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# Sulfur-mediated radical cyclisation reactions on solid support

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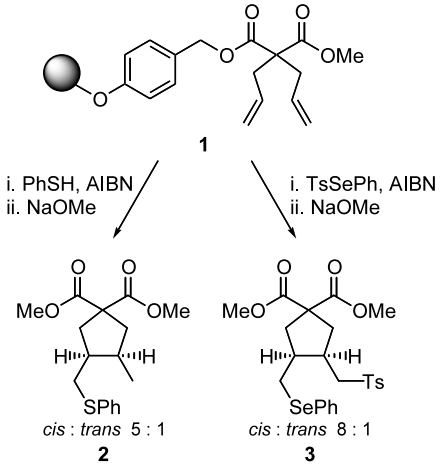
**Abstract**—Two methods for effecting radical cyclisation reactions of solid-supported 1,6-dienes are described. Additions of thiophenol and *p*-tolyl benzeneselenosulfonate have each been achieved with a concomitant 5-*exo*-trig radical cyclisation leading to the formation of highly functionalised cyclopentanes. 

The most common mediator of radical reactions in synthetic organic chemistry is tributyltin hydride.[1] Though problems of toxicity and expense are frequently highlighted as reasons to avoid the reagent,[2] for most small-scale work these are of little consequence. Where the removal of even traces of an organotin residue from a product is of critical importance, as is the case for substances prepared for biological assay,[3] the use of solid-supported reagents or substrates can provide a convenient solution to the toxicity problem.

Few 'non-tin' radical cyclisation reactions have been conducted on solid supported substrates.[4–7] Armstrong et al. have shown that samarium(II) iodide can be effectively used in this context,[4] while Ganesan and Zhu have used the photolytic decomposition of Barton-type esters to trigger both intermolecular addition and cyclisation reactions with solid-supported substrates.[5,7] In a related study, Naito et al. induced cyclisation reactions through the addition of an alkyl radical to an alkene, the former being generated by the decomposition of triethylborane or diethylzinc in the presence of an alkyl iodide.[6] In this letter we report two further methods for effecting the cyclisation of solid-supported 1,6-dienes. The first relies on the addition of a thiyl radical to an alkene to induce ring closure, viz. **1**→**2**,[8] while the second method achieves this through the addition of a tosyl radical formed from *p*-tolyl benzeneselenosulfonate, viz. **1**→**3** (Scheme 1).[9]

Our first task was to establish a convenient method for preparing 1,6-dienes on a solid support. To that end, dimethyl diallylmalonate **5** was synthesised from dimethyl malonate **4** and then saponified to half acid **7**.[10] A DIC-HOBt coupling to PS-Wang then gave **1**,[11] a carbonyl stretching frequency at 1732 $cm^{-1}$ in the reflectance IR spectrum confirming that loading had been successful.

Substrates **10a**–**d** were then prepared in a similar fashion. Thus, dimethyl allylmalonate **6a** and dimethyl methallylmalonate **6b** were prepared and saponified to their respective half acids **8a** and **8b**. These materials were then coupled to PS-Wang using the DIC-HOBt procedure leading to **9a** and **9b**, respectively.[11] Again, characteristic IR signals at 1734 $cm^{-1}$ for **9a** and 1731 $cm^{-1}$ for **9b** confirmed a successful loading of the malonate group. Each of these resin bound substrates was then alkylated with prenyl bromide giving, **10a** and **10d**, and with cinnamyl bromide, giving **10b** and **10c** (Scheme 2).




**Scheme 1.**

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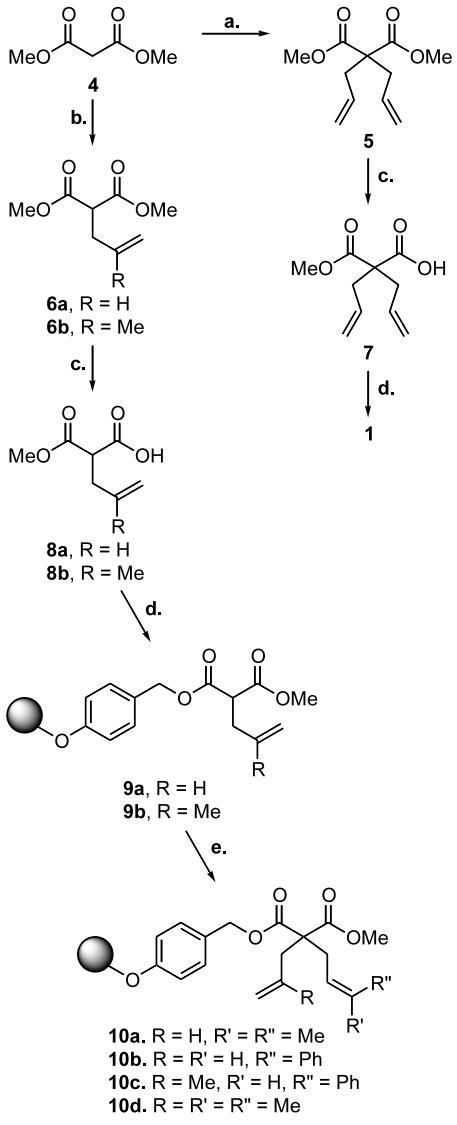



**Scheme 2.** *Reagents and conditions*: (**a**) NaH, THF, 0°C→rt; 2 equiv. allyl bromide, reflux, 15 h, 97%; (**b**) NaH, THF, 0°C→rt; 1 equiv. allyl or methallyl bromide, reflux, 15 h [**4**→**6a**, 94%; **4**→**6b**, 85%]; (**c**) KOH, MeOH, reflux [**5**→**7**, 6 h, 48%; **6a**→**8a**, 6 h, 49%; **6b**→**8b**, 15 h, 49%]; (**d**) HOBt, PS-Wang, 25% DMF in DCM, 30 min; DIC, DMAP, rt, 15 h; (**e**) prenyl or cinnamyl bromide, DBU, 40% acetone in dioxane, 90°C, 36 h.

We were now in a position to investigate the thiyl-mediated radical cyclisation reactions. Initial attempts to effect a co-cyclisation of **1** using *t*-butylthiyl radicals (generated by irradiation of *t*-butyl disulfide) met with failure:[8a] cleavage of the substrate from the resin with sodium methoxide returning only dimethyl diallylmalonate **5**. Using thiophenol in conjunction with AIBN proved more rewarding. Simply heating a five-fold excess of the thiol and 2.3 equiv. of AIBN,[12] in toluene at 80°C for 15 h, effected the desired cyclisation reaction. Cleavage of the product from the resin using sodium methoxide then gave a 5:1 mixture of *cis*-**2** and *trans*-**2** in an overall yield of 78% from the point of resin immobilisation (Table 1).

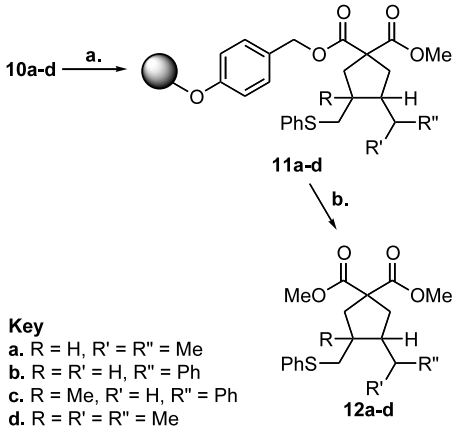
**Table 1.** Details of reactions highlighted in Schemes 1 and 3

| Reaction | Yield (from **7** or **8**) (%) | *cis*:*trans* |
|---|---|---|
| **1**→**2** | 78 | 5:1 |
| **10a**→**12a** | 75 | 3:1 |
| **10b**→**12b** | 76 | 7:2 |
| **10c**→**12c** | 69 | 1:1 |
| **10d**→**12d** | 69 | 1:1 |

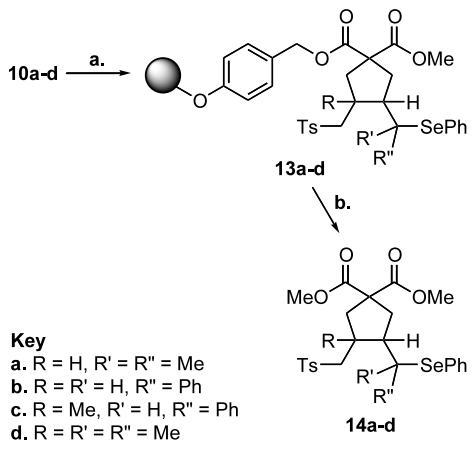
Supported dienes **10a–d** were now treated similarly. In each case the expected cyclopentanes **12a–d** were obtained in good overall yield following cleavage from the PS-resin. Notably, and in line with the Beckwith model for predicting the stereochemical course of 5-*exo*-trig radical cyclisation reactions,[13] the allylated substrates **10a** and **10b** showed a preference for cyclisation to *cis*-**11a** and *cis*-**11b**, respectively. The methallylated substrates **10c** and **10d**, as would be expected, gave equal proportions of *cis*- and *trans*-**12c** and **12d**, respectively (Scheme 3, Table 1).[14]

Our attention now turned to cyclisation reactions mediated by *p*-tolyl benzeneselenosulfonate.[9] The method seemed particularly suitable for library generation as both sulfone and selenide functions are introduced into the product, providing further opportunity for diversification post-cyclisation. Treatment of **1** with 2 equiv. of *p*-tolyl benzeneselenosulfonate and AIBN for 20 h at reflux in chloroform, followed by cleavage of the product from the support with sodium methoxide, gave **3** as an 8:1 mixture of *cis*- and *trans*-diastereoisomers.[14] The overall yield from the point of resin loading to cleavage was a pleasing 74%.

Related cyclisation and cleavage reactions were then performed using **10a–d**. In all cases good conversions were realised. Again, the stereochemical outcome of the cyclisation reactions followed Beckwith's guidelines.[13] One complication associated with dienes **10b** and **10c** was the formation of a third stereogenic centre when




**Scheme 3.** *Reagents and conditions*: (**a**) 5 equiv. PhSH, 2.5 equiv. AIBN, PhMe, 90°C, 26 h; (**b**) NaOMe, 20% MeOH in THF, reflux, 18 h (see Table 1).




**Scheme 4.** *Reagents and conditions*: (**a**) 2 equiv. TsSePh, 2–3 equiv. AIBN, $CHCl_3$, reflux, 15 h; (**b**) NaOMe, 20% MeOH in THF, reflux, 18 h (see Table 2).

**Table 2.** Details of reactions highlighted in Schemes 1 and 4

| Reaction | Yield (from **8**) (%) | *cis*:*trans* |
|---|---|---|
| **1→3** | 74 | 8:1 |
| **10a→14a** | 72 | 3:1 |
| **10b→14b** | 66 | ~[3:3]:[1:1] |
| **10c→14c** | 69 | ~[1:1]:[1:1] |
| **10d→14d** | 68 | 1:1 |

the 2°-alkyl radical intermediate is trapped with SePh. As this step proceeds in an indiscriminate manner, complex product mixtures comprising four diastereoisomers were given in each case. These products could be partially separated by HPLC, allowing us to show that cyclisation of **10b** favoured the *cis*-1,2-substitution pattern (Scheme 4, Table 2).

In conclusion, we have shown that solid supported 1,6-dienes may be transformed into cyclopentanes through the action of either thiyl or sulfonyl radical intermediates. Good yields are attained using PS-Wang as the support and stereochemical outcomes mirror those of the analogous solution phase reactions.[15]

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## References

1. 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*, 301–856; (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, pp. 779–831; (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237–1286; (d) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press, 1991.
2. 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.
3. Lee, S.; Robinson, G. *Process Development*: *Fine Chemicals from Grams to Kilograms*, *OUP*; 1995.
4. (a) Du, X. H.; Armstrong, R. W. *J. Org. Chem*. **1997**, *62*, 5678–5679; (b) Du, X. H.; Armstrong, R. W. *Tetrahedron Lett*. **1998**, *39*, 2281–2284.
5. Ganesan, A.; Zhu, X. *J. Combinatorial Chem*. **1999**, *1*, 157–162.
6. (a) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun*. **2001**, 831–832; (b) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett*. **2000**, *2*, 1443–1445.
7. For further examples of intermolecular radical reactions involving solid supported substrates, see: (a) Caddick, S.; Hamza, D.; Wadman, S. N. *Tetrahedron Lett*. **1999**, *40*, 7285–7588; (b) Plourde, R., Jr.; Johnson, L. L., Jr.; Longo, R. K. *Synlett* **2001**, 439–441; (c) Taddei, M.; Attardi, M. E. *Tetrahedron Lett*. **2001**, *42*, 3519–3522; (d) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett*. **1999**, *40*, 8387–8390; (e) Yim, A. M.; Vidal, Y.; Viallefont, P.; Martinez, J. *Tetrahedron Lett*. **1999**, *40*, 4535–4538.
8. For examples of thiyl radical induced cyclisation reactions, see: (a) Harrowven, D. C.; Hannam, J. C.; Lucas, M. C.; Newman, N. A.; Howes, P. D. *Tetrahedron Lett*. **2000**, *41*, 9345–9349; (b) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 791–804; (c) Harrowven, D. C.; Hannam, J. C. *Tetrahedron* **1999**, *55*, 9341–9346; (d) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett*. **1999**, *40*, 4443–4444; (e) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19–26; (e) Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem*. **1992**, *57*, 111–115; (f) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Synthesis* **1990**, 1123–1125; (g) Ichinose, Y.; Wakamatsu, K.; Nozaki, K.; Birbaum, J.-L.; Oshima, K.; Utimoto, K. *Chem. Lett*. **1987**, 1647–1650; (h) Kuehne, M. E.; Damon, R. E. *J. Org. Chem*. **1977**, *42*, 1825–1832; (i) Oswald, A. A.; Griesbaum K. In *The Chemistry of Organic Sulfur Compound*; Kharasch, N.; Meyers, C. Y., Eds.; Pergamon: Oxford, 1966; Vol. 2, Chapter 9, pp. 233–256.
9. Chuang, C.-P. *Synth. Commun*. **1992**, *22*, 3151–3158.
10. Semmelhack, M. F.; Foos, J. S.; Katz, S. *J. Am. Chem. Soc*. **1973**, *95*, 7325–7336.
11. Bennet, W. D.; Christensen, J. W.; Hamaker, L. K.; Peterson, M. L.; Rhodes, M. R.; Saneii, H. H. *Handbook of Combinatorial and Solid Phase Organic Chemistry*; Advanced ChemTech Inc.: Louisville, 1998.
12. AIBN was added hourly from the commencement of each reaction in nine equal portions.

13. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941; (b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545–546; (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959–974.
14. Whitesell, J. K.; Minton, M. A. *Stereochemical Analysis of Alicyclic Compounds by C-13 NMR Spectroscopy*; Chapman and Hall: London, 1987.
15. Solution phase analogues of all the solid supported radical reactions outlined in this paper were conducted using the appropriate dimethyl diallylmalonate derivative. The products derived from both the solid and solution phase experiments gave near identical stereochemical outcomes.