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Synthesis of Cyclic Sulfonamides via Intramolecular Copper-Catalyzed Reaction of Unsaturated Iminoiodinanes

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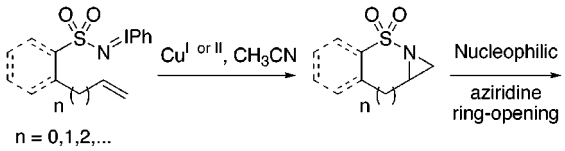
ABSTRACT



Olefinic primary sulfonamides were treated with iodobenzene diacetate and potassium hydroxide in methanol to give intermediate iminoiodinanes. Catalytic copper(I) or (II) triflate then provided intramolecular nitrene delivery leading to aziridine formation except in one case where a rare copper-catalyzed C–H insertion was observed. The aziridines could be opened by various nucleophiles (methanol, thiophenol, allylmagnesium bromide, benzylamine) to give the corresponding substituted cyclic sulfonamides.

Since the initial discovery of the antibacterial activity of the dye Prontosil **1** and its clinical use in 1933 against a case of staphylococcal septicemia,[1] the sulfonamide function has been incorporated in a still growing number of biologically active compounds,[2] one of the most famous examples today being the well-known Sildenafil (Viagra) **2**. In addition to being a carboxyl isostere, the introduction of the SO_2-N moiety induces an increase of stability, for example, toward protease-catalyzed degradation in the case of sulfonamide-containing peptidomimetics.[3] High interest has also been directed to their cyclic counterparts, the sultams, which display a vast array of biological activities. Oxicams (e.g., Ampiroxicam **3**)[4] are a large family of nonsteroidal anti-inflammatory agents. *N*-Alkylated saccharin derivatives act as agonists of 5-HT_{1A} receptors and have therefore found applications as neuroprotectants[5a] or anxiolytics (e.g., Ipsaspirone **4**).[5b] They also selectively inhibit serine proteases (tryptase[6a] or elastase[6b]). Development of cyclic sulfonamides as selective inhibitors of the zinc enzyme carbonic anhydrase has led to the discovery of antiepileptic agents (e.g., Sulthiame **5**)[7] and recently to the approval of Brinzolamide **6** for the topical treatment of glaucoma in the United States.[8] Diuretic,[9a] anticonvulsant,[9b] cardiotonic,[9c] β-blocking,[9d] or herbicidal[9e] activities have also been claimed in patents.

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(1) Domagk, G. *Dtsch. Med. Wochenschr.* **1935**, *61*, 250.
(2) For a review, see: (a) Hansch, C.; Sammes, P. G.; Taylor, J. B. *Comprehensive Medicinal Chemistry*; Pergamon Press: Oxford, 1990; Vol. 2, Chapter 7.1. For a compilatory list of recent biological applications, see (b) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett.* **1999**, *40*, 4761.
(3) de Bont, D. B. A.; Sliedregt-Bol, K. M.; Hofmeyer, L. J. F.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **1999**, *7*, 1043.
(4) *Drugs Future* **1992**, *17*, 451.
(5) (a) *Drugs Future* **1997**, *22*, 341. (b) *Drugs Future* **1986**, *11*, 565.
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(7) Tanimukai, H.; Inoui, M.; Hariguchi, S.; Kaneko, Z. *Biochem. Pharmacol.* **1965**, *14*, 961.
(8) (a) *Drugs Future* **1998**, *23*, 365. (b) Silver, L. H. *Am. J. Ophthalmol.* **1998**, *126*, 400.
(9) (a) Becking, J. B.; Sprague, J. M. U.S. Patent 3,113,075, 1963; *Chem. Abstr.* **1964**, *60*, 5514g. (b) Sianesi, E.; Da Re, P.; Setnikar, I.; Massarani, E. U.S. Patent 3,770,733, 1973; *Chem. Abstr.* **1974**, *80*, 48016p. (c) Tamada, S.; Fujioka, T.; Ogawa, H.; Teramoto, S.; Kondo, K. *Chem. Abstr.* **1990**, *112*, 35887e. (d) *Chem. Abstr.* **1985**, *102*, 78901p. (e) Pasteris, R. J. U.S. Patent 4,842,639, 1989; *Chem. Abstr.* **1990**, *112*, 179032t.

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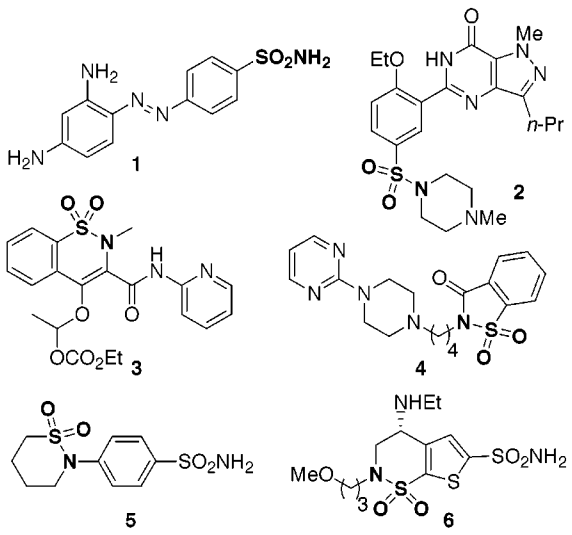
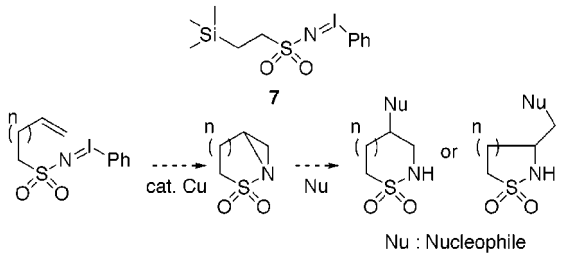
Finally, from a chemical point of view, sultams have served as efficient chiral auxiliaries[10] or reagents.[11]



In this communication, we wish to report a new strategy for the preparation of cyclic sulfonamides based on intramolecular copper-catalyzed nitrene delivery. Recent publications bear witness to a renewed interest in synthetic approaches to sultams. While most previously described methods rely on nucleophilic or electrophilic substitutions, as well as on thermal or photochemical decomposition of azides,[12] new preparations involve ring-closing metathesis[2b] or radical processes.[13] Further to our work on the [*N*-(alkylsulfonyl)-imino]phenyliodinane (PhI═NSes) **7**[14] and in connection with biological studies, we aimed to study the possibility of intramolecular copper-catalyzed aziridinations,[15] never reported before, as a route to substituted cyclic sulfonamides (Scheme 1). The success of such a cyclization would strongly

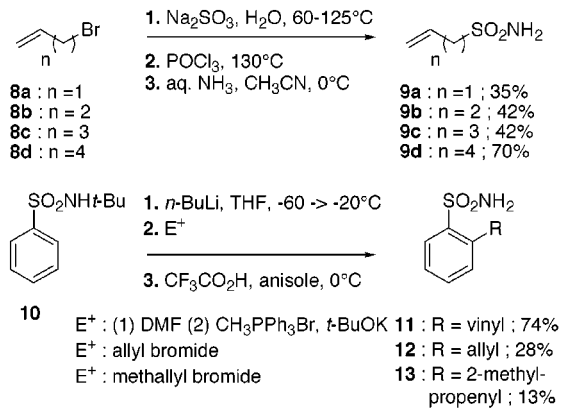
Scheme 1



depend first on the stability of the intermediate iminoiodinanes, particularly their compatibility with a double bond. Second, their aggregate structures[16] could inhibit any intramolecular process and only lead to polymeric materials.

The starting ω-alkene-1-sulfonamides **9a**−**d** were prepared by aminolysis in acetonitrile of ω-alkene-1-sulfonyl chlorides, themselves easily obtained from the corresponding bromides **8a**−**d** using previously published protocols.[17] The *ortho*-substituted benzenesulfonamides **11**−**13** were synthesized in a two-step procedure involving an *ortho*-metalation of *N*-*tert*-butylbenzenesulfonamide **10**[18] followed by acidic cleavage of the *tert*-butyl group (Scheme 2). In the case of

Scheme 2



2-vinylbenzenesulfonamide **11**, the Schlosser procedure[19] prevented any cyclization to 1,2-benzisothiazole 1,1-dioxide. On the other hand, acidic cleavage of the protected 2-methallylbenzenesulfonamide isolated after the *ortho*-metalation step afforded compound **13** in minor quantity, the major product being the six-membered ring-cyclized product.

Following our previously reported procedure,[14] reaction of the unsaturated sulfonamides with iodobenzene diacetate and potassium hydroxide in methanol afforded the intermediate iminoiodinanes, which were isolated simply by extraction with dichloromethane followed by cold aqueous wash. The resulting amorphous yellow solids were immediately treated with a catalytic amount of copper triflate in acetonitrile.[20,21] Results are summarized in Table 1.

Not surprisingly, allylsulfonamide **9a** did not lead to the highly strained bicyclic [2.1.0] structure **14**. In contrast, the

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(11) (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (b) Differding, E.; Lang, R. *Helv. Chim. Acta* **1989**, *72*, 1248.
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(14) Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1999**, *64*, 5304.
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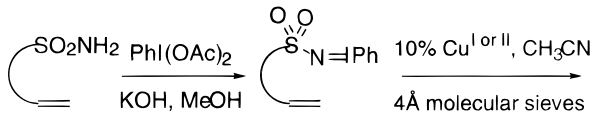
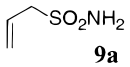
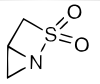
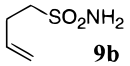
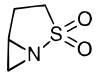
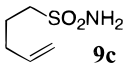
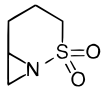
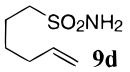
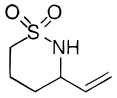
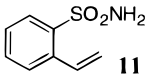
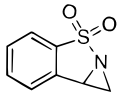
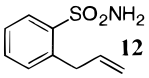
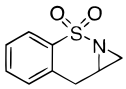
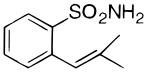
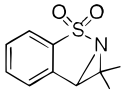
(17) (a) King, J. F.; Harding, D. R. K. *J. Am. Chem. Soc.* **1976**, *98*, 3312. (b) Culshaw, P. N.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2*, **1991**, 1201.
(18) Lombardino, J. G. *J. Org. Chem.* **1971**, *36*, 1843.
(19) Wang, Q.; Wei, H.-X.; Schlosser, M. *Eur. J. Org. Chem.* **1999**, 3263
(20) The formation and the purity (>90%) of the iodinanes were verified by their ^{1}H NMR spectra in which aromatic protons of the iodobenzene moiety were observed together with the disappearance of those of the sulfonamide function and the upfield shift of the alkane protons. For example, for the iminoiodinane derived from sulfonamide **9c**: δ 1.26 (m, 2H), 1.76 (m, 2H), 2.00 (m, 2H), 4.95 (m, 2H), 5.64 (m, 1H), 7.39 (m, 2H), 7.54 (m, 1H), 7.96 (d, 1H).

Table 1. Intramolecular Copper-Catalyzed Reactions



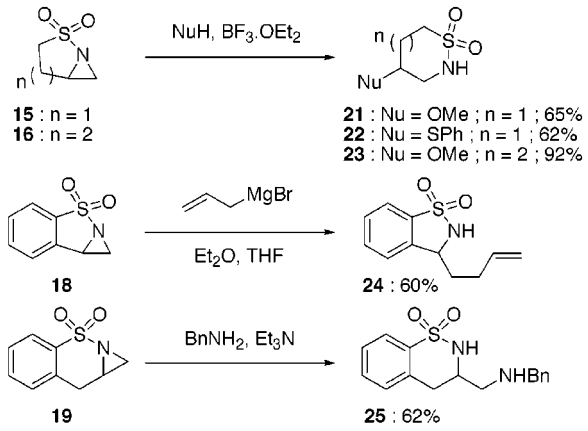
Substrate	Catalyst (Conc°)	Yield[a]	Product
 **9a**	CuOTf	**14** : 0	
 **9b**	CuOTf (0.05 M) CuOTf (0.1 M) CuOTf (0.25 M)	**15** : 33 **15** : 38[b] **15** : 32	
 **9c**	CuOTf (0.05 M) CuOTf (0.1 M) Cu(OTf)2	**16** : 34 **16** : 61[b] **16** : 50	
 **9d**	CuOTf (0.1 M) Cu(OTf)2	**17** : 51[b] **17** : 45	
 **11**	CuOTf PTAB	**18** : 0 **18** : 70[c]	
 **12**	CuOTf	**19** : 60	
 **13**	CuOTf	**20** : 80	

[a] Isolated yield after flash chromatography based on starting sulfonamides. [b] Average of three runs. [c] Bromine-catalyzed aziridination (PTAB, phenyltrimethylammonium tribromide).

higher homologues **9b,c** gave the expected bicyclic aziridines **15** and **16**, respectively. In both cases, best results were obtained using moderately dilute reaction mixtures (i.e., $c = 0.1$ M), while acetonitrile was found to be the solvent of choice. Moreover, both $Cu^{(I)}OTf$ and $Cu^{(II)}(OTf)_2$ catalyzed the intramolecular process, although the latter appeared to be less efficient. However, when applied to sulfonamide **9d**, these conditions gave rise exclusively to the allylic insertion product **17**. Although not unprecedented,[22] such a copper-catalyzed C−H insertion has only been rarely observed in analogous intermolecular aziridination reactions. Another unexpected result came from the benzenesulfonamides. While substrates **12** and **13** could be efficiently transformed into the aziridines **19** and **20**, respectively, no reaction occurred with the iminoiodinane derived from vinylic compound **11**. This is probably related to the nature of this intermediate, which proved to be highly unstable. However, application of the bromine-catalyzed aziridination procedure[23] to **11** led to formation of aziridine **18** in good yield.

We next turned our attention to the synthetic opportunities provided by these new bicyclic sultams. Preliminary experiments with different types of nucleophiles (methanol, thiophenol, allylmagnesium bromide, benzylamine) afforded aziridine ring-opened products in good yields with concomitant C−O, C−S, C−C, or C−N bond formation (Scheme 3). In the case of compounds **15** and **16**, exclusive opening

Scheme 3



of the aziridine at the more substituted site was observed, leading to six- and seven-membered ring products **21**, **22**, and **23**. It should be pointed out that no reaction took place in the absence of boron trifluoride etherate. In contrast, aziridines **18** and **19** preferentially reacted at their less substituted carbon atom, forming benzo[*d*]isothiazole **24** and benzo[*e*]thiazine **25**, respectively, as the major products.

In conclusion, the intramolecular copper-catalyzed reaction of an iminoiodinane bearing an olefinic bond represents a new synthetic route to cyclic sulfonamides. Moreover, in contrast to most previously described procedures, the present methodology allows introduction of additional functionality on the sultam via nucleophilic opening of the intermediate aziridine. The full scope and limitations of this novel methodology are currently under investigation.

Acknowledgment. This paper is dedicated to Prof. P. Potier, recipient of this year's Ernest Guenther Award.

Supporting Information Available: Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The iodinanes were used as soon as they were isolated in order to optimize the yield of the aziridination. However, they could be stored at 4 °C under argon for several days. Their stability is therefore comparable to that of PhINTs or PhINSes.

(22) To the best of our knowledge, there is only one example of the preparative use of such a Cu-catalyzed C−H insertion: Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 4039. In other cases, such compounds were isolated as minor byproducts. For example, see: (a) ref 15. (b) Albone, D. P.; Aujla, P. S.; Taylor, P. C.; Challenger, S., Derrick, A. M. *J. Org. Chem.* **1998**, *63*, 9569.

(23) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.