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Valine-mediated borane reduction of ketones

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Acetophenone, 3,3-dimethyl-2-butanone, 3-methyl-2-butanone, and 2-pentanone were reduced with (*S*)-valine-mediated borane in very good yields (86–91 %) giving predominantly alcohols of the (*R*)-configuration (80, 64, 55, and 36 % *ee*, respectively).

Keywords: valine-mediated borane, chiral reduction, acetophenone.

INTRODUCTION

Amino acids are very important starting materials used as enantioselective auxiliaries.[1] A great many outstanding homogeneous chiral catalysts are derived from amino acids.[2]

We previously reported that the reagent prepared from (*S*)-proline and borane in a mole ratio of 1:7 reduced 10 mol-equivalents of acetophenone in tetrahydrofurane (THF) at room temperature to (*R*)-1-phenyletan-1-ol with 85 % enantiomeric excess (*ee*).[3] Brunel *et al.* found that better results could be obtained by applying catalytic amounts of (*S*)-proline in refluxing toluene (81–95 % *ee*), however, at room temperature the reaction yields (*R*)-1-phenylethan-1-ol in only 8 % *ee*.[4]

Economic reasons and chemical interest led us to investigate unfunctionalized amino acids-mediated borane reductions of ketones. A simple method of reduction of some representative ketones by means of valine-mediated borane[5] are described in this paper.

EXPERIMENTAL

All operations concerning air sensitive materials were carried out under Ar. Tetrahydrofurane was dried over 4 Å molecular sieves and distilled from sodium benzophenone ketyl prior to use. Acetophenone, 3,3-dimethyl-2-butanone, 3-methyl-2-butanone, 10 M borane-methyl sulfide complex, and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) were all obtained from Aldrich. (*S*)-Valine was obtained from Fluka and used without purification. Specific rotations were

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determined on a Perkin-Elmer 241 polarimeter. Analytical gas chromatography (GC) was carried out on a Hewlett-Packard 5890A gas chromatograph using SPB-5 capillary columns. The alcohols were purified by preparative GC on a Carbowax 20M column. The optical purities of alcohols were determined by analysis of MTPA esters of the corresponding alcohols.[7] In general terms the chiral reagent was prepared as follows and used *in situ* for reduction.

Typical experimental procedure

An oven dried 100 mL round-bottom flask equipped with a magnetic stirring bar and septum was cooled to room temperature in a stream of argon. Valine (0.82 g, 7 mmol) was transferred to the flask in a glove bag and THF was added (15 mL). Then, 1.4 mL of 10 M borane-methyl sulfide complex was added dropwise, from syringe, at a rate of 1 mL/min. After stirring for an additional 2.5 h, acetophenone (0.84 g, 7 mmol) in THF (1.4 M) was added in portions of 0.5 mL every 5 min, and the resulting reaction mixture was stirred for 1 h at room temperature. Then, 10 mL of aqueous 3 M NaOH was added. When the evolution of hydogen was complete, the aqueous layer was extracted with ether (2×10 mL), the combined organic phase dried over Na_2SO_4 and distilled. 1-Phenylethan-1-ol, bp 98 °C (20 mm Hg) was obtained (0.77 g, 91 % yield: 97 % glc purity). The optical rotation, after further purification by preparative GC, was estimated to be $[\alpha]_D = +34.27$ (neat) {lit. $[\alpha]_D = +42.85$ (neat)}[6] to reveal an excess of the (*R*)-enantiomer of 1-phenylethan-1-ol. The obtained alcohol was converted to MTPA ester. The ester was prepared using a literature procedure, and analyzed by GC chromatography to reveal an *ee* of 80 % in the (*R*)-isomer.[7]

(*S*)-Valine (0.73 g, 89 %) was recovered by adjusting the acidity of the remaining aqueous solution to pH 6.02, filtering off, washing with ethanol and ether, and drying.

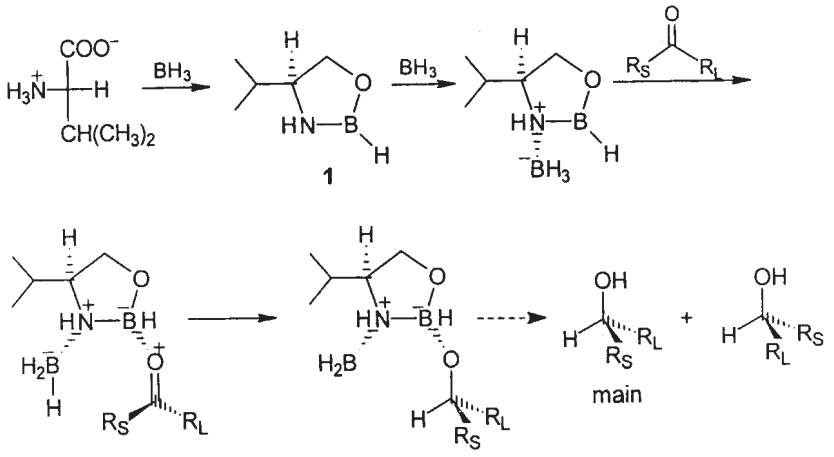
The other ketones were reduced in an analogous manner. The chemical yields and % *ee* of the alcohols are shown in Table II.

RESULTS AND DISCUSSION

In order to explore the influence of the reaction conditions on the reduction of acetophenone by means of valine-mediated borane the (*S*)-valine/BH_3/$PhCOCH_3$ mole ratio was varied, as summarized in Table I.The time of preparation of the reagent was 2.5 h.

$$R^1COR^2 + (S)\text{-Valine} + BH_3\cdot THF \rightarrow R^1CH(OH)R^2$$

When the mole ratio of valine, borane and acetophenone was 0.05:1:1, the conversion of the ketone to the corresponding alcohol, after 8 h, was very good (entry 1, Table I), but the optical yield was only 3 %. The total conversion of the ketone was accomplished with 0.1:0.7:1 valine/borane/ketone (entry 2, Table I), after only 10 min, and the *ee* was increased to 62 %. In the case of the proline-mediated borane reduction of acetophenone, with the same amino acid/borane/ketone mole ratio, a better *ee* of 1-phenylethan-1-ol (85 %) was obtained. Two additional sets of parallel experiments (3/4 and 5/1, Table I) clearly indicate that the mode of addition might be very important for achieving better enantioselectivity. The best mole valine/borane/acetophenone ratio was estimated to be 1:2:1, in the variant with a slower addition of ketone (entry 6, Table I). Itsuno *et al.* found that the reagent prepared from (*S*)-valinol and borane (1:1) in THF at 30 °C yielded 1-phenylethan-1-ol with 49 % *ee*.[8] In the phenyl *n*-alkyl series, this reagent led to higher enantioselectivity, as follows (% enantioselectivity in parentheses): methyl (49), ethyl (61), *n*-propyl (69),



Scheme 1.

n-butyl (73). It must be pointed out that the reagent prepared from valinol was totally soluble in THF. However, our reaction mixture was in the form of a suspension. In addition, 89 % of the starting valine could be recovered after reduction of the ketone. Therefore, the role of valine might be accounted for by the formation of oxazaborolidine **1** (Scheme 1), at least in catalytical amounts. The further reactions presumably occur in the following sequence: (a) complexation of borane to the ring nitrogen; (b) coordination of the ketone oxygen to the ring boron; (c) hydrogen transfer from the NBH_3^- unit to the carbonyl carbon *via* a six-membered cyclic transition state.[2a,4] The enantioselectivity observed in these reactions is thought to be controlled by steric factors. Corey *et al.* achieved excellent results in the reduction of acetophenone by using as the catalyst diphenyl-3-oxa-1-aza-2-borabicyclo [3.3.0] (prepared from prolinole).[2a] The steric factors of this reaction apparently force the large group (R_L) to occupy the less hindered exo face of the ring system.

We reduced several more reactive ketones than acetophenone (Table II). The asymmetric induction with this reagent was within the range of 36 % to 80 % *ee*. It is known that the selectivity decreases in the case of more reactive ketones. This could be overcome to some extent by changing the mode of addition. It was expected that the worst result would be obtained with 2-pentanone. It is interesting that Itsuno *et al.* reduced octan-2-one (as an example of a methyl *n*-alkyl ketone), with valinol-mediated borane (valinol/borane = 2:1), to octan-2-ol with only 10 % *ee*.[9]

Linney *et al.* found in the THF-borane reduction of propanone catalysed by the oxazaboralidine from proline that the transition structure for the ketone coordination is almost as high in energy as that for the rate-limiting hydride-transfer step.[10] Thus, for a better understanding of enantioselectivity it will be necessary to perform theoretical investigations of the complete catalytic cycle, including all transition structures.

CONCLUSION

This study concerning the valine-borane reduction of ketones gave the expected low enantioselective results in comparison with better reagents of more sophisticated structure.

TABLE I. Influence of the reaction conditions[a,b,c] on the reduction of acetophenone by means of valine-mediated borane

Entry	Valine/BH_3/$PhCOCH_3$ mole ratio	Reduction time h	Conversion of ketone %	% *ee*
1	0.05:1:1	8[d]	94	3
2	0.1:0.7:1	10 min[e]	100	62
3	1:1:1	8[d]	100	22
4	1:1:1	8[f]	100	70
5	1:2:1	8[d]	100	53
6.	1:2:1	1[g]	100	80

[a]All reactions were carried out in THF solution at room temperature. [b]The source of borane was $BH_3 \cdot SMe_2$. [c]The reagent preparation time was 2.5 h. [d]7 mmol of ketone was added during a 1 min period. [e]7 mmol of ketone in THF (1.4 M) was added during a period of 10 min. [f]7 mmol. of ketone in THF (1.4 M) was added in portions of 1.25 mL every 2 h . [g]7 mmol of ketone in THF (1.4 M) was added in portions of 0.5 mL every 5 min (main procedure).

TABLE II. Reduction of some ketones with (*S*)-valine-mediated borane[a,b,c,d]

Ketone	Yield isolated (and % *ee*) of alcohols
2-Pentanone	86 (36)
3-Methyl-2-butanone	82 (55)
3,3-Dimethyl-2-butanone	83 (64)
Acetophenone	91 (80)

[a]Valine/$BH_3 \cdot SMe_2$/ketone mole ratio = 1:2:1; [b]Reagent preparation time = 2.5 h; [c]Conversion of ketone = ~ 100 %; [d]In all cases the (*R*)-configuration of the alcohols was predominant based on the sign of rotation.

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ИЗВОД

РЕДУКЦИЈЕ КЕТОНА ПОМОЋУ ВАЛИН-МОДИФИКОВАНОГ БОРАНА

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Редуковани су ацетофенон, 3,3-диметил-2-бутанон, 3-метил-2-бутанон и 2-пентанон помоћу валин-модификованог-борана. Овај реагенс је припремљен од (*S*)-валина и боран-метил-сулфидног комплекса, у различитом моларном односу, употребљавајући тетрахидрофуран као растварач. Реакција редукције кетона се изводи на собној темпе-

ратури. Конверзија супстрата у алкохолни производ је потпуна, а принос изолованог производа дестилацијом износи 86–91 %, при чему (*R*)-конфигурација превлађује (80, 64, 55 и 36 % *ee*, респективно). Сматра се да је активна редукујућа компонента у облику оксазаборолидина.

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