CHEMISTRY
A European Journal

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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201701979

Link to VoR: http://dx.doi.org/10.1002/chem.201701979

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New Approach to 1,4-Benzoxazin-3-ones by Electrochemical C,H-Amination

Lars Julian Wesenberg,[a] Sebastian Herold,[a, b] Akihiro Shimizu,[c] Jun-ichi Yoshida,[c] and Siegfried R. Waldvogel*[a, b]

Dedicated to Hans J. Schäfer on the occasion of his 80th birthday

Abstract: 1,4-Benzoxazin-3-ones are important structural motifs in natural products and bioactive compounds. Usually the synthesis of benzoxazinones requires transition metal catalysts and pre-functionalized substrates, e.g. aryl halides. However, the anodic C,H amination of phenoxy acetates offers a very efficient and sustainable access to these heterocycles. The herein presented electrochemical protocol can be applied to a broad scope of alkylated substrates. Even *tert*-butyl moieties or halogen substituents are compatible with this versatile method.

The 1,4-benzoxazin-3-one scaffold has been recognized as an important heterocyclic motif in natural products as well as in pharmaceutically active compounds.[1] Naturally occurring benzoxazin-3-ones, like 2,4-dihydroxy-1,4-benzoxazin-3-one (DIBOA, **1**) and 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA, **2**) were found in gramineous plants like maize, wheat, rye, and rice (Figure 1).[2,3] Biosynthesis of DIMBOA (**2**) is accomplished via hydroxylation of indole derivatives by P450 monooxogenase. Intermediates of this reaction pathway can also be found in tryptophan biosynthesis.[4] On the other hand, benzoxazinones **3** and **4** are interesting compounds for pharmaceutical applications. The former is an inhibitor of bacterial histidine protein kinase,[5] whereas the latter is a potential agent for the treatment of anxiety and depression symptoms (Figure 1).[6,7]

Common synthetic strategies to construct benzoxazin-3-ones employ *ortho*-substituted nitrophenols or halophenols as starting materials.[2,8] Recently, El Kaïm *et al.* reported a three component reaction to access the benzoxazinone scaffold *via* a Passerini-Smiles rearrangement, followed by hydrogenation and *in-situ* cyclization.[9] Moreover, Liu and co-workers developed a copper(I)-catalyzed one-pot synthesis of benzoxazinones.[6] In this approach, *ortho*-halophenols react with α-chloroacetamides

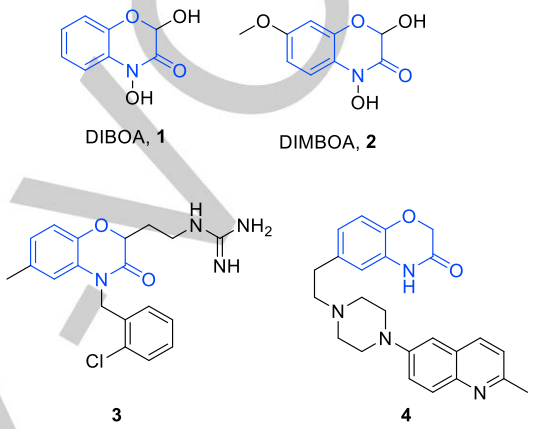
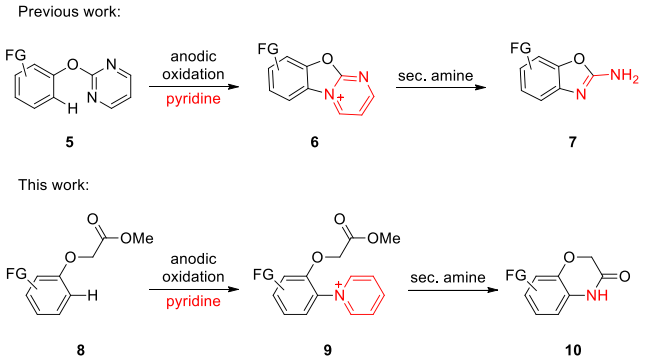


Figure 1. Naturally occurring 1,4-benzoxazin-3-ones DIBOA (**1**) and DIMBOA (**2**) and pharmaceutically relevant compounds **3** and **4** with the benzoxazinone scaffold.

in the presence of a metal promoter. However, a disadvantage of such approaches is the need for transition metal catalysts as well as pre-functionalized substrates, e.g. aryl halogenides or nitroaromatic compounds. In particular, nitroaromatic starting materials are sometimes difficult to obtain selectively, since nitration usually leads to regioisomeric mixtures.[10] Purification of such mixtures often is a tedious process. Recently, Yoshida and co-workers reported in a series of accounts a powerful and selective electrochemical C,N bond formation reactions[11,12,13] including a novel method for the synthesis of benzoxazoles **7** (Scheme 1).[14]



Scheme 1. Electrochemical synthesis of oxazoles **7**[14] and oxazinones **10**.

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10.1002/chem.201701979

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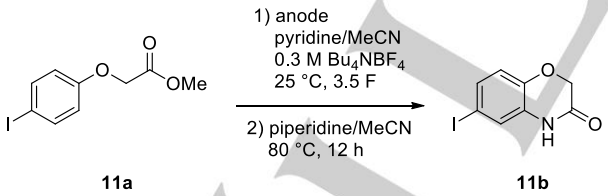
The phenolic substrates for the electrochemical synthesis of oxazoles **7** were initially modified with a pyrimidine moiety. This promotes an intramolecular electrochemical C,N coupling reaction. The anodic amination proceeds *via* positively charged Zincke intermediates **6** and **9**, which prevent a further anodic degradation, thus increasing the selectivity. The corresponding amino moieties can be liberated in a later step at non-electrolytic conditions.

In this work, we present a novel and innovative synthetic approach to the benzoxazinone scaffold by means of electrochemistry. Electrosynthetic conversions usually are considered sustainable as they take place at ambient conditions and avoid the use of stoichiometric amounts of oxidizing or reducing agents. As direct C,H functionalization can be achieved, pre-functionalized starting materials are not necessary. Thus, electro-synthetic processes can offer a higher atom economy compared to traditional methodologies.[15] As extraordinary reaction pathways can be realized by electrochemical oxidation or reduction, electrosynthesis has recently experienced a renaissance.[16,17]

Phenoxyacetate derivatives **8** served as starting materials for the envisioned electrochemical conversion to benzoxazinones. Anodic oxidation of such phenoxyacetates **8** in the presence of pyridine should lead to the positively charged pyridinium intermediates **9** (Zincke-type salts).[11,18] Upon treatment with piperidine the released primary aniline immediately attacks the ester moiety to form the desired benzoxazinones **10**. However, the anodic functionalization by pyridine needs to take place at the position *ortho* to the carboxymethoxy substituent. Only in this case, the desired fused heterocycle with the 1,4-oxazin-3-one substitution pattern will be formed. Therefore, an accessible and activated *ortho* position is required for the direct electrochemical C,H amination.

At first, a screening for suitable electrode materials was carried out, since previous studies revealed a significant impact of the anode material onto the anodic amination.[19] For this investigation, methyl 4-iodophenoxyacetate (**11a**) was chosen as test substrate (Scheme 2).



Scheme 2. Electrochemical amination of methyl 4-iodophenoxyacetate (**11a**); as test substrate for electrochemical synthesis of benzoxazinone (**11b**).

Phenoxyacetate **11a** fulfilled all requirements, such as good access to the position *ortho* of the phenoxy moiety and additionally, a leaving group for subsequent functionalization reactions. The optimization experiments were conducted in divided Teflon cells with a porous glass-frit as separator (see Supporting Information). This screening methodology is simple and allows the variation of different important electrolysis parameters, e.g. current density and applied charge, in a time efficient manner.[20] As anode materials, different carbon felts, carbon fleeces, boron-doped diamond as well as isostatic graphite were employed. The outcome of these screening reactions was quantified by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as internal standard (ISTD).

Porous electrode materials like carbon fleece and carbon felt can be beneficial in electrosynthetic transformations since they exhibit a high surface area. However, anodically generated highly reactive intermediates need to diffuse into the bulk solution for desired follow-up reactions. This diffusion can be inhibited by absorption of the intermediates by the porous material. For carbon felt and carbon fleece as anode materials, a current of 8 mA was applied. These conditions were adopted from previous studies by Yoshida and co-workers.[11] With an applied charge of 3.5 F, a maximum yield of 37% (NMR, ISTD) of **11b** was obtained. Next, boron-doped diamond, which has recently attracted a lot of attention in electrosynthesis, was evaluated.[17,21] Initially, a current density of 10 mA·cm^{-2} and an applied charge of 3.5 F were investigated. At these conditions, the desired benzoxazinone **11b** was formed in 45% yield (NMR, ISTD). So far best results were obtained by using an isostatic graphite anode at similar reaction conditions as used before. Therefore, this anode material was investigated in detail. First, the current density was altered in the range of 0.5-13 mA·cm^{-2} at an applied charge of 3.5 F. We anticipated that a low current density might be beneficial for the selectivity as the amount of reactive intermediates generated is lower than at a high current density (Figure 2).

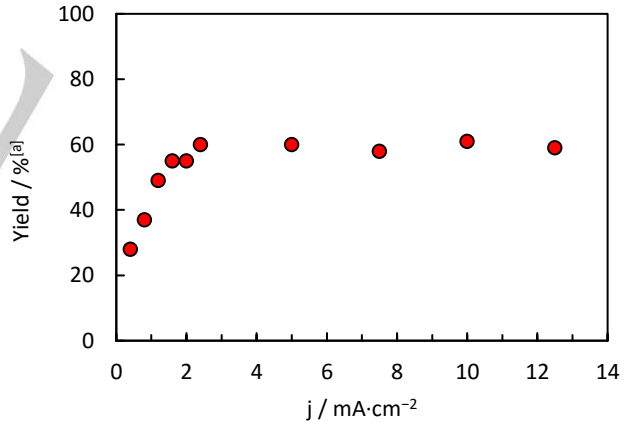


Figure 2. Electrochemical amination of methyl 4-iodophenoxy acetic acid (**11a**); screening of current density at isostatic graphite. [a] ^{1}H NMR yield, internal standard: 1,1,2,2-tetrachloroethane.

However, low current densities of up to 1 mA·cm^{-2} resulted in moderate yields of up to 45% (^{1}H NMR, ISTD). The best performance was observed at an elevated current density of 10 mA·cm^{-2} with 61% yield of **11b** (^{1}H NMR, ISTD). Thus, for further experiments, a current density of 10 mA·cm^{-2} was used. Furthermore, the applied charge was varied in a range of 2.0-5.0 F in steps of 0.5 F (see Supporting Information). Best results were obtained at an applied charge of 3.5 F (61% of **11b**).

10.1002/chem.201701979

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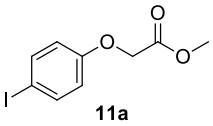
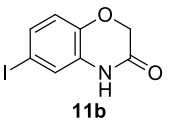
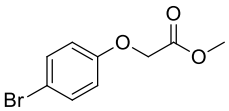
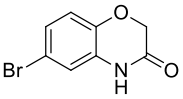
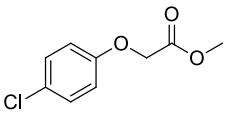
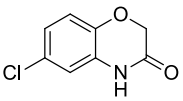
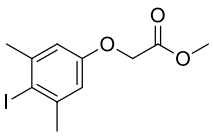
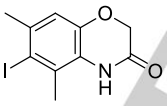
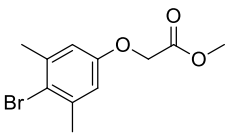
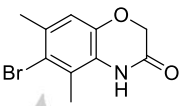
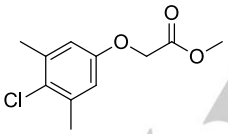
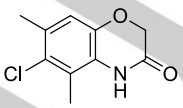
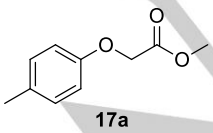
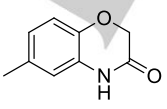
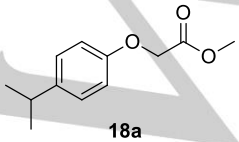
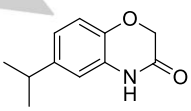
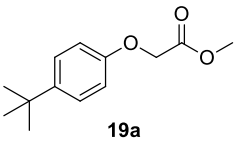
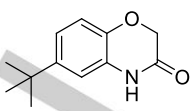
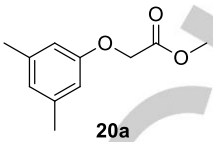
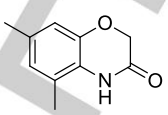
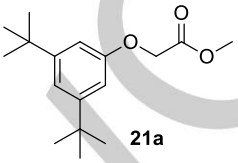
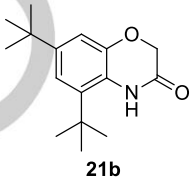
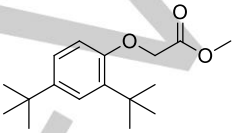
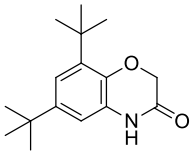
At lower applied charge the yield decreased drastically to approx. 30% of **11b** (^{1}H NMR, ISTD). In this case, an incomplete conversion was observed. Application of more charge, e.g. 5 F led to roughly 40% of benzoxazinone **11b**. The identified, optimized electrolysis conditions consist of an isostatic graphite anode, a current density of 10 mA·cm^{-2}, and an applied charge of 3.5 F. These optimized reaction conditions were then subjected to a collection of phenoxy acetates (**Table 1**).

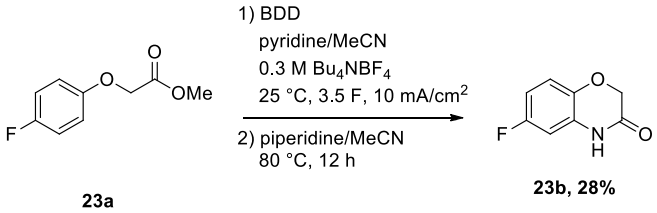
Table 1. Scope of the anodic benzoxazinone formation.

Entry	Substrate	Product	Yield/ %[b]
1	 **11a**	 **11b**	51
2	 **12a**	 **12b**	38
3	 **13a**	 **13b**	39
4	 **14a**	 **14b**	54
5	 **15a**	 **15b**	66
6	 **16a**	 **16b**	78
7	 **17a**	 **17b**	42
8	 **18a**	 **18b**	58
9	 **19a**	 **19b**	62
10	 **20a**	 **20b**	12
11	 **21a**	 **21b**	22
12	 **22a**	 **22b**	23

Anode: isostatic graphite, j = 10 mA·cm^{-2}, Q = 3.5 F, T = 25 °C, divided cell; [b] isolated yield.

As illustrated by Table 1, the electrochemical protocol is applicable to a broad scope of phenoxy acetates. Halide derivatives, e.g. chloro, bromo, and iodo phenoxy acetates (**11a**-**16a**), were compatible with this methodology. The corresponding benzoxazinones (**11b**-**16b**) were obtained in moderate to good yields of up to 78% (Table 1, Entries 1-6). Para-substituted alkyl derivatives **17a**, **18a**, and **19a** were transformed to the corresponding heterocycles **17b**, **18b**, and **19b** in yields of up to 62% (Table 1, Entries 7-9). Despite the cationic nature of intermediates, this method is even suitable for *tert*-butyl groups in which case the corresponding benzoxazinone **19b** was obtained in a good yield of 62% (Table 1, Entry 9). Substrates as **19a** might undergo dealkylation processes upon anodic treatment thus causing by-products. However, this seemed not to be the case. Starting materials **20a** and **21a** exhibit two alkyl substituents in both *meta* positions, leading to a lower yield than the congener with a single substituent (Table 1, Entries 10 and 11). Surprisingly, even the more sterically demanding alkyl substrate **21a** with two *tert*-butyl groups was better accessible compared to phenoxy acetate **20a**. However, to circumvent more hindered adjacent locations, we tested different substitution patterns. Unfortunately, an *ortho* and *para* alkyl substituent did not result in better yields (Table 1, Entry 12). Furthermore, we investigated the less-activated fluoro derivative **23a** as substrate. However, in this case the use of an isostatic graphite anode did not lead to the desired benzoxazinone **23b**. Next, we used boron-doped diamond as anode since this material proved to be a powerful tool for the electroconversion of electron deficient starting materials.[19] Indeed, by employing boron-doped diamond as anode **23b** was obtained in a moderate yield of 28% (Scheme 3).

10.1002/chem.201701979



Scheme 3. Electrochemical transformation of electron-deficient phenoxyacetate **23a** using boron-doped diamond electrodes.

In conclusion, the use of phenoxy acetates as substrates for the electrochemical amination reaction results in the formation of 1,4-benzoxazinones, which are valuable scaffolds in natural products as well as pharmaceutically active compounds. The sequence includes the electrochemical amination via Zincke intermediates followed by liberation of the aniline function, which finally undergoes the ring closure by condensation reaction. The protocol presented allows a simple access to the benzoxazinone skeleton at ambient conditions highlighting the performance of electrosynthetic approaches to such complex heterocycles.

Experimental Section

For experimental details, setup and analytical data see Supporting Information.

Acknowledgements

The support by The Advanced Lab for Electrochemistry and Electrosynthesis – ELYSION (Carl Zeiss Stiftung) is highly appreciated.

Keywords: amination • electrochemistry • nitrogen heterocycles • benzoxazinone • sustainable chemistry

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10.1002/chem.201701979

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Layout 1:

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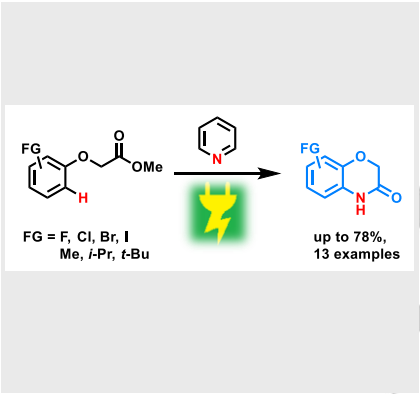
An electrified amination provides direct and highly selective access to 1,4-benzoxazin-3-ones starting from simple and readily available phenoxy acetates. This approach allows the generation of complex fused heterocycles by electro-organic synthesis.



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New Approach to 1,4-Benzoxazin-3-ones by Electrochemical C,H-Amination