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1,3-SYN DIASTEREOSELECTIVE REDUCTION OF β-HYDROXYKETONES UTILIZING ALKOXYDIALKYLBORANES

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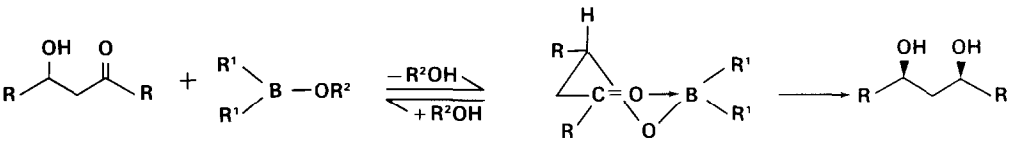
Summary: Sodium borohydride reduction of β-hydroxyketones in presence of alkoxydialkylboranes 1-7 as complexing agents, produced 1,3-syn diols in at least 98:2 ratio. As illustrated with examples 8-17 this method is quite general and superior to those described in the literature.

The diastereoselective reduction of β-hydroxyketones to the corresponding 1,3-syn diols has attracted a great deal of attention from synthetic organic chemists due to the frequent occurrence of 1,3-dioxygenated fragments in biologically active natural products like compactin, macrolides etc. There are several methods mentioned in the literature for the formation of 1,3-syn diols starting from β-hydroxyketones, although most of them do not achieve high stereoselectivity. One exception is the trialkylborane method[1-4] which uses trialkylboranes as complexing agents with hydroxyketones in the presence of activators like air[1,2] or pivalic acid[3,4]. However, to our knowledge, the use of alkoxydialkylboranes as complexing agents in the above reductions has not been reported in the literature, even though many such reagents had been synthesized by Köster and co-workers[5].

Alkoxydialkylboranes, in principle, could interact with hydroxyketones without air or acid activation, leading to the formation of a boron chelate intermediate which on subsequent reduction could give selectively the desired syn diols as shown in Scheme I. In



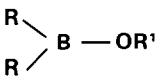
SCHEME I

this communication, we describe a versatile method for the selective formation of 1,3-syn diols in diastereomeric ratios[6] of at least 98:2.

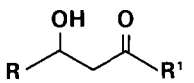
General procedure: To a solution of hydroxyketone (1 mmol) in dry tetrahydrofuran (8 mL) and anhydrous methanol (2 mL) at -70°C under argon, was added dropwise alkoxydialkylborane (1.1 mmol), and the resulting mixture was stirred for 15 min. Then sodium borohydride

(1.1 mmol) was added, and the mixture was stirred for 3-5 h, depending on the substrate used, followed by the addition of 1 mL of acetic acid. The quenched reaction mixture was diluted with ethyl acetate, washed with aqueous sodium bicarbonate solution, dried and evaporated to dryness. The residue thus obtained was azeotroped a few times with methanol until the hydrolysis of the boronate was complete, then chromatographed on silica gel using ethyl acetate/hexane as eluent, to give 1,3-diols.

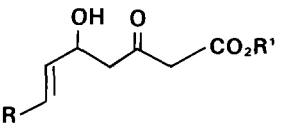
The results obtained in the reduction of ketones[7] 8-17 with sodium borohydride in the presence of methoxydiethylborane[8] 1 are listed in Table 1. It is evident from these results that our method is superior to those described in the literature. For example in case of 8, the trialkylborane method was reported[1] to yield syn and anti diols in the ratio of 88:12 at -78°C compared to our result of 99:1 at -70°C using alkoxyborane 1. The same can be said about examples 10-13 where the selectivity observed is much higher than the literature results[2]. In addition, the trialkylborane[1,2] method fails to give consistent results on scale-up in contrast to our method which is also safer as alkoxydialkylboranes are less pyrophoric than trialkylboranes.

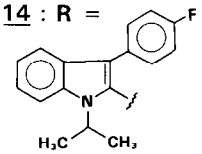
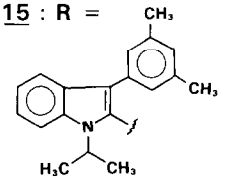


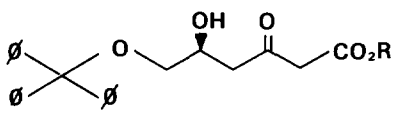
1 : R = ethyl, R¹ = methyl
2 : R = ethyl, R¹ = ethyl
3 : R = ethyl, R¹ = n-butyl
4 : R = ethyl, R¹ = allyl
5 : R = ethyl, R¹ = isopropyl
6 : R = ethyl, R¹ = t-butyl
7 : R = n-butyl, R¹ = methyl



8 : R = R¹ = n-butyl
9 : R = R¹ = phenyl
10 : R = phenyl, R¹ = $CH_2CO_2CH_2CH_3$
11 : R = isopropyl, R¹ = $CH_2CO_2CH_2CH_3$



12 : R = R¹ = methyl
13 : R = phenyl, R¹ = methyl
14 : R =  R¹ = methyl
15 : R =  R¹ = ethyl



16 : R = ethyl
17 : R = allyl

Table 1: Diastereoselective reduction of β-hydroxyketones with sodium borohydride in the presence methoxydiethylborane 1.

Ketone No.	Reaction time (h)	Yield (%)	Product Ratio[6] syn	anti	^{13}C chemical shifts of the two stereogenic C-atoms syn C(δ)	syn C(β)	anti C(δ)	anti C(β)
8	3	99	99	1	73.15	73.15	69.35	69.35
9	3	95	99	1	74.87	74.87	71.60	71.60
10	5	85	98	2	74.28	68.53	71.04	65.50
11	5	80	98	2	76.91	69.15	73.32	65.76
12	3	82	98	2	72.57	68.12	69.70	65.42
13	5	90	98	2	72.51	68.16	69.78	65.49
14	5	90	98	2	71.96	68.12	69.69	65.52
15	5	70	98	2	72.21	68.30	69.70	65.44
16	5	72	98	2	70.99	68.21	68.07	65.35
17	5	68	98	2	70.99	68.15	?	?

Methoxydiethylborane 1 can be replaced with other alkoxy derivatives like 2-7[8] without affecting the selectivity[9], as shown in Table 2. Although we use an alcohol as a co-solvent, it is not essential for it to match the alkoxyborane that is used for complexation. The rate of reduction was slower when t-butanol was used as a co-solvent (Table 2; example 6). The selectivity could perhaps be further increased by carrying out the reduction at temperatures below -70°C, but then the anti isomer would be outside the detection limit of our analytical method[6].

Table 2: Reduction[a] of 17 with $NaBH_4$ in the presence of different alkoxyboranes.

Borane No.	Solvent (ratio 4:1)	Time (h)	Yield (%)	Product Ratio[6] syn	anti
1	THF/methanol	5	85	98	2
2	THF/ethanol	5	80	98	2
3	THF/n-butanol	5	85	98	2
4	THF/allyl alcohol	5	80	98	2
5	THF/isopropanol	8	80	98	2
6	THF/t-butanol	72	75	99	1
7	THF/methanol	5	82	98	2

a) Other conditions are as mentioned in the general procedure

The use of stoichiometric amounts of alkoxyborane is not essential for obtaining high degree of selectivity at least with certain substrates (example 14, Table 3).

Table 3: Reduction of 14 in the presence of varying amounts of 1.

molar equivalents of 1	Product Ratio[6] syn	anti
0.15	70	30
0.50	98	2
1.10	98	2
1.60	98	2

The high diastereoselectivity that was observed in the present studies can be explained on the basis of a chelate model[1,2] shown in Scheme I.

Further work on the mechanism of this reduction method is in progress.

References and Notes

1. K. Narasaka and F.-C. Pai, Tetrahedron, **40,** 2233 (1984) and references cited therein.

2. F.G. Kathawala, B. Prager, K. Prasad, O. Repic, M.J. Shapiro, R.S. Stabler and L. Widler, Helv. Chim. Acta, **69,** 803 (1986).

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6. The syn/anti ratios were calculated on the basis of the relative intensity of the two sets of ^{13}C signals of the two stereogenic carbon atoms, except in the case of example 17 in which the signals overlap; in this case, the syn/anti ratios were determined on the basis of the relative intensities of the α and γ C-atoms. The precision of the ^{13}C NMR method was counterchecked by HPLC with the products obtained from compounds 8, 14 and 15, but the accuracy of either method is only ± 0.5%. For this reason, the values were rounded off to the nearest whole number.

7. Compounds 8 and 9 were prepared following Ref. 1; 10-13 were prepared according to Ref. 2; 14 and 15 were prepared following Ref. 10; 16 and 17 were prepared from (S)-malic acid (Ref. 11).

8. Alkoxyboranes 1-7 were prepared according to Ref. 5. Compounds 5 (bp 115-117°C, yield 78%) and 7 (bp 80-85°C/35 mm, yield 70%) were not described in the literature.

9. At the outset of our investigations we examined dimethoxybutylborane and trimethyl borate, but the results were not stereoselective.

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