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Formation of five- and six-membered heterocyclic rings under radical cyclisation conditions

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Contents

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Abbreviations: ACN, 1,1′-azobis(cyclohexanecarbonitrile); AIBN, azobis(isobutyronitrile); AMBN, azobis(methylisobutyronitrile); ATRA, atom transfer radical addition; ATRC, atom transfer radical cyclisation; CAN, ceric ammonium nitrate; CTAB, cetyltrimethylammonium bromide; CTAN, cerictetra-*n*-butylammonium nitrate; DBU, 1,8-diazabicyclo[5.4.0]undecene-7; DCE, 1,2-dichloroethane; DEPO, diethylphosphineoxide; DFT, density functional theorem; DLP, dilauroyl peroxide; DME, dimethoxyethane; DMF, dimethylformamide; EPHP, *N*-ethylpiperidine hypophosphite; FMO, frontier molecular orbital; HOMO, highest occupied molecular orbital; HMPA, hexamethylphosphoramide; LUMO, lowest unoccupied molecular orbital; MW, microwave; OTBS, *tert*-butyldimethylsilyloxy; PMB, *para*-methoxybenzyl; PMDTA, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylene triamine; PRC, polarity reversal catalysis; SET, single-electron transfer; SH^i, intramolecular homolytic substitution; SOMO, singly occupied molecular orbital; TBHP, tetra-butyl hydroperoxide; TBTH, tributyltin hydride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMEDA, *N*,*N*,*N*,*N*-tetramethyl-1,2-ethylenediamine; TMS, trimethylsilyl; TOCO, thiol-olefin co-oxygenation; $TTMSH/(TMS)_3SiH$, tris(trimethylsilyl)silane; VA-061, 2,2′-azobis[2-(2-imidazoline-2-yl)propane]; VOL(OEt), 2,4-di-*tert*-butyl-6({[(1*S*)-1-(hydroxymethyl)-3-(methylthio)propyl]imino}methyl)phenol.

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1. Introduction

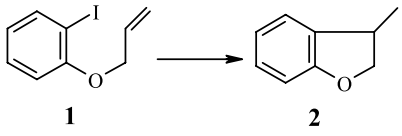
The chemistry of radical cyclisation has been at the forefront of research in a significant number of disciplines.[1] These results underscore the importance of developing new methods for the synthesis of various heterocycles and this may be done by constructing five- and six-membered rings, either in separate or in multistep processes. Rapid progress in free-radical reactions and their applications in organic synthesis have been achieved during the last three decades[2] and, due to this extraordinary development, carbon–carbon bond formation[1,3] is nowadays routinely considered in retrosynthetic analysis. Acyl radicals[4] take part in a large range of inter- and intramolecular reactions and, hence, they are useful synthetic intermediates.[5] Ryu and co-workers have shown that acyl radicals can also be generated by the reaction of alkyl radicals with carbon monoxide.[4,6,7] Primary, secondary, and tertiary radicals can be effectively carbonylated to transform them into carbonyl derivatives such as aldehydes,[8] ketones,[9] esters,[10] lactones,[11] thiolactones,[12] amides,[13] lactams,[14] and acyl selenides.[15] Some of these transformations are associated with atom or group transfer, inter- or intramolecular radical addition, cascade reactions, radical translocation, one-electron oxidation, or ionic chemistry. Intramolecular radical *ipso*-substitution has not received much attention in organic synthesis.[16] Alkyl radicals obtained by the treatment of thiocarbamates of conformationally favourable 3-alkyl-3-arylpropan-1-ols with tris(trimethylsilyl)silane and AIBN were found to undergo intramolecular *ipso*-substitution of the methoxy group, producing the corresponding cyclised products. On the other hand, either conformationally favourable or flexible 1-arylalkan-3- or 4-ones easily cyclised into five- or six-membered condensed rings by treatment with SmI_2 via ketyl radical intermediates.[17] Spirocycles can be effectively synthesised by a radical cyclisation procedure employing an intramolecular radical attack onto a cyclic olefin,[18] intramolecular addition of tertiary cyclic radicals to an alkene[19] or alkyne,[20] or cyclisation of a radical species containing a preoccupied quaternary carbon centre.[21]

Radical reaction is emerging as one of the leading methods in many industrial processes especially for producing a whole class of useful plastics or polymers such as polyethylene, teflon, polystyrene etc. Radical reactions are of vital importance in biology and medicine. The search for various heterocycles and many new methodologies has been a central goal for free-radical chemists in recent years. This review has the same goal as its predecessors to provide the most effective literatures in the particular area. The main aim of this review is to reflect upon, and to summarise, the main developments that have taken place in the application of free-radical chemistry to synthesise five- and six-membered heterocycles and to stimulate further studies in this continually evolving field. In order to keep the review to a reasonable length, coverage has been focused[22] only on five- and six-membered heterocyclic ring constructions and has largely excluded heterocyclic syntheses in which the heterocyclic ring(s) are not part of a radical cyclisation.

2. Reagents, solvents and radical initiators used in radical cyclisation

Tributyltin hydride has proved to be an excellent radical-generating reagent for the development of modern synthetic radical chemistry, but, due to its high toxicity[‡], it is not useful in pharmaceutical synthesis. Additionally, it is very difficult to remove the tributyltin residues from the reaction mixtures and this reagent is very unstable and decomposes steadily, even if carefully stored. Tributylgermanium hydride (Bu_3GeH)[23] is a superior alternative to Bu_3SnH, devoid of all these problems. The use of tris(trimethylsilyl)silane [$(TMS)_3SiH$ or TTMSH][23] and polymethylhydrosiloxanes[24] has been extensively developed. Triphenylgermanium hydride-mediated radical carbonylation/cyclisation reactions[25] are also very useful.

Bowman et al. reported[26] the cyclisation of 2-iodo-1-(prop-2-enyloxy)benzene **1** to give a similar yield of 3-methyl-2,3-dihydrobenzofuran **2** using Bu_3GeH and Bu_3SnH, respectively, but the reaction is slightly slower with Bu_3GeH (Scheme 1).



1 **2**

Reaction conditions	Yield of **2**
Bu_3SnH (1.2 equiv), ACN, PhMe, reflux, 2 h	86%
Bu_3GeH (1.2 equiv), ACN, PhMe, reflux, 3 h	91%

Scheme 1.

The radical cyclisation reactions of 1-iodo-**3a** and 1-bromo-2-[(3-phenylprop-2-enyl)oxy]benzene **3b** were also studied using Bu_3SnH and Bu_3GeH. The rate of bromine abstraction from bromobenzene by $Bu_3Ge^{\cdot}$ radicals at ambient temperature is relatively slow, but will be faster at higher temperature and the rate of abstraction of iodine (k_1) will be faster. Bowman et al. observed[26] that Bu_3SnH-mediated radical cyclisation of the radical precursors **3a** and **3b** gave the cyclised product **6** in good yield, whereas the yields with Bu_3GeH were extremely low. Various reaction conditions and initiators failed to improve the yield of the cyclised product **6**. The poor reactions with Bu_3GeH were due to the slow rate of H-abstraction (k_2) by the intermediate benzyl radical **5** (via **4**) from Bu_3GeH; the rate of H-abstraction from Bu_3GeH is too slow (20–30-fold slower than that with Bu_3SnH) to facilitate propagation and, hence, the chain reaction was inhibited. This is a drawback of Bu_3GeH, compared to Bu_3SnH. The yield of the cyclisation product **6** was increased to 75% by using the polarity reversal catalysis (PRC) technique developed by Roberts,[27] in which the nucleophilic benzylic radical intermediate **5** reacts relatively rapidly (k_3) with the electrophilic source of hydrogen (PhSH). This was the first example of the use of PRC with a triorganogermanium hydride (Scheme 2).

[‡] Tributyltin compounds can be handled safely on a small scale in the lab, provided that good lab practice is observed (see: Thomas, E. J., Science of Synthesis; Georg Thieme: Stuttgart, 2003; Vol. 5, pp 200–201).

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