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SELECTIVE DEPROTECTION OF ALKYL *t*-BUTYLDIMETHYLSILYL ETHERS IN THE PRESENCE OF ARYL *t*-BUTYLDIMETHYLSILYL ETHERS

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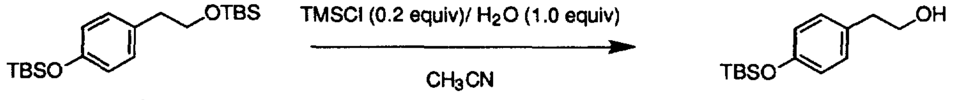
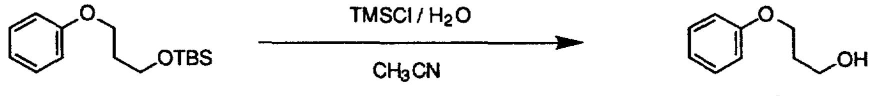
Abstract: Alkyl TBS ethers can be selectively cleaved in high yield in the presence of aryl TBS ethers employing either *in situ* generated hydrogen chloride or hydrogen iodide.

Few methods exist for the selective deprotection of alkyl *t*-butyldimethylsilyl (TBS) ethers in the presence of aryl TBS ethers.[1] It has been shown that 2.0 equiv of 40% aqueous HF in acetonitrile under carefully controlled conditions selectively cleaves alkyl TBS ethers in the presence of aryl TBS ethers.[1a] More recently, Lipshutz[1b] reported on the use of 1% by weight of I_2 in methanol in order to effect a similar selective deprotection of an alkyl TBS ether. We wish to disclose our results on the use of either catalytic HCl or HI (generated *in situ*) in acetonitrile for the selective cleavage of alkyl TBS ethers in the presence of aryl TBS ethers (cf. **1** → **2**).



1 87% **2**

In conjunction with another ongoing project in our laboratory, we had observed that alkyl TBS ethers can be efficiently cleaved with *in situ* generated HCl in acetonitrile (cf. **3** → **4**). For example, exposure [13h, ambient temperature] of a 0.1 M solution of silyl ether **3** in acetonitrile to catalytic HCl [generated *in situ* from TMSCl and water] gave rise to **4** in 91% yield.



3 91% **4**

Attempts to selectively cleave the alkyl TBS ether in substrate **1** with HCl [generated *in situ* from 1.0 equiv of TMSCl and 1.0 equiv of water] in acetonitrile gave rise after 6.5 h to only a 55% yield of **2** along with 31% of the fully deprotected material and 7% of recovered **1**. Surprisingly, use of 0.2 equiv of TMSCl in the above reaction led to exclusive cleavage of the alkyl TBS ether. Thus, exposure [5h, ambient temperature] of a 0.1 M solution of bis-TBS ether **1** in acetonitrile to catalytic HCl, generated *in situ* from 0.2 equiv of TMSCl and 1.0 equiv of water, provided **2** in 87% yield (99% based on recovered **1**) with no trace of the dideprotected material.

The reaction rate for the selective desilylation of the alkyl TBS ether **1** can be accelerated by the addition of 0.1 equiv of NaI to the reaction mixture. Thus, treatment of a 0.1 M solution of **1** in acetonitrile containing 0.2 equiv of TMSCl and 0.1 equiv of NaI at ambient temperature with 1.0 equiv of water gave rise, after 1.3h, to an

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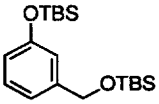
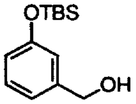
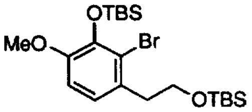
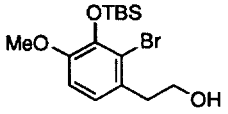
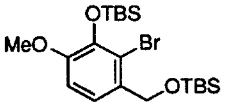
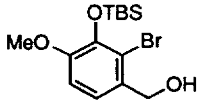
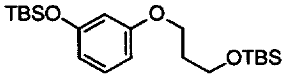
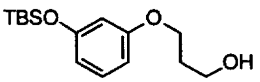
86% yield (93% based on recovered **1**) of **2**. No trace of the fully deprotected material could be detected. The observed increase in reaction rate for the conversion of **1** into **2** is undoubtedly due to the *in situ* formation of HI. When 0.2 equiv of NaI was employed, the fully deprotected material was isolated in ca. 5% yield.[2]

A number of substrates have been examined (Table 1) using the *in situ* generated HCl protocol [Method A: TMSCl (0.2 equiv) / H_2O (1.0 equiv)] and the *in situ* generated HI procedure [Method B: TMSCl (0.2 equiv) / NaI (0.1 equiv) / H_2O (1.0 equiv)]. Reactions were carried out 0.1 M in acetonitrile at ambient temperature. In all cases, only monodesilylation of the alkyl TBS ether was observed.

Table 1. Selective Deprotection of bis-t-Butyldimethylsilyl Ethers.[a]

bis-TBS ether	method / time	product	yield[b]
	A / 6h B / 2h		83 (94) 86 (94)
	A / 13h B / 4h		94 (98) 86 (92)
	A / 16h B / 3.5h		78 (97) 83 (99)
	A / 21h B / 2h		86 (96) 84 (95)

[a] Reactions were conducted 0.1 M in acetonitrile using either Method A [TMSCl (0.2 equiv) and H_2O (1.0 equiv)] or Method B [TMSCl (0.2 equiv), NaI (0.1 equiv) and H_2O (1.0 equiv)]. [b] Yield of isolated, pure material. Yield in parentheses is based on recovered bis-TBS ether.

Typical Experimental Procedure: To a solution of bis-TBS ether **1** (43 mg, 0.12 mmol) in acetonitrile (1.2 mL) was added water (2.1 µL, 0.12 mmol) followed by the addition of TMSCl (2.9 µL, 0.024 mmol). After 5h at ambient temperature, the reaction was quenched by the addition of a saturated aqueous sodium bicarbonate solution (2.0 mL) and diluted with water (10 mL). The product was isolated by extraction with ethyl acetate. The combined organic extracts were washed with brine and concentrated *in vacuo*. The crude product was purified on silical gel. Elution with hexane:ethyl acetate (2:1) afforded 25 mg (87%) of **2** along with 5 mg (12%) of **1**.[3]

References.

1. (a) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681. (b) Lipshutz, B. H.; Keith, J. *Tetrahedron Lett.* **1998**, *39*, 2495. (c) Oriyama, T.; Kobayashi, Y.; Noda, K. *Synlett.* 1998. 1047.
2. Lipshutz (reference 1b) has shown that exposure (<5 min) of a 0.1 M solution of **1** in MeOH containing one drop of 47% aqueous HI led to complete monodeprotection along with <5% of fully deprotected material.
3. This research was supported by a grant from the National Institute of General Medical Sciences (GM 33605).