Synthesis of Oxazolyl- and Furanyl-substituted Imidazole Hydrochlorides and Methiodides

John Boulos*

Department of Chemistry, Barry University, Miami Shores, FL 33161

Jerome Schulman

Department of Chemistry and Biochemistry, Queens College, NY 11367

Received July 1, 1997

Oxazolyl-5- and furanyl-2-substituted imidazoles have been synthesized by coupling the two ring systems *via* the dipolar cycloaddition of tosyl methyl isocyanide to the corresponding oxazolyl and furanyl aldimines in basic media. These substituted oxazolyl and furanylimidazole bases obtained in this manner were then subjected to hydrogen chloride gas and to methyl iodide to form the corresponding hydrochlorides and methyliodides, respectively. All compounds were purified, characterized and then tested for muscarinic binding affinity. Biological test results revealed low muscarinic receptor affinity and selectivity.

J. Heterocyclic Chem., **35**, 859 (1998).

Introduction.

In the ongoing search for selective M_1 muscarinic receptor agonists, oxazolyl- and furanyl-substituted imidazole hydrochloride and methiodide salts were synthesized and then tested for biological activity. Muscarinic M_1 receptors are currently therapeutic targets for the symptomatic treatment of Alzheimer's disease. Biological test results obtained from several pharmaceutical organizations revealed no significant binding affinity of these compounds for muscarinic receptors. Nevertheless, these compounds presented interesting synthetic challenges and their chemistry is the focus of this paper.

Synthetic Strategies and Results.

The strategy employed in the synthesis of these substituted-imidazole salts is illustrated in Schemes 1 and 2.

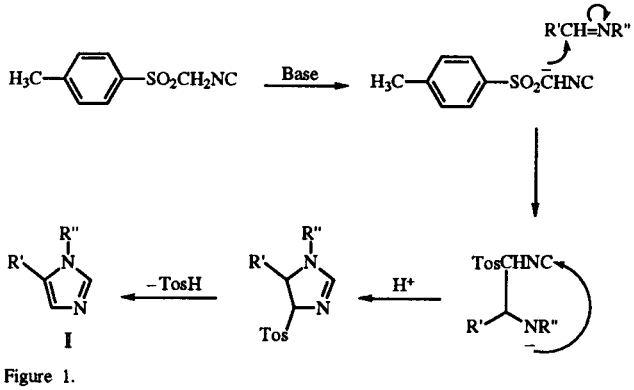
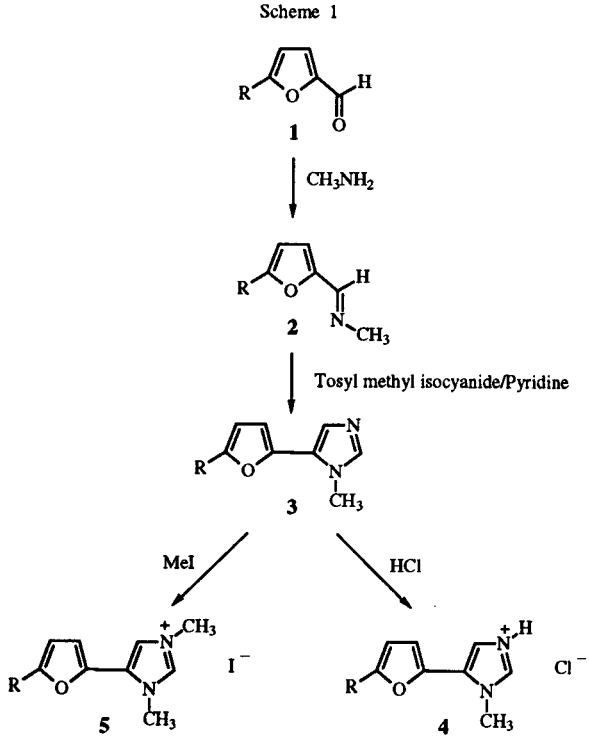


Figure 1.

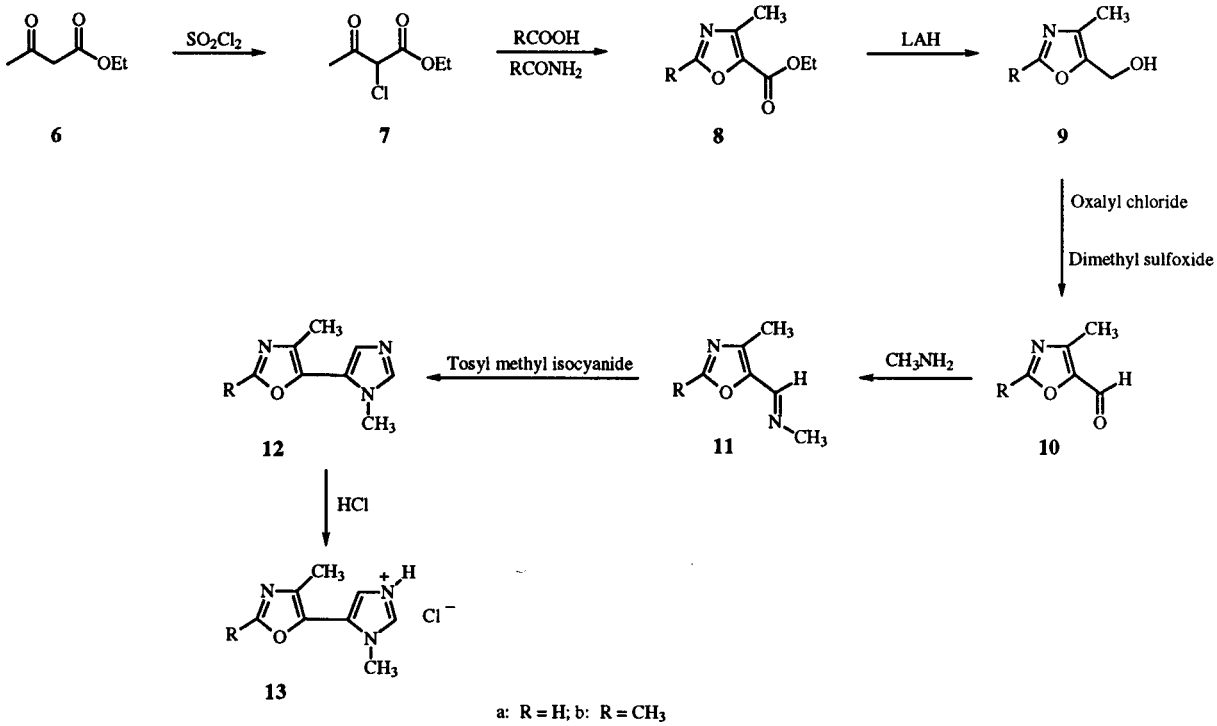
Although substituted imidazoles can be prepared by several synthetic methods, only a few offer a straight forward route to 1,5-disubstituted imidazoles **I** (Figure 1) since the 2-position is susceptible to alkylation [1]. The dipolar cycloaddition of tosyl methyl isocyanide to aldimines provides a successful route to **I**. In this reaction, the CH_2NC moiety of tosyl methyl isocyanide adds to the polarized imine double bond [2]. In the synthesis of the furanyl-substituted imidazoles (Scheme 1), furfural **1b** and 2-methylfurfural **1a** were both converted to the corresponding aldimines **2a,b** in about 72-76% yield. These aldimines were then treated with tosyl methyl isocyanide in pyridine to form the corresponding imidazole bases

Scheme 1



a: R = CH_3; b: R = H

Scheme 2



3a,b [3]. Both furanyl imidazole bases **3a,b** were obtained in low yields (26-38%) with significant amounts of product being lost during workup and purification. The imidazole bases were then converted to their hydrochloride salts **4a,b** with hydrogen chloride gas in dichloromethane and to their methyl iodide salts **5a,b** with methyl iodide in acetonitrile. All structures were confirmed by nmr, mass spectroscopy and elemental analysis.

The first step in the synthesis of the oxazolyl-substituted imidazole bases (Scheme 2) was to construct the oxazole moiety. One convenient method is the treatment of alkylamides with α-chlorocarbonyl compounds in acidic media [4]. In this reaction, ethyl chloroacetoacetate **7** (obtained from the chlorination of ethyl acetoacetate **6**) was treated with the appropriate amides to form the corresponding esters **8a,b** in about 25-26% yield. These esters were then reduced with lithium aluminium hydride in anhydrous ether at -10° to the corresponding alcohols **9a,b** in 60-80% yield. The alcohols were then oxidized to the corresponding aldehydes **10a,b** by the Swern method (dimethyl sulfoxide/oxalyl chloride) in 50-65% yield [5]. Attempts at oxidizing the alcohols by other methods such as Moffat oxidation, pyridinium dichromate, manganese dioxide, or nitric acid resulted either in a very low yield of product or recovery of starting materials. The aldehydes were then treated with 40% aqueous methylamine to obtain the aldimines **11a,b** in 38-49% yield.

Reaction time was crutial for obtaining appreciable amounts of aldimines from **10a**. The reaction mixture was extracted five minutes after the addition of the amine to the aldehyde. With longer reaction times, the yield dropped considerably. It is believed that position 2 of the oxazole ring is susceptible to nucleophilic attack and prolonged exposure to methylamine may lead to by-products. While the structures of the by-products were not confirmed in our laboratory, we observed that methyl substitution at position 2 of the oxazole ring, which would block such nucleophilic attack, indeed furnished a yield independent of reaction time. Therefore, the yield of **11b** from **10b** was unaffected by reaction time. Further studies in this area are needed to confirm the structures of the by-products. The aldimines were then treated with tosyl methyl isocyanide in pyridine and the imidazole bases **12a,b** were obtained in 3-20% yield. The imidazole bases were then converted to their hydrochloride salts with hydrogen chloride gas in dichloromethane. All structures were confirmed by nmr, mass spectroscopy and elemental analysis.

EXPERIMENTAL

General Experimental Procedures.

Reagents were purchased from Aldrich Chemical Company unless otherwise noted and all starting liquid materials were dis-

tilled before use. Silica gel (230-400 mesh) and neutal alumina (Brockman activity I, 80-200 mesh) were used for flash chromatography. Solvents were used without further distillation except for methanol which was distilled over magnesium metal. All nmr spectra were recorded on a 60 MHz EM360 Varian and on a 200 MHz IBM-Bruker WP200SY spectrometer. A Perkin-Elmer 1600 Series FT-IR was used to record ir spectra. Mass spectra were obtained on a Hewlett-Packard 5988A GC/quadrupole MS with HP 1000 data system. Elemental analyses were carried out by Galbraith Laboratories (Knoxville, Tennessee) and all biological assays at Beth Israel Hospital (Boston), Lederle Laboratories (Pearl River, NY), Mitsubishi Kasei Corporation, and by Lilly Research Laboratories.

5-Methylfuran-2-(*N*-methylcarboxaldimine) (**2a**).

About 59.6 g of 40% aqueous methylamine were placed in a 125 ml Erlenmeyer flask containing a magnetic stirrer. This solution was submerged in an ice-bath and to it were added 55.3 g (0.50 mole) of 5-methylfurfural **1a** over 30 minutes, keeping the temperature between 15-20°. After 5 minutes of additional stirring in the ice-bath, the mixture was allowed to stir for an additional 30 minutes at room temperature. About 45 g of potassium hydroxide pellets were added to the mixture with cooling and stirring, keeping the temperature below 15°. Two layers developed, a lower aqueous layer and an upper amber organic layer. The aqueous layer was extracted with dichloromethane; all organic extracts were combined and dried over potassium hydroxide pellets. The solution was filtered, concentrated and distilled. The fraction boiling at 82-83°/16-17 mm Hg afforded 46.4 g of the aldimine (76%); ^{1}H nmr (deuteriochloroform): δ 1.9 (s, 3H), 3.0 (s, 3H), 5.7 (d, 1H), 6.3 (d, 1H), 7.6 (s, 1H).

5-(5-Methyl-2-furyl)-1-methylimidazole (**3a**).

A solution containing 11.18 g (60 mmoles) of tosyl methyl isocyanide, 8.20 g of the aldimine **2a** (70 mmoles) and 70 ml of pyridine was stirred at room temperature for 12 days. The mixture was then concentrated, dissolved in dichloromethane and extracted with 10% hydrochloric acid solution. All aqueous extracts were combined and then made basic with potassium hydroxide pellets to *p*H 8. The solution was extracted three times with dichloromethane, and the combined extracts dried over magnesium sulfate. The solution was filtered and concentrated to afford a crude residue of the base with traces of pyridine. This residue was further concentratred to yield 2.54 g of crystals (26%), mp 30-33°, R_f 0.5 in ethyl acetate. The crystals were chromatographed on a silica gel column (230-400 mesh) eluted with ethyl acetate in 12 fractions (50 ml each). Fractions 7-12 were combined and concentrated to yield 1.6 g of clear yellow crystals (16%), mp 33-35°; ^{1}H nmr (deuteriochloroform): δ 2.2 (s, 3H), 3.7 (s, 3H), 6.0 (d, 1H), 6.2 (d, 1H), 7.1 (s, 1H), 7.3 (s, 1H).

5-(5-Methyl-2-furyl)-1-methylimidazole Hydrochloride (**4a**).

Hydrogen chloride gas was bubbled slowly into a solution of 0.75 g of the base **3a** (5 mmoles) in 20 ml of dichloromethane for about 5 minutes. The solution was concentrated. The residue was recrystallized from 1-butanol to afford 0.50 g of the salt (60%), mp decomposed at 235-237°; ^{1}H nmr (deuterium oxide): δ 2.2 (s, 3H), 3.8 (s, 3H), 6.1 (d, 1H), 6.6 (d, 1H), 7.5 (s, 1H), 8.6 (s, 1H); ms: m/z 162 (M^+) consistent with anticipitated structure upon loss of hydrogen chloride.

Anal. Calcd. for $C_9H_{11}N_2OCl$: C, 54.41; H, 5.58; N, 14.10; Cl, 17.85. Found: C, 53.98; H, 5.57; N, 14.17; Cl, 17.83.

5-(5-Methyl-2-furyl)-1,3-dimethylimidazolium Iodide (**5a**).

To a solution containing 0.80 g of the base **3a** (5 mmoles) in 12 ml of acetonitrile, 2.2 g of methyl iodide (7 mmoles) was added. The solution was stirred to room temperature for 30 minutes, then concentrated, and the residue was recrystallized from *t*-butyl alcohol to afford 0.75 g of the salt (50%). The crystals were dried in a drying pistol, mp 174-177°; ^{1}H nmr (deuteriochloroform): δ 2.4 (s, 3H), 4.1 (s, 6H), 6.1 (d, 1H), 6.7 (d, 1H), 7.7 (s, 1H), 10.1 (s, 1H).

Anal. Calcd. for $C_{10}H_{13}N_2OI$: C, 39.49; H, 4.31; N, 9.21; I, 41.70. Found: C, 39.33; H, 4.34; N, 9.10; I, 41.67.

Furan-2-(*N*-methylcarboxaldimine) (**2b**).

The procedure was the same as described for **2a**, using the following reagents: 17.4 g of furfural (0.18 mole) and 20 ml of 40% aqueous methylamine solution. The reaction afforded 14.1 g of the aldimine (72%), bp 70-76°/15-20 mm Hg; ^{1}H nmr (deuteriochloroform): δ 2.8 (s, 3H), 5.8 (m, 1H), 6.2 (d, 1H), 7.0 (s, 1H), 7.4 (d, 1H).

5-(2-Furyl)-1-methylimidazole (**3b**).

A solution containing 6.72 g of the aldimine **2b** (60 mmoles), 10 g of tosyl methyl isocyanide (50 mmoles) and 75 ml of pyridine was stirred at room temperature for 12 days. Workup is the same as described for **3a**. The reaction afforded 3.5 g of crude base (38%) which was chromatographed on silica gel (230-400 mesh) with ethyl acetate. A total of 20 fractions (50 ml each) was collected. Fractions 4-12 were combined and concentrated to yield 1.9 g of pure base; ^{1}H nmr (deuteriochloroform): δ 3.7 (s, 3H), 6.4 (s, 2H), 7.2 (s, 1H), 7.4 (s, 2H).

5-(2-Furyl)-1-methylimidazole Hydrochloride (**4b**).

The same procedure as in **4a** was followed. Compound **3b** (1.05 g) afforded 0.47 g of pure salt after recrystallization from 1-butanol, mp 228-229°; ^{1}H nmr (deuterium oxide): δ 3.9 (s, 3H), 6.6 (m, 1H), 6.8 (d, 1H), 7.6 (s, 2H), 8.6 (s, 1H).

Anal. Calcd. for $C_8H_9N_2OCl$: C, 52.04; H, 4.91; N, 15.17; Cl, 19.20. Found: C, 52.30; H, 5.00; N, 15.15; Cl, 18.53.

5-(2-Furyl)-1,3-dimethylimidazolium Iodide (**5b**).

To a solution containing 0.6 g of the base **3b** (4 mmoles) in 20 ml of acetonitrile was added 0.9 g (6 mmoles) of methyl iodide. The reaction mixture was stirred at room temperature for about 30 minutes, then concentrated, and the residue was recrystallized from a mixture of *t*-butyl alcohol and 1-butanol (5:1) to yield 0.5 g of the salt, mp 152-153°; ^{1}H nmr (deuterium oxide) δ 3.9 (2s, 6H), 6.6 (m, 1H), 6.9 (d, 1H), 7.7 (m, 2H). ms: m/z 148 (M^+) consistent with anticipitated structure upon loss of methyl iodide.

Anal. Calcd. for $C_9H_{11}N_2OI$: C, 37.26; H, 3.82; N, 9.66; I, 43.74. Found: C, 37.25; H, 3.94; N, 9.58; I, 44.73.

Ethyl Chloroacetoacetate (**7**).

Ethyl acetoacetate **6** (130 g, 1 mole) was added to a 500 ml 3-necked flask fitted with a dropping funnel, mechanical stirrer and a gas-absorption trap. Sulfuryl chloride (135 g, 1 mole) was then added dropwise with external cooling (ice-bath) for 2 hours. The solution was allowed to stand overnight, and the remaining sulfur dioxide and hydrogen chloride were removed by evaporation. The resulting solution was then distilled using a Vigreux column at 25 mm Hg, and the fraction boiling between 95-100°

was collected to afford 95 g of ethyl chloroacetoacetate (64%), lit [4] bp 85-89°/17 mm Hg, (93-97%); ^{1}H nmr (deuteriochloroform): δ 1.1-1.5 (t, 3H), 2.4 (s, 3H), 4.1-4.5 (q, 2H), 4.8 (s, 1H).

Ethyl 4-Methyloxazole-5-carboxylate (**8a**).

A mixture of ethyl chloroacetoacetate (66.1 g, 0.40 mole), formamide (36.3 g, 0.80 mole) and 88% aqueous formic acid (110 g) was refluxed between 140-145° for 6 hours. The residual dark solution was allowed to cool to room temperature, then submerged in an ice-bath and made alkaline with 6*N* sodium hydroxide. The mixture was extracted with ether, and the extracts were combined and dried over sodium sulfate. After filtration, the ether was removed, and the remaining black residue (30 g) was distilled under vacuum at 75°/4-5 mm Hg to give 18.8 g of a colorless liquid. The distillate was shaken with 25 ml of ice cold half-concentrated sulfuric acid. Two layers were formed, the upper one unreacted ethyl chloroacetoacetate and the lower sulfuric acid-containing the oxazole. The sulfuric acid layer was diluted with cold water and made alkaline with *6N* potassium hydroxide. The solution was then extracted with ether, and the combined ether extracts were dried over magnesium sulfate. The solvent was removed, and the residue was distilled between 60-62°/1-2 mm Hg to afford 15 g of the ester (25%), lit [1]: bp 98°/13 mm Hg, (35%); ^{1}H nmr (deuteriochloroform): δ 1.3-1.6 (t, 3H), 2.6 (s, 3H), 4.3-4.7 (q, 2H), 8.0 (s, 1H); ir (carbon tetrachloride): 1720 (C=O), 1610, 1490, 1450 cm^{-1}.

5-Hydroxymethyl-4-methyloxazole (**9a**).

To about 50 ml of anhydrous ether at -100° under nitrogen were added simultaneously, with mechanical stirring, a solution of the ester **3a** (11.5 g, 74 mmoles) in 15 ml of anhydrous ether and a solution of lithium aluminum hydride (2.66 g, 70 mmoles) in 56 ml of anhydrous ether. After 2.5 hours (including one hour for initial dropwise addition), ethyl acetate (11 ml) was added slowly. The solution was allowed to warm to room temperature, and excess lithium aluminum hydride was destroyed with 95% ethanol. The reaction mixture was hydrolyzed with tartaric acid (l9 g in water) and then made alkaline with *6N* sodium hydroxide. The solution was saturated with potassium carbonate, and the two layers were separated. The aqueous layer was extracted with benzene, and the benzene solution was dried over magnesium sulfate. The ether layer was also dried over magnesium sulfate. Both organic layers were concentrated, and the residues combined and distilled, the fraction boiling between 119-120°/13-14 mm Hg afforded 4.3 g of alcohol (60%), lit [1] bp 120°/13 mm Hg, (63%); ^{1}H nmr (deuteriochloroform): δ 2.2 (s, 3H), 3.1 (bs, 1H), 4.6 (s, 2H), 7.8 (s, 1H); ir (carbon tetrachloride): 3600-3200 (OH), 1600, 1490, 1440 cm^{-1}.

4-Methyloxazole-5-carboxaldehyde (**10a**).

A solution containing 75 ml of dichloromethane and 3 ml (33 mmoles) of oxalyl chloride was added to a 250 ml 3-necked flask equipped with a mechanical stirrer and two pressure-equalizing funnels. One contained a solution of 5.1 ml of dimethyl sulfoxide (66 mmoles) in 15 ml of dichloromethane; the other contained a solution of 3.4 g (30 mmoles) of **9a** in 30 ml of dichloromethane. The flask was submerged in a dry ice-acetone bath and the dimethyl sulfoxide solution was added over 5 minutes. Immediately thereafter, the alcohol was added over 5 minutes; stirring was continued for an additional 15 minutes. Triethylamine (21 ml, 50 mmoles) was then added and the reaction mixture was allowed to warm to room temperature. Water (150 ml) was then added to the mixture with stirring. The solution was transferred to a separatory funnel, and the two layers were separated. The aqueous layer was extracted with dichloromethane, and all organic extracts were combined and washed successively with saturated sodium chloride, 5% hydrochloric acid, water, dilute sodium carbonate, and water again. The organic solution was then dried over magnesium sulfate, filtered and concentrated to afford 2.2 g of the aldehyde (65%); ^{1}H nmr (deuteriochloroform): δ 2.6 (s, 3H), 8.2 (s, 1H), 9.9 (s, 1H); ir (carbon tetrachloride): 1690 (C=O), 1595, 1490, 1475, 1440 cm^{-1}.

4-Methyloxazole-5-(*N*-methylcarboxaldimine) (**11a**).

A solution containing 10 g of **10a** (90 mmoles) in water was added slowly to excess 40% aqueous methylamine solution with stirring and cooling. After 5 minutes of additional stirring, the solution was quickly extracted with dichloromethane, and the combined organic extracts were dried over magnesium sulfate, filtered, concentrated and distilled. The fraction boiling at 40-41°/3mm Hg was collected to afford 4.24 g of the aldimine (38%); ^{1}H nmr (deuteriochloroform): δ 2.3 (s, 3H), 3.5 (s, 3H), 7.8 (s, 1H), 8.2 (s, 1H). ir (CCl_4) 1655, 1640, 1490, 1430 cm^{-1}.

5-(1-Methyl-5-imidazolyl)-4-methyloxazole (**12a**).

A solution containing 4.1 g of the aldimine **11a** (33 mmoles), 7.4 g of tosyl methyl isocyanide (38 mmoles) and 56 ml of pyridine was stirred at room temperature for 7 days. The reaction product was monitored by tlc. The mixture was then concentrated, diluted with 40 ml of dichloromethane, and extracted twice with 40 ml of 10% aqueous hydrochloric acid. The combined aqueous extracts were backwashed with dichloromethane and then made alkaline with 6*N* potassium hydroxide solution with stirring and cooling. The basic mixture was extracted with dichloromethane, and the organic extracts were combined and dried over magnesium sulfate, filtered and then concentrated to afford 0.9 g of crude base. The base was chromatographed on a silica gel column (grade 950, 60-200 mesh) and eluted with a mixture of 2:1:1 ethanol/hexane/dichloromethane. A total of 23 fractions (20 ml each) were collected. Fractions 2-22 showed a single spot on the tlc plate and together afforded 0.6 g of pure base **12a** (11%); ^{1}H nmr (deuteriochloroform): δ 2.3 (s, 3H), 3.8 (s, 3H), 7.2 (s, 1H), 7.5 (s, 1H), 7.9 (s, 1H).

5-(1-Methyl-5-imidazolyl)-4-methyloxazole Hydrochloride (**13a**).

Hydrogen chloride gas was slowly bubbled into a solution containing 0.6 g (36 mmoles) of **12a** in 20 ml of dichloromethane. After 5 minutes of addition, the solution was concentrated and the residual solid was recrystallized twice from a 1:1 mixture of butanol and hexane to afford 0.36 g of the hydrochloride salt (yellowish, mp 226-229°). Sublimation under vacuum afforded 0.24 g of the pure salt (white, mp 232-234°); ^{1}H nmr (deuterium oxide): δ 2.2 (s, 3H), 3.8 (s, 3H), 4.8 (s, deuterium oxide), 7.7 (s, 1H), 8.2 (s, 1H), 8.8 (s, 1H); ms: m/z 163 (M^+) consistent with anticipated structure upon loss of hydrogen chloride.

Anal. Calcd. for $C_8H_{10}N_3OCl$: C, 48.12; H, 5.01; N, 21.05; Cl, 17.79. Found: C, 48.10; H, 4.93; N, 20.71; Cl, 17.78.

Ethyl 2,4-Dimethyloxazole-5-carboxylate (**8b**).

A mixture of ethyl chloroacetoacetate (33.05 g, 0.20 mole), acetamide (23.7 g, 0.40 mole), and glacial acetic acid (73 g, 1.20 moles) was refluxed for 22 hours. Workup was the same as described in **3a**. The ester was collected at 60°/4-5 mm Hg, 8.9 g (26%); ^{1}H nmr (deuteriochloroform): δ 1.2-1.6 (t, 3H), 2.4 (s, 3H), 2.5 (s, 3H), 4.2-4.6 (q, 2H); ir (carbon tetrachloride): 1720 (C=O), 1610, 1560, 1440 cm^{-1}.

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.96; H, 6.57; N, 8.19.

5-Hydroxymethyl-2,4-dimethyloxazole (**9b**).

The ester **8b** (13 g, 70 mmoles) and lithium aluminum hydride (3.47 g, 90 mmoles) were used. The procedure was the same as described in **8a**. About 7.67 g of the alcohol was recovered (80%) at 95°/3-4 mm Hg; ^{1}H nmr (deuteriochloroform): δ 2.1 (s, 3H), 2.4 (s, 3H), 4.1-4.3 (broad singlet, 1H), 4.6 (s, 2H); ir (carbon tetrachloride): 3600-3200 (OH), 1640, 1570, 1440 cm^{-1}.

Anal. Calcd. for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.75; H, 6.98; N, 11.15.

2,4-Dimethyloxazole-5-carboxaldehyde (**10b**).

Procedure was same as described in **10a**. From 7.67 g of **9b** used, 3.7 g of aldehyde was recovered as yellowish crystals (49%), mp 29-30°; ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H), 2.6 (s, 3H), 9.8 (s, 1H); ir (carbon tetrachloride): 1690 (C=O), 1670, 1590, 1550, 1440 cm^{-1}.

Anal. Calcd. for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.83; H, 5.58; N, 11.09.

2,4-Dimethyloxazole-5-(*N*-methylcarboxaldimine) (**11b**).

A solution containing 3.7 g of **10b** (30 mmoles) in 5 ml of water was added dropwise to excess 40% aqueous methylamine solution with cooling and stirring. After 30 minutes of additional stirring at room temperature, the mixture was cooled again, and potassium hydroxide pellets were added slowly until two layers developed. The aqueous layer was extracted with dichloromethane and all organic extracts were combined and dried over potassium hydroxide pellets. The solution was filtered, concentrated and distilled at 65-66°/4-5 mm Hg to afford 1.84 g of the aldimine (49%); ^{1}H nmr (deuteriochloroform): δ 2.3 (s, 3H), 2.5 (s, 3H), 3.6 (s, 3H), 8.2 (d, 1H); ir (carbon tetrachloride): 1650, 1615, 1560, 1440 cm^{-1}.

5-(1-Methyl-5-imidazolyl)-2,4-dimethyloxazole (**12b**).

A solution containing 2.5 g of the aldimine **11b** (20 mmoles), 8.8 g of tosyl methyl isocyanide, and 45 ml of pyridine was stirred for 5 days. Workup was same as described in **12a**. About 2.2 g of crude base was recovered. This base was chromatographed on 25 g of silica gel (grade 950, 60-200 mesh) eluted with 1-butanol. A total of 39 fractions (8 ml each) were collected. Fractions 4 to 23 were combined and concentrated to afford 1.4 g of pure base (40%); ^{1}H nmr (deuteriochloroform): δ 2.2 (s, 3H), 2.5 (s, 3H), 3.7 (s, 3H), 7.2 (bs, 1H), 7.5 (bs, 1H).

5-(1-Methyl-5-imidazolyl)-2,4-dimethyloxazole Hydrochloride (**13b**).

Excess 20% aqueous hydrochloric acid was added to 1.4 g of the chromatographed base **12b**, and the mixture was stirred for 10 minutes. The reaction mixture was then concentrated, and the residue was recrystallized from a mixture of ethyl acetate and dimethyl sulfoxide. First, 10 ml of warm ethyl acetate was added to the solid, and then warm dimethyl sulfoxide was added dropwise until all dissolved. The solution was allowed to cool to room temperature; the crystals were filtered, washed with ethyl acetate, and dried under vacuum to afford 0.68 g of pure hydrochloride salt (40%); ^{1}H nmr (deuteriochloroform): δ 2.2 (s, 3H), 2.5 (s, 3H), 4.0 (s, 3H), 7.5 (s, 1H), 10 (s, 1H); ms: m/z 177 (M^+) consistent with expected structure upon loss of hydrogen chloride.

Anal. Calcd. for $C_9H_{12}N_3OCl$: C, 50.59; H, 5.66; N, 19.67; Cl, 16.59. Found: C, 50.44; H, 5.72; N, 19.67; Cl, 16.63.

Acknowledgments.

Financial support from the Department of Chemistry and Biochemistry of Queens College is gratefully acknowledged. Personal thanks to Dr. George Fisher and Michael Elliott for reviewing this manuscript.

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