3586 J. Org. Chem. **1996,** *61,* 3586−3587

Stereoselective Nucleophilic Epoxidation of Vinyl Sulfoxides: A Novel Route to Enantiopure Sulfinyl Oxiranes[†,1]

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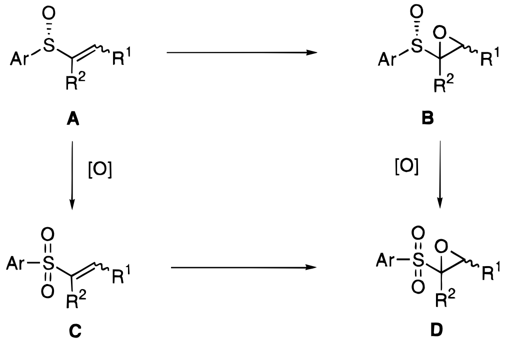
Received February 27, 1996

Enantiopure sulfinyl oxiranes are versatile synthetic intermediates[2] available by condensation of α-chloroalkyl *p*-tolyl sulfoxides with aldehydes or ketones and subsequent cyclization. However, this process results in the formation of two diastereomers due to low 1,3-asymmetric induction.[2b] On the other hand, Jackson has recently shown that (*E*)-*N*-[(*p*-tolylsulfonyl)vinyl]sulfoximines undergo nucleophilic epoxidation with LiOO-*t*-Bu with complete geometric and facial selectivity to produce the corresponding oxiranes.[3,4] Jackson's results conclusively established that a chiral sulfoximine sulfur atom may be a powerful element of stereocontrol in this process. Within the context of an ongoing project addressing multiple sulfur to carbon chirality transfer operations using vinyl sulfoxides, we required an efficient route to enantiopure vinyl epoxy sulfoxides of general structure **B**, R^2 = vinyl (Scheme 1), with high regiocontrol, *E*−*Z* stereocontrol, and diastereofacial selectivity. We envisioned that the nucleophilic epoxidation of readily available[5] 2-sulfinyl dienes **A**, R^2 = vinyl, could be a viable albeit challenging route, and aware of the synthetic usefulness of sulfinyl oxiranes,[2] we undertook the development of such a process as a general reaction of alkenyl sulfoxides. In this paper, we describe our preliminary results of the unprecedented direct epoxidation of simple vinyl sulfoxides.

At the inception of this research we recognized two difficulties associated with our approach to epoxy sulfoxides **B** (Scheme 1), namely, alkenyl sulfoxides, **A**, are only moderately electron deficient[6] and they are readily oxidized to the corresponding sulfones **C** which may undergo nucleophilic epoxidation to yield racemic **D**. In contrast, vinyl sulfoximines are powerful Michael acceptors and cannot be oxidized readily. In addition, the desired sulfinyl oxiranes **B** should undergo oxidation even more readily to produce epoxy sulfones **D**. Since most Weitz−Scheffer reaction conditions are also relatively strongly oxidizing, the viability and, at best, the facial selectivity of this epoxidation became a matter of concern. Considering this, we selected simple vinyl sulfoxides **1**−**6** and dienyl sulfoxides **7** and **8**[5,7] as substrates for this study, and the results obtained are shown in Table 1.

Scheme 1



At the initial stage of this research we focused our efforts on keto vinyl sulfoxide **1** to establish whether a sufficiently activated substrate could undergo epoxidation without significant oxidation to the sulfone. Indeed, treatment of **1** with LiOO-*t*-Bu led to a mixture of four diastereomeric epoxy sulfoxides, presumably geometric and facial isomers, with low selectivity. This disappointing result demonstrated that, at least for short reaction times, these conditions were compatible with the sulfinyl functionality.

The reactivity of simple *E* alkenyl sulfoxides **2** and **3** was then studied. Phenyl-substituted sulfoxide **2** was found to be totally unreactive under a number of experimental conditions.[8] The well-known lack of reactivity of **2** with nucleophiles[9] prompted us to study **3**, but unfortunately, our initial efforts led to almost exclusive formation of sulfone **9**. After considerable experimentation,[10] we succeeded in obtaining the desired epoxy sulfoxides **10** and **11** (Table 1, entry 3) albeit in low selectivity and accompanied by relatively large amounts of sulfone **9**.

The influence of the alkene geometry on the process was then addressed (Table 1, entries 4 and 5), and both *Z* substrates studied, **4** and **5**, afforded good yields of epoxy sulfoxides **13** and **16** with remarkable stereoselectivities. Furthermore, overoxidation to sulfones **12** and **15** was hardly a problem in these cases.[11] In view of the high reactivity displayed by **5**, we studied *tert*-butyl sulfoxide **6** and, while the reaction was somewhat slower than for the *p*-tolyl analogue **5**, practically a single isomer of an epoxy sulfoxide was obtained in excellent yield.[12]

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(1) Taken in part from the M.S. Theses of S.C., P.M., and J.P., Instituto de Química Orgánica, CSIC.

(2) (a) For a review, see: Satoh, T.; Yamakawa, K. *Synlett* **1992**, 455−468. (b) Satoh, T.; Oohara, T.; Ueda, Y.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3130−3136. (c) For an isolated example of an alternative method, see: Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Tetrahedron Lett.* **1974**, 455−458.

(3) Briggs, A. D.; Jackson, R. F. W.; Clegg, W.; Elsegood, M. R. J.; Kelly, J.; Brown, P. A. *Tetrahedron Lett.* **1994**, *35*, 6945−6948.

(4) For leading references on related nucleophilic epoxidations, see: (a) Jackson, R. F. W.; Standen, S. P.; Clegg, W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 149−156. (b) Linderman, R. J.; Claasen, R. J., II; Viviani, F. *Tetrahedron Lett.* **1995**, *36*, 6611−6614. (c) Ambroise, L.; Jackson, R. F. W. *Tetrahedron Lett.* **1996**, *37*, 2311−2314.

(5) See: Paley, R. S.; Weers, H. L.; Fernández de la Pradilla, R.; Castro, S. *Tetrahedron Lett.* **1995**, *36*, 3605−3608 and references cited therein.

(6) Simple vinyl sulfoxides display a relatively low reactivity with nucleophiles. See, for instance: *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. H., Eds.; John Wiley & Sons: New York, 1988.

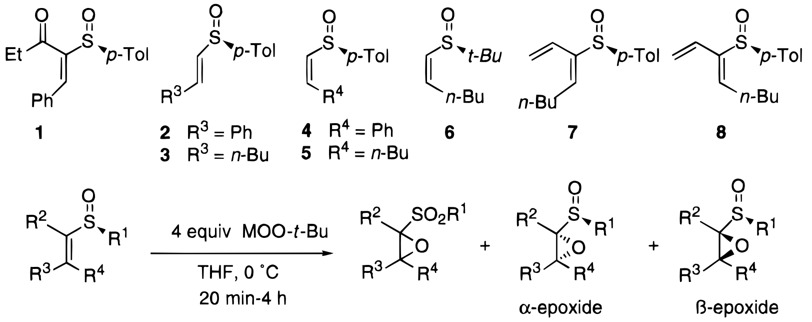
(7) Substrates **2**−**5** were prepared in one step from commercially available reagents by the method of Craig. See: Craig, D.; Daniels, K.; McKenzie, A. R. *Tetrahedron* **1993**, 49, 11263−11304. Alternatively, **3** could be prepared with high selectivity in two steps according to: Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078−1082. For the preparation of **1** see: Marino, J. P.; Viso, A.; Fernández de la Pradilla, R.; Fernández, P. *J. Org. Chem.* **1991**, *56*, 1349−1351. Racemic **6**, available in our laboratories from a previous project, was prepared from 1-hexyne by free radical addition of 2-methyl-2-propanethiol and oxidation. All new products reported here have been fully characterized by spectroscopic techniques.

(8) Forcing reaction conditions (long reaction times, higher temperatures) led to oxidation to the vinyl sulfone and, in some cases, subsequent epoxidation. For the oxidation of sulfoxides with *t*-BuOOH, see: Breton, G. W.; Fields, J. D.; Kropp, P. J. *Tetrahedron Lett.* **1995**, *36*, 3825−3828.

(9) Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, 55, 1086−1093.

S0022-3263(96)00384-2 CCC: $12.00

Table 1. Diastereoselective Epoxidation of Vinyl Sulfoxides



entry	substrate	M	time (min)	sulfone[a]	α-epoxide[a,b]	β-epoxide[a,b]	yield[c] (%)
1	**1**	Li	20		see text		
2	**2**	Li					NR
3	**3**	Li	240	**9** (25)	**10** (17)	**11** (58)	70
4	**4**	Li	240	**12** (6)	**13** (86)	**14** (8)	84
5	**5**	Li	20	**15** (−)	**16** (98)	**17** (2)	74
6	**6**	Li	210	**18** (−)	**19** (98)	**20** (2)	79
7	**7**	Li	120	**21** (trace)	**22** (20)	**23** (80)	75
8	**8**	Li	120	**24** (−)	**25** (77)	**26** (23)	83
9[d]	**3**	Na	90	**9** (13)	**10** (4)	**11** (83)	75
10[d]	**4**	Na	60	**12** (3)	**13** (96)	**14** (1)	77
11[e]	**8**	Li	120	**24** (100)[f]	**25** (−)	**26** (−)	92

[a] Ratios of products measured by integration of the 300 MHz ^{1}H NMR spectra of crude reaction mixtures are in parentheses. [b] Tentative assignments except for **22**, **23**, **25**, and **26**. See ref 15. [c] Unoptimized combined yields of pure products. [d] Generated from NaH and HOO-*t*-Bu. [e] Reaction conducted in Et_2O. [f] Sulfone **24** had 84% ee.

Finally, we focused on the epoxidation of 2-sulfinyl dienes **7** and **8** (Table 1, entries 7 and 8), which displayed moderate stereoselectivities under standard reaction conditions to produce good yields of vinyl epoxy sulfoxides **22**, **23**, **25**, and **26**.

The effect of the metal cation and solvent on this epoxidation was then briefly examined. The use of NaOO-*t*-Bu (Table 1, entries 9 and 10) resulted in a substantial enhancement of the stereoselectivity along with less overoxidation to the sulfones (compare with entries 3 and 4 of Table 1).[13] On the other hand, the epoxidation of diene **8** with LiOO-*t*-Bu in Et_2O (Table 1, entry 11) led to an excellent yield of vinyl epoxy sulfone **24** (83% ee).[14]

While the general structure and geometry of these epoxy sulfoxides could be readily established from their ^{1}H and ^{13}C NMR spectral features, determination of their relative configuration required a chemical correlation which was carried out for vinyl epoxides **23** and **25**.[15] The stereochemistry of the other epoxides gathered in Table 1 was tentatively assigned by analogy with that of **23** and **25**.

The observed stereochemical outcome of this process may be rationalized in terms of the different reactive conformations proposed by Pyne.[9] Thus, a *syn* coplanar S=O/C=C conformation would lead to preferred β-attack for *E* substrates. Alternatively, *Z* sulfoxides would undergo selective α-attack due to a conformational change to an *s-trans* coplanar S=O/C=C conformation. While these selectivities may be accounted for by steric considerations, some directing effect of the sulfinyl oxygen by coordination with the metal cannot be ruled out at this point.

In summary, these results conclusively demonstrate that readily available vinyl sulfoxides may undergo clean nucleophilic epoxidation with moderate to excellent diastereofacial selectivity and complete preservation of the geometry of the starting material and in synthetically useful yields. This methodology should allow for expedient access to a variety of enantiopure epoxy sulfoxides and epoxy sulfones, versatile synthetic intermediates.[2,3,16] We are currently exploring the scope, limitations, and possible improvements of this protocol as well as applications of our vinyl epoxy sulfoxides in synthesis.

Acknowledgment. This research was supported by DGICYT (Grant Nos. PB93-0154 and PB94-0104). We thank Professors B. Rodríguez and S. Valverde for encouragement and support.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds (10 pages).

JO9603845

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(10) The qualitative influence of stoichiometry, temperature, concentration, and reaction time on this process was screened. In many cases, very careful monitoring of the reaction by TLC was crucial since vinyl and epoxy sulfoxides present very similar chromatographic mobilities.

(11) An authentic sample of enantiomerically pure sulfone **15** was prepared by oxidation (MMPP, MeOH, rt) of epoxy sulfoxide **16**.

(12) The use of *tert*-butyl sulfoxides allows for improved stereocontrol *vs* their *p*-tolyl analogues in some cases. For the preparation of optically pure *tert*-butyl sulfoxides, see: Khiar, N.; Fernández, I.; Alcudia, F. *Tetrahedron Lett.* **1994**, 35, 5719−5722 and references cited therein.

(13) To the best of our knowledge, NaOO-*t*-Bu has not been used previously for related processes.

(14) The optical purity was determined by comparison of the optical rotation of **24** (entry 11, [α] = +82.8) with that of an enantiomerically pure sample ([α] = +99.5) obtained from sulfinyl epoxide **25** (Oxone, MeOH). This observation suggests that in Et_2O the epoxidation occurs with better selectivity (*ca.* 90:10) than in THF (77:23) and that sulfoxides **25** and **26** are oxidized very readily to **24**. Efforts to control this undesired oxidation in Et_2O are underway.

(15) This correlation entailed hydrogenation of unsaturated epoxides **23** and **25** and comparison of the data of the resulting sulfinyl oxiranes with that of enantiomeric or diastereomeric epoxides prepared from (R_s)-1-chloro-*n*-propyl *p*-tolyl sulfoxide and *n*-pentanal by the method of Yamakawa (ref 2) of known stereochemical course. These experiments will be described in detail in a full account of this research.

(16) (a) For the α-lithiation of sulfonyl oxiranes, see: Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 897−908. (b) For the generation of oxiranyllithium reagents from sulfinyl oxiranes by ligand exchange, see: Satoh, T.; Horiguchi, K. *Tetrahedron Lett.* **1995**, *36*, 8235−8238.