The First Solvent-directed Regioselective Ketal Reduction of Unsymmetrical Glycols

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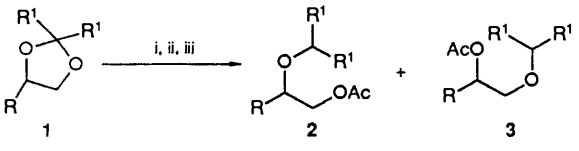
Borane–dimethyl sulphide/TMSOTf in THF reduces ketals of unsymmetrical vicinal diols with much higher regioselectivity than with CH_2Cl_2 as solvent.

Considerable interest has been shown recently in the chemoselective protection of unsymmetrical vicinal diols to afford the thermodynamically and kinetically less stable secondary protected derivative. All of the procedures owe their success to the site selectivity of the oxygen attached to the primary carbon atom of an appropriate cyclic derivative towards an electrophilic reagent. Cyclic derivatives studied to date have been stannylene derivatives,[1] phosphoranes,[2] and acetals and ketals.[3,4] We have recently reported[5] that borane–dimethyl sulphide/trimethylsilyl trifluoromethanesulphonate (TMSOTf) is a novel, highly potent reagent combination for reductive ketal opening. In this communication we report on the use of this reagent in the first solvent controlled regioselective ketal reduction and comment on the mechanistic implications (Scheme 1).



Scheme 1 *Reagents and conditions:* i, BH_3·SMe_2/THF or CH_2Cl_2/TMSOTf/−78 °C; ii, $NaHCO_3/H_2O$; iii, Ac_2O/pyridine/DMAP (cat).

A study was undertaken to ascertain the influence of various reaction conditions and substrate structure on the reaction outcome. The dimethyl and diethyl ketals of 1-phenylethane-1,2-diol and the diethyl and dibenzyl ketals of hexane-1,2-diol were reduced in both THF and CH_2Cl_2, and as seen in Table 1 the isomer ratio improved in favour of the secondary protected derivatives **2** with increasing steric bulk of the ketal groups. Furthermore, improvement in regioselectivity for **2** was more pronounced in THF. The reaction product was acetylated in each case and isomer ratios were ascertained using ^1H NMR and GC. Use of bulkier reagents, *e.g. tert*-butyldimethylsilyl trifluoromethanesulphonate (TBDMSOTf) or 1,1,2-trimethylpropylborane (thexylborane) resulted in a modest preference for the unwanted primary protected derivative **3**.

The most pronounced regioselectivity was observed using THF as solvent which resulted in higher regioselectivities compared with CH_2Cl_2 in spite of the higher temperature required for reaction. For instance, the product ratio for the reduction of the diethyl ketal of 1-phenylethane-1,2-diol improved from 63:37 to 98:2 in favour of the desired secondary protected derivative **2** by changing from CH_2Cl_2 to THF (Entries 3 and 4, Table 1). Similarly, for hexane-1,2-diol diethyl ketal it improved from 27:73 to 83:17. The glycerol dioxolane derivatives (Entries 9 and 10) with R as CH_2OBn were reduced in CH_2Cl_2 to afford almost exclusively[6] the primary protected derivative **3** derived by chelation controlled (*via* CH_2OBn) silylation of the oxygen bonded to the secondary carbon. By comparison, in THF (entry 11), the ratio shifts significantly to give some secondary protected derivative **2** in which the directing influence of THF competes with the chelation controlled process.

Other solvents (toluene, acetonitrile, diisopropyl ether, diethyl ether) did not influence the isomer ratio in favour of the secondary protected derivative. Slightly higher ratios were obtained by adding the borane dimethyl sulphide first, while use of 2 equiv. of borane did not influence the isomer ratio significantly, but did help to reduce the reaction time.

Table 1 Product yields and isomer ratios from reductive cleavage of ketals **1** using borane dimethyl sulphide and TMSOTf (2 equiv.) followed by acetylation

Entry	R	R^1	Solvent	T/°C	Ratio **2**–**3**	Yield (%)
1	Ph	Me	CH_2Cl_2	−78	63:37	60
2	Ph	Me	THF	−78 to +10	81:19	67
3	Ph	Et	CH_2Cl_2	−78 to −30	63:37	84
4	Ph	Et	THF	−78 to +10	98:2	88
5	Bu	Et	CH_2Cl_2	−78 to −20	27:73	73
6	Bu	Et	THF	−78 to +4	83:17	72
7	Bu	CH_2Ph	CH_2Cl_2	−78 to −20	31:69	91
8	Bu	CH_2Ph	THF	−78 to RT	90:10	87
9	CH_2OBn	Me	CH_2Cl_2	−78 to −70	5:95	86
10	CH_2OBn	CH_2Ph	CH_2Cl_2	−78 to −30	5:95	69
11	CH_2OBn	Me	THF	−78 to −70	27:73	72
12	Ph	Et	ether	−78 to 0	63:37	76
13	Ph	Et	diisopropyl ether	−78 to 0	62:38	84
14	Bu	CH_2Ph	ether	−78 to RT	38:62	83

Mechanistically, the most plausible explanation for the solvent effect is that the Lewis basic THF assists in the silylation process, acting as a sterically demanding silylating agent. Other ethereal solvents (diethyl and diisopropyl ether, Entries 12–14) gave approximately the same ratio as the corresponding CH_2Cl_2 cases which may be due to their lower Lewis basicity compared with THF. The THF is unlikely to exert a steric influence in the reduction step since this probably involves $TfO\bar{B}H_3$. This is also borne out by the result with thexylborane in which no improvement in isomer ratio was observed favouring the desired isomer. Hence, increasing the steric bulk of the reductant does not result in production of more of the secondary protected derivative. Yamamoto[7] has recently shown that solvent has a marked effect on the stereoselectivity of reduction of a symmetrical bicyclic ketal using diisobutylaluminium hydride (DIBAH), but in this case the two oxygen atoms were equivalent and oxygen site selectivity was not an issue.

In conclusion, this result highlights the importance of solvent in this reaction for controlling site selectivity and points the way towards the design of more effective reagents for the transformation. We are currently working towards a more useful protecting group using this reagent and results will be communicated in due course.

Experimental

Typical Procedure.—To a solution of ketal (1 mmol) in dry THF or CH_2Cl_2 (3 cm^3) at −78 °C was added TMSOTf (2 mmol) followed by borane dimethyl sulphide (2 mmol). The reduction was followed to completion by TLC whereupon saturated aqueous sodium hydrogencarbonate (5 cm^3) was added and the organic material extracted into ethyl acetate and dried ($MgSO_4$). Removal of solvent gave an oil which was acetylated using pyridine (1 cm^3) and acetic anhydride (1 cm^3) with a catalytic amount of 4-dimethylaminopyridine. After the normal work-up, the final product was isolated by column chromatography and analysed by ^1H NMR and GC in appropriate cases.

Acknowledgements

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References and notes

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6 In the original paper (ref. 5 above), it was stated that **3** was obtained exclusively for the bis-dibenzyl dioxolane. The ratio has now been more accurately determined to be **2**/**3** = 5:95. We apologise for this error.
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