



HAL
open science

Electrochemical sulfonylation of imidazoheterocycles under batch and continuous flow conditions

Elise Leclercq, Maxime Boddaert, Mathieu Beaucamp, Maël Penhoat, Laetitia Chausset-Boissarie

► **To cite this version:**

Elise Leclercq, Maxime Boddaert, Mathieu Beaucamp, Maël Penhoat, Laetitia Chausset-Boissarie. Electrochemical sulfonylation of imidazoheterocycles under batch and continuous flow conditions. *Organic & Biomolecular Chemistry*, 2021, 19 (43), pp.9379-9385. 10.1039/D1OB01822A . hal-03440235

HAL Id: hal-03440235

<https://hal.science/hal-03440235v1>

Submitted on 20 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

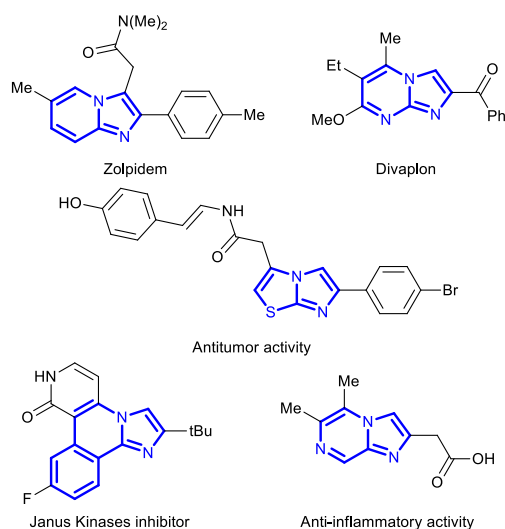
Electrochemical sulfonylation of imidazoheterocycles in Batch and continuous Flow

Elise Leclercq,^a Maxime Boddart,^a Mathieu Beaucamp,^a Maël Penhoat,^a Laëticia Chausset-Boissarie*^a

An efficient and versatile protocol for the C-H sulfonylation of imidazoheterocycles *via* electrochemical activation was established in batch and in flow. The selective C-H bond functionalization proceeded under catalyst- and oxidant-free conditions and tolerated a wide range of functional group. Various sodium sulfonates as well as imidazo[1,2-*a*]-pyridines, -pyrimidine, -quinoline, -isoquinoline, imidazo[1,2-*b*]pyridazine, imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[1,2-*b*]thiazoles reacted successfully. Interestingly, significant acceleration and higher yields were obtained under microfluidic conditions.

Over the last years, electrochemically-induced reactions have re-emerged as a powerful tool for initiating various organic transformations under mild conditions,¹ and thus gained significance in the field of sustainable chemistry.² Indeed, it provides a clean and traceless energy source to notably induced oxidative cross-coupling.³ Nevertheless, the use of this versatile energy source has been hampered in the chemical industry mainly due to its limited scale-up potential.⁴ In recent years, great progress has been made with regard to electrochemical continuous processes using microreactor technology. Owing to small length scales, mass and heat transfer can be significantly accelerated in electrosynthesis flow cells. Moreover, this technology enables high current densities due to small electrode distance, increases reaction efficiency and selectivity and facilitates upscaling efforts.⁵

Imidazoheterocycles are important structural motif present in various biologically active compounds showing important bioactivities like anti-inflammatory,⁶ antiviral,⁷ antibacterial,⁸ anticancer,⁹ and antifungal,¹⁰ in marketed drugs including Zolpidem¹¹ (a hypnotic drug), Alpidem,¹² Divaplon¹³ (anxiolytics), Zolimidine¹⁴ (an antiulcer drug), Olprinone¹⁵ (a cardiotonic agent), and Minodronic acid¹⁶ (used for treatment of osteoporosis) as well as in organic materials¹⁷ (Scheme 1). As a consequence, the functionalization of imidazoheterocycles has been intensively studied in the past decades.¹⁸



Scheme 1 Representative drugs and bioactive compounds containing imidazoheterocycle unit.

Surprisingly, until lately, few methods described the direct sulfonylation of imidazoheterocycles. Moreover, these methodologies require either the use of stoichiometric amount of oxidant,¹⁹ transition metal catalyst,²⁰ high temperature²¹ or extended reaction time.²² Therefore, further development of a practical and direct methodology to synthesize sulfonylated imidazoheterocycles is of great interest since the introduction of sulfonyl group impacts the biological activities as well as the photophysical properties of parent molecules.²³ Very recently, the group of Kim and Wu,²⁴ Lei²⁵ and Oh²⁶ concurrently, reported an oxidative electrochemical sulfonylation protocol. However, despite the synthetic value of these electrochemical approaches, the scope of the imidazoheterocycles coupling partners remains restricted to a limited set of imidazo[1,2-*a*]-pyridines. As part of our interest to develop efficient continuous flow protocols as environmentally benign tools,²⁷ herein we report our efforts to develop a direct electrochemical sulfonylation protocol of imidazoheterocycles in batch and in flow.

^a Univ. Lille, CNRS, USR 3290 - MSAP - Miniaturisation pour la Synthèse l'Analyse et la Protéomique F-59000 Lille, France. E-mail: Laetitia.boissarie@univ-lille.fr

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Optimization studies for the electrochemical sulfonation of imidazoheterocycles in Batch^a or Continuous Flow^b

Entry	Electrodes	Electrolyte (M)	Solvent	Current (mA)	Yield (%) ^c
Batch Conditions^a					
1	C(+) Pt(-)	LiClO ₄ (0.4)	CH ₃ CN/H ₂ O (5:2)	10	68
2 ^d	C(+) Ni(-)	LiClO ₄ (0.4)	CH ₃ CN/H ₂ O (5:2)	10	60
3 ^e	C(+) C(-)	LiClO ₄ (0.4)	CH ₃ CN/H ₂ O (5:2)	10	56
4	C(+) Pt(-)	LiClO ₄ (0.4)	CH ₃ CN/H ₂ O (6:4)	10	18
5	C(+) Pt(-)	LiClO ₄ (0.4)	CH ₃ CN/H ₂ O (8:2)	10	63
6	C(+) Pt(-)	LiClO ₄ (0.1)	CH ₃ CN/H ₂ O (5:2)	10	49
7	C(+) Pt(-)	<i>n</i> Bu ₄ NClO ₄ (0.1)	CH ₃ CN/H ₂ O (5:2)	10	70
8	C(+) Pt(-)	<i>n</i> Bu ₄ NPF ₆ (0.1)	CH ₃ CN/H ₂ O (5:2)	10	68
9	C(+) Pt(-)	<i>n</i> Bu ₄ NBF ₄ (0.1)	CH ₃ CN/H ₂ O (5:2)	10	20
10 ^f	C(+) Pt(-)	<i>n</i>Bu₄NClO₄ (0.1)	CH₃CN/H₂O (5:2)	6	88
11	C(+) Pt(-)	<i>n</i> Bu ₄ NClO ₄ (0.1)	CH ₃ CN/H ₂ O (5:2)	15	61
12 ^f	C(+) Pt(-)	-	CH ₃ CN/H ₂ O (5:2)	6	62
13	C(+) Pt(-)	<i>n</i> Bu ₄ NClO ₄ (0.1)	CH ₃ CN/H ₂ O (5:2)	0	0
Continuous Flow Conditions^b					
14 ^g	C(+) Pt(-)	<i>n</i> Bu ₄ NClO ₄ (0.1)	CH ₃ CN/H ₂ O (5:2)	6	72
15	C(+) Pt(-)	<i>n</i>Bu₄NClO₄ (0.1)	CH₃CN/H₂O (5:2)	6	91
16	C(+) Pt(-)	<i>n</i> Bu ₄ NClO ₄ (0.03)	CH ₃ CN/H ₂ O (5:2)	6	79
17 ^h	C(+) Pt(-)	<i>n</i> Bu ₄ NClO ₄ (0.1)	CH ₃ CN/H ₂ O (5:2)	6	12

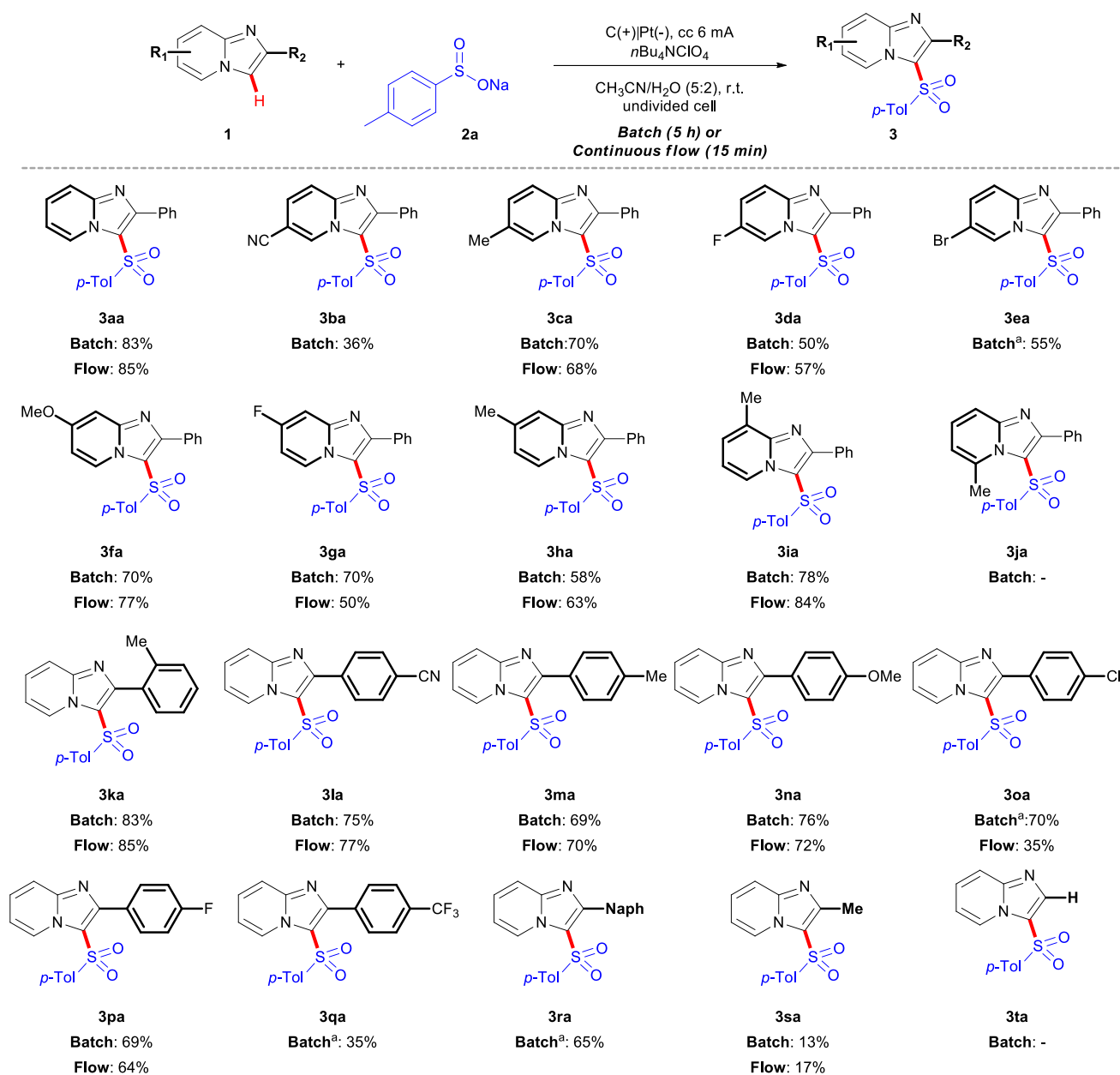
^aReaction condition in batch: **1a** (0.257 mmol, 1 equiv), **2a** (0.514 mmol, 2 equiv), electrolyte and solvent (10 mL), IKA undivided cell, graphite plate anode (8 × 2 × 40 mm) and Pt plate as cathode (8 × 40 mm). constant current, r.t for 2 h. ^bReaction conditions in continuous flow: **1a** (0.207 mmol, 1 equiv), **2a** (0.358 mmol, 1.7 equiv), *n*Bu₄NClO₄ and solvent (8 mL), IKA ElectraSyn undivided Flow cell (0.6 mL) with graphite plate anode (20 × 60 mm) and Pt plate cathode (20 × 60 mm), EPDM gasket 0.5 mm, constant current, r.t for 15 min (40 μL/min). ^cYield was determined by ¹H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. ^dGraphite plate anode (8 × 2 × 40 mm) and Ni foam plate cathode (8 mm × 2 × 40 mm). ^eGraphite plate (8 × 2 × 40 mm) as electrodes. ^f5 h. ^g10 min. ^hIKA divided cell, graphite plate anode (8 × 40 mm) and Pt plate as cathode (8 × 40 mm), EPDM gaskets 0.5 mm, Nafion 324 separator.

We commenced our investigation with 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and sodium *p*-toluenesulfonate (**2a**) as

benchmark substrates (Table 1). The initial reaction was performed in an undivided cell with C(+)|Pt(-) as the electrodes and LiClO₄ as the supporting electrolyte in a mixed solvent system CH₃CN/H₂O (v/v 5:2) under galvanostatic conditions at 10 mA at room temperature for 2 h, delivering the desired product **3aa** in 68% yield (Table 1, entry 1). By investigating different material for the electrodes, we found that the reaction yield decreased when the Pt cathode was replaced with a graphite or a Ni plate (Table 1, entries 2-3). Other ratio of solvent mixtures delivered lower yield (Table 1, entries 4-5). A reduced amount of electrolyte resulted in the deteriorative production of **3aa** (Table 1, entry 6). The effect of *n*-butyl quaternary salt was better than that of Li salt, since the expected product **3aa** was obtained in 70 % when using *n*Bu₄NClO₄ as an electrolyte (Table 1, entry 7). Additionally, the use of *n*Bu₄NPF₆ and *n*Bu₄NBF₄ as electrolyte resulted in lower reaction efficiency (Table 1 entries 8-9). Decreasing the current to 6 mA and extending the reaction time to 5 h afforded the desired product in 88% of yield (Table 1, entry 10) while increasing the current to 15 mA led to a reduced yield (Table 1, entry 11). In the absence of electrolyte, the product is formed but in lower yield (entry 12). It is noteworthy that there is no reaction in the absence of electric current (entry 13).

In order to reduce the required reaction times and to enable scalability of the process, we optimized a flow protocol (Table 1, entries 14-16) by using the commercially available electrochemical reactor Ika Electrasyn²⁸ (see SI). In flow, the reaction time could be reduced significantly due to a small interelectrode gap and enhanced mass transfer yielding the product in 91% after 15 min of reaction (Table 1, entries 14-15). A decreased of the electrolyte loading decreased the kinetics of the reaction (Table 1, entry 15). However, it should be noted that it was possible to recover the starting material quantitatively, which can be subsequently reintroduced into the flow cell enabling higher overall conversions while maintaining a low concentration of electrolyte. Only 12% yield of the desired product was detected in a divided mode by using two spacers (0.5 mm) between the electrodes and a Nafion 324 separator, indicating a close presence of the cathode was essential (entry 17).

With optimal conditions in hand, we probed the generality of this protocol for the sulfonation of a diverse set of C2-substituted imidazo[1,2-*a*]pyridines **1** with sodium *p*-toluenesulfonate (**2a**) in both batch and flow (Scheme 2). Sulfonation with 2-phenylimidazo[1,2-*a*]pyridines bearing alkyl substituent and halogen atoms on the C-7 position on the pyridine ring were well-tolerated, providing the corresponding products **3ca-3ea** in 55–70% yields. However, the presence of an electron-withdrawing groups such as cyano decreased the reaction efficiency (**3ba**), possibly due to side reactions. Bearing an electron-donating substituent (OMe) or a fluorine atom on the C-7 position afforded substrate **3fa** and **3ga** in good isolated yields of 70%. It should be noted that the position of an alkyl substituent on the pyridine ring showed an effect on the electrochemical process.

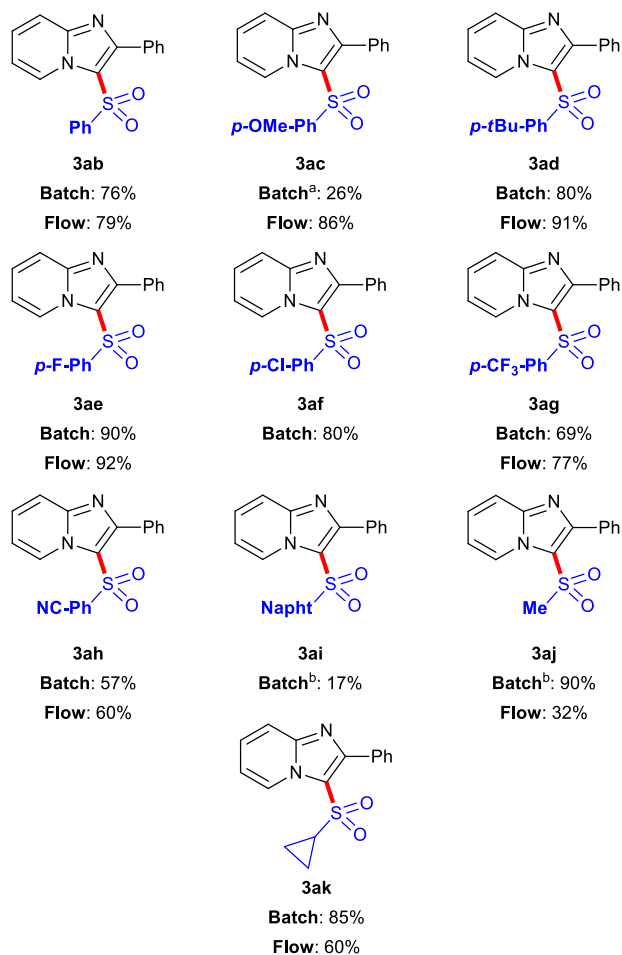
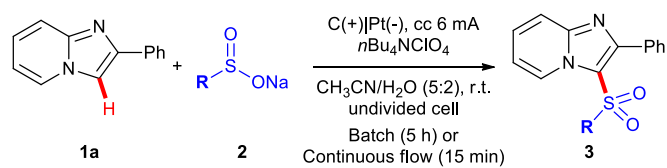


Scheme 2 Substrate Scope of C2-substituted-imidazo[1,2-*a*]pyridines. Reaction condition in batch: **1a** (0.257 mmol, 1 equiv), **2a** (0.514 mmol, 2 equiv), $n\text{Bu}_4\text{NClO}_4$ [0.1 M], $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10 mL), IKA undivided cell, graphite plate anode ($8 \times 2 \times 40$ mm) and Pt plate as cathode (8×40 mm), constant current = 6 mA, under air at room temperature for 5 h. Reaction conditions in continuous flow: **1a** (0.207 mmol, 1 equiv), **2a** (0.358 mmol, 1.7 equiv), $n\text{Bu}_4\text{NClO}_4$ [0.1 M] and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (8 mL), IKA ElectroSyn undivided Flow cell (0.6 mL) with graphite plate anode (20×60 mm) and Pt plate cathode (20×60 mm), EPDM gasket 0.5 mm, constant current = 6 mA, room temperature for 15 min (40 $\mu\text{L}/\text{min}$).^a6 h of reaction time

Indeed, 2-phenylimidazo[1,2-*a*]pyridines with a methyl group at the C-6, C-7 and C-8 positions reacted smoothly yielding the desired products (**3ca**, **3ha** and **3ia**) in 58–78% yields. However, when imidazo[1,2-*a*]pyridine with methyl substitution on the C-9 position was employed the desired product **3ja** could not be prepared under the electrochemical conditions possibly due to steric hindrance. The influence of the substituents on the phenyl ring of 2-phenylimidazo[1,2-*a*]pyridines was also evaluated. Various functional groups, including electron-donating (Me, OMe) and moderate electron-withdrawing

groups (F and CF_3), did not prevent the smooth formation of the expected products **3ma**, **3na**, **3pa** and **3qa** in moderate to high yields (35–76%). Moreover, halide (**3oa**) and cyanide (**3la**) substituents are well tolerated under these mild conditions, which provide opportunities for further functionalization of the molecule. *Ortho* substitution (**3ka**) and 2-naphthyl group (**3ra**) did not affect the efficiency of the reaction. The sulfonation of 2-methylimidazo[1,2-*a*]pyridine furnished the corresponding sulfonated products **3ra** albeit in low yield. Unfortunately, when using imidazo[1,2-*a*]pyridine as the substrate, no desired

product **3ta** was obtained under standard conditions mainly due to its relatively high oxidation potential.



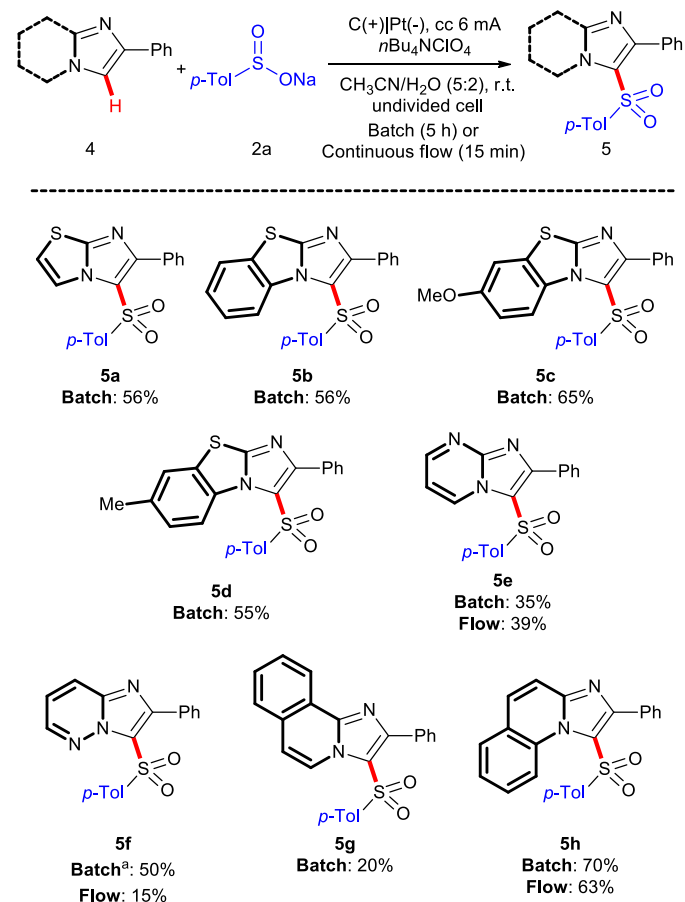
Scheme 3 Scope of sodium sulfonate salts. Reaction condition in batch: **1a** (0.257 mmol, 1 equiv), **2a** (0.514 mmol, 2 equiv), $n\text{Bu}_4\text{NClO}_4$ [0.1 M], $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10 mL), IKA undivided cell, graphite plate anode (8 × 2 × 40 mm) and Pt plate as cathode (8 × 40 mm), constant current = 6 mA, under air at room temperature for 5 h. Reaction conditions in continuous flow: **1a** (0.207 mmol, 1 equiv), **2a** (0.358 mmol, 1.7 equiv), $n\text{Bu}_4\text{NClO}_4$ [0.1 M] and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (8 mL), IKA ElectroSyn undivided Flow cell (0.6 mL) with graphite plate anode (20 × 60 mm) and Pt plate cathode (20 × 60 mm), EPDM gasket 0.5 mm, constant current = 6 mA, room temperature for 15 min (40 $\mu\text{L}/\text{min}$).^a2 h of reaction time.^b6 h of reaction time

In general, it was observed that in addition to the reduced reaction time, the obtained isolated yields were slightly higher under microflow conditions when compared to the batch counterparts. However, in some cases since the product precipitates the transposition in flow was impossible due to clogging of the system (**3ba**, **3ea**, **3ja**, **3qa** and **3ra**).

To further examine the scope of the sulfonylation reaction, various sodium sulfonates were tested, as summarized in Scheme 3. The reaction tolerates different aromatic sulfonates bearing electron-donating (*t*Bu, OMe) and withdrawing groups (F, Cl, CF_3 and CN) in para positions (**3ab–3ah**), the

corresponding sulfonylated products being smoothly obtained in 60–92% yields. Steric hindrance was observed when 2-naphthylsulfinate was introduced (**3ak**). Moreover, the reactivity of alkylsulfonates was tested, which gave products **3aj** and **3ak** in 90% and 85% yield respectively. However, since the sulfonylation rate of compounds **3aj** and **5f** is slower, lower yields were obtained in flow due to too short residence times within the flow cell.

In an endeavour to expand the scope of the methodology, we sought to demonstrate its potential for the sulfonylation of some other imidazoheterocycles (Scheme 4).

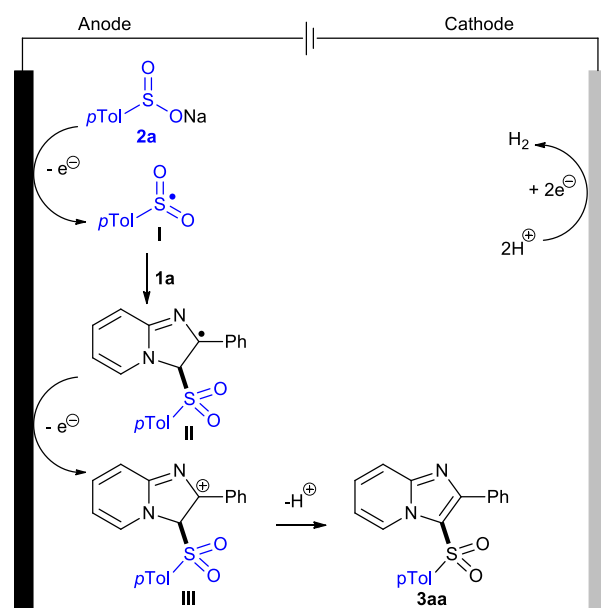


Scheme 4 Substrate scope of imidazoheterocycles. Reaction condition in batch: **1a** (0.257 mmol, 1 equiv), **2a** (0.514 mmol, 2 equiv), $n\text{Bu}_4\text{NClO}_4$ [0.1 M], $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10 mL), IKA undivided cell, graphite plate anode (8 × 2 × 40 mm) and Pt plate as cathode (8 × 40 mm), constant current = 6 mA, under air at room temperature for 5 h. Reaction conditions in continuous flow: **1a** (0.207 mmol, 1 equiv), **2a** (0.358 mmol, 1.7 equiv), $n\text{Bu}_4\text{NClO}_4$ [0.1 M] and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (8 mL), IKA ElectroSyn undivided Flow cell (0.6 mL) with graphite plate anode (20 × 60 mm) and Pt plate cathode (20 × 60 mm), EPDM gasket 0.5 mm, constant current = 6 mA, room temperature for 15 min (40 $\mu\text{L}/\text{min}$).^a10 h of reaction time

To our satisfaction, a similar process occurred with 4-phenylimidazo[2,1-*b*]thiazole and substituted 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazoles, providing the desired products **5a–5d** in 55–65% yields. Due to solubility issue a continuous flow protocol was not developed. It should be noted that, 2-phenylimidazo[1,2-*a*]pyrimidine, and 2-phenylimidazo[1,2-*b*]pyridazine were also suitable for this transformation, nonetheless the reaction was not complete and the desired product **5e–5f** were obtained in 35–50% yields in batch. 2-phenylimidazo[1,2-*a*]isoquinoline and 2-

phenylimidazo[1,2-*a*]quinoline gave the expected products (**5g** and **5h**) in 20% and 70% yields respectively. Moreover, these reactions also showed excellent regioselectivity. These findings are noteworthy because, to the best of our knowledge, this is the first time that benzo[*d*]imidazo[1,2-*b*]thiazoles imidazo[1,2-*a*]-pyrimidines and imidazo[1,2-*a*]-pyridazines are used as substrates in electrochemical sulfonylation protocol.

Cyclic voltammetry (CV) analysis of *p*-toluenesulfinate (**2a**) in CH₃CN/H₂O (v/v 5:2) with *n*Bu₄CIO₄ as electrolyte showed irreversible anodic oxidation waves (Figure 1, SI) at a potential lower than that of 2-phenylimidazo[1,2-*a*]pyridine **1a** (0.74 and 1.12 V vs Ag/AgCl, respectively). The CV measurement of the reaction mixture (1 mM each) showed only one oxidation peak, coherent in potential and current with **1a** alone, whereas the **2a** peak disappeared. Based on the literature reports²⁴⁻²⁶ and our results, a plausible mechanism was illustrated in Scheme 5.

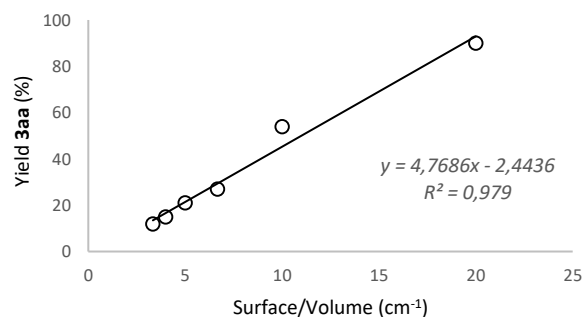


Scheme 5 Proposed mechanism.

Sodium *p*-toluenesulfinate (**2a**) loses one electron at the anode to access the radical intermediate **I**. The attack of the sulfonyl radical onto the double bond of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) provided radical intermediate **II**, which could be further oxidized and transformed to a cationic species **III** on the surface of an anode. Subsequently, the deprotonation of intermediate **III** afforded the desired product **3aa**. The cathodic reduction of protons to hydrogen gas, confirmed by detection at the outlet of the flow-cell using a Dräger X-am 5000 gaz detector, completes the overall electrochemical process.

Moreover, in order to develop a continuous flow gram-scale experiment to demonstrate the practical utility of the developed protocol we studied kinetics of the reaction in an IKA flow cell. The reaction kinetics were evaluated; the flow rates were varied from 35 $\mu\text{L}\cdot\text{min}^{-1}$ to 600 $\mu\text{L}\cdot\text{min}^{-1}$ to give residence time of 1 to 17 min. An apparent zero-order kinetics was determined (Table 3, SI). These results suggested that the kinetics of the electrochemical process was likely to be governed by surface phenomena at the electrode, the rate limiting step during electrolysis therefore involving the

oxidation of the substrate by surface absorption. In a flow-cell, the two electrodes are combined and separated by a hollow PTFE or EPDM gasket. We studied the impact of the spacer thickness on the reaction efficiency by adding multilayers of spacer, the cell volume varying from 0.6 to 3.6 mL, at optimum conditions (15 min of residence time). A larger interelectrode distance slowed down the reaction kinetics (Fig 2, SI). Moreover, the yield of the electrochemical process is proportional to 1/(interelectrode distance), which corresponds to the surface to volume ratio (Scheme 6).



Scheme 6 (2a). Plot of Yield of **3aa** versus Surface/Volume IKA ElectroSyn undivided Flow cell (0.6 mL) with graphite plate anode (20 × 60 mm) and Pt plate cathode (20 × 60 mm), EPDM and Teflon gasket.

Thus, to maintain a high level of conversion for a fixed residence time, an increase of the volume cell must be accompanied by an increase in the surface area of the electrodes or by parallelization of reactors. In addition, if an increase in the diffusional pathway is required the residence time must be increased. To improve the productivity of the IKA flow-cell (PTFE gasket = 0.5 mm, V = 0.6 mL, 15 min of residence time, 12 $\text{mg}\cdot\text{h}^{-1}$), both the volume of the cell (2.4 mL) and the residence time (45 min of residence time) were increased but unfortunately since a moderate yield was obtained (45%) due to over-degradation the productivity was not improved. A modification of the geometry of the flow cell is therefore necessary in order to facilitate the scale up of the reaction.

Conclusions

In summary, a mild and environmentally benign electrochemical C3 sulfonylation protocol for imidazoheterocycles was developed. The reaction was conducted both in batch and flow and is compatible with a wide variety of functional groups. The protocol could be extended from imidazo[1,2-*a*]-pyridines -pyrimidine, -quinoline, -isoquinoline to both imidazo[1,2-*a*]-pyrimidines and benzo[*d*]imidazo[1,2-*b*]thiazoles with moderate to excellent yields demonstrating the generality of our method. Continuous-flow chemistry proved its effectiveness by decreasing the reaction time up to 20 times (5 h vs 15 min) while increasing the yields. Moreover, combining flow process with electrochemical process reduces energy consumption of the reaction by nearly 30 % (3.12 $\text{kW}\cdot\text{g}^{-1}$ in flow vs 4.2 $\text{kW}\cdot\text{g}^{-1}$ in batch).

Conflicts of interest

There are no conflicts to declare

Acknowledgements

This work was financially supported by the Région Hauts-de-France (Implicite-191012) and the CNRS.

Notes and references

- (a) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230-13319; (b) A. Wiebe, T. Gieshoff, S. Moehle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594-5619; (c) S. Mohle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe, S. R. Waldvogel, T. Gieshoff, S. R. Waldvogel, A. Wiebe and S. R. Waldvogel, *Angew Chem Int Ed Engl*, 2018, **57**, 6018-6041; (d) D. Pollok and S. R. Waldvogel, *Chem. Sci.*, 2020, **11**, 12386-12400; (e) C. Zhu, N. W. J. Ang, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Cent. Sci.*, 2021, **7**, 415-431.
- (a) B. A. Frontana-Uribe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099-2119; (b) S. Cembellin and B. Batanero, *Chem. Rec.*, 2021, hem. Rec. 2021, **21**, 1-20; (c) H. J. Schaefer, *C. R. Chim.*, 2011, **14**, 745-765; (d) E. J. Horn, B. R. Rosen and P. S. Baran, *ACS Cent. Sci.*, 2016, **2**, 302-308.
- (a) S. Tang, Y. Liu and A. Lei, *Chem*, 2018, **4**, 27-45; (b) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086-7103; (c) Y. Yuan, J. Qiao, Y. Cao, J. Tang, M. Wang, G. Ke, Y. Lu, X. Liu and A. Lei, *Chem. Commun.*, 2019, **55**, 4230-4233.
- D. S. P. Cardoso, B. Slijkic, D. M. F. Santos and C. A. C. Sequeira, *Org. Process Res. Dev.*, 2017, **21**, 1213-1226.
- For recent reviews see: (a) A. A. Folguez-Amador and T. Wirth, *J. Flow Chem.*, 2017, **7**, 94-95; (b) D. Pletcher, R. A. Green and R. C. D. Brown, *Chem. Rev.*, 2018, **118**, 4573-4591; (c) M. Atobe, H. Tatenno, and Y. Matsumura, *Chem. Rev.*, 2018, **118**, 4541-4572; (d) T. Noel, Y. Cao and G. Laudadio, *Acc. Chem. Res.*, 2019, **52**, 2858-2869; (e) M. Elsherbini and T. Wirth, *Acc. Chem. Res.*, 2019, **52**, 3287-3296; (f) S. Maljuric, W. Jud, C. O. Kappe and D. Cantillo, *J. Flow Chem.*, 2020, **10**, 181-190.
- M. G. Rimoli, L. Avallone, P. de Caprariis, E. Luraschi, E. Abignente, W. Filippelli, L. Berrino and F. Rossi, *Eur. J. Med. Chem.*, 1997, **32**, 195-203.
- C. Moog, A. Wick, P. Le Ber, A. Kirn and A.-M. Aubertin, *Antiviral Res.*, 1994, **24**, 275-288.
- N. M. Shukla, D. B. Salunke, E. Yoo, C. A. Mutz, R. Balakrishna and S. A. David, *Bioorg. Med. Chem.*, 2012, **20**, 5850-5863.
- (a) A. T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S. K. Guchhait, C. N. Kundu, U. C. Banerjee and P. V. Bharatam, *J. Med. Chem.*, 2011, **54**, 5013-5030; (b) E. Guersoy and N. U. Guezeldemirci, *Eur. J. Med. Chem.*, 2007, **42**, 320-326.
- M. H. Fisher and A. Lusi, *J. Med. Chem.*, 1972, **15**, 982-985.
- T. S. Harrison and G. M. Keating, *CNS Drugs*, 2005, **19**, 65-89.
- S. Z. Langer, S. Arbilla, J. Benavides and B. Scatton, *Adv. Biochem. Psychopharmacol.*, 1990, **46**, 61-72.
- M. Feely, P. Boyland, A. Picardo, A. Cox and J. P. Gent, *Eur. J. Pharmacol.*, 1989, **164**, 377-380.
- R. Chermat, Y. Minaire, M. C. Chesneau and P. Simon, *Therapie*, 1977, **32**, 643-648.
- K. Mizushige, T. Ueda, K. Yukiiri and H. Suzuki, *Cardiovasc. Drug Rev.*, 2002, **20**, 163-174.
- S. Hegde and M. Schmidt, *Annu. Rep. Med. Chem.*, 2010, **45**, 467-537.
- A. Douhal, F. Amat-Guerri and A. U. Acuna, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1514-1516.
- (a) Z. Tashrifi, M. Mohammadi-Khanaposhtani, B. Larijani and M. Mahdavi, *Eur. J. Org. Chem.*, 2020, 269-284; (b) C.-H. Ma, M. Chen, Z.-W. Feng, Y. Zhang, J. Wang, Y.-Q. Jiang and B. Yu, *New J. Chem.*, 2021, **45**, 9302-9314.
- D. C. Mohan, S. N. Rao, C. Ravi and S. Adimurthy, *Asian J. Org. Chem.*, 2014, **3**, 609-613.
- D. Yang, P. Sun, W. Wei, F. Liu, H. Zhang and H. Wang, *Chem. - Eur. J.*, 2018, **24**, 4423-4427.
- Y.-J. Guo, S. Lu, L.-L. Tian, E.-L. Huang, X.-Q. Hao, X. Zhu, T. Shao and M.-P. Song, *J. Org. Chem.*, 2018, **83**, 338-349.
- C. Breton-Patient, D. Naud-Martin, F. Mahuteau-Betzer and S. Pignuel, *Eur. J. Org. Chem.*, 2020, 6653-6660.
- For selected reviews, see: (a) T. G. Back, K. N. Clary and D. Gao, *Chem. Rev.*, 2010, **110**, 4498-4453; (b) B. M. Trost and C. A. Kalnals, *Chem.-Eur. J.*, 2019, **25**, 11193-11213; (c) D. Yadav and R. S. Menon, *Org. Biomol. Chem.* 2020, **18**, 365-378.
- L. Han, M. Huang, Y. Li, J. Zhang, Y. Zhu, J. K. Kim and Y. Wu, *Org. Chem. Front.*, 2021, **8**, 3110-3117.
- J. Zhu, Z. Chen, M. He, D. Wang, L. Li, J. Qi, R. Shi and A. Lei, *Org. Chem. Front.*, 2021, **8**, 3815-3819.
- W. Kim, H. Y. Kim, and K. Oh, *J. Org. Chem.*, DOI: 10.1021/acs.joc.1c00873, Ahead of Print.
- (a) N. El Achi, Y. Bakkour, W. Adhami, J. Molina, M. Penhoat, N. Azaroual, L. Chausset-Boissarie and C. Rolando, *Front. Chem.*, 2020, **8**, 740; (b) M. Roseau, N. Dhaouadi, C. Rolando, L. Chausset-Boissarie and M. Penhoat, *J. Flow Chem.*, 2020, **10**, 347-352; (c) F. Gelat, M. Roger, C. Penverne, A. Mazzad, C. Rolando and L. Chausset-Boissarie, *RSC Adv.*, 2018, **8**, 8385-8392; (d) N. El Achi, M. Penhoat, Y. Bakkour, C. Rolando and L. Chausset-Boissarie, *Eur. J. Org. Chem.*, 2016, 4284-4288.
- C. Gütz, A. Stenglein and S. R. Waldvogel, *Org. Process Res. Dev.*, 2017, **21**, 771-778.