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Article

Scalable Electrochemical Hofmann Rearrangement as Platform for Orthogonally Protected Aminoketone Synthons

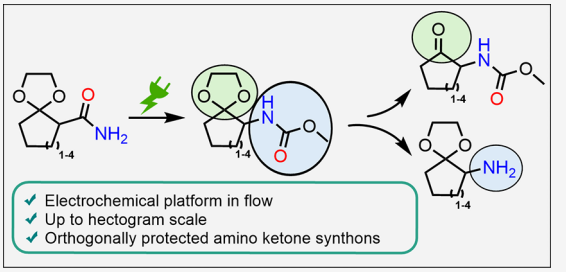
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ABSTRACT: The Hofmann rearrangement is among the most reliable methods for the conversion of primary carboxamides into amines and carbamates, yet access to free α-aminoketone building blocks through this transformation remains elusive. Under the oxidative and basic conditions required, non-protected enolizable ketones are incompatible with oxidative halo species and basic environment necessary for this transformation, whereas the resulting α-amido compounds are chemically and configurationally labile. Here, we show that masking β-ketoamides as cyclic acetals enables electrochemical Hofmann rearrangement in flow with an orthogonal deprotection pathway to the carbamate generated during the transformation. Under galvanostatic conditions, using sodium bromide as both mediator and supporting electrolyte, acetal-protected β-ketoamides are converted into the corresponding methyl carbamates in good to excellent yields. The process established avoids stoichiometric chemical oxidizers and has been demonstrated on gram to hectogram scale (100 g) without loss of efficiency, allowing recovery and reuse of the bromide as mediator. The resulting orthogonally protected carbamates serve as versatile divergent intermediates: chemoselective cleavage of either protecting group, grants access to ketones and amines, whereas sequential deprotection furnishes free 2-aminocycloalkanones and fused azaheterocycles by telescoped, purification-free sequences. The integration of electrochemistry and flow processes thus provides a scalable and sustainable platform for accessing orthogonally protected aminoketone synthons as versatile carbonyl-containing nitrogen building blocks.

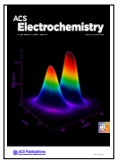


KEYWORDS: *electrosynthesis, scale-up, Hofmann rearrangement, flow process*

INTRODUCTION

Over the past decades, the development of more sustainable chemical processes has become a central objective, particularly in industrial research.[1] Among the key principles of green chemistry is the minimization or elimination of hazardous reagents, which are still widely employed in many fundamental transformations.[2] Amines and carbamates are ubiquitous in pharmaceuticals, agrochemicals, and material science since the operational simplicity, broad functional-group tolerance, and substrate availability of the reaction have sustained its use for more than a century.[3,4] The Hofmann rearrangement remains one of the most dependable methods for converting primary amides into amines and carbamates, effecting a single carbon-to-nitrogen migration on readily available substrates.[5] Despite these advantages, traditional protocols rely on (super-)stoichiometric amounts of highly reactive and hazardous halogenating agents, such as elemental bromine or hypohalites.[6] This reliance raises significant concerns in terms of safety, environmental impact, and waste generation, especially when considering large-scale applications. To address these challenges, organic electrosynthesis has emerged as a powerful and sustainable alternative, enabling the direct use of electricity to drive redox transformations.[7g] Indeed, by replacing conventional oxidants and reducing agents by electrons, electrochemical methods offer improved atom efficiency.[7,8] In this context, the in-cell anodic generation of reactive halogen species from simple halide salts, as supporting electrolyte and mediator, represents an elegant strategy to promote halogen-mediated transformations, without the need for terminal oxidizers.[9,10] In recent years, electrochemical Hofmann rearrangements have been progressively developed in conventional batch electrolysis and flow systems, employing different reactor designs (Scheme 1).[11] Initial reports by Zhang et al. demonstrated the feasibility of the transformation under batch electrolysis conditions on a milligram scale, affording the corresponding carbamates in good yields. Subsequently, Cantillo et al. improved the productivity of the process by

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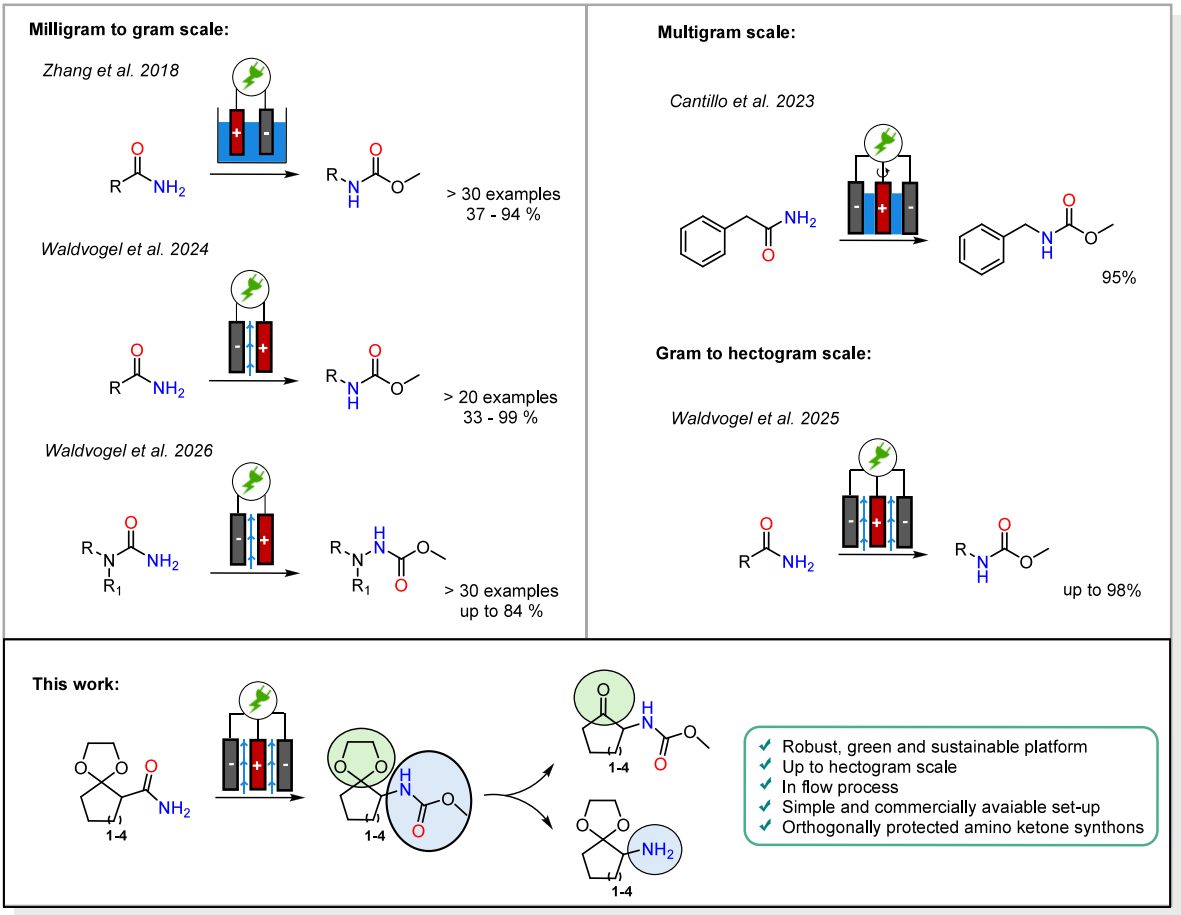


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Scheme 1. Different Setups Employed for the Electrochemical Hofmann Rearrangement



employing a spinning graphite anode, enabling multigram-scale synthesis with enhanced efficiency.[12] Building on these advances, the implementation of flow electrolysis has further expanded the potential of this transformation. More recently, our group successfully demonstrated that the use of high current densities with in flow electrolysers enables a substantial increase in productivity, allowing the scale-up of the electrochemical Hofmann rearrangement from milligram to multigram and even hectogram quantities for both aliphatic and aromatic amides. Furthermore, the versatility of this high-current-density approach was demonstrated by its successful application to urea substrates, providing protected hydrazines under analogous flow conditions.[7g] However, despite these advances, the application of electrochemical Hofmann rearrangements to substrates bearing sensitive carbonyl functionalities in addition to the targeted carboxamide remains underexplored. Among these, ketone-containing amides remain particularly challenging, as ketones are susceptible to competing side reactions under both chemical and electrochemical conditions. Consequently, direct access to versatile amino carbonyl building blocks by electrochemical Hofmann-type rearrangements has remained elusive. To address this limitation, we envisioned the use of acetal-protected 1,3-ketocarboxamides as masked substrates. This modification restores compatibility with the electrochemical conditions and installs a protecting group orthogonal to the carbamate, generated during the rearrangement. Such compounds constitute versatile orthogonally protected synthons, in which chemoselective deprotection of the carbamate and acetal moieties unleashes tunable and complementary reactivity profiles. Herein, we establish a scalable electrochemical platform for the preparation of orthogonally functionalized carbonyl-nitrogen building blocks.

RESULTS AND DISCUSSION

With the aim of establishing a modular platform for orthogonally functionalized amino carbonyl synthons, acetal-protected β-ketoamide **1a** was selected as a model substrate. Given the envisioned downstream transformations and the synthetic utility of the resulting carbamates **2a**, their efficient and scalable preparation using a simple flow setup was considered essential. To this end, a commercial plate and frame electrolyzer was employed (Figure 1a).[13] The reactor consists of a sandwich-type configuration featuring a central glassy carbon anode flanked by two stainless-steel cathodes, arranged in two separate flow compartments. Each compartment provides an anodic electrode surface area of 83 cm^2 with an interelectrode gap of 2 mm, corresponding to a cell volume of 16 mL. The two electrolysis compartments use different sides of the same anode, ensuring complete physical separation of the reaction media throughout the electrolysis (Figure 1b). As a result, the reaction solution is circulated sequentially through both compartments, providing a total anodic surface area of 166 cm^2. This configuration was selected to enable high-current-density electrolysis

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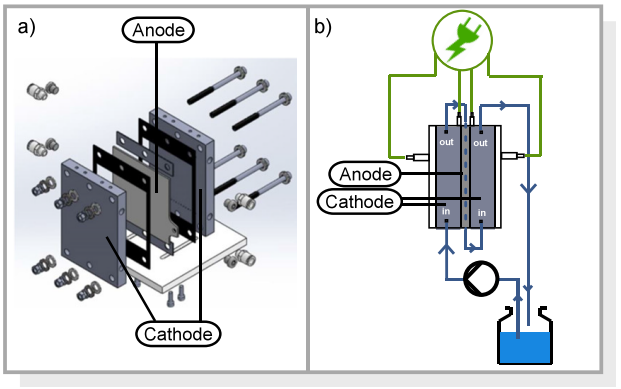


Figure 1. (a) Schematic drawing of the sandwich cell type. (b) Schematic drawing of the electrochemical setup from the side.

under flow galvanostatic conditions. Accordingly, the electrochemical Hofmann rearrangement was initially investigated using acetal-protected β-ketoamide **1a** under galvanostatic conditions (Table 1). Notably, the constant current of 60 mA cm^{-1} and the electrode material have been selected based on our previous studies.[8a]

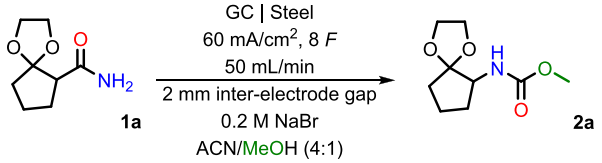
Sodium bromide was selected as an inexpensive bromine source and supporting electrolyte, while a 4:1 mixture of acetonitrile and methanol was employed as the reaction medium. Accordingly, while the anodic oxidation generates Br_2, hydrogen evolution at the cathode surface delivers methoxide as base, necessary for the transformation.[14] To assess the influence of the electrochemical parameters, the amount of applied charge was systematically varied between 4 and 8 *F*. Lower amounts of applied charges resulted in incomplete conversion and diminished yields, with carbamate **2a** being obtained in 61% and 89% yield at 4 and 6 *F*, respectively (entries 2 and 3). These results suggest that maintaining sufficient concentrations of the electrochemically generated brominating species is crucial for efficient conversion. Indeed, full consumption of the starting material was achieved upon applying 8 *F*, providing carbamate **2a** in 96% isolated yield at a flow rate of 50 mL min^{-1} (Entry 1).

Next, the influence of the flow rate was subsequently examined by reducing it to 25 mL min^{-1} while maintaining a charge input of 4 *F*. However, no relevant change in yield was observed (entry 4 and entry 2), indicating that mass transport does not limit the transformation under the applied electrochemical conditions. Encouraged by the high efficiency observed under flow conditions, we next evaluated the scalability of the electrochemical transformation using acetal-protected β-ketoamide **1a**, targeting a 50 g scale reaction within the analogous setup (Table 2).

For this purpose, we selected a recirculatory flow process, where the electrolyte solution, contained in one reservoir, is pumped into the first electrode compartment and then into the second one of the same sandwich-type electrolyzer, operating as two electrochemical flow cells in series (Figure 2a). Under these conditions, 50 g scale electrolysis of **1a** was successfully performed over 6.5 h, followed by overnight postelectrolysis stirring, affording carbamate **2a** in 98% isolated yield after simple distillation of the crude reaction mixture. Noteworthy, simple work-up and reusing electrolyte components are important for the economic and ecological attractivity of an electrochemical process.[15] Accordingly, NaBr was recovered in 87% yield by filtration after solvent evaporation and reused in seven consecutive electrolysis cycles (Figure 2c). In each case, the mediator, recovered from the previous run, was directly employed in the subsequent reaction, consistently affording high ^{1}H NMR yields (97−93%), thereby demonstrating the robustness of the recycling protocol.

Motivated by these results, we next aimed to perform a hectogram scale electrolysis using amide **1a.** To efficiently run the process at this scale, a numbering-up approach using two sandwich-type electrolyzers, identical in design and configuration, was employed. The cells were connected in series, and the electrolyte solution was pumped through all the electrolysis compartments in series from the bottom, representing a system with a total of 324 cm^2 of anode surface area (Figure 2b). Additionally, to maintain the same residence time and an efficient mixing, the flow rate was doubled from 50 to 100 mL min^{-1}. As a result, the processing of 100 g of **1a** was enabled within the same 6.5 h electrolysis and overnight postelectrolysis stirring. Notably, the electrolysis was conducted at room temperature; however, the electric current provides a Joule heating that increases the cell temperature to 35 °C. Carbamate **2a** was successfully obtained in 96% yield after distillation of the crude reaction mixture, providing a robust, efficient, and scalable electrochemical protocol under flow conditions. The performance of the process at the hectogram scale was further evaluated in terms of electrochemical efficiency and productivity. A current efficiency of 24% was achieved, together with a productivity of 17.33 g h^{-1} while maintaining the excellent isolated yield of

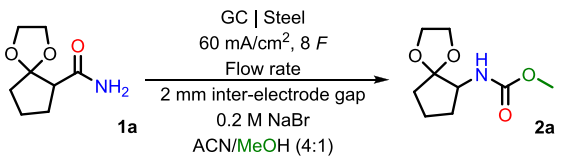
Table 1. Electrochemical Reaction Conditions[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	96
2	4 *F* instead of 8 *F*	61
3	6 *F* instead of 8 *F*	89
4	25 mL/min applying 4 *F*	66
5	no electricity	0

[a]Reaction conditions: **1a** (40 mmol, 6. 85 g, 1 equiv), 0.1 M NaBr (80 mmol, 8.23 g, 2 equiv), ACN/MeOH 4:1, (+) GC|Steel (−), interelectrode gap 2 mm, 60 mA cm^{-1}, 8 *F*, galvanostatic conditions, sandwich-type flow cell, 3 h of postelectrolysis stirring. [b]Isolated yield by column chromatography on silica gel.

Table 2. Electrochemical Hofmann Rearrangement on 50 and 100 g Scale Reaction



1a	flow rate (mL min^{-1})	anode surface (cm^2)	yield (%)[a]
50 g scale	50	162	98
100 g scale	100	324	96

[a]Isolated yields by distillation of the crude reaction mixture.

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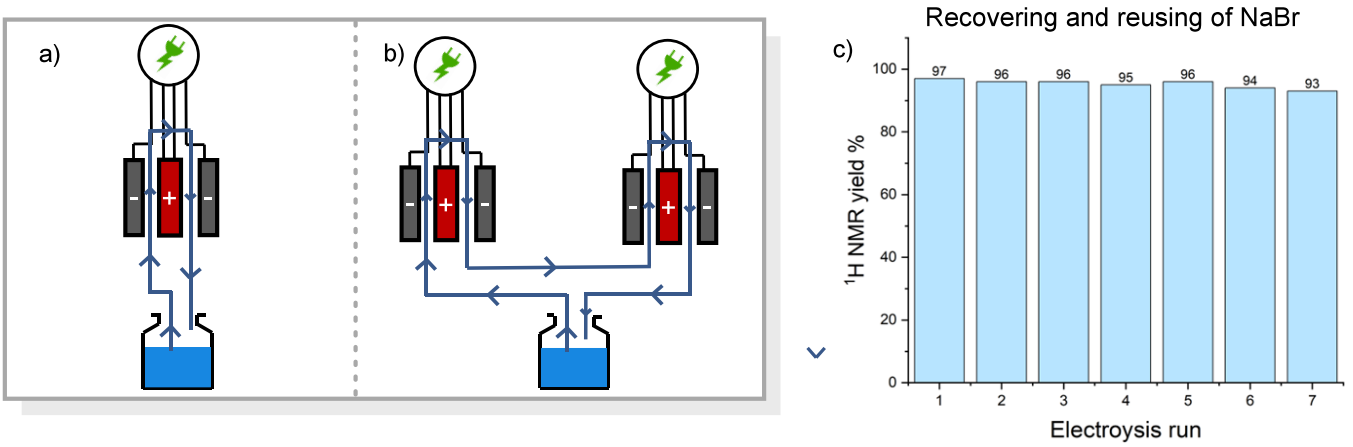
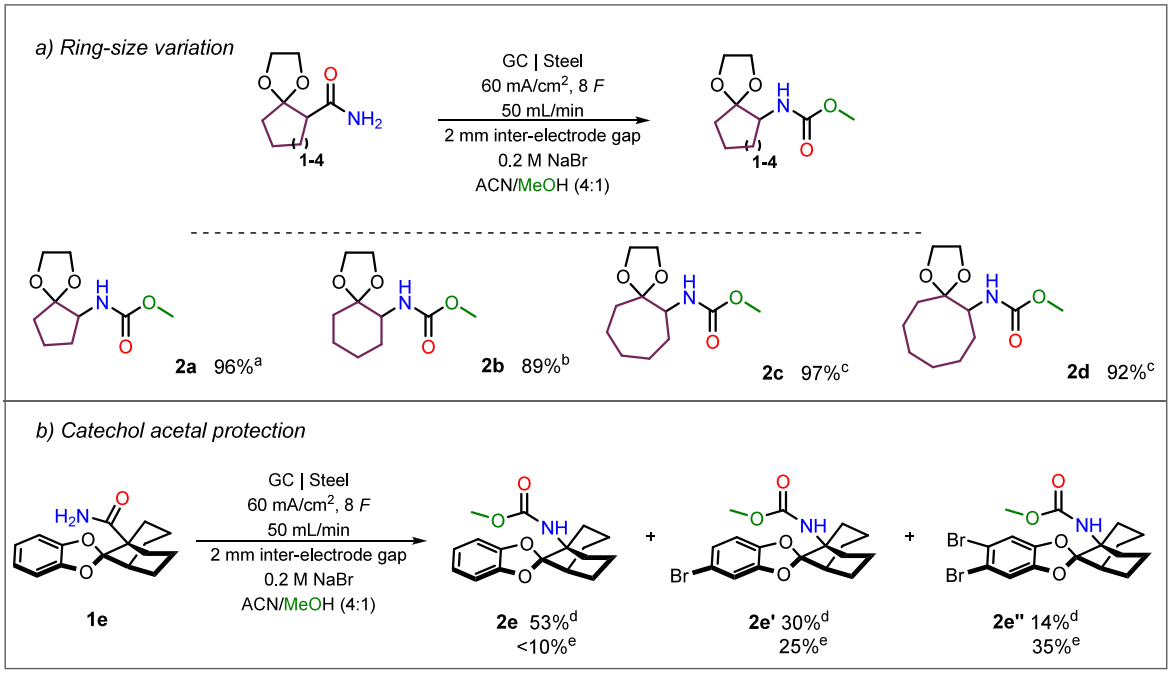


Figure 2. (a) Schematic drawing of the used setup for 50 g scale reaction. (b) Schematic drawing of the hectogram scale reaction using a numbering-up approach. (c) Electrolysis performed on 40 mmol of **1a**. ^{1}H NMR yield determined by 1,3,5-trimethoxybenzol as internal standard.

96% (See Supporting Information for calculations). We next sought to probe its generality and structural tolerance by varying the aliphatic ring size of the substrate. To this end, acetal-protected 1,3-ketocarboxamide **1b**, **1c**, and **1d** were studied under the optimized reaction conditions (Scheme 2a).

All substrates underwent high conversion to the corresponding carbamates **2b**, **2c**, and **2d** in good to excellent isolated yields, highlighting the applicability across different ring sizes. To further examine the scope of the protecting group strategy, the catechol-derived spirocyclic β-ketoamide **1e** was subjected to the optimized reaction conditions (Scheme 2b). This substrate was selected to evaluate whether a structurally distinct cyclic acetal protecting group could be accommodated under the electrochemical Hofmann conditions. Noteworthy, such rearrangement at very bulky carbonyl substrates was performed in the past by the Shioiri reagent. Such entities are important for the construction of artificial receptors for caffeine and explosive.[16] The resulting carbamate **2e** was successfully obtained in 53% isolated yield, confirming the feasibility of the rearrangement with an alternative cyclic acetal protecting group. However, competitive electrophilic bromination of the electron-rich ring resulted in the formation of the corresponding mono- and dibrominated derivatives (**2e′** and **2e″**) in 30% and 14% yield, respectively, illustrating a limitation of highly electron-rich aromatic acetals under bromine-mediated electrochemical conditions compared to the ethylene-glycol

Scheme 2. (a) Variation of the Ring Size for the Electrochemical Hofmann Rearrangement



[a]Reaction performed on 6.85 g scale. [b]Reaction performed on 9 g scale. [c]Reaction performed on 3 g scale. (b) Catechol acetal-protected electrolysis. [d]Reaction performed in 5 g scale. [e]Reaction performed with 12 *F* as amount of the applied charge and 0.3 M NaBr.

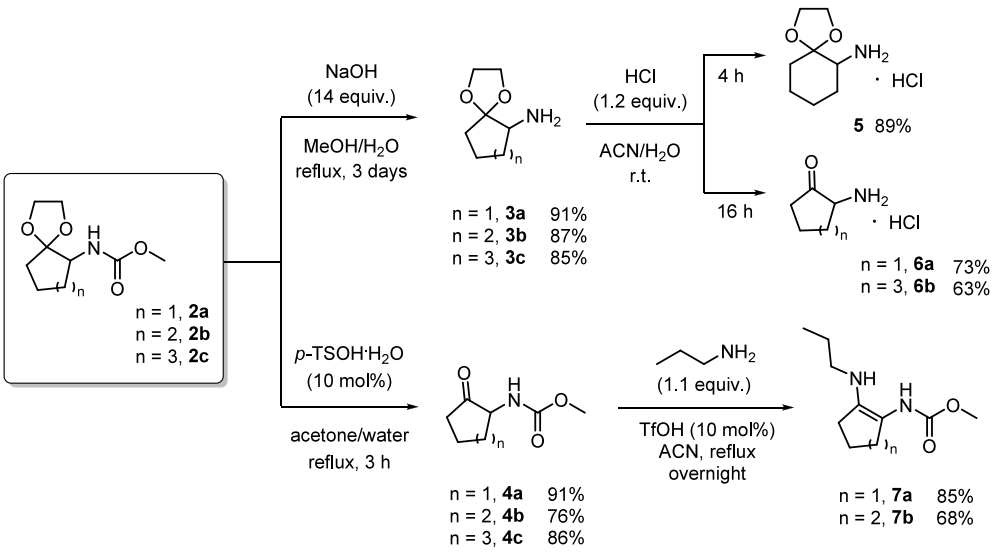
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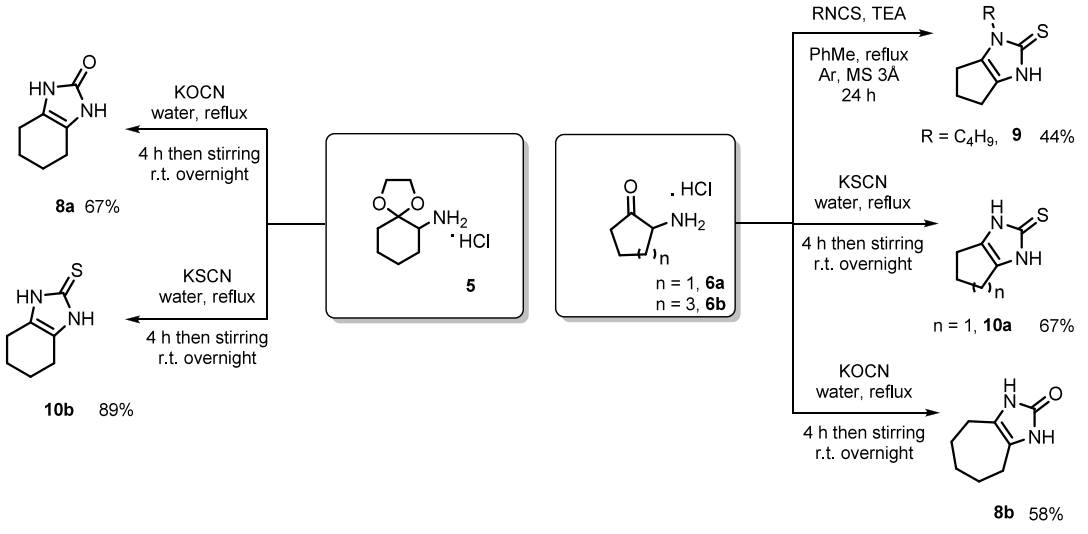
acetals. Additional experiment was conducted trying to increase the selectivity for carbamate **2e″** increasing NaBr concentration and enhancing the amount of applied charge up to 12 *F*. Interestingly, under these electrochemical conditions, **2e′** and **2e″** were isolated in 25% and 35% yield. Although the selectivity toward the desired product could be further improved, this required increasing the amount of the applied charge to 12 *F*. As expected, the higher applied charge resulted in a decrease in current efficiency, which dropped to 12%.

Importantly, the electrochemically generated carbamates provide access to orthogonally protected synthons that enable complementary downstream transformations by chemoselective deprotection strategies (Scheme 3). On one hand, chemoselective acidic deprotection of the acetal moiety provided access to the corresponding ketones **4a−c** in good yields, which were directly converted, without purification, into enamines **7a−b** upon treatment with propylamine in the presence of a strong acid. On the other hand, alkaline hydrolysis of **2a−c** efficiently cleaved the carbamate group to afford the corresponding free amines **3a−c** in good to high yields. Subsequent treatment of these compounds with HCl in acetonitrile generated the corresponding hydrochloride salts. Upon overnight stirring, acidic conditions promoted concomitant acetal deprotection to deliver the hydrochloride salts of the corresponding 2-aminocycloketones **6a−b**, which were isolated by simple precipitation. Interestingly, filtration of the precipitate after 4 h allowed the selective isolation of the hydrochloride salt of the acetal-protected 2-aminoketone **5** in 89% yield, demonstrating that the synthetic sequence can be intercepted at different stages to access complementary products. This intermediate was further converted into imidazolidinone **8a** and imidazolidinthione **10b** upon treatment with KOCN and KSCN, respectively (Scheme 4). To further demonstrate the robustness and practical utility of the methodology, the preparation of **6a** was successfully translated to gram scale, delivering 10 g of product in 73% yield. Having established straightforward access to free

Scheme 3. Synthetic Pathway to Unleash the Desired Reactivity by Selective Deprotection of the Orthogonal Group



Scheme 4. Synthetic Pathway to Afford Versatile Heterocycles



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2-aminocycloketones, we next explored their value as versatile precursors to fused azaheterocycles. Treatment of **6a** with butyl isothiocyanate in the presence of triethylamine (TEA) in toluene under argon atmosphere afforded the corresponding N-substituted imidazolidinthione **9** in moderate yield. In contrast, a more operationally simple and efficient protocol for **6a−c** was identified using KOCN and KSCN under aqueous conditions to provide direct access to imidazolidinthiones **10a** and imidazolidinone **8b** through simple precipitation. Noteworthy, compounds **10a**, **10b**, and **9** constitute valuable heterocyclic frameworks frequently encountered in biologically active molecules for the treatment of cancer, neurodegenerative diseases, and inflammatory disorders.[17] Likewise, compounds **8a** and **8b** belong to a class of fused imidazolidine-2-thiones found in biologically active molecules that selectively bind to γ-aminobutyric acid (GABA) receptors for the treatment of anxiety and sleep disorders.[18] Therefore, their sustainable synthesis through purification-free sequences highlights the potential of the present platform to provide medicinally relevant scaffolds by operationally simple precipitation-based protocols.

EXPERIMENTAL SECTION

General Protocol for the Electrochemical Hofmann Rearrangement

In a 500 mL Schott bottle, 1,4-dioxaspiro[4.4]nonane-6-carboxamide **1a** (6.847 g, 1 equiv 40 mmol) and NaBr (8.231 g, 2 equiv 80 mmol) were dissolved in a mixture 400 mL of ACN/MeOH (4:1). The homogeneous solution was pumped into the sandwich-type electrolyzer using a flow rate of 50 mL min^{-1}. The amount of applied charge for each cell is 4 *F*, and a galvanostatic current of 5 A (60 mA/cm^2) was employed. Notably, the electrolysis was conducted at room temperature; however, the electric current provides a Joule heating that increases the cell temperature to 35 °C. After the end of the electrolysis, the reaction was stirred for additional 3 h, monitoring the disappearance of the starting material by TLC. The solvent was removed under reduced pressure, and the crude was dissolved in CH_2Cl_2 and filtered off. The remaining solid was washed with additional CH_2Cl_2 (3× 30 mL) leaving NaBr to be recovered. The organic layer was washed with water and the aqueous phase was extracted with CH_2Cl_2 (3× 100 mL) and washed two times with brine solution. After solvent removal, the resulting crude product was purified by distillation of the crude, affording **2a** as a red oil in 96% yield.

General Protocol for the Hectrogram-Scale Electrochemical Hofmann Rearrangement

In an 8 L bottle, 1,4-dioxaspiro[4.4]nonane-6-carboxamide **1a** (100 g, 1 equiv 584 mmol) and NaBr (120.17 g, 2 equiv 1.168 mol) were dissolved in a mixture 5.9 L of ACN/MeOH (4:1). The homogeneous solution was pumped into the sandwich-type electrolyzer using 100 mL min^{-1} as flow rate. The amount of applied charge for each cell is 4 *F*, and a galvanostatic current of 5 A (60 mA/cm^2) was employed. Notably, the electrolysis was conducted at room temperature. The electric current provides a Joule heating that increases the temperature at 35 °C. After the end of the electrolysis, the reaction was stirred overnight, monitoring the disappearance of the starting material by TLC. The solvent was removed under reduced pressure, and the crude was suspended in CH_2Cl_2 and filtered off and washed with additional CH_2Cl_2 (3× 700 mL) to recover NaBr. The organic layer was extracted with CH_2Cl_2 (3× 1000 mL) and washed two times with brine solution. After solvent removal, the resulting crude product was purified by distillation of the crude, affording **2a** as a red oil in 96% yield.

CONCLUSIONS

In summary, we have developed a robust and scalable electrochemical Hofmann rearrangement that enables the conversion of acetal-protected β-ketoamides into orthogonally protected carbamates. The flow conditions allow practical scale-up. The protocol combines operational simplicity, inexpensive reagents, and excellent scalability, reaching the hectogram scale while maintaining high isolated yield and substantial productivity. A Faradaic efficiency of 24% was achieved at this scale, indicating that further improvements in charge utilization may still be possible. Nevertheless, the high synthetic efficiency and productivity demonstrate the robustness of the process under preparative flow conditions. Together with the easy recovery and reuse of the bromide mediator, these features provide a practical and sustainable alternative to conventional Hofmann protocols. Beyond the rearrangement itself, the electrochemically generated carbamates constitute a versatile family of orthogonally protected synthons that can be selectively transformed into ketones, enamines, free 2-aminocycloketones, and fused azaheterocycles by complementary deprotection pathways. More broadly, this work demonstrates how the combination of electrochemistry and flow processes can expand the synthetic utility of classical rearrangements, enabling the development of modular and scalable platforms for the preparation of value-added nitrogen-containing building blocks.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acselectrochem.6c00365.

Detailed description of the electrochemical setup and experimental conditions (PDF)

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Author Contributions

S.A., D.F.N., B.W., and S.R.W. conceptualized the project. S.A., D.F.N., R.Z., and J.B conducted the experimental work and analyzed the data. S.A., D.F.N., and S.R.W prepared the manuscript, which was revised by all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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