

0040-4039(95)00820-9

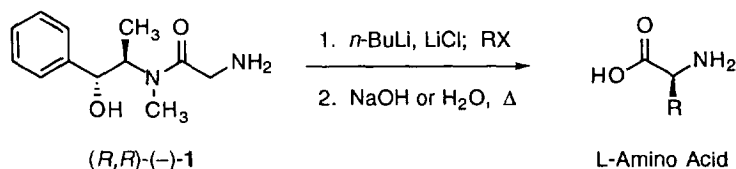
A One-Step Synthesis of Pseudoephedrine Glycinamide, a Versatile Precursor for the Synthesis of α -Amino Acids.

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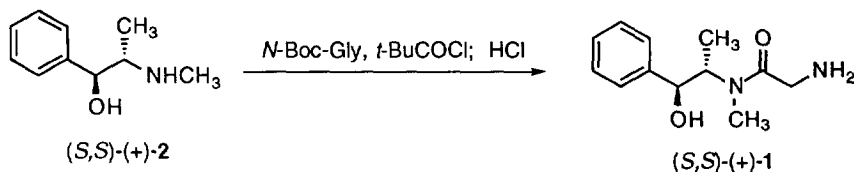
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Abstract: Both enantiomers of pseudoephedrine glycinamide [(+)- or (-)-**1**] were synthesized by either of two procedures: (1) a standard two-step coupling of *N*-Boc-Gly with pseudoephedrine followed by deprotection, or (2) a more economical one-step coupling reaction of Gly-OMe with pseudoephedrine mediated by LiCl and base.

We have recently found that the enantiomeric pseudoephedrine glycinamides (**1**) serve as versatile precursors for the synthesis of α -amino acids of either D- or L-configuration. Enantiomers (+)- or (-)-**1** undergo highly diastereoselective alkylation reactions, without the need for protective groups, and the resulting alkylated products are readily transformed into highly enantiomerically enriched D- or L- α -amino acids, respectively.¹ To maximize the utility of the method, we sought an economical and rapid procedure for the



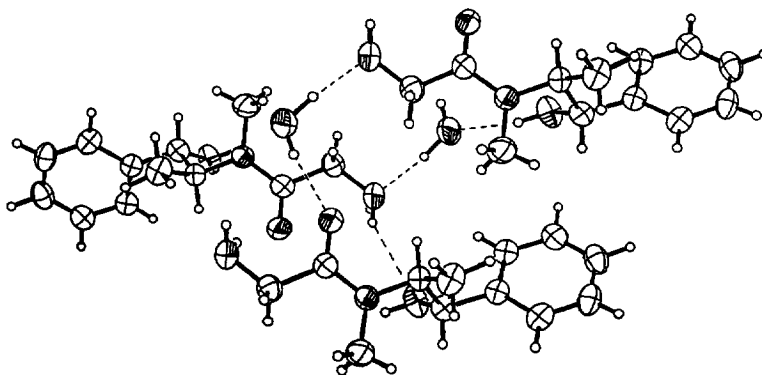
synthesis of the starting materials, (*S,S*)-(+)-**1** and (*R,R*)-(-)-**1**, from the inexpensive commodity chemicals (*S,S*)-(+)-pseudoephedrine [(*S,S*)-(+)-**2**] and (*R,R*)-(-)-pseudoephedrine [(*R,R*)-(-)-**2**], respectively. Conventional synthetic procedures for amide bond formation with the carboxyl group of glycine (and amino acids in general) generally utilize an *N*-protected, carboxyl-activated glycine (amino acid) derivative in the coupling reaction, and thus require a second step to deprotect the amino group. Such a procedure provided (+)- and (-)-**1** for our initial studies and proved amenable to large-scale preparation, as detailed in the following protocol:



extensive precipitation within the reaction mixture in large-scale reactions (>10 g) and a concomitant decrease in the yield of product. As little as 0.2 equiv of *n*-butyllithium may be used to promote the reaction, with only a 10% decrease in the yield of product.

The success of the coupling reaction relied critically upon the use of lithium chloride as an additive. In the absence of lithium chloride the rate of the coupling reaction was markedly slower and self-condensation of glycine (resulting in the incomplete consumption of **2**) and overglycylation of the product competed significantly, diminishing the yield of **1**. The accelerating effect of lithium chloride is believed to result from activation of glycine methyl ester by bidentate coordination to the lithium cation. This coordination is also believed to diminish the nucleophilicity of the amino groups of glycine and the product **1**, thereby slowing the two major processes which decrease the yield of **1**: the oligomerization of glycine and the overglycylation of **1** (producing **3**). If the nucleophilicity of the amino group of pseudoephedrine were similarly attenuated by coordination to lithium, there would be no net improvement in the production of **1**. That this is not the case is hypothesized to be due to the operation of a mechanism wherein glycine methyl ester undergoes initial transesterification with the alkoxy group of lithiated pseudoephedrine (hence the role of *n*-butyllithium in the reaction), followed by rapid intramolecular *O*→*N* acyl transfer. The transesterification of amino acid esters is known to be a facile process under basic conditions.³ Furthermore, it is known that *O*→*N* acyl transfer within pseudoephedrine esters is a very rapid reaction under neutral or basic conditions and strongly favors the *N*-acyl products.⁴

Even under optimum conditions, minor amounts of the by-product **3** (<10%) were present in the reaction product. This by-product was difficult to remove by direct recrystallization or by chromatography. Further investigation revealed that **1** forms a highly crystalline hydrate that is easily purified by recrystallization from wet tetrahydrofuran (mp 84-86 °C). The composition of this crystalline material as **1**•H₂O was supported by elemental analysis (Calcd for C₁₂H₁₈N₂O₂•H₂O: C, 59.93; H, 8.32; N, 11.66; Found: C, 59.85; H, 8.58; N, 11.58) and was established unequivocally by X-ray crystallographic analysis. In the X-ray crystal structure of the hydrate, the water molecule is observed to form hydrogen bonds with three different functional groups



(hydroxyl hydrogen, amide oxygen, and amino nitrogen) of three different molecules in the crystal lattice. Dehydration of the hydrate was readily accomplished in either of two ways, as detailed in the procedures which follow. In both methods a final dehydration step involving heating at 50 °C in vacuo for 2 d was employed. It was found that deletion of this step in method B produced only a slight decrease in the yield of the subsequent alkylation reactions of **1**.¹ The following experimental procedures have provided large quantities of both enantiomers of pseudoephedrine glycinamide for the synthesis of D- or L- α -amino acids.

Synthesis of (S,S)-(+)-**1** from Glycine Methyl Ester and (S,S)-(+)-**2**

n-Butyllithium (25.0 mL, 10 M in hexane, 0.250 mol, 0.830 equiv) was added dropwise to an ice-cold solution of (S,S)-(+)-pseudoephedrine (50.0 g, 0.300 mol, 1 equiv) and anhydrous lithium chloride (25.0 g, 0.590 mol, 1.97 equiv) in tetrahydrofuran (500 mL). After 10 min, a solution of glycine methyl ester (32.0 g, 0.360 mol, 1.20 equiv)² in tetrahydrofuran (50 mL) was added dropwise to the reaction mixture over a 1.5-h period. After completed addition, the mixture was further stirred at 0 °C for 1 h. Water (50 mL) was added, and the reaction mixture was concentrated in vacuo to remove tetrahydrofuran. The liquid residue was diluted with 1 N aqueous sodium hydroxide solution (200 mL) and the product was extracted with three 200-mL portions of a 10:1 mixture of dichloromethane:isopropanol. The combined organics were dried (sodium sulfate), filtered, and concentrated. The residue was dissolved in hot tetrahydrofuran (120 mL), water was added (6 mL), and the solution was allowed to cool, whereupon extensive crystallization of the product occurred. Crystallization was completed by allowing the flask to stand for 24 h at -20 °C. The crystals were collected and air-dried to give 53.0 g of (S,S)-(+)-**1**·H₂O (73%, mp 84-86 °C). Further crystallization from the mother liquors provided an additional 2.20 g of product (3%). The spectral data (¹H NMR and IR) are identical to those listed above for anhydrous **1**; [α]_D²⁰ = +96.6° (c = 2.0, CH₃OH).

Dehydration of **1**·H₂O. Method A

A suspension of **1**·H₂O (14.2 g) in dichloromethane (100 mL) was stirred with anhydrous potassium carbonate (13.0 g) at 23 °C for 12 h. The resulting cloudy solution was filtered through Celite and the clear filtrate was concentrated in vacuo. The residue was dissolved in hot toluene (50 mL). Upon cooling, anhydrous **1** precipitated from solution. The solid was collected by filtration and was further dried in vacuo at 50 °C for 2 d to afford 12.4 g of anhydrous **1** (94%, mp 78-80 °C. Calcd for C₁₂H₁₈N₂O₂: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.63; H, 8.16; N, 12.58). Chloroform may be used in lieu of dichloromethane in this procedure, requiring much less time for the initial drying with potassium carbonate (<10 min).

Dehydration of **1**·H₂O. Method B

A solution of **1**·H₂O (50.3 g) in warm acetonitrile (ca. 200 mL) was concentrated in vacuo. The residue was dissolved in toluene (250 mL) and the resulting solution was concentrated. Anhydrous **1** was obtained by precipitation of the residue from toluene and was dried as in Method A to give 45.7 g of anhydrous **1** (98%). Calcd for C₁₂H₁₈N₂O₂: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.56; H, 8.13; N, 12.57.

Acknowledgment This research was generously supported by the National Science Foundation and the National Institutes of Health. JLG acknowledges postdoctoral fellowship support from the National Institutes of Health.

References and Notes

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(Received in USA 21 April 1995; accepted 5 May 1995)