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

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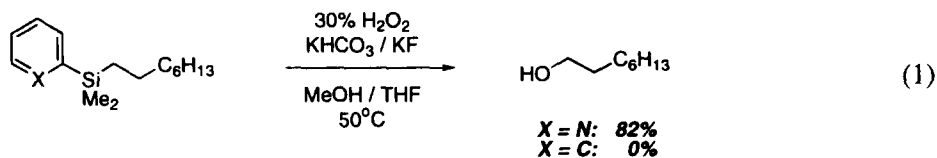
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Abstract

(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 $\text{H}_2\text{O}_2/\text{KF}$ 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-PyMe₂Si) group is the versatile silyl group that is convertible to the hydroxyl group with much milder conditions compared to the well-known PhMe₂Si group (Eq. 1).⁴



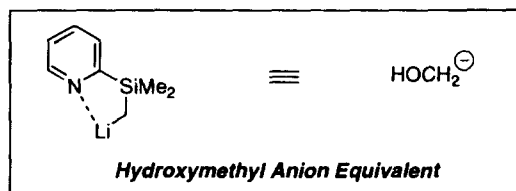
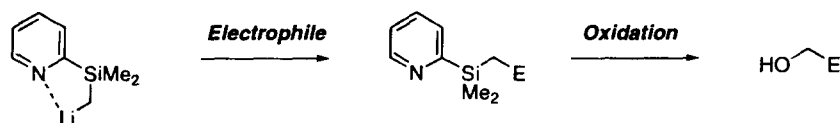
In the preceding paper,⁵ we demonstrated that the (2-pyridyldimethylsilyl)methyl lithium (2-PyMe₂SiCH₂Li) reagent can be easily prepared by the deprotonation of the trimethylsilyl group of 2-pyridyltrimethylsilane. Thus, we have embarked on its reactions toward various electrophiles. We envisioned that, when connected with our previous findings of the oxidative cleavage of 2-PyMe₂Si group (Eq. 1),³ 2-PyMe₂SiCH₂Li can be regarded as a novel nucleophilic hydroxymethylating agent (Eq. 2).⁶

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Table 1
Reactions of 2-PyMe₂SiCH₂Li with various electrophiles^a

entry	electrophile	product	yield ^b	entry	electrophile	product	yield ^b
1	Me ₃ SiCl	2-PyMe ₂ Si-CH ₂ -SiMe ₃	93% ^c	6	PhCHO	2-PyMe ₂ Si-CH(Ph)-CH ₂ OH	85%
2	CH ₂ =CHCH ₂ Br	2-PyMe ₂ Si-CH ₂ -CH=CH ₂	95% ^c	7	PhCH ₂ CHO	2-PyMe ₂ Si-CH(Ph)-CH ₂ CH ₂ OH	63%
3	PhCH ₂ Br	2-PyMe ₂ Si-CH ₂ -Ph	99% ^c	8	Cyclohexanone	2-PyMe ₂ Si-CH ₂ -cyclohexanol	64%
4	PhCH ₂ CH ₂ Br	2-PyMe ₂ Si-CH ₂ -CH ₂ -Ph	84% ^c	9	PhC(=O)Me	2-PyMe ₂ Si-CH(Ph)-CH ₂ OH	55%
5	ClCH ₂ CH ₂ CH ₂ Br	2-PyMe ₂ Si-CH ₂ -CH ₂ CH ₂ Cl	86% ^c	10	2-PyMe ₂ SiH	2-PyMe ₂ Si-CH ₂ -SiMe ₂ Py-2	63%

^a All reactions were performed in dry Et₂O using 2-PyMe₂SiCH₂Li and electrophiles (1.2 equiv.) at -78°C under argon. ^b Isolated yields. ^c Isolated only by acid-base extraction.



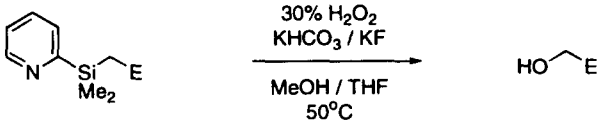
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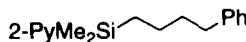
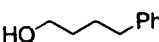
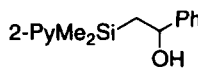
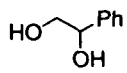
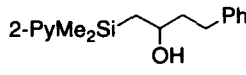
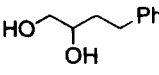
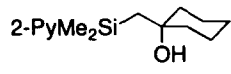
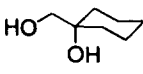
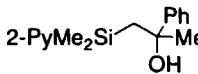
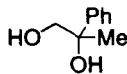
First, we examined the reactions of 2-PyMe₂SiCH₂Li with various electrophiles and the results are listed in Table 1.⁷ Allyl, benzyl, and alkyl bromides were found to be excellent electrophiles for this purpose (entries 2–5). Unfortunately, secondary and tertiary alkyl halides were not applicable in this reaction, partially due to the high basicity of 2-PyMe₂SiCH₂Li. 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 procedure³ using H₂O₂ (30 equiv.), KHCO₃ (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-PyMe₂SiCH₂Li as a novel nucleophilic hydroxymethylating agent

Table 2
H₂O₂ 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% H₂O₂ (30 equiv.), KHCO₃ (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-PyMe₂SiCH₂Li 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. Transmetalations to the other metals as well as the development of new selective reactions utilizing the intramolecular pyridyl group coordination are currently under investigation.

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7. Typical procedure: to a solution of (2-pyridyldimethylsilyl)methyl lithium (1.0 mmol) (see Ref. 5) in dry Et₂O (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 NH₄Cl (5 mL) was added and then made neutral with saturated NaHCO₃. 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: ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 KHCO₃ (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. H₂O₂ (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 Et₂O (4×10 mL) and the combined organic phase was washed successively with 15% aq. Na₂S₂O₃ (10 mL). Drying over MgSO₄ and subsequent silica gel chromatography (hexane:EtOAc=1:1 to 1:2) afforded phenyl-1,2-ethanediol (66 mg, 96%) as a white solid.