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Synthesis of Fused and Bridged Bicyclic Diazenium Salts by Intramolecular Cycloaddition

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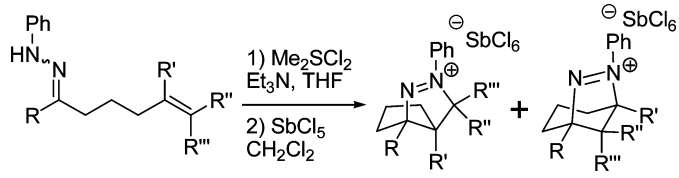
ABSTRACT



Bicyclic diazenium salts were efficiently prepared by a Lewis acid mediated intramolecular cycloaddition. Terminal olefins provided mixtures of fused and bridged bicyclic diazenium salts. The α-chloroazo cycloaddition precursors were conveniently prepared from the corresponding phenyl hydrazones by treatment with chlorodimethylsulfonium chloride.

Structurally complex nitrogen-containing heterocycles are ubiquitous in biologically active compounds,[1,2] and synthetic chemists continually look for efficient ways to prepare these beneficial scaffolds.[3] Cyclic trisubstituted diazenium salts (e.g., **5**, Table 2) are more reactive than their nonionic diazene analogs[4] and can serve as azomethinimine 1,3-dipole precursors[5] or can be reduced to the corresponding trisubstituted hydrazines.[6] However, these cationic species have received less attention from the synthetic community than most classes of nitrogen-containing heterocycles, and few methods exist for their preparation.[7]

Nelsen and co-workers[8−11] have prepared bridged bicyclic diazenium salts by alkylation of the corresponding diazene and have thoroughly studied the redox properties, structure, and charge distribution of these salts. In related work, Nelsen has also studied the [4 + 2] cycloaddition of bicyclic diazenium cations with dienes.[12,13] More recently, Jochims and colleagues[14,15] reported that α-chloroazo compounds react with halophilic Lewis acids to provide 1-aza-2-azoniaallene cation intermediates that in turn can undergo intermolecular [3 + 2] cycloadditions with alkenes to provide diazenium salts by a process reminiscent of the reactivity of Huisgen-type 1,3-dipolar compounds.[16] Despite this pioneer-

(1) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.
(2) (a) *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: New York, 2008; Vol. 43. (b) *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: New York, 2007; Vol. 42. (c) Landquist, J. K. Application as Pharmaceuticals. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 1, pp 143−183.
(3) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.
(4) For a recent example of bicyclic diazene preparation by intramolecular cycloaddition of diazo compounds, see: Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *73*, 9479.
(5) (a) Cauquis, G.; Chabaud, B. *Tetrahedron* **1978**, *34*, 903. (b) Snyder, J. P.; Heyman, M.; Gundestrup, M. *J. Org. Chem.* **1978**, *43*, 2224.
(6) Nelsen, S. F.; Parmelee, W. P.; Goebl, M.; Hiller, K.-O.; Veltwisch, D.; Asmus, K.-D. *J. Am. Chem. Soc.* **1980**, *102*, 5606.
(7) Kuznetsov, M. A. *Russ. Chem. Rev.* **1979**, *48*, 1054.
(8) Nelsen, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 1788.
(9) Nelsen, S. F.; Landis, R. T. *J. Am. Chem. Soc.* **1973**, *95*, 2719.
(10) Nelsen, S. F.; Blackstock, S. C. *J. Org. Chem.* **1984**, *49*, 1134.
(11) Nelsen, S. F.; Chang, H.; Wolff, J. J.; Powell, D. R. *J. Org. Chem.* **1994**, *59*, 6558.
(12) Nelsen, S. F.; Blackstock, S. C.; Frigo, T. B. *J. Am. Chem. Soc.* **1984**, *106*, 3366.
(13) Nelsen, S. F.; Blackstock, S. C.; Frigo, T. B. *Tetrahedron* **1986**, *42*, 1769.
(14) Wirschun, W. G.; Al-Soud, Y. A.; Nusser, K. A.; Orama, O.; Maier, G. M.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4356.
(15) Wang, Q. R.; Amer, A.; Mohr, S.; Ertel, E.; Jochims, J. C. *Tetrahedron* **1993**, *49*, 9973.
(16) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.

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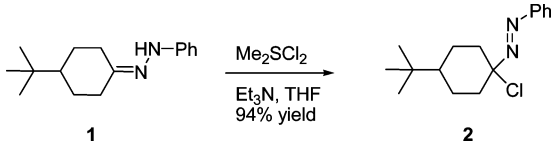
ing work, only simple diazenium salts have been prepared by Jochims' method, and no intramolecular cycloadditions of this type have been reported.

Intramolecular reactions are a particularly efficient way to increase structural complexity.[17] Tethering reactive species together can enforce conformational constraints that result in high levels of stereoselectivity or regioselectivity, and because of the proximity of the reacting groups, it is sometimes possible to effect intramolecular reactions that normally do not occur intermolecularly. In this Letter we report our preliminary results on the preparation of fused and bridged bicyclic diazenium salts by Lewis acid mediated intramolecular cycloaddition reactions.

During studies on the reactivity of hydrazones with sulfonium salts[18−20] we discovered that treating phenyl hydrazones with chlorodimethylsulfonium chloride provided phenyl-α-chloroazo products[21] (e.g., **2**, Scheme 1) in high

Scheme 1. Sulfonium Salt Mediated α-Chloroazo Formation



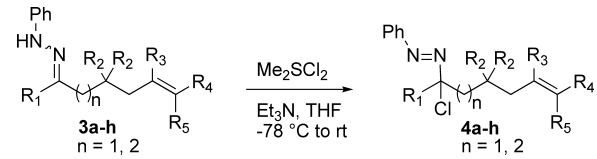
1 **2**

yield. This route to α-chloroazo compounds is more mild and functional-group-compatible than previous routes to these species, which involve treating hydrazones with chlorine gas or *tert*-butyl hypochlorite.[22,23]

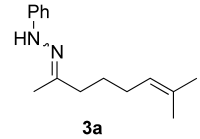
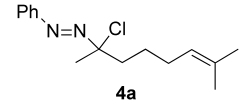
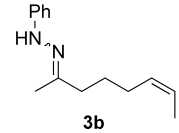
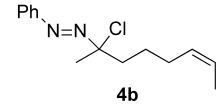
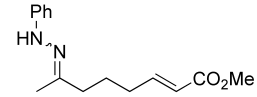
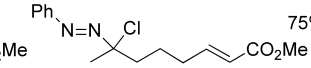
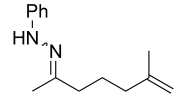
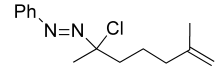
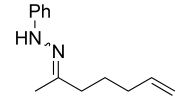
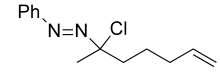
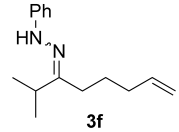
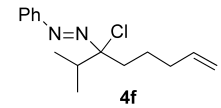
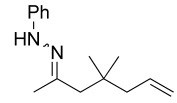
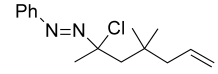
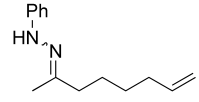
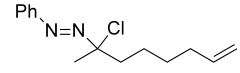
The sulfonium salt mediated formation of α-chloroazo compounds is completely tolerant of alkenes, and by this method we prepared α-chloroazo **4a** (Table 1), one of the first examples of an α-chloroazo compound containing a pendent alkene, in 94% yield.[24] In view of the functional group combination present in α-chloroazo **4a**, we considered the possibility that this compound might serve as a precursor to a bicyclic diazenium salt. In fact, treating α-chloroazo **4a** with antimony pentachloride resulted in an intramolecular cycloaddition in which a new carbocyclic and a new heterocyclic ring were formed to provide fused bicyclic diazenium salt **5a** as a single diastereomer in 71% isolated yield (entry 1, Table 2).

To assess the scope of this intramolecular cycloaddition reaction and to probe for differences between the intermolecular and intramolecular variants of this reaction, we prepared a preliminary set of α-chloroazo compounds with

Table 1. Formation of α-Chloroazos Bearing a Pendent Alkene



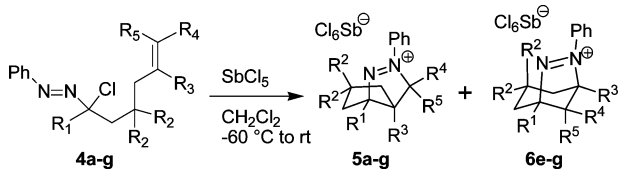
3a-h n = 1, 2 **4a-h** n = 1, 2

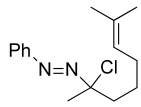
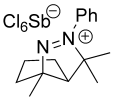
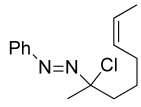
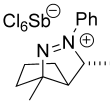
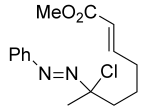
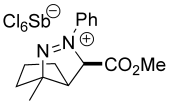
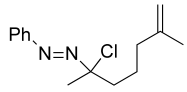
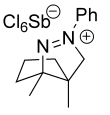
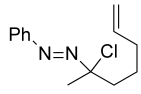
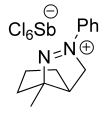
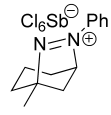
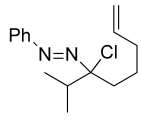
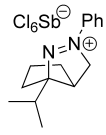
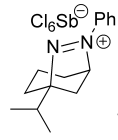
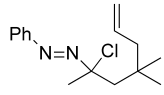
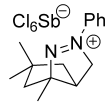
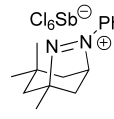
entry	hydrazone	product	yield
1	 **3a**	 **4a**	94%
2	 **3b**	 **4b**	89%
3	 **3c**	 **4c**	75%
4	 **3d**	 **4d**	87%
5	 **3e**	 **4e**	83%
6	 **3f**	 **4f**	88%
7	 **3g**	 **4g**	80%
8	 **3h**	 **4h**	85%

varying steric and electronic properties (Table 1) and subjected these to Lewis acid mediated intramolecular cyclization (Table 2). In each case, the requisite α-chloroazo was isolated in good yield with no apparent degradation of the alkene by treating the corresponding phenyl hydrazone with chlorodimethylsulfonium chloride.

(17) Evans, D. A.; Scheerer, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6038.
(18) Brewer, M. *Tetrahedron Lett.* **2006**, *47*, 7731.
(19) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789.
(20) Javed, M. I.; Brewer, M. *Org. Synth.* **2008**, *85*, 189.
(21) Wyman, J. M.; Jochum, S.; Brewer, M. *Synth. Commun.* **2008**, *38*, 3623.
(22) Moon, M. W. *J. Org. Chem.* **1972**, *37*, 386.
(23) Moon, M. W. *J. Org. Chem.* **1972**, *37*, 383.
(24) An α-chloroazo containing a pendant alkene was described in the following patent: Unsymmetrical *tert*-aliphatic azoalkanes. MacLeay, R. E.; Sheppard, C. S. *74-453444, 4007165*, 1977.

Table 2. Bicyclic Diazenium Salt Formation

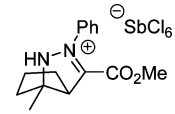


entry	α-chloroazo	product	yield (ratio **5**:**6**)[a]
1	 **4a**	 **5a**	71%
2	 **4b**	 **5b**[b]	88%
3	 **4c**	 **5c**[b]	83%
4	 **4d**	 **5d**	0%
5	 **4e**	 **5e**  **6e**	87% 1: 0.2
6	 **4f**	 **5f**  **6f**	88% 1 : 0.05
7	 **4g**	 **5g**  **6g**	75% 1: 0.09

[a] Diazenium salts **5** and **6** were isolated as mixtures. [b] Diazenium salts **5b** and **5c** were formed as single diastereomers. The relative configurations of **5b** and **5c** were assigned by NOE experiments.

Upon treatment with $SbCl_5$, *cis*-disubstituted alkene **4b** (entry 2, Table 2) was transformed into diazenium salt **5b** as a single diastereomer in 88% yield. The diastereoselectivity of this process further supports the notion that the cycloaddition occurs by a concerted process.[14]

Of particular note, electron-deficient alkene **4c** reacted with $SbCl_5$ to provide diazenium salt **5c** in 83% yield (entry 3, Table 2). This result is important because electron-deficient alkenes do not participate in intermolecular cyclizations of this type,[14] and this result broadens the useful substrate range of this transformation. On handling, diazenium salt **5c** readily tautomerized to hydrazonium salt **7**.


7

A limitation to the intramolecular cyclization became apparent on treating disubstituted terminal alkene **4d** with $SbCl_5$ (entry 4, Table 2). In this case, NMR analysis of the crude reaction mixture showed a complex mixture of products and no resonances characteristic for diazenium salts were observed. The expected diazenium salt product (**5d**) would contain adjacent quaternary centers, and steric encumbrance likely inhibits cyclization.

We were surprised to observe that treating terminal alkene **4e** with $SbCl_5$ provided a mixture of ring-fused diazenium salt **5e** and bridged diazenium salt **6e** in a 1:0.2 ratio (entry 5, Table 2). The corresponding intermolecular cyclizations consistently provided products having the more substituted carbon adjacent to the nitrogen bearing the positive charge,[14] which can be attributed to a preferred electronic arrangement in the transition state. On the basis of this electronic preference, the major product would be expected to be bridged bicyclic diazenium salt **6e**, which would form via transition state **8** (Figure 1). However, it appears that the

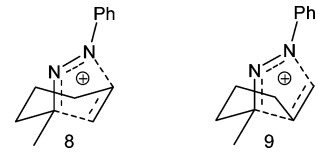


Figure 1. Possible transition sates leading to the formation of diazenium salts **5e** and **6e**.

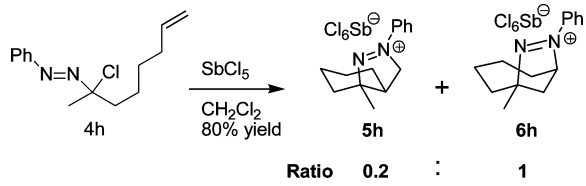
underlying electronic bias for transition state **8** is overcome by the fact that the tether provides a more facile alignment of the reactive partners in transition state **9** leading to fused diazenium **5e** as the major product. It is not clear to us at this point why the bridged diazenium salt did not form from disubstituted terminal alkene **4d**.

Other terminal alkenes also provided a mixture of fused and bridged diazenium salts (entries 6 and 7, Table 2), and the ratio of these products appears to be affected by steric factors. For example, Lewis acid induced cyclization of isopropyl derivative **4f** provided a 1:0.05 ratio of fused (**5f**) to bridged (**6f**) products, and incorporation of a *gem*-dimethyl

group within the chain (**4g**) provided the fused (**5g**) and bridged (**6g**) products in a 1:0.09 ratio. In each case, steric interactions imparted by the additional substituents likely destabilize the transition state leading to the bridged diazenium salt.

Of final note, extending the length of the tether by one carbon had a dramatic effect on the outcome of the cyclization reaction. The Lewis acid mediated cyclization of α-chloroazo **4h** (Scheme 2) favored formation of the bridged bicycle **6h** in which a new seven-membered ring has been formed; only small quantities of the 5,6-fused bicyclic product **5h** were observed in this reaction (1:0.2 ratio).

Scheme 2. Preferential Formation of Bridged Bicyclic 7-Membered-Ring-Containing Diazenium Salt



In conclusion, the mildness and simplicity of the sulfonium salt mediated formation of phenyl α-chloroazo species provides ready access to tethered α-chloroazo alkenes, which in turn undergo Lewis acid catalyzed intramolecular cycloadditions in which a new carbocyclic and a new heterocyclic ring are formed. Overall, this two-step sequence is an efficient way to make structurally complex bicyclic heterocycles from simple linear hydrazone starting materials. Tethering the cycloaddition partners together allows electron-deficient alkenes to participate in the reaction, which is not the case in intermolecular processes. Terminal alkenes provide mixtures of fused and bridged bicyclic diazenium salt products, and the ratio of these products depends primarily on the length of the tether. Further studies on the scope of this intramolecular cycloaddition and synthetic applications of the diazenium salt products are underway.

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Supporting Information Available: Experimental details and characterization data including copies of ^{1}H and ^{13}C NMR spectra for compounds **4a**−**h**, **5a**−**c**, **5e**−**h**, and **6e**−**h**. This information is free of charge via the Internet at http://pubs.acs.org.

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