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Synthesis of pyrido[1,2-*a*]benzimidazoles by electroreductive heterocyclization of 1-(2-nitroaryl)pyridinium chlorides

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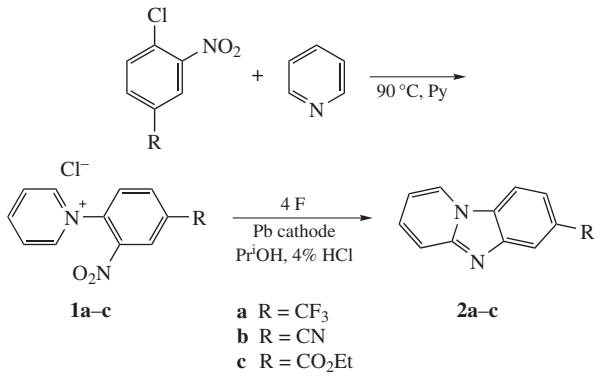
The electrochemical reduction of *N*-(2-nitro-4-R-phenyl)pyridinium chlorides (R = CF_3, CN, CO_2Et) at a lead cathode in HCl/Pr^iOH/H_2O affords the corresponding 7-R-pyrido[1,2-*a*]benzimidazoles in 70–94% yields.

The development of novel methods for the synthesis of substituted pyrido[1,2-*a*]benzimidazoles is topical[1–6] since they are of interest, *e.g.*, as DNA intercalators,[4] antibacterial, antifungal, antitumor and antiviral drugs.[1–3] Since *N*-(2-nitrophenyl)pyridinium chlorides can be readily obtained from pyridines and the corresponding *o*-nitrochlorobenzenes, they were transformed into pyrido[1,2-*a*]benzimidazoles by their reductive heterocyclization, in particular, by the action of tin(II) chloride,[7–10] phenylhydrazine, or by catalytic hydrogenation.[11] It is assumed[12] that the mechanism of these transformations includes the reduction of the nitro group into hydroxyamino one followed by heterocyclization. Since *N*-arylhydroxylamines are typical products of electrochemical reduction of nitroaromatic compounds in protic media,[13] it could be assumed that the electrolysis of *N*-(2-nitrophenyl)pyridinium chlorides would be accompanied by the formation of pyrido[1,2-*a*]benzimidazoles.

N-(2-Nitrophenyl)pyridinium chlorides containing trifluoromethyl (**1a**), nitrile (**1b**) or ethoxycarbonyl (**1c**) substituents in the *para*-position of the benzene ring were prepared by heating of the corresponding *o*-nitrochloro derivatives in pyridine (Scheme 1).†

In literature,[12] the best yields of **1** → **2** transformation (see Scheme 1) were achieved when the $SnCl_2$-assisted heterocyclization was carried out in mixtures of alcohols (MeOH, EtOH, Pr^iOH) and dilute (2–6%) HCl on gentle (~40 °C) heating. Similar conditions are often used for the electroreduction of nitroaromatic compounds,[13] when hydrochloric acid simultaneously provides electroconductivity of the solution and serves as a proton donor. Therefore, for electroreduction of **1a–c**, a mixture of isopropanol and 4% hydrochloric acid (1 : 1) was of choice. Lead was used as a cathode, since it is one of the most suitable materials for transformations of this type, in particular, having a high overvoltage of hydrogen.[13] Electrolysis was carried out in a galvanostatic mode in a divided cell.‡ The point of exhaustive electrolysis was the beginning of intense hydrogen evolution, which occurred on passing of 4 F electricity. Then, the catholyte was treated with a 25% ammonia solution to neutral pH and extracted with chloroform. The corresponding pyrido[1,2-*a*]benzimidazoles **2a–c** were obtained in high (70–94%) yields‡ (see Scheme 1).



Scheme 1

† *Synthesis of* N-*(2-nitrophenyl)pyridinium chlorides* **1a–c**. 2-Nitro-4-R-chlorobenzene (0.022 mol) was added to pyridine (0.154 mol), and the mixture was stirred at 90 °C for 1 h. The precipitate formed was filtered off and washed with acetone (30 ml).

For **1a**: yield 98%; mp 260–262 °C. ^{1}H NMR (300 MHz, D_2O) δ: 9.09 (d, 2H), 8.90 (s, 1H), 8.87 (t, 1H), 8.41 (d, 1H), 8.31 (t, 2H), 8.09 (d, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 148.88, 145.45, 137.35, 133.26, 130.38, 128.37, 124.85. HRMS, *m/z*: 269.0543 $[M]^+$ (calc. for $C_{12}H_8F_3N_2O_2$: 269.0532).

For **1b**: yield 99%; mp 263–265 °C. ^{1}H NMR (300 MHz, D_2O) δ: 9.10 (d, 2H), 8.99 (s, 1H), 8.88 (t, 1H), 8.46 (d, 1H), 8.32 (t, 2H), 8.09 (d, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 215.33, 149.05, 145.36, 139.92, 131.23, 130.39, 128.41, 116.91, 115.86, 30.23. HRMS, *m/z*: 226.0626 $[M]^+$ (calc. for $C_{12}H_8N_3O_2$: 226.0611).

For **1c**: yield 87%; mp 191–193 °C. ^{1}H NMR (300 MHz, D_2O) δ: 9.10 (d, 2H), 9.02 (s, 1H), 8.86 (t, 1H), 8.62 (d, 1H), 8.30 (t, 2H), 8.01 (d, 1H), 4.47 (q, 2H), 1.40 (t, 3H). ^{13}C NMR (75 MHz, D_2O) δ: 164.99, 148.73, 145.41, 137.72, 136.49, 135.04, 129.73, 128.31, 127.71, 63.52, 13.31. HRMS, *m/z*: 273.0878 $[M]^+$ (calc. for $C_{14}H_{13}N_2O_4$: 273.0870).

‡ A B-5-71/1 power source (Profigrupp, St. Petersburg, Russia) was used. Cathode was a lead plate with a surface area of 50 cm^2. In a typical experiment, a substrate (1 g) was taken, the catholyte was a mixture of isopropanol (40 ml) and 4% HCl (aq., 40 ml). Anolyte was 15% H_2SO_4. Anode was a platinum mesh. Electrolysis was carried out at I = 0.2 A and 40–45 °C.

For **2a**: yield 94%; mp 233–235 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, 1H), 8.20 (s, 1H), 7.98 (d, 1H), 7.76 (d, 1H), 7.60 (d, 1H), 7.53 (t, 1H), 6.96 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.29, 142.75, 131.17, 130.23, 128.63, 128.20, 126.32, 125.57, 117.99, 117.31, 111.82, 111.33. HRMS, *m/z*: 237.0637 $[M + H]^+$ (calc. for $C_{12}H_8F_3N_2$: 237.0634).

For **2b**: yield 70%; mp 242–244 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.56 (d, 1H), 8.08 (s, 1H), 8.00 (d, 1H), 7.62 (d, 1H), 7.49 (d, 1H), 7.45 (t, 1H), 6.90 (t, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.02, 140.52, 132.02, 130.02, 126.17, 123.31, 122.51, 118.26, 116.08, 112.48, 111.88, 108.40. HRMS, *m/z*: 194.0713 $[M + H]^+$ (calc. for $C_{12}H_8N_3$: 194.0713).

For **2c**: yield 74%; mp 179–182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.65 (s, 1H), 8.50 (d, 1H), 8.08 (d, 1H), 7.93 (d, 1H), 7.76 (d, 1H), 7.51 (t, 1H), 6.94 (t, 1H), 4.45 (q, 2H), 1.45 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.75, 149.18, 142.97, 131.22, 130.75, 128.44, 125.59, 122.54, 121.86, 118.05, 111.56, 110.45, 61.27, 14.43. HRMS, *m/z*: 241.0974 $[M + H]^+$ (calc. for $C_{14}H_{13}N_2O_2$: 241.0972).

The herein developed protocol for the synthesis of pyrido-[1,2-*a*]benzimidazoles is characterized by simple processing and control, therefore our results can stimulate its further use for the synthesis of this type of compounds.

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