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A Dearomatizing, Thionium Ion Cyclization for the Synthesis of Functionalized, Azaspirocyclic Cyclohexadienones

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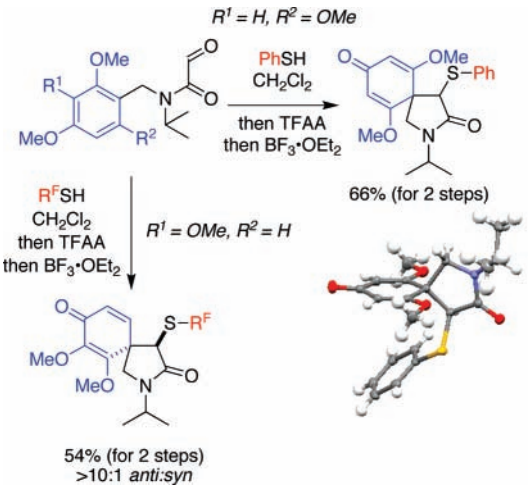
ABSTRACT



Thionium ions, generated by the addition of thiols to *N*-benzylglyoxamides, undergo a dearomatizing spirocyclization. The alkyl or arylsulfanyl group introduced during the thionium ion cyclization can act as a synthetic handle and a stereochemical control element during modifications of the azaspirocyclic frameworks ($R^F = CH_2CH_2C_8F_{17}$).

Pummerer reactions,[1] involving nucleophilic additions to thionium ions, are a useful tool for the synthesis of heterocyclic compounds.[2] We have recently investigated the utility of a Pummerer-type[3] reaction in which thionium ions are generated by the addition of thiols to aldehydes[4] and have exploited the connective nature of the process in a fluorous approach to *N*-heterocycles where a fluorous tag is introduced and a heterocyclic scaffold is constructed in a single step.[5]

We wished to exploit thionium ions generated in this way in cyclization reactions to access unusual *N*-heterocyclic

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(1) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282.

(2) (a) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, *274*, 35. (b) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003. (c) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401. (d) Padwa, A.; Danca, D. M.; Ginn, J. D.; Lynch, S. M. *J. Braz. Chem. Soc.* **2001**, *12*, 571. (e) Padwa, A.; Waterson, A. G. *Curr. Org. Chem.* **2000**, *4*, 175. (f) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353.

(3) We describe these reactions as "Pummerer-type" processes to show their relationship to "Pummerer" reactions in which similar thionium ions are generated from sulfoxides. See ref. 2.

(4) Miller, M.; Tsang, W.; Merritt, A.; Procter, D. J. *Chem. Commun.* **2007**, 498.

(5) (a) McAllister, L. A.; McCormick, R. A.; Brand, S.; Procter, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 452. (b) McCormick, R. A.; James, K. M.; Willetts, N.; Procter, D. J. *QSAR Comb. Sci.* **2006**, *25*, 709. (c) McAllister, L. A.; McCormick, R. A.; James, K. M.; Brand, S.; Willetts, N.; Procter, D. J. *Chem. Eur. J.* **2007**, *13*, 1032.

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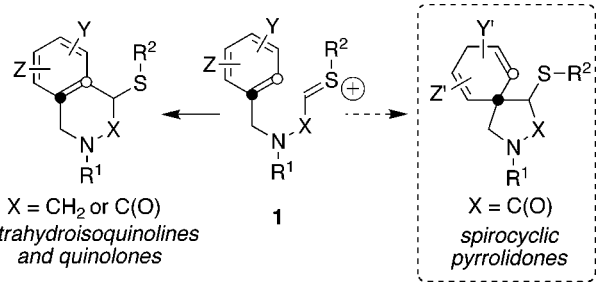
scaffolds. Although cyclizations of thionium ions **1** have been used for the synthesis of tetrahydroisoquinolines and tetrahydroisoquinolones,[6] we envisaged that appropriate aromatic substitution in thionium ions **1** would allow access to functionalized, azaspirocyclic cyclohexadienes via a dearomatizing spirocyclization.[7] The spirocyclic products would be useful intermediates for the synthesis of targets possessing the 2-azaspiro[4.5]decane skeleton (Scheme 1).

Scheme 1. Dearomatizing Spirocyclizations of Thionium Ions



The 2-azaspiro[4.5]decane skeleton is found in a wide variety of natural and unnatural products. The motif is found in synthetic compounds displaying activity as HIV-1 protease inhibitors[8a] and compounds with antiarthritic[8b] and antigastrin[8c] activity. The azaspirocyclic framework is also found in the natural products spirostaphylotrichin A,[8d] annosqualine,[8e] and alkaloids isolated from *didymeles madagascariensis*[8f] (Figure 1).

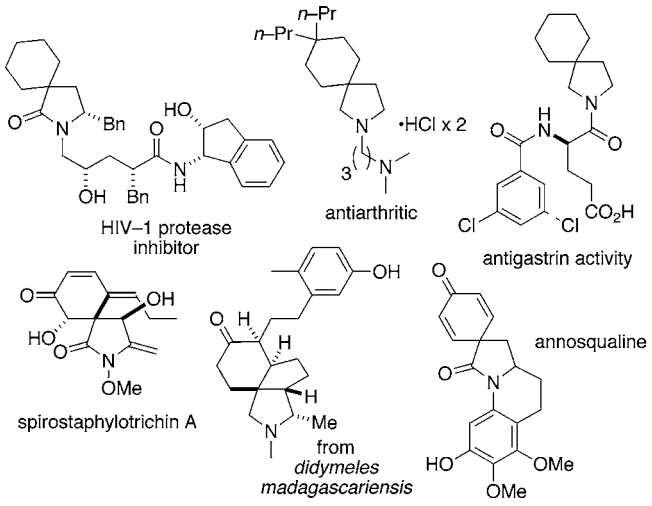


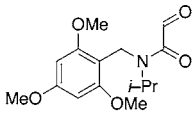
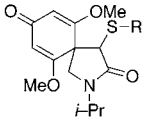
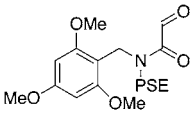
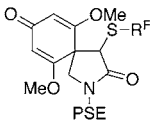
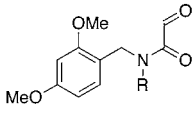
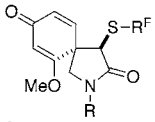
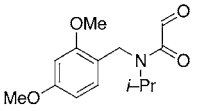
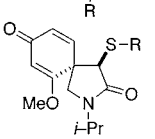
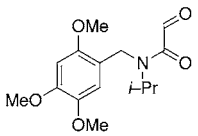
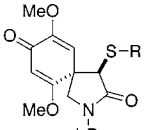
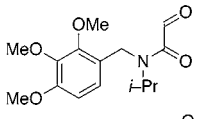
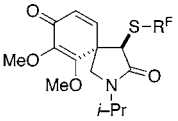
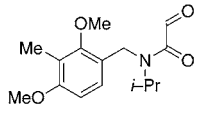
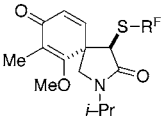
Figure 1. 2-Azaspiro[4.5]decane skeleton.

Few methods for the synthesis of azaspirocyclic cyclohexadiene systems have been reported.[9] Strategies include acid-catalyzed cyclizations of electron-rich aromatic diazoacetamides,[9a] intramolecular additions of nitrenes to electron-rich benzenes,[9b] carbanion additions to arene ruthenium complexes,[9c] and more recently, oxidative radical cyclizations of xanthates.[9d]

Here we report a thionium ion approach to azaspirocyclic cyclohexadienones. In contrast to several of the existing methods for constructing this motif,[9a,d] the thionium ion cyclization is accompanied by an increase in functionality: carbon−carbon and carbon−sulfur bonds and up to two new stereocentres are formed during construction of the azaspirocyclic framework. To our knowledge, this constitutes the first example of the dearomatization of a *benzene* derivative by intramolecular addition of a thionium ion.[7]

N-Benzylglyoxamides **2**−**9** were prepared from readily-available benzylamines using Bartlett's convenient and scalable route,[10] and the cyclization of these substrates was studied using a range of thiols. One-pot cyclizations were carried out by stirring thiol with the crude glyoxamide followed by addition of trifluoroacetic anhydride then BF_3·OEt_2 (Table 1). At least two electron-releasing groups on

Table 1. Dearomatizing Spirocyclizations of Thionium Ions[a]

N–benzylglyoxamide	product	overall isolated yield[b]
 **2**		**10** R = Ph 66% **11** R = R^F 73% **12** R = Et 87% **13** R = *n*–Hex 78% **14** R = *i*–Pr 94% **15** R = *c*–C_6H_{11} 88%
 **3**		**16** 51%
 **4** R = PSE **5** R = *t*–Bu		**17** 69%[c] **18** 54%[c]
 **6**		**19** R = R^F 70%[c] **20** R = Et 60%[c]
 **7**		**21** R = R^F 72%[c] **22** R = Et, 54%[c]
 **8**		**23** 54%[d]
 **9**		**24** 50%[d]

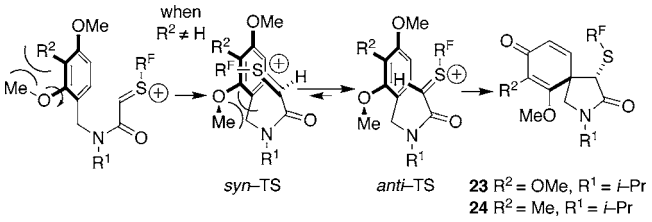
[a] RSH, CH_2Cl_2, then TFAA, then BF_3·OEt_2. [b] Isolated yields are for 2 steps as glyoxamides are not purified. [c] Approximately 2:1 to 3:1 mixture of diastereoisomers. [d] Only one diastereoisomer was isolated (PSE = 2-phenylsulfonylethyl, R^F= $-CH_2CH_2C_8F_{17}$)

(6) (a) Saitoh, T.; Shikiya, K.; Horiguchi, Y.; Sano, T. *Chem. Pharm. Bull.* **2003**, *51*, 667. (b) Hanaoka, M.; Hirasawa, T.; Cho, W. J.; Yasuda, S. *Chem. Pharm. Bull.* **2000**, *48*, 399.

the benzene ring are required for successful isolation of spirocyclic products. The azaspirocyclic structure of **10** was confirmed by X-ray crystallography.[11] In all cases, reaction mixtures develop a bright coloration that we attribute to cationic intermediates and give the expected spirocycles in good overall yield after two steps. Substrates **4**−**7** give azaspirocycles **17**−**22** with moderate selectivity for the *anti* product[12] (approximately 2:1 to 3:1 dr). Interestingly, only a single diastereoisomer was isolated from the cyclization of substrates **8** and **9**. The *anti* stereochemistry of **23** and **24** was confirmed by NOE studies. When the commercial fluorous thiol, $C_8F_{17}CH_2CH_2SH$, was used, fluorous solid-phase extraction (FSPE)[13] provides an additional option for purification. The cyclization of substrates **3** and **4** illustrates that the 2-phenylsulfonylethyl (PSE) group[14] is suitable for the synthesis of azaspirocycles with a protecting group on nitrogen. We have also found that $Sc(OTf)_3$ can be employed as the Lewis acid in the cyclization: the reaction of **4** using $Sc(OTf)_3$ (0.5 equiv) gave **17** in 55% yield (2 steps).

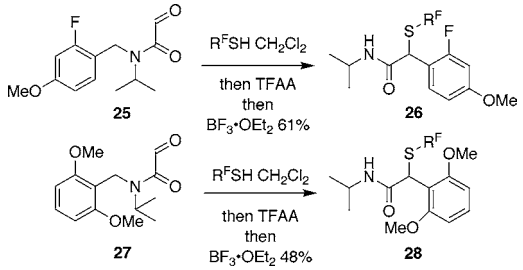
The high diastereoselectivity observed in the cyclization of **8** and **9** appears to arise from steric interactions rather than electronic effects: the *meta* substituent (R^2) increases the steric presence of the *ortho*-methoxy group through a buttressing effect thus favoring the *anti* transition structure (Scheme 2). With a hydrogen in the *meta* position (R^2= H) the methoxy group has a lower steric influence on the course of the cyclization and both *syn* and *anti* transition structures are accessible leading to a lower preference for the *anti* diastereoisomers.

Scheme 2. Origin of Diastereoselectivity ($R^F = -CH_2CH_2C_8F_{17}$)



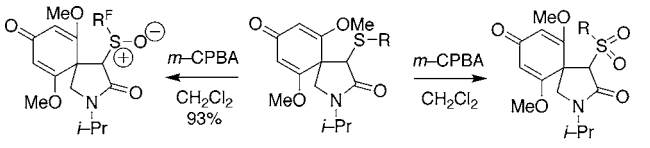
In some cases, the azaspirocyclic motif was not isolated from the reaction, for example, exposure of 2-fluoro-4-methoxybenzylglyoxamide **25** to the reaction conditions gave amide **26** in which the aryl group has undergone migration to the position α- to sulfur, in 61% yield (Scheme 3). This migration occurs via fragmentation of the expected spirocyclic, cationic intermediate, and hydrolysis of the resultant *N*-acyl iminium ion.[15] 2,6-Dimethoxybenzylglyoxamide **27** also underwent cyclization−aryl migration to give **28**. This intramolecular arylation of thionium ions provides a valuable alternative to the intermolecular additions of electron-rich benzenes to thionium ions.[2]

Scheme 3. Spirocyclization-Aryl Migration ($R^F = -CH_2CH_2C_8F_{17}$)



The azaspirocyclic frameworks resulting from the cyclization are rich in functionality and have significant synthetic potential. For example, the alkylsulfanyl group introduced during the spirocyclization is a valuable synthetic handle particularly as the oxidation state of sulfur can easily be adjusted: oxidation of **11** with *m*CPBA (1 eq) gave sulfoxide **29** whereas oxidation of **11** and **12** with *m*CPBA (2 eq) gave sulfones **30** and **31** (Scheme 4). The structure of **31** was confirmed by X-ray crystallographic analysis.[11]

Scheme 4. Adjusting the Oxidation State of Sulfur in the Azaspirocycles ($R^F = -CH_2CH_2C_8F_{17}$)



Conversion to the sulfone facilitates modification of the azaspirocyclic framework, for example, hydrogenation

(7) Previously reported Pummerer spirocyclizations involve addition to indole derivatives. For selected examples, see: (a) Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70. (b) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792. (c) Catena, J.; Valls, N.; Bosch, J.; Bonjoch, J. *Tetrahedron Lett.* **1994**, *35*, 4433. (d) Feldman, K. S.; Vidulova, D. B.; Karatjas, A. G. *J. Org. Chem.* **2005**, *70*, 6429. (e) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2006**, *8*, 4137.

(8) (a) Kazmierski, W. M.; Furfine, E.; Spaltenstein, A.; Wright, L. L. *Biorg. Med. Chem. Lett.* **2002**, *12*, 3431. (b) Badger, A. M.; Schwartz, D. A.; Picker, D. H.; Dorman, J. W.; Bradley, F. C.; Cheeseman, E. N.; DiMartino, M. J.; Hanna, N.; Mirabelli, C. K. *J. Med. Chem.* **1990**, *33*, 2963. (c) Makovec, F.; Peris, W.; Revel, L.; Giovanetti, R.; Mennuni, L.; Rovati, L. C. *J. Med. Chem.* **1992**, *35*, 28. (d) Sandmeier, P.; Tamm, C. *Helv. Chim. Acta* **1989**, *72*, 784. (e) Yang, Y.; Chang, F.; Wu, Y. *Helv. Chim. Acta* **2004**, *87*, 1392. (f) Sánchez, V.; Ahond, A.; Guilhem, J.; Poupat, C.; Potier, P. *Bull. Soc. Chim. Fr.* **1987**, 877.

(9) (a) Rishton, G. M.; Schwartz, M. A. *Tetrahedron Lett.* **1988**, *29*, 2643. (b) Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortíz, J. A. *Tetrahedron Lett.* **2003**, *44*, 2587. (c) Pigge, F. C.; Coniglio, J. J.; Dalvi, R. *J. Am. Chem. Soc.* **2006**, *128*, 3498. (d) Ibarra-Rivera, T. R.; Gámez-Montano, R.; Miranda, L. D. *Chem. Commun.* **2007**, 3485.

(10) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153. See also refs 4 and 5.

(11) See supporting information for CCDC numbers.

(12) The stereochemistry was determined by NOE studies on the major diastereoisomers of **21** and **22** and inferred for the remainder.

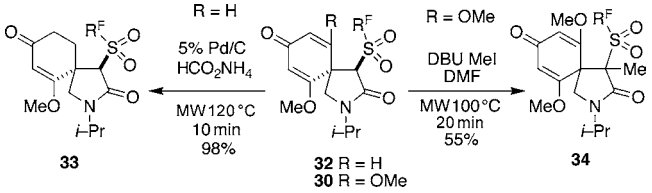
(13) For recent reviews; see: (a) Curran, D. P. In *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley-VCH: Weinheim, 2004. (b) Zhang, W. *Tetrahedron* **2003**, *59*, 4475.

(14) DiPietro, D.; Borzilleri, R. M.; Weinreb, S. M. *J. Org. Chem.* **1994**, *59*, 5856.

(15) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256.

of **32** under microwave irradiation gave **33** in excellent yield whereas attempted hydrogenation of the corresponding sulfide **19** was unsuccessful. Sulfones can also be elaborated through alkylation reactions, for example, treatment of **30** with MeI and DBU under microwave irradiation gave **34** (Scheme 5).

Scheme 5. Modification of the Azaspirocyclic Framework ($R^F = CH_2CH_2C_8F_{17}$)

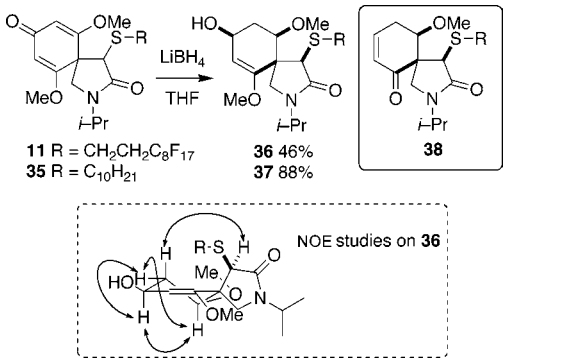


Oxidation of sulfur has an added benefit in that spirocyclic products that are obtained as a mixture of diastereoisomers with only modest preference for the *anti* diastereoisomer, for example **19** (~2:1, *anti*:*syn*), undergo equilibration upon conversion to the sulfones, giving products, such as **32** (85%) greatly enriched in the *anti* diastereoisomers (>12:1, *anti*:*syn* by ^{1}H NMR).

Further preliminary studies on the modification of the azaspirocyclic structures have been carried out. Treatment of spirocycles **11** and **35** with $LiBH_4$ results in a reductive sequence that generates three stereocentres giving allylic alcohols **36** and **37**, respectively, as single diastereoisomers (Scheme 6).

This sequence illustrates how the alkylsulfanyl group introduced in the thionium ion cyclization can function as a stereochemical control element, orchestrating the generation of stereochemistry elsewhere in the system. Allylic alcohols **36** and **37** are unstable; for example, **36** converted to enone **38** upon standing in $CDCl_3$ (Scheme 6). The conversion of **11** to **38** illustrates how the electron-

Scheme 6. Diastereoselective, Sequential Reduction of Azaspirocycles



releasing groups required for cyclization can be removed to access less-oxygenated systems.

In summary, the addition of thiols to *N*-benzylglyoxamides triggers a diastereoselective, dearomatizing cyclization to give functionalized azaspirocyclic cyclohexadienones. The alkyl or arylsulfanyl group introduced during the thionium ion cyclization can play multiple roles, acting as a diversity element, a synthetic handle, and a stereochemical control element in modifications of the azaspirocyclic frameworks.

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Supporting Information Available: Full 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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