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FACILE DEPROTECTION OF SILYL NUCLEOSIDES WITH POTASSIUM FLUORIDE/ 18-CROWN-6

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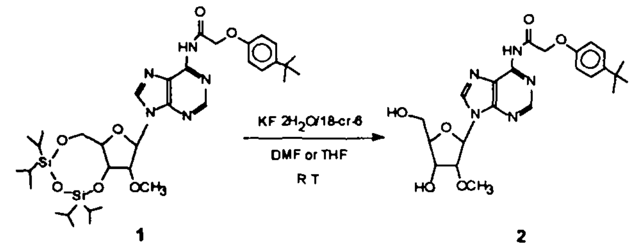
Abstract: *Silyl ethers can be removed under mild conditions by treatment with a mixture of potassium fluoride dihydrate and 18-crown-6 in DMF or THF at room temperature. Both acid and base-labile protecting groups are unaffected.*

Silyl ethers are one of the most common classes of compounds for the protection of hydroxyl groups.[1] In nucleoside chemistry, the 3',5'-tetraisopropyldisiloxyl[2] (TIPS) and the *tert*-butyldimethylsilyl (*t*BDMS) groups[3a,b] are particularly important. Fluoride ion is typically used for removal, the most common reagent being tetra-*n*-butylammonium fluoride (TBAF).[4] Although this is quite specific and rapid , the isolation of the product can often be tedious due to the difficulty in removing residual TBA salts by extraction or chromatography; thus, many different systems have been developed for this transformation, including tetrafluoroborate salts[5a], methylammonium fluoride,[5b] DIBAH,[5c] KF-Al_2O_3,[5d] fluorosilicic acid,[5e,f] and triethylamine trihydrofluroide.[5g] As part of an on-going program to develop efficient syntheses of modified nucleosides, we required a mild deprotection reagent that was amenable to economic large-scale chromatographic purification.



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It occurred to us that potassium fluoride, in the presence of a phase transfer catalyst such as 18-crown-6, would be well suited for our needs. *We were quite surprised to discover that despite references to the contrary, there has been no reported example of using the KF/18-crown-6 system as a desilylation reagent*[5]. Cited most often are papers by Stork[6], Liotta[7] and Torisawa[8], all of which deal with only peripherally related subjects. There are references to the solubilization of anhydrous KF in acetonitrile or benzene by 18-crown-6 and its' utility in S_N2 displacements[7] under phase transfer conditions. Carpino *et al.*[9] have reported $KF \cdot 2H_2O$ and nBu_4NCl is a source of active fluoride, presumably by producing TBAF *in situ*. We report here the use of potassium fluoride dihydrate combined with 18-crown-6 as a convenient and mild reagent system for silyl ether cleavage that simplifies greatly the isolation of pure nucleoside products; we also wish to call attention to the mistakes present in the literature.

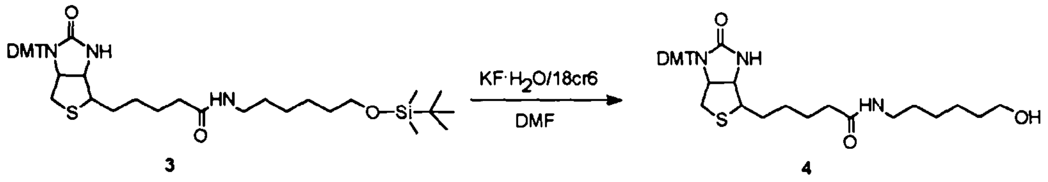
The reaction is general and as the accompanying table illustrates, has been carried out on several different TIPS-protected nucleosides, as well as primary and secondary *t*BDMS derivatives. The procedure is quite simple: the substrate, dissolved in DMF or THF, is treated with commercially available $KF \cdot 2H_2O$ and a catalytic amount of 18-crown-6, then stirred at room temperature. No reaction occurs in the absence of the crown ether (entry 5). Using anhydrous potassium fluoride likewise gives no reaction until some water or other proton donor such as tetrazole is added (data not shown).

ENTRY	SUBSTRATE[a]	SOLVENT[b]	TIME(hr)	KF/cr(eq)	YIELD
1	DMT-2'-OCH_3-C^{Bz}-3'-O-tBDMSi	DMF	12	5/ 2	80
2	DMT-A^{Bz}-2',3'-(O-*t*BDMSi)$_2$	DMF	18	6/ 3	89[c]
3	DMT-A^{tBPA}-2',3'-(O-tBDMSi)$_2$	DMF	18	6/ 3	93[c]
4	TIPS-2'-OCH_3-A^{tBPA}	THF	3	6/ 3	80
5	TIPS-2'-OCH_3-A^{tBPA}	THF	3	6/0	--
6	TIPS-2'-OCH_3-A	THF	18	3/ 2	81
7	TIPS-2'-OCH_3-D[d]	THF	4	6/ 2	60
8	TIPS-2'-O-ALLYL-G^{tBPA}-O^6-NPE[e]	DMF	5	6/ 3	58
9	TIPS-2'-OCH_3-G^{tBPA}-O^6-NPE[e]	DMF	5	6/ 3	55
10	DMT-TpdA^{Bz}-3'-O-tBDMSi[f]	DMF	5	6/ 2	90[c]
11	4	DMF	6	6/.3	77

a All products gave satisfactory analytical and spectral data b All sovlents are HPLC grade used with no further purification c Yield determined by HPLC d. D=2,6-diaminopurine e NPE=p-nitrophenylethyl f p=-OP(=O)(OCH_2CH_2CN)O-

The broad usefulness of the reaction is demonstrated by the stability of both the base-labile *tert*-butylphenoxyacetyl (*t*BPA), a group used in the protection of the exocyclic amine of nucleosides[10] (entries 3,4,8, and 9) and the acid-sensitive 5'-dimethoxytrityl groups (entries 1,2,3 and 10). The bis(*tert*-butyldimethylsilyl)nucleosides, produced as by-products during the large-scale monosilylation reactions[11], along with the undesired 3'-O-*t*BDMS derivatives (entries 2 and 3), regenerate the fully desilylated products which are recycled for subsequent production runs. A deoxynucleoside dimer, with the cyanoethylphosphite triester linkage (entry 10) was produced cleanly with no evidence of internucleotide bond cleavage or other side-reactions.

Apart from its' application for nucleoside chemistry, we have used this reagent system for the removal of the primary silyl group of the DMT-protected biotin derivative **3** described by Pon.[12] Using



the standard TBAF reagent to regenerate the primary alcohol gave adequate, though variable (55-85%) yields; however, it proved extremely difficult to remove residual TBA salts, even with repeated chromatography. The presence of this salt led to decomposition of the subsequently produced biotin phosphoramidite. The new procedure avoided these complications and gave reproducibly pure alcohol **4**.

General Procedure A 1000 mL round bottom flask equipped with a magnetic stirrer was charge with 27 gm. (37.5 mmol) 3',5'-O-(1,1,3,3-tetraisopropyldisiloxy-1,3-diyl)-2'-O-methyl-N^6-*p*-(*tert*-butylphenoxy)acetyladenosine **1**. The nucleoside was dissolved in 200mL tetrahydrofuran and treated with 21 gm (225 mmol) KF 2H_2O (Aldrich Chemical Co., 98%) and 3 gm. (11.3 mmol) 18-crown-6, and stirred at room temperature. After 3 hours, the reaction appeared to be complete by TLC (10% MeOH/$CHCl_3$). The mixture was filtered and the solids washed with THF. The filtrate was concentrated, re-dissolved in ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered and evaporated. The product was purified by flash chromatography[13] with 7% MeOH/$CHCl_3$ to afford 14 gm. diol **2**.

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