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SYNTHESIS OF L and D α-AMINO ACIDS FROM CHIRAL AMIDALS

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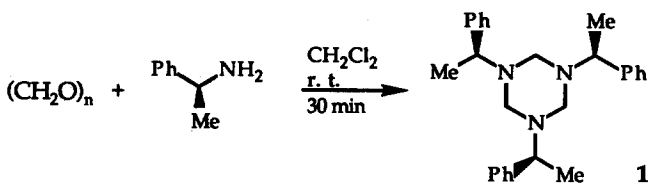
Summary : A new synthesis of D- and L-alanine is described, by means of the mercury cyclisation of the chiral amidal obtained from the reaction of 1,3,5-tri-(S)-phenylethyl-hexahydrotriazine and acryloyl chloride.

1,3,5-Hexahydrotriazines are highly reactive heterocycles that can be prepared from primary amine and formaldehyde under mild conditions and in high yield. [1] It is known from the literature that N-substituted hexahydrotriazine react with acyl chlorides [2] to afford the corresponding N-alkyl-N-chloromethylamides in quantitative yield.

We thought that, utilising as a starting material a hexahydrotriazine bearing an asymmetric centre on the nitrogens, a new synthesis of enantiomerically pure α-amino acids could be envisaged. [3] For this purpose the 1,3,5-tri-(S)-phenylethylhexahydrotriazine **1** has been synthetised by coupling (S)-1-phenylethylamine with paraformaldehyde in dichloromethane. The triazine **1** has been obtained practically pure in quantitative yield as a low melting solid (Scheme 1).



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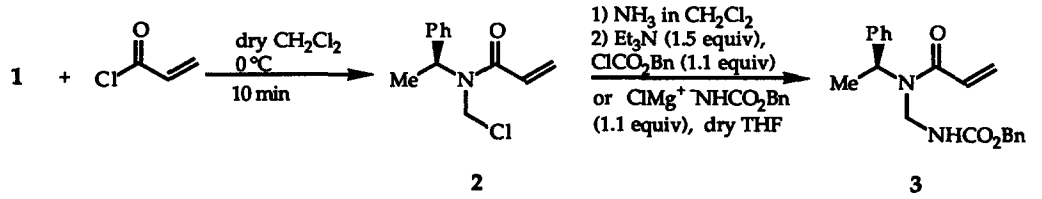
Scheme 1

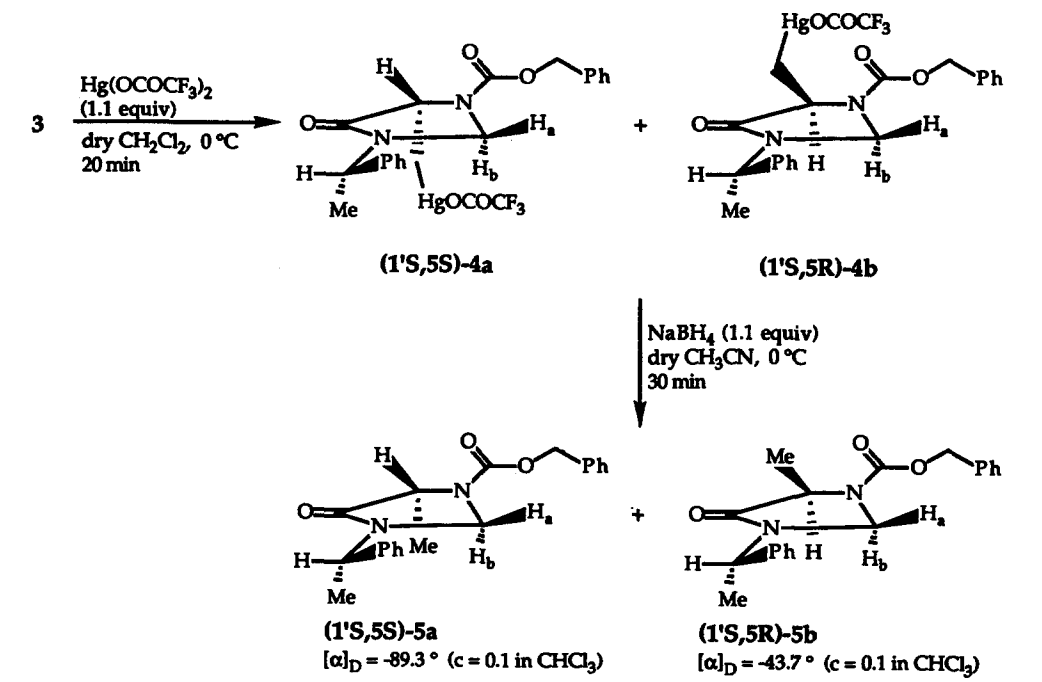
By addition of acryloyl chloride (3 equiv) to a solution of the triazine **1** in dry dichloromethane at 0 °C under argon, the N-(S)-phenylethyl-N-chloromethylacrylamide **2** was quantitatively formed and changed in situ into the corresponding amino derivative by bubbling gaseous ammonia in the reaction mixture at room temperature. After filtration of

the ammonium chloride, the solvent was evaporated under reduced pressure. The amidal **3** was then obtained by reaction with benzyl chloroformate (1.1 equiv) in dry dichloromethane and triethylamine (1.5 equiv) (Scheme 2). Following an alternative pathway **3** was obtained directly by addition of the N-chloromethylamide **2** to a solution of the magnesium salt of benzyl carbamate in dry tetrahydrofuran at 0 °C. The amidal **3** was purified on a column of neutral alumina and obtained in about 70% overall yield from **2** in both cases.



Scheme 2

In order to synthesise the optically active N-substituted imidazolidin-4-ones **5**, protected form of α-aminoacids, the amidal **3** was cyclised [4] in dry dichloromethane, utilising $Hg(OCOCF_3)_2$ as electrophile (1.1 equiv) (Scheme 3). [5]

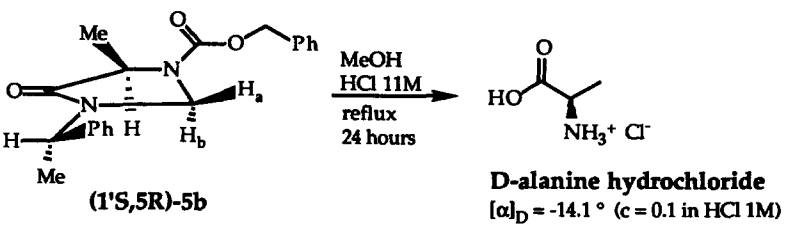


Scheme 3

After 20 minutes the reaction was complete, the solvent was evaporated and replaced with dry acetonitrile. Sodium borohydride (1.1 equiv) was added to the solution under argon at 0 °C and the mixture was stirred for 30 minutes. After filtration of the mercury and evaporation of the solvent, the imidazolidin-4-ones **5a** and **5b** were obtained in quantitative yield and 1:1 diastereomeric ratio. The diastereomeric mixture was easily separated on silica gel to afford enantiomerically pure **5a** and **5b**.

Although both compounds **5a** and **5b** were found at ^1H NMR to be 2 : 1 mixtures of rotamers in $CDCl_3$ (determined on the basis of the doublets of the C_5 methyl group), the absolute configuration of C_5 [6] was attributed on the basis of the non equivalence of H_a and H_b, due to the shielding effect of the phenyl group of the N_3 substituent on H_a. In fact the preferential conformation of the N_3 substituent with the hydrogen eclipsing the carbonyl of the ring has been previously observed. [7] An additional effect is exerted by the C_5 methyl group that shifts upfield H_b in compound **5a** and H_a in compound **5b**. [8]

The correct attribution of the stereochemistry is confirmed by the hydrolysis of **5b** in methanol and HCl 11M at reflux for 24 hours (Scheme 4). The reaction mixture was separated on a column of BIO-RAD AG 50W-X2 resin [9] (NH_4OH 0.015M as eluent): D-alanine was firsty eluted, then (S)-1-phenylethylamine that was completely recovered. With this technique no racemisation of the α-amino acid was remarked as shown by the $[\alpha]_D$ of its hydrochloric salt.



(1'S,5R)-5b

D-alanine hydrochloride
$[\alpha]_D$ = -14.1 ° (c = 0.1 in HCl 1M)

Scheme 4

With the same method L-alanine has been synthetised simply by hydrolysing the imidazolidin-4-one **5a**.

In conclusion, the developed procedure offers a convenient and inexpensive way for a practical preparation of both D and L α-amino acids under mild conditions and in good yield. Moreover the separation of the intermediate imidazolidin-4-ones **5a** and **5b** is very easy and the possibility of recovering the chiral auxiliary is a further advantage of this synthetic method.

Acknowledgement

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8 **(1'S,5S)-5a**: 300 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.44 (d, 3H, J = 6.8 Hz, major rotamer), 1.50 (d, 3H, J = 6.8 Hz, minor rotamer), 1.56 (d, 3H, J = 7.1 Hz), 4.20 (q, 1H, J = 6.8 Hz), 4.41 (d, 1H, H_a, J = 6.5 Hz, minor rotamer), 4.48 (d, 1H, H_a, J = 6.5 Hz, major rotamer), 4.70 (d, 1H, H_b, J = 6.5 Hz), 5.09 (AB, 2H, minor rotamer), 5.16 (AB, 2H, major rotamer), 5. 54 (q, 1H, J = 7.1 Hz), 7.32 (m, 10 H).
(1'S,5R)-5b: 300 MHz ^{1}H NMR ($CDCl_3$) δ (ppm) 1.38 (d, 3H, J = 6.4 Hz, major rotamer), 1.46 (d, 3H, J =6.4 Hz, minor rotamer), 1.56 (d, 3H, J = 7.1 Hz), 4.24 (q, 1H, J = 6.4 Hz), 4.31 (d, 1H, H_a, J = 6.5 Hz), 4.74 (d, 1H, H_b, J = 6.5 Hz, minor rotamer), 4.81 (d, 1H, H_b, J = 6.4 Hz, major rotamer), 5.13 (AB, 2H, minor rotamer), 5.17 (AB, 2H, major rotamer), 5.54 (q, 1H, J = 7.1 Hz), 7.33 (m, 10H).

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