The Use of Methoxy(phenyldimethylsilyl)methyl-lithium as a Formyl Anion Equivalent[1]

David J. Ager,[a] James E. Gano,[b] and Shyamal I. Parekh[b]

[a] NutraSweet Research and Development, 601 E. Kensington Road, Mount Prospect, Illinois 60056, U.S.A.
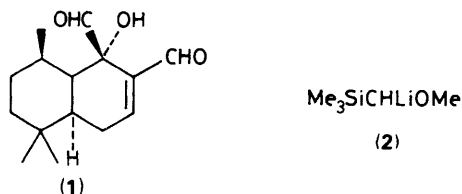[b] Department of Chemistry, Bowman-Oddy Laboratories, University of Toledo, Toledo, Ohio 43606, U.S.A.

Methoxy(phenyldimethylsilyl)methyl-lithium provides a new formyl anion equivalent which affords
α-hydroxyaldehydes via an oxidative desilylation procedure.

Many formyl anion equivalents have been advocated.[2] In contrast, the number of acetal anion equivalents [$(RO)_2CH^-$], which are still umpolung reagents, is rather limited.[3] As part of our approach to the insect antifeedant, warburganal (**1**), we required a formyl anion equivalent which was relatively

sterically demanding yet could be removed under mild conditions.

Magnus has demonstrated the utility of methoxy(trimethyl-silyl)methyl-lithium (**2**) as a vehicle for the homologation of carbonyl compounds.[4] This anion (**2**) has even been used in a
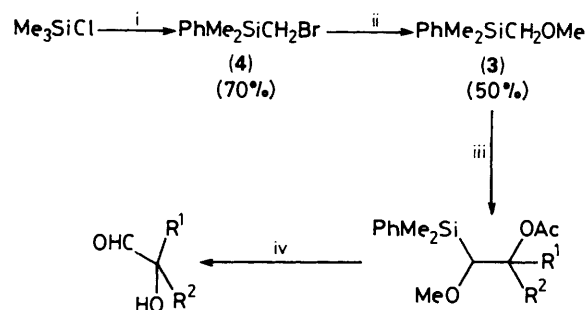
Scheme 1. *Reagents and conditions*: i, (a) Br_2, SO_2Cl_2, azoisobutyronitrile; (b) PhMgBr, Et_2O; ii, MeOH, $AgNO_3$, NEt_3, reflux, 16 h; iii, (a) s-BuLi, THF, TMEDA, $-70\,°C$; (b) R^1R^2CO; (c) Ac_2O; iv, H_2O_2, AcOH, MCPBA, Br_2 or KBr.

(5) a; $R^1 = R^2 = $ Me

b; $R^1 = Pr^i$, $R^2 = $ H

c; $R^1 = R^2 = $ Et

d; R^1, $R^2 = (CH_2)_3CH=CH-$

e; R^1, $R^2 = (CH_2)_5$

f; $R^1 = n\text{-}C_6H_{13}$, $R^2 = $ H

g; $R^1 = $ Ph, $R^2 = $ H

h; $R^1 = $ Ph, $R^2 = $ Me

i; $R^1 = R^2 = $ Ph

synthesis of warburganal.[5] The observation that a phenyl-silane can be converted to a hydroxy group,[6—9] led us to believe that a useful reagent could be derived from a combination of these methodologies, in the form of methoxy(phenyldimethylsilyl)methane (3).

Although the ether (3) has been reported,[10,11] we required a preparation which was amenable to scale up and did not require difficult separations. The final route is shown in Scheme 1. The halogenation[12] and Grignard displacement of the more reactive silyl halide afforded the bromide (4). The cleanest method for the introduction of the methoxy group was a silver induced substitution. Although the yield of the ether (3) (b.p. 70—76 °C/1 mmHg) was only 50%, the only other silicon-containing component in the mixture was the starting material which could be separated and, recovered (47%) by fractional distillation.

As with the trimethylsilyl analogue,[4] the silane (3) requires s-butyl-lithium to effect deprotonation. The resultant anion reacts with a wide variety of aldehydes and ketones (Table 1 and Scheme 1).† In the cases of a carbonyl electrophile, the β-hydroxysilanes (5) were isolated, despite the presence of N,N,N',N'-tetramethylethylenediamine (TMEDA), which was necessary to obtain good yields of the adducts, in the reaction mixture; this chelation agent usually promotes a Peterson elimination.[13] The diastereoisomer ratios of these adducts (5) were not far removed from 1 : 1, with the exception of n-heptanal, which had a *threo* : *erythro* isomer ratio of 3 : 1.

---

† As an example of a typical procedure: a solution of methoxymethyl-dimethylphenylsilane (3) (0.5 mmol) in anhydrous tetrahydrofuran (THF) (5 ml) and TMEDA (1 ml) was cooled to −78 °C, and s-butyl-lithium (0.57 mmol as a solution in cyclohexane) added. The reaction mixture was allowed to warm to 0 °C, then after 0.25 h, was cooled back to −78 °C. Benzaldehyde (0.5 mmol) was added, and the resultant solution allowed to warm to room temperature. The reaction was quenched with saturated ammonium chloride solution, diluted with ether, washed with water and brine, and dried (Na_2SO_4) to give, after chromatography, the adduct (5g) (87%) as an oil. The diastereoisomers were separated by preparative h.p.l.c. ^1H n.m.r. ($CDCl_3$) *erythro* isomer; δ 7.53—7.2 (m, 10H), 5.05 (dd, J 5.0 Hz, 1H), 3.28 (d, J 5.0 Hz, 1H), 3.24 (s, 3H), 2.32 (d, J 2.5 Hz, 1H), 0.21 (s, 3H), and 0.06 (s, 3H); *threo* isomer δ 7.55—7.24 (m, 10H), 4.69 (dd, J 6.2 and 2.4 Hz, 1H), 3.23 (d, J 6.2 Hz, 1H), 3.17 (s, 3H), 2.87 (d, J 2.4 Hz, 1H), 0.20 (s, 3H), and 0.19 (s, 3H). Satisfactory elemental analysis was obtained.

The conversion to the α-hydroxyaldehyde was achieved by quenching the reaction above with acetic anhydride (1 mmol). The crude ester was dissolved in acetic acid, and treated with 30% hydrogen peroxide (2.5 mmol) in the presence of *m*-chloroperbenzoic acid (MCPBA) (0.1 mmol) and potassium bromide (0.6 mmol), at 0 °C. When the evolution of gas had subsided, more hydrogen peroxide (5 mmol) was added, and the mixture stirred at 0 °C for 0.5 h. The resultant slurry was allowed to warm to room temperature overnight, then warmed to 40 °C for 1 h. Upon cooling, ether was added, and the mixture washed with 0.1 M hydrochloric acid, saturated $NaHCO_3$, and NaCl, dried (Na_2SO_4) and evaporated to give a mixture of the α-hydroxyaldehyde and the corresponding acetate. The latter compound was converted to α-hydroxyphenylacetaldehyde by treatment of the mixture with sodium carbonate in methanol. The overall yield was 61%.
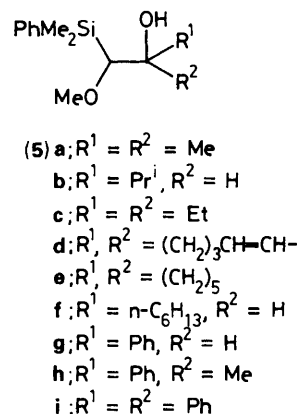
Table 1. Reaction of methoxy(phenyldimethylsilyl)methyl-lithium with electrophiles.

Electrophile	Product	Yield (%)[a]
Me_2CO	(5a)	80 (68)[b]
Pr^iCHO	(5b)	85 (70)[c]
Et_2CO	(5c)	70 (61)
Cyclohexenone	(5d)	57[d]
Cyclohexanone	(5e)	68 (60)
$n\text{-}C_6H_{13}CHO$	(5f)	88 (85)[c]
PhCHO	(5g)	95 (87)[c]
PhCOMe	(5h)	76 (70)[c]
Ph_2CO	(5i)	87

[a] N.m.r. spectroscopic yields are given. Isolated yields are quoted in parentheses. [b] This adduct was isolated as the acetate rather than β-hydroxysilane. [c] A mixture of isomers was formed. [d] 1,2-Addition was observed.

Peterson elimination from the hydroxysilanes (5) may be accomplished with sodium hydride. An alternative procedure to an aldehyde, which does not involve loss of the hydroxy group, requires oxidation of the silyl group with peroxide in the presence of bromine; yields for this step were typically around 60%.[9] It is necessary to protect the hydroxy group as an acetate ester. This can be accomplished through the addition of acetic anhydride to quench the condensation reaction of the formyl anion equivalent with the carbonyl electrophile. This approach provides a useful addition to

formyl anion equivalents as no transition metal ion, or strong acid catalysis is required to unmask either the aldehyde or acetal functionality.

Received, 7th February 1989; Com. 9/00586B

References

1 Taken, in part, from the PhD thesis of Shyamal Parekh, University of Toledo, March 1989.
2 D. J. Ager, in 'Umpoled Synthons: A Survey of Uses and Sources in Synthesis,' ed. T. A. Hase, Wiley, New York, 1987, pp. 19ff.
3 *E.g.* B. M. Trost and C. H. Miller, *J. Am. Chem. Soc.*, 1975, **97**, 7182.
4 P. Magnus and G. Roy, *Organometallics*, 1982, **1**, 553; *J. Chem. Soc., Chem. Commun.*, 1979, 822.
5 A. S. Kende and T. J. Blacklock, *Tetrahedron Lett.*, 1980, **21**, 3119.
6 K. Tamao and M. Kumada, *Tetrahedron Lett.*, 1984, **25**, 321.
7 I. Fleming, R. Henning, and H. Plant, *J. Chem. Soc., Chem. Commun.*, 1984, 29.
8 I. Fleming, R. Henning, and H. Plant, *Tetrahedron Lett.*, 1985, **26**, 397.
9 I. Fleming and P. E. J. Sanderson, *Tetrahedron Lett.*, 1987, **28**, 4229.
10 C. Eaborn and J. C. Jeffrey, *J. Chem. Soc.*, 1957, 137.
11 H. Shechter, K. Kreeger, P. R. Menard, and E. A. Sans, *Tetrahedron Lett.*, 1985, **26**, 1115.
12 H. Sattlegger, W. Simmer, W. Noll, and H. Niederpruern, Ger. Pat. 1 242 615; *Chem. Abstr.*, 1967, **67**, 90931q.
13 For a review see D. J. Ager, *Synthesis*, 1984, 384.