Pergamon

Tetrahedron Letters 41 (2000) 949–951

TETRAHEDRON LETTERS

A practical protocol for chemoselective *N*-methylation of vicinal amino alcohols

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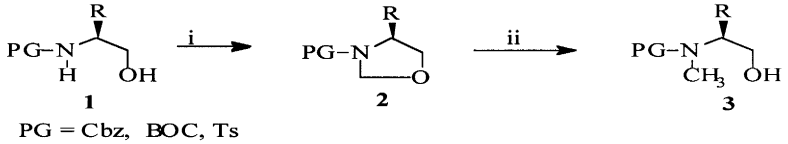
Received 28 June 1999; accepted 10 November 1999

Abstract

A practical method for the chemoselective *N*-methylation of vicinal amino alcohols is described.

Keywords: amino alcohols; oxazolines; aminoacids; protecting groups.

A vicinal *N*-methyl amino alcohol core structure is found in several bioactive molecules including hapalosin[1] and dolastatin,[2] ephedrine and pseudoephedrine.[3] Recently, *N*-protected-*N*-methyl amino alcohol precursors have been used in the synthesis of *N*-methyl-α-amino-oxiranes,[4] which are versatile intermediates in the synthesis of HIV-protease inhibitors. These synthons were also used in the synthesis of luzopeptins, a class of cyclo-depsipeptide antibiotics.[5,6] In connection with our work on the synthesis of (1*S*,2*S*)-pseudoephedrine, we have developed a methodology for the *N*-methylation of vicinal amino alcohols. Herein, we report a general and practical protocol for chemoselective *N*-methylation of vicinal amino alcohols via reductive cleavage of the corresponding oxazolines using $NaCNBH_3$/TMSCl (Scheme 1).



Scheme 1. Reagents and conditions: (i) $(CH_2O)_n$, PTSA, C_6H_6, reflux; (ii) $NaCNBH_3$/TMSCl/CH_3CN, rt

Recently, we have reported a practical method for the preparation of *N*-protected amino alcohols from α-amino acids.[7] The *N*-protected amino alcohols (**1**) obtained by our methodology were treated with paraformaldehyde in the presence of catalytic PTSA under reflux in benzene to give quantitative yields (94–98%) of *N*-protected oxazolines (**2**). Treatment of the resulting oxazoline with $NaCNBH_3$/TMSCl in acetonitrile under N_2 atmosphere smoothly afforded the corresponding *N*-methyl amino alcohols in

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0040-4039/00/$ - see front matter
PII: S0040-4039(99)02105-X

excellent yields (92–95%) (Scheme 1). These reactions were rapid and complete within 20–30 min. A variety of amino alcohols with different *N*-protecting groups were subjected to the present reaction conditions to give excellent yields of *N*-methyl amino alcohols. All *N*-protecting groups used were compatible. The results are summarised in Table 1. All the products obtained were fully characterised by ^{1}H NMR, IR, mass spectral data and microanalysis.† The characteristic signal in the ^{1}H NMR of **3** at δ 2.75 (s, 3H) clearly indicates the presence of an *N*-methyl group. Optical purities of the *N*-methyl amino alcohols were determined by ^{19}F NMR analysis of the corresponding (*R*)-Mosher esters and are found to have >99% ee.[8]

Table 1
N-Methylation of vicinal amino alcohols

Sl. No	PG	R	$[\alpha]_D$ 2	$[\alpha]_D$ 3	Yield* (%)	Sl. No	PG	R	$[\alpha]_D$ 2	$[\alpha]_D$ 3	Yield* (%)
1	Cbz	CH_2PH	+9.00 (c=1)	+11.4 (c=0.5)	97	6	Ts	$CH(CH_3)CH_2CH_3$	+156.8 (c=1)	+ 34.8 (c=1)	97
2	Cbz	$CH(CH_3)_2$	+25 (c=1)	-6.4 (c=1)	94	7	Ts	CH_3	+122.2 (c=1)	+16.4 (c=1)	95
3	Cbz	$CH2CH(CH_3)_2$	+38.8 (c=1)	+3.20 (c=1)	96	8	BOC	CH_2Ph	+63.6 (c=0.5)	+2.0 (c=1)	96
4	Ts	CH_3	+28.0 (c=1)	+4.6 (c=1)	95	9	BOC	$CH_2CH(CH_3)_2$	+55.4 (c=1)	+7.8 (c=1)	94
5	Ts	$CH(CH_3)_2$	+127 (c=1)	-5.6 (c=1)	94	* Isolated yields. Rotations were taken in Methanol					

Typical procedure: The *N*-protected amino alcohol (2 mmol), paraformaldehyde (6 mmol) and PTSA in benzene (10 ml) were refluxed for 30 min using a Dean–Stark apparatus. The solvent was removed under reduced pressure to give a crude residue which was purified on a silica gel column to give pure *N*-protected oxazolines (**2**). *N*-Protected oxazolines (**2**) (2 mmol) in acetonitrile (8 ml) under nitrogen atmosphere were treated with $NaCNBH_3$ (2 mmol) followed by TMSCl (2 mmol). The resulting reaction mixture was stirred at rt until the completion of the reaction (monitored by TLC, 20–30 min). The solvent was removed under reduced pressure followed by the usual workup to afford crude *N*-methyl amino alcohols (**3**), which were purified by silica gel column chromatography.

In summary, we have developed and demonstrated a novel, convenient and practical method for chemoselective *N*-methylation of vicinal amino alcohols. The method is rapid and gives excellent yields. The present method, with its high selectivity and short reaction times, will find application to the preparation of a wide variety of substrates. Further work is in progress and will be reported in due course.

Acknowledgements

We thank Dr. K. V. Raghavan, Director IICT, for the facilities and encouragement. G. V. S. Reddy and G. V. Rao thank CSIR (India) for fellowships.

† Selected data for (*S*)-*N*-Cbz-*N*-Me-phenyl alaninol: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.78–3.10 (m, 2H, $PhCH_2$), 2.80 (s, 3H, N-CH_3), 3.30–3.70 (m, 2H, CH_2OH), 4.15 (br s, 1H, OH), 4.35–4.50 (m, 1H, CHN), 5.10 (s, 2H, $PhCH_2O$), 7.15–7.40 (m, 10H, Ph); IR (KBr, CM-1), 1675, 3435; FABMS (*m/z*) 300 ($M^{+\cdot}$), 301 (M+H); anal. found: C, 72.09; H, 7.23; N, 4.68. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.67. All other *N*-methyl amino alcohols were characterised in a similar manner.

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