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A Simple and Highly Chemoselective Desilylation of *tert*-Butyldimethylsilyl Ethers

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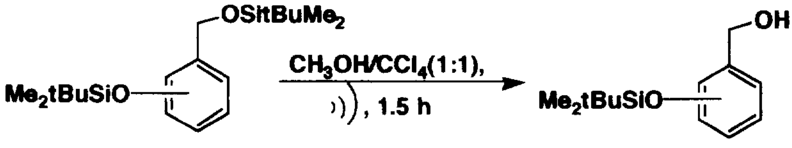
Abstract: The use of a 0.25M CH_3OH/CCl_4 (1:1) solvent mixture under ultrasound for the selective deprotection of *tert*-butyldimethlysilyl ethers of benzyl alcohols is described. This method enables to deprotect *tert*-butyldimethlysilyl ethers of primary alcohols, whereas *tert*-butyldimethlysilyl ethers of secondary and tertiary alcohols were stable under the reaction condition.

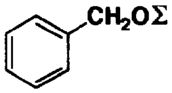
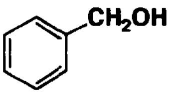
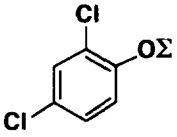
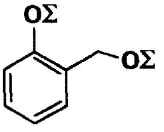
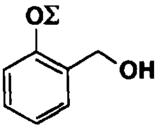
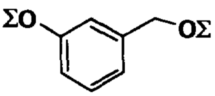
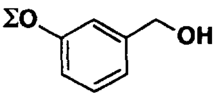
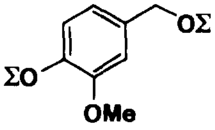
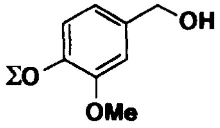
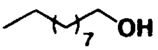
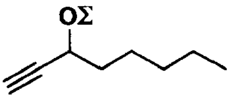
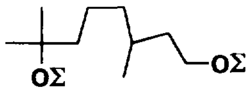
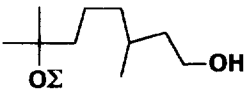
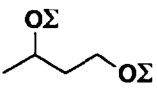
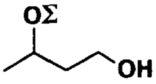
In order to synthesize more complicated molecules, chemists have developed increasingly satisfactory protective groups and effective methods for the formation and cleavage of protected compounds. The selective method to remove protective groups is an important tool in organic synthesis.[1,2] Transformation 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.[3,4] There are a number of papers reporting selective desilylating methods of *tert*-butyldimethylsilyl ethers.[5-14] The cleavage of the Si-O bond of *tert*-butyldimethylsilyl ether is typically performed with fluoride ion or under acidic or basic conditions. Even though a few desilylating methods are reported, a highly selective desilylating method is valuable for silylated alcohols in organic synthesis. Herewith, we wish to report highly chemoselective desilylations of alcoholic *tert*-butyldimethylsilyl ethers under ultrasonic conditions (Scheme 1).

Scheme 1



The typical procedure for desilylating *tert*-butyldimethylsilyl ether to its corresponding alcohol follows: A solution (0.25M) of *tert*-butyldimethylsilyl ether in CH_3OH/CCl_4 (1:1, v/v) is sonicated for 1.5 - 3 h in a commercial ultrasonic cleaning bath (Crest 575-D, 39 kHz) at around 40-50 °C. After the reaction is completed (monitored by TLC), the solvent is removed under reduced pressure. This procedure features a non-quenching treatment and the product after removal of solvent is clean enough that further purification is unnecessary. The results are shown in Table 1. In many cases, sonification for one and half hour is enough, but whenever it is not

Table 1 Desilylation of *tert*-butyldimethylsilyl ethers (Σ = Si*t*BuMe$_2$)[a]

Entry	Substrate	Product	Reaction Time (h)	Yield
1			1.5	93%
2			3	N.R.[b]
3			1.5 3	51% 90%
4			1.5	94%
5			1.5	93%
6			1.5	92%
7			3	N.R.[b]
8			1.5	96%
9			1.5 3	~ 50% 93%

(a)The general reaction conditions are described in the text.
(b) No reaction and 100% recovery of starting material.

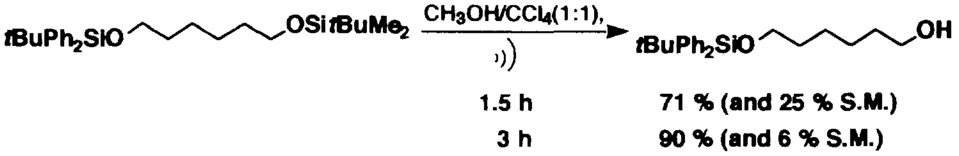
satisfactory, the reactions for three hours gave the product, primary alcohol in very good yields. Under these conditions, *tert*-butyldimethylsilyl ethers of phenols, and secondary and tertiary alcohols are not hydrolyzed (Entries 2-5 and 7-9). In addition, our investigations show that numerous functionalities are resistant to this desilylating method (e.g. $-CO_2R$, -OR, $-NR_2$, -Cl, -COR, -CHO, $-CONR_2$, etc.). It is interesting to note that 0.1M and 0.5M CH_3OH/CCl_4 (1:1) solvent mixture produce a lower yield of desilylation and the desilylating reaction becomes much slower when the methanol is replaced with more steric hindered alcohol, such as isopropyl alcohol or *tert*-butyl alcohol.

In the past, ultrasonic irradiation was considered only as a simple laboratory device, limited to use as a stirring improvement or as an exotic field of chemistry with only phenomenological interest. Recently, however, it became widely used as an energy source to generate radicals and initiate the electron transfer process in organic synthesis,[15] the cleavage of the Si-O bond performed under ultrasounic conditions is little reported.[14] Since earlier studies showed that sonication of CCl_4 in distilled water led to a reduction to pH 2 almost immediately and additional treatment produced no further effect,[16] the mixture of alcohol and carbon tetrachloride as a reagent and an organic solvent was investigated. The resulting desilylation reactions performed well under ultrasound and produced a high yield. Thus, based on the results, we estimate that the CH_3OH/CCl_4 mixture turns to a solution of pH 2 during cavitation, similar to a H_2O/CCl_4 mixture under similar condition.

Our results showed that the primary *tert*-butyldimethylsilyl ether was selectively deprotected to the corresponding alcohol, whereas secondary and tertiary *tert*-butyldimethylsilyl ethers were stable under the reaction condition (Table 1). *ortho*-di-*tert*-Butyldimethylsilyl alcohol (Entry 3) and 1,3-di-*tert*-butyldimethylsilyloxybutane (Entry 9) were selectively deprotected to benzyl alcohols about 50% under the reaction condition. A highly chemoselective desilylation and high yield was achieved with reaction for 3 h. Fluoride-induced desilylation generated a mixture of alcohols,[13] because of silyl migration from a six-membered intramolecular chelation of silicon between the two oxygen atoms.[17,18]

We further investigated the desilylation between *tert*-butyldimethylsilyl ether and *tert*-butyldiphenylsilyl ether. 1-*tert*-Butyldimethylsilyloxy-6-*tert*-butyldiphenylsilyloxyhexane was sonicated under the reaction condition for 1.5 h to afford a chemoselectively desilylated product (yield 71% and recovery 25% of starting material after chromatograph, Scheme 2). The yield of the selective desilylated product increased to 90% with 6% starting material recovery after sonication for 3 h.

Scheme 2



These results lead us to further investigate this extremely highly chemoselective desilylating process of different silyl groups (e.g. $SiEt_3$, $SiPh_3$, $Si{\it i}Pr_3$) and the studies are underway.

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