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Facile Synthesis of Highly Functionalized *N*-Methyl Amino Acid Esters without Side-Chain Protection

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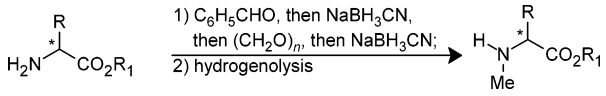
ABSTRACT



The facile, two-pot synthesis of *N*-methyl amino acid esters by way of reductive amination is presented. Side chain protection schemes are not required, the starting materials are all commercially available, and the synthetic method is straightforward and affords desired product in very high yield.

The occurrence of *N*-methyl amino acids (NMA) and their derivatives in natural products[1] and proteins[2] has attracted an interest in these compounds as valuable synthetic building blocks. Indeed, incorporation of NMA into synthetic peptides has been shown to afford increased resistance to proteolysis, unique membrane permeability, and uncommon conformational preferences dictated by the decreased hydrogen bonding capability. However, while various procedures for the production of NMA have been developed over the years,[3] few syntheses effectively combine the elements of simplicity and generality, particularly when dealing with amino acids bearing functionalized side chains.

Work in our laboratory synthesizing models of the active site of cytochrome *c* oxidase[4] required us to have a viable and efficient source of *N*-methyl L-histidine esters. A recent procedure by Hughes and co-workers produced the desired material, albeit with side-chain protection, in a six-step procedure with an overall yield of 30%.[5] In our hands, this procedure was less successful, affording the desired material in approximately 12% yield. Thus, we set out to develop an alternative route that would be amenable to the production of significant quantities of desired material in synthetically useful yields.

Herein, we report the preparation of *N*-methyl derivatives of side-chain-functionalized amino acid esters in high yield through facile laboratory manipulations. The procedure is performed, without resorting to side-chain protection, via consecutive reductive amination reactions, first with benzaldehyde, then with paraformaldehyde. Both sequences of imine (iminium) formation/reduction are performed in the same flask without isolation. Following isolation of the *N*-benzyl-*N*-methyl amino acid derivative, removal of the benzyl protecting group affords desired material. This method, which shows no trace of racemization, employs commercially available and relatively inexpensive amino acid esters as starting materials and affords the desired *N*-methylated compounds in a two flask sequence.

As shown in Scheme 1, our method involves treatment of the amino acid ester, in methanol, first with benzaldehyde

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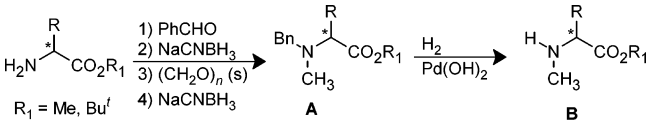
Scheme 1



1 R = CH_2(3-indolyl), *L*-tryptophan
2 R = CH_2(2-imidazolyl), *L*-histidine
3 R = CH_2CONH_2, *L*-asparagine
4 R = CH_2OH, *L*-serine
5 R = (*R*)-$CH(OH)CH_3$, *L*-threonine
6 R = $(CH_2)_3$(guanidyl), *L*-arginine
7 R = CH_2(4-phenolyl), *L*-tyrosine
8 R = CH_2(4-phenolyl), *D*-tyrosine
9 R = $CH_2CH_2CONH_2$, *L*-glutamine

for 1 h, followed by overnight reduction with sodium cyanoborohydride.[6] The thus-formed benzylamine is then treated in situ with solid paraformaldehyde. The initially formed suspension gradually dissolves in the methanol solution at a rate that is amino acid dependent; times are shown in Table 1. Once full dissolution is observed, another

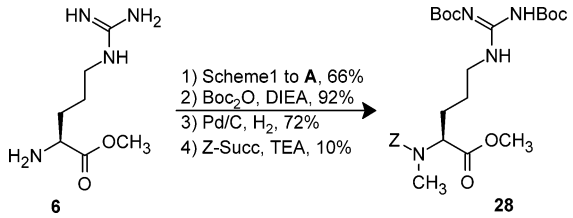
Table 1. *N*-Methylation of Functionalized Amino Acids

amino acid (R_1)	dissolution of $(CH_2O)_n$, h	**A**, %	**B**, %
1 (Me)	3	**10**, 89	**19**, 99
2 (Me)	5	**11**, 99	**20**, 99
3 (Bu^t)	3	**12**, 83	**21**, 99
4 (Me)	5	**13**, 90	**22**, 79
5 (Me)	4	**14**, 99	**23**, 67
6 (Me)	2	**15**, 66	**24**, 85
7 (Me)	3	**16**, 94	**25**, 96
8 (Me)	3	**17**, 95	**26**, 79
9 (Bu^t)	2	**18**, 99	**27**, 82

equivalent of sodium cyanoborohydride is added and again allowed to react overnight to furnish the *N*-benzyl-*N*-methyl amino acid ester (**A**).[7] Following isolation, the benzyl group can be removed via catalytic hydrogenolysis to afford the title compound (**B**). No diastereomers were detected in the formation of threonine amino esters **14** and **23**.

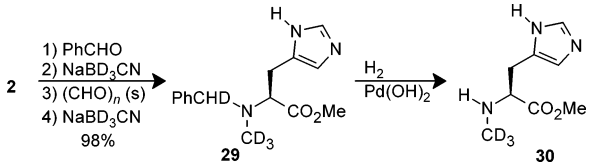
Methyl esters are not required; commercially available asparagine and glutamine *tert*-butyl esters, L-**3** and L-**9**, were employed. We were pleasantly surprised to find that these reaction conditions were successful for the direct *N*-methylation of the amino group in the presence of the basic guanidine functionality of arginine **6**. To verify the success of the reaction, compound **15** was transformed to known product **28**[5b] (Scheme 2) and compared with the reported analytical data of this highly protected derivative.

Scheme 2



Finally, the versatility of this technique is demonstrated by the production of CD_3-labeled histidine **30** through the use of $(CD_2O)_n$ and $NaBD_3CN$ in excellent yield and high deuterium incorporation (Scheme 3).[8]

Scheme 3



In conclusion, we have presented an exceedingly simple and high-yield method for the production of *N*-methyl amino acid esters that requires no protection for functionalized amino acid side chains. While we have not pursued the experiments, we believe these protocols will be successful with amino acids bearing simple alkyl group side chains as well. The procedures are simple, practical, and scaleable and produce the desired material without racemization.[9]

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) No effort was made to lower this reaction time. We opted, rather, for the simplicity of a procedure that requires little oversight.

(7) In a single experiment, resin-bound cyanoborohydride was employed in place of the standard reagent. While the outcome was identical, the expense of this reagent on a mole basis precluded further experimentation.

(8) See the Supporting Information for MS and NMR data.

(9) As we were preparing to submit this paper, Biron and Kessler published a complementary method for synthesizing *N*-methylamino acids with side-chain protection. Biron, E.; Kessler, H. *J. Org. Chem.* **2005**, *70*, 5183−5189.