

A NEW ROUTE TO SECONDARY AMINES FROM BIS-(ALKOXYMETHYL)-ALKYLAMINES - THE ACTIVATION OF AN AMINOMETHYL GROUP AND PROTECTION OF THE PRODUCT BY THE SAME FUNCTIONAL GROUP†

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Summary: Treatment of *N,N*-bis(alkoxymethyl)alkylamines with a variety of acidic reagents affords good yields of *N*-alkoxymethyl-*N*-alkylmethylenimine salts which react with trimethylsilyl enol ethers, and nucleophilic aromatic substrates to form protected secondary amines or tertiary amines by domino reactions; silyl ketene acetals afford tertiary amines only.

Although the formation of tertiary amines using Mannich reactions is extensively documented, the method has been applied only infrequently to the preparation of secondary amines.¹ The development of new methods for the preparation of secondary amines is a desirable objective.² The formation of benzoxazines³ by the interaction of phenols with *N,N*-bis-(alkoxymethyl)amines suggested the use of these latter compounds as precursors to protected secondary amines as well as bis(aminoalkylating) reagents with a wide range of nucleophiles. As far as we are aware the Grignard-Reformatsky reaction of bis(*n*-butoxymethyl)-*t*-butylamine is the only example where an *N*-alkyl-*N*-alkoxymethylmethylenimine salt has been a suggested intermediate.⁴ In that case it was suggested that magnesium bromide functions as the Lewis acid that is involved in the formation of the reactive intermediate. Our interest in Mannich reactions⁵ suggested an investigation of these interesting reagents and we present herein some of our results.

A range of *N,N*-bis(alkoxymethyl)amines was conveniently prepared by the interaction of a solution of a primary amine and paraformaldehyde in ethanol or methanol in the presence of potassium carbonate.⁶ The conversion into iminium salts can be achieved using a number of procedures. For example, a solution of *N,N*-bis(ethoxymethyl)-*iso*-propylamine in light petroleum gave, after several hours at room temperature, a crystalline salt on treatment with acetyl chloride. Reactions of *t*-butyl-bis(ethoxymethyl)amine with ethereal HCl or chlorotrimethyl silane in pentane gave the same iminium salt. A similar result was obtained using *t*-butyl-bis-(methoxymethyl)amine: the iminium methylene- group was observed at $\delta_{\text{H}} = 8.23$ and $\delta_{\text{C}} = 154.9$ in the former case and at $\delta_{\text{H}} = 8.53$ and $\delta_{\text{C}} = 152.7$ ppm in the latter case. We have also generated these and other iminium salts using other Lewis acids. A qualitative indication that this class of iminium salts is more reactive than *N,N*-dialkylmethylenimine salts is evident from the representative examples shown in the TABLE. Thus a reaction of *N,N*-dimethylmethylenimine chloride with *m*-dimethoxybenzene at room temperature gave less than 5% of the expected product whereas much better yields are indicated in the TABLE.

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Similarly, good yields of secondary amines in reactions with *N*-methylindole, *N*-methylpyrrole, and enol trimethylsilyl ethers, were only obtained when the reactions were conducted at low temperatures.

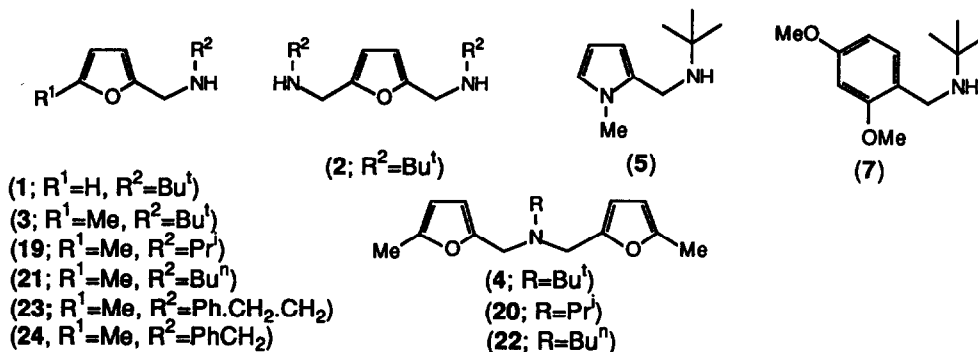
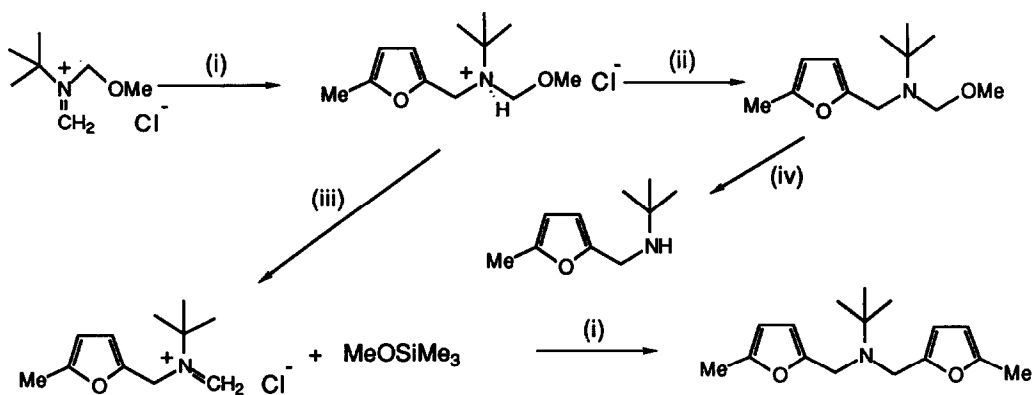


TABLE
 Reactions of N-Alkyl-N-alkoxymethyl(methylene)iminium salts

N-Alkyl	Co-reactant(mol)	Solvent	Temperature (°C)	Time	Products [Yield %]
t-Butyl-	Furan (1)	CH ₃ CN	RT	3h	(1)[31](2)[20]
t-Butyl-	Furan (10)	CH ₃ CN	-22	15h	(1)[51]
t-Butyl-	2-Methylfuran (1)	CH ₃ CN	RT	3h	(3)[80](4)[13]
t-Butyl-	1-Methylpyrrole (1)	CH ₂ Cl ₂	-78	2h	(5)[56]
t-Butyl-	1-Methylindole (1)	CH ₂ Cl ₂	-78	2h	(6)[80]
t-Butyl-	<i>m</i> -Dimethoxybenzene (1)	CH ₃ CN	RT	24h	(7)[32]
t-Butyl-	<i>m</i> -Dimethoxybenzene (5)	CH ₃ CN	RT	5 days	(7)[66]
t-Butyl-	3,3-Dimethyl-2-trimethylsilyloxy-but-1-ene (1)	CH ₂ Cl ₂	-10	2h	(8)[72]
t-Butyl-	1-Trimethylsilyloxy-cyclohexene (1)	CH ₂ Cl ₂	-10	2h	(9)[71]
<i>iso</i> -Propyl-	1-Trimethylsilyloxy-cyclohexene (1)	CH ₂ Cl ₂	-10	1h	(12)[63](13)[24]
<i>iso</i> -Propyl-	3,3-Dimethyl-2-trimethylsilyloxy-but-1-ene (1)	CH ₃ CN	-40	6h	(10)[54](11)[36]
<i>iso</i> -Propyl-	2-Methylfuran (1)	CH ₃ CN	RT	2h	(19)[77](20)[15]
<i>n</i> -Butyl-	2-Methylfuran (1)	CH ₃ CN	RT	22h	(21)[53.5](22)[13]
β-Phenethyl-	2-Methylfuran (1)	CH ₃ CN	RT	18h	(23)[55]
Benzyl-	2-Methylfuran (1)	CH ₃ CN	RT	21h	(24)[41]

A reaction of the iminium salt generated from bis(ethoxymethyl)-*iso*-propylamine using ethereal HCl gave, with *N*-methylindole, a mixture of the secondary and tertiary amines (14) and (15) in 64% and 30% respectively. However, when a similar reaction was carried out with the salt generated by using trichloromethyl silane, the compound (15) was isolated in 67.5% yield. The secondary amine (14) was not detected in this latter reaction. Similarly, a reaction involving *N*-methylpyrrole gave the tertiary amine (16) in >67% yield when the iminium salt was generated using trichloromethyl silane. These results suggested that the formation of iminium salts using

chloro-silanes result in some of the silane being occluded in the precipitated salt and further that the formation of a second iminium salt from the secondary amine in its protected form occurs more rapidly using a chlorosilane than when hydrogen chloride is the only acid present in the reaction mixture. This effect was confirmed by carrying out duplicate reactions of *N*-methoxymethyl-*N*-*t*-butylmethylene-iminium chloride with 2-methylfuran, to one of which we added bis(trimethylsilyl)-acetamide (**Scheme**). In the control experiment the yields of the compounds (3) and (4) were 80% and 13% respectively while in the presence of the HCl scavenger the yields of (3) and (4) were 12% and 80% respectively. These results evidently reflect the fact that whereas the silicon reagents are oxophilic, hydrogen chloride is an azophile. We were able to confirm the intermediacy of the aminol ether (17) by ^1H n.m.r. spectroscopy in a reaction which was worked up under non hydrolytic conditions and the aminol ether (18) was isolated in 47% yield from another reaction mixture. We have routinely used reactions of 2-methylfuran to evaluate new Mannich reagents and we report some other typical reactions in the TABLE.



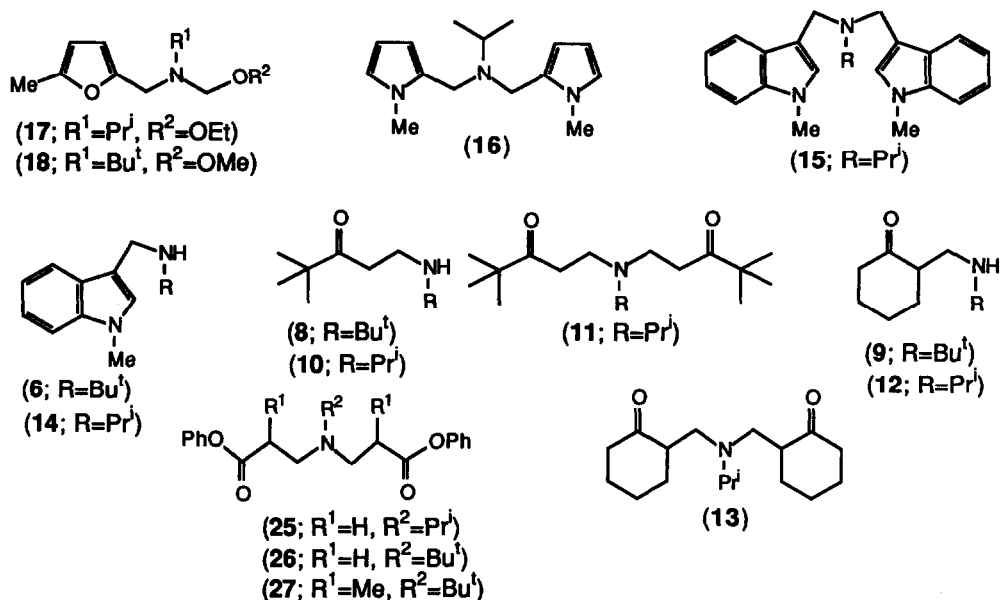
Scheme

(i), 2-methylfuran; (ii), Hunig's base; (iii), bis(trimethylsilyl)acetamide; (iv), water

The yields of secondary amines obtained also depend on the structure of the *N*-alkyl residue. The more sterically demanding alkyl group apparently inhibits the formation of tertiary amine. Whether this is due to inhibition of formation of the second iminium salt (**Scheme**) is not clear at this stage. It is interesting to note that in preliminary experiments using silyl ketene acetals we only isolated tertiary amines. Reactions of 1-phenoxy-1-trimethylsilyloxyethene with *N*-*iso*-propyl-*N*-ethoxymethylmethyleneiminium chloride (-45°C, 3h) and with *N*-*t*-butyl-*N*-methoxymethylmethyleneiminium chloride (-10°C, 2h) gave the amino-esters (25) and (26) in 27% and 39% yields respectively. A reaction of 1-phenoxy-1-trimethylsilyloxyprop-1-ene with *N*-*t*-butyl-*N*-methoxymethylmethyleneiminium chloride (-45°C, 4h) gave the compound (27) in 30% yield.

"In situ" reactions were also carried out in which 2-methylfuran was allowed to interact with a number of different bis(aminol ethers) in the presence of various acidic reagents. *N*-*iso*-propyl-bis(ethoxymethyl)amine gave the products (19) and (20) in variable amounts. The isolated yields were (19) (63%) and (20) (19%) using ethereal HCl, (58%) and (15%) using 25 mol % of TiCl₄, (22%) and (21%) using SO₂, and (38%) and (56%) using TMSCl. We will report other examples in the full paper. It is noteworthy that using β-phenylethylamine bis(aminol ethers) intramolecular

reaction was not observed. In our further studies we will explore the possibility that electron releasing substituents on the β -aryl residue will allow the formation of tetrahydro-isoquinoline derivatives.



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