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Ring-contraction of hantzsch esters and their derivatives to pyrroles *via* electrochemical extrusion of ethyl acetate out of aromatic rings†

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Electrochemical ring-contraction of HEs and theirs pyridine derivatives is developed to obtain polysubstituted pyrroles. This process provides an orthogonal utilization of Hantzsch esters for the well-documented application as side chain or hydrogen donors. The formal transformation shows an extrusion of ethyl acetate out of the pyridine ring in a single step. In addition to the novel transformation, we also discovered the Lewis acid's intermolecular control of regioselectivity during an intramolecular electrochemical process. The reaction provides a number of polysubstituted pyrroles that have never been accessed, including pharmaceutical intermediates and photoswitches. An unusual 4-electron continuous reduction drives the unprecedented anionic dearomatization/ring-contraction/rearomatization pathway.

Introduction

Pyrroles are five-membered nitrogen heterocycles with intrinsic hydrogen bonding ability.[1] Their electronic and steric properties can be regulated by the introduction of multiple substituents onto their carbon skeletons, and tetra- and penta-substituted pyrrole moieties are present in molecular photoswitches[2] and numerous pharmaceuticals (Fig. 1).[3] The established methods for pyrrole synthesis involve condensation reactions, but the synthesis of pyrroles with multiple different types of functional groups poses a challenge and requires careful selection of the substrates and condensation conditions.[4] Therefore, a versatile, modular method for polysubstituted pyrrole synthesis that would allow full modification of the carbon skeleton would be highly desirable.

We speculated that Hantzsch esters (HEs) might be useful for this purpose. HEs are polysubstituted heterocycles that can be prepared by modular, multicomponent condensation reactions. HEs are widely used as hydride donors in organocatalysis and Lewis acid catalysis.[5] In addition, they have been utilized as hydrogen atom donors in various catalytic radical reactions.[6] Recently, 4-substituted HEs have emerged as highly reactive radical donors in Lewis acid catalysis,[7] photoredox catalysis,[8] thermal radical reactions,[9] and electrochemical reactions.[10] In all these innovative transformations, only one substituent on the HE, either a hydrogen or an alkyl group, ends up in the target molecule; the aromatized pyridine ester byproduct is separated and then discarded (Scheme 1a).[11] However, in terms of atom economy and functional group diversity, the pyridine core structure would be ideal for the construction of heterocyclic compounds. Along these lines, we speculated that ring-contraction reactions of HE-derived pyridine derivatives could provide a new strategy for accessing polysubstituted pyrroles. However, this strategy presents two challenges. First, because of the electron deficiency of the HE pyridine ring, the ester groups are stable under various conditions, and therefore, activation of these groups and the subsequent ring contraction would necessitate a tremendous driving force. Second, pyrroles tend to be more reactive than pyridines. In a pioneer-

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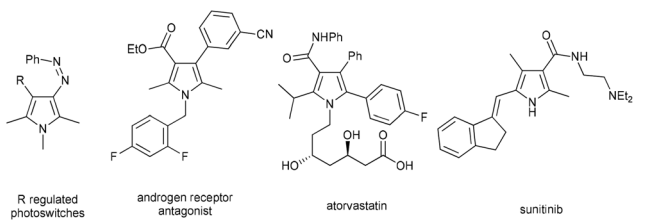
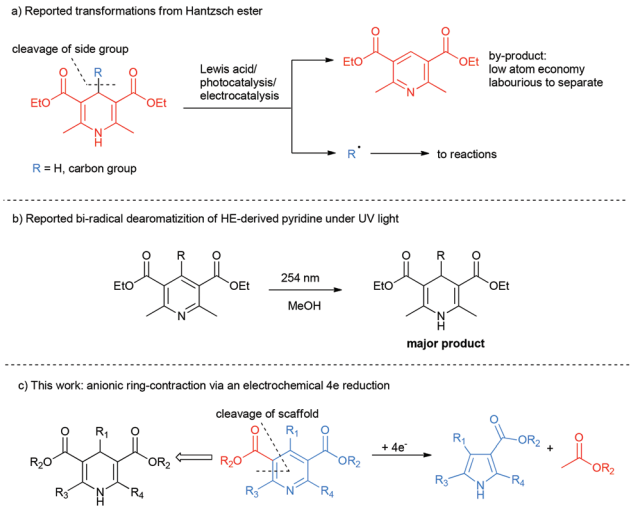


Fig. 1 Polysubstituted-pyrrole-containing photoswitches and pharmaceuticals.



Scheme 1 Utilization of 2H-pyridines as radical donors and pyrrole precursors.

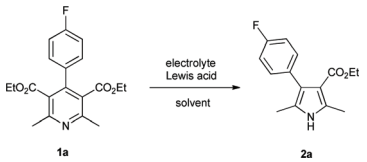
ing study, the Kellogg group reported a protocol for the dearomatization of pyridine diesters under UV irradiation, which gave rise to dihydropyridines as major products *via* a bis-radical pathway (Scheme 1b).[12] In this report, only one example showed pyrrole as the minor product, providing a clue for both the possibility and the challenge of the proposed ring-contraction transformation.

Given the need for a strong driving force, we envisioned that an electrochemical process would be a good option as electrochemical methods have been successfully used for various types of transformations.[13] Specifically, we speculated that a cathode reduction might lead to a new pathway involving an anion intermediate instead of a bis-radical species. This speculation was supported by a number of previously reported cathodic reduction reactions. For example, the Baran group developed an electrochemical Birch reduction chemistry that involves rapid electron transfer to arenes and gives rise to unsaturated carbocycles.[14] In addition, activation of various functional groups, including CO_2,[15] unsaturated C–C bonds,[16] aryl–CN bonds,[17] C–halogen bonds,[18] chlorosilane,[19] nitrones,[20] nitroarenes,[21] diazo compounds,[22] and ketones,[23] by means of innovative cathodic reduction chemistry have been demonstrated recently. Despite of these achievements, however, the dearomative cleavages of C–C/C=C bonds and re-aromatization cascade reaction still remain elusive to known protocols (Scheme 1c). Herein, we report the first example of ester abstraction from pyridines *via* such electrochemical reduction reaction.

Results and discussion

To explore the reaction conditions, we chose pyridine derivative **1a** as the model substrate (Table 1). First, we carried out an electrochemical reaction (20 mA) in THF in an undivided cell with Zn as a sacrificial anode, graphite felt (GF) as the

Table 1 Optimization of conditions for ring contraction of HE-derived pyridine **1a**[a]

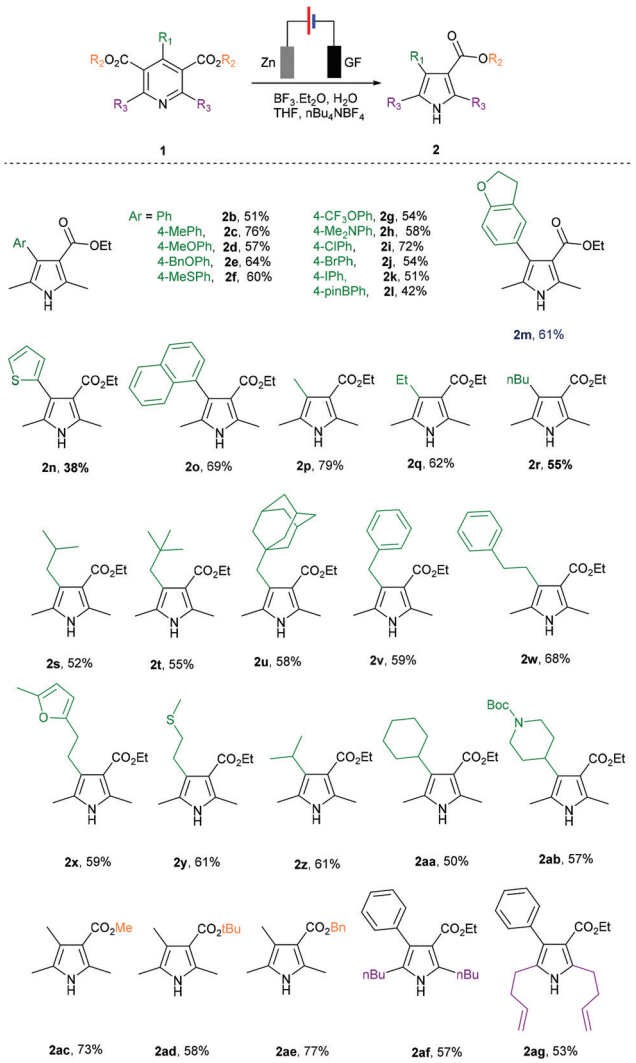


Entry	Electrolyte	Lewis acid (equiv.)	Solvent	Yield[b] (%)
1	$LiClO_4$	$BF_3{\cdot}Et_2O$ (3)	THF	26
2	$LiClO_4$	—	THF	0
3[c]	$LiClO_4$	$BF_3{\cdot}Et_2O$ (3)	THF	0
4[d]	nBu$_4$NBF$_4$	$BF_3{\cdot}Et_2O$ (5)	THF	0
5	nBu$_4$NBF$_4$	$BF_3{\cdot}Et_2O$ (3)	THF	35
6	nBu$_4$NBF$_4$	$Zn(OTf)_2$ (3)	THF	0
7	nBu$_4$NBF$_4$	$BF_3{\cdot}Et_2O$ (3)	MeCN	Trace
8	nBu$_4$NBF$_4$	$BF_3{\cdot}Et_2O$ (3)	MeOH	Trace
9	nBu$_4$NBF$_4$	$BF_3{\cdot}Et_2O$ (3)	DMF	15
10	**nBu$_4$NBF$_4$**	**$BF_3{\cdot}Et_2O$ (5)**	**THF**	**90[e] (75)**
11[f]	nBu$_4$NBF$_4$	$BF_3{\cdot}Et_2O$ (5)	THF	0
12	*hv* 254 nm, MeOH	—	—	0 (12% HE)

[a] Reaction conditions, unless otherwise noted: **1a** (0.2 mmol), electrolyte (0.1 mmol), Lewis acid, H_2O (40 equiv.), solvent (5 mL), Zn(+)/GF(−), 20 mA, rt, 12 h. [b] Yields were determined by gas chromatography. [c] No H_2O. [d] No electricity. [e] Isolated yield. [f] GF(+)/GF(−).

cathode, $LiClO_4$ as a supporting electrolyte, a Lewis acid ($BF_3{\cdot}Et_2O$) as a promoter, and water as the hydrogen source. To our delight, these conditions afforded pyrrole **2a** in 26% yield by gas chromatography (entry 1). In the absence of the Lewis acid, water, or electricity (entries 2–4), the conversion of **1a** failed to proceed. Using n-Bu_4NBF_4 instead of $LiClO_4$ boosted the yield slightly (to 35%, entry 5), whereas there was no reaction when $Zn(OTf)_2$ was employed as the Lewis acid promoter (entry 6). Several solvents that are widely applied in electrochemical synthesis showed inferior results (entries 7–9). However, we found that increasing the amount of $BF_3{\cdot}Et_2O$ to 5 equiv. dramatically improved the yield to 90% by gas chromatography and 75% isolated yield (entry 10). None of the desired product was obtained when the Zn anode was replaced with inert graphite felt (entry 11), suggesting that the Zn anode was essential to prevent the oxidation of **2a** in this undivided cell configuration. Finally, using the de-aromatization protocol reported by Kellogg, UV irradiation of **1a** afforded the corresponding HE (**2H-1a**) in 12% isolated yield, and pyrrole **2a** was not detected (entry 12). A reaction at a concentration of 1.6 mol L^{-1} could afford a faradaic efficiency of 59% (ESI, section 2.1†).

Having optimized the conditions (Table 1, entry 9), we extended the reductive ring-contraction reaction to additional pyridines **1** (Scheme 2). Pyrroles **2b–2l**, which bear phenyl groups with various substitution patterns, were obtained in 42–76% yields; functionality such as a thioether group, an aniline ring, a bromine atom, and a borate group were well tolerated. Dihydrobenzofuryl-substituted pyrrole **2m** was synthesized in 61% yield, and thienyl-substituted pyrrole **2n** could be obtained as well, although the yield was only 43% owing in part to the formation of its corresponding dihydropyridine

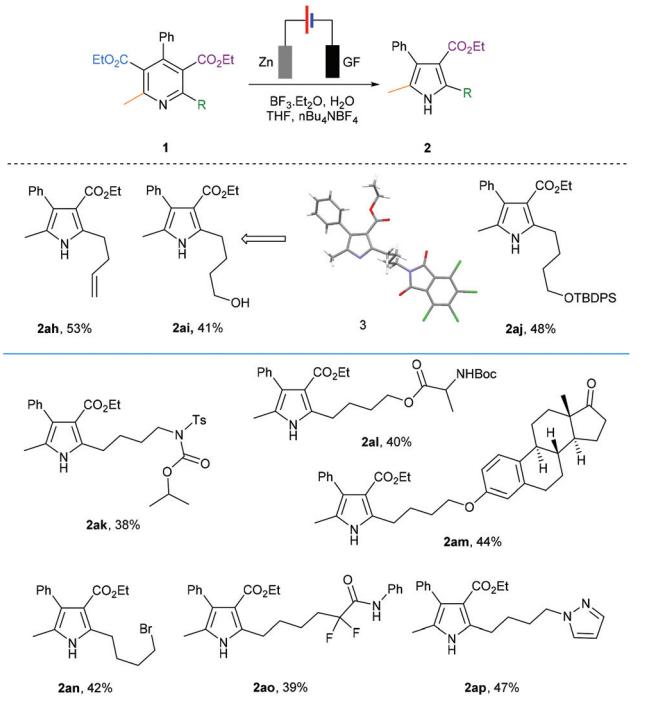


Scheme 2 Synthesis of polysubstituted pyrroles by ring contraction of pyridines derived from symmetrical HEs. Conditions: **1** (0.2 mmol), electrolyte (0.1 mmol), BF_3 etherate (1 mmol), H_2O (8 mmol), solvent (5 mL), Zn(+)/GF(−), 20 mA, rt, 12 h.

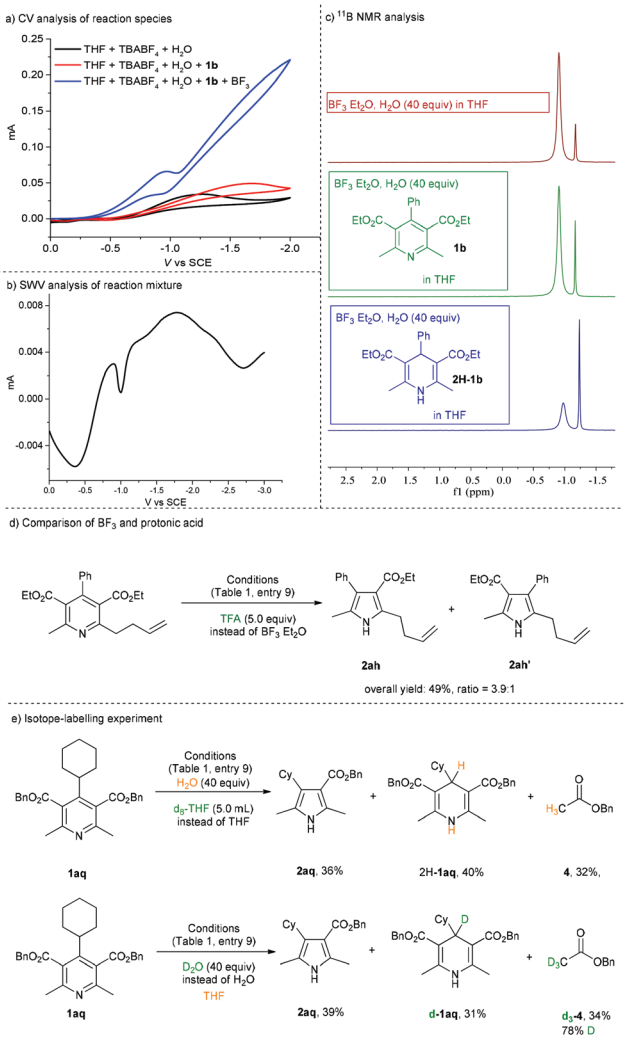
2H-1n. A pyrrole with a bulky α-naphthenyl group (**2o**) was produced in 69% yield. We also screened pyridine substrates derived from alkyl-substituted HEs. We were pleased to find that pyrrole **2p** could be synthesized in 79% yield by our method; in contrast, in the only previously reported synthesis,[12] which was achieved by UV irradiation, the yield of this compound was only 16%. Alkyl-substituted pyrroles **2p–2w** were prepared in moderate yields, and furyl (**2x**) and dialkyl thioether (**2y**) groups remained intact under the reaction conditions. Products **2z–2ab**, which have bulkier secondary alkyl groups, were obtained in similar yields. We also evaluated the effect of the steric bulk of the ester groups and found that larger esters showed slightly diminished yields (compare the yields of **2ac–2ae**). Pyrroles **2af** and **2ag**, which have long carbon chains instead of a methyl group, were also accessible (57% and 53%, respectively).

Next we determined whether our method could be used to obtain pyrroles with four different substituents from unsymmetrical pyridine substrates, which requires that the regioselectivity of the ring-contraction step be controlled (Scheme 3). To our delight, the reaction of **1ah** under the standard conditions afforded pyrrole **2ah**, which has four different substituents on the ring, in 53% yield. Next we evaluated the effects of various R groups. We found that a free hydroxyl group (**2ai**, 41%), an O-silyl group (**2aj**, 48%), an imidate (**2ak**, 38%), a Boc-protected amide (**2al**, 40%), and an estrone (**2am**, 44%) all survived the reduction conditions and had little effect on the reaction yields. The regioselectivity was confirmed by X-ray analysis of a crystal of **3**,[24] which was derived from pyrrole **2ai**. The method was also compatible with a primary alkyl bromide (**2an**, 42%). In contrast, the difluoroamide group of **2ao** decreased the product yield because of the strong affinity of the group for silica gel, which was used during purification. The product **2ap**, which has a pyrazole group, was obtained in 47% isolated yield.

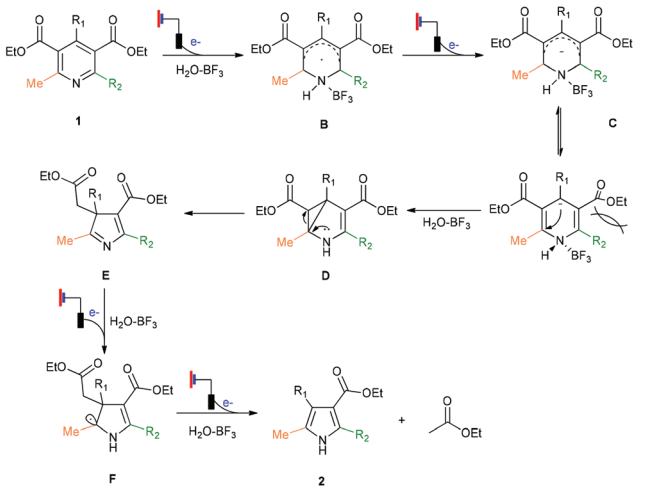
To elucidate the reaction mechanism, we carried out a series of experiments under controlled conditions. First, cyclic voltammetry analysis showed that in aqueous THF, $BF_3{\cdot}Et_2O$ substantially decreased the barrier to the anodic reduction of **1b** (by 0.7 V, Scheme 4a). In addition, a square wave voltammetry experiment indicated that multiple electron transfers were involved in the reduction (Scheme 4b). Comparison of the ^{11}B NMR spectrum of aqueous BF_3 with the spectra of aqueous



Scheme 3 Synthesis of polysubstituted pyrroles by ring contraction of pyridines derived from unsymmetrical HEs. Conditions: **1** (0.2 mmol), electrolyte (0.1 mmol), BF_3 etherate (1 mmol), H_2O (8 mmol), solvent (5 mL), Zn(+)/GF(−), 20 mA, rt, 12 h.



Scheme 4 Analysis of reactants and control experiments.

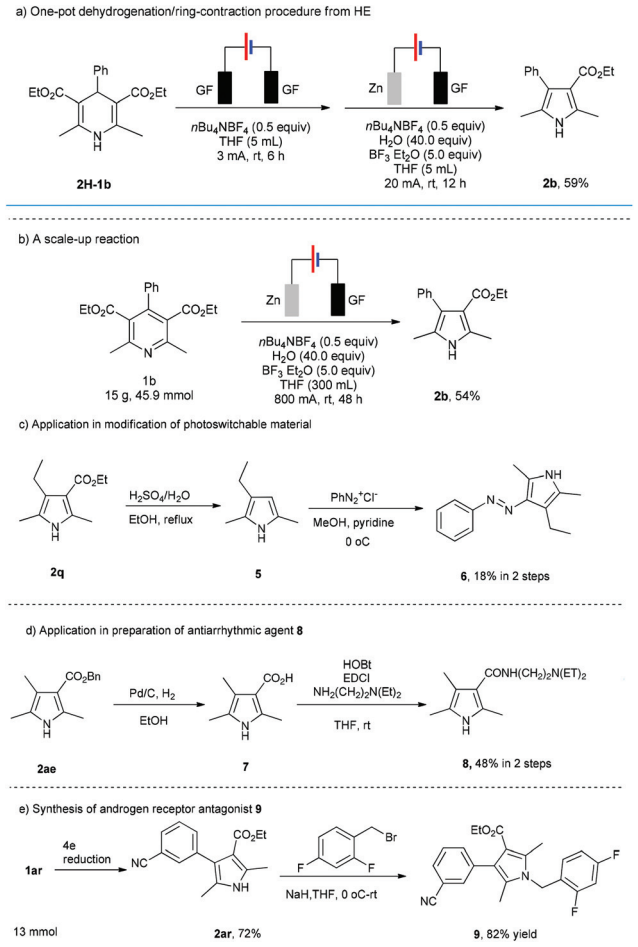


Scheme 5 Plausible pathway for anionic ring-contraction reactions involving four-electron cathodic reduction.

mixtures of BF_3 and **1b** or **2H-1b** revealed that the pyridine did not bind strongly to BF_3, whereas **2H-1b** interacted strongly with BF_3 (Scheme 4c). If $BF_3{\cdot}Et_2O$ was replaced with trifluoroacetic acid (a protonic acid), the reaction gave a 3.9 : 1 mixture of pyrroles **2ah** and **2ah′** in a combined yield of 49% (Scheme 4d). This result suggests that BF_3 played an important role at the ring-contraction stage. Because a reaction of pyridine **1aq** gave both dihydropyridine **2H-1aq** and pyrrole **2aq** as products, we used this substrate to elucidate the intermediate in the transformation. Specifically, when the reaction of **1aq** was carried out in THF-d_8, no deuterium was found in either **2aq**, **2H-1aq**, or benzyl acetate **4** (Scheme 4e). In addition, in a reaction of **1aq** in THF containing D_2O, benzyl acetate d_3-**4** was isolated as the major product by means of gas chromatography–mass spectrometry and NMR analysis. The outcomes of both of these labelling experiments suggest that the hydrogen source was not THF but water.

On the basis of the above-described results, we propose the reaction pathway shown in Scheme 5. First, coupled with the protonation by water-BF_3, an electron is transferred from the graphite felt cathode to pyridine **1** to generate radical **B**. Transfer of a second electron from the cathode forms anionic intermediate **C**. At this stage, steric repulsion between complexed BF_3 and the adjacent alkyl groups distorts the ester group on the side of the molecule with the larger alkyl group; this distortion leads in turn to greater disruption of the conjugation between the ester and the double bond in the ring. Therefore, intramolecular Michael addition of the carbanion occurs selectively at the less hindered side of the nitrogen atom and is followed by a second protonation to afford bicyclic species **D**. Opening of the cyclopropane ring of **D** generates a five-membered-ring structure **E**, which has an imine group. Next a third electron transfer from the cathode takes place, coupled with a third protonation, giving rise to radical **F**. Finally, the cleavage of a C–C bond, transfer of a fourth electron, and protonation furnish pyrrole **2** and ethyl acetate. In this sequence, the water could provide protons for the activation of pyridine and formation of acetate.

Subsequently, we attempted to achieve direct electro-chemical conversion of a HE to a pyrrole in one pot (Scheme 6a). When we used graphite felt for both the anode and the cathode, dehydrogenative oxidation of HE **2H-1b** in THF containing *n*$BuNBF_4$ gave pyridine intermediate **1b**, which then underwent the ring-contraction reaction when we switched to a zinc anode and added $BF_3{\cdot}Et_2O$ and water to the reaction mixture. This one-pot procedure provided **2b** in 59% yield over two steps. The ring-contraction reaction could also be carried out on a 15 g scale to generate **2b** with no loss in yield relative to that obtained from the submillimolar-scale reaction (Scheme 6b). Furthermore, pyrrole **2q** was used to prepare a modified photoswitch **6** in 18% yield, which is comparable to the reported yield of trimethyl pyrrole azobenzene (Scheme 6c).[2] This result suggests that our method could provide a substrate pool for the development of photoswitch-



Scheme 6 Synthetic applications of the electrochemical ring-contraction method.

able materials. Next, an antiarrhythmia agent **8**[25] was synthesized from **2ad** in two steps with a 48% overall yield (Scheme 6d). Finally, an androgen receptor antagonist **9**[26] was obtained from pyridine **1aq** *via* the four-electron reduction (72% yield) and a subsequent benzylation reaction (82% yield) (Scheme 6e).

Conclusions

In summary, we have developed a method for the first time for the electrochemical preparation of polysubstituted pyrroles from HE-derived pyridines. This method, which is unique as it involves four electron transfers, is complementary to the established applications of HEs. More than 40 pyrroles with a diverse array of functional groups were synthesized in moderate to good yields. A Lewis acid, $BF_3{\cdot}Et_2O$, was found to be essential for controlling the regioselectivity of the ring-contraction step in transformations of unsymmetrical pyridines. The transformation from HEs to pyrroles could be accomplished in one pot by means of a two-electron dehydrogenative oxidation/four-electron reductive ring-contraction procedure.

Author contributions

Xu Liu and Chang Liu contributed equally to this work.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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