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# 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

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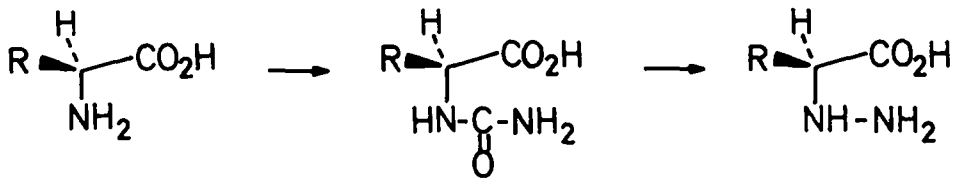
**Summary :** Simple amino acids (1) can be converted in fair to good yield into hydrazino acids (3) of like configuration by using KOCl instead of NaOCl to promote the Shestakov rearrangement of the intermediate hydantoic acids (2).

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 rearrangement[4] 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 → 3.[1,2,5]




1 2 3

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→2→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 peptides[12-14] 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 synthesis[18] 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 proposed[26] 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-products[1] were ascertained by 200 MHz $^1$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 1X2 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 observed[6] 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 $Ca(OCl)_2$ 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 $Ca(OCl)_2$ 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, $^1$H-NMR spectra were obtained at 200.13 MHz on a Brucker 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 $Ca(OCl)_2$ 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 **2b**[5] (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 $D_2O$ ( δ(DOH) = 4.7 ppm) : 0.90, d, J=7.5 Hz, 6H, $Me_2C$), 2.0-2.17 (m, 1H, C<u>H</u>$Me_2$), 3.37 (d, 1H, J=4.5 Hz, CH(α); $C_5H_{12}N_2O_2$, 0.5 $H_2O$ calc C 42.50, H 9.28, N 19.84, found C 42.6, H 9.4, N 19.9.

<u>D-3,3-dimethyl-2-ureido-butanoic acid **2d**</u>. To a solution of D-terleucine[31] (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-$d_6$ ( δ from int. TMS) : 0.89 (s, 9H, tBu), 3.88 (d, 2H, CH), 5.58 (s, 2H, $NH_2$), 6.19 (d, 1H, NH); $C_7H_{14}N_2O_3$ calc. C 48.26, H 8.10, N 16.08, found C 48.0, H 8.1, N 15.8.

<u>D-hydrazinoterleucine **3d**</u>. 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); $[\alpha]_D$ +19.3° (c 0.7 in $H_2O$) (rotation in HCl, see Table 2); NMR (in $D_2O$, δ(DOH) = 4.7 ppm) : 0.92 (s, 9H, tBu) and 3.22 (s, CH); $C_6H_{14}N_2O_2$, 0.5 $H_2O$ 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; $C_6H_{14}N_2O_2$.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 of 2 | (lit) | hydantoic acids 2 $[\alpha]_D$ | [lit] | mp (°C) |
|---|---|---|---|---|---|
| **1a** L-alanine | 61 | (27)[2] | -8.3° (c 1.5, $H_2O$) | [-7.9° (c 1.8, $H_2O$)][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 KOCl | (NaOCl) | hydrazino acids 3 $[\alpha]_D$ (in 6N HCl) | [lit] | abbreviated names[3] |
|---|---|---|---|---|---|
| **2a** (L) | 62 | (20-27)[2] | -26.5° (c 1.2) | [-28.6° (c 1.1)][2] | HAla |
| **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) | | HTle |
| **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).

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