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Selective Deprotection of Silyl-Protected Phenols Using Solid NaOH and a Phase Transfer Catalyst

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Abstract: Aryl silyl ethers can be deprotected to yield phenols in good to excellent yields using a biphasic system of 10 equivalents of NaOH and catalytic Bu_4NHSO_4 in 1,4-dioxane. Alkyl silyl ethers prepared using a variety of silyl protecting groups survive under these conditions, allowing selective deprotection of silyl-protected phenols in the presence of silyl-protected alcohols.

Protection/deprotection protocols using silyl protecting groups are among the most widely used methods for temporarily masking alcohols.[1,2] As synthetic targets have become increasingly complex, methods to selectively remove one such silyl group in the presence of another have been developed.[3] Although discrimination between two silyl ethers derived from alcohols is common, relatively few techniques have been developed to deprotect aryl silyl ethers in the presence of alkyl silyl ethers.[3] Although camphorsulfonic acid / methanol[4] and aqueous DMSO[5] have been used to cleave aryl TBS ethers in the presence of alkyl TBS ethers, a survey of the methods reported to effect selective desilylation of aryl silyl ethers reveals basic conditions to be the norm.[3] Davies has demonstrated that, while the desilylation of the TBS ether of *p*-cresol in 5% NaOH / 95% MeOH has a half-life of 3.5 minutes, the TBS ether of *n*-hexanol is stable over 24 hours.[6] Among the systematically-studied basic reagents reported to effect selective removal of silyl groups from phenols are: TBAF,[7,8] KF / 18-crown-6,[8] KF / alumina,[9] K_2CO_3 / Kryptofix 222,[10] K_2CO_3 / aqueous EtOH[11] and Dowex 1-X8 (OH^- form).[12] Other methods employing TBAF have been reported as parts of total syntheses.[13-16] Some of these methods require elevated reaction temperatures,[5,10,11,17] lengthy reaction times[5,8] and aqueous workup. We have developed a system that allows selective deprotection of aryl silyl ethers in the presence of alkyl silyl ethers at mild temperatures and with relatively short reaction times and wish to report our findings.

Phenols have been reported to undergo selective acylation in the presence of alcohols using powdered NaOH and Bu_4NHSO_4 in a number of organic solvents.[18] We examined this system as a possible means to deliver OH^- ions[19] to silyl-protected phenols in a non-aqueous medium, thereby effecting desilylation. Initial studies (Table 1) on bis-silyl ether **1** showed 10

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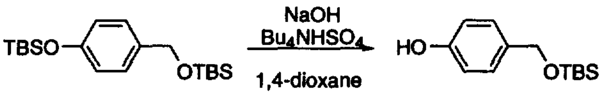
equivalents of NaOH and catalytic Bu_4NHSO_4 in 1,4-dioxane to be the most effective conditions. The identity of the retained silyl group was established by comparing the chemical shift of the *t*-butyl groups before and after the reaction. The *t*-butyl group of the aryl silyl ether is known to be downfield of the *t*-butyl group of the alkyl silyl ether.[10] In this example, the *t*-butyl group of the aryl silyl ether appears at 0.98 ppm and the *t*-butyl group of the alkyl silyl ether appears at 0.93 ppm; only the latter signal is retained in the product. In preparing substrate 1, the silyl-protected phenol bearing an unprotected alcohol (i.e. - the product of selective *alkyl* desilylation) was isolated and characterized, allowing a comparison with the product actually obtained using this method.

Table 1
Selective Desilylation Under a Variety of Conditions



1 **2**

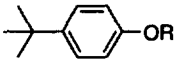
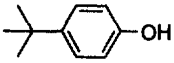
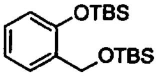
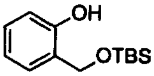
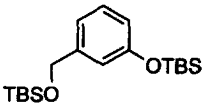
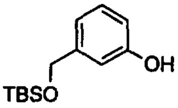
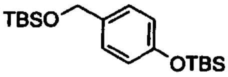
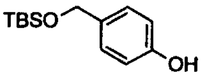
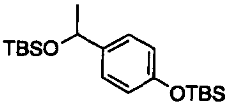
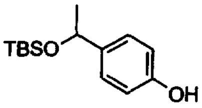
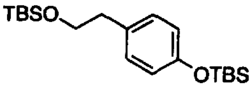
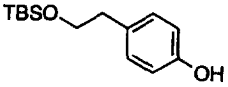
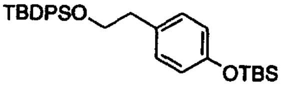
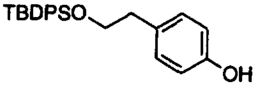
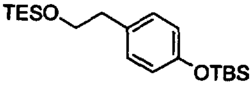
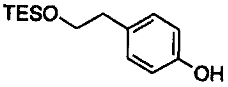
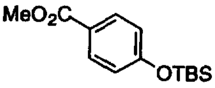
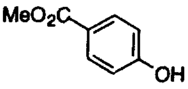
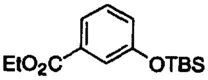
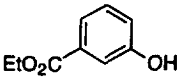
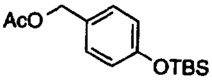
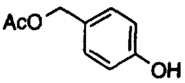
trial	equiv of NaOH	solvent	isolated yield
1	5	1,4-dioxane	56%
2	8	1,4-dioxane	66%
3	10	1,4-dioxane	81%
4	10	THF	63%
5	10	CH_2Cl_2	no desired product

The phase transfer catalyst, Bu_4NHSO_4, is necessary. While desilylation of the aryl silyl ether occurs in 3 hours at room temperature with the catalyst, in the absence of Bu_4NHSO_4, monosilyl ether **2** was isolated in only 18% yield *after 3 days*. Use of more than 10 equivalents of NaOH failed to improve the isolated yield.

A typical procedure is as follows: The bis-silyl ether (1.0 equivalent), powdered NaOH (10 equivalents), Bu_4NHSO_4 (0.5 equivalents) and 1,4-dioxane (5 mL / mmol of substrate) were combined in a flame-dried, round bottom flask and stirred under Argon at room temperature. When TLC indicated disappearance of the bis-silyl ether (typically 2.5 - 3 hours), the mixture was filtered through a plug of Celite, washing with Et_2O. Evaporation of solvent followed by column chromatography yielded the desired product. Powdered NaOH was prepared by grinding NaOH pellets in a mortar and pestle in a glovebox or glovebag under an inert atmosphere and stored in a desiccator. 1,4-Dioxane was obtained from Aldrich in Sure/Seal™ bottles and used as received.

Our results are summarized in Table 2. Monosilylated phenols (entry 1) are deprotected cleanly and in very high yield. More importantly, good yields were obtained for the selective deprotection of the aryl silyl ether in the presence of an alkyl silyl ether in a series of bis-silyl ether substrates (entries 2 - 8). Reaction yields were consistent when the protected alcohol is 1°, 2° or benzylic and regardless of the proximity of the protected alcohol

Table 2
Selective Desilylation of Phenolic Silyl Ethers

entry	substrate	product	yield
1			
	R = TBS		99%
	= TBDPS		99%
	= TES		91%
	= TIPS		88%
2			76%
3			82%
4			81%
5			81%
6			85%
7			78%
8			83%
9			29%
10			79%
11			0%

to the phenolic oxygen. In addition to the alkyl TBS ether, other alkyl silyl ethers survive these conditions (entries 7,8). The possibility of side reactions due to the presence of OH^- was briefly investigated. Although considerable hydrolysis of the methyl ester was observed (entry 9), an ethyl ester survived (entry 10). Acetate-protected alcohols, however, do not survive these conditions (entry 11).

In summary, we have developed a method for the selective deprotection of silyl-protected phenols in the presence of silyl-protected alcohols. The advantages of this method include operational simplicity, non-aqueous conditions or workup, mild reaction temperatures and relatively short reaction times.

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