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SYNTHESIS OF UNNATURAL AMINO ACIDS : SPIRO[4.5]-2-AZA-DECAN-3-CARBOXYLIC ACID

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Summary:

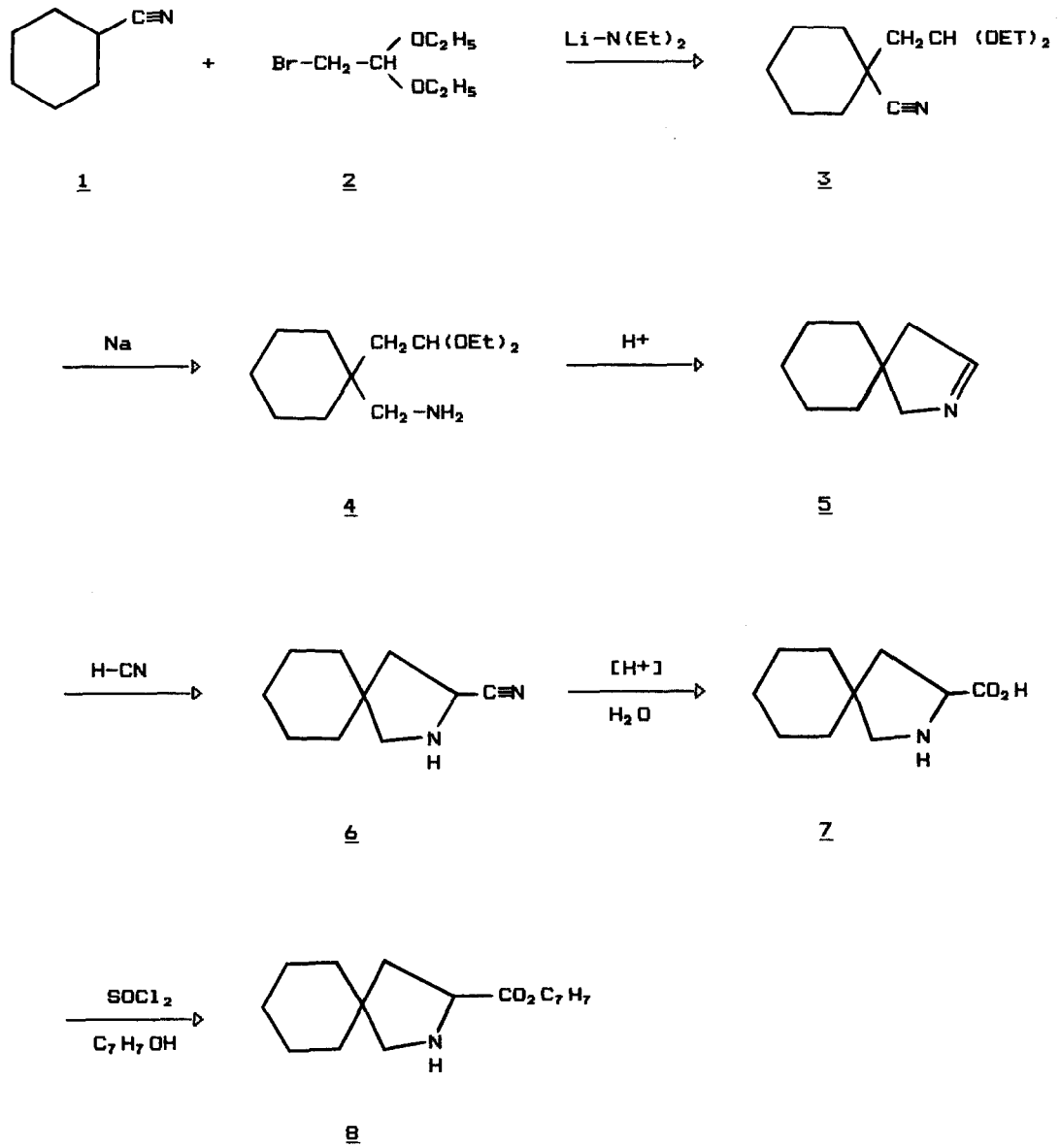
Spiro[4.n]-2-aza-alkan-carboxylic acids represent bulky proline analogues with increased lipophilicity. They are readily available from cyclic nitriles via alkylation with bromoacetaldehyde acetals, reduction to the corresponding amine, cyclisation to the imine and subsequent Strecker synthesis.

Introduction:

Hydrophobic interactions are known to play an important role in the binding of substrates or inhibitors to the active site of an enzyme. In persuit of this general knowledge we synthesized some lipophilic and sterically demanding amino acids [1] in order to substitute proline-residues in peptides. Recently powerful inhibitors of the angiotensin converting enzyme have been found which contain the spiro-proline substructure [2,3]. The synthesis of the spiro[4.5]-compound described here can be used to prepare related systems in a similar and rather convenient manner.

Chemistry:

The anion of cyclohexanecarbonitrile 1 can be obtained with lithiumdiethyl-amide [4] and alkylated with bromoacetaldehyde diethylacetal 2 at -70°C in high yield [8]. Subsequent reduction of the nitrile 3 is performed best with sodium in ethanol to give the amine 4, which is purified by distillation (90% yield, b.p. 69-72 °C at 8 torr (10^3 Pa)). Cleavage of the acetal groups leads to the cyclic imine 5 which should not be isolated but rather converted to the aminonitrile 6 by means of the Strecker synthesis [5, 9].



Scheme

Synthesis of (R,S)-spiro[4.5]-2-aza-decan-3-carboxylic acid

Complete transformation of the imine is checked by thin-layer chromatography and the reaction is performed under nitrogen or argon. The raw aminonitrile 6 is then saponified to the amino acid 7 by heating in 4N HCl for five hours. Precausion should be taken for traces of HCN escaping from the mixture. Evaporation of the butanol extract of the aqueous solution leaves the racemic amino acid hydrochloride, which can be recrystallized from ethanol or other solvents like chloroform/butanol/diisopropyl ether to yield 82% (m.p. 205 °C (decomposition)). The free amino acid 7 can be obtained by treatment with an ion exchange resin e.g. amberlite™ IR45 (acetate form) in water and recrystallisation from ethanol/ether. Transformation of the amino acid 7 to the benzyl-ester 8 (m.p. 145 °C) via the thionyl chloride procedure [1, 6] gives a derivative (77% yield) suitable for peptide synthesis.
Experiments concerning the optical resolution of 8 via a diastereomeric salt have not been successful yet.

References and Footnotes

[1] V.Teetz, R.Geiger and H.Gaul, this journal (1984).
[2] Schering Corporation, EPA 50800 (1982).
[3] Hoechst Aktiengesellschaft, DOS 3211397 (1983).
[4] M.Larcheveque and Th.Cuvigny, Tetrahedron Letters 44, 3851 (1975).
[5] A.Strecker, Liebigs Ann.Chem.130, 217 (1864).
[6] J.Ramachandran and C.H.Li, J.Org.Chem.28, 173 (1963).
[7] 'Pinner' synthesis; see D.B.Neilson, in Patai, The Chemistry of Amidines and Imidates, pp.385-489, Wiley New York (1975).

[8] 1-(Di-(ethyloxy)ethyl)-cyclohexanecarbonitrile 3 :
51.7 ml (0.5 mol) dry diethylamine are added to 312.5 ml (0.5 mol) of a 15% solution of n-butyllithium in hexane at -10°C under nitrogen. The solution is stirred for 20 min. then cooled to -70°C. Within 30 min. 54.6 g cyclohexanecarbonitrile 1 are added, the mixture is stirred for additional 30 min. and 98.5 g bromoacetaldehyde diethylacetal 2 are added dropwise within 1 hour. The reaction is left for 24 h. at low temperature then warmed up to room temperature and poured onto 100 g ice. After twofold extraction with 500 ml ethyl acetate the organic layer is dried over sodium sulfate, concentrated i.vac. and submitted to a vacuum distillation. Yield: 90 g (80%) ; b.p. 78-79 °C at 8 torr (10^3 Pa).

[9] Spiro[4.5]-2-aza-decan-3-carbonitrile 6 :
80.2 g Aminomethyl-di-(ethyloxy)ethyl-cyclohexane 4 are stirred in a mixture of 300 ml ethanol and 300 ml 1 N HCl under nitrogen or argon for 1 h.. After complete cleavage of the starting material the solution is cooled to 0 °C and quickly adjusted to p_H5 with 2 N NaOH. Immediately afterwards the mixture is cooled to -10 °C, 300 ml glacial acetic acid and 17.5 g sodium cyanide (NaCN) are added and the reaction vessel is closed for 5 h.. Complete transformation to the aminonitrile 6 is checked by thinlayer chromatography on silica gel; solvent: ethyl acetate / petrol ether 2:1 (v/v). The R_f-values differ substantially (0.65 versus 0.3 for the nitrile). The solution is then evaporated to dryness. This raw material should soon be saponified to the free amino acid 7 or directly converted to an ester [7].

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