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# MANNICH REACTIONS OF OXAZOLIDINES†

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**Summary:** 3-Methyl-1,3-oxazolidine and 3,4-dimethyl-5-phenyloxazolidine react with acidic reagents under aprotic conditions to afford reactive intermediates that interact with nucleophilic aromatic substrates and enolsilyl ethers to afford good yields of Mannich bases.

Although 3-substituted-1,3-oxazolidines[1] have been known for many years the only studies reported until recently have involved reactions with Grignard reagents.[2] The possibility of ring-chain tautomerism in the presence of acids has been studied recently by $^1$H n.m.r. spectroscopy,[3] and hydroxy Schiff base - oxazolidine tautomerism has been discussed in terms of the apparent breakdown of Baldwin's rules.[4] The series of investigations by Griengl's group appears to be the only use in synthesis of these potentially interesting imonium ions.[5]

Our recent[6] work has been concerned with the use of a number of ethoxydialkylaminomethanes and bis(dialkylamino)methanes in "in situ" Mannich reactions using chlorosilanes. We now record the first use of oxazolidines in Mannich reactions.‡ Excellent yields of the anticipated Mannich bases can be obtained using a wide range of nucleophilic aromatic substrates and enol trimethylsilyl ethers. We have improved the published procedures for the preparation of, for example 3-methyl-1,3-oxazolidine to 70% by heating N-methylethanolamine, paraformaldehyde, and potassium carbonate in the absence of a solvent. We also prepared 3,4-dimethyl-5-phenyloxazolidine from (1R,2S)-ephedrine.

It is interesting to speculate whether the published Mannich reactions involving the reactions of phenols with formaldehyde and N-methylethanolamine[7] involve the intermediacy of 3-methyl-1,3-oxazolidine (1). It occurred to us that reactions of (1) with t-butylchlorodimethylsilane (TBDMSCl) in the presence of suitable aromatic substrates would allow us to carry out Mannich reactions and simultaneously protect the resulting alcoholic function. Analogy for our proposal is the cleavage of tetrahydrofuran by TBDMSCl in the presence of sodium iodide and which results in the formation of 1-iodo-4-t-butyldimethylsilyloxybutane.[8]

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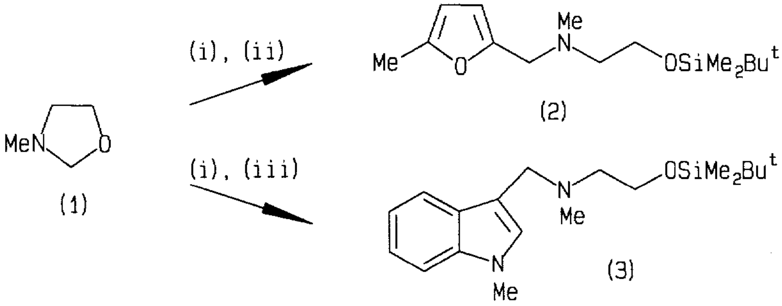
‡ All of the new compounds reported in this letter have been fully characterised by spectroscopic methods and elemental analysis or accurate mass measurement of molecular ions.

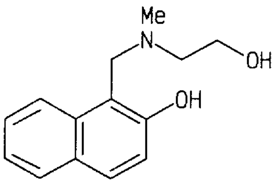
A reaction using 2-methylfuran confirmed that reasoning and led to the formation of the compound (2) in 33% yield. The relatively poor yield prompted an investigation of potential methods of improving the efficiency of the reaction. A reagent that is more electrophilic than TBDMSCl was evidently required. Although the rate of formation of TBDMS ethers derived, for example from tertiary alcohols, is dramatically increased by using TBDMS triflate in the presence of 2,6-lutidine,[9] we found that 2-methylfuran is rapidly destroyed by trialkylsilyl triflates and so we looked for an alternative strategy. A number of catalysts have been recommended.[10] Although the earliest method[11] used imidazole more recent procedures use DMAP in the presence of a base such as triethylamine[12] or imidazole.[13] 1,2,4-Triazole has been recommended,[14] as also has DBU.[15] The product of a Mannich reaction of 3-methyl-1,3-oxazolidine is a tertiary amine which is able to remove the hydrogen chloride generated. The use of 1,2,4-triazole in the reaction with 2-methylfuran resulted in an increase in the yield of the product (2) **Scheme 1** to 61%. A reaction of 1-methylindole without the use of a catalyst resulted in the formation of the derivative (3) in 34% yield. The addition of 1,2,4-triazole or DMAP gave (3) in similar yields (51 and 53% respectively).



**Scheme 1**

(i), t-$BuMe_2SiCl$ - 1,2,4-triazole ; (ii), 2-methylfuran; (iii), 1-methylindole

In the majority of our reactions we have used the cheaper reagents, chlorotrimethyl-, dichlorodimethyl-, and trichloromethyl- silanes to bring about the cleavage of oxazolidines. In these reactions the silyl residue is, of course, lost during the work-up procedure. Very nucleophilic phenols may be sufficiently acidic to react in the absence of an activating reagent. Thus 2-naphthol and 3-methoxyphenol react with (1) and gave (4) and (5) in 96% and 50% yields respectively; (4) was characterised as its hydrochloride and (5) as its methyl ether. Less reactive phenols, for example 2,4-dimethylphenol, gave lower yields (*ca.* 25%).



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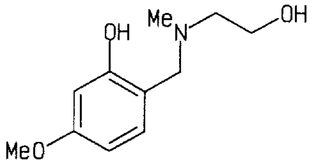


(5)

Reactions of the enoltrimethylsilyl ethers derived from acetophenone, pinacolone, and pentan-3-one with 3-methyl-1,3-oxazolidine (**1**) were investigated. No attempt has been made to optimise the yields which ranged from 33-66%. All of the reactions were initially carried out at room temperature for 18h. The best yields of the products (**6**) (55%) and (**7**) (66%) were obtained using dichlorodimethylsilane *while the best yield of the ketone (**8**) from 1-ethyl-1-*trimethylsilyloxypropene (55%) was obtained using trichloromethylsilane. In the reactions of enoltrimethylsilylethers a balance must be struck between the rate of formation of an imonium salt and the rate of fragmentation of the product, which results in the formation of an unsaturated ketone. Thus in the cases of the ketones (**6**) and (**7**) acid catalysed enolisation can readily result in the formation of the fragmentation product. On the other hand, kinetic deprotonation of the ketone (**8**) does not lead to a fragmentation product and, presumably for this reason, trichloromethylsilane affords the best yield of the compound (**8**).

$Ph-CO-CH_2-CH_2-N(Me)-CH_2-CH_2OH$

(**6**) ($Me_3SiCl$ 47%)
($Me_2SiCl_2$ 55%)
($MeSiCl_3$ 39%)

$t-Bu-CO-CH_2-CH_2-N(Me)-CH_2-CH_2OH$

(**7**) ($Me_3SiCl$ 33%)
($Me_2SiCl_2$ 66%)
($MeSiCl_3$ 52%)

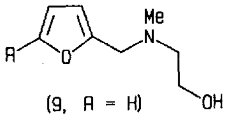
$Me-CH_2-CO-CH(Me)-CH_2-N(Me)-CH_2-CH_2OH$

(**8**) ($Me_3SiCl$ 39%)
($Me_2SiCl_2$ 48%)
($MeSiCl_3$ 55%)

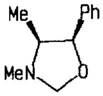
The possibility that the yields obtained in the reaction of 1-trimethylsilyloxy-1-phenylethene using trichloromethylsilane may be low due to fragmentation of the product under the strongly acidic reaction conditions was checked by carrying out a reaction for a reduced period. When a reaction was terminated after 2h the product (**6**) was isolated in 51% yield. This result confirms our view that further improvements to techniques must be sought.

Reactions of furan and 2-methylfuran have been used by us[6] to assess the value of reagent systems and so we carried out reactions with these latter substrates. As expected, the yield of the product (**9**) obtained using 3-methyl-1,3-oxazolidine (**1**), furan, and chlorotrimethylsilane was low (30%) but was significantly improved (to 75%) when using trichloromethylsilane.

In reactions of 2-methylfuran and 3-methyl-1,3-oxazolidine good yields of the alcohol (**10**) were obtained using either chlorotrimethylsilane (73%) or trichloromethylsilane (87%), and a reaction of 2-methylfuran and the oxazolidine (**11**), obtained from (1R,2S)-ephedrine, gave (**12**) in 80% yield using trichloromethylsilane. A reaction of 3-methyl-1,3-oxazolidine with trichloromethylsilane in the presence of N-methylpyrrole gave the mono- and di-substitution products (**13**) and (**14**) in 54 and 12% yields respectively. A similar reaction using chlorotrimethylsilane gave (**13**) in 73% yield. N-Methylindole gave the expected ethanolamine derivative (**15**) in 91% yield using the oxazolidine (**1**) and trichloromethylsilane.



(9, R = H)
(10, R = Me)



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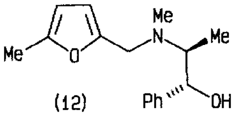
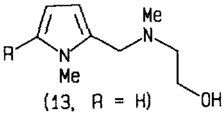
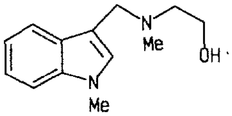


(12)

Dehaloalkylation of 2-haloethyl ethers and 2-dimethylaminoethyl chloride with metals has been reported,[16] but the isolation of a secondary amine does not appear to have been reported. Preliminary experiments show that the alcohol (**10**) affords, with tris(dimethylamino)phosphine-carbon tetrachloride,[17] the expected chloride in 55% yield. When the chloro-derivative (**16**) was heated under reflux with zinc in acetic acid for 1.75h in the presence of sodium iodide the secondary amine (**17**) was isolated in 61% yield.



(13, R = H)
(14, R = $CH_2NMeCH_2CH_2OH$)



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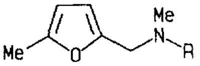

(16, R = $CH_2CH_2Cl$)
(17, R = H)

Our further studies will be directed towards exploiting the use of other cyclic aminals and aminol ethers in Mannich reactions and the further elaboration of the products.

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