Monatshefte für Chemie 123, 565 – 570 (1992)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

5-Substituted (5*S*)-Imidazolidin-4-ones as Effective Chiral Auxiliary for Hydrogenation of α-Keto Amides

Igor Solodin

Institute of Organic Synthesis, Latvian Academy of Sciences 226006-Riga, Latvia

Summary. The title chiral auxiliary was used for asymmetric catalytic hydrogenation of amides derived from phenylglyoxylic acid to give mandelamides with high diastereoselectivity (diastereoisomeric excess, d.e. up to 96%).

Keywords. Asymmetric hydrogenation; Chiral auxiliary; Imidazolidin-4-one; α-Keto Amide.

5-Substituierte (5*S*)-Imidazolidin-4-one als effektive chirale Hilfssubstanzen bei der Hydrierung von α-Ketoamiden

Zusammenfassung. Die asymmetrische katalytische Hydrierung von Phenylglyoxalsäureamiden liefert bei Verwendung der im Titel genannten chiralen Hilfssubstanz Mandelsäureamide mit hoher Diastereoselektivität (diastereomerer Überschuß, d.e. bis zu 96%).

Introduction

Derivatives of optically active α-hydroxy acids are versatile building blocks for the synthesis of various natural products [1]. Diastereoselective reduction of α-keto acids derivatives bearing appropriate chiral auxiliary with complex metal hydrides and hydrogenation over metallic catalysts is the conventional route to optically active α-hydroxy acids [2]. Application of nitrogen containing heterocycles as the chiral auxiliary (proline [3, 4] *trans*-2,5-disubstituted pyrrolidines [5]) seems to be a very promising approach due to the well-known planarity of the amide group and, consequently, the lower number of possible conformers in the transition state as compared to the chiral α-keto esters. We have communicated [6] the high stereodifferentiating ability of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one [7] as chiral auxiliary in reduction of amides derived from phenylglyoxylic acid via fluoride ion-induced hydrosilylation. In the present communication the reduction of chiral amides (5*S*)-**3** derived from 5-substituted (5*S*)-imidazolidin-4-ones (5*S*)-**2** and phenylglyoxylic acid with sodium borohydride and hydrogenation over Pd on carbon and Ni-Raney is described.

Results and Discussion

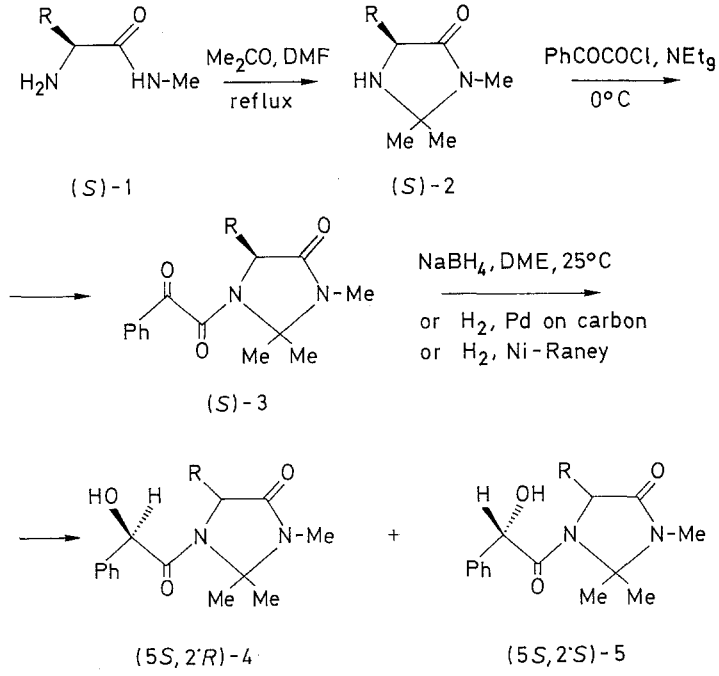
Chiral heterocycles (5*S*)-**2** were prepared by reacting natural (*S*)-α-amino acids N-methyl amides [8] and acetone (Scheme 1) in dimethylformamide under reflux with a good condenser. The subsequent

Table 1. Diastereoisomeric ratios of α-hydroxy amides **4** and **5**

Products[a]	R	Reduction with $NaBH_4$	Catalytic hydrogenation over Pd-C	over Ni-Raney
(2′*R*)-**4a**:(2′*S*)-**5a**	*Me*	77:23	93:7	85:15
(2′*R*)-**4b**:(2′*S*)-**5b**	Me_2CHCH_2	90:10	98:2	93:7
(2′*R*)-**4c**:(2′*S*)-**5c**	$PhCH_2$	90.5:9.5[b]	87:13	90:10

[a] Always-(5*S*)
[b] See Ref. [6]

N-acylation with phenylglyoxylic acid chloride [9] gives α-keto amides (5*S*)-**3**. Reduction of (5*S*)-**3** with sodium borohydride or hydrogenation over Pd-C or Ni-Raney gives a mixture of α-hydroxy amides (5*S*, 2′*R*)-**4** and (5*S*, 2′*S*)-**5** in good yields with a considerable excess of one of the diastereoisomers. Diasteroselectivities of reduction and hydrogenations are summarised in Table 1. Diastereoisomeric α-hydroxy amides (5*S*, 2′*R*)-**4** and (5*S*, 2′*S*)-**5** are resolved by preparative high performance liquid chromatography (Table 2).



1-5	R
a	Me
b	CH_2CHMe_2
c	CH_2Ph

Scheme 1

The direction of asymmetric induction in these reactions was established by hydrolysis of the predominant diastereoisomer (5*S*, 2′*R*)-**4** to mandelic acid and comparing the sign of optical rotation with literature data [10]. The rate of hy-

Table 2. Physico-chemical properties of compounds **2**–**5**

Product	R	Yield (%)	M.p. (°C)	Molecular formula[a]	$[\alpha]_D^{25}$ (*c*) *Et*OH	IR solvent: $\nu_{C=O}$ (cm^{-1})	^1H–NMR ($CDCl_3$ / *TMS*) δ (ppm), *J* (Hz)
2a	*Me*	89	63	$C_7H_{14}N_2O$ (142.2)	+10.5° (4.95)	nujol: 1665	1.32 (s, 3H, C^2-CH_3), 1.41 (d, 3H $J=7$, C^5-CH_3), 1.43 (d, 3H, $J=3$, C^2-CH_3), 1.91 (br s, 1H, NH), 2.80 (s, 3H, NCH_3), 3.55 (q, 1H, $J=7$, C^5H)
2b	Me_2CHCH_2	91	oil	$C_{10}H_{20}N_2O$ (184.3)	−9.6° (2.60)	film: 1695	0.93 and 1.00 (2d, 3H, $J=3$, $CH_3-CH-CH_3$), 1.31 and 1.42 (2s, 3H, $CH_3-C^2-CH_3$), 1.55–2.11 (m, 4H, CH_2-CH, NH), 2.80 (s, 3H, NCH_3), 3.37–3.60 (m, 1H, C^5H)
2c[b]	$PhCH_2$	82	–	–	–	–	–
3a	*Me*	70	oil	$C_{15}H_{18}N_2O_3$ (274.3)	+83.9° (2.97)	$CHCl_3$: 1660, 1700	1.29 (d, 3H, $J=7$, C^5-CH_3), 1.84 (s, 6H, $CH_3-C^2-CH_3$), 2.91 (s, 3H, NCH_3), 4.40 (q, 1H, $J=7$, C^5H), 7.35–8.11 (m, $5H_{arom}$)
3b	Me_2CHCH_2	75	103	$C_{18}H_{24}N_2O_3$ (316.4)	+166.2° (5.05)	$CHCl_3$: 1655, 1700	0.60 and 0.71 (2d, 3H, $J=7$, $CH_3-CH-CH_3$), 0.89–1.78 (m, 3H, $CH-CH_2$), 1.84 (s, 6H, $CH_3-C^2-CH_3$), 2.89 (s, 3H, NCH_3), 4.29–4.53 (m, 1H, C^5H), 7.22–8.15 (m, $5H_{arom}$)
3c[b]	$PhCH_2$	72	–	–	–	–	–
4a	*Me*	85[c] 96[d] 97[e]	oil	$C_{15}H_{20}N_2O_3$ (276.3)	−7.7° (3.37)	$CHCl_3$: 1655, 1705	1.60 (d, 3H, $J=7$, C_5-CH_3), 1.69 (d, 3H, $J=9$, C^2-CH_3), 1.95 (s, 3H, C^2-CH_3), 2.78 (s, 3H, NCH_3), 3.80 (q, 1H, $J=7$, C^5H), 4.62 (br s, 1H, OH), 5.13 (s, 1H, CH–OH), 7.29 (s, $5H_{arom}$)
5a	*Me*		oil		+21.2° (0.76)	$CHCl_3$: 1655, 1705	0.98 (d, 3H, $J=7$, C^5-CH_3), 1.73 and 1.80 (2s, 3H, $CH_3-C^2-CH_3$), 2.83 (s, 3H, NCH_3), 3.95 (br s, 1H, OH), 4.33 (q, 1H, $J=7$, C^5H), 5.11 (s, 1H, **CH**–OH), 7.29 (s, $5H_{arom}$)
4b	Me_2CHCH_2	80[c] 95[d] 96[e]	oil	$C_{18}H_{26}N_2O_3$ (318.4)	+22.9° (4.52)	$CHCl_3$: 1660, 1705	0.98 and 1.05 (2d, 3H, $CH_3-CH-CH_3$), 1.62 and 1.75 (2s, 3H, $CH_3-C^2-CH_3$), 1.69–1.95 (m, 3H, $CH-CH_2$), 2.77 (s, 3H, NCH_3), 3.69–3.93 (m, 1H, C^5H), 4.55 and 5.11 (AB, $J=7$, CH–OH), 7.31 m(s, $5H_{arom}$)
5b	Me_2CHCH_2		oil		+32.9° (2.47)	$CHCl_3$: 1660, 1705	0.42 and 0.79 (2d, 3H, $CH_3-CH-CH_3$), 0.89–1.56 (m, 3H, $CH-CH_2$), 1.75 and 1.82 (2s, 3H, $CH_3-C^2-CH_3$), 2.84 (s, 3H, NCH_3), 3.73 (br s, 1H, OH), 4.35–4.47 (m, 1H, C^5H), 5.11 (s, 1H, **CH**–OH), 7.40 (s, $5H_{arom}$)
4c[b]	$PhCH_2$	85[c] 91[d]	–	–	–	–	–
5c[b]	$PhCH_2$	95[e]	–	–	–	–	–

[a] Satisfactory microanalysis obtained: C±0.35, H±0.16, N±0.19

[b] Physico-chemical properties of compounds **2c**–**5c** were communicated in Ref. [6]

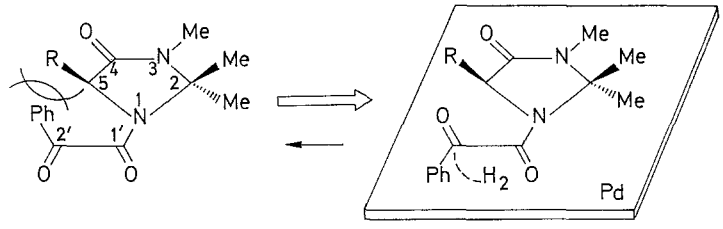
[c] Obtained in reduction of (*S*)–**3** with $NaBH_4$

[d] Obtained in catalytic hydrogenation of (*S*)–**3** over Pd–C

[e] Obtained in catalytic hydrogenation of (*S*)–**3** over Ni–Raney

drolysis performed under usual conditions (1 normal hydrochloric acid, 100°) was rather small (several days for 50% conversion), therefore it was performed using a modified technique [11]: 1 normal hydrochloric acid + ion-exchange resin - Amberlyst-15 (this was used instead of Dowex-50 W × 8).

Preferential formation of (2′*R*)-hydroxy amide, for example, in hydrogenation of (5*S*)-**3** over Pd may be explained by the fact that the *trans*-coplanar conformation of the two carbonyl goups in the phenylglyoxcylic residue is energetically more favored than a *cis*-coplanar conformation, due to interference between the phenyl group and substituents in 2 and 5 positions of the imidazolidinone ring (Scheme 2), which is analogous to the situation for *trans*-2,5-disubstituted pyrrolidines [5].



Scheme 2

The α-keto amide (5*S*)-**3** in this predominant conformation would be absorbed, followed by hydrogenation on the palladium surface from the less bulky side to give (2′*R*)-hydroxy amide.

Thus, the catalytic hydrogenation of amides (5*S*)-**3** proceeded with high diastereoselectivity [d. e. up to 96% for (5*S*)-**3b**] which exceeded results achieved when phenylglyoxylic acid chiral amides were hydrogenated over Pd-C with (*S*)-α-alkyl aryl amines (d. e. 1.3 − 7.7%) [9] and (2*R*,5*R*)-*trans*-2,5-bis(methoxymethoxymethyl) pyrrolidine (d. e. up to 56%) [5] used as chiral sources.

The reduction of (5*S*)-**3** by sodium borohydride proceeded with somewhat lower d. e. (54 − 81%) which is comparable with the case when proline [3] was used as chiral source (d. e. 69%). It should be noted that in the case of more bulky complex hydride - LiB*Et*$_3$H and (2*R*,5*R*)-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine hydride - LiB*Et*$_3$H and (2*R*,5*R*)-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine [5] as chiral auxiliary the diastereoselectivity of the reduction was very good (d. e. 98%).

In summary, it was found that 5-substituted (5*S*)-imidazolidin-4-one is an effective chiral auxiliary for asymmetric catalytic hydrogenation of amides derived from phenylglyoxylic acid.

Experimental Part

^{1}H-NMR spectra were recorded at 90 MHz on a Bruker, mod. WH-90 spectrometer for solutions in deuteriochloroform, chemical shifts (δ) are given in ppm from tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer, mod. 580 B spectrometer. Optical rotations were measured on a Perkin-Elmer, mod. 141 polarimeter at 25°C using ethyl alcohol as the solvent. Microanalyses were determined by the Microanalytical Service Division of this Institute. In analytical thin-layer chromatography Silufol UV-254 (CSFR) plates were used with ethyl acetate as eluent. Spots were visualised in UV light or in iodine vapour. Analytical and preparative high performance liquid chromatography (HPLC) was performed using a HPP, mod. 5001 chromatograph (CSFR), LCI-30 injector, RIDK, mod. 102 RI detector and columns: analytical - Zorbax SIL 4.6 mm × 15 cm,

preparative – Zorbax SIL 9.4 mm × 25 cm. Eluent was hexane:dioxane = 8 : 2 (by volume); flow rate for the analytical HPLC 2.0 ml min^{-1}, for the preparative HPLC 10 ml min^{-1}. Flash-chromatography was carried out on 3 cm × 10 cm column filled with LACHEMA (CSFR) silica gel L 40/100. Natural amino acids were obtained from the REANAL (Hungary). M. p. s are uncorrected.

Synthesis of 5-Substituted Imidazolidin-4-ones (5*S*)-**2**: *General Procedure*

(*S*)-α-Amino acid N-methyl amide [8] (**1**) (0.1 mol) and acetone (10 ml) are refluxed in *DMF* (150 ml) for 5 h. The mixture is concentrated on a rotatory evaporator, the concentrate then is coevaporated with isopropyl alcohol (3 × 50 ml) for complete removing of *DMF*. The residue is flash-chromatographed on silica gel (CH_3CN as eluent). Evaporation of the solvent gave a pure product (5*S*)-**2** (Table 2).

Synthesis of α-Keto-Amides (5*S*)-**3**: *General Procedure*

Freshly prepared phenylglyoxylic acid chloride [9] (7.72 g, 0.055 mol) in dry benzene (10 ml) is added dropwise at 0°C to a solution of (5*S*)-**2** (0.05 mol) and dry Et_3N (7.7 ml, 0.055 mol) in dry CH_2Cl_2 (150 ml). The mixture is stirred for 30 min and then washed with 0.1 *N* HCl (3 × 50 ml). The resulting solution, which contains a little amount of phenylglyoxylic acid is stirred with aqueous sat. $NaHCO_3$ solution (100 ml) for 30 min. The organic phase is separated, dried (Na_2SO_4) and evaporated. The residue is flash-chromatographed on silica gel (hexan/ethyl acetate, 7 : 3, as eluent) to give (5*S*)-**3** (Table 2).

Reduction of α-Keto Amides (5*S*)-**3** *by* $NaBH_4$: *General Procedure*

To a magnetically stirred solution of $NaBH_4$ (0.38 g, 0.01 mol) in dimethoxyethane (50 ml) at 0°C a solution of (5*S*)-**3** (0.01 mol) in dimethoxyethane (10 ml) is added dropwise. The solution is stirred for 30 min and then quenched with 1 *N* HCl (2 ml). The resulting mixture is evaporated on a rotavapor and the viscous residue is extracted with ether (3 × 20 ml). Extracts are combined, evaporated and flash-chromatographed on silica gel (hexane/ethyl acetate, 7 : 3) to give a mixture of α-hydroxy amides (5*S*,2′*R*)-**4** and (5*S*,2′*S*)-**5**, which are resolved by preparative HPLC (Table 1 and 2). The diastereoisomeric ratio of α-hydroxy amides (5*S*,2′*R*)-**4** and (5*S*,2′*S*)-**5** was established by analytical HPLC before flash-chromatography.

Catalytic Hydrogenation of α-Keto Amides (5*S*)-**3**: *General Procedure*

A stirred solutian of (5*S*)-**3** (0.001 mol) in 96% ethyl alcohol (10 ml) is hydrogenated in presence of 0.1 g of 2% palladium on carbon or 0.05 g of Ni-Raney at 20°C under atmospheric pressure. After 5 h of hydrogenation the catalyst is filtered off and the filtrate is evaporated to give α-hydroxy amides (5*S*,2′*R*)-**4** and (5*S*,2′*S*)-**5**. Chemical yields and diastereomeric ratios of the hydrogenation products are determined by analytical HPLC (Tables 1 and 2).

Hydrolysis of α-Hydroxy Amides (5*S*,2′*R*)-**4**: *General procedure*

α-Hydroxy amide (5*S*,2′*R*)-**4** (0.001 mol) is dissolved in 1 *N* HCl (5 ml), 0.5 g of Amberlyst-15 (H^+-Form, 20 – 50 mesh) is added and the magnetically stirred mixture is heated at 100°C for 5 h in a stoppered microreactor "Pierce". After that, the mixture is filtered and water is evaporated on the rotavapor. Preparative HPLC of the oily residue affords partially racemized (*R*)-(–) mandelic acid (~ 90% e. e. in all cases).

References

[1] Hanessian S. (1983) Total Synthesis of Natural Products. In: The Chiral Approach, Ch. 2 Pergamon Press, New York

[2] Morrison J. D., Mosher H. S. (1971) Asymmetric Organic Reactions, Ch. 2 Prentice Hall Englewood Cliffs, N. J.; Harada K. (1985) In: Morrison J. D. (ed.) Asymmetric Synthesis, Vol. 5. Academic Press, New York, p. 345

[3] Soai K., Hasegawa H. (1985) J. Chem. Soc. (Perkin Trans. 1): 769; Soai K., Isoda T., Hasegawa H., Ishizaki M. (1986) Chem. Lett.: 1897

[4] Munegumi T., Fujita M., Maruyama T., Shiono S., Takasaki M., Harada K. (1987) Bull. Chem. Soc. Jpn. **60**: 249

[5] Kawanami Y., Fujita I., Asahara S., Katsuki T., Yamaguchi M. (1989) Bull. Chem. Soc. Jpn. **62**: 3598

[6] Solodin I., Goldberg Yu., Zelčans G., Lukevics E. (1990) J. Chem. Soc. (Chem. Commun.): 1321

[7] For other applications of imidazolidin-4-one derivatives, easily available from natural amino acids, in asymmetric synthesis see: Polt R., Seebach D. (1989) J. Am. Chem. Soc. **111**: 2622; Gander-Coquoz M., Seebach D. (1988) Helv. Chim. Acta **71**: 224

[8] For (S) -Ala-$NHCH_3$, see: Iqbal M., Nagaraj R., Balaram P. (1981) Int. J. Peptide Protein Res. **18**: 208; for (S) -Leu-$NHCH_3$: Okada Y., Iguchi S., Hirai T., Goto Y., Yagyu M., Yajima H. (1984) Chem. Pharm. Bull. **32**: 4608; for (S) -Phe-$NHCH_3$: Santi V., Danenberg P. V. (1971) Biochemistry **10**: 4813

[9] Harada K., Munegumi T. (1984) Bull. Chem. Soc. Jpn. **57**: 3203

[10] Aldrich (1990) Catalog-Handbook of Fine Chemicals 1990 – 1991, p. 815

[11] Fitzi R., Seebach D. (1988) Tetrahedron **44**: 5277

Received July 24, 1991. Accepted October 16, 1991