

A Novel, Highly Efficient and Selective Desilylating Method for Trialkylsilyl Ethers

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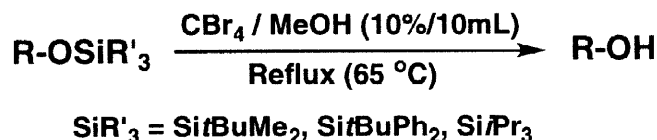
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Abstract: A series of *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl and triisopropylsilyl ethers are hydrolyzed to their corresponding alcohols in $\text{CBr}_4 / \text{CH}_3\text{OH}$ (0.1 eq. / 10mL) reaction system under refluxing condition. The chemoselectivity can be achieved between primary and secondary triisopropylsilyl ethers when more hindered 2-propanol is used instead of methanol.

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In order to synthesize more complicated molecules, chemists have developed increasingly satisfactory protective groups and effective methods for the formation and cleavage of protected compounds.^{1,2} The selective method to remove protective groups is an important tool in organic synthesis.³ Transformation of an alcohol to its corresponding silyl ether is a common and useful method for protecting hydroxyl groups. Within the silyl ethers, *tert*-butyldimethylsilylation is the most commonly used protecting method.^{4–6} More acid inert silyl ethers⁷ such as *tert*-butyldiphenylsilyl and triisopropylsilyl ethers recently receive much more attentions and extensive applications in organic synthesis.^{8–14} Our previous studies showed that a selective desilylation between primary and secondary *tert*-butyldimethylsilyl ethers is achieved in $\text{CCl}_4 / \text{MeOH}$ mixture under ultrasound whereas *tert*-butyldiphenylsilyl ether is resistant under the reaction condition.¹⁵ A few selective desilylating methods for *tert*-butyldiphenylsilyl and triisopropylsilyl ethers have been reported.^{16–24} The cleavage of the Si–O bond of these acidic resistant trialkylsilyl ethers is typically performed with fluoride ion or harsh basic reaction conditions. Herewith, we wish to report a mild, highly efficient and selective desilylations for alcoholic trialkylsilyl ethers under $\text{CBr}_4 / \text{MeOH}$ reaction conditions (Scheme 1).

Scheme 1



The typical procedure for desilylating trialkylsilyl ether to its corresponding alcohol follows: A solution of trialkylsilyl ether (1.0 mmol) and CBr₄ (0.1 mmol) in anhydrous CH₃OH (10 mL) is refluxed at 65 °C. After the reaction is completed (monitored by TLC), the solution was cooled to room temperature and the organic solvent was directly removed under reduced pressure. Further purification was achieved on a flash chromatograph with silical gel and ethyl acetate/hexane. A series of *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl and triisopropylsilyl ethers are deprotected and the results are shown in Table 1.

Table 1. Desilylations of trialkylsilyl ethers

Entry	Substrate	Product	Σ	Time (h)	Yield ^a
1			Si <i>t</i> BuMe ₂	1	95%
			Si <i>i</i> Pr ₃	3	97%
			Si <i>t</i> BuPh ₂	4	81%
2			Si <i>t</i> BuMe ₂	2	83%
			Si <i>i</i> Pr ₃	7	82%
			Si <i>t</i> BuPh ₂	7	87%
3			Si <i>t</i> BuMe ₂	2	90%
			Si <i>i</i> Pr ₃	5	93%
			Si <i>t</i> BuPh ₂	11	84%
4			Si <i>t</i> BuMe ₂	13	93%
			Si <i>i</i> Pr ₃	48	41%(50%) ^b
			Si <i>t</i> BuPh ₂	72	44%(47%) ^b
5			Si <i>t</i> BuMe ₂	2	91%(7%) ^c
			Si <i>i</i> Pr ₃	6	80%
			Si <i>t</i> BuPh ₂	12	85%

(a) The yields were determined after chromatographic purification.

(b) The recovery yield of starting material.

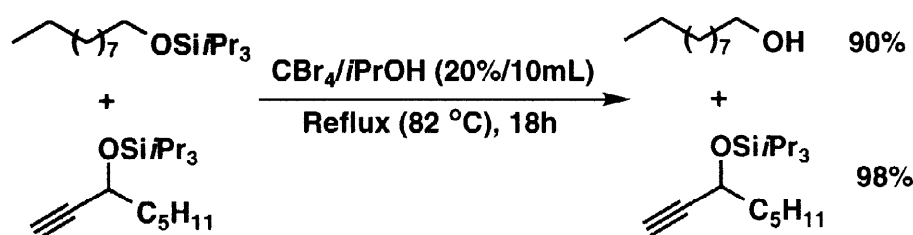
(c) The 7% yield of diol was produced.

Primary and secondary *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl and triisopropylsilyl ethers were deprotected to their corresponding alcohols with high yields under the reaction conditions (Entries 1, 2). *tert*-Butyldiphenylsilyl and triisopropylsilyl ethers of phenols are not hydrolyzed at short time and only about 40% desilylated to alcohols at prolonged reaction time (Entry 4). Thus, *ortho*-di-*tert*-Butyldimethylsilyl, *ortho*-di-*tert*-butyldiphenylsilyl and *ortho*-di-triisopropylsilyl ethers of benzyl and phenolic alcohols were prepared for

selective desilylating investigation. The results showed that benzyl silyl ether was selectively deprotected to benzyl alcohol whereas phenolic silyl ether was stable under the reaction condition (Entry 5). It should be noted that fluoride-induced desilylation generated a mixture of alcohols,²⁵ because of silyl migration from a six-membered intramolecular chelation of silicon between the two oxygen atoms.^{26,27}

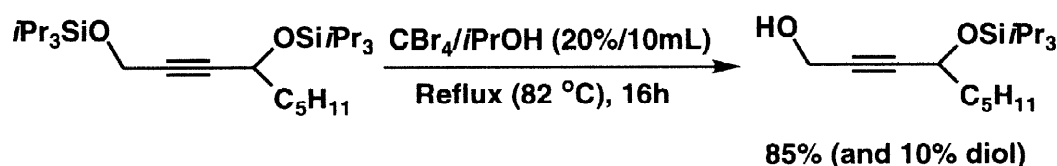
It is interesting to note that the desilylating reaction becomes much slower when the methanol is replaced with more steric hindered alcohol, such as *isopropyl* alcohol or *tert*-butyl alcohol. These results lead us to investigate this highly chemoselective desilylating process between primary and secondary triisopropylsilyl ethers. A mixture of primary and secondary triisopropylsilyl ethers in CBr_4 / *i*PrOH (0.2 eq./ 10 mL) was refluxed at 82 °C for 18 hours (Scheme 2). Primary triisopropylsilyl ether was deprotected to its corresponding alcohol in 90% yield, whereas secondary triisopropylsilyl ether was stable under refluxing condition for 18 hours and a 98% recovery was achieved after chromatography.

Scheme 2



A simple and selective desilylation between primary and secondary trialkylsilyl ethers is valuable in organic synthesis. Based on our knowledge, only a few selective desilylating methods between primary and secondary triisopropylsilyl ethers are reported.^{9,18} Therefore, we further investigate the desilylation of di-triisopropylsilyloxyl compound under the reaction condition. 1,4-Di-triisopropylsilyloxyl-2-nonyne was refluxed in CBr_4 / *i*PrOH reaction mixture for 16 h to afford a chemoselective desilylated product with 85% yield and 10% yield of diol after chromatographic purification (Scheme 3).

Scheme 3



This method enables to deprotect triisopropylsilyl ether of primary alcohol, whereas triisopropylsilyl ether of secondary alcohol was stable under the reaction condition. The chemoselective studies among trialkylsilyl ethers such as triethylsilyl, triphenylsilyl, *t*-butyldimethylsilyl, triisopropylsilyl and *t*-butyldiphenylsilyl ethers are underway. In addition, our investigations show that numerous functionalities are hydrolyzed by this reaction system (e.g. acetal/ketal, tetrahydropyranyl ether, silyl ester, etc.). These results lead us to further investigate this new hydrolyzing method and the studies are underway.

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