Asymmetric Reduction of Chiral Pyruvamide with Sodium Borohydride

Toratane Munegumi and Kaoru Harada*

Department of Chemistry, University of Tsukuba, Sakura-Mura, Niihari, Ibaraki 305

(Received August 2, 1982)

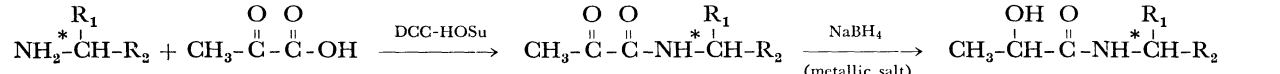
Several amides of pyruvic acid with (*S*)-amines were reduced with sodium borohydride (NBH) in several alcohols and *N*-[(*R*)-lactoyl]-(*S*)-amines were obtained in excess. When the reductions were carried out in methanol or ethanol in the presence of metallic salt, *N*-[(*S*)-lactoyl]-(*S*)-amines were obtained in asymmetric yields up to 22%.

Many studies[1-4] on the homogeneous reduction of chiral esters of α-keto acids have been performed, while few studies[4] on that of chiral α-keto acid amides have been reported. In the former case, an empirical rule was found between the absolute configuration of the chiral source and that of the product. This rule is called the Prelog's rule[2] and has been applied to the determination of the absolute configuration of chiral alcohols. In the latter, enough data have not been obtained to establish such a rule. The reduction of *N*-[(*S*)-α-methylbenzyl]benzoylformamide with sodium borohydride (NBH) was carried out by Mitsui and Kanai,[4] and (*R*)-mandelic acid was obtained in optical purity of 5.1%. According to the stereochemical consideration using a molecular model of the substrate, it seems unlikely that the benzoyl and the carbamoyl group coexist on the same plane, because of the steric repulsion between the phenyl and the carbamoyl group. In such a case the discussion on the steric course of the NBH reduction is more difficult compared with that of the esters.

In this paper, the NBH reduction of chiral amides of pyruvic acid, in which the above-stated steric repulsion is smaller than that of benzoylformamide, is described. The chiral amines used are (*S*)-α-methylbenzylamine, (*S*)- and (*R*)-α-ethylbenzylamine, and (*S*)- and (*R*)-1-(1-naphthyl)ethylamine. The substrates **2a**—**c** and **2b′**—**c′** were prepared by the condensation of the chiral amines and pyruvic acid with dicyclohexylcarbodiimide and *N*-hydroxysuccinimide (Fig. 1). The solvent used in the NBH reduction were methanol, ethanol, 2-propanol, *t*-butanol. The chemical and asymmetric yields of the products were determined by gas chromatographic analysis. The reduction of the substrate was also carried out in methanol and ethanol in the presence of a metallic salt.

Experimental

All the melting points were uncorrected. Optical rotations were measured with a JASCO DIP-181 Digital Polarimeter. All the GC analyses were carried out with a Hitachi 163 gas chromatograph, and the peaks on the chromatogram were integrated with a Hitachi 834-30 chromatoprocessor.



1

1a: $R_1=CH_3$, $R_2=Ph$ (*S*)
1b: $R_1=C_2H_5$, $R_2=Ph$ (*S*)
1b′: $R_1=C_2H_5$, $R_2=Ph$ (*R*)
1c: $R_1=CH_3$, $R_2=Naph$ (*S*)
1c′: $R_1=CH_3$, $R_2=Naph$ (*R*)

2

2a: $R_1=CH_3$, $R_2=Ph$ (*S*)
2b: $R_1=C_2H_5$, $R_2=Ph$ (*S*)
2b′: $R_1=C_2H_5$, $R_2=Ph$ (*R*)
2c: $R_1=CH_3$, $R_2=Naph$ (*S*)
2c′: $R_1=CH_3$, $R_2=Naph$ (*R*)

3

3a: $R_1=CH_3$, $R_2=Ph$ (*S*)
3b: $R_1=C_2H_5$, $R_2=Ph$ (*S*)
3b′: $R_1=C_2H_5$, $R_2=Ph$ (*R*)
3c: $R_1=CH_3$, $R_2=Naph$ (*S*)
3c′: $R_1=CH_3$, $R_2=Naph$ (*R*)

Fig. 1. (*S*) or (*R*): Absolute configuration of chiral amine. **3a**—**c** and **3b′**—**c′**: Diastereomer mixture.

Table 1. Elementary analyses of the substrates

Substrate	Yield %	Mp θ_m/°C	Optical rotation (ethanol)		Elementary analysis C (%)	H (%)	N (%)
2a	16	76—77	$[\alpha]_D^{16}$ −116° (*c* 1.0)	Found	69.91	6.85	7.31
				Calcd ($C_{11}H_{13}NO_2$)	69.09	6.85	7.32
2b	16	84.5—85.5	$[\alpha]_D^{14}$ −117° (*c* 1.0)	Found	70.31	7.32	6.80
				Calcd ($C_{12}H_{15}NO_2$)	70.22	7.36	6.82
2b′	19	84—85	$[\alpha]_D^{18}$ +122° (*c* 1.1)	Found	70.29	7.40	6.80
				Calcd ($C_{12}H_{15}NO_2$)	70.22	7.36	6.82
2c	33	(Oil)	$[\alpha]_D^{24}$ −3.6° (*c* 1.0)	Found	73.94	6.30	5.88
				Calcd ($C_{15}H_{15}NO_2$)	74.66	6.26	5.80
2c′	29	(Oil)	$[\alpha]_D^{18}$ +3.1° (*c* 1.0)	Found	74.20	6.61	6.09
				Calcd ($C_{15}H_{15}NO_2$)	74.66	6.26	5.80

Table 2. Retention times of O-TFA lactamides

Lactamide	Retention time/min		Separation factor
	First peak	Second peak	
3a	13.2(*R,S*)[a]	13.8(*S,S*)	1.045
3b′	16.8(*R,R*)	17.6(*S,R*)	1.017
3c′	28.8(*R,R*)	29.1(*S,R*)	1.010

a) ( ): Configuration of diastereomeric lactamide.

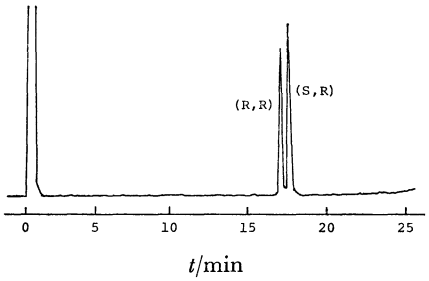


Fig. 2. Typical gas chromatographic peaks of O-TFA derivatives of lactamide **3b′**.

*N-[(S)-α-Methylbenzyl]pyruvamide(**2a**) and Other Substrates **2b**—**c** and **2b′**—**c′**.* To a cooled ethyl acetate solution (200 ml), in which pyruvic acid(5.00 g, 0.0567 mol), (*S*)-α-methylbenzylamine(6.87 g, 0.0567 mol), and *N*-hydroxylsuccinimide(7.84 g, 0.0681 mol) were dissolved, dicyclohexylcarbodiimide(12.9 g, 0.0624 mol) was added. The reaction mixture was stirred for 2 h at 0 °C and for 12 h at room temperature and filtered. The filtrate was extracted with three 100 ml portions of 1 mol dm^{-3} HCl, three 100 ml portions of an aquous $NaHCO_3$ solution(10%), and three 100 ml portions of a saturated aquous NaCl solution. The ethyl acetate layer was dried with anhydrous magnesium sulfate. The solvent was removed *in vacuo*, and a crude oily product was obtained. This product was purified by means of silica gel flash chromatography[5] (column: 15 cm×4 cm i.d., eluting solvent: ethyl acetate–hexane(1:5)).

The other four pyruvamide were prepared in a similar method. The optical rotations, elementary analyses, yields and melting points of the products are summarized in Table 1.

*NBH Reduction of the Substrates **2a**—**c** and **2b′**—**c′** without Metallic Salt.* Substrates **2a**—**c** and **2b′**—**c′** (20 mg, 1×10^{-4} mol) were dissolved in a solvent(methanol, ethanol, isopropanol, and *t*-butanol), and were reduced by NBH (10 mg, 2.6×10^{-4} mol) at 30 °C for 90 min. After the reduction was over, the boron complex was decomposed by addition of 1 mol dm^{-3} HCl (2 ml). An aquous solution (20 ml) of saturated sodium chloride was added in the reaction mixture, and the resulted solution was extracted by three 20 ml portions of ethyl acetate. After drying the ethyl acetate layer, the solvent was removed and an oily product was obtained. Both the reaction yield and the ratio of each diastereomer were determined by gas chromatography.

*NBH Reduction of Substrate **2a**—**c** and **2b′** with Metallic Salt.* The NBH reduction with a metallic salt(magnesium chloride or zinc chloride) was carried out by addition of NBH (10 mg, 2.6×10^{-4} mol) to 3 ml of a methanol or an ethanol solution of the substrate(20 mg, 1×10^{-4} mol) and the metallic salt(1×10^{-4} mol). The amount of the metallic salt in the reaction mixture of the substrate **2b′** was changed from 10 mg (1×10^{-4} mol) to 100 mg(1×10^{-3} mol). The reaction conditions, the work-up of the reaction mixture, and the analysis of the product was carried out in a similar manner as in the reduction without metallic salt.

Determination of the Reaction Yield. The oily product obtained by reduction was redissolved in chloroform(0.5 ml), and a part of the solution was injected into a gas chromatograph with a stainless column(4 m×3 mm i.d.), which was filled with Chromosorb W AW DMCS coated with 5% SE-52. Column temperature was raised from 100 °C to 250 °C at a rate of 5 °C per minute. The flow rate of carrier gas(nitrogen) was 39 ml/min and the temperature of injection port was 300 °C. The detector was flame-ionization detector.

Determination of the Diastereoisomeric Purity. TMS-Im Method:[6] Ten seconds after the injection of the pyridine solution of *N*-trimethylsilylimidazole, a 3 μl portion of the chloroform solution of the product was applied into the gas chromatograph equipped with the same column(SE-52) as described in the previous section. The column temperature was raised from 100 °C to 250 °C at a rate of 2 °C per minute. The other analytical conditions were same as those of the determination of the chemical yield. The diastereomeric lactamides were separated, and the diastereoisomeric purity was determined from the ratio of the integrated values of the diastereomeric peaks. This TMS-Im method was applied to the analyses of the entries 1—4, 6—9, 12—20, and 26—28.

TFA Method: To the NBH reduction product, trifluoroacetic acid (3 ml) saturated with HCl was added, and the resulting solution was refluxed for 15 min. The residue obtained by the evaporation of trifluoroacetic acid was redissolved in chloroform. The chloroform solution was injected into the gas chromatograph equipped with a glass capillary column(25 m×0.3 mm i.d.) coated with a chiral stationary phase, Chirasil-Val.[7] The O-TFA derivatives of the two diastereomers of each lactamide were separated on the chromatogram. The column temperature was raised from 90 °C to 180 °C at 4 °C per minute. The temperature of the injection port was 250 °C. This method was applied to the analyses of the reactions of entries 5, 10, 11, and 21—25 in Table 3 or 4. The retention times of O-TFA derivatives of the diastereomeric lactamides(**3a**, **3b′**, and **3c′**) are summarized in Table 2, and typical chromatographic peaks of O-TFA derivatives of lactamide **3b′** are shown in Fig. 2. The analyzed asymmetric yields were found to be similar by both TMS-Im and TFA methods.

Results and Discussion

The results of the NBH reduction without and with a metallic salt are shown in Tables 3 and 4, respectively.

In the NBH reduction without metallic salt, *N*-[(*R*)-lactoyl]-(*S*)-amine ((*R,S*)-lactamide) was obtained in excess over *N*-[(*S*)-lactoyl]-(*S*)-amine ((*S,S*)-lactamide) from the pyruvamide in which the chiral source was (*S*)-amine. The asymmetric yields were equal to or less than 11%, and substrate **2a** gave the lowest values. In the NBH reduction with metallic salts, the substrate in which the chiral source was (*S*)-amine gave (*S,S*)-lactamide in excess. Thus, the configuration of the lactoyl moiety of the resulting lactamide was reversed to the opposite structure in the reduction with metallic salts. When magnesium chloride was added to the reaction mixture, the asymmetric yield of (*R,R*)-lactamide increased with the increase of the concen-

TABLE 3. NBH REDUCTION WITHOUT METALLIC SALT

Entry	Substrate	Configuration[a]	Solvent	Yield/%	*Dp*/%[b]	Configuration[c]
1	**2a**	*S*	MeOH	39	0	
2	**2a**	*S*	EtOH	45	1	*R*
3	**2a**	*S*	*i*-PrOH	40	0	
4	**2a**	*S*	*t*-BuOH	40	1	*R*
5	**2a**	*S*	MeOH	58	0	
6	**2b**	*S*	MeOH	39	2	*R*
7	**2b**	*S*	EtOH	48	11	*R*
8	**2b**	*S*	*i*-PrOH	48	7	*R*
9	**2b**	*S*	*t*-BuOH	41	8	*R*
10	**2b′**	*R*	MeOH	58	3	*S*
11	**2b′**	*R*	EtOH	39	9	*S*
12	**2c**	*S*	MeOH	46	2	*R*
13	**2c**	*S*	EtOH	45	10	*R*
14	**2c**	*S*	*i*-PrOH	47	7	*R*
15	**2c**	*S*	*t*-BuOH	54	7	*R*
16	**2c′**	*R*	EtOH	41	10	*S*

a) Configuration of chiral amine. b) Diastereomeric purity. c) Configuration of newly formed asymmetric moiety.

TABLE 4. NBH REDUCTION WITH METALLIC SALT

Entry	Substrate	Configuration[a]	Solvent	Metal(mg)	Yield/%	*Dp*/%[b]	Configuration[c]
17	**2a**	*S*	MeOH	$MgCl_2$(10)	48	7	*S*
18	**2a**	*S*	EtOH	$MgCl_2$(10)	50	15	*S*
19	**2a**	*S*	MeOH	$ZnCl_2$(14)	57	3	*S*
20	**2b**	*S*	MeOH	$MgCl_2$(10)	49	19	*S*
21	**2b′**	*R*	EtOH	$MgCl_2$(10)	51	16	*R*
22	**2b′**	*R*	EtOH	$MgCl_2$(20)	43	18	*R*
23	**2b′**	*R*	EtOH	$MgCl_2$(50)	36	21	*R*
24	**2b′**	*R*	EeOH	$MgCl_2$(100)	27	22	*R*
25	**2b**	*S*	MeOH	$ZnCl_2$(14)	56	22	*S*
26	**2c**	*S*	MeOH	$MgCl_2$(10)	45	18	*S*
27	**2c**	*S*	EtOH	$MgCl_2$(10)	52	19	*S*
28	**2c**	*S*	MeOH	$ZnCl_2$(14)	70	20	*S*

a) Configuration of chiral amine. b) Diastereomeric purity. c) Configuration of newly formed asymmetric moiety.

tration of magnesium chloride in the reaction mixture (entries 21—24 in Table 4).

From these results, the conformation of the substrate in the solution and the steric course of the NBH reduction could be discussed as follows. Because of the electrostatic repulsion between the two carbonyl groups in the molecule, these carbonyl groups and the N–H bond should be on the same plane. Therefore, the asymmetric induction in the reduction without metallic salts could be discussed only by the consideration of the conformation of the chiral amine moiety.

The conformation of the pyruvamide in solution could be a mixture of the two conformers A and B shown in Fig. 3. The (*R,S*)-lactamide is formed in excess from conformer A, and the (*S,S*)-lactamide from conformer B in excess. Therefore, the observed asymmetric yield would be interpreted as the combined asymmetric induction of the reduction of each conformer. Since conformer A is more stable than conformer B, the (*R,S*)-lactamide could be formed in excess over the (*S,S*)-lactamide through the reduction. The X-ray crystallographic study[8,9] and the NMR measurement[10] of similar amides indicate that conformer A is more stable than conformer B. On the other hand, the asymmetric yield of the reduction of substrate **2b** was larger than that of **2a**. This could be explained by the steric repulsion between the ethyl group in the chiral source and the carbonyl group of the amide. Thus, the population of conformer B

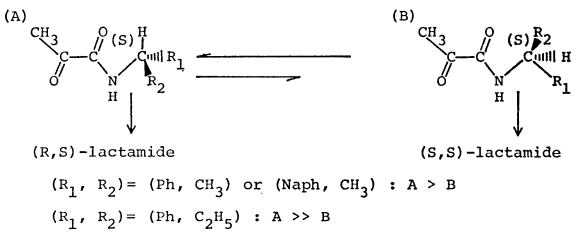


Fig. 3. Steric courses of the reduction without metallic salt.

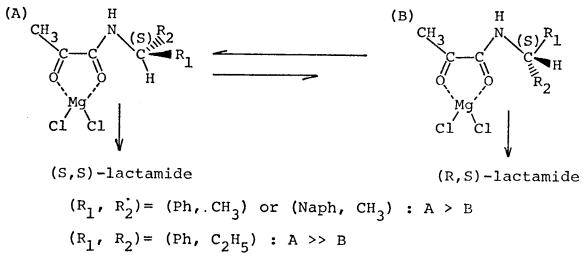


Fig. 4. Steric courses of the reductions with metallic salt.

is much smaller than that of conformer A as shown in Fig. 3, and the reduction of conformer A governs the asymmetric yield of the whole reaction. In the reduction of substrate **2c**, the asymmetric yield would be larger than the reduction of substrate **2a**, because of the difference in the bulkiness between the naphthyl and phenyl groups in substrates **2a** and **2c**.

The reduction with metallic salts may be explained in terms of the formation of a chelated substrate. The two carbonyl groups in the substrate could coordinate to the metallic salt and be fixed weakly in a *s*-cis conformation as shown in Fig. 4. And the asymmetric induction could be determined by the conformation of the asymmetric moiety of the substrate. The most preferred conformation could be that where the C–H bond of the asymmetric moiety is on the same plane with the chelated part of the substrate (Fig. 4). The hydrogenation of the substrate resulted in the formation of the (*S*,*S*)-lactamide. Thus, the configuration of the lactoyl moiety of the product ((*S*,*S*)-lactamide) reversed to the opposite structure from that obtained in the NBH reduction without metallic salt. The asymmetric yields of the NBH reduction with metallic salt were larger than those without metallic salt, possibly because of the fixation of the conformation by the chelation of the two carbonyl groups with the metallic salt.

References

1) V. Prelog, M. Wilhelm, and D. B. Bright, *Helv. Chim. Acta*, **37**, 221 (1954).
2) S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, **1961**, 168.
3) M. S. Kubitscheck and W. A. Bonner, *J. Org. Chem.*, **26**, 2194 (1961).
4) S. Mitsui and A. Kanai, *Nippon Kagaku Zasshi*, **86**, 627 (1965).
5) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
6) T. Munegumi, S. Nomoto, and K. Harada, *J. Chromatogr.*, **237**, 469 (1982).
7) H. Frank, G. J. Nicolson, and E. Bayer, *J. Chromatogr.*, **146**, 197 (1978).
8) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **41**, 801 (1976).
9) A. T. Hagler, L. Leiseroruitz, and M. Tuval, *J. Am. Chem. Soc.*, **98**, 4600 (1976).
10) G. Helmchen, R. Ott, and K. Sauber, *Tetrahedron Lett.*, **1972**, 3873.