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Electrochemical transformation of 4-cyanocinnolines into 4(1*H*)-cinnolones

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Abstract

Electrochemical transformation of 4-cyanocinnolines into 4(1*H*)-cinnolones has been achieved, for the first time, in 70∼100% yield.

Keywords: cyano compounds; electrochemical reaction; nitrogen heterocycles.

Recent interest in the molecular functions of cinnolines has been focused on their biological activity and functions.[1,2] To clarify their structure–activity relationship, it should be necessary to develop new methods for synthesis and functional group transformation which provide various kinds of cinnolines. Very recently, we reported a versatile, single-step synthesis of cyanocinnolines from aromatic hydrazones and TCNE.[3] Among the possible functional group transformation of cyanocinnolines, we were interested in the behavior of 4-cyanocinnolines (**1**) toward electrochemical reduction.

Electrode reaction of cinnolines in acidic media is reported to give indole derivatives via the 1,4-dihydro derivatives.[4] Electrochemical reduction of cyanopyridines having the same structural moiety as **1** in alkaline media is known to afford pyridine and cyanide ion by C–CN bond fission.[5]

In marked contrast to these examples, we report here that cyanocinnolines (**1**) can be selectively converted into 4(1*H*)-cinnolones by electrochemical reduction (electrode: Pt). The reaction of **1a**–**f** (which were prepared according to our method[3]) was conducted at ambient temperature for 2 h under constant voltage (−8 V) in benzonitrile in the presence of O_2 and H_2O. Workup gave **2a**–**f** in good to high yields.[6] In the absence of O_2 and H_2O, formation of **2a**–**f** was not observed.

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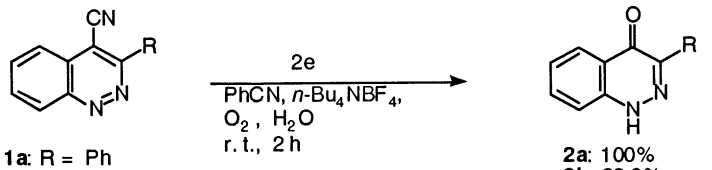
Benzonitrile as solvent and n-Bu_4NBF_4 as supporting electrolyte were the best choice for the synthetic purpose.

When acetonitrile was used instead of benzonitrile, the yield of cinnolones decreased in 30∼40%, and formation of cinnoline-4-carboxylic acid amides (CN→$CONH_2$) was observed.

As exemplified below, the transformation is general for cyanocinnolines, and occurs efficiently irrespective of kind of substituent (R).



1a: R = Ph
1b: R = *p*-Cl-C_6H_4
1c: R = *p*-CH_3O-C_6H_4
1d: R = 2-Naphthyl
1e: R = $PhCH_2CH_2$
1f: R = $CH_3(CH_2)_3$

2a: 100%
2b: 82.0%
2c: 71.5%
2d: 73.5%
2e: 80.9%
2f: 84.0%

Cyclic voltammograms of **1**, O_2, and O_2+**1** in PhCN are considered to be useful for disclosing the initial step of the reaction. As shown in Fig. 1(A), the cyclic voltammogram of **1a** demonstrates only one reversible one electron reduction wave.[7] The cyclic voltammogram of O_2 shows also one reversible wave (Fig. 1(B)). On the contrary, the cyclic voltammogram of an O_2-saturated PhCN solution of **1a** shows an irreversible wave of **1a**, where the cathodic peak corresponding to **1a**→**1a**$^{-\bullet}$ is shifted to cathodic side by 0.13 V, presumably because of complex formation with O_2, and the anodic peak corresponding to **1a**$^{-\bullet}$→**1a** disappears. No reduction wave of O_2 is observed. These data indicate the initial step of the reaction to be the formation **1a**$^{-\bullet}$, followed by its reaction of O_2.

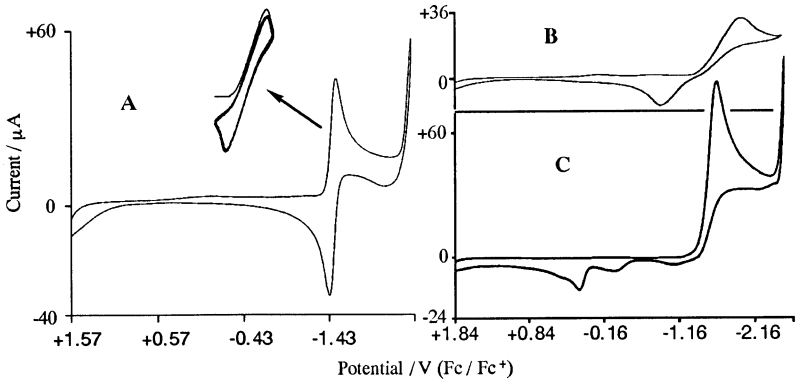
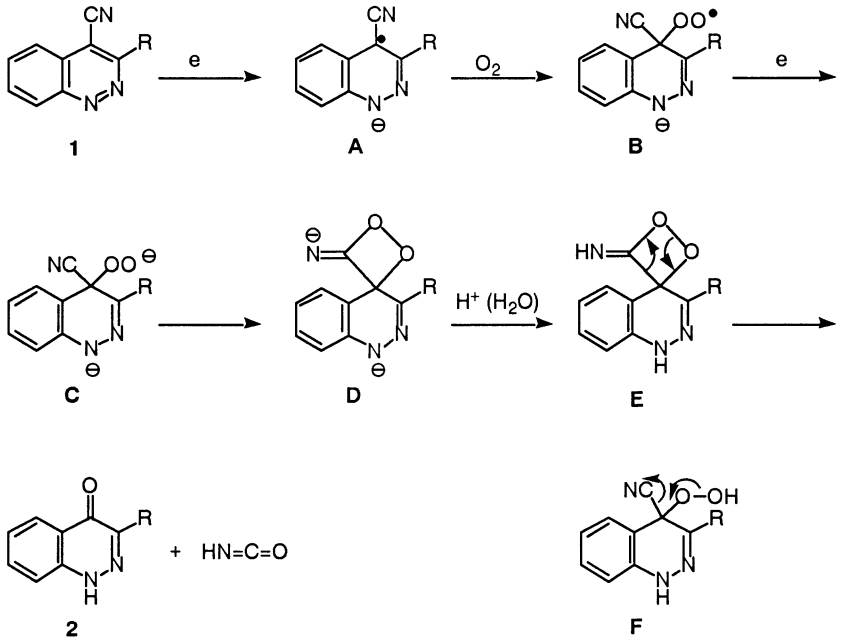


Figure 1. Cyclic voltammograms of **1a** (A), O_2 (B), and **1a**+O_2 (C). Potentials were measured in benzonitrile at 25°C with a scan rate 100 mV s^{-1} using Pt electrode. An Ag/AgCl electrode was used as a reference electrode, and ferrocene was added as an internal reference. n-Bu_4NBF_4 was added as a supporting electrolyte

HPLC and TLC monitoring of the reaction demonstrated 1,4-dihydro derivatives of **1** not to be detected. In the presence of methanol the reaction provided methylcarbamate besides **2**, indicating the formation of isocyanic acid (HNCO).

Thus the transformation of **1** into **2** is considered to proceed according to the following scheme.



It is certain that the reaction proceeds via an intermediate **C**, because we observe that the reaction of **1a** with Na_2O_2 in the presence of 18-crown-6 in PhCN gives **2a** exclusively.

As for the final step leading to **2a**, a concerted ring fission of the dioxetane type intermediate **E** is more conceivable than a nonconcerted decomposition of the noncyclic intermediate **F** (protonated **C**) judging from (1) nature of the both processes; (2) detection of isocyanic acid during the reaction, and (3) large strain energy difference (**E**>**F**, 28 kcal/mol) between both structural isomers, **E** and **F**, which have small heat of formation differences (**E**>**F**, 9 kcal/mol).[12]

Since the electrochemical transformation of **1** into **2** is a safety reaction compared with chemical transformation using Na_2O_2, and proceeds efficiently under mild conditions, this reaction could be useful as a new tool for 4(1*H*)-cinnolone synthesis.[13]

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6. Into a cathodic chamber of an electrolysis cell equipped with a platinum cathode (2×2 cm) was added a solution of **1a** (1 mmol) in benzonitrile (30 ml) containing *n*-Bu_4NBF_4 (0.5 g) as supporting electrolyte. The anodic solution was 10 ml of benzonitrile containing *n*-Bu_4NBF_4 (0.5 g), and a platinum anode (2×2 cm) was used. The electroreduction was carried out under constant voltage conditions (−8 V) at room temperature in the presence of O_2 and H_2O. After 2 h, the reaction mixture was evaporated under reduced pressure. The residue was purified by recrystallization from methanol to give **2a** in quantitative yield, pale orange crystals, mp 268–270.5°C (lit.[8] 268–270°C); IR (KBr, cm^{-1}) 2893, 1549; ^1H NMR (DMSO-d_6) δ 13.64 (s, 1H), 8.15 (d, 1H), 8.08 (d, 2H), 7.78 (dd, 1H), 7.63 (d, 1H), 7.43 (d, 2H), 7.42 (dd, 1H), 7.41 (m, 1H); HRMS found: *m*/*z* 222.0758, calcd for $C_{14}H_{10}N_2O$ 222.0793. Further reaction of **2a** (known compound) with methyl iodide in the presence of potassium hydroxide led to 1-methyl-3-phenyl-4(1*H*)-cinnolone (isolated yield 90%), pale orange crystals, mp 106.5–110.5°C (lit.[9] 107–108°C); HRMS found: *m*/*z* 236.0931, calcd for $C_{15}H_{12}N_2O$ 236.0950. **2b** (known compound): white crystals, yield 82.0%; mp 328–330°C (lit.[8] 329–330°C); FT-IR (KBr pellet, cm^{-1}) 2894, 1546; ^1H NMR (DMSO-d_6) δ 13.79 (s, 1H), 8.16 (d, 1H), 8.15 (d, 2H), 7.80 (dd, 1H), 7.64 (d, 1H), 7.50 (d, 2H), 7.45 (dd, 1H); HRMS found: *m*/*z* 256.0396, calcd for $C_{14}H_9ClN_2O$ 256.0403. **2c** (new compound): pale orange crystals, yield 71.5%; mp 266.5–268°C; FT-IR (KBr pellet, cm^{-1}) 2834, 1542; ^1H NMR (DMSO-d_6) δ 13.61 (s, 1H), 8.13 (d, 1H), 8.09 (d, 2H), 7.77 (dd, 1H), 7.61 (d, 1H), 7.41 (dd, 1H), 7.00 (d, 2H), 3.80 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.25, 159.49, 145.08, 140.69, 133.51, 129.59, 127.38, 124.66, 123.19, 116.42, 113.27, 109.02, 55.16; HRMS found: *m*/*z* 252.0877, calcd for $C_{15}H_{12}N_2O_2$ 252.0899. **2d** (new compound): pale orange crystals, yield 73.5%; mp 299–301°C; FT-IR (KBr pellet, cm^{-1}) 2920, 1544; ^1H NMR (DMSO-d_6) δ 13.86 (s, 1H), 8.87 (s, 1H), 8.20 (d, 1H), 8.17 (d, 1H), 7.99 (d, 1H), 7.97 (d, 1H), 7.93 (d, 1H), 7.82 (dd, 1H), 7.67 (d, 1H), 7.57–7.52 (m, 2H), 7.47 (dd, 1H); ^{13}C NMR (DMSO-d_6) δ 169.42, 144.93, 140.71, 133.50, 132.76, 132.63, 132.42, 128.40, 127.71, 127.35, 127.07, 126.37, 126.08, 125.60, 124.82, 124.63, 123.59, 116.47; HRMS found: *m*/*z* 272.0921, calcd for $C_{18}H_{12}N_2O$ 272.0950. **2e** (new compound): pale yellow crystals, yield 80.9%; mp 210.5–212.0°C; FT-IR (KBr pellet, cm^{-1}) 2882, 1542; ^1H NMR (DMSO-d_6) δ 13.28 (s, 1H), 8.04 (d, 1H), 7.73 (dd, 1H), 7.53 (d, 1H), 7.37 (dd, 1H), 7.23 (s, 5H); ^{13}C NMR (DMSO-d_6) δ 169.57, 149.63, 141.62, 141.11, 133.42, 128.30, 128.26, 125.79, 124.18, 124.09, 121.22, 116.17, 32.44, 31.53; HRMS found: *m*/*z* 250.1124, calcd for $C_{18}H_{12}N_2O$ 250.1106. **2f** (known compound): pale yellow crystals, yield 84.0%; mp 178.5–180°C (lit.[10] 178–180°C); FT-IR (KBr pellet, cm^{-1}) 2868, 1548; ^1H NMR (DMSO-d_6) δ 13.20 (s, 1H), 8.01 (d, 1H), 7.72 (dd, 1H), 7.52 (d, 1H), 7.34 (dd, 1H), 2.68 (t, 2H), 1.59 (m, 2H), 1.33 (m, 2H), 0.89 (t, 3H); HRMS found: *m*/*z* 202.1109, calcd for $C_{12}H_{14}N_2O$ 202.1106.
7. From observed E_p value (0.029 V) and $E_p = E_{1/2} + 0.0285/n$ (at 25°C) equation[11], *n* becomes 1.
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12. AM1 calculation for both structural isomers, **E** and **F**, indicates that heat of formation (kcal/mol) is 112.8 for **E** and 103.1 for **F** ($\Delta\Delta H_f$ 9 kcal/mol), but strain energy (kcal/mol) is 28.6 for **E** and zero for **F** (ΔSE 28 kcal/mol).
13. Chemical reduction of **1** afforded quite different products from electrochemical reduction. For example, reaction of **1a** with zinc dust in acetic acid at 25°C gave 3-cyano-2-phenylindole in quantitative yield. Reaction of **1** with $NaBH_4$ in ethanol under reflux provided 3-phenylcinnoline in almost quantitative yield.