N,N-Bis(trimethylsilyl)methoxymethylamine as a Convenient Synthetic Equivalent for +CH₂NH₂: Primary Aminomethylation of Organometallic Compounds

Toshiaki Morimoto, Toshio Takahashi, and Minoru Sekiya*

Shizuoka College of Pharmacy, Oshika, Shizuoka 422, Japan

The introduction of the primary aminomethyl unit at carbon through *N,N*-bis(trimethylsilyl)aminomethylation of Grignard and organolithium compounds can be achieved in good yield using *N,N*-bis(trimethylsilyl)methoxymethylamine (1).

Efficient new methods for introducing the primary aminomethyl unit at carbon in organic molecules are of interest, since the existing methods are not convenient, requiring many steps, or are limited to specific classes of compound. † We now describe a simple procedure for this purpose. The new reagent, *N,N*-bis(trimethylsilyl)methoxymethylamine (1), formally a source of †CH₂NH₂, was readily attacked by Grignard and organolithium reagents, the latter in the presence of magnesium bromide, affording *N,N*-bis(trimethylsilyl)aminomethyl compounds, simple solvolytic work-up of which gave the corresponding primary amines.

RX
$$\begin{array}{c} \text{RM} & \xrightarrow{\text{(Me}_3\text{Si)}_2\text{NCH}_2\text{OMe (1)}} \\ \text{Bu}^{\text{n}}\text{Li} & \xrightarrow{\text{(MgBr}_2)} \\ \text{RH} & & \text{RCH}_2\text{N(SiMe}_3)_2 \\ \\ \text{RH} & & \text{RCH}_2\text{NH}_2 \\ \\ \text{M = Li, MgX} \end{array}$$

The procedure demonstrates how aminomethyl compounds may be readily prepared from organic halides and aromatic compounds through metallation, N,N-bis(silyl)aminomethylation, and solvolysis. This method is useful not only for the preparation of one-carbon-enlarged primary amines, but also for the preparation of N,N-bis(trimethylsilyl)amines,

[†] The Mannich and related reactions do not achieve primary aminomethylation, but mostly tertiary aminomethylation. (For a review see M. Tramontini, *Synthesis*, 1973, 703.)

Table 1. Reactions of organometallic compounds with N,N-bis-(trimethylsilyl)methoxymethylamine (1).

Organometallic	N, N-Bis(trimethylsilyl)aminee	% Yield ^r
EtMgBra	$Pr^{n}N(SiMe_{3})_{2}$	72
c-C ₆ H ₁₁ MgBr ^a	$c-C_6H_{11}CH_2N(SiMe_3)_2$	52
CH ₂ =CHCH ₂ MgBr ^a	$CH_2=CH[CH_2]_2N(SiMe_3)_2$	88
PhCH ₂ MgBr ^a	$Ph[CH_2]_2N(SiMe_3)_2$	87
Me ₃ SiCH ₂ MgCl ^a	$Me_3Si[CH_2]_2N(SiMe_3)_2$	50
PhMgBr ^a	$PhCH_2N(SiMe_3)_2$	75
(2-Thienyl)MgBra	$(2-Thienyl)CH_2N(SiMe_3)_2$	92
PhC≡CMgBrʰ	$PhC \equiv CCH_2N(SiMe_3)_2$	61
Bu ⁿ Li ^c	$n-C_5H_{11}N(SiMe_3)_2$	85
(2-Furyl)Li ^{c,d}	$(2-Furyl)CH_2N(SiMe_3)_2$	81
(2-Thienyl)Lic.d	$(2-Thienyl)CH_2N(SiMe_3)_2$	67
o-MeOC ₆ H₄Lic.d	o-MeOC ₆ H ₄ CH ₂ N(SiMe ₃) ₂	56
(Fluoren-9-yl)Lic.d	$(Fluoren-9-yl)CH_2N(SiMe_3)_2$	80

^a Prepared in normal fashion directly from the parent halide and Mg in diethyl ether; c-C₆H₁₁ = cyclohexyl. ^b Prepared by metal-proton exchange of phenylacetylene with EtMgBr. Because of the lower reactivity of this reagent, the reaction was carried out in tetrahydrofuran under reflux. ^c Anhydrous MgBr₂ was added, which was prepared from 1,2-dibromoethane and Mg in diethyl ether. ^d Prepared by directed lithiation of the parent aromatic compound with BuⁿLi. ^e The *N*,*N*-bis(trimethylsilyl)amines have been fully characterized by n.m.r. spectra and elemental analysis. ^f Isolated yields based on the reagent (1).

which are obtained prior to the solvolytic procedure. The synthetic utility of the latter class of compound has been noted,² but their previous syntheses are generally of low yields and limited in scope.³

The reagent (1) was obtained in 86% yield, by treating chloromethyl methyl ether‡ with lithium bis(trimethylsilyl)-amide in tetrahydrofuran-hexane at 0 °C, as a colourless liquid [b.p. 91—92 °C at 86 mmHg; 1 H n.m.r., δ (CDCl₃) 0.14 (s, 18H, 2 × Me₃Si), 3.17 (s, 3H, MeO), and 4.28 (s, 2H, CH₂); 13 C n.m.r., δ 1.9 (q, MeSi), 53.4 (q, MeO), and 80.9 (t, CH₂)], which is stable to long storage.

With a variety of Grignard and organolithium compounds the N,N-bis(trimethylsilyl)aminomethylation proceeded in good yields as shown in Table 1. A typical procedure is as

follows: an ethereal solution of the reagent (1) (1.0 equiv.) was added to an ethereal solution of the organometallic compound (1.0—1.1 equiv.), to which, in the case of the organolithium compounds, anhydrous magnesium bromide (1.0 equiv.) in diethyl ether had been added. The mixture was stirred at room or at reflux temperature for 1—20 h and then treated with 30% aqueous sodium hydroxide. The usual work-up followed by distillation gave pure N.N-bis(trimethylsilyl)amines. The N.N-bis(trimethylsilyl)amines were easily desilylated by heating in methanol in the presence of toluene-p-sulphonic acid or silica gel as catalyst to afford the corresponding primary amines in good yields.

The Grignard reaction of (1) is similar to that of N-(alkoxymethyl)dialkylamines, resulting in N,N-dialkylaminomethylation, but few papers have described the reaction with organolithium compounds, which results in a low yield of the N,N-dialkylaminomethylation product. Because of the lower Lewis acidity of lithium salts, addition of magnesium bromide is necessary to promote the reaction.

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[‡] Chloromethyl methyl ether is carcinogenic and must be used with appropriate precautions.