The First Examples of Bridgehead Bicyclic Sultams

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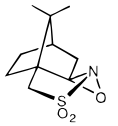
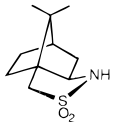
The sulfonamide antibiotics hold the prestigious position of being the first synthetic compounds to have had utility in human therapy.[1] These exciting developments spawned considerable interest in their use in veterinary practice and in the preparation of many hundreds of cyclic variants (i.e., sultams).[2] In recent years, reagents containing the important sultam functionality as a key structural feature have emerged. Representative examples include Davis's stereoselective oxidizing agent **1**,[3] the *N*-acyl and *N*-enoyl derivatives of 10,2-camphorsultam (**2**) developed by Oppolzer,[4] and Differding's saccharin-based electrophilic fluorinating agent **3**.[5]



1



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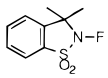
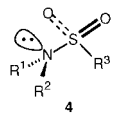


3

Despite the extent of attention accorded this class of compounds, the literature holds no report of any small bridgehead bicyclic sultam. The few carbonyl analogues (lactams) that are known[6] are highly prone to hydrolysis.[7] The angle strain and enforced torsional distortion, which combine to orient the nonboned nitrogen lone pair orthogonal to the C═O π-bond and inhibit resonance interaction, contribute to this uncharacteristic reactivity. With amide resonance energy amounting to 16−22 kcal/mol depending on structure [8] and N−C═O overlap being subject to a cos θ relationship,[9] it is obvious that energy costs rise steeply as resonance interaction is progressively curtailed in lactams.

The corresponding situation in *N,N*-disubstituted sulfonamides is much less clear. Their stabilization is derived quite differently. A search of the Cambridge Crystallographic Data Base for this compound class furnished more than 200 examples for which coordinates are available.[10] Although the $-SO_2NR_2$ types ranged from cyclic to cycloaromatic and from amide to amidine, with resultant notable differences in the geometry at N,[11] a decided preference for orienting the nitrogen lone pair in the bisector of the O−S−O internuclear angle as in **4** is seen. This structural



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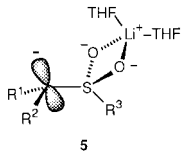
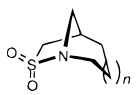
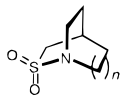


5

feature closely parallels the staggered conformation adopted by α-sulfonyl carbanions (see **5**), where the lone pair orbital is likewise gauche to the two oxygens that are engaged in contact ion-pairing to the metal ion.[12−14] It is not clear, at this point, if changes in the orientation of the nitrogen lone pair relative to the O−S−O internuclear angle will translate into altered reactivity. This intriguing structural question could be addressed by the synthesis of small bridgehead sultams. Our expectations are that such molecules will be very weak bases, comparable to aliphatic congeners,[15] and may exhibit a chemical robustness appreciably greater than that of their carbonyl analogues. A direct synthetic entry to title compounds offering the structural features given by **6**−**10** is recorded herein.



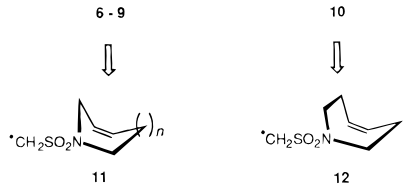
6, $n = 1$
7, $n = 2$
8, $n = 3$



9, $n = 1$
10, $n = 2$

The operational strategy was based on the expectation that the five- and six-membered heterocyclic subunits would prove amenable to generation by free radical cyclization (Scheme 1). While 5-*exo* regioselectivity as in **11** is adopted with widespread facility in many hexenyl systems,[16] other observations suggested that **12** should respond in parallel 6-*exo* fashion.[17] Furthermore, although displacement reactions on α-halosulfonyl compounds are generally not feasible for steric and stereoelectronic reasons,[18] such compounds are amenable to efficient conversion into reactive electrophilic radicals. Since α-sulfonyl radicals are not stabilized,[19] they should be prone to rapid intramolecular cyclization.[20]

Scheme 1



11 **12**

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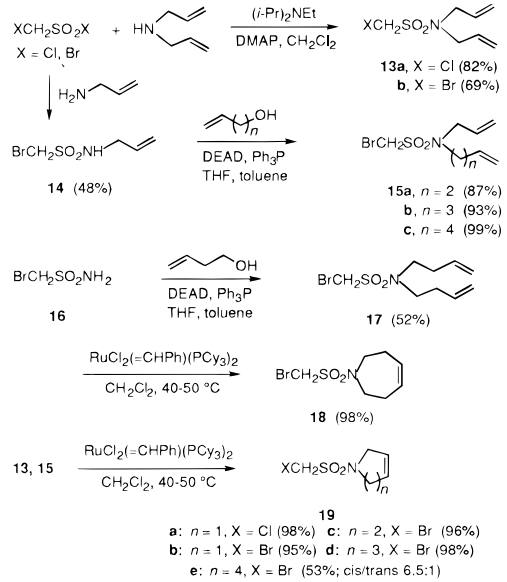
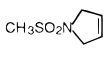
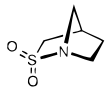
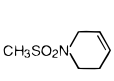
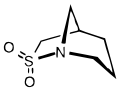
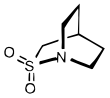
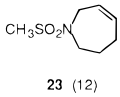
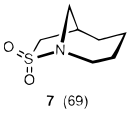
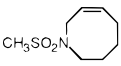
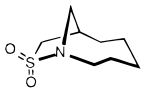
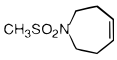
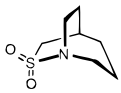
Scheme 2



A salient feature of the present plan is the ready availability of $ClCH_2SO_2Cl$[21] and $BrCH_2SO_2Br$[22] by halogenation of *s*-trithiane under aqueous conditions. Admixture of these reagents with diallylamine in CH_2Cl_2 containing Hünig's base and DMAP generated **13a** and **13b**, respectively (Scheme 2). Subjection of **14** to Mitsunobu alkylation[23] involving terminal alkenols led in high yield to **15a**−**c**. Comparable treatment of the known **16**[24] with 3-buten-1-ol provided **17**. Ring-closing metathesis[25] of all the doubly unsaturated sulfonamides proceeded smoothly and efficiently in the presence of the Grubbs catalyst[26] to give **18** and **19**.

While the heating of **19a** with tri-*n*-butyltin hydride (1.2 equiv) and AIBN (0.07 equiv) in benzene under syringe pump conditions resulted simply in reductive dehalogenation (Table 1), more fruitful results emerged from the comparable handling of the higher homologues **18** and **19c**−**e**. The elevated strain energy resident in bridgehead sultam **21** was expected to deter the ring closure step leading to its formation. Indeed, none of this product was seen. In the case of **19c**, cyclization begins to exhibit the capacity to compete at a reasonable level with reduction. Interestingly, both the [3.2.1] and [2.2.2] bicyclic sultams are generated, the latter product stemming from 6-*endo* C−C bond formation. Their relative ratio is 2.2:1. The most favorable state of affairs is manifested with **18** and **19d**, which undergo ring closure to give **10** and **7**, respectively, in preparatively attractive yields. The drop-off in ring-forming efficiency observed for **8** was not entirely expected. The prominent workability of the 6-*exo* pathway involving **12** could represent a useful feasibility calibration point.

Table 1. Products of Free Radical Cyclization of Halomethylsulfonamides[a,b]

compd	reduction prod (%)	cyclization prod (%)
19a	 **20** (74)	 **21** (0)
19c	 **22** (47)	 **6** (16) +  **9** (7)
19d	 **23** (12)	 **7** (69)
19e	 **24** (49)	 **8** (37)
18	 **25** (10)	 **10** (79)

[a] Reaction conditions: Bu_3SnH, AIBN, C_6H_6, 60 °C, syringe pump. [b] All compounds exhibited spectra fully compatible with the indicated assignment.

The crystal structure of the smallest bicyclic sultam available to us has been determined by single-crystal diffraction analysis. Several features of this molecule are of interest. The cyclohexane substructure is not impeded by the sulfonyl group from adopting a chairlike conformation. Also, the exo and endo orientations of the two oxygens are well defined. More significantly, although the N lone pair electrons on the bridgehead nitrogen cannot be located exactly, proper approximations indicate them to be projected in a plane that bisects the O−S−O angle into very uneven sectors. The values are −90° and 40°. Thus, the geometry inherent to **6** results in a significant distortion away from the equilibrium state represented by **4**.

Nevertheless, all five members of the homologous set are white, hydrolytically stable crystalline solids, readily amenable to chromatographic purification[27] and long-term storage in the atmosphere. Clearly, structural enforcement of less than ideal electronic interactions in these sultams is not being reflected in hyperreactivity.

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Supporting Information Available: Crystallographic experimental details for **6**, including tables of bond lengths, bond angles, atomic coordinates, and isotropic/anisotropic displacement parameters (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992161C

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(27) The separation of **9** from **6** is challenging because of its relative percentage in the mixture and the closely similar R_f values.