SYNTHESIS OF ENANTIOMERICALLY PURE CYCLOHEXYLGlyCINE

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Abstract: (S)-cyclohexylglycine (1) is prepared in high yield by hydrogenation of (S)-phenylglycine (2) using rhodium on carbon as the catalyst.

Cyclohexylglycine (α-amino-cyclohexaneacetic acid) (1) is used as a non-natural amino acid in pharmaceutical studies and in peptide chemistry. Apart from its close analogy to phenylglycine (2), it functions as a structural mimic of the natural amino acids valine and isoleucine. In connection with the synthesis of non-natural amino acids, we were looking for a method to prepare multigram quantities of (S)-1.
A number of strategies has been used to prepare racemic 1.\(^3\) One of them comprises of a Strecker reaction starting from cyclohexane-carboxaldehyde, followed by hydrolysis of the resulting amino nitrile.\(^4\) Also several enantioselective syntheses\(^5\) and enzymatic resolutions\(^6\) are known, which lead to enantiomerically enriched material.

An obvious method for the preparation of enantiomerically pure 1, is the hydrogenation of phenylglycine 2 (Scheme 1). Both enantiomers of 2 are readily available and hydrogenation leads, in principle, directly to 1. However, an important drawback of this approach, is the partial hydrogenolysis of the benzylic amino group. This leads, after reduction of the aromatic ring, to the formation of cyclohexaneacetic acid. A reported\(^7\) hydrogenation of 2, using palladium hydroxide on charcoal (Pd(OH)\(_2\)/C) as a catalyst, gives low yields due to this side-reaction. In addition, partial racemisation of the product was reported.

Several procedures for the hydrogenation of 2 using Adam’s catalyst (PtO\(_2\))\(^8\) or platinum on carbon (Pt/C)\(^9\) have been reported.\(^10\) In addition, a patent has recently been published describing the hydrogenation of 2 with 30 bar of hydrogen pressure and catalytic amounts of ruthenium on carbon.\(^11\) In this procedure, 1 is
isolated as its hydrochloride salt in a moderate 65% yield, without racemisation. The reduction of 4-hydroxy-phenylglycine using Raney Nickel as the catalyst has also been described.\textsuperscript{12}

Contrary to Pd and Pt catalysts, rhodium promotes hydrogenolysis to a much lesser extent. Until now, the use of rhodium on a support has not been reported in connection with the synthesis of 1. Rhodium black has been used,\textsuperscript{13} but gives a very slow reaction. On the contrary, the structurally related mandelic acid has been hydrogenated successfully using Rh on alumina.\textsuperscript{14} The reaction gave high yields and hydrogenolysis was not observed. However, the e.e. of the product appeared to be slightly lower than the e.e. of the starting material.

We decided to use rhodium on carbon (Rh/C) as the hydrogenation catalyst for the preparation of (S)-1. Using 0.05 equiv. of 5% Rh/C and 3.6 bar of H\textsubscript{2}-pressure, the hydrogenation proceeded smoothly at 50 °C in aqueous HCl. After removal of the catalyst, the product (S)-1 was easily isolated by neutralising the reaction mixture, followed by filtration. After drying, pure (S)-1 was isolated in 92% yield.\textsuperscript{15} Determination of the e.e. by HPLC showed that no racemisation had occurred. So, Rh/C can be used as an effective catalyst for the hydrogenation of phenylglycine to 1 without racemisation or significant hydrogenolysis. This method will probably also be effective in the hydrogenation of other aromatic amino acids such as 4-hydroxy-phenylglycine, phenylalanine and tyrosine.

**Experimental**

The rhodium catalyst was obtained from Johnson Matthey Chemicals. Hydrogenation’s were performed in a stirred 1L Büchi autoclave. Determination
of the e.e. was performed on HPLC using a Daicel Crown ether (+) column at 15 °C with aqueous HClO₄ (pH = 2) as the eluent. Post-column reaction of the components with 1,2-phthalic dicarboxaldehyde / mercapto ethanol reagent at pH = 10 was followed by fluorescence detection.

(S)-cyclohexylglycine (1).

A slurry of 20.0 gram (0.132 mol, 99% e.e.) of (S)-phenylglycine in 25 gram (0.208 mol, 1.6 eq.) of 30% aqueous HCl and 90 gram of water was placed in an autoclave. 2.10 Gram of 5% Rh/C (moisture content 59%) was added and the slurry was stirred at 50 °C. After 30 min. the starting material had completely dissolved and stirring was continued at 50 °C for 40 h under 3.6 bar of H₂-pressure. The reaction was monitored with TLC. After completion of the reaction, the catalyst was filtered off and the reaction mixture was allowed to come to room temperature. 27 Gram (0.203 mol) of 30% aqueous NaOH was added dropwise and the resulting white suspension was filtered. The white solid was washed with water and dried in vacuo giving 19.1 gram (0.122 mol, 92% yield, 99% e.e.) of (S)-1. The ¹H-NMR data corresponded with those reported in the literature. Anal. Calcd for C₈H₁₅N₁O₂: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.10; H, 9.42; N, 8.95.

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References


For reduction of the \( N \)-methyl amino derivative, see ref. 1a.


10. In our hands, hydrogenation of \( (S) \)-2 with Pt/C in aqueous HCl afforded a greenish solution and large amounts of catalyst were needed for the reaction to reach completion.


15. Analysis of the mother liquor showed that 1% of cyclohexaneacetic acid had been formed, so the reaction has a selectivity of 99%.

16. The catalyst was re-used without loss of activity.

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