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Electroreductive heterocyclization of *ortho*-piperidino substituted nitro(het)arenes

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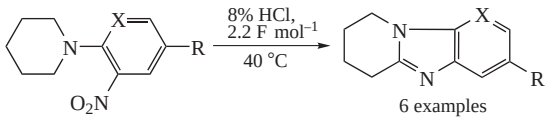
Electrochemical reduction of *ortho*-piperidino substituted nitro(het)arenes in an undivided cell on a lead cathode in 8% HCl gave either 1,2,3,4-tetrahydropyrido[1,2-*a*]-benzimidazoles or 6,7,8,9-tetrahydropyrido[3′,2′:4,5]-imidazo[1,2-*a*]pyridines. The reductive heterocyclization mechanism involves the initial formation of a nitroso derivative followed by the formation of an imidazole ring.



Keywords: nitroarenes, piperidines, pyrido[1,2-*a*]benzimidazoles, pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines, electrochemical reduction, heterocyclization, cyclic voltammetry.

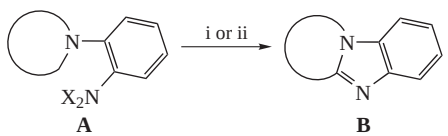
Benzimidazole derivatives containing saturated heterocycles annulated to an imidazole ring are widely used in the development of new efficient drugs.[1–5] Quinones based on 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole exhibit high antitumor activity,[4–7] for example, 1,2,3,4-tetrahydropyrido-[1,2-*a*]benzimidazole-6,9-dione is 300 times more cytotoxic toward hypoxic cancer cells of human skin than Mitomycin C, a clinically used drug.[5]

Numerous methods for synthesizing heterocyclic compounds with similar structures are known.[8–13] Noteworthy is the C–N heterocyclization of *N*-[*o*-nitro(amino)aryl] substituted pyrrolidines, piperidines, and similar compounds **A** (Scheme 1).[4,14–24] It is important that a CH_2 group adjacent to the nitrogen atom participates in the process, and in products **B** it is converted into amidine carbon atom.

The use of a nitro substrate (X=O) is preferable. A variety of starting compounds can be easily obtained by S_NAr reactions from available *o*-halonitroarenes and secondary cyclic amines. The formation of an imidazole ring occurs under mild conditions in one stage that involves a cascade of reactions, including the nitro group reduction and cyclization. Various reducing agents are used for this purpose, such as metal salts,[18,19] carbon monoxide,[20] molecular hydrogen[21] or molecular iodine.[22] The highest yield of cyclization products was observed in the reduction of *N*-(2-nitroaryl)hetarenes in 36% HCl at 80 °C with Ti^{3+} and Sn^{2+} chlorides that were gradually added over 1 h to the reaction mixture.[18,19] Despite the high yield, the isolation the reaction product is difficult, and disposal or regeneration of the reducing agent is required.

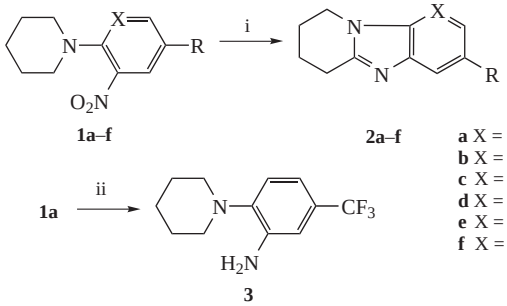
The use of electrochemical reduction for intramolecular heterocyclization provides an efficient solution to these problems.[25–30] The difficulty in applying this synthetic approach stems from the fact that the reductive cyclization of *N*-(2-nitroaryl)hetarenes most likely occurs through the stage of nitroso compounds[18,22] that are not typical of the electrochemical reduction of nitroarenes in protic media.[31] At the same time, hydroxylamino derivatives were postulated as process intermediates.[21]

In this work, we studied the main features of the electroreduction of *N*-[2-nitro(het)aryl]hetarenes. The electrolysis was carried out in a cylindrical undivided cell, which provides a number of advantages,[29,30] in galvanostatic mode with vigorous magnetic stirring. The conditions for the electrosynthesis of 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazoles were selected using *N*-[2-nitro-4-(trifluoromethyl)phenyl]piperidine **1a** as the model compound (Scheme 2). Lead was used as the cathode



A **B**

Scheme 1 *Reagents and conditions:* i, X = H, oxidation[4,14–17]; ii, X = O, reduction.[18–24]



1a–f **2a–f** **3**

a X = CH, R = CF_3
b X = CH, R = H
c X = CH, R = CN
d X = CH, R = Cl
e X = CH, R = NO_2
f X = N, R = H

Scheme 2 *Reagents and conditions*: i, HCl (8%), 40 °C, Pb cathode, 2.2 F mol^{-1}; ii, HCl (36%), 80 °C, Pd cathode, 6.0 F mol^{-1}.

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material since it proved efficient in the reductive cyclization of *N*-(2-nitroaryl)pyridinium salts.[26,27] A graphite plate served as the anode.

In our experiments, electroreduction of **1a** was performed in 36% HCl at 80 °C and at a current density of 50 mA cm^{-2}. After passing 2 F mol^{-1} of electricity (as calculated to obtain a nitroso compound), the presence of a nitro substrate in the reaction mixture was detected polarographically. It was completely consumed upon passing additional 2 F mol^{-1} of electricity. 7-Trifluoromethyl-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole **2a** and 2-(piperidin-1-yl)-5-(trifluoromethyl)aniline **3** (see Scheme 2) were isolated from the reaction mixture. Varying the current density did not allow us to obtain individual compound **2a** since it was always contaminated with much aniline **3**. Apparently, in strongly protogenic environments a competition between cyclization and reduction of the intermediate would occur. Therefore, a number of experiments were conducted to study the effect of HCl concentration on the reaction outcome (see Online Supplementary Materials, Table S1). Less amine **3** was formed upon passage of 2.2 F mol^{-1} of electricity through a solution of **1a** in 8% HCl. The solubility of the nitro substrate decreased in 4% HCl, and therefore the undissolved portion remained intact. Electrolysis was carried out in the temperature range of 20–80 °C. The highest yield of **2a** and minimum of side products were achieved at 40 °C in 8% HCl and at current density of 25 mA cm^{-2}.

These conditions were applied to the syntheses of 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazoles **2a–e** and 6,7,8,9-tetrahydropyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridine **2f** (see Scheme 2), with the yields of cyclization products having been 91–97%. Amino product **3**, which is a precursor of the antileukemic compound SRPIN340,[32] was synthesized in individual form in 94% yield by six-electron reduction of **1a** at 80 °C in 36% HCl at a current density of 50 mA cm^{-2}.

The high yield of amine **3** (94%) and cyclization products **2a–f** upon passage of a nearly theoretical amount of electric current indicates that anodic oxidation of the electrolyte that could lead to chlorination products did not practically occur. This can be explained by the fact that the reduction of substrate **1** proceeds at low potentials (–375 mV), whereas oxidation of chloride ions into dichlorine should occur at larger potentials of > 1200 mV.

The formation of fused products **2a–f** upon passage of 2.2 F mol^{-1} of electricity could mean that cyclization occurred at the stage of reduction of the nitro group to a nitroso group. An alternative mechanism for the formation of products **2** may assume the reduction of the nitro group to a hydroxylamino one followed by intramolecular cyclization to afford 1,2,3,4,4a,5-hexahydropyrido[1,2-*a*]benzimidazole. Its further oxidation with another molecule of the nitro compound results in 1,2,3,4-tetrahydro analogue and a nitroso compound. The latter would add two electrons to give hydroxylaminoarene, which undergoes cyclization and oxidation. In this way, the process occurs until the nitro substrate is consumed completely. Importantly, this path would require the same amount of electricity.

To prove the nitro group reduction step where the cyclization product is formed, we used cyclic voltammetry (see Online Supplementary Materials) to study the mechanism of **1a** electroreduction and the electrochemical behavior of the possible products of its reduction, *i.e.*, fused heterocycle **2a** and the corresponding amino compound **3**. The curves obtained in 8% HCl are presented in Figure 1.

One can see that compound **1a** is reduced easily at –375 mV (curve *1*). The current of this peak corresponds to the two-electron level matching the formation of a nitroso compound that undergoes heterocyclization. There are no other peaks in the

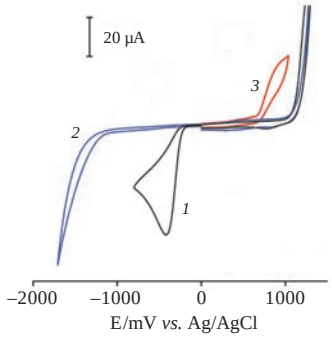

Figure 1 Cyclic voltammetric curves of (*1*) nitro compound **1a**, (*2*) a product of its reductive heterocyclization **2a** and (*3*) amino derivative **3**; 5×10^{-3} M in 8% HCl, glassy carbon working electrode (d = 1.7 mm), potential sweep rate of 100 mV s^{-1}, T = 298 K.

entire potential region available under these conditions. The heterocyclization product **2** is electrochemically inactive and there are no reduction or oxidation signals on its voltammetric curves (see Figure 1, curve *2*). This indicates that it is formed upon the electroreduction of **1** whose curve does not contain peaks of any products, either. On the other hand, the product of possible exhaustive six-electron reduction, amine **3**, is electrochemically active and its oxidation corresponds to the peak at ~850 mV (curve *3*). The absence of this signal on the curve of **1a** electroreduction indicates that compound **3** is not formed in this process. Also, the curve of **1a** does not contain peaks at smaller potentials that could be attributed to the oxidation of the four-electron reduction product, the hydroxylamino derivative, which is characterized by thermodynamically easier oxidation compared to the corresponding amines.[33,34]

Thus, the two-electron current level of the reduction peak of the nitro compound corresponds to the formation of a nitroso compound rather than other possible products, *viz.*, a hydroxylamino derivative (a four-electron product) or an amino derivative (a six-electron product). This confirms that the heterocyclization process includes the initial formation of a nitroso derivative followed by the formation of a ring. The unusual completion of the electrochemical reduction of the nitroaromatic compound at the stage of a nitroso derivative, though such derivatives generally tend to be reduced at smaller potentials than a substrate and undergo subsequent reduction reactions,[35,36] can be explained by the fact that under these sufficiently acidic conditions, the nitro derivative is in a more easily reducible protonated form, while the less basic nitroso derivative is not protonated.

The structures of 7-trifluoromethyl-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole **2a** (Figure 2) and 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole-7-carbonitrile **2c** (Figure 3) were established by single crystal X-ray diffraction analysis.[†] All the carbon and nitrogen atoms in both molecules, except for C(2) and C(3), lie in the same plane. Each of the fluorine atoms of the trifluoromethyl group in **2a** is disordered over four positions due

[†] X-Ray diffraction data were collected at 100 K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator, shutterless φ- and ω-scan technique), using MoKα-radiation (0.71073 Å). The intensity data were integrated by the SAINT program[37] and corrected for absorption and decay using SADABS.[38] The structure was solved by direct methods using SHELXT[39] and refined on F^2 using SHELXL-2018.[40] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were found from the electron density-difference map, but placed geometrically and refined as riding atoms with relative isotropic displacement parameters. The SHELXTL program suite was used for molecular graphics.

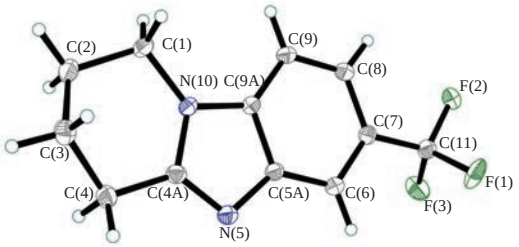

Figure 2 Molecular structure of **2a** (p = 50%). The disordering of the CF_3 group is not shown.

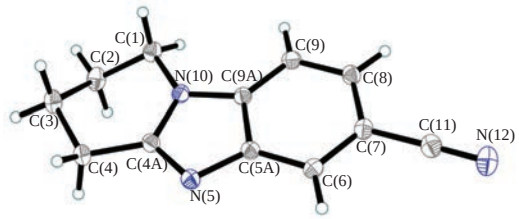

Figure 3 Molecular structure of **2c** (p = 50%). The disordering of the C(2) and C(3) atoms is not shown.

to rotation around a single bond. The $(CH_2)_4$ moiety in **2c** demonstrates conformational rigidity: the C(2) and C(3) atoms are disordered over two positions (see Online Supplementary Materials).

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.027.

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Crystal data for **2a**. $C_{12}H_{11}F_3N_2$, M = 240.23, triclinic, space group $P\bar{1}$, a = 6.2608(2), b = 8.2336(3) and c = 10.2971(4) Å, α = 85.4144(10)°, β = 89.7475(10)°, γ = 79.8077(10)°, V = 520.73(3) Å^3, Z = 2, d_{calc} = = 1.532 g cm^{-3}, $F(000)$ = 248, μ(MoKα) = 0.130 mm^{-1}, θ_{min} = 1.98°, θ_{max} = 32.03°, 22692 reflections measured, 3618 independent reflections (R_{int} = 0.0392), R_1 = 0.0467, wR_2 = 0.1071 for 2939 reflections with $I > 2\sigma(I)$; R_1 = 0.0618, wR_2 = 0.1183 for all data, 181 parameters and 84 restraints, GOF = 1.040, ρ_{max} / ρ_{min} = 0.431 / –0.353 e Å^{-3}.

Crystal data for **2c**. $C_{12}H_{11}N_3$, M = 197.24, orthorhombic, space group *Pbca*, a = 7.1674(2), b = 11.8345(4) and c = 22.7718(8) Å, V = = 1931.56(11) Å^3, Z = 8, d_{calc} = 1.356 g cm^{-3}, $F(000)$ = 832, μ(MoKα) = 0.084 mm^{-1}, θ_{min} = 3.36°, θ_{max} = 31.25°, 49378 reflections measured, 3144 independent reflections (R_{int} = 0.0672), R_1 = 0.0467, wR_2 = 0.1096 for 2504 reflections with $I > 2\sigma(I)$; R_1 = 0.0640, wR_2 = = 0.1234 for all data, 155 parameters and 3 restraints, GOF = 1.033, ρ_{max} / ρ_{min} = 0.336 / –0.242 e Å^{-3}.

CCDC 1991687 and 1991688 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

See Online Supplementary Materials for geometric parameters and refinement details.

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