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

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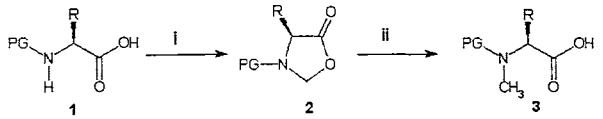
A two step strategy for optically pure N-Protected-N-methyl-α-amino acids starting from N-protected-α-amino acids *via* reductive cleavage of oxazolidinones using $NaCNBH_3$/TMSCl is described.

N-Methyl–α-amino acids are an important class of compounds present in a wide variety of naturally occuring 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 products[13] 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 oxazolidinones[15] **2** using $NaCNBH_3$/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 ^{1}H-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) $(CH_2O)n$, PTSA(Cat), C_6H_6, reflux (ii) $NaCNBH_3$, Me_3SiCl, CH_3CN, RT

Typical Procedure: To a mixture of N-protected oxazolidinone **2** (2 mmol) and $NaCNBH_3$ (2.2 mmol) in 10 ml of dry CH_3CN was added Me_3SiCl (2.2 mmol) dropwise under N_2 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 and extracted with ethyl acetate. Organic layer was washed thoroughly with water and dried over anhydrous Na_2SO_4. 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.

Table1. Preparation of N-protected-N-methyl-α-amino acids

Entry	PG	R	Time /min	[a]Yield/ %
1	Cbz	CH_3	15	94
2	"	$(CH_3)_2CH$	10	92
3	"	$(CH_3)_2CHCH_2$	10	96
4	"	$CH_3CH_2CHCH_3$	10	94
5	"	$PhCH_2$	5	98
6	"	$CH_3SCH_2CH_2$	10	91
7	"	p-BnO-$C_6H_4CH_2$	5	95
8	Boc	$(CH_3)_2CH$	10	91
9	"	$(CH_3)_2CHCH_2$	10	94
10	"	$CH_3CH_2CHCH_3$	10	92
11	"	$PhCH_2$	5	96
12	"	$CH_3SCH_2CH_2$	15	96
13	"	p-BnO-$C_6H_4CH_2$	10	93
14	Ts	$(CH_3)_2CH$	5	93
15	"	$(CH_3)_2CHCH_2$	5	92
16	"	$CH_3CH_2CHCH_3$	5	92
17	"	$PhCH_2$	5	97
18	"	$CH_3SCH_2CH_2$	5	94
19	"	p-BnO-$C_6H_4CH_2$	5	91

[a]Isolated yield.

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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17 Representative data for (S)-N-Benzyloxycarbonyl-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), ^{1}H NMR ($CDCl_3$) 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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