A New Synthesis of 2-(2-Hydroxyalkyl)- and 2-(2-Aminoalkyl)-morpholines *via* 3-Morpholinones

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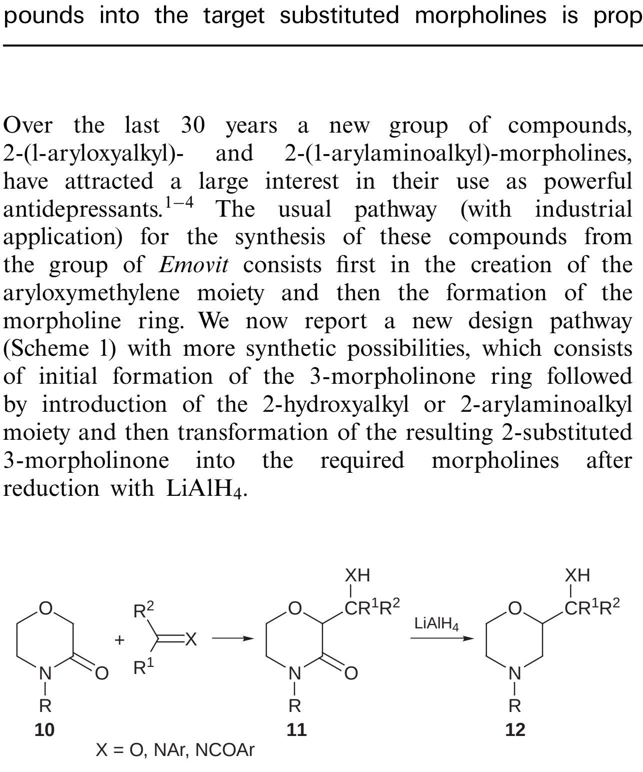
A new pathway for the synthesis of 2-(1-hydroxyalkyl)- and 2-(1-arylaminoalkyl)-morpholines *via* reaction of α-hydroxy- or α-amino-alkylation of 3-morpholinones followed by reduction with $LiAlH_4$ of the intermediate compounds into the target substituted morpholines is proposed.

Over the last 30 years a new group of compounds, 2-(l-aryloxyalkyl)- and 2-(l-arylaminoalkyl)-morpholines, have attracted a large interest in their use as powerful antidepressants.[1–4] The usual pathway (with industrial application) for the synthesis of these compounds from the group of *Emovit* consists first in the creation of the aryloxymethylene moiety and then the formation of the morpholine ring. We now report a new design pathway (Scheme 1) with more synthetic possibilities, which consists of initial formation of the 3-morpholinone ring followed by introduction of the 2-hydroxyalkyl or 2-arylaminoalkyl moiety and then transformation of the resulting 2-substituted 3-morpholinone into the required morpholines after reduction with $LiAlH_4$.



X = O, NAr, NCOAr

Scheme 1

Starting from a large number of 4-alkyl-3-morpholinones **10** with or without additional substituents, we found that their lithium salts, prepared by means of LDA in THF at −80 °C, react readily with carbonyl compounds. The expected 2-(l-hydroxyalkyl)-4-alkyl-3-morpholinones **11** (X = O) were obtained in good yields, even for acetophenone and benzophenone, which do not react with the analogous 3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzothiazines.[29–32] Our attempts to carry out the reaction with paraformaldehyde or trioxymethylene failed. The same reaction also occurs with the corresponding 2-methyl and 2-phenyl substituted 3-morpholinones giving the expected sterically hindered products **11** in good yields.

According to the obtained data, the nucleophilic addition of the lithiated 4-alkyl-3-morpholinones to prochiral carbonyl compounds occurs with well pronounced *syn*-stereoselectivity. Our result can be explained on the basis of the formation of a transition state with twist boat configuration as proposed by Heathcock *et al.*[41] and Seebach *et al.*[42] for the reaction of the lithium derivatives of some cyclic lactones and amides such as dioxalonones, oxazolidinones and imidazolidinones.

The lithium derivatives of **10** also react successfully with a series of arylidenearylamines and *N*-acylimines under the reaction conditions given above.[33] In all cases the addition products, 2-(1-aryl-1-phenylaminomethyl)-4-alkyl-3-morpholinones **11** (X = NAr or NCOAr) were obtained in good to high yields as a mixture of diastereoisomers. With some of the 2-phenyl substituted 3-morpholinones we carried out reactions with some Schiff bases under PTC conditions (50% aqueous sodium hydroxide in the presence of TEBA).

All new products were identified by their microanalysis, IR and ^1H NMR spectra as well as, in some cases, by mass spectra. Absorption bands at 1625–1650 cm^{-1}, corresponding to a carbonyl group, at 3350–3420 cm^{-1} for OH and at 3400-3440 cm^{-1} for NH are present in the IR spectra of the obtained 2-substituted 4-alkyl-3-morpholinones. The observed signals in the ^1H NMR spectra are in accordance with the proposed structure of the products.

The acylation of the 3-morpholinones provides a new indirect pathway for the preparation of 2-(l-hydroxyalkyl)-morpholines after hydrogenation of the corresponding 2-acyl-3-morpholinones. When the reaction of the lithium derivative of **17** with benzoyl chloride was carried out in THF at −78 °C, the corresponding tertiary alcohol **19** (38%) was isolated in addition to the expected ketone **18** (48%). Doubling the quantity of the deprotonating agent LDA gave rise to 57% yield of ketone **18** while the yield of alcohol **19** remained at 19%.[34]

Acylation of the lithium derivatives of 4-alkyl-3-morpholinones with ethyl chloroformate and isobutyl chloroformate produced a mixture of mono- and di-acylated products. For other acylating reagents, such as *N,N*-diphenylcarbamoyl chloride, however, the reaction resulted in the formation of only one product (the corresponding *N,N*-diphenylamides of the 4-alkyl-3-oxo-2-morpholinecarboxylic acid) probably because of steric hindrance. Acylation with a bulky reagent, di(*tert*-butyl) dicarbonate, gave also only the monoacylated derivatives, the *tert*-butyl esters of 4-alkyl-3-oxo-2-morpholinecarboxylic acids. The products were isolated and their structures confirmed by IR, ^1H NMR and mass spectra as well as by microanalysis.

The treatment of the corresponding morpholinones **11** (Scheme 1) with an excess of $LiAlH_4$ in anhydrous diethyl ether gives smoothly a series of 2-(1-hydroxyalkyl)- and 2-(1-arylaminoalkyl)-4-alkylmorpholines **12** in high yields. Their structure was confirmed by microanalytical as well as by their IR, ^1H NMR and mass spectra. It is interesting that after the reduction we did not observe any change in the *syn/anti* ratios of the diastereoisomer which remained the same as in the starting 2-substituted 3-morpholinones.

Reduction of the 2-benzoyl-derivative **18** with $LiAlH_4$ afforded 2-(1-hydroxyalkyl)morpholines prepared already from the corresponding 2-(1-hydroxyalkyl)morpholinone.

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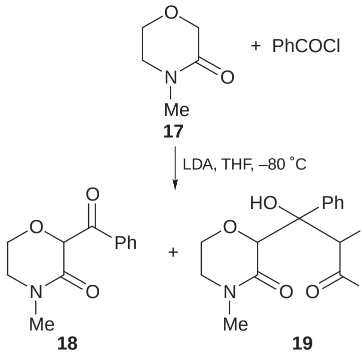

Scheme 2

On the other hand the reduction of the *tert*-butyl ester of 4-benzyl-3-oxo-2-morpholinecarboxylic acid afforded the target 4-benzyl-2-hydroxymethylmorpholine in high yield (73%).

All these results presented above demonstrate a new pathway for the synthesis of 2-(1-hydroxyalkyl)- or 2-(1-arylaminoalkyl)-derivatives of 4-alkylmorpholines consisting of the creation of a functionalized lateral chain at position 2 of the 3-morpholinone ring and subsequent transformation by reduction with $LiAlH_4$ to the target 2-substituted 4-alkylmorpholines.

Techniques used: ^{1}H NMR, IR, mass spectrometry

Tables: 2

References: 48

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