A Novel Sequence of Radical Rearrangements involving the 5-*Exo* Cyclisation of a 3-(Methylenecyclopropyl)propyl Radical

Christine Destabel and Jeremy D. Kilburn*

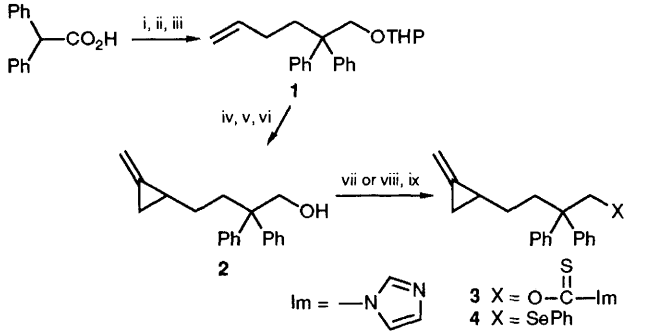
Department of Chemistry, University of Southampton, Highfield, Southampton SO9 5NH, UK

Radical **10**, generated from the corresponding imidazolethiocarbonyl derivative **3** or the phenyl selenide **4**, rearranges in a six-step process to give the cyclohexene **5**, after reduction; this rearrangement sequence includes the selective 5-*Exo* cyclisation of a (methylenecyclopropyl)propyl radical and opening of the intermediate cyclopropylmethyl radical to give a ring-expanded product.

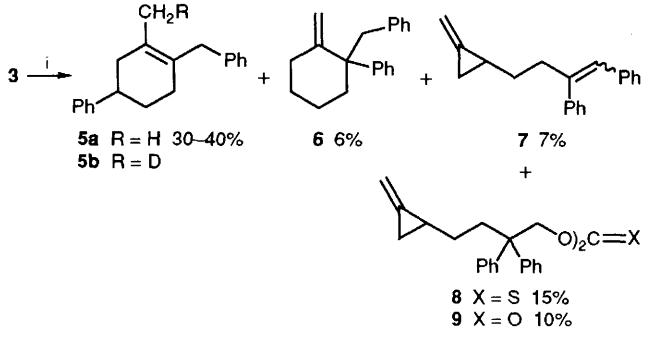
In an effort to develop new and efficient approaches to ring systems, using radical cyclisation methodology,[1] we decided to study cyclisations of methylenecyclopropylalkyl radicals. As part of our investigations into such radical systems we have come across a remarkable sequence of radical rearrangements in the conversion of **3** to give the cyclohexene **5**, which, along with other results, indicates that (methylenecyclopropyl)-propyl radicals, such as **11**, undergo almost exclusive *Exo*-cyclisation, and the intermediate cyclopropylmelthyl radicals, such as **12**, are converted cleanly *via* ring expansion into methylenecyclohexanes.

In our first efforts to prepare a radical precursor we chose to synthesise alcohol **2** according to Scheme 1.† Thus, diphenyl-acetic acid was converted to the protected alcohol **1** which was then reacted with chloromethylcarbene followed by a base-catalysed elimination, using methodology first outlined by Binger,[2] and used more recently by Motherwell.[3] Deprotec-

† THF = tetrahydrofuran; DHP = dihydropyran; *p*Ts = *p*-$MeC_6H_4SO_2$; DMSO = dimethyl sulfoxide; AIBN = azoisobutyronitrile; THP = tetrahydropyran-2-yl.



Scheme 1 *Reagents and conditions*:† i, a, BuLi (2.2 equiv.), THF, −15 °C, b, $BrCH_2CH_2CH{=}CH_2$; ii, $LiAlH_4$, Et_2O, 47% over two steps; iii, DHP, *p*TsOH, CH_2Cl_2, 77%; iv, $MeCHCl_2$, BuLi, Et_2O, −35 °C, 78%; v, KOBu^t, DMSO, 70 °C, 95%; vi, *p*TsOH, MeOH, 50 °C 85%; vii, $Im_2C{=}S$, THF, reflux, 95%; viii, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 93%; ix, PhSeSePh, Na, THF, reflux, 38%

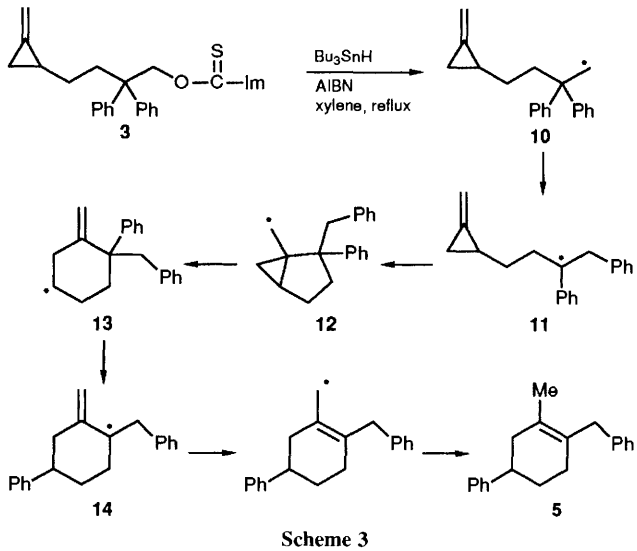


Scheme 2 *Reagents and conditions*:† i, Bu_3SnH and cat. AIBN (syringe pump addition), xylene, reflux

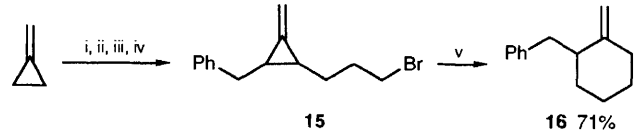
tion gave the alcohol **2**, which we were unable to convert into the corresponding bromide owing to competing phenyl migration, but it could be converted to the imidazolethiocarbonyl derivative **3** or to the phenyl selenide **4** *via* the mesylate (although this transformation was low-yielding, with large amounts of mesylate being recovered).

In order to encourage efficient generation of the primary carbon-centred radical **10**, from the imidazolethiocarbonyl derivative **3**, tributyltin hydride and a catalytic amount of AIBN were added *via* syringe pump, over 6 h, to a refluxing 0.014 mol dm^{-3} solution of **3** in xylene, according to Barton's reported procedure.[4] The reaction gave a mixture of largely unexpected products which were eventually identified‡ as the cyclohexene **5a** (40%), the methylenecyclohexane **6** (6%), the diene **7** (7%) and the two dimers **8** (15%) and **9** (10%). The diene **7** was presumably formed by a simple eliminative 1,2 phenyl migration and although the mechanism for the formation of the two dimeric compounds **8** and **9** is not entirely clear, we do not believe that it involves the intermediacy of the primary radical **10** which is obviously not formed very readily from **3**, even under such high-dilution and high-temperature conditions. However, it seems that when this radical is formed, it is converted with reasonable efficiency to the two products **5a** and **6**. This is further supported by the cyclisation of the phenyl selenide **4** with tributyltin hydride and a catalytic amount of AIBN (syringe pump addition) in refluxing toluene which gave **5a** (*ca.* 25%) and **6** (*ca.* 25%) along with recovered starting selenide **4** (33%).

‡ The structures of all compounds were confirmed by NMR (including ^1H–^{13}C correlation and COSY–NOESY experiments for **5** and **6**), IR and mass spectroscopy. The structure of the cyclohexene **5** was further confirmed by ozonolysis to give a more readily identifiable diketone, and an authentic sample of **6** was prepared from 2-benzylcyclohexanone (i, Et_3N, Me_3SiCl, CH_2Cl_2; ii, $Ph_2I^+F^-$, THF;[10] iii, $MePPh_3^+ I^-$, BuLi, THF).



Scheme 3



Scheme 4 *Reagents and conditions*:† i, a, BuLi, THF, −78 °C, b, $PhCH_2Br$, 44%; ii, a, BuLi, THF, −78 °C, b, $Br(CH_2)_3OTHP$; iii, *p*TsOH, MeOH, 45% over two steps; iv, CBr_4, Ph_3P, CH_2Cl_2, 76%; v, Bu_3SnH (0.016 mol dm^{-3}), cat. AIBN, toluene, reflux, 71%

In order to elucidate the mechanism of formation of **5a** and **6** we repeated the cyclisation of **3** using tributyltin deuteride, which gave the product **5b** in 17% yield, and identified for us the final radical intermediate in the reaction. We therefore believe that the formation of cyclohexene **5** occurs *via* the sequence of steps outlined in Scheme 3. Thus, the initially formed primary radical **10** first undergoes a 1,2 phenyl migration to give the more stable benzylic radical **11**. Such migrations are well established in the literature.[5] The radical **11** then cyclises in 5-*Exo* fashion to give an intermediate cyclopropylmethyl radical **12** which appears to open to give exclusively the methylenecyclohexyl radical **13**. The regioselectivity of the kinetically controlled opening of cyclopropanemethyl radicals has been investigated in some detail,[6] and the reaction is generally deemed to proceed *via* the stereoelectronically preferred conformer. However, we are unable to identify any clear stereoelectronic preference which would lead to exclusive '*Endo*' opening in our system, so it is probably that, under the high dilution conditions employed here, the opening is reversible and thus under thermodynamic control,[6] to give preferentially the six-membered ring. In any event, radical **13** is either reduced to give small quantities of the methylenecyclohexane **6**, or undergoes a transannular 1,4 phenyl shift, to give the tertiary allylic radical **14**. Such phenyl shifts across cyclohexane rings (*via* a boat transition state) are also well documented in the literature,[7] and are particularly favourable when a more stable radical results, the rate constant for such a process being estimated at *ca.* $1–5 \times 10^4\ s^{-1}$ at 150 °C. Finally, radical **14** is reduced, at the sterically more accessible allylic position, to give the major cyclohexene product. Although the 5-*Exo* closure–ring opening sequence, converting radical **11** to **13**, is unprecedented,[8] we were able to carry out a much less ambiguous cyclisation using bromide **15**, which was conveniently prepared by sequential deprotonation and alkylation of methylenecyclopropane,[9] as a 9 : 1 mixture of diastereoisomers (Scheme 4). Cyclisation of this bromide gave the methylenecyclohexane **16** in a very clean 71% yield, which is presumably formed by a sequence identical to that for the conversion of **11** to **13**.

The results indicate that the 5-*Exo* cyclisation and ring opening may be a general process, providing a novel route to methylenecyclohexanes. We are currently continuing our investigations to look at the possibility of synthesising larger rings, and at the use of the intermediate methylene cyclohexyl radicals in further cyclisations to give bicyclic products.

We thank W. B. Motherwell (Imperial College) and John Knight (Glaxo Group Research) for helpful discussions, Dr John Langley for the mass spectra, Ms Joan Street for the NMR spectra and Glaxo Group Research for supporting this work.

Received, 28th January 1992; Com. 2/00463A

References

1 For leading references on the use of radical reactions in organic synthesis see D. P. Curran, *Synthesis*, 1988, 417 and 489; B. Giese, *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon Press, Oxford, 1986.
2 S. Arora and P. Binger, *Synthesis*, 1974, 801.
3 S. A. Bapuji, W. B. Motherwell and M. Shipman, *Tetrahedron Lett.*, 1989, **30**, 7107; W. B. Motherwell, personal communication.
4 D. H. R. Barton, W. B. Motherwell and A. Stange, *Synthesis*, 1981, 743.
5 A. L. J. Beckwith and K. U. Ingold, in *Rearrangements in Ground and Excited States*, ed. P. de Mayo, Academic Press, New York, 1980, vol. 1, p. 170.
6 A. L. J. Beckwith and G. Moad, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1473 and references therein; M. Castaing, M. Pereyre, M. Ratier, P. M. Blum and A. G. Davies, *J. Chem. Soc., Perkin Trans. 2*, 1979, 287; P. M. Blum, A. G. Davies, M. Pereyre and M. Ratier, *J. Chem. Soc., Chem. Commun.*, 1976, 814; A. G. Davies, B. Muggleton, J.-Y. Godet, M. Pereyre and J.-C. Pommier, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1719.
7 See ref. 5, p. 175 and J. W. Wilt, R. A. Dabek and K. C. Welzel, *J. Org. Chem.*, 1972, **37**, 425.
8 The cyclisation of a β-methylenecyclopropylaminyl radical has been reported, and led exclusively to the 1-azabicyclo[4.1.0]heptane product *via Endo*-cyclisation: J.-L. Stein, L. Stella and J.-M. Surzur, *Tetrahedron Lett.*, 1980, **21**, 287.
9 For original work on the alkylation of methylenecyclopropane, see E. W. Thomas, *Tetrahedron Lett.*, 1983, **24**, 1467.
10 K. Chen and G. F. Koser, *J. Org. Chem.*, 1991, **56**, 5764.