), 112.60 (C_1-CH = CH-), 55.53 (C_4-OCH$_3$), 48.38 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{12}H_{11}NO_3H$; 218.0817; found: 218.0795.

Cyanomethyl (*E*)-3-(4-hydroxyphenyl)acrylate (**3 cd**). White solid; yield: 74% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 79% (32 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 89:11, mp = 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 1H, C_1-CH = CH-), 7.43 (d, 2H, J = 8.4 Hz, H-2, H-6), 6.87 (d, 2H, J = 8.4 Hz, H-3, H-5), 6.30–6.26 (m, 1H, C_1-CH = CH-), 4.85 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 165.69 (C_1-COOCH$_2$CN), 158.65 (C-4), 147.64 (C_1-CH = CH-), 130.56 (C-2, C-6), 126.48 (C-1), 116.14 (C-3, C-5), 115.39 (-OCH$_2$CN), 112.45 (C_1-CH = CH-), 48.41 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{11}H_9NO_3H$; 204.0661; found: 204.0677.

Cyanomethyl (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)acrylate (**3ce**). White solid; yield: 87% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 138–139 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.69 (d, 1H, J = 15.6 Hz, C_1-CH = CH-), 7.46 (d, 1H, J = 1.2 Hz, H-2), 7.26–7.24 (m, 1H, H-5), 6.97 (d, 1H, J = 8.0 Hz, H-6), 6.59 (d, 1H, J = 16 Hz, C_1-CH = CH-), 6.09 (s, 2H, -OCH_2O-), 5.07 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.33 (C_1-COOCH$_2$CN), 149.86 (C-3), 148.11 (C-4), 146.74 (C_1-CH = CH-), 128.11 (C-1), 125.77 (C-2), 116.19 (-OCH$_2$CN), 113.63 (C-4), 108.51 (C-5), 106.85 (C-6), 101.73 (-OCH_2O-), 49.01 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{12}H_9NO_4H$; 232.0610; found: 232.0622.

Cyanomethyl 3-phenylpropiolate (**3cf**). White solid; yield: 86% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 84% (33 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 90:10, mp = 74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 2H, H-2, H-6), 7.53–7.48 (m, 1H, H-4), 7.43–7.39 (m, 2H, H-3, H-5), 4.86 (s, 2H, C_1-C ≡ C-COOCH_2-) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 152.20 (C_1-COOCH$_2$-), 133.42 (C-2, C-6), 131.58 (C-4), 128.89 (C-3, C-5), 118.78 (C-1), 113.77 (-OCH$_2$CN), 90.06 (C_1-C ≡ C-), 78.81 (C_1-C ≡ C-), 49.30 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_{11}H_7NO_2H$; 186.0555; found: 186.0569.

Cyanomethyl nicotinate (**3 da**). Blackish brown liquid; yield: 86% (28 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (29 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (s, 1H, H-2), 8.84 (d, 1H, J = 4.0 Hz, H-4), 8.33 (d, 1H, J = 8.0 Hz, H-6), 7.47–7.44 (m, 1H, H-5), 5.01 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.83 (C_3-COOCH$_2$CN), 154.48 (C-2), 151.13 (C-4), 137.70 (C-6), 124.25 (C-3), 123.77 (C-5), 114.13 (-OCH$_2$CN), 49.21 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_8H_6N_2O_2H$; 163.0508; found: 163.0527.

Cyanomethyl 2-methylnicotinate (**3db**). White solid; yield: 88% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 60:40, mp = 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, 1H, J = 3.6 Hz, H-2), 8.25 (d, 1H, J = 8.0 Hz, H-6), 7.29–7.27 (m, 1H, H-4), 4.98 (s, 2H, -OCH_2CN), 2.87 (s, 3H, C_2-CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.56 (C_3-COOCH$_2$CN), 161.00 (C-2), 153.07 (C-4), 138.88 (C-6), 122.97 (C-3), 121.21 (C-5), 114.36 (-OCH$_2$CN), 49.00 (-OCH$_2$CN), 25.06 (C_2-CH$_3$) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_8H_8N_2O_2H$; 177.0664; found: 177.0668.

Cyanomethyl 6-chloronicotinate (**3dc**). White semi-solid; yield: 81% (32 mg, 0.2 mmol scale, Sonochemistry), yield: 86% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 83:17. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.02 (d, 1H, J = 2.0 Hz, H-2), 8.28–8.25 (m, 1H, H-4), 7.47 (d, 1H, J = 8.4 Hz, H-5), 5.00 (s, 2H, -OCH_2CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.10 (C_3-COOCH$_2$CN), 157.11 (C-6), 151.57 (C-2), 139.93 (C-4), 124.72 (C-5), 123.10 (C-3), 113.96 (-OCH$_2$CN), 49.34 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): m/z [M + H]$^+$ calcd. for $C_8H_5ClN_2O_2H$; 197.0118; found: 197.0127.

Cyanomethyl 2-aminonicotinate (**3dd**). White solid; yield: 82% (31 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (30 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 65:35, mp = 148–150 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (d, 1H, J = 5.2 Hz, H-4), 6.97 (s. 1H, H-6), 6.90–6.88 (m, 1H,

H-5), 6.39 (s, 2H, C_2-NH_2), 5.21 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 164.28 (C_3-COOCH$_2$CN), 160.59 (C-2), 149.30 (C-4), 136.15 (C-6), 115.87 (-OCH$_2$CN), 109.90 (C-3), 107.56 (C-5), 50.12 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_8H_7N_3O_2H$; 178.0617; found: 178.0601.

Cyanomethyl 2-aminoisonicotinate (**3de**). White solid; yield: 79% (30 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (31 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 50:50, mp = 165–166 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.27 (m, 1H, H-3), 8.13–8.10 (m, 1H, H-5), 6.67–6.64 (m, 1H, H-6), 4.92 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.33 (C_4-COOCH$_2$CN), 159.79 (C-2), 155.24 (C-3), 140.36 (C-5), 114.50 (-OCH$_2$CN), 113.07 (C-6), 103.87 (C-4), 48.75 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_8H_7N_3O_2H$; 178.0617; found: 178.0638.

Bis(cyanomethyl) pyridine-2,6-dicarboxylate (**3df**). White solid; yield: 77% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 73% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 55:45, mp = 144 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, 2H, *J* = 8.0 Hz, H-3, H-5), 8.17–8.13 (m, 1H, H-4), 5.07 (s, 4H, C_2-OCH_2CN, C_6-OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.99 (C_2-COOCH$_2$CN, C_6-COOCH$_2$CN), 146.79 (C-2, C-6), 139.21 (C-4), 129.64 (C-3, C-5), 113.91 (2 × -OCH$_2$CN), 49.91 (2 × -OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7N_3O_4H$; 246.0515; found: 246.0529.

Cyanomethyl 1*H*-indole-2-carboxylate (**3dg**). White solid; yield: 90% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (35 mg, 0.2 mmol scale, Mechanochemistry), mp = 163–164 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.13 (s, 1H, C_1-N*H*), 7.69 (d, 1H, *J* = 8.0 Hz, H-3), 7.47 (d, 1H, *J* = 8.4 Hz, H-7), 7.32–7.29 (m, 2H, H-5, H-6), 7.13–7.09 (m, 1H, H-4), 5.26 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 160.00 (C_2-COOCH$_2$CN), 137.90 (C-9), 126.64 (C-8), 125.45 (C-3), 125.12 (C-3), 122.42 (C-4), 120.57 (C-7), 116.15 (-OCH$_2$CN), 112.75 (C-5), 109.50 (C-6), 49.50 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_8N_2O_2H$; 201.0664; found: 201.0645.

Cyanomethyl 1*H*-indole-3-carboxylate (**3dh**). Violet solid; yield: 82% (33 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (34 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 83:17, mp = 172–174 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.18 (s, 1H, C_1-N*H*), 8.23 (s, 1H, H-2), 7.99 (d, 1H, *J* = 4.4 Hz, H-4), 7.53–7.52 (m, 1H, H-7), 7.25–7.23 (m, 2H, H-5, H-6), 5.17 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 162.83 (C_3-COOCH$_2$CN), 136.48 (C-9), 133.86 (C-3), 125.53 (C-8), 122.81 (C-4), 121.81 (C-7), 120.24 (C-5), 116.66 (-OCH$_2$CN), 112.65 (C-6), 104.34 (C-3), 48.34 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_8N_2O_2H$; 201.0664; found: 201.0657.

Cyanomethyl benzofuran-2-carboxylate (**3di**). White solid; yield: 87% (35 mg, 0.2 mmol scale, Sonochemistry), yield: 89% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 112–113 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, 1H, *J* = 8.0 Hz, H-3), 7.66–7.65 (m, 1H, H-7), 7.60 (d, 1H, *J* = 8.4 Hz, H-4), 7.53–7.49 (m, 1H, H-5), 7.35 (t, 1H, *J* = 7.6 Hz, H-6), 5.02 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.81 (C_2-COOCH$_2$CN), 156.26 (C-9), 143.24 (C-8), 128.75 (C-3), 126.65 (C-2), 124.36 (C-4), 123.32 (C-7), 116.42 (C-5), 114.08 (-OCH$_2$CN), 112.59 (C-6), 49.01 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7NO_3H$; 202.0504; found: 202.0529.

Cyanomethyl benzo[*b*]thiophene-2-carboxylate (**3dj**). White solid; yield: 85% (37 mg, 0.2 mmol scale, Sonochemistry), yield: 87% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 80:20, mp = 104–106 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (s, 1H, H-3), 7.92–7.88 (m, 2H, H-4, H-7), 7.53–7.49 (m, 1H, H-5), 7.46–7.43 (m, 1H, H-6), 4.99 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.22 (C_2-COOCH$_2$CN), 142.85 (C-9), 138.50 (C-8), 132.69 (C-3), 130.55 (C-2), 127.87 (C-4), 126.06 (C-7), 125.42 (C-5), 122.94 (C-6), 114.26 (-OCH$_2$CN), 49.17 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7NO_2SH$; 218.0276; found: 218.0289.

Cyanomethyl benzo[*b*]thiophene-3-carboxylate (**3dk**). White solid; yield: 78% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 81% (35 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 75:25, mp = 95 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, 1H, *J* = 8.4 Hz, H-2), 8.48 (s, 1H, H-7), 7.89 (d, 1H, *J* = 8.0 Hz, H-4), 7.54–7.50 (m, 1H, H-5), 7.47–7.43 (m, 1H, H-6), 4.99 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 160.62 (C_3-COOCH$_2$CN), 139.90 (C-8), 138.85 (C-2), 136.38 (C-9), 125.97 (C-7), 125.59 (C-4), 124.56 (C-3), 124.47 (C-5), 122.72 (C-6), 114.67 (-OCH$_2$CN), 48.56 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7NO_2SH$; 218.0276; found: 218.0282.

Cyanomethyl quinoline-3-carboxylate (**3dl**). White solid; yield: 80% (34 mg, 0.2 mmol scale, Sonochemistry), yield: 85% (36 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 75:25, mp = 137–138 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.42 (d, 1H, *J* = 1.6 Hz, H-2), 8.87 (d, 1H, *J* = 2.0 Hz, H-4), 8.17 (d, 1H, *J* = 8.4 Hz, H-8), 7.95 (d, 1H, *J* = 8.0 Hz, H-5), 7.89–7.86 (m, 1H, H-6), 7.67–7.64 (m, 1H, H-7), 5.07 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.96 (C_3-COOCH$_2$CN), 150.29 (C-10), 149.63 (C-2), 139.82 (C-4), 132.83 (C-8), 129.66 (C-5), 129.38 (C-6), 128.02 (C-7), 126.66 (C-9), 120.90 (C-3), 114.28 (-OCH$_2$CN), 49.24 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_8N_2O_2H$; 213.0664; found: 213.0679.

Cyanomethyl isoquinoline-3-carboxylate (**3dm**). Pale brown solid; yield: 85% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 90% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 55:45, mp = 133–134 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.34 (s, 1H, H-4), 8.64 (s, 1H, H-1), 8.08 (d, 1H, *J* = 7.6 Hz, H-8), 8.00 (d, 1H, *J* = 7.6 Hz, H-5), 7.86–7.78 (m, 2H, H-6, H-7), 5.09 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 164.34 (C_3-COOCH$_2$CN), 153.17 (C-4), 139.55 (C-10), 135.32 (C-9), 131.73 (C-1), 130.52 (C-8), 130.35 (C-3), 128.29 (C-5), 127.94 (C-6), 125.52 (C-7), 114.39 (-OCH$_2$CN), 49.46 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_8N_2O_2H$; 213.0664; found: 213.0681.

Cyanomethyl quinoxaline-2-carboxylate (**3dn**). White solid; yield: 89% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 91% (39 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30, mp = 125 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.55 (s, 1H, H-3), 8.29–8.27 (m, 1H, H-5), 8.22–8.19 (m, 1H, H-8), 7.98–7.93 (m, 1H, H-6), 7.93–7.89 (m, 1H, H-7), 5.15 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.94 (C_2-COOCH$_2$CN), 144.99 (C-3), 144.22 (C-9), 141.57 (C-10), 140.60 (C-2), 133.32 (C-5), 131.67 (C-8), 130.73 (C-6), 129.61 (C-7), 113.86 (-OCH$_2$CN), 49.85 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{11}H_7N_3O_2H$; 214.0617; found: 214.0606.

Cyanomethyl 2-oxo-2*H*-chromene-3-carboxylate (**3do**). Pale brown solid; yield: 83% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 81% (37 mg, 0.2 mmol scale, Mechanochemistry), mp = 81–82 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.68–8.67 (m, 1H, H-4), 7.70–7.65 (m, 2H, H-5, H-8), 7.38–7.36 (m, 2H, H-6, H-7), 4.98 (s, 2H, -OCH_2CN) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.62 (C_3-COOCH$_2$CN), 156.17 (C_2-CO), 155.60 (C-10), 151.13 (C-4), 135.64 (C-8), 130.14 (C-5), 125.37 (C-7), 117.62 (C-9), 117.09 (C-6), 115.76 (C-3), 114.13 (-OCH$_2$CN), 49.43 (-OCH$_2$CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{12}H_8NO_4H$; 230.0453; found: 230.0438.

Cyanomethyl 6-(methyl)-2-oxo-2*H*-chromene-3-carboxylate (**3dp**). Pale brown solid; yield: 86% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 82% (40 mg, 0.2 mmol scale, Mechanochemistry), mp = 171 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.83 (s, 1H, H-4), 7.74 (s, 1H, H-8), 7.61–7.59 (m, 1H, H-5), 7.36 (d, 1H, *J* = 8.4 Hz, H-7), 5.21 (s, 2H, -OCH_2CN), 2.38 (s, 3H, C_6-CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 161.55 (C_3-COOCH$_2$CN), 155.79 (C_2-CO), 153.03 (C-10),

150.58 (C-4), 136.19 (C-8), 134.36 (C-3), 130.07 (C-5), 117.45 (C-3), 116.05 (C-7), 115.85 (C-9), 115.55 (-OCH$_2$*C*N), 49.91 (-O*C*H$_2$CN), 20.19 (C$_6$-*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_9NO_4H$, 244.0610; found: 244.0628.

Cyanomethyl 6-(*tert*-butyl)-2-oxo-2*H*-chromene-3-carboxylate (**3dq**). Pale brown solid; yield: 91% (52 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (50 mg, 0.2 mmol scale, Mechanochemistry), mp = 132–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1H, H-4), 7.77–7.74 (m, 1H, H-8), 7.61 (d, 1H, *J* = 2.4 Hz, H-5), 7.31 (d, 1H, *J* = 8.8 Hz, H-7), 4.99 (s, 2H, -O*C*H$_2$CN), 1.36 (s, 9H, C$_6$-C(*C*H$_3$)$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.70 (C$_3$-*C*OOCH$_2$CN), 156.51 (C$_2$-*C*O), 153.71 (C-10), 151.64 (C-4), 148.64 (C-9), 133.63 (C-8), 126.20 (C-5), 117.11 (C-6), 116.64 (C-7), 115.30 (C-3), 114.18 (-OCH$_2$*C*N), 49.36 (-O*C*H$_2$CN), 34.75 (C$_6$-*C*(CH$_3$)$_3$), 31.28 (C$_6$-C(*C*H$_3$)$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{16}H_{15}NO_4H$, 286.1079; found: 286.1097.

Cyanomethyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate (**3dr**). Brown solid; yield: 73% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 75% (37 mg, 0.2 mmol scale, Mechanochemistry), mp = 214–215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.81 (s, 1H, H-4), 7.80 (d, 1H, *J* = 8.4 Hz, H-8), 6.87–6.84 (m, 1H, H-5), 6.74–6.73 (m, 1H, H-6), 5.17 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.93 (C$_3$-*C*OOCH$_2$CN), 161.85 (C$_2$-*C*O), 157.57 (C-7), 156.11 (C-10), 151.24 (C-4), 132.67 (C-6), 116.02 (-OCH$_2$*C*N), 114.33 (C-8), 113.50 (C-9), 110.43 (C-3), 101.88 (C-5), 49.62 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_7NO_5H$, 246.0402; found: 246.0422.

Cyanomethyl 6-methoxy-2-oxo-2*H*-chromene-3-carboxylate (**3ds**). Pale yellow solid; yield: 81% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 77% (40 mg, 0.2 mmol scale, Mechanochemistry), mp = 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1H, H-4), 7.30 (s, 2H, H-5, H-7), 7.04 (s, 1H, H-8), 4.98 (s, 2H, -O*C*H$_2$CN), 3.87 (C$_6$-O*C*H$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.76 (C$_3$-*C*OOCH$_2$CN), 156.62 (C$_2$-*C*O), 156.41 (C-6), 150.93 (C-4), 150.27 (C-10), 124.18 (C-5), 118.23 (C-7), 117.89 (C-9), 115.93 (C-3), 114.14 (-OCH$_2$*C*N), 110.86 (C-8), 56.09 (C$_6$-O*C*H$_3$), 49.43 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_9NO_5H$, 260.0559; found: 260.0549.

Cyanomethyl 7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (**3dt**). Pale brown solid; yield: 73% (38 mg, 0.2 mmol scale, Sonochemistry), yield: 71% (37 mg, 0.2 mmol scale, Mechanochemistry), mp = 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1H, H-4), 7.73–7.65 (m, 2H, H-6, H-8), 7.39–7.36 (m, 1H, H-5), 4.99 (s, 2H, -O*C*H$_2$CN), 2.61 (C$_7$-O*C*H$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.60 (C$_3$-*C*OOCH$_2$CN), 156.17 (C$_2$-*C*O), 155.57 (C-7), 151.10 (C-4), 135.89 (C-10), 135.61 (C-6), 130.13 (C-8), 125.36 (C-5), 117.62 (C-9), 115.75 (C-3), 114.13 (-OCH$_2$*C*N), 49.41 (-O*C*H$_2$CN), 40.89 (C$_7$-O*C*H$_3$) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{13}H_9NO_5H$, 260.0559; found: 260.0567.

Cyanomethyl 6-fluoro-2-oxo-2*H*-chromene-3-carboxylate (**3du**). Pale brown semi-solid; yield: 73% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 77% (38 mg, 0.2 mmol scale, Mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.86 (s, 1H, H-4), 7.86–7.84 (m, 1H, H-5), 7.69–7.64 (m, 1H, H-7), 7.54–7.51 (m, 1H, H-8), 5.22 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.29 (C$_3$-*C*OOCH$_2$CN), 158.05 (d, $J^1_{C\text{-}F}$ = 239 Hz, C-6), 155.46 (C$_2$-*C*O), 151.33 (C-9), 149.65 (d, $J^4_{C\text{-}F}$ = 3 Hz, C-4), 122.49 (d, $J^2_{C\text{-}F}$ = 25 Hz, C-5), 118.58 (d, $J^3_{C\text{-}F}$ = 10 Hz, C-3), 118.41 (d, $J^3_{C\text{-}F}$ = 8 Hz, C-7), 115.83 (-OCH$_2$*C*N), 115.48 (d, $J^2_{C\text{-}F}$ = 24 Hz, C-8), 50.07 (-O*C*H$_2$CN) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −117.38 ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NFO_4H$, 248.0359; found: 248.0344.

Cyanomethyl 6-chloro-2-oxo-2*H*-chromene-3-carboxylate (**3dv**). Pale brown solid; yield: 80% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 78% (41 mg, 0.2 mmol scale, Mechanochemistry), mp = 178–180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.85 (s, 1H, H-4), 8.09 (s, 1H, H-5), 7.80 (d, 1H, *J* = 8.4 Hz, H-7), 7.49 (d, 1H, *J* = 8.8 Hz, H-8), 5.23 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.27 (C$_3$-*C*OOCH$_2$CN), 155.28 (C$_2$-*C*O), 153.50 (C-10), 149.40 (C-4), 134.57 (C-5), 129.46 (C-7), 128.65 (C-6), 119.10 (C-9), 118.37 (C-8), 116.87 (C-3), 115.84 (-OCH$_2$*C*N), 50.10 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NClO_4H$, 264.0064; found: 264.0077.

Cyanomethyl 6-bromo-2-oxo-2*H*-chromene-3-carboxylate (**3dw**). Pale brown solid; yield: 68% (42 mg, 0.2 mmol scale, Sonochemistry), yield: 65% (40 mg, 0.2 mmol scale, Mechanochemistry), mp = 176–178 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.85 (s, 1H, H-4), 8.23 (d, 1H, *J* = 2.4 Hz, H-5), 7.94–7.91 (m, 1H, H-7), 7.44 (d, 1H, *J* = 9.2 Hz, H-8), 5.23 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 160.91 (C$_3$-*C*OOCH$_2$CN), 154.89 (C$_2$-*C*O), 153.56 (C-6), 148.97 (C-4), 136.97 (C-5), 132.12 (C-7), 119.26 (C-10), 118.26 (C-8), 116.48 (C-9), 116.07 (-OCH$_2$*C*N), 115.47 (C-3), 49.72 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NBrO_4H$, 307.9558; found: 307.9552.

Cyanomethyl 6-nitro-2-oxo-2*H*-chromene-3-carboxylate (**3dx**). Yellow liquid; yield: 66% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 69% (38 mg, 0.2 mmol scale, Mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.08 (s, 1H, H-4), 8.98 (d, 1H, *J* = 2.0 Hz, H-5), 8.55–8.53 (m, 1H, H-7), 7.68 (d, 1H, *J* = 9.2 Hz, H-8), 5.26 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.00 (C$_3$-*C*OOCH$_2$CN), 158.32 (C$_2$-*C*O), 154.75 (C-6), 149.53 (C-4), 143.74 (C-9), 129.16 (C-5), 126.44 (C-7), 118.09 (C-10), 117.87 (C-8), 117.65 (C-3), 115.76 (-OCH$_2$*C*N), 50.18 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6N_2O_6H$, 275.0304; found: 275.0321.

Cyanomethyl 6,8-dichloro-2-oxo-2*H*-chromene-3-carboxylate (**3dy**). White solid; yield: 74% (44 mg, 0.2 mmol scale, Sonochemistry), yield: 72% (43 mg, 0.2 mmol scale, Mechanochemistry), mp = 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.86 (s, 1H, H-4), 8.11–8.10 (m, 1H, H-7), 8.08–8.07 (m, 1H, H-5), 5.24 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 160.99 (C$_3$-*C*OOCH$_2$CN), 154.46 (C$_2$-*C*O), 149.32 (C-8), 149.12 (C-7), 133.79 (C-5), 128.59 (C-7), 128.53 (C-6), 120.94 (C-10), 120.19 (C-9), 117.64 (C-3), 115.79 (-OCH$_2$*C*N), 50.21 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_5NCl_2O_4H$; 297.9674; found: 297.9678.

Cyanomethyl 6,8-dibromo-2-oxo-2*H*-chromene-3-carboxylate (**3dz**). Brownish-yellow semi-solid; yield: 83% (64 mg, 0.2 mmol scale, Sonochemistry), yield: 80% (62 mg, 0.2 mmol scale, Mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.84 (s, 1H, H-4), 8.29 (d, 1H, *J* = 2.0 Hz, H-7), 8.23 (d, 1H, *J* = 2.0 Hz, H-5), 5.24 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 160.93 (C$_3$-*C*OOCH$_2$CN), 154.56 (C$_2$-*C*O), 150.75 (C-10), 149.09 (C-4), 139.06 (C-7), 132.09 (C-5), 120.58 (C-6), 117.46 (C-8), 116.43 (C-9), 115.76 (-OCH$_2$*C*N), 110.20 (C-3), 50.17 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{12}H_6NBrO_4H$; 307.9558; found: 307.9572.

Cyanomethyl 3-oxo-3*H*-benzo[*f*]chromene-2-carboxylate (**3da′**). Greenish yellow solid; yield: 72% (40 mg, 0.2 mmol scale, Sonochemistry), yield: 70% (39 mg, 0.2 mmol scale, Mechanochemistry), mp = 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.48 (m, 1H, H-4), 8.60 (d, 1H, *J* = 8.4 Hz, H-8), 8.35 (d, 1H, *J* = 9.2 Hz, H-7), 8.09 (d, 1H, *J* = 8.0 Hz, H-2′), 7.81–7.77 (m, 1H, H-5′), 7.69–7.65 (m, 1H, H-3′), 7.59 (d, 1H, *J* = 8.8 Hz, H-4′), 5.26 (s, 2H, -O*C*H$_2$CN) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 161.87 (C$_3$-*C*OOCH$_2$CN), 155.77 (C$_2$-*C*O), 146.04 (C-4), 136.97 (C-8), 129.83 (C-5, C-6), 129.26 (C-7), 129.14 (C-2′), 129.10 (C-5′), 126.65 (C-4′), 122.39 (C-3′), 116.56 (C-4′), 115.92 (C-9), 114.33 (-OCH$_2$*C*N), 111.97 (C-10), 49.92 (-O*C*H$_2$CN) ppm. HRMS (ESI − TOF): *m/z* [M + H]$^+$ calcd. for $C_{16}H_9NO_4H$; 280.0610; found: 280.0619.

Cyanomethyl 2-hydroxy-2,2-diphenylacetate (**3ea**). White solid; yield: 86% (46 mg, 0.2 mmol scale, Sonochemistry), yield: 88% (47 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 70:30, mp = 125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.40 (m, 4H, H-3, H-4, H-5, H-6), 7.39–7.36 (m, 6H, H-2, H-2′, H-3′, H-4′, H-5′, H-6′), 4.82 (s, 2H, -O*C*H$_2$CN),

3.86 (s, 1H, -O*H*) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 173.13 (C_1-$COOCH_2CN$), 140.83 (C-1, C-1′), 128.74 (C-2, C-2′), 128.54 (C3, C-4, C-3′, C-4′), 127.33 (C-5, C-6, C-5′, C-6′), 113.59 (-OCH_2CN), 81.55 (C_1-*C*(OH)$COOCH_2CN$), 49.84 (-OCH_2CN) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{16}H_{13}NO_3H$; 268.0974; found: 268.0997.

Cyanomethyl 2-(4-isobutylphenyl)propanoate (3eb). White semi-solid; yield: 73% (36 mg, 0.2 mmol scale, Sonochemistry), yield: 78% (38 mg, 0.2 mmol scale, Mechanochemistry), eluent used for the flash column was hexane/EtOAc 96:4. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.18 (d, 2H, *J* = 7.6 Hz, H-2, H-6), 7.12 (d, 2H, *J* = 8.0 Hz, H-3, H-5), 4.95 (s, 2H, -O*C*H_2CN), 3.90–3.85 (m, 1H, -*CH*$COOCH_2CN$), 2.41 (d, 2H, -*C*H_2CH$(CH_3)_2$), 1.85–1.74 (m, 1H, -CH_2*CH*$(CH_3)_2$), 1.39 (d, 3H, *J* = 6.8 Hz, -*C*H_3CHCOOCH_2CN), 0.84 (d, 6H, *J* = 6.4 Hz, -CH_2CH(*C*$H_3)_2$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 173.10 (C_1-$COOCH_2CN$), 140.24 (C-1, C-1′), 137.05 (C-2, C-2′), 129.32 (C3, C-4, C-3′, C-4′), 127.15 (C-5, C-6, C-5′, C-6′), 115.90 (-OCH_2CN), 49.31 (-O*C*H_2CN), 44.28 (-CH_3*C*HCOOCH_2CN), 43.65 (-*C*H_2CH$(CH_3)_2$), 29.68 (-CH_2*C*H$(CH_3)_2$), 22.21 (-*C*H_3CHCOOCH_2CN), 18.48 (-CH_2CH(*C*$H_3)_2$) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_{15}H_{19}NO_2H$; 246.1494; found: 246.1481.

Benzyl 1*H*-tetrazole-5-carboxylate (**6ab**). White semi-solid; yield: 69% (28 mg, 0.2 mmol scale), eluent used for the flash column was hexane/EtOAc 97:3. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.29–8.28 (m, 2H, Ar-H), 8.04 (s, 1H, Ar-H), 7.59 (s, 3H, Ar-H & -*C*H_2), 6.82 (s, 1H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ = 156.18 (Ar*C*OO-), 154.75 (*C*), 131.18 (*C*H), 129.11 (2 × *C*H), 127.46 (2 × *C*H), 103.60 (*C*), 97.46 (-*C*H_2-) ppm. HRMS (ESI − TOF): *m/z* $[M + H]^+$ calcd. for $C_9H_8N_4O_2H$; 205.0726; found: 205.0743.

Supporting Information

Electronic Supporting Information (ESI) available: scanned copies of ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR (for compounds **3ao**, **3ap**, **3aq**, **3ab′**, **3ak′**, **3am′**, and **3du**) for all the synthesized compounds **3** (**3aa**-**3az**, **3aa"-3av"**, **3ba**-**3bc**, **3ca**-**3cf**, **3da**-**3dz**, **3da′**, **3ea**, and **3eb**) and **6ab** are supplied (PDF).

FAIR data, including the primary NMR FID files, for all the synthesized compounds **3** and **6ab** (ZIP).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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Sono- and mechanochemical dual syntheses of bio-relevant aryldiazenyl-substituted phosphine oxides/phosphonates *via* P(O)–H functionalisation†‡

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We herein disclose a dual-synthetic approach involving sonochemical and mechanochemical strategies for diversely functionalised (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates. Both methods offer highly efficient, practical and straightforward alternative routes for accessing this important class of biologically promising phosphoramide derivatives containing phosphorus–nitrogen (P–N) bonds. Significant advantages of the newly developed methods include mild reaction conditions, avoidance of any catalysts and additives, shorter reaction times, good to excellent yields, broad substrate scope, gram-scale applicability, operational simplicity, low *E*-factors, and eco-friendliness.

Green foundation

1. The described research outcomes highlight the fruitful application of ultrasonics and ball-milling as useful green energy tools in exploring highly efficient, practical and straightforward alternative routes for accessing an important class of biologically promising phosphoramide derivatives containing phosphorus–nitrogen (P–N) bonds. The notable green chemistry advances in this endeavour include mild reaction conditions, avoidance of any catalysts and additives, shorter reaction times, good to excellent yields with low *E*-factors, and gram-scale synthetic applicability.
2. The green chemistry achievements for this research are quantitative regarding the reduction in reaction times (5–7 minutes compared to 12–24 h in earlier methods), lowering in *E*-factors (0.36–0.89 g/g), and gram-scale synthetic applications. Qualitatively, these alternative methods avoid using any catalysts/additives, reduce the use of solvents, and do not require external heating, making them energy-efficient.
3. Further research in the direction of making the processes more energy-efficient, avoidance of column chromatographic purifications, and kilogram-scale synthetic applications is prescribed.

1. Introduction

Organophosphorus compounds not only play a vital role in life processes,[1] but plenty of such phosphorus-containing derivatives are known to have applications in asymmetric catalysis,[2] flame retardants,[3] materials science,[4] agricultural science,[5] and medicinal chemistry[6] due to their interesting structural, physical and biological properties. Although organophosphorus molecules are ubiquitous in bioactive natural and synthetic compounds, those bearing phosphorus–nitrogen (P–N) bonds are rare.[7] Fig. 1 offers examples of three natural phosphoramides (**I–III**)[8a–c] with antibiotic properties and a set of arylaza phosphonates (**IV** and **V**)[8d,e] as synthetic polymeric analogues with useful materials properties, especially excimer laser ablation. Hence, the design and synthesis of functionalised phosphoramide derivatives have recently become an emerging field of research in organophosphorus chemistry for synthetic organic chemists due to their promising medicinal and materials properties.

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†This paper is dedicated to Professor Hiriyakkanavar Ila on the occasion of her 80th birthday.

‡Electronic supplementary information (ESI) available: Scanned copies of ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{31}P NMR, ^{19}F NMR (for **4ga** and **4gd**), 2D NMR (for one representative compound, **4gd**), and single-crystal X-ray crystallographic information for **4ib** are provided as supplementary materials. Copies of HRMS for trapped adducts **5–8** are also documented. CCDC 2393356. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4gc05501b

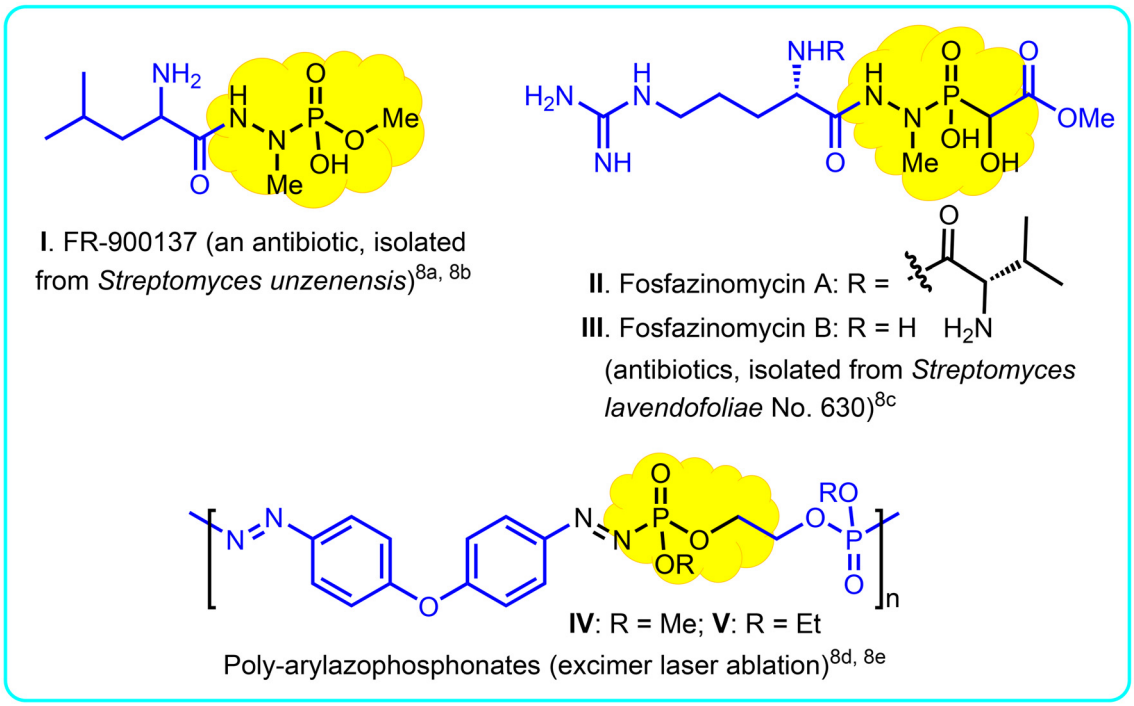
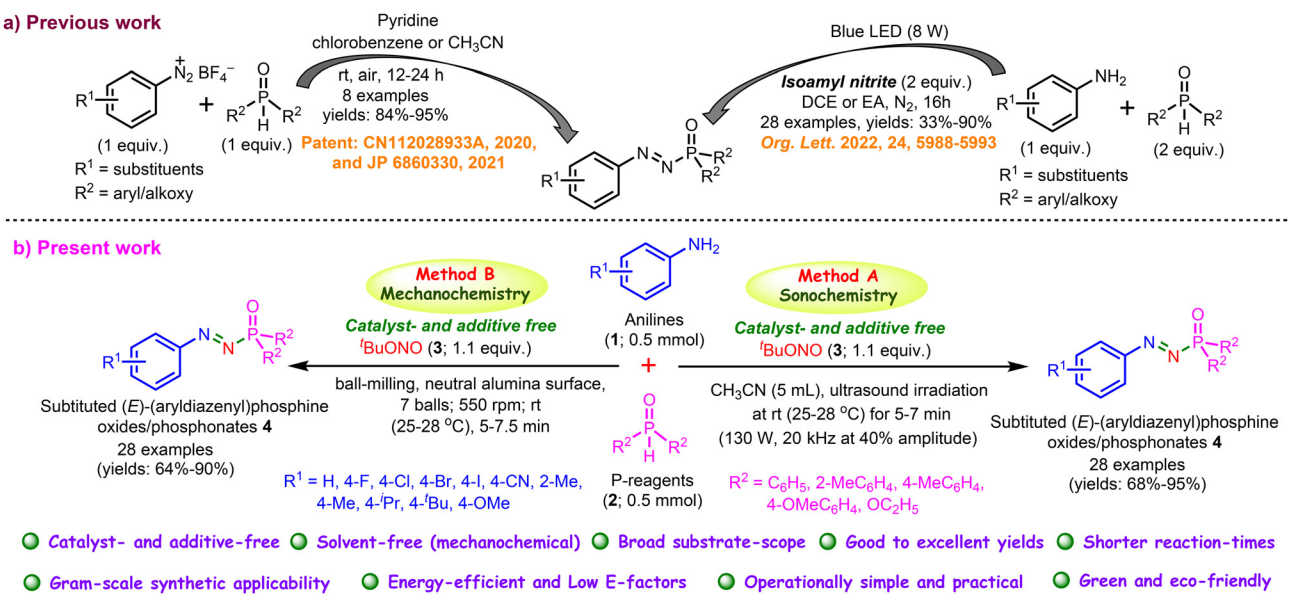


Fig. 1 Examples of a few bioactive natural and synthetic phosphoamidates.[8]

(*E*)-Aryldiazenyl-substituted phosphine oxides and phosphonates belong to a sub-group of phosphoamidates, and a literature survey reveals that there are only two previous synthetic reports for accessing these molecules. In 1998, Nuyken and co-workers[9] first synthesised only eight derivatives of phosphoamidates by stirring a mixture of aryl diazonium salts and phosphine oxides/phosphonates in the presence of pyridine as a base in a dichloromethane/acetonitrile solvent at room temperature for 12–24 h (Scheme 1a). Recently, in 2022, Lee and co-workers[10] reported a visible-light-induced alternative route for the synthesis of a series of such compounds from the one-pot three-component reaction between substituted anilines, phos-



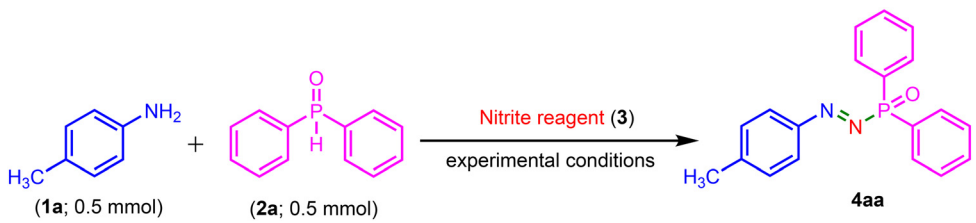
Scheme 1 (a) Earlier reports on the synthesis of (*E*)-aryldiazenyl-substituted phosphine oxides/phosphonates; and (b) sonochemical and mechanochemical syntheses of diversely substituted (*E*)-aryldiazenyl-substituted phosphine oxides/phosphonates.

phine oxides/phosphonates and isoamyl nitrite dissolved in either dichloroethane or ethyl acetate upon irradiation with blue light for 16 h under a nitrogen atmosphere (Scheme 1a). Although this visible-light-assisted protocol seems more advantageous than the previous one, mainly regarding substrate scope, it still suffers from a long reaction time (16 h), low yields of products in most cases, and use of non-aerial systems. Under this purview, designing and developing more efficient, eco-friendly, and practical synthetic routes to functionalised phosphoamidates is highly warranted. As part of our green chemistry-driven organic synthesis,[11] we eventually succeeded in developing a dual approach, both sonochemical and mechanochemical strategies, to access a series of diversely substituted (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates, as outlined in Scheme 1b. The salient features of these newly developed methods are the avoidance of any catalysts and additives, mild reaction conditions, good to excellent yields within shorter reaction times of minutes, low *E*-factors, scalability, practicality and eco-friendliness. The sonochemical method uses acetonitrile as solvent, whereas the mechanochemical process is solvent-free. The applications of sonochemical[12] and mechanochemical[13] strategies are well-documented in synthetic organic chemistry.

2. Results and discussion

We commenced our investigation with our model reaction involving a one-pot, three-component reaction between *p*-toluidine (**1a**), diphenylphosphine oxide (**2a**) and *tert*-butyl nitrite (**3**) targeting the desired product, (*E*)-diphenyl(*p*-tolyldiazenyl) phosphine oxide (**4a**), upon stirring the reactants dissolved in acetonitrile (CH_3CN) under ambient conditions, and we were delighted to isolate the desired product **4a** from this reaction, although in a low yield of 29% after 120 min (Table 1, entry 1). We also observed that this reaction is highly solvent-specific – the model reaction was found not to occur in dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, ethanol, and water when stirred under ambient conditions (Table 1, entries 2–6). Now, we turned our attention to enhancing the reaction yield (Table 1, entry 1), and we envisioned using ultrasound might do the job. Accordingly, we applied ultrasound at 30% amplitude to the model entry for 10 min, which helped in increasing the isolated yield up to 44% (Table 1, entry 7). Hence, we then increased the ultrasonic power to 40% amplitude when we isolated **4a** in 95% yield at 5 min (Table 1, entry 8). At this stage, we performed a set of twelve more reactions by varying ultrasonication power and time, nitrite reagents and their equivalency, and solvents

Table 1 Optimisation of the reaction conditions under ultrasonication[a,b]



(**1a**; 0.5 mmol) (**2a**; 0.5 mmol) **4aa**

Entry	Nitrite reagent (**3**) (equiv.)	Solvent (5 mL)	Conditions (amplitude %)	Time (min)	Yield[a,b] (%)
1	^{t}BuONO (1.1)	CH_3CN	Stirring at rt	120	29
2	^{t}BuONO (1.1)	DMSO	Stirring at rt	120	—
3	^{t}BuONO (1.1)	DMF	Stirring at rt	120	—
4	^{t}BuONO (1.1)	1,4-Dioxane	Stirring at rt	120	—
5	^{t}BuONO (1.1)	EtOH	Stirring at rt	120	Trace
6	^{t}BuONO (1.1)	H_2O	Stirring at rt	120	—
7	^{t}BuONO (1.1)	CH_3CN	Ultrasound (30%)	10	44
8	**^{t}BuONO (1.1)**	**CH_3CN**	**Ultrasound (40%)**	**5**	**95**
9	^{t}BuONO (1.1)	CH_3CN	Ultrasound (40%)	10	88
10	^{t}BuONO (1.1)	CH_3CN	Ultrasound (40%)	3	43
11	^{t}BuONO (1.1)	CH_3CN	Ultrasound (50%)	5	72
12	^{t}BuONO (0.75)	CH_3CN	Ultrasound (40%)	5	74
13	^{t}BuONO (1.5)	CH_3CN	Ultrasound (40%)	5	89
14	^{t}BuONO (1.1)	DMSO	Ultrasound (40%)	10	Trace
15	^{t}BuONO (1.1)	DCM	Ultrasound (40%)	10	42
16	^{t}BuONO (1.1)	Dioxane	Ultrasound (40%)	10	—
17	^{t}BuONO (1.1)	DMF	Ultrasound (40%)	10	—
18	^{t}BuONO (1.1)	EtOH	Ultrasound (40%)	10	64
19	^{t}BuONO (1.1)	H_2O	Ultrasound (40%)	10	69
20	$NaNO_2$ (1.1)	CH_3CN	Ultrasound (40%)	10	53

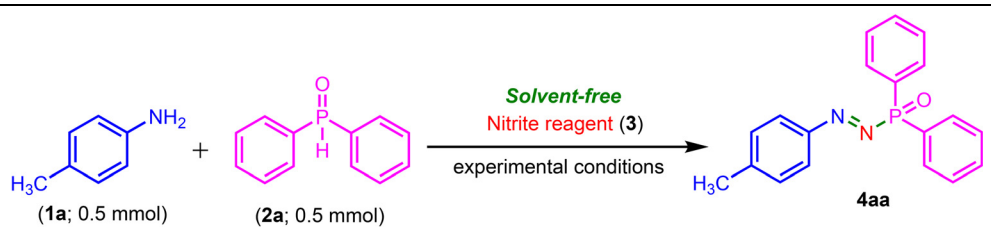
[a] Reaction conditions: a mixture of *p*-toluidine (**1a**; 0.5 mmol) and diphenylphosphine oxide (**2a**; 0.5 mmol) was reacted with *tert*-butyl nitrite or sodium nitrite in the absence of any catalyst in 5 mL of varying solvent(s) under either room temperature (rt, 25–28 °C) stirring or ultrasound irradiation (US; 130 W, 20 kHz at 40–50% amplitude). [b] Isolated yields.

(Table 1, entries 9–20) when the best-suited reaction conditions for our model reaction came out as irradiating the reaction mixture of *p*-toluidine (**1a**, 0.5 mmol), diphenylphosphine oxide (**2a**, 0.5 mmol) and *tert*-butyl nitrite (**3**, 0.55 mmol, 1.1 equiv.) in acetonitrile (5 mL) with ultrasound at 40% amplitude for 5 min, thereby furnishing the target product, (*E*)-diphenyl(*p*-tolyldiazenyl)phosphine oxide (**4aa**), in 95% yield (Table 1, entry 8). Compound **4aa** is a new compound fully characterised by its detailed spectral (^{1}H-, ^{13}C- and ^{31}P-NMR, DEPT-135, and HRMS) studies. The overall results are summarised in Table 1.

Upon establishing the optimised sonochemical conditions for our model reaction, we were motivated to investigate the applicability of a ball-mill as another widely used green tool in organic synthesis. We envisioned that the mechanochemical transformation might be implemented solvent-free, and accordingly, we performed the model reaction with *p*-toluidine (**1a**, 0.5 mmol), diphenylphosphine oxide (**2a**, 0.5 mmol) and *tert*-butyl nitrite (**3**, 0.55 mmol, 1.1 equiv.) by grinding the reaction mixture in a ball-mill using neutral alumina as a surface and seven stainless steel balls at 550 rpm for just 5 min, when we were able to isolate the targeted product **4aa** in an excellent yield of 90% (Table 2, entry 1), almost a similar yield obtained out of the sonochemical method. We carried out 15 more trial reactions (Table 2, entries 2–16) with the model entry under varying conditions (such as variations in surface materials, nitrating agents, number of balls, rotation-speed, *etc*.) to validate the best-suited mechanochemical conditions. We also performed a control experiment using a tungsten carbide jar and balls to rule out any catalytic intervention by a stainless steel jar and balls (Table 2, entry 17). Eventually, we were delighted to unearth another alternative and efficient method for the same transformation under ball-milling using neutral alumina (2.0 g) as the surface and seven stainless steel balls (10 mm in diameter) milled for 5 min (rotation in an inverted direction with a 5 s break at 2.5 min interval) at 550 rpm, from where we isolated **4aa** in 90% yield (Table 2, entry 1). All these results are summarised in Table 2.

Thus, we have now accomplished a dual approach for the direct P–H functionalisation of phosphine oxides/phosphonates as practical and useful alternative green synthetic routes to access biologically promising diverse series of aryldiazenyl-substituted phosphine oxides/phosphonates by using sonochemical (Method A) and mechanochemical (Method B) strategies (Scheme 1b). Having established the optimised reaction conditions for both methods, we planned to explore the scope of the developed protocols and compare their efficacies in terms of respective yields and reaction times of this one-pot, three-component transformation. As part of this endeavour, we first conducted a set of nine reactions by treating the aniline derivatives (**1b–1j**), bearing both electron-donating and electron-withdrawing functionalities (such as methyl, iso-propyl, *tert*-butyl, methoxy, cyano, fluoro, chloro, bromo, and iodo), with diphenylphosphine oxide (**2a**) and *tert*-butyl nitrite (**3**)

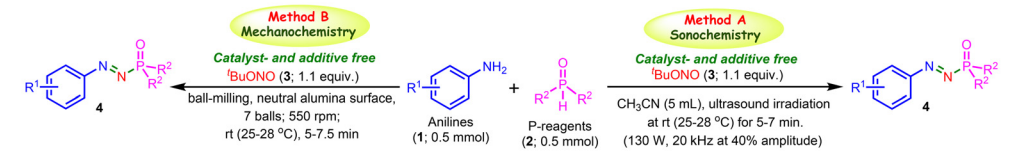
Table 2 Optimisation of the reaction conditions under ball-milling

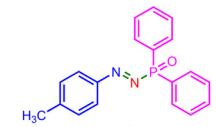


Entry	Surface (2 g)	Nitrite reagent (3) (equiv.)	Conditions	No. of balls/rpm	Time (min)	Yield[a,b] (%)
1	**Neutral alumina**	**^{t}BuONO (1.1)**	**Ball-milling**	**7/550**	**5**	**90**
2	Neutral alumina	^{t}BuONO (0.5)	Ball-milling	7/550	10	39
3	Neutral alumina	^{t}BuONO (0.75)	Ball-milling	7/550	10	64
4	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	7/600	5	90
5	Neutral alumina	^{t}BuONO (1.5)	Ball-milling	7/550	5	89
6	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	8/550	5	88
7	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	6/550	10	86
8	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	7/450	15	72
9	Neutral alumina	$NaNO_2$ (1.1)	Ball-milling	7/550	10	66
10	Basic alumina	^{t}BuONO (1.1)	Ball-milling	7/550	10	80
11	Acidic alumina	^{t}BuONO (1.1)	Ball-milling	7/550	10	81
12	Silica	^{t}BuONO (1.1)	Ball-milling	7/550	10	Trace
13	NaCl	^{t}BuONO (1.1)	Ball-milling	7/550	10	Trace
14	—	^{t}BuONO (1.1)	Stirring at rt	—	120	Trace
15	—	$NaNO_2$ (1.1)	Stirring at rt	—	120	Trace
16	Neutral alumina	—	Ball-milling	7/550	60	—
17[c]	Neutral alumina	^{t}BuONO (1.1)	Ball-milling	7/550	5	90

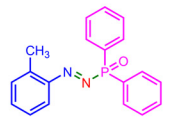
[a] Reaction conditions: a mixture of *p*-toluidine (**1a**; 0.5 mmol) and diphenylphosphine oxide (**2a**; 0.5 mmol) was reacted with either *tert*-butyl nitrite or sodium nitrite under ball-milling (using a 25 mL stainless-steel jar and balls of 10 mm diameter, and rotation in an inverted direction with a break of 5 s at 2.5 min intervals) in the absence of additives. [b] Isolated yields. [c] Using tungsten carbide jar and balls.

Table 3 Sonochemical and mechanochemical syntheses of diversely functionalised (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates (**4**)[a,b]

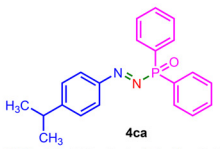




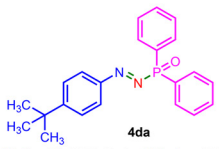
4aa
Method A: 95%; 5 min; **E-factor:** 0.36
Method B: 90%; 5 min; **E-factor:** 0.43



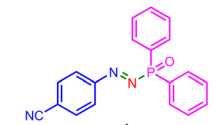
4ba
Method A: 71%; 5 min; **E-factor:** 0.82
Method B: 69%; 7.5 min; **E-factor:** 0.87



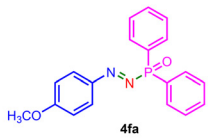
4ca
Method A: 79%; 5 min; **E-factor:** 0.59
Method B: 77%; 7.5 min; **E-factor:** 0.62



4da
Method A: 77%; 5 min; **E-factor:** 0.62
Method B: 73%; 7.5 min; **E-factor:** 0.71

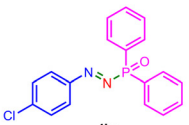


4ea
Method A: 70%; 5 min; **E-factor:** 0.82
Method B: 68%; 7.5 min; **E-factor:** 0.89

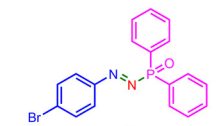


4fa
Method A: 77%; 5 min; **E-factor:** 0.66
Method B: 71%; 7.5 min; **E-factor:** 0.79

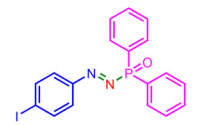
4ga
Method A: 80%; 7 min; **E-factor:** 0.60
Method B: 78%; 7.5 min; **E-factor:** 0.65



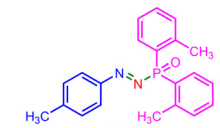
4ha
Method A: 75%; 5 min; **E-factor:** 0.67
Method B: 72%; 7.5 min; **E-factor:** 0.77



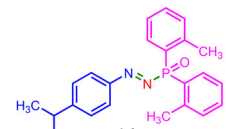
4ia
Method A: 77%; 5 min; **E-factor:** 0.60
Method B: 73%; 7.5 min; **E-factor:** 0.70



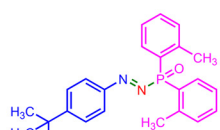
4ja
Method A: 68%; 5 min; **E-factor:** 0.78
Method B: 64%; 7.5 min; **E-factor:** 0.89



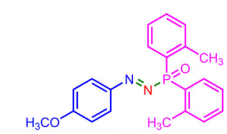
4ab
Method A: 81%; 5 min; **E-factor:** 0.56
Method B: 78%; 5 min; **E-factor:** 0.62



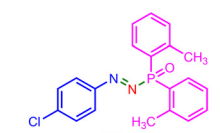
4cb
Method A: 83%; 5 min; **E-factor:** 0.50
Method B: 75%; 5 min; **E-factor:** 0.58



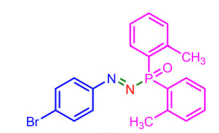
4db
Method A: 84%; 5 min; **E-factor:** 0.47
Method B: 77%; 5 min; **E-factor:** 0.61



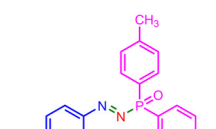
4fb
Method A: 80%; 5 min; **E-factor:** 0.56
Method B: 74%; 7.5 min; **E-factor:** 0.67



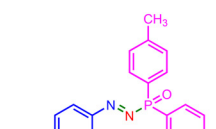
4hb
Method A: 75%; 5 min; **E-factor:** 0.67
Method B: 69%; 7.5 min; **E-factor:** 0.81



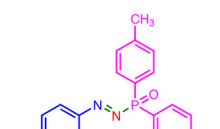
4ib
Method A: 81%; 7 min; **E-factor:** 0.51
Method B: 77%; 7.5 min; **E-factor:** 0.58



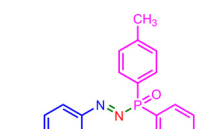
4ac
Method A: 88%; 5 min; **E-factor:** 0.44
Method B: 81%; 5 min; **E-factor:** 0.56



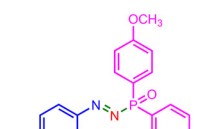
4fc
Method A: 82%; 5 min; **E-factor:** 0.53
Method B: 77%; 7.5 min; **E-factor:** 0.63



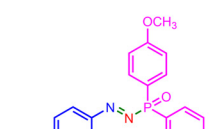
4hc
Method A: 76%; 7 min; **E-factor:** 0.64
Method B: 71%; 7.5 min; **E-factor:** 0.76



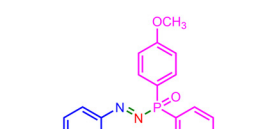
4ic
Method A: 83%; 5 min; **E-factor:** 0.48
Method B: 80%; 7.5 min; **E-factor:** 0.53



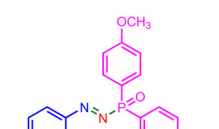
4ad
Method A: 87%; 5 min; **E-factor:** 0.43
Method B: 84%; 5 min; **E-factor:** 0.48



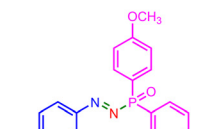
4cd
Method A: 78%; 7 min; **E-factor:** 0.56
Method B: 71%; 7.5 min; **E-factor:** 0.72



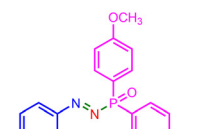
4dd
Method A: 79%; 5 min; **E-factor:** 0.54
Method B: 75%; 7.5 min; **E-factor:** 0.63



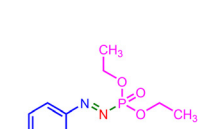
4gd
Method A: 84%; 7 min; **E-factor:** 0.48
Method B: 80%; 7.5 min; **E-factor:** 0.53



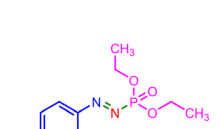
4hd
Method A: 80%; 5 min; **E-factor:** 0.54
Method B: 74%; 7.5 min; **E-factor:** 0.66



4jd
Method A: 73%; 5 min; **E-factor:** 0.62
Method B: 67%; 7.5 min; **E-factor:** 0.76



4ke
Method A: 77%; 5 min; **E-factor:** 0.79
Method B: 73%; 5 min; **E-factor:** 0.89



4ae
Method A: 77%; 5 min; **E-factor:** 0.76
Method B: 74%; 5 min; **E-factor:** 0.83

[a] Reaction conditions: a mixture of anilines (**1**; 0.5 mmol) and phosphine oxides/phosphonate (**2**; 0.5 mmol) was reacted with *tert*-butyl nitrite (**3**; 0.55 mmol, 1.1 equiv.) under both ultrasonication (Method A) and ball-milling (Method B) reaction conditions, respectively. [b] Isolated yields.

separately under the optimised conditions for sonochemical (Method A) and mechanochemical (Method B) processes. All the reactions took place smoothly in both methods, furnishing the desired (*E*)-diphenyl(aryldiazenyl)phosphine oxides (**4ba–4ja**) in good yields ranging from 68–95% in the sonochemical method and 64–90% in the mechanochemical method, within respective reaction time periods of 5–7 min and 5–7.5 min (Table 3, compounds **4ba–4ja**). Encouraged by these results, we then planned to extend the scope of diarylphosphine oxide **2**; we thus performed a set of sixteen more reactions between substituted diarylphosphine oxides (*viz.* di-*o*-tolylphosphine oxide **2b**, di-*p*-tolylphosphine oxide **2c**, and bis(4-methoxyphenyl)phosphine oxide **2d**), diversely functionalised aromatic primary amines (**1a**, **1c**, **1d**, and **1f–1j**) and *tert*-butyl nitrite (**3**) under identical reaction conditions, following both methods individually. All the reactions occurred satisfactorily both sono- and mechanochemically. We isolated the corresponding differently substituted (*E*)-diaryl(aryldiazenyl)phosphine oxides **4** (Table 3, compounds **4ab**, **4cb**, **4db**, **4fb**, **4hb**, **4ib**, **4ac**, **4fc**, **4hc**, **4ic**, **4ad**, **4cd**, **4dd**, **4gd**, **4hd**, and **4jd**) in good yields ranging from 73–88% under ultrasonication (Method A) within 5–7 min, and 67–84% under ball-milling (Method B) within 5–7.5 min. Delightfully, diethyl phosphonate (**2e**) also participated in the transformation in both methods under similar reaction conditions, thereby affording aryldiazenyl-substituted phosphonate derivatives, such as diethyl (*E*)-(phenyldiazenyl)phosphonate (**4ke**) and diethyl (*E*)-(*p*-tolyldiazenyl)phosphonate (**4ae**), with an identical yield of 77% for **4ke** at 5 min following both methods, and with 73% and 74% yields for **4ae** at 5 min under sonication and ball-milling, respectively (Table 3, compounds **4ke** and **4ae**). However, dialkylphosphine oxide was highly reluctant to undergo this reaction, as evidenced by our experimental observations that we could not detect the formation of the desired product when the model reaction was performed with dimethylphosphine oxide [$Me_2P(O)H$] in both methods (Methods A and B) even after 30 minutes of operation. This is perhaps because the alkyl groups cannot stabilise the proposed *in situ*-generated phosphonyl radical from the P-reagent. All the experimental results are shown in Table 3.

All the isolated products, **4**, synthesised following both Method A (sonochemical) and Method B (mechanochemical), were purified using the column chromatographic technique (see the Experimental section). All are new compounds except **4ea**, **4fa**, **4ke** and **4ae**. Each synthesised compound was fully characterised based on their detailed spectral studies, including ^{1}H-NMR, ^{13}C-NMR, DEPT-135, ^{31}P-NMR, ^{19}F-NMR (for **4ga** and **4gd**), 2D-NMR (for one representative compound, **4gd**), and HRMS (see the Experimental section). Further confirmation of the structural framework, as deduced from the spectral analyses, was established from the single-crystal X-ray diffraction studies for a representative entry, (*E*)-((4-bromophenyl)diazenyl)di-*o*-tolylphosphine oxide (**4ib**; CCDC 2393356‡); space group: $P\bar{1}$; unit cell parameters: a 6.9964(6) Å, b 8.4138 (8) Å, c 17.0464(18) Å; α 86.124(8)°, β 89.703(8)°, γ 73.686(8)° (see the ESI‡). Fig. 2 shows the ORTEP diagram of the molecule **4ib**.

To evaluate the greenness of these two newly developed methods, we herein calculated (see the ESI‡) *E*-factor (g/g)[14] for all the synthesised compounds **4**. The calculated *E*-factors were found to be in the range of 0.82–0.36 for the sonochemical method and 0.89–0.43 for the mechanochemical method. The calculated parameters indicate the considerable greenness of both methods; the respective *E*-factors for each entry are shown in Table 3. Again, to determine the synthetic practicality of both approaches, we carried out gram-scale synthetic applications (5.0 and 10.0 mmol-scales; 10- and 20-fold enhancement; Scheme 2) for our model compound, (*E*)-diphenyl (*p*-tolyldiazenyl)phosphine oxide (**4aa**). The sonochemical method (Method A) furnished the product **4aa** with a satisfactory yield of 91% after 5 min in both experiments (see the Experimental section). The mechanochemical method (Method B) afforded 84% and 81% yields in the 5.0 mmol and 10.0 mmol reactions, respectively, after 7.5 min (see the Experimental section). The yields and the reaction times observed in the gram-scale synthesis were almost identical to those for the millimolar scale reactions.

Finally, we performed a set of control experiments with our model reaction in the presence of three different radical scavengers, such as TEMPO, BHT and *p*-benzoquinone (BQ), to pursue an idea of the possible mechanistic pathway of this one-pot, three-component reaction between anilines (**1**), substituted phosphine oxides/phosphonates (**2**) and *tert*-butyl nitrite (**3**) following either ultrasonication or ball-milling processes, resulting in the formation of (*E*)-diaryl(aryldiazenyl) phosphine oxides/phosphonates (**4**). The results of the control experiments are depicted in Scheme 3. Each of the radical scavengers was found to inhibit the reaction when carried out either sonochemically or mechanochemically, thereby

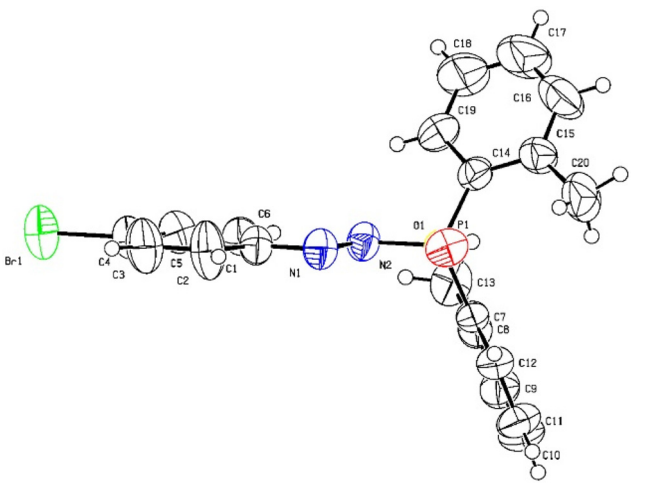
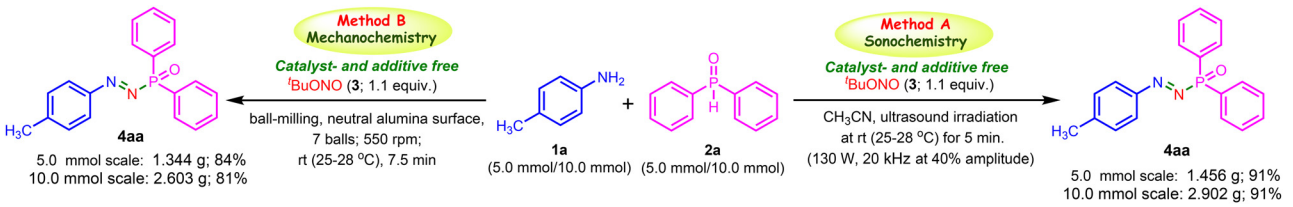
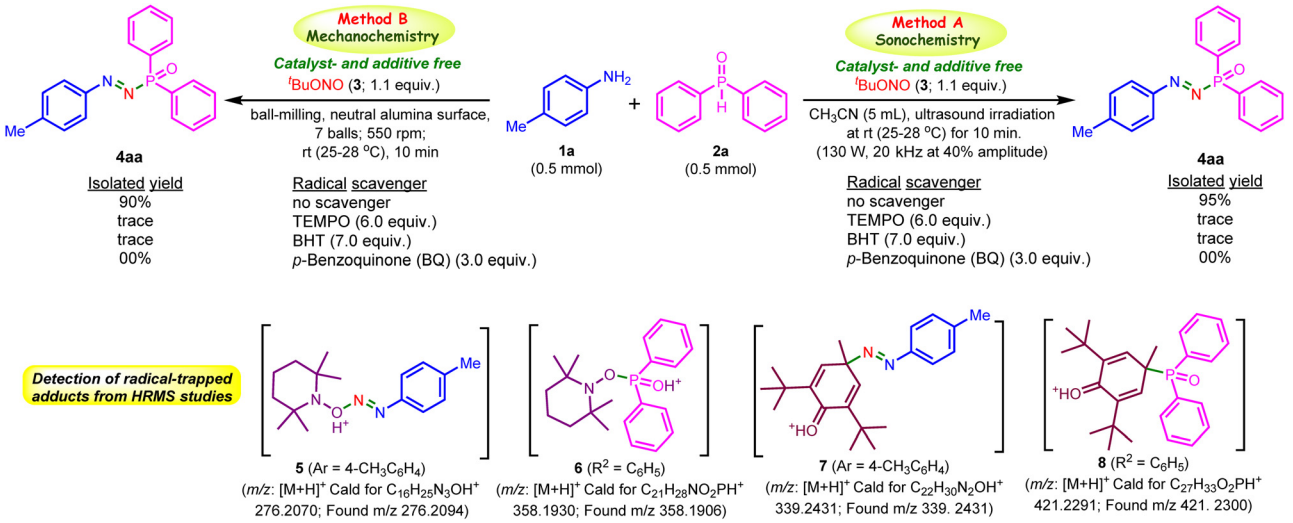


Fig. 2 ORTEP view of molecule **4ib** (CCDC 2393356‡), showing the atom-labeling scheme (displacement ellipsoids are drawn at the 50% probability level).



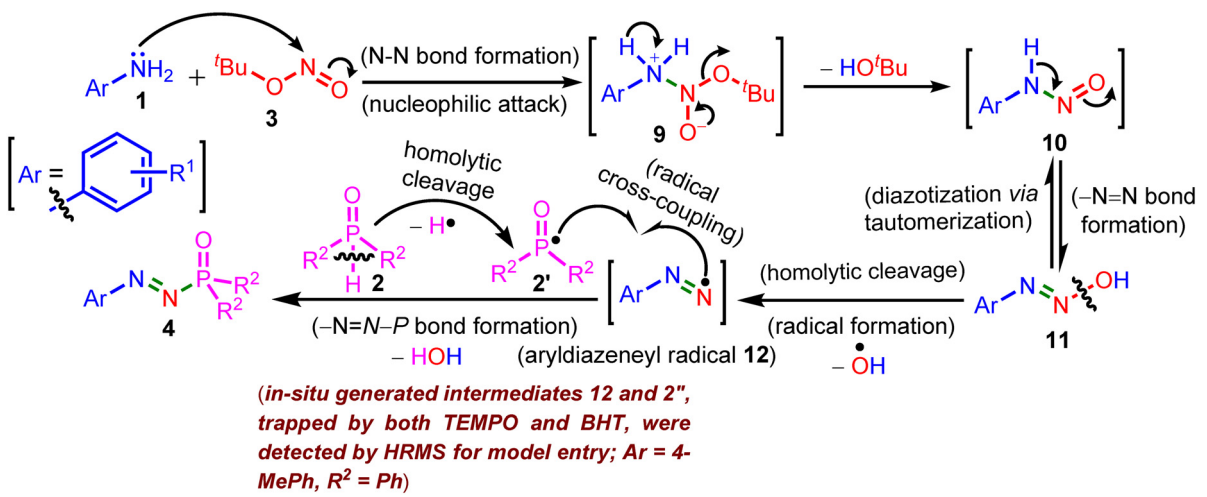
Scheme 2 Gram-scale synthetic applications under both sono- and mechanochemical methods.



Scheme 3 Control experiments with radical scavengers.

suggesting that the transformation follows a radical pathway in both processes. Delightfully, we successfully detected the TEMPO-adducts **5** and **6** and the BHT-adducts **7** and **8** (Scheme 3) from the HRMS analysis, which supported our presumption of the generation of possible radical intermediates, such as aryldiazenyl radical **12** (trapped adducts **5** and **7**) and phosphonyl radical **2′** (trapped adducts **6** and **8**).

Based on the results of the control experiments (Scheme 3), we herein proposed a possible mechanism (Scheme 4) for the sono- and mechanochemical transformations. Aromatic primary amine **1** and *tert*-butyl nitrite (**3**) first react together under the reaction conditions to form (*E*)-1-hydroxy-2-aryldiazene (**11**),[10,15] which then undergoes a homolytic cleavage of its N–OH bond to generate an aryldiazenyl radical inter-



Scheme 4 Proposed reaction mechanism.

mediate (**12**, as trapped by TEMPO and BHT). Simultaneously, phosphine oxide **2** also forms a phosphonyl radical intermediate **2′** (as trapped by TEMPO and BHT). Finally, these *in situ*-generated radical intermediates **12** and **2′** undergo rapid hetero-cross-coupling to afford the desired product **4** (Scheme 4).

3. Conclusions

We have developed practical and straightforward alternative synthetic protocols for diversely functionalised (*E*)-diaryl(aryldiazenyl)phosphine oxides/phosphonates (**4**) based on sonochemical and mechanochemical strategies as a dual approach from the three-component one-pot reaction between substituted anilines (**1**), diarylphosphine oxides/dialkyl phosphonates (**2**) and *tert*-butyl nitrite (**3**). The sonochemical method utilises the advantages of ultrasound irradiation under catalyst- and additive-free conditions under ambient conditions, while the mechanochemical process implements the chemical transformation with the same efficiency under high-speed solvent-free ball-milling conditions. The key advantages of the newly developed methods are mild reaction conditions that use ultrasound and ball-milling as green tools, avoidance of any catalysts and additives, shorter reaction times, good to excellent yields, broad substrate scope and tolerance of various functional groups, scalability, operational simplicity, low *E*-factors, and eco-friendliness.

4. Experimental section

4.1. General method

Chemicals and solvents used in this work were purchased from reputed companies. ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded at 400, 100, and 162 MHz, respectively, using a Bruker DRX spectrometer. $CDCl_3$ and DMSO-d_6 were used as solvents, and TMS was used as an internal standard for recording the NMR spectra. The ^{1}H-NMR signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet), and the chemical shift values for both ^{1}H- and ^{13}C-NMR spectra are presented in δ (ppm). Coupling constants are reported as J values in Hz. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. A Waters (G2-XS Q-TOF) high-resolution mass spectrometer was utilised to record the HRMS spectra. X-ray single-crystal crystallographic data were collected using an X′ Calibur CCD area-detector diffractometer. The melting points were recorded on a Chemiline CL-725 melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was performed using silica gel 60 F254 (Merck) plates. A Sonics-made ultrasound probe-sonicator (model: VCX 130) with a frequency of 20 kHz and energy of 130 W was used for sonication. A PM 100 (Retsch GmbH, Germany) ball-milling apparatus was used for mechanochemical reactions. Safety statement on the procedures: We did not detect/encounter any unexpected, new, and/or significant hazards or risks associated with the reported work.

4.2. General procedure for the synthesis of functionalised (*E*)-(aryldiazenyl)phosphine oxides/phosphonates (4) under the sonochemical method (Method A)

Anilines (**1**; 0.5 mmol), diarylphosphine oxides/dialkyl phosphonates (P-reagents, **2**; 0.5 mmol), and *tert*-butyl nitrite (^{t}BuONO, **3**; 1.1 equivalent) were added sequentially to an oven-dried glass vessel (20 mL). 5 mL of acetonitrile was then added to the vessel. The mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 5–7 minutes (monitored by TLC). Upon completion of the reaction, the whole content was transferred into a 25 mL separating funnel, followed by addition of 20 mL of a mixture (3 : 1 v/v) of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the crude mass, which was then subjected to column chromatographic purification using EtOAc–hexane mixtures as eluents to isolate the desired products (*E*)-(aryldiazenyl)phosphine oxides/phosphonates **4** (**4aa–4ja**, **4ab**, **4cb**, **4db**, **4fb**, **4hb**, **4ib**, **4ac**, **4fc**, **4hc**, **4ic**, **4ad**, **4cd**, **4dd**, **4gd**, **4hd**, **4jd**, **4ae**, and **4ke**). The synthesised compounds were fully characterised by spectroscopic studies, including ^{1}H-NMR, ^{13}C-NMR, DEPT-135, ^{31}P-NMR, ^{19}F-NMR (for compounds **4ga** and **4gd**), 2D-NMR (for compound **4gd**), single-crystal X-ray diffraction (XRD) studies (for compound **4ib**) and HRMS. The physical and spectral data for known compounds (*viz.* **4ea**, **4fa**, **4ae** and **4kl**) were consistent with previously reported data[10] (see the ESI‡).

4.3. Gram-scale synthesis of one representative compound 4aa under the sonochemical method (Method A)

p-Toluidine (**1a**; 5.0 mmol/10.0 mmol), diphenylphosphine oxide (**2a**; 5.0 mmol/10.0 mmol), and *tert*-butyl nitrite (^{t}BuONO, **3**; 1.1 equivalent) were added sequentially to an oven-dried glass vessel (20 mL), followed by adding 5 mL/10 mL of acetonitrile. Each reaction mixture was then irradiated with ultrasound (130 W, 20 kHz at 40% amplitude) for 5 minutes (monitored by TLC). Upon completion of each reaction, the resultant reaction mixture was worked up and purified following the same procedure as mentioned in the general method (Method A) to obtain pure product **4aa** in 91% yield for both 5.0 mmol-scale (1.456 g of **4aa**) and 10.0 mmol-scale (2.902 g of **4aa**) experiments.

4.4 General procedure for the synthesis of functionalised (*E*)-(aryldiazenyl)phosphine oxides/phosphonates (4) under ball-milling (Method B)

A mixture of anilines (**1**; 0.5 mmol), P-reagent (**2**; 0.5 mmol), and ^{t}BuONO (**3**; 1.1 equivalent) was subjected to ball-milling in the presence of neutral alumina (1.5 g) as the surface at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) made of the same material for 5–7.5 minutes. The ball-milling operation was conducted with an inverted

rotation direction, with intervals of 2.5 minutes and breaks of 5 seconds. After completion of the reaction (monitored by TLC), the entire content was transferred into a 250 mL separating funnel, followed by adding 30 mL of a mixture (3 : 1 v/v) of ethyl acetate and water. The resulting mixture was then shaken well; the organic layer was separated and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to obtain a crude mass, which was subjected to column chromatographic purification using EtOAc–hexane mixtures as eluents to yield pure products of substituted (*E*)-(aryldiazenyl)phosphine oxides/phosphonates **4** (**4aa–4ja**, **4ab**, **4cb**, **4db**, **4fb**, **4hb**, **4ib**, **4ac**, **4fc**, **4hc**, **4ic**, **4ad**, **4cd**, **4dd**, **4gd**, **4hd**, **4jd**, **4ae**, and **4ke**).

4.5 Gram-scale synthesis of one representative compound 4aa under ball-milling (Method B)

A mixture of *p*-toluidine (**1a**; 5.0 mmol/10.0 mmol), diphenylphosphine oxide (**2a**; 5.0 mmol/10.0 mmol), and *tert*-butyl nitrite (^{t}BuONO, **3**; 1.1 equivalents) were subjected to ball-milling in the presence of neutral alumina (1.5 g for 5.0 mmol-scale/6.0 g for 10.0 mmol-scale) as the surface at 550 rpm using a 25 mL (5.0 mmol-scale)/50 mL (10.0 mmol-scale) stainless steel jar with seven balls (10 mm in diameter) made of the same material for 7.5 minutes (monitored by TLC). The ball-milling operation was conducted with an inverted rotation direction, with intervals of 2.5 minutes and breaks of 5 seconds. Upon completion of each reaction, the resultant reaction mixture was worked up and purified following the same procedure as mentioned in the general method (Method B) to obtain a pure product **4aa** in 84% yield for 5.0 mmol-scale (1.344 g of **4aa**) and 81% yield for 10.0 mmol-scale (2.603 g of **4aa**) experiments.

4.6. The physical and spectral data of the synthesised (*E*)-aryldiazenyl-substituted phosphine oxides/phosphonates 4

(*E*)-Diphenyl(*p*-tolyldiazenyl)phosphine oxide (4aa). Light reddish solid; yield: 95% (152 mg, 0.5 mmol scale, sonochemistry), yield: 90% (144 mg, 0.5 mmol scale, mechanochemistry), mp = 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 4H, Ar–H), 7.88 (d, 2H, J = 8.0 Hz, Ar–H), 7.58–7.54 (m, 2H, Ar–H), 7.52–7.47 (m, 4H, Ar–H), 7.30 (d, 2H, J = 8.0 Hz, Ar–H), 2.42 (s, 3H, Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.15 (d, $J_{C–P}$ = 44 Hz, *C*), 145.19 (*C*), 132.62 (2 × *C*H), 132.50 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 130.08 (d, $J_{C–P}$ = 176 Hz, 2 × *C*), 129.92 (2 × *C*H), 128.74 (d, $J_{C–P}$ = 12 Hz, 4 × CH), 123.41 (2 × *C*H), 21.82 (Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.84 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2OPH^+$, 321.1151; found: *m*/*z* 321.1133.

(*E*)-Diphenyl(*o*-tolyldiazenyl)phosphine oxide (4ba). Red oil; yield: 71% (113 mg, 0.5 mmol scale, sonochemistry), yield: 69% (110 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.89 (m, 4H, Ar–H), 7.59–7.56 (m, 2H, Ar–H), 7.52–7.43 (m, 6H, Ar–H), 7.35 (d, J = 6.8 Hz, 1H, Ar–H), 7.24–7.20 (m, 1H, Ar–H), 2.64 (s, 3H, Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 154.65 (d, $J_{C–P}$ = 43 Hz, *C*), 141.51 (*C*), 134.22 (2 × *C*H), 132.62 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 131.94 (2 × *C*H), 128.79 (2 × *C*), 128.67 (2 × *C*H), 126.40 (2 × *C*H), 113.37 (2 × *C*H), 17.48 (Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.38 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2OPH^+$, 321.1151; found: *m*/*z* 321.1158.

(*E*)-((4-Isopropylphenyl)diazenyl)diphenylphosphine oxide (4ca). Black semi-solid; yield: 79% (138 mg, 0.5 mmol scale, sonochemistry), yield: 77% (135 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.86 (m, 6H, Ar–H), 7.44–7.40 (m, 6H, Ar–H), 7.29–7.26 (m, 2H, Ar–H), 2.90–2.82 (m, 1H, Ar–C*H*$(CH_3)_2$) 1.17–1.14 (m, 6H, Ar–CH$(CH_3)_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.59 (*C*), 153.06 (d, $J_{C–P}$ = 44 Hz, *C*), 132.36 (d, $J_{C–P}$ = 2 Hz, 2 × *C*H) 132.14 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 129.42 (d, $J_{C–P}$ = 116 Hz, 2 × *C*), 128.47 (d, $J_{C–P}$ = 12 Hz, 4 × *C*H), 127.05 (2 × *C*H), 123.23 (2 × *C*H) 34.07 (Ar–*C*H$(CH_3)_2$), 23.45 (Ar–CH(*C*H$_3$)$_2$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.73 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2OPH^+$, 349.1464; found: *m*/*z* 349.1472.

(*E*)-((4-(*tert*-Butyl)phenyl)diazenyl)diphenylphosphine oxide (4da). Dark reddish semi-solid; yield: 77% (140 mg, 0.5 mmol scale, sonochemistry), yield: 73% (133 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.89 (m, 6H, Ar–H), 7.49–7.41 (m, 8H, Ar–H), 1.28 (s, 9H, 3CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.85 (*C*), 152.66 (d, J = 43 Hz, *C*), 132.44 (d, $J_{C–P}$ = 2 Hz, 2 × *C*H), 132.23 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 129.47 (d, $J_{C–P}$ = 116 Hz, 2 × *C*), 128.55 (d, $J_{C–P}$ = 12 Hz, 4 × CH), 126.02 (2 × *C*H), 122.97 (2 × *C*H), 35.14 (Ar–*C*(CH_3)), 30.96 (3 × Ar–C(*C*H$_3$)) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.76 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2OPH^+$, 363.1612; found: *m*/*z* 363.1626.

(*E*)-4-((Diphenylphosphoryl)diazenyl)benzonitrile (4ea).[10] Purple solid; yield: 70% (116 mg, 0.5 mmol scale, sonochemistry), yield: 68% (112 mg, 0.5 mmol scale, mechanochemistry), mp = 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–7.96 (m, 6H, Ar–H), 7.83 (d, 2H, J = 8.4 Hz, Ar–H), 7.63–7.60 (m, 2H, Ar–H), 7.57–7.52 (m, 4H, Ar–H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.43 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}N_3OPH^+$, 332.0947; found: *m*/*z* 332.0930.

(*E*)-((4-Methoxyphenyl)diazenyl)diphenylphosphine oxide (4fa).[10] Dark reddish solid; yield: 84% (68 mg, 0.5 mmol scale, sonochemistry), yield: 76% (62 mg, 0.5 mmol scale, mechanochemistry), mp = 101–103 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (d, 2H, J = 9.2 Hz, Ar–H), 7.87–7.83 (m, 4H, Ar–H), 7.65–7.61 (m, 2H, Ar–H), 7.59–7.54 (m, 4H, Ar–H), 7.13 (d, 2H, J = 8.8 Hz, Ar–H), 3.85 (Ar–OCH_3), ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 25.22 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O_2PH^+$, 337.1100; found: *m*/*z* 337.1103.

(*E*)-((4-Fluorophenyl)diazenyl)diphenylphosphine oxide (4ga). Pinkish red solid; yield: 80% (130 mg, 0.5 mmol scale, sonochemistry), yield: 78% (126 mg, 0.5 mmol scale, mechanochemistry), mp = 147–149 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.05–8.02 (m, 2H, Ar–H), 7.94–7.89 (m, 4H, Ar–H), 7.67–7.61 (m, 6H, Ar–H), 7.46 (t, J = 8.4 Hz, 2H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.66 (d, $J_{C–F}$ = 252 Hz, *C*), 150.96 (d, $J_{C–P}$ = 45 Hz, *C*), 132.96 (2 × *C*H), 131.99 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H) 129.45 (d, $J_{C–P}$ = 116 Hz, 2 × *C*), 129.11

(d, J_{C-F} = 12 Hz, 2 × *C*H), 125.61 (d, J_{C-P} = 9 Hz, 4 × *C*H), 116.88 (d, J_{C-F} = 23 Hz, 2 × *C*H) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 25.73 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −104.39 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FN_2OPH^+$, 325.0901; found: *m*/*z* 325.0921.

(*E*)-((4-Chlorophenyl)diazenyl)diphenylphosphine oxide (4ha). Reddish semi-solid; yield: 75% (128 mg, 0.5 mmol scale, sonochemistry), yield: 72% (122 mg, 0.3 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.91 (m, 4H, Ar–H), 7.61–7.57 (m, 2H, Ar–H), 7.54–7.47 (m, 6H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 152.81 (d, J_{C-P} = 43 Hz, *C*), 140.29 (2 × *C*), 132.84 (2 × *C*H), 132.50 (d, J_{C-P} = 9 Hz, 4 × *C*H) 129.23 (d, J_{C-P} = 116 Hz, 2 × *C*), 129.65 (2 × *C*H), 128.86 (d, J_{C-P} = 15 Hz, 4 × *C*H), 124.52 (2 × *C*H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.66 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}ClN_2OPH^+$, 341.0605; found: *m*/*z* 341.0591.

(*E*)-Diphenyl(*p*-tolyldiazenyl)phosphine oxide (4ia). Red solid; yield: 77% (149 mg, 0.5 mmol scale, sonochemistry), yield: 73% (140 mg, 0.5 mmol scale, mechanochemistry), mp = 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.94 (m, 4H, Ar–H), 7.84 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.67–7.65 (m, 2H, Ar–H), 7.61–7.57 (m, 2H, Ar–H), 7.54–7.49 (m, 4H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.16 (d, J_{C-P} = 44 Hz, *C*), 132.89 (d, J_{C-P} = 2 Hz, 4 × *C*H), 132.70 (2 × *C*H) 132.54 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.22 (d, J_{C-P} = 116 Hz, 2 × *C*), 129.09 (*C*), 128.90 (d, J_{C-P} = 12 Hz, 4 × *C*H), 124.66 (2 × *C*H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.75 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}BrN_2OPH^+$, 385.0100; found: *m*/*z* 365.0089.

(*E*)-((4-Iodophenyl)diazenyl)diphenylphosphine oxide (4ja). Red solid; yield: 68% (147 mg, 0.5 mmol scale, sonochemistry), yield: 64% (138 mg, 0.5 mmol scale, mechanochemistry), mp = 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.93 (m, 4H, Ar–H), 7.88 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.67 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.61–7.57 (m, 2H, Ar–H), 7.54–7.49 (m, 4H, Ar–H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.69 (d, J_{C-P} = 44 Hz, *C*), 138.74 (2 × *C*H), 132.89 (2 × *C*H), 132.52 (d, J_{C-P} = 8 Hz, 4 × *C*H) 129.14 (d, J_{C-P} = 117 Hz, 2 × *C*), 128.89 (d, J_{C-P} = 12 Hz, 4 × *C*H), 124.56 (2 × *C*H), 102.01 (C) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.66 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}IN_2OPH^+$, 432.9961; found: *m*/*z* 432.9952.

(*E*)-Di-*o*-tolyl(*p*-tolyldiazenyl)phosphine oxide (4ab). Dark red semi-solid; yield: 81% (141 mg, 0.5 mmol scale, sonochemistry), yield: 78% (136 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.83–7.74 (m, 4H, Ar–H), 7.56 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.45–7.41 (m, 2H, *J* = 7.6 Hz, Ar–H), 7.40–7.35 (m, 4H, Ar–H), 2.41 (s, 3H, Ar–C*H*$_3$), 2.29 (s, 6H, 2Ar–C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 152.61 (d, J_{C-P} = 43 Hz, *C*), 145.46 (*C*), 141.66 (d, J_{C-P} = 9 Hz, 2 × *C*), 133.08 (2 × *C*H), 132.95 (d, J_{C-P} = 6 Hz, 2 × *C*H), 131.76 (d, J_{C-P} = 11 Hz, 2 × *C*H), 130.37 (2 × *C*H), 128.69 (d, J_{C-P} = 110 Hz, 2 × *C*), 126.11 (d, J_{C-P} = 12 Hz, 2 × *C*H), 122.83 (2 × *C*H), 21.31 (Ar–*C*H$_3$), 21.29 (d, *J* = 4 Hz, 2 × Ar–*C*H$_3$)ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 31.33 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2OPH^+$, 349.1464; found: *m*/*z* 349.1459.

(*E*)-((4-Isopropylphenyl)diazenyl)di-*o*-tolylphosphine oxide (4cb). Reddish semi-solid; yield: 83% (165 mg, 0.5 mmol scale, sonochemistry), yield: 75% (141 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.86 (m, 4H, Ar–H), 7.47 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.38 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.32–7.27 (m, 4H, Ar–H), 3.05–2.95 (m, 1H, Ar–C*H*(CH$_3$)$_2$), 2.49 (s, 6H, (2 × Ar–C*H*$_3$)), 1.29 (d, *J* = 7.2 Hz, 6H, Ar–CH(C*H*$_3$)$_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.72 (*C*), 153.47 (d, J_{C-P} = 44 Hz, *C*), 142.66 (d, J_{C-P} = 9 Hz, 2 × *C*) 133.80 (d, J_{C-P} = 10 Hz, 2 × *C*H) 132.69 (d, J_{C-P} = 2 Hz, 2 × *C*H), 131.71 (d, J_{C-P} = 10 Hz, 2 × *C*H), 128.87 (d, J_{C-P} = 112 Hz, 2 × *C*), 127.40 (2 × *C*H), 125.84 (d, J_{C-P} = 13 Hz, 2 × *C*H), 123.58 (2 × *C*H) 34.47 (Ar–*C*H(CH$_3$)$_2$), 23.81 (Ar–CH(*C*H$_3$)$_2$), 22.12 (d, *J* = 2 Hz, 2 Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.00 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{25}N_2OPH^+$, 377.1777; found: *m*/*z* 377.1753.

(*E*)-((4-(*tert*-Butyl)phenyl)diazenyl)di-*o*-tolylphosphine oxide (4db). Reddish semi-solid; yield: 84% (164 mg, 0.5 mmol scale, sonochemistry), yield: 77% (150 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.91–7.86 (m, 2H, Ar–H), 7.55 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.48–7.45 (m, 2H, Ar–H), 7.32–7.27 (m, 4H, Ar–H), 2.44 (s, 6H, 2Ar–C*H*$_3$), 1.36 (s, 9H, Ar–C(C*H*$_3$)$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.88 (*C*), 153 (d, J_{C-P} = 44 Hz, *C*), 142.65 (d, J_{C-P} = 9 Hz, 2 × *C*), 133.77 (d, J_{C-P} = 10 Hz, 2 × *C*H), 132.66 (d, J_{C-P} = 2 Hz, 2 × *C*H), 131.69 (d, J_{C-P} = 9 Hz, 2 × *C*H), 128.87 (d, J_{C-P} = 112 Hz, 2 × *C*), 126.28 (2 × *C*H), 125.82 (d, J_{C-P} = 12 Hz, 2 × *C*H), 123.18 (2 × *C*H), 35.40 (Ar–*C*(CH$_3$)$_3$), 31.22 (Ar–C(*C*H$_3$)$_3$), 22.08 (d, *J* = 3 Hz, 2 ×Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.97 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}N_2OPH^+$, 391.1934; found: *m*/*z* 391.1924.

(*E*)-((4-Methoxyphenyl)diazenyl)di-*o*-tolylphosphine oxide (4fb). Reddish semi-solid; yield: 80% (146 mg, 0.5 mmol scale, sonochemistry), yield: 74% (135 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.77–7.72 (m, 2H, Ar–H), 7.53 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.39–7.32 (m, 4H, Ar–H), 7.13 (d, 2H, *J* = 9.2 Hz, Ar–H), 3.85 (Ar–OC*H*$_3$), 2.25 (s, 6H, 2Ar–C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 164.95 (*C*), 149.51 (d, J_{C-P} = 44 Hz, *C*), 141.96 (d, J_{C-P} = 9 Hz, 2 × *C*), 133.32 (d, J_{C-P} = 9 Hz, 4 × *C*H), 132.09 (d, J_{C-P} = 11 Hz, 2 × *C*H), 129.06 (d, J_{C-P} = 111 Hz, 2 × *C*), 126.39 (d, J_{C-P} = 11 Hz, 2 × *C*H), 125.81 (2 × *C*H), 115.33 (2 × *C*H), 56.34 (Ar–O*C*H$_3$), 21.63 (2 × Ar–*C*H$_3$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 29.31 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2PH^+$, 365.1419; found: *m*/*z* 365.1404.

(*E*)-((4-Chlorophenyl)diazenyl)di-*o*-tolylphosphine oxide (4hb). Reddish semi-solid; yield: 75% (138 mg, 0.5 mmol scale, sonochemistry), yield: 69% (127 mg, 0.3 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.81–7.76 (m, 2H, Ar–H), 7.70 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.59–7.55 (m, 2H, Ar–H), 7.42–7.36 (m, 4H, Ar–H), 2.30 (s, 6H, (2 × Ar–C*H*$_3$)) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 152.47 (d, J_{C-P} = 44 Hz, *C*), 141.71 (d, J_{C-P} = 9 Hz, 2 × *C*), 139.20 (*C*), 133.10–133.00 (m, 4 × *C*H), 129.60 (2 × *C*H), 131.80

(d, J_{C-P} = 9 Hz, 2 × *C*H), 130.02 (2 × *C*H), 128.26 (d, J_{C-P} = 109 Hz, 2 × *C*), 126.16 (d, J_{C-P} = 12 Hz, 2 × *C*H), 21.27 (*J* = 3 Hz, Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 30.12 ppm. HRMS (ESI-TOF): *m*/*z* [M + H + 2]$^+$ calcd for $C_{20}H_{18}ClN_2OPH^+$, 371.0889; found: *m*/*z* 371.0897.

(*E*)-((4-Bromophenyl)diazenyl)di-*o*-tolylphosphine oxide (4ib). Brick red solid; yield: 81% (167 mg, 0.3 mmol scale, sonochemistry), yield: 77% (160 mg, 0.3 mmol scale, mechanochemistry), mp = 156–158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.829 (s, 4H, Ar–H), 7.77–7.72 (m, 2H, Ar–H), 7.58–7.54 (m, 2H, Ar–H), 7.41–7.35 (m, 4H, Ar–H), 2.25 (s, 6H, 2 Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 153.08 (d, J_{C-P} = 43 Hz, *C*), 142.10 (d, J_{C-P} = 10 Hz, 2 × *C*), 133.61 (2 × *C*H), 133.37 (d, J_{C-P} = 6 Hz, 4 × *C*H), 132.24 (d, J_{C-P} = 12 Hz, 2 × *C*H), 128.88 (d, J_{C-P} = 15 Hz, 2 × *C*), 127.70 (*C*), 125.59 (d, J_{C-P} = 12 Hz, 2 *C*H), 124.89 (2 × *C*H), 21.63 (Ar–*C*H_3), 21.60 (Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 30.72 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}BrN_2OPH^+$, 413.0413; found: *m*/*z* 413.0405.

(*E*)-Di-*p*-tolyl(*p*-tolyldiazenyl)phosphine oxide (4ac). Dark red semi-solid; yield: 88% (153 mg, 0.5 mmol scale, sonochemistry), yield: 81% (141 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.81 (m, 6H, Ar–H), 7.31–7.28 (m, 2H, Ar–H), 2.42 (s, 3H, Ar–CH_3), 2.39 (s, 6H, 2Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.10 (d, J_{C-P} = 43 Hz, *C*), 144.04 (d, J_{C-P} = 173 Hz, 2 × *C*), 132.50 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.87 (2 × *C*H), 129.48 (d, J_{C-P} = 13 Hz, 4 × *C*H), 126.54 (d, J_{C-P} = 118 Hz, 2 × *C*), 123.37 (2 × *C*H), 121.26 (*C*), 21.80 (3 × Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.05 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2OPH^+$, 349.1464; found: *m*/*z* 349.1467.

(*E*)-((4-Methoxyphenyl)diazenyl)di-*p*-tolylphosphine oxide (4fc). Dark reddish semi-solid; yield: 82% (149 mg, 0.5 mmol scale, sonochemistry), yield: 77% (140 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, 2H, *J* = 9.2 Hz, Ar–H), 7.84–7.79 (m, 4H, Ar–H), 7.27 (dd, 4H, *J* = 2.8 Hz, *J* = 8 Hz, Ar–H), 6.95 (d, 2H, *J* = 8.8 Hz, Ar–H), 3.85 (Ar–OCH_3), 2.37 (s, 6H, 2 × Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.35 (*C*), 149.67 (d, J_{C-P} = 445 Hz, *C*), 142.96 (d, J_{C-P} = 2 Hz, 2 × *C*), 132.39 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.37 (d, J_{C-P} = 13 Hz, 4 × *C*H), 126.84 (d, J_{C-P} = 119 Hz, 2 × *C*), 125.69 (2 × *C*H), 114.22 (2 × *C*H), 55.78 (Ar–O*C*H_3), 21.72 (2 × Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.60 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2PH^+$, 365.1413; found: *m*/*z* 365.1424.

(*E*)-((4-Chlorophenyl)diazenyl)di-*m*-tolylphosphine oxide (4hc). Red liquid; yield: 76% (140 mg, 0.5 mmol scale, sonochemistry), yield: 71% (131 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, 2H, *J* = 4.8 Hz, Ar–H), 7.85–7.81 (m, 4H, Ar–H), 7.46 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.31–7.29 (m, 4H, Ar–H), 2.39 (s, 6H, 2 Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 152.73 (d, J_{C-P} = 43 Hz, *C*), 143.40 (d, J_{C-P} = 3 Hz, 2 × *C*), 139.96 (*C*), 132.45 (d, J_{C-P} = 9 Hz, 4 × *C*H), 129.60 (2 × *C*H), 129.50 (d, J_{C-P} = 5 Hz, 4 × *C*H), 125.95 (d, J_{C-P} = 120 Hz, 2 × *C*), 124.40 (2 × *C*H), 21.77 (Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.75 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2OPH^+$, 369.0918; found: *m*/*z* 369.0903.

(*E*)-((4-Bromophenyl)diazenyl)di-*p*-tolylphosphine oxide (4ic). Dark reddish liquid; yield: 80% (165 mg, 0.5 mmol scale, sonochemistry), yield: 83% (171 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.81 (m, 6H, Ar–H), 7.79 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.32–7.29 (m, 4H, Ar–H), 2.39 (s, 6H, 2 × Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 153.10 (d, J_{C-P} = 42 Hz, *C*), 143.45 (d, J_{C-P} = 3 Hz, 2 × *C*), 132.57 (d, J_{C-P} = 4 Hz, 4 × *C*H), 132.46 (2 × *C*H), 129.59 (d, J_{C-P} = 13 Hz, 4 × CH), 128.76 (*C*), 125.98 (d, J_{C-P} = 118 Hz, 2 × *C*), 124.56 (2 × *C*H), 21.82 (2 × Ar–*C*H_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.80 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{18}BrN_2OPH^+$, 413.0409; found: *m*/*z* 413.0413.

(*E*)-Bis(4-methoxyphenyl)(*p*-tolyldiazenyl)phosphine oxide (4ad). Black semi-solid; yield: 87% (165 mg, 0.5 mmol scale, sonochemistry), yield: 84% (159 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.78–7.73 (m, 6H, Ar–H), 7.35 (d, 2H, *J* = 8.0 Hz, Ar–H), 7.07 (d, *J* = 6.8 Hz, 4H, Ar–H), 3.77 (s, 6H, (2 × Ar–OCH_3)), 2.35 (s, 1H, Ar–CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 162.90 (*C*), 152.64 (d, J_{C-P} = 43 Hz, *C*), 145.37 (2 × *C*), 134.15 (d, J_{C-P} = 10 Hz, 4 × *C*H), 130.38 (2 × *C*H), 122.95 (2 × *C*H), 120.82 (d, J_{C-P} = 122 Hz, 2 × *C*), 114.80 (d, J_{C-P} = 13 Hz, 4 × *C*H), 55.68 (2 Ar–O*C*H_3), 21.50 (Ar–*C*H_3), ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 27.09 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_3PH^+$, 381.1363; found: *m*/*z* 381.1386.

(*E*)-((4-Isopropylphenyl)diazenyl)bis(4-methoxyphenyl)phosphine oxide (4cd). Dark reddish semi-solid; yield: 78% (160 mg, 0.5 mmol scale, sonochemistry), yield: 71% (145 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.84 (m, 6H, Ar–H), 7.34 (d, 2H, *J* = 8.0 Hz, Ar–H), 6.99–6.97 (m, 4H, Ar–H), 3.82 (s, 6H, 2 Ar–OCH_3), 3.01–2.91 (m, 1H, Ar–C*H*(CH_3)$_2$), 1.25 (d, 6H, *J* = 7.2 Hz, Ar–CH(CH_3)$_2$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.96 (*C*), 155.46 (2 × *C*), 153.22 (d, J_{C-P} = 44 Hz, *C*) 134.26 (d, J_{C-P} = 10 Hz, 2 × *C*H) 127.24 (2 × *C*H), 123.42 (2 × *C*H), 120.97 (d, J_{C-P} = 123 Hz, 2 × *C*), 114.32 (d, J_{C-P} = 13 Hz, 4 × *C*H), 55.43 (2 Ar–O*C*H_3), 34.38 (Ar–*C*H(CH_3)$_2$), 23.76 (Ar–CH(*C*H_3)$_2$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.14 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{25}N_2O_3PH^+$, 409.1676; found: *m*/*z* 409.1667.

(*E*)-((4-(*tert*-Butyl)phenyl)diazenyl)bis(4-methoxyphenyl) phosphine oxide (4dd). Yellowish semi-solid; yield: 79% (167 mg, 0.5 mmol scale, sonochemistry), yield: 75% (158 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.85 (m, 6H, Ar–H), 7.52 (d, 2H, *J* = 8.8 Hz, Ar–H), 6.99 (dd, 4H, *J* = 2.8 Hz, *J* = 8.8 Hz, Ar–H), 3.84 (s, 6H, 2Ar–OCH_3), 1.34 (s, 9H, 3CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.99 (d, J_{C-P} = 3 Hz, 2 × *C*), 157.67 (*C*), 152.82 (*J* = d, 43 Hz, *C*), 134.42 (d, J_{C-P} = 9 Hz, 4 × *C*H), 126.19 (2 × *C*H), 123.11 (2 × *C*H), 121.08 (J_{C-P} = 124 Hz, 2 × *C*), 114.36 (J_{C-P} = 14 Hz, 4 × *C*H), 55.48 (2 × Ar–O*C*H_3), 35.39 (Ar–*C*(CH_3)), 31.25 (3 × Ar–C(*C*H_3)) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 28.07 ppm. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}N_2O_3PH^+$, 423.1832; found: *m*/*z* 423.1852.

(*E*)-((4-Fluorophenyl)diazenyl)(3-methoxyphenyl)(4-methoxyphenyl)phosphine oxide (4gd). Reddish semi-solid; yield: 84% (162 mg, 0.5 mmol scale, sonochemistry), yield: 76% (154 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99–7.96 (m, 2H, Ar–H), 7.80 (t, 4H, J = 9.2 Hz, Ar–H), 7.413 (t, 2H, J = 8 Hz, Ar–H), 7.12 (d, 4H, J = 4.8 Hz, Ar–H), 3.79 (s, 6H, 2Ar–OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 165.54 (d, $J_{C–F}$ = 252 Hz, *C*), 162.78 (d, $J_{C–P}$ = 2 Hz, *C*), 150.90 (d, $J_{C–P}$ = 45 Hz, *C*), 134.04 (d, $J_{C–F}$ = 90 Hz, 2 × *C*H), 125.44 (d, $J_{C–P}$ = 9 Hz, 4 × *C*H), 120.57 (d, $J_{C–P}$ = 122 Hz, 2 × *C*) 116.85 (d, $J_{C–F}$ = 23 Hz, 2 × *C*H), 114.73 (d, $J_{C–P}$ = 13 Hz, 4 × *C*H), 55.52 (2 × Ar–O*C*H$_3$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 27.32 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = −104.90 ppm. HRMS (ESI-TOF): m/z [M + H + 1]$^+$ calcd for $C_{20}H_{18}FN_2O_3PH^+$, 386.1145; found: m/z 386.1157.

(*E*)-((4-Chlorophenyl)diazenyl)bis(4-methoxyphenyl)phosphine oxide (4hd). Reddish semi-solid; yield: 80% (160 mg, 0.5 mmol scale, sonochemistry), yield: 74% (148 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, 2H, Ar–H), 7.81 (s, 4H, Ar–H), 7.43 (s, 2H, Ar–H), 7.13 (s, 4H, Ar–H), 3.80 (s, 6H, 2Ar–OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ = 162.67 (d, $J_{C–P}$ = 2 Hz, *C*), 152.27 (d, $J_{C–P}$ = 43 Hz, *C*), 138.43 (2 × *C*), 133.96 (d, $J_{C–P}$ = 10 Hz, 4 × *C*H), 129.83 (2 × CH), 124.23 (2 × *C*H), 120.40 (d, $J_{C–P}$ = 122 Hz, 2 × *C*), 114.64 (d, $J_{C–P}$ = 12 Hz, 4 × *C*H), 54.42 (2 × Ar–O*C*H$_3$) ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 27.42 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2O_3PH^+$, 401.0836; found: m/z 401.0826.

(*E*)-((4-Iodophenyl)diazenyl)bis(4-methoxyphenyl)phosphine oxide (4jd). Red semi-solid; yield: 73% (180 mg, 0.5 mmol scale, sonochemistry), yield: 67% (166 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.83 (m, 6H, Ar–H), 7.65 (d, 2H, J = 8.8 Hz, Ar–H), 6.99 (dd, 4H, J = 2.4 Hz, J = 8.0 Hz, Ar–H), 3.83 (s, 6H, 2Ar–OCH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.16 (d, $J_{C–P}$ = 2 Hz, 2 × *C*), 152.61 (d, $J_{C–P}$ = 44 Hz, *C*), 137.62 (2 × *C*H), 133.41 (d, $J_{C–P}$ = 10 Hz, 4 × *C*H), 123.47 (2 × *C*H), 119.36 (d, $J_{C–P}$ = 124 Hz, 2 × *C*), 113.46 (d, $J_{C–P}$ = 13 Hz, 4 × *C*H), 100.50 (*C*), 54.47 (2 × Ar–O*C*H$_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.14 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{20}H_{18}IN_2O_3PH^+$, 493.0172; found: m/z 493.0169.

Diethyl (*E*)-(*p*-tolyldiazenyl)phosphonate (4ae).[10] Red oil; yield: 77% (99 mg, 0.5 mmol scale, sonochemistry), yield: 74% (95 mg, 0.5 mmol scale, mechanochemistry). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, J = 8.4 Hz, Ar–H), 7.31 (d, 2H, J = 8.0 Hz, Ar–H), 4.39–4.30 (m, 4H, 2 × –OCH_2CH$_3$), 2.43 (s, 3H, Ar–CH_3) 1.42–1.38 (m, 6H, 2 × –OCH$_2$CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.04 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{11}H_{17}N_2O_3PH^+$, 257.1050; found: m/z 257.1029.

Diethyl (*E*)-(phenyldiazenyl)phosphonate (4ke).[10] Red oil; yield: 77% (93 mg, 0.5 mmol scale, sonochemistry), yield: 73% (88 mg, 0.5 mmol scale, mechanochemistry), mp = 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, 2H, J = 7.2 Hz, Ar–H), 7.59–7.56 (m, 1H, Ar–H), 7.53–7.49 (m, 2H, Ar–H), 4.42–4.29 (m, 4H, 2 × –OCH_2CH$_3$), 1.42–1.38 (m, 6H, 2 × –OCH$_2$CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.49 ppm. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{10}H_{15}N_2O_3PH^+$, 243.0893; found: m/z 243.0881.

Data availability statement

The data underlying this study are available in the published article and its ESI.‡

Conflicts of interest

There are no conflicts of interest to declare.

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Electro- and Mechanochemical Strategy as a Dual Synthetic Approach for Biologically Relevant 3-Nitro-imidazo-[1,2-*a*]pyridines

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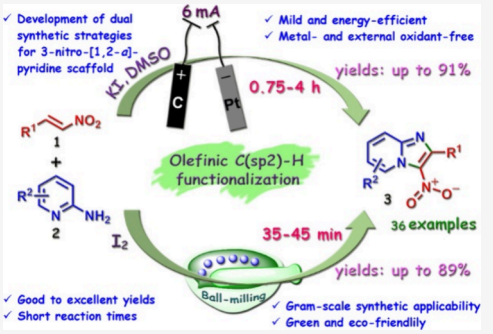
ABSTRACT: We herein disclose a dual synthetic approach involving electrochemical and mechanochemical strategies for diversely functionalized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines. Both methods offer a practical and straightforward alternative route for accessing this important class of biologically promising nitrogen-containing heterocycles. Significant advantages of the newly developed methods include mild and energy-efficient reaction conditions, avoidance of transition metal catalysts, external heating and additional oxidants, shorter reaction times, good to excellent yields, broad substrate scope, gram-scale applicability, operational simplicity, and eco-friendliness. Furthermore, a synthetic application was extended by successfully reducing synthesized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines to their corresponding amino derivatives.



1. INTRODUCTION

Imidazo[1,2-*a*]pyridines represent a group of nitrogen-containing heterocycles with valuable applications in pharmaceutical and medicinal chemistry, agrochemistry, and materials sciences.[1] This functional structural motif is abundantly found in bioactive natural products[2] and their synthetic analogues.[3] Figure 1 shows a few bioactive imidazo[1,2-*a*]pyridine derivatives and marketed drug molecules bearing this scaffold.[4,5]

Due to their promising multifaceted applications, several synthetic endeavors for accessing functionalized imidazo[1,2-*a*]pyridine derivatives are reported in the literature.[6] Still, the design and development of alternative eco-friendly and more practical methodologies for such an important organic scaffold are warranted. As part of our ongoing green chemistry research,[7] we felt it pertinent to design and develop practical and efficient alternative synthetic protocols for polyfunctionalized imidazo-[1,2-*a*]pyridines using *β*-nitrostyrenes and 2-aminopyridines as the readily available starting materials. Upon a literature survey, we encountered just a few such previous reports[8] on the preparation of 2-aryl-3-nitro-imidazo-[1,2-*a*]pyridines with the aid of CuBr/air/DMF,[8a] TBAI/TBHP/DMF,[8b] $NaICl_2$/DMF,[8c] I_2/H_2O_2/DMSO,[8d] I_2/TBHP/pyridine,[8e] and Au/Al_2O_3 (γ-Al_2O_3)[8f] under heating conditions in all cases, and also out of a three-component raection between substituted 2-aminopyrines, benzaldehydes, and nitromethane upon refluxing for 6 h in acetonitrile under *N*-iodo-succinamide (NIS) catalysis[8g] (Scheme 1). To avoid using any metal catalysts, additional oxidants, and high temperature, coupled with enabling the transformation to be more energy-efficient, eco-friendly, and fast-going with a better substrate scope, we thus engaged ourselves to explore alternative protocols for the targeted compounds. As an outcome of our sincere endeavors, we eventually succeeded in developing a dual approach, both electrochemical and mechanochemical strategies, to have a series of diversely functionalized 2-aryl-3-nitro-imidazo-[1,2-*a*]pyridines, as outlined in Scheme 1. Mild and energy-efficient reaction conditions, avoidance of transition metal catalysts, external heating and additional oxidants, good to excellent yields within shorter reaction times, scalability, and eco-friendliness are the notable advantages of these newly developed methods. Both electrochemical[7a,c,9] and mechanochemical[7b,10] strategies in synthetic organic chemistry are now growing rapidly.

2. RESULTS AND DISCUSSION

We started our investigation to optimize the reaction conditions first for the electrochemically promoted cyclization between (*E*)-(2-nitrovinyl)benzene (**1a**) and pyridin-2-amine (**2a**) as our model reaction. Initially, we checked the reaction simply by stirring the reaction mixture of **1a** and **2a** in dimethyl sulfoxide (DMSO) at ambient temperature (25−28 °C) when the reaction was found not to occur even at 4 h (Table 1, entry 1). A similar result was observed when we performed the reaction by adding 0.04 M potassium iodide (KI) (Table 1, entry 2). We then opted for an electrochemical condition for the model reaction by using a pair of undivided C||Pt electrodes and a direct current (DC) of 6 mA, keeping KI (0.04 M) as the electrolyte (Table 1, entry 3); gratifyingly, the reaction took

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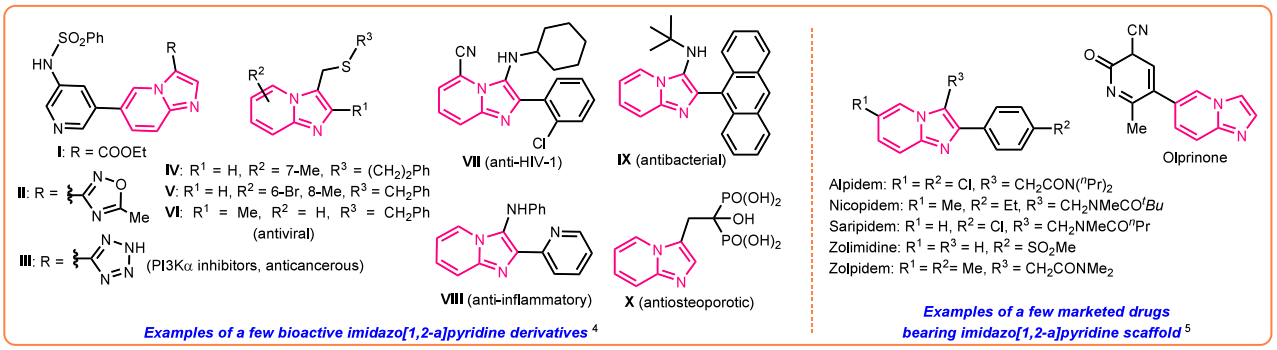
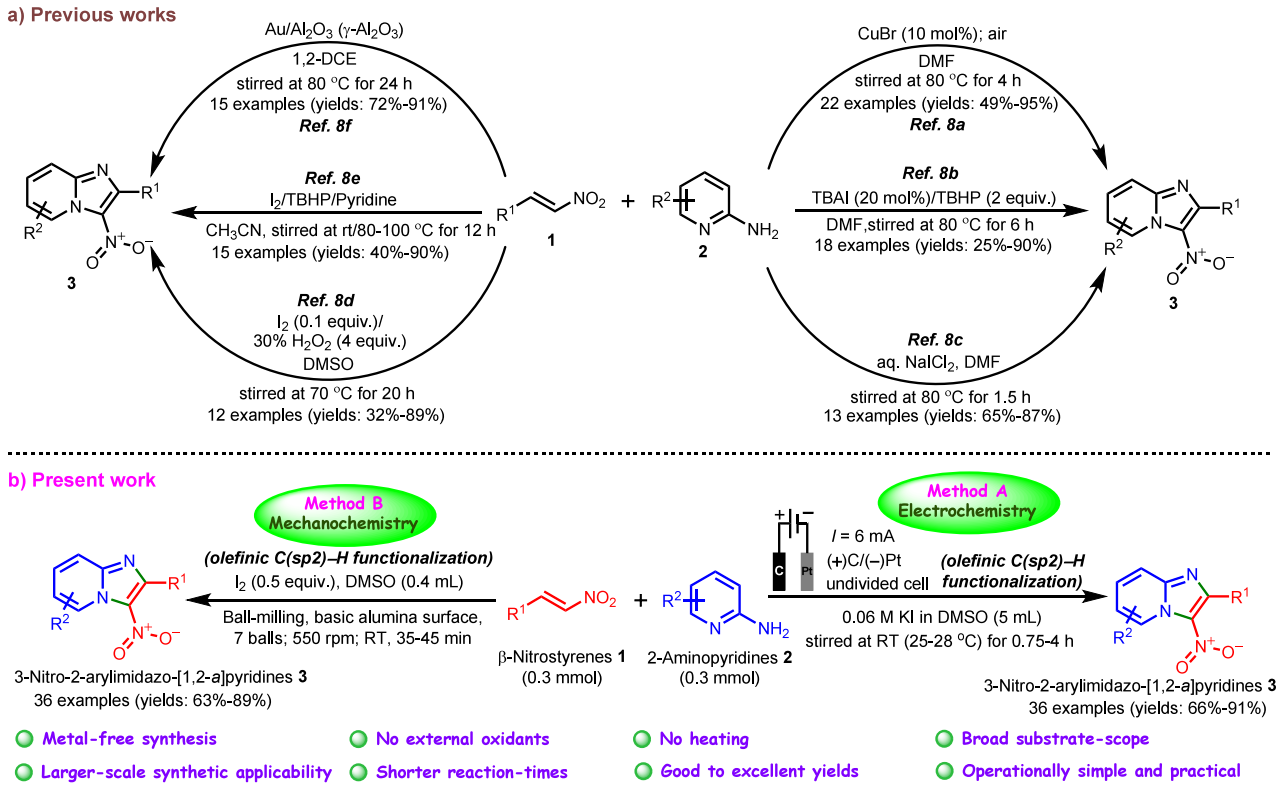


Figure 1. Examples of a few bioactive imidazo[1,2-*a*]pyridine derivatives[4] and marketed drug molecules[5] bearing this scaffold.

Scheme 1. (a) Earlier Reports on the Synthesis of 3-Nitro-imidazo-[1,2-*a*]pyridines; and (b) Electrochemical and Mechanochemical Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines



place under this electrochemical condition, resulting in the formation of the desired cyclized product, 3-nitro-2-phenylimidazo[1,2-*a*]pyridine (**3a**), in good yields of 86% at 2 h at ambient temperature (25−28 °C). Encouraged by this result, we carried out three more reactions electrochemically using the KI electrolyte in its three varying molar concentrations of 0.05, 0.06, and 0.07 M in DMSO, retaining all other parameters the same (Table 1, entries 4−6) when we isolated the product **3a** in 88% yield at 2 h in the first case (Table 1, entry 4) and in an identical yield of 91% at 45 min in the other two reactions (Table 1, entries 5 and 6). Lowering the flow of current (DC) resulted in a decrease in the isolated product (71% yield upon passing a DC of 3 mA; Table 1, entry 7), while no incremental effect on the reaction was observed upon enhancing the flow of current (89% yield upon passing a DC of 12 mA; Table 1, entry 8). The alteration in using the pair of electrodes, such as Pt||Pt (Table 1, entry 9), Pt||C (Table 1, entry 10), and C||C (Table 1, entry 11), was also found not to work well. We then performed a set of 10 more reactions with varying solvents, such as acetonitrile (CH_3CN), *N*,*N*-dimethylformamide (DMF), ethanol (EtOH), methanol (MeOH), water, aqueous ethanol (1:1), 1,2-dichloroethane (1,2-DCE), 1,1-dichloromethane (DCM), 1,4-dioxane, and tetrahydrofuran (THF), retaining other parameters constant (Table 1, entries 12−21). None of these reactions proceeded even at 4 h, except isolating a 71% yield of the product **3a** at 3 h in acetonitrile solvent (Table 1, entry 12).

For further exploration of the best-suited reaction conditions, we then performed a series of trial reactions with the model reaction using different supporting electrolytes (such as KBr, KCl, NaCl, ^{n}Bu$_4$NBF$_4$, ^{n}Bu$_4$NPF$_6$, LiClO$_4$, ^{n}Bu$_4$NI, and ^{n}Bu$_4$NBr$_3$), each at a concentration of 0.12 M DMSO, under the galvanostatic mode (C||Pt as the pair of electrodes; I = 6 mA) at ambient temperature (25−28 °C) (Table 1, entries 22−29). Also, an alternating current (AC) was tested in place of a direct current (DC) (Table 1, entry 30). Again, it was observed that an

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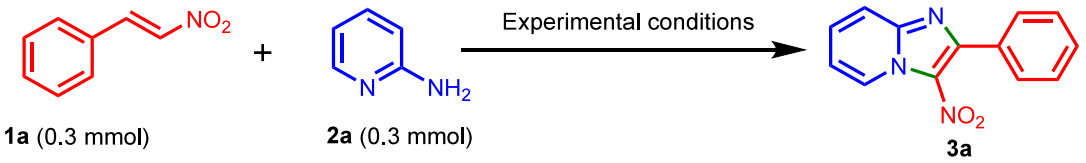
Table 1. Optimization of Reaction Conditions under Electrosynthesis[a]



1a (0.3 mmol) **2a** (0.3 mmol) **3a**

entry	electrolyte (M)	cell (+ ‖ −)	solvent (5 mL)	current (mA)	time (min)	yield (%)[a,b]
1			DMSO		240	
2	KI (0.04)		DMSO		240	
3	KI (0.04)	C ‖ Pt	DMSO	6	120	86
4	KI (0.05)	C ‖ Pt	DMSO	6	120	88
5	**KI (0.06)**	**C ‖ Pt**	**DMSO**	**6**	**45**	**91**
6	KI (0.07)	C ‖ Pt	DMSO	6	45	91
7	KI (0.06)	C ‖ Pt	DMSO	3	240	71
8	KI (0.06)	C ‖ Pt	DMSO	12	40	89
9	KI (0.06)	Pt ‖ Pt	DMSO	6	120	29
10	KI (0.06)	Pt ‖ C	DMSO	6	120	82
11	KI (0.06)	C ‖ C	DMSO	6	120	85
12	KI (0.06)	C ‖ Pt	CH_3CN	6	180	71
13	KI (0.06)	C ‖ Pt	DMF	6	240	trace
14	KI (0.06)	C ‖ Pt	EtOH	6	240	
15	KI (0.06)	C ‖ Pt	MeOH	6	240	
16	KI (0.06)	C ‖ Pt	H_2O	6	240	
17	KI (0.06)	C ‖ Pt	EtOH:H_2O	6	240	
18	KI (0.06)	C ‖ Pt	1,2-DCE	6	240	
19	KI (0.06)	C ‖ Pt	DCM	6	240	
20	KI (0.06)	C ‖ Pt	1,4-dioxane	6	240	
21	KI (0.06)	C ‖ Pt	THF	6	240	
22	KBr (0.12)	C ‖ Pt	DMSO	6	240	
23	KCl (0.12)	C ‖ Pt	DMSO	6	240	
24	NaCl (0.12)	C ‖ Pt	DMSO	6	240	
25	$^nBu_4NBF_4$ (0.12)	C ‖ Pt	DMSO	6	240	
26	$^nBu_4NPF_6$ (0.12)	C ‖ Pt	DMSO	6	240	
27	$LiClO_4$ (0.12)	C ‖ Pt	DMSO	6	240	
28	TBAI (0.12)	C ‖ Pt	DMSO	6	240	trace
29	TBATB (0.12)	C ‖ Pt	DMSO	6	240	
30[c]	KI (0.06)	C ‖ Pt	DMSO	6	240	
31[d]	KI (0.06)	C ‖ Pt	DMSO	6	45	91

[a]Reaction conditions: A mixture of (*E*)-(2-nitrovinyl)benzene (**1a**; 0.3 mmol) and pyridin-2-amine (**2a**; 0.3 mmol) dissolved in a different electrolyte solution(s) at a constant current in an undivided cell at 0.5 cm distance at room temperature (25−28 °C). Electrode size: 0.7 cm × 0.7 cm × 0.2 cm. [b]Isolated yields. [c]Alternating current (AC). [d]Reaction under nitrogen atmosphere. M = molarity.

inert atmosphere (after evacuation of the air, the reaction chamber was refilled with nitrogen gas) did not affect the reaction (Table 1, entry 31). Eventually, we arrived at the optimized reaction conditions for this electrochemical reaction between (*E*)-(2-nitrovinyl)benzene (**1a**) mmol) and pyridin-2-amine (**2a**) as a model entry, in terms of yield and time, when a graphite plate was used as the anode and a platinum plate as the cathode in an undivided cell using 0.06 M KI-electrolyte in DMSO [viz. 1.0 equiv of KI (i.e., 50 mg of KI) dissolved in 5 mL of DMSO] at ambient temperature at a constant current of 6 mA (DC). The target product **3a** was isolated with a yield of 91% in 45 min (Table 1, entry 5). All of the trial reactions for the electrosynthetic process were compiled in Table 1. Compound **3a** was fully characterized by its detailed spectral (^{1}H NMR, ^{13}C NMR, DEPT-135, and HRMS) studies, and its physical and spectral properties are similar to those reported in the literature.[8]

Upon optimizing the reaction conditions for the electrochemically promoted cyclization between *β*-nitrostyrenes and 2-aminopyridines, we then focused on gaining insight into the mechanistic pathway of this transformation. For this purpose, we first conducted cyclic voltammetry (CV) experiments of the reactants used in the model reaction [viz. (*E*)-(2-nitrovinyl)-benzene (**1a**), pyridin-2-amine (**2a**), and potassium iodide (KI); see the Supporting Information], and also performed a series of control experiments (Scheme 3). Figure 2 summarizes the CV results. The cyclic voltammograms of both pyridin-2-amine (**2a**) and KI exhibited oxidation peak(s): **2a** recorded its oxidation peak at +1.53 V (vs Ag/Ag^+), while KI showed its two oxidation peaks at +0.91 V (vs Ag/Ag^+) and +1.09 V (vs Ag/Ag^+), thereby suggesting that both of them become oxidized at the anode surface. Hence, we propose that 2-aminopyridine **2** and KI simultaneously expel an electron each to the anode and produce an amino radical-cation **2′** and an iodine radical, respectively. The in situ generated amino radical-cation **2′** then undergoes deprotonation, followed by a regioselective attack at the *α*-carbon center of the olefinic double bond of *β*-nitrostyrene **1** via the radical pathway to form a secondary carbon-radical adduct **4** that is immediately attacked by the in situ formed iodine radical,

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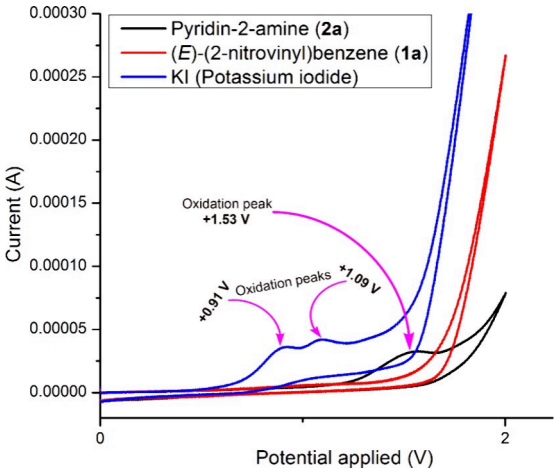


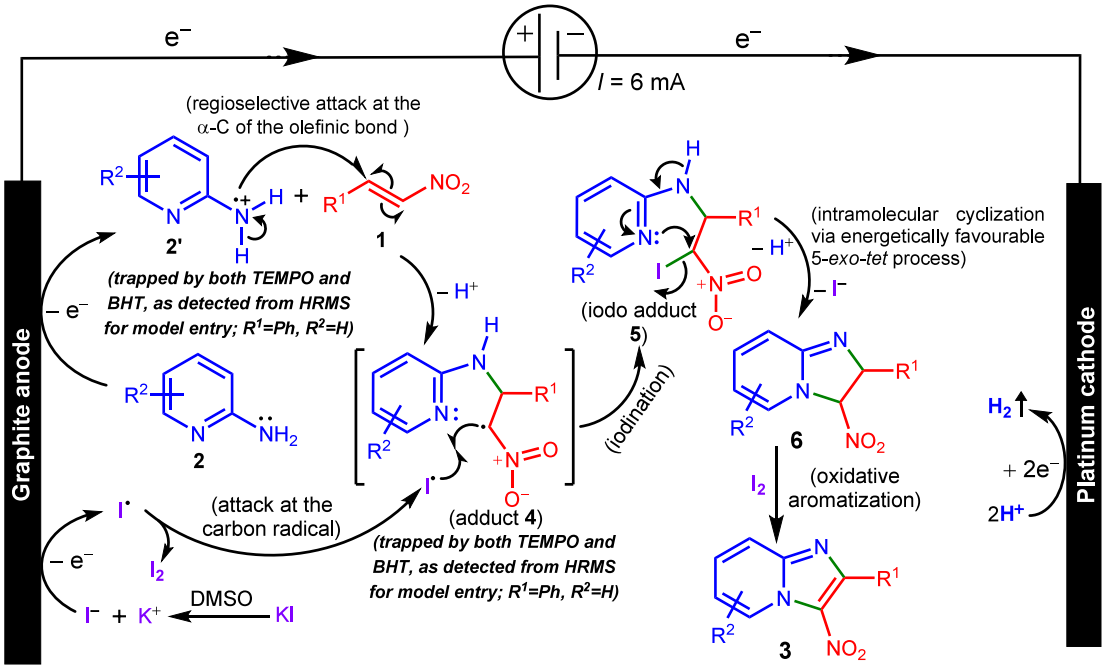
Figure 2. Cyclic voltammetry of (*E*)-(2-nitrovinyl)benzene (**1a**), pyridin-2-amine (**2a**), and potassium iodide (KI) (for detailed experimental details, see the Supporting Information).

thereby resulting in the formation of an iodo-adduct **5**. This iodoadduct **5**, in turn, undergoes an intramolecular cyclization via an energetically 5-*exo*-*tet* process to form intermediate **6**; the iodide ion, as regenerated in this step, takes part in the next cycle. In the final step, intermediate **6** undergoes oxidative aromatization by molecular iodine (I_2 formed in the reaction mixture out of the radical recombination of the in situ generated iodine radicals) under the reaction conditions, thus affording the desired product, 3-nitro-imidazo-[1,2-*a*]pyridine **3**. At the cathode surface, hydrogen is liberated upon reduction of the free protons (Scheme 2).

The proposed mechanism received good support from the results of our control experiments with the model reaction (Scheme 3). All of the radical scavenging agents, such as TEMPO, butylated hydroxytoluene (BHT), and *p*-benzoquinone (BQ), inhibited the reaction completely (Scheme 3a), thereby supplementing the radical pathway for the electrochemical conversion. To our delight, we detected both the TEMPO- and the BHT-trapped adducts **8**−**11** for the proposed in situ formed amino radical upon deprotonation of **2′** and carbon-radical adduct **4** from the HRMS spectral studies of the respective reaction mixtures (Scheme 3b; see the Supporting Information). Again, the in situ generation of molecular iodine during the current flow is evidenced by the fact that the reaction was deterred by adding sodium thiosulfate solution to the reaction mixture (Scheme 3a). This molecular iodine, in turn, implements oxidative aromatization of intermediate **6**, not by the air, as evidenced by the fact that the reaction took place under an inert (nitrogen gas) atmosphere (Table 1, entry 31). Potassium iodide thus acts as an electrolyte, redox-mediator, and oxidizing agent in implementing the conversion.

Considering the role of in situ generated iodine radical and molecular iodine from potassium iodide used as the electrolyte in the DMSO solvent under electrochemical conditions, we then envisioned that the use of molecular iodine in DMSO might be effective in carrying out the transformation under mechanochemical conditions. Accordingly, we performed the model reaction with (*E*)-(2-nitrovinyl)benzene (**1a**; 0.3 mmol) and pyridin-2-amine (**2a**; 0.3 mmol) by grinding the reaction mixture in a ball-mill in the presence of molecular iodine (0.5 equiv) and DMSO (0.4 mL) using seven stainless steel balls at 550 rpm for 1 h, when we were able to isolate the targeted product **3a** just in 28% yield (Table 2, entry 1). Encouraged by this result, we decided to optimize this mechanochemical transformation, and accordingly, we carried out a total of 25 trial reactions with the model entry under varying conditions. We also performed a control experiment using a tungsten carbide jar and balls to rule out any catalytic intervention by the stainless steel jar and balls (Table 2, entry 26). Subsequently, we were delighted to unearth another alternative and efficient method for the same transformation under ball-milling using basic alumina (2.0 g) as the surface and seven stainless steel balls (10 mm in diameter) milled for 35 min (rotation in an inverted direction

Scheme 2. Proposed Mechanism for the Electrosynthesis of 3-Nitro-imidazo-[1,2-*a*]pyridines 3



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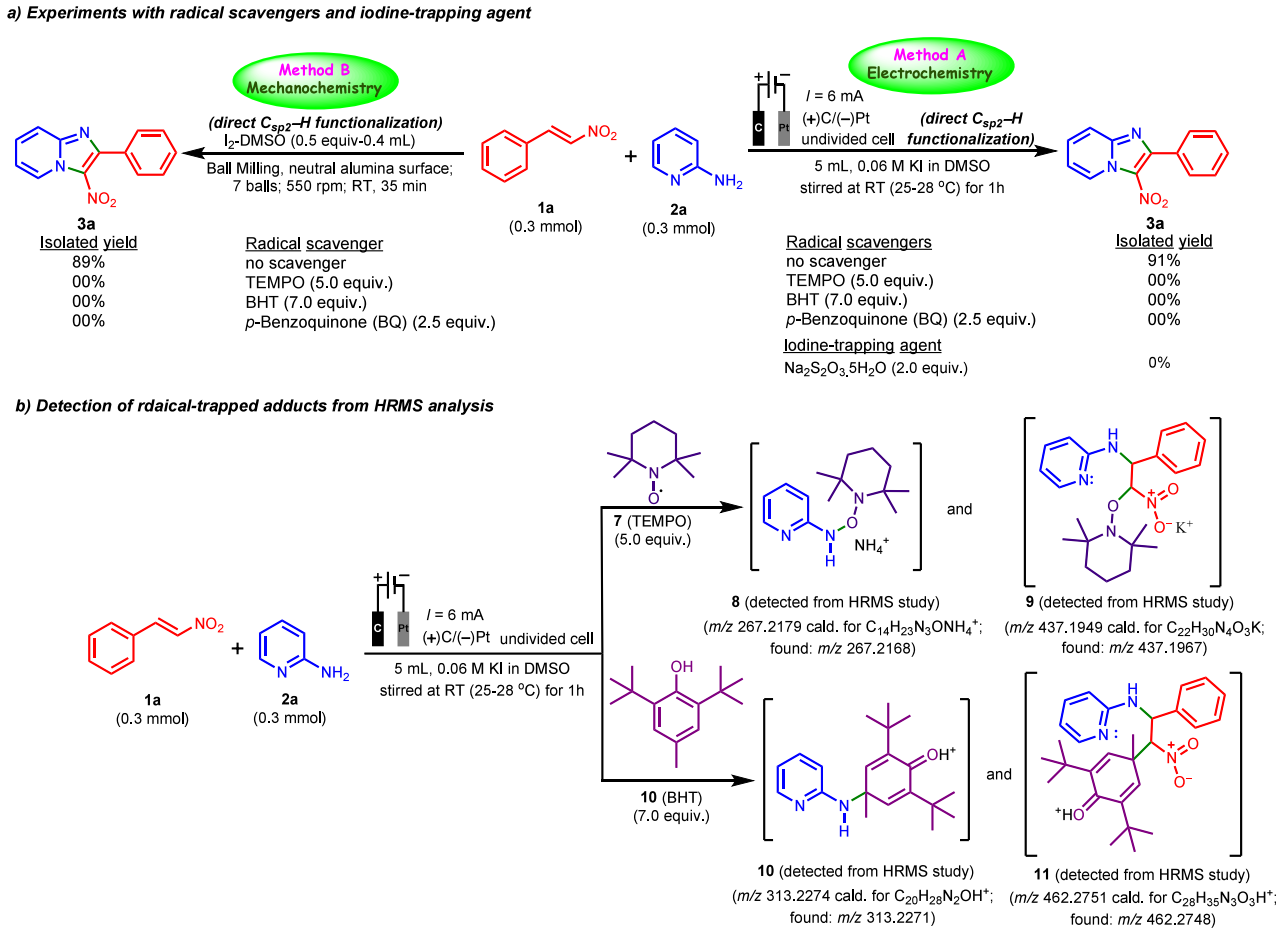
Scheme 3. Control Experiments



with a 5 s break at 5 min intervals) at 550 rpm in the presence of 0.5 equiv of I_2 as an additive and DMSO (0.4 mL) as the solvent, from where we isolated **3a** in an excellent yield of 89% (Table 2, entry 5). All of these results are summarized in Table 2.

Scheme 4 illustrates our proposed mechanism for this ball-mill-assisted mechanochemical transformation. Under ball-milling, an iodine molecule generates two iodine radicals, one of which snatches a hydrogen radical from the amino ($-NH_2$) group of 2-aminopyridines **2** to form amino radical **2″** (detected from the HRMS study), which in turn attacks at the α-carbon of the olefinic double bond of β-nitrostyrenes **1** in a regioselective manner to furnish a secondary carbon radical **4** (also detected by HRMS study). Another iodine radical adds to this carbon radical intermediate **4** to iodo-adduct **5**, which undergoes rapid intramolecular ring-closure via an energetically favorable 5-*exo-tet* process to form the cyclized species **6**. This intermediate **6**, in the final step, undergoes an oxidative aromatization by molecular iodine oxidant under the reaction conditions, thus furnishing desired product **3** (Scheme 4). The hydroiodic acid, formed during the reaction, is converted to molecular iodine once again upon reacting with alumina under ball-milling conditions.

Thus, we have now explored a dual approach for accessing biologically promising functionalized 3-nitro-imidazo-[1,2-*a*]-pyridines by using an electrosynthetic strategy (method A) and mechanochemical design (method B), both of which are effective and useful as the alternative synthetic routes (Scheme 1). Having optimized reaction conditions for both methods, we planned to explore the scope of the developed protocols and compare their efficacies in terms of respective yields and reaction times. As part of this endeavor, we first performed a set of eight reactions by treating various β-nitrostyrene derivatives (**1b**–**1i**), containing phenyl rings substituted with both electron-donating and electron-withdrawing functionalities (such as methyl, dimethyl, methoxy, 3,4-methylenedioxy, bromo, chloro, and fluoro) and 2-furyl as a heteroaryl ring, with pyridin-2-amine (**2a**) separately under the optimized conditions for electrosynthesis (method A) and the mechanochemical process (method B). All of the reactions took place smoothly in both methods, furnishing the desired 3-nitro-imidazo-[1,2-*a*]pyridines derivatives (**3b**–**3i**) in good yields ranging from 68–88% in the electrochemical and 66–86% in the mechanochemical method, within respective reaction times of 0.75–4 h and 35–45 min (Table 3, compounds **3b**–**3i**). We further extended the scope of both methods by conducting a set of 25 more reactions between diversely substituted β-nitrostyrenes (**1a**–**1c** and **1e**–**1l**) and 2-aminopyridines (viz., 4-methylpyridin-2-amine **2b**, 5-methylpyridin-2-amine **2c**, and 6-methylpyridin-2-amine **2d**) under identical reaction conditions using both strategies. Gratifyingly, all of these varieties of reactions proceeded efficiently, and the targeted products **3j**–**3z** and **3a′** were isolated with good to excellent yields ranging from 64–83% within 0.75–4 h under the electrochemical method and ranging from 62–80% within 35–45 min under the ball-milling method (Table 3, compounds **3j**–**3z** and **3a′**). Encouraged by these experimental outcomes, we synthesized another set of seven more functionalized 3-nitro-

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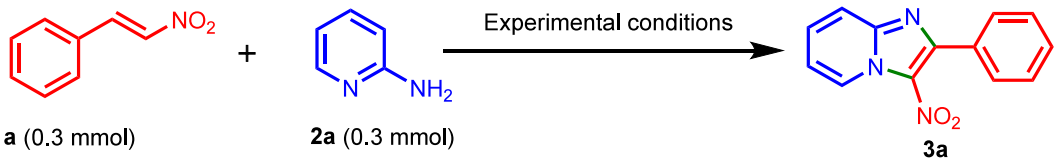
Table 2. Optimization of Reaction Conditions under Ball-Milling[a]

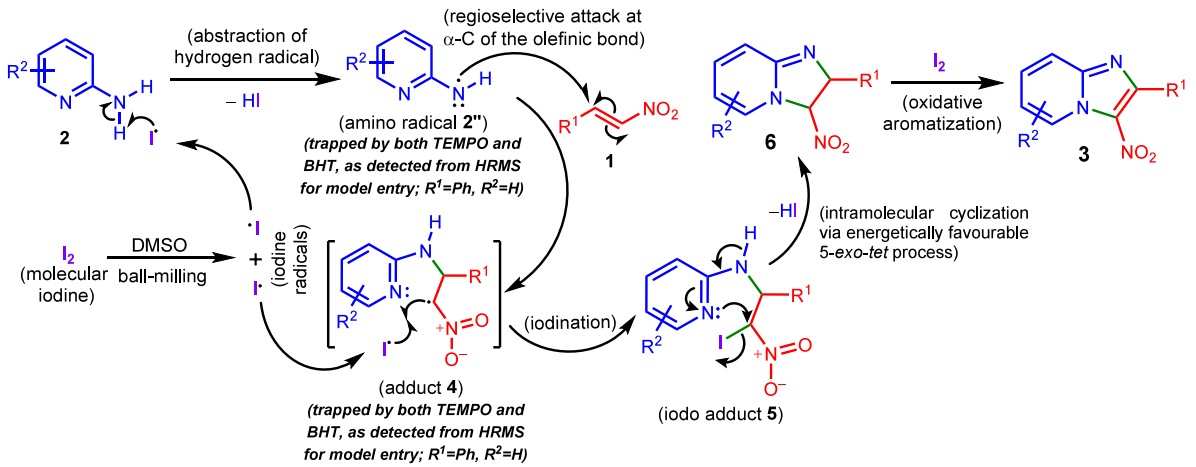


1a (0.3 mmol) **2a** (0.3 mmol) **3a**

entry	solvent (mL)	surface (2 g)	I_2 (equiv)	condition	no. of balls/rpm	time (min)	yield (%)[a,b]
1	DMSO (0.4)		I_2 (0.5)	ball-milling	7/550	60	28
2	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	10	34
3	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	20	48
3	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	10	34
4		basic alumina	I_2 (0.5)	ball-milling	7/550	60	trace
5	DMSO (0.4)	**basic alumina**	**I_2(0.5)**	**ball-milling**	7/550	**35**	**89**
6	DMSO (0.3)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	25
7	DMSO (0.5)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	46
8	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	29
9	DMSO (0.4)	basic alumina	I_2 (1.0)	ball-milling	7/550	35	60
10	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	8/550	35	88
11	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	6/550	35	86
12	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/450	35	72
13	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/600	35	66
14	DMSO (0.4)	neutral alumina	I_2 (0.5)	ball-milling	7/550	35	25
15	DMSO (0.4)	acidic alumina	I_2 (0.5)	ball-milling	7/550	35	
16	DMSO (0.4)	silica	I_2 (0.5)	ball-milling	7/550	35	
17	DMSO (0.4)	NaCl	I_2 (0.5)	ball-milling	7/550	35	
18	CH_3CN (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	85
19	THF (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
20	1,4-dioxane (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
21	EtOH (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	45
22	DMF (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
23	H_2O (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	
24	DMSO (3 mL)		I_2 (0.5)	stirring at rt		120	
25	DMSO (3 mL)	basic alumina	I_2 (0.5)	stirring at rt		360	60
26[c]	DMSO (0.4)	basic alumina	I_2 (0.5)	ball-milling	7/550	35	88

[a]Reaction conditions: A mixture of (*E*)-(2-nitrovinyl)benzene (**1a**; 0.3 mmol) and pyridin-2-amine (**2a**; 0.3 mmol) was reacted either under ball-milling (using a 25 mL stainless-steel jar and balls of 10 mm in diameter, and rotation in an inverted direction with a break of 5 s at each 5 min interval) in the presence or absence of additives or by simple stirring with iodine in various solvents (2 mL) at room temperature (25−28 °C). [b]Isolated yields. [c]Using tungsten carbide jar and balls.

Scheme 4. Proposed Mechanism for the Mechanochemical Synthesis of 3-Nitro-imidazo-[1,2-*a*]pyridines 3



imidazo-[1,2-*a*]pyridines **3b′−3h′** from the reactions between substituted *β*-nitrostyrenes and 4-ethylpyridin-2-amine (**2e**) by both methods (methods A and B) keeping all of the reaction parameters intact. The products **3b′−3h′** were obtained in good yields of 69−84% within 2−4 h in method A and 67−83% within 35−45 min in method B (Table 3, compounds **3b′−3h′**). 7-Ethyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-*a*]pyridine (**3i′**) and 7-ethyl-2-(naphthalen-2-yl)-3-nitroimidazo[1,2-*a*]pyridine

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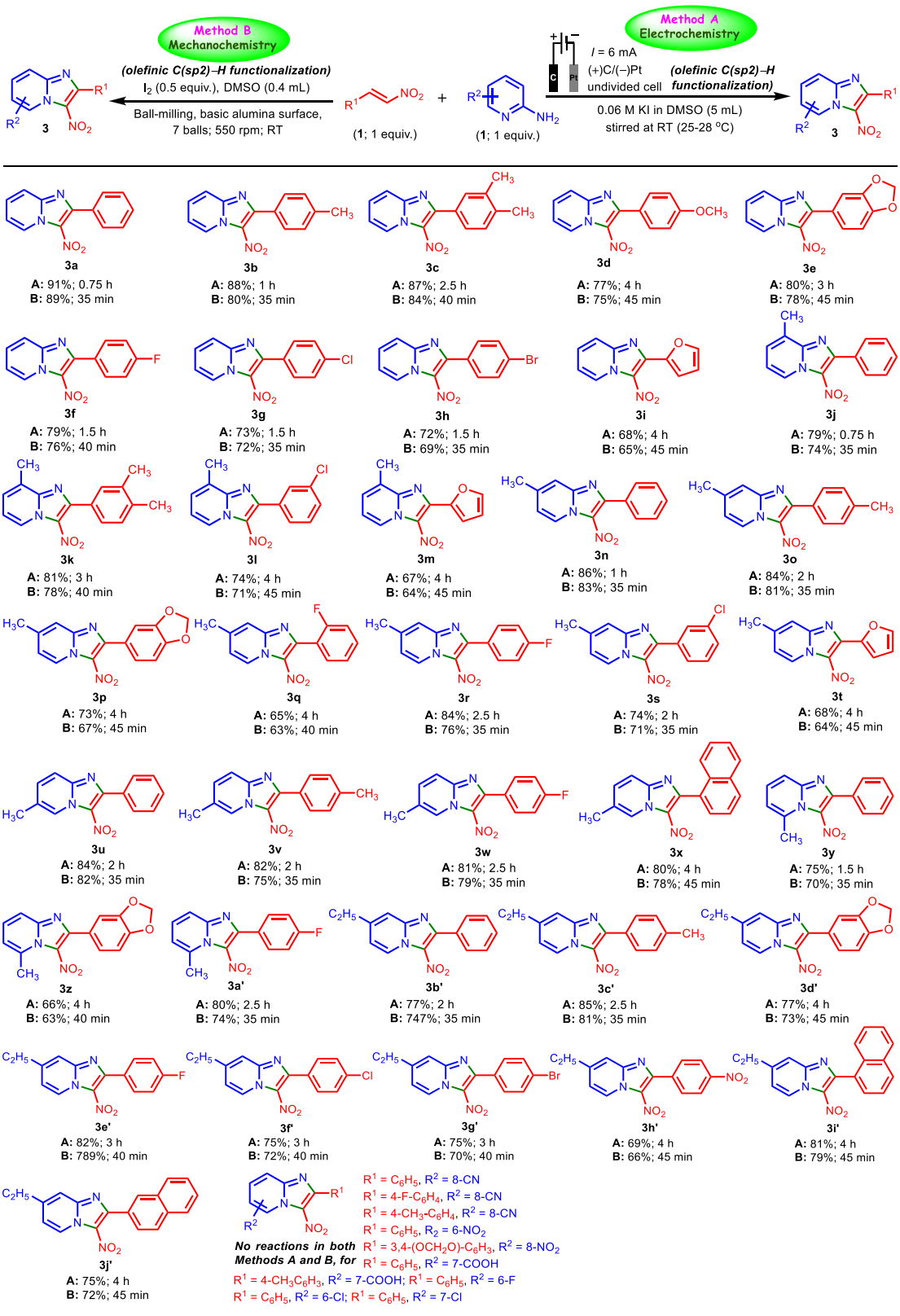
Table 3. Electrochemical and Mechanochemical Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines (3)[a,b]



[a]Standard conditions: Method A: Graphite plate as anode and platinum plate as cathode placed in an undivided cell at 0.5 cm distance, electrode size: 0.7 cm × 0.7 cm × 0.2 cm, constant current (I = 6 mA), β-nitrostyrene derivatives **1** (0.3 mmol), 2-aminopyridines **2** (0.3 mmol), KI (0.06 M), DMSO (5.0 mL), rt (28−30 °C). Method B: A mixture of β-nitrostyrene derivatives **1** (0.3 mmol) and 2-aminopyridines **2** (0.3 mmol) was reacted under ball-milling using seven stainless steel balls (10 mm in diameter) within a 25 mL stainless-steel jar at 550 rpm (rotation in an inverted direction with a break of 5 s at each 5 min interval) in the presence of 0.5 equiv of I_2 and 0.4 mL of DMSO using a solid basic alumina surface. [b]Isolated yields.

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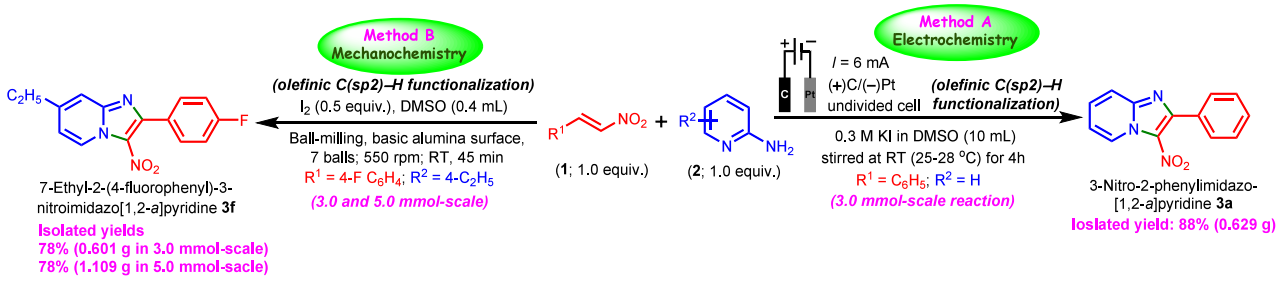
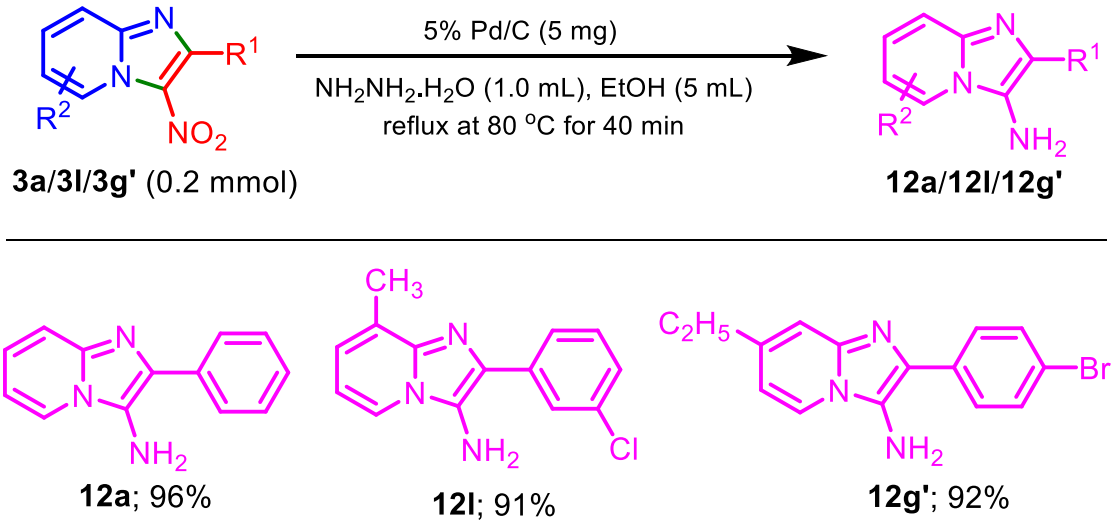
Scheme 5. Larger-Scale Synthetic Application at the Electrochemical Cell and Ball-Milling Conditions



Scheme 6. Reduction to 3-Amino-2-aryl-immidazo[1,2-*a*]pyridines (12)[a]



[a](a) Reaction conditions: A mixture of 3-nitro-2-aryl-immidazo[1,2-*a*]pyridine (**3a**/**3l**/**3g**′; 0.2 mmol), hydrazine hydrate (1.0 mL, 80% solution in water), a catalytic amount (5 mg) of 5% palladium on activated charcoal, and ethanol (5 mL) was refluxed for 40 min, and upon completion of each reaction, the desired product (**12a**/**12l**/**12g**′) was isolated following standard procedure.[11] (b) Isolated yields.

(**3j**′), the two more 3-nitro-imidazo-[1,2-*a*]pyridine derivatives, were successfully synthesized from the reaction of 4-ethyl-pyridin-2-amine (**2e**), respectively, with (*E*)-1-(2-nitrovinyl)-naphthalene (**1l**) and (*E*)-2-(2-nitrovinyl)naphthalene (**1m**), in the respective yields of 81% and 75% at 4 h under the electrochemical process (method A), and 79% and 72% yields, respectively, under ball-milling (method B) (Table 3, compounds **3i**′ and **3j**′). However, 2-aminopyridine derivatives containing electron-withdrawing groups, such as 3-CN, 5-NO_2, 4-COOH, 5-F, 4-Cl, and 5-Cl, did not undergo the reaction with varying *β*-nitrostyrenes in both electrochemical (method A) and mechanochemical (method B) processes. The presence of electron-withdrawing groups within the 2-aminopyridine nucleus possibly retards the generation and stabilization of amino radical cation **2**′ in the initial mechanistic step (Schemes 2 and 4). All of these experimental results are shown in Table 3.

Column chromatographic purification (see Experimental Section) was required to purify all of the synthesized products **3** (**3a**−**3z** and **3a**′−**3j**′ in both methods). All are new compounds except **3a**−**3e**, **3g**−**3j**, **3u**, and **3y**. Each synthesized compound was fully characterized based on their detailed spectral studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **3f**, **3q**, **3r**, **3w**, **3a**′, and **3e**′), 2D-NMR (for **3u**), and HRMS (see Experimental Section).

To verify the efficacy of both methods for somewhat higher-scale synthetic applications, we performed larger-scale reactions in each case (see Experimental Section). First, we carried out a 3.0 mmol scale (10-fold enhancement) reaction with the model entry under the electrochemical method and successfully obtained the desired 3-nitro-2-phenylimidazo-[1,2-*a*]pyridine **3a** in almost similar yield (88%; 0.629 g) compared to the submillimolar scale (Table 3, entry 1); although this reaction was completed with 1.0 equiv of KI (dissolved in 10 mL of DMSO solvent), it required substantially more time (4 h) than that for the submillimolar. Afterward, we conducted two larger-scale reactions (3.0 and 5.0 mmol; 10-fold and 16.7-fold enhancements, respectively) with a representative entry under the mechanochemical process, and delightfully, we isolated the target product, 7-ethyl-2-(4-fluorophenyl)-3-nitroimidazo[1,2-*a*]pyridine **3f**, with almost identical yields (78% yield in both cases) and time (45 min), compared to the respective submillimolar scale (Table 3, entry 5), with the optimized conditions. Scheme 5 delineates the experimental observations.

To extend the synthetic application of our synthesized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines, we then planned to reduce a set of three representative compounds, such as **3a**, **3l**, and **3g**′, to their respective amino derivatives, following the standard N_2H_4/Pd−C procedure[11] when we isolated the targeted aromatic primary amines product **12a**/**12l**/**12g**′ in excellent yields (Scheme 6), which may find many applications as synthones.

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3. CONCLUSIONS

We have developed practical and straightforward alternative synthetic protocols for diversely functionalized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines (**3**) based on electrochemical and mechanochemical strategies as a dual approach from the reaction between *β*-nitrostyrenes (**1**) and 2-aminopyridines (**2**). The transformation involves direct olefinic C(sp^2)−H functionalization of *β*-nitrostyrenes and an intramolecular ring closure. The electrochemical method exploits iodide salt as an electrolyte, redox-mediator, and oxidizing agent in an efficient manner. At the same time, the mechanochemical process also uses molecular iodine as an effective catalyst and oxidant under high-speed ball-milling conditions. Thus, both methods avoid using transition metals and additional oxidants. The key advantages of the newly developed methods are mild and energy-efficient reaction conditions that use electrochemical cells and ball-mill as green tools, avoidance of transition metal catalysts, external heating and additional oxidants, shorter reaction times, good to excellent yields, broad substrate scope and tolerance of various functional groups, scalability, operational simplicity, and eco-friendliness. Furthermore, a few representatives of the synthesized 3-nitro-2-aryl-immidazo[1,2-*a*]pyridines were reduced to their corresponding amino derivatives, which may find possible applications as valuable intermediates for some organic reactions.

4. EXPERIMENTAL SECTION

4.1. General. All chemicals (analytical grade) were purchased from reputed companies and used without further purification. All of the starting *β*-nitrostyrene derivatives used in this study were synthesized following the previously reported methods.[12] ^{1}H, ^{13}C, and ^{19}F NMR spectra were collected at 400, 100, and 376 MHz, respectively, on a Bruker DRX spectrometer using $CDCl_3$ as the solvent. Chemical shifts were reported in *δ* (ppm), relative to the internal standard TMS. The signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants are reported as *J* value in Hz. Structural assignments were made using additional information from gCOSY, gHSQC, and gHMBC experiments. Mass spectrometry was obtained using a Waters (G2-XS Q-TOF) high-resolution mass spectrometer. Cyclic voltammetry was carried out in a conventional three-electrode electrochemical cell with a Metrohm Autolab potentiostat (type: PGSTAT204; serial no. AUT52241). The melting points were recorded on a Chemiline CL-725 melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using 60 F254 (Merck) silica gel plates. A DC-regulated power supply machine (brand: Metravi; model: RPS-3005; power details − input: 220/110 V 10%, 50−60 Hz, variable output: 0−30 V DC, variable output current: 0−5 A), and Pt, graphite (C), stainless steel (SS) Ag, Zn, and Cu plate-electrodes were used to perform the electrochemical cell reactions. A PM 100, Retsch GmbH, Germany, ball-milling apparatus was used for mechanochemical reactions. Safety statement of the procedure: We did not detect/encounter any unexpected, new, and/or significant hazards or risks associated with the reported work.

4.2. General Procedure for the Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines (3) under Electrochemical Cell. *β*-Nitrostyrenes (**1**; 0.3 mmol), 2-aminopyridines (**2**; 0.3 mmol), 5 mL of 0.06 M potassium iodide (KI) electrolyte solution in DMSO, and a magnetic stir bar were successively sequentially transferred into an oven-dried glass-vessel. The reaction vessel was then capped with the graphite electrodes plate as an anode (dimensions of 0.7 × 0.7 × 0.2 cm) and platinum plate as a cathode (dimensions of 0.7 × 0.7 × 0.7 × 0.01 cm) with a distance of 0.5 cm, constructing an undivided electrochemical cell. Here, an uninterrupted flow of direct current (6 mA) was maintained through the reaction mixture with stirring at ambient temperature (25−28 °C) for 0.75−4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, 20 mL of a mixture of ethyl acetate and saturated aqueous sodium thiosulfate solution in a proportion of 3:1 (v/v) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the crude mass, which was then subjected to column chromatographic purification using an EtOAc−hexane mixture as eluent to obtain the desired products **3** (**3a**−**3z** and **3a′**−**3j′**). The synthesized compounds were fully characterized by spectroscopic studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F-NMR (**3f**, **3q**, **3r**, **3w**, **3a′**, and **3e′**), 2D-NMR (**3u**), and HRMS; the physical and spectral data for known compounds (viz. **3a**−**3e**, **3g**−**3j**, **3u**, and **3y**) are well-matched with those reported earlier[8] (see the Supporting Information).

4.3. General Procedure for the Synthesis of Functionalized 3-Nitro-imidazo-[1,2-*a*]pyridines (3) under Ball-Milling. *β*-Nitrostyrenes (**1**; 0.3 mmol), 2-aminopyridines (**2**; 0.3 mmol), in the presence of molecular iodine (0.5 equiv) and DMSO (0.4 mL) and basic alumina (1.5 g) used as the solid surface, was subjected to ball-milling at 550 rpm using a 25 mL stainless steel jar with seven balls (10 mm in diameter) of the same material for 35−45 min. The ball-milling operation was performed using an inverted rotation direction, with an interval of 5 min and taking a break of 5 s. On completion of the reaction (monitored by TLC), 30 mL of ethyl acetate and saturated aqueous sodium thiosulfate solution in a proportion of 3:1 (v/v) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was then removed under reduced pressure to obtain a white crude mass, which was then subjected to column chromatographic purification using EtOAc−hexane mixture as eluent to have pure products of 3-nitro-imidazo-[1,2-*a*]pyridines **3** (**3a**−**3z** and **3a′**−**3j′**).

4.4. Physical and Spectral Data of the Synthesized 3-Nitro-imidazo-[1,2-*a*]pyridine 3 (Including the Model Compound 3a and All of the New Compounds; These Data for Known Compounds 3b, 3c, 3d, 3e, 3g, 3h, 3i, 3j, 3u, and 3y Are Given in the Supporting Information) and the Reduced Amino Derivatives 12a, 12l, and 12g′. *3-Nitro-2-phenylimidazo[1,2-a]pyridine (**3a**).* Pale yellow solid; yield: 91% (65 mg, 0.3 mmol scale, electrochemistry), yield: 89% (64 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 170−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 9.52 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.92−7.89 (m, 2H, Ar−H), 7.84 (d, 1H, *J* = 8.8 Hz, Ar−H), 7.66−7.64 (m, 1H, Ar−H), 7.52−7.50 (m, 3H, Ar−H), 7.30−7.27 (m, 1H, Ar−H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* = 150.4 (*C*), 145.3 (*C*), 131.9 (*C*), 131.0 (CH), 130.4 (CH), 130.2 (2 × CH), 128.9 (*C*), 128.3 (CH), 128.3 (2 × CH), 118.5 (CH), 116.6 (CH) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_9N_3O_2H^+$, 240.0773; found, *m*/*z* 240.0765.

*2-(4-Fluorophenyl)-3-nitroimidazo[1,2-a]pyridine (**3f**).* Pale yellow solid; yield: 79% (61 mg, 0.3 mmol scale, electrochemistry), yield: 76% (59 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 9.51 (d, 1H, *J* = 6.8 Hz, Ar−H), 7.95−7.92 (m, 2H, Ar−H), 7.83 (d, 1H, *J* = 8.8 Hz, Ar−H), 7.69−7.65 (m, 1H, Ar−H), 7.31−7.26 (m, 1H, Ar−H), 7.21−7.17 (m, 2H, Ar−H), ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* = 164.1 (d, J^1_{C-F} = 249 Hz, *C*), 149.4 (*C*), 145.3 (*C*), 143.1 (*C*), 132.5 (d, J^3_{C-F} = 8 Hz, 2 × CH), 131.2 (CH), 128.4 (CH), 118.4 (CH), 116.7 (CH), 116.2 (d, J^2_{C-F} = 22 Hz, *C*), 115.5 (d, J^2_{C-F} = 22 Hz, 2 × CH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): *δ* = −109.88 ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_8FN_3O_2H^+$, 258.0673; found, *m*/*z* 258.0660.

*2-(3,4-Dimethylphenyl)-8-methyl-3-nitroimidazo[1,2-a]pyridine (**3k**).* Dark brown semisolid; yield: 81% (68 mg, 0.3 mmol scale, electrochemistry); yield: 78% (66 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 9.35 (d, 1H, *J* = 6.8 Hz, Ar−H), 7.68−7.64 (m, 2H, Ar−H), 7.42 (d, 1H, *J* = 7.2, Ar−H), 7.27−7.25 (s, 1H, Ar−H), 7.14 (t, 1H, *J* = 6.8 Hz, Ar−H), 2.71 (s, 3H, Ar−CH_3), 2.34 (d, 6H, *J* = 4 Hz, 2 × Ar−CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* = 149.2 (*C*), 144.3 (*C*), 138.1 (*C*), 135.5 (2 × *C*), 130.1 (CH), 128.9 (CH), 128.7 (*C*), 128.5 (CH), 127.5 (*C*), 126.7 (CH), 125.0 (CH), 115.4

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(*C*H), 18.9 (2 × Ar−*C*H$_3$), 15.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_3O_2H^+$, 282.1237; found, *m*/*z* 282.1221.

*2-(3-Chlorophenyl)-8-methyl-3-nitroimidazo[1,2-a]pyridine (**3l**).* Yellow solid; yield: 74% (64 mg, 0.3 mmol scale, electrochemistry); yield: 71% (61 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 93:7; mp = 175−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.89 (s, 1H, Ar−H), 7.80−7.78 (m, 1H, *J* = 1.2 Hz, Ar−H), 7.47−7.41 (m, 3H, Ar−H), 7.22−7.18 (m, 1H, Ar−H), 2.72 (s, 3H, Ar−CH_3, Ar−H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 147.1 (*C*), 144.2 (*C*), 133.2 (*C*), 133.0 (*C*), 129.2 (*C*H), 129.2 (*C*H), 129.2 (*C*H), 128.5 (*C*H), 127.9 (2 × *C*), 127.5 (*C*H), 124.9 (*C*H), 115.9 (*C*H), 15.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}ClN_3O_2H^+$, 288.0534; found, *m*/*z* 288.0520.

*2-(Furan-2-yl)-8-methyl-3-nitroimidazo[1,2-a]pyridine (**3m**).* Greenish yellow solid; yield: 67% (49 mg, 0.3 mmol scale, electrochemistry); yield: 64% (47 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 184−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.91 (d, 1H, *J* = 3.2 Hz, Ar−H), 7.76 (d, 1H, *J* = 1.2 Hz, Ar−H), 7.46 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.18−7.15 (m, 1H, Ar−H), 6.66 (qt, 1H, *J* = 1.6 Hz, *J* = 3.6 Hz, Ar−H), 2.76 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 146.1 (*C*), 146.1 (*C*), 145.9 (*C*H), 137.8 (*C*), 130.7 (*C*H), 126.1 (*C*H), 118.4 (*C*H), 116.5 (*C*H), 115.5 (*C*), 112.6 (*C*H), 109.7 (*C*), 14.1 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9N_3O_3H^+$, 244.0717; found, *m*/*z* 244.0701.

*7-Methyl-3-nitro-2-phenylimidazo[1,2-a]pyridine (**3n**).* Pale yellow solid; yield: 86% (65 mg, 0.3 mmol scale, electrochemistry); yield: 83% (63 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 164−166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.92−7.89 (m, 2H, Ar−H), 7.59 (br s, 1H, Ar−H), 7.49 (t, 3H, *J* = 3.2 Hz, Ar−H), 7.11−7.09 (m, 1H, Ar−H), 2.55 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.8 (*C*), 145.8 (*C*), 143.1 (2*C*), 132.2 (*C*), 130.3 (*C*H), 130.2 (2 × *C*H), 128.2 (2 × *C*H), 127.6 (*C*H), 119.0 (*C*H), 117.2 (*C*H), 21.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}N_3O_2H^+$, 254.0924; found, *m*/*z* 254.0918.

*7-Methyl-3-nitro-2-(p-tolyl)imidazo[1,2-a]pyridine (**3o**).* Yellowish white solid, 84% yield (67 mg, 0.3 mmol scale, electrochemistry), 81% yield (65 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 148−150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.82 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.58 (s, 1H, Ar−H), 7.30 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.09−7.08 (m, 1H, Ar−H), 2.54 (s, 3H, Ar−C*H*$_3$), 2.44 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.9 (*C*), 145.8 (*C*), 143.2 (*C*), 140.6 (2C), 130.1 (2 × *C*H), 129.2 (*C*), 128.9 (2 × *C*H), 127.6 (*C*H), 118.9 (*C*H), 117.1 (*C*H), 21.7 (Ar−*C*H$_3$), 21.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_3O_2H^+$, 268.1081; found: *m*/*z* 268.1070.

*2-(Benzo[d][1,3]dioxol-5-yl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3p**).* Yellow solid; yield: 73% (65 mg, 0.3 mmol scale, electrochemistry); yield: 67% (60 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 162−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.56 (s, 1H, Ar−H), 7.52−7.49 (m, 1H, Ar−H), 7.42−7.41 (m, 1H, Ar−H), 7.08 (dd, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz, Ar−H), 6.92 (d, 1H, *J* = 8.0 Hz, Ar−H), 6.04 (s, 2H, Ar−H), 2.53 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 149.5 (*C*), 147.5 (*C*), 145.7 (*C*), 143.4 (*C*), 127.6 (*C*H), 126.7 (*C*), 125.7 (*C*), 125.2 (*C*H), 122.9 (*C*), 118.9 (*C*H), 116.9 (*C*H), 110.6 (*C*H), 108.2 (*C*H), 101.6 (*C*H$_2$), 21.7 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}N_3O_4H^+$, 298.0822; found, *m*/*z* 298.0810.

*2-(2-Fluorophenyl)-5-methyl-3-nitroimidazo[1,2-a]pyridine (**3q**).* Yellowish brown viscous oil; yield: 65% (53 mg, 0.3 mmol scale, electrochemistry); yield: 63% (51 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9; mp = 160−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.37 (d, 1H, *J* = 6.8, Ar−H), 7.68−7.64 (m, 1H, Ar−H), 7.62 (s, 1H, Ar−H), 7.53−7.47 (m, 1H, Ar−H), 7.30 (d, 1H, *J* = 7.6, Ar−H), 7.23−7.19 (m, 1H, Ar−H), 7.13 (qt, 1H, *J* = 6.8 and 1.2, Ar−H), 2.56 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 160.7 (d, J^1_{C-F} = 250 Hz, *C*), 142.9 (2 × *C*), 135.1 (2 × *C*), 131.9 (d, J^3_{C-F} = 8 Hz, *C*H), 131.2 (d, J^3_{C-F} = 3 Hz, CH), 130.1 (*C*), 127.1 (*C*H), 124.3 (d, J^3_{C-F} = 3 Hz, *C*H), 119.2 (*C*H), 117.3 (*C*H), 115.9 (d, J^2_{C-F} = 21 Hz, *C*H), 21.8 (Ar−*C*H$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −109.99 ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, *m*/*z* 272.0824.

*2-(4-Fluorophenyl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3r**).* Yellowish white solid; yield: 84% (68 mg, 0.3 mmol scale, electrochemistry); yield: 76% (62 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9; mp = 160−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 7.2, Ar−H), 7.95−7.91 (m, 2H, Ar−H), 7.59−7.58 (m, 1H, Ar−H), 7.21−7.16 (m, 2H, Ar−H), 7.13−7.10 (m, 1H, Ar−H), 2.55 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.1 (d, J^1_{C-F} = 249 Hz, *C*), 149.8 (*C*), 143.4 (*C*), 132.5 (d, J^3_{C-F} = 9 Hz, 2 × *C*H), 128.2 (*C*), 127.6 (*C*H), 124.8 (*C*), 123.2 (*C*), 119.1 (*C*H), 117.2 (*C*H), 115.4 (d, J^2_{C-F} = 22 Hz, 2 × *C*H), 21.7 (Ar−*C*H$_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −109.99 ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, *m*/*z* 272.0831.

*2-(3-Chlorophenyl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3s**).* Gray solid; yield: 74% (64 mg, 0.3 mmol scale, electrochemistry); yield: 71% (61 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 93:7; mp = 183−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (d, 1H, *J* = 6.8 Hz, Ar−H), 7.89 (s, 1H, Ar−H), 7.79 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.64 (s, 1H, Ar−H), 7.49−7.41 (m, 2H, Ar−H), 7.15 (d, 1H, *J* = 7.2 Hz, Ar−H), 2.56 (s, 3H, Ar−CH_3) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 148.6 (*C*), 145.4 (*C*), 143.8 (*C*), 134.2 (*C*), 133.4 (*C*), 131.9 (*C*), 130.5 (*C*H), 130.2 (*C*H), 129.6 (*C*H), 128.5 (*C*H), 127.5 (*C*H), 119.5 (*C*H), 117.1 (*C*H), 21.8 (Ar−CH_3) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}ClN_3O_2H^+$, 288.0534; found, *m*/*z* 288.0519.

*2-(Furan-2-yl)-7-methyl-3-nitroimidazo[1,2-a]pyridine (**3t**).* Greenish brown solid; yield: 68% (50 mg, 0.3 mmol scale, electrochemistry); yield: 64% (47 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 222−224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (d, 1H, *J* = 7.2 Hz, Ar−H), 7.93 (d, 1H, *J* = 3.6 Hz, Ar−H), 7.73 (d, 1H, *J* = 1.2 Hz, Ar−H), 7.59 (s, 1H, Ar−H), 7.08 (dd, 1H, *J* = 7.2 Hz, *J* = 1.2 Hz, Ar−H), 6.66 (dd, 1H, *J* = 3.6 Hz, *J* = 1.6 Hz, Ar−H), 2.54 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 146.3 (*C*), 145.9 (*C*H), 143.9 (*C*), 140.4 (2 × *C*), 138.4 (*C*), 127.5 (*C*H), 118.9 (*C*H), 118.7 (*C*H), 117.0 (*C*H), 112.7 (*C*H), 21.8 (Ar−*C*H$_3$) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9N_3O_3H^+$, 244.0717; found, *m*/*z* 244.0709.

*6-Methyl-3-nitro-2-(p-tolyl)imidazo[1,2-a]pyridine (**3v**).* Greenish yellow solid, 82% yield (66 mg, 0.3 mmol scale, electrochemistry); 75% yield (60 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 172−174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1H, Ar−H), 7.80 (d, 2H, *J* = 8.0 Hz, Ar−H), 7.72 (d, 1H, *J* = 8.8 Hz, Ar−H) 7.49 (dd, 1H, *J* = 8.8 Hz, *J* = 1.6 Hz, Ar−H), 7.30 (d, 2H, *J* = 8.0 Hz, Ar−H), 2.50 (s, 3H, Ar−C*H*$_3$), 2.43 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 150.5 (*C*), 144.3 (*C*), 140.5 (2*C*), 138.8 (*C*), 133.8 (*C*H), 130.1 (2 × *C*H), 128.9 (*C*H), 126.4 (*C*H), 125.1 (*C*), 117.6 (*C*H), 116.7 (*C*H), 21.7 (Ar−CH_3), 18.8 (Ar−CH_3) ppm. HRMS (ESI−TOF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}N_3O_2H^+$, 268.1081; found, *m*/*z* 268.1071.

*2-(4-Fluorophenyl)-6-methyl-3-nitroimidazo[1,2-a]pyridine (**3w**).* Gray amorphous powder, 81% (66 mg, 0.3 mmol scale, electrochemistry); 79% (64 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9; mp = 196−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.33 (s, 1H, Ar−H), 7.94−7.90 (m, 2H, Ar−H), 7.72 (d, 1H, *J* = 9.2 Hz, Ar−H), 7.51 (dd, 1H, *J* = 8.8 Hz, *J* = 1.2 Hz, Ar−H), 7.20−7.16 (m, 2H, Ar−H), 2.52 (s, 3H, Ar−C*H*$_3$) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 164.0 (d, J^1_{C-F} = 248 Hz, *C*), 149.3 (*C*), 144.3 (*C*), 138.9 (*C*), 134.0 (*C*H), 133.0 (d, J^3_{C-F} = 9 Hz, *C*), 132.4 (d, J^3_{C-F} = 8 Hz, 2 × *C*H), 126.4 (*C*H), 117.6 (*C*H), 116.2 (d, J^2_{C-F} = 22 Hz, *C*), 115.4 (d, J^2_{C-F} = 21 Hz, 2 × *C*H), 18.8 (Ar−

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CH_3)ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.17 ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, m/z 272.0825.

*6-Methyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-a]pyridine (**3x**).* Yellow solid; yield: 80% (73 mg, 0.3 mmol scale, electrochemistry); yield: 78% (71 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 198−200 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.37 (s, 1H, Ar−H), 7.99 (d, 1H, J = 8.0 Hz, Ar−H), 7.93 (d, 1H, J = 8.4 Hz, Ar−H), 7.77 (d, 1H, J = 8.8 Hz, Ar−H), 7.71−7.69 (m, 2H, Ar−H), 7.60−7.57 (m, 1H, Ar−H), 7.60−7.57 (m, 1H, Ar−H), 7.52−7.48 (m, 1H, Ar−H), 7.44 (t, 1H, J = 7.2 Hz, Ar−H), 2.51 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.2 (2 × C), 144.3 (C), 133.8 (CH), 133.5 (C), 131.3 (C), 130.2 (CH), 128.7 (CH), 128.3 (CH), 127.2 (2 × C), 126.9 (CH), 126.1 (CH), 126.0 (CH), 125.1 (CH), 124.9 (CH), 117.7 (CH), 21.8 (Ar−CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{18}H_{13}N_3O_2H^+$, 304.1081; found, m/z 304.1065.

*2-(Benzo[d][1,3]dioxol-5-yl)-5-methyl-3-nitroimidazo[1,2-a]-pyridine (**3z**).* Brown viscous oil; yield: 66% (59 mg, 0.3 mmol scale, electrochemistry); yield: 63% (56 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (s, 1H, Ar−H), 7.56 (d, 1H, J = 8.8 Hz, Ar−H), 7.49−7.46 (m, 2H, Ar−H), 7.18−7.14 (m, 1H, Ar−H), 7.88 (d, 1H, J = 8.0 Hz, Ar−H), 6.63 (d, 1H, J = 6.8 Hz, Ar−H), 5.99 (s, 2H, Ar−H), 2.61 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 148.2 (C), 147.7 (C), 145.9 (C), 145.3 (C), 134.4 (C), 127.9 (C), 125.4 (C), 120.1 (CH), 114.6 (CH), 111.9 (CH), 108.8 (CH), 106.8 (CH), 104.8 (CH), 101.3 (CH_2), 18.9 (Ar−CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{11}N_3O_4H^+$, 298.0822; found, m/z 298.0821.

*2-(4-Fluorophenyl)-5-methyl-3-nitroimidazo[1,2-a]pyridine (**3a′**).* Yellow viscous oil; yield: 80% (65 mg, 0.3 mmol scale, electrochemistry); yield: 74% (60 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 91:9. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1H, Ar−H), 7.67 (s, 1H, Ar−H), 7.55 (d, 1H, J = 8.0 Hz, Ar−H), 7.18−7.08 (m, 3H, Ar−H), 6.64 (d, 1H, J = 6.0 Hz, Ar−H), 2.60 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 162.8 (d, J^1_{C-F} = 245 Hz, C), 146.1 (2 × C), 144.6 (C), 134.6 (C), 129.9 (C), 127.9 (d, J^3_{C-F} = 7 Hz, 2 × CH), 125.5 (CH), 115.8 (d, J^2_{C-F} = 22 Hz, CH), 114.8 (CH), 112.0 (CH), 105.2 (CH), 18.9 (Ar−CH_3)ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −113.98 ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{10}FN_3O_2H^+$, 272.0830; found, m/z 272.0830.

*7-Ethyl-3-nitro-2-phenylimidazo[1,2-a]pyridine (**3b′**).* Yellow amorphous solid, yield: 77% (62 mg, 0.3 mmol scale, electrochemistry); yield: 74% (59 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 90:10; mp = 150−152 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, 1H, J = 7.2 Hz, Ar−H), 7.91−7.89 (m, 2H, Ar−H), 7.61 (s, 1H, Ar−H) 7.49 (t, 3H, J = 7.2 Hz, Ar−H), 7.13−7.11 (m, 1H, Ar−H), 2.83 (qt, 2H, J = 7.2 Hz, Ar−CH_2CH_3), 1.35 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.7 (C), 148.1 (2 × C), 144.9 (C), 131.1 (C), 129.2 (CH), 129.1 (2 × CH), 127.2 (2 × CH), 126.7 (CH), 117.0 (CH), 114.7 (CH), 27.6 (Ar−CH_2CH_3), 13.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_3O_2H^+$, 268.1081; found, m/z 268.1057.

*7-Ethyl-3-nitro-2-(p-tolyl)imidazo[1,2-a]pyridine (**3c′**).* Pale yellow solid, 85% yield (72 mg, 0.3 mmol scale, electrochemistry); 81% yield (68 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 90:10; mp = 115−117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, 1H, J = 6.8 Hz, Ar−H), 7.82 (d, 2H, J = 8.4 Hz, Ar−H), 7.60 (s, 1H, J = 8.4 Hz, Ar−H), 7.30 (d, 2H, J = 8.0 Hz, Ar−H) 7.17−7.10 (m, 1H, Ar−H), 2.84 (q, 2H, J = 7.6 Hz, Ar−CH_2CH_3), 2.44 (s, 3H, Ar−CH_3) 1.35 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.1 (C), 140.6 (C), 130.3 (C), 130.2 (2 × CH), 129.2 (C), 129.0 (2 × CH), 127.8 (CH), 124.1 (C), 119.6 (C), 117.9 (CH), 115.7 (CH), 28.7 (Ar−CH_2CH_3), 21.7 (Ar−CH_3) 14.2 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_3O_2H^+$, 282.1237; found, m/z 282.1243.

*2-(Benzo[d][1,3]dioxol-5-yl)-7-ethyl-3-nitroimidazo[1,2-a]-pyridine (**3d′**).* Yellow solid; yield: 77% (72 mg, 0.3 mmol scale, electrochemistry); yield: 73% (68 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 134−136 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, 1H, J = 6.8 Hz, Ar−H), 7.56 (s, 1H, Ar−H), 7.51−7.49 (m, 1H, J = 8.0 Hz, Ar−H), 7.41 (d, 1H, J = 1.2 Hz, Ar−H), 7.11−7.08 (m, 1H, Ar−H), 6.91 (d, 1H, J = 8.0 Hz, Ar−H), 6.03 (s, 2H, Ar−H), 2.84−2.79 (m, 2H, Ar−CH_2CH_3), 1.34 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.4 (C), 148.5 (2 × C), 148.2 (C), 146.5 (C), 144.8 (C), 126.8 (CH), 124.7 (C), 124.2 (CH), 116.9 (CH), 114.5 (CH), 109.6 (CH), 107.2 (CH), 100.6 (CH_2), 27.6 (Ar−CH_2CH_3), 13.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{16}H_{13}N_3O_4H^+$, 312.0979; found, m/z 312.0976.

*7-Ethyl-2-(4-fluorophenyl)-3-nitroimidazo[1,2-a]pyridine (**3e′**).* Yellow solid, 82% (70 mg, 0.3 mmol scale, electrochemistry), 79% (68 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 89:11; mp = 145−147 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, 1H, J = 7.2 Hz, Ar−H), 7.95−7.92 (m, 2H, Ar−H), 7.61 (s, 1H, Ar−H), 7.23−7.13 (m, 3H, Ar−H), 2.87−2.82 (m, 2H, Ar−CH_2CH_3), 1.38−1.34 (m, 3H, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 164.1 (d, J^1_{C-F} = 249 Hz, C), 149.3 (2 × C), 132.4 (d, J^3_{C-F} = 8 Hz, 2 × CH), 127.8 (CH), 127.1 (C), 119.0 (C), 118.1 (CH), 116.2 (C), 115.7 (CH), 115.5 (CH), 115.3 (CH), 28.7 (Ar−CH_2CH_3), 14.2 (Ar−CH_2CH_3)ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −110.17 ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}FN_3O_2H^+$, 286.0986; found, m/z 286.0966.

*2-(4-Chlorophenyl)-7-ethyl-3-nitroimidazo[1,2-a]pyridine (**3f′**).* Reddish gray solid; yield: 75% (68 mg, 0.3 mmol scale, electrochemistry); yield: 72% (65 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 115−117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.37 (d, 1H, J = 7.2 Hz, Ar−H), 7.85 (d, 2H, J = 8.4 Hz, Ar−H), 7.59 (s, 1H, Ar−H), 7.45 (d, 1H, J = 7.6 Hz, Ar−H), 7.15−7.12 (m, 1H, Ar−H), 2.83 (q, 2H, J = 7.6 Hz, Ar−CH_2CH_3, Ar−H), 1.34 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3, Ar−H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.4 (2 × C), 145.8 (C), 136.4 (C), 131.9 (CH), 131.6 (CH), 130.5 (2 × C), 129.2 (CH), 128.5 (CH), 127.7 (CH), 118.2 (CH), 115.7 (CH), 28.6 (Ar−CH_2CH_3), 14.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}ClN_3O_2H^+$, 302.0691; found, m/z 302.0679.

*2-(4-Bromophenyl)-7-ethyl-3-nitroimidazo[1,2-a]pyridine (**3g′**).* Orangish brown solid; 75% (78 mg, 0.3 mmol scale, electrochemistry); yield: 70% (73 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 92:8; mp = 105−107 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.36 (d, 1H, J = 7.2 Hz, Ar−H), 7.78 (d, 2H, J = 8.4 Hz, Ar−H), 7.61 (d, 3H, J = 8.8 Hz, Ar−H), 7.13 (dd, 1H, J = 8.0 Hz, J = 7.2 Hz, Ar−H), 2.83 (q, 2H, J = 7.6 Hz, Ar−CH_2CH_3), 1.36−1.32 (m, 3H, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.4 (2 × C), 145.9 (C), 132.2 (C), 131.8 (2 × CH), 131.4 (2 × CH), 130.9 (C), 127.7 (CH), 124.9 (C), 118.2 (CH), 115.7 (CH), 28.6 (Ar−CH_2CH_3), 14.1 (Ar−CH_2CH_3) ppm. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}BrN_3O_2H^+$, 346.0186; found, m/z 346.0173.

*7-Ethyl-3-nitro-2-(4-nitrophenyl)imidazo[1,2-a]pyridine (**3h′**).* Gray amorphous powder, yield: 69% (65 mg, 0.3 mmol scale, electrochemistry); yield: 66% (62 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 172−174 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.40 (d, 1H, J = 7.2 Hz, Ar−H), 8.35 (d, 2H, J = 7.2 Hz, Ar−H), 8.08 (d, 2H, J = 8.8 Hz, Ar−H), 7.65 (s, 1H, Ar−H) 7.21−7.19 (m, 1H, Ar−H), 2.89−2.84 (m, 2H, Ar−CH_2CH_3), 1.37 (t, 3H, J = 7.6 Hz, Ar−CH_2CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.7 (C), 147.9 (C), 131.3 (2 × CH), 127.9 (C), 127.6 (C), 124.3 (CH), 123.4 (2 × CH), 121.6 (C), 118.8 (CH), 116.0 (CH), 115.5 (C), 28.7 (Ar−CH_2CH_3), 14.1 (Ar−CH_2CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_4O_4H^+$, 313.0931; found, m/z 313.0922.

*7-Ethyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-a]pyridine (**3i′**).* Brown solid; yield: 81% (77 mg, 0.3 mmol scale, electrochemistry); yield: 79% (75 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 82−84 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.47 (d, 1H, J = 7.2 Hz, Ar−H), 8.00 (d, 1H, J =

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8.0 Hz, Ar−H), 7.94 (d, 1H, J = 7.2 Hz, Ar−H), 7.72−7.68 (m, 3H, Ar−H), 7.61−7.56 (m, 1H, Ar−H), 7.53−7.49 (m, 1H, Ar−H), 7.46−7.42 (m, 1H, Ar−H), 7.21−7.19 (m, 1H, Ar−H), 2.87 (q, 2H, J = 7.6 Hz, Ar−CH_2CH$_3$), 1.38 (t, 3H, J = 7.6 Hz, Ar−CH$_2$$CH_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 149.7 (*C*), 149.2 (2 × *C*), 145.9 (*C*), 133.5 (*C*), 131.3 (*C*), 130.3 (*C*H), 130.2 (*C*), 128.7 (*C*H), 128.3 (*C*H), 127.5 (*C*H), 126.9 (*C*H), 126.2 (*C*H), 125.1 (*C*H), 125.0 (*C*H), 118.2 (*C*H), 115.8 (*C*H), 28.7 (Ar−CH_2CH$_3$), 14.2 (Ar−CH$_2$$CH_3$) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{15}N_3O_2H^+$, 318.1237; found, m/z 318.1225.

*7-Ethyl-2-(naphthalen-1-yl)-3-nitroimidazo[1,2-a]pyridine (**3j′**).* Yellowish brown solid; yield: 75% (71 mg, 0.3 mmol scale, electrochemistry), yield: 72% (69 mg, 0.3 mmol scale, mechanochemistry); eluent used for flash column was hexane/EtOAc 88:12; mp = 91−93 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.41 (d, 1H, J = 7.2 Hz, Ar−H), 8.46 (s, 1H, Ar−H), 7.98−7.93 (m, 3H, Ar−H), 7.89 (d, 1H, J = 7.6 Hz, Ar−H), 7.64 (s, 1H, Ar−H), 7.56−7.52 (m, 2H, Ar−H), 7.14−7.12 (m, 1H, Ar−H), 2.83 (q, 2H, J = 7.6 Hz, Ar−CH_2CH$_3$), 1.35 (t, 3H, J = 7.6 Hz, Ar−CH$_2$$CH_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 155.9 (*C*), 150.8 (*C*), 149.3 (*C*), 145.9 (*C*), 134.1 (*C*), 132.9 (*C*), 130.4 (*C*H), 129.4 (*C*), 129.0 (*C*H), 127.8 (*C*H), 127.7 (2 × *C*H), 127.4 (*C*H), 126.9 (*C*H), 126.5 (*C*H), 118.1 (*C*H), 115.7 (*C*H), 28.6 (Ar−CH_2CH$_3$), 14.1 (Ar−CH$_2$$CH_3$) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{15}N_3O_2H^+$, 318.1237; found, m/z 318.1230.

*2-Phenylimidazo[1,2-a]pyridin-3-amine (**12a**).* Brown solid; yield: 96% (40 mg, 0.2 mmol scale); mp = 100−102 °C. ^1H NMR (400 MHz, $CDCl_3$): d = 7.99−7.95 (m, 3H, Ar−H), 7.53 (d, 1H, J = 8.8 Hz, Ar−H), 7.45 (t, 2H, J = 7.6 Hz, Ar−H), 7.33−7.29 (m, 1H, Ar−H), 7.12−7.08 (m, 1H, Ar−H), 6.79 (t, 1H, J = 6.8 Hz, Ar−H), 3.43 (s, 2H, Ar−NH_2) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.0 (*C*), 134.4 (2 × *C*), 128.9 (2 × *C*H), 127.3 (*C*H), 127.2 (2 × *C*H), 123.5 (*C*H), 122.8 (*C*), 121.9 (*C*H), 117.4 (*C*H), 111.9 (*C*H) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{13}H_{11}N_3H^+$, 210.1026; found, m/z 210.1007.

*2-(3-Chlorophenyl)-8-methylimidazo[1,2-a]pyridin-3-amine (**12l**).* Brown semisolid; yield: 91% (47 mg, 0.2 mmol scale). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1H, Ar−H), 7.89−7.85 (m, 2H, Ar−H), 7.37−7.33 (m, 2H, Ar−H), 6.94 (d, 1H, J = 6.8 Hz, Ar−H), 6.76 (t, 1H, J = 6.8 Hz, Ar−H), 3.47 (s, 2H, Ar−NH_2), 2.60 (s, 3H, Ar−CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.7 (*C*), 135.4 (*C*), 134.7 (2 × *C*), 129.9 (*C*H), 127.4 (*C*), 127.3 (*C*H), 126.9 (*C*), 125.5 (*C*H), 123.9 (*C*H), 120.2 (*C*H), 113.1 (*C*H), 112.8 (*C*H), 16.9 (Ar−CH_3) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{14}H_{12}ClN_3H^+$, 258.0793; found, m/z 258.0780.

*2-(4-Bromophenyl)-7-ethylimidazo[1,2-a]pyridin-3-amine (**12g′**).* Yellow solid; yield: 92% (58 mg, 0.2 mmol scale); mp = 134−136 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94−7.86 (m, 3H, J = 7.2 Hz, Ar−H), 7.52 (d, 1H, J = 7.2 Hz, Ar−H), 7.29−7.26 (m, 2H, Ar−H), 6.68 (d, 1H, J = 5.2 Hz, Ar−H), 3.35 (s, 1H, Ar−NH_2), 2.70−2.65 (m, 2H, Ar−CH_2CH$_3$), 1.25 (s, 3H, Ar−CH$_2$$CH_3$) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.4 (*C*), 133.3 (*C*), 131.8 (*C*H), 129.9 (*C*), 128.8 (*C*H), 128.6 (*C*H), 127.3 (*C*), 127.2 (*C*H), 122.3 (*C*), 121.5 (*C*H), 114.2 (*C*H), 114.0 (*C*), 113.9 (*C*H), 28.5 (Ar−CH_2CH$_3$), 14.5 (Ar−CH$_2$$CH_3$) ppm. HRMS (ESI−TOF): m/z $[M + H]^+$ calcd for $C_{15}H_{14}BrN_3H^+$, 316.0444; found, m/z 316.0424.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00881.

Experimental procedures, compound characterization data for known molecules, and scanned copies of respective ^1H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **3f**, **3q**, **3r**, **3w**, **3a′**, and **3e′**), 2D NMR (for one representative compound, **3u**), and HRMS (all new compounds) spectra for all of the synthesized compounds, along with those of cyclic voltammograms (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a−3z**, **3a′−3j′**, and **12a**, **12l**, and **12g′** (ZIP)

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Notes

The authors declare no competing financial interest.

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Visible-Light-Promoted Intramolecular C−O Bond Formation via C_{sp^3}−H Functionalization: A Straightforward Synthetic Route to Biorelevant Dihydrofuro[3,2-*c*]chromenone Derivatives

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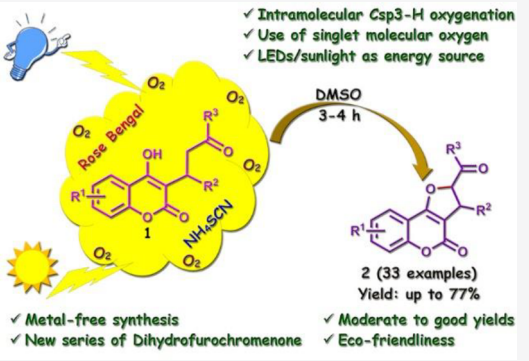
ABSTRACT: A photochemical method for the synthesis of functionalized dihydrofuro[3,2-*c*]chromenones via intramolecular C_{sp^3}−H *cross*-dehydrogenative oxygenation within a warfarin framework has been unearthed. Advantages of this protocol include abundant sunlight or low-energy visible light as the energy source, mild reaction conditions, and avoidance of metal catalysts.



1. INTRODUCTION

In recent times, intramolecular C−O bond formation via direct C−H functionalization has gained much importance in organic synthesis because of several benefits associated with this strategy, including the use of starting materials without their prefunctionalization, reduction in the number of reaction steps, minimization of byproduct formation, clean reaction profiles, and enhanced atom economy.[1] Such a smart strategy opens a new avenue for the straightforward synthesis of *O*-heterocyclic scaffolds finding much importance in medicinal and industrial fields.[2] Although this spectacular research field is developing rapidly,[3] intramolecular *cross*-dehydrogenative C_{sp^3}−O coupling is still limited.[3a−c] As part of our ongoing endeavors in developing green-chemistry-directed protocols for biologically interesting molecules,[4] we were motivated to explore a new synthetic route to furochromenones. This important class of *O*-heterocyclic scaffolds is ubiquitously present in natural and unnatural compounds with potential applications in medicinal, agricultural, and material sciences.[5] To our delight, we have successfully explored a visible-light-promoted protocol for accessing a new series of functionalized dihydrofuro[3,2-*c*]chromenones from warfarin analogues based on intramolecular C−O bond formation via direct C−H functionalization at ambient temperature (Scheme 1). Both blue LEDs and direct sunlight implemented the transformation with equal ease. Rose bengal photocatalyst executed the reaction in association with molecular oxygen as the oxidant. Visible-light-promoted photocatalysis is currently a hot research area in organic synthesis.[6] This strategy has already shown immense potential to successfully perform many organic conversions under mild and green conditions, which may be otherwise nonfeasible. Accordingly, the newly developed protocol also offers several advantages: one-pot and one-step conversion, making good use of sunlight or low-energy visible-light, metal-free synthesis under mild reaction conditions, and eco-friendliness.

Scheme 1. Visible-Light-Induced Intramolecular C_{sp^3}−H *cross*-Dehydrogenative Oxygenation with a Warfarin Framework

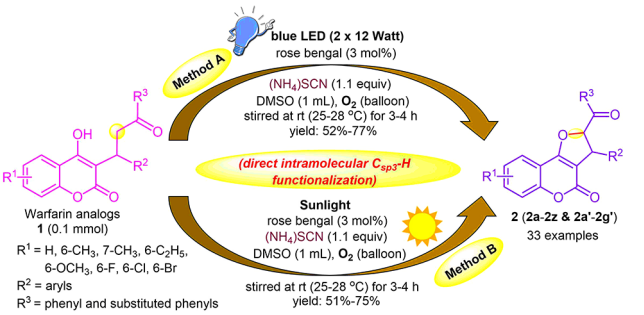


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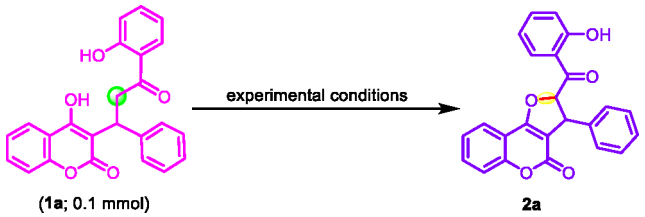
Table 1. Optimization of Reaction Conditions[b]



(1a; 0.1 mmol) 2a

entry	photocatalyst(mol %)	additive	visible light	solvent (1 mL)	time (h)	yield[b,c] (%)
1[d]	RB (3)		white LED	DMSO	12	trace
2[d,e]	RB (3)	ATS	white LED	DMSO	4	55
3[d,e]	–	ATS	white LED	DMSO	12	
4[d,e]	RB (3)	ATS	Dark	DMSO	12	
5[d,e]	**RB (3)**	**ATS**	**blue LED**	**DMSO**	**4**	**63**
6[d,f]	RB (3)	ATS	blue LED	DMSO	4	63
7[e,g]	RB (3)	ATS	blue LED	DMSO	7	52
8[e,h]	RB (3)	ATS	blue LED	DMSO	12	
9[d,e]	RB (3)	ATS	green LED	DMSO	12	23
10[d,e,I]	RB (3)	ATS	sunlight	DMSO	12	
11[d,e,j]	**RB (3)**	**ATS**	**Sunlight**	**DMSO**	**4**	**63**
12[d,e]	RB (5)	ATS	blue LED	DMSO	4	63
13[d,e]	RB (1)	ATS	blue LED	DMSO	5	60
14[d,k]	RB (3)	ATS	blue LED	DMSO	4	63
15[d,e]	RB (3)	KTS	blue LED	DMSO	4	60
16[d,e]	RB (3)	TMTS	blue LED	DMSO	12	
17[d,e]	RB (3)	TBN	blue LED	DMSO	12	
18[d,l]	RB (3)	ATS	blue LED	DMSO	5	57
19[d,e]	EY (3)	ATS	blue LED	DMSO	12	
20[d,e]	EB (3)	ATS	blue LED	DMSO	12	trace
21[d,e]	RHB (3)	ATS	blue LED	DMSO	12	
22[d,e]	FC (3)	ATS	blue LED	DMSO	12	
23[d,e]	RB (3)	ATS	blue LED	DCE	12	trace
24[d,e]	RB (3)	ATS	blue LED	DMF	12	trace
25[d,e]	RB (3)	ATS	blue LED	dioxane	12	
26[d,e]	RB (3)	ATS	blue LED	toluene	12	
27[d,e]	RB (3)	ATS	blue LED	H_2O	12	
28[d,e]	RB (3)	ATS	blue LED	TFE	12	
29[d,e]	Ru-cat (3)	ATS	blue LED	DMSO	12	trace
30[d,e]	IR-cat (3)	ATS	blue LED	DMSO	12	

[a]Ru-cat = $Ru(bpy)_3Cl_2·6H_2O$; Ir-cat = $[Ir(dtbbpy)(ppy)_2]PF_6$; FC = fluorescence; ATS = NH_4SCN; KTS = KSCN; TMTS = TMSCN; TBN = *tert*-butyl nitrite. [b]Reaction conditions: Warfarin analogue **1a** (0.1 mmol) was reacted under the influence of different visible lights and atmospheres using various photocatalysts and additives in the presence of solvent(s) at room temperature (25−28 °C). [c]Isolated yields. [d]Oxygen (balloon). [e]Additive (1.1 equiv). [f]Additive (2.0 equiv). [g]Aerial. [h]N_2 atmosphere. [I]Diffused sunlight. [j]Direct sunlight. [k]Additive (2.0 equiv); [l]Additive (0.5 equiv). White LEDs: 2 × 9 W. Blue LEDs: 2 × 12 W. Green LEDs: 2 × 12 W. RB = rose bengal; EY = eosin Y; EB = eosin B; RhB = rhodamine B.

2. RESULTS AND DISCUSSION

We commenced our investigation with 4-hydroxy-3-(3-(2-hydroxyphenyl)-3-oxo-1-phenylpropyl)-2*H*-chromen-2-one (**1a**) as our model substrate to explore the standard reaction conditions for visible-light-induced intramolecular C_{sp^3}−H *cross*-dehydrogenative oxygenation. For this purpose, we performed a series of trial experiments under the influence of visible lights (*viz*. white LEDs, blue LEDs, green LEDs, and also diffused/direct sunlight) using different organic dyes and metal photocatalysts in varying amounts in an aerial/oxygen (balloon)/nitrogen atmosphere (Table 1, entries 1−30). We also studied the effect of different solvents (*viz*. dimethyl sulfoxide, 1,2-dichloroethane, *N*,*N*-dimethylformamide, 1,4-dioxane, toluene, trifluoroethane, and water) and additives (*viz*. ammonium thiocyanate, potassium thiocyanate, trimethylsilyl cyanide, and *tert*-butyl nitrite). The best result for this transformation was obtained using 3.0 mol % of rose bengal photocatalyst in DMSO in the presence of NH_4SCN (1.1 equiv) as the additive under an O_2 atmosphere (balloon) at an ambient temperature either upon passing light from blue LEDs (2 × 12 W) (Table 1, entry 5; *Method A*) or under direct sunlight (Table 1, entry 11, *Method B*). The target product, 2-(2-hydroxybenzoyl)-3-phenyl-2,3-dihydro-4*H*-furo[3,2-*c*]-chromen-4-one (**2a**), was isolated in 63% yields in both events within an identical time frame of 4 h (Table 1, entries 5 and 11). KSCN also behaved as an effective additive, yielding 60% of the product at 4 h (Table 1, entry 15). As revealed, no product **2a** was observed without use of lights, photocatalysts, or additives (Table 1, entries 1, 3, and 4). Compound **2a** was characterized by its detailed spectral (^{1}H NMR, ^{13}C NMR, DEPT-135, and HRMS) studies (see Experimental Section). Table 1 summarizes the overall results.

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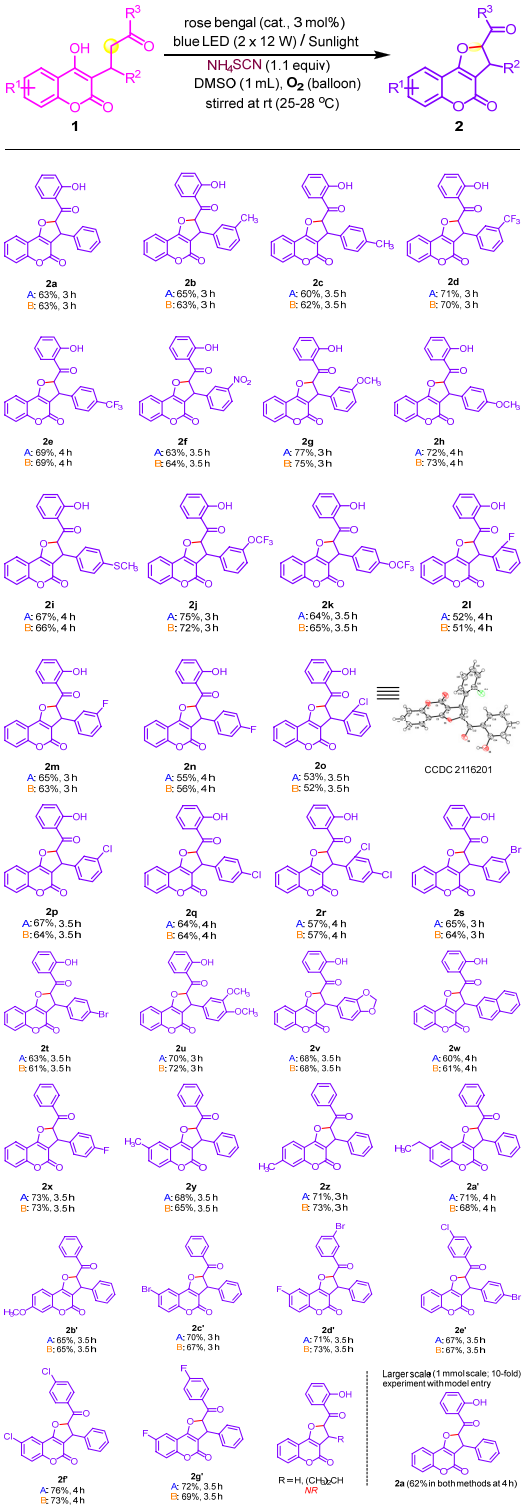
Once we optimized the standard reaction conditions for the photochemical *cross*-dehydrogenative cyclization of warfarin derivatives, the feasibility, as well as the applicability of this protocol, was examined by performing a set of five reactions with 4-hydroxy-3-(3-(2-hydroxyphenyl)-3-oxo-1-(*m*-tolyl)-propyl)-2*H*-chromen-2-one (**1b**), 4-hydroxy-3-(3-(2-hydroxyphenyl)-3-oxo-1-(*p*-tolyl)propyl)-2*H*-chromen-2-one (**1c**), 4-hydroxy-3-(3-(2-hydroxyphenyl)-3-oxo-1-(3-(trifluoromethyl)-phenyl)propyl)-2*H*-chromen-2-one (**1d**), 4-hydroxy-3-(3-(2-hydroxyphenyl)-3-oxo-1-(4-(trifluoromethyl)phenyl)propyl)-2*H*-chromen-2-one (**1e**), and 4-hydroxy-3-(3-(2-hydroxyphenyl)-1-(3-nitrophenyl)-3-oxopropyl)-2*H*-chromen-2-one (**1f**) under optimized conditions using both light sources, blue LEDs (*Method A*) and direct sunlight (*Method B*). All the reactions took place efficiently, giving rise to the desired dihydrofuro[3,2-*c*]chromenones **2b**−**2f** with respective yields of 65%, 60%, 71%, 69%, and 63% upon irradiation with blue LEDs (Method A) and with 63%, 62%, 70%, 69%, and 64% yields, respectively, under direct sunlight (Method B), within 3−4 h (Table 2, compounds **2b**−**2f**). We then carried out another set of five reactions with 4-hydroxy-3-(3-(2-hydroxyphenyl)-1-(3-methoxyphenyl)-3-oxopropyl)-2*H*-chromen-2-one (**1g**), 4-hydroxy-3-(3-(2-hydroxyphenyl)-1-(4-methoxyphenyl)-3-oxopropyl)-2*H*-chromen-2-one (**1h**), 4-hydroxy-3-(3-(2-hydroxyphenyl)-1-(4-(methylthio)phenyl)-3-oxopropyl)-2*H*-chromen-2-one (**1i**), 4-hydroxy-3-(3-(2-hydroxyphenyl)-3-oxo-1-(3-(trifluoromethoxy)phenyl)propyl)-2*H*-chromen-2-one (**1j**), and 4-hydroxy-3-(3-(2-hydroxyphenyl)-3-oxo-1-(4-(trifluoromethoxy)phenyl)propyl)-2*H*-chromen-2-one (**1k**) under both methods, and with all the cases, the target products **2g**−**2k** were isolated with respective yields of 77%, 72%, 67%, 75%, and 64% with Method A (blue LED) and with respective yields of 75%, 73%, 66%, 72%, and 65% Method B (sunlight) within 3−4 h.

Encouraged by these results, we then extended the scope of the reaction with another set of 13 more warfarin analogues (**1l**−**1x**) containing varying substituents (*viz*. Br, Cl, F, di-Cl, di-OCH_3, 3,4-methylenedioxyphneyl, and 2-naphthyl). To our delight, all these substrates afforded the desired products **2l**−**2x** with moderate to good yields ranging from 51% to 73% within a reasonable time frame of 3−4 h with both Methods A and B (Table 2, compounds **2l**−**2x**). The substrate scope was further elaborated by synthesizing a set of 9 warfarin derivatives **1y**−**1z** and **1a′**−**1g′**, bearing both electron-donating and electron-withdrawing substituents in the coumarin part and also in the benzoyl ring of the substrate molecules (see the Experimental Section). All these warfarin derivatives underwent the transformation very smoothly under either blue light irradiation or direct sunlight, affording the dihydrofuro[3,2-*c*]chromenones **2y**−**2z** and **2a′**−**2g′**, with good yields ranging from 65% to 76%, within the same time frame (Table 2, compounds **2y**−**2z** and **2a′**−**2g′**). However, it was observed that warfarin analogues with a C-3 side chain being unsubstituted or substituted with an alkyl group at C-1 do not undergo the reaction using either method. Table 2 summarizes all these experimental outcomes.

Column chromatographic purification (see Experimental Section) was required to purify all the synthesized products **2a**−**2z** and **2a′**−**2g′**. All are new compounds and were fully characterized based on their detailed spectral studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **2d**, **2e**, **2j**−**2n**, **2d′**, and **2g′**), 2D-NMR (for **2v**), and HRMS. The structural framework received further confirmation from the single-crystal X-ray analysis for a representative entry, 3-(2-chlorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4*H*-furo[3,2-

Table 2. Photochemical Synthesis of Functionalized Dihydrofuro[3,2-*c*]chromenones (2)



[a]Reaction conditions: warfarin derivatives (**1**; 0.1 mmol) in the presence of NH_4SCN (0.11 mmol) dissolved in 1 mL of DMSO under the influence of visible light (blue LED; 2 × 12 W; Method A)/direct sunlight (Method B) using rose bengal (3 mol %) as a photocatalyst in an oxygen atmosphere (in a balloon) at ambient temperature (25−28 °C). [b]Isolated yields. NR: No reaction.

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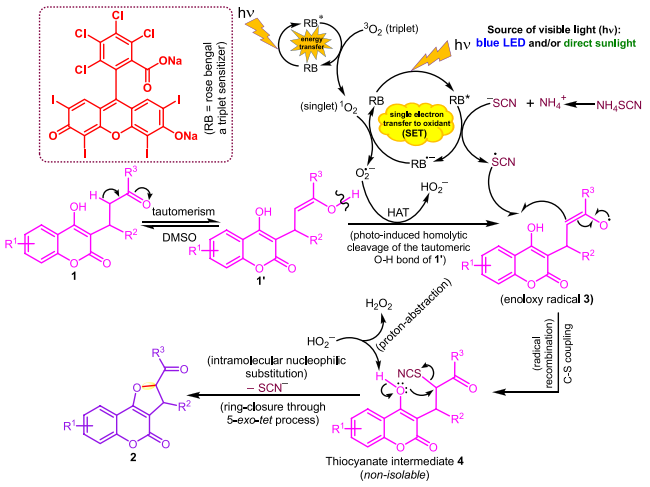
c]chromen-4-one (**2o**; CCDC 2116201) (see Supporting Information). The X-ray analysis indicates a *trans*-fusion at the C_2,C_3 junction; however, enantioselectivity has not been attained, and we isolated all products as racemic mixtures of (2*R*,3*R*)- and (2*S*,3*S*)-isomers under the present reaction conditions. Furthermore, we carried out the model reaction on a somewhat larger scale (1.0 mmol; 10-fold) that proceeded smoothly (both Methods A and B) with similar yields and time to those of the submillimolar scale (see Experimental Section).

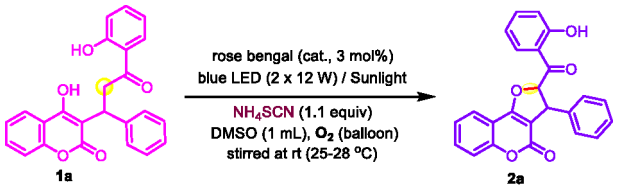
We herein propose a plausible mechanism for this photochemical transformation in Scheme 2. Upon irradiation

Scheme 2. Proposed Mechanism



with blue light/direct sunlight, one molecule of activated rose bengal (RB*) photosensitizer[7] takes part in generating singlet oxygen ($^1O_2$) from its triplet state ($^3O_2$),[8] and another molecule snatches an electron from the thiocyanate ion (SCN^-), thereby giving rise to the photocatalyst radical anion ($RB^{\bullet-}$)[9] and thiocyanate radical (SCN).[10] The photocatalyst radical anion gives up its extra electron to singlet oxygen through the SET process and enters the catalytic cycle, forming a peroxide radical anion ($O_2^{\bullet-}$)[11] that snatches hydrogen radical from the tautomeric O–H bond of **1′** through the HAT process when an enoloxy radical **3** and a hydroperoxide (HO_2^-) ion are formed. Next, a thiocyanate intermediate **4** (nonisolable) is produced via C–S coupling between the radicals **3** and thiocyanate (SCN). The C_4-hydroxy proton within **4** is then abstracted by the hydroperoxide (HO_2^-) ion to form H_2O_2 (detected by KI/starch color reaction),[12] and the *in situ* generated enolate undergoes an intramolecular nucleophilic substitution reaction, removing the thiocyanate ion and thereby yielding the desired *O*-heterocycle **2** via the thermodynamically feasible 5-*exo*-*tet* process. In support of our mechanistic proposition, we conducted a set of control experiments (Scheme 3) with our model reaction in the presence of radical-trapping reagents such as TEMPO, *p*-benzoquinone (BQ), and DDQ. Each of them inhibited the transformation, which indicates the involvement of a radical pathway. The reaction is also deterred by DABCO (Scheme 3), a well-known singlet oxygen quencher,[13] which supports the generation of *in situ* generated singlet oxygen in the process.

Scheme 3. Control Experiments



Radical scavenger	Isolated yield
no scavenger	63%
TEMPO (0.5, 1.0, and 2.0 equiv.)	39%, 23%, 0%
p-Benzoquinone (BQ) (0.25, 0.5, and 1.0 equiv.)	44%, 21%, 0%
DDQ (1.0 and 2.0 equiv)	26%, 0%
DABCO (1.5 and 3.0 equiv)	36%, 0%

3. CONCLUSIONS

In conclusion, a facile and straightforward synthetic route for accessing a new series of biorelevant dihydrofuro[3,2-*c*]-chromenones has been designed via visible light (blue LED/direct sunlight)-induced photocatalytic intramolecular C_{sp^3}–H *cross*-dehydrogenative oxygenation within the warfarin framework at ambient temperature. The use of abundant sunlight or a low-energy visible-light source, energy-efficient mild reaction conditions, metal-free synthesis, low-cost and nontoxic rose bengal as a photosensitizer, moderate-to-good yields, and eco-friendliness are the notable advantages of this method.

4. EXPERIMENTAL SECTION

4.1. General. All fine chemicals and photocatalysts (analytical grade) except starting warfarin analogues were purchased from reputed companies and used without further purification. Warfarin derivatives **1a**–**1w** used as substrates in this study were synthesized as per our previously reported method.[14] The remaining warfarin derivatives **1x**–**1z** and **1a′**–**1g′** were prepared following the protocol reported by Talhi et al.[15] ^{1}H, ^{13}C, and ^{19}F NMR spectra were collected at 400, 100, and 376 MHz, respectively, on a Bruker DRX spectrometer using $CDCl_3$ as the solvent. ^{1}H and ^{13}C NMR chemical shifts were reported in δ (ppm), relative to the internal standard, TMS. The observed ^{19}F NMR chemicals shifts were not calibrated using a reference standard. The signals observed are described as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants are reported as *J* values in Hz. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Mass spectrometry was obtained using a Bruker maXis Impact (Q-TOF) high-resolution mass spectrometer. X-ray single crystallographic data were collected on an X'CaliburCCD area-detector diffractometer. The melting points were recorded on a Chemiline CL-725 melting point apparatus and are uncorrected. TLC was performed using silica gel 60 F_{254} (Merck) plates. Sparc Light 12 W Blue LEDs (manufacturer, Sparc Light; part number, G Light-02-BLU_12W; luminous, 3000 Lumen; color temperature, 3000 K) were used for the light source. For accessing direct sunlight, all reactions were carried out on an open rooftop (Chemistry Building).

4.2. General Procedure for the Synthesis of Dihydrofuro-[3,2-*c*]chromenone Derivatives (2). An oven-dried tripod standard-joint glass vessel was charged with warfarin analogues (**1**; 0.1 mmol), ammonium thiocyanate (0.11 mmol, 9.0 mg), rose bengal photocatalyst (3.0 mol %, 3 mg), DMSO (1 mL), and a magnetic stir bar sequentially. Oxygen (O_2) was bubbled through the reaction mixture for about 10 s, and the reaction vessel was then capped with a stopper having a vertical channel fitted with an O_2 balloon. This reaction system was then placed under the influence of blue LEDs (2 × 12 W) within a specially designed wooden box. Afterward, the reaction mixture then started to stir at room temperature for a stipulated time frame (3–4 h) with occasional TLC monitoring to judge the progress of the reaction. On completion of the reaction, 20 mL of EtOAc-H_2O (3:1 v/v) was added to the resulting mixture and shaken well in a separating funnel. The organic layer was separated,

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dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to obtain a white crude mass, which was finally purified with the help of column chromatography using mixtures of EtOAc-hexane as eluents, to furnish pure products, dihydrofuro[3,2-*c*]chromenones **2** (**2a**−**2z** and **2a′**−**2g′**). Each set of reactions (entries **2a**−**2z** and **2a′**−**2g′**) were also performed similarly, replacing the blue light source with direct sunlight on the rooftop of our chemistry building, thereby isolating desired products **2** with almost identical yields and within the same time frame (3−4 h). The structures of the isolated compounds were confirmed by spectral studies, including ^{1}H NMR, ^{13}C NMR, DEPT-135 NMR, ^{19}F NMR (for **2d**, **2e**, **2j**−**2n**, **2d′**, and **2g′**), 2D NMR (for **2v**), and HRMS. Further structural confirmation was done by single X-ray crystallographic studies with a representative entry, 3-(3-chlorophenyl)-2-(2-hydroxybenzoyl)-2*H*-furo[3,2-*c*]chromen-4(3*H*)-one (**2o**).

The amount of the warfarin analogues **2** used for the 0.1 mM scale reaction: **1a**, 39 mg; **1b**, 40 mg; **1c**, 40 mg; **1d**, 45 mg; **1e**, 45 mg; **1f**, 43 mg; **1g**, 42 mg; **1h**, 42 mg; **1i**, 43 mg; **1j**, 47 mg; **1k**, 47 mg; **1l**, 40 mg; **1m**, 40 mg; **1n**, 40 mg; **1o**, 42 mg; **1p**, 42 mg; **1q**, 42 mg; **1r**, 46 mg; **1s**, 47 mg; **1t**, 47 mg; **1u**, 45 mg; **1v**, 43 mg; **1w**, 44 mg; **1x**, 39 mg; **1y**, 38 mg; **1z**, 38 mg; **1a′**, 40 mg; **1b′**, 40 mg; **1c′**, 45 mg; **1d′**, 47 mg; **1e′**, 48 mg; **1f′**, 44 mg; **1g′**, 41 mg.

4.3. Larger-Scale (1.0 mmol scale) Synthesis of Compound 2a. The starting warfarin derivative **1a** (1.0 mmol, 386 mg), rose bengal photocatalyst (3 mol %, 30 mg), and NH_4SCN (1.1 equiv, 84 mg), and DMSO (4 mL) were placed in a reaction glass vessel, already having a magnetic stir bar, and then capped with a stopper having a vertical channel fitted with an O_2 balloon. One reaction set was placed (2 cm from the light source) under the influence of blue LEDs (2 × 12 W) fitted within the wooden box, and another set was placed in open (direct) sunlight. The reaction mixture in each group was then stirred at ambient temperature to complete the conversion (at 4 h in both cases as monitored by TLC), followed by a workup of the resulting crude product as described in the general method. Upon drying, pure **2a** was isolated in practically identical yields (62%, 238 mg); its physical and spectral properties were found to be identical to those obtained in a 0.1 mmol scale reaction.

4.4. Physical and Spectral Data for All the Synthesized Compounds 2 (2a−2z and 2a′−2g′). *4.4.1. 2-(2-Hydroxybenzoyl)-3-phenyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2a**).* White amorphous powder, yield: 63% (24 mg, blue LEDs; 0.10 mmol scale), 63% (24 mg, sunlight; 0.10 mmol scale), and the eulent used for flash column was hexane/EtOAc 84:16; mp = 220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H, Ar−O*H*), 7.88−7.86 (m, 1H, Ar−H), 7.66−7.61 (m, 1H, Ar−H), 7.58−7.54 (m, 1H, Ar−H), 7.47−7.45 (m, 1H, Ar−H), 7.43−7.39 (m, 3H, Ar−H), 7.37−7.32 (m, 4H, Ar−H), 7.08 (d, 1H, *J* = 8.8 Hz, Ar−H), 6.90−6.86 (m, 1H, Ar−H), 6.21 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.81 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 197.4 (*C*O), 166.5 (lactone *C*O), 163.7 (*C*), 159.3 (*C*), 155.5 (*C*), 139.3 (*C*), 137.8 (*C*H), 133.2 (*C*H), 129.8 (*C*H), 129.5 (2 × *C*H), 128.5 (*C*H), 127.7 (2 × *C*H), 124.4 (*C*H), 123.3 (*C*H), 119.5 (*C*H), 119.3 (*C*H), 117.2 (*C*H), 116.3 (*C*), 112.1 (*C*), 105.5 (*C*), 91.6 (ArCOCH<), 50.2 (ArCH<) ppm. HRMS (ESI): *m*/*z* 385.1071 [M + H]$^+$ calcd for $C_{24}H_{16}O_5H$, found *m*/*z* 385.1076; *m*/*z* 407.0890 [M + Na]$^+$ calcd for $C_{24}H_{16}O_5Na$, found *m*/*z* 407.0898; *m*/*z* 423.0629 [M + K]$^+$ calcd for $C_{24}H_{16}O_5K$, found *m*/*z* 423.0638.

*4.4.2. 2-(2-Hydroxybenzoyl)-3-(m-tolyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2b**).* White amorphous powder; yield: 65% (26 mg, blue LEDs, 0.10 mmol scale), 63% (25 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H, Ar−O*H*), 7.88−7.86 (m, 1H, Ar−H), 7.65−7.61 (m, 1H, Ar−H), 7.58−7.54 (m, 1H, Ar−H), 7.48−7.46 (m, 1H, Ar−H), 7.42 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.38 (t, 1H, *J* = 7.6 Hz, Ar−H), 7.29 (d, 1H, *J* = 7.6 Hz, Ar−H), 7.16 (d, 1H, *J* = 7.6 Hz, Ar−H), 7.13−7.07 (m, 3H, Ar−H), 7.89−7.86 (m, 1H, Ar−H), 6.19 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.76 (d, 1H, *J* = 4.8 Hz, ArC*H*<), 2.35 (s, 3H, Ar−CH_3) ppm. ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 197.5 (*C*O), 166.5 (lactone *C*O), 163.8 (*C*), 159.3 (*C*), 155.6 (*C*), 139.3 (*C*), 139.2 (*C*), 137.8 (*C*H), 133.2 (*C*H), 129.9 (*C*H), 129.4 (*C*H), 129.3 (*C*H), 128.3 (*C*H), 124.9 (*C*H), 124.4 (*C*H), 123.3 (*C*H), 119.5 (*C*H), 119.3 (*C*H), 117.3 (*C*H), 116.3 (*C*), 112.2 (*C*), 105.6 (*C*), 91.7 (ArCOCH<), 50.2 (ArCH<), 21.6 (Ar-CH_3) ppm. HRMS (ESI): *m*/*z* 399.1227 [M + H]$^+$ calcd for $C_{25}H_{18}O_5H$, found *m*/*z* 399.1214; *m*/*z* 421.1046 [M + Na]$^+$ calcd for $C_{25}H_{18}O_5Na$, found *m*/*z* 421.1033; *m*/*z* 437.0786 [M + K]$^+$ calcd for $C_{25}H_{18}O_5K$, found *m*/*z* 437.0773.

*4.4.3. 2-(2-Hydroxybenzoyl)-3-(p-tolyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2c**).* White amorphous powder; yield: 60% (24 mg, blue LEDs, 0.10 mmol scale), 62% (25 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.58 (s, 1H, Ar−O*H*), 7.79−7.76 (m, 1H, Ar−H), 7.56−7.44 (m, 2H, Ar−H), 7.38−7.26 (m, 3H, Ar−H), 7.17−7.09 (m, 4H, Ar−H), 6.98 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.81−6.77 (m, 1H, Ar−H), 6.09 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.66 (d, 1H, *J* = 4.8 Hz, ArC*H*<), 2.27 (s, 3H, Ar−CH_3) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 197.5 (*C*O), 166.4 (lactone *C*O), 163.7 (*C*), 159.3 (*C*), 155.5 (*C*), 138.3 (*C*), 137.7 (*C*H), 136.27 (*C*), 133.1 (*C*H), 130.2 (2 × *C*H), 129.8 (*C*H), 127.6 (2 × *C*H), 124.4 (*C*H), 123.3 (*C*H), 119.5 (*C*H), 119.3 (*C*H), 117.3 (*C*H), 116.3 (*C*), 112.2 (*C*), 105.7 (*C*), 91.7 (ArCOCH<), 50.1 (ArCH<), 21.3 (Ar-CH_3) ppm. HRMS (ESI): *m*/*z* 399.1227 [M + H]$^+$calcd for $C_{25}H_{18}O_5H$, found *m*/*z* 399.1240; *m*/*z* 421.1046 [M + Na]$^+$ calcd for $C_{25}H_{18}O_5Na$, found *m*/*z* 421.1063; *m*/*z* 437.0786 [M + K]$^+$ calcd for $C_{25}H_{18}O_5K$, found *m*/*z* 437.0802.

*4.4.4. 2-(2-Hydroxybenzoyl)-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2d**).* White amorphous powder; yield: 71% (32 mg, blue LEDs, 0.10 mmol scale), 70% (31 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 85:15; mp = 187 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.60 (s, 1H, Ar−O*H*), 7.87−7.85 (m, 1H, Ar−H), 7.68−7.62 (m, 2H, Ar−H), 7.60−7.53 (m, 4H, Ar−H), 7.48 (dd, 1H, *J* = 9.6 and 1.2 Hz, Ar−H), 7.43 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.41−6.37 (m, 1H, Ar−H), 7.09 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.92−6.88 (m, 1H, Ar−H), 6.16 (d, 1H, *J* = 5.2 Hz, ArCOC*H*<), 4.97 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 196.7 (*C*O), 166.9 (lactone *C*O), 163.9 (*C*), 159.1 (*C*), 155.7 (*C*), 140.3 (*C*), 138.1 (*C*H), 133.5 (*C*H), 131.4 (*C*H), 129.9 (d, J_{CF} = 35 Hz, *C*H), 125.5 (*C*H), 125.4 (*C*H), 124.6 (*C*H), 124.5 (*C*H and CF_3), 124.4 (*C*H), 123.4 (*C*H), 119.5 (d, J_{CF} = 15 Hz, *C*H), 117.4 (*C*H), 116.4 (*C*), 111.9 (*C*), 104.7 (*C*), 91.3 (ArCOCH<), 49.5 (ArCH<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.6 ppm. HRMS (ESI): *m*/*z* 453.0944 [M + H]$^+$ calcd for $C_{25}H_{15}F_3O_5H$, found *m*/*z* 453.0950; *m*/*z* 475.0764 [M + Na]$^+$ calcd for $C_{25}H_{15}F_3O_5Na$, found *m*/*z* 475.0776; *m*/*z* 491.0503 [M + K]$^+$ calcd for $C_{25}H_{15}F_3O_5K$, found *m*/*z* 491.0514.

*4.4.5. 2-(2-Hydroxybenzoyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2e**).* White amorphous powder; yield: 69% (31 mg, blue LEDs, 0.10 mmol scale), 69% (31 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 85:15; mp = 215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.60 (s, 1H, Ar−O*H*), 7.86−7.84 (m, 1H, Ar−H), 7.67−7.63 (m, 3H, Ar−H), 7.60−7.56 (m, 1H, Ar−H), 7.47 (d, 3H, *J* = 7.6 Hz, Ar−H), 7.43−7.39 (m, 1H, Ar−H), 7.38−7.36 (m, 1H, Ar−H), 7.08 (dd, 1H, *J* = 8.4 and 0.8 Hz, Ar−H), 6.93−6.89 (m, 1H, Ar−H), 6.19−6.18 (m, 1H, ArCOC*H*<), 4.95−4.94 (m, 1H, ArC*H*<) ppm. ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 196.7 (*C*O), 166.8 (lactone *C*O), 163.9 (2 × *C*), 159.2 (*C*), 155.6 (*C*), 143.2 (*C*), 138.0 (*C*H), 133.5 (*C*H), 129.6 (*C*H), 128.2 (2 × *C*H), 126.6 (*C*H), 126.5 (*C*H), 126.5 (CF_3), 124.6 (*C*H), 123.32 (*C*H), 119.7 (*C*H), 119.5 (*C*H), 117.4 (*C*H), 116.3 (*C*), 111.9 (*C*), 104.9 (*C*), 91.2 (ArCOCH<), 49.5 (ArCH<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.6 ppm. HRMS (ESI): *m*/*z* 453.0944 [M + H]$^+$ calcd for $C_{25}H_{15}F_3O_5H$, found *m*/*z* 453.0961; *m*/*z* 475.0764 [M + Na]$^+$ calcd for $C_{25}H_{15}F_3O_5Na$, found *m*/*z* 475.0780; *m*/*z* 491.0503 [M + K]$^+$ calcd for $C_{25}H_{15}F_3O_5K$, found *m*/*z* 491.0518.

*4.4.6. 2-(2-Hydroxybenzoyl)-3-(3-nitrophenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2f**).* White amorphous powder; yield: 63% (27 mg, blue LEDs, 0.10 mmol scale), 64% (27 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 217 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.57 (s, 1H, Ar−O*H*), 8.23−8.19 (m, 2H, Ar−H), 7.85 (dd, 1H, *J* = 8.0 and 1.2

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Hz, Ar−H), 7.70 (d, 1H, J = 7.6 Hz, Ar−H), 7.68−7.64 (m, 1H, Ar−H), 7.61−7.57 (m, 2H, Ar−H), 7.55−7.53 (m, 1H, Ar−H), 7.42 (d, 1H, J = 8.4 Hz, Ar−H), 7.39 (t, 1H, J = 7.6 Hz, Ar−H), 7.09 (d, 1H, J = 8.0 Hz, Ar−H), 6.94−6.90 (m, 1H, Ar−H), 6.19 (d, 1H, J = 5.2 Hz, ArCOC*H*<), 5.09 (d, 1H, J = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 196.2 (*C*O), 166.9 (lactone *C*O), 163.9 (*C*), 159.1 (*C*), 155.6 (*C*), 149.0 (*C*), 141.3 (*C*), 138.2 (*C*H), 134.3 (*C*H), 133.7 (*C*H), 130.5 (*C*H), 129.7 (*C*H), 124.6 (*C*H), 123.6 (*C*H), 123.4 (*C*H), 122.6 (*C*H), 119.7 (*C*H), 119.5 (*C*H), 117.4 (*C*H), 116.4 (*C*), 111.8 (*C*), 104.5 (*C*), 91.1 (ArCOCH<), 48.9 (ArCH<) ppm. HRMS (ESI): m/z 430.0921 $[M + H]^+$ calcd for $C_{24}H_{15}NO_7H$, found m/z 430.0925; m/z 452.0741 $[M + Na]^+$ calcd for $C_{24}H_{15}NO_7Na$, found m/z 452.0744; m/z 468.0480 $[M + K]^+$ calcd for $C_{24}H_{15}NO_7K$, found m/z 468.0481.

*4.4.7. 2-(2-Hydroxybenzoyl)-3-(3-methoxyphenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2g**).* White amorphous powder; yield: 77% (32 mg, blue LEDs, 0.10 mmol scale), 75% (31 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 86:14; mp = 211 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H, Ar−O*H*), 7.87−7.84 (m, 1H, Ar−H), 7.65−7.61 (m, 1H, Ar−H), 7.58−7.54 (m, 1H, Ar−H), 7.50−7.48 (m, 1H, Ar−H), 7.41 (d, 1H, J = 8.0 Hz, Ar−H), 7.39−7.35 (m, 1H, Ar−H), 7.34−7.29 (m, 1H, Ar−H), 7.09−7.07 (m, 1H, Ar−H), 6.92−6.84 (m, 4H, Ar−H), 6.20 (d, 1H, J = 4.8 Hz, ArCOC*H*<), 4.77 (d, 1H, J = 4.8 Hz, ArC*H*<), 3.79 (s, 3H, Ar−OCH_3) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 197.4 (*C*O), 166.6 (lactone *C*O), 163.8 (*C*), 160. (*C*), 155.6 (*C*), 140.8 (*C*), 137.8 (*C*H), 136.3 (*C*), 133.2 (*C*H), 130.6 (*C*H), 129.9 (*C*H), 124.4 (*C*H), 123.3 (*C*H), 119.9 (*C*H), 119.5 (*C*H), 119.4 (*C*H), 117.3 (*C*H), 116.3 (*C*), 113.8 (*C*H), 113.6 (*C*H), 112.2 (*C*), 105.4 (*C*), 91.5 (ArCOCH<), 55.5 (Ar−OCH_3), 50.2 (ArCH<) ppm. HRMS (ESI): m/z 437.0996 $[M + Na]^+$ calcd for $C_{25}H_{18}O_6Na$, found m/z 437.1008; m/z 453.0735 $[M + K]^+$ calcd for $C_{25}H_{18}O_6K$, found m/z 453.0745.

*4.4.8. 2-(2-Hydroxybenzoyl)-3-(4-methoxyphenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2h**).* White amorphous powder; yield: 72% (30 mg, blue LEDs, 0.10 mmol scale), 73% (30 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 86:14; mp = 192 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.69 (s, 1H, Ar−O*H*), 7.89−7.88 (m, 1H, Ar−H), 7.67−7.63 (m, 1H, Ar−H), 7.60−7.56 (m, 1H, Ar−H), 7.49−7.47 (m, 1H, Ar−H), 7.43 (d, 1H, J = 8.4 Hz, Ar−H), 7.41−7.37 (m, 1H, Ar−H), 7.27 (d, 2H, J = 8.8 Hz, Ar−H), 7.09 (d, 1H, J = 8.4 Hz, Ar−H), 6.95 (d, 2H, J = 8.8 Hz, Ar−H), 6.92−6.88 (m, 1H, Ar−H), 6.19 (d, 1H, J = 4.8 Hz, ArCOC*H*<), 4.76 (d, 1H, J = 4.8 Hz, ArC*H*<), 3.84 (s, 3H, Ar−OCH_3) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 197.6 (*C*O), 166.3 (lactone *C*O), 163.7 (*C*), 159.7 (*C*), 159.3 (*C*), 155.5 (*C*), 137.7 (*C*H), 133.1 (*C*H), 131.3 (*C*), 129.6 (*C*H), 128.8 (2 × *C*H), 124.4 (*C*H), 123.2 (*C*H), 119.5 (*C*H), 119.3 (*C*H), 117.2 (*C*H), 116.3 (*C*), 114.9 (2 × *C*H), 112.2 (*C*), 105.6 (*C*), 91.7 (ArCOCH<), 55.5 (Ar−OCH_3), 49.8 (ArCH<) ppm. HRMS (ESI): m/z 437.0996 $[M + Na]^+$ calcd for $C_{25}H_{18}O_6Na$, found m/z 437.0990; m/z 453.0735 $[M + K]^+$ calcd for $C_{25}H_{18}O_6K$, found m/z 453.0727.

*4.4.9. 2-(2-Hydroxybenzoyl)-3-(4-(methylthio)phenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2i**).* White amorphous powder; yield: 67% (29 mg, blue LEDs, 0.10 mmol scale), 66% (28 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 84:16; mp = 226 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H, Ar−O*H*), 7.88−7.86 (m, 1H, Ar−H), 7.66−7.62 (m, 1H, Ar−H), 7.59−7.55 (m, 1H, Ar−H), 7.46 (dd, 1H, J = 8.0 and 1.6 Hz, Ar−H), 7.42 (d, 1H, J = 8.0 Hz, Ar−H), 7.39−7.36 (m, 1H, Ar−H), 7.29−7.24 (m, 4H, Ar−H), 7.08 (d, 1H, J = 8.4 Hz, Ar−H), 6.91−6.88 (m, 1H, Ar−H), 6.18 (d, 1H, J = 4.8 Hz, ArCOC*H*<), 4.77 (d, 1H, J = 5.2 Hz, ArC*H*<), 2.49 (s, 3H, Ar−SCH_3) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 197.3 (*C*O), 166.5 (lactone *C*O), 163.8 (*C*), 159.3 (*C*), 155.6 (*C*), 139.1 (*C*), 137.8 (*C*H), 135.9 (*C*), 133.2 (*C*H), 129.7 (*C*H), 128.1 (2 × *C*H), 127.4 (2 × *C*H), 124.4 (*C*H), 123.3 (*C*H), 119.6 (*C*H), 119.4 (*C*H), 117.3 (*C*H), 116.3 (*C*), 112.1 (*C*), 105.4 (*C*), 91.5 (ArCOCH<), 49.9 (ArCH<), 15.8 (Ar−SCH_3) ppm. HRMS (ESI): m/z 453.0767 $[M + Na]^+$ calcd for $C_{25}H_{18}O_5SNa$, found m/z 453.0770; m/z 469.0507 $[M + K]^+$ calcd for $C_{25}H_{18}O_5SK$, found m/z 469.0506.

*4.4.10. 2-(2-Hydroxybenzoyl)-3-(3-(trifluoromethoxy)phenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2j**).* White amorphous powder; yield: 75% (35 mg, blue LEDs, 0.10 mmol scale), 72% (34 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 203 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.60 (s, 1H, Ar−O*H*), 7.87−7.84 (m, 1H, Ar−H), 7.67−7.63 (m, 1H, Ar−H), 7.60−7.56 (m, 1H, Ar−H), 7.49 (dd, 1H, J = 8.0 and 1.2 Hz, Ar−H), 7.46−7.41 (m, 2H, Ar−H), 7.40−7.36 (m, 1H, Ar−H), 7.28−7.22 (m, 2H, Ar−H), 7.17 (s, 1H, Ar−H), 7.09 (d, 1H, J = 8.4 Hz, Ar−H), 6.93−6.89 (m, 1H, Ar−H), 6.16 (d, 1H, J = 4.8 Hz, ArCOC*H*<), 4.88 (d, 1H, J = 4.8 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 196.8 (*C*O), 166.9 (lactone *C*O), 163.8 (*C*), 159.1 (*C*), 155.6 (*C*), 150.0(*C*), 141.6 (*C*), 138.0 (*C*H), 133.5 (*C*H), 131.0 (*C*H), 129.7 (*C*H), 126.1 (*C*H), 124.5 (*C*H), 123.3 (*C*H), 121.8 (O*C*F_3), 120.8 (*C*H), 120.5 (*C*H), 119.6 (*C*H), 119.5 (*C*H), 117.4 (*C*H), 116.3 (*C*), 111.9 (*C*), 104.7 (*C*), 91.3 (ArCOCH<), 49.6 (ArCH<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.7 ppm. HRMS (ESI): m/z 491.0713 $[M + Na]^+$ calcd for $C_{25}H_{15}F_3O_6Na$, found m/z 491.0715; m/z 507.0452 $[M + K]^+$ calcd for $C_{25}H_{15}F_3O_6K$, found m/z 507.0455.

*4.4.11. 2-(2-Hydroxybenzoyl)-3-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2k**).* White amorphous powder; yield: 64% (30 mg, blue LEDs, 0.10 mmol scale), 65% (31 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 180 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.62 (s, 1H, Ar−O*H*), 7.86−7.84 (m, 1H, Ar−H), 7.67−7.62 (m, 1H, Ar−H), 7.59−7.56 (m, 1H, Ar−H), 7.49−7.47 (m, 1H, Ar−H), 7.42 (d, 1H, J = 8.4 Hz, Ar−H), 7.39−7.36 (m, 3H, Ar−H), 7.24 (s, 2H, Ar−H), 7.08 (dd, 1H, J = 8.4 and 0.8 Hz, Ar−H), 6.93−6.89 (m, 1H, Ar−H), 6.17 (d, 1H, J = 5.2, ArCOC*H*<), 4.89 (d, 1H, J = 5.2, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 196.9 (*C*O), 166.6 (lactone *C*O), 163.8 (*C*), 159.2 (*C*), 155.6 (*C*), 149.3 (*C*), 137.9 (*C*H), 137.9 (*C*), 133.4 (*C*H), 129.7 (*C*H), 129.2 (2 × *C*H), 124.5 (*C*H), 123.3 (2 × *C*H), 121.9 (*C*H and O*C*F_3), 119.6 (*C*H), 119.5 (*C*H), 117.3 (*C*H), 116.3 (*C*), 112.0 (*C*), 105.1 (*C*), 91.4 (ArCOCH<), 49.2 (ArCH<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.8 ppm. HRMS (ESI): m/z 469.0893 $[M + H]^+$ calcd for $C_{25}H_{15}F_3O_6H$, found m/z 469.0891; m/z 507.0452 $[M + K]^+$ calcd for $C_{25}H_{15}F_3O_6K$, found m/z 507.0450.

*4.4.12. 3-(2-Fluorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2l**).* White amorphous powder; yield: 52% (21 mg, blue LEDs, 0.10 mmol scale), 51% (20 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 92:8; mp = 216 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H, Ar−O*H*), 7.83 (dd, 1H, J = 8.0 and 1.2 Hz, Ar−H), 7.65−7.61 (m, 1H, Ar−H), 7.58−7.53 (m, 2H, Ar−H), 7.42 (d, 1H, J = 8.4 Hz, Ar−H), 7.38−7.28 (m, 3H, Ar−H), 7.19−7.16 (m, 1H, Ar−H), 7.14−7.09 (m, 1H, Ar−H), 7.07 (d, 1H, J = 8.4 Hz, Ar−H), 6.92−6.88 (m, 1H, Ar−H), 6.23 (d, 1H, J = 5.2 Hz, ArCOC*H*<), 5.17 (d, 1H, J = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 196.9 (*C*O), 166.7 (lactone *C*O), 163.8 (*C*), 162.1 (*C*), 159.2 (*C*), 155.6 (*C*), 137.8 (*C*H), 133.2 (*C*H), 130.2 (d, J_{CF} = 8 Hz, *C*H), 130.0 (*C*H), 129.9 (*C*H), 129.8 (*C*H), 125.1 (*C*H), 124.4 (*C*H), 123.3 (*C*H), 119.4 (d, J_{CF} = 28 Hz, *C*H), 117.2 (*C*H), 116.6 (*C*), 116.5 (*C*H), 116.3 (*C*H), 112.1 (*C*), 103.8 (*C*), 90.2 (ArCOCH<), 43.9 (ArCH<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.1 ppm. HRMS (ESI): m/z 425.0796 $[M + Na]^+$ calcd for $C_{24}H_{15}FO_5Na$, found m/z 425.0791; m/z 441.0535 $[M + K]^+$ calcd for $C_{24}H_{15}FO_5K$, found m/z 441.0529.

*4.4.13. 3-(3-Fluorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2m**).* White amorphous powder; yield: 65% (26 mg, blue LEDs, 0.10 mmol scale), 63% (25 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 195 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.62 (s, 1H, Ar−OH), 7.86−7.84 (m, 1H, Ar−H), 7.66−7.62 (m, 1H, Ar−H), 7.59−7.55 (m, 1H, Ar−H), 7.49 (dd, 1H, J = 8.0 and 1.2 Hz, Ar−H), 7.43−7.35 (m, 3H, Ar−H), 7.13 (d, 1H, J = 7.6 Hz, Ar−H), 7.09−7.02 (m, 3H, Ar−H), 6.93−6.89 (m, 1H, Ar−H), 6.18 (d, 1H, J

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= 4.8 Hz, ArCOC*H*<), 4.85 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 196.9 (*C*O), 166.7 (lactone *C*O), 163.8 (*C*), 163.4 (d, J_{CF} = 247 Hz, *C*), 159.2 (*C*), 155.6 (*C*), 141.8 (*C*), 141.7 (*C*), 137.9 (*C*H), 133.4 (*C*H), 131.1 (d, J_{CF} = 9 Hz, *C*H), 129.7 (*C*H), 124.5 (*C*H), 123.5 (d, J_{CF} = 3 Hz, *C*H), 123.3 (*C*H), 119.5 (d, J_{CF} = 19 Hz, *C*H), 117.3 (*C*H), 116.3 (*C*), 115.6 (d, J_{CF} = 21 Hz, *C*H), 114.7 (d, J_{CF} = 22 Hz, *C*H), 112.0 (*C*), 105.0 (*C*), 91.3 (ArCOCH<), 49.6 (ArCH<) ppm.^{19}F NMR (376 MHz, $CDCl_3$): δ −111.3 ppm. HRMS (ESI): *m*/*z* 425.0796 $[M + Na]^+$ calcd for $C_{24}H_{15}FO_5Na$, found *m*/*z* 425.0784; *m*/*z* 441.0535 $[M + K]^+$ calcd for $C_{24}H_{15}FO_5K$, found *m*/*z* 441.0528.

*4.4.14. 3-(4-Fluorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2n**).* White amorphous powder; yield: 55% (22 mg, blue LEDs, 0.10 mmol scale), 56% (23 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 84:16; mp = 187 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.64 (s, 1H, Ar−O*H*), 7.85 (dd, 1H, *J* = 7.6 and 1.2 Hz, Ar−H), 7.66−7.62 (m, 1H, Ar−H), 7.59−7.55 (m, 1H, Ar−H), 7.46 (dd, 1H, *J* = 8.0 and 0.8 Hz, Ar−H), 7.42 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.39−7.36 (m, 1H, Ar−H), 7.33−7.29 (m, 2H, Ar−H), 7.09 (t, 3H, *J* = 8.4 Hz, Ar−H), 6.91−6.88 (m, 1H, Ar−H), 6.16 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.83 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 197.1 (*C*O), 166.5 (lactone *C*O), 163.8 (2 × *C*), 162.8 (d, J_{CF} = 246 Hz, *C*), 157.5 (*C*), 155.6 (*C*), 137.9 (*C*H), 135.1 (*C*), 133.3 (*C*H), 129.7 (*C*H), 129.4 (d, J_{CF} = 9 Hz, 2 × *C*H), 124.5 (*C*H), 123.3 (*C*H), 119.5 (d, J_{CF} = 13 Hz, 2 × *C*H), 117.3 (*C*H), 116.6 (*C*H), 116.4 (*C*H), 112.1 (*C*), 105.3 (*C*), 91.5 (ArCOCH<), 49.5 (ArCH<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.5 ppm. HRMS (ESI): *m*/*z* 425.0796 $[M + Na]^+$ calcd for $C_{24}H_{15}FO_5Na$, found *m*/*z* 425.0805; *m*/*z* 441.0535 $[M + K]^+$ calcd for $C_{24}H_{15}FO_5K$, found *m*/*z* 441.0548.

*4.4.15. 3-(2-Chlorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2o**).* White amorphous powder; yield: 53% (22 mg, blue LEDs, 0.10 mmol scale), 52% (21 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 90:10; mp = 201 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H, Ar−O*H*), 7.76−7.74 (m, 1H, Ar−H), 7.62−7.51 (m, 4H, Ar−H), 7.41−7.39 (m, 2H, Ar−H), 7.31 (t, 1H, *J* = 7.6 Hz, Ar−H), 7.25−7.24 (m, 2H, Ar−H), 7.04 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.90−6.86 (m, 1H, Ar−H), 6.16 (m, 1H, *J* = 4.8 Hz, ArCOC*H*<), 5.48 (m, 1H, *J* = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 196.5 (*C*O), 166.8 (lactone *C*O), 163.8 (*C*), 159.2 (*C*), 155.5 (*C*), 137.8 (*C*H), 136.6 (*C*), 133.7 (*C*), 133.3 (*C*H), 130.4 (*C*H), 130.2 (*C*H), 129.6 (*C*H), 129.5 (*C*H), 127.8 (*C*H), 124.4 (*C*H), 123.2 (*C*H), 119.6 (*C*H), 119.1 (*C*H), 117.2 (*C*H), 116.9 (*C*), 112.0 (*C*), 104.3 (*C*), 90.1(ArCOCH<), 46.0 (ArCH<) ppm. HRMS (ESI): *m*/*z* 441.0500 $[M + Na]^+$ calcd for $C_{24}H_{15}ClO_5Na$, found *m*/*z* 441.0503; *m*/*z* 457.0240 $[M + K]^+$ calcd for $C_{24}H_{15}ClO_5K$, found *m*/*z* 457.0243.

*4.4.16. 3-(3-Chlorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2p**).* White amorphous powder; yield: 67% (28 mg, blue LEDs, 0.10 mmol scale), 64% (27 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 177 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.61 (s, 1H, Ar−O*H*), 7.85 (dd, 1H, *J* = 7.6 and 1.2 Hz, Ar−H), 7.67−7.62 (m, 1H, Ar−H), 7.59−7.56 (m, 1H, Ar−H), 7.49 (dd, 1H, *J* = 8.0 and 0.8 Hz, Ar−H), 7.42 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.38 (t, 1H, *J* = 7.6 Hz, Ar−H), 7.34−7.33 (m, 2H, Ar−H), 7.30 (s, 1H, Ar−H), 7.24−7.21 (m, 1H, Ar−H), 7.08 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.93−6.89 (m, 1H, Ar−H), 6.17 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.84 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 196.8 (*C*O), 166.7 (lactone *C*O), 163.8 (*C*), 159.2 (*C*), 155.6 (*C*), 141.3 (*C*), 137.9 (*C*H), 135.4 (*C*), 133.4 (*C*H), 130.7 (*C*H), 129.7 (*C*H), 128.8 (*C*H), 127.7 (*C*H), 126.2 (*C*H), 124.5 (*C*H), 123.3 (*C*H), 119.6 (*C*H), 119.4 (*C*H), 117.3 (*C*H), 116.3 (*C*), 111.9 (*C*), 104.9 (*C*), 91.3 (ArCOCH<), 49.5 (ArCH<) ppm. HRMS (ESI): *m*/*z* 441.0500 $[M + Na]^+$ calcd for $C_{24}H_{15}ClO_5Na$, found *m*/*z* 441.0499; *m*/*z* 457.0240 $[M + K]^+$ calcd for $C_{24}H_{15}ClO_5K$, found *m*/*z* 457.0237.

*4.4.17. 3-(4-Chlorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2q**).* White amorphous powder; yield: 64% (27 mg, blue LEDs, 0.10 mmol scale), 64% (27 mg, sunlight; 0.10 mmol scale); eulent used for flash column, hexane/EtOAc 88:12; mp = 194 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.63 (s, 1H, Ar−O*H*), 7.85 (dd, 1H, *J* = 8.0 and 1.2 Hz, Ar−H), 7.67−7.62 (m, 1H, Ar−H), 7.59−7.55 (m, 1H, Ar−H), 7.45 (dd, 1H, *J* = 8.0 and 1.2 Hz, Ar−H), 7.42 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.39−7.36 (m, 3H, Ar−H), 7.28−7.27 (m, 2H, Ar−H), 7.08 (d, 1H, *J* = 8.0 Hz, Ar−H), 6.92−6.88 (m, 1H, Ar−H), 6.16 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.82 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, CDCl3): δ 196.9 (*C*O), 166.6 (lactone *C*O), 163.8 (*C*), 159.2 (*C*), 155.6 (*C*), 137.9 (*C*H), 137.8 (*C*), 134.5 (*C*), 133.4 (*C*H), 129.7 (2 × *C*H), 129.6 (*C*H), 129.1 (2 × *C*H), 124.5 (*C*H), 123.3 (*C*H), 119.6 (*C*H), 119.4 (*C*H), 117.3 (*C*H), 116.3 (*C*), 112.0 (*C*), 105.1 (*C*), 91.4 (ArCOCH<), 49.5 (*C*H) ppm. HRMS (ESI): *m*/*z* 441.0500 $[M + Na]^+$ calcd for $C_{24}H_{15}ClO_5Na$, found *m*/*z* 441.0525; *m*/*z* 457.0240 $[M + K]^+$ calcd for $C_{24}H_{15}ClO_5K$, found *m*/*z* 457.0268.

*4.4.18. 3-(2,4-Dichlorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2r**).* White amorphous powder; yield: 57% (26 mg, blue LEDs, 0.10 mmol scale), 57% (26 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 90:10; mp = 210 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H, Ar−O*H*), 7.78−7.76 (m, 1H, Ar−H), 7.66−7.62 (m, 1H, Ar−H), 7.60−7.56 (m, 2H, Ar−H), 7.46−7.42 (m, 2H, Ar−H), 7.37−7.33 (m, 1H, Ar−H), 7.29−7.27 (m, 1H, Ar−H), 7.21 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.08 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.95−6.91 (m, 1H, Ar−H), 6.14 (d, 1H, *J* = 5.2 Hz, ArCOC*H*<), 5.47 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 196.2 (*C*O), 166.9 (lactone *C*O), 163.9 (*C*), 159.2 (*C*), 155.6 (*C*), 138.0 (*C*H), 135.3 (*C*), 134.9 (*C*), 134.4 (*C*), 133.5 (*C*H), 130.4 (*C*H), 130.3 (*C*H), 130.0 (*C*H), 128.2 (*C*H), 124.5 (*C*H), 123.2 (*C*H), 119.7 (*C*H), 119.2 (*C*H), 117.3 (*C*H), 116.8 (*C*), 111.9 (*C*), 103.9 (*C*), 89.9 (ArCOCH<), 45.6 (ArCH<) ppm. HRMS (ESI): *m*/*z* 453.0291 $[M + H]^+$ calcd for $C_{24}H_{14}Cl_2O_5H$, found *m*/*z* 453.0283; *m*/*z* 475.0110 $[M + Na]^+$ calcd for $C_{24}H_{14}Cl_2O_5Na$, found *m*/*z* 475.0100; *m*/*z* 490.9850 $[M + K]^+$ calcd for $C_{24}H_{14}Cl_2O_5K$, found *m*/*z* 490.9840.

*4.4.19. 3-(3-Bromophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2s**).* White amorphous powder; yield: 65% (30 mg, blue LEDs, 0.10 mmol scale), 64% (29 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 88:12; mp = 181 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.62 (s, 1H, Ar−O*H*), 7.85 (d, 1H, *J* = 8.0 Hz, Ar−H), 7.65 (t, 1H, *J* = 8.0 Hz, Ar−H), 7.60−7.56 (m, 1H, Ar−H), 7.50−7.36 (m, 5H, Ar−H), 7.28−7.27 (m, 2H, Ar−H), 7.09 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.92 (t, 1H, *J* = 7.6 Hz, Ar−H), 6.17−6.16 (m, 1H, ArCOC*H*<), 4.84−4.82 (m, 1H, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 196.8 (*C*O), 166.7 (lactone *C*O), 163.8 (*C*), 159.1 (*C*), 155.6 (*C*), 141.5 (*C*), 137.9 (*C*H), 133.4 (*C*H), 131.7 (*C*H), 131.0 (*C*H), 130.6 (*C*H), 129.8 (*C*H), 126.7 (*C*H), 124.5 (*C*H), 123.6 (*C*), 123.3 (*C*H), 119.6 (*C*H), 119.4 (*C*H), 117.3 (*C*H), 116.3 (*C*), 112.0 (*C*), 104.9 (*C*), 91.3 (ArCOCH<), 49.4 (ArCH<) ppm. HRMS (ESI): *m*/*z* 484.9995 $[M + Na]^+$ calcd for $C_{24}H_{15}BrO_5Na$, found *m*/*z* 484.9979; *m*/*z* 500.9734 $[M + K]^+$ calcd for $C_{24}H_{15}BrO_5K$, found *m*/*z* 500.9722; *m*/*z* 502.9734 $[M + 2 + K]^+$ calcd for $C_{24}H_{15}BrO_5K$, found *m*/*z* 502.9701.

*4.4.20. 3-(4-Bromophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2t**).* White amorphous powder; yield: 63% (29 mg, blue LEDs, 0.10 mmol scale), 61% (28 mg, sunlight; 0.10 mmol scale); eulent used for flash column hexane/EtOAc 84:16; mp = 230 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 11.62 (s, 1H, Ar−O*H*), 7.86−7.83 (m, 1H, Ar−H), 7.66−7.62 (m, 1H, Ar−H), 7.59−7.55 (m, 1H, Ar−H), 7.52 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.47−7.44 (m, 1H, Ar−H), 7.41 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.39−7.35 (m, 1H, Ar−H), 7.21 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.08 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.92−6.88 (m, 1H, Ar−H), 6.16 (d, 1H, *J* = 5.2 Hz, ArCOC*H*<), 4.80 (d, 1H, *J* = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 196.9 (*C*O), 166.6 (lactone *C*O), 163.8 (*C*), 159.2 (*C*), 155.6 (*C*), 138.3 (*C*), 137.9 (*C*H), 133.4 (*C*H), 132.7 (2 × *C*H), 129.6 (*C*H), 129.4 (2 × *C*H), 124.5 (*C*H), 123.3 (*C*H), 122.6 (*C*), 119.6 (*C*H), 119.4 (*C*H), 117.3 (*C*H), 116.3 (*C*), 112.0 (*C*), 105.1 (*C*), 91.3 (ArCOCH<), 49.6 (ArCH<) ppm. HRMS (ESI): *m*/

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z 484.9995 $[M + Na]^+$ calcd for $C_{24}H_{15}BrO_5Na$, found *m*/*z* 485.0017; *m*/*z* 486.9995 $[M + 2 + Na]^+$ calcd for $C_{24}H_{15}BrO_5$ Na, found *m*/*z* 487.0001; *m*/*z* 500.9734 $[M + K]^+$ calcd for $C_{24}H_{15}BrO_5K$, found *m*/*z* 500.9755; *m*/*z* 502.9734 $[M + 2 + K]^+$ calcd for $C_{24}H_{15}BrO_5K$, found *m*/*z* 502.9737.

*4.4.21. 3-(3,4-dimethoxyphenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2u**).* White amorphous powder; yield: 70% (31 mg, blue LEDs, 0.10 mmol scale), 72% (32 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 84:16; mp = 208−209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.67 (s, 1H, Ar−O*H*), 7.87 (dd, 1H, *J* = 7.6 and 1.2 Hz, Ar−H), 7.65−7.61 (m, 1H, Ar−H), 7.58−7.54 (m, 1H, Ar−H), 7.48−7.46 (m, 1H, Ar−H), 7.42 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.39−7.35 (m, 1H, Ar−H), 7.09−7.07 (m, 1H, Ar−H), 6.89−6.85 (m, 3H, Ar−H), 6.80 (s, 1H, Ar−H), 6.19 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.74 (d, 1H, *J* = 5.2 Hz, ArC*H*<), 3.88 (s, 3H, Ar−OCH_3), 3.84 (s, 3H, Ar−OCH_3) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 197.5 (CO), 166.4 (lactone CO), 163.8 (*C*), 159.3 (*C*), 155.6 (*C*), 149.7 (*C*), 149.2 (*C*), 137.8 (CH), 133.2 (CH), 131.7 (*C*), 129.9 (CH), 124.4 (CH), 123.3 (CH), 119.8 (CH), 119.4 (CH), 119.3 (CH), 117.3 (CH), 116.3, 112.2, 112.0 (CH), 110.9 (CH), 105.3 (*C*), 91.6 (ArCOCH<), 56.2 (Ar−OCH_3), 56.1 (Ar−OCH_3), 50.2 (ArCH<) ppm. HRMS (ESI): *m*/*z* 467.1107 $[M + Na]^+$calcd for $C_{26}H_{20}O_7Na$, found *m*/*z* 467.1112.

*4.4.22. 3-(Benzo[d][1,3]dioxol-5-yl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2v**).* White amorphous powder; yield: 68% (29 mg, blue LEDs, 0.10 mmol scale), 68% (29 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 86:14; mp = 210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H, Ar−O*H*), 7.87−7.84 (m, 1H, Ar−H), 7.65−7.61 (m, 1H, Ar−H), 7.59−7.54 (m, 1H, Ar−H), 7.48 (d, 1H, *J* = 8.0 Hz, Ar−H), 7.41 (d, 1H, *J* = 8.0 Hz, Ar−H), 7.37 (d, 1H, *J* = 7.6 Hz, Ar−H), 7.07 (d, 1H, *J* = 8.4 Hz, Ar−H), 6.93−6.89 (m, 1H, Ar−H), 6.82−6.77 (m, 3H, Ar−H), 6.15 (d, 1H, *J* = 4.4 Hz, ArCOC*H*<), 5.98 (d, 2H, *J* = 2.4 Hz, −OCH_2O−), 4.71 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 197.4 (CO), 166.5 (lactone CO), 163.7 (*C*), 159.3 (*C*), 155.5 (*C*), 148.7 (*C*), 147.9 (*C*), 137.8 (CH), 133.2 (CH), 132.9 (*C*), 129.7 (CH), 124.4 (CH), 123.3 (CH), 121.4 (CH), 119.6 (CH), 119.4 (CH), 117.3 (CH), 116.2 (*C*), 112.1 (*C*), 108.9 (CH), 107.7 (CH), 105.4 (*C*), 101.5 (−OCH_2O−), 91.6 (ArCOCH<), 50. (ArCH<) ppm. HRMS (ESI): *m*/*z* 429.0969 $[M + H]^+$ calcd for $C_{25}H_{16}O_7H$, found *m*/*z* 429.0968; *m*/*z* 451.0788 $[M + Na]^+$ calcd for $C_{25}H_{16}O_7Na$, found *m*/*z* 451.0787; *m*/*z* 467.0528 $[M + K]^+$ calcd for $C_{25}H_{16}O_7K$, found *m*/*z* 467.0528.

*4.4.23. 2-(2-Hydroxybenzoyl)-3-(naphthalen-2-yl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2w**).* White amorphous powder; yield: 60% (26 mg, blue LEDs, 0.10 mmol scale), 61% (27 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 92:8; mp = 219 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.65 (s, 1H, Ar−O*H*), 7.86 (d, 1H, *J* = 7.6 Hz, Ar−H), 7.65−7.61 (m, 1H, Ar−H), 7.58−7.54 (m, 1H, Ar−H), 7.48−7.32 (m, 9H, Ar−H), 7.26 (s, 1H, Ar−H), 7.08 (d, 1H, *J* = 8.4 Hz, Ar−H),6.89−6.86 (m, 1H, Ar−H), 6.20 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.81 (d, 1H, *J* = 4.4 Hz, ArC*H*<) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 197.4 (CO), 166.5 (lactone CO), 163.8 (*C*), 159.3 (*C*), 155.6 (*C*), 139.3 (2 × *C*), 137.8 (2 × CH), 133.2 (CH), 129.8 (2 × CH), 129.5 (2 × CH), 128.5 (2 × CH), 127.7 (2 × CH), 124.4 (CH), 123.3 (CH), 119.5 (CH), 119.3 (CH), 117.3 (CH), 116.3 (*C*), 112.2 (*C*), 105.5 (*C*), 91.6 (ArCOCH<), 50.3 (ArCH<) ppm. HRMS (ESI): *m*/*z* 435.1227 $[M + H]^+$ calcd for $C_{28}H_{18}O_5H$, found *m*/*z* 435.1211; *m*/*z* 457.1046 $[M + Na]^+$ calcd for $C_{28}H_{18}O_5Na$, found *m*/*z* 457.1029; *m*/*z* 473.0786 $[M + K]^+$ calcd for $C_{28}H_{18}O_5K$, found *m*/*z* 473.0769.

*4.4.24. 2-Benzoyl-3-(4-fluorophenyl)-2,3-dihydro-4H-furo[3,2-c]-chromen-4-one (**2x**).* White amorphous powder; yield: 73% (28 mg, blue LEDs, 0.10 mmol scale), 73% (28 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 80:20; mp = 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.88 (m, 2H, Ar−H), 7.83−7.81 (m, 1H, Ar−H), 7.68−7.58 (m, 2H, Ar−H), 7.49 (t, 2H, *J* = 7.6 Hz, Ar−H), 7.39 (d, 1H, *J* = 8.4 Hz, Ar−H), 7.34 (t, 1H, *J* = 7.6 Hz, Ar−H), 7.28−7.25 (m, 2H, Ar−H), 7.08−7.03 (m, 2H, Ar−H), 6.12 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.81 (d, 1H, *J* = 5.2 Hz, ArC*H*<) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 192.1 (CO), 166.5 (lactone CO), 162.6 (d, J_{CF} = 246 Hz, *C*), 159.4 (*C*), 155.5 (*C*), 135.5 (d, J_{CF} = 2 Hz, *C*), 134.7 (CH), 133.3 (*C*), 133.2 (CH), 129.4 (CH), 129.3 (CH), 129.2 (2 × CH), 124.4 (2 × CH), 123.3 (2 × CH), 117.2 (CH), 116.4 (d, J_{CF} = 22 Hz, 2 × CH), 112.2 (*C*), 105.3 (*C*), 92.7 (ArCOCH<), 48.7 (ArCH<) ppm. HRMS (ESI): *m*/*z* 387.1027 $[M + H]^+$ calcd for $C_{24}H_{15}FO_4H$, found *m*/*z* 387.1026; *m*/*z* 409.0847 $[M + Na]^+$ calcd for $C_{24}H_{15}FO_4Na$, found *m*/*z* 409.0849; *m*/*z* 425.0586 $[M + K]^+$ calcd for $C_{24}H_{15}FO_4K$, found *m*/*z* 425.0589.

*4.4.25. 2-Benzoyl-8-methyl-3-phenyl-2,3-dihydro-4H-furo[3,2-c]-chromen-4-one (**2y**).* White amorphous powder; yield: 68% (26 mg, blue LEDs, 0.10 mmol scale), 65% (25 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 78:22; mp = 195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 2H, *J* = 7.4 Hz, Ar−H), 7.68−7.64 (m, 2H, Ar−H), 7.52−7.48 (m, 2H, Ar−H), 7.43−7.33 (m, 4H, Ar−H), 7.31−7.28 (m, 3H, Ar−H), 6.17 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.78 (d, 1H, *J* = 4.8 Hz, ArC*H*<), 2.45 (s, 3H, Ar−CH_3) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 192.3 (CO), 166.5 (lactone CO), 159.6 (*C*), 153.7 (*C*), 139.8 (*C*), 134.6 (CH), 134.1 (CH), 133.3 (*C*), 129.4 (2 × CH), 129.2 (2 × CH), 129.2 (2 × CH), 128.3 (CH), 127.7 (2 × CH), 122.9 (CH), 116.9 (CH), 111.9 (*C*), 105.4 (*C*), 92.7 (ArCOC*H*<), 49.6 (ArC*H*<), 20.9 (Ar−CH_3) ppm. HRMS (ESI): *m*/*z* 383.1278 $[M + H]^+$ calcd for $C_{25}H_{18}O_4H$, found *m*/*z* 383.1285; *m*/*z* 405.1097 $[M + K]^+$ calcd for $C_{25}H_{18}O_4K$, found *m*/*z* 405.1104.

*4.4.26. 2-Benzoyl-7-methyl-3-phenyl-2,3-dihydro-4H-furo[3,2-c]-chromen-4-one (**2z**).* White amorphous powder; yield: 71% (27 mg, blue LEDs, 0.10 mmol scale), 73% (28 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 78:22; mp = 152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.89 (m, 2H, Ar−H), 7.72 (d, 1H, *J* = 8.0 Hz, Ar−H), 7.67−7.63 (m, 1H, Ar−H), 7.51−7.48 (m, 2H, Ar−H), 7.39−7.32 (m, 3H, Ar−H), 7.31−7.29 (m, 2H, Ar−H), 7.19 (s, 1H, Ar−H), 7.16 (d, 1H, *J* = 8.0 Hz, Ar−H), 6.15 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.78 (d, 1H, *J* = 5.2 Hz, ArC*H*<), 2.48 (m, 3H, Ar−CH_3) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 192.3 (CO), 166.7 (lactone CO), 159.7 (*C*), 155.7 (*C*), 144.5 (*C*), 139.9 (*C*), 134.5 (CH), 133.3 (*C*), 129.4 (2 × CH), 129.2 (2 × CH), 129.1 (2 × CH), 128.2 (CH), 127.7 (2 × CH), 125.5 (CH), 122.9 (CH), 117.3 (CH), 109.8 (*C*), 104.4 (*C*), 92.8 (ArCOC*H*<), 49.4 (ArC*H*<), 22.1 (Ar−CH_3) ppm. HRMS (ESI): *m*/*z* 383.1278 $[M + H]^+$ calcd for $C_{25}H_{18}O_4H$, found *m*/*z* 383.1286; *m*/*z* 405.1097 $[M + Na]^+$ calcd for $C_{25}H_{18}O_4Na$, found *m*/*z* 405.1107; *m*/*z* 421.0837 $[M + K]^+$ calcd for $C_{25}H_{18}O_4K$, found *m*/*z* 421.0847.

*4.4.27. 2-Benzoyl-8-ethyl-3-phenyl-2,3-dihydro-4H-furo[3,2-c]-chromen-4-one (**2a′**).* White amorphous powder; yield: 71% (28 mg, blue LEDs, 0.10 mmol scale), 68% (27 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 75:25; mp = 161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91−7.89 (m, 2H, Ar−H), 7.68−7.64 (m, 2H, Ar−H), 7.52−7.48 (m, 2H, Ar−H), 7.46−7.44 (m, 1H, Ar−H), 7.40−7.3 (m, 4H, Ar−H), 7.31−7.29 (m, 2H, Ar−H), 6.18 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.76 (d, 1H, *J* = 4.8 Hz, ArC*H*<), 2.75 (dd, 2H, *J* = 15.2 and 7.6 Hz, Ar−CH_2−), 1.29 (d, 3H, *J* = 15.2 and 7.6 Hz, Ar−CH_2CH_3) ppm. ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 192.3 (CO), 166.7 (lactone CO), 159.7 (*C*), 153.9 (*C*), 140.5 (*C*), 139.8 (*C*), 134.6 (CH), 133.2 (*C*), 133.1 (CH), 129.4 (2 × CH), 129.2 (2 × CH), 129.2 (2 × CH), 128.3 (CH), 127.7 (2 × CH), 121.8 (CH), 117.0 (CH), 111.9 (*C*), 105.3 (*C*), 92.7 (ArCOC*H*<), 49.6 (ArC*H*<), 28.4 (CH_2), 15.7 (CH_3) ppm. HRMS (ESI): *m*/*z* 397.1434 $[M + H]^+$ calcd for $C_{26}H_{20}O_4H$, found *m*/*z* 397.1450; *m*/*z* 419.1254 $[M + Na]^+$ calcd for $C_{26}H_{20}O_4Na$, found *m*/*z* 419.1270; *m*/*z* 435.0993 $[M + K]^+$ calcd for $C_{26}H_{20}O_4K$, found *m*/*z* 435.1010.

*4.4.28. 2-Benzoyl-7-methoxy-3-phenyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2b′**).* White amorphous powder; yield: 65% (26 mg, blue LEDs, 0.10 mmol scale), 65% (26 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 80:20; mp = 163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 2H, *J* = 7.2 Hz, Ar−H), 7.74 (d, 1H, *J* = 8.8 Hz, Ar−H), 7.67−7.63 (m, 1H, Ar−H), 7.51−7.47 (m, 2H, Ar−H), 7.39−7.32 (m, 3H, Ar−H), 7.29 (d, 2H, *J* = 6.8 Hz, Ar−H), 6.98−6.89 (m, 1H, Ar−H), 6.87 (br s, 1H, Ar−H), 6.15 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.75 (d, 1H, *J* = 4.8 Hz,

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ArC*H*<), 3.88 (s, 3H, Ar−OCH_3) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 192.4 (*C*O), 166.9 (lactone *C*O), 163.9 (*C*), 159.8 (*C*), 157.5 (*C*), 139.9 (*C*), 134.5 (*C*H), 133.3, 129.4 (2 × *C*H), 129.2 (2 × *C*H), 129.1 (2 × *C*H), 128.2 (*C*H), 127.6 (2 × *C*H), 124.3 (*C*H), 112.8 (*C*H), 105.4 (*C*), 102.5 (*C*), 100.9 (*C*H), 92.7 (ArCOC*H*<), 55.9 (Ar−O*C*H_3), 49.3 (ArC*H*<) ppm. HRMS (ESI): *m*/*z* 399.1227 $[M + H]^+$ calcd for $C_{25}H_{18}O_5H$, found *m*/*z* 399.1228; *m*/*z* 421.1046 $[M + Na]^+$ calcd for $C_{25}H_{18}O_5Na$, found *m*/*z* 421.1054; *m*/*z* 437.0786 $[M + K]^+$ calcd for $C_{25}H_{18}O_5K$, found *m*/*z* 437.0791.

*4.4.29. 2-Benzoyl-8-bromo-3-phenyl-2,3-dihydro-4H-furo[3,2-c]-chromen-4-one (**2c′**).* White amorphous powder; yield: 70% (31 mg, blue LEDs, 0.10 mmol scale), 67% (30 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 82:18; mp = 202 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 1H, *J* = 2.4 Hz, Ar−H), 7.89 (d, 2H, *J* = 2.4 Hz, Ar−H), 7.70−7.65 (m, 2H, Ar−H), 7.53−7.49 (m, 2H, Ar−H), 7.41−7.34 (m, 3H, Ar−H), 7.29−7.26 (m, 3H, Ar−H), 6.20 (d, 1H, *J* = 5.2 Hz, ArCOC*H*<), 4.79 (d, 1H, *J* = 4.8 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 191.9 (*C*O), 165.3 (lactone *C*O), 158.8 (*C*), 154.2 (*C*), 139.2 (*C*), 135.9 (*C*H), 134.7 (*C*H), 132.9 (*C*), 129.5 (2 × *C*H), 129.2 (2 × *C*H), 129.2 (2 × *C*H), 128.4 (*C*H), 127.6 (2 × *C*H), 125.8 (*C*H), 118.9 (*C*H), 117.0 (*C*), 113.8 (*C*), 106.4 (*C*), 92.8 (ArCOC*H*<), 49.4 (ArC*H*<) ppm. HRMS (ESI): *m*/*z* 447.0226 $[M + H]^+$ calcd for $C_{24}H_{15}BrO_4H$, found *m*/*z* 447.0239; *m*/*z* 449.0226 $[M + 2 + H]^+$ calcd for $C_{24}H_{15}BrO_4H$, found *m*/*z* 449.0226; *m*/*z* 469.0046 $[M + Na]^+$ calcd for $C_{24}H_{15}BrO_4Na$, found *m*/*z* 469.0058; *m*/*z* 471.0226 $[M + 2 + Na]^+$ calcd for $C_{24}H_{15}BrO_4Na$, found *m*/*z* 471.0047.

*4.4.30. 2-(3-Bromobenzoyl)-8-fluoro-3-phenyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2d′**).* White amorphous powder; yield: 71% (33 mg, blue LEDs, 0.10 mmol scale), 73% (34 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 78:22; mp = 177 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (br s, 1H, Ar−H), 7.81−7.77 (m, 2H, Ar−H), 7.49 (dd, 1H, *J* = 7.6 and 2.8 Hz, Ar−H), 7.41−7.32 (m, 6H, Ar−H), 7.31−7.28 (m, 2H, Ar−H), 6.11 (d, 1H, *J* = 5.2 Hz, ArCOC*H*<), 4.81 (d, 1H, *J* = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 190.8 (*C*O), 165.5 (lactone *C*O), 158.9 (*C*), 158.6 (d, J_{CF} = 244 Hz, *C*), 151.7 (*C*), 139.0 (*C*), 137.5 (2 × *C*H), 134.9 (*C*), 132.2 (*C*H), 130.7 (*C*H), 129.5 (2 × *C*H), 128.5 (*C*H), 127.6 (2 × *C*H), 123.5 (*C*), 120.7 (d, J_{CF} = 25 Hz, *C*H), 118.9 (d, J_{CF} = 9 Hz, *C*H), 112.7 (d, J_{CF} = 10 Hz, *C*), 108.9 (d, J_{CF} = 26 Hz, *C*H), 106.2 (*C*), 92.8 (ArCOC*H*<), 49.3 (ArC*H*<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.4 ppm. HRMS (ESI): *m*/*z* 465.0132 $[M + H]^+$ calcd for $C_{24}H_{14}BrFO_4H$, found *m*/*z* 465.0146; *m*/*z* 467.0132 $[M + 2 + H]^+$ calcd for $C_{24}H_{14}BrFO_4H$, found *m*/*z* 467.0134.

*4.4.31. 3-(4-Bromophenyl)-2-(4-chlorobenzoyl)-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2e′**).* White amorphous powder; yield: 67% (33 mg, blue LEDs, 0.10 mmol scale), 67% (33 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 76:24; mp = 177 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.82−7.79 (m, 1H, Ar−H), 7.66−7.61 (m, 1H, Ar−H), 7.52−7.49 (m, 2H, Ar−H), 7.48−7.46 (m, 1H, Ar−H), 7.43−7.40 (m, 2H, Ar−H), 7.38−7.34 (m, 1H, Ar−H), 7.26−7.25 (m, 2H, Ar−H), 6.06 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.86 (d, 1H, *J* = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 190.8 (*C*O), 166.4 (lactone *C*O), 159.3 (*C*), 155.5 (*C*), 141.7 (*C*), 141.4 (*C*), 133.4 (*C*H), 131.6 (*C*H), 130.9 (*C*H), 130.7 (2 × *C*H), 130.5 (*C*H), 129.6 (2 × *C*H), 128.8 (*C*), 126.7 (*C*H), 124.4 (*C*H), 123.6 (*C*), 123.3 (*C*H), 117.3 (*C*H), 112.0 (*C*), 104.8 (*C*), 92.4 (ArCOC*H*<), 48.5 (ArC*H*<) ppm. HRMS (ESI): *m*/*z* 480.9842 $[M + H]^+$ calcd for $C_{24}H_{14}BrClO_4H$, found *m*/*z* 480.9849; *m*/*z* 482.9842 $[M + 2 + H]^+$ calcd for $C_{24}H_{14}BrClO_4H$, found *m*/*z* 482.9851.

*4.4.32. 8-Chloro-2-(4-chlorobenzoyl)-3-phenyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2f′**).* White amorphous powder; yield: 76% (33 mg, blue LEDs, 0.10 mmol scale), 73% (32 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 82:18; mp = 195 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.78 (d, 1H, *J* = 2.4 Hz, Ar−H), 7.55 (dd, 1H, *J* = 8.8 and 2.4 Hz, Ar−H), 7.49 (d, 2H, *J* = 8.4 Hz, Ar−H), 7.42−7.38 (m, 2H, Ar−H), 7.37−7.32 (m, 2H, Ar−H), 7.30−7.28 (m, 2H, Ar−H), 6.13 (d, 1H, *J* = 4.8 Hz, ArCOC*H*<), 4.81 (d, 1H, *J* = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 190.8 (*C*O), 165.1 (lactone *C*O), 158.7 (*C*), 153.8 (*C*), 141.4 (*C*), 139.1 (*C*), 133.1 (*C*H), 131.5 (*C*), 130.6 (2 × *C*H), 129.9 (*C*), 129.6 (2 × *C*H), 129.7 (2 × *C*H), 128.5 (*C*H), 127.6 (2 × *C*H), 122.7 (*C*H), 118.7 (*C*H), 113.3 (*C*), 106.4 (*C*), 92.7 (ArCOC*H*<), 49.3 (ArC*H*<) ppm. HRMS (ESI): *m*/*z* 437.0342 $[M + H]^+$ calcd for $C_{24}H_{14}Cl_2O_4H$, found *m*/*z* 437.0351; *m*/*z* 459.0161 $[M + Na]^+$ calcd for $C_{24}H_{14}Cl_2O_4Na$, found *m*/*z* 437.0168.

*4.4.33. 8-Fluoro-2-(4-fluorobenzoyl)-3-phenyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (**2g′**).* White amorphous powder; yield: 72% (29 mg, blue LEDs, 0.10 mmol scale), 69% (28 mg, sunlight; 0.10 mmol scale); eulent used for flash column was hexane/EtOAc 84:16; mp = 155 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96−7.92 (m, 2H, Ar−H), 7.49 (dd, 1H, *J* = 7.6 and 2.8 Hz, Ar−H), 7.42−7.35 (m, 4H, Ar−H), 7.34−7.32 (m, 1H, Ar−H), 7.31−7.29 (m, 2H, Ar−H), 7.20−7.18 (m, 2H, Ar−H), 6.14 (d, 1H, *J* = 5.2 Hz, ArCOC*H*<), 4.82 (d, 1H, *J* = 5.2 Hz, ArC*H*<) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 190.4 (*C*O), 166.6 (d, J_{CF} = 257 Hz, *C*), 165.5 (lactone *C*O), 158.7 (d, J_{CF} = 244 Hz, *C*), 157.4 (*C*), 151.7 (*C*), 139.2 (*C*), 132.0 (d, J_{CF} = 9 Hz, 2 × *C*H), 129.7 (d, J_{CF} = 3 Hz, *C*), 129.5 (2 × *C*H), 128.5 (*C*H), 127.6 (2 × *C*H), 120.7 (d, J_{CF} = 24 Hz, *C*H), 118.9 (d, J_{CF} = 8 Hz, *C*H), 116.5 (d, J_{CF} = 22 Hz, 2 × *C*H), 112.9 (d, J_{CF} = 9 Hz, *C*), 108.9 (d, J_{CF} = 25 Hz, *C*H), 106.4 (*C*), 92.7 (ArCOC*H*<), 49.4 (ArC*H*<) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ −101.8, −116.5 ppm. HRMS (ESI): *m*/*z* 405.0933 $[M + H]^+$ calcd for $C_{24}H_{14}F_2O_4H$, found *m*/*z* 405.0914.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00059.

Scanned copies of respective ^1H NMR, ^{13}C NMR, DEPT-135, ^{19}F NMR (for **2d**, **2e**, **2j**−**2n**, **2d′**, and **2g′**), 2D NMR (for one representative compound, **2v**), and HRMS spectra for all of the synthesized compounds (**2a**−**2v**) and single-crystal X-ray analysis for a representative entry, 3-(2-chlorophenyl)-2-(2-hydroxybenzoyl)-2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-one (**2o**) (PDF)

FAIR data, including the primary NMR FID files, for compounds **2a**, **2a′**, **2b**, **2b′**, **2c**, **2c′**, **2d**, **2d′**, **2e**, **2e′**, **2f**, **2f′**, **2g**, **2g′**, **2h**, **2i**, **2j**, **2k**, **2l**, **2m**, **2n**, **2o**, **2p**, **2q**, **2r**, **2s**, **2t**, **2u**, **2v**, **2w**, **2x**, **2y**, and **2z** (ZIP)

Accession Codes

CCDC 2116201 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Sopherone A and B: Two new biologically relevant dibenzo-α-pyrones from *Cassia sophera*

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ABSTRACT

Sopherone A (**1**) and B (**2**), two new biologically relevant dibenzo-α-pyrones, were isolated from the stems of *Cassia sophera* Linn. (Caesalpiniaceae). Their structures were elucidated by detailed analysis of their spectroscopic data, including 1D and 2D NMR.

1. Introduction

Dibenzo-α-pyrones, also called as 6*H*-benzo[*c*]chromen-6-ones or 6*H*-dibenzo[*b*,*d*]pyran-6-ones, belong to an important group of naturally occurring heptaketide coumarins of biological promise [1–4]. A handful of these natural molecules have been reported to exhibit considerable biological and pharmaceutical properties that include antioxidant [5], cytoxicity [6], antitumor and antibiotics [7,8], antimicrobial [9], antiallergic [10], anti-Alzheimer's [11], antidyslipidemic [12], and many more [13–18]. In addition, dibenzo-α-pyrones are found to play the key role of intermediates in the synthesis of pharmaceutically valuable compounds, such as cannabinoids [19], progesterone, androgen, and glucocorticoid receptor agonists [20,21]. Furthermore, certain benzo[*c*]chromen-6-ones are known to exhibit interesting optical properties as blue-green fluorescing dyes [22]. Fig. 1 offers a glimpse of few naturally occurring potentially bioactive dibenzo-α-pyrones [6,10,23–31].

In the course of our work in search of new biologically relevant natural products [32–48], we herein wish to report the occurrence of two new dibenzo-α-pyrones, named as sopherone A (**1**) and B (**2**) (Fig. 2), from the stems of *Cassia sopera* Linn. (Caesalpiniaceae), a traditionally used Indian medicinal plant [49–51] for the treatment of various diseases such as asthma, allergy, inflammation, pain, arthritis, liver-infections, diabetes, and convulsions [52–55]. The structures of the dibenzo-α-pyrones **1** and **2** were elucidated based on their detailed spectral studies, including 1D- and 2D- NMR analyses.

2. Experimental

2.1. Chemicals and instrumentation

All chemicals used in this study were purchased from reputed companies. The solvents were dried before use following standard procedure [56]. Melting point was recorded on a Chemiline CL-726 apparatus and is uncorrected. Infrared spectra were recorded on a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using KBr disc. The ^{1}H, ^{13}C and 2D-NMR spectra were obtained at 400 MHz and 100 MHz, respectively, on a Bruker DRX spectrometer using $CDCl_3$ as the solvent. Mass spectra (ESI-HRMS) were recorded on a QTOF Micro mass spectrometer. Elemental analyses were performed on an ElementarVario EL III Carlo Erba 1108 micro analyzer instrument. Chromatography was carried on silica gel flash columns (Merck 60–120 mesh) and TLC was performed on silica gel 60 F_{254} (Merck) plates.

2.2. Plant material

Whole plants (aerial parts and roots) *C. sophera* Linn. (Caesalpiniaceae) were collected during October - November 2016 in the vicinity of Santiniketan, West Bengal, India. The stems were separated from the whole plants and dried for using in this work. The plant material was identified by Dr. H. R. Chowdhury (Botany Department, Visva-Bharati University) and a voucher specimen (V/AM/8/2016) kept in the Laboratory of Natural Products and Organic Synthesis of this University.

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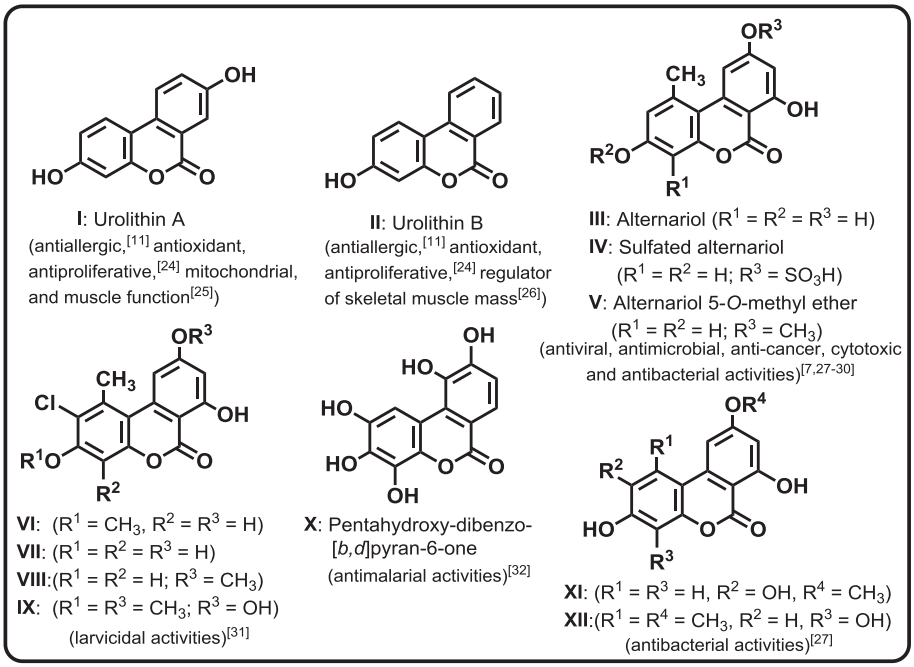

Fig. 1. Examples of few bioactive natural dibezo-α-pyrones [6,10,23–31].

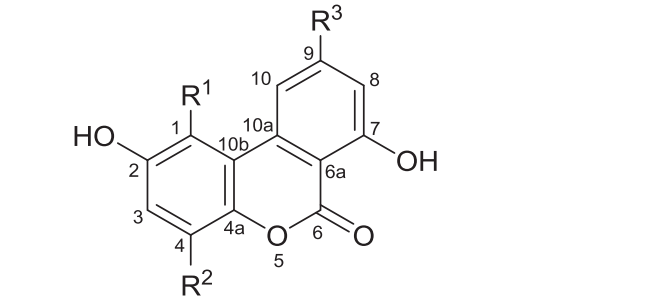

Fig. 2. Structures of dibenzo-α-pyrones **1** and **2**.

2.3. Extraction and isolation

Dried stems (1.5 kg) of *C. sophera* were crushed into powder and extracted in a Soxhlet apparatus with methanol for 72 h. The methanol extract (4.5 L) was then concentrated under reduced pressure in a rotary evaporator (EYELA, JAPAN) to give a greenish gummy residue (66 g) which was washed with cold hexane (100 mL) to dissolve out certain low-polar gummy substances. The residual portion (52 g) was then subjected to column chromatography (column diameter 5.72 cm; length: ~14.5 in.) on silica gel (60–120 mesh, 410 g) using mixtures of petroleum ether and ethyl acetate in varying proportions. Upon elution with petroleum ether-ethyl acetate (91:9 *v*/v) sopherone A (**1**; 61 mg; 0.004%) was obtained as a yellow solid, while the eluent at a ratio of 84:16 furnished sopherone B (**2**; 45 mg; 0.003%) as a yellow solid.

Sopherone A (**1**): Yellow amorphous solid; mp 177–180 °C; UV (MeOH) λ_{max} 205, 225, 255, 287 nm; FT-IR (KBr) ν_{max}: 3238, 2951, 1690, 1651, 1601, 1509, 1440, 1389, 1290, 1206, 1084, 1015, 927, 825, 745, 681, 573, 436 cm^{-1}; ^1H, ^{13}C, DEPT-135 and 2D-NMR (COSY-45, HMQC, HMBC) data are described in Tables 1; HRESIMS: *m/z* 265.0469 $[M + Na]^+$ (calcd for $C_{14}H_{10}O_4Na$, 265.0477). Anal. calcd. For $C_{14}H_{10}O_4$: C, 69.42; H, 4.16; found: C, 69.21; H, 4.15.

Sopherone B (**2**): Yellow amorphous solid; mp 199–200 °C; UV (MeOH) λ_{max} 261, 297, 383 nm; FT-IR (KBr) ν_{max}: 3340, 2921, 2852, 2358, 1732, 1675, 1627, 1563, 1464, 1371, 1275, 1209, 1164, 1084, 902, 867, 754, 673, 544, 501, 451 cm^{-1}; ^1H, ^{13}C, DEPT-135 and 2D-NMR (COSY-45, HMQC, HMBC) data are described in Tables 2; HRESIMS: *m/z* 323.0523 $[M + Na]^+$ (calcd for $C_{16}H_{12}O_6Na$, 323.0532); *m/z* 301.0705 $[M + H]^+$ (calcd for $C_{16}H_{13}O_6$, 301.0712). Anal. calcd. For $C_{16}H_{12}O_6$: C, 64.00; H, 4.03; found: C, 63.93; H, 4.01.

3. Results and discussion

Sopherone A (**1**) was obtained as yellow amorphous solid. Its molecular formula was determined as $C_{14}H_{10}O_4$ by elemental analysis, high resolution mass spectral (HRMS) measurement at *m/z* 265.0469 $[M + Na]^+$ (calcd for $C_{14}H_{10}O_4Na$, 265.0477) and ^{13}C NMR data, indicating 10 indices of hydrogen deficiency (IDHs). The molecule showed characteristic UV absorptions at λ_{max} 205, 225, 255 and 287 nm. Its IR spectrum also recorded characteristic absorption bands for phenolic (3238 cm^{-1}), aromatic unsaturation (1650, 1601, 1509 and 1440 cm^{-1}), and α,β-unsaturated lactone carbonyl (1690 cm^{-1}) group. The ^1H NMR spectrum (*see* Table 1) displayed signals for two phenolic protons at δ_H 12.13 (1H, s) and 12.02 (1H, s), five aromatic protons at δ_H 7.11 (1H, d, J = 1.2 Hz), 7.29 (1H, dd, J = 8.2, 1.2 Hz), 7.65–7.67 (1H, m), 7.69 (1H, br s) and 7.83 (1H, dd, J = 7.6, 1.2 Hz), and one aromatic methyl at δ_H 2.47 (3H, s). Analysis of the ^{13}C NMR data (Table 1) revealed the presence of 14 carbon signals, including one lactone carbonyl carbon [δ_C 156.46 (C-6)], one aromatic methyl carbon (δ_C 22.41 at C-4), five methine carbons [δ_C 137.10 (C-1), 124.53 (C-3), 124.72 (C-8), 121.52 (C-9), and 120.08 (C-10)], and eight quaternary carbons [δ_C 162.90 (C-2), 132.44 (C-4), 156.46 (C-6), 162.60 (C-7), 149.61 (C-4a), 133.48 (C-6a), 116.10 (C-10a), and 134.05 (C-10b)]. The 10 IHDs in **1** are, thus, satisfied with the presence of one carbonyl, one lactone ring, and two benzene rings having a total of six double bonds. The observed spectral data for **1** are found to be comparable with those reported for molecules having identical skeleton [57,58]. The relatively high value for C-1 (H-1, 7.69 ppm and C-1, 137.10 ppm) as compared to the other carbons carrying a hydrogen atom in compound **1** is suggestive of the fact that C-1 is possibly affected by the anisotropic cone of the carbonyl group at C-6 [59–61].

For further confirmation of the proposed structure **1**, we analyzed

Table 1
1D and 2D-NMR data for sopherone A (2,7-dihydroxy-4-methyl-6*H*-benzo[*c*]chromen-6-one; **1**).

Carbon	^{1}H (ppm/δ)	^{13}C (ppm/δ)	DEPT-135	^{1}H–^{1}H COSY-45	^{1}H- [13]C HMQC	^{1}H–^{13}C HMBC
C-1	7.69 (1H, br s, Ar–H)	137.10	CH	–	δ 7.69 (H-1) *vs* δ 137.10 (C-1)	δ 7.69 (H-1) *vs* δ 124.53 (C-3), 116.10 (C-10a)
C-2	–	162.90	C	–	–	–
C-3	7.11 (1H, d, *J* = 1.2 Hz, Ar–H)	124.53	CH	–	δ 7.11 (H-3) *vs* δ 124.53 (C-3)	–
C-4	–	132.44	C	–	–	–
C-6	–	156.46	C	–	–	–
C-7	–	162.60	C	–	–	–
C-8	7.29 (1H, dd, *J* = 8.2, 1.2 Hz, Ar–H)	124.72	CH	H-8 (δ 7.29) *vs* H-9 (δ 7.65–7.67)	δ 7.29 (H-8) *vs* δ 124.72 (C-8)	–
C-9	7.65–7.67 (1H, m, Ar–H)	121.52	CH	H-9 (δ 7.65–7.67) *vs* H-8 (δ 7.29) & H-10 (δ 7.83)	δ 7.65–7.67 (H-9) *vs* δ 121.52 (C-9)	–
C-10	7.83 (1H, dd, *J* = 7.6, 1.2 Hz, Ar–H)	120.08	CH	H-10 (δ 7.83) *vs* H-9 (δ 7.65–7.67)	δ 7.83 (*H* – 10) *vs* δ 120.08 (C-10)	δ 7.83 (H-10) *vs* δ 133.48 (C-6a), 134.05 (C-10b)
C-4a	–	149.61	C	–	–	–
C-6a	–	133.48	C	–	–	–
C-10a	–	116.10	C	–	–	–
C-10b	–	134.05	C	–	–	–
C_4-CH_3	2.47 (3H, s, Ar-C*H*$_3$)	22.41	CH_3	–	δ 2.47 (C*H*$_3$) *vs* δ 22.41 (CH_3)	δ 2.47 (C*H*$_3$) *vs* δ 124.53 (C-3), 149.61 (C-4a)
C_2-OH	12.13 (1H, s, Ar-O*H*)	–	–	–	–	δ 12.13 (C_2-O*H*) *vs* δ 124.53 (C-3), 162.90 (C-2)
C_7-OH	12.02 (1H, s, Ar-O*H*)	–	–	–	–	δ 12.02 (C_7-O*H*) *vs* δ 162.60 (C-7), 124.72 (C-8), 116.10 (C-10a)

its detailed 2D-NMR (^{1}H–^{1}H-COSY-45, HMQC and HMBC) spectral properties. All respective homo- and hetero-nuclear interactions are shown in Fig. 2, and the results are summarized in Table 1. As expected, ^{1}H–^{1}H-COSY-45 spectrum of **1** showed the interactions of H-8 (δ_H 7.29) with H-9 (δ_H 7.65–7.67), H-9 (δ_H 7.65–7.67) with H-8 (δ_H 7.29) and H-10 (δ_H 7.83) and *vice versa*. The HMQC spectrum also demonstrated the expected ^{1}H- [13]C correlations between carbon atoms and the protons directly attached to them. Thus, H-1 (δ_H 7.69) correlates with C-1 (δ_C 137.10), H-3 (δ_H 7.11) with C-3 (δ_C 124.53), H-8 (δ_H 7.29) with C-8 (δ_C 124.72), H-9 (δ_H 7.65–7.67) with C-9 (δ_C 121.52), H-10 (δ_H 7.83) with C-10 (δ_C 120.08) and the methyl protons (δ_H 2.47) at C-4 with the methyl carbon at δ_C 22.41 ppm. The results from the hetero-nuclear multiple bond correlation (HMBC) spectral studies also unambiguously confirmed the structure of molecule **1**. In the HMBC spectrum, H-1 at δ_H 7.69 showed interactions with C-3 (δ_C 124.53) and C-10a (δ_C 116.10), H-10 (δ_H 7.83) with C-6a (δ_C 133.48) and C-10b (δ_C 134.05), methyl protons (δ_H 2.47) at C-3 with C-3 (δ_C 124.53) and C-4a (δ_C 149.61). The C-2 hydroxyl proton at (δ_H 12.13) showed expected HMBC interactions with C-2 (δ_C 162.90) and C-3 (δ_C 124.53); similarly, C-7 hydroxyl proton at (δ_H 12.02) experienced HMBCs with C-7, C-8 and C-10a at δ_C 162.60, 124.72 and 116.10, respectively. All these observed HMBC interactions, as depicted in Fig. 3, are compatible with the structure proposed for **1**. Based on detailed 1D- and 2D-NMR spectral analyses, the proposed structure for compound **1** was formulated as 2,7-dihydroxy-4-methyl-6*H*-benzo[*c*]chromen-6-one (named as sopherone A).

Sopherone B (**2**) was also isolated as a yellow amorphous solid. The molecular formula, $C_{16}H_{12}O_6$, was established by its elemental analysis coupled with HRESIMS which showed a $[M + Na]^+$ ion-peak at *m/z* 323.0523 (calcd for $C_{16}H_{12}O_6Na$, 323.0532) and also a $[M + H]^+$ ion-peak at *m/z* 301.0705 $[M + H]^+$ (calcd for $C_{16}H_{13}O_6$, 301.0712), and ^{13}C NMR data, thereby indicating 11 indices of hydrogen deficiency (IDHs). In its UV spectrum, the molecule recorded absorption bands at λ_{max} 261, 297 and 383 nm, in accordance of its molecular framework. The IR spectrum of **2** showed characteristic absorption bands for phenolic hydroxyl (3340 cm^{-1}), ester carbonyl (1732 cm^{-1}), α,β-unsaturated lactone (1675 cm^{-1}), and aromatic unsaturation (1627, 1563 and 1472 cm^{-1}). The ^{1}H and ^{13}C NMR spectroscopic data (Table 2) implied that **2** also possesses a dibenzo-α-pyrone moiety, closely related to **1**, with just a difference in substitution pattern of the aromatic rings. The compound **2** showed ^{1}H NMR resonances for four aromatic protons – two at δ_H 7.36 (1H, d, *J* = 8.8 Hz) and 7.46 (1H, d, *J* = 9.2 Hz) for one ring, and other two at δ_H 6.62 (1H, br s) and 6.73 (1H, br s) for another. Comparison of both ^{1}H and ^{13}C NMR data of **2** with those of **1** revealed the presence of a carbomethoxyl (-$COOCH_3$) function as an extra substituent group in the former – the carbomethoxyl protons recorded ^{1}H NMR signal at δ_H 4.00 (3H, s) while the ester carbonyl and carbomethoxyl carbon showed ^{13}C NMR resonances at δ_C 169.27 and 53.27, respectively. The 11 IHDs in **2** are, thus, satisfied with the presence of two carbonyls, one lactone ring, and two benzene rings having a total of six double bonds. The spectral data for **2** are found to be comparable with those reported for molecules having identical skeleton [6,62].

Finally, the structure of **2** received concrete supports from detailed analysis of its 2D-NMR (^{1}H–^{1}H-COSY-45, HMQC and HMBC) spectral properties. All respective homo- and hetero-nuclear interactions are shown in Fig. 4 and the results are summarized in Table 2. The ^{1}H–^{1}H-COSY-45 spectrum of **2** recorded interactions of H-3 (δ_H 7.46) with H-4 (δ_H 7.36) and *vice-versa*. The HMQC correlations were observed as: H-3 (δ_H 7.46) correlates with C-3 (δ_C 122.27), H-4 (δ_H 7.36) with C-4 (δ_C 125.55), H-8 (δ_H 6.73) with C-8 (δ_C 107.40), H-10 (δ_H 6.62) withC-10 (δ_C 111.54), methoxy proton (δ_H 4.00) of ester group at C-1 with the methoxyl carbon at δ_C 53.27,and the methyl protons (δ_H 2.43) at C-9 with the methyl carbon at δ_C 22.74 ppm. The results from the hetero-nuclear multiple bond correlation (HMBC) spectral studies unambiguously confirmed the structure of molecule **2**. In the HMBC spectrum, H-3 at δ_H 7.46 showed interactions with C-2 (δ_C 152.25) and

Table 2
1D and 2D-NMR data for sopherone B (methyl 2,7-dihydroxy-9-methyl-6-oxo-6*H*-benzo[*c*]chromene-1-carboxylate; **2**).

Carbon	^{1}H (ppm/δ)	^{13}C (ppm/δ)	DEPT-135	^{1}H–^{1}H COSY-45	^{1}H–^{13}C HMQC	^{1}H–^{13}C HMBC
C-1	–	114.16	C	–	–	–
C-2	–	152.25	C	–	–	–
C-3	δ 7.46 (1H, d, *J* = 9.2 Hz, Ar—H)	122.27	CH	H-3 (δ 7.46) *vs* H-4 (δ 7.36)	δ 7.46 (H-3) *vs* δ 122.27 (C-3)	δ 7.46 (H-3) *vs* δ 152.25 (C-2), 118.70 (C-10b)
C-4	δ 7.36 (1H, d, *J* = 8.8 Hz, Ar—H)	125.55	CH	H-4 (δ 7.36) *vs* H-3 (δ 7.46)	δ 7.36 (H-4) *vs* δ 125.55 (C-4)	δ 7.36 (H-4) *vs* δ 114.16 (C-1), 150.88 (C-4a), 149.02 (C-10a)
C-4a	–	150.88	C	–	–	–
C-6	–	161.28	C	–	–	–
C-6a	–	118.70	C	–	–	–
C-7	–	152.25	C	–	–	–
C-8	δ 6.73 (1H, br s, Ar—H)	107.40	CH	–	δ 6.73 (H-8) *vs* δ 107.40 (C-8)	δ 6.73 (H-8) *vs* δ 111.54 (C-10)
C-9	–	149.02	C	–	–	–
C-10	δ 6.62 (1H, br s, Ar—H)	111.54	CH	–	δ 6.62 (H-10) *vs* δ 111.54 (C-10)	δ 6.62 (H-10) *vs* δ 107.40 (C-8)
C-10a	–	149.02	C	–	–	–
C-10b	–	118.70	C	–	–	–
C-11	–	169.27	C	–	–	–
C_9-CH_3	δ 2.43 (3H, s, Ar-C*H*$_3$)	22.74	CH_3	–	δ 2.43 (C*H*$_3$) *vs* δ 22.74 (*C*H$_3$)	δ 2.43 (C*H*$_3$) *vs* δ 107.40 (C-8), 149.02 (C-9), 111.54 (C-10), 149.02 (C-10a)
C_2-OH	–	–	–	–	–	–
C_7-OH	δ 12.19 (1H, s, Ar-O*H*)	–	–	–	–	δ 12.19 (OH) *vs* δ 161.28 (C-6), 107.40 (C-8)
C_{11}-OCH_3	δ 4.00 (3H, s, OC*H*$_3$)	53.27	OCH_3	–	δ 4.00 (OC*H*$_3$) *vs* δ 53.27 (O*C*H$_3$)	δ 4.00 (OC*H*$_3$) *vs* δ 169.27 (C-11)

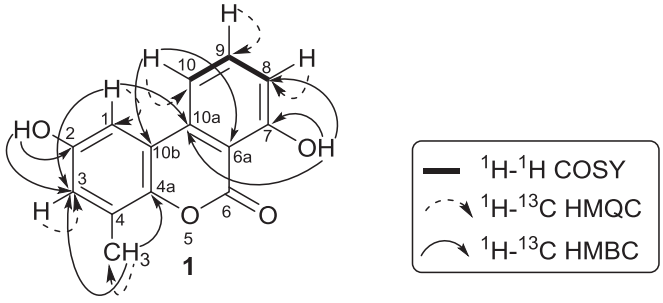

Fig. 3. ^{1}H – ^{1}H COSY, ^{1}H – ^{13}C HMQC, and ^{1}H – ^{13}C HMBC interactions for **1** (COSY, correlation spectroscopy; HMQC, hetero-nuclear multiple quantum coherence; HMBC, hetero-nuclear multiple bond correlation).

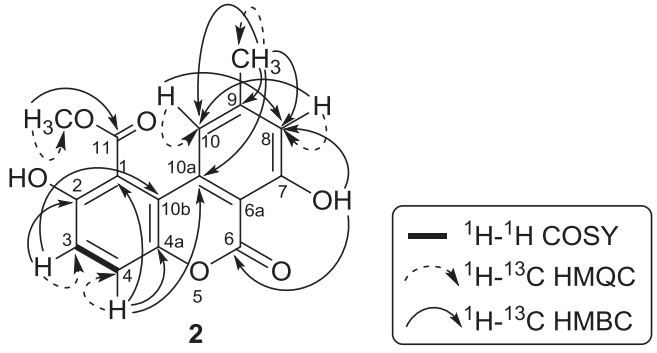

Fig. 4. ^{1}H – ^{1}H COSY, ^{1}H – ^{13}C HMQC, and ^{1}H – ^{13}C HMBC interactions for **2** (COSY, correlation spectroscopy; HMQC, hetero-nuclear multiple quantum coherence; HMBC, hetero-nuclear multiple bond correlation).

C-10b (δ_C 118.70), H-4 (δ_H 7.36) with C-1 (δ_C 114.16), C-4a (δ_C 150.88) and C-10a (δ_C 149.02), H-8 (δ_H 6.73) with C-10 (δ_C 111.54), H-10 (δ_H 6.62) with C-8 (δ_C 107.40), methyl protons (δ_H 2.43) at C-9 with C-9 and C-10a (δ_C 149.02), C-8 (δ_C 107.40), and C-10 (δ_C 111.54). The C-7 hydroxyl proton at (δ_H 12.19) experienced HMBCs with C-6 and C-8 at δ_C 161.28 and 107.40, respectively. In HMBCs, methoxyl protons (δ_H 4.00) interact with C-11 (δ_C 169.27) which indicate that a carbomethoxy group is present. All these observed HMBC interactions, as depicted in Fig. 4, are compatible with the structure proposed for **2**. Therefore, compound **2** was assigned as methyl 2,7-dihydroxy-9-methyl-6-oxo-6*H*-benzo[*c*]chromene-1-carboxylate (named as sopherone B).

4. Conclusion

In conclusion, two new biologically relevant natural dibenzo-α-pyrones, here referred to as sopherone A (**1**) and sopherone B (**2**), were successfully isolated for the first time from *Cassia sophera* (Caesalpiniaceae) stems and their structure were unequivocally determined as 2,7-dihydroxy-4-methyl-6*H*-benzo[*c*]chromen-6-one and methyl 2,7-dihydroxy-9-methyl-6-oxo-6*H*-benzo[*c*]chromene-1-carboxylate, respectively, from 1D- and 2D-NMR analyses. The dibenzo-α-pyrone scaffold represents a key structural motif for a considerable number of pharmaceutically prominent molecules exhibiting a wide range of multi-faceted biological properties, and hence, this set of two newly reported biomolecules would provoke the attentions of both medicinal and synthetic chemists at large.

Conflict of interests

The authors declare no conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Scanned copies of 1D- and 2D-NMR spectra of the natural dibenzo-α-pyrone isolates [sopherone A (**1**) and sopherone B (**2**)] are supplemented as Supporting Information Electronic File. Supplementary data to this article can be found online at https://doi.org/10.1016/j.fitote.2019.05.008.

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