Pergamon

Tetrahedron Letters 39 (1998) 1985–1986

TETRAHEDRON
LETTERS

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

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Received 24 November 1997; revised 31 December 1997; accepted 9 January 1998

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 dolastatins[1] 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 yields[6] (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.

IICT Communication No. 3934

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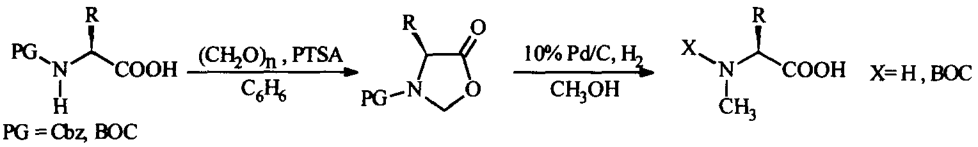
PII: S0040-4039(98)00111-7

Table 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	"	$(CH_3)_2CHCH_2$	10	"	$(CH_3)_2CHCH_2$
4	"	$CH_3CH_2CHCH_3$	11	"	$CH_3CH_2CHCH_3$
5	"	$PhCH_2$	12	"	$PhCH_2$
6	"	$HO\text{-}C_6H_4CH_2$	13	"	$TBDPSOCH_2$
7	"	$TBDPSOCH_2$			

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

Acknowledgements : One of the authors (G.V.S.R.) thank CSIR, New Delhi, India for the award of a fellowship.

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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 Et_3SiH and trifluoro acetic acid with reaction times ranging from 20-100 hr. (ref. 4d)