SELECTIVE DEPROTECTION OF ALCOHOLIC AND PHENOLIC SILYL ETHERS

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ABSTRACT: Hydrofluoric acid and tetrabutylammonium fluoride will selectively deprotect alcoholic and phenolic silyl ethers respectively.

One of the most common hydroxyl protecting functions presently in use is the t-butyldimethylsilyl moiety[1]. This group is easy to introduce[2] and of a variety of reagents[3] that exist for its removal the most useful is tetrabutylammonium fluoride. More recently[4] it has been suggested that the use of aqueous hydrofluoric acid is complementary; specifically it allows the removal of the silyl groups from the highly sensitive PGD_2 precursor (1).

(1) R=Sit-BuMe$_2$ PGD$_2$

We have discovered that these fluorine containing reagents can be used to effect selective desilylation of compounds containing both phenolic and alcoholic t-butyldimethylsilyl ethers. Thus, under carefully controlled conditions, aqueous hydrofluoric acid in acetonitrile selectively regenerates the alcohol function whereas tetrabutylammonium fluoride in tetrahydrofuran liberates the corresponding phenol (Scheme 1). As expected the use of an excess of either reagent eventually results in complete deprotection.

Scheme 1

Conditions A

aq HF / MeCN

Conditions B

^{n}Bu$_4$NF / THF

R = Sit-BuMe$_2$

Generally both reactions proceed very cleanly although the deprotections with hydrofluoric acid give reduced yields when the substrates are acid sensitive (Table, entries 4 and 7) or the masked hydroxyl group is sterically hindered (entry 9). In some instances reduced yields were also observed with the fluoride ion-mediated desilylations because concomitant removal of the alcoholic silyl moiety also occurred (entries 3 and 8). However, the use of short contact times (1-2 mins.) and toluene as solvent circumvented these problems and significantly improved the amount of desired product.

Interestingly, both types of products were isolated when the saligenin derivative (entry 3) was treated with tetrabutylammonium fluoride in toluene. This is rationalised on the basis of a fluoride ion-assisted silyl group migration[5] (Scheme 2) rather than a non-selective deprotection process. This postulate is supported by the observation that where intramolecular silyl migration is not possible (entry 2) then no deprotection of the alcoholic silyl moiety occurs.

Scheme 2

The selective deprotection is also successful with the t-butyldiphenylsilyl group[6] although more drastic conditions are required to liberate the free alcohol function (Scheme 3). Similar attempts with the trimethylsilyl moiety failed and only fully deprotected compounds were recovered.
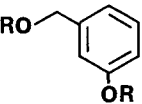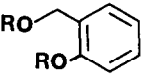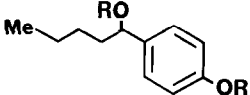
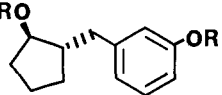### Scheme 3

$HF/MeCN/50^{o}$
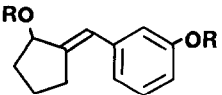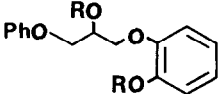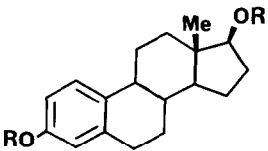
92%

$^{n}Bu_{4}NF/THF/0^{o}$

83%
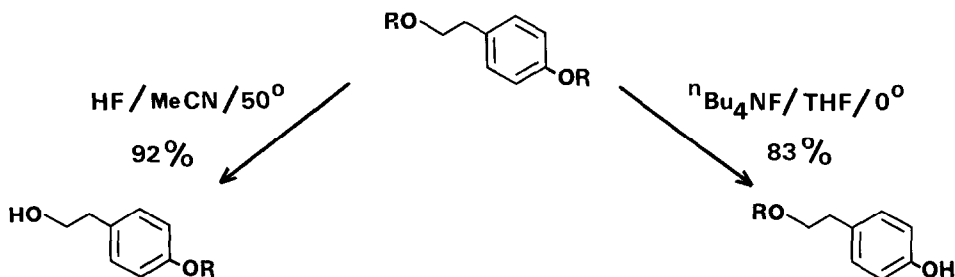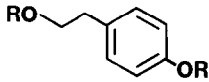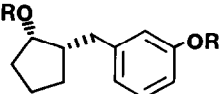
Conditions A

2 equivalents of 40% aqueous HF are added to a solution of the substrate in MeCN at either 0° or room temperature. When the reaction is complete by t.l.c. analysis (~30 mins.) an excess of 8% $NaHCO_3$ is added and the product is extracted into ether. Purification is carried out by flash chromatography[7] on silica gel.

Conditions B

1 equivalent of 1M Bu_4NF/THF is added to a solution of the substrate in THF at 0°. After ~15 mins. an excess of aqueous NH_4Cl is added and the product isolated as in A.
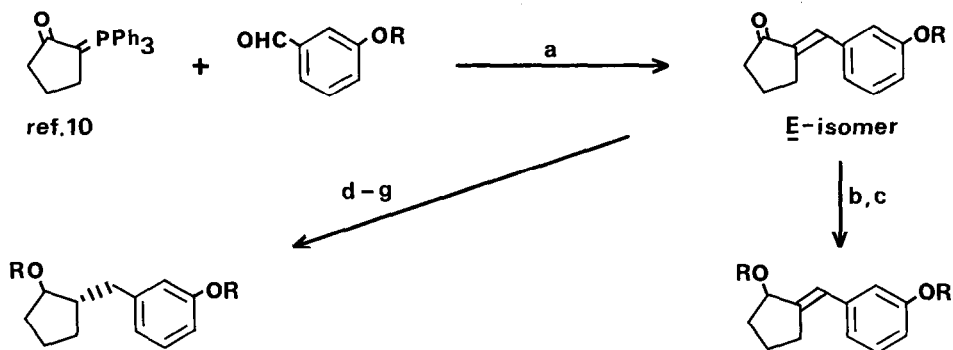
Table

SUBSTRATE [8,9] (R = ^{t}BuMe$_2$Si)	DEPROTECTION CONDITIONS	
	A PRODUCT TYPE,(% Yield)	B PRODUCT TYPE,(% Yield)
1. RO—CH$_2$CH$_2$—C$_6$H$_4$—OR	A (96)	B (96)
2. RO—CH$_2$—C$_6$H$_4$—OR (meta)	A (98)	B (98)
3. RO—CH$_2$—C$_6$H$_4$—OR (ortho)	A (98)	B (0–38)[b] B (74) A (4)[c]
4. Me(CH$_2$)$_3$CH(OR)—C$_6$H$_4$—OR	A (37)[a]	B (99)
5. RO-cyclopentane–CH$_2$–C$_6$H$_4$–OR	A (95)	B (100)
6. RO-cyclopentane–CH$_2$–C$_6$H$_4$–OR	A (95)	B (97)
7. RO-cyclopentene=CH–C$_6$H$_4$–OR	A (40)[a]	B (100)
8. PhO–CH$_2$–CH(OR)–CH$_2$–O–C$_6$H$_4$–OR	A (46)	B (~50)[d] B (94)[e]
9. steroid (Me, OR; RO)	A (64) B (4)	B (99)

a. Evidence for olefin containing by-products.
b. Complete deprotection to the corresponding diol was observed with 1eq Bu$_4$NF. 38% Yield of product B was obtained with 0.5eq Bu$_4$NF.
c. Toluene/0°/2 mins. Amount of product A increases with increased reaction time.
d. 50% Yield of corresponding diol also produced.
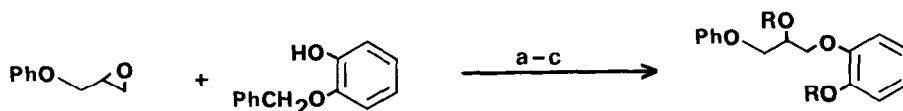e. Toluene/0°/2 mins.

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8. The silyl ethers were prepared by conventional methods (ref. 2) and were obtained in
    yields of 75-99%. All new compounds possessed satisfactory spectroscopic and
    analytical data.
9. Substrates for entries 5-7 were prepared as follows:-

a. Δ/toluene; 93%   b. NaBH$_4$/EtOH; 82%   c. RCl/DMF/Imidazole; 86%
d. H$_2$/Pd; 75%   e. NaBH$_4$/EtOH; 90%   f. separate isomers
g. RCl/DMF/Imidazole; cis, 96%; trans, 97%

Substrate for entry 8 was prepared as follows:-

a. KF/Al$_2$O$_3$; 89%   b. H$_2$/Pd; 95%   c. RCl/DMF/Imidazole; 83%

R = ^{t}BuMe$_2$Si

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