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Electrochemical Synthesis of Benzoxazoles from Anilides – A New Approach to Employ Amidyl Radical Intermediates

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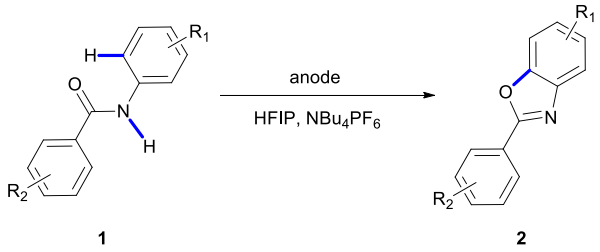
A novel electrochemical method for the synthesis of benzoxazoles from readily available anilides is reported. Various functionalities are tolerated and good yields can be achieved. By employing common electrode materials and a simple constant current protocol, this method is an attractive new alternative to conventional pathways.

Benzoxazoles represent an important structure in heterocyclic chemistry and are key motifs of several natural products, pharmaceuticals, and biologically active compounds.[1] Thus, they are a significant topic of contemporary research, and efficient synthetic strategies starting from simple starting materials are highly desired. Traditionally, benzoxazoles have been synthesized by treating 2-aminophenols with activated acids or aldehydes under oxidative conditions.[2] In recent years, this approach has been complemented by methods capitalizing on anilide or benzoxazole core scaffolds that can be employed as substrates in a variety of coupling reactions. Coupling strategies using substrates prefunctionalized with a leaving group and capitalizing on CH-activation have been reported.[3]

The use of electrochemistry can offer a mechanistically distinct and significantly sustainable approach to benzoxazoles.[4] In addition, this method can be considered as inherently safe. In an electrochemical reaction, electric current serves as an inexpensive and potentially renewable reagent that avoids the need to a stoichiometric redox reagent. This both minimizes the waste produced in the reaction and removes the limitations on redox potential associated with every chemical reagent. This later point is important because it enables electrochemical reactions to readily access extraordinary reaction pathways.[5,6] This combination of sustainability and mechanistic opportunity has led to the recent development of a variety of valuable electrolysis protocols.[5,7,8–10]

Here, we report the first direct, reagent-free electroorganic synthesis of benzoxazoles based on alkyl and aryl anilides in a simple electrochemical set-up cell (Scheme 1). The reaction employs easily accessible starting materials, inexpensive electrode materials, and a low concentration of supporting electrolyte. The result is a synthetically attractive alternative to conventional methods for synthesizing the target structure. We anticipate that amidyl radicals act as intermediates, which are directly generated at the anode.[5,10] The efficient formation of amidyl radicals has been of great interest for the chemical community.[11] Their structure and reactivity has been mostly explored in the context of rearrangements and hydroamination reactions.[8,12]



1 2

Scheme 1 Electrochemical synthesis of benzoxazoles.

The transformation illustrated in Scheme 1 was discovered in the course of our studies concerning the electrochemical formation of N,N bonds.[5] The addition of an amidyl radical to a neighbouring aryl ring was observed in cases wherein the desired N,N bond formation was slow. In these cases, a mixture of N,N bond coupling and the formation of benzoxazoles was obtained. The mixture issue was quickly resolved by using monoanilides in order to exclude the intramolecular N,N bond formation.

N-(4-Chlorophenyl)benzamide (**1a**) was then chosen as a test substrate for optimization studies. The aromatic substitution

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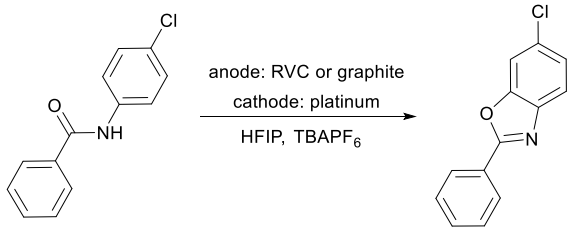
pattern was known to afford high yields for reactions leading to N,N bond formation,[5] a scenario that suggested the systems compatibility with the formation of a reactive amidyl radical. When the reaction was screened for its compatibility with different electrolyte systems,[13] only the use of hexafluoroisopropyl alcohol (HFIP) as a solvent enabled the desired formation of the benzoxazole. Methanol and other solvents commonly applied in electrochemical transformations lead to degradation of the anilides, even though conventional and electrochemical reactions of amidyl radicals in methanol are described in literature.[8–10,14] This result suggested that the cyclization was slow and thus required sufficient stabilization by the solvent. HFIP is able to effectively stabilize radical intermediates.[15] The almost quantitative recovery of this particular solvent (b.p. 56 °C) allows minimization of the fluorine footprint.[5,16] By employing a low concentration of tetrabutylammonium hexafluorophosphate (0.01 M) as supporting electrolyte, the atom economy and work-up are significantly improved.

Electrochemical reactions are usually sensitive to the current density applied and the electrode geometry.[10] Hence, we optimized the applied current for the two most commonly used laboratory scale electrochemical set-ups. Set-up A relies on a 25 mL three-necked flask, wherein a reticulated vitreous carbon (RVC) anode and a platinum wire cathode are placed angular to each other. Set-up B is a beaker-type cell with a flat isostatic graphite anode and a platinum plate cathode, which are orientated parallel to each other.[5] The latter provides a more defined and homogenous electric field. More detailed information about both reaction setups can be found within the supporting information.

Table 1 Optimization of electrolysis parameters



1a **2a**

Entry	Set-up[a]	j [mA/cm²]	I [mA]	Isolated yield [%]
1	A	-	1.1	31
2	A	-	4.1	54
3	A	-	8.4	56
4	A	-	12.4	49
5	B	1.3	-	50
6	B	1.9	-	53
7	B	2.5	-	66
8	B	5.0	-	57

[a] Set-up **A**: 25 mL three-necked flask, RVC (100 PPI) anode, platinum wire cathode, 0.4 mmol substrate, 0.01 M $TBAPF_6$ in 10 mL HFIP, amount of charge = 2 F; Set-up **B**: beaker-type cell, isostatic graphite anode, platinum cathode, 8 cm^2 electrode surface, 1.0 mmol substrate, 0.01 M $TBAPF_6$ in 25 mL HFIP, 2 F amount of charge.

With the optimized electrolysis conditions in hand, the scope of this electrosynthetic method was elucidated.

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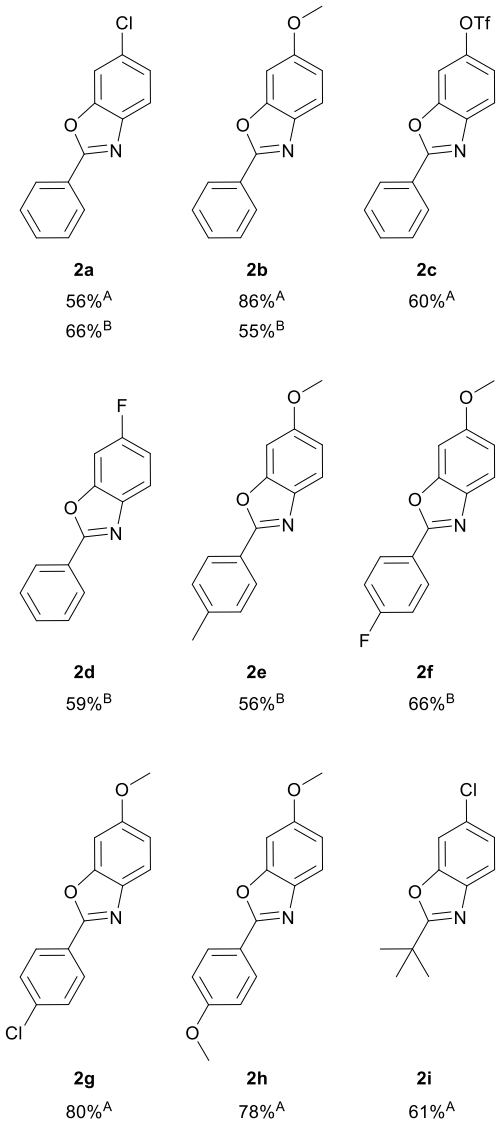
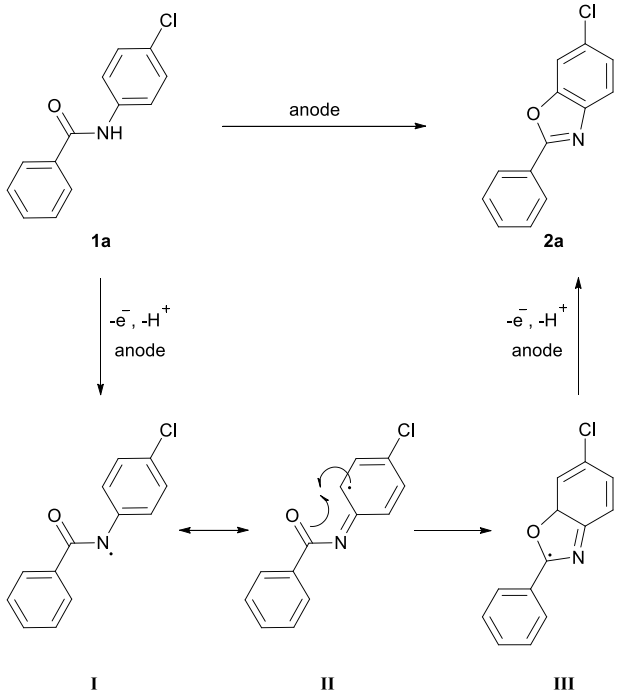


Scheme 2 Scope. A: Set-up A, B: Set-up B.

Several valuable functionalities are tolerated by the method leading to the synthesis of a variety of benzoxazoles in good to very good yield. Electron donating substituents on either the amide or the anilide part of the substrate have a beneficial effect onto the yield (**2b**, **2g** and **2h**). In addition, typical leaving group functionalities are also tolerated. In particular, chloro and triflate moieties are compatible with the reactions opening up the opportunity to further functionalize and diversify the scaffolds make using an assortment of subsequent transformations, i.e. cross-coupling reactions. On the amide part of the substrate, aromatic systems and quaternary alkyls are tolerated, while α hydrogens lead to unselective degradation processes. The different anilides were converted with both electrolysis set-ups **A** and **B**. The respective yields for these set-ups were compared using substrates **1a** and **1b**. The formation of **2a** afforded a higher yield using set-up **B**, while the

formation of **2b** proceeded better with set-up **A**. Two points about this finding deserve comment. First, note that both setups generated product and could be used to determine the synthetic potential of the reaction. So, for exploratory purposes the nature of the reaction setup is not important. However, when optimizing the reactions the observations underscore the need to pay attention to electrochemical conditions. Electrochemical reactions depend not only on how the reactive intermediates are generated, but also on how those intermediates interact with the chemical environment immediately surrounding the electrode, diffuse away from the electrode involved in their generation, and the gradient of chemical environments encountered during that diffusion process. All of these things depend on the nature of the electrochemical field in the cell, a field that relies on electrode configuration, spacing, etc. The point is simple. If the yield of a desired electrochemical reaction is lower than one might prefer, then one should look at alterations of the electrolysis set-up and the electrode geometry as one means of influencing that yield.

Regarding the mechanism of the transformations observed, we propose that oxidation of the substrate leads to an amidyl radical that is stabilized by the neighboring aromatic ring by resonance.[17] This first oxidation step might be facilitated by deprotonation of the amide via in-situ generated alcoholate anions derived from HFIP at the cathode. Bond formation between the amidic oxygen and the ortho carbon of the aromatic ring leads to the formation of a heterocyclic radical. A second oxidation followed by the loss of a proton then completes product formation. It is also possible that the reaction proceeds through a second oxidation that occurs prior to the cyclization followed by an electrocyclic oxa-Nazarov-type reaction.[18]



Scheme 3 Proposed mechanism.

The proposed mechanism suggests that the aromatic ring has substantial radical nature. This observation is supported by experimental data. An aryl radical would be expected to undergo significant coupling chemistry at the position *para* to the amidyl group. In practice, this occurs, and a substituent is required at the *para*-position of the N-substituted aryl-ring in order to prevent side reactions at this position. [5] The mechanism also explains why electron-releasing substituents on the ring favor the observed reaction since they both aid in the oxidation steps and stabilize the intermediate radical. Interestingly, if an *ortho* position is blocked by a substituent in the substrate, no product is formed. Evidently, a substituent in this position prevents rotation along the carbon nitrogen bond to generate the planar orientation required for resonance of the N-based radical into the aromatic ring.[19]

In conclusion, we have developed a straightforward and sustainable electrochemical synthesis for the direct construction of benzoxazoles from easy accessible anilides. A variety of functional groups are tolerated by the reaction, and these groups a well-positioned to enable further synthetic manipulation of the products. The comparison of the two most commonly used electrolysis set-ups in synthetic labs demonstrate that the method can be readily adopted by others.

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