Lewis Acid-catalyzed Reductive Etherification of Carbonyl Compounds with Alkoxyhydrosilanes[1]

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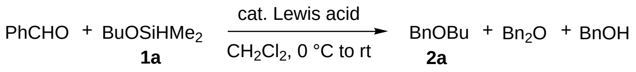
Abstract: The TMSI-catalyzed reaction of aldehydes and ketones with alkoxydimethylsilanes gave unsymmetrical ethers in good to high yields. This reductive etherification is superior to the conventional method using two kinds of silicon reagents in terms of atom efficiency and ease of operation.

Key words: Lewis acids, reductive etherifications, ethers, aldehydes, bifunctional silicon reagents

Reductive etherification of aldehydes and ketones, that is, reduction of in situ-generated acetals and oxocarbenium ions provides a convenient route to a variety of ethers.[2–6] Particularly, the Lewis acid-catalyzed reaction with alkoxysilanes and hydrosilanes is valuable for the highly efficient synthesis of unsymmetrical ethers.[6] In the course of our studies on tandem reactions using bifunctional silicon reagents,[7,8] we have recently reported the Lewis acid-catalyzed reductive amination of aldehydes and ketones with aminohydrosilanes.[9] Thus, our interest was focused on reductive etherification with alkoxyhydrosilanes. Such a tandem reaction is expected to be advantageous in terms of atom efficiency and ease of operation in comparison with the conventional method using two kinds of silicon reagents.[6] We herein disclose that alkoxydimethylsilanes ($ROSiHMe_2$) efficiently work for the Lewis acid-catalyzed reductive etherification of various aldehydes and ketones.

Initially, the reaction of benzaldehyde with butoxydimethylsilane **1a** was run to screen Lewis acids (Table 1).[10] The use of $TiCl_4$, which is effective in the reductive amination with aminodimethylsilanes,[9] gave the desired ether **2a** in moderate yield along with dibenzyl ether and benzyl alcohol (entry 1).[11] Lowering the reaction temperature completely suppressed the formation of these by-products to improve the yield of **2a** (entry 2). The ZnI_2-catalyzed reaction with **1a** resulted in selective formation of benzyl alcohol (entry 3). In contrast, 5 mol% of TMSI, TMSOTf, and Ph_3CClO_4 effectively promoted the reductive etherification at 0 °C to room temperature to give **2a** in high yields (entries 4–6).

Table 1 Reductive Etherification of Benzaldehyde with **1a**[a]



$$PhCHO + \underset{\textbf{1a}}{BuOSiHMe_2} \xrightarrow[CH_2Cl_2,\ 0\ °C\ to\ rt]{cat.\ Lewis\ acid} \underset{\textbf{2a}}{BnOBu} + Bn_2O + BnOH$$

Entry	LA (equiv)	Time (h)	Yield (%)		
			2a	Bn_2O	BnOH
1	$TiCl_4$ (0.2)	16	64	13	20
2[b]	$TiCl_4$ (0.2)	96	91	< 1	0
3	ZnI_2 (0.2)	70	12	4	71
4	TMSI (0.05)	2	quant.	0	0
5	TMSOTf (0.05)	2	94	0	0
6	Ph_3CClO_4 (0.05)	2	97	0	0

[a] The reactions were carried out with 1.2 (entries 1–3) or 1.1 equiv (entries 4–6) of **1a**. For general procedure, see ref.[12]
[b] At –50 °C.

As shown in Table 2, the TMSI-catalyzed reductive etherification with **1** was applicable to various aldehydes and ketones.[12] In the reaction of substituted benzaldehydes, the para substituent affected the reactivity to **1a**. Introduction of an electron-donating group decelerated the reductive etherification (entries 2 and 3), while 4-halobenzaldehydes as well as benzaldehyde exhibited high reactivity (entries 4 and 5). The reactions of 4-nitro- and 4-cyanobenzaldehyde resulted in comparably low yields of **2** (entries 7 and 8), which is probably due to deactivation of the Lewis acid by the polar functionalities. The unsatisfactory yields could be improved by increased amounts of **1a** and TMSI (method B). Aromatic ketones were much less reactive than aromatic aldehydes (entries 9 and 10). Particularly, the reductive etherification of benzophenone was quite slow even under the conditions of method B. Cinnamaldehyde smoothly reacted with **1a** to give **2** in high yield (entry 11). In contrast, the reaction of α,β-unsaturated ketones such as (*E*)-4-phenyl-3-buten-2-one and 2-cyclohexen-1-one did not form the desired allyl ethers. Aliphatic aldehydes and ketones were not as reactive as benzaldehyde, but they could be efficiently converted into **2** by method B (entries 12–14).

We also examined the reaction of other alkoxydimethylsilanes **1b**–**d**. As a result, **1b** and **1c** were successfully utilized for the TMSI-catalyzed reductive etherification (entries 15–18). Unfortunately, the etherification with **1d** was too slow to attain satisfactory results (entries 19 and 20). In entry 20, the low reactivity caused reductive

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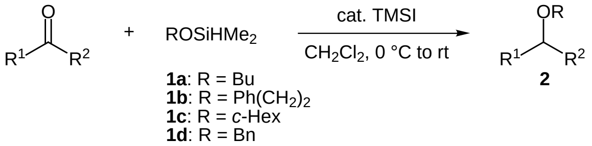
Table 2 Reductive Etherification of Aldehydes and Ketones[a]



Entry	Carbonyl Compound		1	Method[a]	Time	Yield
	R^1	R^2			(h)	(%)
1	Ph	H	**1a**	A	2	quant.
2	4-MeC$_6$H$_4$	H	**1a**	A (B)	18 (2)	84 (88)
3	4-MeOC$_6$H$_4$	H	**1a**	A (B)	18 (12)	65 (67)
4	4-ClC$_6$H$_4$	H	**1a**	A	2	96
5	4-BrC$_6$H$_4$	H	**1a**	A	2	98
6	4-MeO$_2$CC$_6$H$_4$	H	**1a**	A	12 (2)	90 (90)
7	4-O$_2$NC$_6$H$_4$	H	**1a**	A (B)	18 (3)	69 (82)
8	4-NCC$_6$H$_4$	H	**1a**	A (B)	36 (3)	74 (96)
9	Ph	Me	**1a**	A (B)	18 (18)	24 (73)
10	Ph	Ph	**1a**	B	24	21
11	(*E*)-PhCH=CH	H	**1a**	A	3	88
12	Ph(CH$_2$)$_2$	H	**1a**	A (B)	18 (2)	79 (95)
13	Ph(CH$_2$)$_2$	Me	**1a**	A (B)	24 (2)	68 (96)
14	-(CH$_2$)$_2$CH*t*-Bu(CH$_2$)$_2$-[b]		**1a**	A (B)	18 (3)	85 (96)
15	Ph	H	**1b**	A	2	92
16	-(CH$_2$)$_5$-[c]		**1b**	A (B)	2	91 (94)
17	Ph	H	**1c**	A	2	quant.
18	Ph(CH$_2$)$_2$	H	**1c**	A (B)	2 (2)	80 (85)
19	Ph	H	**1d**	A (B)	24 (24)	35 (45)
20	Ph(CH$_2$)$_2$	H	**1d**	A (B)	24 (24)	41 (48)[d]

[a] Method A: **1** (1.1 equiv), TMSI (0.05 equiv). Method B: **1** (1.2 equiv), TMSI (0.2 equiv). For general procedure, see ref.[12].

[b] 4-*t*-Butylcyclohexanone.

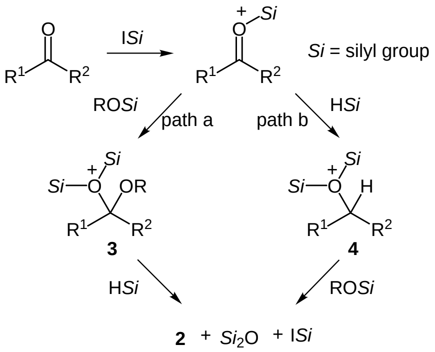
[c] Cyclohexanone.

[d] Di(3-phenylpropyl) ether was obtained in ca. 40% yield in both cases of methods A and B.

dimerization to di(3-phenylpropyl) ether as a side reaction.

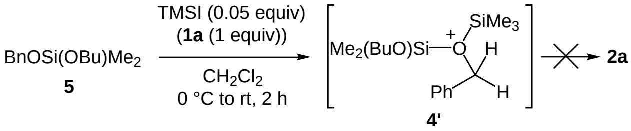
Judging from the report by Olah et al.,[6b] the present reductive etherification would pass through nucleophilic attack of the alkoxy group of **1** or an alkoxysilane arising from **1** and the subsequent reduction with a hydride species (path a in Scheme 1). Another possible mechanism is that the substrate undergoes hydride reduction in the initial step, then the resultant silyl ether **4** is converted into **2** by nucleophilic substitution of the alkoxy group (path b). To examine the latter possibility, dialkoxysilane **5** was prepared from dimethyldichlorosilane and subjected to a catalytic amount of TMSI (Scheme 2). As a result, the expected ether **2a** was not obtained at all. The reaction of **5** was carried out in the presence of an equimolar amount of **1a**, but it resulted in no formation of **2a** again. Thus path b is unlikely in the present reductive etherification.

We further performed the TMSI-catalyzed reaction of benzaldehyde with an equimolar mixture of **1a** and deuteriosilane **1e** to gain mechanistic insight into the reaction (Scheme 3). GC-MS analysis of the reaction mixture revealed that the reductive etherification formed all of the four possible benzyl ethers with no selectivity (Scheme 3). This result shows that a hydrogen atom and

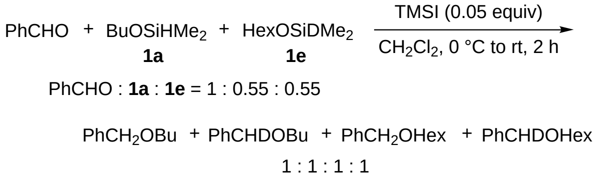


Scheme 1

an alkoxy group introduced into a substrate molecule by the present reaction are not originated from the same molecule of **1**. Accordingly, the reduction of **3** to **2** may proceed intermolecularly rather than by the action of an internal hydride species.



Scheme 2



Scheme 3

In summary, we have demonstrated that alkoxydimethylsilanes **1** work as bifunctional silicon reagents to enable the Lewis acid-catalyzed reductive etherification of aldehydes and ketones. The present reaction is superior to the conventional method using two kinds of silicon reagents in terms of atom efficiency and ease of operation.

Acknowledgement

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References

(1) Studies on Organosilicon Chemistry. No. 156.

(2) (a) Miura, K.; Hosomi, H. In *Lewis Acid Reagents*; Yamamoto, H., Ed.; Oxford University Press: Oxford, **1999**, 159. (b) Brewster, J. H. In *Comprehensive Organic Synthesis*, Vol. 8; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 211.

(3) Reductive etherification by catalytic hydrogenation in alcoholic acidic media: Verzele, M.; Acke, M.; Anteunis, M. *J. Chem. Soc.* **1963**, 5598.

(4) Reductive etherification with alcohols and hydrosilanes: (a) Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 3659. (b) Loim, N. M.; Parnes, Z. N.; Vassilyeva, S. P.; Kursanov, D. N. *Zh. Org. Khim.* **1972**, *8*, 896. (c) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136.

(5) Reductive dimerization of carbonyl compounds with hydrosilanes: (a) Doyle, M. P.; DeBruyn, D. J.; Donnelly, S. J.; Kooistra, D. A.; Odubela, A. A.; West, C. T.; Zonnebelt, S. M. *J. Org. Chem.* **1974**, *39*, 2740. (b) Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129. (c) Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **1988**, *44*, 3771; and ref.[6b].

(6) Lewis acid-catalyzed reductive etherification with alkoxysilanes and hydrosilanes (Lewis acid): (a) Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1985**, 743; (Ph_3CClO_4). (b) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314; (TMSI). (c) Hatakeyama, S.; Mori, H.; Kitano, K.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1994**, *35*, 4367; (TMSOTf). (d) Komatsu, N.; Ishida, J.; Suzuki, H. *Tetrahedron Lett.* **1997**, *38*, 7219; ($BiBr_3$).

(7) Miura, K.; Nakagawa, T.; Suda, S.; Hosomi, A. *Chem. Lett.* **2000**, 150.

(8) Review on tandem reactions: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(9) Miura, K.; Ootsuka, K.; Suda, S.; Nishikori, H.; Hosomi, A. *Synlett* **2001**, 1617.

(10) Alkoxydimethylsilanes **1** were prepared from alcohols, chlorodimethylsilane, and triethylamine (50–60% yield) or from alcohols and(diethylamino)dimethylsilane (50–70% yield).

(11) For the formation of dibenzyl ether (reductive dimerization), see ref.[5c] and ref.[6b]

(12) **General Procedure for the TMSI-catalyzed Reductive Etherification (Method A)**: To a solution of **1** (1.10 mmol) and a carbonyl compound (1.00 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added TMSI (1.0 M in CH_2Cl_2, 0.05 mL, 0.05 mmol). The mixture was stirred for 10 min and warmed to r.t. After a given reaction time, the reaction mixture was poured into water (20 mL) and extracted with *t*-BuOMe (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The residual oil was purified by silica gel column chromatography.