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A facile, selective KF/Al_2O_3 mediated method for the deprotection of aryl silyl ethers and preparation of aryl SEM ethers

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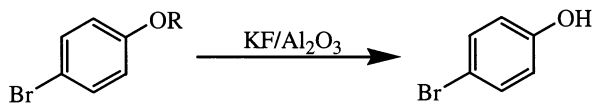
Abstract—A selective, solvent dependent KF/Al_2O_3 mediated method for the cleavage of aryl silyl ethers and the preparation of SEM aryl ethers is reported.

Over the past century, the science of organic chemistry has made great strides forward in part due to the development of effective protecting group strategies. Organosilicon reagents have played an important role in this area, due to their stability under a broad range of reaction conditions. Although originally introduced in the late 1950s as tools to facilitate gas chromatography and mass spectrometry, the utility of organosilicon reagents in organic synthesis was not recognized until the early 1970s.[1] Since that time, their use has undergone an explosive growth, and numerous methods for the preparation and subsequent removal of organosilyl ethers have been developed. The most common methods for the deprotection of silyl ethers include the use of mild acids (e.g. TFA, formic acid) and fluoride reagents (e.g. TBAF, HF/pyridine, KF/18-crown-6).[2] Recently, we have examined the application of solid supported reagents, in particular, potassium fluoride on alumina (KF/Al_2O_3), and their potential utility in deprotection of silyl ethers. We now wish to report that neutral KF/Al_2O_3 efficiently, selectively, and cleanly removes a variety of silyl protecting groups from phenols. The process is solvent dependent, allowing for the selective cleavage of TMS, TBDMS, or TDBPS groups. It is also possible to differentiate between electron rich and electron poor phenolic ethers, as this reaction shows strong solvent effects. In addition, carbon/silicon bonds are not affected, as the SEM protecting group is stable to this reagent under a variety of conditions. For example, we have found that neutral KF/Al_2O_3 can replace tertiary amine bases in the preparation of phenolic SEM ethers. This new method is simpler than most of those available, as there is no aqueous work-up and the products are isolated by filtration and removal of the solvent.

Potassium fluoride on alumina (KF/Al_2O_3) was initially reported in 1981 by Yamawaki as a base for functional-

Table 1. Solvent effects of KF/Al_2O_3 mediated deprotection of silyl ethers[10]



Entry	R	DME/time	DCE/time	1,4-Dioxane/time	Temp. (°C)
1	TMS	95%/4 h	95%/4 h[a]	95%/4 h	25
2	TBDMS	92%/4 h	0%/16 h	94%/16 h	25
3	TBDPS	95%/4 h	0%/16 h	0%/16 h	25
4	SEM	0%/16 h	0%/16 h	0%/16 h	75

[a] After completion, the reaction was diluted with an equivalent volume of DME to dissolve the product.

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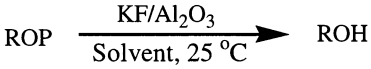
Table 2. Representative examples of KF/Al_2O_3 mediated deprotection of silyl ethers



Entry	R	Protecting group	Solvent	Time (h)	Temp. (°C)	Conversion (%)	Yield (%)
1	2-Br-C_6H_4	TBDMS	DME	4	25	100	92
2	4-NO_2-C_6H_4	TBDMS	DME	4	25	100	93[a]
3	4-CO_2Bn-C_6H_4	TBDMS	DME	4	25	100	92
4	4-Ph-C_6H_4	TBDMS	DME	4	25	100	95
5	4-TBDMSO$(CH_2)_2C_6H_4$	TBDMS	DME	4	25	100	87
6	2-Br-C_6H_4	TBDMS	1,4-Dioxane	16	25	100	92
7	4-NO_2-C_6H_4	TBDMS	1,4-Dioxane	16	25	100	93[a]
8	4-CO_2Bn-C_6H_4	TBDMS	1,4-Dioxane	16	25	100	95
9	4-Ph-C_6H_4	TBDMS	1,4-Dioxane	16	25	0	N/A
10	4-TBDMSO$(CH_2)_2C_6H_4$	TBDMS	1,4-Dioxane	16	25	0	N/A
11	*n*-C_8H_{17}	TBDMS	DME	16	25	0	N/A
12	*n*-C_8H_{17}	TBDMS	1,4-Dioxane	16	25	0	N/A

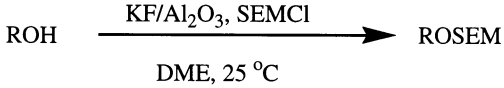
[a] After completion, 24 equivalents of acetic acid was added assist in product recovery.

ization of amides.[3] Morgan has reported the KF/Al_2O_3 mediated alkylation of 2,4-dinitrophenylhydrazones,[4] and Tius recently demonstrated that KF/Al_2O_3 is useful for the preparation of α-heterosubstituted Weinreb amides.[5] We have reported our findings that this reagent can facilitate the functionalization of 2-oxazolidinones[6] and also allows selective alkylation of benzodiazepin-2,5-diones.[7] In an effort to extend the utility of this versatile reagent, we have examined its ability to cleave silyl ethers under a variety of conditions. Sawyer has reported that both acidic and basic KF/Al_2O_3 can cleave phenolic TBDMS ethers in acetonitrile, and that the reaction rates were generally higher for basic alumina. In addition, ultrasound was found to increase the rate of cleavage of the silyl ether.[8] We have since found that neutral KF/Al_2O_3 can effectively remove a wide range of silyl ethers in a solvent dependent manner, without the aid of ultrasound. The reaction can also be fine tuned to allow for differentiation between various silyl ethers, as the rates of cleavage of TMS, TBDMS, TBDPS, and SEM[9] phenolic ethers vary greatly depending on the choice of solvent. Thus, trimethylsilyl-4-bromophenol (Table 1, entry 1) was readily deprotected with neutral KF/Al_2O_3 in DME, DCE or 1,4-dioxane after only 4 hours at 25°C. *t*-Butyldimethylsilyl-4-bromophenol (Table 1, entry 2), however, was found to be stable after 16 hours in DCE in the presence of neutral KF/Al_2O_3. Switching solvents to DME facilitated cleavage of the TBDMS group, which was accomplished after only 4 hours at 25°C. The solvent dependence of this reaction is further demonstrated by the decrease in the reaction rate when the solvent is changed to 1,4-dioxane. The conversion of *t*-butyldimethylsilyl-4-bromophenol to the corresponding phenol in 1,4-dioxane requires 16 hours. The TBDPS analog is stable to these conditions. Removal of the TBDPS group can, however, be accomplished in 4 hours in DME. Interestingly, the SEM protected analog of 4-bromophenol is stable to all of the aforementioned conditions, and no product was detected in DCE, DME or 1,4-dioxane after 16 hours at 75°C.

Upon examination of a broader array of silyl protected ethers (Table 2), we discovered some additional aspects of this reaction. First, alkyl silyl ethers are not cleaved under any of the conditions examined, as indicated by the recovery of starting materials in examples 11 and 12. Differentiation between alkyl and aryl silyl ethers is clearly displayed by the selective deprotection of entry 5, which produced the monosilylated phenol, rather than the diol.[11] Second, while electron poor TBS phenolic ethers are cleaved in 1,4-dioxane after 16 hours (Table 2, entries 6–8), electron rich TBS phenolic ethers are stable, as indicated by the recovery of starting materials in entries 9 and 10.

The unusually strong solvent dependence of this reaction and the stability of the SEM protected phenols to these conditions suggested that KF/Al_2O_3 might also be suitable for the preparation of SEM ethers. This would provide a simplified method of preparation of SEM ethers, as removal of the base (in this case, KF/Al_2O_3) would not require an aqueous work-up. Treatment of a series of phenols with 1.0 equivalents of SEM-Cl in the presence of KF/Al_2O_3 in DME produced the desired SEM ether in high yield, as indicated in Table 3. This procedure is effective for both electron rich and poor phenols, but as indicated by entry 7, alkyl SEM ethers can not be prepared using this method.

Table 3. Representative examples of KF/Al_2O_3 mediated SEM ether preparation[12]



Entry	R	Yield (%)
1	4-Br-C_6H_4	94
2	2-Br-C_6H_4	92
3	2,4-Di-Br-C_6H_4	96
4	4-Ph-C_6H_4	89
5	4-NO_2-C_6H_4	88
6	4-CO_2Bn-C_6H_4	95
7	*n*-C_8H_{17}	0

The solvent effects observed in these reactions could be explained by a solvent dependence on the basicity of the KF/Al_2O_3. In less polar, non-chelating solvents, such as DCE, ion pairing of the KF is high. This limits the ability of KF/Al_2O_3 in DCE to cleave silyl ethers, and as a result, only the weakest silyl protecting group, TMS, is removed. As the polarity and chelating ability of the solvent is increased, the ion pairing of the KF is decreased via chelation of the potassium, thus allowing more stable silyl protecting groups (e.g. TBS and TBDPS) to be removed. The limitation of this are clearly indicated by the stability of the SEM group, which is stable to all of the conditions we examined.

In summary, we have developed a new, selective method for the cleavage of aryl silyl ethers in the presence of alkyl silyl ethers. Furthermore, the method can be used to selectively remove less bulky aryl silyl ethers in the presence of their more sterically hindered counterparts. Finally, the method can be used to prepare aryl SEM ethers. The products are obtained in excellent yields, and the selectivity of the reaction can be tuned by the appropriate choice of solvents.

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9. TMS = trimethylsilyl, TBDMS = *tert*-butyldimethyl silyl, TBDPS = *tert*-butyldiphenyl silyl, SEM = 2-(trimethylsilyl)ethoxy methyl.
10. Typical experimental procedure: *t*-Butyldimethylsilyl-4-bromophenol (32.1 mg, 27.3 μL, 0.11 mmol) is dissolved in 2.0 ml of DME and 172 mg of KF/Al_2O_3 (40% wt. KF) is added. The reaction is stirred at room temperature for 4 hours, filtered and stripped to an oily solid. Chromatography with 3/1 hexane/ethyl acetate provided 17.5 mg of 4-bromophenol.
11. Removal of the aryl silyl ether was confirmed by analysis of mass spectral fragmentation patterns.
12. Typical experimental procedure: 4-Bromophenol (100 mg, 0.56 mmol) and 890 mg of KF/Al_2O_3 (40% wt. KF) are dissolved/suspended in 5.0 ml of DME and 102 μL of SEM-Cl (96.2 mg, 0.56 mmol) is added. The reaction is then stirred 2 hours, filtered and stripped to yield 165 mg (94%) of the desired product. No further purification was required.