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Synthesis of Sulfur-Containing Heterocycles through Oxidative Carbon–Hydrogen Bond Functionalization

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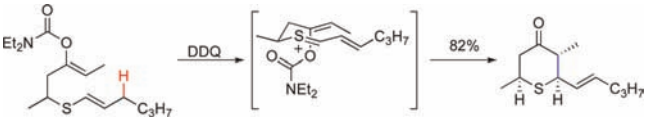
ABSTRACT



Vinyl sulfides react rapidly and efficiently with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to form α,β-unsaturated thiocarbenium ions through oxidative carbon–hydrogen bond cleavage. These electrophiles couple with appended π-nucleophiles to yield sulfur-containing heterocycles through carbon–carbon bond formation. Several nucleophiles are compatible with the procedure, and the reactions generally proceed through readily predictable transition states.

Organic sulfides display a remarkable range of properties in comparison to their oxygen-containing analogs. They are more nucleophilic, less basic, and less polar, and they can be oxidized to form sulfoxides and sulfones that provide additional opportunities for structural diversification. Moreover sulfides can be converted to substrates for [2,3]-sigmatropic rearrangements[1] that have proven to be useful in complex molecule synthesis. Sulfur's versatility has been exploited significantly in drug discovery efforts, as evidenced by the fact that several of the 200 top-selling pharmaceutical agents in 2010[2] contain sulfur and, in many cases, the sulfur atom is contained in a ring. Thus developing new methods for the stereoselective synthesis of sulfur-containing heterocycles is clearly a worthy objective.

Thiocarbenium ions are attractive intermediates for the synthesis of sulfur-containing compounds.[3] The vast majority of cyclization reactions that proceed through thiocarbenium ions provide *exo*-products in which the sulfur is not contained in a ring. Designing reactions of thiocarbenium ions in which the nucleophilic addition proceeds through an *endo*-pathway would provide a preparative method for sulfur-containing heterocycles. This strategy is rarely employed for thia-Prins-type reactions in which ring formation occurs through carbon–carbon bond formation.[4] The limited number of reported examples of this type of transformation[5] and the potential for preparing sulfur analogs of biologically active tetrahydropyran natural products[6] led us to explore the synthesis of tetrahydrothiopyrans[7] through intramolecular additions of π-nucleophiles into oxidatively generated thiocarbenium ions.[8]

Our approach was designed to mirror our route to the formation of oxygen-containing heterocycles,[9] whereby allylic or benzylic ethers react with 2,3-dichloro-5,

(1) (a) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (b) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.

(2) For a list of the top selling drugs in 2010 with structures, see: http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.

(3) (a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832. (b) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003. (c) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.

(4) For recent reviews of Prins-type cyclization reactions, see: (a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413. (b) Pastor, I.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925.

(5) (a) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739. (b) Dobbs, A. P.; Guesné, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880. (c) Bondalapati, S.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2012**, *77*, 2508.

(6) (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053. (b) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237.

(7) For recently reported alternate strategies for sulfur-containing heterocycle synthesis, see: (a) Li, F.; Calabrese, D.; Brichacek, M.; Lin, I.; Njardarson, J. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1938. (b) Robertson, F. J.; Wu, J. *J. Am. Chem. Soc.* **2012**, *134*, 2775.

(8) For a similar approach to thiocarbenium ion formation, see: Li, Z.; Li, H.; Guo, X.; Cao, L.; Yu, R.; Li, H.; Pan, S. *Org. Lett.* **2008**, *10*, 803.

10.1021/ol3002877
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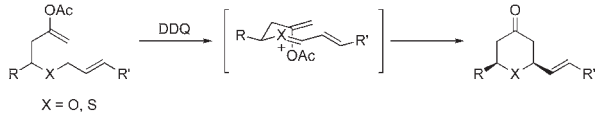
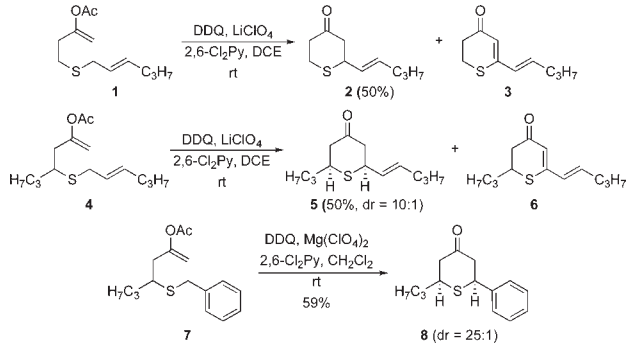
6-dicyano-1,4-benzoquinone (DDQ) to yield oxocarbenium ions that react with enol acetate nucleophiles (Scheme 1).[10] Sulfur is a larger and less electronegative atom than oxygen, making the relative stabilities of intermediate thiocarbenium and oxocarbenium ions difficult to predict, though comparative studies have shown that the energetic difference between these species is small.[11] Additionally the longer bonds between carbon and sulfur indicate that the strong preference for the *E*-geometry of oxocarbenium ions[12] could be eroded for thiocarbenium ions, leading to lower stereocontrol.

Scheme 1. Heterocycle Synthesis through Oxidative Carbon–Hydrogen Bond Cleavage



We demonstrated the viability of allylic sulfide substrates in these reactions (Scheme 2) through the DDQ-mediated conversion of **1** to **2**. This transformation led to the formation of variable amounts of enone **3** as a result of the oxidation of **2**. The addition of $LiClO_4$ to the reaction mixture reduced the formation of **3** to 4%, presumably due to the stabilization of the radical anion that forms from the initial electron transfer. Secondary sulfide **4** reacted with DDQ to yield **5** as a satisfactory 10:1 ratio of diastereomers, confirming that the *E*-thiocarbenium ion is the dominant reactive species. The product of overoxidation (**6**) was also formed in this transformation in 4% yield. Benzyl sulfide **7** was converted to tetrahydrothiopyrone **8** with excellent stereocontrol. No overoxidation was observed in this reaction. We postulate that the benzylic carbon–hydrogen bond in the product does not overlap the p-orbitals of the aromatic ring, thereby slowing product oxidation.

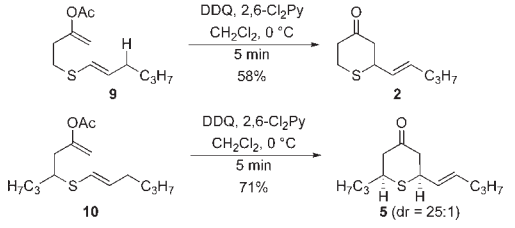
Scheme 2. Allylic and Benzylic Sulfide Substrates



The formation of overoxidized products and our desire to expand the scope of nucleophilic groups led us to explore vinyl sulfide substrates. Mechanistic studies in our group have revealed that oxidation rates are influenced by the oxidation potential of the substrate and the stability of the cation.[13] Although allyl sulfides and isomeric vinyl sulfides form the same thiocarbenium ion upon DDQ oxidation, the lower oxidation potential of vinyl sulfides[14] was expected to provide higher radical cation concentrations and faster cation formation. This strategy has been shown to be effective for acyliminium ion formation,[15] whereby allylic amides are unreactive toward DDQ while vinyl amides react quickly. Vinyl sulfides are attractive substrates for these processes because of their increasing accessibility through a number of new metal mediated protocols for their formation.[16]

Vinyl sulfide **9** was prepared through a sequence in which the key step was a palladium-mediated coupling between a thiol and a vinyl iodide.[17] Exposing **9**[18] to DDQ provided **2** in 58% isolated yield within 10 min at 0 °C through the same thiocarbenium ion that was formed from allyl sulfide **1** (Scheme 3). Vinyl sulfide **10** also proceeded through the oxidative cyclization reaction smoothly, forming **5** with excellent diastereocontrol. No overoxidation was observed. These results validated the strategy of employing vinyl sulfides rather than allyl sulfides as substrates for oxidative thiocarbenium ion formation.

Scheme 3. Cyclizations of Vinyl Sulfide Substrates



(9) (a) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184. (b) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567. (c) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069. (d) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5894.

(10) For recent examples of carbon–carbon bond formation through DDQ-mediated carbon–hydrogen bond oxidation, see: (a) Benfatti, F.; Capdavila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun.* **2009**, 5919. (b) Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3920. (c) Ghosh, A. K.; Cheng, X. *Org. Lett.* **2011**, *13*, 4108. (d) Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429. (e) Son, Y. W.; Kwon, T. H.; Lee, J. K.; Pae, A. N.; Lee, J. Y.; Cho, Y. S.; Min, S.-J. *Org. Lett.* **2011**, *13*, 6500. (f) Reddy, B. V. S.; Borkar, P.; Jadav, J. S.; Reddy, P. P.; Kunwar, A. C.; Sridhar, B.; Gree, R. *Org. Biomol. Chem.* **2012**, *10*, 1349. (g) Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949.

(11) (a) Osapay, K.; Delhalle, J.; Nsunda, K. M.; Rolli, E.; Houriet, R.; Hevesi, L. *J. Am. Chem. Soc.* **1989**, *111*, 5028. (b) Apeloig, Y.; Karni, M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 625. (c) Grützmacher, H.; Marchand, C. M. *Coord. Chem. Rev.* **1997**, *163*, 287.

(12) Broecker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006.

(13) Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830.

(14) Directly appending electron donating groups to alkenes results in a substantial lowering of the oxidation potential. See: Schepp, N. P.; Johnston, L. J. *J. Am. Chem. Soc.* **1996**, *118*, 2872.

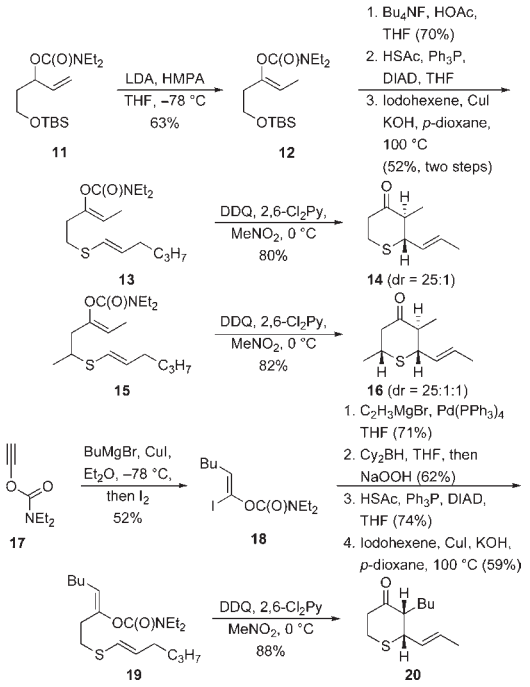
(15) (a) Brizgys, G. J.; Jung, H. H.; Floreancig, P. E. *Chem. Sci.* **2012**, *3*, 438. (b) Liu, L.; Floreancig, P. E. *Org. Lett.* **2009**, *11*, 3152.

Increasing the level of substitution in the products can be achieved by employing substituted nucleophiles. Controlling the stereochemical outcome of reactions with highly substituted nucleophiles requires the preparation of enolate surrogates with a high degree of geometrical control. The geometry of enol acetates and enolsilanes is difficult to control, but enol carbamates can be prepared with the appropriate level of control. The preparation and cyclization of enol carbamate substrates is shown in Scheme 4. The isomerization of allyl carbamate **11** with LDA in the presence of HMPA[19] provided (*Z*)-enol carbamate **12**. The vinyl sulfide was formed through a sequence of silyl ether cleavage, Mitsunobu displacement with thioacetic acid,[20] and coupling with (*E*)-1-iodo-1-hexene using the recently reported conditions from Kao and Lee[21] to yield substrate **13**. Although these conditions were developed for thiols, we observed the useful result whereby thioesters could be used in the coupling reactions with equal efficiency to thiols, presumably due to *in situ* thioester cleavage. Oxidation of **13** with DDQ resulted in the smooth conversion to **14** with high stereocontrol. Branched vinyl sulfide **15** was also an excellent participant in the reaction, providing **16** in 82% yield as a 25:1:1 mixture of products, with the major product arising from the expected chair transition state with an (*E*)-thiocarbenium ion. The minor products can be attributed to a boat transition state and a transition state with a (*Z*)-thiocarbenium ion.

The (*E*)-carbamate was accessed by exposing alkynyl carbamate **17** to Marek's carbocupration/iodination sequence[22] to form **18**. Cyclization substrate **19** was prepared through a straightforward sequence. Oxidation of **19** with DDQ provided 2,3-*cis*-product **20** in 72% yield as a single stereoisomer. These results demonstrated that complementary stereocontrol can be accessed by the appropriate selection of enolate surrogate geometry.

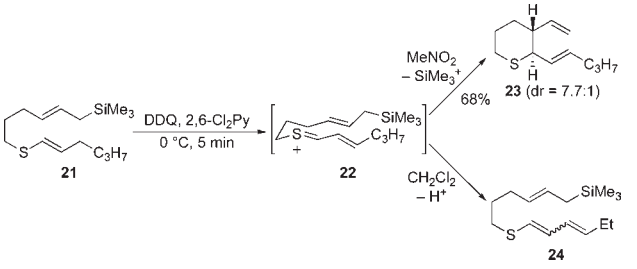
Allylsilanes are also effective nucleophiles for this reaction,[23] as shown by the conversion of **21** to **23** in Scheme 5. This process required that $MeNO_2$ be used as the solvent[24] since reactions in CH_2Cl_2 led to the formation of dienyl sulfide **24** from the deprotonation of thiocarbenium ion **22**. The more polar solvent allows for nucleophilic addition to be competitive with proton transfer, presumably by stabilizing the silyl-substituted carbocation intermediate that forms during the carbon–carbon bond forming step. The *trans*-relationship between the two alkenyl groups in the product can be attributed to the

Scheme 4. Cyclization with Enol Carbamate Nucleophiles



predominance of a chair transition state in which the thiocarbenium ion has an (*E*)-geometry and the allylsilane group occupies a pseudoequatorial orientation. The minor diastereomer can be formed from the (*Z*)-thiocarbenium ion, from the allylsilane group occupying a pseudoaxial orientation, or from a competitive twist boat transition state.

Scheme 5. Ring Closure by Allylsilane Addition



Several additional allylsilane substrates were prepared to probe the transition state of these reactions. The results are shown in Table 1. Cyclizations of vinyl sulfides that contain (*Z*)-allylsilane or trisubstituted allylsilane nucleophiles (entries 1 and 2) proceeded with much lower diastereocontrol than the cyclization of **21**. Incorporating a branched alkyl group into the substrate led to the formation of four diastereomeric products (entries 3–6), with the (*E*)-allylsilane substrates again reacting with higher levels of stereocontrol than the corresponding (*Z*)-allylsilane substrates. Tetrahydrothiophenes are also accessible through allylsilane additions to thiocarbenium ions, as

(16) (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (b) Bichler, P.; Love, J. A. *Top. Organomet. Chem.* **2010**, *31*, 39.

(17) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133.

(18) Please see the Supporting Information for details regarding substrate syntheses.

(19) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; van Hülsen, E. *Chem. Ber.* **1985**, *118*, 2822.

(20) Mitsunobu, O. *Synthesis* **1981**, 1.

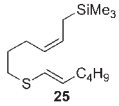
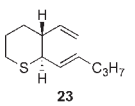
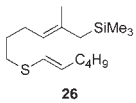
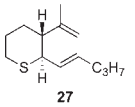
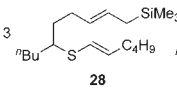
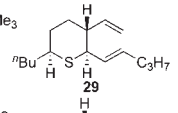
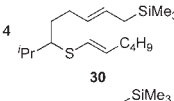
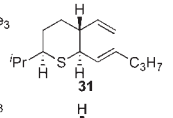
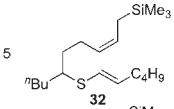
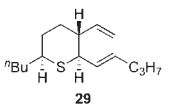
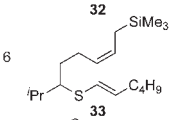
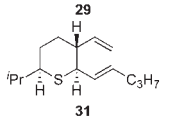
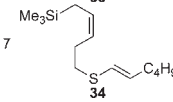
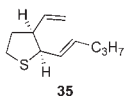
(21) Kao, H.-L.; Lee, C.-F. *Org. Lett.* **2011**, *13*, 5204.

(22) Chechik-Lankin, H.; Marek, I. *Org. Lett.* **2003**, *5*, 5087.

(23) (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.

(24) **CAUTION!** The flash point of $MeNO_2$ is 35 to 44 °C.

Table 1. Stereocontrol in Allylsilane Addition Reactions[a]

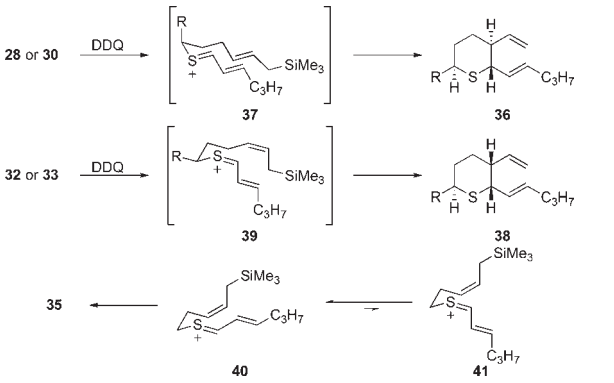
entry	substrate	major product	yield (%)[b]	dr[c]
1	 **25**	 **23**	75%	1.9:1
2	 **26**	 **27**	72%	2.0:1
3	 **28**	 **29**	68%	1.0:0.2:0.1:0.05[d]
4	 **30**	 **31**	79%	1.0:0.15:0.1:0.05[d]
5	 **32**	 **29**	68%	1.0:0.8:0.2:0.2[d]
6	 **33**	 **31**	79%	1.0:1.0:0.1:0.1[d]
7	 **34**	 **35**	77%	20:1

[a] Representative procedure: DDQ (1.05 equiv) was added to a solution of the vinyl sulfide in $MeNO_2$ (~0.1 M) at 0 °C. The reaction was stirred for 5 min and then purified by flash chromatography. [b] Yield refers to the mixture of isomeric products. [c] Determined by NOESY experiments and coupling constants in ^1H NMR spectra. [d] See text for details.

shown in entry 7 where the (*Z*)-allylsilane substrate provides the product with good stereocontrol. The facility of the unusual 5-*endo* cyclization can be attributed to the longer carbon−sulfur bonds in comparison to carbon−oxygen bonds. The origin of the striking differences between the selectivities of the (*E*)- and (*Z*)-allylsilanes is illustrated in Scheme 6. The most abundant minor product in the cyclization of substrates **28** and **30** is **36**. This compound most likely arises through transition state **37**, in which the alkyl group occupies a pseudoaxial orientation. This is reasonable based on the diminished energetic penalty for axial substituents in sulfur-containing heterocycles in comparison to oxygen-containing heterocycles.[25] The most abundant byproduct in the cyclizations of **32** and **33**, however, is **38**. This arises from cyclization through (*Z*)-thiocarbenium ion **39**. We note that the formation of tetrahydrothiophene **35** proceeds cleanly through (*E*)-thiocarbenium ion **40**. While we do not currently understand the origin of the effect, a comparison of **39**, **40**, and the disfavored intermediate **41** infers the potential for an attractive interaction between the nucleophile and the vinyl group of the thiocarbenium ion in **39** that would not be present in **41**.

(25) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1.

Scheme 6. Origins of Minor Products with Allylsilane Nucleophiles



We have demonstrated that stabilized thiocarbenium ions can be prepared through the oxidation of unsaturated sulfides with DDQ. The oxidations proceed most quickly for vinyl sulfides due to their lower oxidation potentials. The oxidatively generated electrophiles react with appended nucleophiles to form tetrahydrothiopyrans and tetrahydrothiophenes. In most cases these transformations proceed with good levels of stereocontrol through transition states that mirror those of the corresponding oxygen analogs, although (*Z*)-allylsilanes react with poor stereocontrol for the formation of six-membered rings. Enol carbamates were shown to be very effective nucleophiles for the preparation of highly substituted heterocycles with excellent stereocontrol.

Acknowledgment. We thank the National Institutes of Health (GM062924) for generous support of this work.

Supporting Information Available. Synthetic schemes for substrate syntheses, experimental procedures for cyclization reactions, and characterization data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.