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Synthesis of 4*H*-1,3-Benzoxazines via Metal- and Oxidizing Reagent-Free Aromatic C−H Oxygenation

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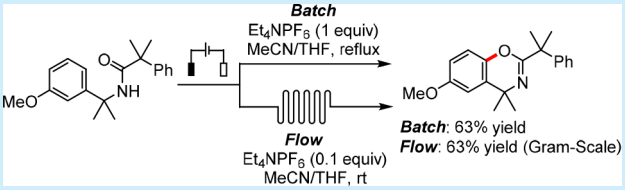
Supporting Information

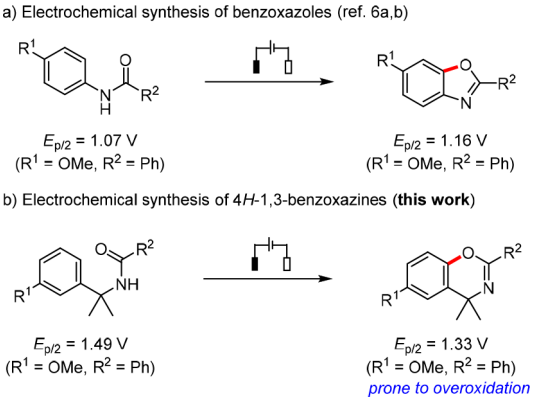
ABSTRACT: An unprecedented electrochemical aromatic C−H oxygenation reaction for the synthesis of 4*H*-1,3-benzoxazines from easily available *N*-benzylamides is reported. These oxidative cyclization reactions proceed in a transition metal- and oxidizing reagent-free fashion and produce H_2 as only theoretical byproduct. Adapting the C−H oxygenation reaction in an electrochemical microreactor has been demonstrated.



The development of more efficient and environmentally friendly synthetic methods to construct heterocycles is highly desirable and relevant due to the prevalence of heterocyclic motifs in natural products and bioactive compounds.[1] Furthermore, the generation of novel heterocyclic scaffolds could also open up chemical space that has yet to be explored.[2] While transition metal-catalyzed C−H functionalization has been widely employed in heterocycle construction,[3] contamination of trace metals in products and the frequent need for stoichiometric oxidants often pose significant challenges to environment sustainability, operational safety and downstream processing. As a result, the development of alternative metal-free strategies has recently gained considerable traction.[4]

Electroorganic synthesis[5] has been used in a variety of studies to achieve oxidizing reagent-free C−H functionalization reactions.[6] Despite considerable advances in this field, electrochemical oxygenation of aromatic C−H bonds remains underexplored. Waldvogel has recently reported an elegant electrochemical method for the synthesis of benzoxazoles through C−H oxygenation of easily available *N*-aryl amides (Scheme 1a),[6a] which the authors suggested involved a key amidyl cation intermediate.[6b] One of the important factors contributing to the success of the reaction is that the benzoxazole product is slightly more difficult to oxidize than the starting amide. In contrast, functionalization of aryl C−H bonds to form C−N or C−O bonds often would afford products with lower oxidation potentials than their precursors due to the introduction of electron-releasing heteroatom substituents to the aryl ring. In these scenarios, the products could quickly undergo oxidative degradation. To address this issue, Yoshida developed aromatic C−H amination reactions that featured the formation of a cationic, electron-deficient intermediate resistant to further oxidation.[7] The method has recently been applied for the synthesis of heterocycles.[7a] Mei and Zhang reported the first examples of Pd-catalyzed electrochemical aromatic C−H acetoxylation reactions.[8] While these strategies succeeded in the formation of the oxidation-labile products, they required the use of a divided cell probably to avoid the cathodic reduction of the cationic intermediate or the Pd catalyst.[7,8]

Scheme 1. Synthesis of Heterocycles through Metal- and Oxidizing Reagent-Free Electrochemical C−H Oxygenation



We have reported the synthesis of several classes of heterocycles through electrochemical dehydrogenative cyclization reactions.[9] Herein we report an unprecedented C−H oxygenation reaction featuring the direct electrolysis of *N*-benzylamides to prepare a wide range of substituted 4*H*-1,3-benzoxazines[10] with lower redox potentials than their precursors (Scheme 1b). The synthesis can also be conducted in an electrochemical microreactor,[11] which not only reduces the amount of supporting electrolyte required, but also allows the reaction to proceed at rt.

We began our study by first optimizing the electrolysis conditions for the cyclization of amide **1** (Table 1). The reaction was conducted at a constant current in an undivided cell (a three-necked round-bottomed flask) equipped with a

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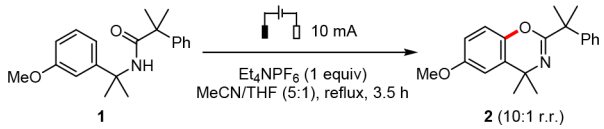
Table 1. Optimization of Reaction Conditions[a]



1 2 (10:1 r.r.)

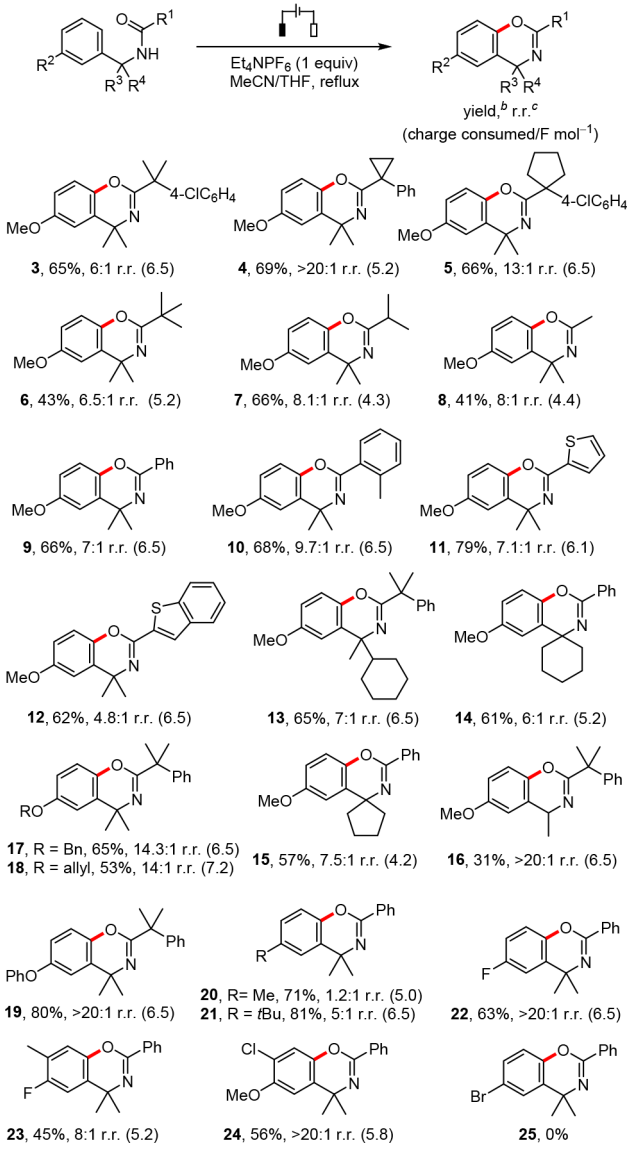
entry	conditions	yield (%)[b]
1[c]	none	63 (23)
2[c]	reaction for 4.5 h	55 (12)
3	entry 1 but MeCN as solvent	47 (13)
4	entry 1 but MeOH as solvent	<5 (95)
5	entry 1 but HFIP as solvent	<5 (0)
6	entry 1 but reaction at rt	18 (42)
7	entry 1 but reaction at 50 °C	47 (16)
8[d]	entry 1 but 20 mA	54 (23)
9	entry 1 but under air	30 (40)
10	entry 1 but with 0.5 equiv of Et_4NPF_6	56 (38)
11	entry 1 but with 0.1 equiv of Et_4NPF_6	26 (60)

[a]Reaction conditions: RVC anode (j = 0.15 mA cm^{-2}), Pt cathode, **1** (0.2 mmol), solvent (6 mL), argon, 6.5 F mol^{-1}. [b]Yield determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. The unreacted **1** was shown in parentheses. [c]Isolated yield. [d]Reaction time = 1.7 h. r.r. = regioisomeric ratio.

reticulated vitreous carbon (RVC) anode and Pt plate cathode. After screening a variety of solvents and reaction temperatures, the best results were obtained when the electrolysis was performed in a mixture of MeCN/THF (5:1) under reflux. Under these conditions, the benzoxazine product **2** was formed in 63% yield at 71% conversion with good regioselectivity (10:1 r.r.) that favored the reaction of the aromatic hydrogen *para* to the methoxy group (entry 1). Extending the reaction time from 3.5 to 4.5 h increased the conversion, but also the oxidative degradation of **2**, which is more susceptible to oxidation than **1** ($E_{p/2}$ = 1.55 and 1.45 V for compounds **1** and **2**, respectively), and consequently lowered the yield to 55% (entry 2).[12] The use of other solvents, such as MeCN (entry 3), MeOH (entry 4) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)[13] (entry 5) diminished the reaction efficiency to varying degrees. Similarly, conducting the electrocatalysis at rt (entry 6) or 50 °C (entry 7), using higher current density (entry 8), or under air (entry 9) also blunted product formation considerably. Attempt to reduce the amount of the electrolyte employed to 0.5 (entry 10) or 0.1 equiv (entry 11) led to reduced conversion and yield.

We next explored the substrate scope of the reaction (Scheme 2). The reaction showed broad compatibility with different tertiary (**3**–**6**), secondary (**7**) and primary (**8**) alkyl substituents as R^1 in the starting amide. In addition, aryl (**9**–**10**) and heteroaryl groups, such as thiophene (**11**) and benzothiophene (**12**), were also well tolerated. On the other hand, the benzylic position (R^3 and R^4) could be substituted with a cyclohexyl group (**13**) or a spiro ring (**14**–**15**). However, the reaction was greatly inhibited or even completely abolished if there was only one (**16**) or no (data not shown) alkyl substituent at the benzylic position. The aromatic ring that underwent C–H functionalization could be substituted with a host of electron-donating functionalities, such as an alkoxy (**17**, **18**), a phenoxy (**19**), or an alkyl group (**20**, **21**), or halogens such as fluoro (**22**, **23**) or a chloro group (**24**). The regioselectivity of the reaction was found to be affected by the choice of substituents at R^1–R^4. In addition, both electronic

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: Table 1, entry 1 unless otherwise mentioned. [b]Isolated yield. [c]Regioisomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture.

and steric properties of the aryl substituents (R^2) affected the regioisomeric ratios (**19**–**22**).

Compared to batch reactors, the use of electrochemical microreactors can reduce the need for supporting electrolytes, improve reaction efficiency and offer ease of scalability.[11] Indeed, passing a MeCN/THF solution containing 1.07 g (3.44 mmol) of **1** and 0.1 equiv of Et_4NPF_6 through a microflow electrolysis cell at rt furnished **2** in 63% yield (Scheme 3). In comparison, the same synthesis, when performed in a flask, necessitated the use of 1 equiv of Et_4NPF_6 and heating to reflux and afforded only 40% yield on a 0.56 g (1.8 mmol) scale. The mild temperature required by the flow reactor could also be a key contributing factor to the regioselectivity improvement that we observed (>20:1 r.r. in flow vs 10:1 r.r. in batch).

Recently, several other research groups have demonstrated that aryl methyl ethers can participate in transition metal-catalyzed cross-coupling reactions to form C–C and C–heteroatom bonds.[14] Indeed, the methoxy group in **2** could be

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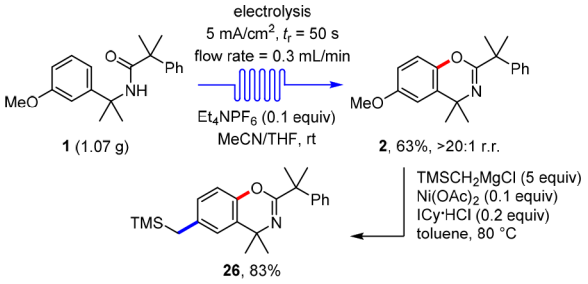
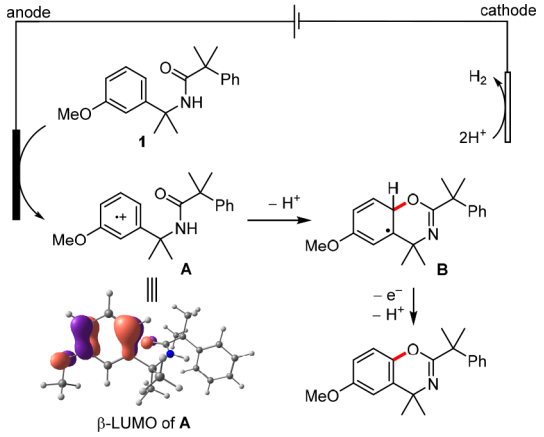
Scheme 3. Synthesis in Flow and Product Transformation



efficiently cleaved and replaced with a synthetically useful trimethylsilylmethyl group in the presence of a Ni catalyst (Scheme 3).[14d]

A possible mechanism for the electrolytic C−H oxygenation of amide **1** was illustrated in Scheme 4. The electrolytic

Scheme 4. Proposed Mechanism



reaction begins with the anodic oxidation of the electron-rich methoxylated phenyl ring in **1** to form the radical cation **A**. The regioselective cyclization of **A** at the position *para* to the methoxy group, which is sterically less hindered than the *ortho* position and also where the SOMO is mainly located,[7b,15] furnishes the cyclohexadienyl radical **B** after deprotonation. Rearomatization of **B** via electron and proton elimination furnishes the final product **2**.

In summary, we have developed an electrochemical method that can be used to prepare a variety of 4*H*-1,3-benzoxazines via the aromatic C−H functionalization of *N*-benzylamides. The reaction showed a broad substrate scope and satisfactory regioselectivity despite the susceptibility of the benzoxazine products to overoxidation. We also demonstrated that a microflow electrolysis cell could be employed to achieve easy reaction scale-up and to reduce the use of supporting electrolyte.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03152.

Experimental procedure and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(12) The product **2** is less polar than the starting amide **1**, which probably reduces its solubility in the highly polarized double layer and contributes to its survival of the electrolysis.

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