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Selective Reductions of Oxazolidinones : New Protocol for Diastereoselective Synthesis of Vicinal Amino Alcohols

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Abstract : **Selective reductions of oxazolidinones using sodium borohydride and their application to the diastereoselective synthesis of vicinal amino alcohols are described.** © 1999 Elsevier Science Ltd. All rights reserved.

Key words : Oxazolidinones; asymmetric synthesis; amino alcohols; amino aldehydes

Optically pure α-amino alcohols and α-amino aldehydes are versatile compounds and constitute an important class in asymmetric synthesis [1] and pharmaceutical chemistry [2]. Although, N-protected amino alcohols are quite stable compounds, N-protected amino aldehydes are chemically and configurationally highly labile. In view of their high demand in organic synthesis, numerous methods have been reported for their preparation. Earlier methods for their preparation [2-5] involve reduction of α-amino acids using complex metal hydrides or $NaBH_4$ in conjunction with strong acids and require an inert atmosphere. N-Protected α-amino aldehydes have been synthesized by either DIBAL-H reduction of N-protected α-amino esters or oxidation of N-protected amino alcohols [6]. In this letter, we wish to report the sodium borohydride reduction of oxazolidinones and its application in the synthesis of α-amino alcohols [7-11]. The N-protected oxazolidinones **2** [12] obtained by the treatment of N-protected-α-amino acids with paraformaldehyde in presence of cat. PTSA

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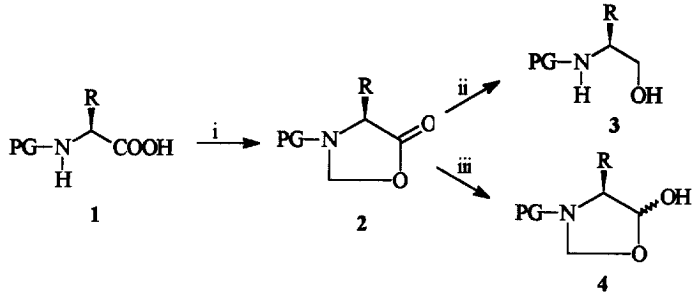
were treated with sodium borohydride in methanol (Scheme-1). Thus, using 2.4 eq of sodium borohydride, oxazolidinone **2** furnished N-protected α-amino alcohols **3**, whereas 1 eq. of sodium borohydride afforded corresponding lactols† **4** in excellent yields. The selectivity of the reaction totally depends on the amount of sodium borohydride employed. The reaction was complete within 2-3 h. for lactols, whereas aminoalcohols required 2-6 h. The results obtained with a variety of N-protected-oxazolidinones are summarized in Table-1 and Table-2. All the compounds were fully characterized# by ^{1}H NMR, Mass spectrometry and specific rotations.



Reagents and conditions : i) $(CH_2O)n$, PTSA, C_6H_6, reflux, 1h. ii) 2.4 eq. $NaBH_4$, CH_3OH, 0°C-RT. iii) 1 eq. $NaBH_4$, CH_3OH, 0°C-RT.

Scheme-1

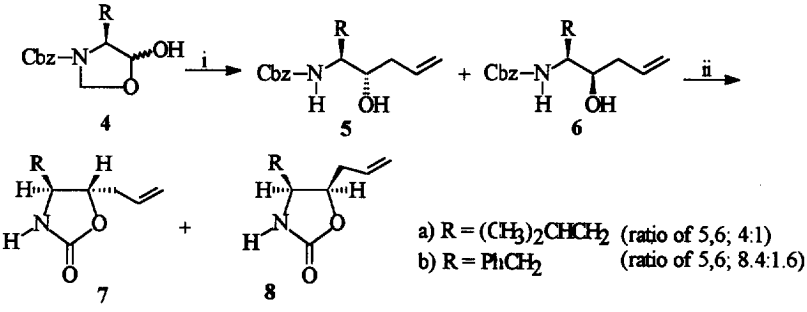
Table-1 : $NaBH_4$ reduction of oxazolidinones 2 to Lactols 4

Entry	PG	R	$[\alpha]_D^{25}$	Reaction time (h.)	Yield (%)
a	Cbz	$(CH_3)_2CHCH_2$	-2.2	1	96
b	Cbz	$PhCH_2$	-60.6	2	93
c	Cbz	$(CH_3)_2CH$	-10.8	2	94
d	Cbz	$CH_3CH_2CHCH_3$	-6.2	2	92
e	BOC	$PhCH_2$	26.6	2	94
f	BOC	$(CH_3)_2CH$	21.4	2	95
g	BOC	$(CH_3)_2CHCH_2$	-5.8	3	93

Table-2 : $NaBH_4$ Reduction of oxazolidinones 2 to aminoalcohols 3

Entry	PG	R	Reaction time (h.)	Yield (%)
a	Cbz	$(CH_3)_2CHCH_2$	3	92
b	Cbz	$PhCH_2$	2	94
c	Cbz	$(CH_3)_2CH$	3	93
d	Cbz	$CH_3CH_2CHCH_3$	4	97
e	BOC	$PhCH_2$	3	95
f	BOC	$(CH_3)_2CH$	5	92
g	BOC	$(CH_3)_2CHCH_2$	5	94
h	Ts	CH_3	4	92

The lactols obtained in the present study are important substitutes for highly unstable amino aldehydes. This was demonstrated by reacting lactols (**4a** and **4b**) with Grignard reagents to give vicinal amino alcohols (**5a,6a** and **5b,6b**) with high diastereoselectivity; these are useful precursors in the synthesis of protease inhibitors as shown in Scheme-2.



Reagents and conditions : i) CH_2CHCH_2MgBr, THF, N_2, 0°C-RT, 2h.; ii) KOH, MeOH-THF, RT, 1h.

Scheme-2

Thus, treatment of lactols (**4a** and **4b**) with allylmagnesiumbromide in THF afforded a mixture of amino alcohols. The ratios and absolute configuration of newly created stereo centre in both isomers were determined by converting the mixture into easily separable, known oxazolidinones, **7a**, colourless solid, m.p. 70°C, $[\alpha]_D^{25}$ = -52.8 (c=1, $CHCl_3$), lit. [13] m.p. 69-70°C. $[\alpha]_D^{25}$ = -51.73 (c=0.88, $CHCl_3$); **8a**, colourless solid, m.p. 79-80°C. $[\alpha]_D^{25}$ = +15.7 (c=1, $CHCl_3$) lit. [13] m.p. 78-81°C, $[\alpha]_D^{25}$ = +13.32 (c=1.09, $CHCl_3$); **7b**, colourless oil $[\alpha]_D^{25}$ = -68.1 (c=1, $CHCl_3$) lit. [13] $[\alpha]_D^{25}$ = -67.2 (c=0.97, $CHCl_3$); **8b**, colourless oil $[\alpha]_D^{25}$ = -69.2 (c=1, $CHCl_3$) lit. [13] $[\alpha]_D^{25}$ = -68.9 (c=1.47, $CHCl_3$),

(Scheme-2) and by comparing specific rotations with literature values which were found to be in good agreement. The products were also characterized by spectral data, thereby confirming structure assignments and configurations.

In summary, we have developed a facile and practical protocol for obtaining optically pure amino alcohols and masked amino aldehydes (lactols) from readily accessible oxazolidinones. The synthetic application of the lactols was demonstrated by reacting them with a Grignard reagent to give amino alcohols with good diastereoselectivity, key precursors of protease inhibitors. Since this is a novel methodology, it has wide scope and enables the synthesis of analogous series of compounds. Further work is in progress and will be reported in due course.

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† While our work was in progress, phenyl alanine derived N-BOC oxazolidinone reduction with Dibal-H to give mixture of products was reported [14].

Selected data

Compound 3a : δ 0.75-0.95 (m, 6H, $(C\underline{H}_3)_2CH$), 1.15-1.65 (m, 3H, $C\underline{H}(CH_3)_2$ & $C\underline{H}_2CH$), 3.30-3.70 (m, 2H, $C\underline{H}_2OH$), 4.05-4.20 (brs, 1H, OH), 4.35-4.55 (m, 1H, C<u>H</u>N), 5.10 (s, 2H, $PhC\underline{H}_2O$), 5.30-5.40 (brs, 1H, NH), 7.15-7.35 (m, 5H, Ph), FABMS : 252 (M^+ +H).

Compound 4a : δ 0.80-1.00 (m, 6H, $(C\underline{H}_3)_2CH$), 1.20-1.80 (m, 3H, $C\underline{H}(CH_3)_2$ & $C\underline{H}_2CH$), 3.35-3.60 (m, 2H, C<u>H</u>N & OH), 4.40-4.60 (m, 1H, C<u>H</u>OH), 4.85-5.25 (m, 4H, $NC\underline{H}_2O$ and $PhC\underline{H}_2O$ also overlapped), 7.20-7.40 (m, 5H, Ph), FABMS : 280 (M^+ +H).

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