

Cyclopropanes via an Efficient 3-Exo Trig Radical Cyclisation Reaction¹

Adusumilli Srikrishna,* G. Veera Raghava Sharma and Parthasarathy Hemamalini

Department of Organic Chemistry, Indian Institute of Science, Bangalore - 560 012, India

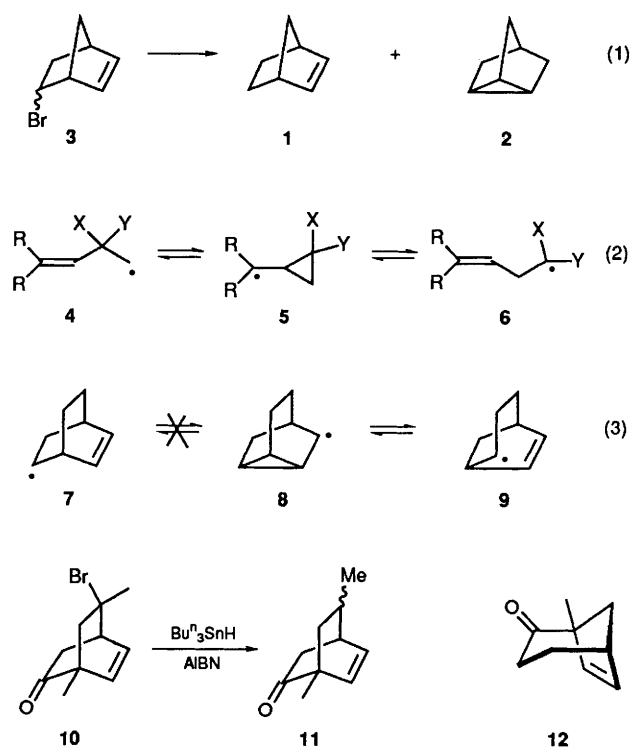
The first examples of an exclusive formation of a cyclopropane via the 3-*exo trig* radical cyclisation of homoallyl bromides **13** and **14** are reported.

The formation of a 1:1 mixture of norbornene **1** and nortricyclene **2** from norbornenyl bromide **3** (eqn. 1) is, perhaps, the only example of a homoallyl-cyclopropylmethyl radical rearrangement (via 3-*exo trig* cyclisation, eqn. 2),^{2,3} where a stable cyclopropane system was isolated in reasonable yields under standard radical cyclisation conditions.⁴ One reason extended for the isolation of **2** in this reaction is the large strain in norbornene itself.[†] However, the higher homologue, the bicyclo[2.2.2]octenyl system **7**, did not undergo cyclisation (eqn. 3).^{4b†} The presence of stabilising

groups, such as phenyl (eqn. 2, R = Ph) induced the cyclopropane formation, albeit in low yield ($\leq 10\%$).³ Indeed, radicals were conveniently used to cleave cyclopropanes to homoallyl systems.⁵ We now report the first examples of the ready formation of a cyclopropane, in the tricyclo[3.2.1.0^{2,7}]octane system **8**, starting from either a bicyclo[2.2.2]oct-5-en-2-yl radical **7** or a bicyclo[3.2.1]oct-6-en-2-yl radical **9** via 3-*exo trig* radical cyclisation.

In line with the earlier observation (eqn. 3)^{4b} radical reaction of the bromide **10**, obtained from (*S*)-carvone as depicted in Scheme 1, under standard radical cyclisation conditions [Bu^n_3SnH , AIBN (AIBN = azoisobutyronitrile), 0.02 mol dm^{-3} in benzene] resulted in only the reduced product **11** as a mixture of diastereoisomers. The absence of any detectable amount of **12** indicates the nonexistence of any equilibrium between the initial radical formed with a cyclised radical (e.g., eqn. 3). However, the presence of a stabilising group (e.g., aryl) on the alkene changed the situation.

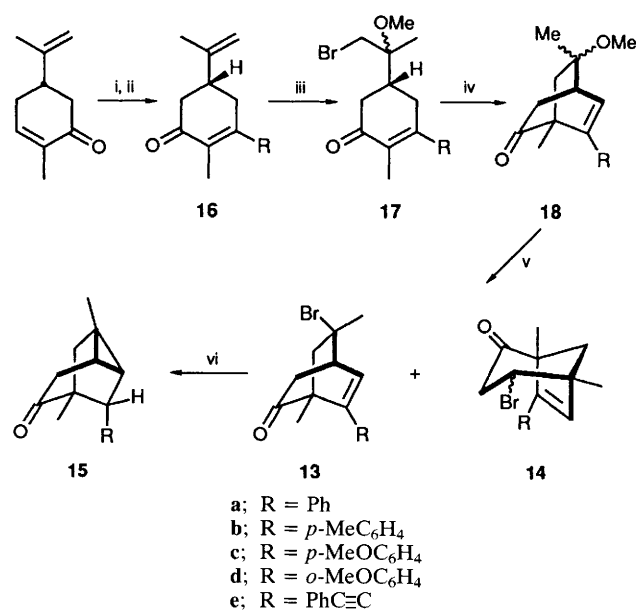
[†] According to molecular mechanics calculations, the strain energy (ΔSE) increase going from norbornene to nortricyclene is $21.43 \text{ kcal mol}^{-1}$ as against an increase of $26.93 \text{ kcal mol}^{-1}$ for the simple but-1-ene to cyclopropylmethane ($1 \text{ cal} = 4.184 \text{ J}$). The strain energy increase from bicyclo[2.2.2]octene ($\Delta\text{SE} 23.49 \text{ kcal mol}^{-1}$) and from bicyclo[3.2.1]octene ($\Delta\text{SE} 23.38 \text{ kcal mol}^{-1}$) to tricyclo[3.2.1.0^{2,7}]octane is intermediate between these values.



Refluxing a 0.02 mol dm⁻³ benzene solution of a 3 : 1 mixture of bromides **13a** and **14a** with Buⁿ₃SnH (1.1 equiv.) in the presence of a catalytic amount of AIBN furnished exclusively the cyclopropane product **15a**, in 85% yield, in a stereospecific manner (Scheme 1).[‡] The structure of **15a** was clearly delineated from its spectral data§ in particular the absence of alkenic protons and carbons (except the aromatic signals) in the ¹H and ¹³C NMR spectra, and further confirmed by comparison of the ¹H and ¹³C NMR data with those of unsubstituted compound.⁶ The cyclisation takes place so readily that even the presence of 20 equivalents of a radicalophile, e.g., methyl acrylate, in the medium was not able to trap the initial radical and stop the cyclopropane formation. The generality of this cyclisation was established by the preparation of **15a–e** and the results are summarized in Table 1. Interestingly not only aryl groups, but even an acetylene group (entry e) stabilise the radical enough to produce only **15e**.

[‡] The ¹H NMR spectrum of the crude reaction mixture (no alkenic signals) ruled out the presence of any trace amounts of uncyclised products. The ¹³C NMR spectrum of the compound **15a** clearly established the presence of only one stereoisomer and we assigned, tentatively, the phenyl group as *endo*, since the *endo*-isomer is slightly more stable than the *exo*-isomer.

§ Selected spectroscopic data: 1,5-Dimethyl-6-phenyltricyclo-[3.2.1.0^{2,7}]octan-4-one **15a**. The stereochemistry of the phenyl group is tentative. Low melting (below room temperature) solid, b.p. 180 °C (bath temperature), at 0.2 torr; [α]_D -140° (CHCl₃, c 1.1); IR (neat) ν/cm⁻¹ 3060, 1720, 760 and 710; ¹H NMR (270 MHz, CDCl₃): δ 7.25 (5H, br s, ArH), 3.45 (1H, d, J 2.5 Hz, 6-H), 2.68 (1H, dd, J 20.5, 2.2 Hz, 3a-H), 2.53 (1H, dd, J 20.5, 2.7 Hz, 3b-H), 1.93 and 1.99 (2H, ABq, J 12.9 Hz, 8-H), 1.48 (1H, dd, J 7.3, 2.9 Hz, 7-H), 1.35 (3H, s, 1-Me), 1.19 (1H, m, 2-H) and 1.11 (3H, s, 5-Me); ¹³C NMR (22.5 MHz, CDCl₃) δ 210.9 (s, C-4), 139.1, (s), 128.1 (2C, d), 127.5 (2C, d) and 126.8 (d) (aromatic), 55.9 (s, C-5), 53.7 (d, C-6), 43.2 (t, C-3), 34.8 (t, C-8), 26.7 (d, C-7), 20.2 (s, C-1), 19.5 (q, Me), 18.2 (d, C-2) and 17.3 (q, Me); Mass *m/z* 226 (100, M⁺), 198 (18), 184 (25), 183 (31), 169 (35), 157 (47), 129 (32), 115 (33), 107 (25), 96 (89), 91 (61) and 77 (27); M, 226.1362.



Scheme 1 Reagents and conditions: i, RMgBr, Et₂O, 0 °C to room temp., 6 h, or RLi, THF, -78 °C to room temp., 6 h; ii, PCC, silica gel, CH₂Cl₂, room temp., 8 h; iii, *N*-bromosuccinimide, CH₂Cl₂-MeOH (3:2), 0 °C to room temp., 16 h; iv, K⁺ -OBu^t, 1:1 Bu^tOH-THF (0.5 mol dm⁻³), 0 °C to room temp., 16 h; v, BBr₃, CH₂Cl₂, -60 °C, 1 h; vi, Buⁿ₃SnH, AIBN, C₆H₆ (0.02 mol dm⁻³), reflux, 2.5 h

Table 1 Yields of various compounds (%)^a

Entry	R	16 ^b	17 ^c	18 ^c	13 and 14 [¶]	15
a	Ph	75	60	76	78	85
b	<i>p</i> -tolyl	70	68	90	50	93
c	<i>p</i> -anisyl	55	87	70	45	85
d	<i>o</i> -anisyl	60 ^d	70	60	55	60
e	-C≡C-Ph	50	70	68	55	82

^a Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited satisfactory analytical and spectral data.
^b Overall yield from (*S*)-carvone. ^c 1 : 1 mixture of diastereoisomers.
^d The corresponding RLi was prepared *via* orthometallation of anisole in THF (tetrahydrofuran) and TMEDA (tetramethylethylene diamine).

The radical precursors **13** and **14** were obtained from (*S*)-carvone as depicted in Scheme 1. Alkylative 1,3-enone transposition⁷ of (*S*)-carvone, *i.e.*, 1,2 addition of RLi (or RMgBr) followed by oxidation [pyridinium chlorochromate (PCC)-silica gel] of the resulting allylic tertiary alcohol, furnished β-substituted carvones **16**. Transformation of **16** to the bicyclic compound **18** was achieved according to the recently developed⁸ procedure, *via* regioselective bromomethoxylation (to **17**) followed by an intramolecular alkylation (K⁺ -OBu^t-Bu^tOH-THF) reaction of the thermodynamic enolate. Treatment of **18** with BBr₃ generated an inseparable mixture[¶] of bromides **13** and **14**. The composition of this mixture varied with the nature of R. Structures of **13** and **14** were derived from their ¹H and ¹³C NMR spectroscopic

[¶] The composition of the bromides **13** and **14** varied from batch to batch. However, typical observations are as follows: when R = H, only **10** was formed; when R = Ph, a 3 : 1 mixture of **13a** and **14a**; when R = *p*-tolyl, *p*-anisyl or *o*-anisyl a 1 : 6 mixture of **13** and **14** (**14** as a mixture of diastereoisomers); and when R = -C≡C-Ph only **13e** were obtained.

data. Radical cyclisation of the bromide mixtures under standard conditions (except when R = H) furnished, exclusively, the cyclised products **15** irrespective of the composition of **13** and **14**. The yields of various intermediates along with the final radical cyclisations are listed in Table 1.

In conclusion, we have described the first examples of the formation of a cyclopropane product *via* an efficient homoallyl-cyclopropyl methyl radical cyclisation, potentially of synthetic value, which we are investigating.

Received, 7th August 1990; Com. 0/03649H

References

- 1 For Part 4 of the series, Chiral Synthons from Carvone, see A. Srikrishna and P. Hemamalini, *J. Org. Chem.*, 1990, **55**, 4883.
 - 2 M. Newcomb, A. G. Glenn and W. G. Williams, *J. Org. Chem.*, 1989, **54**, 2675 and references cited therein. See also, J. Masnovi, E. G. Samsel and R. M. Bullock, *J. Chem. Soc., Chem. Commun.*, 1989, 1044; J. M. Tanko and R. E. Drumright, *J. Am. Chem. Soc.*, 1990, **112**, 5362.
 - 3 V. W. Bowry, J. Luszyk and K. U. Ingold, *J. Chem. Soc., Chem. Commun.*, 1990, 923; T. A. Halgren, M. E. H. Howden; M. E. Medof and J. D. Roberts, *J. Am. Chem. Soc.*, 1967, **89**, 3051. See also, Z. Cekovic and R. Saicic, *Tetrahedron Lett.*, 1986, **27**, 5893. In all the reports where reasonable yields of cyclopropanes were reported, the corresponding radical was generated directly from the cyclopropyl compound and not *via* the cyclisation of the homoallyl radical, *e.g.*, see reference 2.
 - 4 (a) C. R. Warner, R. J. Strunk and H. G. Kuivila, *J. Org. Chem.*, 1966, **31**, 3381; (b) J. W. Wilt and A. A. Levin, *J. Org. Chem.*, 1962, **27**, 2319; (c) M. M. Martin and D. C. DeJongh, *J. Am. Chem. Soc.*, 1962, **84**, 3526; (d) T. A. Halgren, J. L. Firkins, T. A. Fujimoto, H. H. Suzukawa and J. D. Roberts, *Proc. Nat. Acad. Sci., USA*, 1971, **68**, 3216; (e) P. C. Wong and D. Griller, *J. Org. Chem.*, 1981, **46**, 2327.
 - 5 D. L. J. Clive and S. Daigneault, *J. Chem. Soc., Chem. Commun.*, 1989, 332.
 - 6 A. J. Ragauskas and J. B. Stothers, *Can. J. Chem.*, 1983, **61**, 2254.
 - 7 G. Büchi and B. Egger, *J. Org. Chem.*, 1971, **36**, 2021; A. Srikrishna and P. Hemamalini, *Indian J. Chem., Sect B.*, 1990, **29**, 152.
 - 8 A. Srikrishna and P. Hemamalini, *Indian J. Chem., Sect B.*, 1990, **29**, 201.
-