Pergamon

Tetrahedron Letters 40 (1999) 5537–5540

TETRAHEDRON
LETTERS

(2-Pyridyldimethylsilyl)methyl lithium as a novel hydroxymethylating reagent

Kenichiro Itami, Koichi Mitsudo and Jun-ichi Yoshida *

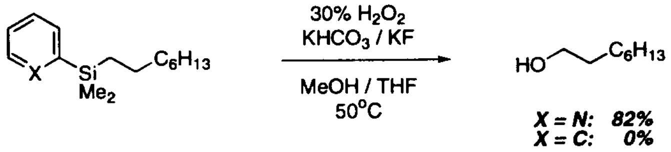
Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Yoshida, Kyoto 606-8501, Japan

Received 30 April 1999; revised 20 May 1999; accepted 21 May 1999

Abstract

(2-Pyridyldimethylsilyl)methyl lithium was found to react with organic bromides, aldehydes, ketones, and hydrosilanes in good to excellent yields. The resultant adducts were further oxidized with H_2O_2/KF to give the corresponding alcohols in excellent yields. Thus, this two-step transformation provides an efficient method for hydroxymethylation. © 1999 Elsevier Science Ltd. All rights reserved.

During the past two decades, intensive efforts have been devoted to develop the new silicon-based reagents in organic synthesis.[1] Since the discovery of the facile oxidative cleavage of the carbon–silicon bond to afford the corresponding alcohol (Tamao–Fleming oxidation), certain silyl groups have been well recognized as important hydroxyl group surrogates in modern organic synthesis.[2] Quite recently,[3] we have found that the 2-pyridyldimethylsilyl (2-$PyMe_2Si$) group is the versatile silyl group that is convertible to the hydroxyl group with much milder conditions compared to the well-known $PhMe_2Si$ group (Eq. 1).[4]



(1)

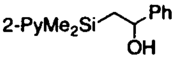
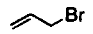
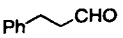
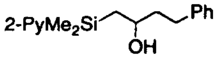
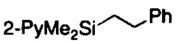
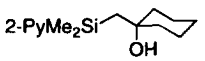
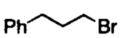
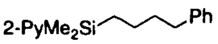
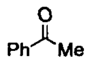
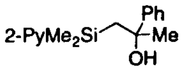
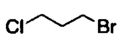
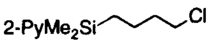
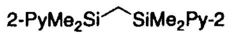
In the preceding paper,[5] we demonstrated that the (2-pyridyldimethylsilyl)methyl lithium (2-$PyMe_2SiCH_2Li$) reagent can be easily prepared by the deprotonation of the trimethylsilyl group of 2-pyridyltrimethylsilane. Thus, we have embarked on its reactions toward various electrophiles. We envisioned that, when connected with our previous findings of the oxidative cleavage of 2-$PyMe_2Si$ group (Eq. 1),[3] 2-$PyMe_2SiCH_2Li$ can be regarded as a novel nucleophilic hydroxymethylating agent (Eq. 2).[6]

---

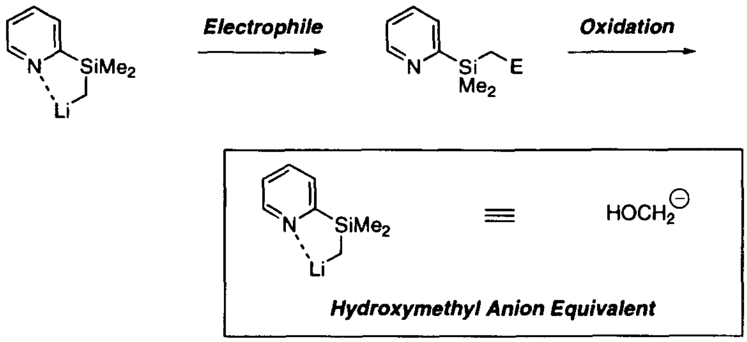
* Corresponding author.

PII: S0040-4039(99)01028-X

Table 1
Reactions of $2\text{-PyMe}_2\text{SiCH}_2\text{Li}$ with various electrophiles[a]

entry	electrophile	product	yield[b]	entry	electrophile	product	yield[b]
1	Me_3SiCl		93%[c]	6	PhCHO		85%
2			95%[c]	7			63%
3			99%[c]	8	Cyclohexanone		64%
4			84%[c]	9			55%
5			86%[c]	10	$2\text{-PyMe}_2\text{SiH}$		63%

[a] All reactions were performed in dry Et_2O using $2\text{-PyMe}_2\text{SiCH}_2\text{Li}$ and electrophiles (1.2 equiv.) at –78°C under argon. [b] Isolated yields. [c] Isolated only by acid-base extraction.



(2)

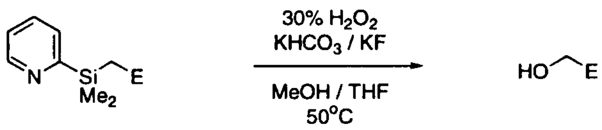
First, we examined the reactions of $2\text{-PyMe}_2\text{SiCH}_2\text{Li}$ with various electrophiles and the results are listed in Table 1.[7] Allyl, benzyl, and alkyl bromides were found to be excellent electrophiles for this purpose (entries 2–5). Unfortunately, secondary and tertiary alkyl halides were not applicable in this reaction, partially due to the high basicity of $2\text{-PyMe}_2\text{SiCH}_2\text{Li}$. Aromatic and aliphatic aldehydes were also found to be applicable (entries 6 and 7). Ketones also gave their adducts, albeit with lower yields (entries 8 and 9). Although chlorosilanes were excellent electrophiles, hydrosilane was also found to be effective in this reaction (entry 10).

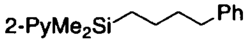
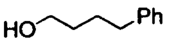
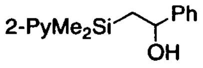
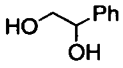
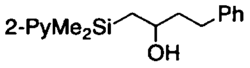
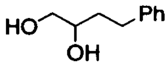
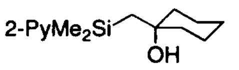
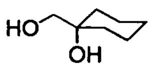
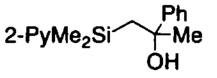
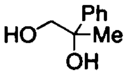
Next, we examined the oxidative cleavage of carbon–silicon bonds of (2-pyridyldimethylsilyl)methylated products in Table 1. Listed in Table 2 are the representative results.[8] The oxidations were performed by modified Tamao procedure[3] using H_2O_2 (30 equiv.), $KHCO_3$ (2.0 equiv.), and KF (2.0 equiv.) in MeOH:THF (1:1) at 50°C. In all cases, the oxidation proceeded well to give the corresponding alcohols, which are regarded as overall hydroxymethylated products of the electrophiles. Noteworthy was that these oxidative conditions were also applicable to β-hydroxysilanes which are prone to undergo Peterson-type elimination to form alkenes.

In conclusion, we have developed $2\text{-PyMe}_2\text{SiCH}_2\text{Li}$ as a novel nucleophilic hydroxymethylating agent

Table 2

H_2O_2 oxidation of (2-pyridyldimethylsilyl)methylated products[a]



entry	substrate	product	yield
1			98%
2			96%
3			90%
4			95%
5			93%

[a] All reactions were performed in MeOH/THF using substrates, 30% H_2O_2 (30 equiv.), $KHCO_3$ (2.0 equiv.), and KF (2.0 equiv.) at 50°C under argon. Given yields are isolated yields.

for various electrophiles. Compared to the other existing hydroxymethylating agents, $2\text{-}PyMe_2SiCH_2Li$ significantly outperforms in its availability. Moreover, the present methodology alleviates some of the problems encountered in others, in which the *silylmethylated* intermediate cannot always be easily isolated. This advantage of the isolation would allow the intervention of several synthetic manipulations between the silylmethylation and oxidation. Transmetallations to the other metals as well as the development of new selective reactions utilizing the intramolecular pyridyl group coordination are currently under investigation.

References

1. (a) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. (b) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.
2. For excellent reviews on oxidative cleavage of carbon–silicon bond, see: (a) Tamao, K. *Advances in Silicon Chemistry*; JAI Press Inc., 1996; Vol. 3, p. 1. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.
3. (a) Yoshida, J.; Itami, K.; Mitsudo, K.; Suga, S. *Tetrahedron Lett.* **1999**, *40*, 3403. (b) Itami, K.; Mitsudo, K.; Yoshida, J., submitted for publication.
4. For a review, see: Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.
5. Itami, K.; Mitsudo, K.; Yoshida, J. *Tetrahedron Lett.* **1999**, *40*, 5533.

6. (a) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120. (b) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4245. (c) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249. (d) Boons, G. J. P. H.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1989**, *30*, 229. (e) Chan, T. H.; Pellon, P. *J. Am. Chem. Soc.* **1989**, *111*, 8737. (f) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96. (g) Gais, H.-J.; Bülow, G. *Tetrahedron Lett.* **1992**, *33*, 461. (h) van Delft, F. L.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 1091. (i) Corey, E. J.; Chen, Z. *Tetrahedron Lett.* **1994**, *35*, 8731. (j) van Delft, F. L.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1995**, 1069.
7. Typical procedure: to a solution of (2-pyridyldimethylsilyl)methyl lithium (1.0 mmol) (see Ref. 5) in dry Et_2O (2 mL) was added benzaldehyde (127 mg, 1.2 mmol) at –78°C and stirred for 1 h. After stirring at 0°C for 3 h, saturated NH_4Cl (5 mL) was added and then made neutral with saturated $NaHCO_3$. Extractive work-up and subsequent silica gel chromatography (hexane:EtOAc=5:1 to 5:2 as eluents) afforded (2-hydroxy-2-phenyl)ethyl-(2-pyridyl)dimethylsilane (219 mg, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.27 (s, 3H), 0.38 (s, 3H), 1.39 (dd, J=14.7, 3.3 Hz, 1H), 1.57 (dd, J=14.7, 10.2 Hz, 1H), 5.05 (dd, J=10.2, 3.3 Hz, 1H), 7.16–7.26 (m, 2H), 7.31 (t, J=7.8 Hz, 2H), 7.44 (d, J=7.8 Hz, 2H), 7.54 (dm, J=7.8 Hz, 2H), 7.63 (tm, J=7.8 Hz, 1H), 8.70 (dm, J=5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ –3.0, –2.7, 28.1, 70.0, 123.1, 125.2, 126.4, 128.0, 129.3, 135.0, 148.0, 148.9, 166.5.
8. Typical procedure: to a mixture of KF (58 mg, 1.0 mmol) and $KHCO_3$ (100 mg, 1.0 mmol) in MeOH (1 mL) and THF (1 mL) was added (2-hydroxy-2-phenyl)ethyl-(2-pyridyl)dimethylsilane (129 mg, 0.5 mmol) and then 30% aq. H_2O_2 (1.71 g, 15 mmol) under argon. The mixture was stirred at 50°C for 6 h. After cooling to room temperature, the reaction mixture was treated with water (10 mL). The mixture was extracted with Et_2O (4×10 mL) and the combined organic phase was washed successively with 15% aq. $Na_2S_2O_3$ (10 mL). Drying over $MgSO_4$ and subsequent silica gel chromatography (hexane:EtOAc=1:1 to 1:2) afforded phenyl-1,2-ethanediol (66 mg, 96%) as a white solid.