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A STEREOSELECTIVE SYNTHESIS OF α,β-DIHYDROXY KETONES. AN ALDOL REACTION OF ENEDIOL-TYPE CYCLIC VINYLOXYBORANES

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α,β-Dihydroxy ketones are synthesized stereoselectively by the aldol reaction of 1,3,2-dioxaboroles, formed from α-hydroxy ketones and phenylboronic acid, and aldehydes.

During our continuous investigations on the streoselective construction of the framework of various sugar derivatives[1], the one-step preparation of α,β-dihydroxy carbonyl compounds from α-hydroxy carbonyls turned out to be a quite useful method for the synthesis of these polyoxygenated organic molecules. Though several reports[2] appeared in the aldol reaction of α-hydroxy esters, few investigation has been done for the utilization of α-hydroxy ketones[3].

We now wish to report a stereoselective aldol reaction of α-hydroxy ketones with aldehydes to synthesize α,β-dihydroxy ketones via enediol-type cyclic vinyloxyboranes, based on the knowledge of the vinyloxyboranes we have previously explored[4].

A toluene solution of 3-hydroxy-2-butanone (1) and phenylboronic acid was refluxed for 1h removing the water azeotrope[5], and 1,3,2-dioxaborole (2), an enediol-type cyclic vinyloxyborane, was obtained in 50% yield by distillation (bp 76°C/0.4mmHg) as shown in Scheme I. In this condensation reaction, endo-enediol (2) was the only product, and no exo-vinyloxyborane (3) was detected by NMR. The 1,3,2-dioxaborole (2), thus obtained, reacted readily with 1.0 equivalent of various aldehydes in tetrahydrofuran (THF) at 0°C to form the adducts, 1,3,2-dioxaborolanes (4 and 5), in good yield (Scheme II, Table I). When benzaldehyde was employed, the major isomer formed was determined to have cis-configuration concerning the phenyl and the methyl groups based on the NMR spectra assuming a large shielding effect of benzene ring on the cis-methyl group (major isomer δ 0.93, minor isomer δ 1.66 or 1.71 (One of these peaks corresponds to the acetyl protons.)). By analogy, the configuration of the main products of the aldol reaction of aliphatic aldehydes were considered to be cis.

As the solvent effect on the yield and the stereochemistry of the adducts (4 and 5) is rather small, various solvents such as toluene, petroleum ether, acetonitrile or methylene chloride are available in the present reaction.

Though ketones did not react with 2 at 0°C, at an elevated temperature, 2 added to cyclohexanone to form the spiro-adduct in moderate yield.

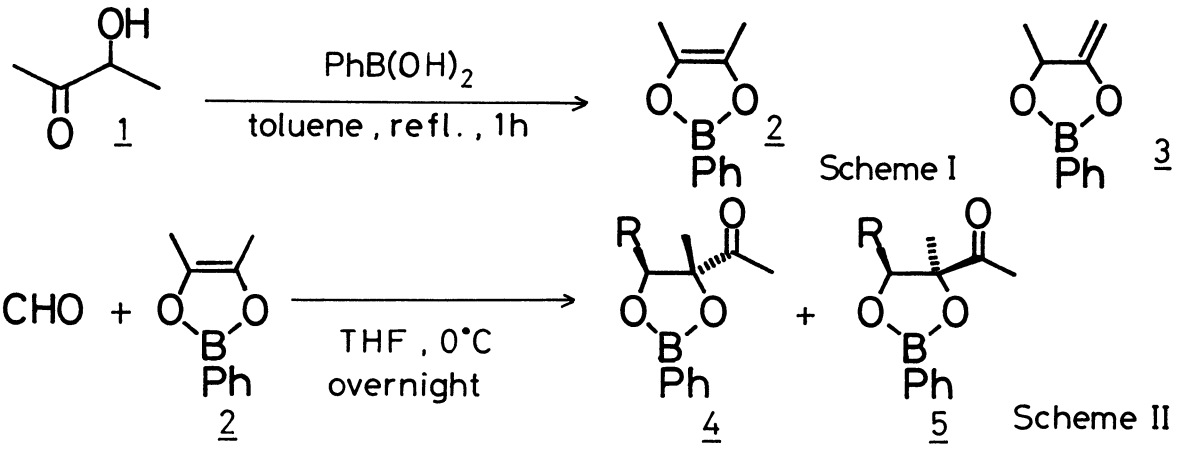
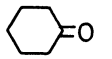


Table I The Addition Reaction of the 1,3,2-Dioxaborole to Aldehydes.

RCHO	yield (%)[a]	4:5[b]	NMR spectra($CDCl_3$, δ)[d]
PhCHO	90	4:1	0.93, 2.34
n-C_7H_{15}CHO	79	3:1	1.49, 2.25
Et_2CHCHO	87	7:1	1.52, 2.65
	44[c]	—	1.34, 2.29

a) All the products gave satisfactory 'H-NMR and IR spectra.
b) Determined by ^{13}C-NMR.
c) Reacted at room temperature.
d) Selected spectral data of the major isomers.

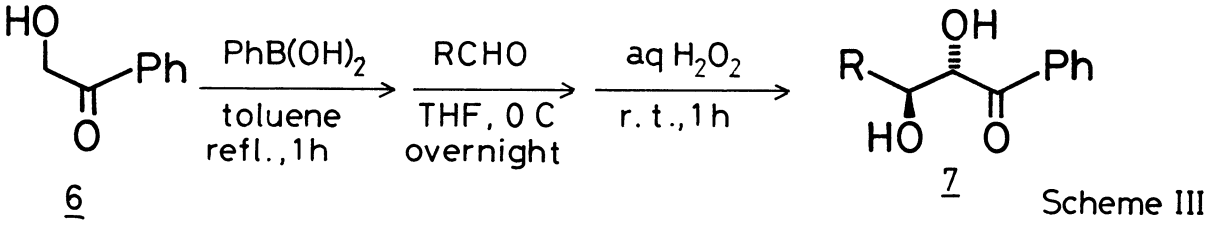


Table II The Aldol Reaction.

R	yield (%)[a]	diastereomer ratio	NMR Spectra($CDCl_3$, δ)[c]
Ph	95	8:1[b]	4.99(d, J=4Hz) 5.33(d, J=4Hz)
n-C_8H_{17}	quant.	>9:1	5.25(d, J=4Hz)
$PhCH_2CH_2$	81	>9:1	see text

a) All the products gave satisfactory NMR and IR spectra.
b) Each isomer was isolated.
c) Selected NMR spectral data of the major isomers.

1,3-Dioxaphosphole, prepared by the redutive treatment of 2,3-butanedione with trimethylphosphite, was already known to react with aldehydes to give 1,3-dioxaphospholanes[6]. Compared with the reaction, the present method has several synthetic advantages: 1) The enediol derivatives are synthesized from readily available α-hydroxy ketones: 2) Cis-adducts concerning two alkyl groups are obtained from 2, while trans-isomers result from the dioxaphosphole: 3) As will be seen later, the adducts are easily hydrolyzed under mild reaction conditions to give α,β-dihydroxy ketones.

Next, we studied the one-pot synthesis of α,β-dihydroxy ketones starting from an α-hydroxy ketone and aldehydes without isolating the intermediates. 2-Hydroxy-1-phenylethanone (6) was treated with phenylboronic acid in refluxing toluene for 1h, and after the removal of the solvent, a THF solution of aldehydes was added to react at 0°C overnight. Finally the mixture was treated with aqueous hydrogen peroxide to hydrolyze boronic esters and α,β-dihydroxy ketones (7) were isolated in good yields, which consisted almost exclusively of one isomer (Scheme III, Table II). The stereochemistry was determined based on the NMR spectrum of the intermediate. Namely, 1,3,2-dioxaborolane synthesized from benzaldehyde was found to have cis-configuration (major isomer δ 5.78, 6.08; minor isomer δ 5.44, 5.78), and was considered to afford an α,β-dihydroxy ketone with anti-configuration.

A typical procedure is described for the synthesis of (2R, 3R)- and (2S, 3S)-2,3-dihydroxy-1,5-diphenyl-1-pentanone; Under an argon atomosphere, a toluene (20 ml) solution of 2-hydroxy-1-phenylethanone (68 mg, 0.5 mmol) and phenylboronic acid (72 mg, 0.6 mmol) was refluxed for 1h removing the water azeotrope. After the solution was cooled, the solvent was evaporated under reduced pressure, and a THF (2 ml) solution of 3-phenylpropanal (34 mg, 0.25 mmol) was added to react overnight. The mixture was diluted with ethyl acetate and treated with aqueous hydrogen peroxide for 1h. Organic materials were extracted with ethyl acetate, and combined extracts were washed with brine and dried over $MgSO_4$. After the solvent was evaporated, (2R, 3R)- and (2S, 3S)-2,3-dihydroxy-1,5-diphenyl-1-pentanone (56 mg, 81%) was isolated by thin layer chromatography on silica gel.

Mp. 91°C (hexane-benzene recryst.). NMR ($CDCl_3$) δ 1.3-2.1 (2H, m), 2.4-2.8 (2H, m), 3.88 (1H, dt, J=9,4Hz), 5.16 (1H, d, J=4Hz), 3.4-5.1 (2H, broad), 6.7-8.3 (10H, m). IR (KBr) 1660, 3410 cm^{-1}. Found:C, 75.47; H, 6.62%. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

It should be noted that α,β-dihydroxy ketones are prepared stereoselectively by the aldol reaction of 1,3,2-dioxaboroles, formed in situ from α-hydroxy ketones and phenylboronic acid, and aldehydes.

A further synthetic investigation based on the useful reaction is now in progress.

References

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