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AN EXCELLENT REAGENT FOR THE REMOVAL OF THE t-BUTYLDIMETHYLSILYL PROTECTING GROUP

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Summary: Aqueous hydrofluoric acid is an excellent reagent for the removal of t-butyldimethylsilyl protecting groups.

The t-butyldimethylsilyl moiety is in common use as a protecting group for hydroxyl functionality.[1] Regeneration of the alcohol can be effected using aqueous acid[2], tetrabutylammonium fluoride[3], or boron trifluoride[4]. However, these methods are generally unsuitable for the regeneration of β-ketols due to concurrent dehydration under the reaction conditions.

Now we have discovered that aqueous hydrofluoric acid[5] in acetonitrile is a mild and efficient method for the cleavage of t-butyldimethylsilyl ethers and is particularly useful for the formation of β-ketols. A selection of our results is illustrated in the Table.

The following points are noteworthy:-

a) Unhindered silyl ethers are cleaved rapidly and cleanly at ambient temperature by acetonitrile containing 5% of a 40% aqueous solution of HF.

b) Bulky alkyl silyl ethers react more slowly, however higher concentrations of HF and/or higher reaction temperatures leads to an increase in reaction rate, often without loss of product.

c) In some cases nitromethane or ethanol are satisfactory alternative solvents.

d) Sensitive β-ketols are produced in very high yield, however elevated temperatures are detrimental and promote further acid catalysed decompositions of the products.

e) A simple extraction procedure affords the desired alcohol since the organic side-product is presumably a volatile silyl fluoride. Complementary work has shown that trimethylsilyl and n-butyldimethylsilyl ethers are susceptible to cleavage under the reaction conditions outlined in Method A while ketones are regenerated from ethylene ketals under these conditions.

Method A - The substrate was dissolved in acetonitrile containing a suitable amount (5-30%) of a 40% aqueous solution of HF. T.l.c. monitoring was carried out by spotting aliquots directly onto a silica gel plate. When deprotection was complete chloroform and water were added. The organic phase was removed and evaporated to give pure alcohol (n.m.r., t.l.c.).

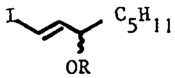
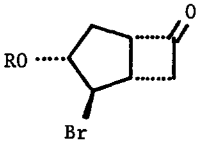
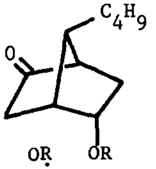
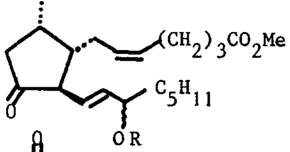
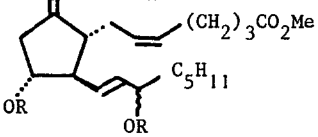
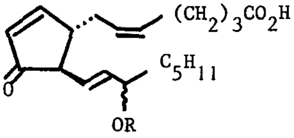
Method B - As above except the product was purified by short column chromatography.

Method C - As for method A except the reaction mixture was heated to reflux.

Method D _ As for method C except nitromethane was used instead of acetonitrile.

Method E - As for method C except ethanol was used instead of acetonitrile.

Table: Reaction of some t-butyldimethylsilyl ethers with aqueous HF in acetonitrile.

System	Substrate	Product	Conc. of HF*	Method	Time	Yield
	$R=Si(Me)_2{}^tBu$	R=H	5%	A	0.5	100
	$R=Si(Me)_2{}^tBu$	R=H	"	A	24	100
	"	"	"	C	1	100
	"	"	"	D	2	100
	"	"	"	E	2	95
	$R=Si(Me)_2{}^tBu$	R=H	"	A	1	100
	$R=Si(Me)_2{}^tBu$	R=H	30%	B	2.5	70
	$R=Si(Me)_2{}^tBu$	R=H	5%	B	2	96
	"	"	15%	A	1	100
	$R=Si(Me)_2{}^tBu$	R=H	5%	A	1	100

*HF refers to a 40% aqueous solution of hydrofluoric acid.

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