Angewandte Highlights

Electroorganic Synthesis

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Renaissance of Electrosynthetic Methods for the Construction of Complex Molecules

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electrochemistry · natural products ·
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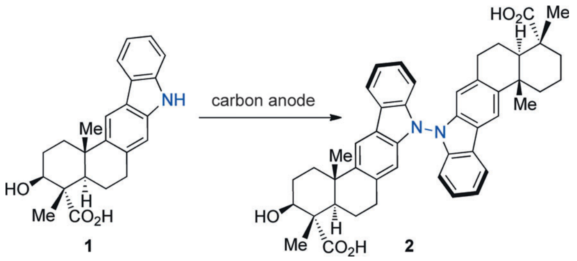
Electrochemical synthesis is an attractive method for the construction of organic compounds, as it allows C−C coupling reactions, functional-group interconversion, and installation of heteroatom moieties.[1] Since only electrons serve as the reagents and the electrodes employed are not consumed, electrochemistry complies with all the criteria of "green chemistry".[2] Large quantities of stoichiometric oxidizers and reductive reagents can be avoided, even when mediators are employed. Consequently, the waste originating from the reagents used is almost negligible. Since renewable energy will play a major role in future industrial societies, there will definitely be a surplus of electric energy, which can best be used for the conversion of chemicals into valuable products. Therefore, new electrosynthetic transformations are highly welcome. Electrosynthesis is usually associated with inorganic or small organic molecules with a known technical significance.[3] Unfortunately, this method is not yet very common for the construction of larger organic compounds, most probably because electrosynthesis is not covered in most curricula and the experimental setup seems too sophisticated at first glance. Consequently, in the preparation of complex organic molecules, electrochemistry is commonly considered as the last option when all other conventional chemical methods have failed.

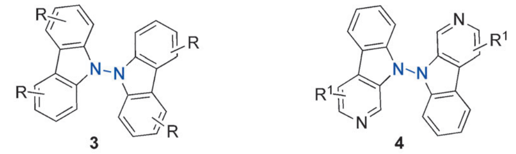
An impressive and convincing example is the recent total synthesis of the N,N-linked dimeric indole alkaloid dixiamycin B (**2**; Scheme 1).[4] Interestingly, the N,N-linked dimeric atropisomeric species **2** exhibits a distinctly higher antibacterial activity than the monomeric xiamycin A (**1**).[5] The Baran research group tested a plethora of oxidizers to effect the N,N-linkage through oxidative coupling, although most of these reagents failed completely. $KMnO_4$ or $(PhCO_2)_2$ provided detectable amounts of **2**, but accumulation of sufficient amounts for the preparation of dixiamycin was not possible because of decomposition during the reaction. To meet this challenge, an electrochemical oxidative dimerization procedure was developed, which serves as the pivotal step in the first total synthesis of **2**.



Scheme 1. Synthesis of dixiamycin B by anodic coupling. Reagents and conditions: undivided cell, carbon electrodes, +1150 mV, Et_4NBr, DMF, MeOH.

The electroorganic synthesis results in a 28% yield of the product and the formation of a bromo derivative of subunit **1**. Interestingly, the application of the conventional oxidizers resulted in both diastereomeric isomers of **2** being detected, whereas the electrochemical approach provides only the atropisomer displayed in Scheme 1. It is not yet clear if both atropisomers are formed and the other one degraded during the course of the electrolysis.

The electroorganic method turned out to be general and practical for the N,N dimerization of substituted carbazoles **3** and β-carbolines **4** (Figure 1). The method tolerates alkyl moieties as well as electron-withdrawing groups on the heterocyclic substrate. The yields reach 66% of the isolated material, the parent N,N-linked carbazole **3** was obtained in 61% yield even on a gram-scale. The established electrochemical procedure seems more robust than would be



3

$R = H$, ^tBu, CF_3, CO_2CH_3, SO_2CH_3
up to 66%

4

$R^1 = H$, CO_2CH_3
up to 66%

Figure 1. Electrochemical N,N dimerization of carbazoles and carbolines. Reagents and conditions: carbon anode, +1.2 V versus Ag/AgCl, Et_4NClO_4, DMF/MeOH (19:1).

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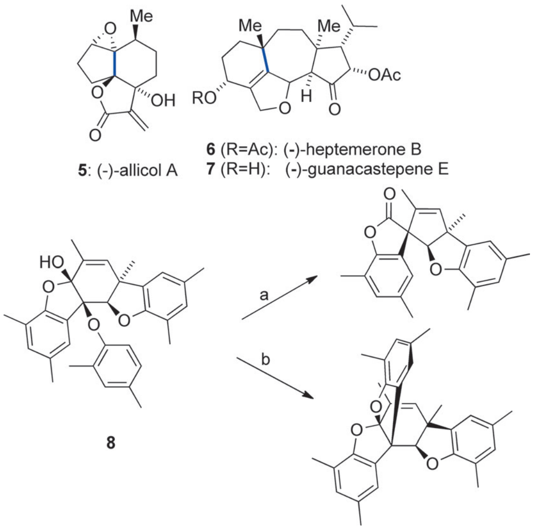
expected, since from an electrosynthetic point of view the experimental set-up is not optimal: The alignment of the electrode rods is expected to lead to an inhomogeneous electrical field and consequently a certain continuous electrical potential is applied to the electrolyte. However, the authors use NBu_4Br as a supporting electrolyte, which definitely serves as a mediator and acts as a kind of redox filter. The coformation of the bromo by-product of **1** in the generation of **2** is also indicative of this. The application of mediators in electrochemical conversions is a common electroorganic approach.[6] The anodic treatment of aromatic amines usually provides oligomeric or polymeric products, and only in a few cases can an N,N linkage be selectively achieved.[7] Very specific substrates are required for the generation of hydrazobenzene[8] or azo moieties.[9] Carbazoles can be constructed by anodic treatment, which indicates a certain stability of this particular moiety under electroorganic conditions.[10] This finding strongly underlines the value of the electrosynthesis developed by Baran and coworkers.

Previous applications of electroorganic methods in the synthesis of larger natural products are mostly intramolecular anodic treatments, with anodic C–C coupling being the dominant transformation. Representative examples are the natural products **5–7** (Scheme 2, the electrochemically formed bonds are depicted in blue).[11]



5: (-)-allicol A

6 (R=Ac): (-)-heptemerone B
7 (R=H): (-)-guanacastepene E

8

Scheme 2. Natural products formed using an electrochemical step and the diversity of their polycyclic scaffolds. Reagents and conditions: a) conc. H_2SO_4, toluene, RT, 4 h, 75%; b) BF_3OEt_2, CH_2Cl_2, −78 °C, 83%.

Electroorganic methods also provide access to molecular diversity. Anodic treatment of 2,4-dimethylphenol in an undivided cell results directly in the dehydrotetrameric compound **8** in 54–60% yield. Subsequent transformations selectively provide—depending on the reaction conditions—different molecular architectures.[12] Some of these polycyclic scaffolds are close to naturally occurring compounds.

It is noteworthy that the examples discussed deal with anodic conversions; cathodic transformations for the construction of complex molecular architectures are far rarer. This can be attributed to the lack of suitable electrolyte/electrode combinations. Consequently, in the area of cathodic transformations there is still a significant demand for research. The impressive example from the Baran research group, as well as the other electroorganic syntheses discussed, underline the value and power of this method. Recent electrochemical developments in selective C–C bond formation, such as the cation-pool method or exploitation of solvent effects using fluorinated alcohols, provide new tools for efficient cross-coupling reactions which are essentially metal and reagent free.[13] The encouraging results underline the potential of electroorganic synthesis and pave the way for the renaissance of this method.

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