Reagents for Bioorganic Synthesis. 2. Methyl *N*-(Dicarbomethoxymethyl)methanimidate[1]

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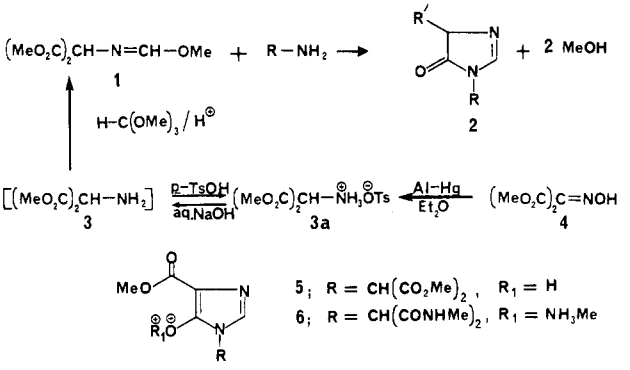
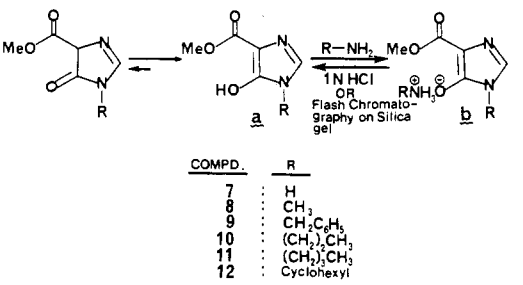
Preparation, properties, and reactions of the reagent methyl *N*-(dicarbomethoxymethyl)methanimidate (**1**) are reported. Dropwise addition of dimethyl aminomalonate to refluxing trimethyl orthoformate/TFA afforded **1**. Treatment of **1** with ammonia and various primary amines gave the corresponding unsubstituted and 1-substituted 4-carbomethoxy-5-hydroxyimidazoles **7–12**, either as the parent hydroxy compounds (**a**) or as the (alkyl)ammonium salts (**b**). The reaction of **1** with water and sodium hydrosulfide provided dimethyl *N*-formylaminomalonate (**13**) and dimethyl *N*-(thioformyl)aminomalonate (**14**), respectively. The reaction of **1** with excess sodium hydrosulfide resulted in the formation of methyl *N*-(thioformyl)aminoacetate (**17**). Conversions of methylammonium 4-carbomethoxy-1-methylimidazol-5-olate (**8b**) and benzylammonium 4-carbomethoxy-1-benzylimidazol-5-olate (**9b**) into 5-(benzylamino)-4-(benzylcarbamoyl)-1-methylimidazole (**18**) and 1-benzyl-5-(benzylamino)-4-(benzylcarbamoyl)imidazole (**19**), respectively, were each accomplished in a single-pot procedure, employing phenylphosphonic dichloride as the key reagent.

Esters of imidic acids are an important class of reagents which have found wide use in organic/bioorganic synthesis.[2] As a further demonstration of their versatility, we present here the preparation, properties, and reactions of methyl *N*-(dicarbomethoxymethyl)methanimidate (**1**). This reagent permits the incorporation of a synthetic fragment $CNC(CO_2Me)CO$- onto nucleophiles in a single step. With amine nucleophiles, in particular, the reaction leads to the formation of 1-substituted 4-carbomethoxy-2-imidazolin-5-ones (**2**, R = alkyl; R′ = CO_2Me) (Scheme I). Imidazolinones bearing the general structure **2** are important as (a) catabolites in the biological degradation of xanthine to *N*-(iminomethyl)glycine,[3,4] (b) labile entities in the microbial degradation of a variety of imidazole derivatives,[5] and (c) as analogues of the naturally occurring potent antiviral/antitumor nucleoside, bredinin (**2**, R = β-D-ribofuranosyl; R′ = $CONH_2$).[6] However, little is known on the chemistry of imidazolinones. While a few mono- and disubstituted imidazolin-4-ones have been prepared,[7a] attempts to synthesize the parent **2** (R = R′ = H) have met with failures,[3,7b,c] and the only reported synthesis of **2** (R = H, R′ = CO_2Et) suffers from poor yields and is not general.[8] The reagent **1** provides an access to this important class of heterocycles.

Scheme I



Scheme II



COMPD.	R
7	H
8	CH_3
9	$CH_2C_6H_5$
10	$(CH_2)_2CH_3$
11	$(CH_2)_3CH_3$
12	Cyclohexyl

Compound **1** was prepared (Scheme I) by the slow dropwise addition of dimethyl aminomalonate (**3**) to a large excess of refluxing trimethyl orthoformate, containing catalytic amounts of trifluoroacetic acid. The amine **3**, in turn, was obtained from the corresponding isonitrosomalonate (**4**)[9a] by convenient reduction with aluminum amalgam[9b] instead of catalytic hydrogenation at 1800 psi.[9a] The amine **3** being unstable was stored as a stable, crystalline salt of *p*-toluenesulfonic acid (**3a**) and was regenerated, as necessary, upon treatment with aqueous sodium hydroxide. The reagent **1** was a colorless liquid which could be stored as a low-melting solid in a refrigerator, with protection from moisture, for several months. The ^1H NMR, IR, mass spectral, and microanalytical data of **1** (see

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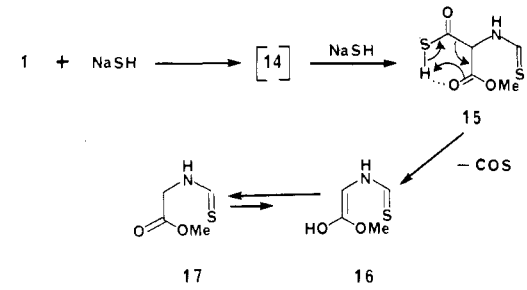
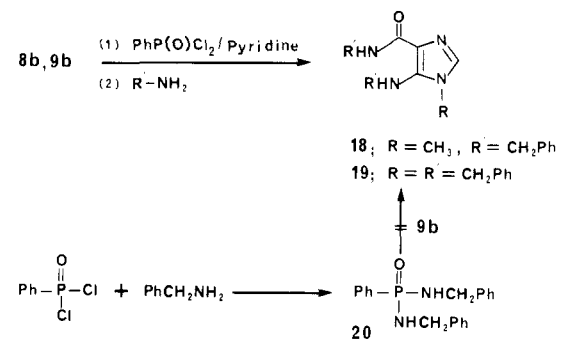
Scheme III



Scheme IV

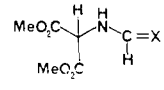


Experimental Section) were consistent with the assigned structure.

The mode of addition of the reactants played a crucial role in the formation of the reagent **1**. For example, when the reactants **3**, the ortho ester, and the acid were simply mixed and heated at reflux or when a weaker acid such as glacial acetic acid was employed as a catalyst in the dropwise addition procedure described above, a different product was obtained whose spectral and microanalytical data (see Experimental Section) led to the assignment of its structure as 4-carbomethoxy-1-(dicarbomethoxymethyl)-5-hydroxyimidazole (**5**) (Scheme I). Treatment of **5** with methylamine yielded a diamide derivative, isolated as its methylammonium salt (**6**). Compound **5** is apparently formed via condensation of the preformed **1** with the unreacted **3** and the subsequent ring-closure of the intermediate amidine.

The reagent **1** was treated with six primary amines at room temperature: ammonia and methyl-, benzyl-, propyl-, butyl-, and cyclohexylamine. The respective imidazolinones **7–12** (Scheme II) were isolated as theiry hydroxy tautomers, as detected by ^{1}H NMR, either in the parent forms (a) or as the ammonium (alkylammonium) salts (b) or both. The formation of **a** or **b** was dependent upon whether an equivalent or an excess of the amine was employed in the ring-closure reaction. The two forms were interconvertible: **a** → **b** by treatment with excess amine and **b** → **a** by 1 N hydrochloric acid or by flash chromatography on silica gel or more conveniently by heating with phenylphosphonic dichloride, followed by hydrolysis. In general, the ^{1}H NMR resonances of both the ester methyls and the imidazole CH's showed upfield shifts of ~0.1 and 1 ppm, respectively, in salts (**b**) as compared with those in the parent compounds (**a**). While the mass spectra of **a** exhibited the molecular ion peaks, those of **b** revealed the loss of R–NH_2 from the molecular ions. Both **a** and **b** displayed a characteristic fragmentation pattern: the initial loss of methanol from the parent ion, followed by the loss of carbon monoxide.

Reactivity of **1** toward oxygen and sulfur nucleophiles was also investigated. Thus, the reaction of **1** with water yielded dimethyl *N*-formylaminomalonate (**13**) and that with sodium hydrosulfide hydrate ($NaSH \cdot xH_2O$) provided dimethyl *N*-(thioformyl)aminomalonate (**14**). The product



13; X = O

14; X = S

structures were consistent with their IR, NMR, and mass spectral data and their melting points were in agreement with the reported values.[10,11]

The reaction of **1** with excess sodium hydrosulfide yielded a low-melting solid which had a lower mobility than **14** [silica gel, $CHCl_3$:acetone (9:1)]. The same product was obtained by treatment of **14** with excess NaSH. The assigned structure, methyl *N*-(thioformyl)aminoacetate (**17**) (Scheme III) for this product was in agreement with its ^{1}H NMR, IR, mass spectrum, and microanalyses. Thiolysis of the intermediate **14** (to yield **15**), followed by the loss of carbonyl sulfide (to form **16**) and subsequent tautomerization, explains the formation of **17** in the above reaction.

The compounds **8b** and **9b** were converted into **18** and **19**, respectively (Scheme IV), upon reaction with phenylphosphonic dichloride in pyridine, followed by treatment with benzylamine. This reaction required an initial high heating of the hydroxyimidazoles with $PhP(O)Cl_2$ prior to the addition of the primary amine, otherwise the undesired **20** would be formed. Since the separate reactions of **20** with **9b** failed to produce **19** under a variety of experimental conditions, **20** is not believed to be an intermediate in this conversion. The study of the mechanism of this conversion and its potential applicability to other heterocyclic systems bearing vinylogous hydroxy ester groups is under investigation.

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) and integration. The electron impact (EI) mass spectra were performed at the School of Pharmacy, University of Maryland at Baltimore, on a DuPont 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 spectrometer or a Perkin-Elmer 1420 ratio recording instrument. Elemental microanalyses were performed by (a) Galbraith Laboratories, Inc., Knoxville, TN, or (b) Atlantic Microlab, Inc., Atlanta, GA.

Methyl *N*-(Dicarbomethoxymethyl)methanimidate (1). (Dicarbomethoxymethyl)ammonium *p*-toluenesulfonate (**3a**) (10 g, 31 mmol) was neutralized with 2 N NaOH (15 mL), and the aqueous mixture was extracted with $CHCl_3$ (4 × 150 mL). The combined extracts were dried over anhydrous $CaSO_4$ and filtered, and the filtrate was evaporated on a rotary evaporator by using a water bath whose temperature did not exceed 30 °C. The residual yellow oil was dissolved in dry acetonitrile (40 mL) and added portion-wise (0.34 mL/min), with the aid of a syringe-drive pump, to the refluxing mixture, under N_2, of trimethyl orthoformate (100 mL, 0.9 mol) and trifluoroacetic acid (0.2 mL, 2.6 mmol), during a total period of ~5 h. The reaction mixture was cooled and evaporated to a thick oil which was distilled in a Kügelröhr apparatus [95–120 °C (oven temperature)/0.7 mmHg] to obtain a colorless liquid (2.6–3.0 g, 13.8–15.9 mmol, 44–51%): ^{1}H NMR (Me_2SO-d_6) δ 3.68 (s, 3, imidate CH_3), 3.71 (s, 6, two ester CH_3), 4.99 (s, 1, malonate CH), 7.91 (s, 1, imine CH); IR (neat) 3000 (=CH), 1770–1740 (C=O) cm^{-1}; mass spectrum (70 eV), *m/e* 174 ($M^+ - CH_3$), 130 ($M^+ - CO_2CH_3$).

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Anal. Calcd for $C_7H_{11}NO_5$: C, 44.45; H, 5.86; N, 7.40. Found: C, 44.34; H, 6.01; N, 7.19.

(Dicarbomethoxymethyl)ammonium *p*-Toluenesulfonate (3a). Aluminum foil (14 g, 0.51 mol) was cut into $^1/_2$ in. squares and was covered with a 5% aqeuous solution of mercuric chloride until mercury coating was visible on the aluminum (approximately 30 s). The mercuric chloride solution was decanted, and the amalgamated aluminum was washed with water (300 mL) twice, with 95% ethanol (300 mL) once, and with tetrahydrofuran (300 mL) twice. The amalgamated aluminum was transferred to a 1000-mL three-necked round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, a thermometer, and a 250-mL addition funnel and was immediately covered with 500 mL of ether. The reaction mixture was cooled and maintained at ≃9 °C with an ice–water bath, and a solution of dimethyl isonitrosomalonate (4) (55 g, 0.32 mol) in 250 mL of ether was added in a period of 15 min. After the addition, 25 mL of water was introduced during 30 min while maintaining a gentle reflux. The reaction mixture was stirred for an additional 30 min. The mixture was cooled to room temperature and filtered through a pad of Celite. The Celite cake was washed with ether (4 × 100 mL). To the combined filtrates was added a slurry of *p*-toluenesulfonic acid monohydrate (62 g, 0.33 mol) in a mixture of ether (300 mL) and EtOH (50 mL) to afford a precipitate which was filtered in vacuo and dried to obtain **3a** which was recrystallized from acetonitrile to give colorless crystals (52.5 g, 0.163 mol, 51%), mp 163.5–165.5 °C: ^{1}H NMR (Me_2SO-d_6) δ 2.3 (s, 3 CH_3 of tosylate), 3.75 (s, 6, two OMe), 5.15 (s, 1, CH of malonate), 7.1 (d, J = 8.0 Hz, 2, CH of Ph), 8.0–9.5 (br, 3, NH_3, exchangeable with D_2O); IR (KBr) 3300–2400 (NH_3^+), 2000 (NH_3^+), 1775–1740 (C=O) cm^{-1}; mass spectrum (70 eV) m/e 172 (*p*-TsOH$^+$·), 142 (M^+ – *p*-TsOH).

Anal. Calcd for $C_{12}H_{17}O_7NS$: C, 45.13; H, 5.37; N, 4.39. Found: C, 45.18; H, 5.40; N, 4.39.

4-Carbomethoxy-1-(dicarbomethoxymethyl)-5-hydroxyimidazole (5). A mixture of dimethyl aminomalonate (liberated from the corresponding *p*-toluenesulfonic acid salt, as described above) (38.5 g, 0.26 mol), dry acetonitrile (100 mL), trimethyl orthoformate (200 mL), and glacial acetic acid (5 mL) was heated at reflux, under N_2, for 9 h. The reaction mixture was cooled and evaporated to dryness on a rotary evaporator. The residue was triturated with ethanol to obtain a solid which was recrystallized from acetonitrile into colorless crystals of **5** (32.5 g, 0.12 mol, 46%), mp 177–178 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.65 (s, 3, 4-CO_2Me), 3.77 (s, 6, two malonate CO_2Me), 5.88 (s, 1, malonate CH), 8.39 (s, 1, imidazole CH); IR (KBr) 3180 (OH), 2960 (CH), 1775–1745 (C=O) cm^{-1}; mass spectrum (70 eV), m/e 272 (M^+), 240 (M^+ – CH_3OH), 213 (M^+ – CO_2Me).

Anal. Calcd for $C_{10}H_{12}N_2O_7$: C, 44.14; H, 4.44; N, 10.29. Found: C, 44.24; H, 4.48; N, 10.27.

Methylammonium 4-Carbomethoxy-1-[bis(methylcarbamoyl)methyl]imidazol-5-olate (6). The suspension of 4-carbomethoxy-1-(dicabomethoxymethyl)-5- hydroxyimidazole (**5**) (5 g, 18 mmol) in absolute methanol (45 mL) was warmed to form a clear solution. The solution was cooled to room temperature, a saturated solution of methanolic methylamine (15 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. The solid formed was filtered and recrystallized from acetonitrile (5.4 g, 17.92 mmol, 99.6%), mp 192–194 °C: ^{1}H NMR (Me_2SO-d_6) δ 2.38 (s, 3, salt N–CH_3), 2.59 (d, J_{NH,CH_3} = 4.3 Hz, 6, two amide $NHCH_3$), 3.55 (s, 3, OCH_3), 5.49 (s, 1, malonate CH), 7.24 (s, 1, imidazole CH), 6.87 (br, 3, NH_3^+, exchangeable with D_2O), 8.35 (q, J_{NH,CH_3} = 4.3 Hz, 2, two amide NH's, exchangeable with D_2O); IR (KBr) 3320–3060, 2610, 2500 (NH + NH_3^+), 2945 (CH), 1735–1640 (C=O) cm^{-1}; mass spectrum (70 eV); m/e 213 (M^+ – $CH_3NH_2CH_3N$=C=O), 156 (M^+ – CH_3NH_2 – $2CH_3N$=C=O), 142 (M^+ + 1 – CH_3NH_2 – $2CH_3N$=C(O)CH_3), 124 (M^+ – CH_3NH_2 – $2CH_3N$=C=(O)CH_3OH).

Anal. Calcd for $C_{11}H_{19}N_5O_5$: C, 43.85; H, 6.31; N, 23.25. Found: C, 43.88; H, 6.29; N, 22.69.

General Method for the Synthesis of 1-Substituted 4-Carbomethoxy-5-hydroxyimidazoles 7a–12a and Ammonium (Alkylammonium) 1-Substituted 4-Carbomethoxyimidazol-5-olates 7b–12b. To a solution of methyl *N*-(dicarbomethoxymethyl)methanimidate (**1**, 5.3 mmol) in either dry acetonitrile (for compounds **9–12**) (40 mL) or in absolute methanol (for compounds **7** and **8**) (40 mL) was added primary amine (5.2 and 11.6 mmol for **a** and **b**, respectively), dropwise, under N_2. The reaction mixture was stirred at room temperature, under N_2, for an additional 2 h, and the precipitated solid was collected by filtration, dried, and recrystallized from appropriate solvents mentioned below (for compounds **a** only) or simply washed with excess acetonitrile, and dried (for salts **b**). The percentage yields, melting points, recrystallization solvents (where appropriate), and spectral data for compounds **7–12** are given as follows.

4-Carbomethoxy-5-hydroxyimidazole (7a): from **1** plus NH_3; colorless crystals from H_2O; 65%; mp >250 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.67 (s, 3, OCH_3), 7.63 (s, 1, CH); mass spectrum (70 eV), m/e 142 (M^+), 110 (M^+ – CH_3OH), 82 (M^+ – CH_3OH–CO).

Anal. Calcd for $C_5H_6N_2O_3$: C, 42.26; H, 4.26; N, 19.71. Found: C, 42.16; H, 4.31; N, 19.66.

Ammonium 4-Carbomethoxyimidazol-5-olate (7b): from **1** plus NH_3; colorless crystals; 67%; mp 191–192 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.59 (s, 3, CH_3), 5.87 (br, 4, NH_4^+, exchangeable with D_2O), 7.19 (s, 1, CH); mass spectrum (70 eV), m/e 142 (M^+ – NH_3), 110 (M^+ – NH_3-CH_3OH), 83 (M^+ – NH_3CO_2Me).

4-Carbomethoxy-5-hydroxy-1-methylimidazole (8a): from **1** plus methylamine; colorless crystals from acetonitrile; 90%, mp 147–148 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.20 (s, 3, NCH_3), 3.62 (s, 3, OCH_3), 8.09 (s, 1, CH); mass spectrum (70 eV), m/e 156 (M^+), 124 (M^+ – CH_3OH), 96 (M^+ – CH_3OHCO).

Anal. Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 45.93; H, 5.18; N, 17.99.

Methylammonium 4-Carbomethoxy-1-methylimidazol-5-olate (8b): from **1** plus methylamine; colorless crystals; 90%; mp 160–162 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.36 (s, 3, salt NCH_3), 3.07 (s, 3, ring NCH_3), 3.52 (s, 3, OCH_3), 6.3 (br, 3, NH_3^+, exchangeable with D_2O), 6.97 (s, 1, CH); mass spectrum (70 eV), m/e 156 (M^+ – CH_3NH_2), 124 (M^+ – $CH_3NH_2CH_3OH$), 96 (M^+ – $CH_3NH_2CH_3OHCO$).

1-Benzyl-4-carbomethoxy-5-hydroxyimidazole (9a): from **1** plus benzylamine; colorless crystals from acetonitrile; 70%; mp 180 °C dec, ^{1}H NMR (Me_2SO-d_6) δ 3.63 (s, 3, CH_3), 4.87 (s, 2, CH_2), 7.31 (s, 5, Ph), 8.31 (s, 1, CH); mass spectrum (70 eV), m/e 232 (M^+), 200 (M^+ – CH_3OH).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.05; H, 5.21; N, 12.07. Found: C, 61.97; H, 5.21; N, 12.02.

Benzylammonium 1-Benzyl-4-carbomethoxyimidazol-5-olate (9b): from **1** plus benzylamine; colorless crystals; 78%; mp 144–146 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 3.55 (s, 3, CH_3), 3.94 (s, 2, salt NCH_2), 4.74 (s, 2, ring NCH_2), 7.19 (s, 1, CH), 7.38–7.25 (m, 10, 2 Ph); mass spectrum (70 eV), m/e 232 (M^+ – $C_6H_5CH_2NH_2$), 200 (M^+ – $C_6H_5CH_2NH_2CH_3OH$).

Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.05; H, 6.19; N, 12.49.

4-Carbomethoxy-5-hydroxy-1-propylimidazole (10a): from **1** plus propylamine; colorless crystals from acetonitrile; 65%; mp 152–154 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.83 (t, J = 7.1 Hz, 3, CCH_3), 1.63 (m, J = 7.1 Hz, 2 CCH_2C), 3.62 (t, J = 7.1 Hz, 2, NCH_2C), 3.62 (s, 3, OCH_3), 8.2 (s, 1, CH); mass spectrum (70 eV), m/e 184 (M^+), 152 (M^+ – CH_3OH), 124 (M^+ – CH_3OHCO).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.07; H, 6.57; N, 15.16.

Propylammonium 4-Carbomethoxy-1-propylimidazol-5-olate (10b): from **1** plus propylamine; colorless crystals; 74%; mp 187 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.72–0.96 (two overlapping t, J = 7.0 Hz, 6, two CCH_3), 1.3–1.76 (m, 4, two CCH_2C), 2.7 (t, J = 7.0 Hz, 2, salt NCH_2), 3.4 (t, J = 7.0 Hz, ring NCH_2), 3.53 (s, 3, OCH_3), 6.97 (s, 1, CH), 7.52 (br, 3, NH_3^+, exchangeable with D_2O); mass spectrum (70 eV), m/e 184 (M^+ – $CH_3CH_2CH_2NH_2$), 152 (M^+–$CH_3CH_2CH_2NH_2CH_3OH$), 124 (M^+ – $CH_3CH_2CH_2NH_2CH_3OHCO$).

1-Butyl-4-carbomethoxy-5-hydroxyimidazole (11a): from **1** plus butylamine; colorless crystals from acetonitrile; 58%; mp 177–179 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.87 (t, J = 7.1 Hz, 3, CCH_3), 1.06–1.79 (m, 4, 2 CCH_2C), 3.64 (t, J = 7.1 Hz, 3, NCH_2C), 3.64 (s, 3, OCH_3), 8.22 (s, 1, CH); mass spectrum (70 eV), m/e 198 (M^+), 166 (M^+ – CH_3OH), 138 (M^+ – CH_3OHCO).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.40; H, 7.15; N, 14.09.

Butylammonium 1-Butyl-4-carbomethoxyimidazol-5-olate (11b): from **1** plus butylamine; colorless crystals; 65%; mp 185

°C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.7–1.0 (two overlapping t, J = 7.1 Hz, 6, two CCH_3), 1.05–1.75 (m, 8, two CCH_2CH_2C), 2.72 (t, J = 7.1 Hz, 2, salt NCH_2), 3.48 (t, J = 7.1 Hz, 2, ring NCH_2), 3.52 (s, 3, OCH_3), 6.95 (s, 1, CH), 7.5 (br, 3, NH_3^+, exchangeable with D_2O); mass spectrum (70 eV), m/e 198 (M^+ – $CH_3CH_2CH_2CH_2NH_2$), 166 (M^+ – $CH_3CH_2CH_2CH_2NH_2CH_3OH$), 138 ($M^+$ – $CH_3CH_2CH_2CH_2NH_2CH_3OHCO$).

4-Carbomethoxy-1-cyclohexyl-5-hydroxyimidazole (12a): from 1 plus cyclohexylamine; colorless crystals from acetonitrile; 44%, mp 200–202 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1–2 (br, 11, cyclohexyl H's), 3.63 (s, 3, CH_3), 8.27 (s, 1, CH); mass spectrum (70 eV), m/e 224 (M^+), 192 (M^+ – CH_3OH), 164 (M^+ – CH_3OHCO).

Anal. Calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.99; H, 7.21; N, 12.45.

Cyclohexylammonium 4-Carbomethoxy-1-cyclohexylimidazol-5-olate (12b): from 1 plus cyclohexylamine; colorless crystals; 77%, mp 144–146 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1–2 (br, 22, cyclohexyl H's), 3.53 (s, 3, CH_3), 6.92 (br, 3, NH_3^+, exchangeable with D_2O), 7.12 (s, 1, CH).

General Method for the Conversion of 1-Substituted (Unsubstituted) 4-Carbomethoxy-5-hydroxyimidazoles 7a–12a into Alkylammonium (Ammonium) 1-Substituted 4-Carbomethoxyimidazol-5-olates 7b–12b. Compound **9a** (1 g, 4.3 mmol) was suspended in acetonitrile (30 mL), and the suspension was heated at reflux to form a clear solution. Benzylamine (1 mL, 9.2 mmol) was introduced, and the reaction mixture was continued to reflux for an additional 2 h. The reaction was cooled to room temperature, and the white solid that separated was filtered in vacuo and air-dried to obtain **9b** (1.3 g, 3.8 mmol, 88%), mp 144–146 °C dec. The ^{1}H NMR of this compound was superimposable with that of **9b** obtained from the reaction of **1** and excess benzylamine.

General Method for the Conversion of Alkylammonium (Ammonium) 1-Substituted 4-Carbomethoxyimidazol-5-olates 7b–12b into 1-Substituted (Unsubstituted) 4-Carbomethoxy-5-hydroxyimidazoles 7a–12a. Method A. Treatment with 1 N Hydrochloric Acid. Compound **12b** (1.9 g, 5.8 mmol) was neutralized with 1 N HCl, and the aqueous mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were dried over anhydrous $CaSO_4$ and filtered, and the filtrate was evaporated to dryness to obtain a solid which was recrystallized from acetonitrile into colorless crystals of **12a** (0.9 g, 4.0 mmol, 69%), mp 200–202 °C. The ^{1}H NMR of this compound was superimposable with that of **12a** prepared from the reaction of **1** and cyclohexylamine as described above.

Method B. Flash Chromatography on Silica Gel. Compound **11b** (1.0 g, 3.7 mmol) was dissolved in MeOH (30 mL), and the solution was mixed with 5 g of silica gel (40–63 μm) and evaporated to dryness. The residue was suspended in 10 mL of $CHCl_3$, the suspension was loaded onto a column of silica gel (40–63 μm, 50 g), made in $CHCl_3$, and the column was eluted with a mixture of $CHCl_3$–MeOH (9:1) (1 L) at a flow rate of 10 mL/min at 6 psi. The UV absorbing fractions were pooled and evaporated to obtain **11a** as a white solid (0.5 g, 2.52 mmol, 68%), mp 177–179 °C dec. The ^{1}H NMR of this compound was identical with that of **11a** obtained from the reaction of **1** and butylamine as described above.

Method C. Treatment with Phenylphosphonic Dichloride. A mixture of **9b** (339 mg, 1 mmol), phenylphosphonic dichloride (0.14 mL, 1 mmol), and dry pyridine (5 mL) was heated at reflux for 25 min. The reaction mixture was cooled, evaported to dryness on a rotary evaporator, and poured onto ice-cold water (20 mL). The precipitate separated was filtered in vacuo and recrystallized from acetonitrile into colorless crystals of **9a** (200 mg, 0.86 mmol, 86%), mp 180 °C dec. The ^{1}H NMR of this compound was identical with that of **9a** prepared from the reaction of **1** and benzylamine as described (vide supra).

Dimethyl *N*-Formylaminomalonate (13). A mixture of **1** (1 g, 5.3 mmol) and H_2O (15 mL) was stirred at room temperature for 5 h. The solvent was removed on a rotary evaporator azeotropically with toluene (10 mL). The residual dense oil was distilled in a Kügelrohr apparatus [130–135 °C (oven temperature)/0.5 mmHg] to obtain a white solid which was recrystallized from ethyl acetate–ligroin into colorless crystals of **13** (0.4 g, 2.28 mmol, 43%), mp 79–80 °C (lit.[10] mp 85.5 °C): ^{1}H NMR (Me_2SO-d_6) δ 3.63, 3.75 (two s, 6, 2 CH_3), 5.18 (d, J = 7.06 Hz, 1, malonate CH), 8.3 (s, 1, amide CH), 9.03 (br, 1, NH, exchangeable with D_2O); IR (KBr) 3300 (NH), 1750, 1660 (C=O) cm^{-1}; mass spectrum (70 eV), m/e 147 (M^+ – CO), 132 (M^+ – NHCO), 116 (M^+ – CO_2Me).

Anal. Calcd for $C_6H_9NO_5$: C, 41.15; H, 5.18; N, 8.0. Found: C, 41.16; H, 5.19; N, 7.97.

Dimethyl *N*-(Thioformyl)aminomalonate (14). A solution of $NaSH{\cdot}xH_2O$ (0.28 g, ~5.0 mmol) in absolute MeOH (5 mL) was added dropwise to the well-stirred solution of **1** (1 g, 5.3 mmol) in absolute MeOH (30 mL). The reaction mixture was stirred at room temperature for an additional 2 h, mixed with silica gel (60–200 mesh) (7 g), and evaporated to dryness. The residue was suspended in $CHCl_3$ (10 mL), and the resulting slurry was loaded onto a column of silica gel (60–200 mesh, 75 g), prepared in $CHCl_3$, and eluted with the same solvent (1 L). The UV-absorbing fractions were pooled and evaported to obtain a solid which was recrystallized from benzene–petroleum ether (30–60 °C) into colorless crystals of **14** (0.79 g, 4.13 mmol, 78%), mp 74 °C (lit.[11] mp 71–72 °C): ^{1}H NMR (Me_2SO-d_6) δ 3.76 (s, 6, 2 CH_3), 5.76 (s, 1, malonate CH), 9.39 (s, 1, thioamide CH), 11.04 (br, 1, NH, exchangeable with D_2O); IR (KBr) 3225 (NH), 1750 (C=O) cm^{-1}; mass spectrum (70 eV), m/e 191 (M^+), 159 (M^+ – CH_3OH), 131 (M^+ – NHCH=S).

Anal. Calcd for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33. Found: C, 37.72; H, 4.78; N, 7.31.

Methyl *N*-(Thioformyl)aminoacetate (17). To the stirring solution of **1** (1.5 g, 7.9 mmol) in absolute MeOH (30 mL) was added $NaSH{\cdot}xH_2O$ (2 g, ~35 mmol) dissolved in absolute MeOH (15 mL). The reaction mixture was stirred at room temperature for 20 min and then heated at reflux for 2 h. The solid formed was filtered off, and the filtrate was mixed with silica gel (60–200 mesh) (7 g) and evaporated to dryness on a rotary evaporator. The residue was suspended in chloroform (15 mL), and the resulting slurry was loaded onto a preformed column of silica gel (60–200 mesh, 100 g), prepared in $CHCl_3$, and eluted with the same solvent. The appropriate fractions were pooled and evaporated to obtain a solid which was recrystallized from benzene–petroleum ether (30–60 °C) into colorless crystals of **17** (0.72 g, 5.4 mmol, 68%), mp 46–48 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.68 (s, 3, OMe), 4.40 (d, J_{NH,CH_2} = 5.7 Hz, 2, CH_2), 9.38 (d, $J_{NH,CH}$ = 6.0 Hz, 1, CH), 10.48 (br, 1, NH, exchangeable with D_2O); IR (KBr) 3340 (NH), 2950 (CH), 1750–1720 (C=O), 1521, 1508 (C=S) cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 133 (M^+, 100), 101 (M^+ – MeOH).

Anal. Calcd for $C_4H_7NO_2S$: C, 36.08; H, 5.30; N, 10.52. Found: C, 36.18; H, 5.31; N, 10.51.

General Procedure for the Preparation of 1-Substituted 5-(Substituted-amino)-4-(*N*-substituted-carbamoyl)-imidazoles. In a 100-mL, three-necked flask, fitted with a reflux condenser, a thermometer, and a serum cap, was suspended alkylammonium 4-carbomethoxyimidazol-5-olate (5.34 mmol) in dry pyridine (20 mL) under N_2. Phenylphosphonic dichloride (11.8 mmol) was introduced via hypodermic syringe, and the reaction mixture was stirred at room temperature for 5 min to form a clear solution. The flask was then submerged into an oil bath preheated to 115–120 °C. After 25 min, the primary amine (23 mmol) was introduced *cautiously*, and the reaction mixture was continued to heat at the above temperature for an additional 15 h. The resulting dark solution was concentrated to a thick oil which was then mixed with MeOH (30 mL) and evaporated to dryness. The residue was triturated with H_2O (25 mL), the aqueous suspension was extracted with AcOEt (4 × 75 mL), and the combined extracts were dried over $CaSO_4$ and filtered. The filtrate was mixed with 5 g of silica gel (40–63 μm) and evaporated to dryness. The residue was suspended in $CHCl_3$ (10 mL), and the resulting slurry was loaded onto a flash chromatography column, made of silica gel (40–63 μm, 35 g) in $CHCl_3$. The column was eluted with a mixture of $CHCl_3$–acetone (9:1) (600 mL) at a flow rate of 10 mL/min at 6 psi. The appropriate UV-absorbing fractions were pooled and evaporated. The residue was recrystallized from the appropriate solvents. The percentage yields, melting points, solvents of recrystallization, and spectral data for compounds **18** and **19** are listed below.

5-(Benzylamino)-4-(benzylcarbamoyl)-1-methylimidazole (18): from **8b** and benzylamine; colorless needles from toluene;

50%; mp 155–156 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.1 (s, 3, CH_3), 4.78–5.1 (br, 5, two $NHCH_2$ + one NH), 7.0 (s, 1, imidazole CH), 7.27 (s, 10, two Ph); mass spectrum (70 eV), m/e 320 (M^+), 229 ($M^+ - CH_2Ph$).

Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.38; H, 6.36; N, 17.27.

1-Benzyl-5-(benzylamino)-4-(benzylcarbamoyl)imidazole (19): from **9b** and benzylamine; colorless needles from EtOH–H_2O (1:1); 53%; mp 140 °C; ^{1}H NMR (Me_2SO-d_6) δ 4.74 (s, 2, NCH_2), 4.82–5.13 (br, 5, two $NHCH_2$ + one NH), 7.11 (s, 1, imidazole CH), 7.28 (s, 15, three Ph); mass spectrum (70 eV), m/e 396 (M^+), 305 ($M^+ - CH_2Ph$).

Anal. Calcd for $C_{25}H_{24}N_4O$: C, 75.73; H, 6.10; N, 14.13. Found: C, 75.63; H, 6.10; N, 14.09.

Phenylphosphonic Bis(*N*-benzylamide) (20). A mixture of phenylphosphonic dichloride (0.14 mL, 1 mmol) and dry pyridine (5 mL) was immersed in an oil bath maintained at 70 °C. Benzylamine (1 mL, 9.15 mmol) was introduced through a serum cap, and the reaction mixture was heated at the above temperature, under N_2, for 4.5 h. The reaction mixture was cooled, the precipitated benzylamine hydrochloride was filtered, and the filtrate was evaporated to dryness on a rotary evaporator. The residue was poured over H_2O (50 mL), and the aqueous mixture was extracted with AcOEt (3 × 35 mL). The combined extracts were dried over anhydrous $CaSO_4$ and filtered, and the filtrate was evaporated to obtain a white solid. The solid was further purified by flash chromatography on a silica gel (40–63 μm) column (30 g), employing a mixture of $CHCl_3$–acetone (1:1) (500 mL) as the eluting solvent, at a flow rate of 10 mL/min at 9 psi. Recrystallization from benzene–hexane provided colorless, fluffy needles of **20** (275 mg, 0.82 mmol, 82%), mp 99–100 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.91 (d, J = 7.3 Hz, 2, CH_2), 4.04 (d, J = 7.4 Hz, 2, CH_2), 4.78–5.20 (br m, 2, two NH, exchangeable with D_2O), 7.15–7.95 (m, 15, three Ph); mass spectrum (70 eV), m/e 336 (M^+), 230 ($M^+ - NHCH_2Ph$).

Anal. Calcd for $C_{20}H_{21}N_2PO$: C, 71.40; H, 6.29; N, 8.32. Found: C, 71.05; H, 6.51; N, 8.26.

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Synthesis of Halogenated Pyridines via the CuCl-Catalyzed Addition of Polyhaloacetonitriles to Olefins

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Halogenated acetonitriles add smoothly to acrolein, methacrolein, and methacrolein dimethyl acetal in the presence of a catalytic amount of CuCl and triphenylphosphine, tri-*n*-butylphosphine, or triethylamine to give halogenated difunctional adducts. The adducts have been cyclized in high yields under acidic conditions to halogenated pyridines.

Historically, very few methods have been described that provide for the multiple introduction of halogens at specific positions on the pyridine ring.[1] Vapor-phase halogenations typically give indiscriminate substitutions,[2a-d] and isolation of specific isomers is often a laborious process. Electrophilic substitution of halogens on the pyridine ring affords some selectivity but frequently requires excessive amounts of Lewis acid catalysts.[3ab] The Schiemann reaction has been used to prepare 2,6-difluoro- and 2,3-difluoropyridine from 6-amino- and 3-amino-2-fluoropyridines.[4] Recently, Martin and co-workers[5a-c] have reported the Cu- and CuCl[6]-catalyzed addition of polychloro aldehydes to acrylonitrile and methacrylonitrile. The resulting adducts were cyclized to afford 2,3-dichloro-5-methylpyridine and 2,3,5-trichloropyridine.[5a] We report an alternative method for the synthesis of halogenated pyridines. We have found that polyhaloacetonitriles add smoothly, under mild conditions, to acrolein and methacrolein in the presence of cuprous chloride and a cocatalyst to afford adducts that readily cyclize to give halogenated pyridines. We have found that this reaction affords a diversity of halogen and mixed-halogen substituents on the pyridine ring and can be attained by the suitable selection of the halogens on acetonitrile. The reaction conditions for the experiments are summarized in Table I.

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