



A thiyl radical mediated cascade sequence for the co-cyclisation of 1,6-hexadienes with sulfur atom transfer

David C. Harrowven,^{a,*} Joanne C. Hannam,^a Matthew C. Lucas,^a Nicola A. Newman^a
and Peter D. Howes^b

^aDepartment of Chemistry, The University, Southampton S017 1BJ, UK

^bMedicinal Chemistry 2, GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts. SG1 2NY, UK

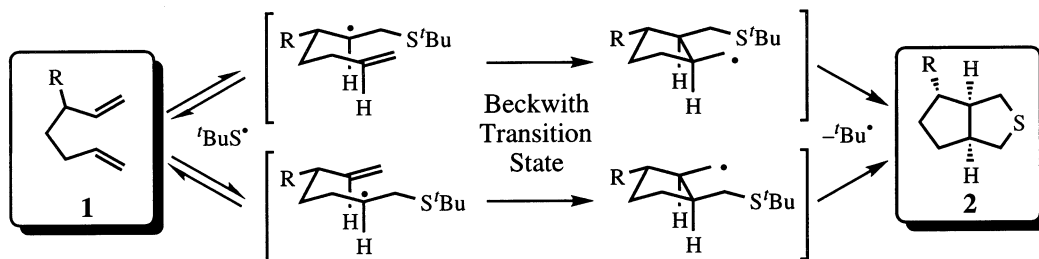
Received 31 August 2000; accepted 27 September 2000

Abstract

The paper describes a method for effecting the co-cyclisation of 1,6-dienes with concomitant sulfur atom transfer. The key step is a cascade reaction involving the addition of a thiyl radical to an alkene, cyclisation through a chair-like transition state and termination by homolytic substitution at sulfur. It has been used to synthesise a broad range of fused thiabicyclo[3.3.0]octanes. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: cyclisations; photochemistry; radicals and radical reactions; sulfur heterocycles.

Radical reactions mediated by sulfur have many potential advantages over trialkylstannane methodologies.^{1,2} In particular, the lower cost of reagents, the ease of work up and the reduced toxicity of both reagents and residues are attractive features.³ In practice, sulfur-centred radical reactions are often capricious. Indeed, the reversible nature of thiyl radical additions to alkenes, the efficiency of hydrogen atom abstraction from thiols, and regiochemical issues that arise when unsymmetrical dienes are employed as substrates ensure that complex product mixtures are produced in most cases (Scheme 1).²

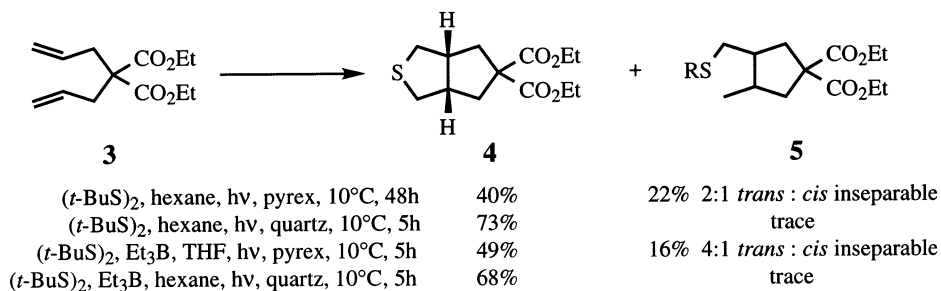


Scheme 1.

* Corresponding author.

We reasoned that sulfur-mediated radical cyclisations involving 1,6-dienes would be more efficient if hydrogen atom abstraction was slowed. In particular, provided Beckwith's guidelines for ring closure were followed,⁴ cyclisation would favour generation of a radical intermediate suitably disposed to effect an S_H2 reaction at sulfur.^{5,6} A second cyclisation to sulfur would then produce a *cis*-fused thiabicyclo[3.3.0]octane (e.g. **2**) as the major product (Scheme 1).^{7,8}

Initially our attention focused on the co-cyclisation of the commercially available 1,6-diene **3**. We found that photolysing a hexane solution of **3** and di-*tert*-butyl disulfide in a water cooled quartz photochemical cell for 5 h gave the corresponding tetrahydrothiophene **4** in good yield together with some baseline material. Reactions were much slower and less efficient when a Pyrex photochemical cell was employed. In such cases the addition of triethylborane was found to accelerate the reaction rate dramatically (Scheme 2).



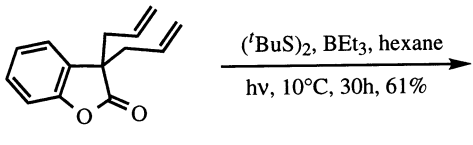
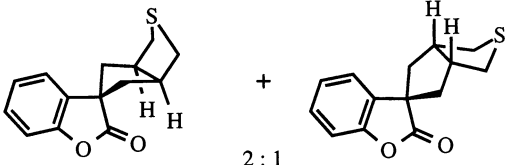
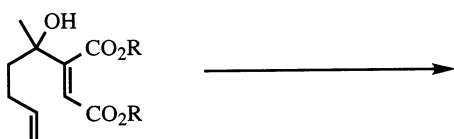

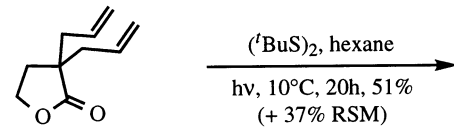
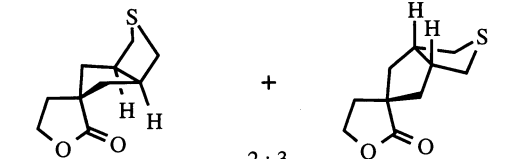
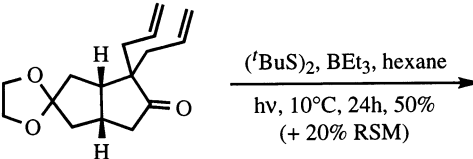
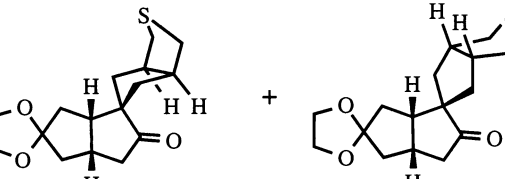
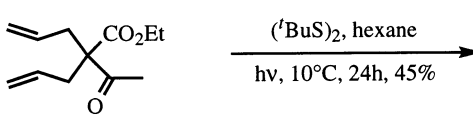
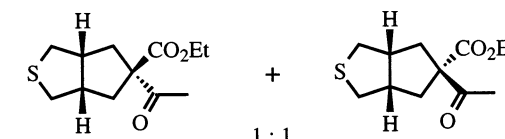
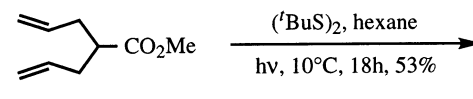
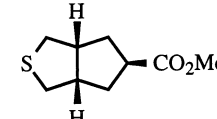
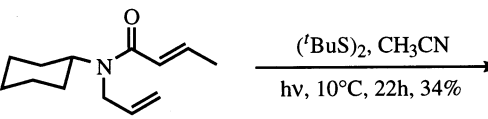
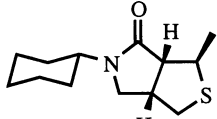
Scheme 2.

Table 1
Examples of 1,6-diene co-cyclisation with a sulfur atom transfer

<p>A</p> <p style="text-align: center;">hexane, 10°C, 18h, 55% (+ 10% RSM)</p>	<p>B</p> <p style="text-align: center;">BEt₃, hexane, 10°C, 9h, 55% (+ 31% RSM)</p>
<p>C</p> <p style="text-align: center;">hexane, 10°C, 20h, 46%</p>	<p>D</p> <p style="text-align: center;">BEt₃, hexane, 10°C, 6h, 33% (+ 22% RSM)</p>
<p>E</p> <p style="text-align: center;">BEt₃, hexane, 10°C, 20h, 45%</p>	<p>F</p> <p style="text-align: center;">R = fmoc: BEt₃, hexane, 10°C, 9h, 42%</p> <p style="text-align: center;">R = Ts: BEt₃, hexane, 10°C, 4h, 33%</p>

Several related cyclisations were then conducted to explore the generality of the method and these results are summarised in Tables 1 and 2. In general, reasonable yields were obtained for the co-cyclisation of heptadiene derivatives and heteroatoms could be tolerated in the linking

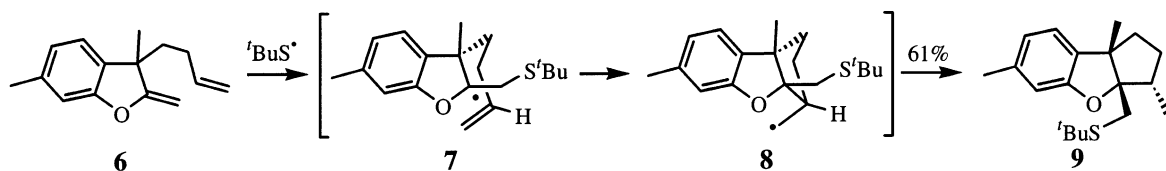
Table 2
Examples of 1,6-diene co-cyclisation leading to diastereoisomeric products

A	 <p>$(^t\text{BuS})_2$, BEt_3, hexane hv, 10°C, 30h, 61%</p>	 <p>2 : 1</p>
B & C	 <p>R = Me: $(^t\text{BuS})_2$, hexane, hv, 10°C, 20h, 52% R = Et: $(^t\text{BuS})_2$, hexane, hv, 10°C, 24h, 61%</p>	 <p>4 : 1 2 : 1</p>
D	 <p>$(^t\text{BuS})_2$, hexane hv, 10°C, 20h, 51% (+ 37% RSM)</p>	 <p>2 : 3</p>
E	 <p>$(^t\text{BuS})_2$, BEt_3, hexane hv, 10°C, 24h, 50% (+ 20% RSM)</p>	 <p>2 : 3</p>
F	 <p>$(^t\text{BuS})_2$, hexane hv, 10°C, 24h, 45%</p>	 <p>1 : 1</p>
G	 <p>$(^t\text{BuS})_2$, hexane hv, 10°C, 18h, 53%</p>	
H	 <p>$(^t\text{BuS})_2$, CH_3CN hv, 10°C, 22h, 34%</p>	

chain. The role of quaternary stereogenic centres on the course of the reaction was also examined (Table 2).

In conclusion, we have developed a method for effecting the co-cyclisation of 1,6-dienes with concomitant sulfur atom transfer.⁷ The key step is a cascade reaction involving the addition of a thiyl radical to an alkene, cyclisation through a chair-like transition state and termination by homolytic substitution at sulfur. A broad range of fused tetrahydrothiophenes have been synthesised using the method and we are currently seeking to exploit the reaction in target oriented synthesis.

Finally, it should be noted that reactions which favour chair-like transition states leading to a *trans* relationship between the newly formed radical centre and the sulfide (e.g. **7**→**8**) can also be efficient processes.⁹ In such cases cyclisation to sulfur is prohibited, as evinced by our cyclisation of diene **6** to sulfide **9** in a recent synthesis of (±)-aplysin (Scheme 3).



Scheme 3.

Acknowledgements

The authors would like to thank GlaxoWellcome and the EPSRC for financial support, the EPSRC X-ray service at Southampton for help with the assignment of relative stereochemistries (in Table 2) and the EPSRC mass spectrometry service at Swansea for the provision of HRMS data.

References

- For recent overviews of radical cyclisation reactions, see: (a) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301; (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, p. 779; (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237; (d) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: New York, 1991.
- For overviews and representative examples of sulfur mediated radical cyclisation reactions, see: (a) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19; (b) Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem.* **1992**, *57*, 111; (c) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *Heterocycles* **1991**, *32*, 2319; (d) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Synthesis* **1990**, 1123; (e) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1987**, 1647; (f) Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825; (g) Oswald, A. A.; Griesbaum, K. In *The Chemistry of Organic Sulfur Compounds*; Kharasch, N.; Meyers, C. Y., Eds.; Pergamon: Oxford, 1966; Vol. 2, Chapter 9, p. 233.
- For a detailed report on the toxicity of tin reagents, see: *Occupational Exposure to Organotin Compounds*; US Department of Health, Education and Welfare: Washington, Nov. 1976.

4. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925; (b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545; (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
5. For reviews concerned with homolytic substitution reactions, see: (a) Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265; (b) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, 143; (c) Ingold, K. U.; Roberts, B. P. *Free Radical Substitution Reactions*; Wiley-Interscience: New York, 1971.
6. For recent studies involving S_H2 reactions at sulfur, see: (a) Schiesser, C. H.; Wild, L. M. *J. Org. Chem.* **1999**, *64*, 1131; (b) Boros, E. E.; Hall, W. R.; Harfenist, M.; Kelley, J. L.; Reeves, M. D.; Styles, V. L. *J. Heterocyclic Chem.* **1998**, *35*, 699; (c) Ryu, I.; Okuda, T.; Nagahara, K.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1997**, *62*, 7550; (d) Harrowven, D. C.; Browne, R. *Tetrahedron Lett.* **1995**, *36*, 2861; (e) Tada, M.; Sugano, K.; Yoshihara, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2969; (f) Schiesser, C. H.; Smart, B. A. *Tetrahedron* **1995**, *51*, 10651; (g) Beckwith, A. L. J.; Duggan, S. A. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1509; (h) Harrowven, D. C. *Tetrahedron Lett.* **1993**, *34*, 5653.
7. The conversion of germacrene D into mintsulfide by photolysis in the presence of sulfur may proceed by a similar mechanism. See: (a) Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971; (b) Takahashi, K.; Muraki, S.; Yoshida, T. *Agric. Biol. Chem.* **1981**, *45*, 129; (c) Uyehara, T.; Ohnuma, T.; Saito, T.; Kato, T.; Yoshida, T.; Takahashi, K. *J. Chem. Soc., Chem. Commun.* **1981**, 127. Also see: (d) Padwa, A.; Nimmegern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.
8. For a related sequence induced by silicon centred radicals, see: (a) Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 23487; (b) Kulicke, K. J.; Chatgililoglu, C.; Kopping, B.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 935; (c) Miura, K.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1992**, 247.
9. Cyclisations leading to radical intermediates incapable of undergoing intermolecular S_H2 reactions at sulfur are generally quenched by hydrogen atom abstraction or homolytic substitution with a disulfide. See: (a) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, *40*, 4443; (b) Kuehne, M. E.; Damon, R. E. *J. Org. Chem.* **1977**, *42*, 1825.