TETRAHEDRON LETTERS

Pergamon

Tetrahedron Letters 43 (2002) 6709–6713

In-situ generation of Et_3SiBr from $BiBr_3$ and Et_3SiH and its use in preparation of dialkyl ethers

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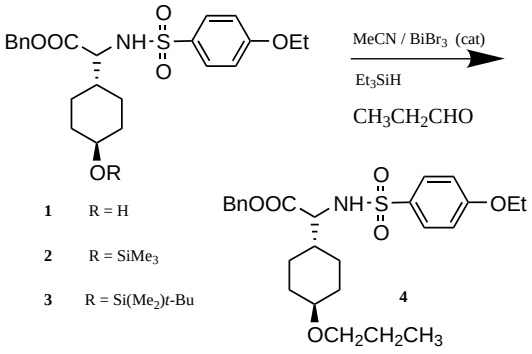
Received 9 July 2002; revised 23 July 2002; accepted 24 July 2002

Abstract—The reported $BiBr_3$–Et_3SiH catalyzed reductive etherifications of silyl ethers with carbonyl compounds are shown to be catalyzed by the in situ formed Et_3SiBr and verified by an independent use of the commercial reagent. As Et_3SiBr is moisture sensitive and is not readily available, this in situ generation is still recommended as the method of choice. Utilizing this method, several alcohols were transformed under very mild conditions into dialkyl ethers via their silyl intermediates, such as TES, TBDMS, and TIPS. © 2002 Elsevier Science Ltd. All rights reserved.

The preparation of ethers has been accomplished almost exclusively by means of the Williamson ether synthesis involving alkylation of an alkoxy anion with an alkyl halide or sulfonate. However, olefin formation (elimination) can sometimes become an alternative pathway under these basic conditions. Another method for the synthesis of ethers is the reductive coupling of carbonyl compounds with trialkyl silanes to give symmetrical and unsymmetrical ethers.[1] In the latter approach, emphasis has been placed on the conversion of a carbonyl compound to the corresponding ether, a transformation which has not been widely applied in the context of etherification of alcohols. However, when considered from the point of view of the alcohol component, transformation of an alcohol into an ether via its silyl ether can potentially be a very useful and desired transformation in organic synthesis. In addition, we were intrigued by the fact that the bismuth bromide that was claimed as a catalyst[2] was always used in combination with triethylsilane. These factors prompted us to investigate this chemistry in detail with special emphasis on the role of $BiBr_3$ in these etherifications. While our work was in progress, Wada et al. reported[3] their results on reductive etherification of alcohols using $BiCl_3$ as a catalyst. In the present communication, we show that in the reductive alkylation of silyl ethers with $BiBr_3/Et_3SiH$, the catalyst is actually triethylsilyl bromide. In addition, stable silyl ethers like triethylsilyl (TES), triisopropylsilyl (TIPS), and *t*-butyldimethylsilyl (TBDMS) can also be used in these transformations with equal ease.

Our work started with the objective of finding an efficient method for converting alcohol **1** to its corresponding *n*-propyl ether **4**[4] (Scheme 1). Substrate **1** represented a demanding case owing to the hindered nature of a secondary alcohol and the presence of an additional base-sensitive functionality such as the α-aminoester, which is susceptible to epimerization. Not surprisingly, several attempts to alkylate the hydroxyl group of **1** under a variety of basic conditions[5] failed to give the desired product **4**. The palladium catalyzed[6] reaction of **1** with diallyl carbonate afforded the *N*-allylated compound as the only product.[7] Also the reaction of **1** with allyl 2,2,2-trichloroacetimidate[8] under Lewis-



Scheme 1.

Keywords: bismuth bromide; triethylsilane; triethylsilyl bromide; silyl ethers; reductive etherification.

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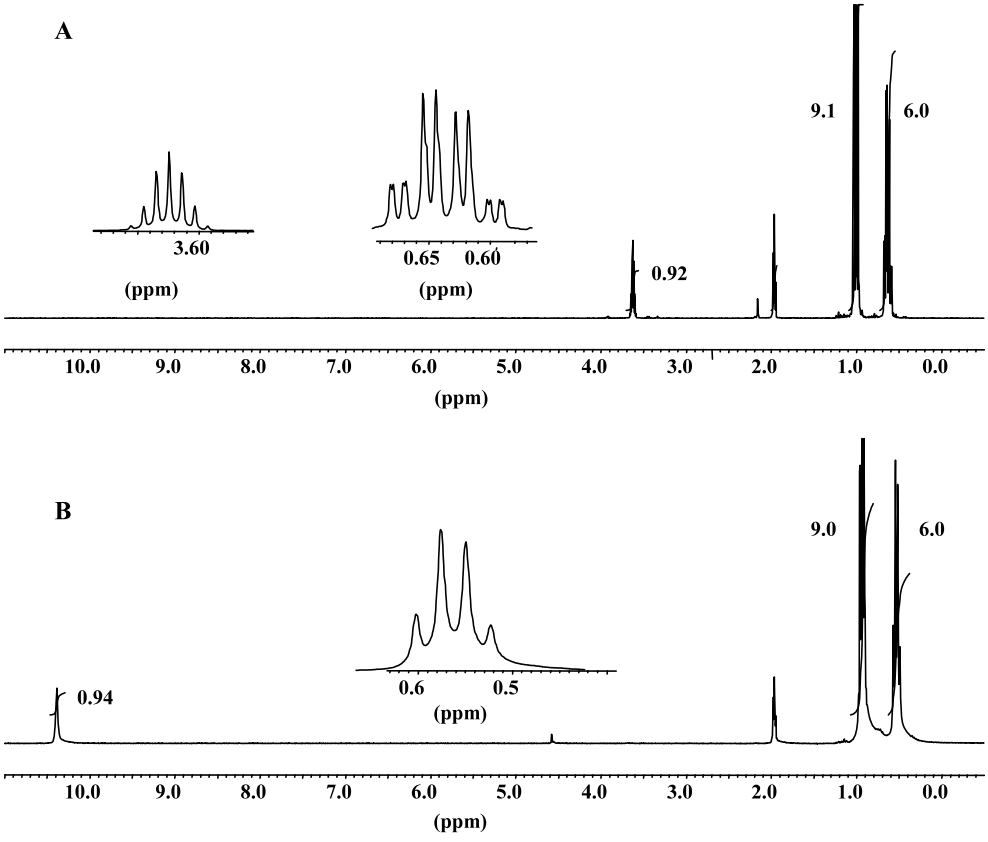
PII: S0040-4039(02)01532-0

acid catalysis led to the formation of trichloroacetimidate[9] of the alcohol **1**. Thus, it became apparent that standard methods of ether synthesis were not readily amenable to the conversion of **1** to **4**. However, reaction of TMS ether **2** derived from alcohol **1** with propionaldehyde and triethylsilane in the presence of 7 mol% of $BiBr_3$ under conditions similar to those described by Komatsu,[2] gave the desired ether **4** in 70% yield along with 15% of alcohol **1**. On a scale of 1 mmol, the reaction was found to be quite exothermic and was completed in less than 5 min. Recovery of starting alcohol **1** was demonstrated to be the result of hydrolysis of TMS ether **2** due to the non-anhydrous nature of the solvent acetonitrile.[10] Extension of this reaction to more stable TBDMS ether **3** resulted in a higher yield (88%) of the propyl ether **4**. This reaction has been successfully scaled up to 50 kg.

While studying this reaction, we always noticed precipitation of gray solids during the reaction. This solid was filtered off and was shown by elemental analysis to be bismuth metal and did not have any catalytic activity. Instead, the catalytic activity was retained by the filtrate.

To understand the actual process that is occurring under these conditions, we monitored the interaction of Et_3SiH with $BiBr_3$ by NMR. In Scheme 2, part A is the proton spectrum of Et_3SiH in CD_3CN. As expected, the signal for the methylene protons of Et_3SiH is observed as a multiplet at δ 0.61 ppm and the -Si<u>H</u> is observed as a multiplet at δ 3.60 ppm. After adding excess of $BiBr_3$ to the above solution, the proton spectrum was recorded again (Scheme 2, part B). It is interesting to note that the signal at δ 3.60 ppm disappeared while a new signal appeared at δ 10.36 ppm. Furthermore, the peak at δ 0.61 ppm changed from a multiplet to a simple quartet. All these results are consistent with the reaction shown below.

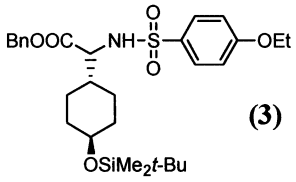
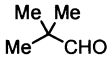
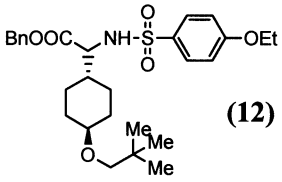
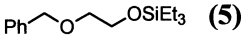
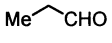
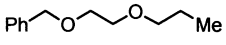
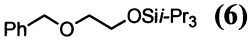
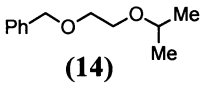
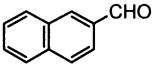
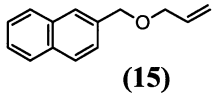
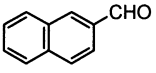
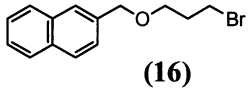
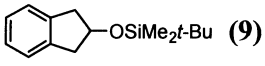
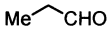
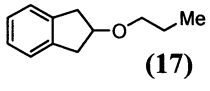
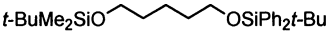
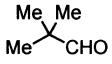
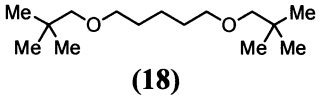
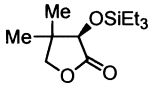
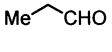
The hydrogen bromide generated in situ reacts with the solvent acetonitrile to give acetimidoyl bromide.[11] This adduct was generated independently (by passing dry hydrogen bromide through acetonitrile) and was ineffective in catalyzing *O*-alkylations. However, commercial triethylsilyl bromide when used in catalytic amounts together with Et_3SiH worked as effectively as $BiBr_3/Et_3SiH$ combination in these reductive etherifications of silyl ether **3**, thus confirming our conclusions from NMR experimentation. By analogy, the use of TMS triflate and TMS iodide for reductive alkylations is well documented in the literature.[1a,b] The known sensitivity of triethylsilylbromide towards moisture during routine handling and its scarce availability makes the in situ generation starting from $BiBr_3$ and Et_3SiH still the most convenient method. Therefore, the in situ method is used for all further work reported in this publication.



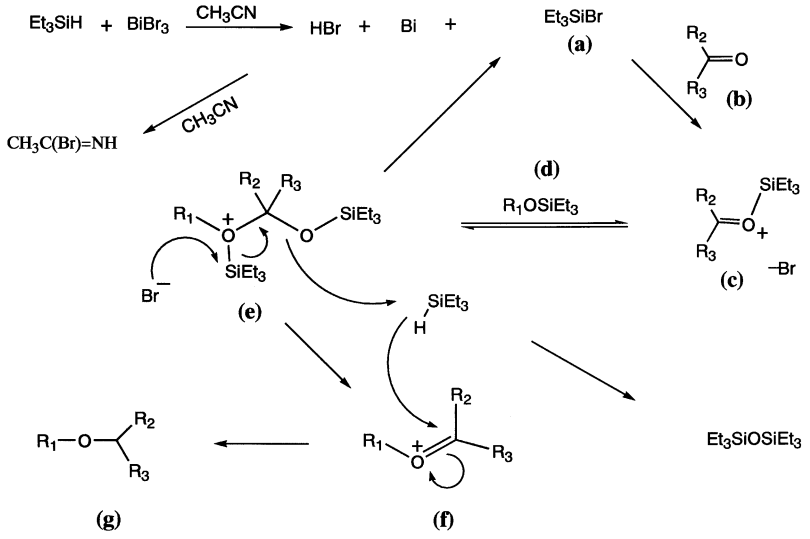
Scheme 2. (A) ^1H NMR spectrum of $Et_3SiH+CD_3CN$; (B) ^1H NMR spectrum of $Et_3SiH+CD_3CN+BiBr_3$.

To ascertain the generality of these reductive etherifications, we examined the coupling reactions of a variety of silyl ethers with several carbonyl compounds including both aldehydes and a ketone. These results are summarized in Table 1. As can be seen, the reaction works well with a wide variety of primary and secondary silyl ethers including bulky stable silyl ethers such as TBDMS (entries 1, 4, 5 and 6) and TIPS (entry 3). However, the reaction is much slower with TBDPS ether (entry 7). Neopentyl ethers, not readily accessible by conventional methods involving nucleophilic substitution, are easily obtained in high yield (entry 1). The reaction conditions are also compatible with potentially reducible functions such as that of bromides (entry 5)

Table 1. Transformation of silyl ethers into dialkyl ethers[a]

Entry	Silyl ether	Aldehyde or ketone	Time (min)	Product[b]	Yield (%)[c]
1	 **(3)**		20	 **(12)**	92
2	 **(5)**		15	 **(13)**	90
3	 **(6)**		30	 **(14)**	85
4	 **(7)**		10	 **(15)**	92
5	 **(8)**		10	 **(16)**	81
6	 **(9)**		15	 **(17)**	87
7	 **(10)**		30	 **(18)**	45
8	 **(11)**		18 h	No reaction	0

[a] The reaction was carried out following the general procedure described in the text.
[b] All products were fully characterized by spectroscopic methods, and the selected spectral data are given in Ref. 13.
[c] Isolated yields.



Scheme 3. Reductive etherification of silyl ethers.

and olefins (entry 4). However, silyl ethers such as pentalactone (entry 8) that are both sterically hindered and electronically deactivated, proved to be unreactive.

A likely mechanistic pathway for these transformations is shown in Scheme 3. It is reasonable to assume that the in-situ formed catalyst triethylsilyl bromide (a) activates the aldehyde (b) towards the nucleophilic attack by the silyl ether (d) to give an intermediate (e), which undergoes a fragmentation to give an oxonium species (f), which undergoes reduction with triethylsilane leading to the formation of the product (g). It is presumed that when other silyl ethers are used, the corresponding bromides are the catalysts.

A typical experimental procedure is as follows: A solution of TBDMS ether **3** (56.2 g, 100 mmol) in acetonitrile (600 mL) was partially distilled off at atmospheric pressure to remove 100 mL of solvent. The mixture was then cooled to 20°C and triethyl silane (24 mL, 150 mmol) was added slowly followed by bismuth bromide (3.0 g, 6.7 mmol). When the addition was complete, a dark black suspension was obtained. To this suspension, was added propionaldehyde (10.8 mL, 150 mmol) at such a rate[12] that the internal temperature does not rise above 25°C. The reaction mixture was stirred at 20–23°C till the HPLC indicated completion of reaction (30 min). To the reaction mixture was added 5% sodium bicarbonate solution (375 mL) and ethyl acetate (320 mL). The black mixture was filtered through a pad of Hyflo Super Cel® (10 g). The organic layer was separated from the aqueous layer. The organic phase was washed with 300 mL of 1% sodium chloride solution and 300 mL of water. The organic phase was evaporated under vacuum and the residue dissolved in 245 mL of ethyl acetate and diluted with 1470 mL of heptane. The suspension was heated to reflux to give a clear colorless solution. The solution was cooled to 0–5°C and held at this temperature for 30 min with continuos stirring. The white solid was filtered with suction and the cake washed with ice cold (0–5°C) 190 mL of ethyl acetate/heptane (1:5). The wet cake was dried at 40–45°C/37 mbar for 24 h to give **4** (41.53 g, 84.8% yield).

In conclusion, the initial interaction of $BiBr_3$ with triethylsilane was shown by NMR studies to produce triethylsilyl bromide. This in situ generated Et_3SiBr was indeed found to be the catalyst in the reductive etherification of silyl ethers with carbonyl compounds.

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4. Parker, D. U.S. Patent 5,770,624, 1998.
5. The following reaction conditions were tried: (a) NaH/THF/*n*-PrBr/rt/24 h; (b) NaH/THF/allyl bromide/rt/24 h; (c) NaH/THF/*n*-PrBr/18-crown-6/rt/24 h; and (d) NaH/DMF/allyl bromide/rt/24 h.
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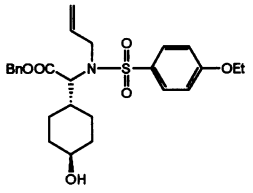
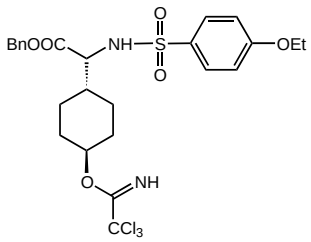
7. Reaction of **1** with $(CH_2{=}CH\text{-}CH_2\text{-}O)_2CO/Pd_2(dba)_3$-THF/reflux gave the following product:



8. Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2250.
9. The structure of the product was found to be as follows:



10. Alkyl TBDMS ethers are hydrolyzed with a catalytic amount of $BiBr_3$ in wet acetonitrile: Bajwa, J. S.; Vivelo, J.; Slade, J.; Repic, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021–6024.
11. Janz, G. L.; Danyluk, S. S. *J. Am. Chem. Soc.* **1959**, *81*, 3850–3854.
12. On large scale, the exotherm of the reaction was controlled by the rate of addition of propionaldehyde solution in acetonitrile to the reaction mixture and by external cooling.
13. Spectroscopic data for selected compounds:
(α*R-trans*)-α-[[(4-Ethoxyphenyl)sulfonyl]amino]-4-propoxycyclohexaneacetic acid phenylmethyl ester (4). mp 97–99°C; ^{1}H NMR δ 7.70 (d, $J=9.0$ Hz, 2H), 7.30–7.38 (m, 3H), 7.13–7.21 (m, 2H), 6.87 (d, $J=9.0$ Hz, 2H), 5.07 (d, $J=10.0$ Hz, 1H), 4.91 (AB, $J=12.1$ Hz, 1H), 4.86 (AB, $J=12.1$ Hz, 1H), 4.05 (q, $J=6.97$ Hz, 2H), 3.76 (dd, $J_1=10$ Hz, $J_2=5.1$ Hz, 1H), 3.37 (t, $J=6.79$ Hz, 2H), 3.08 (m, 2H), 2.03 (m, 2H), 1.48–1.73 (m, 5H), 1.44 (t, $J=6.97$ Hz, 3H), 0.96–1.38 (m, 4H), 0.90 (t, $J=7.4$ Hz, 3H); ^{13}C NMR δ 171.2, 162.4, 134.8, 130.8, 129.4, 128.6, 128.2, 114.5, 77.1, 69.9, 67.2, 63.9, 59.9, 40.3, 31.6, 27.4, 25.7, 23.3, 14.6, 10.6. Anal. calcd for $C_{26}H_{35}NO_6S$: C, 63.78; H, 7.21; N, 2.86. Found: C, 63.73; H, 7.22; N, 2.68.
(α*R-trans*)-4-(2,2-Dimethylpropoxy)-α-[[(4-ethoxyphenyl)-sulfonyl]amino]cyclohexaneacetic acid phenylmethyl ester (12). mp 128–129°C; ^{1}H NMR δ 7.70 (d, $J=9.0$ Hz, 2H), 7.29–7.39 (m, 3H), 7.12–7.21 (m, 2H), 6.87 (d, $J=9.0$ Hz, 2H), 5.06 (d, $J=10.0$ Hz, 1H), 4.90 (AB, $J=12.1$ Hz, 1H), 4.85 (AB, $J=12.1$ Hz, 1H), 4.05 (q, $J=7.0$ Hz, 2H), 3.75 (dd, $J_1=10$ Hz, $J_2=5.1$ Hz, 1H), 3.05 (s, 2H), 2.95–3.04 (m, 2H), 1.95–2.08 (m, 2H), 1.51–1.73 (m, 3H), 1.44 (t, $J=7.0$ Hz, 3H), 0.98–1.37 (m, 4H), 0.87 (s, 9H); ^{13}C NMR δ 171.2, 162.4, 134.8, 130.8, 129.4, 128.6, 128.2, 114.5, 78.8, 78.0, 67.2, 63.9, 59.9, 40.4, 32.0, 31.5, 31.4, 27.4, 26.7, 14.6. Anal. calcd for $C_{28}H_{39}NO_6S$: C, 64.96; H, 7.59; N, 2.71. Found: C, 64.80; H, 7.50; N, 2.54.
[(2-Propoxyethoxy)methyl]benzene (13). ^{1}H NMR δ 7.23 (m, 5H), 4.58 (s, 2H), 3.62 (s, 4H), 3.43 (t, $J=6.78$, 2H), 1.54–1.69 (m, 2H), 0.92 (t, $J=7.44$ Hz); ^{13}C NMR δ 138.8, 128.7, 128.1, 127.9, 73.6, 73.5, 70.5, 69.9, 23.3, 11.0;
[[2-(1-Methylethoxy)ethoxy]methyl]benzene (14). ^{1}H NMR δ 7.24–7.38 (m, 5H), 4.58 (s, 2H), 3.57–3.67 (m, 5H), 1.17 (d, $J=6.22$ Hz); ^{13}C NMR δ 137.5, 127.2, 126.5, 126.3, 72.0, 70.6, 68.8, 66.4, 21.0;
2-[(2-Propenyloxy)methyl]naphthalene (15). ^{1}H NMR δ 7.77–7.86 (m, 4H), 7.42–7.51 (m, 3H), 5.91–6.06 (m, 1H), 5.19–5.37 (m, 2H), 4.69 (s, 2H), 4.05–4.10 (m, 2H); ^{13}C NMR δ 136.4, 135.3, 133.9, 133.6, 128.7, 128.4, 128.3, 126.9, 126.6, 126.4, 126.3, 117.6, 72.7, 71.7;
2-[(3-Bromopropoxy)methyl]napthalene (16). ^{1}H NMR δ 7.75–7.87 (m, 4H), 7.43–7.52 (m, 3H), 4.68 (s, 2H), 3.65 (t, $J=5.93$ Hz, 2H), 3.56 (t, $J=6.0$ Hz, 2H), 2.16 (m, 2H); ^{13}C NMR δ 135.7, 133.2, 132.9, 128.1, 127.8, 127.6, 126.2, 126.0, 125.7, 125.5, 73.0, 67.6, 32.8, 30.6;
2,3-Dihydro-2-propoxy-1*H*-indene (17). ^{1}H NMR δ 7.10–7.24 (m, 4H), 4.33 (m, 1H), 3.45 (t, $J=6.78$ Hz, 2H), 3.16 (dd, $J=16.0$, 6.7 Hz, 2H), 2.97 (dd, $J=16$, 5.1 Hz, 2H), 1.53 (m, 2H), 0.93 (t, $J=7.43$, 3H); ^{13}C NMR δ 141.0, 126.4, 124.7, 80.3, 70.9, 39.3, 23.1, 10.7;
1,5-Bis(2,2-dimethylpropoxy)pentane(18). ^{1}H NMR δ 3.41 (t, $J=6.4$ Hz, 4H), 3.04 (s, 4H), 1.53–1.65 (m, 4H), 1.35–1.47 (m, 2H), 0.90 (s, 18H); ^{13}C NMR δ 81.8, 71.9, 32.4, 29.9.