Practical synthesis of optically active α -hydrazino acids from α -amino acids

Joelle Pérard-Viret, Jacqueline Gabard, André Collet

► To cite this version:

Joelle Pérard-Viret, Jacqueline Gabard, André Collet. Practical synthesis of optically active α -hydrazino acids from α -amino acids. *Tetrahedron*, 1987, 43 (5), pp.891-894. 10.1016/S0040-4020(01)90026-2 . hal-03373639

HAL Id: hal-03373639

<https://hal.science/hal-03373639>

Submitted on 19 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

PRACTICAL SYNTHESIS OF OPTICALLY ACTIVE α -HYDRAZINO ACIDS FROM α -AMINO ACIDS

Joëlle Viret, Jacqueline Gabard and André Collet

Chimie des Interactions moléculaires, E.R. C.N.R.S. 285, Collège de France,
11, place Marcelin-Berthelot, 75005 Paris, France

Summary : Simple amino acids (1) can be converted in fair to good yield into hydrazino acids (3) of like configuration by using KOCl instead of NaOCl to promote the Shestakov rearrangement of the intermediate hydantoic acids (2).

It was shown fifteen years ago by Karady et al.,¹ and later by Gustafsson,² that simple amino acids (1) can be converted into α -hydrazino carboxylic acids (3) ("hydrazino acids")³ of like configuration via Shestakov rearrangement⁴ of intermediate hydantoic acids (2) in the presence of sodium hypochlorite. This simple route to L- (or D-) hydrazino acids would seem particularly attractive because hydantoic acids can be easily obtained from L- (or D-) amino acids in excellent yield, and their transformation to 3 takes place without racemization;² it is of low practical value, however, in view of the poor yields (20-30%) usually obtained in the last step 2 $\rightarrow$ 3.^{1,2,5}

We wish to report that the use of KOCl instead of NaOCl can improve the yield of this reaction to 70% and therefore makes the sequence 1 $\rightarrow$ 2 $\rightarrow$ 3 one of the simplest and often most efficient processes for the preparation of simple optically pure L- (or D-) hydrazino acids. The use of KOCl was suggested by recent observations by Enders et al.⁶ and by Brienne et al.⁷ that this reagent was superior to NaOCl in Hofmann degradation (SAMP synthesis) and in olefin epoxidation.

The importance of L- and D-hydrazino acids has been recognized in several fields, particularly in view of their close relationship to natural amino acids. As such, these compounds exhibit strong biological activities as inhibitors of amino acid decarboxylases,⁸⁻¹¹ and some of them have been used as building units in modified peptides¹²⁻¹⁴ and semi-synthetic β -lactam antibiotics,¹⁵⁻¹⁷ or as intermediates in the synthesis of antimalarial pyrazoles.² Moreover, chiral hydrazino acids (and, in general, chiral hydrazines) are potentially useful reagents for asymmetric synthesis¹⁸ or for optical resolution of carbonyl compounds.¹⁹

Thus far, optically active hydrazino acids have rarely been obtained by optical resolution methods,²⁰⁻²² and the conversion of L-amino acids to D-hydrazino acids via hydrazinolysis of intermediate L- α -halogeno acids proved satisfactory in only a few instances;^{20,23-25} alternatively, a synthesis of

L-hydrazino acids involving nitrosation/reduction of N-benzyl L-amino esters has been proposed²⁶ but this procedure involves six steps from 1 to 3; very recently, three elegant asymmetric syntheses which may be useful for the preparation of certain L- or D-hydrazino acids have also been reported.²⁷⁻²⁹

Results. Some relevant data on the conversion of amino acids 1a-f into hydantoic acids 2a-f and on the Shestakov rearrangement of the latter to hydrazino acids 3a-f are assembled in Tables 1 and 2, respectively.

Hydantoic acids were obtained by reaction of amino acid hydrochlorides with KOCN (H_2O , 60°C, 4 h) and were isolated in essentially pure form by crystallization from the reaction mixture on acidification (concd. HCl). The structures of 2a-f and the absence of possible hydantoin by-products¹ were ascertained by 200 MHz $^1\text{H-NMR}$.

Potassium hypochlorite solutions for the Shestakov reaction were prepared from calcium hypochlorite pellets containing 65% chlorine. The concentration of the KOCl solutions (measured iodometrically) must be ca. 1.5-2 M. Hydrazino acids 3a-f were conveniently isolated by percolation of the reaction mixture through a Dowex IX2 anion exchange resin as described in the experimental section, and washed with ethanol (usually, no further purification was necessary).³⁰ The observed specific rotations (Table 2) are close to the reported values (whenever available) for optically pure products. D-Hydrazino terleucine (3d) is a new compound which could be useful as a building block for artificial peptides and for asymmetric synthesis; we have recently described a simple optical resolution procedure for the parent amino acid terleucine.³¹ Surprisingly, our attempts to synthesize the hitherto unknown L-hydrazino proline from the corresponding hydantoic acid only afforded intractable mixtures, which is in contrast to the excellent yield observed⁶ in the analogous degradation of the urea of 2-methoxymethyl pyrrolidine to SAMP.

Comments. When direct comparison is possible, the yields of 3 by the present procedure are ca. 2-3 times better than those previously reported and are especially good in the case of hydrazino valine 3b. These results seem to confirm the earlier observations,^{6,7} although the reasons for this difference between KOCl and NaOCl have not been clearly established. Potassium hypochlorite solutions have been shown to decompose faster (hence could be more reactive) than sodium and lithium hypochlorite solutions under alkaline, neutral, or slightly acidic conditions.³² Moreover, a high hypochlorite concentration seems to be important if not essential, and the KOCl solutions prepared from $\text{Ca}(\text{OCl})_2$ are usually more concentrated than the NaOCl solutions thus far employed in these reactions. In our hands, however, control experiments using concentrated NaOCl solutions prepared from $\text{Ca}(\text{OCl})_2$ proved to be significantly less efficient than KOCl solutions in promoting the conversion of 2b to 3b (ca. 40% instead of 70% yield).

Experimental Section

Melting points were measured on a Kofler hotbench apparatus, routine IR spectra were recorded in nujol mulls on a Perkin-Elmer 297 spectrometer, $^1\text{H-NMR}$ spectra were obtained at 200.13 MHz on a Bruker AM200SY instrument; rotations were measured on a Perkin-Elmer 241 polarimeter in thermostated (25°C) 1-dm quartz cells. Technical calcium hypochlorite purchased from Aldrich-Chimie was used for the preparation of the KOCl solutions.

Potassium hypochlorite solutions : 100 g of powdered $\text{Ca}(\text{OCl})_2$ in water (300 ml) were vigorously shaken (or sonicated) for ca. 15 min, then a solution of KOH (20 g) and K_2CO_3 (70 g) in water (125 ml) was added. After 10-15 min stirring and separation of the solid (mostly CaCO_3) a green-yellow solution of KOCl (1.5 to 2.0 M) was obtained (such solutions can be stored at 4°C for several weeks).

General procedure for the Shestakov reaction : L-hydrazino valine 3b. L-Hydantoic acid 2b⁵ (1.2 g, 7.5 mmol) was dissolved at 0°C in 4.5 ml of a 5N KOH solution, and 6 ml of 1.8 M KOCl solution were added. After overnight stirring at r.t. in the dark the excess reagent was destroyed (solid Na_2SO_3), 5 ml of ether were added and the solution was brought to pH 1-2 by slow addition of concentrated HCl (gas evolution!). Then the solution was extracted twice with ether and the aqueous phase was percolated through

a Dowex 1X2 (OH⁻) column (20 x 5 cm). The resin was washed with water until the eluate was neutral then the hydrazino acid was recovered by elution with 1N acetic acid; the fractions containing **3b** (ninhydrin test : pale pink) were evaporated to dryness and the crystalline solid washed with cold ethanol; yield 0.72 g (70%) (Table 2); NMR in D₂O (δ (DOH) = 4.7 ppm) : 0.90, d, J=7.5 Hz, 6H, Me₂C), 2.0-2.17 (m, 1H, CHMe₂), 3.37 (d, 1H, J=4.5 Hz, CH(α); C₅H₁₂N₂O₂, 0.5 H₂O calc C 42.50, H 9.28, N 19.84, found C 42.6, H 9.4, N 19.9.

D-3,3-dimethyl-2-ureido-butanoic acid 2d. To a solution of D-terleucine³¹ (655 mg) in water (10 ml) was added 3 g of KOCN; after 4 h at 60°C the mixture was cooled to r.t. and some insoluble material was filtrated off. The ice-cooled solution was then acidified by adding 5.4 ml of 12 N HCl. The precipitate was collected in the usual way, washed with cold water, and dried in air; yield 786 mg (90%) (Table 1); NMR in DMSO-d₆ (δ from int. TMS) : 0.89 (s, 9H, tBu), 3.88 (d, 2H, CH), 5.58 (s, 2H, NH₂), 6.19 (d, 1H, NH); C₇H₁₄N₂O₃ calc. C 48.26, H 8.10, N 16.08, found C 48.0, H 8.1, N 15.8.

D-hydrazinoterleucine 3d. A solution of 348 mg of **2d** in 1.2 ml of 5 N KOH was treated with 2 ml of 1.6 M KOCl as described above for the conversion of **2b** to **3b**; yield 130 mg of **3d** (45%), for which no mp could be measured (decomp. above 200°C); [α]_D +19.3° (c 0.7 in H₂O) (rotation in HCl, see Table 2); NMR (in D₂O, δ (DOH) = 4.7 ppm) : 0.92 (s, 9H, tBu) and 3.22 (s, CH); C₆H₁₄N₂O₂, 0.5 H₂O calc C 46.43, H 9.74, N 18.05, found C 46.2, H 9.8, N 17.4. The corresponding hydrochloride had mp 208°C; C₆H₁₄N₂O₂·HCl calc. C 39.45, H 8.28, N 15.34, Cl 19.41, found C 39.1, H 8.2, N 14.8, Cl 19.3.

Table 1 - Optically active hydantoic acids **2a-f** from amino acids **1a-f**

Starting material 1 (hydrochloride)	% yield		hydantoic acids 2		mp (°C)
	of 2	(lit)	[α] _D	[lit]	
1a L-alanine	61	(27) ²	-8.3° (c 1.5, H ₂ O)	[-7.9° (c 1.8, H ₂ O)] ²	183
1b L-valine	80	(84) ⁵	+16.9° (c 1, EtOH)	[+16° (c 0.5, aq. EtOH)] ⁵	209
1c L-leucine	96	-	+0.6° (c 1.5, NaOH)		234dec
1d D-terleucine	90	-	-4.5° (c 0.5, EtOH)		260dec
1e L-phenylalanine	94	-	+45.0° (c 1, EtOH)	[+36.3° (c 1, aq. NH ₃)] ³³	189
1f D-phenylglycine	89	(87) ⁵	-160.0° (c 0.9, EtOH)	[-131.5° (c 1, aq. NH ₃)] ⁵	230

Table 2 - Optically active hydrazino acids **3a-f** from hydantoic acids **2a-f**

Starting material 2	% yield of 3		hydrazino acids 3			abbreviated names ³
	KOCl	(NaOCl)	[α] _D	(in 6N HCl)	[lit]	
2a (L)	62	(20-27) ²	-26.5° (c 1.2)		[-28.6° (c 1.1)] ²	HA1a
2b (L)	70	(20) ⁵	-17.1° (c 0.8) ^a		[-17.6° (c 1)] ²	HVal
2c (L)	50	-	-13.2° (c 1.0)		[+13.4° (D isomer)] ²⁷	HLeu
2d (D)	45	-	+11.0° (c 0.6)			HT1e
2e (L)	54	-	-15.8° (c 0.5)		[-16.0° (c 0.7)] ²⁶	HPhe
2f (D)	40	(20) ⁵	-153.0° (c 0.4)		[-154° (c 3)] ⁵	HPGly

a) corrected for the water of crystallization (hemihydrate).

References and Notes

- 1) S. Karady, M.G. Ly, S.H. Pines, and M. Sletzing J. Org. Chem. 1971, **36**, 1949.
- 2) H. Gustafsson and U. Ragnardsson Acta Pharm. Suecica 1974, **11**, 493; H. Gustafsson Acta Chem. Scand. 1975, **B29**, 93.
- 3) For convenience the hydrazino analogues of natural amino acids are called by the name of the amino acid preceded by the word hydrazino : e.g., hydrazino alanine, hydrazino valine etc. See : E. Ronwin, J.V. Roach, and B.L. Tucker Can. J. Chem. 1968, **46**, 3013.
- 4) P. Shestakov Z. Angew. Chem. 1903, **16**, 1061; this reaction (i.e., the conversion of ureas to hydrazines) has been occasionally^{2,6} called "Hofmann rearrangement" (amides to amines).
- 5) G. LiBassi, P. Ventura, R. Monguzzi, and G. Pifferi Gazz. Chim. Ital. 1977, **107**, 253.
- 6) D. Enders, P. Fey, and H. Kipphardt Org. Prep. and Proc., int. 1985, **17**, 1.
- 7) M.J. Brienne, D. Varech, M. Leclercq, J. Jacques, N. Radembino, M.-C. Dessalles, G. Mahuzier, C. Gueyouche, C. Bories, P. Loiseau, and P. Gayral (to be published).
- 8) C.R. Creveling, J.W. Daly, and B. Witkop J. Med. Chem. 1966, **9**, 284.
- 9) C.C. Porter, L.S. Watson, D.C. Titus, J.A. Totaro and S.S. Byer Biochem. Biopharm. 1962, **11**, 284.
- 10) S.I. Harik and S.H. Snyder Biochim. Biophys. Acta 1973, **327**, 501.
- 11) E.J. Glamkowski, G. Gal, M. Sletzing, and C.C. Porter J. Med. Chem. 1967, **10**, 852.
- 12) H. Niedrich Chem. Ber. 1967, **100**, 3273.
- 13) R. Grupe and H. Niedrich Chem. Ber. 1967, **100**, 3283.
- 14) P.H. Bentley and J.S. Morley J. Chem. Soc. (C), 1966, 60.
- 15) G. LiBassi, R. Monguzzi, R. Broggi, and G. Broccali J. Antibiot. 1977, **30**, 376.
- 16) A. Balsamo, B. Macchia, F. Macchia, A. Rossello, R. Giami, G. Pifferi, M. Pinga, and G. Broccali J. Med. Chem. 1983, **26**, 1648.
- 17) P.H. Bentley and E. Hunt Tetrahedron Letters 1976, 3731.
- 18) E.J. Corey, R.M. McCaully, and H. Sachdev J. Am. Chem. Soc. 1970, **92**, 2476; E.J. Corey, H.S. Sachdev, J.Z. Gougoutas, and W. Saenger J. Am. Chem. Soc. 1970, **92**, 2488.
- 19) J. Jacques, A. Collet, and S.H. Wilen "Enantiomers, Racemates, and Resolutions", J. Wiley & Sons, New York, 1981, p. 336.
- 20) A. Darapsky J. Prakt. Chem. 1919, **99**, 198.
- 21) L.M. Stephenson and D.L. Mattern J. Org. Chem. 1976, **41**, 3614.
- 22) S. Karady, M.G. Ly, S.H. Pines, and M. Sletzing J. Org. Chem. 1971, **36**, 1946.
- 23) M. Sletzing, R.A. Firestone, D.F. Reinhold, C.S. Rooney, and W.H. Nicholson J. Med. Chem. 1968, **11**, 261.
- 24) H. Niedrich and R. Grupe J. Prakt. Chem. 1965, **27**, 108.
- 25) J.G. Johanson, R.M. Parkhurst, and W.A. Skinner Indian J. Chem. 1976, **14B**, 209; T. Sawayama, H. Kinugasa, and H. Nishimura Chem. Pharm. Bull. 1976, **24**, 326.
- 26) K. Achiwa and S. Yamada Tetrahedron Letters 1975, 2701.
- 27) C. Gennari, L. Colombo, and G. Bertolini J. Am. Chem. Soc. 1986, **108**, 6394.
- 28) D.A. Evans, T.C. Britton, R.L. Dorow, and J.F. Dellaria J. Am. Chem. Soc. 1986, **108**, 6395.
- 29) L.A. Trimble and J.C. Vederas J. Am. Chem. Soc. 1986, **108**, 6397.
- 30) The hydrazino acids isolated at this step showed only minor amounts of non-identified impurities (200 MHz ¹H-n.m.r. in D₂O); final purification could be effected by crystallization from EtOH/H₂O.
- 31) J. Viret, H. Patzelt, and A. Collet Tetrahedron Letters 1986, **27**, 5865.
- 32) P. Pierron Bull. Soc. chim. Fr. 1943, **10**, 445.
- 33) H.D. Dakin and H.W. Dudley J. Biol. Chem. 1913, **17**, 29.