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KHF₂, a mild and selective desilylating agent for phenol *t*-butyldimethylsilyl (TBDMS) ethers

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Abstract

TBDMS (*t*-BuMe₂Si, *t*-butyldimethylsilyl) ethers of a variety of phenols have been deprotected with KHF₂ in MeOH, at room temperature. Carboxylic ester and labile phenolic acetate were unaffected under these conditions. In competition reactions between TBDMS ethers of a phenol and two primary benzylic alcohols, the phenolic ether underwent cleavage whereas the alcohol ethers remained intact. From a substrate containing both a phenolic hydroxyl group and a secondary, doubly benzylic hydroxyl group protected as TBDMS ethers, the phenol was rapidly and selectively released. Cleavage of TBDMS, TBDPS, and TIPS ethers of a phenol was also compared. TBDMS and TBDPS ethers underwent cleavage at room temperature within 30 min, whereas removal of the TIPS ether required 2.5 hours. Ease of cleavage appears to be TBDMS ≈ TBDPS > TIPS. At 60 °C, TBDMS ethers of primary benzylic, allylic, and unactivated alcohols can be efficiently desilylated over a prolonged period (13–17 h). Thus, KHF₂ proves to be a mild and effective reagent for the selective desilylation of phenol TBDMS ethers at room temperature.

Graphical Abstract

Keywords

deprotection; desilylation; silicon; fluoride; potassium bifluoride

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Primary Data

NO

Supporting Information

YES

Silyl ethers, a large class of hydroxyl protecting groups, are a staple in contemporary organic synthesis.¹ Among these, the trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), *t*-butyldimethylsilyl (TBDMS), and *t*-butyldiphenylsilyl (TBDPS) are routinely employed. The relative rates of hydrolysis of *O*-silyl ethers in acidic and alkaline media are different and can be exploited for selective deprotection. For example, under acidic conditions, the general order of hydrolytic lability is TMS > TES > TBDMS > TIPS > TBDPS, and under basic conditions it is TMS > TES > TBDMS $\approx$ TBDPS > TIPS.² Generally, phenol silyl ethers are more rapidly cleaved under basic conditions as compared to acidic conditions. For example, the half-life for the deprotection of the TBDMS ether of *p*-cresol is 3.5 min with 5% NaOH in 95% EtOH and $\sim$ 4.5 h with 1% HCl in 95% EtOH.² In a similar trend, half-lives for hydrolysis of the TIPS and TBDPS ethers of *p*-cresol are >100 h with 1% HCl in 95% EtOH.² On the other hand, with 5% NaOH in 95% EtOH, the half-lives for hydrolysis of these TIPS and TBDPS ethers are $\sim$ 3.1 h and 6.5 min, respectively.² The greater lability of phenol silyl ethers to basic conditions is consistent with both the greater electrophilicity of the silicon center, due to delocalization of the oxygen atom lone pair, as well as the fact that phenoxide is a good leaving group. However, basic conditions can pose problems when base-labile functionalities such as esters are present.

Fluoride ion is an exceptional agent for deprotection of silyl ethers,³ and $n\text{Bu}_4\text{N}^+\text{F}^-$, NH_4F , CsF, HF complexes such as HF-pyridine, HF- Et_3N , difluorosilicates such as tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and tetrabutylammonium difluorotriphenylsilicate (TBAT) have all found applications. Key to F-mediated desilylations is the significantly stronger Si-F bond compared to the Si-O bond, and the formation of a fluorosiliconate intermediate. Among the methods developed for cleavage of *O*-TBDMS groups, there are generally fewer ones for accomplishing desilylation of phenol TBDMS ethers. Some of these include use of KF/18-Cr-6 in MeCN,⁴ KF-alumina in MeCN under ultrasound conditions,⁵ K_2CO_3 and Kryptofix 222,⁶ $\text{PdCl}_2(\text{MeCN})_2$ in acetone at 75 °C,⁷ K_2CO_3 in wet EtOH at reflux,⁸ DMSO/ H_2O at 90 °C,⁹ NaOH/ $n\text{Bu}_4\text{NHSO}_4$ in 1,4-dioxane,¹⁰ LiOH in DMF,¹¹ tetramethylguanidine in MeCN,¹² KOH in EtOH,¹³ Cs_2CO_3 in wet DMF,¹⁴ SbCl_5 in wet MeCN,¹⁵ DBU in MeCN- H_2O ,¹⁶ LiOAc in DMF- H_2O ,¹⁷ KF in tetraethylene glycol,¹⁸ $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$ in MeOH under microwave conditions (130 °C) or conventional heating (60 °C),¹⁹ and NaH in DMF.²⁰ In the context of deprotecting alkyl silyl ethers in the presence of phenolic silyl ethers, catalytic $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ in MeOH or *i*PrOH has been investigated for removal of phenolic TBDMS groups.²¹ Catalytic $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ in MeOH has been used to deprotect four phenolic TBDMS groups, but the method gave a low yield with an electron deficient phenol.²²

In connection with ongoing work on desilylations of some nucleoside substrates, we found the compounds to be exceptionally sensitive to a variety of conventional fluoride reagents. This necessitated the evaluation of alternate reagents and we have found that KHF_2 in MeOH is a mild reagent for cleavage of phenolic TBDMS groups. A major consideration in the use of silyl protecting groups for hydroxyl functionalities is the selective cleavage of one silyl ether over others, and particularly when different hydroxyl groups bear an identical silyl protection.^{23–25} Thus, we also wanted to ascertain the selectivity of KHF_2 for removal of a phenolic TBDMS protection over comparable protection of 1° and 2° alkanols, and evaluate removal of a phenolic TBDMS group in the presence of a carboxylic ester and a

phenolic acetate. Related to this work, a single report exists wherein a fluoride buffer prepared from 0.1 M HF and 0.1 M NaF was used to desilylate a relatively sensitive phenolic TBDMS ether.²⁶

Several phenol TBDMS ethers were synthesized and subjected to desilylation with KHF₂ in MeOH at room temperature. Although in initial assessments with (4-bromophenoxy)(*t*-butyl)dimethylsilane, 1.5 equivalents of KHF₂ gave a high 91% yield of **1** in 0.5 h, 2.5 equivalents were used to ensure rapid and complete cleavage in all cases. Scheme 1 shows products, reaction times, and yields obtained. All reactions, with the exception of one (see below), proceeded efficiently at room temperature.

A methyl ester was unaffected in product **6**. Deprotection of the sterically congested TBDMS ether of 2,6-dimethylphenol required heating at 50 °C, but this reaction was complete within 2 h. Bis-TBDMS ethers were also evaluated. Hydroquinone bis-TBDMS ether was cleaved readily to yield hydroquinone (**8**) within 1 h. In contrast, the bis-TBDMS ether of 1,1'-bi(2-naphthol) required a long reaction time at room temperature, nevertheless, a good yield of product **9** was obtained. The reaction time for the 1,1'-binaphthol derivative appears to be unique to this system because, just as with the bis-TBDMS derivative of hydroquinone, bisphenol F (**10**) could be obtained by cleavage of the corresponding bis-TBDMS ether within 2 h.

Next, we investigated the suitability of the reaction conditions for removal of a phenolic TBDMS group, in the presence of a phenolic acetate. For this, hydroquinone (**8**) was converted to 4-[(*t*-butyldimethylsilyl)oxy]phenol (**11**)²⁷ by monosilylation using excess hydroquinone. Compound **11** upon acetylation gave 4-[(*t*-butyldimethylsilyl)oxy]phenyl acetate (**12**).²⁸ Exposure of this differentially diprotected hydroquinone **12** to the desilylation conditions gave hydroquinone monoacetate **13**²⁹ in an excellent 97% yield (Scheme 2). This clearly showed that highly labile phenolic acetate is stable under the reaction conditions.

Competitive desilylation of TBDMS ethers of a phenol and two benzylic alcohols was then evaluated. First, an equimolar mixture of (4-bromophenoxy)(*t*-butyl)dimethylsilane (**14**) and *t*-butyl[(2,3-dimethoxybenzyl)oxy]dimethylsilane (**15**) was exposed to the desilylation conditions for 30 min. In this period, only compound **14** underwent complete desilylation, and this situation remained unaltered even after 1 h (Scheme 3). From this reaction 4-bromophenol (**1**) was isolated in 91% yield and 97% of unreacted **15** was reisolated.

Competitive desilylation was also evaluated with (4-bromophenoxy)(*t*-butyl)dimethylsilane (**14**) and ((4-bromobenzyl)oxy)(*t*-butyl)dimethylsilane (**16**), both containing a comparable bromine substituent (Scheme 3). As in the previous example, after 30 min and 1 h of reaction, only the phenolic silyl group had undergone cleavage. From this reaction, 87% yield *p*-bromophenol (**1**) was obtained and 91% of unreacted **16** was reisolated. These experiments clearly indicated high selectivity for phenolic TBDMS cleavage in the presence of a comparable benzylic ether.

The next evaluation was the selective release of a phenolic hydroxyl group from a compound that contained TBDMS ethers of the phenol and a doubly benzylic secondary alcohol, within a single molecule (Scheme 4). For this, benzhydrol **17** was synthesized by lithiation of TBDMS-protected *p*-bromophenol (**14**) and reaction with 2,3-dimethoxybenzaldehyde. The secondary alcohol was silylated to yield compound **18**, which upon exposure to the desilylation conditions gave phenol **19** in an excellent 96% yield.

Using silyl ethers of *p*-bromophenol, the ability to cleave *t*-butyldiphenylsilyl (TBDPS) and triisopropylsilyl (TIPS) ethers with KHF_2/MeOH , and in comparison to the corresponding TBDMS derivative, was evaluated. Three reactions were conducted, one with each of the silyl ethers, and were stopped after 30 min. The mixtures were chromatographed and the data from these experiments are shown in Table 1.

Data in Table 1 show that both TBDMS and TBDPS groups undergo complete cleavage within 30 minutes but that deprotection of the TIPS group is significantly slower. However, within 2.5 h the TIPS group was fully removed with an ensuing *p*-bromophenol yield of 92% (with silyl ether **21**). A separate competitive desilylation reaction of silyl ethers **14** and **20**, gave a 95% yield of *p*-bromophenol (**1**). These collective results indicate that TBDMS and TBDPS groups are removed with similar ease. Thus, order of removal of the three silyl groups is TBDMS $\approx$ TBDPS > TIPS. Whereas this order is similar to that for removal of these groups under basic conditions,² it is notable that phenolic acetate and ester groups are unaffected.

We then evaluated the utility of KHF_2/MeOH for cleavage of alkanol TBDMS ethers. It was discovered that secondary alcohol TBDMS ethers were recalcitrant to cleavage, even at 60 °C. However, at 60 °C, TBDMS ethers of primary benzylic, an allylic, and an unactivated alcohol underwent desilylation reasonably efficiently (Scheme 5), but clearly slower than deprotection of phenolic TBDMS ethers.

In summary, phenolic TBDMS groups are readily deprotected by KHF_2 in MeOH at room temperature.³⁰ With appropriate handling care,^{30,31} this solid reagent is convenient to use and is highly selective for desilylation of phenolic TBDMS groups in the presence of comparable silyl ethers of primary and secondary alcohols. Carboxylic esters and the relatively labile phenolic acetate are stable under the desilylation conditions. TIPS and TBDPS ethers of *p*-bromophenol are also cleaved at room temperature and the ease of deprotection is TBDMS $\approx$ TBDPS > TIPS. Although this parallels the order for basic cleavage,² ester and phenolic acetate remain unaffected. At elevated temperature (60 °C), KHF_2 does cause deprotection of benzylic, allylic, and unactivated primary alcohol TBDMS ethers, albeit quite slowly. Also notably, KHF_2 (>99%) costs ~\$17/mol and is cheaper than KF (>99%) that costs ~\$23/mol.³² Thus, KHF_2 should find broad applications in the desilylations of a range of phenolic TBDMS compounds,³⁰ even in the presence of primary and secondary alcohols protected with the same silyl group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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30. **Caution!** *KHF₂ can produce HF upon contact with water and MeOH. It has been shown to etch glass in repeated use of glassware for the synthesis of organotrifluoroborates.*³¹ **Representative procedure for desilylation of phenol TBDMS ethers: 4-hydroxyphenyl acetate (**13**).**²⁹ In an oven dried 25 mL round bottom flask, a mixture of silyl ether **12** (0.266 g, 1 mmol) and KHF₂ (0.195 g, 2.5 mmol) in anhydrous MeOH (10.0 mL) was stirred at room temperature. The reaction was monitored by TLC using 40% EtOAc in hexanes and was found to be complete within 1 hour. The mixture was evaporated under reduced pressure and loaded onto a silica column (100–200 mesh) packed with hexanes (adequate caution was exercised to ensure complete transfer of the crude material). Elution with hexanes, followed by 30% EtOAc in hexanes gave 0.148 g (97% yield) of 4-hydroxyphenyl acetate (**13**) as a white powder. *R_f* (40% EtOAc in hexanes): 0.37. ¹H NMR (500 MHz, CDCl₃): δ = 6.95 (d, *J* = 8.8 Hz, 2H, ArH), 6.81 (d, *J* = 8.8 Hz, 2H, ArH), 4.69 (br s, 1H, OH), 2.28 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃): δ = 170.4, 153.7, 144.5, 122.6, 116.3, 21.2. HRMS (ESI/TOF): *m/z* calcd for C₈H₈O₃Na [M + Na]⁺: 175.0366; found 175.0380
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Scheme 1.

Results from the deprotection of several phenol TBDMS ethers

Scheme 2.

Synthesis and desilylation of the monoacetoxy mono TBDMS ether of hydroquinone to yield 4-hydroxyphenyl acetate

Scheme 3.

Competitive deprotection of TBDMS ethers of a phenol and two benzylic alcohols

Scheme 4.

Selective deprotection of a phenolic TBDMS ether in the presence of a TBDMS ether of a secondary, doubly benzylic alcohol

Scheme 5.

Deprotection of TBDMS ethers of two benzylic, an allylic, and an unactivated alcohol

Table 1Comparison of the deprotection of TBDMS, TBDPS, and TIPS ethers of *p*-bromophenol^a

Substrate	PG =	Yield of 1	SM ^b recovered
14	<i>t</i> -BuMe ₂ Si	95%	None
20	<i>t</i> -BuPh ₂ Si	92%	None
21	(iPr) ₃ Si	25%	65%

^aYields reported are of isolated materials obtained by chromatography.^bSM = starting material.