Tetrahedron Letters, Vol. 34, No. 19, pp. 3151-3154, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# Radical Cyclisations of Methylenecyclopropane Derivatives

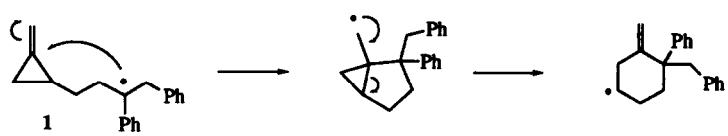
**Christine Destabel,[a] Jeremy D Kilburn[a*] and John Knight[b]**

a Department of Chemistry, University of Southampton, Southampton, SO9 5NH, UK

b Glaxo Group Research Limited, Park Road, Ware, Hertfordshire, SG12 0DP, UK

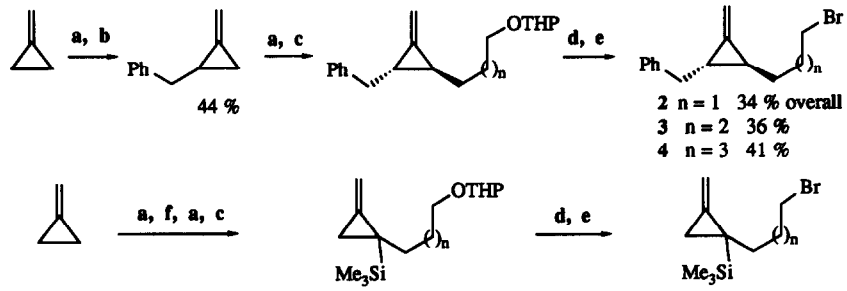
**Abstract** - Radical cyclisations of various methylenecyclopropane derivatives have been studied and it has been found that methylenecyclopropyl propyl radicals undergo exclusive 5-*exo* cyclisation while methylenecyclopropyl butyl radicals give a mixture of products resulting from 6-*exo* and 7-*endo* cyclisation. Attempted cyclisations of methylenecyclopropyl pentyl radicals leads to reduced products only.

While the cyclisation of hexenyl radicals to give cyclopentane products is well established,[1] the cyclisation of heptenyl radicals to give six-membered rings is not as generally successful since the reaction is often less regioselective than analogous hexenyl radical cyclisations, and associated problems such as abstraction of allylic hydrogen atoms have to be considered.[2] Furthermore, synthesis of medium-sized rings using radical cyclisations remains a problem because such cyclisations suffer from slow reaction rates, so that competing reduction, and other pathways, begin to dominate the reaction. We recently reported a novel radical rearrangement which involved the 5-*exo* cyclisation of a methylenecyclopropyl propyl radical **1**, (eq. 1) followed by opening of the resulting cyclopropylmethyl radical, to give finally a cyclohexene product.[3] The potential for radical cyclisations of strained methylene cyclopropane systems to provide novel routes to larger carbocycles has led us to look at the cyclisations of a number of methylene cyclopropane derivatives, as a function of chain length, and we report the results of these studies in this Letter.




(eq. 1)

The radical precursors, bromides **2-7**, were prepared by successive deprotonation and alkylation, or silylation, of methylenecyclopropane following the work of Binger[4] and Thomas[5] (scheme 1), followed by conversion of the protected alcohols into the desired bromides. The 1,2 disubstituted methylenecyclopropanes **2**, **3** and **4** were obtained as predominantly the *trans* isomers (> 5 : 1). For the synthesis of **5**, **6**, and **7** the sequence involving deprotonation of methylenecyclopropane, silylation, deprotonation and alkylation could be carried out in one pot.

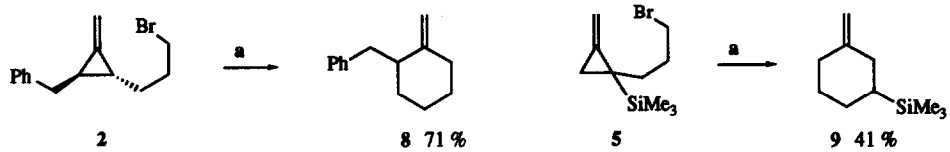



a) BuLi, b) $PhCH_2Br$, c) $BrCH_2(CH_2)_nCH_2OTHP$,
d) Amberlite IR-120, MeOH,
e) $CBr_4$, $Ph_3P$, f) $Me_3SiCl$

SCHEME 1

*Methylenecyclopropyl propyl radicals*

Cyclisation of bromide **2** (0.015 M in toluene) gave methylene cyclohexane **8** (Scheme 2) as the only identifiable product[6] in 71 % isolated yield (> 95 % by GC analysis) *via* initial 5-*exo* cyclisation followed by ring-opening of the cyclopropyl methyl radical as for radical **1** (eq.1).




**2** **8** 71 % **5** **9** 41 %

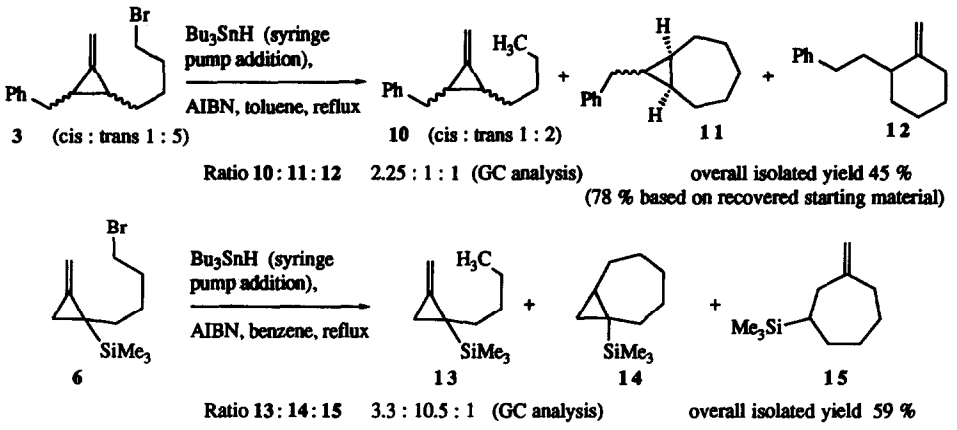
SCHEME 2 a) $Bu_3SnH$, AIBN, toluene, reflux

Cyclisation of bromide **5** (0.028 M in toluene) similarly led to a methylenecyclohexane product **9** in an extremely clean reaction by GC analysis (> 85 % yield), although the volatility of the product made isolation difficult.

*Methylenecyclopropyl butyl radicals*

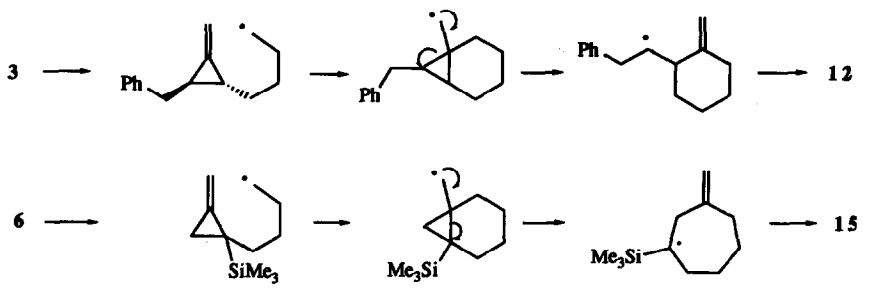
Cyclisation of **3** (toluene, syringe pump) (Scheme 3) gave a mixture of products, inseparable by column chromatography, but which were identifiable by NMR and by GC analysis with independently synthesised materials,[6] as a 1:1 mixture of **11** and **12** resulting from initial 7-*endo* or 6-*exo* cyclisation respectively, along with reduced, uncyclised **10**. Carrying out the cyclisation at lower temperature (benzene, 80 °C) merely increased the yield of **10**

Cyclisation of **6** (benzene, syringe pump), however, proceeds in predominantly 7-*endo* fashion to give the bicyclo [1.5.0] octane **14**, with small amounts of methylenecycloheptane derived from initial 6-*exo* cyclisation. The trimethylsilyl moiety on **6** may be electronically promoting *endo* attack[7] and also blocking hydrogen atom abstraction from the methylenecyclopropane ring.




**SCHEME 3**

It is noteworthy that the 6-*exo* cyclisation of **3** was followed by an "*endo*" ring opening of the intermediate cyclopropyl methyl radical (to give **12**), as opposed to the "*exo*" opening found in the case of methylenecyclopropyl propyl radicals (Scheme 1), but in both cases this led to six membered rings as the final products. These observations, and the lack of any conformational restriction on the intermediate cyclopropyl methyl radical,[8] suggest that this opening is reversible,[9] and under thermodynamic control (Scheme 4).



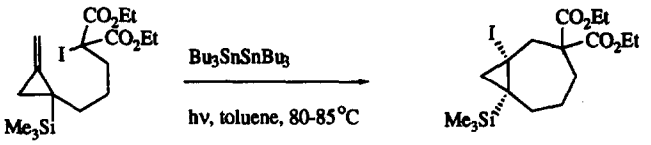

**SCHEME 4**

The thermodynamic preference for ring opening can be biased by placement of suitable functionality. Thus, the small amount of 6-*exo* cyclised product from **6** leads, *via* an "*endo*" opening of the intermediate cyclopropyl methyl radical, to a seven membered ring **15**, with the final radical intermediate presumably stabilised by the silyl group.[10]

*Methylenecyclopropyl pentyl radicals*

Attempted cyclisation of bromides **4** and **7** gave reduced, uncyclised products only.

The high yielding cyclisations of methylenecyclopropyl propyl radicals **2** and **5** suggests that the sequence leading to methylene cyclohexanes is general for such systems. The cyclisation of the homologous methylenecyclopropyl butyl radicals, particularly **6**, provides access to medium sized rings although reduction, without cyclisation, is a problem. In order to increase the yield of cyclised product we are now looking at cyclisations using Curran's atom transfer chemistry.[11] Thus cyclisation of iodomalonate **16** using catalytic $Bu_3SnSnBu_3$ gives bicyclic **17** as a single isomer in >85 % isolated yield (Scheme 5).




**16** **SCHEME 5** **17.**

Further studies involving radical cyclisations of methylenecyclopropane systems and their use in tandem cyclisations will be reported in due course.

**Acknowledgements**

We thank Glaxo Group Research for supporting this work.

**References**

1. For leading references see: a) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, Academic Press, **1992**; b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem Rev*, **1991**, *91*, 1237; c) Curran, D. P. *Synthesis*, **1988**, 417 and 489; d) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, Oxford, **1986**.
2. See, for example, Leonard, W. R.; Livinghouse, T. *Tetrahedron Lett*, **1985**, *26*, 6431.
3. Destabel, C; Kilburn, J. D. *J Chem Soc, Chem Commun*, **1992**, 596-598
4. Sternberg, E.; and Binger, P. *Tetrahedron Lett*, **1985**, *26*, 301
5. Thomas, E. W. *Tetrahedron Lett.*, **1983**, *24*, 1467.
6. Compounds **8**, **9**, **10**, **12**, **13** and **15** have been unambiguously identified by independent synthesis and comparison of NMR data and GC retention times. Bicycles **11** and **14** have not been independently synthesised, but $^{13}C$ and $^{1}H$ NMR signals are consistent with the proposed structures and reported data for related bicyclic compounds. Full details will be reported in due course.
7. The presence of a silyl group within a radical forming ring can have a profound effect on the regioselectivity of ring closure: Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J Am Chem Soc*, **1988**, *110*, 281; Wilt, J. W. *Tetrahedron*, **1985**, *41*, 3979. A study of the effect of a silyl group *exo* to the ring as in the case of **6** does not appear to have been carried out.
8. For conformationally locked cyclopropyl methyl radicals, the kinetic ring opening is generally considered to be under stereoelectronic control. See Batey, R. A.; Grice, P.; Harling, J. D.; Motherwell, W. B.; Rzepa, H. S. *J Chem Soc, Chem Commun*, **1992**, 942 and references therein.
9. For examples of this phenomenon see Stork, G.; Mook Jr, R. *Tetrahedron Lett*, **1986**, *27*, 4529 and Beckwith, A. L. J.; O'Shea, D. M. *ibid*, **1986**, *27*, 4525.
10. Direct evidence for stabilisation of a radical by a silyl group has been reported: Miura, K; Oshima, K; Utimoto, K. *Tetrahedron Lett*, **1989**, *30*, 4413.
11. Curran, D. P., Chang, C.-T. *J Org Chem.*, **1989**, *54*, 3140.

(Received in UK 8 March 1993)