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Radicals in organic synthesis. Part 1

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Abbreviations: (S,S)-BDPP, (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane; ABCVA, 4,4'-azobis(4-cyanovaleric acid); ACCN, 1,1'-azobis(cyclohexanecarbonitrile); AIBN, azobisisobutyronitrile; AMBN, azobismethylisobutyronitrile or 2-(1-cyano-1-methyl-propylazo)-2-methyl-butynitrile; ATRA, atom transfer radical addition; ATRC, atom transfer radical cyclisation; ATRP, atom transfer radical polymerisation; BDPP, 2,4-bis(diphenylphosphino)pentane; bipy, 2,2'-bipyridine; BPO, benzoyl peroxide; BTAC, benzyltriethylammonium chloride; CAN, cerium(IV) ammonium nitrate or ceric ammonium nitrate or diammonium cerium(IV) nitrate; Cat, catechol; COD, 1,5-cyclo-octadiene; Coll, collidine or 2,4,6-trimethylpyridine; CTAB, cetyltrimethylammonium bromide; DBPB, 2,2-bis(*tert*-butylperoxy)butane; DCP, dicumyl peroxide; DEPO, diethylphosphine oxide; dHbipy, 4,4'-di-*n*-heptyl-2,2'-dipyridyl; DLP, dilauroyl peroxide or lauroyl peroxide or dodecanoyl peroxide; DMA, *N,N*-dimethylacetamide; DMDO, dimethyl dioxirane; DMF, dimethylformamide; DMP, 1,4-dimethylpiperazine; DMSO, dimethylsulfoxide; DPPB, 1,4-bis(diphenylphosphino)butane; DPPE, 1,2-bis(diphenylphosphino)ethane; DPPP, 1,3-bis(diphenylphosphino)propane; DTBP, di-*tert*-butyl peroxide; EH, 2-ethylhexanoate; EPHP, 1-ethylpiperidinium hypophosphite; HMDS, hexamethyldisilazane or bis(trimethylsilyl)amine; HMPA, hexamethylphosphoramide; HWEE, Horner–Wadsworth–Emmons; IBX, 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide; MAP, 4-methoxyacetophenone; MOM, methoxymethyl; MW, microwave; NHPI, *N*-hydroxyphthalimide; PMB, *para*-methoxybenzyl; PMDETA, *N,N,N',N''*-pentamethyldiethylenetriamine; PMP, *para*-methoxyphenyl; PRC, polarity-reversal catalyst/catalysis; PRE, persistent-radical effect; PTOC-OME, *N*-methoxycarbonyloxypyridine-2-thione; quin, quinuclidine; SET, single electron transfer; SEM, 2-(trimethylsilyl)methoxymethyl; TAHP-1, hexadecanyltrimethylammonium hypophosphite; TBADT, tetrabutylammonium decatungstate; TBDPS, *tert*-butyldiphenylsilyl; TBHN, di-*tert*-butyl hyponitrite; TBHP, *tert*-butyl hydrogen peroxide; TBPP, *tert*-butyl peroxyphosphate; TBS, *tert*-butyldimethylsilyl; TBST, tri-*tert*-butoxysilanethiol; TBTH, tributyltin hydride; TEMPO, 2,2,6,6-tetramethylpiperidine-1-oxyl radical; Tf, trifluoromethanesulfonyl or triflyl; THP, tetrahydropyran; TMEDA, *N,N,N',N'*-tetramethylethylenediamine; TMS, trimethylsilyl; TPA, tripyridylamine; Tr, trityl; Ts, toluenesulfonyl or tosyl; TSE, 2-tosylethyl; TTMS, tris(trimethylsilyl)silane; xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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1. Introduction

From its humble origins as a mere ‘chemical curiosity,’ radical chemistry has developed into one of the most powerful tools for preparative organic synthesis. Initially considered too reactive to be of use in synthesis, to quote Chatgililoglu, ‘...most chemists have avoided radical reactions as messy, unpredictable, unpromising, and essentially mysterious,’¹ radicals now play a dominant role in the development of novel methodology and have found widespread use in the synthesis of complex natural products. In fact, far from being too reactive to give clean reactions, it is clear that radicals are frequently more selective and predictable than ionic reactions. Radical processes show numerous advantages over their ionic counterparts, including greater functional-group tolerance, the frequent use of pH-neutral conditions and a capability to be incorporated into elaborate reaction cascades that rapidly increase molecular complexity. Furthermore, radical chemistry is amenable to ‘green’ chemistry; there are many examples of radical reactions being performed in water and with a variety of cheap, environmentally benign reagents. Research into radical chemistry continues to blossom and, with the move away from tin-based methodologies, its future is well assured.

The aim of the following two articles is to highlight recent developments in the use of radical reagents and reactions in organic synthesis; as such, it is not intended to be an all-inclusive review. The review is loosely based on the material covered by the author’s contributions to *Annual Reports on the Progress of Chemistry: Section B*,^{2a–f} covering the literature from 2002 to 2007; key publications from 2008 have been included, but the year was not meticulously surveyed. The review concentrates on radical reactions that aid the synthetic chemist and can be performed in any standard organic research laboratory; discussion of both electro- and photochemistry, with the exception of simple UV-light initiation, is limited. Photochemical reactions that do not proceed by a chain process, i.e., the combination of biradicals, have not been included. Similarly, due to the intended practical bias, there is little discussion of fundamental research on the physical properties of radicals and their reactions, such as kinetic experiments. Regrettably, these restrictions mean that many elegant publications are not included; hopefully, the review will stimulate the reader to seek these papers out.

There have been a number of specialist reviews providing comprehensive coverage of various aspects of radical chemistry published over the last five years; topics covered include free-radical cascade processes,³ the synthesis of heterocycles by radical cyclisations,⁴ the synthesis of five- and six-membered heterocycles,^{5a,b} 5-*endo-trig* cyclisations,⁶ the formation of five-membered rings by

translocation–cyclisation,⁷ unusual radical cyclisations,⁸ radical reactions in aqueous media,⁹ the chemistry of ketyl radical anions formed by photoinduced electron transfer,¹⁰ the addition of radicals to C=N bonds,^{11,12} ‘clean’ radical reagents,¹³ phosphorus-based radical methodology,¹⁴ indium and indium reagents in organic synthesis,^{15a,b} dichloroindane as a versatile reducing agent,¹⁶ titanium-mediated radical reactions,^{17a,b} copper(I)-catalysed atom transfer radical cyclisations,¹⁸ atom transfer radical polymerisations (ATRP),^{19a,b} samarium(II) iodide in organic synthesis,^{20–22} samarium(II) iodide in asymmetric synthesis,²³ transition metal generated radicals,²⁴ cerium reagents in synthesis,²⁵ the persistent radical effect,^{26a,b} cyclohexa-1,4-diene-based radical reagents,²⁷ radical additions to aromatic systems,²⁸ diastereoselective radical reactions,^{29a,b} enantioselective radical reactions,^{30–32} stereoselective conjugate additions,^{33,34} radical carbonylations,³⁵ O-centred radicals in C–O bond formation,³⁶ inorganic radical reagents,³⁷ radical chemistry of organoboranes,^{38a,b} the addition of phosphorus compounds to unactivated hydrocarbons,³⁹ nitrogen-directed radical rearrangements,⁴⁰ thiol-mediated radical cyclisations,⁴¹ the chemistry of N-centred radicals,⁴² chirality control in photochemical reactions⁴³ and the carbometallation of unactivated alkenes by zinc enolate derivatives.⁴⁴ An issue of *Tetrahedron: Asymmetry* was dedicated to stereoselective radical reactions.⁴⁵ The nature of the current review means there will be overlap with some of these publications; in all cases, the interested reader is directed towards the specialist review for a more detailed insight.

It is impossible to organise such a substantial body of work to please every reader, or even the author; the original draft of this review was over 350 pages and considerable editing has led to its current structure. To emphasise the synthetic uses of radicals, the review has been divided into two sections; reagents and transformations. Due to the size of the topic, there is an uneven division of material over two issues of *Tetrahedron*, with reagents and intermolecular additions following this introduction whilst radical cyclisations and rearrangements are found in a forthcoming issue. The first section is not a comprehensive list of every radical initiator and hydride source available, but concentrates on new technologies that aid clean radical reactions. Examples of the utility of each reagent will be given in this section, but the majority of the chemistry will be contained in the subsequent sections. The ability of radicals to partake in cascade reactions and multi-component couplings results in potential overlap between the various sections; for example, a cyclisation could also involve a conjugate addition. Regrettably, this is unavoidable and the author has organised such reactions by the ‘key’ step. A lenient definition of the term ‘radical reaction’ has been employed and, thus, a number

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