Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3955–3958

TETRAHEDRON: *ASYMMETRY*

Chiral oxazolidinones from α-hydroxy oxazolidines: a new access to 1,2-amino alcohols

Claude Agami, Franck Amiot, François Couty,* Luc Dechoux, Christophe Kaminsky and Olivier Venier

Laboratoire de Synthèse Asymétrique (UMR CNRS 7611), Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France

Received 29 September 1998; accepted 12 October 1998

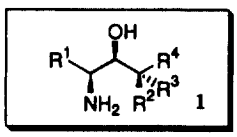
Abstract

N-Carbamoyl-α-hydroxy oxazolidines prepared from *N*-Boc-2-acyl oxazolidines or *N*-Boc-2-alkenyl oxazolidines, using phenyl glycinol as the chiral source, are converted into bicyclic oxazolidinones. Reactions of these compounds with different nucleophiles under conditions suitable for the production of *N*-acyliminium ions were studied. Allylsilane reacted very stereoselectively in all cases, and this reaction provides a new flexible entry for the preparation of enantiopure *syn*-2-amino alcohols, possibly bearing an additional stereocenter α to the hydroxyl moiety.

1. Introduction

Synthetic efforts towards the preparation of enantiomerically pure 1,2-amino alcohols still receive considerable attention.[1] Not only is this class of compounds frequently found as a substructure in bioactive molecules,[2] but it also allows the formation of heterocycles which rank among the most popular chiral auxiliaries.

We wish to report herein a new entry to either enantiomer of enantiomerically pure *syn*-1,2-amino alcohols, bearing, if desired, a third stereocenter adjacent to the hydroxyl moiety, according to the general structure **1** shown below:



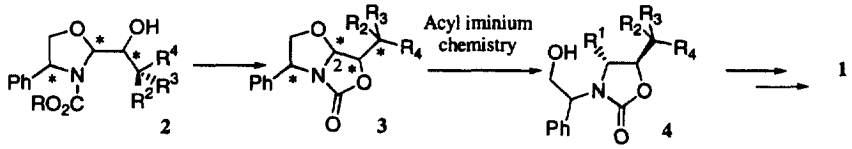
1

* Corresponding author. Fax: 33 1 44 27 26 20; e-mail: couty@ccr.jussieu.fr

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00414-5

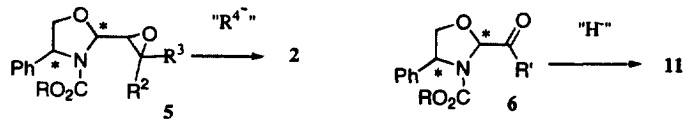
This framework is often encountered in important bioactive molecules, such as MeBmt, an unusual β-amino acid present in cyclosporin,[3] phytosphingosin,[4] or dolaproin, the key building block of dolastatin.[5] Our strategy to prepare these molecules[6] relies on our previously reported methodologies using *N*-Boc-2-alkenyl[7] or 2-acyl[8] oxazolidines, phenyl glycinol being the chiral starting material.

N-Carbamoyl-α-hydroxy oxazolidines **2**, readily accessible, were found to be valuable starting materials for the preparation of **1**. The key step of this transformation is the diastereoselective formation of a C–C bond at C-2 in intermediate **3** via *N*-acyliminium chemistry.[9] Compound **3** results from transcarbamoylation of substrate **2**, and the desired amino alcohol **1** is prepared from oxazolidinone **4** by removal of the phenyl glycinol residue and hydrolysis of the heterocycle (Scheme 1).



Scheme 1.

Synthesis of compounds **2** is performed through the nucleophilic opening of the α,β-epoxy oxazolidine **5**,[7] and in this case, the configuration of the stereogenic center adjacent to the hydroxyl moiety is controlled owing to the stereospecificity of this process. Alternatively, diastereoselective reduction of an acyl oxazolidine **6**[8] provides starting materials suitable for this study, but devoid of an additional stereocenter adjacent to the hydroxyl moiety (Scheme 2).



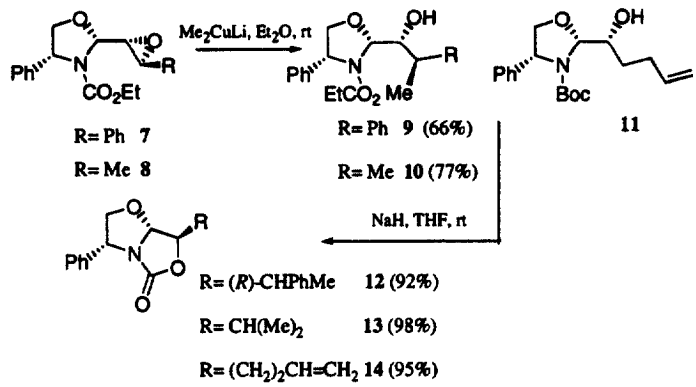
Scheme 2.

2. Results and discussion

The starting α-hydroxy oxazolidines were prepared from α,β-epoxy oxazolidines **7** and **8**. Nucleophilic opening of these compounds with lithium dimethylcuprate[10] gave **9** and **10** in a highly regioselective way. Alternatively, **11** was prepared through reduction of the corresponding *N*-Boc-2-acyl-oxazolidine, following a previously reported procedure.[11] Transcarbamoylation was smoothly performed by treating these compounds with sodium hydride in THF. It should be mentioned that this operation required only 2 h at rt for **9** and **10**, bearing a carboethoxy group on the nitrogen, but 12 h were necessary to reach completion in the case of **11**, protected by a *t*-Boc moiety, probably due to the steric hindrance (Scheme 3).

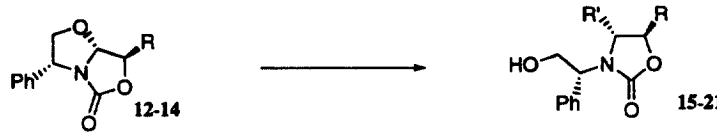
Having in hand the required bicyclic oxazolidinones **12–14**, we turned our attention to the C–C bond formation, α to the nitrogen atom, by taking advantage of the electrophilic reactivity of a transient *N*-acyliminium ion. Results are summarized in Table 1.

Allylsilane reacted very stereoselectively in the presence of $TiCl_4$ with either **12**, **13** or **14** (entries 1, 2, 6), yielding *trans*-disubstituted oxazolidinones, in accordance with previous reports[12] performed on similar substrates. On the other hand, TMSCN reacted less stereoselectively. This result can be ascribed to the small size of the nucleophile involved, and similar lack of stereoselectivity in analogous cases has been already reported.[13]



Scheme 3.

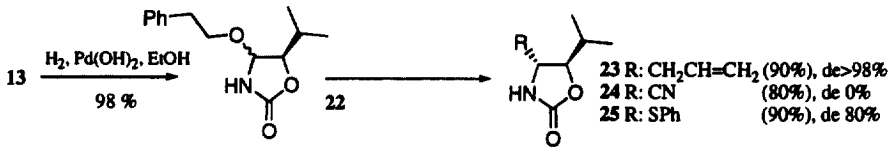
Table 1
Reaction of oxazolidinones **12–14** with different nucleophiles in the presence of Lewis acids



Entry	Substrate	Conditions[a]	Product	de[b]	yield[c]
1	**12**	Allyltrimethylsilane, $TiCl_4$	**15** R= (*R*)-$CHCH_3Ph$ R'= $CH_2CH=CH_2$	>98	82
2	**13**	Allyltrimethylsilane, $TiCl_4$	**16** R= $CH(CH_3)_2$ R'= $CH_2CH=CH_2$	>98	85
3	**13**	Et_3SiH, $BF_3.OEt_2$	**17** R= $CH(CH_3)_2$ R'= H	-	80
4	**13**	TMSCN, $BF_3.OEt_2$	**18** R= $CH(CH_3)_2$ R'= CN	70	70
5	**13**	PhSH, BF_3 OEt_2	**19** R= $CH(CH_3)_2$ R'= SPh	>98	95
6	**14**	Allyltrimethylsilane, $TiCl_4$	**20** R= $(CH_2)_2CH=CH_2$ R'= $CH_2CH=CH_2$	>98	80
7	**14**	TMSCN, $BF_3.OEt_2$	**20** R= $(CH_2)_2CH=CH_2$ R'= CN	52	82

a: a 1/2/3 molar ratio of substrate, Lewis acid and nucleophile respectively was used in each case b: determined by ^1H NMR on the crude reaction products. c: yields of isolated products

The reactivity of an *N*-debenzylated oxazolidinone was then briefly examined. Thus, hydrogenolysis of **13** gave oxazolidinone **22** as a 6:4 ratio of diastereomers. Treatment of **22**, under the conditions described above gave oxazolidinones **23–25** (Scheme 4).

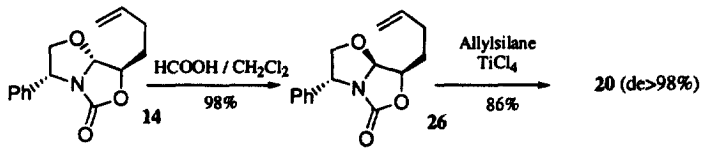


Scheme 4.

The loss of stereoselectivity during the formation of **24** and **25** from **22**, compared to the corresponding

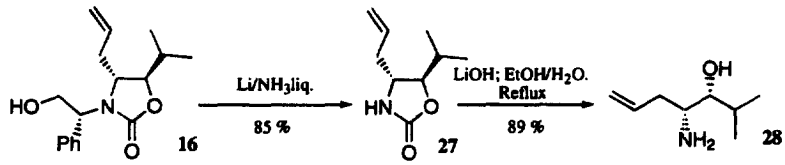
reactions leading to **18** and **19** from the *N*-alkylated product **13**, suggests that reliable and high diastereoselectivity in these reactions requires a chiral benzylic nitrogen substituent.

From a mecanistical point of view, Meyers and Burgess[14] already stated that there is no clear-cut experimental distinction between S_N1 and S_N2 processes in related acetal or oxazolidine substrates. Actually an acidic treatment of compound **14** led completely to its epimer **26** whose reaction under the same conditions described above for **14** produced the same allylated product **20** (Scheme 5). This clearly shows an S_N1 process is operating since the identical course of allylation starting from substrates **14** and **26** strongly suggests the intermediacy of an acyliminium ion.



Scheme 5.

Finally, the phenyl glycinol residue was easily cleaved, as exemplified below for oxazolidinone **16**, by reaction with lithium in ammonia, and the produced oxazolidinone **27** was saponified to give the corresponding 2-amino alcohol in good yield (Scheme 6).



Scheme 6.

In conclusion, the above-described method extends the scope of the use of *N*-Boc oxazolidines in asymmetric synthesis. Application of this methodology for the total synthesis of natural products is currently underway.

References

1. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
2. Scott, J. S. In *Asymmetric Synthesis*; Morrisson, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 4, pp. 1–226.
3. Durand, J. O.; Genet, J. P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 612–619.
4. Kobayashi, S.; Hayashi, T.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 9573–9576.
5. Pettit, G. R.; Burkett, D. B.; Barkoczy J.; Breneman, G. L.; Pettit, W. E. *Synthesis* **1996**, 719–725.
6. For another recently disclosed strategy based on radical additions, see: Morita, T.; Matsunaga, H.; Sugiyama, E.; Ishisuka, T.; Kunieda, T. *Tetrahedron Lett.* **1998**, *39*, 7131–7134.
7. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *J. Org. Chem.* **1997**, *62*, 2106–2112.
8. Agami, C.; Couty, F.; Lequesne, C. *Tetrahedron* **1995**, *51*, 4043–4056.
9. For some exemples, see: (a) Dhimane, H.; Vanucci, C.; Lhommet, G. *Tetrahedron Lett.* **1997**, *38*, 1415–1418. (b) Sadakane, M.; Vahle, R.; Schierle, K.; Kolter, D.; Steckhan, E. *Synlett* **1997**, 95–96. (c) Danielmeier, K.; Schierle, K.; Steckhan, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2247–2248. (d) Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1987**, *26*, 373–376. (e) Moolenar, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2391–2393.
10. Agami, C.; Couty, F.; Venier, O. *Synlett* **1996**, 511–512.
11. Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783–8796.
12. See: Ishiguza, T.; Ishibushi, S.; Kunieda, T. *Tetrahedron* **1993**, *49*, 1841–1852 and Ref. 9b–d.
13. (a) Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77–82. (b) Tung, R. D.; Rich, D. H. *Tetrahedron Lett.* **1987**, *28*, 1139–1142.
14. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294–2296, footnote 12.