Reagents for Bioorganic Synthesis: Preparation, Properties, and Reactions of Ethyl and Methyl *N*-(Cyanomethyl)methanimidates[1,2]

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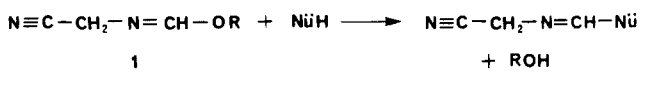
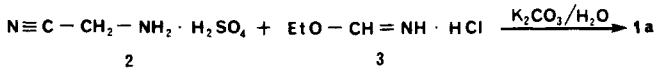
An efficient procedure for the preparation of the reagents ethyl and methyl *N*-(cyanomethyl)methanimidates ($NCCH_2N{=}CHOR$) (**1a**, R = Et; **1b**, R = Me) is presented, along with their preliminary properties and reactions. The reaction of aminoacetonitrile hydrochloride with trialkyl orthoformate gave 4(5)-imidazolone. The reaction of aminoacetonitrile (free base) with the ortho ester, catalyzed by formic acid, gave methyl *N*-7*H*-imidazo[1,5-*a*]imidazol-2-ylmethanimidate (**6**). The reaction of **1b** with 2-aminothiazole and 2-aminopyrimidine, catalyzed by trimethylsilyl triflate, gave 2-(5′-imino-2′-imidazolin-1′-yl)thiazole (**9**) and 2-(5′-imino-2′-imidazolin-1′-yl)-pyrimidine (**10**), respectively. Compound **10** underwent facile acid hydrolysis to form 2-(formylamino)pyrimidine (**11**). The reactions of 2-aminothiazole with 2 equiv of **1b** or that of **10** with 1 equiv of **1b** both provided 2-[5′-(5″-imino-2″-imidazolin-1″-yl)imidazol-1′-yl]thiazole (**12**).

N-(Cyanomethyl)methanimidates (**1**) are potentially



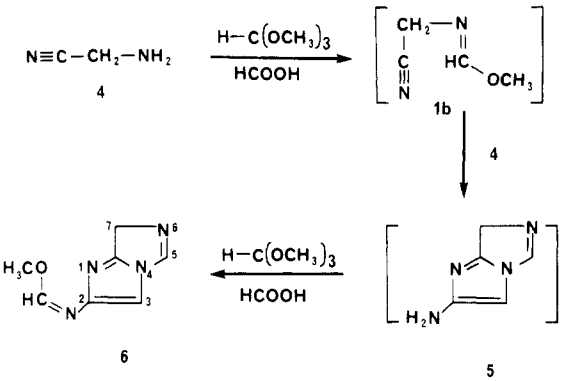
useful reagents in bioorganic synthesis, permitting incorporation of a CNCCN synthetic fragment onto nucleophiles in one step. The ethyl ester **1a** (R = Et) has been prepared in a very low yield in aqueous solution by the reaction of aminoacetonitrile bisulfate (**2**) with ethyl formimidate hydrochloride (**3**) in the presence of potassium carbonate.[3] We now report an improved procedure for preparing **1** in practical yields by using a nonaqueous medium and some reactions of these imidates.



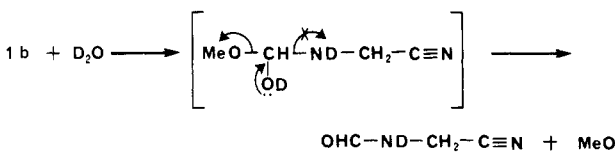
In our initial attempt to prepare **1**, the reaction of aminoacetonitrile hydrochloride with trimethyl orthoformate led, in >90% yield, to a product whose properties established the structure as 4(5)-imidazolone,[4] evidently arising by the initial formation of the intermediate **1**, followed by alcoholysis of the nitrile function of **1** and ring closure to form 5-methoxy-4*H*-imidazole (or its 1*H* tautomer), and the subsequent dealkylation by HCl. This mechanism was supported by the reaction of **1** with methanolic hydrogen chloride, which, in fact, gave the above imidazolone.[4] This compound, which is speculated to be an intermediate in the biological degradation of xanthine to formiminoglycine but has not been isolated,[5,6] could not be obtained from the reaction of glycinamide with the ortho ester.

Condensation of the free aminoacetonitrile (**4**) with trimethyl orthoformate in the presence of formic acid gave methyl *N*-7*H*-imidazo[1,5-*a*]imidazol-2-ylmethanimidate (**6**) (Scheme I), presumably by sequential incorporation

Scheme I

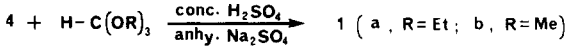


Scheme II



of a 2nd mol of aminoacetonitrile into the intermediate **1b** to form **5**, which further reacts with the ortho ester. The substitution of the more reactive dialkoxymethyl acetate[7] for trialkyl orthoformate only afforded (acetylamino)acetonitrile.[8]

The successful synthesis of **1** was accomplished by the reaction of **4** with trialkyl orthoformates, with concentrated



sulfuric acid as a catalyst. Both **1a** and **1b** are colorless, resonably stable liquids which could be stored, free of moisture, in a refrigerator for several months.

The reactivity of **1b**[9] was investigated employing H_2O/D_2O as a nucleophile. The ^1H NMR spectrum of the mixture of **1b** and D_2O was monitored with time, and by separate external addition of the products of the reaction, it was concluded that methanol, and not aminoacetonitrile,

(1) Presented to Professor Nelson J. Leonard of the University of Illinois, Urbana, on his birthday.
(2) (a) This paper has been presented, see: "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept 2, 1983; American Chemical Society: Washington, DC, 1983; Abstr ORGA 168. (b) Communication: Hosmane, R. S. *Tetrahedron Lett.* **1984**, *25*, 363.
(3) Shaw, G.; Warrener, R. N.; Butler, D. N.; Ralph, R. K. *J. Chem. Soc.* **1959**, 1648.
(4) Hosmane, R. S. *Liebigs Ann. Chem.*, in press.
(5) Freter, K.; Rabinowitz, J. C.; Witkop, B. *Ann. Chem.* **1957**, *607*, 174.
(6) Oien, H. G.; Wright, L. D. *J. Bacteriol.* **1971**, *105*, 1229.
(7) Montgomery, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 1928.
(8) Johnson, T. B.; Gatewood, E. *J. Am. Chem. Soc.* **1929**, *51*, 1815.
(9) Our preference for reagent **1b** over **1a** lies in the ease of preparation of the former. Trimethyl orthoformate, with its low enough boiling point, coud be conveniently removed on a rotary evaporator after the reaction was complete.

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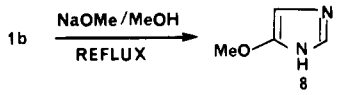
was the leaving group from the intermediate adduct (7) (Scheme II) formed from **1b** with nucleophiles.

The reagent **1b** reacted only slowly with sodium meth-



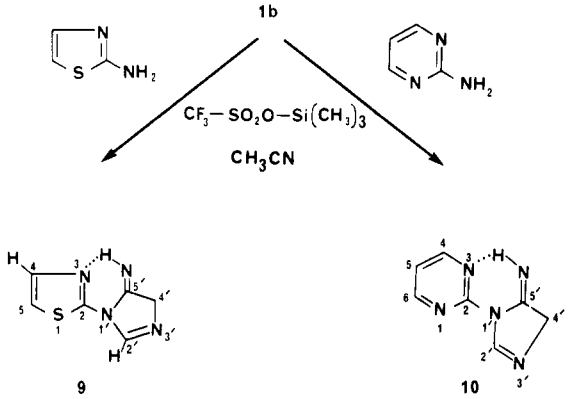
oxide/methanol at room temperature but at reflux rapidly provided 4(5)-methoxyimidazole (**8**),[10] thus pointing to the susceptibility of the nitrile function of **1b** to strong base/nucleophile under strenuous reaction conditions.

Reactions of the reagent **1a** with methyl- and ethylamines are reported to yield the respective 1-methyl- and 1-ethyl-4(5)-aminoimidazoles (as their picrate derivatives) in low yields.[3] Analogous reactions of **1a** or **1b** with heterocyclic amines, e.g., 2-aminothiazole and 2-aminopyrimidine, under a variety of experimental conditions led to the recovery of the starting materials or resulted in intractable mixtures of products. However, the use of trimethylsilyl triflate[11] as a Lewis acid catalyst[12] facilitated the reactions of 2-aminothiazole and 2-aminopyrimidine (Scheme III) with **1b**, and new products were isolated in excellent yields. The ^{1}H NMR, ^{13}C NMR, and mass spectral analyses, coupled with the microanalytical data of the compounds, established their structures as 2-(5′-imino-2′-imidazolin-1′-yl)thiazole (**9**) and 2-(5′-imino-2′-imidazolin-1′-yl)pyrimidine (**10**), respectively. The infrared spectra of both **9** and **10** exhibited a strong hydrogen-bonded imine NH stretching frequency in the region 3100–2700 cm^{-1}.

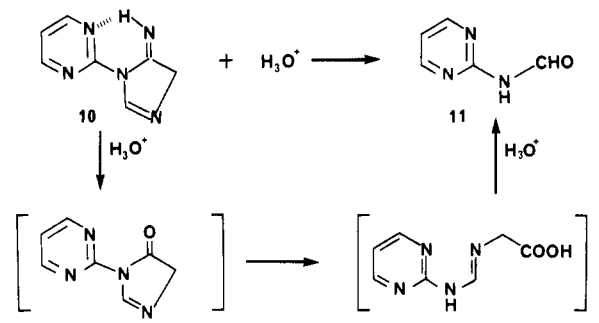
Compound **10** underwent slow decomposition at room temperature over a period of several days. It also underwent facile hydrolysis, catalyzed by formic acid, to yield 2-(formylamino)pyrimidine (**11**).[13] A reaction pathway for the hydrolysis sequence is proposed in Scheme IV. Compound **9** on the other hand, revealed no apparent change when subjected to the identical hydrolysis conditions employed for **10**. The reason for the difference in the reactivity of **9** and **10** toward hydrolysis is not known at this point.[14]

The above results with 1 equiv of **1b** prompted us to attempt the reaction of the heterocyclic amines with ad-

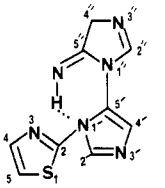
Scheme III



Scheme IV



ditional equivalents of this reagent. As expected, the reaction of 2-aminothiazole with 2 equiv of **1b** or the reaction of **9** with 1 equiv of **1b** both gave rise to **12**. The ^{1}H NMR



12

spectrum of **12** (in deuterated dimethyl sulfoxide) revealed three CH singlets at δ 6.93, 7.66, and 8.3 assignable to H-4′, H-2″, and H-2′, respectively, two CH doublets (J = 3.5 Hz) at δ 7.30 and 7.53 corresponding to the thiazole H-4 and H-5, a CH_2 singlet at δ 5.27, and a broad imine NH signal, exchangeable with D_2O, at δ 11.7. The infrared spectrum of the compound once again revealed a strong hydrogen-bonded NH stretching frequency ranging from 3100 to 2700 cm^1. The elemental microanalyses, in conjunction with the mass spectral data [m/e 232 (M^+)], confirmed 2-[5′-(5″-imino-2″-imidazolin-1″-yl)imidazol-1′-yl]thiazole (**12**) as the product.

Implications of the formation of **12** in the above reaction are intriguing in view of the anticipated imidazole ring propagation with additional equivalents of the reagent **1b**. We are presently investigating the possibility of forming heterocyclic polymers by reacting 2-aminothiazole and other heterocyclic amines with several equivalents of the reagent **1b**.

Experimental Section

Proton nuclear magnetic resonance spectra were recorded on an IBM NR/80 spectrometer. ^{13}C NMR spectra were run on an IBM 200SY instrument at the University of Maryland, College Park. Data are reported as follows: chemical shift, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet), integration. The electron-impact (EI) mass spectra were performed at the School of Pharmacy, University of Maryland, 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 Hitachi Perkin-Elmer 700 instrument. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

***N*-7*H*-Imidazo[1,5-*a*]imidazol-2-ylmethanimidate (6).** Aminoacetonitrile hydrochloride (9.25 g, 0.1 mol) was added portionwise to a solution of potassium carbonate (16 g, 0.116 mol) in water (20 mL) and stirred vigorously for 5 min. The aqueous solution was extracted with AcOEt (3 × 200 mL), the combined extracts were dried over anhydrous potassium carbonate, and the solvent was evaporated to dryness on a rotary evaporator at 37 °C. The residual oil was mixed with trimethyl orthoformate (50 mL, 0.46 mol), and 5 drops of formic acid and the mixture were heated at reflux under anhydrous conditions (guard tube) for 23 h. TLC (4:1 $CHCl_3$/MeOH) showed that a new, less polar, UV-absorbing compound had formed. The reaction mixture was evaporated to dryness on a rotary evaporator at 37 °C to obtain

(10) An examination of the literature revealed that this simple imidazole derivative is still unknown.

(11) See, for example: Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71.

(12) Stang, P. J.; White, M. R. *Aldrichim. Acta* **1983**, *16*, 15.

(13) Kondo, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1443.

(14) One of the referees offered the following explanation: Thiazole is orders of magnitude more basic than pyrimidine; thus, **9** would protonate on the thiazole ring, and this would deactivate the imidazole toward protonation and subsequent hydrolysis. The less basic pyrimidine **10** would protonate on the imidazole and, thus, be prone to hydrolysis.

an oil, which was distilled in a Kügelrohr apparatus at 160–175 °C (oven temperature) at 350 μmHg. The colorless distillate crystallized into a white solid upon cooling to room temperature. Resublimation of the solid in the Kügelrohr at 90–100 °C (oven temperature) and 300 μmHg afforded **6** as white crystals, which were recrystallized from dry toluene (4 g, 0.024 mol, 24%): mp 101–102 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.86 (s, 3, OMe), 5.2 (s, 2, CH_2), 6.78 (d, J = 0.9 Hz, 1, H-3), 7.6 (d, J = 0.9 Hz, 1, H-5), 8.37 (s, 1, side-chain CH); IR (KBr) 2900 (CH), 1640 (C=C) cm^{-1}; mass spectrum (relative intensity) (70 eV), m/e 164 (M^+, 100), 133 (M^+ – OMe, 4.7), 124 (13.3), 109 (4.9), 94 (25.3), 80 (16.2), 67 (41), 42 (13.4), 39.8 (19.5), 28 (13.2).

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.36;, H, 5.02, N, 34.28.

Methyl *N*-(Cyanomethyl)methanimidate (1b). Potassium carbonate (17 g, 0.123 mol) was dissolved in water (20 mL), and aminoacetonitrile hydrochloride (23 g, 0.25 mol) was added portionwise with stirring. After most of the effervescence subsided, the aqueous mixture was extracted with AcOEt (5 × 300 mL). The combined extracts were dried over anhydrous K_2CO_3, and the solvent was evaporated to dryness on a rotary evaporator at 40 °C to obtain an oil, which was distilled in a Kügelrohr apparatus at 40–60 °C (oven temperature) and 140 μmHg to obtain a colorless liquid, aminoacetonitrile (**4**, free base) (11.5 g, 0.21 mol, 82%): ^{1}H NMR (Me_2SO-d_6) δ 3.49 (s, 2, CH_2), 2.06 (s, 2, NH_2, exchangeable with D_2O); IR (neat) 3400 (NH), 2990 (CH) 2300 (C≡N), 1620 (NH) cm^{-1}.

The above oil (8 g, 0.14 mol) was added dropwise with the aid of a hypodermic syringe to the gently distilling suspension of trimethyl orthoformate (200 mL), anhydrous sodium sulfate (20 g, 0.14 mol), and concentrated H_2SO_4 (2 drops), contained in a 300-mL three-necked flask protected from atmospheric moisture and fitted with a distillation setup, serum cap, and a magnetic stirrer. The rate of distillation was maintained at 55 drops/min. The addition took a total time of 10 min. The distillation was continued for an additional 15 min. The reaction mixture had turned into a yellow-orange solution. The mixture was cooled, and the supernatant liquid was transferred to a clean, dry flask and evaporated to dryness on a rotary evaporator at 40 °C to obtain an oil, which was distilled in vacuo on a Kügelrohr apparatus at 30–40 °C (oven temperature) and 150–200 μmHg to obtain **1b** as a colorless liquid (12.9 g, 0.13 mol, 94%): ^{1}H NMR (Me_2SO-d_6) δ 3.65 (s, 3, CH_3), 4.35 (s, 2, CH_2), 7.9 (s, 1, CH); IR (neat) 3000 (=CH), 2300 (C≡N), 1680–1660 (C=N) cm^{-1}; mass spectrum (relative intensity) (70 eV) m/e 98 (M^+, 8) 67 (M^+ – OCH_3, 93), 58 (M^+ – CH_2CN, 100).

Anal. Calcd for $C_4H_6N_2O$: C, 48.97; H, 6.16; N, 28.55. Found: C, 48.97; H, 6.18; N, 28.46.

Ethyl *N*-(Cyanomethyl)methanimidate (1a). This reagent was prepared by following the procedure described abbove for **1b**, in >90% yield: bp 60 °C (1 mm/Hg) [lit.[3] 51 °C (0.8 mm)]; ^{1}H NMR (Me_2SO-d_6) δ 1.22 (t, J = 7.0 Hz, 3, CH_3), 4.08 (q, J = 7.0 Hz, 2, CH_2 of OEt), 4.33 (s, 2, CH_2), 7.85 (s, 1, CH).

4(5)-Methoxyimidazole (8). A solution of sodium methoxide, prepared from sodium (230 mg, 10 mmol) and MeOH (15 mL), was heated to reflux under N_2. The reagent **1b** (1 g, 10.2 mmol) was introduced through a hypodermic syringe during a period of 10 min. The reaction mixture was continued to reflux for 2 h to form a clear orange solution, which was cooled and carefully neutralized with concentrated HCl. The precipitated NaCl was filtered, and the filtrate was evaporated to dryness. The residue was purified by flash chromatography on a column of silica gel (particle size 40–63 μm, 30 g) with $CHCl_3$/acetone (1:1) as the eluting solvent (flow rate 6 mL/min at 4 psi). The appropriate fractions were pooled and evaporated to obtain crystalline **8** (600 mg, 6.1 mmol, 60%): mp 115–116 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.65 (s, 3, OMe), 6.37 [d, J 1.5 Hz, 1, H-4(5)], 7.23 (d, J = 1.5 Hz, 1, H-2); mass spectrum (70 eV), m/e 98 (M^+).

Anal. Calcd for $C_4H_6N_2O$: C, 48.97; H, 6.16; N, 28.55. Found: C, 48.72; H, 6.21; N, 28.79.

2-(5′-Imino-2′-imidazolin-1′-yl)thiazole (9). A mixture of 2-aminothiazole (0.5 g, 5 mmol) and dry CH_3CN (15 mL) was stirred under N_2 on a magnetic stirrer at room temperature to form a clear solution. Methyl *N*-(cyanomethyl)methanimidate (**1b**; 0.5 g, 5.1 mmol) was introduced through a hypodermic syringe during a period of 2 min, followed by trimethylsilyl triflate (0.025 mL, 0.13 mmol). The whole reaction mixture was stirred under N_2 for an additional 2 h. TLC ($CHCl_3$/acetone, 1:1) indicated the formation of a UV-absorbing compound, which was slightly less polar than the starting material. The reaction mixture was evaporated to dryness on a rotary evaporator, and the residue was triturated with H_2O (25 mL) and stirred for 0.5 h. The precipitate was filtered in vacuo, air-dried, and recrystallized from toluene to afford **9** as colorless needles (760 mg, 4.58 mmol, 91%): mp 126 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 4.33 and 4.39 (2 pseudo s, 2, CH_2), 7.13 (d, J = 3.7 Hz, 1, thiazole H-4), 7.35 (d, J = 3.7 Hz, 1, thiazole H-5), 8.34 (br s, 2, H-2′ and NH of iminoimidazoline); ^{13}C NMR (Me_2SO-d_6) δ 28.55 (t, $^1J_{C_4'-H_4'}$ = 148 Hz, C-4′), 113.99 (d, $^1J_{C_4-H_4}$ = 191 Hz, C-4), 116.98 (s, C-5′), 139.67 (d, $^1J_{C_5-H_5}$ = 191 Hz, C-5), 153.06 (d, $^1J_{C_2'-H_2'}$ = 181 Hz, C-2′), 173.29 (s, C-2); IR (KBr) 3100–2700 cm^{-1}; mass spectrum (70 eV), m/e 166 (M^+), 139 (M^+ – HCN), 126 (M^+ – CH_2CN).

Anal. Calcd for $C_6H_6N_4S$: C, 43.36; H, 3.64; N, 33.71. Found: C, 43.49; H, 3.61; N, 33.53.

2-(5′-Imino-2′-imidazolin-1′-yl)pyrimidine (10). 2-Aminopyrimidine (475 mg, 5 mmol) was suspended in dry CH_3CN (10 mL) and stirred at room temperature under N_2 to form a clear solution. The reagent **1b** (0.5 g, 5.1 mmol) was introduced through a hypodermic syringe over a period of 1–2 min with stirring, followed by trimethylsilyl triflate (0.025 mL, 0.13 mmol). The whole reaction mixture was allowed to stir for an additional 1 h. Any precipitate that formed was removed by filtration [Note: This solid was identified as 2-(formylamino)pyrimidine, and its yield varied, depending upon how anhydrous conditions were maintained: see below], and the filtrate was evaporated to dryness on a rotary evaporator to afford a solid. This solid was triturated with 10 mL of H_2O, stirred for $^1/_2$ h, filtered in vacuo, and dried to obtain **10** as a white solid (660 mg, 4.09 mmol, 82%): mp 158 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 4.42 and 4.49 (2 pseudo s, 2, CH_2), 7.05 (dd, J = 4.8 and 4.7 Hz, 1, pyrimidine H-5), 8.55 (2 overlapping d, J = 4.8 and 4.7 Hz, 2, pyrimidine H-4 and H-6), 8.79 (s, 1, iminoimidazoline H-2′), 10.45 (br, 1, NH, exchangeable with D_2O); IR (KBr) 3100–2700 cm^{-1}; mass spectrum (70 eV), m/e 161 (M^+), 134 (M^+ – HCN), 121 (M^+ – CH_2CN).

Anal. Calcd for $C_7H_7N_5$: C, 52.00; H, 4.37; N, 43.33. Found: C, 52.29; H, 4.54; N, 43.13.

Hydrolysis of 2-(5′-Imino-2′-imidazolin-1′-yl)pyrimidine (10). A mixture of **10** (100 mg, 0.62 mmol), CH_3CN (20 mL), H_2O (0.3 mL, 16.7 mmol), and HCO_2H (0.025 mL, 0.66 mmol) was stirred at room temperature for 6 h. TLC (silica gel; $CHCl_3$/acetone, 1:1) indicated the formation of a less polar (than **10**), UV-absorbing compound. The reaction mixture was evaporated to dryness on a rotary evaporator, and the residue was recrystallized from EtOH/ligroin to give 2-(formylamino)pyrimidine (**11**) as colorless needles (72 mg, 0.59 mmol, 94%): mp 200–202 °C (lit.[13] mp not reported); ^{1}H NMR (Me_2SO-d_6) δ 7.21 (dd, J = 4.8 and 4.7 Hz, 1, H-5), 8.62 (2 overlapping d, J = 4.8 and 4.7 Hz, 2, H-4 and H-6), 9.39 (d, J = 9.9 Hz, 1, CHO, collapsing to a singlet with D_2O exchange), 11.0 (br, 1, NH, exchangeable with D_2O).

2-[5′-(5″-Imino-2″-imidazolin-1″-yl)imidazol-1′-yl]thiazole (12). Method A. A mixture of 2-aminothiazole (1.0 g, 10 mmol) and dry CH_3CN (30 mL) was stirred under N_2 for 10 min. The reagent **1b** (2.0 mL, 20.4 mmol) was introduced through a hypodermic syringe over a period of 4 min, followed by trimethylsilyl triflate (0.05 mL, 0.26 mmol). This mixture was stirred under N_2 for 4 days, and the solvent was evaporated to dryness. The residue was triturated with 50 mL of H_2O and stirred for $^1/_2$ h, and the resulting solid was filtered, washed with H_2O, and air-dried. The solid thus obtained was suspended in 50 mL of toluene, heated to boiling, and filtered while hot. The precipitate was recrystallized from AcOEt into white crystals of **12** (1.2 g, 5.2 mmol, 52%): mp 206 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 5.27 (s, 2, CH_2), 6.93 (s, 1, imidazole H-4′), 7.30 (d, J = 3.5 Hz, 1, thiazole H-4), 7.53 (d, J = 3.5 Hz, 1, thiazole H-5), 7.66 (s, 1, iminoimidazoline H-2″), 8.3 (s, 1, imidazole H-2′), 11.7 (br, s, 1, imine NH, exchangeable with D_2O); IR (KBr) 3100–2700 cm^{-1}; mass spectrum (70 eV), m/e 232 (M^+).

Anal. Calcd for $C_9H_8N_6S$: C, 46.54; H, 3.47; N, 36.19. Found: C, 46.48, H, 3.47; N, 36.04.

Method B. The procedure adopted was essentially the same as described above in method A, except that 2-(5′-imino-2′-

imidazolin-1′-yl)thiazole (9) (instead of 2-aminothiazole) and 1 equiv of the reagent 1b (instead of 2 equiv as used in method A) were employed. The yields were comparable within ±5% to that obtained by method A.

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Registry No. 1a, 88945-40-8; 1b, 88945-41-9; 4, 540-61-4; 4·HCl, 6011-14-9; 6, 88945-42-0; 8, 88945-43-1; 9, 88945-44-2; 10, 88945-45-3; 11, 31354-57-1; 12, 88945-46-4; 2-aminothiazole, 96-50-4; 2-aminopyrimidine, 109-12-6.

Reduction of Aromatic Nitro Compounds by Ethylenediamine. A New Selective Reagent for the Synthesis of Symmetric Azo Compounds

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Ethylenediamine selectively reduces aromatic nitro compounds $RC_6H_4NO_2$ (R = H, *m*-CH_3, *p*-CH_3, and *m*-Ph) at 150 °C to symmetric azo compounds $RC_6H_4N{=}NC_6H_4R$ in good yield but does not reduce their ortho-substituted analogues. The diamine does not react with *o*- or *p*-nitroanilines but reduces the meta isomer to 1,3-diaminobenzene and 3,3′-diaminoazobenzene. Its reaction with *o*- and *p*-halonitrobenzenes gives substitution products $H_2NCH_2CH_2NHC_6H_4NO_2$. Nitrosobenzene is reduced to aniline and azobenzene, while α-nitroso-β-naphthol is converted to 1,4-phenanthroline. Among a variety of other amines tested, only 1,3-propylenediamine reduces nitrobenzene to azobenzene. A mechanism for the reaction is proposed.

Introduction

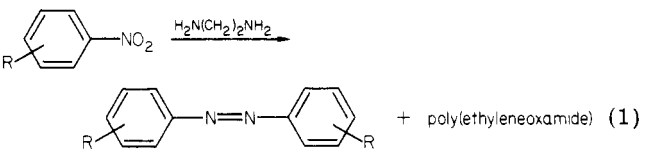
Methods for selective reduction of aromatic nitro compounds to azo compounds are of continuing interest.[1-5] Although many reagents have been developed for this reduction, most of them give low yields of azo compounds. An exception is zinc powder in basic solution, which converts nitrobenzene to azobenzene in 85% yield.[1b] $NaBH_4$,[1h] $LiAlH_4$, $NaAlH_4$,[1e-j] and $NaH_2Al(OCH_3)(OC_2H_5)$[1f] have also been used for this reduction. While both boron and aluminum hydrides reduce nitro compounds to azo compounds in good yields, the former are less reactive and require a much higher temperature for the reduction.

In our studies on the catalytic reduction of aromatic nitro compounds by alcohols and alkyl amines[6] we have discovered that ethylenediamine reduces aromatic nitro compounds to the corresponding azo compounds in good yield (eq 1). We now report the results of this investigation.

Table I. Reduction of Aromatic Nitro Compounds by Ethylenediamine

nitro compd	product and yield[a]
nitrobenzene	azobenzene 75%, aniline (10%)
p-nitrotoluene	4,4′-azotoluene 97%
m-nitrotoluene	3,3′-azotoluene 86%, *m*-toluidine (12%)
o-nitrotoluene	no reaction
p-nitroaniline	no reaction
m-nitroaniline	3,3′-diaminoazobenzene 24%, phenylenediamine 75%
o-nitroaniline	no reaction
m-nitrobiphenyl	3,3′-diphenylazobenzene 68%
nitrosobenzene	azobenzene (16%), aniline (83%)
α-nitroso-β-naphthol	1,4-phenanthroline (65%)

[a] Isolated yields; yield in parentheses were estimated by NMR.



(1)

Results and Discussion

The reduction is performed by heating a mixture of the nitro compound and 4–10 equiv of ethylenediamine at 150 °C for 10–22 h. The reaction is carried out in a vessel that can contain the pressure (~2 atm) developed by the ethylenediamine. Yields of azo compounds prepared by this method are presented in Table I. Nitrobenzene is reduced mainly to azobenzene and ca. 10% aniline as shown by NMR spectroscopy. The attachment of a methyl

(1) (a) Tabei, K.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1538. (b) Bigelow, E.; Robinson, D. B. "Organic Syntheses"; Wiley: New York, 1955; Collect Vol 3, p 103. (c) Nystron, R. F.; Brown, W. J. *J. Am. Chem. Soc.* **1948**, *70*, 3738. (d) Dewar, M. J. S.; Goldberg, R. S. *Tetrahedron Lett.* **1966**, 2717. (e) Finholt, A. E.; Jacobson, E. C.; Ogard, A. E.; Thompson, P. *J. Am. Chem. Soc.* **1955**, *77*, 4136. (f) Corbett, J. F. *Chem. Commun.* **1968**, 1257. (g) Meltsner, M.; Greenstein, L.; Gross, G.; Cohen, M. *J. Am. Chem. Soc.* **1937**, *59*, 2660. (h) Goerrig, D. *Neth. Appl.* 6,409,225. (i) Alper, H.; Paik, H.-N. *J. Organomet. Chem.* **1978**, *144*, C18. (j) Knipe, A. C.; McGuinness, J.; Watts, W. E. *J. Organomet. Chem.* **1979**, *172*, 463.

(2) (a) Landesberg, J. M.; Katz, L.; Olsen, C. *J. Org. Chem.* **1970**, *37*, 930. (b) Knifton, J. F. *J. Org. Chem.* **1973**, *38*, 3296. (c) Watanabe, Y.; Mitsudo, T.; Yamashita, M.; Takegami, Y. *Bull Chem. Soc. Jpn.* **1975**, *48*, 1478. (d) Alper, H.; Hashem, K. E. *J. Am. Chem. Soc.* **1981**, *103*, 6514 and references cited therein.

(3) Bigelow, H. E.; Palmer, A. "Organic Syntheses"; Wiley: New York, 1943; Collect Vol 2, p 57 and references therein.

(4) Fox, B. A.; Threlfall, T. L. "Organic Syntheses"; Wiley: New York, 1973; Collect Vol 5, p 346.

(5) Lindsay, R. J. "Comprehensive Organic Chemistry"; Pergamon Press: Oxford, 1979; Vol 2.

(6) Liou, K. F.; Cheng, C. H. *J. Org. Chem.* **1981**, *47*, 3018. Unpublished results.

0022-3263/84/1949-1215$01.50/0