

A Practical Approach for the Optically Pure N-Methyl-α- Amino Acids

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Abstract: A new practical synthesis of N-Methyl-α-amino acids by racemization free methodology has been developed. The method involves the reductive cleavage of N-protected oxazolidinones using hydrogen in the presence of Pd/C to give the title compounds in quantitative yields. © 1998 Elsevier Science Ltd. All rights reserved.

Optically pure N-Methyl-α-amino acids constitute an important part of several biologically active natural products such as dolastatins¹ and didemnins.² They are also useful for obtaining information about the backbone conformations and structure activity of the peptides.³ Although several methods have been reported,⁴ there is no satisfactory method available for synthesis of optically pure N-methyl-α-amino acids under neutral conditions.

Partial racemisation,^{4a} longer reaction times and the use of harsh exotic reagents^{4b,f,g} makes the earlier methods unsatisfactory. In view of the importance of N-methyl- α -amino acids and lack of a satisfactory practical method under neutral conditions, we have developed a practical and efficient method for the preparation of N-methyl- α -amino acids under mild conditions.

The present methodology features a two step strategy starting from N-BOC or N-Cbz amino acids via oxazolidinones. Reaction of paraformaldehyde with N-protected- α - amino acids in the presence of PTSA furnished the required oxazolidinones in excellent yields.⁵ Using reduction protocol under hydrogenolic conditions the oxazolidinones are cleaved to give the desired N-methyl- α -amino acids with high optical purity in quantitative yields⁶ (Scheme 1). Under similar conditions the N-BOC-oxazolidinones gave N-BOC-N-methyl- α -amino acids quantitatively. The generality of this methodology is illustrated in Table-1. This is the first report on the reductive cleavage of the N-protected-oxazolidinones using hydrogen in the presence of Pd/C to N-methyl- α -amino acids.⁷ The important feature of this methodology for N-methyl- α -amino acids is its lack of racemisation and neutral reaction conditions.

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TAUK 1					
Entry	P.G.	R	Entry	P.G.	R
1	cbz	CH ₃	8	BOC	CH ₃
2	"	$(CH_3)_2CH$	9	**	$(CH_3)_2CH$
3	"	(CH ₃) ₂ CHCH ₂	10	H	(CH ₃) ₂ CHCH ₂
4	**	CH ₃ CH ₂ CHCH ₃	11	11	CH ₃ CH ₂ CHCH ₃
5	"	PhCH ₂	12	tt	PhCH ₂
6	"	HO-C ₆ H ₄ CH ₂	13	***	TBDPSOCH ₂
7	"	TBDPSOCH.			

Table 1

In conclusion, we have developed an efficient, simple and practical methodology for the synthesis of optically pure N-methyl- α -amino acids starting from readily accessible N-protected oxazolidinones. This will be useful for making N-methyl- α -amino acids containing both acid and base labile protecting groups.

Scheme 1

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- 6. All the compounds were characterized by ¹H NMR, mass spectra and optical rotations were in agreement to the literature values. (ref. 4e)
- 7. Earlier report from Freidinger et al described the conversion of oxazolidinones to the N-methyl-α-amino acids using large excess of Et₃SiH and trifluoro acetic acid with reaction times ranging from 20-100 hr. (ref. 4d)