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Anodic Cyanation of 1-Methylimidazoles

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The electrooxidation of several 1-methylimidazoles was performed in MeOH that contains NaCN at a platinum anode in a divided cell. Replacement of an aromatic hydrogen by a cyano group occurred. With 1,2,4,5-tetramethylimidazole, the 2,5-addition of cyano groups to the imidazole ring was achieved, and besides side-chain substitution occurred concurrently.

It has been shown that an electrochemical technique makes possible the direct introduction of cyano groups either by substitution or addition into aromatic compounds.[1,2] This method is especially useful for five-membered heterocycles.[3]

The present paper describes synthetic application of the method to 1-methylimidazoles. The possible products α-amino nitriles are useful as the synthetic intermediates. Heretofore, in electrooxidation reactions, imidazoles were often used as nucleophiles rather than as substrates.[4,5]

Results

Controlled-Potential Electroreaction (CPE). The potentiostatic oxidations of 1-methylimidazoles were performed in a divided cell with a Pt anode at room temperature. The reference electrode was an SCE. The electroreaction medium was MeOH–0.4 M NaCN (1 M=1 mol dm^{-3}). After the theoretically calculated amount of charge had passed, the solvent was removed. The residue was triturated with chloroform, filtered, concentrated, and analyzed by GLC. The products reported in Table 1 were isolated by preparative GLC. They were identified by the elemental and ^{1}H NMR, IR, and mass spectroscopic analyses and by comparison with the authentic samples prepared by other routes. Current efficiencies (CEs) are based on the total charge passed; the formation of 1 mol of each product is assumed to require 2 F.

The replacement of an aromatic hydrogen by a cyano group occurred at a position lacking the substituent on the imidazole ring. MI gives all three possible ring-substitution products, 5-, 2-, and 4-cyano isomers in an approximate ratio of 5:2:1. A similar product distribution has been reported for the electroreaction in aqueous cyanide (presumably as a potassium salt, experimental details including melting points of some products were not furnished).[6] The reaction point in the present anodic reaction is of particular interest because conventional electrophilic substitution by a cyano group occurs exclusively at the 2 position.[7]

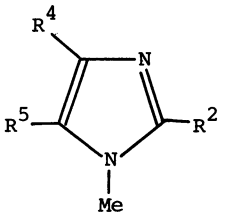
For TEMI obstructed all of the replaceable positions by the methyl substituents, the 2,5-addition of cyano groups across the diene system of an imidazole was achieved, and besides side-chain substitution occurred concurrently at the substituent methyl group in the 5 position. The transformation of the adduct **2** to the side-chain-cyanation product **1h** during GLC analysis was not observed. For the 2,5-dicyano adduct of 1,2,5-trimethylpyrrole, such a rearrangement of a cyano group has been reported.[8]

The CE for the formation of these carbonitriles

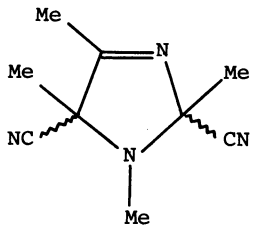
Table 1. Anodic Cyanation of 1-Methylimidazoles. Voltammetric Data and Products

Reactant	E_p[a] / V	PCPE[b] / V	n[c] / F mol^{-1}	Product	CE[d] / %
1-Methylimidazole (MI)	≈1.75	1.80	2.7	1-Methyl-2-imidazolecarbonitrile (**1a**)	17
				1-Methyl-4-imidazolecarbonitrile (**1b**)	8
				1-Methyl-5-imidazolecarbonitrile (**1c**)	42
1,2-Dimethylimidazole (1,2-DIMI)	1.54	1.54	2.1	1,2-Dimethyl-4-imidazolecarbonitrile (**1d**)	7.5
				1,2-Dimethyl-5-imidazolecarbonitrile (**1e**)	79
1,5-Dimethylimidazole (1,5-DIMI)	1.47	1.47	2.1	1,5-Dimethyl-2-imidazolecarbonitrile (**1f**)	32
				1,5-Dimethyl-4-imidazolecarbonitrile (**1g**)	36
1,2,4,5-Tetramethylimidazole (TEMI)	1.12	1.10	2.1	2,5-Dihydro-1,2,4,5-tetramethyl-2,5-imidazoledicarbonitrile (**2**)	13
				1,2,4-Trimethylimidazole-5-acetonitrile (**1h**)	11

a) Peak potential for cyclic voltammetry; Pt anode, MeOH, 0.4 M NaCN, SCE. Scan rate is 0.1 V s^{-1}. Substrate concentration is 2×10^{-2} M. All voltammograms showed no cathodic peak corresponding to reversible reduction of an initially formed cation radical. b) Potential for controlled-potential electroreaction. c) Controlled-potential coulometry. d) Current efficiency (based on **2e** process). This value corresponds to the yield based on imidazole used since the reaction was terminated at the stage when 2 F mol^{-1} of electricity was passed.



1a, R^2=CN; R^4=R^5=H
b, R^2=R^5=H; R^4=CN
c, R^2=R^4=H; R^5=CN
d, R^2=Me; R^4=CN; R^5=H
e, R^2=Me; R^4=H; R^5=CN
f, R^2=CN; R^4=H; R^5=Me
g, R^2=H; R^4=CN; R^5=Me
h, R^2=R^4=Me; R^5=CH_2CN



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increases with decreasing amounts of passed electricity. It would be ascribable to that, the oxidation of the background solvent-electrolyte system becomes conspicuous with decreasing concentration of the electroactive substrate.

The GLC retention time of 4-carbonitriles is remarkably long compared with that of the other positional isomers (e.g., t_R=14, 14, and 98 min for **1a**, **1c**, and **1b**, respectively; PEG 6000 column, 190 °C).

The intensity of C≡N stretching vibration in IR spectra varied with structure. Ring substitution products have a strong band in the region of the C≡N stretching vibration, whilst the intensity of the nitrile absorption band in 2,5-addition or side-chain-substitution product is weaker.

Preparative-Scale Electroreaction. The larger preparative electroreactions were conducted at constant current of 0.05 A. After usual workup, the products were separated by column chromatography. The CEs for constant-current electroreaction were lower than those for CPE. There was some difference in product ratios using the different reaction conditions. At the nonpotentiostatic conditions, a portion of the primary product would be consumed by further oxidations.

Experimental

General. Spectrometers and electrochemical equipment have been described previously.[9]

Materials. MeOH and reagent grade NaCN were used without purification.

MI and 1,2-DIMI were obtained commercially and were purified by distillation. TEMI was also a commercial sample and was purified by column chromatography on silica gel using pentane-chloroform (1:2) as an eluent and by recrystallization; mp 58.0—61.0 °C (from petroleum ether, lit,[10] mp 51—54 °C).

1,5-DIMI was prepared by the hydrazine reduction of 1-methyl-5-imidazolecarbaldehyde according to the method of Martin, et al.[11] The desired aldehyde was obtained by oxidation of the corresponding alcohol with activated manganese dioxide in benzene according to the method of Loozen, et al.[12] The procedures of Jones and McLaughlin were followed for the preparation of 1-methyl-5-(hydroxymethyl)-imidazole.[13-15]

^{1}H NMR ($CDCl_3$): MI, δ=3.66 (3H, s), 6.84 (1H, m), 7.00 (1H, m), 7.38 (1H, br s); 1,2-DIMI, δ=2.37 (3H, s), 3.56 (3H, s), 6.78 (1H, d, J=1.2), 6.86 (1H, d, J=1.2); 1,5-DIMI, δ= 2.17 (3H, d, J=1.0), 3.50 (3H, s), 6.72 (1H, br s), 7.32 (1H, s); TEMI, δ=2.07 (3H, s), 2.09 (3H, s), 2.30 (3H, s), 3.35 (3H, s).

The following reference materials were obtained by dehydration of the oximes with acetic anhydride according to the procedure of Anderson,[16] which describes the preparation of 2-pyrrolecarbonitrile from the corresponding oxime: **1a—c** and **1e**. Their precursors aldehydes were prepared according to the literature. 1-Methyl-2-imidazolecarbaldehyde[12] was obtained from oxidation of the corresponding alcohol[17,18] with active manganese dioxide. 1-Methyl-4-imidazolecarbaldehyde was prepared by an eight-step method of Martin, et al.[11] The desired α-acetamidoacrylic acid was obtained according to the literature.[19,20] The preparation of 1-methyl-5-imidazolecarbaldehyde was described above. 1,2-Dimethyl-5-imidazolecarbaldehyde was made by the literature procedure.[12,21]

Cyclic Voltammetry. Voltammograms were recorded for each compound as described previously.[9] The E_p value are in Table 1.

CPE. The cell and general procedure have been described.[9] Oxidations in MeOH, 0.4 M NaCN were performed at controlled potentials as indicated in Table 1. The reactions were usually terminated after passage of ≈2 F mol^{-1} of added imidazole. The workup procedure consisted of evaporation of much of the MeOH (*caution*: HCN), addition of chloroform, and filtration of NaCN. The chloroform extract was concentrated and analyzed by GLC using a PEG 6000 column. Each isomeric product was separated in pure form by preparative GLC.[22] They were identified by the elemental and ^{1}H NMR, IR, and mass spectroscopic analyses (Table 2).

Preparative-Scale Electroreaction of MI. The electroreaction was carried out in a two-compartment H-type cell with glass frit separating the compartments fitted with Pt foil electrodes (2×2 cm). The anolyte was made up of 3.3 g (0.04 mol) of MI, 2.5 g (0.05 mol) of NaCN, and 50 ml of MeOH. The catholyte was the same medium in the absence of the substrate. The anode and cathode compartments were kept under a nitrogen atmosphere and the anolyte was stirred magnetically. The reaction was performed at 0.05 A of constant current by using a direct-current power supply at room temperature until ≈2 F mol^{-1} of added imidazole had passed through the electrolyte, which generally took 24 h.

After completion of the oxidation, the solvent was removed under aspirator vacuum. The residue was triturated with chloroform, filtered, concentrated,[25] and chromatographed on silica-gel column using chloroform as the eluant. The elution of products was followed by IR spec-

troscopy. The first product to elute was **1a**, the second **1c**, followed by unreacted substrate and successive elution of **1b**. Separation of the isomers was accomplished without loss.

Preparative-Scale Electroreaction of TEMI. The method of oxidation, workup, and product isolation was identical to that described for MI. 2,5-Dihydro-1,2,4,5-tetramethyl-2,5-imidazoledicarbonitrile (**2**; 0.35 g, 5% CE) was isolated as the first fraction by column chromatography, followed by unidentified substances. 1,2,4-Trimethylimidazole-5-acetonitrile (**1h**) as well as the adduct **2** could be separated from the reaction mixture by preparative GLC using a PEG 6000 column at 190 °C.

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22) The isomeric **1a** and **1c** could not be separated by GLC. The mixed isomers were taken out by preparative GLC and their ratio was determined by NMR spectroscopy. Separation to the individual isomers was made by column chromatography on silica gel with chloroform (see

Table 2. Melting points and Spectroscopic Data of Cyanation Products

Product	Mp θ_m/°C	^{1}H NMR,[a] δ/ppm (J in Hz)	MS m/z (M^+)	IR[b] ν/cm^{-1}
1a	Oil (bp 65—70 °C/0.4 mmHg[c] (1 mmHg=133.322 Pa))	3.86 (3H, s) 7.08 (1H, d, J=0.8) 7.13 (1H, d, J=0.8)	107	2210 (C≡N)
1b	73.5—74.5, from $CHCl_3$-hexane (72—73[d])	3.78 (3H, s) 7.46 (2H, br s)[e]	107	2240 (C≡N)
1c	53.0—53.5, from CCl_4 (48—50[f])	3.80 (3H, s) 7.57 (1H, s) 7.61 (1H, s)	107	2260 (C≡N)
1d	139.0—140.0, from hexane	2.38 (3H, s) 3.60 (3H, s) 7.32 (1H, s)	121	2240 (C≡N)
1e	66.0—67.0, from CCl_4 (54—57[g])	2.44 (3H, s) 3.66 (3H, s) 7.50 (1H, br s)	121	2260 (C≡N)
1f	75.0—78.0, from CCl_4	2.23 (3H, d, J=0.8) 3.69 (3H, s) 6.90 (1H, m)	121	2240 (C≡N)
1g	94.0—97.0, from $CHCl_3$-CCl_4 (1 : 5)	2.37 (3H, s) 3.60 (3H, s) 7.40 (1H, br s)	121	2220 (C≡N)
1h	32.5—33.5, from hexane	2.16 (3H, br s) 2.32 (3H, s) 3.38 (3H, s) 3.56 (2H, br s)	149	2240 (C≡N)
2	79.5—81.5, from petroleum ether	1.84 (3H, s) 1.86 (3H, s) 2.01 (3H, s) 2.90 (3H, s)	176	2220 (C≡N) 1590 (C=N)

a) 100 MHz, $CDCl_3$ solution. b) Uncorrected. c) Ref. 7. d) Ref. 23. e) Divided into two peaks in the dilute solution, δ 7.47 (1H, s), 7.45 (1H, s). f) Ref. 6. g) Ref. 24.

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25) At this stage, yields were estimated by GLC combined with NMR spectral analysis (**1a**, 0.26 g, 6% CE; **1b**, 0.20 g, 4.6% CE; **1c**, 0.58 g, 13.5% CE).[22]