Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2311-2314, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00252-3

Stereoselective Synthesis of *anti*-β-Amino-α-Hydroxy Acid Derivatives using Nucleophilic Epoxidation of 1-Arylthio-1-Nitroalkenes

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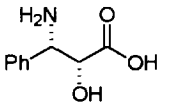
Abstract: Reaction of lithium t-butylperoxide with 1-arylthio-1-nitroalkenes 5, prepared by condensation of (4-tolylthio)nitromethane with N-(Boc)-protected α-amino aldehydes, leads to the formation of oxazolidinones rather than the expected oxiranes. Initially, a mixture of cis 8 and trans 9 diastereoisomers is formed, but upon exposure to silica gel complete conversion to the cis-diastereoisomers 8 takes place.

Much effort has recently been devoted to the development of efficient stereocontrolled synthetic routes for the preparation of enantiomerically pure β-amino-α-hydroxy acid derivatives,[1] principally due to the presence of this unit in a variety of biologically important targets. Specific examples of these targets include the β-phenylisoserine side-chain **1** of taxol[2,3] and components, such as allophenylnorstatine **2**,[4] of a wide variety of protease inhibitors.



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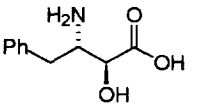

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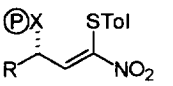


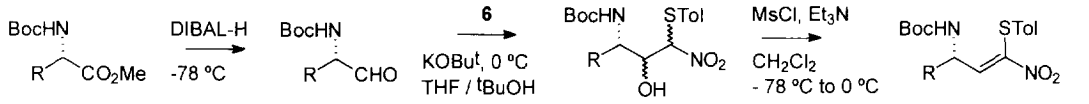
3

Ⓟ = protecting group

We have been interested for some time in investigating the control of stereochemistry in nucleophilic epoxidation of 1-arylthio-1-nitroalkenes using metal alkylperoxides, specifically in cases where the alkene has an allylic stereogenic centre.[5] It has already been established that useful levels of stereochemical control may be obtained when the 1-arylthio-1-nitroalkene contains an allylic stereocentre bearing oxygen (**3**, X = O) (Scheme 1),[6] and we have therefore initiated a study of the nucleophilic epoxidation of 1-arylthio-1-nitroalkenes bearing allylic nitrogen functionality, **3** (X = HN), which has lead to the discovery of a new method for the synthesis of *anti*-α-hydroxy-β-amino acid derivatives.

Scheme 1

In view of the ease of preparation and relative stability (both chemical and stereochemical) of *t*-butoxycarbonyl α-amino aldehydes **4**,[7] we initially chose to investigate the nucleophilic epoxidation of the corresponding 1-arylthio-1-nitroalkenes **5a-c**. These compounds were prepared by condensation of the aldehydes **4** with (4-tolylthio)nitromethane **6** to give a diastereoisomeric mixture of β-hydroxy nitroalkanes **7**, followed by elimination to give the alkenes **5** (Scheme 2).[8] Although the method was effective in two cases, the additional instability of the aldehyde **4c** resulted in a lower overall yield for this example.



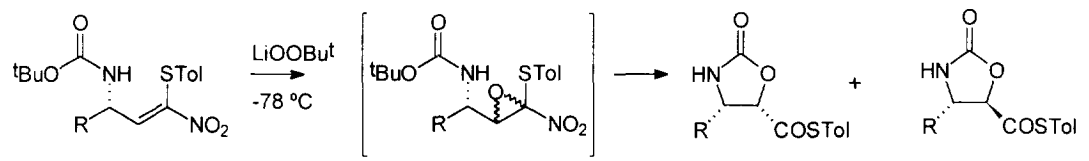
Scheme 2

Table 1. Preparation of γ-*tert*-Butoxycarbonylamino 1-Tolylthio-1-Nitroalkenes 5

R	Amino Aldehyde	β-Hydroxy Nitroalkane	Yield, %	Tolylthionitroalkene	Yield, %
Me	**4a**	**7a**	60	**5a**	63
$PhCH_2$	**4b**	**7b**	68	**5b**	61*
Ph	**4c**	**7c**	44	**5c**	41

* An overall yield of 58% may be obtained, provided the alcohol **7b** is used without purification.

Epoxidation of the alkenes **5** was initially investigated using lithium *tert*-butylperoxide at -78 °C. However, this reaction lead in each case to a diastereoisomeric mixture of *cis*-oxazolidinones **8** and *trans*-oxazolidinones **9**, rather than the expected oxiranes **10** and **11** (Scheme 3). It seems reasonable to postulate that, under the conditions of the reaction, the carbamate group is sufficiently nucleophilic to attack the oxirane. Subsequent loss of *tert*-butyl cation would then give the observed product. When a reaction was quenched shortly after addition of the reagents, some evidence for formation of an intermediate oxirane was obtained. Although the stereoselectivity of this reaction was disappointingly low, good yields of a single crystalline oxazolidinone were obtained after purification by flash chromatography on silica gel, Table 2. While the products obtained from epoxidation of **5a** and **5b** were enantiomerically pure,[9] the product derived from **5c** was found to be racemic. We presume that this is due to racemisation of the α-amino aldehyde **4c** either during its preparation, or during the subsequent condensation reaction with (4-tolylthio)nitromethane.[10]



Scheme 3

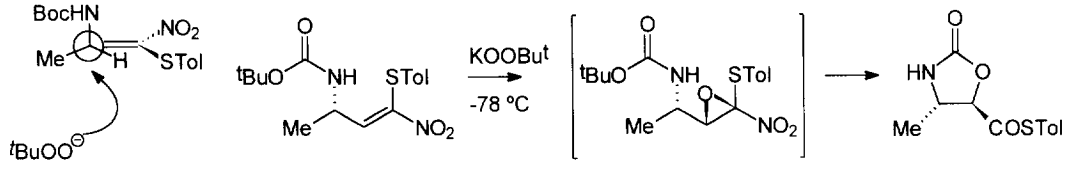
The usual method for assignment of stereochemistry in such cases requires comparison of ^1H-^1H coupling constants between H-4 and H-5 in the oxazolidinone for each stereoisomer.[11] However, in this case, the coupling constants were so similar as to make an unambiguous assignment impossible (Table 2). The relative stereochemistry of each of the products **8a**, **8b**[12] and **8c** was unambiguously established by X-ray crystallography.[13] The apparent greater thermodynamic stability of the *cis*-oxazolidinones **8** is of some note,[14] although we do not yet have a good explanation for the phenomenon.[15] Nevertheless, this process does provide access to precursors to *anti*-β-amino-α-hydroxy acid derivatives.

Table 2. Epoxidation of 1-Arylthio-1-Nitroalkenes 5 using Lithium *tert*-Butylperoxide

1-Arylthio-1-Nitroalkene	Crude Ratio **8**:**9**	$J_{H\text{-}4/H\text{-}5}$ for **8**	$J_{H\text{-}4/H\text{-}5}$ for **9**	Product	Yield, %
5a	1:1	9.0 Hz	9.8 Hz	**8a**	72
5b	2:1	8.9 Hz	9.7 Hz	**8b**	62
5c	only **8**	9.3 Hz	-	**8c**	43

In an attempt to develop conditions which would allow the preparation of the *trans*-diastereoisomers **9** selectively, we have investigated the nucleophilic epoxidation of the alkene **5a** using potassium *tert*-butylperoxide. In the ^1H NMR spectra of the crude reaction product, it was evident that the *trans*-diastereoisomer **9a** was the major isomer (d.e. > 90%). However, all attempts thus far to isolate and purify this compound have been unsuccessful. In all cases either partial (alumina chromatography) or complete (silica gel chromatography) isomerisation to the *cis*-diastereoisomer **8a** was observed. Efforts to establish methods for isolating the *trans*-diastereoisomer **9a** are continuing.

The stereoselectivity observed in the epoxidation using potassium *tert*-butylperoxide can be rationalised using a similar argument to that which we have already used to explain the stereochemical outcome in the epoxidation of γ-oxygenated 1-arylthio-1-nitroalkenes.[5] Thus, a reactive conformation **A** in which the allylic hydrogen occupies the inside position so as to minimize allylic strain,[16] followed by nucleophilic attack of the *tert*-butylperoxide anion *anti* to the bulky, electronegative nitrogen-substituent[17] would lead, *via* the *anti*-oxirane **11a**, to the *trans*-oxazolidinone **9a** (Scheme 4).



Scheme 4

Acknowledgements: We thank the Commission of the European Union for support (ERBCHRXCT930141, "*The Rational Design of New Organic Molecules and Synthetic Methods*"), Miss C.L. Elston for the chiral phase HPLC analysis, Glaxo-Wellcome for the gift of HPLC equipment and Professor W. Clegg and Dr M.R.J. Elsegood for the X-ray crystal structure determinations.

References

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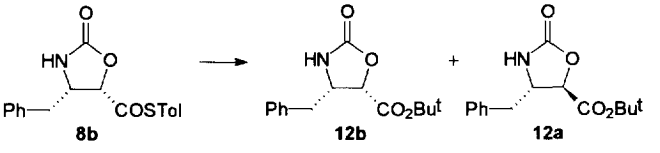
9. Determined in the case of **8b** by chiral phase HPLC analysis using a sample prepared from *D*-phenylalanine for comparison.
10. Dondoni (reference 2) has reported the condensation of the aldehyde **4c** (ee = 84%) with 2-(trimethylsilyl)-thiazole, which proceeds with no loss of optical purity, so we believe that it is the conditions of our condensation reaction which result in racemisation.
11. For a recent discussion of the coupling constants observed in related oxazolidinones, see: Kise, N.; Inakoshi, N.; Matsumura, Y. *Tetrahedron Lett.* **1995**, *36*, 909.
12. Compound **8b** is a potential precursor to allophenylnorstatine **2**, and we have converted it (t-BuOH, AgO_2CCF_3) to the corresponding *tert*-butyl ester **12b** for comparison with a known compound, see reference 4 above. A small amount of the corresponding *trans*-oxazolidinone **12a**, which could not be separated by chromatography, was always present, so direct comparison of specific rotation with the literature value could not be made.



8b **12b** **12a**

13. Clegg, W. and Elsegood, M.R.J., unpublished work. The details of these crystal structure determinations will be published separately.
14. It is interesting to note that an isomerisation in the opposite sense has been observed in the preparation of Taxotere® using an isopropylidene protected derivative of *anti*-phenylisoserine: Denis, J.-N.; Kanazawa, A.M.; Greene, A.E. *Tetrahedron Lett.* **1994**, *35*, 105. See also reference 10 above.
15. Both diastereoisomers of closely related esters, in contrast to the thioesters which we have prepared, are reported in reference 11 above to be stable to silica gel chromatography. It therefore appears that the thioester group is responsible for the observed isomerisation to the *cis*-oxazolidinones.
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(*Received in UK* 2 *February* 1996; *accepted* 9 *February* 1996)