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REDUCTION OF ACTIVATED KETALS WITH BORANE-DIMETHYL SULPHIDE

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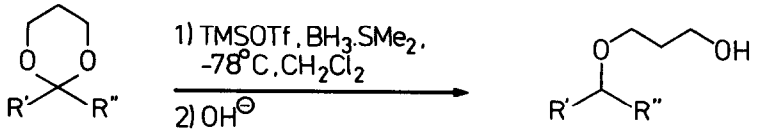
Abstract:

Borane-Dimethyl sulphide reduces ketals activated with TMSOTf at -78 °C in dichloromethane. The scope and selectivity of the reagent has been investigated.

The reduction of a ketone to a secondary alcohol stands out as one of the most important transformations in organic chemistry. A multitude of chemoselective reducing agents are available for this reaction and in recent times considerable effort has been directed towards the rational design of asymmetric reducing agents.[1,2] By comparison, the history of reduction of acetals and ketals is far more recent with several reagents having been investigated including $LiAlH_4/BF_3$[3], $LiAlH_4/AlCl_3$[4], DIBAH[5], B_2H_6[6], $NaBH_3CN$-HCl(g)[7], $Zn(BH_4)_2/Me_3SiCl$[8], Me_3SiH/Me_3SiOTf[9], Et_3SiH/acids[10], H_2/Rh[11].

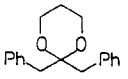
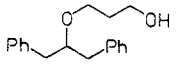
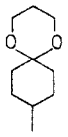
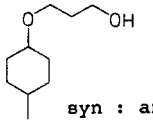
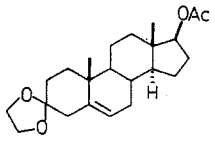
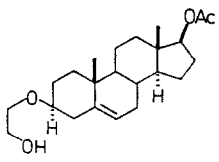
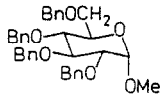
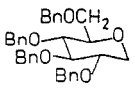
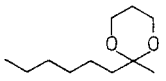
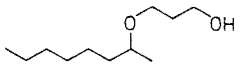
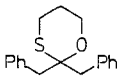
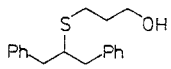
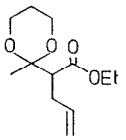
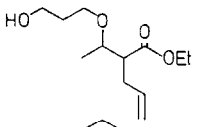
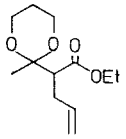
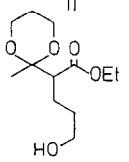
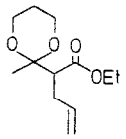
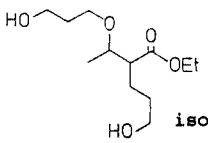
More recently Yamamoto and co-workers[12] have established that diisobutylaluminium hydride (DIBAH) and triethylsilane/titanium tetrachloride are complementary reagents for the diastereoselective reductive opening of chiral ketals via syn and anti mechanisms respectively. Borane-THF has been reported to reduce acetals to ethers at room temperature but ketals react sluggishly requiring higher temperatures and giving lower yields.[6] In this communication we would like to report on the chemoselectivity of borane dimethyl sulphide and trimethylsilyl trifluoromethanesulphonate (TMSOTf) as a novel reagent combination for reduction of ketals to protected secondary alcohols in high yield.

Scheme 1.



A range of substrates were selected to test out the scope of the reagent and the results are shown in Table 1.

Table 1

Entry	Ketal	Product(s)	Yield(%)[a]
1			95
2			97 syn : anti = 1:6
3			83
4			50
5			53
6			72
7			77
8[b]			80
9[c]			36 isomer ratio = 3:2

a: Isolated yields after column chromatography

b: No TMSOTf, $^{-}$OOH work-up

c: $BH_3.SMe_2$ followed by TMSOTf

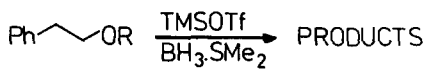
A typical experimental procedure is as follows: To a stirred solution of acetal (1 mmol) in dry dichloromethane (3 mls) at -78 °C is added, via syringe, TMSOTf (1.2 mmol) and borane dimethyl sulphide (1.2 mmol). On completion of reaction (monitored by t.l.c.) saturated sodium bicarbonate (10 mls) is added and the organic product extracted into dichloromethane (3 x 25 ml). Drying ($MgSO_4$) and evaporation of solvent furnishes the protected alcohol as an oil which is purified by column chromatography.

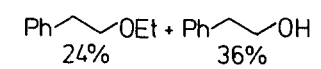
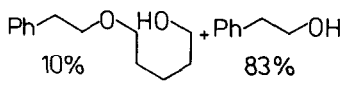
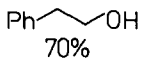
Several features about the reaction deserve mentioning. Dichloromethane proved generally to be superior to THF owing to the latter's susceptibility towards polymerisation with TMSOTf at room temperature. Similarly, borane dimethyl sulphide proved to be practically more suitable than the THF complexed reagent although both gave similar isolated yields. Other Lewis acids screened required higher reaction temperatures, e.g. for substrate (1) $TiCl_4$: 0 °C , $SnCl_4$: 0 °C , $BF_3.Et_2O$: 25 °C. One equivalent of TMSOTf was essential for complete conversion of ketal while use of a substituted borane, e.g. thexylborane, required a higher reaction temperature.

As evidenced from Table 1 the chemoselectivity of the borane may be controlled by the choice and order of addition of reagents. Entry 9 indicates the possibility of intramolecular reduction, a pathway not readily available to other reagents for ketal reduction.

As an extension of the chemoselectivity study, four common hydroxyl protecting groups were examined with the reagent and the results are shown in Table 2. 2-Phenylethanol was chosen as the parent alcohol. Only the benzyl ether group showed any resistance to the reagent, while acetate reduced partially to the ethyl ether.

Table 2.



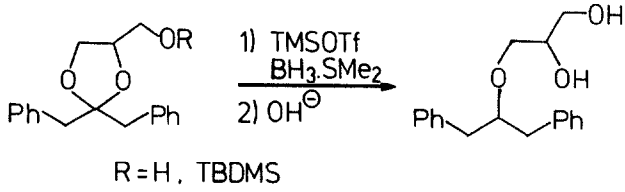
Entry	R	Conditions	Products / Yields[a]
1		25°C/24h	
2		-78°C/3h	
3	$-CH_2Ph$	25°C	no reaction
4		-78°C/4h	

a: Isolated yields after column chromatography

Finally, the influence of proximal functionality on the selectivity of C-O bond fission was investigated.

Both the unprotected and the silyl protected derivatives of the bis-benzyl dioxolane of glycerol gave the unsymmetrical diol in 74% and 84% yield respectively as the only identifiable product.

Scheme 2.



R=H, TBDMS

Further studies are continuing on the mechanistic and selectivity aspects of this reagent.

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