JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 11
1993

Control of Diastereoselectivity in the Nucleophilic Epoxidation of 1-Arylthio-1-nitroalkenes: Synthesis of Diastereoisomerically Pure γ-Hydroxy Threonine Derivatives

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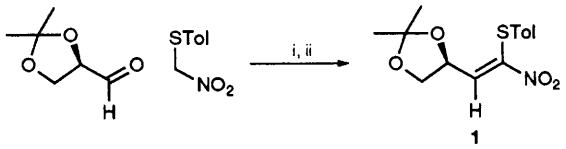
Epoxidation of the 1-nitro-1-(*p*-tolylthio)alkene **1** derived from D-isopropylideneglyceraldehyde with lithium *tert*-butyl peroxide affords the *syn* epoxide **2** with moderate selectivity, whereas epoxidation with potassium *tert*-butyl peroxide affords the *anti* diastereoisomer **3** preferentially; treatment of each of the epoxides **2** and **3** with amines, including ammonia, gives diastereoisomerically pure α-amino thioesters with no trace of stereoisomeric contamination.

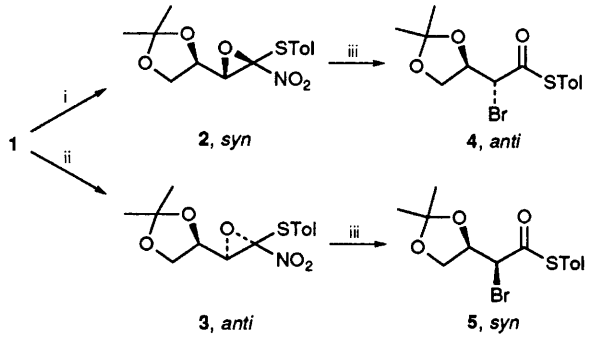
We have shown recently that 2-nitro-2-phenylthiooxiranes, prepared by nucleophilic epoxidation of 1-nitro-1-phenylthioalkenes, react with oxygen and halide nucleophiles to give α-substituted *S*-phenyl thioesters under mild conditions.[1] Prompted by our recent investigations into the control of stereochemsitry in nucleophilic epoxidation of γ-hydroxy α,β-unsaturated sulfones by the allylic stereocentre,[2] we have investigated the stereoselectivity in nucleophilic epoxidation of the 1-nitro-1-(*p*-tolylthio)alkene **1**.

The alkene **1** was prepared from D-isopropylideneglyceraldehyde by condensation with (*p*-tolylthio)nitromethane (Scheme 1),[3] and appeared to be a single isomer (*Z*) as judged by ^{1}H NMR spectroscopy. Epoxidation of **1** with lithium *tert*-butyl peroxide gave a mixture of *syn* and *anti* epoxides **2** and **3** (ratio 5 : 1), from which the major *syn* isomer **2** could be obtained pure (60%) by crystallisation from light petroleum. An X-ray crystal structure analysis of the epoxide **2** established its structure unambiguously.[4] Epoxidation of **1** with potassium *tert*-butyl peroxide resulted in a reversal in diastereoselectivity, with the *anti* epoxide **3** now the major isomer (ratio of **2** to **3** 1 : 6.5). Column chromatography, followed by crystallisation of the minor component, afforded **3** as a pure diastereoisomer (63%). The two epoxides **2** and **3** were converted into the stereoisomeric *anti* and *syn* α-bromo *S*-tolyl thioesters **4** (85%) and **5** (83%), respectively (Scheme 2). An X-ray crystal structure analysis[4] of the α-bromo *S*-tolyl thioester **4** confirmed that it possessed the *anti* configuration, and, therefore, that the epoxide ring-opening reaction had proceeded with inversion of configuration.

We believe that the stereochemical outcome of the epoxidation process can be rationalised on the basis of a reactive conformation in which the allylic hydrogen occupies the inside position (to minimise allylic strain),[5] and coordination by the γ-oxygen substituent directs attack by lithium *tert*-butyl peroxide to the same face (Fig. 1). In contrast, reaction with potassium *tert*-butyl peroxide is likely to be under stereoelectronic control, in which nucleophilic attack occurs *anti* to the allylic C–O bond (Fig. 2). Related diastereoselective additions to 1-nitro-1-phenylthioalkenes have been reported,[6] and attention has been drawn to the steric bulk of the nucleophile in controlling the stereochemical sense of such reactions.[7]



Scheme 1 *Reagents and conditions*: i, KOBu^t, Bu^{t}OH–THF, 0 °C; ii, $MeSO_2Cl$ (3 equiv.), NEt_3 (3 equiv.), −78 °C to 0 °C, 54% overall yield†



Scheme 2 *Reagents and conditions*: i, LiOOBu^t, THF, −78 °C, 2 h; ii, KH–Bu^{t}OOH, THF, −78 °C, 2 h; iii, $MgBr_2 \cdot Et_2O$, Et_2O (1.2 equiv.), room temp., 2 h

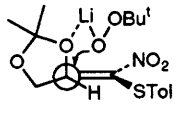


Fig. 1

† *Abbreviations used*: Tol = *p*-MeC_6H_4, Bn = $PhCH_2$, Boc = Bu^{t}OCO, Z = $PhCH_2OCO$.

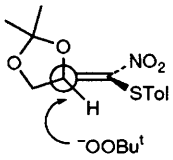
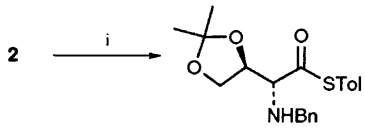
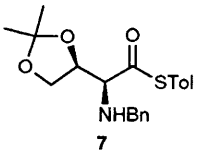
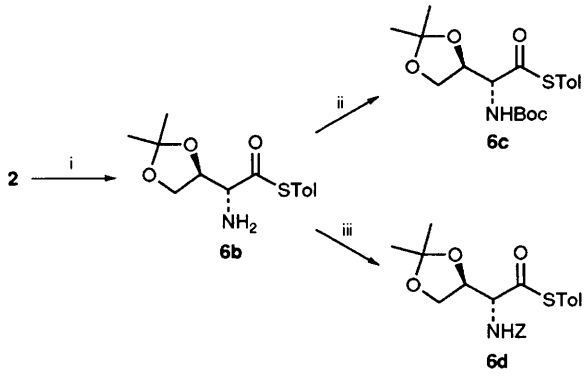


Fig. 2

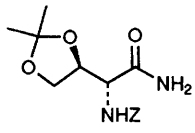


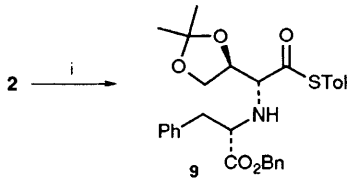
Scheme 3 *Reagents and conditions*: i, $BnNH_2$ (2 equiv.), CH_2Cl_2, room temp. 2 h





Scheme 4 *Reagents and conditions*: i, NH_3 (*d* 880 aq., 5 equiv.), CH_2Cl_2, room temp., 2 h; ii, Boc_2O (10 equiv.), room temp., 2 h; iii, ZCl (10 equiv.), room temp, ½ h





Scheme 5 *Reagents and conditions*: i, (*S*)-$PhCH_2CH(NH_2)CO_2Bn$ (2 equiv.), CH_2Cl_2, room temp., 24 h

In our initial study on ring-opening reactions of 2-nitro-2-phenylthiooxiranes,[1] we had not investigated the possibility of using nitrogen nucleophiles, and we now report that a variety of primary amines, including ammonia, react with the oxiranes **2** and **3** under mild conditions to give the corresponding α-amino *S*-tolyl thioesters **6** and **7** in a completely stereospecific manner. For example, treatment of **2** with benzylamine in dichloromethane gave the diastereoisomerically pure γ-hydroxy threonine derivative **6a** (88%) (Scheme 3).[8,9] Reaction of the stereoisomer **3** under the same conditions gave **7** (80%). More usefully, treatment of **2** with ammonia (880, aqueous solution) in dichloromethane gave the free *anti* α-amino *S*-tolyl thioester **6b**, which could be isolated either as the *tert*-butoxycarbonyl derivative **6c** (67%) or the benzyloxycarbonyl derivative **6d** (69%), by addition either of *tert*-butyl pyrocarbonate or benzyloxycarbonyl chloride, respectively, after TLC had indicated complete consumption of the oxirane **2** (Scheme 4). The stereochemistry of the *Z*-protected derivative **6d** was confirmed by an X-ray crystal structure analysis,[4] and also by conversion to the corresponding amide **8** (by extended treatment with ammonia) followed by comparison of ^1H NMR data for this compound with those in the literature.[9] It is noteworthy that reaction of the *S*-tolyl thioester to give a primary amide is significantly slower than the original ring opening of the 2-nitro-2-(tolylthio)oxirane group, testifying to its very high reactivity towards nucleophiles.

As a final example, reaction of oxirane **2** with phenylalanine benzyl ester gave the secondary amine **9** (80%) as a single stereoisomer as judged by ^1H NMR spectroscopy (Scheme 5). This result not only illustrates a novel route to enzyme inhibitors, but also confirms that no significant racemisation had occurred in the formation of the 1-nitro-1-(*p*-tolylthio)-alkene **1**.

We thank the SERC for a CASE award (N. J. P.) and a Quota award (J. M. K.), Professor W. Clegg and Dr M. R. J. Elsegood for determining the X-ray crystal structures and Pfizer Central Research and Zeneca Pharmaceuticals for support.

Received, 17th March 1993; Com. 3/01559I

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