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Direct Electroreductive Preparation of Indolines and Indoles from Diazonium Salts

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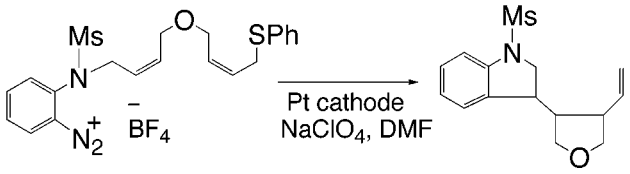
ABSTRACT

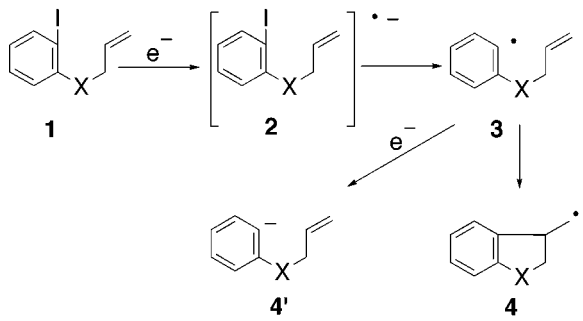


Indolines and indoles are prepared for the first time by direct electrochemical reduction of arenediazonium salts.

The pressing need to develop clean methodology ("green chemistry") for synthetic reactions is widely recognized[1]. One aspiration of green chemistry is to replace current methods of forming C−C bonds that use toxic reagents with "reagentless" reactions that are induced simply by energy: electrical, thermal, photochemical, or other. This paper deals with electrochemistry; although it is a valuable tool in synthesis[2], there are many areas of organic chemistry where it has not yet been applied. Here we describe a new application of controlled potential electrochemistry to the synthesis of indolines and indoles, both of which are important pharmacophores.

Cathodic reduction of an aryl halide **1** could occur by an initial one-electron reduction to form the radical anion **2**, which could dissociate into an aryl radical and a halide anion. This radical could then cyclize onto appropriate unsaturated side-chains to form the five-membered heterocyclic ring in **4**. However a second reductive step, converting the aryl radical **3** to an anion equivalent, **4′**, could also occur. Selectivity for formation of the radical **4** versus the anion **4′** then depends on the energy separation between the two electron-transfer steps.

Scheme 1



It has been reported[3] that direct electrochemical reduction of aryl halides such as **1** does not lead to radical cyclization but instead to products resulting from the formation of anionic intermediates. However, this may depend on the

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(1) See special issue: *Pure Appl. Chem.* **2000**, *72*, 1207−1403.
(2) For a review, see: Eberson, L.; Schäfer, H. *Fortschr. Chem. Forsch.* **1971**, *21*, 5.
(3) Olivero, S.; Clinet, J. C.; Dunach, E. *Tetrahedron Lett.* **1995**, *36*, 4429.

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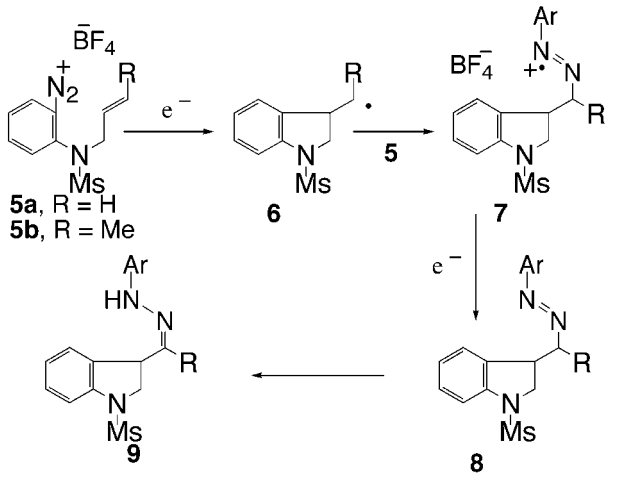
Scheme 2



conditions used and on the properties of the individual substrates, since a number of electrochemical cyclizations of aryl halides onto arenes have been reported by Grimshaw et al.[4] and by Gottlieb and Neumeyer.[5] Very recently, Munusamy et al.[6] also reported elegant work on the cathodic cyclization of iodophenyl alkylcinnamides.

In cases where difficulties occur in selectively generating the aryl radicals by electrochemical means, successful radical generation and cyclization can often be achieved in an indirect electrochemical way by using nickel or cobalt complexes to mediate the reactions.[3,7] In these cases, an added nickel or cobalt complex is reduced electrochemically in situ, and the reduced complex then carries out the desired radical-forming reaction.

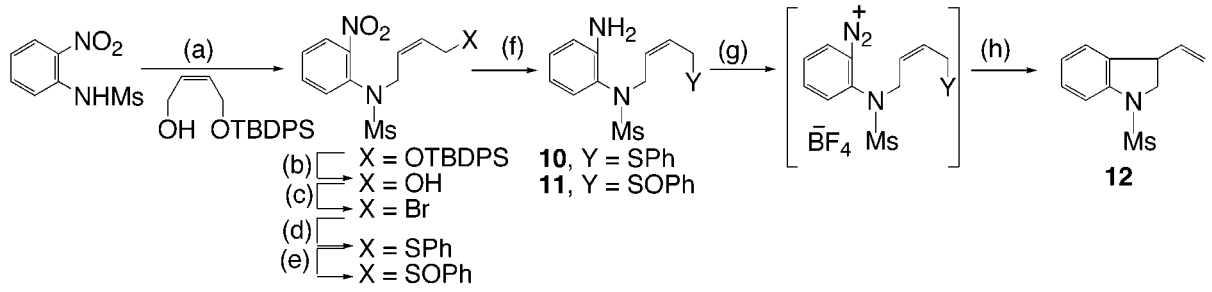
Regardless of the substrate dependencies of these reactions, electrochemical reduction of aryl halides (or of the metal mediators described above) generally occurs at a highly reductive −1.5 to −2.5 V relative to SCE. These are brutal conditions to use on sensitive substrates. By contrast, arenediazonium salts are excellent single-electron acceptors, and polarographic studies by Elofson et al.[8] Atkinson et al.,[9] and Kochi[10] have confirmed this. Therefore, in contrast to aryl halides, controlled potential reduction of arenediazonium salts should allow extremely mild and selective formation of aryl radicals for cyclization reactions. Surprisingly, the only report of electrochemical activation of a diazonium salt for cyclization relates to a Pschorr reaction[11]. Notably, electrolysis was conducted at a very mild 0 V vs SCE.

We began with a study of simple arenediazonium salts **5a** and **5b**.[12] Using a platinum cathode, the cyclic voltammogram showed the first reductive half-wave potential at −0.2V vs SCE. In the preparative experiments, maintaining the potential at −0.4V vs SCE and using a divided cell afforded a complex mixture as seen by NMR spectroscopy. From the ^{1}H NMR spectrum, it was clear that the diazonium group was no longer present. Some aryl radical cyclization had taken place, but alkene peaks remained in the crude product. The presence of alkene protons, despite the complete absence of diazonium salts, was curious. If the diazonium salt had converted to an aryl radical, a very rapid cyclization would have followed, thereby removing both groups. The data suggested that a side-reaction had consumed some of the diazonium groups. A clue came from the report by Minisci et al.[13] that carbon radicals can add efficiently to arenediazonium salts in normal (i.e., nonelectrochemical) solution; in our case, this would be a very likely reaction at the cathode because of the expected high local concentration of diazonium cations. Thus, cyclized radical **6** attacks diazonium salt **5** to afford coupled azo radical-cation **7**. Facile electrochemical reduction of **7** would yield neutral azo compound **8**; in turn, this could undergo tautomerism to afford the hydrazone **9**. (The alternate sequence of attack by cyclized radical **6** on an aryldiazo radical, may also be valid.[14])

Although it was not possible to isolate any pure compound from these experiments, the working hypothesis just discussed proved very useful in focusing on the need to terminate the cyclized radical **6** before intermolecular reaction could occur. Hence substrates **10** and **11** were synthesized bearing a sulfide and sulfoxide group, respectively (Scheme 3).

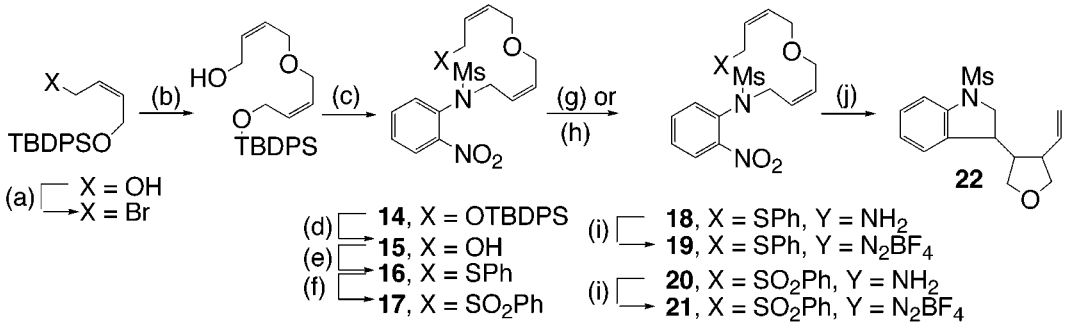
These were converted into diazonium tetrafluoroborates that were used in situ and afforded an excellent 90% of

Scheme 3[a]



[a] Reagents and conditions: (a) DEAD, PPh_3, THF, 0° to rt, 96%. (b) TBAF, THF, 95%. (c) PBr_3, THF, 0 °C to rt, 80%. (d) PhSH, NaH, THF, 98%. (e) $NaIO_4$, MeOH, H_2O, 91%. (f) $Cu(acac)_2$, $NaBH_4$, EtOH, 85% for sulfide, 65% for sulfoxide. (g) $NOBF_4$. (h) Pt cathode, −1.1 V vs SCE, 0.06−0.08 M $[ArN_2]BF_4$ in 0.1 M $NaClO_4$/DMF, reaction scale = 0.7 mmol to 1 mmol of $[ArN_2]BF_4$, 90% for sulfide, 70% for sulfoxide.

Scheme 4[a]



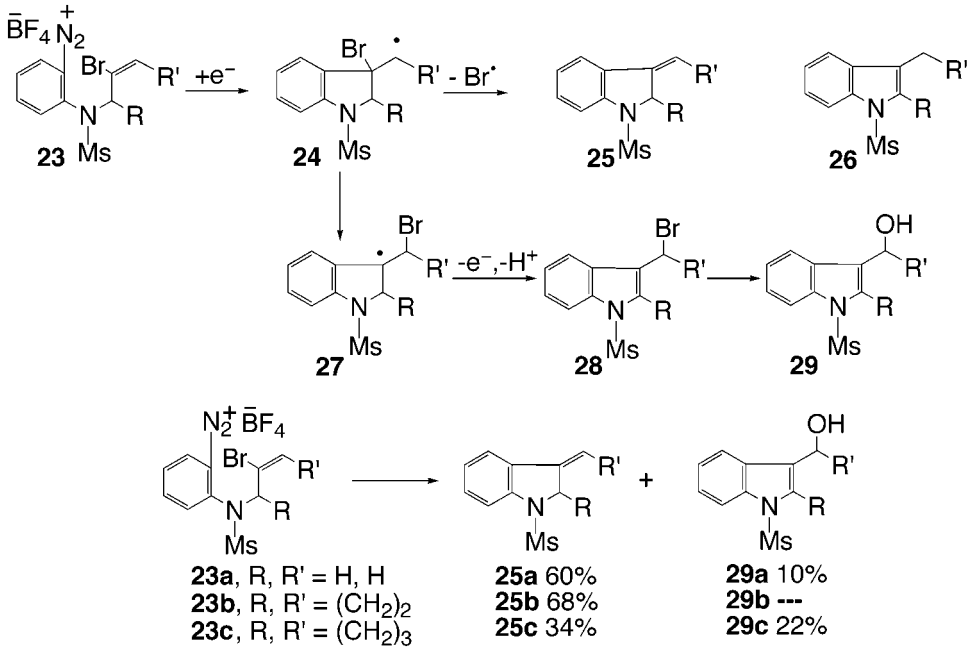
[a] Reagents and conditions: (a) NBS, Me_2S, DCM, 0 °C to rt, 95%. (b) NaH, THF, *cis*-but-2-en-1,4-diol, 0 °C to rt, 60%. (c) 2-nitrobenzenesulfonamide, DEAD, PPh_3, THF, 98%. (d) TBAF, THF, 95%. (e) NBS, Me_2S, DCM, 0 °C to rt, then NaH, PhSH, THF, 84%. (f) $NaIO_4$, 2 equiv, H_2O, MeOH, rt, 59%. (g) $SnCl_2$, MeOH, Δ, 82% for sulfide. (h) $Cu(acac)_2$, $NaBH_4$, EtOH, 89% for sulfone. (i) $NOBF_4$, DCM, −5 °C. (j) Pt cathode −1.1 V vs SCE, 0.06 M $[ArN_2]BF_4$ in 0.1 M $NaClO_4$/DMF, reaction scale = 0.1 mmol to 0.7 mmol of $[ArN_2]BF_4$, 76% from sulfide **18**, 65% from sulfone **20**.

vinylindoline **12** from the reaction of sulfide **10**, and 70% from reaction of sulfoxide **11**. (Our preparative experiments were generally conducted at −1.1V vs SCE for the convenience of achieving a rapid preparative conversion, although they could be carried out more slowly at less reducing potentials, as described above for **5a**,**b**. The first reduction potentials seen in the c.v. data for compounds **5a**,**b** were assumed to be also representative for the first reduction potentials of other diazonium salts in our work).

To test whether the electrochemistry could be applied to more complex substrates, sulfide **19** and sulfone **21** were prepared as shown in Scheme 4. The diazonium salts were again used in situ and afforded yields of 76% of **22** from the sulfide and 65% from the sulfone.

Having successfully synthesized a range of indolines, the next step was to prepare indoles using substrates **23** (Scheme 5). Cyclization of the electroreductively generated aryl radical would afford radical **24**, which should cause a rapid elimination of the bromine atom from the adjacent carbon to afford an exocyclic alkene **25**; tautomerism in the presence of a trace of acid[15] would then provide the desired indoles **26**. The substrates **23b,c** were prepared as described previously,[15] and **23a** was prepared analogously. Controlled potential electrolysis of these substrates led to rapid reaction of the diazonium salts. (Reaction scale = 0.2−0.25 mmol of $[ArN_2]BF_4$). Isolation of the products by chromatography on silica gel in each case afforded the exocyclic alkene **25** rather than the thermodynamically more stable indole **26** as

Scheme 5



the principal product. However, and intriguingly, a second product type, alcohol **29**, was also isolated from two of the substrates. The oxidized products **29a,c** are formed in the reductive cathode compartment of a divided cell. Their formation may arise by (direct or indirect) 1,2-bromine shift[15,16] from radical **24**; oxidation of the resulting benzylic radical **27** could occur by electron transfer to a diazonium cation, present in high concentration around the cathode. Proton loss then forms the bromoalkyl indole **28**, which would undergo easy hydrolysis to the observed alcohol **29**.

In summary, arenediazonium salts are easily converted to aryl radicals under controlled potential electrolysis. The aryl radicals are useful precursors of indolines, provided that an appropriate leaving group is present to preempt intermolecular reactions of intermediate radicals **6**. Phenylthio is a very useful leaving group in this context. The aryl radicals are also useful precursors of indoles. However, an unexpected reaction is frequently seen in these reactions, which may arise from initial 1,2-bromine atom shift. Investigation of alternative leaving groups is currently in progress.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra together with combustion analysis and/or high-resolution mass data on all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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