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DERACEMIZATION BY ENANTIOSELECTIVE PROTONATION IV
AN IMPROVED METHOD FOR THE ENANTIOMERIC ENRICHMENT OF α-AMINOACIDS USING METALATION BY MEANS OF CHIRAL AMIDES

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ABSTRACT : *Optically active α-aminoesters are obtained by metalation of the corresponding Schiff bases by chiral lithium amide followed by protonation by an achiral or a chiral acid. 70 % e.e. can be obtained.*

Deracemization by enantioselective protonation is a method for the enantiomeric enrichment of a racemic mixture. It theoretically allows the complete conversion of the racemic in one enantiomer. This procedure was applied to carbonyl compounds [1] and to Schiff bases of α-aminoesters [2].

In this last case, we have shown in our previous report [2] the importance of the structure of the chiral acid **5** used for the protonation of the prochiral enolate **3** . The base used for metalation of the Schiff base **1** was always lithium diisopropylamide.

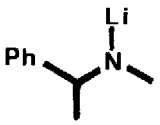
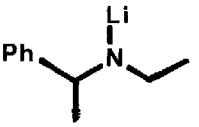
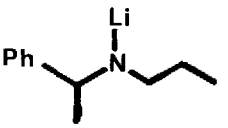
We report an improved procedure based on the use of chiral amides **2** to produce enolate **3** from racemic Schiff base **1** . Protonation of the anion **3** by diacyltartaric acid **5** under the influence of the chiral amine **4** [3], followed by acid hydrolysis and separation of the amine hydrochloride **7** yields the optically active aminoester hydrochloride **6** with an enantiomeric ratio as high as 85 : 15 (70 % e.e.).

We noted that the amine present in the reaction mixture after deprotonation of the Schiff base **1** has an important influence on the selectivity of the protonation of the enolate **3** . In these studies, the couple (2R, 3R) **5** / (R) **4** is favourable to a good selectivity, while the couple (2S, 3S) **5** / (R) **4** decreases the enantiomeric excess of the reaction product.

On the other hand, when the protonation is carried out with a racemic or an achiral acid, influence of the chiral amine is sufficient to induce significant optical yields. These results afford evidence for an interaction between the carbanionic species and secondary amines [4].

The use of chiral amides allows an improvement of the method of deracemization : the enantiomeric ratio of the protonation product by (2R, 3R) dipivaloyltartaric acid increases from 75 : 25 (base : LDA) to 85 : 15 (base : lithium N-ethyl(1-phenylethyl-amide)) [5]. The initial Schiff base can be racemic or optically active (see table 1). So the method allows the conversion of an enantiomer into its antipode. In this last case, the term deracemization is inappropriate.

TABLE 1 : Deracemization by enantioselective protonation of enolate **3** of methyl N-benzylidene phenylglycinate **1** by diacyltartaric acid **5** in the presence of N-alkyl (1-phenylethyl)amines **4** [6]

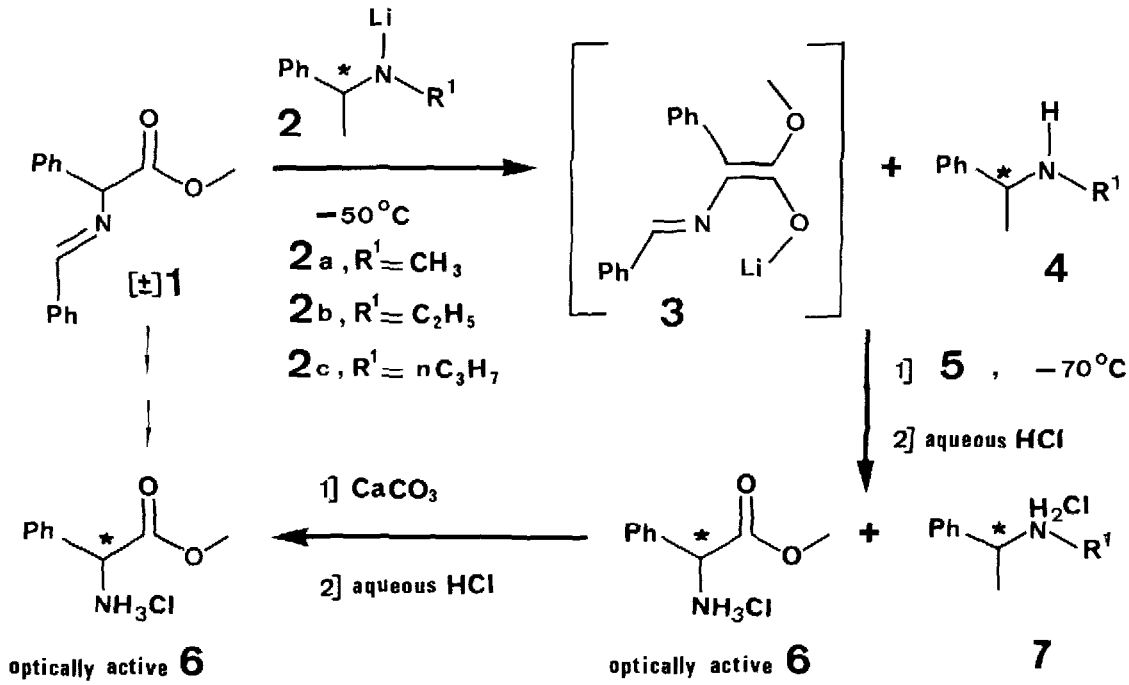
Initial Schiff base	Lithium amide	Acid	Active methylphenylglycinate hydrochloride: Obs $[\alpha]_D^{25}$ deg in CH_3OH (c) [i]	Enantiomeric Ratio S : R [ii]	Chemical Yield [iiii]
Racemic **1**		(2R, 3R) **5** a	+ 79.4° (1)	80 : 20 [iii]	70
		(2S, 3S) **5** a	- 47.1° (1)	32 : 68	70
		racemic **5** a	+ 21.4° (1.3)	58 : 42	80
		meso **5** a	+ 7.7° (1.3)	53 : 47	82
	(R) **2** a	(2R, 3R) **5** b	+ 76.1° (1.6)	79 : 21	87
Racemic **1**	racemic **2** a	(2R, 3R) **5** a	+ 66.8° (1.3)	75 : 25	70
Racemic **1**		(2R, 3R) **5** a	+ 92° (1)	85 : 15	84
		(2S, 3S) **5** a	- 7.3° (1.4)	47 : 53	75
		racemic **5** a	+ 51° (2)	70 : 30	75
		meso **5** a	+ 31.2° (1.5)	62 : 38	85
	(R) **2** b	(2R, 3R) **5** b	+ 91° (2)	85 : 15	92
(R) **1**	(R) **2** b	(2R, 3R) **5** a	+ 89° (1.4)	84 : 16	80
Racemic **1**		(2R, 3R) **5** a	+ 81.6° (1)	81 : 19	75
		(2S, 3S) **5** a	0° (2)	50 : 50	80
	(R) **2** c				

[i] *Reference, (R), **6** , $[\alpha]_D^{25} = -131°$ (c = 1, CH_3OH)[7]. All rotations measured in a 1 ml cell (1 dm) on a Perkin Elmer model 241 polarimeter.*

[ii] *The purification procedure did not include any recrystallization which can affect the enantiomeric ratio of the reaction product.[6] It was applied to a mixture of racemic **1** and (R) **4** a and to a mixture of (R) **6** ($[\alpha]_D^{25} = -131°$, c = 1, CH_3OH) and (R) **4** a. The obtained hydrochlorides **6** gave respectively rotations of $[\alpha]_D^{25} = 0°$, c = 3 , CH_3OH and $[\alpha]_D^{25} = -128°$, c = 1, CH_3OH (98 % e.e.).*

[iii] *This corresponded to an enantiomeric excess (e.e.) of 60 %.*

[iiii] *All products demonstrated spectral data and microanalyses in accord with assigned structure. The purity of the products was found to be from 99 % to 99.5 % by glc analysis of the aminoester set free from hydrochloride **6** after an aqueous NaOH treatment. The major impurity was amine hydrochloride **7** (less than 1 %).*



5 : HOOC — CH(OCOR²) — CH(OCOR²) — COOH ; **5**a, $R^2 = tC_4H_9$ **5**b , R^2 = 1-adamantyl

Theoretically, this study demonstrates the possibility of asymmetric synthesis by means of chiral amides or chiral amines set free from chiral amides [9].

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(1) H. Matsushita, M. Noguchi, M. Saburi, S. Yoshikawa, Bull.Chem.Soc.Japan, 1975, 48, 3715. H. Matsushita, Y. Tsujino, M. Noguchi, S. Yoshikawa, Bull.Chem.Soc.Japan, 1976, 49, 3629. H. Matsushita, Y. Tsujino, M. Noguchi, M. Saburi, S. Yoshikawa, Bull.Chem.Soc.Japan, 1978, 51, 862.- L. Duhamel, C.R.Acad.Sci., 1976, 282C, 125.- L. Duhamel, J.C. Plaquevent, Tetrahedron Letters, 1977, 2285.

(2) L. Duhamel, J.C. Plaquevent, J.Amer.Chem.Soc., 1978, 100, 7415.

(3) Chiral amines were prepared by $LiAlH_4$ reduction of the obtained amide from α-phenylethylamine and HCOOMe, CH_3COCl or C_2H_5COCl. (R) **4** a $(\alpha)_D^{25} = +83.7°$, c = 2, C_6H_6; (R) **4** b $(\alpha)_D^{25} = +60.3°$, c = 3, C_6H_6; (R) **4** c $(\alpha)_D^{25} = +64.4°$, c = 2, C_6H_6.

(4) Similar interpretations were proposed in the field of anions produced by LDA. See for examples : P.L. Creger, J.Amer.Chem.Soc., 1970, 92, 1396.- P.E. Pfeffer, L.S. Silbert, J.M. Chirinko, J.Org.Chem. 1972, 37, 451.- K.G. Davenport, H. Eichenauer, D. Enders,

M. Newcomb, D.E. Bergbreiter, J.Amer.Chem.Soc., 1979, 101, 5654.

(5) In ref. (2), we report a 79 : 21 enantiomeric ratio by protonation of enolate **3** by (2R,3R) dipivaloyltartaric acid in the presence of diisopropylamine. This value was based on the maximum rotation of (R) **1** $[\alpha]_D^{25} = +71.5°$ (c = 3, $CHCl_3$), which was erroneous, and is really (R) **1** $[\alpha]_D^{25} = +84°$ (c = 2, $CHCl_3$), which leads to the enantiomeric ratio of 75 : 25.

(6) In a typical experiment, 0.44 g of (±) **1** (1.75 mmol) in 3 ml of dry THF was added under N_2 at - 50°C to **2** b (2.5 mmol) prepared at - 35°C from 2.5 mmol of n-BuLi in hexane titrated by [8] and 0.38 g of **4** b (2.5 mmol) in 10 ml of dry THF. After 15 mn, protonation was carried out at - 70°C by addition (10 mn) of a solution of 1.6 g of (2R, 3R) **5** a [5 mmol $[\alpha]_D^{25} = -23.8°$ (c = 2, dioxane)] in 5 ml of dry THF. The reaction was continued at - 70°C during a period of 15 mn. The homogeneous reaction mixture was allowed to warm to + 5°C, completed with 15 ml of dry ether, then extracted twice by 10 ml of aqueous HCl N. The aqueous layer was completed by 10 ml H_2O, saturated by 15 g of $CaCO_3$ and extracted at room temperature with 100 ml AcOEt during 4 hours of vigourous stirring. The two layers were separated. The aqueous layer was washed with 40 ml of AcOEt. The organic layers were combined and washed three times with water, then extracted twice with 7 ml of HCl N. This acid solution was concentrated in vacuo an dried in vacuo on P_2O_5 to yield **6** (84 % yield, 70 % e.e.). Chiral acid **5** was retrieved from the ether/THF layer (no racemization, 95 % yield). Chiral amine **4** was retrieved from the aqueous layer after basification by aqueous NaOH (no racemization, 50 % unoptimized yield of distilled product).

(7) E.P. Kyba, J.M. Timko, L.J. Kaplan, F. De Jong, G.W. Gokel, D. Cram, J.Amer.Chem.Soc., 1978, 100, 4555.

(8) L. Duhamel, J.C. Plaquevent, J.Org.Chem., 1979, 44, 3404.

(9) Recently, enantioselective deprotonation by means of chiral amides was reported : J.M. Whitesell, S.W. Felman, J.Org.Chem., 1980, 45, 755.

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