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From screening to the hectogram scale: sustainable electrochemical synthesis of mefenpyr-diethyl†

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To demonstrate the technical application potential of electrochemical reactions, we developed a synthetic method to access the commercially available herbicide safener mefenpyr-diethyl. In a simple undivided electrolysis cell with non-hazardous aqueous sodium iodide as supporting electrolyte and mediator, the target compound was synthesized *via* the (*E*)- or (*Z*)-hydrazone. Environmentally benign solvents or solvent-free conditions ensure a sustainable process and excellent recycling of the excess reagents. Finally, scale-up to the hectogram scale was performed with good to excellent yield.

Introduction

The global climate crisis necessitates action and has caused a shift towards a more sustainable economy. For the chemical industry, this will mean a renunciation of long-practiced processes. Nowadays, highly efficient synthesis with regards to atom economy and energy efficiency is necessary not only from an economical but also an ecological point of view. This has led to a need for a sustainable, circular economy.[1] Furthermore, minimizing risks by circumventing the use of hazardous chemicals and establishing inherently safe processes is of utmost importance for modern synthetic methodologies.[2,3]

Electrochemistry is linked to the principles of green chemistry and can contribute to a more sustainable chemical industry.[3,4] Hazardous and often expensive redox reagents can be substituted with electric current.[5] Electricity contributes not only to the sustainability of a process, but also to its safety.[6] Control over the reaction is simply given by controlling the current density, as the initial electron transfer is confined to the electrode surface and runaway reactions can be avoided.[7] Furthermore, organic electrochemistry facilitates resource efficiency, as unique reactivities can give access to synthetic shortcuts and additives, *e.g.*, supporting electrolytes, can be easily recycled.[8] Thus, a reaction can be considered practically waste- and pollutant-free, if the applied electricity originates from renewable resources.[9]

The structural motifs of pyrazoles and pyrazolines are widely found among biologically active substances. Their potential pharmaceutical applications include antimicrobial,[10] antipsychotic,[11] anti-inflammatory,[12] anti-nociceptive,[13] anti-cancer[14] and anti-obesity drugs.[15] Furthermore, a variety of agrochemicals featuring a pyrazole or pyrazoline moiety have been developed, such as the herbicide benzofenap (**3**)[16] and the herbicide safener mefenpyr-diethyl (**1**)[17] (Chart 1). The latter is commonly used for fenoxaprop-P-ethyl (**2**) detoxifica-

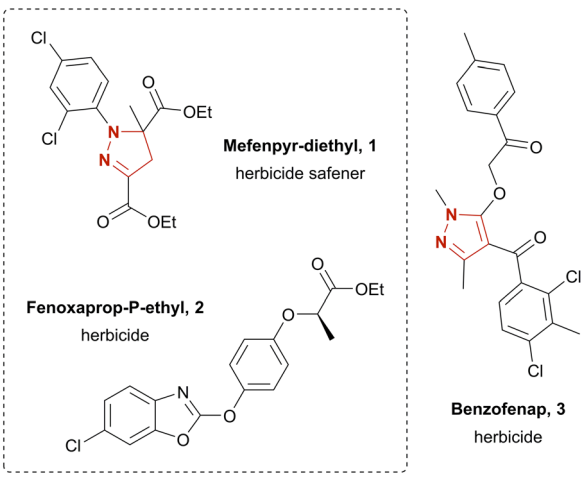

Chart 1 Examples of commercial herbicides and herbicide safeners.

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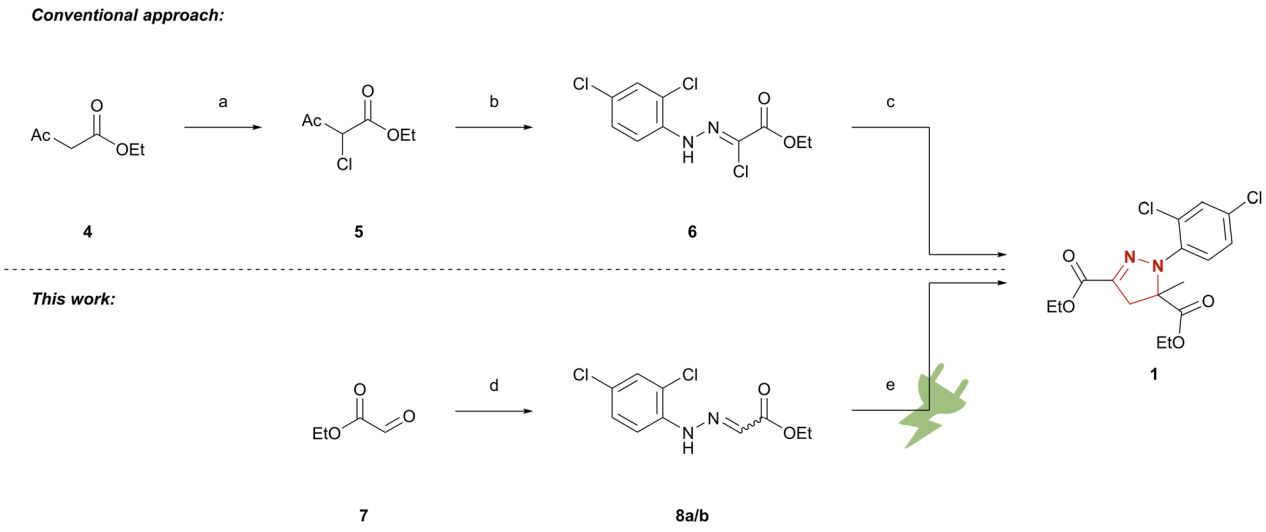
tion in wheat and barley.[18] Conventionally, pyrazolines and pyrazoles are synthesized by condensation of hydrazones with 1,3-diketones,[19,20] 2-ynones,[21] or 2-enones.[22] Yet, these strategies suffer from an often-unsatisfying regioselectivity and difficult-to-obtain starting materials. Other strategies rely on oxidative synthesis of hydrazonoyl halides; subsequent pyrazoline or pyrazole formation is achieved *via* base-promoted liberation of the corresponding nitrile imine and [3 + 2] cycloaddition with a dipolarophile.[19,26,27] The yield for the latter route commonly varies as much as 38–95% over the two steps.[27] However, often hazardous and expensive catalysts and oxidizers, *e.g.*, *N*-chlorosuccinimide[27] (NCS), are employed. Literature has several further examples on the electrochemistry of pyrazolines and pyrazoles. These include intramolecular synthesis,[28] 4-halogenation,[29] dimerization,[30] and *N*-arylation of pyrazoles.[31] Yet, pyrazol(in)e syntheses are rather poorly explored. Reported examples additionally suffer from elaborate starting materials which themselves are borne out of complex synthetic routes.[32] Recently, the electro-chemical generation of stable diazo compounds[33] and a simple and scalable electrosynthesis of pyrazolines and pyrazoles[34] starting from easily accessible hydrazones were published. The latter gave access to a broad variety of pyrazolines in up to excellent yields by using aqueous sodium iodide as mediator and supporting electrolyte in a biphasic system using ethyl acetate as solvent.

The conventional synthetic route to mefenpyr-diethyl (**1**) follows a highly complex pathway.[25,35] First, ethyl acetoacetate (**4**) is chlorinated in position 2. The key intermediate **6** is yielded *via* nucleophilic attack of ethyl 2-chloroacetoacetate (**5**) at the corresponding aryldiazonium species and deacetylation of the formed adduct. The hydrazonoyl chloride **6** is finally converted to mefenpyr-diethyl (**1**) by base-promoted cycloaddition as seen below (Scheme 1). To demonstrate the applicability of electrochemical techniques in modern industrially relevant processes,[36] we developed an electrochemical approach for an environmentally benign synthesis of herbicide safener mefenpyr-diethyl (**1**). Aqueous sodium iodide is used in a dual role as mediator and supporting electrolyte. The use of inexpensive isostatic graphite (C_{gr}) as electrode material in environmentally benign solvents or under solvent-free conditions ensures a sustainable process and excellent recycling potential of the excess reagents. The simple setup of a galvanostatic beaker-type cell allows for easy scale-up to hectogram scale.

Results and discussion

We chose the synthesis of mefenpyr-diethyl (**1**) as an example reaction to highlight the development of a technically relevant electrochemical reaction from screening to scale-up. The previously employed conditions for starting material synthesis led to selective formation of (*Z*)-hydrazone **8a** in an excellent yield of 90% on 15 mmol scale.[34] However, scale-up resulted in a massive decrease in yield of **8a**, as significant amounts of the corresponding (*E*)-hydrazone **8b** were formed according to ^{1}H NMR. However, modification of this method allowed for selective synthesis of **8a** even on larger scale. Therefore, treatment of the hydrazine hydrochloride with triethylamine in THF and filtration prior to addition to the corresponding glyoxylate **7** proved beneficial. Furthermore, an excess of aldehyde **7** was required to supress hydrazinolysis of the ethyl ester, yielding (*Z*)-hydrazone **8a** in a satisfactory yield of 80% on 47 mmol scale. Further scale-up to hectogram scale (0.9 mol) again resulted in a decreased yield of 63%, but maintained the selectivity towards the (*Z*)-hydrazone **8a**. Nevertheless, on this



Scheme 1 Synthetic approaches to mefenpyr-diethyl (**1**). (a) DMSO, NCS, room temperature;[23] (b) 2,4-dichloroaniline, $NaNO_2$, aq. HCl, 0 °C, then **5**, NaOAc, EtOH, room temperature;[24] (c) NEt_3/$KHCO_3$, ethyl methacrylate, 60–65 °C;[25] (d) 2,4-dichlorophenylhydrazine hydrochloride, THF, NEt_3; EtOH 0 °C → room temperature *or* 2,4-dichlorophenylhydrazine hydrochloride, EtOH, AcOH, 80 °C; (e) $C_{gr}||C_{gr}$, 1 M aq. NaI, ethyl methacrylate, 27.9 mA cm^{-2}, 5.4 *F*, 33 °C *or* $C_{gr}||C_{gr}$ EtOH/MeCN 1 : 1 (v/v), ethyl methacrylate, NaI, 4.0 mA cm^{-2}, 4.03 *F*, 25 °C.

scale parameters such as efficient mixing to overcome concentration gradients, changes in temperature due to alteration in heat transfer, and the relative concentration as well as stability of products and starting materials need to be considered. Thus, transferring this synthesis to hectogram scale or beyond does require re-evaluation of the reaction conditions.[37] Another common route to access hydrazones involves refluxing the corresponding hydrazine and aldehyde in methanol or ethanol with catalytic amounts of acid.[38] This method allowed for selective synthesis of the (*E*)- hydrazone **8b** in a very good yield of 89% on hectogram scale (0.75 mol). Thus, selective synthesis of both isomers in satisfactory yields was achieved by controlling solvent, temperature, and additives.

The electrochemical synthesis of mefenpyr-diethyl was initially investigated with the (*Z*)-hydrazone **8a** to re-evaluate the solvent system. Ethyl acetate, *tert*-butyl methyl ether, dichloromethane, and chlorobenzene were tested as organic solvents (phase ratio org. solvent/1 M aq. NaI of 1 : 4). Unfortunately, the chlorinated solvents were observed to give the highest yields (Table S7, ESI†). Thus, further reaction optimization aiming for a sustainable system was necessary. A statistically driven optimization *via Design of Experiments* (DoE)[39] was pursued to ensure a comprehensive investigation of the system. In a two-step optimization *via* fractional factorial designs (both 2^{3-1}, resolution III with central point and rotatable axial points, each data point acquired thrice) regarding the applied amount of charge (*Q*), the current density (*j*), and the amount of acrylate, the following conditions were found: graphite electrodes, 27.9 mA cm^{-2}, 5.4 *F*, 3.21 eq. ethyl methacrylate (Fig. 1). Through further linear optimization, solvent-free electrolytic conditions were achieved, employing 250 mg (0.96 mmol) hydrazone **8a** per 1 mL aqueous phase at 33 °C. This enabled full conversion of 1 g (3.8 mmol) **8a** in a 5 mL screening cell, accessing mefenpyr-diethyl (**1**) in 93% GC-yield. Hence, the reaction was transferred to a 50 mL jacketed beaker-type cell and run on 5 g-scale (19.1 mmol). This allowed for more efficient mixing of the reaction mixture due to more powerful cross-shaped stirring bars and the target compound **1** was obtained in a very good isolated yield of 86%.

Furthermore, the electrochemical conversion of the (*E*)-hydrazone **8b** under previously optimized conditions was tested. Contrary to hydrazone **8a**, application of hydrazone **8b** in the reaction resulted in a rather poor yield of mefenpyr-diethyl (**1**) as well as incomplete conversion. According to LC-MS analysis, both isomers exhibit a pronounced difference in polarity (Fig. S22 and S23, ESI†). Whilst (*Z*)-hydrazone **8a** is more polar than the formed product **1**, the initial oxidation of the hydrazone can occur at the organic/aqueous phase boundary. Thus, even under solvent-free conditions the reaction is thought to follow the initially hypothesized mechanism.[34] In contrast, (*E*)-hydrazone **8b** shows increased lipophilicity compared to **8a** and is even more apolar than mefenpyr-diethyl. This seems to strongly disable efficient oxidation of the hydrazone at the interface, explaining the insufficient conversions and poor yields of **1**. Addition of *tert*-butyl methyl ether as solvent improved the results, but still gave un-satisfactory yields (GC). To circumvent the inhibited oxidation of the lipophilic (*E*)-hydrazone **8b** at the phase boundary, application of a homogeneous system was investigated. Thus, sodium iodide was employed in a dual role as mediator and supporting electrolyte in various organic solvents (acetonitrile, methanol, ethanol, isopropanol). Generally, the homogeneous system proved suitable for conversion of the (*E*)-hydrazone **8b**.

The best results were obtained using a mixture of acetonitrile/ethanol (1 : 1 v/v) as solvent system and further optimization was performed *via DoE*. A fractional factorial design

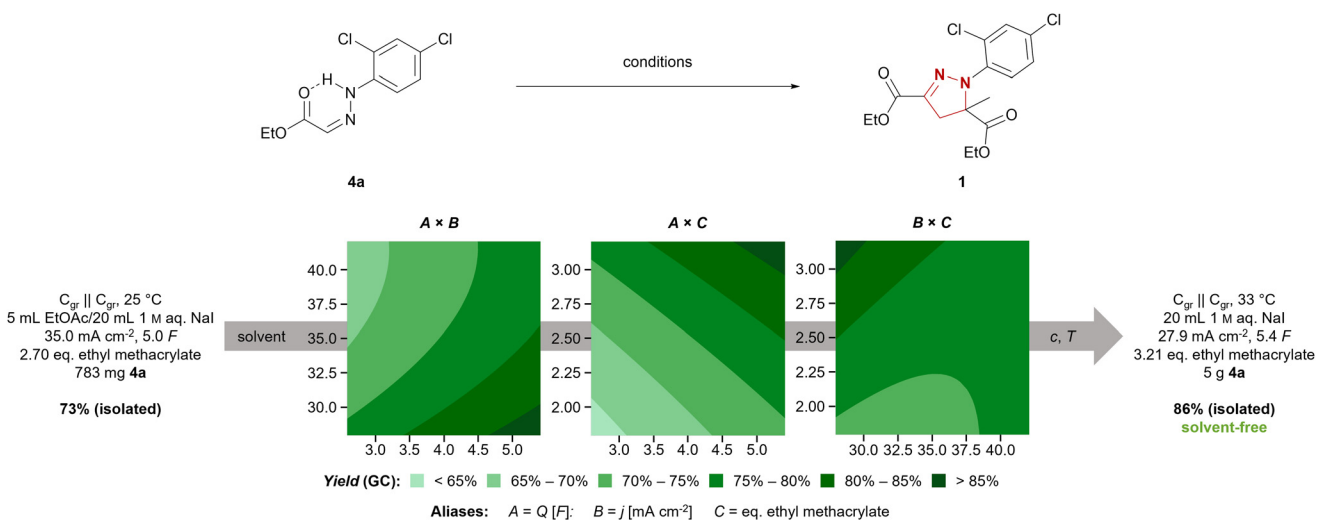


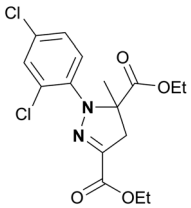
Fig. 1 Contour plots of the yield (GC, 1,3,5-trimethoxybenzene as internal standard) for the optimization process *via* DoE for the synthesis of **1** form (*Z*)-hydrazone **8a**. The solvent, substrate concentration *c* and reaction temperature *T* were optimized in a linear fashion. Synthesis conditions before and after optimization are shown on the left and right, respectively. Holding values: *A* = 5.41 *F*; *B* = 27.9 mA cm^{-2}; *C* = 3.21 eq. GC yields determined with 1,3,5-trimethoxybenzene as internal standard after external calibration.

(2^{5-2}, resolution III with central point and rotatable axial points, each data point acquired once, central point thrice) led to the following optimum conditions: graphite electrodes, acetonitrile/EtOH (1 : 1 v/v), 2.79 eq. NaI, 3.79 eq. ethyl methacrylate, 9.0 mA cm^{-2}, 4.03 *F*, rt. An additional linear optimization of the current density revealed an optimum at 4.0 mA cm^{-2}. With the adjusted conditions, full conversion of hydrazone **8b** was achieved and mefenpyr-diethyl (**1**) was obtained in a satisfactory isolated yield of 71% on 2.85 mmol scale. Hence, the electrosynthesis of herbicide safener **1** seems to be strongly solvent dependent with regards to the substrate configuration.

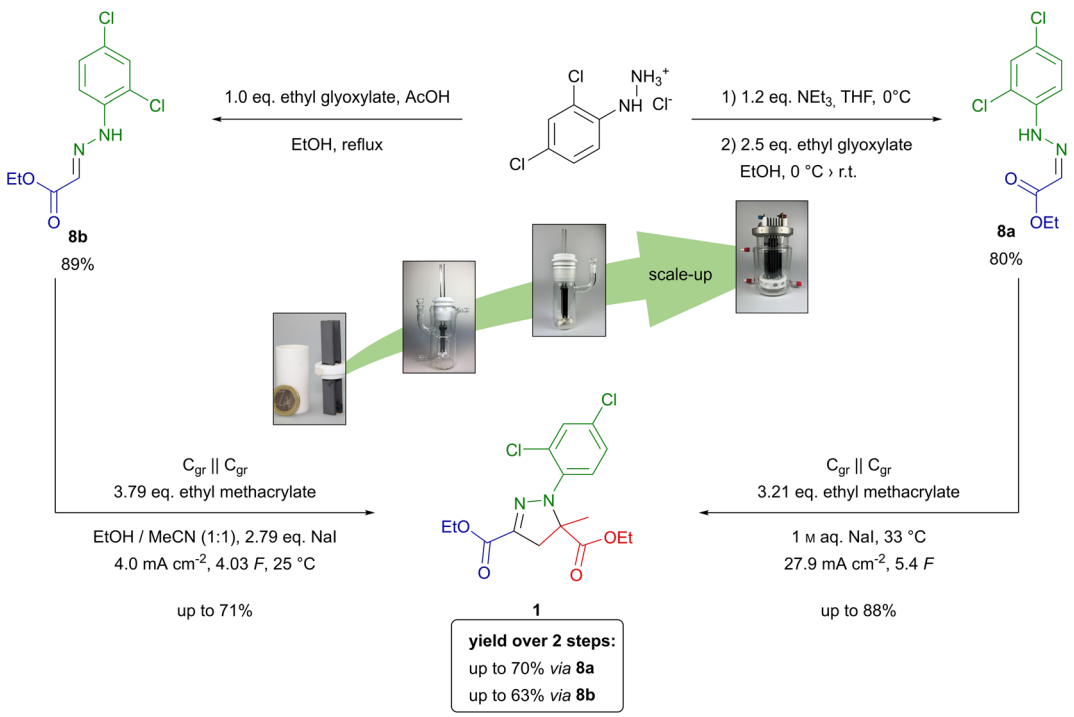
After suitable reaction conditions for both hydrazones **8a** and **8b** were established, the reactions were investigated regarding scalability. The results are summarized in Table 1.

To our delight, both established synthetic routes for conversion of hydrazones **8a** and **8b** to mefenpyr-diethyl (**1**) showed robustness in scale-up. Synthesis of **1** starting from (*E*)-hydrazone **8b** was performed in a satisfactory yield of 66% on multigram-scale. Even on multi-decagram scale in a bipolar cell set-

Table 1 Scale-up of the synthesis of mefenpyr-diethyl (**1**) from hydrazones **8a** and **8b**

Product	Hydrazone			
 **1**	**8a**[a]	**86%** 16.4 mmol 6.13 g	**88%** 88.2 mmol 32.9 g	**66%** 0.528 mol 197 g
	8b[b]	**71%** 2.03 mmol 757 mg	**66%** 14.9 mmol 5.59 g	**63%** 101 mmol 37.8 g

[a] Solvent-free, c = 0.96 M **8a** in 1 M NaI (aq.), 3.21 eq. ethyl methacrylate, graphite electrodes, 33 °C, 27.9 mA cm^{-2}, 5.4 F. [b] c = 0.11 M **8b** in EtOH/MeCN 1 : 1 (v/v), 3.79 eq. ethyl methacrylate, 2.79 eq. NaI, 4.0 mA cm^{-2}, 4.03 F.



Scheme 2 Synthesis from screening to scale-up of mefenpyr-diethyl (**1**) from 2,4-dichlorophenylhydrazone hydrochloride *via* hydrazones **8a** and **8b**.

up,[40] the homogeneous reaction proved to be stable, and mefenpyr-diethyl was obtained in a comparable yield of 63%. Similarly, (*Z*)-hydrazone **8a** underwent the desired conversion smoothly under solvent-free conditions at different scales. Even when going from gram-scale to decagram-scale, no loss in yield was observed and target compound **1** was obtained in an excellent yield of 88%. Thus, we decided to transfer this reaction to even larger scale, employing 209 g (0.8 mol) of (*Z*)-hydrazone **8a**. A stacked electrode setup was used,[40] and mefenpyr-diethyl was obtained in 66% (197 g) on hectogram scale. On these scales, the counter electrode reaction represents an important process which must be taken into consideration. The counter electrode reaction for the represented example is the evolution of hydrogen. This is a well-known and extensively studied reaction, which can be easily controlled.[41]

To compare both approaches to herbicide safener **1**, the yield over two steps including hydrazone formation in the first and electrochemical conversion in the second step must be considered. Overall, mefenpyr-diethyl (**1**) was obtained in a total yield of up to 70% over two steps *via* (*Z*)-hydrazone **8a**. The competing sequence *via* (*E*)-hydrazone **8b** yielded the desired product **1** in up to 63% (Scheme 2).

Overall, the synthesis of mefenpyr-diethyl (**1**) *via* (*Z*)-hydrazone **8a** is slightly more favourable compared to the method using (*E*)-hydrazone **8b**. However, both synthetic strategies demonstrate excellent performance regarding their scalability. Thus, these electro-organic procedures show potential for application on technically relevant scale.

Conclusions

A sustainable two-step protocol for the preparation of the industrially relevant herbicide safener mefenpyr-diethyl was established.

The selective synthesis of (*E*)- or (*Z*)-hydrazone as substrates for the electrochemical conversion was achieved by solvent-control in very good yields. A substantial difference in the polarity of the hydrazones was found to require vastly different reaction conditions for a smooth synthesis of the title compound. Whereas the (*E*)-hydrazone required a homogeneous system for successful conversion, the (*Z*)-hydrazone was converted in a biphasic system under solvent-free conditions. A series of scale-up experiments revealed a good to excellent stability for both processes. Thus, the (*E*)-hydrazone yielded up to 71% mefenpyr-diethyl and a 50-fold scale-up to multi-decagram scale was performed successfully. In parallel, the conversion of the (*Z*)-hydrazone yielded 86–88% in up to multi-decagram scale and even a scale-up to hectogram scale was demonstrated.

In conclusion, the general application potential of this exemplary electrochemical conversion on technically relevant scale was proven. Both reaction sequences captivate with the simplicity of their electrochemical key steps: an undivided beaker-type cell equipped with inexpensive graphite electrodes and excess reagents can be recycled easily. By employing environmentally benign solvents or solvent-free conditions with abundant and non-hazardous sodium iodide in a dual role as supporting electrolyte and mediator, the established protocol offers a sustainable and feasible alternative to conventional synthetic methods.

Author contributions

M. L. and S. H. contributed equally to this work. M. L. and S. H. established the reaction, analysed experimental data, and performed the scale-up reactions. M. L., S. H., and F. N. W synthesized starting materials. M. L., S. H., and F. N. W. conducted the experiments for initial reaction optimization and DoE. M. L., S. H., R. M. B., S. J. K., M. J. F., and S. R. W. wrote the manuscript. All authors discussed the results and agreed to the manuscript.

Conflicts of interest

There are no conflicts to declare.

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References

1 (*a*) I. T. Horváth, *Chem. Rev.*, 2018, **118**, 369; (*b*) N. Jain, *Nat. Rev. Methods Primers*, 2022, **2**, 61.
2 P. T. Anastas, *Green Chem.*, 2003, **5**, G29.
3 P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301.
4 (*a*) J. Seidler, J. Strugatchi, T. Gärtner and S. R. Waldvogel, *MRS Energy Sustain.*, 2020, **7**, E42; (*b*) K. Lam, S. D. Minteer and D. L. Poole, *Org. Biomol. Chem.*, 2023, **21**, 221; (*c*) K. Lam and K. M. P. Wheelhouse, *Org. Process Res. Dev.*, 2021, **25**, 2579.
5 J. L. Röckl, D. Schollmeyer, R. Franke and S. R. Waldvogel, *Angew. Chem., Int. Ed*, 2020, 59, 315.
6 (*a*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230; (*b*) A. Wiebe, T. Gieshoff, S. Möhle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594; (*c*) B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099.
7 S. B. Beil, D. Pollok and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2021, **60**, 14750.
8 (*a*) S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 6018;

(*b*) A. Shatskiy, H. Lundberg and M. D. Kärkäs, *ChemElectroChem*, 2019, **6**, 4067.
9 D. Pollok and S. R. Waldvogel, *Chem. Sci.*, 2020, **11**, 12386.
10 R. Verma, S. K. Verma, K. P. Rakesh, Y. R. Girish, M. Ashrafizadeh, K. S. Sharath Kumar and K. S. Rangappa, *Eur. J. Med. Chem.*, 2021, **212**, 113134.
11 G. Li, Y. Cheng, C. Han, C. Song, N. Huang and Y. Du, *RSC Med. Chem.*, 2022, **13**, 1300.
12 S. Basu, D. A. Barawkar, V. Ramdas, M. Patel, Y. Waman, A. Panmand, S. Kumar, S. Thorat, M. Naykodi, A. Goswami, B. S. Reddy, V. Prasad, S. Chaturvedi, A. Quraishi, S. Menon, S. Paliwal, A. Kulkarni, V. Karande, I. Ghosh, S. Mustafa, S. De, V. Jain, E. R. Banerjee, S. R. Rouduri, V. P. Palle, A. Chugh and K. A. Mookhtiar, *Eur. J. Med. Chem.*, 2017, **134**, 218.
13 I. F. Florentino, D. P. B. Silva, C. S. Cardoso, R. Menegatti, F. S. de Carvalho, L. M. Lião, P. M. Pinto, S. Peigneur, E. A. Costa and J. Tytgat, *Biomed. Pharmacother.*, 2019, **115**, 108915.
14 (*a*) H. Aziz, A. F. Zahoor and S. Ahmad, *J. Chil. Chem. Soc.*, 2020, **65**, 4746; (*b*) F. E. Bennani, L. Doudach, Y. Cherrah, Y. Ramli, K. Karrouchi, M. Ansar and M. E. A. Faouzi, *Bioorg. Chem.*, 2020, **97**, 103470.
15 A. Samat, B. Tomlinson, S. Taheri and G. N. Thomas, *Recent Pat. Cardiovasc. Drug Discovery*, 2008, **3**, 187.
16 W. C. Quayle, D. P. Oliver, S. Zrna and A. Fattore, *J. Agric. Food Chem.*, 2007, **55**, 5199.
17 (*a*) L. Bianchi, S. M. Perissato, V. M. Anunciato, R. C. Dias, D. M. Gomes, C. A. Carbonari and E. D. Velini, *J. Environ. Sci. Health, Part B*, 2021, **56**, 163; (*b*) R. D. C. Dias, L. Bianchi, V. M. Anunciato, L. Tropaldi, P. V. D. Silva, C. A. Carbonari and E. D. Velini, *Ornam. Hortic.*, 2021, **27**, 281.
18 (*a*) L. Yuan, G. Ma, Y. Geng, X. Liu, H. Wang, J. Li, S. Song, W. Pan and Z. Hun, *PLoS One*, 2021, **2**, e0256884; (*b*) E. Hacker, H. Bieringer, L. Willms, W. Rösch, H. Köcher and R. Wolf, *J. Plant Dis. Prot.*, 2000, 493; (*c*) A. C. Cataneo, L. C. Ferreira, M. M. Mischan, E. D. Velini, N. Corniani and A. L. Cerdeira, *Planta Daninha*, 2013, **31**, 387.
19 S. Fustero, A. Simón-Fuentes and J. F. Sanz-Cervera, *Org. Prep. Proced. Int.*, 2009, **41**, 253.
20 (*a*) S. Fustero, R. Román, J. F. Sanz-Cervera, A. Simón-Fuentes, A. C. Cuñat, S. Villanova and M. Murguía, *J. Org. Chem.*, 2008, **73**, 3523; (*b*) S. T. Heller and S. R. Natarajan, *Org. Lett.*, 2006, **8**, 2675.
21 D. B. Grotjahn, S. Van, D. Combs, D. A. Lev, C. Schneider, M. Rideout, C. Meyer, G. Hernandez and L. Mejorado, *J. Org. Chem.*, 2002, **67**, 9200.
22 A. E. Sarhan, A. A. Sediek, N. M. Khalifa and E. E. Hasan, *Heterocycles*, 2022, **104**, 447.
23 B. Sreedhar, P. Surendra Reddy and M. Madhavi, *Synth. Commun.*, 2007, **37**, 4149.
24 S. Altomonte, G. L. Baillie, R. A. Ross and M. Zanda, *RSC Adv.*, 2015, **5**, 13692.
25 G. Schlegel, US5908938A, 1999.
26 D. Li, S. Qiu, Y. Chen and L. Wu, *ChemistrySelect*, 2020, **5**, 12034.
27 L. Song, Y. Lai, H. Li, J. Ding, H. Yao, Q. Su, B. Huang, M.-A. Ouyang and R. Tong, *J. Org. Chem.*, 2022, **87**, 10550.
28 S. A. Paveliev, O. O. Segida, O. V. Bityukov, H.-T. Tang, Y.-M. Pan, G. I. Nikishin and A. O. Terent'ev, *Adv. Synth. Catal.*, 2022, **364**, 3910.
29 (*a*) B. V. Lyalin and V. A. Petrosyan, *Russ. Chem. Bull.*, 2014, **63**, 360; (*b*) B. V. Lyalin, V. A. Petrosyan and B. I. Ugrak, *Russ. J. Electrochem.*, 2008, **44**, 1320; (*c*) B. V. Lyalin, V. A. Petrosyan and B. I. Ugrak, *Russ. Chem. Bull.*, 2010, **59**, 1549; (*d*) S. Zandi and F. Nikpour, *Z. Naturforsch., B: J. Chem. Sci.*, 2022, **77**, 35.
30 F. Pragst and C. Böck, *J. Electroanal. Chem. Interfacial Electrochem.*, 1975, **61**, 47.
31 S. R. Waldvogel, S. Lips, M. Selt, B. Riehl and C. J. Kampf, *Chem. Rev.*, 2018, **118**, 6706.
32 X. Wei and B. Speiser, *Electrochim. Acta*, 1997, **42**, 73.
33 N. Tanbouza, A. Petti, M. C. Leech, L. Caron, J. M. Walsh, K. Lam and T. Ollevier, *Org. Lett.*, 2022, **24**, 4665.
34 M. Linden, S. Hofmann, A. Herman, N. Ehler, R. M. Bär and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2023, e202214820.
35 G. Shi, H. Hu and H. Meng, CN111592493A, 2020.
36 (*a*) D. Pollok, B. Gleede, A. Stenglein and S. R. Waldvogel, *Aldrichimica Acta*, 2021, **54**, 3; (*b*) J. Jörissen, in *Encyclopedia of Electrochemistry*, ed. A. J. Bard, Wiley, 2007; (*c*) J. R. Hitchin, *Nat. Rev. Methods Primers*, 2022, **2**, 28.
37 D. C. Hendershot and A. Sarafinas, *Chem. Health Saf.*, 2005, **12**, 29.
38 (*a*) N. Thamban Chandrika, E. K. Dennis, S. K. Shrestha, H. X. Ngo, K. D. Green, S. Kwiatkowski, A. G. Deaciuc, L. P. Dwoskin, D. S. Watt and S. Garneau-Tsodikova, *Eur. J. Med. Chem.*, 2019, **164**, 273; (*b*) J. R. Hwu, C. C. Lin, S. H. Chuang, K. Y. King, T.-R. Su and S.-C. Tsay, *Bioorg. Med. Chem.*, 2004, **12**, 2509.
39 (*a*) E. Babaoglu and G. Hilt, *Chem. – Eur. J.*, 2020, **26**, 8879; (*b*) M. Dörr, M. M. Hielscher, J. Proppe and S. R. Waldvogel, *ChemElectroChem*, 2021, **8**, 2621; (*c*) M. Dörr, J. L. Röckl, J. Rein, D. Schollmeyer and S. R. Waldvogel, *Chem. – Eur. J.*, 2020, **26**, 10195; (*d*) M. Hielscher, E. K. Oehl, B. Gleede, J. Buchholz and S. R. Waldvogel, *ChemElectroChem*, 2021, **8**, 3904; (*e*) M. Linden, M. M. Hielscher, B. Endrődi, C. Janáky and S. R. Waldvogel, in *Flow Chemistry – Applications*, ed. F. Darvas, G. Dormán, V. Hessel and S. V. Ley, De Gruyter, 2021, pp. 31–68; (*f*) R. Möckel, E. Babaoglu and G. Hilt, *Chem. – Eur. J.*, 2018, **24**, 15781; (*g*) R. Möckel, J. Hille, E. Winterling, S. Weidemüller, T. M. Faber and G. Hilt, *Angew. Chem., Int. Ed.*, 2018, **57**, 442; (*h*) M. Santi, J. Seitz, R. Cicala, T. Hardwick, N. Ahmed and T. Wirth, *Chem. – Eur. J.*, 2019, **25**, 16230.
40 G. H. M. de Kruijff, T. Goschler, N. Beiser, A. Stenglein, O. M. Türk and S. R. Waldvogel, *Green Chem.*, 2019, **21**, 4815.
41 M. Klein and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204140.

