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Electrosynthesis of Substituted 1*H*-Indoles from *o*-Nitrostyrenes

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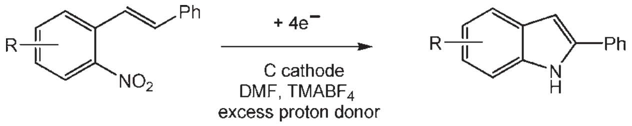
ABSTRACT



A novel procedure has been devised for the synthesis of derivatives of 1*H*-indole that is based on the direct, room-temperature electrochemical reduction of substituted *o*-nitrostyrenes at carbon cathodes in *N,N*-dimethylformamide containing tetramethylammonium tetrafluoroborate as supporting electrolyte and in the presence of a 10-fold molar excess of a proton donor (phenol or methyl 3-oxobutanoate).

Derivatives of 1*H*-indole continue to capture the attention of synthetic chemists because of the diverse uses of these substances as pharmaceutical agents. Although protocols for the synthesis of 1*H*-indoles abound in the literature, comparatively few publications have appeared that involve *o*-substituted nitro aromatic compounds as starting materials.[1] In classic work by Sundberg,[2] β-substituted *o*-nitrostyrenes were heated in boiling triethyl phosphite at 163 °C for 18 h to afford 1*H*-indoles. Metal carbonyl compounds [$Fe(CO)_5$, $Ru_3(CO)_{12}$, and $Rh_6(CO)_{16}$] under CO at 80 atm and 220 °C have been used to promote the reductive cyclization of *o*-nitrostyrenes to 1*H*-indoles.[3] Bartoli and co-workers[4,5] developed a method for the preparation of 7-substituted 1*H*-indoles that is based on the low-temperature treatment of a nitroarene with vinylmagnesium bromide. Palladium(II)-catalyzed reduction of several *o*-nitrostyrenes in the presence of carbon monoxide to afford 1*H*-indoles has been described,[6] and a review by Söderberg[7] includes a discussion of several strategies for the reductive deoxygenation of *o*-substituted nitroarenes that can be utilized to obtain 1*H*-indoles. Substituted 1*H*-indoles have been found as products of the palladium(II) trimethylbenzoate-catalyzed reductive deoxygenation of *o*-nitrostyrenes in tetrahydrofuran under CO at 30 atm.[8] Dobbs[9] demonstrated that 4-bromo-3-nitrotoluene can be employed as a starting material for the preparation of substituted 2-methyl-1*H*-indoles, and Davies and collaborators[10] converted a number of derivatives of *o*-nitrostyrene to 1*H*-indoles by means of a procedure involving the use of 0.1 mol % of palladium(II) trifluoroacetate and 0.7 mol % of 3,4,7,8-tetramethyl-1,10-phenanthroline in dimethylformamide (DMF) at 15 psig CO and 80 °C for a period of 16 h. Each of the preceding references[1−10] cites additional work dealing with *o*-nitrostyrenes as starting materials for the synthesis of 1*H*-indoles. In the arena of electrochemistry, a paper by Mishra and Mishra[11] indicates that some 1*H*-indole is produced during the constant-current electrolytic reduction of (*Z*)-1-nitro-2-(2-nitrovinyl)benzene in an aqueous mixture of acetic acid and sulfuric acid.

In a recent publication[12] from our laboratory, we reported on the room-temperature electrochemical reduction of 1-(2-haloethyl)-2-nitrobenzenes at carbon cathodes in DMF containing 0.10 M tetramethylammonium tetrafluoroborate ($TMABF_4$) as supporting electrolyte. In the absence of

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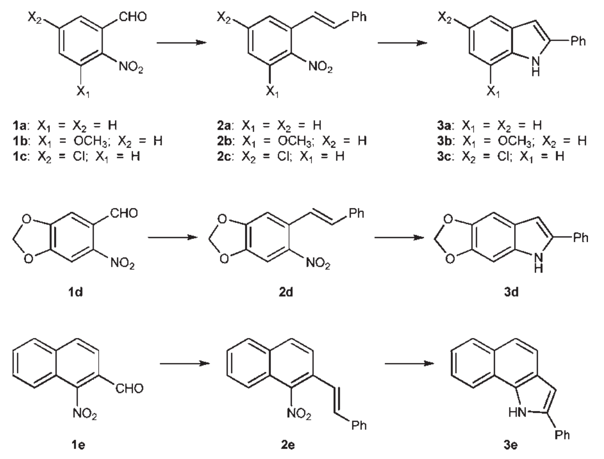

Figure 1. Structures of commercially available starting materials (**1a**–**e**), chemically synthesized *o*-nitrostyrenes (**2a**–**e**), and electrochemically produced 1*H*-indoles (**3a**–**e**).

a deliberately added proton donor (phenol or 2,4-pentanedione), the principal electrolysis product (after a conventional workup procedure) is 1-nitro-2-vinylbenzene, obtained in 70–80% yield, along with small amounts (10–15%) of 1*H*-indole and even smaller quantities (3–7%) of a dimeric species believed to be 1,1′-biindole. A far more interesting finding, however, was that direct electrolysis of 1-nitro-2-vinylbenzene *in the presence of a 5-fold excess of phenol* affords 1*H*-indole in high yield (> 80%), together with traces of 1-amino-2-vinylbenzene and the aforementioned dimer. Accordingly, we became intrigued by the possibility that the direct electroreduction of substituted *o*-nitrostyrenes in the presence of a proton donor might offer a general and straightforward approach to the synthesis of 1*H*-indole derivatives. In this communication, we present early, yet highly promising, results of an electrochemical investigation of five compounds (**2a**–**e**) shown in Figure 1 to evaluate an electrosynthetic procedure for the preparation of **3a**–**e**, respectively.

Substituted *o*-nitrostyrenes (**2a**–**e**) were prepared according to a procedure published by Davies and co-workers;[10] in particular, commercially available **1a**–**e** were each treated separately with diethyl benzylphosphonate in DMF containing sodium methoxide for a period of 14 h, followed by workup, purification, and crystallization. We confirmed the identities of **2a**–**e** with the aid of ^{1}H and ^{13}C NMR spectrometry, along with mass spectrometry, and our experimentally acquired spectral data were in excellent agreement with those reported previously; more details about these syntheses as well as spectroscopic data for each compound are available as Supporting Information. Each *o*-nitrostyrene was investigated by means of cyclic voltammetry and controlled-potential (bulk) electrolysis; information pertaining to electrodes and electrochemical cells as well as the chromatographic and spectrometric procedures for separation, identification, and quantitation of products appears elsewhere.[12]

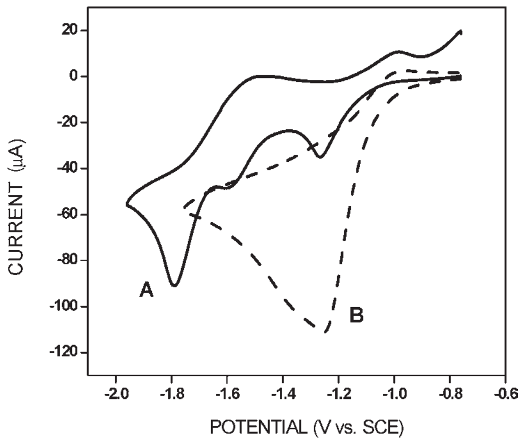

Figure 2. Cyclic voltammograms recorded at 100 mV s^{-1} for reduction of 2.0 mM solutions of **2a** at a glassy carbon electrode (area = 0.077 cm^2) in oxygen-free DMF containing 0.050 M TMABF$_4$: (A) with no phenol; (B) with 20 mM phenol. Potential scan goes from ca. −0.8 to −2.0 to −0.8 V vs SCE for curve A and from ca. −0.8 to −1.8 to −0.8 V vs SCE for curve B.

Cyclic voltammograms were recorded at a scan rate of 100 mV s^{-1} for each *o*-nitrostyrene derivative (**2a**–**e**) at a freshly polished glassy carbon electrode in oxygen-free DMF containing 0.050 M TMABF$_4$ and in the absence or presence of an excess of phenol (introduced as a proton donor). In Figure 2 are cyclic voltammograms for a 2.0 mM solution of **2a** without and with 20.0 mM phenol. Curve A of Figure 2, which depicts a cyclic voltammogram in the absence of phenol, shows three cathodic peaks with peak potentials (E_{pc}) of −1.27, −1.59, and −1.79 V vs SCE and two anodic peaks having peak potentials (E_{pa}) of −1.51 and −0.99 V vs SCE. We attribute the cathodic peak at −1.27 V and the anodic peak at −0.99 V, respectively, to the quasi-reversible one-electron reduction of the nitro group of **2a** to its radical–anion and to the subsequent oxidation of this radical–anion back to the starting material. At more negative potentials, the second redox couple (E_{pc} = −1.59 V, E_{pa} = −1.51 V) is probably associated with reversible one-electron reduction of the nitro radical–anion to the nitro dianion and then one-electron oxidation of the latter species to the radical–anion; in the presence of residual water in the solvent–supporting electrolyte, the nitro dianion can be protonated to initiate further reduction to afford a nitroso compound and eventually a hydroxylamine. All of these processes have been discussed in previous work.[12–16] Finally, we believe that the third cathodic peak at −1.79 V arises from the irreversible reduction of a substituted diphenylethene moiety.[17,18] However, future research, not

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strictly related to the direct electrosynthesis of substituted 1*H*-indoles, would be desirable to clarify these reactions.

When a proton donor (phenol or methyl 3-oxobutanoate) is added to the solution, the cyclic voltammogram changes dramatically, as shown by curve B of Figure 2. Only one very broad cathodic peak is seen at −1.25 V vs SCE, which is in accord with observations made in our earlier study.[12] It is our belief, as revealed below, that this single, large cathodic peak arises principally from the overall four-electron conversion of the *o*-nitrostyrene (**2a**) to the desired 2-phenyl-1*H*-indole (**3a**).

Compiled in Table 1 are cathodic and anodic peak potentials for all five *o*-nitrostyrenes (**2a**−**e**) in the absence of a proton donor as well as cathodic peak potentials for these compounds in the presence of a 10-fold molar excess of phenol. Although there are some differences in the various peak potentials for the five species, the essential interpretation of their electrochemical behavior is quite comparable. It is not unexpected that structural modifications for **2b**−**e** can lead to the appearance of a new voltammetric peak or to the coalescence of two voltammetric peaks.

Table 1. Cyclic Voltammetric Peak Potentials at 100 mV s^{-1} for 2.0 mM Solutions of *o*-Nitrostyrenes at a Glassy Carbon Electrode in DMF Containing 0.050 M $TMABF_4$

o-nitrostyrene	E_{pc}, V[a]	E_{pa}, V[a]	E_{pc}[b], V[a]
2a	−1.27, −1.59, −1.79	−1.51, −0.99	−1.25
2b	−1.54, −1.78	−1.42, −1.25, −0.87	−1.45
2c	−1.14, −1.54, −1.70	−1.37, −0.91	−1.18
2d	−1.25, −1.64, −1.74	−1.38, −1.04, −0.84	−1.33
2e	−1.29, −1.41, −1.68	−1.38, −1.08, −0.82	−1.30

[a] E_{pc} values are cathodic peak potentials, and E_{pa} values are anodic peak potentials with respect to the saturated calomel electrode (SCE); see Supporting Information for details about the actual reference electrode used. [b] 20 mM phenol was added to the solution.

Table 2. Coulometric Data and Product Yields for the Direct Reduction of 5.0 mM Solutions of *o*-Nitrostyrenes at a Reticulated Vitreous Carbon Cathode in DMF Containing 0.050 M $TMABF_4$ and 50 mM Phenol

o-nitrostyrene	electrolysis potential, V[a]	*n*[b]	yield of 1*H*-indole
2a	−1.31	3.92	**3a** (82%)
2b	−1.46	4.13	**3b** (67%)
2c	−1.26	4.10	**3c** (57%)
2d	−1.41	4.20	**3d** (38%)
2e	−1.41	4.20	**3e** (35%)
2e[c]	−1.41	4.20	**3e** (65%)

[a] All potentials are with respect to the saturated calomel electrode (SCE); see Supporting Information for details about the actual reference electrode used. [b] Average number of electrons required to reduce one molecule of each parent *o*-nitrostyrene derivative. [c] Methyl 3-oxobutanoate (50 mM) was used as the proton donor instead of phenol.

On the basis of previous work done with 1-nitro-2-vinylbenzene,[12] separate room-temperature controlled-potential (bulk) electrolyses of 5.0 mM solutions of **2a**−**e** in DMF containing 0.050 M $TMABF_4$ and 50.0 mM phenol were carried out at reticulated vitreous carbon cathodes. We determined the potential needed for each bulk electrolysis by inspecting a cyclic voltammogram for a 2.0 mM solution of each compound in DMF−0.050 M $TMABF_4$ containing 20.0 mM phenol. For example, to carry out the electrolysis of **2a**, the potential chosen from curve B of Figure 2 was −1.31 V vs SCE (Table 2), which is just slightly more negative than the value for E_{pc} (−1.25 V vs SCE) listed in Table 1. Potentials for the electrochemical reductions of **2b**−**e** were similarly selected, as a comparison of data in Tables 1 and 2 reveals. Choosing a potential more positive than E_{pc} will prolong the electrolysis (and may lead to extraneous products), whereas a potential that is significantly more negative than E_{pc} will induce the formation of products (*e.g.*, amines) that are more extensively reduced than the desired 1*H*-indoles. Moreover, at more negative potentials, it is possible that the proton donor itself will undergo some reduction, forming hydrogen gas and competing with direct electrolysis of the chosen *o*-nitrostyrene.

Table 2 summarizes the coulometric data along with yields of the 1*H*-indole derivatives (**3a**−**e**) for at least duplicate electrolyses of each *o*-nitrostyrene; the *n* values indicate the average number of electrons required to reduce each molecule of *o*-nitrostyrene, and the product yield is the percentage of the *o*-nitrostyrene derivative incorporated into each of the 1*H*-indoles (as determined by means of gas chromatography, with a known quantity of an electroinactive internal standard, *n*-dodecane, being added to each solution prior to an electrolysis).[19] At the end of each experiment, none of the starting material remained unreduced. As revealed in Table 2, an interesting observation is that the use of methyl 3-oxobutanoate, which is more acidic than phenol, raised the yield of **3e** from 35% to 65%; in a DMF medium, the pK_a values for phenol and methyl 3-oxobutanoate are close to 18.9 and 15.2, respectively.[20,21] In preliminary experiments a near doubling of the yield of **3d** has been obtained when phenol is replaced by methyl 3-oxobutanoate. Thus, the use of even more potent proton donors should be a fruitful avenue for future exploration. We have begun to explore a larger set of more potent proton donors, including acetic acid ($pK_a^{DMF} = 13.4$) and benzoic acid ($pK_a^{DMF} = 12.1$). Changing the proton donor has little effect on the value of E_{pc} for the single cathodic peak that is governed essentially by reduction of the nitro group, but we have not yet assessed whether these better proton donors affect the yields of 1*H*-indoles.

It should be noted that the coulometric *n* values reported in Table 2 are essentially 4, an observation in accord with the postulate, as articulated by Söderberg,[7] that a nitrene intermediate might be involved in the reductive conversion of *o*-nitrostyrenes to 1*H*-indoles. Finally, **3b** is difficult to isolate in pure form, as discussed in the Supporting Information.

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In conclusion, we are strongly encouraged by the discovery that 1*H*-indoles can be electrosynthesized from *o*-nitrostyrenes in moderate to good yields at room temperature in a relatively short time (40 min) and without the use of harsh reagents or conditions. In future work, we plan to explore how different proton donors and other solvents affect the electrosynthesis of 1*H*-indoles via the reduction of *o*-nitrostyrenes; we are already aware of the facts that the identity of the proton donor and the choice of electrolysis potential influence the yields of 1*H*-indoles. Efforts will be directed to expand the molecular complexity of *o*-nitrostyrenes that can be subjected to electrochemical reduction, and there is the possibility that electrogenerated catalysts can be used to carry out the indirect reduction of *o*-nitrostyrenes to 1*H*-indoles. In addition, a single-pass, flow-through electrochemical reactor has been constructed that features a large reticulated vitreous carbon rod with a surface area of approximately 2 m^2 (100 times greater than the areas of cathodes employed in the present investigation); using this reactor, we hope to electrosynthesize 1*H*-indoles in gram quantities.

Supporting Information Available. Experimental procedures as well as ^1H and ^{13}C NMR, GC–MS, and HRMS data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.