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A Novel Method for the In Situ Generation of Alkoxydialkylboranes and Their Use in the Selective Preparation of 1,3-Syn Diols

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An in situ method for generating Et_2BOCH_3 from triethylborane and methanol without using any other catalysts is described. Using the Et_2BOCH_3 thus generated as a chelating agent, syn 1,3-diols are prepared in $\geq$ 98% stereochemical purity by reducing β-hydroxyketones with sodium borohydride.

We have recently reported[1] a general and efficient method for the synthesis of syn 1,3-diols by $NaBH_4$ reduction of β-hydroxyketones utilizing alkoxydialkylboranes as chelating agents, with the syn diastereoselection exceeding 98%. These results prompted us to search for methods of in situ generation of alkoxydialkylboranes from the commercially available trialkylboranes. Dialkylborylation of alcohols was hitherto achieved in the literature by treating alcohols with the corresponding trialkylboranes in presence of activating reagents like pivalic acid,[2] air[3] etc.

$$R_3B + R'OH \xrightarrow[-RH]{\text{Activators}} R_2BOR'$$

During our work, we found that the desired alkoxyboranes could be generated by mixing Et_3B with CH_3OH in THF in the absence of any further activators.[4] We established the optimum ratio of Et_3B and CH_3OH that is needed for an efficient conversion, by studying the ^{11}B-NMR spectra[5] (Table 1) of the reaction mixtures. From these studies (entries 2-5) it is clear that the desired Et_2BOCH_3 could be generated in situ conveniently and quantitatively just by modulating the relative ratios of Et_3B and CH_3OH: the higher the ratio of CH_3OH/Et_3B the faster the rate of formation of Et_2BOCH_3. The ^{11}B-NMR spectrum of the sample obtained by mixing Et_3B (0.25 mmol) with CH_3OH (0.5 mL) in THF (2 mL) at -78 °C (entry 5) is essentially identical to the one obtained with authentic Et_2BOCH_3 (entry 6).

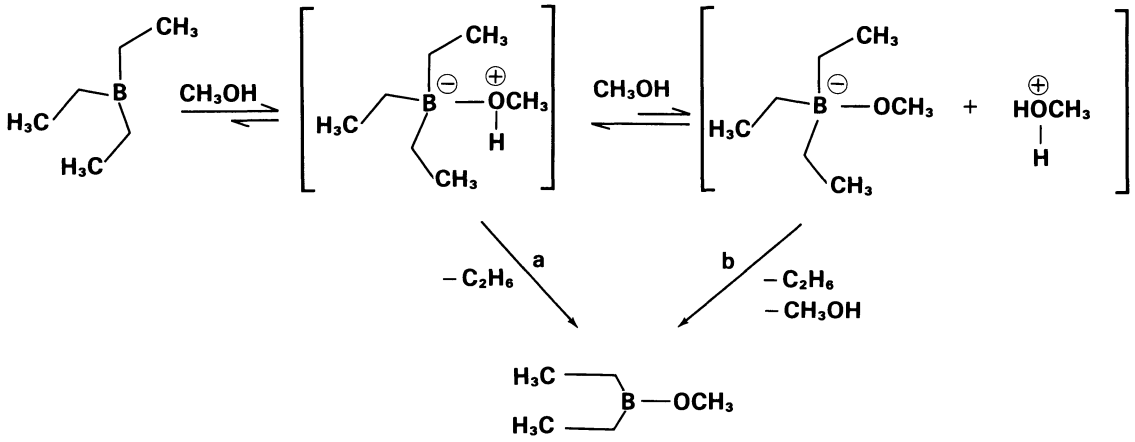
The probable mechanism for the formation of Et_2BOCH_3 from Et_3B and CH_3OH is shown in Scheme 1. The first step in this process is the fast addition of CH_3OH to Et_3B generating an ate complex (^{11}B-NMR δ 11.63 ppm) which in principle could protonolyze either in an inter- or intramolecular fashion (route a) forming Et_2BOCH_3 (^{11}B-NMR δ 35.2 ppm) and ethane. Alternatively, the ate complex, in presence of excess CH_3OH, could equilibrate to borate and methoxonium ions which in turn could generate the Et_2BOCH_3 via protonolysis (route b). The latter route

may be more likely, as the rate of the formation of Et_2BOCH_3 is proportional to methanol concentration (cf. entries 2-5). At higher CH_3OH concentrations (entries 4&5), as the ^{11}B-NMR signal of the ate complex (11.6-11.9 ppm) diminishes due to its conversion to Et_2BOCH_3 (35.2 ppm), the weaker signal of $EtB(OCH_3)_2$ (12.8 ppm) becomes visible.

Table 1. ^{11}B-NMR Study of the Interactions of Et_3B with CH_3OH

Entry No.	Borane	Solvent	Chemical shifts[a] of the boron signal due to Et_3B	Et_2BOCH_3 (Rel. int.)	ate complex and/or $EtB(OCH_3)_2$ (Rel. int.)
1	BEt_3[b]	THF	60.06	-	-
2	BEt_3[c] (2 mmol)	THF:CH_3OH 2 mL 0.5 mL	-	35.27 (20%)	11.63 (80%)
3	BEt_3[c] (1 mmol)	"	-	35.23 (29%)	11.90 (71%)
4	BEt_3[c] (0.5 mmol)	"	-	35.23 (57%)	12.81&11.89(43%)
5	BEt_3[c] (0.25 mmol)	"	-	35.23 (93%)	12.89 (7%)
6	Et_2BOCH_3[d]	THF	-	35.18 (97%)	12.77 (3%)
7	$EtB(OCH_3)_2$[e]	THF	-	-	12.96

a) Chemical shifts are reported in δ ppm with reference to $B(OCH_3)_3$ as an external standard, and the NMR spectra are measured using a 10-mm probe. b) Sample obtained from Aldrich. c) The reagents were mixed at -78 °C, and after 30 min at this temperature the NMR spectra were recorded at 22 °C. d) Authentic sample made by following Köster's procedure.[2] e) Sample kindly supplied by Prof. Köster.



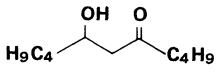
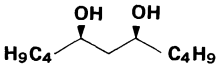
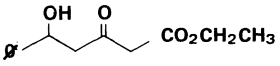
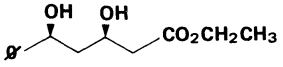
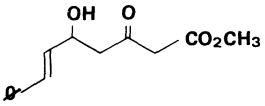
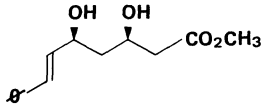
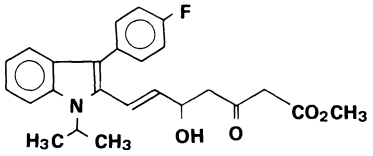
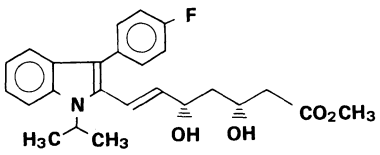
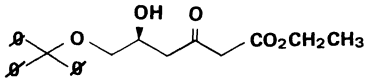
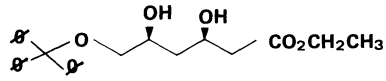
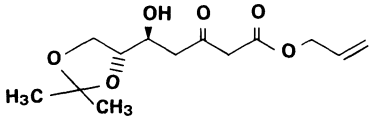
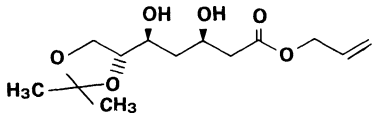
Scheme 1.

The above method of in situ generation of alkoxydialkylboranes was found to be generally applicable to substrates such as triethyl- and tributylboranes in combination with simple alcohols like methanol, ethanol, allyl alcohol etc. The details of these results will be published in due course of time.

In order to check the applicability of this method to the diastereoselective reduction of β-hydroxyketones with $NaBH_4$, we compared the results obtained with

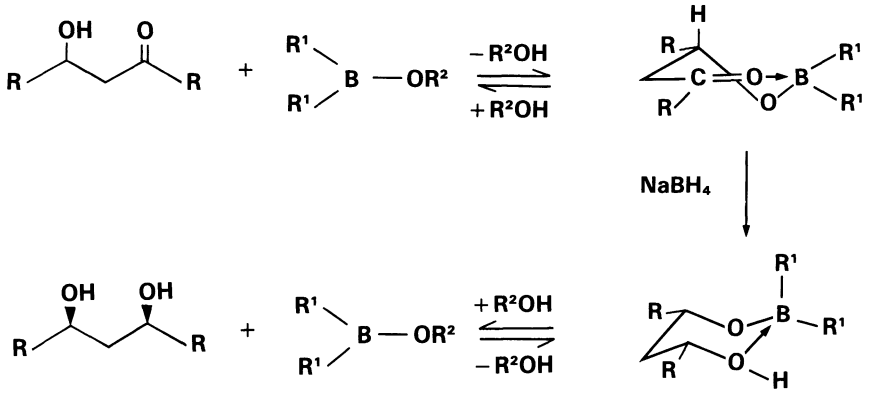
the in situ reagent with those obtained with authentic[1] Et_2BOCH_3. In all cases thus far examined, the syn diastereoselectivity[6] was found to be ≥98% (Table 2). The details of the reaction conditions for the in situ method are described in the general procedure below.

Table 2. Diastereoselective Reductions of β-hydroxyketones with $NaBH_4$ in the Presence of Et_2BOCH_3 (in situ Method)

Example	Reactant	Product	syn/ %	Yield /%
1.			>99	95
2.			>99	80
3.			>99	90
4.			>98	70
5.			>99	75
6.			>99	70

With the intention of monitoring the transformations that take place around boron nucleus during the reduction process (Scheme 2), the ^{11}B-NMR spectra of the reduction mixture with example 4 were measured at different intervals. The signal at δ 35 ppm essentially remained unchanged during the whole course of the reduction presumably due to the fact that solvation, present from the beginning of the experiment, has a similar effect on the ^{11}B-NMR shift as does chelation. Therefore, we could not further prove the presence of the six-membered chelate intermediate,[1,3] the model for explaining the syn diastereoselectivity.

The high degree of diastereoselectivity observed in the reduction of β-hydroxyketones with sodium borohydride by using alkoxydialkyl boranes as chelating agents and the fact that these reagents in turn can be quantitatively generated in situ from the commercially available trialkylboranes, make the above method for the preparation of syn 1,3-diols unique. These results complement well the recently reported anti-selective reductions.[7]



Scheme 2.

A solution of Et_3B (1.1 mL of 1 M solution in THF) was added to a mixture of dry THF (8 mL) and methanol (2 mL) at room temperature under argon. After stirring for one hour, the mixture was cooled to -70 °C followed by the addition of a β-hydroxyketone (1 mmol), and the stirring was continued for 30 min. Then sodium borohydride (1.1 mmol) was added, and the mixture was stirred for 3-5 h, depending on the substrate used. The reaction mixture was diluted with ethyl acetate, quenched with aqueous ammonium chloride solution, and the organic phase was dried and evaporated to dryness. The residue was azeotroped a few times with methanol until boron-containing compounds were removed, then chromatographed on silica gel using ethyl acetate/hexane as eluent to give 1,3-diols.

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References

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2) R. Köster, W. Fenzl, and G. Seidel, Liebigs Ann. Chem., 1975, 352.

3) K. Narasaka and F.-C. Pai, Tetrahedron, 40, 2233 (1984).

4) The possibility that traces of air or peroxide impurities could be responsible for the results was ruled out by carrying out experiments in degassed solvents as well as in the presence of Galvinoxyl,[8] a radical inhibitor. The results were always consistent and reproducible.

5) Trialkyl, dialkyl monooxygenated and monoalkyl dioxygenated boranes can be readily differentiated by ^{11}B-NMR as the boron chemical shifts of these compounds are widely separated and very characteristic.

6) The syn/anti ratios were calculated on the basis of the relative intensity of the two sets of ^{13}C-NMR signals of the two stereogenic carbons.[1]

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