ORGANIC LETTERS

2003
Vol. 5, No. 22
4175−4177

Practical Synthesis of Sultams via Sulfonamide Dianion Alkylation: Application to the Synthesis of Chiral Sultams

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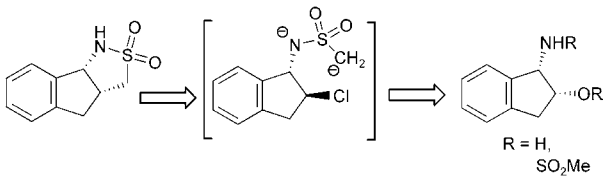
Received August 26, 2003

ABSTRACT



A practical synthesis of sultams was developed via intramolecular sulfonamide dianion alkylation. This method has been applied toward the synthesis of chiral sultams, which are synthetically valuable as chiral auxiliaries.

The sulfonamide functional group stands out as one of the most important pharmacophores and is found in useful therapeutic agents.[1] Recently, cyclic sulfonamides (sultams) have received significant attention due to their biological activity and diverse medicinal uses.[2] Beyond their significance in the treatment of disease, sultams have also been employed with considerable success as chiral reagents and auxiliaries.[3] Despite the utility of these compounds, an efficient route for the preparation of cyclic sulfonamides has not been realized.

The reported syntheses of 1,4-butanesultam and 1,3-propanesultam, which utilized chloroalkanesulfonyl chloride intermediates, required multistep sequences and inconvenient reagents such as PCl_5 and chlorine.[4] Although various protocols for synthesis of the substituted sultams have been developed using as a key ring formation step either C−N bond formation[5] or C−C bond formation,[6] these methods have been limited to a specific class of substrates. Herein, we describe a general and widely applicable solution for the synthesis of sultams via sulfonamide dianion alkylation and application to the preparation of the chiral sultams.

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(2) (a) Zhuang, L.; Wai, J, S.; Embrey, M.; Fisher, T, E.; Egbertson, M, S.; Payne, L, S.; Guare, J, P.; Vacca, J, P.; Hazuda, D, J.; Felock, P, J.; Wolfe, A, L.; Stillmock, K, A.; Witmer, M, V.; Moyer, G.; Schleif, W, A.; Gabryelski, L, J.; Leonard, Y, M.; Lynch, J, J.; Michelson, S, R.; Young, S, S. *J. Med. Chem*. **2003**, *46*, 453. (b) Ries, U. J.; Mihm, G.; Narr, B,; Hasselbach, K. M.; Wittneben, H.; Entzeroth, M.; van Meel, J. C.; Wienen, W.; Hauel, N. H. *J. Med. Chem*. **1993**, *36*, 4040. (c) Inagaki, M.; Tsuri, T.; Jyoyama, H.; Ono, T.; Yamada, K.; Kobayashi, M.; Hori, Y.; Arimura, A.; Yasui, K, Ohno, K.; Kakudo, S.; Koizumi, K.; Suzuki, R.; Kato, M.; Kawai, S.; Matsumoto, S. *J. Med. Chem*. **2000**, *43*, 2040.

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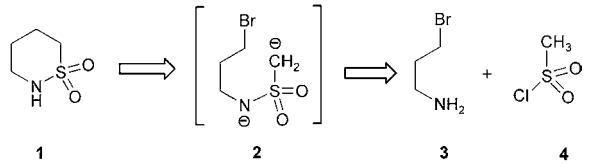
10.1021/ol0356183 CCC: $25.00
Published on Web 10/10/2003

We envisioned a retrosynthetic strategy (Scheme 1) whereby **1** might arise from sulfonamide dianion alkylation

Scheme 1. Retrosynthetic Analysis

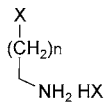
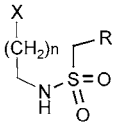
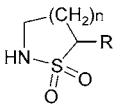


without protection of the nitrogen atom.[7] This approach depended on the desired C−C bond-forming reaction occurring in preference to azetidine (four-membered ring) formation. 3-Bromopropylsulfonamide would be available from methanesulfonylation of bromopropylamine **3**.

To test the proposed hypothesis, 3-bromopropylmethane sulfonamide (**2b**) was prepared by treatment of commercially available bromopropylamine-HBr (**3b**) and methanesulfonyl chloride in the presence of 2 equiv of triethylamine (>98%). Gratifyingly, the intramolecular sulfonamide dianion alkylation was readily initiated with in situ generated LDA[8] by treatment of *n*-BuLi (2.2 equiv) and diisopropylamine (0.25 equiv) in the presence of bromosulfonamide at −30 °C. Subsequent aging of the reaction mixture at 0 °C for 1 h gave the desired *δ*-sultam **1** in 85% overall yield. Exposure of all substrates of haloalkanesulfonamides to the *in situ* generated LDA in THF led to the formation of the desired *δ*-sultams in high yield (Table 1).

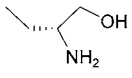
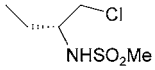
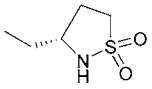
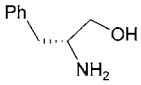
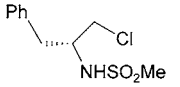
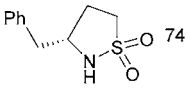
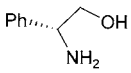
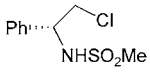
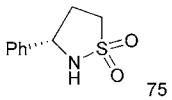
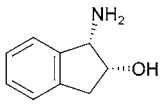
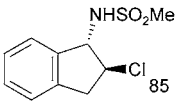
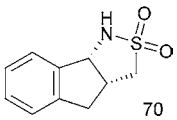
Of particular note is that the formation of the azetidine was not detected in crude reaction mixtures. Thus, protection of the nitrogen atom was not required for the six-membered sultam synthesis.

Table 1. Synthesis of Six- and Five-Membered Sultam from Precursor Haloalkylamine and Sulfonyl Chloride[a]

Entry	n	Substrate	Halosulfonamide[b]	Sultam[c]	Yield (%)[d]
					
1	n=2	**3b**: X = Br	**2b**: R = H , X = Br	**1**: R = H	85
2	n=2	**3b**: X = Br	**2b**: R = H , X = Br	**1**: R = H	89 [e]
3	n=2	**3c**: X = Cl	**2c**: R = H , X = Cl	**1**: R = H	90
4	n=2	**3c**: X = Cl	**5c**: R = Me, X = Cl	**6**: R = Me	72
5	n=2	**3b**: X = Br	**7b**: R = Ph, X = Br	**8**: R = Ph	75
6	n=1	**9b**: X = Br	**10b**: R = H , X = Br	**11**: R = H	55
7	n=1	**9c**: X = Cl	**10c**: R = H , X = Cl	**11**: R = H	75

[a] See the Supporting Information for a detailed procedure. [b] TEA (2 equiv), $MeSO_2Cl$ (1 equiv), THF, 5 to 10 °C, 1.5 h. [c] Diisopropylamine (0.25 equiv), *n*-BuLi (2.2 equiv), THF, −30 to 0 °C, 4 h. [d] Isolated yield. [e] 1.0 equiv of diisopropylamine was used.

Table 2. Synthesis of Five-Membered Chiral Sultams and Halosulfonamides from *β*-Amino Alcohols Precursors

Entry	Starting material	chlorosulfonamide[a] (yield, %)	sultam[b] (yield, %)
1	 **15**	 87 **16**	 68 **17**
2	 **18**	 90 **19**	 74 **20**
3	 **21**	 90 **22**	 75 **23**
4	 **24**	 85 **25**	 70 **26**

[a] CH_3SO_2Cl (2 equiv), TEA, THF; NaCl, DMF, 75 or 95 °C, 16 h. [b] Diisopropylamine (0.25 equiv), *n*-BuLi (2.2 equiv), −50 to 0 °C, 4 h.

The byproduct detected was the anticipated HBr-eliminated olefin. Interestingly, the olefin byproduct was suppressed by employing 1.0 equiv of diisopropylamine (entry 2). Chloropropylethanesulfonamide **5c**, which was derived from a readily available 3-chloropropylamine-HCl (**3c**) and ethanesulfonyl chloride, also afforded the desired cyclization product effectively (entry 4).

Based on the successful six-membered sultam synthesis, we were hopeful that with extension of this methodology it would be possible to perform functionalized five-membered

(6) (a) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126. (b) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761. (c) Wanner, J.; Harned, A, M.; Probst, D. A.; Kevin, W. C.; Poon, Klein, T, A.; Snelgrove, K, A.; Hanson, P, R. *Tetrahedron Lett.* **2002**, *43*, 917. (d) Lee, A. W. M.; Chan, W. H.; Poon, K. W. *Chem. Commun.* **1997**, 611. (e) Chiaccoi, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Graassi, G.; Piperno. A,; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425. (f) Plietker, B.; Seng, D.; Froehlich, R.; Metz, P. *Tetrahedron* **2000**, *56*, 873. For the sultam synthesis via intramolecular monoanion alkylation of *N*-protected sulfonamide, see: (a) Kobayashi, M.; Okahara, M.; Komori, S.; Agawa, T. *Synthesis* **1973**, 667.

(7) Although a sulfonamide *N*,*C*-dianion alkylation is known for substituted sulfonamide synthesis, this intramolecular dianion alkylation method has not been exploited for the cyclic sulfonamide formation. For examples of sulfonamide or sultam dianion, see: (a) Thompson, M, E. *J. Org. Chem.* **1984**, *49*, 1700. (b) Watanabe, H.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 4278. (c) Miller, R. A.; Humphrey, G. R.; Lieberman, D. R.; Ceglia, S. S.; Kennedy, D. J.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **2000**, *65*, 1399. (d) Szymonika, M. J.; Heck, J. V. *Tetrahedron Lett.* **1989**, *30*, 2873.

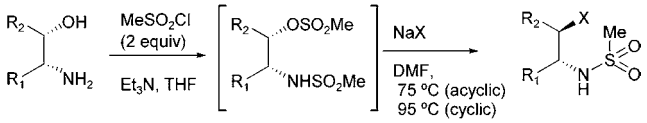
(8) Trecourt, F.; Mallet, M.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 1367.

sultam synthesis using the corresponding bromoethanesulfonamide. Treatment of the bromoethanesulfonamide **10b** with diisopropylamine and *n*-BuLi at −50 °C followed by warming to 0 °C over 4 h gave the desired sultam **11** in 55% yield (entry 6). In the case of the five-membered sultam cyclization reaction, aziridine formation was a competitive reaction pathway even at <−65 °C. This undesired aziridine formation can be suppressed with the use of chloride **10c**, affording **11** in 75% yield.

At this point, we investigated a general method for the efficient preparation of β-haloalkanesulfonamides from β-amino alcohols. Direct halogenation of the unprotected β-amino alcohols using PCl_5 or $SOBr_2$ gave the desired halide in moderate yields and required tedious purification. Attempted selective mono-*N*-sulfonylation of β-amino alcohols with a primary hydroxyl group such as 2-amino-3-phenyl-1-propanol **18** (Table 2) gave mixtures of products which required chromatographic separation.

Fortunately, it was found that *N*,*O*-bis-methanesulfonylation of amino alcohols followed by S_N2 displacement with sodium halide in DMF gave the desired haloalkanesulfonamides in high yield[9] (Scheme 2).

Scheme 2. General Method for the Preparation of a Chiral β-Halosulfonamide



12 **13** **14**

In this way, a variety of β-chlorosulfonamides, including both acyclic (Table 2, entries 1−3) and cyclic (entry 4) were prepared from commercially available chiral β-amino alcohols in high yield. In the case of *cis*-aminoindanol, the hydroxyl group can be converted to its *trans*-β-halo-*N*-sulfonamide (sultam precursors) with inversion of configuration (entry 4).

With chiral chlorosulfonamides in hand, we tried the sulfonamide dianion alkylation as shown in Table 2. Under the optimized reaction conditions, the chlorosulfonamides effectively cyclized to form the five-membered chiral sultams. These results are indicative of the versatility of this methodology for functionalized chiral sultam syntheses. The readily available *cis*-aminoindanol derived chlorosulfonamide gave the *cis*-fused sultam **26** in 70% yield which may have further application in asymmetric synthesis.

In conclusion, we have developed a practical and high-yielding method for the efficient synthesis of sultams. This key sulfonamide dianion alkylation was applied to the synthesis of chiral sultams from available nonracemic amino alcohols.

Supporting Information Available: Information on experimental procedures and compound characterization. ^1H and ^{13}C NMR spectra for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) After *N*,*O*-bis-methanesulfonylation of amino alcohol, an attempted one-pot halogenation with resulting triethylamine−HCl salt under THF or MEK reflux was not effective. *N*-Protected β-halosulfonamide has been prepared via *N*,*O*-bis-sulfonation followed by halide displacement: Bland, D.; Hart, D. J.; Lacoutiere, S. *Tetrahedron* **1997**, *53*, 8871.