



A Convenient Synthesis of Optically Active Phenylglycine

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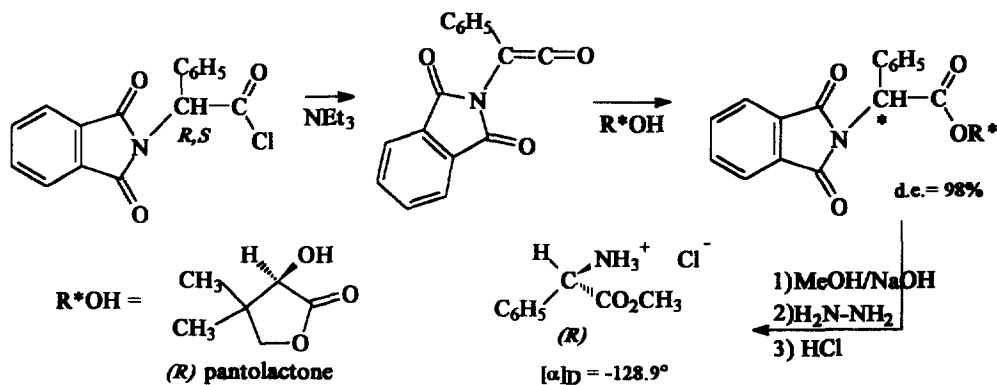
Abstract : *Optically active R phenylglycine methyl ester hydrochloride (ee = 98%) was prepared in 90% yield from racemic phenylglycine. The key step was the base catalysed diastereoselective addition at -78°C of R pantolactone to the N-phthalyl protected phenylglycine ketene*

Optically active phenylglycine is an aminoacid widely used in the preparation of bioactive peptides, and many enantioselective syntheses have been described in the literature¹. We wish to report a novel and convenient synthesis resulting from the total conversion of the racemic mixture *via* its ketene, into one enantiomer (deracemization or retroracemization).

Previous studies have shown that the base catalysed addition of a chiral alcohol to ketenes derived from various racemic aryl propionic acids can afford, depending on the experimental conditions, only one diastereoisomer². We decided to explore this method to prepare optically active phenylglycine, since its structure is very close to that of aryl propionic acids. Amino ketenes are generally generated *in situ*, except in the case of the phthalimido *ter*-butyl ketene which can be isolated as a crystalline solid³. The only reaction involving amino ketenes which has been extensively investigated is the cycloaddition of imines because of its utility particularly in the β -lactam synthesis^{2b}. Only Hegedus *et al*^{4,5} have studied the stereoselective addition of achiral alcohols or amines to chiral chromium amino ketene complexes. These complexes were generated by photolysis of corresponding chromium amino carbene complexes which were prepared from chromium hexacarbonyl and methyl or aryl lithium. High diastereoisomeric excesses were generally obtained, except in the case of arylglycines⁵ (d.e. <76%)

We prepared the phenylglycine ketene more simply and in quantitative yield by dehydrochlorination of the corresponding acyl chloride. The amine function must be previously protected by a phthalyl group in order to avoid NH addition to the ketene. The N-phthalyl phenylglycine acid chloride resulting from treatment at room temperature with oxalyl chloride, was first dehydrochlorinated at low temperature by triethylamine and then *R* pantolactone was added. Both reactions must be carried out at low temperature since at temperatures higher than -30°C undesired side reactions occur. When the reaction was performed at -78°C, the *R,R* pantolactonyl ester was afforded in 98% d.e.⁶, it is worth noting that an increase of temperature to -40°C just

slightly moderated the diastereoselectivity ($d.e.^6 = 95\%$). After transesterification with methanol the phthalyl N-protecting group was cleaved with hydrazine and *R* phenylglycine methyl ester hydrochloride, was isolated without racemization⁷. Next this latter can be easily saponified.



Work is now in progress on extending this new methodology to the asymmetric synthesis of other useful aminoacids.

REFERENCES AND NOTES

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- Determined from the ¹H NMR spectrum (Bruker AC 250) by integration of the H-3 signals of the pantolactonyl moiety of the diastereoisomers and by HPLC (column Chirasphere Merck, 25cmx4mm, flow: 1ml/min, hexane/ isopropanol 80/20, retention times : 14.14 min for the *S,R* isomer and 15.90 min for the *R,R* isomer).
- General procedure: to a stirred solution of N-phthalyl phenylglycine acid chloride (prepared from 1g or 3.56 mmol of acid) in 9.5 ml of anhydrous THF, cooled to -78°C under argon, was first added 0.75 ml (1.5 equiv) of NEt₃ followed by, after 25 minutes, a precooled solution of 0.51 g (3.91 mmol, 1.1 equiv) of *R* pantolactone in 5.6 ml of THF. After 6 h at this temperature a 1N solution of citric acid (15 ml) was added and the reaction mixture was allowed to warm to room temperature. The solution was extracted with AcOEt (25 ml) and the organic layer was washed successively with water and a sodium bicarbonate solution and then dried over sodium carbonate. Evaporation under vacuum gave the pantolactonyl ester. To a solution of this ester in 10 ml of MeOH cooled to 0°C was slowly added 3.2 ml (1 equiv) of a 1M solution of NaOH. The solution was rapidly concentrated in vacuo and the residue was chromatographed (silica gel, hexane-AcOEt 1-1). To a stirred solution of the resulting methyl ester in 4 ml of MeOH and 4 ml of THF, was slowly added a solution of 0.24 ml of hydrazine hydrate in 1 ml of MeOH. Stirring was continued for 3 h and a 1N HCl solution (2 ml) was added. After 2h of additional stirring, the precipitate was filtered off and the filtrate concentrated in vacuo. The optical purity of *R* phenylglycine methyl ester hydrochloride, ee = 98%, [0.64g, Yield = 90%, mp = 189-190°C, $[\alpha]_D = -128.9$ ($c=2$, MeOH)⁸] was verified from the ¹H NMR spectrum (Bruker AC 250) recorded in the presence of Eu(hfc)₃.
- Duhamel L, Fouquay S., Plaquevent J-C., *Tetrahedron Lett.*, 1986, 27, 4975. $[\alpha]_D = -132$ ($c=1$, MeOH)