Pergamon

Tetrahedron Letters 41 (2000) 10071–10074

TETRAHEDRON LETTERS

# Facile inversion of configuration of *N*-Boc-β-aminoalcohols via $S_N2$ cyclization to oxazolidinones

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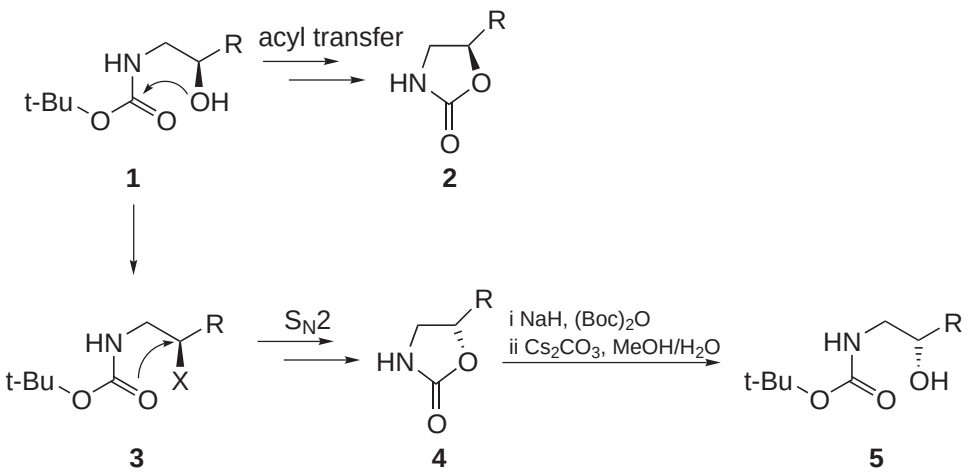
Received 3 October 2000; accepted 9 October 2000

**Abstract**

Oxazolidinones are obtained by the cyclization of mesylates derived from *N*-Boc-β-aminoalcohols. Hydrolysis of the *N*-Boc-oxazolidinones regenerates the protected aminoalcohols with inverted configuration at the hydroxy group. 

*Keywords:* amino alcohols; oxazolidinones; inversion reactions; cyclization.

*N*-Boc-β-Aminoalcohols (**1**) readily cyclize to oxazolidinones (**2**) by a base catalyzed intramolecular acyl transfer (Scheme 1).[1] However, when the hydroxy group is converted into a




Scheme 1.

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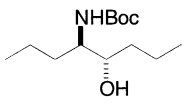
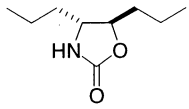
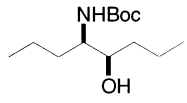
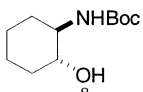
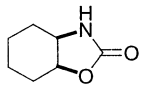
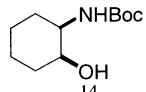
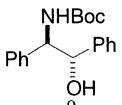
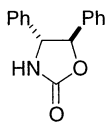
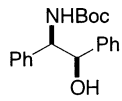
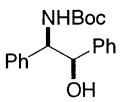
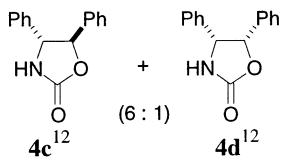
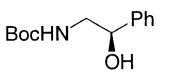
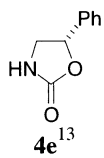
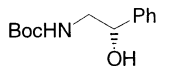
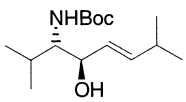
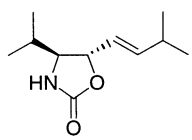
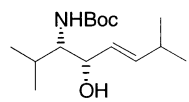
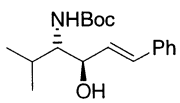
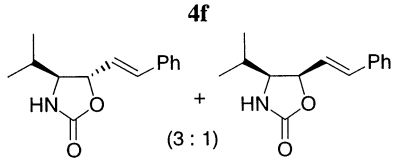
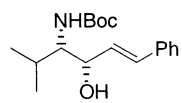
0040-4039/00/$ - see front matter 
PII: S0040-4039(00)01753-6

suitable leaving group, as in **3**, cyclization can take place by an intramolecular $S_N2$ displacement, thus leading to the formation of the epimeric product **4**.[2–4] As oxazolidinones **4** can be readily converted into *N*-Boc aminoalcohols **5**,[5] this reaction sequence (**1**→**5**) can be exploited to invert the configuration of the hydroxy group (Scheme 1).

Recently this approach has been used by Ghosh in the synthesis of the core unit of ritonavir, a potent HIV-protease inhibitor, and cyclization was obtained by treating the *N*-Boc aminoalcohol with thionyl chloride.[6] This prompted us to report on a parallel study which we undertook

Table 1
Inversion of configuration of *N*-Boc aminoalcohols

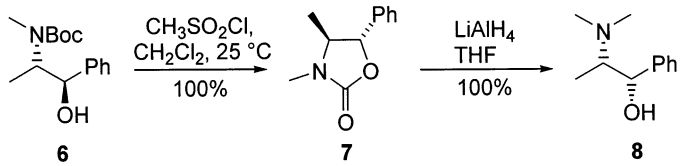
| Entry | *N*-Boc aminoalcohol | Oxazolidinone[a] | Inverted aminoalcohol | Yield %[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **4a**[10] |  **5a** | 47 |
| 2 |  **1b**[8] |  **4b**[11] |  **5b**[14] | 76 |
| 3 |  **1c**[9] |  **4c**[12] |  **5c** | 45 |
| 4 |  **1d** |  **4c**[12] (6 : 1) **4d**[12] | | |
| 5 |  **1e** |  **4e**[13] |  **5e** | 74[c] |
| 6 |  **1f** |  **4f** |  **5f** | 53 |
| 7 |  **1g** |  **4g** (3 : 1) **2g** |  **5g** | 45[d] |

[a] Diastereoisomer ratios were calculated by NMR.
[b] Overall yields of inverted products (single isomers, by NMR).
[c] 97% e.e., from optical rotations.
[d] Based on **1g**. The *N*-Boc derivatives of oxazolidinones **4g** and **2g** were separated by crystallization.

as part of an investigation into the synthesis of dipeptide isosteres. We have found that $S_N2$ cyclization to oxazolidinones takes place smoothly when the β-aminoalcohol **1** is converted in situ into the corresponding mesylate **3** (X = OMs, Scheme 1), thus avoiding the use of thionyl chloride which may lead to undesired side reactions. The inverted *N*-Boc aminoalcohol is then restored by *t*-butoxycarbonylation and hydrolysis of the *N*-Boc oxazolidinones with cesium carbonate.[5,7] The results on a representative series of *N*-Boc β-aminoalcohols are reported in Table 1.[8–14]

It can be seen from the Table that cyclization of the *N*-Boc aminoalcohols is completely stereospecific giving the oxazolidinones with inversion of configuration at $C_5$, with the two exceptions of entries 4 and 7. In the case of the *threo* aminoalcohol **1d** (entry 4), the reaction leads to a 6:1 mixture of isomeric oxazolidinones **4c** and **4d**[12] with retention and inversion of configuration, respectively. The main product **4c** is identical to that obtained from the cyclization (with inversion of configuration) of the *erythro* aminoalcohol **1c**. The $S_N2$ pathway is probably disfavoured in the *threo* isomer **1d** by steric interactions between the *syn* phenyl groups; formation of the *anti* oxazolidinone **4c** is thus preferred, probably via a $S_N1$ cyclization of the benzylic mesylate. Competition between $S_N1$ and $S_N2$ mechanisms is also likely to be responsible for the partial epimerization observed in the cyclization of the very reactive mesylate derived from alcohol **1g** (entry 7) leading to a 3:1 mixture of inverted and retained oxazolidinones **4g** and **2g**, respectively. A similar result was obtained when the cyclization was carried out with thionyl chloride.[6] Entries 5–7 in Table 1 illustrate the application of our methodology to the inversion of configuration of enantiopure 1,2-aminoalcohols. Thus, for example, *N*-Boc aminoalcohol **1e** ($[\alpha]_D^{25} = -2.62$, $c = 4$, EtOH) was smoothly converted into its enantiomer **5e** ($[\alpha]_D^{25} = +2.53$, $c = 4$, EtOH) via known oxazolidinone **4e** ($[\alpha]_D^{25} = +23$, $c = 4.3$, EtOH)[13] in 74% overall yield and 97% e.e. (entry 5). In the case of the allylic alcohol **1f** (entry 6), our methodology proved superior to that described by Ghosh.[6] When the cyclization of this alcohol was performed with thionyl chloride, a 1:1 mixture of oxazolidinone **4f** and the chloride derived by a $S_N1$ displacement at the allylic position was obtained, while under our conditions **4f** is the only product.

The synthetic utility of this method is further illustrated by the two-step synthesis of *N*-methyl-pseudoephedrine **8** from *N*-Boc-ephedrine **6** (Scheme 2). The latter aminoalcohol, when treated with methanesulfonyl chloride, readily cyclizes, at 25°C in 4 hours, to the known[15] oxazolidinone **7**, with complete inversion of configuration. Reduction of the oxazolidinone with lithium aluminium hydride in THF gave *N*-methyl-pseudoephedrine **8**[16] in quantitative yield.




Scheme 2.

1,2-Aminoalcohols are intermediates in the synthesis of biologically active products[17–19] and are widely used as chiral auxiliaries in asymmetric synthesis;[1] the methodology described here may offer a useful tool for the interconversion of stereoisomers of this important class of compounds.

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7. In a typical experiment the *N*-Boc aminoalcohol was treated with 1.5 equiv. of MsCl and 3 equiv. of DIPEA in 1,2-dichloroethane at 25°C for 1 hour and then at 83°C until completion (1 hour at 0°C in $CH_2Cl_2$ was sufficient for the more reactive allylic alcohols of entries 6 and 7). The oxazolidinone thus obtained (50–100% yield), in THF, was treated with 1.1 equiv. of NaH and 1.2 equiv. of di-*tert*-butyl dicarbonate, in that order, for 2 hours at 25°C and then hydrolyzed with 2 equiv. $Cs_2CO_3$ in 4:1 aqueous methanol to regenerate the inverted *N*-Boc aminoalcohol in 82–100% yield. Overall yields are in Table 1.
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