Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4245–4248
Tetrahedron Letters

Regioselective synthesis of N-substituted-4-substituted isothiazolidine-1,1-dioxides

Ed Cleator,* Faye J. Sheen, Matthew M. Bio, K. M. Jos Brands, Antony J. Davies and Ulf-H. Dolling

Department of Process Research, Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU, UK

Received 26 November 2005; revised 2 April 2006; accepted 7 April 2006
Available online 4 May 2006

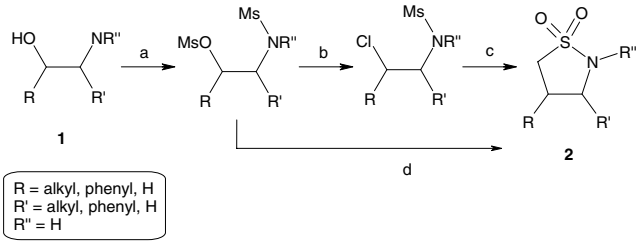
Abstract—A novel and efficient synthesis of a range of racemic and enantioenriched N-substituted-4-substituted isothiazolidine-1,1-dioxides from epoxides and sulfonamides is described. The critical choice of the activating group for the cyclization event is discussed. The application of this methodology to the synthesis of N-substituted-4,5-disubstituted derivatives is also described.

Sulfonamides are prevalent structural features of many pharmaceutical agents.[1] The corresponding cyclic sulfonamides (sultams) have therefore been pursued as potential pharmaceutical scaffolds in their own right.[2] The synthetic strategies towards these important building blocks have, with very few exceptions,[3] relied upon intramolecular cyclization of the corresponding haloalkylsulfonyl chlorides. This approach generally requires multi-step reaction sequences and/or the use of noxious reagents (Cl_2, PCl_5, Bu_3SnH/AIBN).[4]

Lee et al. have recently shown that substituted sultams can be effectively prepared from α-amino alcohols **1**, and used this protocol to generate a range of 3-substituted isothiazolidine-1,1-dioxides **2** in good yields (Scheme 1).[5] A similar strategy had previously been used by Cooper to produce 3,4-disubstituted isothiazolidine-1,1-dioxides, starting from the corresponding 1,2-disubstituted amino alcohols.[6]

Whilst this method has proven general for 3- and 3,4-substituted cyclic sulfonamides there are, to date, no general methods for the preparation of the 4-substituted analogues. Herein we report a novel, efficient and regioselective synthesis of these compounds, using readily available starting materials and mild reaction conditions. The cyclization is also found to be stereoselective, when enantioenriched starting materials are used. The methodology has also been applied to the synthesis of 4,5-disubstituted isothiazolidin-1,1-dioxides.

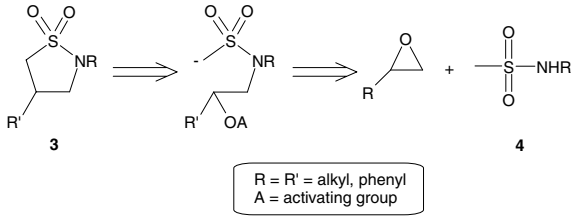
During the course of a research project, a number of N-alkylated-4-substituted isothiazolidine-1,1-dioxides **3** were required. We envisaged that these compounds could be prepared by addition of sulfonamides to epoxides and subsequent ring closure (Scheme 2). Many epoxides are commercially available in both racemic and enantioenriched forms, which makes them very attractive precursors. Additionally, nonracemic epoxides can be readily prepared using methods such as the Jacobsen hydrolytic kinetic resolution (HKR)[7] and the Sharpless epoxidation (SAE).[8]



Scheme 1. Reagents and conditions: (a) MsCl, THF, 0 °C; (b) NaCl, DMF, 80 °C; (c) LDA, THF, −50 °C → rt and (d) *n*-BuLi, (2.2 equiv), THF, −10 °C → rt, 2 h.

Keywords: Sulfonamides; Epoxides; Cyclizations; Ring opening reactions.
* Corresponding author. Tel.: +44 (0)1992 452179; fax: +44 (0)1992 470437; e-mail: edward_cleator@merck.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.038



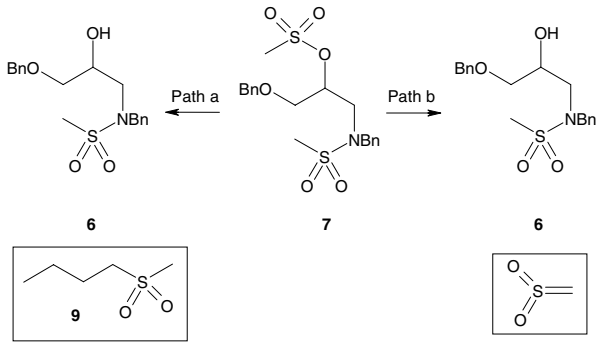
Scheme 2. Retrosynthetic approach to 4-substituted isothiazolidine-1,1-dioxides **3**.

The ring opening of epoxides with sulfonamides has been outlined in the literature.[9] Adapting the conditions of Albanese et al.,[10] we found that heating a solution of a secondary sulfonamide **4**[11] (R = Bn) and an epoxide **5** in 1,4-dioxane at 100 °C gave the desired amino alcohol **6** in good yield. Subsequent activation of the alcohol prior to intramolecular cyclization was accomplished upon treatment of **6** with methanesulfonyl chloride (MsCl) in pyridine at room temperature. The resulting methanesulfonate (mesylate) **7** could, after acidic work-up, be directly cyclized by treatment with *n*-butyllithium (*n*-BuLi) in THF (Scheme 3).

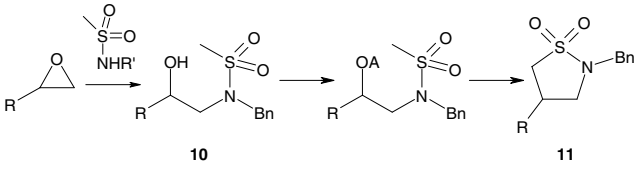
This procedure gave a modest 48% yield of the cyclized product **8**. The remaining material was found to be alcohol **6**, resulting from the loss of the mesyl group from **7**. This was ascribed to the decomposition of the methanesulfonate by the action of *n*-BuLi.

This decomposition could either take place by nucleophilic attack of the organometallic species at the sulfur to give alcohol **6** and sulfone **9** (Scheme 4, path a), or by deprotonation of the α-hydrogen and elimination of a sulfene (Scheme 4, path b). Changing the base to LDA also gave a mixture of **6** and **8**, suggesting that path b was operative. Further evidence for path b was obtained using an activating group with no α-hydrogens. The alcohol **6** was converted to the corresponding benzenesulfonate (besylate) by treatment with benzenesulfonyl chloride (BsCl) in pyridine at 50 °C. Treatment of this benzenesulfonate analogue with *n*-BuLi led to the formation of the desired N-benzylated-4-substituted isothiazolidine-1,1-dioxide in an improved 76% overall yield. In this case, no alcohol **6** was observed.

A range of N-substituted-4-substituted isothiazolidine-1,1-dioxides were prepared using this method (Scheme 5, Table 1).



Scheme 4. Potential pathways for the formation of **6** from **7** upon treatment with *n*-BuLi.



Scheme 5. General approach to N-substituted-4-substituted isothiazolidine-1,1-dioxides. A = Ms (methanesulfonyl), Bs (benzenesulfonyl).

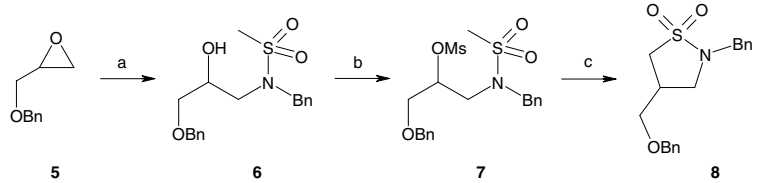
Table 1. *N*-Alkyl-4-substituted isothiazolidine-1,1-dioxides **11** produced via Scheme 5

Entry	R	R′	Yield of **10** (%)	A[a]	Yield **11** over two steps (%)
1	Ph	Bn	87	Ms	42
2	Ph	Bn	87	Bs	78
3	CH_2OPh	Bn	88	Bs	83
4[b]	(*R*)–$(CH_2)_2CHCH_2$	Bn	94	Ms	51
5[b]	(*R*)–$(CH_2)_2CHCH_2$	Bn	94	Bs	82
6	$(CH_2)_2CHCH_2$	Bn	97	Bs	81
7	Ph	Ph	86	Bs	72

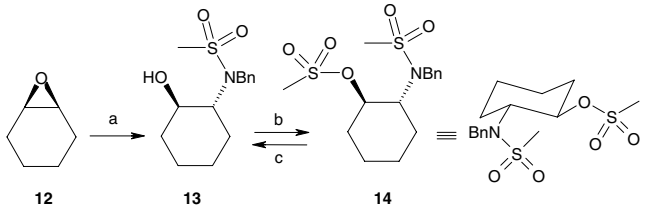
[a] Ms = Methanesulfonyl, Bs = benzenesulfonyl.
[b] Commercially available chiral epoxide (97.4% ee). The chirality was transferred to the product **11**.

In all cases, the overall yield for the two-step activation-cyclization was greatly enhanced when the benzenesulfonates were used as activated intermediates.

Chiral 4-substituted isothiazolidine-1,1-dioxides were also easily accessed using this methodology. When the chiral epoxide (*R*)-1,2-epoxyhex-5-ene (97.4% ee) was



Scheme 3. Initial preparation of 4-substituted isothiazolidine-1,1-dioxide: Reagents and conditions: (a) 1,4-dioxane, K_2CO_3 (10 mol %), tetraethylammonium chloride (10 mol %), **4** (R = Bn), 100 °C, 91%; (b) MsCl (1.2 equiv), pyridine, DMAP (cat.), rt and (c) *n*-BuLi, (2.2 equiv), THF, −78 °C → rt, 2 h, 48% over two steps.



Scheme 6. Reagents and conditions: (a) 1,4-dioxane, K_2CO_3 (10 mol %), tetraethylammonium chloride (10 mol %), **4** (R = Bn), 100 °C, 88%; (b) MsCl (1.2 equiv), pyridine, DMAP (cat.), rt and (c) *n*-BuLi, (2.2 equiv), THF, −78 °C → rt, 2 h, 97% over two steps.

used as the starting material (Table 1, entries 4 and 5), the chirality was faithfully translated to the product through inversion at the sulfonate-bearing carbon.[12] This indicated that the cyclization was occurring exclusively via an S_N2 process.

Attempts to expand this methodology to 1,2-dialkyl epoxides were generally unsuccessful, presumably due to steric hindrance. However, the ring opening of the bicyclic cyclohexene oxide **12** with *N*-benzylmethanesulfonamide gave the desired *trans*-amino alcohol **13** in good yield (Scheme 6). Conversion of **13** to the corresponding mesylate **14** was uneventful; however, when treated with *n*-BuLi, **14** was found to revert exclusively to alcohol **13**. This is thought to be a consequence of **14** having both functionalities in equatorial positions, and thus being unable to attain the correct conformation for a S_N2 reaction. Attempts to cyclize the corresponding besylate were also unsuccessful.

The scope of this methodology was further extended to the synthesis of trisubstituted isothiazolidine-1,1-dioxides: *N*-benzylpropylsulfonamide **15** was added to (*R*)-1,2-epoxyhex-5-ene **16** to give amino alcohol **17** in excellent yield (Scheme 7). The amino alcohol was then converted to the benzenesulfonate **18** which, upon treatment with *n*-BuLi, afforded the isothiazolidine-1,1-dioxides **20a** and **20b** in 52% yield as a 3:1 mixture of diastereomers, respectively.

The observed diastereoselectivity is believed to be a consequence of differing steric environments in the transition states during the cyclization. Abstraction of the α-sulfonamide proton generates intermediates **19a** and **19b**. It has been shown that anions α to a sulfonyl moiety are able to racemize via interaction with the sulfur d-orbitals,[13] hence **19a** and **19b** are in equilibrium. This racemization occurs at a faster rate than ring closure. Cyclization of intermediate **19a** is expected to be faster as, in this case, the bulky R groups are *anti* and not eclipsed as in **19b**. Sultam **20a** is, therefore, observed as the major product.

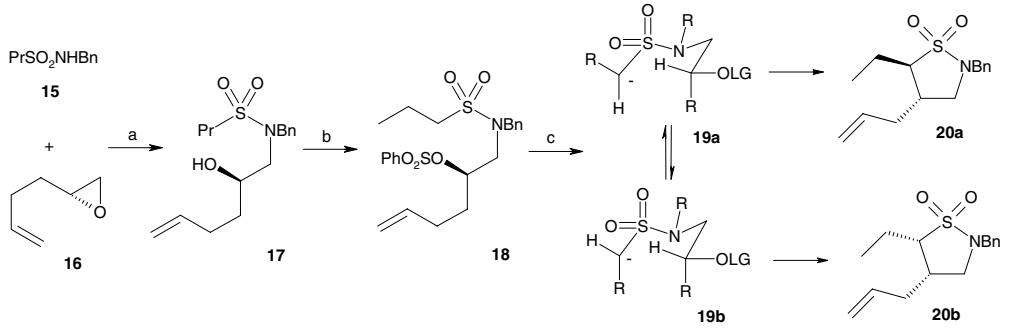
In summary, we have developed an efficient synthesis of N-alkylated-4-substituted isothiazolidine-1,1-dioxides starting from readily available epoxides. Furthermore, the use of an enantiomerically enriched epoxide provides access to the corresponding enantiomerically enriched sultam. We have also demonstrated the extension of this method to the synthesis of trisubstituted isothiazolidine-1,1-dioxides.

Acknowledgements

We would like to thank Sophie Strickfuss from the MSD analytical research group at Hoddesdon for the chiral HPLC analyses.

References and notes

1. Bowman, W. C.; Ram, M. J. *Textbook of Pharmacology*, 2nd ed.; Blackwell: London, 1979; Chapter 34.
2. Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. R. *Bioorg. Med. Chem. Lett.* **2000**, *11*, 1159.
3. Merten, S.; Fröhlich, R.; Kataeva, O.; Metz, P. *Adv. Synth. Cat.* **2005**, *6*, 754.
4. (a) White, E. H.; Lim, H. M. *J. Org. Chem.* **1987**, *52*, 2162; (b) Bliss, A. D.; Cline, W. K.; Hamilton, C. E.; Sweeting, O. *J. Org. Chem.* **1963**, *28*, 3557.
5. Lee, J.; Zhong, Y. L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, *5*, 4175.
6. Cooper, G. F. *Synthesis* **1991**, *10*, 859.
7. Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.
8. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
9. Baker, B. R.; Kadish, A. F.; Querry, M. V. *J. Org. Chem.* **1950**, *2*, 400.



Scheme 7. Reagents and conditions: (a) 1,4-dioxane, K_2CO_3 (10 mol %), tetraethylammonium chloride (10 mol %), **15**, 100 °C, 87%; (b) $PhSO_2Cl$ (1.2 equiv), pyridine, DMAP (cat.), 50 °C and (c) *n*-BuLi, (2.2 equiv), THF, −78 °C → rt, 2 h, 52% over two steps.

10. Albanese, D.; Landini, D.; Penso, M.; Petricci, S. *Tetrahedron* **1999**, *20*, 6387.
11. For initial studies, *N*-benzyl methanesulfonamide (**4**, R = Bn) was prepared in almost quantitative yield by reaction of benzylamine and methanesulfonyl chloride in THF, in the presence of triethylamine.
12. Determined by chiral HPLC. Conditions, Column—Chiral AD; eluant 20% *iso*-propyl alcohol in hexanes containing 0.1% TFA; Retention times—major = 30.5 min, minor = 34.0 min.
13. Corey, E. J.; Kaiser, E. T. *J. Am. Chem. Soc.* **1961**, *83*, 490.