H, aromatic H). The unpurified product was used directly in the next reaction.

Phenyl (*E*)-[2-Chloro-3-methoxy-5-(2-methyl-1-oxo-2-butenyl)phenyl]methylcarbamate (10). Unpurified allylic alcohol **9** (0.072 g, 0.192 mmol) and 0.335 g of activated manganese(IV) oxide (Aldrich) were stirred at room temperature in 4.5 mL of benzene for 20 h. The mixture was filtered over Celite, concentrated, and purified by preparative TLC (R_f 0.30–0.43; 1:1, ether/petroleum ether) to yield pure ketone **10** (89% overall from **8**) as a pale yellow liquid: IR ($CHCl_3$) 1724 (s), 1643 (m), 1570 (m) cm^{-1}; ^1H NMR δ 1.89 (d, 3 H, J = 6.8 Hz, β-Me), 1.97 (s, 3 H, α-Me), 3.32 (s, 3 H, NMe), 3.96 (s, 3 H, OMe), 6.45 (br q, 1 H, J = 6.8 Hz, olefinic H), 6.92–7.61 (m, 7 H, aromatic H); mass spectrum, *m/e* 373 (M^+), 338, 280 (base), 252, 217; exact mass, *m/e* 373.1090 (calcd for $C_{20}H_{20}{}^{35}ClNO_4$, 373.1081).

Acknowledgment. The financial support of this work by NSF-EPSCOR Grant ISP-8011447, Research Corp., and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. The mass spectral data were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska–Lincoln, a National Science Foundation supported Regional Instrumentation Facility. The 60-MHz NMR spectrometer used in this work was purchased with a Research Instrumentation grant (No. CDP-8006650) from the National Science Foundation. We thank Dr. K. L. Loening, Nomenclature Director, Chemical Abstracts Service, for nomenclature advice.

Facile Conversion of 4(5)-Nitro-5(4)-methylimidazoles into 4(5)-Nitro-5(4)-cyanoimidazoles

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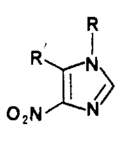
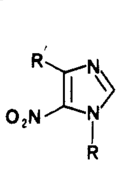
5(4)-Cyano-4(5)-nitroimidazoles (**1**, **2**) are important synthons in the preparation of imidazole fused heterocycles.[1] These compounds offer the option of chain extension either as electrophiles involving their cyano function or as nucleophiles after reduction of their nitro group. While **1** can be prepared from straight-chain precursors, albeit in multisteps and poor yields,[1b] no method to date is available for the synthesis of the (biologically more significant) isomer **2**, which is a potential precursor for the ubiquitous 9-substituted purines. We report here a facile general method for the synthesis of both **1** and **2**, in a three-step procedure, from the readily accessible 5(4)-methyl-4(5)-nitroimidazoles **3** and **4**, respectively.



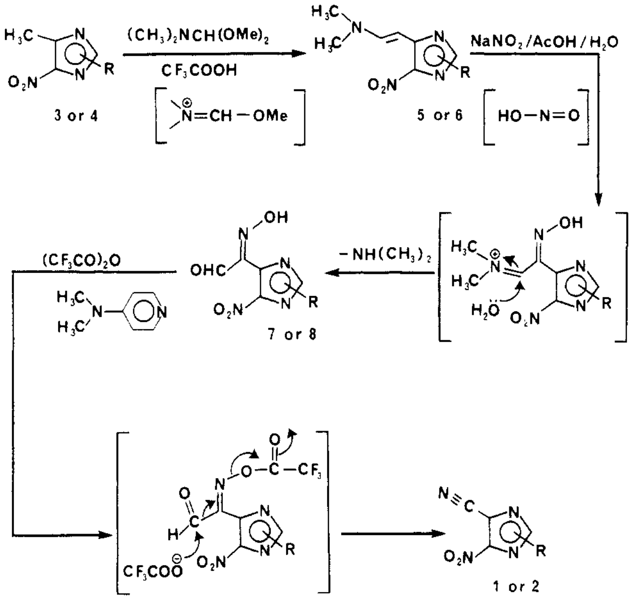
a, R=H
b, R=CH_3
c, R=CH_2Ph



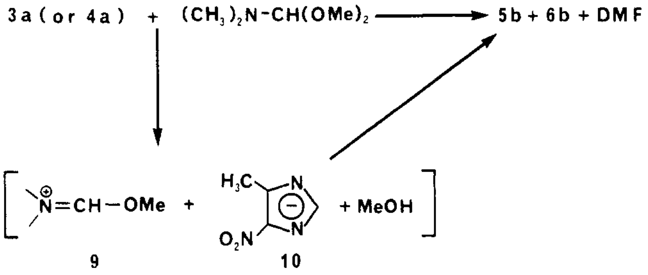
1; R'=CN
3; R'=CH_3

2; R'=CN
4; R'=CH_3

Scheme I



Scheme II



Our method (Scheme I) consists of reacting **3** or **4** (R = alkyl) with dimethylformamide dimethyl acetal, catalyzed by trifluoroacetic acid, to obtain the corresponding 5(4)-β-(*N*,*N*-dimethylamino)ethylene-4(5)-nitroimidazoles **5** or **6**, respectively, in 75–80% yields. The enamine **5** or **6** was further treated with sodium nitrite in aqueous acetic acid to yield the corresponding glyoxal α-oximes **7** or **8**, respectively, in 74–94% yields. The latter compounds, upon treatment with trifluoroacetic anhydride, catalyzed by 4-(*N*,*N*-dimethylamino)pyridine, afforded the title cyanoimidazoles **1** or **2**, respectively, in 60–80% yields. The structures of the products in each step were confirmed by ^1H NMR, IR, mass spectral data and elemental microanalyses. The presumed key intermediates of these reactions are shown in brackets. In general, the proton NMR signals of both the ring alkyl (aralkyl) and the imidazole CH groups were shifted downfield by approximately 0.2–0.3 ppm in **6** as compared with **5**. A similar trend was discernible between **8** and **7**. However, the difference was less dramatic between the signals of **2** and **1**. While in the former two cases only the NO_2 group exerted the proximal deshielding effect, this phenomenon was shared by both C≡N and NO_2 in the last instance, thus causing less difference between the chemical shifts of **2** and **1**. The IR spectra of the final products revealed strong nitrile absorptions in the 2200-cm^{-1} region.

The reaction of the unsubstituted **3** or **4** (R = H) with dimethylformamide dimethyl acetal directly provided a mixture of **5** and **6** (R = Me) in approximately 1:1 ratio (Scheme II). This reaction required no acid catalyst unlike that of the substituted **3** or **4** (R = alkyl) with DMF acetal, as described above. The mixture was separated by either fractional recrystallization or flash chromatography. The positions of alkylation in **5b** and **6b** were established (a)

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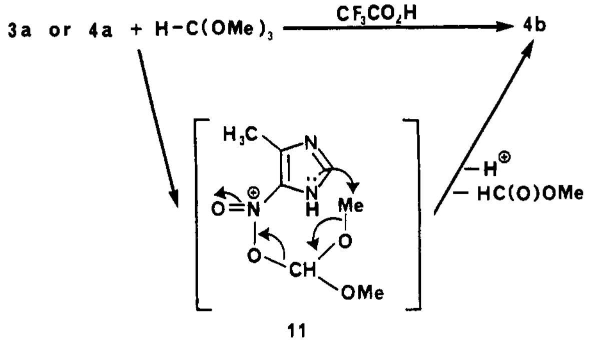
[1] (a) Prasad, R. N.; Robins, R. K. *J. Am. Chem. Soc.* **1957**, *79*, 6401. (b) Sarasin, J.; Wegmann, E. *Helv. Chim. Acta* **1924**, *7*, 713. (c) Mann, F. G.; Porter, J. W. G. *J. Chem. Soc.* **1945**, 751 and the references cited therein.

0022-3263/85/1950-5892$01.50/0 © 1985 American Chemical Society

Scheme III



by spectral and melting point comparison with the authentic samples of **5b** and **6b** prepared as described above and (b) by hydrolysis of **5b** with aqueous NaOH or HCl, which gave 1,5-dimethyl-4-nitroimidazole (**3b**).[2] The ring alkylation[3] of heterocycles by DMF acetals[4] is well established. The absence of any acid catalyst, coupled with the observed nonregiospecific alkylation of the imidazole ring, suggests the intermediacy of the imidate cation **9** and the resonance-delocalized imidazole anion **10** in this reaction.

All the starting materials employed in this investigation were prepared from the commercially available[5] 4(5)-methylimidazole. Nitration[6] of the latter (to yield **3a** or **4a**), followed by base-catalyzed alkylation[7] with methyl iodide and benzyl chloride yielded **3b**, **4b**, and **3c**, **4c**, respectively. As expected,[8] the alkylation yielded predominantly the **3** isomer (the ratio **3**:**4** ≈ 4:1). The less abundant isomer **4b** was, therefore, prepared by an alternative novel route (Scheme III) that involved reacting **3a** (or **4a**) with trimethyl orthoformate, catalyzed by trifluoroacetic acid. This reaction provided **4b** exclusively. The observed regiospecific alkylation is believed to involve an initial condensation between the nitro group and the ortho ester to form an intermediate mixed ortho ester (**11**) that further undergoes intramolecular nucleophilic displacement on its methoxy methyl function by the proximal imidazole nitrogen, yielding **4b** and methyl formate. However, as we have made no attempts to either detect or isolate the intermediate or the byproduct of this reaction, the proposed mechanism is only tentative. Another plausible method for **4**,[10] although not attempted here, involves alkylation with the appropriate alkyl halides in an acid medium.[11]

The title conversion may be applicable to other heterocyclic (and possibly nonheterocyclic) systems bearing vinylogous nitro methyl functions.

Experimental Section

Proton nuclear magnetic resonance spectra were recorded on an IBM NR/80 spectrometer. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), intergration. The electron impact (EI) mass spectra were performed at the School of Pharmacy, University of Maryland at Baltimore, on a Du Pont 21-490 mass spectrometer with a 21-094 data system and an Extranuclear Simulscan GC/MS instrument. Infrared spectra were obtained on a Perkin-Elmer 1420 ratio recording instrument. Elemental microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

General Method for the Preparation of 5(4)-β-(*N*,*N*-Dimethylamino)ethylene-4(5)-nitroimidazoles (5 and 6). A mixture of 4(5)-nitro-5(4)-methylimidazole (**3** or **4**; 15 mmol) and dry DMF (20 mL) was stirred under N_2 to form a clear solution. Dimethylformamide dimethyl acetal (150 mmol) was introduced through a hypodermic syringe needle, followed by trifluoroacetic acid (0.1 mL). The reaction mixture was heated at reflux under N_2 for 15–20 h, cooled, and rotary evaporated to dryness. The residual oil, upon cooling in an ice bath, crystallized into red to maroon solids that were purified by either recrystallization from appropriate solvents or by flash chromatography on Woelm silica gel (particle size 40–63 μm), employing a mixture of chloroform and acetone (9:1) as the eluting solvent system. The recrystallization solvents, percentage yields, melting points, and spectral data for the various **5** and **6** obtained by this procedure are given below:

5-β-(Dimethylamino)ethylene-1-methyl-4-nitroimidazole (5b): from **3b**; red crystals from benzene; 80%; mp 123.5–125 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.79 (d, *J* = 13.65 Hz, 1, side-chain β-CH), 7.50 (s, 1, imidazole CH), 5.38 (d, *J* = 13.57 Hz, 1, side-chain α-CH), 3.62 (s, 3, ring CH_3), 2.96 (s, 6, $N(CH_3)_2$); mass spectrum (70 eV) *m/e* 196 (M^+), 179, 148, 136, 120, 108, 95, 82, 67, 50. Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28.55. Found: C, 49.02; H, 6.18; N, 28.54.

4-β-(Dimethylamino)ethylene-1-methyl-5-nitroimidazole (6b): from **4b**; maroon crystals from benzene; 75%; mp 150–152.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.75 (d, *J* = 12.94 Hz, 1, side-chain β-CH), 7.74 (s, 1, imidazole CH), 5.79 (d, *J* = 12.96 Hz, 1, side-chain α-CH), 3.80 (s, 3, ring CH_3), 2.96 (s, 6, $N(CH_3)_2$); mass spectrum (70 eV) *m/e* 196 (M^+), 181, 179, 163, 149, 135, 120, 108, 94, 81, 66. Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28.55. Found: C, 48.89; H, 6.18; N, 28.46.

1-Benzyl-5-β-(dimethylamino)ethylene-4-nitroimidazole (5c): from **3c**; maroon crystals from toluene; 79%, mp 148.5–149.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.82 (d, *J* = 13.51 Hz, 1, side-chain β-CH), 7.72 (s, 1, imidazole CH), 7.32 (m, 5, Ph), 5.31 (s, 2, CH_2), 5.13 (d, *J* = 13.20 Hz, 1 , side-chain α-CH), 2.83 (s, 6, $N(CH_3)_2$); mass spectrum (70 eV), *m/e* 272 (M^+), 255, 217, 181, 134, 107, 91, 65. Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.83; H, 5.96; N, 20.46.

1-Benzyl-4-β-(dimethylamino)ethylene-5-nitroimidazole (6c): from **4c**; red crystals from benzene–petroleum ether (40–60 °C); 70%; mp 145–148 °C; ^{1}H NMR (Me_2SO-d_6) δ 8.04 (s, 1, imidazole CH), 7.82 (d, *J* = 12.56 Hz, 1, side-chain β-CH), 7.30 (m, 5, Ph), 5.80 (d, *J* = 12.39 Hz, 1 , side-chain α-CH), 5.48 (s, 2, CH_2), 2.97 (s, 6, $N(CH_3)_2$); mass spectrum (70 eV) *m/e* 272 (M^+), 255, 227, 225, 217, 181, 149, 134, 119, 107, 91, 81, 64. Anal. Calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.84; H, 5.97; N, 20.46.

General Procedure for the Preparation of 1-Substituted 4(5)-Nitroimidazo-5(4)-glyoxal α-Oximes (7, 8). The enamine **5** or **6** (15 mmol) was dissolved in a mixture of glacial acetic acid (12 mL) and water (15 mL) in a round-bottom flask, equipped with a thermometer and an addition funnel. The flask was placed in an ice–salt water bath, and a cold solution of granulated $NaNO_2$ (5 g) in 30 mL of water was added in small portions while maintaining the temperature below 10 °C. After approximately 0.5 h, a light yellow precipitate started forming. When the evolution of brown fumes subsided (after about 1 h), the solid formed was filtered in vacuo, washed with H_2O, and dried. The solvents of recrystallization, melting points, and spectral data for various **7** and **8** obtained by this procedure are summarized below:

1-Methyl-4-nitroimidazo-5-glyoxal α-Oxime (7b): from **5b**; off-white flakes from acetonitrile; 74%; mp 206–207 °C; ^{1}H NMR (Me_2SO-D_6) δ 9.73 (s, 1, CHO), 8.01 (s, 1, imidazole CH), 3.64 (s, 3, *N*-CH_3); IR (KBr) 3380 (OH), 1700 (C=O) cm^{-1}; mass spectrum

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[2] *Beilstein* **1936**, *H-23*, 71; **1954**, *E II 23*, 63.

[3] (a) Stanovnik, B.; Tišler, M.; Hribar, A.; Barlin, G. B.; Brown, D. J. *Aust. J. Chem.* **1981**, *34*, 1729. (b) Žemlička, J. *Collect. Czech. Chem. Commun.* **1970**, *35*, 3572 and the references cited therein.

[4] Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

[5] Available from Aldrich Chemical Co., Milwaukee, WI.

[6] Fargher, R. G.; Pyman, F. L. *J. Chem. Soc.* **1919**, *115*, 234.

[7] Chan, E.; Putt, S. R.; Showalter, H. D. H.; Baker, D. C. *J. Org. Chem.* **1982**, *47*, 3457.

[8] See for example: (a) Pyman, F. L. *J. Chem. Soc.* **1922**, *121*, 2621. (b) Wu, D. C. J.; Cheer, C. J.; Panzicka, R. P.; Abushanab, E. *J. Org. Chem.* **1982**, *47*, 2661.

[9] Bhagwat, V. K.; Pyman, F. L. *J. Chem. Soc.* **1925**, *127*, 1832.

[10] This method was suggested by one of the reviewers.

[11] Miller, M. W.; Horwes, H. I.; Kasubick, R. V.; English, A. R. *J. Med. Chem.* **1970**, *13*, 849.

(70 eV) m/e 198 (M^+), 153, 137, 122, 107, 95, 79, 67, 53. Anal. Calcd for $C_6H_6N_4O_4$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.38; H, 3.08; N, 28.33.

1-Methyl-5-nitroimidazo-4-glyoxal α-Oxime (8b): from **6b**; off-white flakes from acetonitrile; 93%; mp 192–193 °C; ^1H NMR (Me_2SO-d_6) δ 9.68 (s, 1, CHO), 8.12 (s, 1, imidazole CH), 3.94 (s, 3, N-CH_3); IR (KBr) 3380 (OH), 1700 (C=O) cm^{-1}; mass spectrum m/e 198 (M^+), 168, 153, 137, 122, 107, 95, 91, 79, 68, 65, 52. Anal. Calcd for $C_6H_6N_4O_4$: C, 36.37; H, 3.05; N, 28.28. Found: C, 36.42; H, 3.09; N, 28.20.

1-Benzyl-4-nitroimidazo-5-glyoxal α-Oxime (7c): from **5c**; pale yellow crystals from acetonitrile; 80% mp 208–209 °C; ^1H NMR (Me_2SO-d_6) δ 9.55 (s, 1, CHO), 8.18 (s, 1, imidazole CH), 7.28–7.09 (m, 5, Ph), 5.25 (s, 2, CH_2); IR (KBr) 3280–3250 (OH), 1700 (C=O) cm^{-1}; mass spectrum (70 eV) m/e 274 (M^+), 105, 91, 77, 65, 51. Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.56; H, 3.68; N, 20.43. Found: C, 52.56; H, 3.72; N, 20.37.

1-Benzyl-5-nitroimidazo-4-glyoxal α-Oxime (8c): from **6c**; pale yellow crystals from acetonitrile; 96%; mp 193 °C; ^1H NMR (Me_2SO-d_6) δ 9.68 (s, 1, CHO), 8.39 (s, 1, imidazole CH), 7.43–7.26 (m, 5, Ph), 5.62 (s, 2, CH_2); IR (KBr) 3300–3120 (OH), 1715–1710 (C=O) cm^{-1}; mass spectrum (70 eV) m/e 274 (M^+), 105, 91, 77, 65, 51. Anal. Calcd for $C_{12}H_{10}N_4O_4$: C, 52.56; H, 3.68; N, 20.43. Found: C, 52.61; H, 3.74; N, 20.39.

General Method for the Preparation of 1-Substituted 5(4)-Cyano-4(5)-nitroimidazoles (1, 2). A mixture of the oxime **7** or **8** (41 mmol) and 4-(N,N-dimethylamino)pyridine (72 mmol) in dry acetonitrile (80 mL) was stirred under N_2 at 0 °C for 15 min. Trifluoroacetic anhydride (43 mmol) was introduced carefully through a serum cap at such a rate as to maintain the temperature below 5 °C. After the addition was complete, the reaction mixture was allowed to warm to room temperature. A TLC [silica gel, $CHCl_3$–MeOH (6:1)], taken after 0.5 h, indicated the formation of a less polar (faster moving than the starting material), UV-absorbing compound. The reaction mixture was continued to stir at room temperature for an additional 1–2 h (except in the case of **8b**, which required heating at reflux for 1 h to effect complete conversion to **2b**), and the contents of the flask were evaporated to dryness. The residue was purified by flash chromatography on silica gel (particle size 40–63 μm, 120 g), using $CHCl_3$ as the eluting solvent. The solvents of recrystallization, percentage yields, melting points, and spectra data for various **1** and **2** are summarized below:

5-Cyano-1-methyl-4-nitroimidazole (1b): from **7b**; white crystals from $CHCl_3$–petroleum ether (40–60 °C); 56–60%; mp 140–142 °C; ^1H NMR (Me_2SO-d_6) δ 7.93 (s, 1, imidazole CH), 3.89 (s, 3, CH_3); IR (KBr) 2240 (C≡N) cm^{-1}; mass spectrum (70 eV) m/e 152 (M^+), 122, 106, 67. Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.83. Found: C, 39.29; H, 2.70; N, 36.73.

4-Cyano-1-methyl-5-nitroimidazole (2b): from **8b**; white crystals from $CHCl_3$–petroleum ether (40–60 °C); 65–80%; mp 118–120 °C; ^1H NMR (Me_2SO-d_6) δ 8.23 (s, 1, imidazole CH), 3.96 (s, 3, CH_3); IR (KBr) 2235 (C≡N) cm^{-1}; mass spectrum (70 eV) m/e 152 (M^+), 135, 122, 106, 92, 79, 77, 67, 65, 64, 52. Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.83. Found: C, 39.53; H, 2.69; N, 36.80.

1-Benzyl-5-cyano-4-nitroimidazole (1c): from **7c**; white needles from $CHCl_3$–petroleum ether (40–60 °C); 65%; mp 125–126 °C; ^1H NMR (Me_2SO-d_6) δ 8.42 (s, 1, imidazole CH), 7.39 (s, 5, Ph), 5.51 (s, 2, CH_2); IR (KBr) 2200 (C≡N) cm^{-1}; mass spectrum (70 eV) m/e 228 (M^+), 91, 65, 51. Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53, N, 24.55. Found: C, 57.81; H, 3.56; N, 24.48.

1-Benzyl-4-cyano-5-nitroimidazole (2c): from **8c**; white needles from $CHCl_3$–petroleum ether (40–60 °C); 42%; mp 119–120 °C; ^1H NMR (Me_2SO-d_6) δ 8.46 (s, 1, imidazole CH), 7.32 (s, 5, Ph), 5.65 (s, 2, CH_2); IR (KBr) 2240 (C≡N) cm^{-1}; mass spectrum (70 eV) m/e 228 (M^+), 211, 105, 91, 77, 64, 51. Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53, N, 24.55. Found: C, 57.70; H, 3.54; N, 24.50.

Reaction of 5(4)-Methyl-4(5)-nitroimidazole (3a or 4a) with Dimethylformamide Dimethyl Acetal. The procedure is the same as the general method described above for the preparation of **5** and **6**, except no catalyst (TFA) was employed in the reaction. The red solid obtained contained a mixture of **5b** and **6b**, which were separated either by fractional recrystallization from benzene–toluene and ligroin or by flash chromatography on Woelm silica gel (40–60 μm), employing a mixture of $CHCl_3$ and acetone (9:1) as the eluting solvent. Compounds **5b** and **6b**, obtained in 27 and 31% yields, respectively, exhibited (a) no depression in the mixture melting point with the authentic **5b** and **6b** prepared from **3b** and **4b**, respectively, as described above and (b) superimposable ^1H NMR and mass spectra with those of the authentic **5b** and **6b**.

Hydrolysis of 5-β-(N,N-Dimethylamino)ethylene-1-methyl-4-nitroimidazole (5b). (a) With 2 N NaOH. A solution of **5b** (250 mg, 1.27 mmol) in 2 N NaOH (50 mL) was stirred at room temperature for 21 h. The progress of the reaction, monitored by TLC [silica gel, $CHCl_3$–MeOH (8:1)], showed gradual formation of a less polar (faster moving than the starting material), UV-absorbing compound. The aqueous reaction mixture was extracted with AcOEt (3 × 50 mL), combined extracts were dried over anhydrous Na_2SO_4, filtered, and rotary evaporated to dryness to obtain **3b** (45 mg, 0.32 mmol, 25%); mp 157 °C (lit.[9] mp 160–161 °C). The ^1H NMR and mass spectral data of this compound were identical with those of the authentic **3b** prepared from **3a** (vide infra).

(b) With 2 N HCl. The procedure is similar to the one described in (a) above, except that the reaction was carried out at reflux temperature.

General Method for the Alkylation of 5(4)-Methyl-4(5)-nitroimidazole (3a, 4a). A suspension of **3a** (or **4a**) (50 g, 0.39 mol) and anhydrous K_2CO_3 (53 g, 0.38 mol) in anhydrous DMF (100 mL) was stirred under N_2 for 30 min. Appropriate alkyl halide (CH_3I, $PhCH_2Cl$) (0.39 mol) was introduced, and the reaction mixture was continued to stir under N_2 for 24 h. A TLC [silica gel, $CHCl_3$–MeOH (8:1)] of the reaction mixture indicated the formation of two new UV-absorbing, less polar (faster moving than the starting material) compounds. The reaction mixture was filtered to remove inorganic solids, and the filtrate was evaporated to dryness. The residue, upon washing with 80 mL of boiling water (to remove traces of inorganic salts) and drying in vacuo, gave an isomeric mixture of **3b**, **4b**, or **3c**, **4c**. The mixture was separated by flash chromatography on Woelm silica gel (40–63 μm), employing either $CHCl_3$ (for **3b**, **4b**) or a mixture of $CHCl_3$–hexane (1:1) (for **3c**, **4c**). The compound **3c** was also separated from **4c** through fractional recrystallization from benzene: while **4c** readily dissolves in benzene, **3c** recrystallizes (moderate solubility) from it. In general, the combined yield of the isomeric mixture was ≥90% and the isomeric ratio 3:4 ≈ 4:1. The physical data for the compounds obtained by this method are given below:

1,5-Dimethyl-4-nitroimidazole (3b): mp 153–157 °C (lit.[9] mp 160–161 °C); ^1H NMR (Me_2SO-d_6) δ 7.71 (s, 1, imidazole CH), 3.64 (s, 3, N-CH_3), 2.55 (s, 3, 5-CH_3); mass spectrum (70 eV) m/e 141 (M^+), 124, 111, 94, 78, 67, 56.

1,4-Dimethyl-5-nitroimidazole (4b): mp 54–56 °C (lit.[8a] mp 57–58 °C); ^1H NMR (Me_2SO-d_6) δ 7.93 (s, 1, imidazole CH), 3.93 (s, 3, N-CH_3), 2.50 (s, 3, 4-CH_3); mass spectrum (70 eV) m/e 141 (M^+), 124, 111, 94, 80, 67, 52.

1-Benzyl-5-methyl-4-nitroimidazole (3c): mp 136.5–137.5 °C; ^1H NMR (Me_2SO-d_6) δ 7.93 (s, 1, imidazole CH), 7.34 (m, 5, Ph), 5.34 (s, 2, CH_2), 2.49 (s, 3, CH_3); mass spectrum (70 eV) m/e 217 (M^+), 200, 172, 170, 91, 65. Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.93;, H, 5.11; N, 19.30.

1-Benzyl-4-methyl-5-nitroimidazole (4c): mp 65–69 °C; ^1H NMR (Me_2SO-d_6) δ 8.18 (s, 1, imidazole CH), 7.30 (m, 5, Ph), 5.56 (s, 2, CH_2), 2.48 (s, 3, CH_3); mass spectrum (70 eV) m/e 217 (M^+), 200, 111, 105, 91, 78, 72, 65. Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.97; H, 5.15; N, 19.34.

Reaction of 5(4)-Methyl-4(5)-nitroimidazole (3a, 4a) with Trimethyl Orthorformate. A mixture of **3a** (or **4a**) (1 g, 8 mmol), dry acetonitrile (15 mL), and trimethyl orthorformate (45 mL, 0.41 mmol) was stirred under N_2 at room temperature to form a clear solution. Trifluoroacetic acid (0.05 mL, 0.64 mmol) was introduced through a serum cap, and the reaction mixture was heated at reflux for 5 h. A TLC [silica gel, $CHCl_3$–MeOH (8:1)] of the reaction mixture indicated the formation of a less polar (faster moving than the starting material), UV-absorbing compound in addition to the starting material. The mixture was cooled and evaporated to dryness on a rotary evaporator, and the residue was purified by flash chromatography on Woelm silica gel (40–63 μm) (30 g), employing $CHCl_3$ as the eluting solvent. Appropriate fractions were pooled and evaporated to obtain **4b**: 400 mg, 2.84 mmol, 35%; mp 54-56 °C (lit.[8a] mp 57-58 °C). The ^1H NMR and mass spectrum of this compound were superimposable with those of the authentic **4b** (vide supra). (Note: The only other compound isolated in this reaction was the unreacted starting material.)

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Selective Chlorination of Toluene by Anodic Oxidation

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Chlorotoluenes are commerically produced by toluene and chlorine in the presence of a Lewis acid catalyst and a cocatalyst.[1] Since *p*-chlorotoluene has a higher market value than its ortho isomer, numerous attempts to develop processes with high para to ortho isomer ratio (para/ortho) can be found in the patent literature. There is, however, little success, and para/ortho is seldom over 1.0.[2,3]

Electrochemical oxidation of chloride ions in the presence of toluene can also yield chlorotoluenes.[6,7] Gourcy, Simonet, and Jaccaud[10] reported that when tetraethylammonium chloride or lithium chloride was oxidized at a platinum anode in acetonitrile at constant current, toluene was monochlorinated with para/ortho ranging from 0.63 to 1.0. The applied potential range was 1.5 to 2.3 V vs. Ag/Ag^+ (0.1 M). If the experiment was done with large excess of a Lewis acid, a para/ortho ratio of 1.8 could be achieved. Osa, Fujihira, Matsue, and Yamauchi[11] claimed that by using an anode made of a carbonaceous material with cyclodextrin or a derivative thereof bonded onto its surface, toluene could be electrochemically chlorinated with para/ortho as high as 4.7. Cyclodextrin, however, is expensive, and the three-step electrode preparation is not trivial. We report that by oxidizing lithium chloride with an *unmodified* platinum electrode at a *constant potential of 1.0 or 1.1 V* vs. Ag/Ag^+ (0.01 M) in acetonitrile, toluene can be chlorinated with relatively high para selectively, with no Lewis acid being required.

Experimental Section

All the experiments were done in a divided cell with a glass frit separator, and the cell was placed in a constant-temperature bath. The working electrode was a 2.2-cm^2 platinum sheet, and a stainless-steel counterelectrode was used. Electrolysis was done at a constant potential set by a Princeton Applied Research 178 potentiostat. Potentials were measured against a Ag/Ag^+ (0.01 M) reference electrode unless specified. The anodic compartment contained 100 mL of an acetonitrile solution and 200 mg of lithium chloride[12] and in most cases 0.1 M supporting electrolyte (Table I). The content of the cathodic compartment was 60 mL. Acetonitrile was purified by distillation over P_2O_5. Glassware, lithium chloride, and supporting electrolytes were dried in an oven before use. Electrolysis was stopped when the desired number of Faradays per mole of toluene was passed. About 80% of the acetonitrile was distilled off with a 24-in. Vigreux column. The residue was partitioned with dichloromethane and water. The organic extracts were combined and dried, and the solvent was removed by distillation. Yield and isomer ratio were determined by a 30-m J and W fused silica capillary column. The GC internal standard was *o*-xylene. The structure of the chlorotoluenes was confirmed by GC-mass spectroscopy.

Results and Discussions

The results are summarized in Table I. *p*-Chlorotoluene to *o*-chlorotoluene ratios varied from 1.7 to 3.0. Less than 1% *m*-chlorotoluene was observed. Lithium perchlorate or tetraethylammonium fluoroborate was added in most cases to increase the conductivity. Only trace amounts (<2%) of benzyl chloride and dichlorotoluenes were detected by GLC when the toluene conversion was about 45%. The *p*-chlorotoluene selectivity increases when the reaction temperature decreases. Para selectivity is only observed in acetonitrile. When toluene was chlorinated by anodic oxidation of lithium chloride in dimethylformamide, the product mixture showed a *p*-chlorotoluene to *o*-chlorotoluene ratio of 0.77. The two isomers ratio was 0.66 in dimethylacetamide. With methanol as solvent, the para/ortho ratio was 1.0.

The first half-wave potential ($E_{1/2}$) of LiCl and toluene in acetonitrile are 0.7[15] and 1.98 V,[16] respectively. In our case, electrolysis was done at 1.0 or 1.1 V, and the chlorinating species must come from the oxidation of chloride ions. Chlorine radicals probably are not involved because they are known to react with toluene to give side-chain substitution and ring addition products[17] whereas we ob-

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[1] Gelfand, S. In "Kirk-Othmer Encyclopedia of Chemical Technology", 3rd ed.; Wiley: New York, 1979; Vol. 5, pp 821-822.

[2] The following patents claimed a para/ortho ratio of about 1.0: (a) Buckholtz, H. E.; Bose, A. C. U.S. Patent 4024198, May 1977; *Chem. Abstr.* **1977**, *87*, 134446*e*. (b) Graham, J. C. U.S. Patent 4031142, June 1977. (c) Graham, J. C. U.S. Patent 4031147, June 1977. (d) Lin, H. C. U.S. Patent 4069263, Jan 1978; *Chem. Abstr.* **1978**, *88*, 190351*C*. (e) Lin, H. C. U.S. Patent 4069264, Jan 1978; *Chem. Abstr.* **1978**, *88*, 120761*n*. (f) Lin, H. C.; Robota, S. U.S. Patent 4250122, Feb 1981; *Chem. Abstr.* **1981**, *95*, 24504*e*. (g) Graham, J. C. U.S. Patent 401373, March 1977; *Chem. Abstr.* **1977**, *87*, 5605*s*. (h) Di Bella, E. P. U.S. Patent 4031144, June 1977; *Chem. Abstr.* **1977**, *87*, 134449*h*. (i) British Patent 1153746, May 1969. (j) British Patent 1163927, Sept 1969. (5) Japan Patent 81/110630, Sept 1981; *Chem. Abstr.* **1982**, *96*, 34810*m*. (l) Saito, R.; Hattori, T.; Kawasuchi, T. Japanese Patent 75/34009, Nov 1975; *Chem. Abstr.* **1976**, *84*, 89792*q*.

[3] When a *stoichiometric amount* of ferric chloride was used as the chlorinating agent, para/ortho ratios as high as 9.0 could be obtained.[4,5]

[4] Sawazai, K.; Fujii, H.; Dehura, M. German Patent 2230369, Jan 1973; *Chem. Abstr.* **1973**, *78*, 84004*a*.

[5] Japan Patent 74/76828, July 1974; *Chem. Abstr.* **1976**, *85*, 46167*t*.

[6] (a) Rifi, M. R.; Covitz, F. H. "Introduction to Organic Electrochemistry"; Marcel Dekker: New York, 1974; pp 296-301. (b) Simonet, J. In "Organic Electrochemistry, An Introduction and a Guide", 2nd ed.; Baizer, M. M., Lund, H., Eds.; Marcel Dekker: New York, 1983; pp 863-865.

[7] Cohen, Dawson, and Crosland[8] reported that anodic oxidations of hydrochloric acid with toluene at refluxing temperature gave *p*-chlorotoluene as the major product. The authors distilled the para isomer out, and *o*-chlorotoluene was left in the residue. The boiling points of *p*-chlorotoluene and *o*-chlorotoluene, however, are 162 and 157-159 °C, respectively.[9] We repeated the experiment and *p*-chlorotoluene to *o*-chlorotoluene to benzyl chloride ratio was 23:51:26.

[8] Cohen, J. B.; Dawson, M. H.; Crosland, P. F. *J. Chem. Soc.* **1905**, *87*, 1034-1037.

[9] West, R. C., Ed. "CRC Handbook of Chemistry and Physics", 62nd ed.; CRC Press, Inc.: Cleveland, OH, 1981.

[10] Gourcy, J.; Simonet, J.; Jaccaud, M. *Electrochimica Acta* **1979**, *24*, 1039-1046.

[11] Osa, T.; Fujihira, M.; Matsue, T.; Yamauchi, T. U.S. Patent 4269674, May 1981.

[12] Lithium chloride was only partially soluble in acetonitrile.

[13] Solvent effects on the isomer distribution in the chlorination of toluene was studied by Stock and Himoe.[14] In acetonitrile, para/ortho = 1.6. The reaction rate, however, was relatively slow, and the reaction was only done for kinetic investigation. Conversion of toluene was very low.

[14] Stock, L. M.; Himoe, A. *Tetrahedron Lett.* **1960**, 9-13.

[15] Kolthoff, I. M.; Coetzer, J. F. *J. Am. Chem. Soc.* **1957**, *79*, 1852-1858. Potentials in,the paper were measured vs. standard calomel electrode (SCE). They are converted to potentials vs. Ag/Ag^+ (0.01 M) for discussion convenience.

[16] Siegerman, H. In "Technique of Electroorganic Synthesis"; Weinberg, N. L., Ed.; Wiley: New York, 1975; Part II, p 690.