Synthesis of Oxazolyl-Substituted Morpholinium Salts

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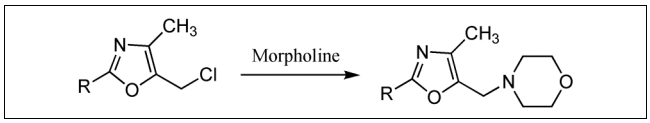

Morpholinium salts coupled to oxazolyl moieties have been synthesized *via* nucleophilic substitution of a series of oxazolyl chlorides with morpholine. The oxazole moieties were first synthesized and then coupled with morpholine. The corresponding hydrochloride and methyl iodide salts were obtained, purified, characterized and then tested for muscarinic receptor binding affinity. Biological test results from MDS Pharma Services revealed no significant muscarinic receptor affinity.

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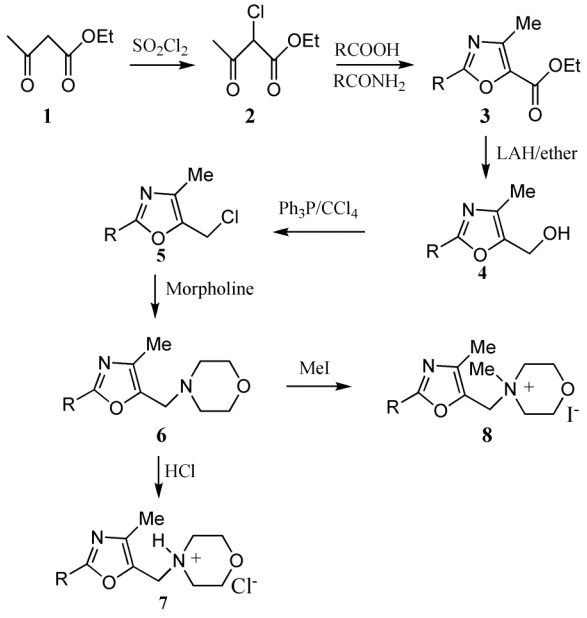
Introduction.

In the search for new selective M_1 muscarinic receptor agonists, hydrochloride and methyl iodide salts of N-substituted oxazolyl morpholine bases were synthesized in our laboratory and then tested for biological activity. Muscarinic M_1 receptors are currently therapeutic targets for the symptomatic treatment of Alzheimer's disease. These compounds were designed to test the cholinergic hypothesis advanced by Schulman *et al* [1]. This hypothesis is based on the fact that while basal forebrain neurons which express the M_2 muscarinic receptor are at risk of degenerating, the cortical neurons expressing the M_1 subtype which synapse with them are not altered. In theory, one could design and synthesize muscarinic selective M_1-agonists that would activate the cortical neurons. These compounds conform to the structural constraints imposed by Schulman's model of the muscarinic pharmacophore and conform to the five-atom rule with the NCCOC backbone, one of the criteria for muscarinic receptor activity. Biological tests conducted by MDS Pharma Services 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.

The strategy employed in the synthesis of these salts is illustrated in Scheme 1. The first step in the synthesis of the N-substituted oxazolyl morpholine bases was to construct the oxazole moiety. Of the many synthetic routes to 4,5-disubstituted oxazoles, one convenient method [2] is the treatment of α-metalated alkyl isocyanides (prepared from isocyanides) with acylating agents such as acyl chlorides, carboxylic esters, and N,N-disubstituted amides. An alternate route [3] is the treatment of alkylamides with α-chlorocarbonyl compounds in acidic media. The latter route was chosen to synthesize the oxazole carboxylic acid esters **3a**, **b**. In this reaction, ethyl chloroacetoacetate **2** (obtained from the chlorination of ethyl acetoacetate **1**) was treated with the appropriate amides to form the corresponding esters in about 25-26% yield. These esters were then reduced with lithium aluminum hydride (LAH) in anhydrous ether at -10 °C to the corresponding hydroxymethyl oxazoles **4a**, **b** in 60-80% yield. It was found that at lower temperatures, these esters precipitated out of solution leading to much lower yields of alcohols. The alcohols were then chlorinated with triphenyl phosphine [4] in carbon tetrachloride to provide the corresponding chloromethyl oxazoles **5a**, **b** in about 55-73% yield. The chlorides were coupled with morpholine to furnish the corresponding N-substituted oxazolyl morpholine bases **6a**, **b**. The bases were then converted to hydrochloride and methyl iodide salts with HCl gas and iodomethane **7a**, **b** and **8a**, **b**, respectively.

Scheme 1



(a: R=H; b: R=Me)

EXPERIMENTAL

General: Reagents were purchased from Aldrich Chemical Company unless otherwise noted and all starting liquid materials were distilled before use. All NMR spectra were obtained using a Varian 300 MHz spectrometer. IR spectra were recorded using a Nicolet Impact 400D FT-IR and mass spectra on a Hewlett Packard 5972 Series MS interfaced with a Hewlett Packard 5890 Series II Plus GC. Elemental analyses were done at Galbraith Laboratories (Knoxville, Tennessee) and all biological assays conducted at MDS Pharma Services. Melting points were determined on a MEL-TEMP II purchased from Laboratory Devices and are uncorrected.

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

To 50 mL of anhydrous ether at -10 °C under nitrogen were added simultaneously, with mechanical stirring, a solution of the ester (**3a**) (11.5 g, 74 mmol) in 15 mL of anhydrous ether and a solution of LAH (2.66 g, 70 mmol) 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 LAH was destroyed with 95% ethanol. The reaction mixture was hydrolyzed with tartaric acid (19 g in water) and then made alkaline with 6 *N* NaOH. The solution was saturated with K_2CO_3, and the two layers were separated. The aqueous layer was extracted with benzene, and the benzene solution was dried over $MgSO_4$; the ether layer was also dried over $MgSO_4$. Both layers were concentrated, and the residues combined and distilled; the fraction boiling between 119-120 °C/13-14 mm Hg afforded 4.3 g of alcohol (60%). Literature values: [3] bp 120 °C/13 mm Hg, (63%). ^{1}H nmr ($CDCl_3$): δ 2.2 (s, 3H), 3.1 (bs, 1H), 4.6 (s, 2H), 7.8 (s, 1H); ir (CCl_4): 3600-3200 (OH), 1600, 1490, 1440 cm^{-1}.

5-Chloromethyl-4-methyloxazole (**5a**).

A mixture of the alcohol (**4a**) (1.21 g, 0.010 mol) in anhydrous carbon tetrachloride (15.33 g, 0.10 mol) was added to a dry, 300-mL single-necked flask furnished with a magnetic stirring bar and a reflux condenser (to which was attached a Drierite-filled drying tube). To this solution, triphenyl phosphine (3.65 g, 0.010 mol) was added, and the reaction mixture was refluxed for 1 hour. The mixture was allowed to cool to room temperature; dry pentane was added (100 mL), and stirring was continued for an additional 5 minutes. The triphenyl phosphine oxide precipitate was filtered, and the residue was washed with 50 ml of dry pentane. The solution was concentrated and then distilled to afford 1.02 g of the chloride (72.8%), bp 47-49 °C/3-4 mm Hg. Literature values: [6] bp 65-67/12 mm Hg). ^{1}H nmr ($CDCl_3$): δ 2.5 (s, 3H), 4.4 (s, 2H), 7.9 (s, 1H).

4-Methyl-5-(4-morpholinomethyl)oxazole (**6a**).

The chloride (**5a**) (1.02 g, 0.008 mol) was added to a mixture of sodium carbonate in 5 mL of benzene and morpholine (0.68 g, 0.008 mol), dissolved in 5 mL of benzene, was added dropwise with stirring. After 12 hours of additional stirring, the reaction mixture was refluxed for about 5 hours. The mixture was cooled to room temperature, diluted with benzene and filtered. The filtrate was concentrated under vacuum to dryness to yield 0.85 g of fairly pure base (58.7%). ^{1}H nmr ($CDCl_3$): δ 2.2 (s, 3H), 2.4 (t, 4H), 3.5 (s, 2H), 3.7 (t, 4H), 7.8 (s, 1H).

4-Methyl-5-(4-morpholinomethyl)oxazole hydrochloride (**7a**).

HCl gas was bubbled through a solution of 0.50 g (0.00274 mol) of the base (**6a**) dissolved in 10 mL of dichloromethane for about 15-20 minutes. About 2 mL of anhydrous methanol was added to dissolve the solid. The resulting solution was concentrated and the solid residue recrystallized from 1-butanol to afford 0.45 g of (**7a**) (60 %). ^{1}H nmr (D_2O): δ 2.1 (s, 3H), 3.2 (bm, 4H), 3.6-3.8 (bm, 4H), 4.4 (s, 2H), 8.1 (s, 1H); ms: m/z 182 (M^+) consistent with anticipated structure upon loss of HCl, 123, 96, 86, 56, 42.

Anal. Calcd. for $C_9H_{15}N_2O_2Cl$: C, 49.43; H, 6.91; N, 12.81; Cl, 16.21. Found: C, 49. 54; H, 6.90; N, 12.79; Cl, 15.98.

4-Methyl-5-(4-morpholinomethyl)oxazole Methyl Iodide Salt (**8a**).

About 5 mL of iodomethane was added to a mixture containing 0.30 g of the base (0.00165 mol) (**6a**) dissolved in 10 mL of acetonitrile. The reaction mixture was stirred at room temperature overnight, concentrated and the residue was recrystallized from n-butanol to afford 0.35 g of the salt (66.0%). ^{1}H nmr (D_2O): δ 2.15 (s, 3H), 3.1 (s, 3H), 3.25-3.6 (m, 4H), 4.0 (m, 4H), 4.65 (s, 2 H), 8.2 (s, 1H).

Anal. Calcd. for $C_{10}H_{17}N_2O_2I$: C, 37.06; H, 5.29; N, 8.64; I, 39.16. Found: C, 36.97; H, 5.19; N, 8.71; I 39.24.

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

The ester (**3b**) (13 g, 70 mmole) and LAH (3.47 g, 90 mmol) were used. The procedure was the same as described in (**4a**). About 7.67 g of the alcohol were recovered (80%) at 95 °C/3-4 mm Hg. ^{1}H nmr ($CDCl_3$): δ 2.1 (s, 3H), 2.5 (s, 3H), 3.0-3.5 (bs, 2H), 4.6 (s, 2H); ir (CCl_4): 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.

5-chloromethyl-2,4-dimethyloxazole (**5b**).

A mixture of the alcohol (**4b**) (6.0 g, 0.047 mol), anhydrous carbon tetrachloride (45 mL) and of triphenyl phosphine (17.04 g, 0.065 mol) was refluxed for 2 hours. The reaction mixture was allowed to cool to room temperature and then diluted with 100 mL of dry pentane. The mixture was filtered, and the filtrate was concentrated to one-fourth of its original volume. The concentrated product was distilled to yield 3.73 g of the chloride (54.6%) which was collected at 53-54 °C/2-3 mm Hg. ^{1}H nmr ($CDCl_3$): δ 2.1 (s, 3H), 2.4 (s, 3H), 4.5 (s, 2H).

2,4-Dimethyl-5-(4-morpholinomethyl)oxazole (**6b**).

The chloride (**5b**) (1.73 g, 0.012 mole) was treated with morpholine as described in (**6a**). About 1.02 g of fairly pure base was recovered (36.6 %). ^{1}H nmr ($CDCl_3$): δ 2.1 (s, 3H), 2.4 (s, 3H), 2.5 (m, 4H), 3.5 (s, 2H), 3.8 (m, 4H).

2,4-Dimethyl-5-(4-morpholinomethyl)oxazole hydrochloride (**7b**).

About 0.80 g of the base (**6b**) (0.00408 mol) was converted to the hydrochloride salt as described in (**7a**); 0.60 g of the salt (63.8%) was recovered after recrystallization from 1-butanol, mp 222-224 °C. ^{1}H nmr (D_2O): δ 2.1 (s, 3H), 2.45 (s, 3H), 3.2-3.4 (bm, 4H), 3.6-4.0 (bm, 4H), 4.4 (s, 2H); ms: m/z 196 (M^+) consistent with the anticipated structure upon loss of HCl, 110, 86, 56, 42.

Anal. Calcd. for $C_{10}H_{17}N_2O_2Cl$: C, 51.61; H, 7.36; N, 12.04; Cl, 15.24. Found: C, 51.85; H, 7.37; N, 11.98; Cl, 14.96.

2,4-Dimethyl-5-(4-morpholinomethyl)oxazole methyliodide (**8b**).

About 0.40 g of the base (**6b**) (0.00204 mol) was converted to the methyl iodide salt as described in (**8a**) to afford 0.35 g of material (50.7%). ^{1}H nmr (D_2O): δ 2.04 (s, 3H), 2.35 (s, 3H), 3.05 (s, 3H), 3.35-3.5 (m, 4H), 4.0 (bm, 4H), 4.6 (s, 2H).

Anal. Calcd. for $C_{11}H_{19}N_2O_2I$: C, 39.07; H, 5.66; N, 8.28; I, 37.53. Found: C, 38.97; H, 5.69; N, 8.21; I, 37.24.

REFERENCES AND NOTES

[1] J. M. Schulman, M. L. Sabio and R. L. Disch, *J. Med. Chem.*, **26**, 817(1983).

[2] U. Schollkopf and R. Schroder, *Angew. Chem. Int. Ed. Engl.*, **10**, 330 (1971).

[3] A. Dornow and H. Hell, *Chem. Ber.*, **94**, 1248 (1961).

[4] Org. Syntheses Coll. Vol. **6**, John Wiley & Sons, New York, NY, 1988, pp 634-637.

[5] Org. Syntheses Coll. Vol. **4**, John Wiley & Sons, New York, NY, 1967, pp 590-593.

[6] U. H. Lindberg and J. Pedersen, B. Ulff, *Acta Pharmaceutica Suecica*, **4**, 5 (1967).