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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

Jason J. Chruma, Dalibor Sames, and Robin Polt*

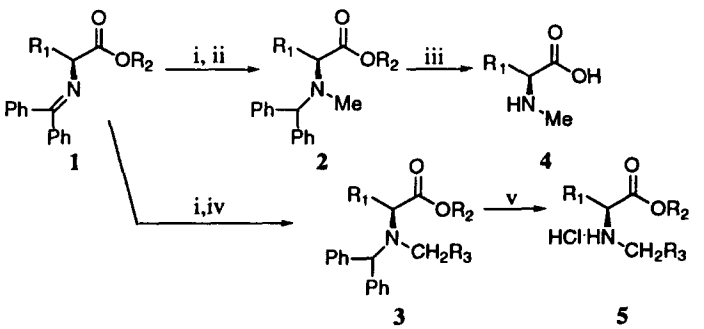
Department of Chemistry, University of Arizona, Tucson, AZ 85721 USA

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 $NaBH_3CN$ and formaldehyde, or the appropriate aldehyde in CH_3CN 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,[1] anticancer,[2,3] antiviral, and immunosuppressive activity.[3] *N*-methyl amino acids are also useful tools for stabilizing various peptide backbone conformations (e.g. β turns), and for obtaining structure-activity information about peptides.[4] Various methods have been developed for the synthesis of optically active *N*-methyl amino acids,[5] as well as the preparation of scalemic *N*-methyl amino acids.[6] However, all of these methods have significant weaknesses, such as the inability to methylate more functionalized amino acids (i.e. histidine, tryptophan, and lysine),[5a,5g] harsh reaction conditions,[5b,5f] lack of generality due to racemization and low reactivity,[5c,5e] and instability of the intermediate products.[5d]

A widely used method for alkylating amines is reductive amination using $NaBH_3CN$ and an aldehyde or ketone.[7] 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 $NaBH_3CN$ led to inseparable mixtures of unmethylated, monomethylated, and dimethylated amino acids.[8] Recently, *N*-monoalkylation of amino esters using sodium triacetoxyborohydride was reported, but *N*-methyl analogs were not prepared.[9]

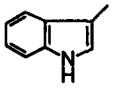
Scheme 1



i. $NaBH_3CN$, ACN or THF, AcOH; ii. $H_2C{=}O$, $NaBH_3CN$, pH~5-7; iii. H_2, Pd/C, MeOH or EtOH; iv. $O{=}CHR_3$, $NaBH_3CN$, pH~5-7; v. H_2, 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/esters[10] and reductive amination with $NaBH_3CN$ 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[13] 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_1	R_2	2 (%)	4 (%)
a	Me	$HCPh_2$	77	91
b	$HOCH_2$	$HCPh_2$	71	71-90
c	MeC(OH)H	$HCPh_2$	63	74
d		Bn	86 / 61[a]	82

[a] Yields for steps i. and ii. recorded separately

Table 2. N-Alkylation of Amino Esters

Entry	R_1	R_2	R_3	3 (%)	5 (%)
e	i-Bu	Et	H	63	92
f	Me	Me	H	90	90
g[b]	Me	Me	$CH_3(CH_2)_4CH_2$	90	91

[b] Steps i. and iv. done in the presence of molecular sieves.

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References and Notes

1. Ebata, M.; Takahashi, Y.; Otsuka, H. *Bull. Chem. Soc. Japan* , **1966**, *39* , 2535-38 and references cited therein.
2. Pettit, G. R.; Kamano, Y.; Herald, C. L.; Fujii, Y.; Kizu, H.; Boyd, M. R.; Boettner, F. E.; Doubek, D. L.; Schmidt, J. M.; Chapuis, J.-C.; Michel, C. *Tetrahedron* , **1993**, *49* , 9151-70.
3. Li, W.-R.; Jouillié, M.M. In *Studies in Natural Products Chemistry, Vol. 10, Stereoselective Synthesis (Part F)* ; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; pp 241-302.
4. (a) Vitoux, B.; Aubry, A.; Cung, M. T.; Marraud, M. *Int. J. Peptide Protein Res.*; **1986**, *27* , 617-632. (b) Goodfellow, V. S.; Marathe, M. V.; Kuhlman, K. G.; Fitzpatrick, T. D.; Cuarado, D.; Hanson, W.; Zuzack, J. S.; Ross, S. E.; Wieczorek, M.; Burkard, M.; Whalley, E. T. *J. Med. Chem.* **1996**, 39, 1472-84.
5. (a) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta*, **1963**, *43*, 327-333. (b) McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 1915-19. (c) Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314-33. (d) Freidinger, R. M.; Hinkle, J. S.; Perlow, D. S.; Arison, B. H. *J. Org. Chem.* **1983**, *48*, 77-81. (e) O'Donnell, M. J.; Bruder, W. A.; Daugherty, B. W.; Liu, D.; Wojciechowski, K. *Tetrahedron Lett.* **1984**, *25*, 3651-4. (f) Olsen, R. K. *J. Org. Chem.* **1970**, *35*, 1912-5. (g) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746-9.
6. Dorow, R. L.; Gingrich, D. E. *J. Org. Chem.* **1995**, *60*, 4986-7.
7. Lane, C. F. *Synthesis*, **1975**, 135 (*Review*).
8. Ohfune, Y.; Kurokawa, N.; Higuchi, N.; Saito, M.; Hashimoto, M; Tanaka, T. *Chem. Lett.*, 1984, 441-4.
9. a.) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah. R. D. *J. Org. Chem.* **1996**, *61*, 3849-62. b.) Ramanjulu, J. M.; Jouillié, M. M. *Syn. Comm.* , **1996**, *26* , 1379-84.
10. O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.*, **1982**, *47* , 2663-6.
11. General Procedure: 100 mg of Schiff-base 1 was dissolved in dry ACN and soln. added, *via* syringe to 1.6 eq. $NaBH_3CN$ stirring under Ar; pH brought to ~ 5-7 with glacial AcOH. Rxn. stirred at RT for ~20 min (TLC). An additional 6 eq. of $NaBH_3CN$, along with 6 eq. $H_2C{=}O$ (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. $H_2C{=}O$ (37.7%) was added and soln. stirred for 1-2 hr. Soln. diluted w/ Et_2O, washed w/ sat. $NaHCO_3$ (aq.) and washed w/ brine. Org. layers collected, dried over K_2CO_3, filtered through Celite,® reduced *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.
12. This method was first applied in our lab in the enantioselective synthesis of *N*-methylfucosamine, Sames, D.; Polt, R. *J. Org. Chem.*, **1994**, *59* , 4596-4601.
13. Borch, R. F.; Hassid, A. I. *J. Org. Chem.*, **1971**, *37* , 1673-4.
14. Czerwinski, K. M.; Deng, L.; Cook, J. M. *Tetrahedron Lett.*, **1992**, *33*, 4721-4.

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