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Synthesis of N- Heterocyclic amides from imidazoheterocycles through convergent paired electrolysis

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AN EFFICIENT RING OPENING OF IMIDAZOHETEROCYCLES INDUCED BY A DIRECT C-H AZIDATION RESULTING IN AN UNUSUAL FORMATION OF N- HETEROCYCLIC AMIDES HAS BEEN SUCCESSFULLY DEVELOPED THROUGH CONVERGENT PAIRED ELECTROLYSIS. A BROAD SCOPE OF PYRIDYLBENZAMIDES COULD BE OBTAINED IN MODERATE TO EXCELLENT YIELDS UNDER EXOGENOUS-OXIDANT, ELECTROLYTE AND METAL FREE ELECTROCHEMICAL CONDITIONS. THE METHODOLOGY WAS TRANSFERRED TO CONTINUOUS FLOW CONDITIONS RESULTING IN NOTABLE IMPROVEMENTS PARTICULARLY IN TERMS OF COST-EFFICIENCY OVER TRADITIONAL BATCH VERSIONS.

In the past few years, organic electrochemistry has been revived as an efficient, safe, and environment-friendly approach since it utilizes electrical energy to drive redox reactions avoiding the use of stoichiometric, toxic and polluting redox reagents.¹ However, most electrochemical processes utilize only a half-reaction with the counterpart being sacrificed.² On the contrary, paired electrolysis (classified in 4 types: convergent, parallel, divergent and linear),³ which involves two productive half reactions to deliver products, is a highly sustainable process that maximizes the energy efficiency of the reaction and minimises waste. In spite of these benefits, paired electrochemical reactions are still greatly underdeveloped with limited synthetic applications.⁴

Amide bond which is one of the most fundamental group in organic chemistry and biology is present in a vast number of bioactive compounds, pharmaceuticals, agrochemicals as well as material sciences.⁵ In particular, heterocyclic benzamides are mainstay building blocks for prevalent structural scaffolds that exhibit a broad spectrum of biological and pharmacological activities.⁶ Common strategies for the synthesis of (hetero)aryl amides involve a direct condensation reaction between a carboxylic acid⁷ or a carboxylic acid surrogate⁸ (esters, amides, acyl halides, ketones, aldehydes...) and amine. However, harsh reaction conditions, low yields and expensive or transition metal catalysts limit the scope of these methodologies. In recent years, new strategies for accessing (hetero)aryl amides from imidazopyridines based on oxidative ring opening *via* C-C and C-N bond cleavage have been developed.⁹ However, all these protocols present certain limitations such as the use of stoichiometric oxidants or a scope restricted to a limited set of imidazo[1,2-*a*]-pyridines. Therefore, the development of greener approaches still remains a major challenge especially for electron-deficient or less nucleophilic amines.

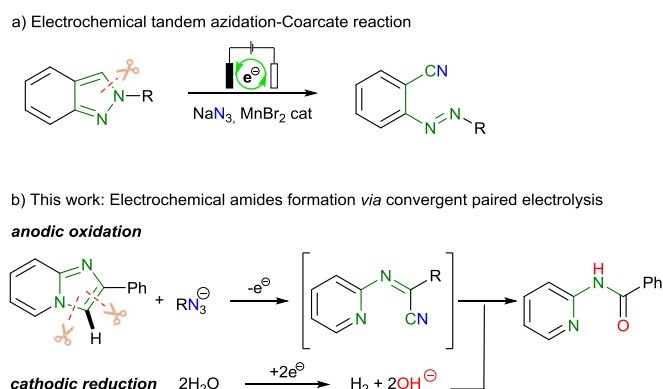


FIGURE 1 APPROACHES FOR THE ELECTROCHEMICAL AMIDE FORMATION

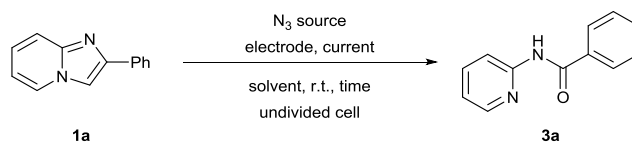
Recently, selective electrochemical induced C-C¹⁰ or C-N¹¹ bond cleavage strategy has gained an increasingly interest. In this context, De Sarka and co-workers reported an appealing methodology for the synthesis of 2-azobenzonitriles based on electrochemical induced azidation of 2*H*-indazoles mediated by manganese salts (Figure 1, a).¹² Thus, inspired by this work we envisaged a novel approach for the synthesis of (hetero)aryl amides through electrochemical generation of α -iminonitriles based on the convergent paired electrolysis¹³ of

imidazoheterocycles, readily available azide source and water. Indeed, we will take advantage of the cathodic reduction of water to generate hydroxide anion¹⁴ which will hydrolyse the anodically formed α -iminonitriles to the respective benzamides¹⁵ in a convergent paired-electrolysis process without electrolyte (Figure 1, b). Moreover, this approach provides a greener alternative toward the synthesis of α -iminonitriles from imidazopyridines which are traditionally obtained *via* radical ring opening with either expensive oxidizing agent or azide sources such as azidobenziodoxolone.¹⁶

Pursuant to our interest in the development of environmentally benign and straightforward methodologies for the synthesis of highly valued molecules,¹⁷ herein, we report an efficient electrochemical protocol for the synthesis of N- Heterocyclic amides.

First, 2-phenylimidazo[1,2-*a*]pyridine **1a** was employed as a model substrate for the electrochemical formation of N-(pyridine-2-yl)benzamide **3a** under various conditions (Table 1). When the reaction was performed in an undivided cell equipped with graphite plate electrodes, sodium azide as azide source under galvanostatic conditions at 3.0 F (8 mA at room temperature for 2 h) in the presence of lithium perchlorate as the supporting electrolyte in a 9:1 acetonitrile/water mixture, the desired product **3a** could be formed with an 62% yield (Table 1, entry 1). Encouraged by the initial result, different solvents were tested, significantly lower yields of **3a** were obtained in the MeCN/H₂O (8:2) mixture (entry 2) or in MeCN (entry 3). No product was obtained with ethanol as co-solvent indicating that water is essential for this electrochemical transformation (entry 4). Next, other electrode materials were tested, when nickel plate was used for anode a slight decreased of the yield was observed (entry 5). Gratifyingly, running the reaction with a platinum plate cathode delivered the desired product in 68% (entry 6). Especially, the yield of the desired product **3a** was significantly reduced to 21% when the electrolysis was performed with platinum plate as anode (entry 7). Replacing lithium perchlorate with tetrabutylammonium perchlorate resulted in the dramatical decrease of the yield of **3a** (entry 8), while no product was obtained in the absence of an electrolyte (entry 9). However, we hypothesized that using tetrabutylammonium azide (*n*Bu₄NN₃) **2** would avoid the need for an additional wasteful supporting electrolyte by acting either as reagent and supporting electrolyte. Fortunately, product **3a** was obtained with a slight decreased of yield (entry 10). Thereafter, the effect of the current density was checked, and it was observed that the variation of the current density did not impact the product formation. Similar yields were obtained when the current was increased to 10 mA (3.7 F) or decreased to 6 mA (2.2 F, entries 11-12). Interestingly, decreasing the current to 4 mA (1.5 F) afforded the desired product in 39% of yield (entry 13), however unreacted starting material could be recovered (43%) due to incomplete conversion. To our delight, a further increase of the reaction time to 5 h (3.7 F) enhanced the yield of **3a** up to 76% (entry 14). It's interesting to note that the yield of **3a** was slightly diminished under air (entry 15). Finally, as expected, the reaction did not take place in the absence of electric current or azide source (entries 16-17). Thus, the optimal reaction conditions were attained using 3 equiv of *n*Bu₄NN₃ in MeCN/H₂O (9:1) solvent mixture in an undivided cell with graphite anode and platinum cathode at 4 mA constant current at room temperature for 5 h (3.7 F).

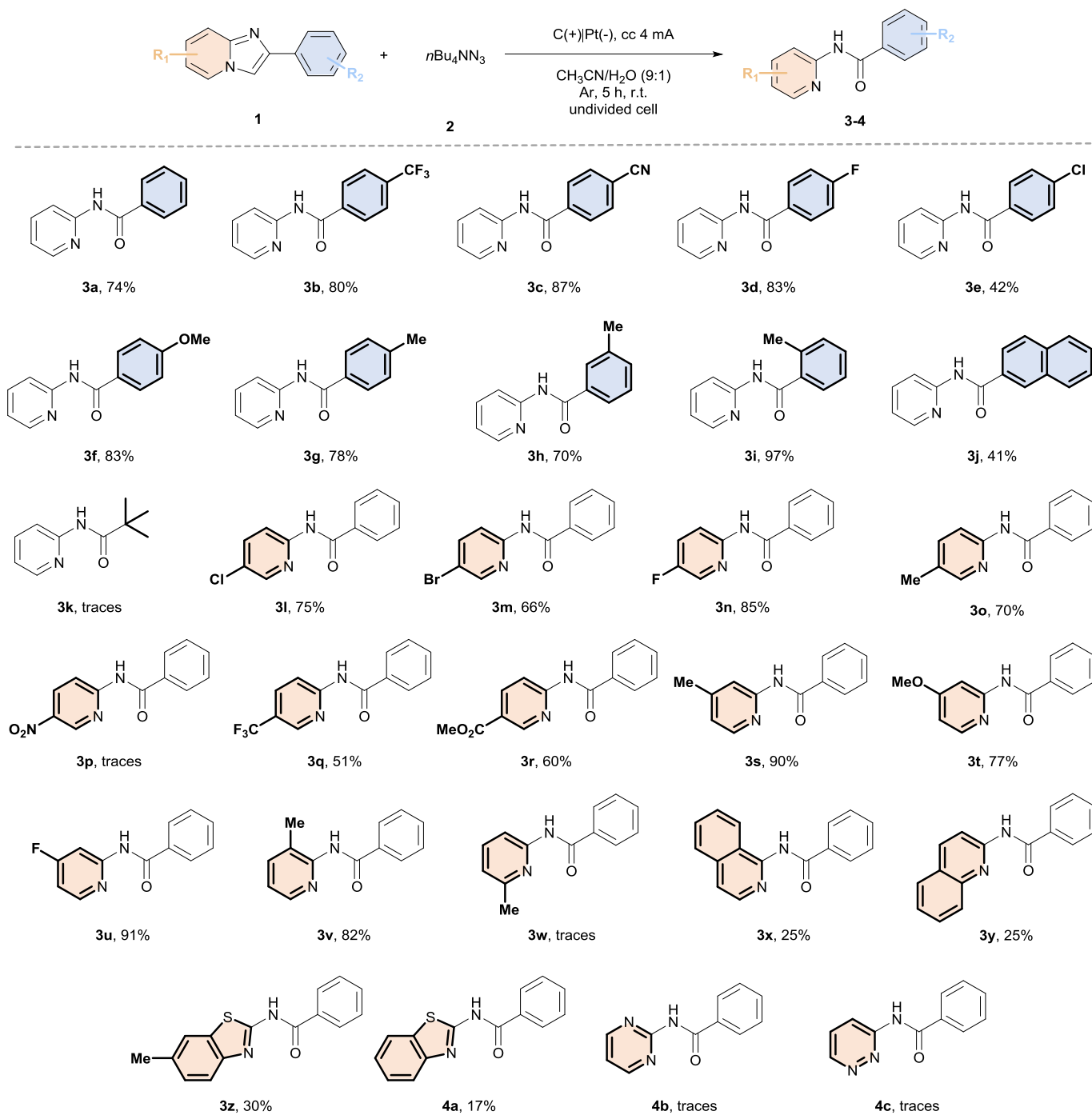
Table 1. Optimization studies for the electrochemical formation of N-(pyridine-2-yl)benzamide **3a**^a



Entry	Electrodes	Azide source	Electrolyte	Current (mA)	Yield (%) ^b
1 ^c	C(+) C(-)	NaN ₃	LiClO ₄	8	62
2 ^d	C(+) C(-)	NaN ₃	LiClO ₄	8	45

3 ^e	C(+) C(-)	NaN ₃	LiClO ₄	8	12
4 ^f	C(+) C(-)	NaN ₃	LiClO ₄	8	N.P.
5 ^g	C(+) Ni(-)	NaN ₃	LiClO ₄	8	58
6 ^h	C(+) Pt(-)	NaN ₃	LiClO ₄	8	68
7	Pt(+) C(-)	NaN ₃	LiClO ₄	8	21
8	C(+) Pt(-)	NaN ₃	<i>n</i> Bu ₄ NClO ₄	8	22
9	C(+) Pt(-)	NaN ₃	-	8	traces
10	C(+) Pt(-)	<i>n</i> Bu ₄ NN ₃	-	8	63
11 ⁱ	C(+) Pt(-)	<i>n</i> Bu ₄ NN ₃	-	10	61
12 ^j	C(+) Pt(-)	<i>n</i> Bu ₄ NN ₃	-	6	62
13 ^k	C(+) Pt(-)	<i>n</i> Bu ₄ NN ₃	-	4	39
14 ^l	C(+) Pt(-)	<i>n</i> Bu ₄ NN ₃	-	4	76
15 ^l m	C(+) Pt(-)	<i>n</i> Bu ₄ NN ₃	-	4	70
16 ^l	C(+) Pt(-)	-	LiClO ₄	4	N.P
17	C(+) Pt(-)	<i>n</i> Bu ₄ NN ₃	-	-	N.R.

^aReaction conditions: **1a** (0.2 mmol, 1 equiv), N₃ source (0.6 mmol, 3 equiv), electrolyte (0.1 M) and solvent (10 mL), IKA undivided cell, plate electrodes, constant current, $J = 2.50 \text{ mA}\cdot\text{cm}^{-2}$, 3.0 F, r.t. for 2 h under argon. ^bYield was determined by ¹H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. ^cGraphite plate electrodes (8 × 2 × 40 mm). ^dCH₃CN/H₂O (v/v 8:2) as solvent. ^eCH₃CN as solvent. ^fCH₃CN/EtOH (v/v 9:1) as solvent. ^gNi plate cathode (8 × 2 × 40 mm). ^hPt plate cathode (20 × 60 mm). ⁱ $J = 3.12 \text{ mA}\cdot\text{cm}^{-2}$, 3.7 F. ^j $J = 1.87 \text{ mA}\cdot\text{cm}^{-2}$, 2.2 F. ^k $J = 1.25 \text{ mA}\cdot\text{cm}^{-2}$, 1.5 F. ^l $J = 1.25 \text{ mA}\cdot\text{cm}^{-2}$, 3.7 F, 5 h. ^munder air.

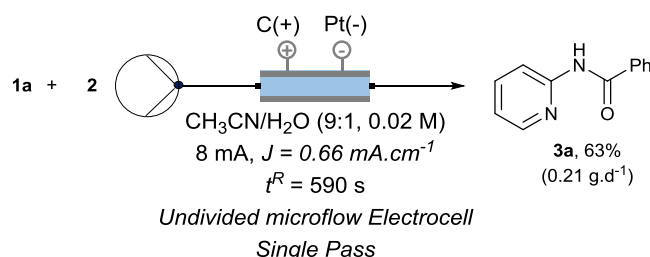


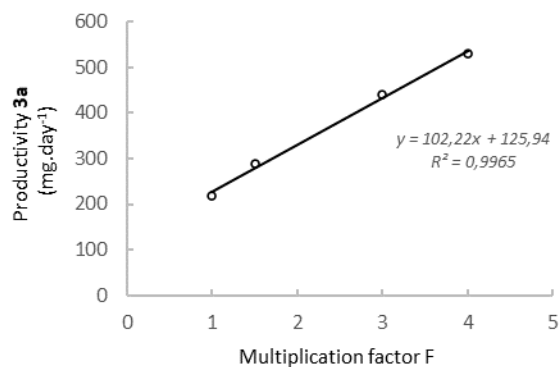
SCHEME 1 Substrate scope of imidazoheterocycles. Reaction conditions: **1** (0.2 mmol, 1 equiv), $n\text{Bu}_4\text{NN}_3$ **2** (0.6 mmol, 3 equiv) and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (v/v 9:1, 10 mL), IKA undivided cell, graphite plate anode ($8 \times 2 \times 40$ mm) and Pt plate cathode (8×40 mm), constant current at 4 mA for 5 h $J = 1.25 \text{ mA}\cdot\text{cm}^{-2}$, 3.7 F, at r.t. under argon.

With the optimized reaction conditions in hand, we next examined the scope of the oxidative ring-opening of various imidazoheterocycles, and the results are summarized in Scheme 2. A variety of substituted imidazopyridines afforded the desired products in moderate to excellent yields (Scheme 1, **3a-3v**). Imidazo[1,2-*a*]pyridines with various substituents on aryl ring were first examined. Imidazo[1,2-*a*]pyridine with strong electron-withdrawing groups such as -CN and -CF₃ or electron-donating substituents such as -OMe and -Me on the aryl ring were well tolerated and provided the corresponding products (**3b**, **3c**, **3f-3g**) in good to excellent yields.

Halogen (-F, and -Cl) substituents resulted in the desired products with yields of 83% and 42% (Scheme 2, **3d** and **3e**, respectively). Regardless of the position of the methyl group on the aromatic ring, products **3h** and **3i** were obtained in good to excellent yields. In addition, naphthyl substituted imidazo[1,2-*a*]pyridine **3j**, also worked under the optimized reaction conditions however in lower yield. Unfortunately, alkyl substituents were not well tolerated, as only trace amounts of the desired product **3k** were obtained, along with unidentified degradation by-products. The effect of different substituents on the pyridine ring of imidazo[1,2-*a*]pyridines was also explored. To our delight, imidazopyridines with halogens (-Cl, Br and -F), and electron-donating (-Me) substituents on the C6 position on the phenyl ring gave the corresponding products **3l-3o** in 66-90% yields. Strongly electron-poor group like NO₂ at the C6 position was ineffective to furnish the product **3p** however other withdrawing groups (-CF₃ and CO₂Me) successfully yielded the desired products **3q** and **3r** in 51 and 60 %, respectively. We found that regardless of the electronic nature of the substituents on the C-7 position, the corresponding products **3s-3u** were obtained in excellent yields (77-91%). Methyl substitution at the C8 position provided the desired product **3v** in 82% yield. However, when imidazo[1,2-*a*]pyridine with methyl substitution on the C-9 position was employed the desired product **3w** was not obtained possibly due to steric hindrance. Interestingly, it is worth noting that in addition to 2-phenylimidazo[1,2-*a*]pyridines, 2-phenylimidazo[1,2-*a*]isoquinoline, 2-phenylimidazo[1,2-*a*]quinoline, 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole and 6-phenylimidazo[2,1-*b*]thiazole were also compatible substrate, delivering the corresponding (hetero)aryl amides however in moderate yields (Scheme 2, **4a-4d**) due to the formation of unidentified side-products. In contrast, 2-phenylimidazo[1,2-*a*]pyrimidine, and 2-phenylimidazo[1,2-*b*]pyridazine were not suitable for this transformation.

Continuous microflow electrocells accelerate electrocatalytic reactions due to their short diffusion distance between electrodes, high electrode surface-to-volume ratios and improved mass transfer efficiency.¹⁸ Thus, in order to reduce the reaction time and improve the process productivity, the reaction was translated under single-pass continuous flow conditions using the commercially available electrochemical microflow cell from IKA (ElectraSyn Flow, inter-electrode gap 0.5 mm and 12 cm² for the surface area of the electrodes).¹⁹ Hence, we optimized the continuous flow process by evaluating different residence times and amounts of charge using the optimized electrodes and solvent mixture (Table S1, Supporting Information).

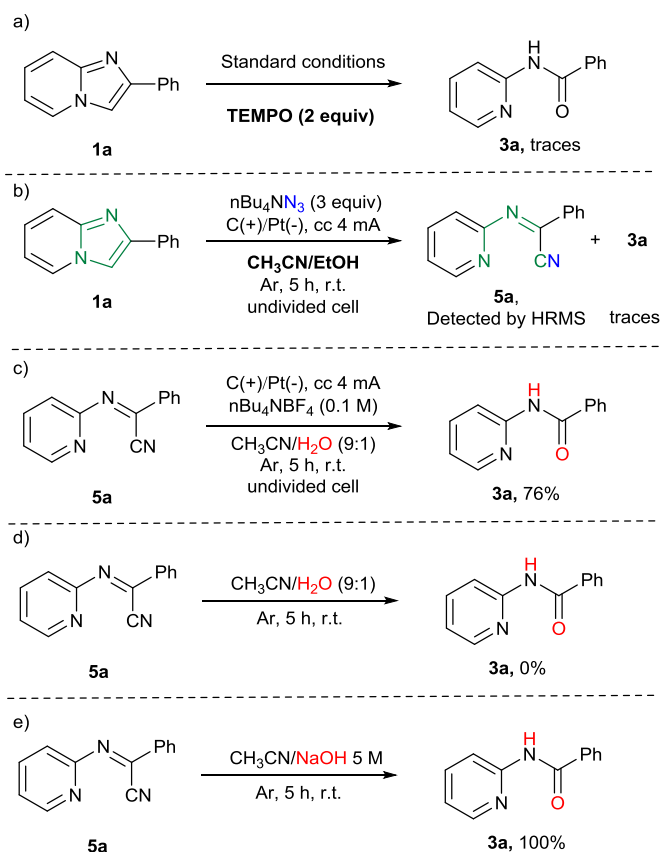




SCHEME 2: A) CONTINUOUS FLOW FORMATION OF N-(PYRIDINE-2-YL)BENZAMIDE **3a** USING AN IKA MICROFLOW ELECTROCELL. B) PLOT of productivity of **3a** versus multiplication factor F of current density and concentration.

We were delighted to find that product **3a** could be obtained in 63% yield with a significant shorter reaction time than in batch (590 s vs 5 h) (Scheme 2a). Moreover, it is worth noting that the use of microfluidic electrocell has reduced energy consumption by almost 20% (10.31 Kw.g⁻¹ under flow conditions vs 8.19 Kw.g⁻¹ in batch)²⁰ with a slightly higher productivity (217 mg.d⁻¹ under flow conditions vs 140 mg.d⁻¹). Then, to improve the productivity of the process without increasing the volume cell or the surface area of the electrodes we studied the impact of an increase of the concentration and the current density for a fixed residence time (590 s of residence time, Table S2, SI). At optimum conditions the productivity is found to be proportional to a factor multiplying both the concentration and the current density (Scheme 2b). Thus, by increasing simultaneously the concentration of **1a** (0.08 M) and the current density (32 mA, $J = 2.66 \text{ mA.cm}^{-2}$) by a factor of 4 we were able to almost quadruple the productivity of the reaction to 0.52 g.day⁻¹. Unfortunately, a multiplication factor above 4 did not allowed to maintain a high level of conversion. Further improvement should be feasible by an increase in the surface area of the electrodes or by parallelization of reactors.²¹

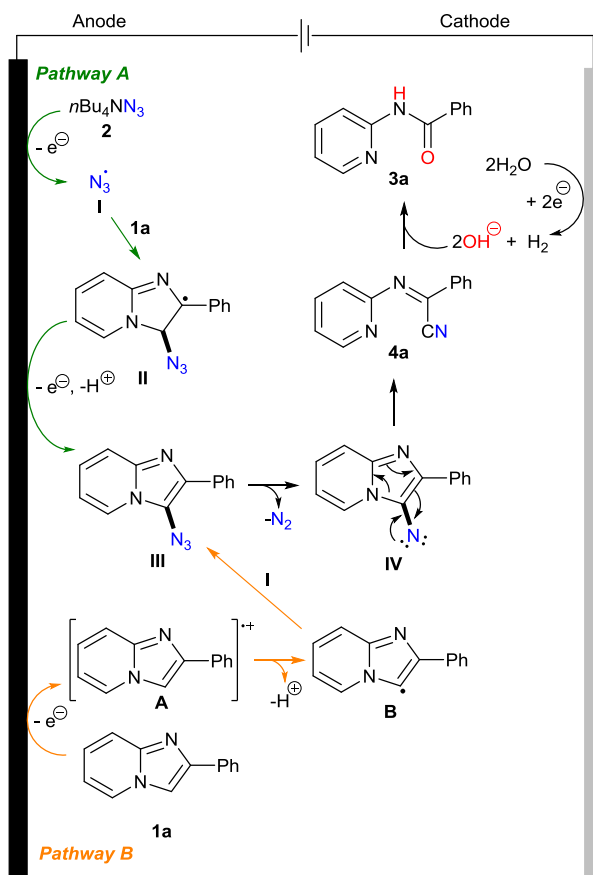
We then performed mechanistic studies to gain more insight into the reaction pathway (Scheme 3).



SCHEME 3 Mechanistic studies.

A few control experiments were performed, in the presence of radical scavengers such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) only a trace amount of product was formed (Scheme 3a). These results indicate that the reaction probably proceeds through a radical pathway.

From the cyclic voltammetry (CV) experiments, it is observed that tetrabutylammonium azide **2** oxidizes (0.88 V vs SCE) slightly more easily at the anode than 2-phenylimidazopyridine **1a** (1.10 V vs SCE) (Figure S2, SI). In addition, α -iminonitrile **5a** was synthesized since α -iminonitriles can be considered as precursors of amides **3a** via hydrolysis.¹⁵ Gratifyingly, the anticipated intermediate **5a** was confirmed from LC-MS analysis of the reaction mixture when ethanol was used as co-solvent instead of water, indicating its crucial role (Scheme 3b). Moreover, when α -iminonitrile **5a** was subjected to the standard conditions, amide **3a** was obtained in 76% (Scheme 3c). Thus, these experiments are consistent with the formation of α -iminonitrile intermediate. In addition, in the absence of electricity the desired product **3a** was not obtained, and only α -iminonitrile **5a** was recovered (Scheme 3d). Conversely, in presence of a sodium hydroxide solution, α -iminonitrile **5a** was completely converted to amide **3a** (Scheme 3e). In light of the above results, and previous literature reports¹² plausible mechanisms are proposed for the electrochemical ring opening of imidazoheterocycles driven by C3 azidation (Scheme 4).



SCHEME 4 Proposed reaction mechanism.

Anodic oxidation of tetrabutylammonium azide **2** furnishes azide radical **I** that further adds selectively at the C3 position of imidazopyridine **1a** to produce intermediate **II**. Next, intermediate **II** undergoes anodic oxidation followed by elimination of proton to afford 3-azidoimidazo[1,2-*a*]pyridine **III** (Scheme 4, pathway A). Subsequently, azide Intermediate **III** undergoes thermal decomposition to form nitrene intermediate **IV**^{16a} which affords α -iminonitriles **5a** after fragmentation and a coarctate reaction. Finally, hydroxide anions which are obtained by cathodic reduction of two molecules of water hydrolyses α -iminonitriles **5a** to the respective benzamides **3a**.

However, as the oxidation potentials of tetrabutylammonium azide **2** and 2-phenylimidazopyridine **1a** are really closed an alternative pathway could be envisaged (Scheme 4, pathway b). 3-azidoimidazo[1,2-*a*]pyridine **III** is produced from the radical coupling reaction of the azide radical **I** with the 2-arylimidazo[1,2-*a*]pyridine radical **B**,²² which is formed *via* anodic oxidation of 2-arylimidazo[1,2-*a*]pyridine **1a** followed by the deprotonation of the 2-arylimidazo[1,2-*a*]pyridine cation radical **A** intermediate.

Conclusions

In conclusion, we have developed a mild and straightforward convergent paired electrolysis method which gives rapid access to *N*- Heterocyclic amides in moderate to high yields. The reaction proceeds through the formation of α -iminonitriles, which is induced by the direct azidation of imidazoheterocycles whereas water plays a dual role as oxidant at the cathode and strong base. Moreover, continuous low protocol enables to reduce the energy consumption by nearly 20 % and facilitate the scale up of the reaction.

Author contributions

E. L. surveyed the substrate scope and optimized the flow protocol; L. C. surveyed the substrate scope; N.D. optimized the reaction conditions; M. D. supervised the project and provided experimental equipment; L. C. B. planned and supervised the project and wrote the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare

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