ORGANIC LETTERS

2004
Vol. 6, No. 8
1313−1315

Synthesis of 1-Aza-8-thiabicyclo[4.2.1]nona-2,4-diene 8,8-Dioxide and Its Conversion to a Strained Spirocycle via Photoinduced SO_2–N Bond Cleavage

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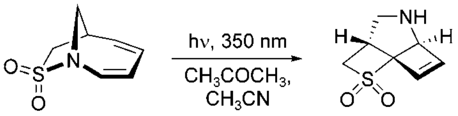
Received February 23, 2004

ABSTRACT

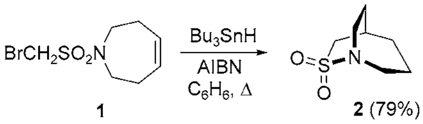


12 **17**

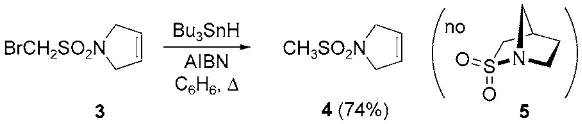
A route to the doubly unsaturated bridgehead sultam 12 has been developed. When irradiated at 350 nm, this conjugated diene is isomerized via a two-photon process to the structurally novel spiro heterocycle 17 constituted of cyclobutene, thietane dioxide, and pyrrolidine rings. A probable mechanism for the generation of 17 and select reactions thereof are reported.

Sulfonamides are of such widespread medicinal importance that the strength of the SO_2−N bond in this compound class has often come into question. Structural studies having their basis in X-ray crystallographic measurements have demonstrated that the nitrogen lone pair in this structural series most often resides in the bisector of the O−S−O internuclear angle and that this state of affairs persists despite notable differences in the geometry at N.[1] Since the possibility always exists that crystal lattice forces may control conformation, quantum mechanical geometry optimization has more recently been utilized to probe energetically preferred conformations in the gas phase.[2] Since sulfonamides perform their therapeutic function in aqueous solution, their hydrolytic stability in acidic and alkaline environments has come under greatest scrutiny.[3] At one end of the scale, acyclic sulfonamides exhibit extreme resistance toward either sulfonyl transfer reaction. In contrast, β-sultams exhibit extraordinary rate enhancements on the order of 10^7−10^9 under both sets of conditions.[4] Presently, the existing evidence appears to favor a mechanism in which bond-making and bond-breaking are discretely different, clearly separated mechanistic steps.[4,5]

Notably absent from this field has been any investigation of possible photoinduced SO_2−N bond homolysis. In a first thrust into gaining insight into sulfonamide photochemistry, we have presently made use of earlier synthetic studies in which bridgehead bicyclic sultams such as **2** were accessed by a free-radical protocol.[6] This direct route is not suited to the preparation of more highly strained members such as **5** because of the slowed rate of cyclization that is now overridden by simple reduction (as **3** to **4**).[7]



1 **2** (79%)



3 **4** (74%) **5**

This chemistry does allow, however, for the development

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(1) Beddoes, R. L.; Dalton, L.; Joule, J. A.; Mills, O. S.; Street, J. D.; Watt, C.; Ian F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 787.

(2) Renko, M. *J. Phys Chem. A* **2003**, *107*, 720 and references therein.

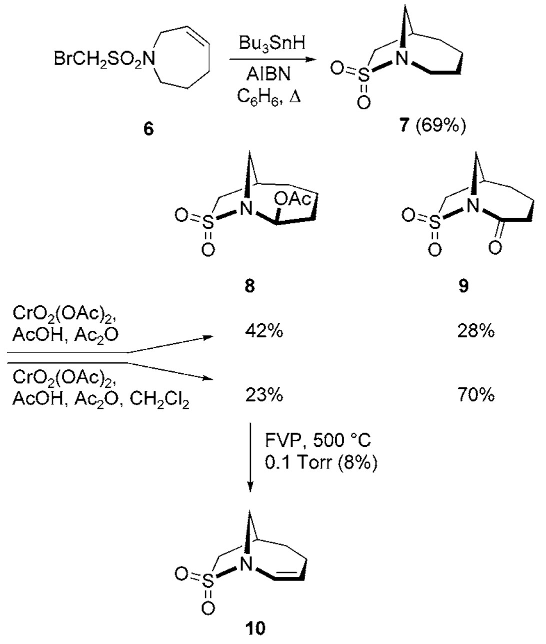
(3) Searles, S.; Nukina, S. *Chem. Rev.* **1959**, *59*, 1077.

10.1021/ol049679s CCC: $27.50

of a synthetic route to the doubly unsaturated [4.2.1] bicyclic sultam **12**. The remarkable photoisomerization of **12** via facile cleavage of its sulfonamide SO_2-N bond in the photoexcited state is documented herein.

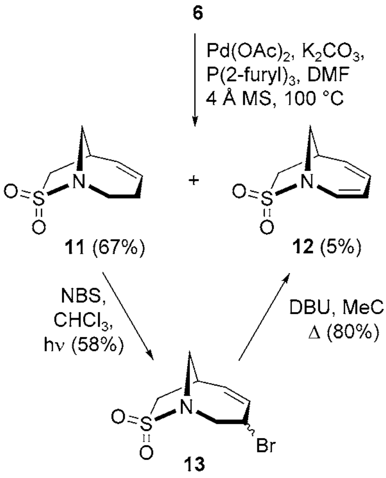
The operational strategy commences with chromyl acetate oxidation[8] of previously described **7**.[6,7] When this reaction is performed in glacial acetic acid admixed with acetic anhydride, the acetate **8** and ketone **9** are isolated in 42% and 28% yields, respectively (Scheme 1). Dilution of the reaction medium with CH_2Cl_2 enhanced the level of ketone production and gave rise to an inverted distribution of **8** and **9** (23%; 70%). Flash vacuum pyrolysis of **8** at 500 °C and 0.1 Torr resulted in inefficient conversion to **10**. When the allylic bromination of **10** with *N*-bromosuccinimide (NBS) was also recognized to be problematic, generation of the isomeric monounsaturated sultam **11** was pursued instead.

Scheme 1



The rather prominent deficiency of Pd(II)-promoted alkenylations involving α-halo ketones and esters[9] was not a deterrent in the application of this methodology to **6**. To our delight, the heating of **6** with palladium acetate in DMF containing K_2CO_3, tri-2-furylphosphine, and 4 Å molecular sieves at 100 °C for 72 h proceeded to furnish **11** (67%), **12** (5%), and a minor amount of reduced product (Scheme 2).

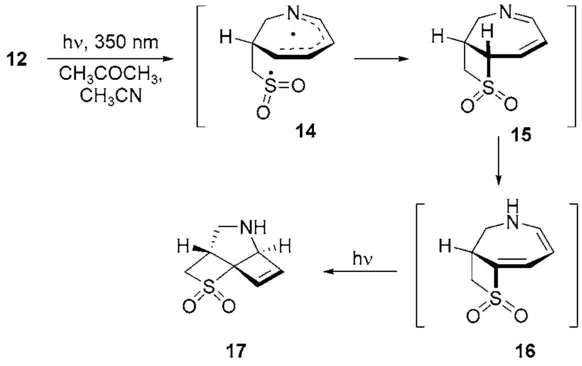
Scheme 2



This favorable state of affairs continued with the demonstration that NBS acted on **11** to deliver chiefly the bromo sultam **13**. The propensity of **13** toward E_2 elimination was sufficiently elevated to bring about its conversion to diene **12** by heating with DBU in acetonitrile. The availability of **12** [λ_{max} ($CHCl_3$) 262 nm (ϵ 5320)] is enhanced by virtue of the fact that this two-step sequence can be performed in series without intermediate purification with no adverse effect on yield.

The irradiation of **12** through Pyrex with 350 nm light in a Rayonet reactor resulted in relatively rapid formation of a more polar isomer during 2 h (Scheme 3). In pure acetone as solvent, photoproduct **17** dominated (52% isolated),[10] although polymer formation was evident on the walls of the reaction vessel. This tendency was significantly reduced upon

Scheme 3



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(4) (a) Baxter, N. J.; Rigoreau, L. J. M.; Laws, A. P.; Page, M. I. *J. Am. Chem. Soc.* **2000**, *122*, 3375. (b) Wood, J. M.; Hinchcliffe, P. S.; Laws, A. P.; Page M. I. *J. Chem. Soc., Perkin Trans. 2* **2002**, 938. (c) Hinchcliffe, P. S.; Wood, J. M.; Davis, A. M.; Austin, R. P.; Beckett, R. P.; Page, M. I. *Org. Biomol. Chem.* **2003**, *1*, 67.

(5) (a) Kice, J. L. *Adv. Phys. Org. Chem.* **1980**, *17*, 65. (b) Ciuffarin, E.; Senatore, L.; Isola, M. *J. Chem. Soc., Perkin Trans. 2* **1972**, 468. (c) Deacon, T.; Farrar, C. R.; Sikkel, B. J.; Williams, A. *J. Am. Chem. Soc.* **1978**, *100*, 2525. (d) Rogne, O. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1486. (e) King, J. F.; Gill, M. S.; Klassen, D. F. *Pure Appl. Chem.* **1996**, *68*, 825.

(6) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126.

(7) Paquette, L. A.; Ra, C. S.; Schloss, J. D.; Leit, S. M.; Gallucci, J. C. *J. Org. Chem.* **2001**, *66*, 3564.

(8) Freeman, F. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, 1995; p 1282.

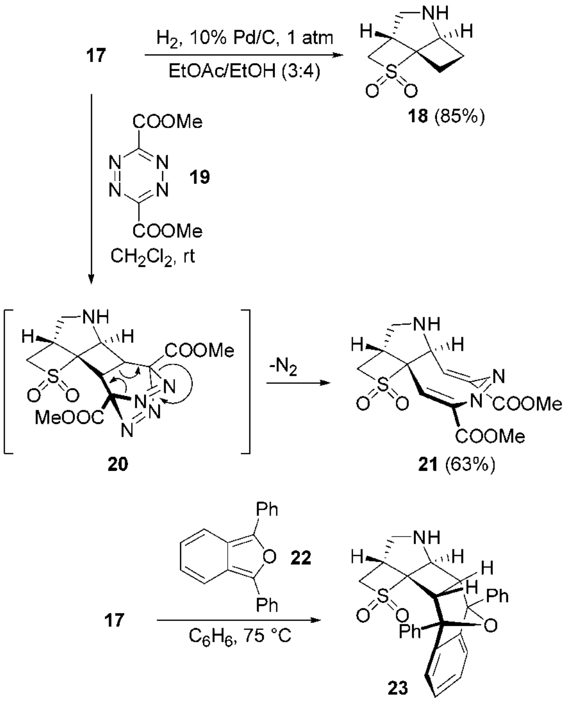
(9) The synthesis of 1,4-diketones and γ-keto esters in this manner by coupling to silyl enol ethers has been reported: (a) Kosugi, M.; Takano, I.; Sakurai, M.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1221. (b) Kimpson, J. H.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 1759.

dilution with acetonitrile (acetone/CH_3CN 2:1), and the photoisomerization was slowed. However, greater throughput was possible because the unreacted **12** can be easily recycled. A yield of 28% (42% based on recovered starting material) is typical.

The 500 MHz ^1H NMR spectrum of **17** in C_6D_6 revealed several key features of its structure, including most notably the presence of two mutually coupled but otherwise isolated vinylic protons (δ 5.72 and 5.59, $J = 2.8$ Hz) and an exchangeable NH group following the addition of D_2O. COSY studies defined the existence of two nonvicinal CH_2 groups, one adjacent to SO_2 and the other neighboring to nitrogen. Particularly informative as well were DEPT measurements that proved diagnostic of the fact that a quaternary carbon (92.6 ppm) had been generated.

The presence of a single site of unsaturation in **17** was corroborated by catalytic hydrogenation over 10% Pd/C at atmospheric pressure to give **18** (Scheme 4). The strained nature of the double bond in question was established by Diels−Alder cycloadditions involving both dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**19**)[11] and diphenylisobenzofuran (**22**).[12] In the first instance, reaction proceeded during 2 h at room temperature to give **21**, presumably via retrograde deazatization of the first-formed [4 + 2] adduct with cleavage of the cyclobutane ring.[13] Our quest of a crystalline substance was rewarded by the formation of **23** (66%) as the predominant stereoisomer from the reaction with **22** at 75 °C in benzene. The *endo* stereochemistry of **23** and the relative configuration of its seven contiguous stereogenic centers were ultimately revealed by X-ray crystallographic analysis (Figure 1).

Scheme 4



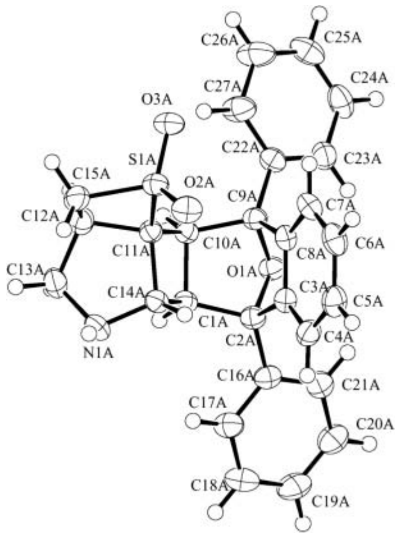


Figure 1. ORTEP diagram of **23**.

With this evidence in hand, the excited-state behavior of **12** is seen to differ appreciably from that of the simple electrocyclic pathway adopted by bicyclo[4.2.0]octa-2,4-dienes.[14] Rather, a series of chemical events is seemingly triggered by unusually facile homolytic rupture of the sulfonamide $SO_2{-}N$ bond to generate biradical **14** under conditions of triplet sensitization. Rebonding to generate the bicyclic isomer **15** appears to be kinetically feasible, thereby making possible the subsequent thermally induced surprafacial [1,5]-sigmatropic shift of hydrogen and accessibility to **16**. Absorption of a second photon at this point eventuates in disrotatory closure with formation of the spirocyclic cyclobutene framework. Generation of the quite unusual structural framework inherent to **17** by the biphotonic pathway outlined in Scheme 3 is unprecedented. We infer from the behavior of **17** that the customarily strong sulfonamide linkage may be generally amenable to facile heterolysis when good stereoelectronic overlap is available. These architectural features form the foundation of current efforts to develop this area of photoisomerization chemistry.

Supporting Information Available: General experimental details and $^1H/^{13}C$ NMR spectral data for all compounds, as well as the crystallographic details for **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] A significantly less stable photoisomer of **12** is also produced in yields below 5%. The characterization of this sensitive substance remains under investigation.

[11] Sauer, J.; Bäuerlein, P.; Ebenbeck, W.; Gousetis, C.; Sichert, H.; Troll, T.; Utz, F.; Wallfahrer, U. *Eur. J. Org. Chem.* **2001**, 2629.

[12] Warrener, R. N.; Wang, S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 3975.

[13] The loss of N_2 and cleavage of the strained ring need not be synchronous events. It will be noted that an alternative two-step pathway to **21** from **20** is also possible.

[14] Jefford, C. W.; Delay, F. *J. Am. Chem. Soc.* **1972**, *94*, 4794.