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## General Method for the Synthesis of N-Methyl Amino Acids and N-Alkyl Amino Esters from O'Donnell's Schiff Bases

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Abstract: N-methyl amino acids, including L-abrine, and N-alkyl amino esters, were synthesized by reductive amination of O'Donnell's Schiff base amino esters with NaBH3CN and formaldehyde, or the appropriate aldehyde in CH3CN or THF in good to excellent yields, and with high purity. © 1997 Elsevier Science Ltd.

N-methyl amino acids are found as natural products and in a wide range of naturally occurring peptides and depsipeptides exhibiting an equally wide range of biological effects, including antibiotic, anticancer, antiviral, and immunosuppressive activity. N-methyl amino acids are also useful tools for stabilizing various peptide backbone conformations (e.g.  $\beta$  turns), and for obtaining structure-activity information about peptides. Various methods have been developed for the synthesis of optically active N-methyl amino acids, as well as the preparation of scalemic N-methyl amino acids. However, all of these methods have significant weaknesses, such as the inability to methylate more functionalized amino acids (i.e. histidine, tryptophan, and lysine), harsh reaction conditions,  $^{50}$ , flack of generality due to racemization and low reactivity,  $^{5c}$ , and instability of the intermediate products.  $^{5d}$ 

A widely used method for alkylating amines is reductive amination using NaBH<sub>3</sub>CN and an aldehyde or ketone.<sup>7</sup> This method has been used by Ohfune, *et al.*, to *N*-monoalkylate amino acids, with MeOH as the solvent, but attempts to *N*-methylate amino acids using formaldehyde and NaBH<sub>3</sub>CN led to inseparable mixtures of unmethylated, monomethylated, and dimethylated amino acids.<sup>8</sup> Recently, *N*-monoalkylation of amino esters using sodium triacetoxyborohydride was reported, but *N*-methyl analogs were not prepared.<sup>9</sup>

Scheme 1

Scheme 1

$$R_1 \longrightarrow OR_2 \longrightarrow i$$
, ii  $R_1 \longrightarrow OR_2 \longrightarrow R_1 \longrightarrow OH$ 
 $Ph \longrightarrow NMe \longrightarrow HN$ 
 $Ph \longrightarrow NMe \longrightarrow HN$ 
 $R_1 \longrightarrow OH$ 
 $R_1 \longrightarrow OH$ 

i. NaBH<sub>3</sub>CN, ACN or THF, AcOH; ii. H<sub>2</sub>C=O, NaBH<sub>3</sub>CN, pH~5-7; iii. H<sub>2</sub>, Pd/C, MeOH or EtOH; iv. O=CHR<sub>3</sub>, NaBH<sub>3</sub>CN, pH~5-7; v. H<sub>2</sub>, Pd/C, AcCl, MeOH or EtOH.

We are pleased to report the successful N-monomethylation of amino acids and amino esters in good to excellent yields using O'Donnell's Schiff bases of the parent amino acids/esters10 and reductive amination with NaBH<sub>3</sub>CN and aqueous formaldehyde. 11 followed by catalytic hydrogenation (Scheme 1). 12 Results are summarized in Tables 1 and 2. In most cases, the aprotic solvent acetonitrile<sup>13</sup> was used, but due to solubility problems, 1b and 1c were done in THF. It is significant to note that this method can be used to synthesize the natural product L-abrine (N-methyl-L-tryptophan, 4d), without competing Pictet-Spengler cyclization. 14 Under anhydrous conditions, this method can be extended to N-monoalkylation of amino esters with longer alkyl chains (5g).

Table 1. N-Methylation of Amino Acids

Entry	R <sub>1</sub>	R <sub>2</sub>	2 (%)	4 (%)
2	Me	HCPh <sub>2</sub>	77	91
b	HOCH <sub>2</sub>	$HCPh_2$	71	71-90
c	МеС(ОН)Н	HCPh <sub>2</sub>	63	74
d		Bn	86 / 61ª	82

Table 2. N-Alkylation of Amino Esters

Entry	Ri	R <sub>2</sub>	R <sub>3</sub>	3 (%)	5 (%)
e	i-Bu	Et	Н	63	92
f	Me	Me	Н	90	90
$\mathbf{g}^{b}$	Me	Me	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub>	90	91

Steps i, and iv. done in the presence of molecular sieves.

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- 11. General Procedure: 100 mg of Schiff-base 1 was dissolved in dry ACN and soln. added, via syringe to 1.6 eq. NaBH3CN stirring under Ar; pH brought to ~ 5-7 with glacial AcOH, Rxn. stirred at RT for ~20 min (TLC). An additional 6 eq. of NaBH3CN, along with 6 eq.  $H_2C=0$  (37.7%) and enough glacial AcOH to bring pH to ~ 5-7 was slowly added to stirred soln. If rxn. was not complete after 3-4 hr (TLC), an additional 1-2 eq. H<sub>2</sub>C=O (37.7%) was added and soln. stirred for 1-2 hr. Soln. diluted w/ Et<sub>2</sub>O, washed w/ sat. NaHCO<sub>3</sub> (aq.) and washed w/ brine. Org. layers collected, dried over K<sub>2</sub>CO<sub>3</sub>, filtered through Celite, ereduced via rotary evaporation, and dried overnight in vacuo. Product (2 or 3) purified via flash chromatography. Generally, 5-19% unmethylated secondary amine, and no 1, is recovered.
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<sup>&</sup>lt;sup>a</sup> Yields for steps i. and ii. recorded separately