Two-carbon Ring Expansion through Free Cyclobutylcarbinyl Radical Fragmentation

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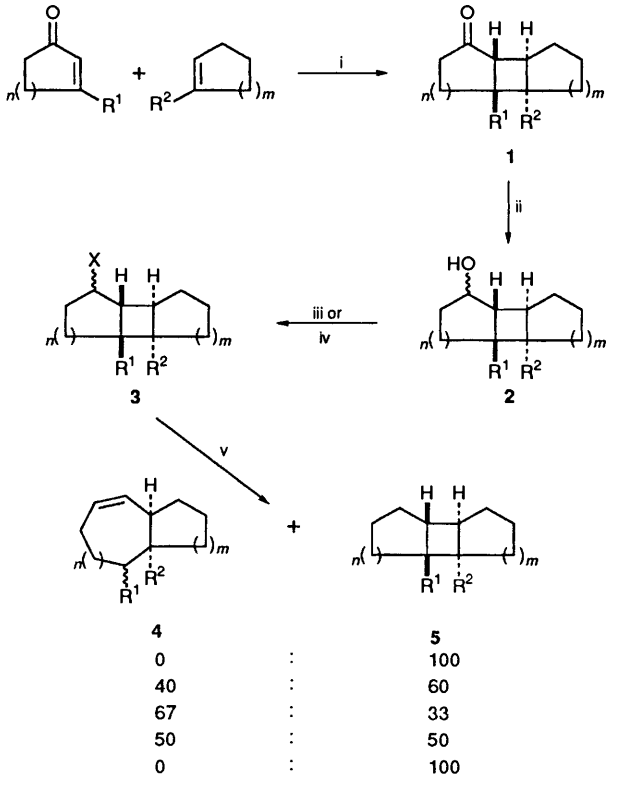
Fragmentation of cyclobutylcarbinyl radicals in suitably substituted cyclobutane derivatives leads to functionalised fused seven- and eight-membered ring systems by way of two-carbon ring expansion.

The importance of radical-based reactions in synthesis is increasingly recognized.[1] However, although the cyclobutylcarbinyl moiety has been variously employed for the construction of carbocyclic rings by way of ionic rearrangements[2] its use in free-radical processes has been little explored until recently.[3] Our interest in the use of the rearrangements of cyclobutane derivatives for the synthesis of natural product skeletons,[4] therefore, encouraged us to study the free-radical reactions of these potential substrates and here we disclose our preliminary results (Scheme 1).

The cyclobutyl derivatives **3a–e** were readily obtained from the corresponding cyclobutyl ketones **1a–e**, prepared by the [2 + 2] photocycloaddition of appropriate enones and olefins by reported procedures,[3b,5] through the sequence; reduction with zinc borohydride[6] and subsequent conversion into the iodide[7] or the xanthate[8] by standard methods. Treatment of the iodo compound **3a** with tributyltin hydride and AIBN (azoisobutyronitrile) in refluxing benzene produced exclusively the corresponding reduced product **5a**, the identity of which was confirmed by comparison with an authentic sample, prepared from the cyclobutyl ketone **1a** by Huang–Minlon reduction. Variations in the experimental conditions of the Bu_3SnH reaction failed to fragment the cyclobutane ring. However, the cyclobutane **3b** with a CO_2Me substituent on treatment with Bu_3SnH and AIBN furnished a mixture containing the olefin **4b** and the reduced product **5b** in a 2:3 ratio (^1H NMR). Clearly, compound **4b** arose by ring expansion of **3b** resulting from scission of the internal cyclobutane bond under free-radical condition. The olefinic product **4b** was separated, purified as its epoxide and then regenerated. The cyclobutane derivatives **3c** and **3d** also underwent fragmentation under free-radical condition to produce **4c** and **5c** (2:1) and **4d** and **5d** (1:1), respectively. Interestingly, however, the cyclobutane **3e** having two CO_2Me substituents failed to undergo scission in the Bu_3SnH/AIBN reaction, the sole product being **5e**, the reduced product.

In general, it seems that efficient fragmentation relies upon good orbital overlap between the radical, the cyclobutane C–C bond and an activating group, failure to achieve this then favouring reduction over fragmentation. As evident from the results, in **3b**, **3c** and **3d** modest overlap is achieved, whilst in **3a** and **3e** it is not, **3a** having no activating group and in **3e** a steric interference of the neighbouring CO_2Me group resisting such orbital overlap.

These results clearly indicate that cyclobutylcarbinyl radical fragmentation in suitably substituted cyclobutane derivatives can generate ring-expanded products, thus, providing a novel approach by two-carbon ring expansion to functionalised fused seven- and eight-membered ring systems.



a $n = 1$, $m = 1$, $R^1 = Me$, $R^2 = H$, X = I
b $n = 1$, $m = 1$, $R^1 = CO_2Me$, $R^2 = H$, X = I
c $n = 2$, $m = 1$, $R^1 = CO_2Me$, $R^2 = H$, X = OC(S)SMe
d $n = 2$, $m = 2$, $R^1 = CO_2Me$, $R^2 = H$, X = I
e $n = 2$, $m = 2$, $R^1 = CO_2Me$, $R^2 = CO_2Me$, X = OC(S)SMe

Scheme 1 *Reagents and conditions:* i, *hν*, CH_2Cl_2, 60–85%; ii, $Zn(BH_4)_2$, DME, room temp., 85-90%; iii, NaI, Me_3SiCl, MeCN, reflux, or Ph_3P, imidazole, I_2, room temp., 60–65%; iv, NaH, CS_2, MeI, THF, room temp. 80–85%; v, Bu_3SnH, AIBN, benzene, reflux, 75–84%

Experimental

Procedure for Free Radical Fragmentation of Cyclobutyl Derivatives: Representative Procedure with **3d**.—To a solution of the iodo compound **3d** (530 mg, 1.52 mmol) in dry benzene (20 cm^3) under nitrogen was added dropwise over 6 h a solution of tributyltin hydride (487 mg, 0.45 cm^3, 1.67 mmol) and AIBN (3 mg) in benzene (80 cm^3). The mixture was refluxed for a further 2 h. After removal of solvent from the reaction mixture under reduced pressure, the residue was chromatographed over silica gel to furnish a mixture (250 mg, 75%) of the olefin **4d** and the reduced product **5d** in a ratio of 1:1 (from ^1H NMR evidence). This mixture, being inseparable by the customary chromatographic techniques, was treated with *m*-chloroperbenzoic acid to convert the olefin into epoxide. Separation of the epoxide and the reduced product by preparative TLC was easy, the former then being converted back into the pure olefin **4d** (homogeneous by GC), a colourless oil; ν_{max}(neat)/

cm^{-1} 1730 and 1600; $\delta(CCl_4)$: 0.93–2.20 (m, 17H), 3.63 (s, 3H) and 5.63–5.80 (m, 2H).

This procedure was followed for the free-radical reactions of **3a**, **3b**, **3c** and **3e**. The products are fully characterised on the basis of spectral and analytical evidence.

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