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An efficient synthesis of 2-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)morpholine: a potent M_1 selective muscarinic agonist

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Abstract—2-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)morpholine is useful for synthesizing potent antimicrobials including the arecoline derivatives, phendimetrazine and polygonapholine and was synthesised in nine steps with an overall yield of 36%. Bromination of 3-acetylpyridine and dehydration of a diol with cyclization were pivotal to the success of the strategy.

Neurochemical examination of the brain material from Alzheimer's patients has demonstrated loss of the presynaptic marker enzyme choline acetyltransferase and the muscarinic receptors of the M_2 subtype which are mainly responsible in causing deficits in central cholinergic transmission in Alzheimer's patients.[1–3] The postsynaptic muscarinic receptors, which primarily are of the M_1 subtype, to a large extent, seem to survive the loss of cholinergic nerve endings.[4] These findings have led to attempts at restoring cholinergic function by means of cholinomimetic drugs such as acetylcholinesterase inhibitors and muscarinic agonists, the hypothesis being that enhancement of cholinergic neurotransmission would alleviate the symptoms of the diseases, particularly the deficits in cognition and memory.[4] Pharmacological investigation of muscarinic receptor subtypes using both functional and binding studies has identified three distinct muscarinic receptor[5] subtypes, M_1, M_2 and M_3. Identifying M_1 selective muscarinic agonists which are capable of crossing the blood–brain barrier is the subject of active research for pharmacological application.[6] Arecoline **1**, an alkaloid obtained from the betel nut (*Areca catechu*), the fruit of a palm tree, has been used previously as a leading structure to design centrally active muscarinic agents.[7] The lack of M_1 selectivity and efficacy due to dose limiting side effects associated with M_2 and M_3 muscarinic receptor subtype stimulation have produced disappointing results.[7] Replacement of the ester functionality of arecoline with either the 3-alkyl-1,2,4-oxadiazole **2** or the 3-alkyl-1,2,4-thiadiazole **3** has produced very potent muscarinic agonists.[8,9]

However, the systematic removal of a heteroatom in the 3-methyl-1,2,4-oxadiazole giving oxazoles and furans caused a decrease in affinity for the agonist binding site. The two isomers, 2-methyl-1,2,4-oxadiazole **4** and 5-methyl-1,2,4-oxadiazole **5** also had lower affinities for muscarinic receptors.[8,9] No muscarinic M_1 subtype selectivity has been reported for 2-(1-methyl-1,2,5,6-tetrahydropyridin-3-yl)morpholine **13**. C-Functionalized morpholines are found in a variety of natural products and biologically active compounds. Since compound **13** is a conformationally restricted arecoline analogue we were encouraged to pursue this compound. Furthermore sulfonylation, amidation and alkylation on the nitrogen atom of the morpholine ring would provide analogues for biological evaluation (see Fig. 1).

C-Functionalized morpholines are found in various naturally occurring products as well as in drugs but,[10] synthetic access is rather restricted since morpholines are often derived from aminoalcohols[11a] and aminoepoxides.[11b] A retrosynthetic analysis of this general target structure leads to an enantiopure epoxide and an aminoalcohol as the starting materials (see Fig. 2).

Keywords: C-Substituted morpholines; 2-Acetyl pyridine; Arecoline.
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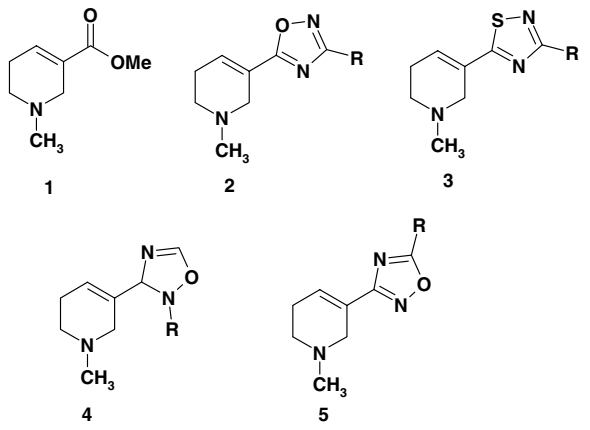


Figure 1. Arecoline **1** and arecoline derivatives **2**–**5**.

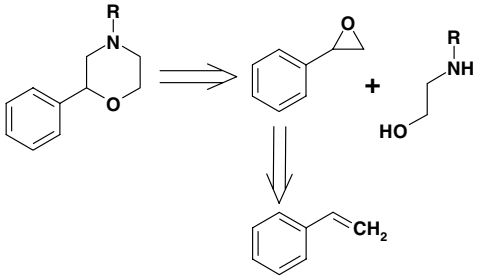


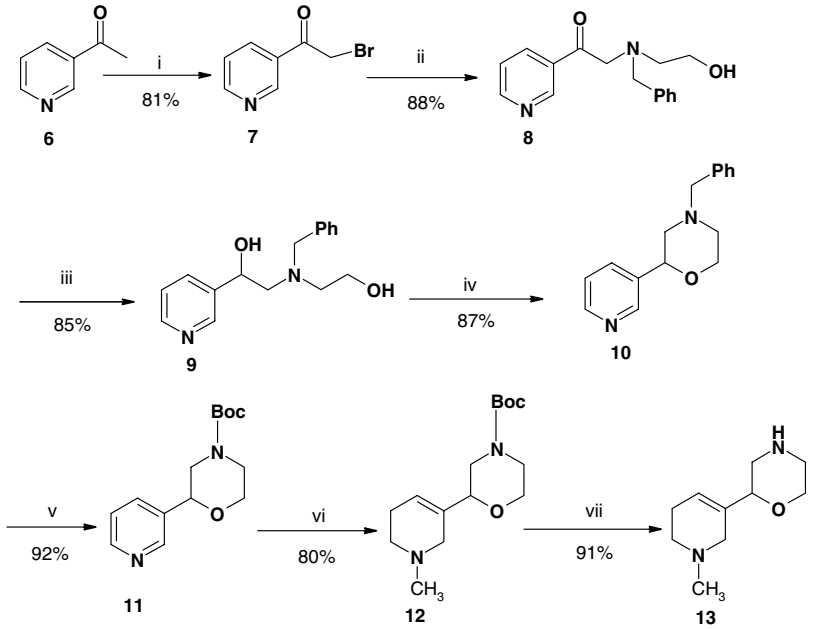
Figure 2. Retrosynthetic pathway for synthesizing 2-aryl substituted morpholine.

We found that implementation of this approach was not straightforward, particularly, for the synthesis of the 2-pyridyl substituted morpholine **10**. Since the pyridyl group contains a nitrogen atom, epoxidation of the 3-vinyl pyridine gave the *N*-oxide,[12] and dihydroxylation of the vinyl pyridine gave the dihydroxylated compound which was highly water soluble. The starting material 3-vinyl pyridine, moreover, undergoes polymerization very quickly.[13] Here we report a novel, efficient and concise synthetic strategy to prepare 2-pyridyl substituted morpholines.

Bromination of 3-acetylpyridine with Br_2/HBr in glacial acetic acid[14] gave the HBr salt of bromoacetylpyridine **7**. This was converted to the amino alcohol **8** by reaction with *N*-benzylaminoethanol in DMF in the presence of K_2CO_3. The keto group of compound **8** was reduced using $NaBH_4$ in methanol to obtain the dihydroxy compound **9**. Treatment of compound **9** with 70% H_2SO_4 under reflux conditions caused dehydration[15] to yield the cyclized product **10** (see Scheme 1).

The *N*-benzyl group was removed by refluxing amine **10** in methanol in the presence of 10% Pd–C and ammonium formate[16] and the resulting free amine was treated with Boc-anhydride in THF in the presence of K_2CO_3 to yield the Boc-protected compound **11**. This was converted to the corresponding methylamine hydroiodide salt by reaction with methyl iodide in acetone. This on treatment with sodium borohydride in methanol[17] gave the reduced product **12**. Finally, the Boc group was removed using methanolic HCl to yield the free amine **13**.

The overall yield of morpholine **13** starting from ketone **6** (nine steps) was 36%. The secondary amine of morpholine **13** can be derivatised to give the corresponding amide, *N*-alkyl and/or sulphonamide derivatives by treatment with acyl chlorides, alkyl bromides and/or sulfonyl chlorides, respectively, and these molecules are being evaluated as potent M_1 selective muscarinic agonists.



Scheme 1. Reagents and conditions: (i) HBr, acetic acid, Br_2; (ii) *N*-benzylaminoethanol, K_2CO_3, DMF; (iii) $NaBH_4$, MeOH; (iv) 70% H_2SO_4, reflux; (v) (a) 10% Pd–C, ammonium formate, MeOH reflux. (b) $(Boc)_2O$, THF, K_2CO_3; (vi) (a) MeI, acetone. (b) $NaBH_4$, MeOH; (vii) HCl, MeOH.

In conclusion, we have described an efficient method for the preparation of a 2-pyridyl substituted morpholine. We believe that this protocol may be of value in the synthesis of other pyridyl substituted morpholine analogues as biologically active molecules. The stereospecific reduction of the keto group[18] of compound **8** to synthesize enantiomerically pure 2-pyridyl substituted morpholines and the testing of acyl, sulfonyl and alkyl derivatives of compound **13** for central muscarinic cholinergic receptor binding affinity using [3H] oxotremorine-M and [3H]QNB as ligands and in a functional assay using guinea pig ileum, are currently in progress.

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Supplementary data

^{1}H NMR and mass spectra of compounds **8**–**12**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.135.

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14. *2-Bromo-1-pyridin-3-yl ethanone* **7**. A solution of 3-acetylpyridine (25 g, 0.206 mol), in 33% HBr in acetic acid (220 mL) was stirred at 70 °C for 5 min. Bromine (33.38 g, 0.208 mol) in 45% aq HBr (30 mL) was added dropwise, and the reaction mixture was stirred for 3 h at the same temperature. The reaction mixture was cooled to room temperature and the white solid obtained was filtered and recrystallized using methanol–hexane (1:1). Yield: 51 g, MS (ESI) m/z 202 ($M+H^+$).
15. *4-Benzyl-2-pyridin-3-yl-morpholine* **10**. Diol **9** (35 g, 0.128 mol) in 70% aqueous sulphuric acid (350 mL) was heated to 100 °C for 24 h. The reaction mixture was basified using 10% aqueous sodium hydroxide and extracted using ethyl acetate (3 × 400 mL). The combined organic layer was washed with water followed by brine and dried over anhydrous Na_2SO_4. The ethyl acetate was removed under reduced pressure and the crude product was purified by column chromatography (silica 60–120) using hexane–ethyl acetate (8:2) as eluent.
Yield: 28.5 g (87%), MS (ESI) m/z 255.1 ($M+H^+$).
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.55 (s, 1H), 8.50 (d, $J = 4.8$ Hz, 1H), 7.63 (d, $J = 5.8$ Hz, 1H), 7.31–7.38 (s, 5H), 7.2–7.22 (t, $J = 4.2$ Hz, 1H), 4.57–4.61 (dd, $J_1 = 10.2$ Hz, $J_2 = 2.1$ Hz, 1H), 3.96 (d, $J = 9.9$ Hz 1H), 3.8–3.84 (t, $J = 10.7$ Hz, 1H), 3.5 (s, 2H), 2.8 (d, $J = 9.3$ Hz, 1H), 2.74 (d, $J = 9.3$ Hz, 1H), 2.26–2.28 (t, $J = 10.7$ Hz, 1H), 2.04–2.12 (t, $J = 10.9$ Hz, 1H). Anal. Calcd for $C_{16}H_{18}N_2O$: Calcd C, 75.56; H, 7.13; N, 11.0%. Found C, 75.60; H, 7.10; N, 11.23%.
16. *N-Boc-2-pyridin-3-yl-morpholine* **11**. To a solution of compound **10** (28 g, 0.11 mol) in methanol, (280 mL) ammonium formate (34.7 g, 0.551 mol) and 10% Pd/C (8.4 g) were added and the mixture refluxed for 5 h. The reaction mixture was filtered through Celite and methanol was removed under reduced pressure. The resulting debenzylated compound (15 g, 0.091 mol) was dissolved in tetrahydrofuran (150 mL), and potassium carbonate (18.9 g, 0.1371 mol) was added followed by Boc-anhydride (23.7 g, 0.109 mol) and the reaction stirred at 45 °C for 6 h. Tetrahydrofuran was removed under reduced pressure and water was added and the reaction mixture was extracted using ethyl acetate (3 × 200 mL). The combined organic layer was dried over anhydrous sodium sulphate. Ethyl acetate was removed under reduced pressure and the crude product was purified by silica gel (60–120 mesh) column chromatography using 8:2 hexane–ethyl acetate as an eluent.
Yield: 22.5 g (93%), MS (ESI) m/z 265.2 ($M+H^+$) ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.60 (s, 1H), 8.53 (d, $J = 4.8$ Hz, 1H), 7.78 (d, $J = 7.2$ Hz, 1H), 7.38–7.40 (t, $J = 4.0$ Hz, 1H), 4.47–4.50 (dd, $J_1 = 12.0$ Hz, $J_2 = 4.0$ Hz, 1H), 3.94–3.97 (m, 2H), 3.78–3.81 (d, $J = 12.0$ Hz, 1H), 3.5–3.56 (t, $J = 12.0$ Hz, 1H), 3.0–3.1 (br m, 1H), 2.8–2.9 (br m, 1H), 1.4 (s, 9H), Anal. Calcd for $C_{14}H_{20}N_2O_3$: Calcd C, 63.6; H, 7.63; N, 10.6%. Found C, 63.56; H, 7.69; N, 10.58%.
N-Boc-2-(pyridin-3-yl) morpholine methyl iodide salt. To a solution of compound **11** (20 g, 0.075 mol) in acetone (200 mL), methyl iodide (32 g, 0.227 mol) was added at 0 °C and the mixture was stirred at 0 °C for 4 h and then at 25 °C for 8 h. The yellow solid formed was filtered and washed using cold acetone.
Yield: 30.0 g (97%), MS (ESI) m/z 407.32 ($M+H^+$), Molecular formula: $C_{15}H_{23}IN_2O_3$, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.37 (d, $J = 6.0$ Hz, 1H), 9.08 (s, 1H), 8.41 (d, $J = 7.8$ Hz, 1H), 8.13–8.17 (t, $J = 6.9$ Hz, 1H), 4.64–4.75 (br m, 4H), 4.2–4.2 (d, $J = 12.9$ Hz, 1H), 4.03–4.07 (d, $J = 11.4$ Hz 1H), 3.96 (br m, 1H), 3.67–3.75 (t, $J = 11.85$ Hz, 1H), 3.09 (br m, 1H), 2.91–2.99 (t, $J = 11.85$ Hz, 1H), 1.43 (s, 9H).
17. *N-Boc-2-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-morpholine* **12**. To a solution of methyl iodide salt **11** (30 g,

0.0738 mol) in methanol (300 mL) at 0 °C, sodium borohydride (7.03 g, 0.185 mol) was added portionwise and the mixture stirred at 30 °C for 8 h. Methanol was removed under reduced pressure, water was added and the mixture extracted using ethyl acetate (3 × 300 mL). The combined organic layer was dried over anhydrous sodium sulphate and purified through silica gel (60–120 mesh) column chromatography using 7:3 hexane–ethyl acetate as an eluent.

Yield: 17.0 g (81%), MS (ESI) *m*/*z* 283.32 ($M+H^+$), ^1H NMR ($CDCl_3$, 300 MHz): δ 5.77 (br s, 1H), 3.71–3.86 (br m, 3H), 3.46–3.50 (m, 1H), 2.89–2.91 (br, 3H), 2.76 (br, 2H), 2.43–2.52 (br m, 2H), 2.22 (s, 3H), 2.02–2.2 (br, 2H), 1.44 (s, 9H). Anal. Calcd for $C_{15}H_{26}N_2O_3$: Calcd C, 63.8; H, 9.28; N, 9.92%. Found C, 63.82; H, 9.30; N, 9.89%.

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