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Practical Electrochemical Anodic Oxidation of Polycyclic Lactams for Late Stage Functionalization**

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Abstract

Electrochemistry provides a powerful tool for the late-stage functionalization of complex lactams. A two-stage protocol for converting lactams, many of which are preparable through the intramolecular Schmidt reaction of keto azides, is presented. In the first step, anodic oxidation in MeOH using a repurposed power source provides a convenient route to lactams bearing a methoxy group adjacent to nitrogen. Treatment of these intermediates with a Lewis acid in DCM permits the regeneration of a reactive acyliminium ion that is then reacted with a range of nucleophilic species.

Keywords

Anodic oxidation; N-acyliminium ion; Lactam; Diversity-oriented synthesis

Late-stage functionalization of complex molecules is an important strategy in both natural product[1] and diversity-oriented synthesis (DOS) programs.[2] A body of creative work toward this end has been steadily building, including metal-mediated C–H activation

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

chemistry,[3] photochemical methods,[4] and electrochemical oxidation reactions.[5] In particular, the application of electrochemistry in organic synthesis has benefited from advances such as cation pool[6] and flow chemistry techniques,[7] Here, we introduce a simple and inexpensive way of carrying out electrochemical oxidations and demonstrate its utility in diversifying polycyclic lactams.

We have developed useful routes to complex lactams using the intramolecular azido-Schmidt reaction, such as the Diels–Alder/Schmidt sequence affording **1a** in Scheme 1.[8] Having adapted this chemistry to diversity-oriented synthesis by using the ketone as a fulcrum for analog synthesis,[9] we felt that a useful alternative would be to generate analogs by modifying the normally unreactive amide linkage. Specifically, we imagined that converting the lactam products into acyliminium ions like **2** would lead to broadly useful intermediates for downstream manipulation. Since many of the chemical oxidants traditionally used for such oxidations,[10] such as ceric ammonium nitrate and dichlorodicyanoquinone, are highly toxic or poorly compatible with other functional groups, we considered electrochemical oxidation as an attractive alternative.[11] Operationally, these reactions are carried out in methanol, where anodic oxidation leads to an iminium ion that is trapped by solvent, e.g., **2** → **1b**. Having stored the higher oxidation state as **1b**, regeneration of **2** can be effected by treatment with a Lewis or protic acid in a non-participating solvent, where it can be trapped by another nucleophile.

Similar electrochemical oxidations have involved proline or pyrrolidinone derivatives, often in the context of peptidomimetic synthesis.[5, 12] In contrast, we are aware of only two examples where bicyclic lactams were used as substrates.[13] Accordingly, a primary goal of the present project was to show the utility of this approach in more complex settings. An important secondary goal was to develop an accessible anodic oxidation method for mainstream laboratory use. In addition to some of the aforementioned efforts toward real-world electrochemistry, Moeller has used 6-volt lantern batteries connected in series or photovoltaic cells for organic electrochemical transformations,[14] and Boydston and coworkers demonstrated the organocatalyzed anodic oxidation of aldehydes to esters powered by D-cell batteries.[15] Here, we report the design and construction of an improvised device for undivided cell electrochemistry using a mobile phone recharger.

We first assembled a simple electrochemical setup repurposing a cell phone charger as the DC power source (Figure 1). Such power sources with different voltage and current outputs are ubiquitous in our technology-driven society. These power sources are sold as accessories with most portable electronic devices and typically outlive the useful life of the device itself. In many cases, simply connecting the output wires from the power source to the electrodes in the reaction cell is all that is necessary to fabricate a useful electrochemical setup. If the current output from the power source is higher than desired, it can be reduced by connecting resistors to the circuit in series, as shown in Figure 1a. Other convenient modifications are the attachment of the lead wires to alligator clips, allowing easier connection to the electrodes (Figure 1b) and the use of #7 mechanical pencil lead refills as electrodes (Figure 1c). This last example has the advantages of further removing the need for any specialized supplies and more importantly, the small diameter electrodes allow for microscale electrochemical oxidations (reaction volumes < 1 mL). CAUTION: we recommend

common-sense precautions when preparing similar devices to avoid electric shock (see Supporting Information for best practice precautions in carrying out these reactions).

We first confirmed the ability of the DC power source to perform known preparative electrochemistry by reproducing the known electrochemical oxidation of the proline derivative **3a**[14c] to give **3b** as well as the acyclic amide **4a** to give **4b** (Table 1, entries 1 and 2, respectively). Our initial experiments were conducted using a 6 V, 30 mA power source with later experiments conducted with a 5.2 V, 800 mA power source. Note that while the rate of electron flow (current) varied, both power sources had a voltage output significantly greater than the typical 1.95 to 2.10 V (vs. Ag/AgCl) oxidation potential of the amide or lactam.[16] Having validated the improvised device on model substrates we turned our attention to more complex amide substrates, readily available by azide methods developed in these laboratories.

In general, the results in Table 1 confirm the utility of this electrochemical oxidation across a range of ring systems. Entries 7 and 8 show that ketone or phenyl groups are tolerated in the electrochemical oxidation. Entries 9 and 10 extend the scope of the method to nonaromatic tricyclic lactam scaffolds. As expected, a diastereomeric mixture of methoxy amide products were obtained in all examples. In one case, reaction of a lactam containing more than one adjacent position with abstractable hydrogens belied a limitation of this method (Table 1, entry 11). Such substrates suffer from competing reactions between potential reactive sites and also the formation of overoxidized products, as previously observed for the electrochemical oxidation of lactams.[13] Thus, the product shown in entry 11 of Table 1 was isolated as a single isomer in 19% yield, while the mass balance was a complex and inseparable mixture of other isomers and side products. Moreover, we observed similar product mixtures when this reaction was performed using the fully-regulated constant current electrochemical setup traditionally used.

The versatility of these methoxyamides for the synthesis of an array of functionalized products was illustrated by the addition of various nucleophiles to the *N*-acyliminium ion generated in situ from either methoxy amide **5b** or **7b** (Scheme 2). Highlights from Scheme 2 include the Friedel-Crafts addition of aromatic compounds (derivative **16**), butenolide or indole side chain introduction (derivatives **14** and **15**), the use of boronic acids as nucleophiles (derivative **18**) and addition of cuprate reagents such as the phenyl acetylide (derivative **20**). The cuprate addition was unsuccessful under several different conditions using methoxy amide substrate **5b**, but proceeded smoothly using the alkyl substrate **7b**. We note here that the stereoselectivity of these substitutions depend on the intrinsic face selectivity of the particular scaffold. Thus, while **5b** and **7b** do not exhibit strong bias, the literature is replete with examples of highly selective additions to acyliminium ions[17] (for another example, see Scheme 4 below). As proposed in Scheme 1, the more complex methoxy amide **1b** was readily converted to the *N*-acyliminium ion **2** and converted to the allyl derivative **21**.

This methodology is attractive for target-oriented synthesis as well, isofar as amide or lactam intermediates are stable species able to survive numerous chemical conditions likely to be encountered in multistep synthesis. To demonstrate these, we targeted the

derivatization of tricyclic lactam **27**, a core skeleton we explored for the synthesis of pinnaic acid and related natural products (Figure 3).[18] Moreover, the recent disclosure that the related derivative **24** possessed potential anti-cancer properties[19] suggests that the tricyclic motif itself could serve as a scaffold for biologically relevant analogs. En route to the formal synthesis of pinnaic acid, we previously reported the selective synthesis of **22** in a 10:1 ratio over **23**.[20] The trivially accessible and previously unreported lactam **27** would provide a blank canvas for the introduction of diversity as exemplified in Scheme 4.

Thus, the known acid **25**, derived in a single step from commercially-available hept-6-enoic acid, underwent a ketene-mediated [2+2] cycloaddition to afford cyclobutanone **26** in 85% yield.[21] Subsequent azide displacement and intramolecular Schmidt reaction achieved the synthesis of tricyclic lactam **27** in 93% yield. The *N*-acyliminium ion intermediate was generated utilizing our electrochemistry apparatus and trapped by methanol as the methoxy amide **28**. Subsequent allylation of the crude product gave lactam **29** as the sole observed product in 56% yield over two steps. The high stereoselectivity most likely arises from top attack of the nucleophile to the more stable conformation **A** (as opposed to the more strained **B**) in the *N*-acyliminium ion chair-like transition state (Scheme 4). The allyl derivative could be utilized directly as a handle to introduce functionality or additional nucleophiles could be introduced via the methoxyamide intermediate as illustrated in Scheme 1.

In summary, we have constructed a simple, improvised device for undivided cell electrochemistry. We have demonstrated how this device can enable the synthesis of novel lactam derivatives via *N*-acyliminium ion diversification and extended this chemistry to lactams of unprecedented complexity. We believe that this apparatus would be a useful addition to the standard methods available to synthetic organic chemists by providing a simple, reliable power source of sufficient voltage to carry out a variety of electrochemical transformations.[22]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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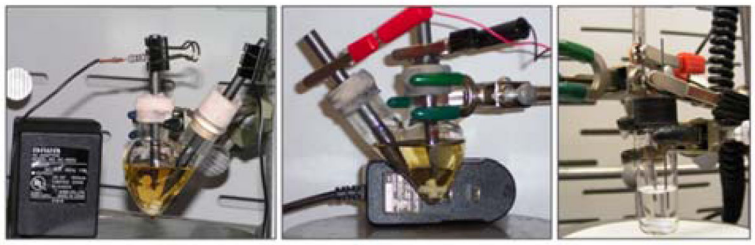
22. CCDC 1403517 and CCDC 1403516 contain the supplementary crystallographic data for compounds **14** and **16**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



(a) (b) (c)

Figure 1.

Improvised electrochemical devices: (a) initial 30 mA prototype device, (b) alternate 800 mA device, and (c) microscale set-up using # 7 pencil leads as electrodes. See Supporting Information for larger photographs and details for the fabrication and use of these devices.

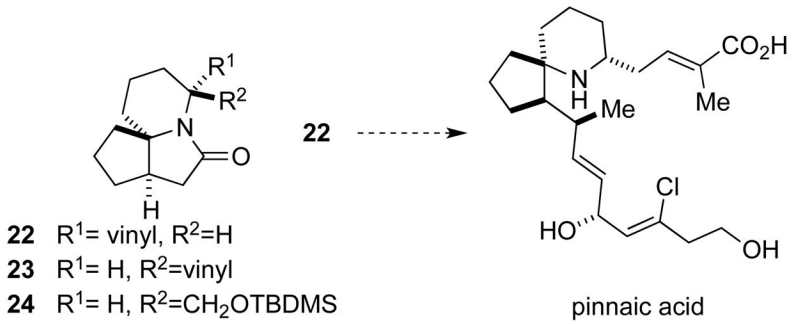
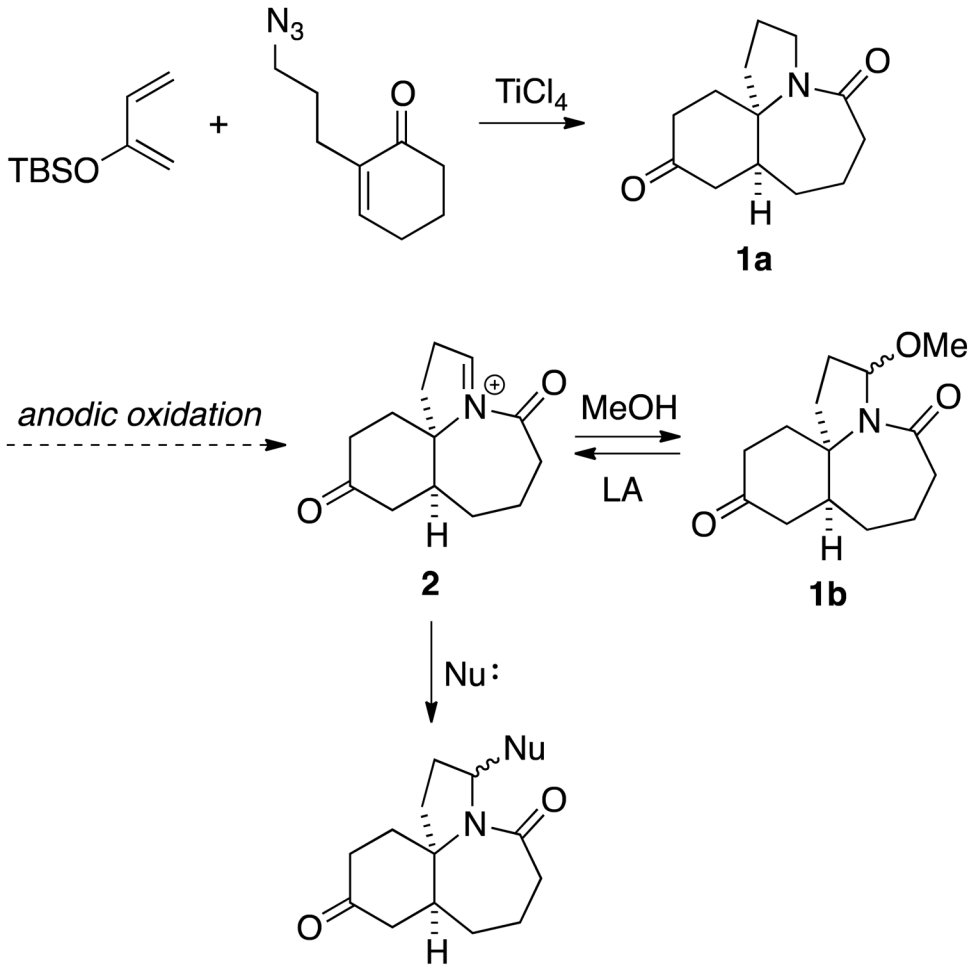
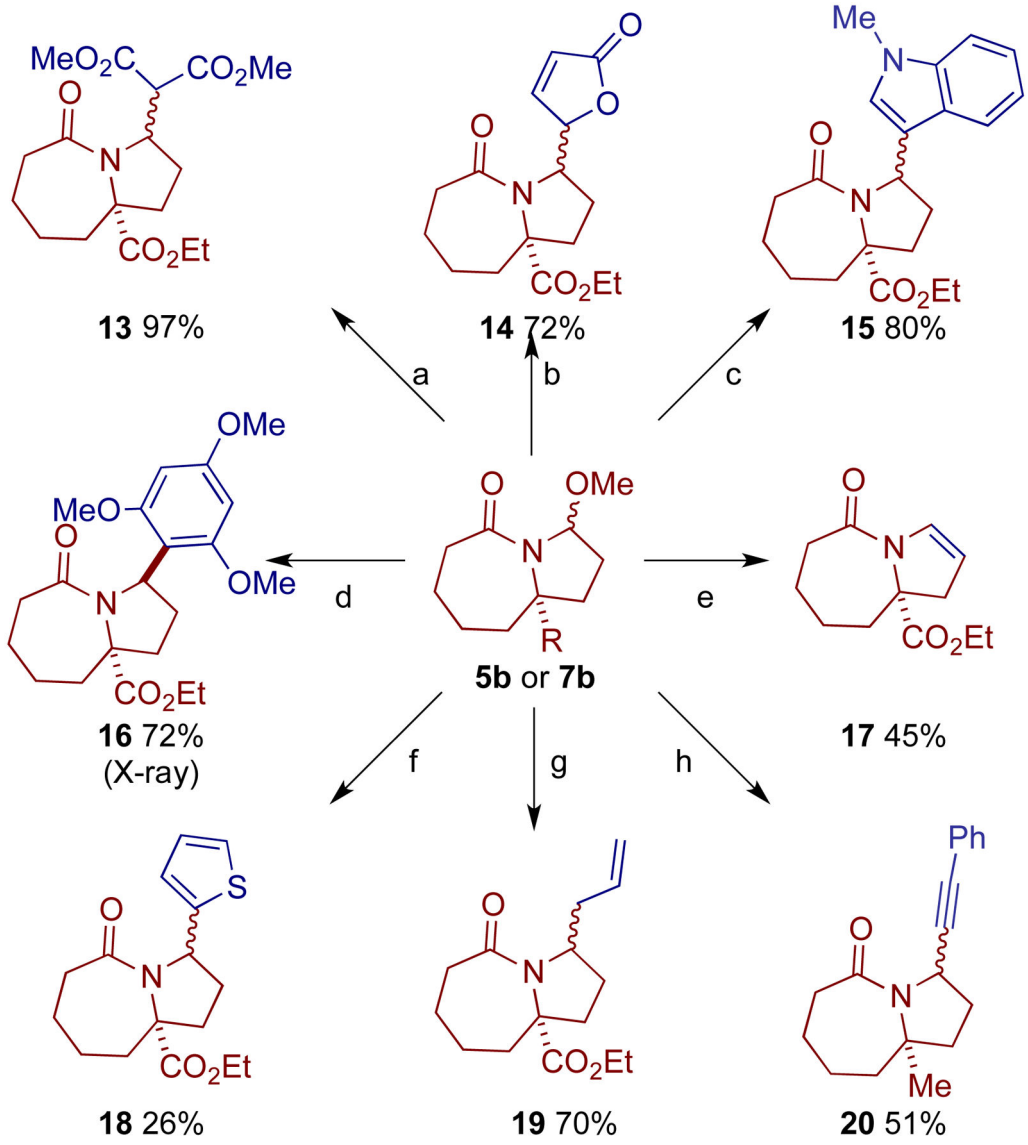


Figure 3.
Tricyclic lactam pinnaic acid precursor and analogs.

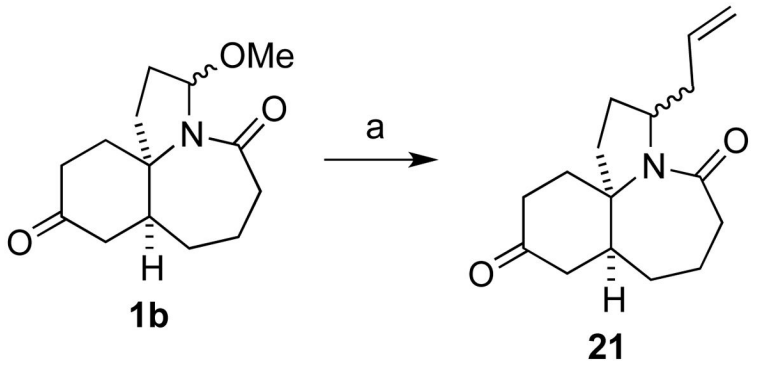


Scheme 1.
Strategy for the modification of polycyclic lactams.



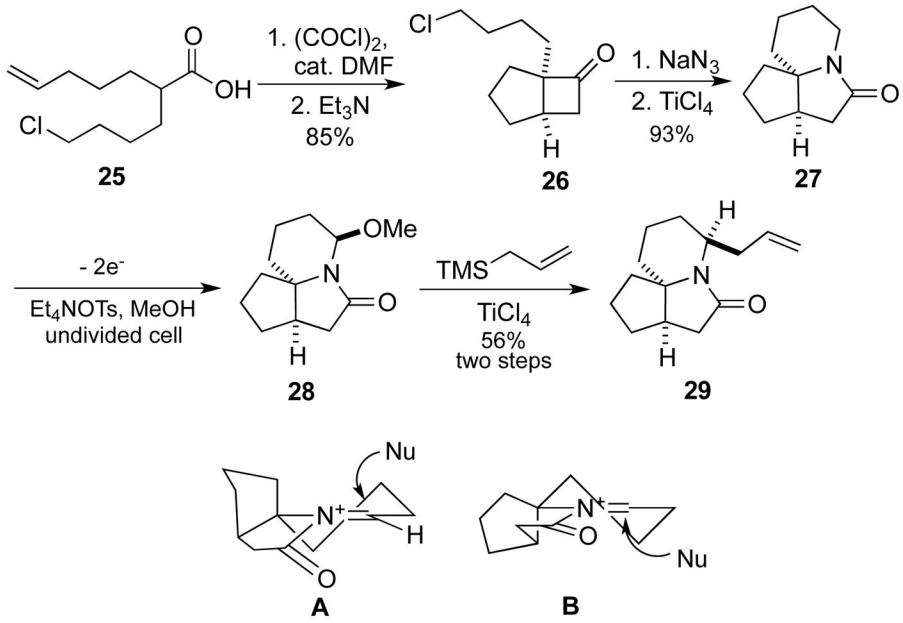
Scheme 2.

Diversification pathways for methoxy amides **5b** or **7b** (a) dimethyl malonate, Et_3N, $TiCl_4$; (b) 2-trimethylsilyloxyfuran, $TiCl_4$; (c) *N*-methylindole, $TiCl_4$; (d) 1,3,5-trimethoxybenzene, $SnCl_4$; (e) $TiCl_4$; Et_3N; (f) thiopheneboronic acid; BF_3•OEt_2 (g) $TiCl_4$; trimethylsilyl allyl silane (h) $TiCl_4$; PhCCMgCuBr.



Scheme 3.

Substitution of methoxy amide **1b**. (a) $TiCl_4$; trimethylsilyl allyl silane.

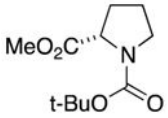
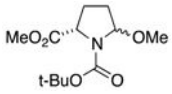
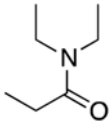
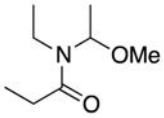
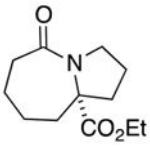
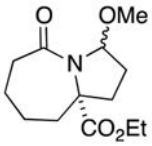
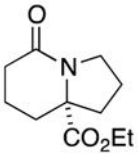
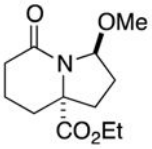
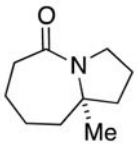
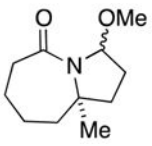
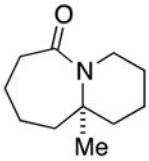
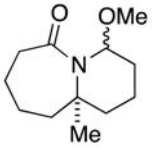
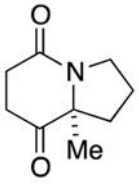
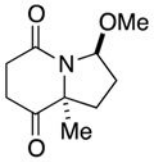


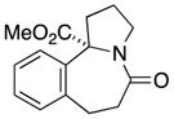
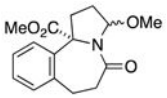
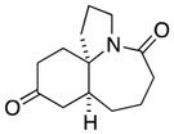
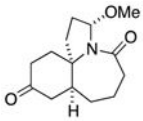
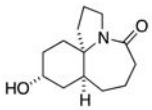
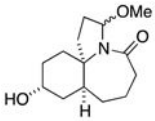
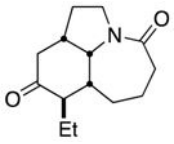
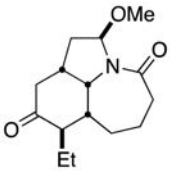
Scheme 4.

Synthesis and functionalization of lactam **27**.

Table 1

Electrochemical Oxidation of Amides[a]

entry	substrate	product	yield, % (ratio[b])
1	 **3a**	 **3b**	93 (1:1)
2	 **4a**	 **4b**	57
3	 **5a**	 **5b**	91 (4:1)
4	 **6a**	 **6b**	63 (single isomer)
5	 **7a**	 **7b**	56 (1.7:1)
6	 **8a**	 **8b**	28 (1.5:1)
7	 **9a**	 **9b**	47 (single isomer)

entry	substrate	product	yield, % (ratio[b])
8	 **10a**	 **10b**	40 (single isomer)
9	 **1a**	 **1b**	78 (single isomer)
10	 **11a**	 **11b**	65 (2.8:1)
11	 **12a**	 **12b**	19 (single isomer)

[a] Conditions: MeOH, undivided cell, C anode/cathode, Et_4NOTs or $LiClO_4$.

[b] Ratios approximated by ^1H NMR; except where shown, diastereomeric structures were not determined.