

A Simple and Rapid Protocol for *N*-Methyl- α -Amino Acids

G. Vidyasagar Reddy and D.S. Iyengar*

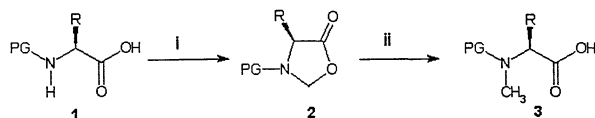
Discovery Laboratory, Organic Division-II, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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A two step strategy for optically pure *N*-Protected-*N*-methyl- α -amino acids starting from *N*-protected- α -amino acids *via* reductive cleavage of oxazolidinones using NaCNBH₃/TMSCl is described.

N-Methyl- α -amino acids are an important class of compounds present in a wide variety of naturally occurring peptides and depsipeptides with broad spectrum activity including antibiotic, antiviral and anti cancer.¹⁻³ They are also very useful compounds for stabilizing several peptide backbone conformations and for obtaining structure activity information about peptides.^{4,5} Due to their importance, quite a number of methods have been reported.⁶⁻¹⁴ However, each method has limitations which include harsh reaction conditions,⁶⁻¹⁰ lack of generality due to partial racemization and low reactivity,^{11,12} greater number of steps required to prepare substrates,^{10,14} instability of intermediate products¹³ and prolonged reaction times.^{6,7,13} Further, there is no satisfactory method available compatible with all types of commonly used *N*-protecting groups. In view of this, there is a considerable interest to develop a milder methodology having general applicability with a variety of *N*-protecting groups, since suitable protection is required in peptide synthesis.

We report here an efficient, rapid two step methodology involving reductive cleavage of *N*-protected oxazolidinones¹⁵ **2** using NaCNBH₃/TMSCl reagent system for optically pure *N*-methyl- α -amino acids **3** starting with readily accessible *N*-protected- α -amino acids **1** (Scheme 1). The reaction was complete within 5–15 min giving yields >90%. The reaction has general applicability with all commonly used *N*-protecting groups (Boc, Cbz, Ts) and results are summarized in Table 1. The *N*-protected-*N*-methyl- α -amino acids obtained were characterized by ¹H-nmr, Mass, IR, specific rotations, and were in good agreement with literature data.⁶⁻⁸ It may be explained that, as TMSCl is good electrophile,¹⁶ oxygen atom of oxazolidinone ring coordinates to TMSCl followed by reduction gives the title compounds.



Scheme 1 : Reagents and conditions

(i) (CH₂O)_n, PTSA(Cat), C₆H₆, reflux (ii) NaCNBH₃, Me₃SiCl, CH₃CN, RT

Typical Procedure: To a mixture of *N*-protected oxazolidinone **2** (2 mmol) and NaCNBH₃ (2.2 mmol) in 10 ml of dry CH₃CN was added Me₃SiCl (2.2 mmol) dropwise under N₂ atmosphere at room temperature with stirring. After completion of the reaction (monitored by tlc, 10–15 min), reaction mixture was quenched by the slow addition of water

Table 1. Preparation of *N*-protected-*N*-methyl- α -amino acids

Entry	PG	R	Time /min	^a Yield/ %
1	Cbz	CH ₃	15	94
2	"	(CH ₃) ₂ CH	10	92
3	"	(CH ₃) ₂ CHCH ₂	10	96
4	"	CH ₃ CH ₂ CHCH ₃	10	94
5	"	PhCH ₂	5	98
6	"	CH ₃ SCH ₂ CH ₂	10	91
7	"	p-BnO-C ₆ H ₄ CH ₂	5	95
8	Boc	(CH ₃) ₂ CH	10	91
9	"	(CH ₃) ₂ CHCH ₂	10	94
10	"	CH ₃ CH ₂ CHCH ₃	10	92
11	"	PhCH ₂	5	96
12	"	CH ₃ SCH ₂ CH ₂	15	96
13	"	p-BnO-C ₆ H ₄ CH ₂	10	93
14	Ts	(CH ₃) ₂ CH	5	93
15	"	(CH ₃) ₂ CHCH ₂	5	92
16	"	CH ₃ CH ₂ CHCH ₃	5	92
17	"	PhCH ₂	5	97
18	"	CH ₃ SCH ₂ CH ₂	5	94
19	"	p-BnO-C ₆ H ₄ CH ₂	5	91

^aIsolated yield.

and extracted with ethyl acetate. Organic layer was washed thoroughly with water and dried over anhydrous Na₂SO₄. Concentration of solvent and crystallization of crude product using ethyl acetate, hexane solvents gave *N*-protected-*N*-methyl- α -amino acids **3**¹⁷ in pure form.

In summary, a convenient and efficient methodology has been developed for the synthesis of optically pure *N*-protected-*N*-methyl- α -amino acids. The major advantages of present method are less number of steps, shorter reaction times, compatible with all *N*-protecting groups, hence superior to the earlier procedures.

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References and Notes

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- 17 Representative data for (S)-N-Benzoyloxycarbonyl-N-methyl-phenyl alanine: colorless crystals, mp 69-71 °C, $[\alpha]_D^{25} -68.3$ (c 1 in EtOH), lit.⁸ mp 67-71 °C, $[\alpha]_D^{25} -67$ (c 1.8 in EtOH), ¹H NMR (CDCl₃) δ 2.80 (s, 3H), 3.10-3.25 (m, 2H), 4.80-4.90 (m, 1H), 5.20 (s, 2H), 7.20-7.25 (m, 10H), 9.60 (br s, 1H).

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