

Preliminary communication

**Primary aminomethylation of organometallic compounds
via *N,N*-bis(trimethylsilyl)methylthiomethylamine ***

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Abstract

The reaction of various organometallic compounds with *N,N*-bis(trimethylsilyl)methylthiomethylamine provides an easy way for the introduction of a primary aminomethyl unit into a variety of organic substrates.

The sustained interest in the aminomethylation of organic molecules has mainly focused on the optimization of *N,N*-dialkylaminomethylations [1]. Very few methods have been so far reported for the introduction of the H_2NCH_2 moiety, in spite of its obvious importance in organic synthesis [2].

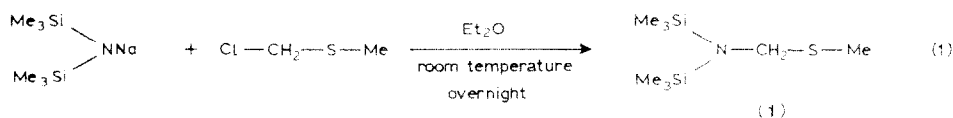
Quite recently however, a new reagent, *N,N*-bis(trimethylsilyl)methoxymethylamine, has been shown almost simultaneously by several authors [3] to act, often in the presence of "acidic catalysts", as an efficient agent for the primary aminomethylation of electron-rich organic molecules.

A possible drawback with the above reagent lies in the carcinogenicity of the intermediate methoxymethylene chloride, so we decided to investigate the synthesis and the possible applications of the corresponding sulphur analogue, *N,N*-bis(trimethylsilyl)methylthiomethylamine (**1**) also with a view to defining the relationships between the reactivity of the C-heteroatom bond to be broken in the aminomethylating reagent and the nature of the organometallic reagent or of the metal catalyst, and thus optimizing the primary aminomethylation reaction.

The reagent **1** was obtained in 50% yield (eq. 1), by treating the commercially available chloromethyl methyl sulphide with sodium bis(trimethylsilyl)amide, as a

* Dedicated to Professor Colin Eaborn in recognition of his important contributions to Organometallic Chemistry.

colourless oil, b.p. 70°C at 3 mmHg: ^1H NMR (CDCl_3): δ 0.20 (s, 18H, $2 \times \text{Me}_3\text{Si}$), 2.00 (s, 3H, MeS) and 4.10 (s, 2H, CH_2) ppm; IR (film): 1440, 1250, 940 and 850 cm^{-1} ; MS m/z 206 ($M^+ - \text{Me}$, 5%), 174 ($M^+ - \text{SMe}$, 69%), 73 (SiMe_3^+ , 100%), 47 (SMe^+ , 5%) *.



The *N,N*-bis(trimethylsilyl)methylthiomethylamine (**1**), was treated with several representative organometallic compounds, with or without catalysts: the relevant results are collected in Table 1.

In a typical procedure, 2.5 mmol of **1** were dissolved in an anhydrous solvent and then added to an equimolar amount of the organometallic reagent in the presence, when required, of a suitable catalyst. After stirring for several hours (see Table 1), the mixture was treated with aqueous sodium hydroxide (entries 1–7), $\text{NH}_3/[\text{NH}_4]\text{Cl}$ saturated aqueous solution (entries 11, 12), or eluted on alumina (entries 8–10). *N,N*-bis(trimethylsilyl)aminomethyl compounds obtained in this way are easily desilylated by solvolytic workup, affording the corresponding primary amines.

The Grignard reaction of **1**, similar to the oxygen analogue, results in a high yield of *N,N*-bis(trimethylsilyl)aminomethylation products from aromatic, aliphatic and heteroaromatic organomagnesium derivatives, under mild conditions. The sole limit in this first group of reactions lies in the availability of several starting Grignard reagents, some of which (entries 4, 5) are obtained only in low yields.

With organolithium derivatives the aminomethylation reaction was unsuccessful, irrespective of the reagent used: the presence of Lewis acid catalysts did not help, in contrast to results previously observed with the oxygen analogues **.

Because organotin compounds are incipient carbanionic species with a highly thiophilic metal centre, it seemed worthwhile to try them in aminomethylation reactions with **1**: among the compounds investigated in this reaction, only 1,3-bis(trimethylstannyl)-2-methylenepropane (entry 8), reacted in a satisfactory way with **1** in the presence of an equimolar ratio of MgBr_2 .

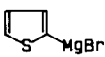
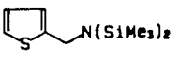
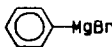
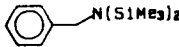
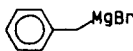
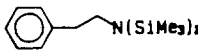
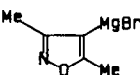
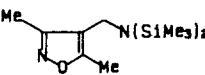
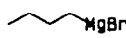
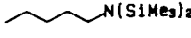
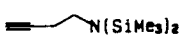
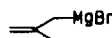
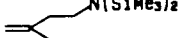
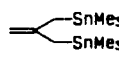
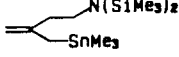
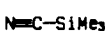
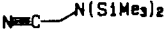
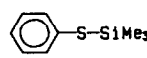
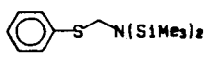
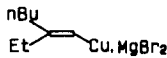
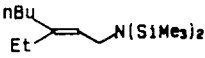
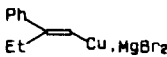
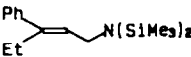
An interesting, but no immediately obvious, principle feature lies in the reactivity of **1** with trimethylsilylnitrile: the reaction occurs under mild conditions (entry 9) and gives very good yields of *N,N*-bis(trimethylsilyl)aminoacetonitrile, a product not easily available otherwise [4], and which has a synthetic interest as a precursor of glycine. A crucial point in this reaction is the catalyst: AlEt_3 appears to be the Lewis acid of choice, whose removal at the end of the reaction can be easily achieved by elution on alumina using CH_2Cl_2 as eluent. Extension of the aminomethylation reaction to other reactive organosilanes proved to be unsuccessful since, even at very low temperature, alkylation of **1** using AlEt_3 gives predominantly propyl-*N,N*-bis(trimethylsilyl)amine. Not even the use of other catalysts allowed extension of the aminomethylation method to organosilicon compounds.

* Compound **1** is, to our knowledge, unknown even though several thiomethylamino derivatives have been prepared recently (ref.3c) by treating thiosilanes with *N,N*-bis(trimethylsilyl)methoxymethylamine

** A plausible explanation lies in the generation, by lithium-hydrogen exchange, of a carbanion highly stabilized by the sulphur atom at the α position.

Table 1.

Reactions of organometallic compounds with *N,N*-bis(trimethylsilyl)methylthiomethylamine

Organometallic reagent	Reaction conditions	Catalyst ^a	Product	Yield ^b
1) 	Et ₂ O/ r. t. 2h	-		95%
2) 	Et ₂ O/ r. t. 48h	-		75%
3) 	Et ₂ O/ r. t. 48h	-		80%
4) 	Et ₂ O/reflux 48h	-		10%
5) 	Et ₂ O/ r. t. 48h	-		80%
6) 	Et ₂ O/ r. t. 48h	-		45% ^c
7) 	Et ₂ O/ r. t. 6h	-		70%
8) 	toluene/reflux 1h	MgBr ₂		75%
9) 	CH ₂ Cl ₂ / -78°C 1h	Al(Et) ₃		95%
10) 	without solvent 70°C, 2h	ZnBr ₂		65%
11) 	THF/ -40°C 4h	-		85%
12) 	THF/ -40°C 12h	-		80%

^a The catalyst is used in a stoichiometric amount. ^b Gas chromatographic yields. ^c Present in a mixture of double bond containing isomers: total conversion yield 65%.

Finally, reactions of **1** with organocuprates can be put to synthetic advantage. Reactions performed with two representative compounds of this series (entries 11, 12) are rapid and lead, in good yields, to the expected products: the organocuprates

exhibit a higher tendency to react with aminothioethers than with aminoethers [5]. The use of **1** is thus favourably competitive with that of the oxygen analogues and gives an easy and straightforward route to various functionalized primary allylic amines.

References

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