

## An Efficient and Highly Chemoselective Method to Desilylate Silyl Ethers

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An efficient and highly chemoselective desilylating method is described. Trimethylsilyl ethers (0.25 M) in a  $\text{CH}_3\text{OH}/\text{CCl}_4$  (1:1) solvent mixture are deprotected to their corresponding alcohols with ultrasound in a commercial ultrasonic cleaning bath. Selective deprotection of *tert*-butyldimethylsilyl ethers of benzyl alcohols and phenols is achieved under ultrasonic conditions. We deprotected also *tert*-butyldimethylsilyl ethers of primary alcohols, whereas *tert*-butyldimethylsilyl ethers of secondary and tertiary alcohols are stable under these conditions.

### INTRODUCTION

To synthesize complicated molecules, chemists have developed increasingly satisfactory protective groups and effective methods to form and to cleave protected compounds. A selective method to remove a protective group is an important tool in organic synthesis.<sup>1</sup> Transformation of an alcohol to its corresponding silyl ether is a common and useful method to protect hydroxyl groups. Within the silyl ethers, trimethylsilylation is used extensively to produce derivatives of most functional groups so as to increase their volatility for gas chromatography and mass spectrometry.<sup>2</sup> Because of its acidic and basic stability, *tert*-butyldimethylsilyl ether is the group most commonly used to protect alcohols. Selective desilylating methods are reported.<sup>3</sup> Cleavage of the Si-O bond is typically performed with a fluoride ion or under acidic or basic conditions. Even though a few desilylating methods are reported, none discriminates completely chemoselectively and in silyoxy functionalities. Thus, a highly selective desilylating method is valuable for silylated alcohols.

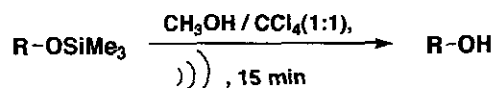
### RESULTS AND DISCUSSION

Much of earlier sonochemical work was done in aqueous solution because cavitation and sonochemical effects had not been observed in most common organic solvents. Ultrasonic irradiation was considered only a simple laboratory device, limited to use as a stirring improvement or as an exotic field of chemistry with only phenomenological interest.<sup>4</sup> Even though ultrasound became used to generate radicals and to initiate electron transfer in organic synthesis,<sup>5</sup> cleavage of the Si-O bond performed under ultrasonic conditions is little reported.<sup>3a</sup> As sonication of  $\text{CCl}_4$  in distilled

water led to a reduction to pH 2 almost immediately and as additional treatment produced no further effect,<sup>6</sup> a mixture of alcohol and carbon tetrachloride as a reagent and an organic solvent was then investigated. We used a commercially available ultrasonic cleaning bath (39 kHz) to investigate desilylation. The resulting reactions worked well under ultrasound and produced a high yield. Thus, we postulate that the  $\text{CH}_3\text{OH}/\text{CCl}_4$  mixture turns to a solution of pH 2 during cavitation, similar to a  $\text{H}_2\text{O}/\text{CCl}_4$  mixture under similar conditions. A mechanism<sup>7</sup> of a  $\text{CH}_3\text{OH}/\text{CCl}_4$  mixture under ultrasonic desilylation is proposed in Scheme II.

We report our results on desilylations with no reagent under ultrasonic conditions (Scheme I and Table 1). Trimethylsilyl ethers (0.25 M) are deprotected to their corresponding alcohols in  $\text{CH}_3\text{OH}/\text{CCl}_4$  (1:1) under sonication for 15 minutes in a commercial ultrasonic cleaning bath (39 kHz). Numerous functional groups resist this desilylating method (e.g.  $-\text{CO}_2\text{R}$ ,  $-\text{OR}$ ,  $-\text{NR}_2$ ,  $-\text{Cl}$ ,  $-\text{COR}$ ,  $-\text{CHO}$ ,  $-\text{CONR}_2$ , etc.).<sup>8</sup> Other solvent systems (e.g.  $\text{MeOH}$ ,  $\text{MeOH}/2$  drops  $\text{H}_2\text{O}$ ,  $\text{THF}/\text{H}_2\text{O}$ ,  $\text{MeOH}/\text{CHCl}_3$ , 95%  $\text{EtOH}$ , 95%  $\text{EtOH}/\text{CCl}_4$ , etc.) led to small yields even with prolonged reaction.

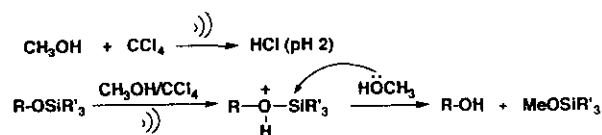
#### Scheme I



R = Alkyl (primary, secondary and tertiary), Aryl

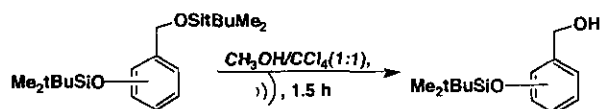
The Si-O bond of *tert*-butyldimethylsilyl ethers under acidic conditions is much more stable than in trimethylsilyl ethers.<sup>1a,3e</sup> This scheme of sonochemical desilylation induced cleavage of the Si-O bond of primary *tert*-butyldimethylsilylether (R-OTBDMS). Of many methods<sup>3a,h,j</sup> to regenerate the free hydroxyl group, aqueous hydrofluoric acid in acetonitrile selectively regenerates the alcohol of the

## Scheme II



compound containing both phenolic and alcoholic *tert*-butyldimethylsilyl ethers. This selective desilylation was processed under carefully controlled conditions including a tedious aqueous treatment. We report our results of highly chemoselective desilylation of alcoholic *tert*-butyldimethylsilyl ethers under ultrasonic conditions (Scheme III and Table 2). The alcoholic *tert*-butyldimethylsilyl ether (0.25 M) is desilylated in  $\text{CH}_3\text{OH}/\text{CCl}_4$  (1:1) under ultrasound, whereas the phenolic *tert*-butyldimethylsilyl ether was stable under similar condition (entries 1-5).

## Scheme III



Ortho-*tert*-butyldimethylsilyloxy, *tert*-butyldimethylsilyloxybenzyl alcohol (entry 3) and 1,3-di-*tert*-butyldimethylsilyloxybutane (entry 9) were selectively deprotected to benzyl alcohols about half under ultrasonic conditions. A highly chemoselective desilylation and high yield was achieved with reaction for 3 h. Fluoride-induced desilylation generated a mixture of alcohols,<sup>3a,b</sup> because of silyl migration from a six-membered intramolecular chelation of silicon between the two oxygen atoms.<sup>9</sup> Aliphatic *tert*-butyldimethylsilyl ethers were also investigated (entries 6-9). Only primary *tert*-butyldimethylsilyl ethers were deprotected to the corresponding alcohols under ultrasonic conditions. These results led us to investigate selective desilylation between *tert*-butyldimethylsilyl ether and *tert*-butyldiphenylsilyl ether.

1-*tert*-Butyldimethylsilyloxy-6-*tert*-butyldiphenylsilyloxyhexane was sonicated for 1.5 h to afford a chemoselectively desilylated product (yield 71% and recovery 25% of starting material after chromatography, Scheme IV). The yield of the selective desilylated product increased to 90% with 6% starting material recovery after sonication for 3 h.

## Scheme IV

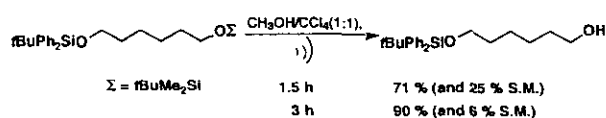


Table 1. Desilylations of Trimethylsilyl Ethers

Entry	Substrate	Product	Method <sup>a</sup>	Yield/%
1			A C D	95 <5 converted <5 converted
2			A	97
3			A	95
4			A D	96 <20 converted
5			A	97
6			A	98
7			A C	96 92 converted
8			B	98
9			B	96
10			B	98

<sup>a</sup> Method A: 0.25 M  $\text{CH}_3\text{OH}/\text{CCl}_4$ , 15 min sonication.

Method B: 0.1 M  $\text{CH}_3\text{OH}/\text{CCl}_4$ , 15 min sonication.

Method C: 0.25 M  $\text{CH}_3\text{OH}$ , 2 h sonication.

Method D: 0.25 M  $\text{CH}_3\text{OH}$  with 2 drops  $\text{H}_2\text{O}$ , 2 h sonication.

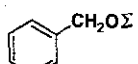
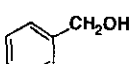
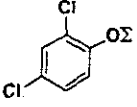
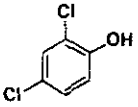
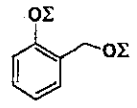
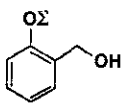
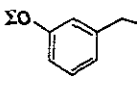
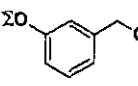
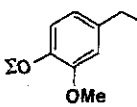
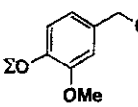
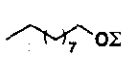
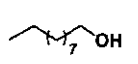
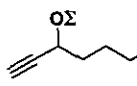
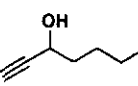
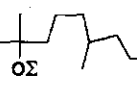
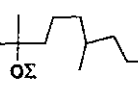
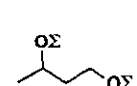
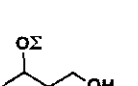
In summary, trimethylsilyl ethers and primary *tert*-butyldimethylsilyl ethers are deprotected to their corresponding alcohols in  $\text{CH}_3\text{OH}/\text{CCl}_4$  (1:1) under ultrasound. Some functional groups  $-\text{CO}_2\text{R}$ ,  $-\text{OR}$ ,  $-\text{NR}_2$ ,  $-\text{Cl}$ ,  $-\text{COR}$ ,  $-\text{CHO}$ ,  $-\text{CONR}_2$ , etc. are resist this method, which features non-quenching treatment; the resulting product after removal of solvent is clean enough that further purification is unnecessary. Desilylation becomes much slower when methanol is replaced with a more sterically hindered alcohol, isopropyl alcohol or *tert*-butyl alcohol. These results led us to investigate further this highly chemoselective desilylation of other silyl groups (e.g.  $\text{SiEt}_3$ ,  $\text{SiPh}_3$ ,  $\text{Si}(\text{Pr})_3$ ); work is in progress.

## EXPERIMENTAL SECTION

## General

All alcohols shown in Table 1 and Table 2 were purchased (Aldrich and Merck, USA); all were transformed to

Table 2. ( $\Sigma = \text{Si}t\text{BuMe}_2$ )

Entry	Substrate	Product	Method <sup>a</sup>	Yield/%
1			A	93
			B	~30
2			B	N.R. <sup>b</sup>
			C	N.R. <sup>b</sup>
3			A	51
			3 h	90
4			A	94
5			A	93
6			A	92
7			C	N.R. <sup>b</sup>
8			A	96
9			A	~50
			3 h	93
			B	N.R. <sup>b</sup>
			D	N.R. <sup>b</sup>

<sup>a</sup> Method A: 0.25 M  $\text{CH}_3\text{OH}/\text{CCl}_4$ , 1.5 h sonication,  $-42^\circ\text{C}$ .

Method B: 0.1 M  $\text{CH}_3\text{OH}/\text{CCl}_4$ , 1.5 h sonication,  $-42^\circ\text{C}$ .

Method C: 0.25 M  $\text{CH}_3\text{OH}/\text{CCl}_4$ , 2 h sonication,  $-46^\circ\text{C}$ .

Method D: 0.5 M  $\text{CH}_3\text{OH}/\text{CCl}_4$ , 1.5 h sonication,  $-42^\circ\text{C}$ .

<sup>b</sup> No reaction and complete recovery of starting material.

their corresponding silylated compounds without further purification.

All experiments were carried out under nitrogen dried primarily on passage through a column of potassium hydroxide (KOH) layered with calcium sulfate ( $\text{CaSO}_4$ ). Tetrahydrofuran was dried before use. Methanol, carbon tetrachloride, chloroform and dichloromethane (spectroscopic grade) were used directly without drying. Flash chromatography was performed using silica gel (Merck 230-400 mesh) or alumina (neutral, Merck) and thin layer chromatography (TLC) was performed on a plastic plate (or aluminium sheet) precoated with silica gel (Merck, 0.25 mm) and developed by spraying with a phosphomolybdic acid ethanolic solution (10%).  $^1\text{H}$  NMR spectra were recorded at 300 MHz (Bruker 300P) with deuteriochloroform ( $\text{CDCl}_3$ , Aldrich 99.8 atom % D) as solvent and internal standard.

### Ultrasonic Desilylating Method

A typical procedure for desilylating trimethylsilyl ether (*tert*-butyldimethylsilyl ether) to its corresponding alcohol follows: A solution (0.25 M) of trimethylsilyl ether in  $\text{CH}_3\text{OH}/\text{CCl}_4$  (1:1, v/v) is sonicated in a commercial ultrasonic cleaning bath (Crest 575D, Frequency 39 kHz). After the reaction is completed (monitored with 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. Purity of the desilylated product was determined with  $^1\text{H}$  NMR spectra. Further purification, if necessary, is achieved on a flash chromatograph with silica gel and ethyl acetate/hexane.

### Typical Synthesis of Trimethylsilyl Ethers

Trimethylsilyl chloride (1.2 equimolar proportions for one hydroxyl group) was added to a solution of alcohol and triethylamine (1.1 equimolar proportions for one hydroxyl group) in tetrahydrofuran (10 mL) about  $25^\circ\text{C}$  under nitrogen. The reaction mixture was stirred for 2 h and diethyl ether (20 mL) was added. The mixture was washed with brine (30 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated. Purification was achieved on a flash chromatograph with  $\text{Al}_2\text{O}_3$  and hexane. All trimethylsilyl ethers possessed satisfactory spectral and analytical data.

### Typical Synthesis of *tert*-Butyldimethylsilyl Ethers

Imidazole (2.6 equimolar proportions for one hydroxyl group) and *tert*-butyldimethylsilyl chloride (1.3 equivalent for one hydroxyl group) was added to a solution of alcohol in tetrahydrofuran (10 mL) about  $25^\circ\text{C}$  under nitrogen. The reaction mixture was stirred for 3 h and diethyl ether (20 mL) was added. The mixture was washed with brine (30 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated. Purification was achieved on a flash chromatograph with  $\text{SiO}_2$  and ethyl acetate/hexane (1-2%). All *tert*-butyldimethylsilyl ethers produced satisfactory spectral and analytical data.

### ACKNOWLEDGMENT

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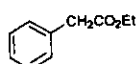
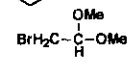
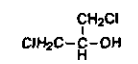
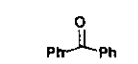
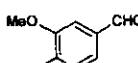
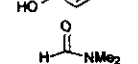
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### Key Words

Sonochemistry; Ultrasound; Cavitation; Desilyla-

tion; Chemoselection; Deprotection.

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|   | $\xrightarrow[\text{)}) , 2 \text{ h}]{\text{CH}_3\text{OH} / \text{CCl}_4(1:1)}$    | starting material was recovered (>99%) |
|   | $\xrightarrow[\text{)}) , 30 \text{ min}]{\text{CH}_3\text{OH} / \text{CCl}_4(1:1)}$ | starting material was recovered (>99%) |
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|   | $\xrightarrow[\text{)}) , 30 \text{ min}]{\text{CH}_3\text{OH} / \text{CCl}_4(1:1)}$ | starting material was recovered (>99%) |
|   | $\xrightarrow[\text{)}) , 1.5 \text{ h}]{\text{CH}_3\text{OH} / \text{CCl}_4(1:1)}$  | starting material was recovered (>99%) |
|  | $\xrightarrow[\text{)}) , 1.5 \text{ h}]{\text{CH}_3\text{OH} / \text{CCl}_4(1:1)}$  | starting material was recovered (>99%) |
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