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ASYMMETRIC HYDROGENATIONS OF N-PYRUVOYL-(S)-AMINO ACID ESTERS BY USING SODIUM BOROHYDRIDE. A SOLVENT EFFECT

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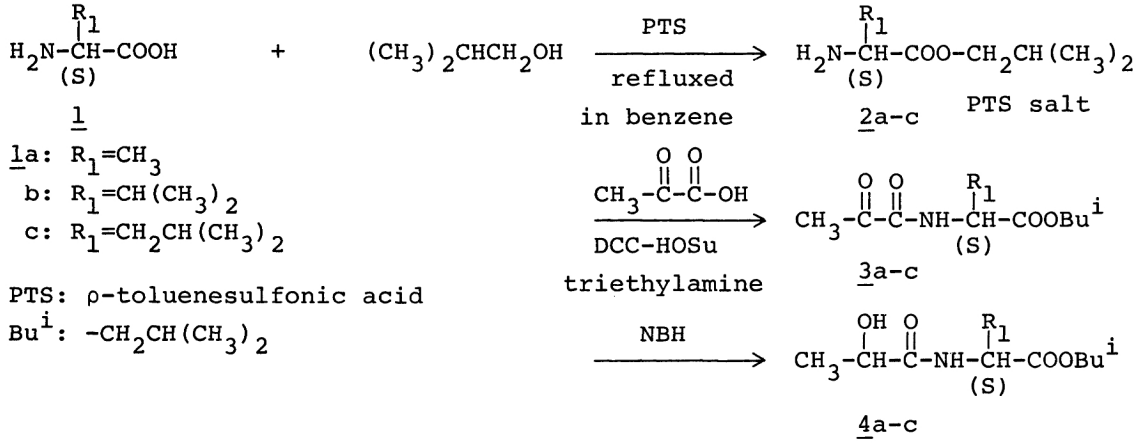
N-Pyruvoyl-(S)-amino acid isobutyl esters were hydrogenated with sodium borohydride(NBH) in several alcoholic solvents, and N-[(R)-lactoyl]-(S)-amino acid esters were obtained with diastereoisomeric purity of up to 44%. Significant solvent effect on the diastereoisomeric purity of the product was observed.

Stereochemistry in sodium borohydride(NBH) hydrogenations of chiral esters of α-keto acids have been investigated by several workers.[1-6] In those studies, the results of the hydrogenations seemed to be explained by a similar steric course as that described in Prelog's rule,[7] which was proposed as an empirical rule of addition reaction of Grignard reagent. However, little study[4,8] has been made on the NBH hydrogenation of chiral amides of α-keto acid and the steric course has not been discussed in detail. Recently, we have reported on the stereochemistry of the NBH hydrogenation of three chiral pyruvamides.[9] We concluded that the direction of the asymmetric induction was determined by the population of the stable conformers of the substrates in the solution.

In this paper, we wish to describe the stereochemistry in the NBH hydrogenation of N-pyruvoyl-(S)-amino acid esters(3a-c) using several alcoholic solvents. The amino acids used as the asymmetric center were (S)-alanine(1a), (S)-valine(1b), and (S)-leucine(1c). Substrates(3a-c) were prepared by the



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1a: $R_1=CH_3$
b: $R_1=CH(CH_3)_2$
c: $R_1=CH_2CH(CH_3)_2$

PTS: p-toluenesulfonic acid
Bu^i: $-CH_2CH(CH_3)_2$

2a-c

3a-c

4a-c

Scheme 1. Asymmetric hydrogenation of N-Pyruvoyl-(S)-amino acid isobutyl esters with sodium borohydride.

coupling of pyruvic acid and the corresponding (S)-amino acid isobutyl esters[10] (2a-c) with dicyclohexylcarbodiimide(DCC) in the presence of N-hydroxysuccinimide (HOSu) (Scheme 1). After the usual coupling reaction, the resulting crude oily products were purified by employing silica gel flash chromatography[11] (eluent: ethyl acetate - hexane (1:10)). The specific rotations were measured, and all of the elemental analyses agreed with the theoretical values. Substrates 3a-c(20 mg, 0.1 mmol) were dissolved in 3 ml of solvents[methanol(MeOH), ethanol(EtOH), 2-propanol(i-PrOH), 2-methyl-2-propanol(t-BuOH), and 2-methyl-2-butanol(t-AmylOH)], and were hydrogenated by addition of NBH(10 mg, 0.26 mmol) at 30 °C for 90 min. After decomposition of the boron complex by addition of 1 mol dm^{-3} HCl, the reaction mixtures were extracted with ethyl acetate and the solutions were evaporated in vacuo to dryness. The residue was redissolved in chloroform. The chemical yields were determined by means of gas-liquid chromatography(column: Silicone gum SE-52, 4 m x 3 mm i.d.). And the diastereoisomeric purities were determined also by the gas chromatographic separation of the diastereomeric lactamides. Ten seconds after injection of the pyridine solution of trimethylsilylimidazole(TMS-Im), the chloroform solution of the hydrogenated products was applied into the gas chromatographic equipped with the same column

Table 1. NBH Reduction of N-pyruvoyl-(S)-amino acid esters.

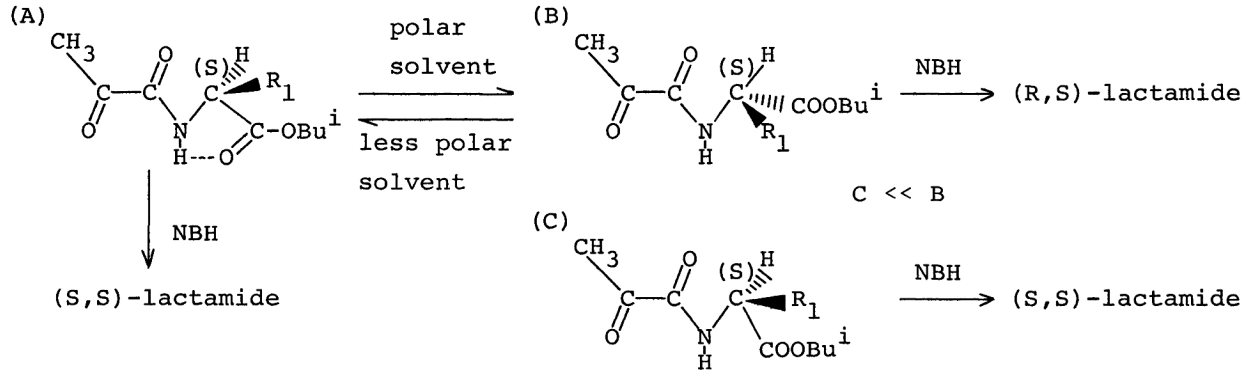
Substrate	$[\alpha]_D^{26}$ a) (EtOH)	Confign.b)	Solvent	Confign.c)	Yield(%)	D.p.(%)d)
3a	-36	S	MeOH	R	42	42
(oil)	(c, 1.2)		EtOH	R	41	39
			i-PrOH	R	31	43
			t-BuOH	S	25	11
			t-AmylOH	S	13	17
3b	-16	S	MeOH	R	65	24
(oil)	(c, 1.3)		EtOH	R	43	17
			i-PrOH	R	36	23
			t-BuOH	S	21	20
			t-AmylOH	S	22	24
3c	-15	S	MeOH	R	40	36
(oil)	(c, 1.6)		EtOH	R	43	38
			i-PrOH	R	36	44
			t-BuOH	S		20
			t-AmylOH	S	10	28

a) Optical rotation of substrate.
b) Configuration of amino acid.
c) Configuration of newly formed lactoyl moiety.
d) Diastereoisomeric purity = [(R,S)-(S,S)]/[(R,S)+(S,S)] x 100
(or [(S,S)-(R,S)]/[(R,S)+(S,S)] x 100)

(SE-52).[12] The diastereomeric lactamides were clearly separated with this method, and each chromatographic area was integrated with a Hitachi 834-30 chromatoprocessor. The retention times of diastereomeric lactamide 4a were 37.5 min (S,S) and 38.3 min (R,S).

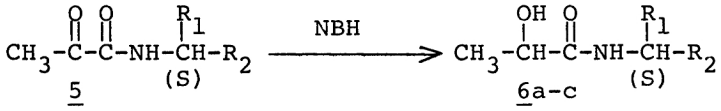
In MeOH, EtOH, and i-PrOH, each substrate gave N-[(R)-lactoyl]-(S)-amino acid ester[(R,S)-lactamide]. Hydrogenation of substrate 3c in i-PrOH gave (R,S)-lactamide with diastereoisomeric purity of 44%. On the other hand, when t-BuOH and t-AmylOH were used as the solvent, each substrate gave N-[(S)-lactoyl]-(S)-amino acid ester[(S,S)-lactamide] in excess(up to 28%) over (R,S)-lactamide, and clear inversion of configuration of the hydrogenation products was observed.

The significant solvent effect could be explained by the possible intramolecular hydrogen bonding between the H of the amide group and the O of the carboxylate group of the substrate in less polar solvents(t-BuOH and t-AmylOH). In polar solvents such as MeOH, EtOH, and i-PrOH, the hydrogen bonding described above is weak, and the populatiion of conformer B and C(C << B)[9] of the substrate would be larger than conformer A as shown in Scheme 2. If this is the case,



Scheme 2. Possible steric course of the NBH hydrogenation of N-pyruvoyl-(S)-amino acid ester.

coformer B would predominate the asymmetric induction of the hydrogenation reaction, and (R,S)-lactamide would be obtained in excess over (S,S)-lactamide. In less polar solvents such as t-BuOH or t-AmylOH, the population of conformer A would increase by the intramolecular hydrogen bonding. The increase of conformer A



5a: R_1=CH_3, R_2=Ph
b: R_1=C_2H_5, R_2=Ph
c: R_1=CH_3, R_2=Naph

Scheme 3. NBH Hydrogenation of simple chiral pyruvamide.

would increase the formation of (S,S)-lactamide by the NBH hydrogenation.

In the NBH hydrogenation of simple pyruvamides 5a-c containing optically

activebenzylic amines(Scheme 3),[9] no marked solvent effect was observed as in the hydrogenation of substrate 3a-c. The results could support the intramolecular hydrogen bonding mechanism described above. Because the pyruvamides 5a-c do not contain carboxylate groups necessary in the formation of intramolecular hydrogen bonding to fix the conformation of the chiral moiety of the substrate, substrates 5a-c gave (R,S)-lactamide in excess in all solvents.

The clear inversion of the configuration of the products obtained by NBH hydrogenation of N-pyruvoyl-(S)-amino acid esters suggests that intramolecular hydrogen bonding of the substrate might be influenced by whether polar or less polar solvents were used.

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