Tetrahedron Letters, Vol.32, No.49, pp 7207-7210, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Selective Desilylation of tert-Butyldimethylsilyl Ethers of Phenols Using Potassium Fluoride-Alumina and Ultrasound

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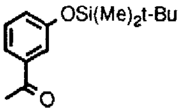
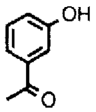
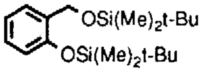
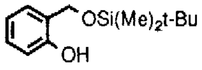
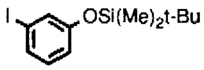
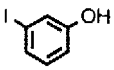
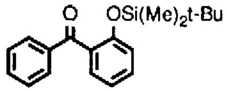
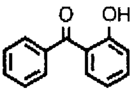
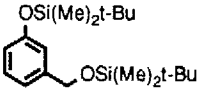
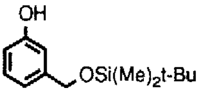
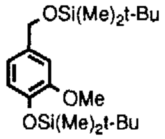
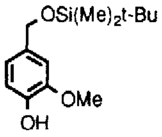
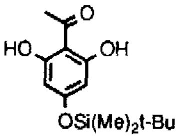
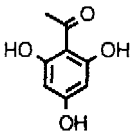
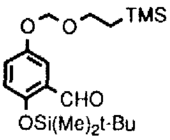
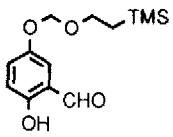
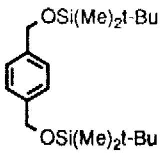
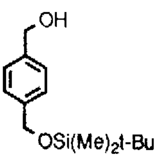
Abstract: *The use of potassium fluoride on basic alumina in acetonitrile with ultrasound for the selective deprotection of tert-butyldimethylsilyl ethers of phenols is described. The method, which features a non-aqueous work-up, readily cleaves tert-butyldimethylsilyl ethers of phenols at room temperature, whereas tert-butyldimethylsilyl ethers of benzyl alcohols or 2-(trimethylsilyl)ethoxymethyl ethers of phenols are stable.*

The tert-butyldimethylsilyl (TBDMS) group, first introduced by Stork in 1968,[1] is one of the most useful protecting groups for the hydroxy functionality.[2] Of the many methods used to regenerate the free hydroxy group,[3] only aqueous hydrofluoric acid/aqueous sodium fluoride[4] and potassium fluoride/48% aqueous hydrobromic acid/dimethylformamide (DMF)[5] were developed specifically for phenolic TBDMS ethers. The standard tetra-n-butylammonium fluoride/tetrahydrofuran (THF) conditions[6, 7] are often incompatible with sensitive TBDMS ethers of phenols.[4,5] In addition, while the general desilylation methods cited above prove satisfactory under most circumstances, each requires a disadvantageous aqueous work-up.

In connection with another project, we recently had need of a deprotection method that would be compatible with a sensitive, water-soluble phenol. Toward this end, we examined alumina-supported potassium fluoride (KF-Al_2O_3) as a potential alternative to the established methods. Alumina appears to be unique among the several KF supports described; in contrast to KF-silica gel, KF-celite, KF-molecular sieves, or free KF, KF-Al_2O_3 exhibits a surprising degree of basicity,[8] a property exploited in several cataylzed and non-catalyzed systems.[9] We reasoned that the high activity associated with KF-Al_2O_3, combined with the possibility of controlled access to fluoride ion, might provide an optimum environment for desilylation.

Treatment of 3M solutions of TBDMS ethers of phenols in acetonitrile with 3 wt. equiv. 37% KF-basic Al_2O_3 at room temperature (Method B) resulted in conversion to the free phenols in good to excellent isolated yields (see Table).[10] In general, higher reactivity was observed with KF-basic Al_2O_3 (Method B) than with KF-acidic Al_2O_3 (Method A), as is evident through comparison of reaction times (Entries 1 and 4). It was subsequently found that the use of ultra-

Table: Reaction of *t*-butyldimethylsilyl ethers with KF-Al_2O_3 in acetonitrile.

Entry	Reactant	Product	Method[a]	Time	%Yield
1			A	48 h	82
			B	45 min	81
2			A	24 h	64[b]
			B	30 min	78
3			A	1 h	55[c]
			B	10 min	55[c]
4			A	24 h	72
			B	1.5 h	85
			C	15 min	87
5			A	4 h	92
			B	3 h	84
			C	15 min	86
6			A	96 h	78
			B	6 h	80
			C	4 h	73
7			B	18 h	86
			C	1 h	85
8			C	1.5 h	70
9			C	48 h	<10[d]

(a) Methods: A = 3 wt. equiv. KF-Al_2O_3 (acidic), acetonitrile, room temperature; B = 3 wt. equiv. KF-Al_2O_3 (basic), acetonitrile, room temperature; C = 3 wt. equiv. KF-Al_2O_3 (basic), acetonitrile, room temperature (reaction time ≤15 min.) or 45-55 °C (reaction time ≥1h.), ultrasound. (b) Ratio of phenol to diol = 1.5:1. (c) The phenol proved difficult to separate from silyl by-product(s). (d) Remainder was starting material.

sound with KF-basic Al_2O_3 (Method C) facilitated the reaction even further (Entries 4 and 7). Selectivity was observed between TBDMS ethers of phenols versus benzyl alcohols (Entries 2, 5, 6, and 9). Differentiation between TBDMS ethers of phenols and alcohols by the judicious use of either aqueous hydrofluoric acid/acetonitrile or tetra-n-butylammonium fluoride has been detailed previously.[7] Of particular interest is the selective deprotection of the phenolic TBDMS group in Entry 2, a system known to give both possible mono-silylated products upon treatment with tetra-n-butylammonium fluoride (presumably due to base-catalyzed intramolecular silyl transfer).[7] Selectivity was also observed between TBDMS and SEM phenolic ethers (Entry 8).[11]

Reaction of TBDMS ethers with non-supported KF in acetonitrile resulted in recovered starting material; similarly, basic alumina alone failed to effect TBDMS cleavage. While DMF could be substituted in place of acetonitrile, purification became problematical due to the aqueous work-up required. Substitution of THF for acetonitrile in Entry 4 (Method C) failed to produce detectable levels (TLC) of phenol after 2 hours.

Despite the presence of the highly basic species associated with KF-Al_2O_3 (potassium hexafluoroaluminate, potassium hydroxide, potassium aluminate, and potassium carbonate),[8] the most likely mechanism of desilylation involves the nucleophilic addition of fluoride ion. The co-operative action of fluoride ion on the alumina surface[12] results in a strong "naked" nucleophilic matrix not possible with KF alone. Evidence that basicity is important, however, follows from consideration of the weaker activity of KF-acidic Al_2O_3. The dispersion and large surface area of KF resulting from the high-load procedure described below (preparation of 37% w/w KF-basic Al_2O_3) appears to provide for an optimum TBDMS-cleavage reagent.

Procedure for the preparation of 37% w/w KF-basic Al_2O_3:

A mixture of potassium fluoride (37 g) and alumina (63 g, Woelm®, alumina basic) in water (100 mL) was stirred at room temperature for 10 min. The resulting suspension was concentrated *in vacuo* (rotary evaporator) and dried in a vacuum oven at 80 °C for 18 h.

General procedure for desilylation of TBDMS ethers of phenols, Method C:

The starting tert-butyldimethylsilyl ether (1 wt. equiv.) in acetonitrile (~3M) was treated with 37% w/w KF-basic Al_2O_3 (3 wt. equiv.) at room temperature with sonication (Bransonic® 2200 ultrasonic cleaner). Upon reaction completion (as judged via thin-layer chromatography) the mixture was filtered. The alumina was washed thoroughly with methanol and the combined fractions were concentrated *in vacuo*; purification of the crude phenol via flash chromatography[13](eluting with hexane/ethyl acetate mixtures) provided pure product.

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(10) Starting TBDMS ethers were prepared via treatment of the phenols with TBDMS-Cl and imidazole in THF or DMF (Hansen, D. W.; Pilipauskas, D. *J. Org. Chem.* **1985**, *50*, 945); all starting materials and products exhibited satisfactory spectral data.

(11) Selective protection of 2,5-dihydroxybenzaldehyde (**i**) was accomplished by treatment

i **ii**

with 1 equiv. sodium hydride in DMF at 0 °C followed by SEM-Cl to provide **ii** in 55% yield: ^{1}H-NMR (CDCl$_3$) 10.44 (s, 1H, CHO), 7.27 (d, J = 1 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.03 (dd, J = 8, 1 Hz, 1H), 5.70 (bs, 1H, OH), 5.29 (s, 2H), 3.80 (t, J = 8 Hz, 2H), 0.99 (t, J = 8 Hz, 2H), 0.02 (s, 9H).

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(Received in USA 27 August 1991)