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

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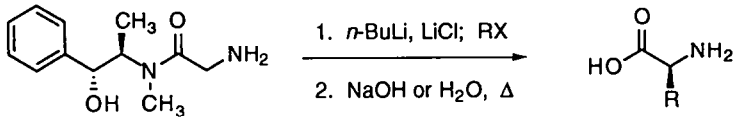
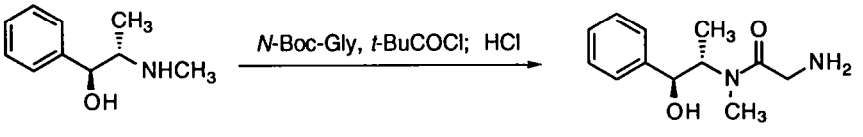
Abstract: Both enantiomers of pseudoephedrine glycinamide [(+)- or (–)-**1**] were synthesized by either of two procedures: (1) a standard two-step coupling of *N*-Boc-Gly with pseudoephedrine followed by deprotection, or (2) a more economical one-step coupling reaction of Gly-OMe with pseudoephedrine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



(*R,R*)-(–)-**1** L-Amino Acid

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:



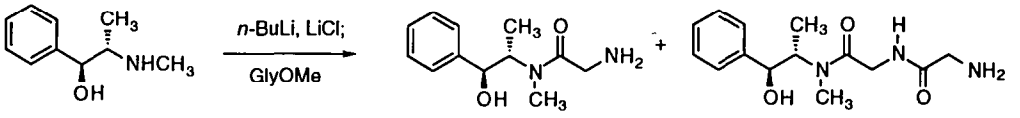
(*S,S*)-(+)-**2** (*S,S*)-(+)-**1**

Synthesis of (*S,S*)-(+)-**1** from *N*-(*tert*-butoxycarbonyl)glycine and (*S,S*)-(+)-**2**

Pivaloyl chloride (14.1 mL, 0.114 mol, 1.00 equiv) was added dropwise to a vigorously stirred solution of *N*-(*tert*-butoxycarbonyl)glycine (20.0 g, 0.114 mol, 1.00 equiv) and triethylamine (19.1 mL, 0.137 mol, 1.20 equiv) in dichloromethane (400 mL) at 0 °C. After 5 min, a fine white solid precipitated from the reaction mixture. After 30 min, a second portion of triethylamine (19.1 mL, 0.137 mol, 1.20 equiv) and solid (*S,S*)-(+)-pseudoephedrine (18.9 g, 0.114 mol, 1 equiv) were added sequentially to the cold reaction mixture. The reaction mixture was stirred for 45 min at 0 °C. Volatiles were removed in vacuo and the resulting slurry was dissolved in 1:1 methanol-water (400 mL). The resulting solution was cooled in an ice bath and concentrated hydrochloric acid (150 mL) was added carefully to the cold solution. Vigorous gas evolution was observed during and immediately following the addition. After stirring for 3 h at 0 °C, the reaction mixture was freed of methanol by concentration in vacuo at 23 °C. The aqueous concentrate was cooled in ice while the pH was adjusted to 14 by the slow addition of 50% aqueous sodium hydroxide solution (Caution! Exotherm). The addition rate was moderated so as to maintain a solution temperature of ≤ 45 °C. The basic aqueous solution was extracted with four 250-mL portions of dichloromethane. The combined organic extracts were dried over solid anhydrous potassium carbonate and the dried solution was filtered through Celite. The filtrate was concentrated in vacuo producing an oily residue. The residue was dissolved in toluene and the resulting solution was concentrated in vacuo. The oily residue obtained upon concentration was dissolved in toluene (80 mL, warming with a heat gun may facilitate this process) and the resulting solution was seeded with anhydrous (*S,S*)-(+)-pseudoephedrine glycinamide. When precipitation of the product appeared to be complete (ca. 2 h), the flask was cooled to 0 °C and was held at that temperature for 1 h. The solid product was collected in two crops and was dried in vacuo (0.2 mm) at 55 °C for 12 h (18.04 g first crop, 4.18 g second crop, 88% combined yield, mp 78–82 °C). IR (neat, cm^{-1}) 3361, 2981, 1633, 1486, 1454, 1312, 1126, 1049, 926, 760, 703; ^1H NMR (1:1 ratio of rotamers, $CDCl_3$, δ) 7.29-7.40 (m, 5H), 4.53-4.63 (m, 1.5H), 3.88 (m, 0.5H), 3.72 (d, 0.5H), 3.46 (d, 1H, *J*=16.6), 3.37 (d, 0.5H, *J*=17.1), 2.97 (s, 1.5H), 2.79 (s, 1.5H), 2.11 (s(br), 3H), 1.09 (d, 1.5H, *J*=6.7), 0.99 (d, 1.5H, *J*=6.7); ^{13}C NMR ($CDCl_3$, δ): 174.1, 173.5, 142.3, 142.1, 128.7, 128.5, 127.9, 126.9, 126.7, 75.8, 74.9, 57.5, 57.2, 43.7, 43.4, 30.1, 27.1, 15.3, 14.4. Calcd for $C_{12}H_{18}N_2O_2$, C, 64.84; H, 8.16; N, 12.60; Found C, 64.54; H, 7.93; N, 12.46; $[\alpha]_D^{20}$ = +102.0° (c = 1.06, CH_3OH). For (*R,R*)-(–)-**1**, $[\alpha]_D^{20}$ = –101.2° (c = 1.2, CH_3OH).

Although the above method provided both (+)- and (–)-**1** in quantity, the expense of *N*-(*tert*-butoxycarbonyl)glycine led us to search for a more economical protocol for the synthesis of **1** and, if possible, one proceeding in a single step. To meet this goal it was necessary to activate the carboxyl group of glycine toward coupling with pseudoephedrine, while avoiding self condensation (with the free amino group of glycine), as well as coupling with the amino group of the reaction product (see structure **3**). This was accomplished by using glycine methyl ester as the glycine transfer reagent, however only after extensive development of the reaction parameters.

The "free-base" form of glycine methyl ester can be obtained in ≥85% yield by neutralization of the hydrochloride salt with ammonia, followed by distillation.[2] Although glycine methyl ester will oligomerize upon standing at ambient temperature, we have stored the neat liquid at –20 °C for at least 2 weeks without noticeable degradation. The condensation of glycine methyl ester with pseudoephedrine is brought about by partial lithiation of pseudoephedrine (1 equiv) with *n*-butyllithium (0.7-0.9 equiv) in tetrahydrofuran at 0 °C in the presence of lithium chloride (≥2 equiv) followed by the slow addition of a solution of glycine methyl ester in tetrahydrofuran. Use of a slight excess of glycine methyl ester (1.2–1.3 equiv) proved optimum for the



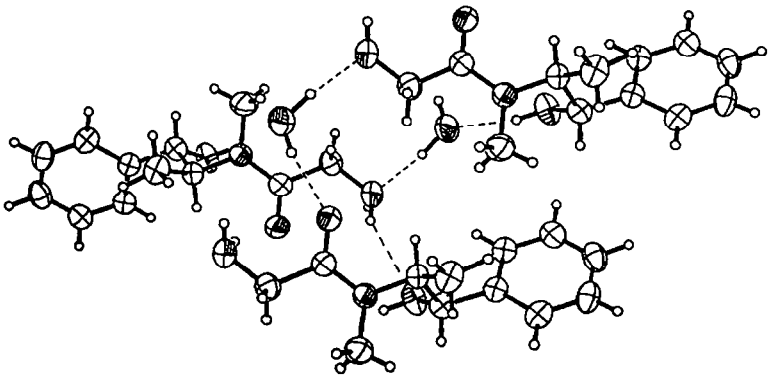
(*S,S*)-(+)-**2** (*S,S*)-(+)-**1** (76%) **3** (<10%)

complete consumption of pseudoephedrine, while minimizing the formation of pseudoephedrine glycylglycinamide (**3**), the major by-product of the reaction (<10%). Substoichiometric amounts of *n*-butyllithium are desirable, with 0.7-0.9 equiv being optimum. Use of a full equivalent of base caused

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 $O \rightarrow N$ acyl transfer. The transesterification of amino acid esters is known to be a facile process under basic conditions.[3] Furthermore, it is known that $O \rightarrow N$ 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**•H_2O was supported by elemental analysis (Calcd for $C_{12}H_{18}N_2O_2$•H_2O: 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**•H_2O (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**; $[\alpha]_D^{20}$ = +96.6° (c = 2.0, CH_3OH).

Dehydration of **1**•H_2O, Method A

A suspension of **1**•H_2O (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 $C_{12}H_{18}N_2O_2$: 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**•H_2O, Method B

A solution of **1**•H_2O (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 $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.56; H, 8.13; N, 12.57.

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