

N-Heterocyclic Carbene-Mediated Microfluidic Oxidative Electrosynthesis of Amides from Aldehydes

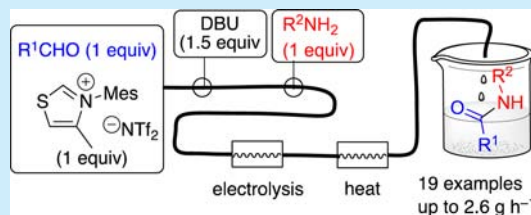
Robert A. Green,[†] Derek Pletcher,[†] Stuart G. Leach,[‡] and Richard C. D. Brown^{*,†}

[†]Department of Chemistry, University of Southampton, Southampton, Hampshire SO17 1BJ, U.K.

[‡]GlaxoSmithKline, Stevenage, Herts SG1 2NY, U.K.

S Supporting Information

ABSTRACT: A flow process for N-Heterocyclic Carbene (NHC)-mediated anodic oxidative amidation of aldehydes is described, employing an undivided microfluidic electrolysis cell to oxidize Breslow intermediates. After electrochemical oxidation, the reaction of the intermediate N-acylated thiazolium cation with primary amines is completed by passage through a heating cell to achieve high conversion in a single pass. The flow mixing regimen circumvented the issue of competing imine formation between the aldehyde and amine substrates, which otherwise prevented formation of the desired product. High yields (71–99%), productivities (up to 2.6 g h⁻¹), and current efficiencies (65–91%) were realized for 19 amides.

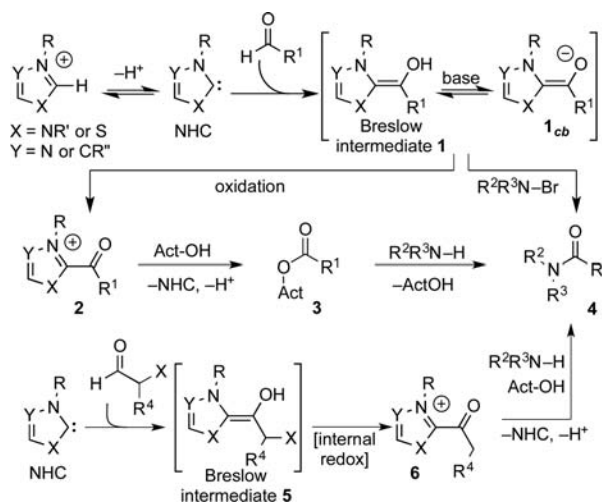


The amide functional group is of fundamental importance as a structural and functional motif present in a vast array of natural and synthetic substances, from small molecule drugs to biopolymers and materials.¹ Consequently, the synthesis of amides is widely practiced and highly relevant across many areas. Traditional approaches to amide formation by means of carboxylate activation are often highly efficient in terms of conversions and yields,² but can exhibit low atom economy or the requirement for corrosive and toxic reagents and intermediates.^{3,4}

A number of alternative methodologies have been proposed, including oxidative conversions of alcohols or aldehydes to amides.⁵ N-Heterocyclic carbenes (NHCs) have been identified as organic catalysts for a range of reactions including the oxidative conversion of aldehydes to amides (Scheme 1).⁶ Reported NHC-mediated acylations from aldehydes require the addition of an external stoichiometric chemical oxidant⁷ or utilize substrates that contain an internal redox system (e.g., α -halo or α,β -unsaturated aldehydes),⁸ to transform Breslow intermediate 1 or 5 to the activated acyl donor 2 or 6 respectively. Direct amidation of aldehydes mediated by NHC salts can be inhibited by a competing reaction between the aldehyde and amine, and formation of water as a byproduct, which may intercept any activated acyl intermediates formed. Solutions to this problem have included the addition of nucleophilic catalysts such as HOBt and imidazole,^{8c,d} or by performing the reaction with the amine as a separate step following the formation of an activated ester intermediate.⁹

Electrochemical oxidation of Breslow intermediates 1 (or 1_{cb}) presents an appealing alternative to the use of a stoichiometric oxidizing equivalent, in the form of either an added reagent or a pre-existing functionality within either substrate. This electrosynthesis approach has been applied to the formation of esters and thioesters in batch, and recently by

Scheme 1. Approaches to the Synthesis of Amides from Aldehydes Mediated by NHCs



us, using a microfluidic electrolysis cell (Figure 1).¹⁰ Herein we describe a flow process for NHC-mediated synthesis of amides from aldehydes using an electrochemical microflow cell in sequence with a heating chip, where high conversions and yields can be achieved in a single pass.

3,4,5-Trimethoxybenzaldehyde (8) and benzyl amine were selected as test substrates for initial investigation of anodic oxidative amidation using the thiazolium bistriflimide 7 as an NHC precursor (Scheme 2), employing a microfluidic electrolysis cell previously described by us.¹¹ Direct application

Received: February 2, 2016

Published: February 17, 2016

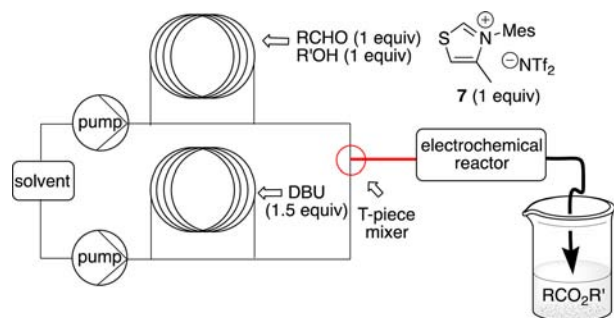
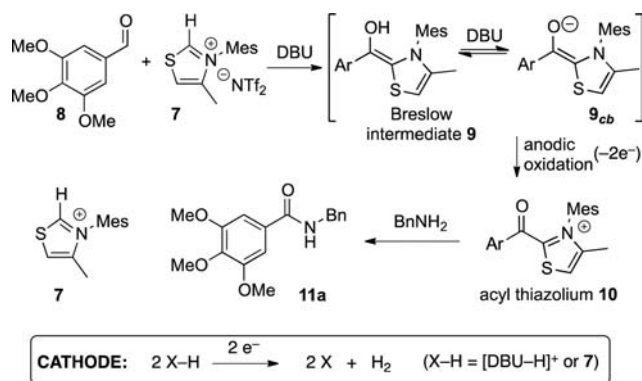


Figure 1. NHC-mediated oxidative synthesis of esters from aldehydes and alcohols using a microfluidic electrolysis cell.^{10d}

Scheme 2. Electrosynthesis of Amide 11a from Aldehyde 8 Mediated by Thiazolium Bistriflimide 7

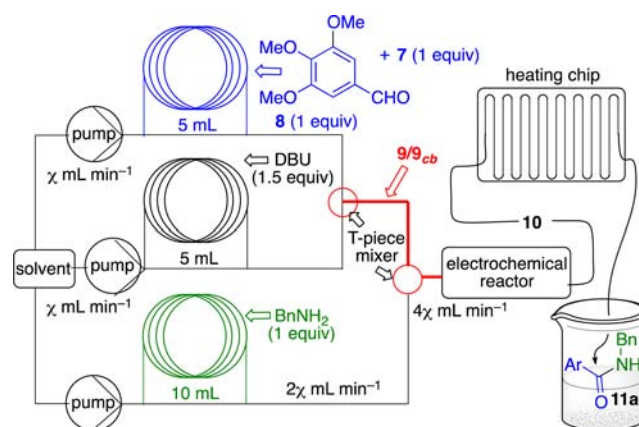


of the conditions for NHC-mediated electrochemical esterification (Figure 1), whereby the alcohol nucleophile was simply replaced with BnNH_2 , failed to deliver any of the desired amide 11a.^{10a} In the esterification process, the solution exiting the mixing T-piece displayed a red coloration, which we consider to be indicative of the formation of the Breslow intermediate 9/9_{cb}. Notably, in the failed amidation attempt, the characteristic red color was absent, presumably as a consequence of competing imine formation.

A significant benefit of performing reactions in flow is the ability to easily control reactant and reagent mixing, which herein enabled formation of the NHC and Breslow intermediate in flow prior to mixing with the amine and before the reaction mixture entered the electrolysis cell (see Table 1). Indeed, this in-flow mixing regimen led to encouraging isolated yields of amide 11a of 30–40% in a THF/DMSO solvent mixture with a total flow rate of 0.12 mL min⁻¹ at rt (entry 1, Table 1). DMF has been suggested as a superior solvent to THF for acyl transfer,^{8b} in addition to being regarded as a favorable electrochemical solvent due to its high dielectric constant, and significantly for the current application, it is effective in solubilizing the thiazolium salt 7. Further improvement followed from a solvent switch to DMF at the same flow rate, resulting in an 80% yield of amide 11a (entry 2, Table 1).

With the objective of increasing the rate of production of amide 11a, the flow rate through the cell was increased to 1.2 mL min⁻¹, with a commensurate adjustment of the cell current (entry 3, Table 1). However, an unexpected drop in the product yield was observed. Further investigation revealed that the reaction of benzylamine with the acyl thiazolium intermediate 10 was incomplete when the reaction mixture exited the flow cell. As a consequence of the increased flow rate

Table 1. Optimization of Electrochemical Formation of Amide 11a^a



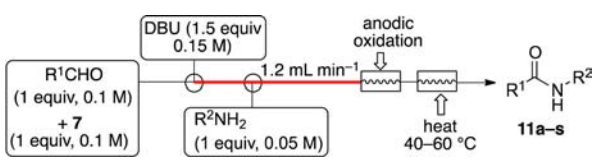
entry	solvent	flow rate (mL/min) ^b	current (mA) ^c	temp (°C) ^d	yield of 11a ^e (%)
1	THF/DMSO	0.12	10–12	rt	40
2	DMF	0.12	10–12	rt	80
3	DMF	1.2	105	rt	39
4	DMF	1.2	105	rt ^f	99
5	DMF	1.2	105	50	80
6	DMF	1.2	105	60	99
7	DMF	1.2	105	100	59

^aReactions performed on 0.5 mmol scale with a final concentration of 8 of 0.025 M at a combined flow rate of 0.12 or 1.2 mL min⁻¹ before entering the electrolysis cell (electrolysis cell residence time <10 s at 1.2 mL min⁻¹). ^bFlow rate represents the total combined flow rate from mixing three streams before entering the electrolysis cell. ^cTotal cell current once the cell is flooded with the reaction mixture. ^dTemperature of heating chip (residence time <50 s at 1.2 mL min⁻¹). ^eIsolated yield of purified amide 11a. ^fThe total reaction mixture was stirred in the collection vessel for 2 h before workup.

of 1.2 mL min⁻¹ the flow run was completed in less time, accounting for the observed decrease in yield/conversion at the time of workup. Complete conversion was achieved when the reaction mixture was held in the collection flask for 2 h before workup (entry 4). However, a more efficient solution was realized by flowing the reaction mixture through a heating chip after exiting the electrolysis cell resulting in quantitative yield at 60 °C (entry 6). Lower, or higher, temperatures at the same flow rate gave incomplete conversion or led to some degradation (entries 5 and 7 respectively).

The results detailed above highlight the remarkably efficient anodic oxidation of thiazolium-derived Breslow intermediates, at residence times of no more than 10 s in the electrolysis cell at 1.2 mL min⁻¹ (this neglects the increased flow rate caused by evolution of hydrogen gas at the cathode). An additional benefit of the process stems from the ability to heat the postelectrolysis flow stream and thereby accelerate and complete the addition of the amine to the acylthiazolium, which is comparatively slower than the corresponding reaction with simple alcohols.^{10a,12}

The optimized conditions were applied to a range of aldehydes and primary amines with productivity rates between 0.3 and 0.6 g h⁻¹ (Table 2). Electron-rich aromatic and heteroaromatic aldehydes underwent amidation in good to excellent isolated yields (94–99%, entries 1, 5, and 7). Furthermore, primary amines containing electron-rich electro-

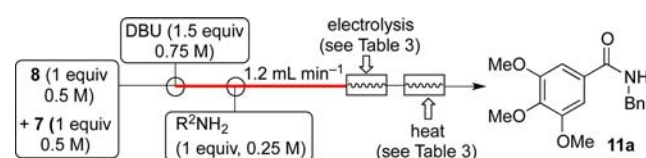
Table 2. Examples of NHC-Mediated Electrochemical Amidation of Aldehydes in Flow^a


entry	R ¹ CHO	R ² NH ₂	temp (°C) ^b	yield of 11a-s ^c (%) [Productivity] ^d
1	8	Bn-NH ₂	60	11a , 99, [540 mg h ⁻¹]
2	Ph-CHO	Bn-NH ₂	60	11b , 98, [371 mg h ⁻¹]
3		Bn-NH ₂	60	11c , 98, [432 mg h ⁻¹]
4		Bn-NH ₂	40	11d , 88, [364 mg h ⁻¹]
5		Bn-NH ₂	60	11e , 99, [432 mg h ⁻¹]
6		Bn-NH ₂	40	11f , 92, [432 mg h ⁻¹]
7		Bn-NH ₂	60	11g , 94, [342 mg h ⁻¹]
8		Bn-NH ₂	60	11h , 91, [349 mg h ⁻¹]
9	<i>n</i> -C ₁₁ H ₂₃ -CHO	Bn-NH ₂	60	11i , 71, [370 mg h ⁻¹]
10		Bn-NH ₂	40	11j , 94, [490 mg h ⁻¹]
11	12		60	11k , 83, [378 mg h ⁻¹]
12	12		60	11l , 86, [414 mg h ⁻¹]
13	12		60	11m , 80, [428 mg h ⁻¹]
14	12		60	11n , 86, [374 mg h ⁻¹]
15	12		60	11o , 86, [432 mg h ⁻¹]
16	12		60	11p , 83, [457 mg h ⁻¹]
17	12		40	11q , 97, [558 mg h ⁻¹]
18	12		60	11r , 78, [450 mg h ⁻¹]
19	12		60	11s , 71, [436 mg h ⁻¹]

^aReactions performed on 0.5 mmol scale with a final concentration of R¹CHO/R²NH₂ of 0.025 M at a combined flow rate of 1.2 mL min⁻¹ before entering the electrolysis cell. ^bTemperature of heating chip. ^cYield is that of purified isolated material. ^dProductivity is based upon 16.67 min run time.

chemically oxidizable functionalities such as indole, furan, and phenol groups afforded amides in 71–86% yields (entries 15, 18, and 19). An unbranched aliphatic aldehyde afforded the corresponding *N*-benzylamide **11i** in 71% yield (entry 9). The conditions of the undivided cell also tolerated the aryl bromide functionality (71–97% yields, entries 10–19). Current efficiencies for the two-electron anodic process were in the range 65–91%, indicating good selectivity with respect to secondary oxidations.¹³ Unfortunately, attempts to use bulkier secondary amines only led to a trace amount of products being isolated, underscoring the lower reactivity of amines with acylthiazoliums.

With the objective of delivering larger quantities of material, efforts to improve the rate of productivity examined increasing initial substrate concentration to 0.5 M along with the cell current required to effect the required chemical conversion (Table 3). At the higher concentration of aldehyde **8** (0.5 M)

Table 3. Increasing the Productivity Rate for the Electrosynthesis of Amide 11a^a


entry	current (mA)	temp (°C) ^d	yield of 11a ^b (%)	productivity ^c (g h ⁻¹)
1	510	60	71	1.9
2	575	60	54	1.5
3	510	80	71	1.9
4	510	110	94	2.5

^aReactions performed on 2.5 mmol scale with a final concentration of **8** of 0.125 M at a combined flow rate of 1.2 mL min⁻¹ before entering the electrolysis cell. ^bYield is that of purified isolated material. ^cProductivity is based upon isolated yields from 16.67 min run time. ^dTemperature of heating chip.

and with the heater chip at 60 °C, the yield of amide **11a** was found to decrease to 71% (entry 1). This can be understood by the significantly increased flow through the heater chip due to the increased cathodic hydrogen gas production at the higher current, and consequent decreased residence time. Further increase of the cell current led to a further reduction in yield of amide **11a** (entry 2). Gratifyingly, excellent yield (94%) and a high rate of production (2.5 g h⁻¹) could be achieved when the heater chip temperature was increased to 110 °C (entry 4), producing 706 mg of amide in 16.7 min.

Finally, to demonstrate the robustness of the process, an extended run over 8.3 h produced 21.5 g (97%) of isolated amide **11a** at a productivity rate of 2.58 g h⁻¹.

In conclusion, an in-flow process for NHC-mediated anodic oxidative amidation of aldehydes has been described, employing an undivided microfluidic electrolysis cell in series with a heater chip to achieve high conversion in a single pass. High yields (71–99%), productivities (up to 2.6 g h⁻¹), and current efficiencies (65–91%) were achieved on scales up to 20 g.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00339.

Experimental details and procedures, compound characterization data, current efficiencies, and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: rcb1@soton.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge financial support from EPSRC (EP/L003325/1 and EP/K039466/1), GlaxoSmithKline for a CASE award (R.A.G.), and the European Regional Development Fund (ERDF) for cofinancing the AI-Chem project through the INTERREG IV A France (Channel)–England cross-border cooperation Programme.

REFERENCES

- (1) (a) Greenberg, A.; Breneman, C. M.; Liebman, J. F.; *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; John Wiley & Sons: New Jersey, USA, 2002. (b) Zabicky, J.; Zabicky Chemistry of Functional Groups: Chemistry of the Amides. In *Patai's Chemistry of Functional Groups*, Vol. 2; John Wiley & Sons: USA, 1970.
- (2) For selected recent reviews: (a) Taylor, J. E.; Bull, S. D. *N-Acylation of Amines*. In *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: Amsterdam, 2014; Vol. 6, pp 427–478. (b) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 2013, 7453. (c) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557. (d) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606.
- (3) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
- (4) For an overview of catalytic reactions of carboxylic acids with amines: Lundberg, H.; Tinnis, F.; Selander, N.; Adolffson, H. *Chem. Soc. Rev.* **2014**, *43*, 2714.
- (5) For selected reviews: (a) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (b) Chen, C.; Hong, S. H. *Org. Biomol. Chem.* **2011**, *9*, 20. For examples of cyanide-mediated oxidative amidation, see: (c) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 2003, 1055. (d) Gilman, N. W. *J. Chem. Soc. D* **1971**, 733.
- (6) (a) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. - Eur. J.* **2013**, *19*, 4664. (b) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (c) Knappke, C. E. I.; Imami, A.; Jacobi von Wangelin, A. *ChemCatChem* **2012**, *4*, 937.
- (7) For an NHC-catalyzed oxidative amidation of aldehydes where the reaction is believed to proceed by reaction of the Breslow intermediate (acyl anion equivalent) with *N*-bromoamines: Alanthadka, A.; Maheswari, C. U. *Adv. Synth. Catal.* **2015**, *357*, 1199.
- (8) (a) Dong, X. Q.; Yang, W.; Hu, W. M.; Sun, J. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 660. (b) Feroci, M.; Chiarotto, I.; Inesi, A. *Electrochim. Acta* **2013**, *89*, 692. (c) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796. (d) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798.
- (9) For amidation via the intermediacy of hexafluoroisopropyl esters formed by NHC-catalyzed oxidative esterification: (a) Zhang, B.; Feng, P.; Cui, Y.; Jiao, N. *Chem. Commun.* **2012**, *48*, 7280. (b) De Sarkar, S.; Studer, A. *Org. Lett.* **2010**, *12*, 1992.
- (10) For NHC-catalyzed esterification in batch: (a) Tam, S. W.; Jimenez, L.; Diederich, F. *J. Am. Chem. Soc.* **1992**, *114*, 1503. (b) Finney, E. E.; Ogawa, K. A.; Boydston, A. J. *J. Am. Chem. Soc.* **2012**, *134*, 12374. (c) Ogawa, K. A.; Boydston, A. J. *Org. Lett.* **2014**, *16*, 1928. (d) Green, R. A.; Pletcher, D.; Leach, S. G.; Brown, R. C. D. *Org. Lett.* **2015**, *17*, 3290.

- (11) For a description of the cell used in this work: (a) Kuleshova, J.; Hill-Cousins, J. T.; Birkin, P. R.; Brown, R. C. D.; Pletcher, D.; Underwood, T. J. *Electrochim. Acta* **2012**, *69*, 197. (b) Green, R. A.; Brown, R. C. D.; Pletcher, D. *J. Flow Chem.* **2015**, *5*, 31.
- (12) Samanta, R. C.; De Sarkar, S.; Frohlich, R.; Grimme, S.; Studer, A. *Chem. Sci.* **2013**, *4*, 2177.
- (13) See [Supporting Information](#) for further details.