

## A Practical Method for the Synthesis of D- or L- $\alpha$ -Amino Acids by the Alkylation of (+)- or (-)-Pseudoephedrine Glycinamide

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The central role of  $\alpha$ -amino acids in chemistry and biology has stimulated the development of numerous methods for their synthesis.<sup>1</sup> Among these, the asymmetric alkylation of chiral glycine derivatives, conceptually one of the simplest and most general strategies, figures prominently.<sup>2</sup> In this work we detail a new method for the synthesis of D- or L- $\alpha$ -amino acids that involves the direct alkylation of (+)- or (-)-pseudoephedrine glycinamide, without the need for protective groups. The methodology we describe offers an exceedingly practical alternative to existing methodology for  $\alpha$ -amino acid synthesis and is noteworthy for its directness and experimental simplicity.

Pseudoephedrine is an inexpensive chiral commodity chemical that is available in quantity in both enantiomeric forms. We have previously shown that amides derived from pseudoephedrine undergo efficient and diastereoselective alkylation reactions and that the alkylated products are readily transformed into chiral carboxylic acids, aldehydes, ketones, and alcohols of high enantiomeric purity.<sup>3</sup> In an important extension of this methodology, we now report the use of pseudoephedrine glycinamide (**1**) as an economical and versatile precursor for the synthesis of a wide range of natural and nonnatural  $\alpha$ -amino acids of high enantiomeric purity.

Both enantiomeric forms of **1** have been synthesized in quantity either by the direct acylation of pseudoephedrine with the mixed anhydride formed from *N*-Boc-glycine and pivaloyl chloride, followed by acidic cleavage of the *N*-Boc group (88%), or, more economically, in a single step by the condensation of glycine methyl ester with pseudoephedrine promoted by *n*-butyllithium and lithium chloride (70%).<sup>4</sup> Anhydrous **1** (mp 78–82 °C) can be weighed and transferred quickly in the laboratory without impairing subsequent alkylation reactions, but will hydrate upon extended exposure to the air.

Addition of a solution of (*S,S*)-(+)- or (*R,R*)-(–)-**1** (1 equiv) in tetrahydrofuran to a slurry of lithium chloride (6.0 equiv) and lithium diisopropylamide (1.95 equiv) in tetrahydrofuran at –78 °C leads to initial deprotonation of the hydroxyl and amino groups of **1**, as evidenced by the observation of products of N-alkylation when alkylating agents are added at this temperature. Upon warming of the *O,N*-dianion solution to 0

°C for 20 min, however, equilibration to the (*Z*)-enolate by C to N proton transfer must take place, for addition of electrophiles at this point efficiently forms products of C-alkylation; N-alkylation is effectively suppressed. A wide range of electrophiles can be utilized successfully in the alkylation reaction (Table 1), including poorly reactive substrates such as isobutyl iodide. Notably, the latter reaction can be conducted at 23 °C (8 h) without apparent decomposition of the enolate, affording **2c** with 90% de (73% yield). With other substrates, alkylation reactions are conveniently conducted at 0 °C. For allylic and benzylic halides, product de's of 91–93% are common, whereas normal or branched alkyl halides typically afford products with higher diastereoselectivity (96–98% de). The sense of asymmetric induction is the same as that previously observed for the alkylation of pseudoephedrine amide enolates: (*R,R*)-(–)-**1** produces L- $\alpha$ -amino acid derivatives, and (*S,S*)-(+)-**1** produces D- $\alpha$ -amino acid derivatives. Many of the alkylation products are crystalline compounds and can be isolated as analytically pure solids of  $\geq 99\%$  de by direct crystallization from the crude reaction mixture (see values in parentheses, Table 1).

The use of slightly less than 2 equiv of base is important not only for anion equilibration but also to avoid the onset of a deleterious side reaction that occurs when >2 equiv of base is added, resulting in the release of free pseudoephedrine (believed to involve an intermediate trianion). For this reason it is important to use solutions of *n*-butyllithium that are accurately titrated when preparing lithium diisopropylamide.<sup>5</sup> In small-scale reactions (<5 mmol) we have found that *n*-butyllithium may be used directly to deprotonate **1** (in lieu of lithium diisopropylamide), but produces an exotherm that leads to partial cleavage of **1** on a larger scale. Lithium diisopropylamide has been found to be effective on both large and small scales.

A major advantage of this methodology is the efficiency and ease with which the auxiliary is removed. Hydrolysis of the alkylation products occurs rapidly in the presence of sodium hydroxide (2 equiv) in water or water–methanol mixtures at reflux. The aqueous hydrolysis mixture is extracted with dichloromethane to remove the pseudoephedrine auxiliary (96% recovery). The alkaline, aqueous product solution is then treated with acylating agents such as di-*tert*-butyl dicarbonate or 9-fluorenylmethyl chloroformate in the presence of sodium bicarbonate (2.0 equiv, to quench excess hydroxide), to afford directly the corresponding Boc or Fmoc *N*-protected  $\alpha$ -amino acids (Table 2). The yield of this hydrolysis/*N*-protection procedure typically exceeds 90%, and, where substrates of  $\geq 99\%$  de are employed, products of  $\geq 99\%$  ee are often obtained. The rate of alkaline hydrolysis of these  $\alpha$ -amino amides is much faster than that of their hydrocarbon counterparts.<sup>3</sup> This is believed to be due to acceleration of the (rate-determining) intramolecular N  $\rightarrow$  O acyl transfer step. Importantly, the rate of epimerization of the  $\alpha$ -center is not correspondingly accelerated. In at least one case, enantiomeric enrichment of the product was actually observed (**2f** of 91% de gave amino acid of 94% ee) due to the slower rate of hydrolysis of the minor diastereomer.

A second cleavage method is available that is ideal for the isolation of free amino acids. Solutions of the alkylation products in pure water are sufficiently basic (pH  $\sim$  10) to undergo hydrolysis at reflux without the need for an external base. Although the rate of hydrolysis is slower, little (<2%) to no racemization is observed. Because the reactions proceed in pure water, no desalting procedures are necessary to isolate the pure amino acids. Extraction of the aqueous reaction mixture with dichloromethane, lyophilization of the aqueous layer, and trituration of the solid residue with ethanol (to remove any remaining pseudoephedrine) then provides the pure  $\alpha$ -amino acid (Table 3).

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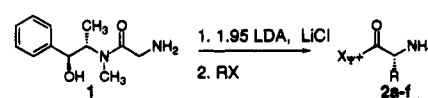
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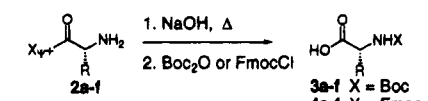
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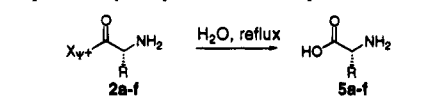
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**Table 1.** Diastereoselective Alkylation of Pseudoephedrine Glycinamide (**1**)<sup>a</sup>


RX	temp (°C)	time (h)	prod.	yield (%)	de <sup>b</sup> (%)
CH <sub>3</sub> CH <sub>2</sub> I	0	1.5	<b>2a</b>	82 (76)	97 (≥99)
CH <sub>2</sub> =CHCH <sub>2</sub> Br	0	0.3	<b>2b</b>	80 (69)	93 (≥99)
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> I	0	48	<b>2c</b>	55	97
	23	8	<b>2c</b>	73 (43)	90 (≥99)
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Br	0	1	<b>2d</b>	79 (68)	91 (≥99)
c-C <sub>3</sub> H <sub>5</sub> CH <sub>2</sub> I	0	10	<b>2e</b>	82 (66) <sup>c</sup>	98 (≥99)
o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> Br	0	2	<b>2f</b>	83	91

<sup>a</sup> Values in parentheses are for products isolated by recrystallization.<sup>b</sup> Determined by capillary GC analysis of the corresponding diacetates using a Chirasil-Val column. <sup>c</sup> Approximately 7% of the homoallylic isomer (S<sub>N</sub>2' product) was produced in this reaction. The isolated product was contaminated with ca. 1% of this byproduct.**Table 2.** Hydrolysis of Pseudoephedrine Amides Followed by N-Protection<sup>a</sup>


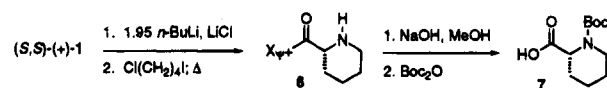
entry	R	time (h)	3a-f		4a-f	
			yield (%)	ee <sup>b</sup> (%)	yield (%)	ee <sup>b</sup> (%)
<b>a</b>	CH <sub>3</sub> CH <sub>2</sub>	1.5	97	≥99	99 <sup>c</sup>	≥99
	CH <sub>2</sub> =CHCH <sub>2</sub>	1.5	91	≥99	75	≥99
<b>c</b>	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	1.5	97	≥99	81	≥99
<b>d</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	3	88	≥99	90	≥99
<b>e</b>	c-C <sub>3</sub> H <sub>5</sub> CH <sub>2</sub>	2	93 <sup>d</sup>	≥98	84 <sup>e</sup>	≥99
<b>f</b>	o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	4-5	86	96 <sup>e</sup>	81 <sup>e</sup>	98 <sup>e</sup>

<sup>a</sup> All starting materials were of ≥99% de except as noted. <sup>b</sup> Enantiomeric excesses (ee's) were determined by HPLC analysis using a Crownpak CR(+) column. <sup>c</sup> Reaction performed using Fmoc-N-hydroxysuccinimide. <sup>d</sup> Isolated product contains ca. 1% of the 2-amino-5-hexenoic acid derivative. <sup>e</sup> Starting material was 91% de. Hydrolysis afforded amino acid of 94% ee; additional ee enrichment of **3f** and **4f** due to recrystallization.**Table 3.** Aqueous Hydrolysis of Pseudoephedrine Amides<sup>a</sup>


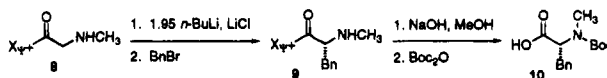
entry	R	time (h)	yield (%)	crude ee <sup>b</sup> (%)	isol ee <sup>c</sup> (%)
<b>a</b>	CH <sub>3</sub> CH <sub>2</sub>	10	88	≥99	≥99
<b>b</b>	CH <sub>2</sub> =CHCH <sub>2</sub>	10	87	98	≥99
<b>c</b>	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	10	86	≥99	≥99
<b>d</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	18	77	98	≥99
<b>e</b>	c-C <sub>3</sub> H <sub>5</sub> CH <sub>2</sub>	12	79 <sup>d</sup>	≥97	≥98
<b>f</b>	o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	22 <sup>e</sup>	71	98	≥99

<sup>a</sup> All starting materials were of ≥99% de except as noted. Enantiomeric excesses (ee's) were determined by HPLC analysis using a Crownpak CR(+) column. <sup>b</sup> Prior to trituration with EtOH. <sup>c</sup> Subsequent to trituration with EtOH. <sup>d</sup> Isolated product was contaminated with ca. 1% 2-amino-5-hexenoic acid. <sup>e</sup> Starting material was 91% de. This reaction was conducted in a 1:1 mixture of water and *p*-dioxane.

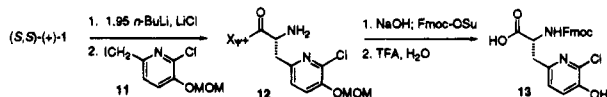
We have extended this methodology to the synthesis of cyclic amino acids and α-N-methylamino acids. For example, treatment of the enolate derived from (S,S)-(+)-**1** with 1-chloro-4-iodobutane followed by heating of the crude reaction product to induce cyclization of the chloroalkylamine forms the D-pipecolinic acid amide **6** in 72% yield (96% de). Alkaline cleavage of the pseudoephedrine auxiliary, acylation of the crude product with di-*tert*-butyl dicarbonate, and recrystallization affords *N*-Boc-D-pipecolinic acid **7** in 77% yield (96% ee). *N*-Methyl α-amino acids are prepared from pseudoephedrine



*N*-methyl glycine amide (**8**), synthesized from *N*-Boc-sarcosine and pseudoephedrine in analogy to **1** above. Alkylations of **8** are similar to those of **1** in yield and diastereoselectivity. For example, alkylation of **8** with benzyl bromide provides amide **9** (mp 119–120 °C) in 79% yield and 91% de (58% yield and ≥99% de after recrystallization). Cleavage of the pseudoephedrine auxiliary (2 equiv of sodium hydroxide, 1:1 methanol/water, reflux, 24 h) and *N*-acylation of the crude product with di-*tert*-butyl dicarbonate provides *N*-Boc-*N*-methyl-D-phenylalanine (**10**) in 88% yield (94% ee from **9** of >99% de).



Finally, we have applied this new methodology to the synthesis of D-β-(6-chloro-5-hydroxy-2-pyridyl)alanine, a constituent of the antitumor antibiotic kedarcidin chromophore.<sup>6</sup> Alkylation of the enolate derived from (S,S)-(+)-**1** (1.3 equiv) with iodide **11** (1 equiv)<sup>7</sup> at –78 °C for 5 h gave the alkylated amide **12** (crude de 93%, chromatographed de 96%, 89% yield). Alkaline cleavage of the auxiliary, as described above, occurs without competing hydrolysis of the chloropyridine group. Protection of the crude product with Fmoc-*N*-hydroxysuccinimide and removal of the methoxymethyl protective group with trifluoroacetic acid affords the acid **13** (mp 185–187 °C) in 73% yield (96% ee).



In conclusion, we have developed a practical, experimentally simple method for the synthesis of D- or L-α-amino acids involving the alkylation of (S,S)-(+)- or (R,R)-(–)-pseudoephedrine glycinamide (**1**). The method features simple preparation of starting materials from commercially available compounds and does not require protective groups. The hydrolysis of the pseudoephedrine auxiliary is easily achieved under mild conditions leading to both free and *N*-protected amino acids of high enantiomeric purity.

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**Supporting Information Available:** Sample experimental procedures for the preparation and alkylation of **1** and for the transformation of the alkylation products into free and *N*-protected (Fmoc and Boc) α-amino acids and a listing of spectroscopic and analytical data for all synthetic compounds (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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