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Expedient Preparation of Nazlinine and a Small Library of Indole Alkaloids Using Flow Electrochemistry as an Enabling Technology

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Supporting Information

ABSTRACT: An expedient synthesis of the indole alkaloid nazlinine is reported. Judicious choice of flow electrochemistry as an enabling technology has permitted the rapid generation of a small library of unnatural relatives of this biologically active molecule. Furthermore, by conducting the key electrochemical Shono oxidation in a flow cell, the loading of electrolyte can be significantly reduced to 20 mol % while maintaining a stable, broadly applicable process.

In the context of organic synthesis an enabling technology can be defined as a technique that permits strategic disconnections that would otherwise be difficult to achieve by alternative means. In addition to this, enabling technology may also permit other benefits such as increased process safety, increased reproducibility, improved reactivity, and scalability of the designed method. In recent years there has been a resurgence of some of the more traditional enabling technologies, such as photo-[1] and electrochemistry,[2] as well as the incorporation and understanding of new techniques such as mesoscale flow chemical methods in the context of natural product synthesis.[3] It is important to continue to explore, develop, and understand what these alternative methods are capable of providing for the modern synthesis chemist, who, as well as being under increased time pressures, must also consider environmental, economical, and safety factors when planning research. Herein we describe how the judicious choice of continuous flow electrochemistry as an enabling tool permits the straightforward preparation of a library of unnatural congeners of the indole alkaloid nazlinine (**1b**).

Nazlinine, first isolated in 1991 from the plant *Nitraria schoberi*, displays serotonergic properties.[4] Nazlinine itself also serves as a platform molecular architecture, from which numerous other indole alkaloids are reported to derive biosynthetically (Figure 1).[5] A structurally related family, the tryptargines, also exhibit neurotoxic capabilities thus making this class of natural products interesting probes for medicinal chemistry programs.[6]

Given the relatively simple structure of nazlinine, we were surprised to find that only two syntheses are reported in the literature, neither of which lends itself to the modular preparation of structural analogues.[7] Here we report a versatile two-step route to the nazlinine scaffold which hinges around the electrochemical oxidation of readily available cyclic amines (or their protected carbamate forms), to provide α-methoxyamine building blocks which feed into the key Pictet–Spengler reaction to furnish a compound library.[8]

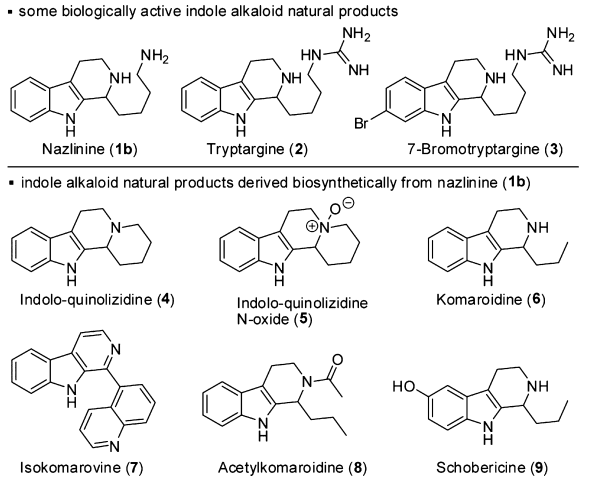

Figure 1. Naturally occurring biologically active tetrahydro-β-carbolines.

Flow electrochemistry is an attractive prospect for synthesis, particulalrly when measured against the green agenda.[9,10] Specifically the narrow distance between electrodes offers excellent potential to minimize or perhaps even eliminate the use of wasteful electrolytes altogether. However, this must be offset against the stability of the working cell, as a narrow distance between electrodes can also lead to increased chances for salt bridging across the divide. We therefore set out to assess the Shono oxidation of *N*-Boc pyrrolidine within the flux electrosynthesis module.[11−13] Initially we found that the use of steel or platinum coated electrodes in conjunction with an equistoichiometric amount of tetraethylammonium tetrafluoroborate electrolyte resulted in no conversion to the desired product (entries 1 and 2, Table 1). Changing this to a carbon anode was suitable to bring about the α-methoxylation reaction (entry 3,

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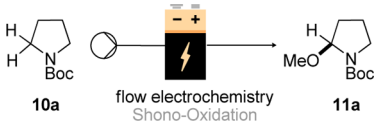
Table 1. α-Methoxylation of *N*-Boc Pyrrolidine Using an Microfluidic Electrolytic Cell[a]



entry	anode	R^+X^- (mol %)	conversion (purity), %[b]
1	steel	Et_4N^+ BF_4^- (100)	0
2	Pt-coated	Et_4N^+ BF_4^- (100)	0
3	carbon	Et_4N^+ BF_4^- (100)	99(90)
4	carbon	Et_4N^+ BF_4^- (20)	98(95)
5[c]	carbon	Et_4N^+ BF_4^- (10)	90(95)
6	carbon	Li^+ BF_4^- (20)	97(85)
7	carbon	Na^+ Cl^- (20)	5

[a]Steel electrode used as a counter electrode; *I* maintained constant at 43 mA; flow rate 120 μL min^{-1}; 0.1 M solution of **10a** in MeOH used. [b]Detected by ^1H NMR. [c]0.2 M solution of **10a** in MeOH used; flow rate 100 μL min^{-1}.

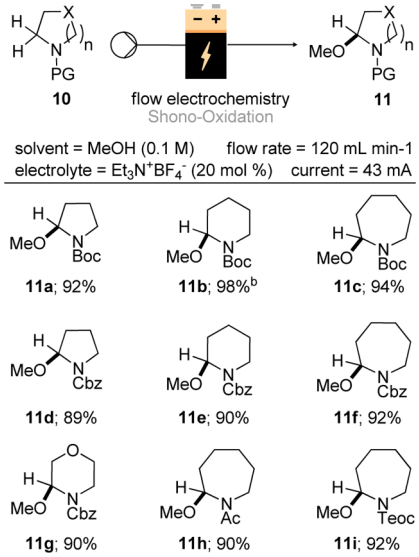
Table 1), a result in agreement with previous studies, which show that *N*-Boc protected amines and methanol have very close redox potentials, such that changing the electrode can easily tip the balance between substrate or solvent oxidation pathways in the system.[7]

It was also found that the electrolyte loading could be lowered to 20 mol % while the conversion and product purity remained high (entry 4, Table 1). The system was shown to be stable under these conditions, and the electrolysis was run continuously to process 10 mmol of material within ∼14 h with no variation in either conversion or the product purity being observed throughout the run. Notably, the electrolyte loading could be lowered still further to 10 mol % (entry 5, Table 1); however, a higher concentration of the starting material and lower flow rates were necessary to offset the poorer conductivity of the reaction media. It was also found that the cell was less stable under these conditions. Regarding alternative electrolytes, it was observed that $LiBF_4$ was effective but provided a low quality product (entry 6, Table 1), whereas simple NaCl provided poor conversion (entry 7, Table 1).

With the optimal procedure in hand (entry 4, Table 1), the continuous flow conditions were applied to the α-methoxylation of a series of cyclic amines varying in ring size and protecting group. It was shown that *N*-protected pyrrolidine, piperidine, azepane, and morpholine can all be successfully methoxylated using the electrochemical apparatus affording the corresponding products **11a−i** with high yields and purity (Scheme 1). Furthermore, several protecting groups, such as *tert*-butylcarbamate, benzylcarbamate, acetyl and trimethylsilylethylcarbamate, can all be carried through the process successfully.

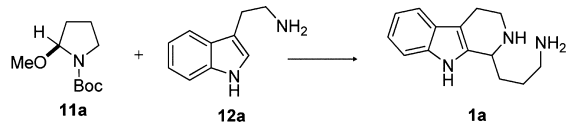
Next, we attempted the Pictet−Spengler reaction between the electro-synthesized imine precursor (**11a**) and tryptamine (**12a**) under the conditions previously reported successful for the reaction of 2,3,4,5-tetrahydropyridine with tryptamine.[7b] Unfortunately these preliminary experiments were unsuccessful (entry 1, Table 2). Working on the hypothesis that 0.2 equiv of acid was not sufficient to deprotect the nitrogen, liberate the imine from the aminal, and buffer the basic tryptamine nitrogen, we increased the loading to 6 equiv of TFA, affording 10% of the desired product (entry 2, Table 2). By contrast, changing the acid to HCl and the solvent to methanol allowed the desired reaction to proceed with 50% conversion at reduced temperatures (entry 3, Table 2). Nonvolatile camphor sulfonic acid (CSA) further

Scheme 1. α-Methoxylation of *N*-Protected Cyclic Amines in the Microfluidic Electrolytic Cell[a]



[a]Electrolysis was performed in an undivided cell with a carbon anode and steel cathode; yields shown are isolated yields after FCC. [b]Isolated yield, no purification by FCC needed.

Table 2. Optimization of the Reaction of *N*-Boc α-Methoxypyrrolidine with Tryptamine[a]



entry	acid (*n* equiv)	time (h)	*t* (°C)	solvent	yield (%)[b]
1	TFA (0.2)	15	90	H_2O	0
2	TFA (6)	15	90	H_2O	10
3	HCl (6)	15	50	MeOH	50
4	CSA (6)	15	50	MeOH	80
5	CSA (6)	0.5	130[c]	MeOH	52
6	**CSA (6)**	**0.5**	**130[c]**	**H_2O**	**90(87)**
7	TFA (6)	0.5	130[c]	H_2O	71
8	H_3PO_4 (6)	0.5	130[c]	H_2O	67

[a]Reaction conditions: Tryptamine (1 equiv, 0.1 M), α-methoxycarbamate (2 equiv), heated in a sealed tube. [b]Detected by ^1H NMR; numbers in parentheses represent isolated yield. [c]Heated in a microwave.

improved this to 80% conversion (entry 4, Table 2). Turning to microwave irradiation as an enabling technology, proven to rapidly increase reaction rates by permitting work at hyperthermal conditions, we were able to reduce the reaction time from 15 h to 30 min, initially with a reduced yield of 52% (entry 5, Table 2). With a change of solvent to water this became a 90% conversion, corresponding to an isolated yield of 87% (entry 6, Table 2). Under these microwave heating conditions neither TFA nor phosphoric acid provided a better reaction than CSA.

Taking these reactions onto a two-step process in which a small library of unnatural analogues could be prepared, the output of the electrochemical cell underwent a simple solvent exchange and filtration before passing into the second tricycle forming step.[14]

It was found that this procedure was suitable for the preparation of several structural relatives, which were furnished

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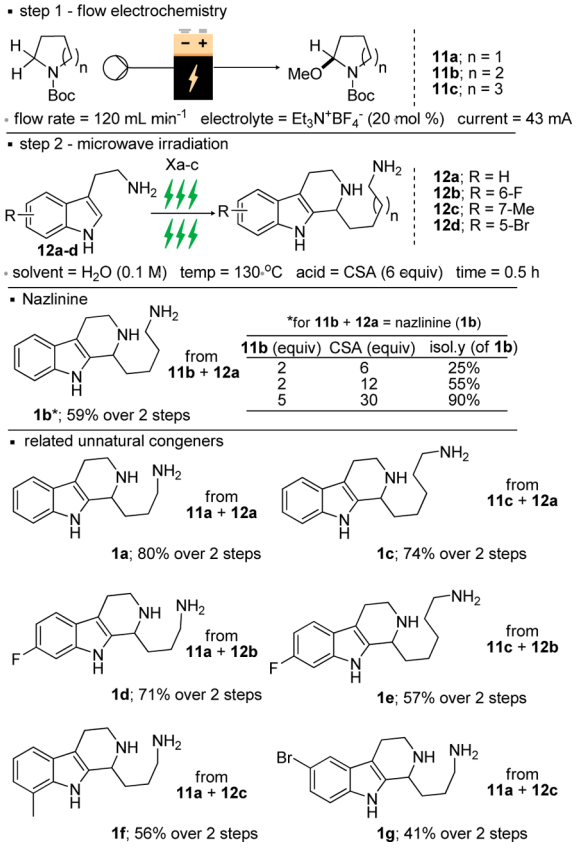
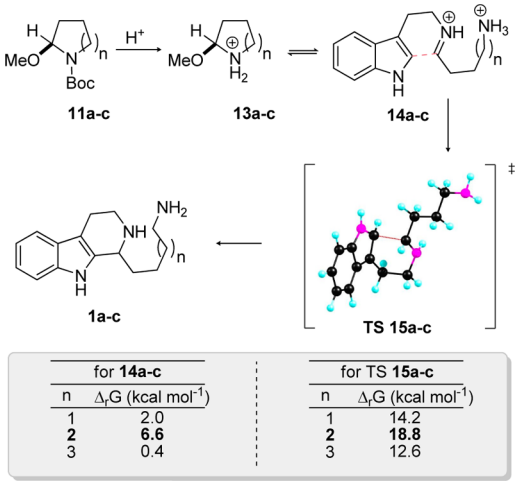
in moderate to excellent yields for the two-step process (Scheme 2). Tryptamines bearing bromo, fluoro, and methyl substituents

Scheme 2. Synthesis of Nazlinine and Unnatural Congeners via Two-Step Method



participated in the reaction without incident. With regard to the ring size of the methoxyamine component, however, there was a notable difference in reactivity between the 5, 6, and 7 membered systems. Indeed, further probing of the second step showed that the optimal conditions for 5 and 7 membered imine precursors (**11a** and **11c**, 2 equiv, microwave, 130 °C, 30 min) were not sufficient for the 6 membered analogue (**11b**), leading to a poor 25% conversion under the same conditions. It was found that this could only be improved by increasing the number of equivalents of the imine precursor to 5 and of CSA to 12, resulting in a 90% conversion (Scheme 2). This interesting phenomenon can be explained by computational studies at the Density Functional Theory (DFT) level (Scheme 3).[15,16] The linear iminium **14** is the key intermediate in the Pictet–Spengler cyclization reaction affording product **1** via a 6-*endo*-cyclization step which is characterized by the single transition state **15** (Scheme 3).[17] It was found that the formation of iminium **14** in the presence of tryptamine **12a** from a 6 membered α-methoxyamine **13**[18] compared to its 5 or 7 membered analogues costs more energy (compare Gibbs free energies of **14** for n = 1–3; Scheme 3). Consequently, this holds up the rate determining cyclization process and instead results in increased decomposition of the intermediate materials.[19] Notably, and perhaps as one might expect, the calculations show that once the intermediate linear iminum is reached the system needs to overcome the same rate limiting barrier of 12.2 kcal mol^{-1} to get to the product, irrespective of the size of the initial imine precursor ring size

Scheme 3. Proposed Mechanism of the Pictet–Spengler Reaction of Cyclic α-Methoxyamines with Tryptamines[a]



[a]Computed (at ωB97XD/PVTZ//ωB97XD/PVDZ level using SMD solvation (water as a solvent) model during geometry optimization) reaction Gibbs free energies are listed; energy of **13** is set as a reference for every entry.[21]

(compare Gibbs free energies of TS **15** for n = 1–3 with the Gibbs free energies required to reach the iminium intermediate **14**).[20]

In conclusion, we have identified flow electrochemistry as a suitable enabling technology to permit the quick generation of a compound library through the rapid preparation of protected cyclic α-methoxyamines. These were then applied in a subsequent Pictet–Spengler reaction, thus leading to an expedient two-step method to access the biologically active natural product nazlinine and related unnatural congeners. The reported scaffolds could lead to the preparation of further unnatural relatives of the indole alkaloids tryptargine, indoloquinolizidine, komaroidine, isokomarvine, and schobercine (Figure 1). We have shown that by using a continuous flow electrochemical cell substoichiometric loadings of electrolyte (20 mol %) are sufficient to effect the desired reaction over a range of substrates and that the system is robust for overnight running.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) *N*-Boc deprotection of carbamates is fast. It is complete within 5 min at 50 °C in either methanol or water in the presence of CSA.

(19) As shown by ^{1}H NMR.

(20) Full computational details of this are reported in the SI

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