Reactivity and Structure Concepts in Organic Chemistry

Volume 7

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Free Radicals in Organic Synthesis

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For Mary and Vivienne

Preface

Free Radical Chemistry has a comparatively long history. Before the acceptance of the quadrivalence of carbon, various attempts were made to prepare trivalent carbon species like methyl and ethyl. Initial investigations involving reaction between alkyl iodides and zinc were thought to be successful[1], but were subsequently branded as failures[2]. In fact free methyl and ethyl were transient radicals involved in the reactions, but because of their short lifetimes the radicals were not detected, and only the hydrocarbons formed by dimerisation of the radicals were isolated. At the beginning of the 20th century Gomberg discovered the stable triarylmethyl radicals[3], and then in the 1920's Paneth[4] showed that free alkyl radicals could have a short lifetime in the gas phase. Free radicals as intermediates in reactions in solution were largely unrecognised until in 1937 Hey and Waters[5] interpreted a number of reactions, which did not fit into the then developing electronic theory of Organic Chemistry[6,7], by suggesting that they involved the intermediacy of free radicals. The other contemporary pioneer Kharasch[8] also proposed free radicals as intermediates in certain reactions in solution, many involving organometallic species. However in the 1930–1950 period free radicals were not universally accepted as respectable reaction intermediates as evidenced by the initial rejection of the work of Koelsch[9] and the stand against free radicals made by Hodgson[10].

Since 1950 there has been an exponential rise in interest in the chemistry of free radicals, and it is now clear that free radicals are important reaction intermediates, which have been shown to be involved in an increasing number of reactions. This growth of knowledge has prompted the publication of a number

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1 Frankland, E.: Ann. *71*, 171, 213 (1849).
2 Watts, H.: A Dictionary of Chemistry, Vol. 6, p. 590. London: Longmans, Green. 1887.
3 Gomberg, M.: J. Am. Chem. Soc. *22*, 757 (1900); Gomberg, M.: Chem. Ber. *33*, 3150 (1900).
4 Paneth, F., Hofeditz, W.: Chem. Ber. *62*, 1335 (1929).
5 Hey, D. H., Waters, W. A.: Chem. Rev. *21*, 169 (1937).
6 Ingold, C. K.: Chem. Rev. *15*, 225 (1934).
7 Robinson, R.: Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions. London: Institute of Chemistry 1932.
8 Waters, W. A.: Vistas in Free-radical Chemistry. Oxford: Pergamon 1959; Intra-science Chemistry Reports *4*, 77 (1970) (M. S. Kharasch Commemorative Issue).
9 Koelsch, C. F.: J. Am. Chem. Soc. *79*, 4439 (1957).
10 Hodgson, H. H.: J. Chem. Soc. *1948*, 348.

of detailed texts on the subject. The early texts of Waters[11] and Walling[12] and the more recent one by Nonhebel and Walton[13] are notable, as is the two-volume work edited by Kochi[14] and the series edited by Williams[15] and by Huyser[16].

The present volume originates from an article[17] we wrote on "Free Radicals in Organic Synthesis" to publicise a symposium on "Synthetic Aspects of Free Radical Chemistry" organised by the CS Perkin Division and the Chilterns and Middlesex Section of the CS/RIC in November 1975. The article prompted Professor C. W. Rees to suggest that it should be expanded to make a small book, and this we have been happy to do. The book commences with a summary of the more important types of free radical reactions, and then successive chapters cover the various classes of compound that can be made by free radical reactions. In each Chapter we do not aim to be comprehensive, but rather to illustrate the synthetic value of particular reactions. A certain amount of duplication between chapters has been included for the convenience of readers. We have tried to provide references to comprehensive reviews and to pertinent papers so that the reader may readily obtain further information

11 Waters, W. A.: The Chemistry of Free Radicals. Oxford: Clarendon Press 1946.
12 Walling, C.: Free Radicals in Solution. New York: Wiley 1957.
13 Nonhebel, D. C., Walton, J. C.: Free-radical Chemistry. Cambridge: Cambridge University Press 1974.
14 Kochi, J. K. (ed.): Free Radicals Vol. 1 and 2. New York: Wiley 1973.
15 Williams, G. H. (ed.): Adv. Free Radical Chem. London: Logos 1965 onwards.
16 Huyser, E. S. (ed.): Methods in Free-radical Chem. New York: Dekker 1969 onwards.
17 Davies, D. I., Parrott, M. J.: Chem. in Britain *11*, 364 (1975).

relating to particular reactions in which he has interest. We hope the book is sufficiently short to enable the Chemist to study it in its entirety and gain thereby an appreciation of the value of free radical reactions in synthetic organic chemistry.

In the photograph Toby Davies is seen guarding his Gomberg bush, on which triarylmethyl radicals grow. For many years he has welcomed free radical chemists to his home, including the editor (Professor C. W. Rees) in 1964 before the Gomberg bush bore fruit. We hope that this book will also bear fruit and be of value to both synthetic and free radical chemists, acting as a spur to the further exploitation of free radical reactions in organic synthesis. We also hope that not only academic and industrial research workers but also postgraduate and advanced undergraduate students, who are interested in synthetic and/or free radical chemistry, will benefit from reading this book.

September, 1977

David I. Davies, London
Maxwell J. Parrott, Manchester

Contents

1. Free Radical Reactions

1.1 Introductory Survey

In recent years many different reactions have been found to involve the intermediacy of free radicals. Such reactions, although diverse in nature, do have a number of common features. In a first stage radicals are usually produced by the thermal or photochemical fission of a covalent bond, or in a redox reaction. Less usual is radical formation by molecule-molecule interaction. In a second stage radicals may combine or disproportionate to give products, substitute for an atom or group in a neutral molecule, add to multiple bonds, fragment or rearrange. When, in successive stages a radical reacts with a substrate to produce a new radical, and this new radical reacts with the original radical source to afford a product, so regenerating the original radical, a chain reaction is set up. This continues until the chain is terminated by radicals being removed from the system. As an alternative to reaction with a substrate, free radicals can also afford products in oxidative processes. Because of the diversity of reaction that a radical may undergo, a number of different products usually results from a reaction involving free radicals. Due to the increase in knowledge of radical reactions (Organic Reaction Mechanisms covering the year 1975 surveys 1,100 papers on radical reactions [1]), and of how they are affected by change in reaction conditions, certain reactions have been developed to give one readily isolated product. Such reactions can often be useful in affording products that are not readily available by other means.

This chapter serves as a brief introduction to free radical reactions. Further details may be obtained from basic texts [2, 3] and also from collections of reviews on the more detailed aspects of free radical chemistry [4, 5]. An early text on the synthetic value of free radical reactions was compiled by Sosnovsky [6], and an interesting review by Gill [7] is also available. Many examples are also given by Buehler and Pearson [8] in their survey of organic syntheses.

1.2 Formation of Radicals

The most familiar and well utilised sources of free radicals are peroxidic and azo compounds. Such compounds tend to readily undergo thermal and/or photolytic decomposition to afford free radicals. Among those in common use [3, 9] are di-*t*-butyl peroxide

$$RO{-}OR \rightarrow 2RO\cdot$$

$$R{-}N{=}N{-}R \rightarrow 2R\cdot + N_2$$

$Me_3CO{-}OCMe_3$, diacetyl peroxide $MeCO.O{-}O.COMe$, benzoyl peroxide $PhCO.O{-}O.COPh$, *t*-butyl peracetate $Me_3CO{-}O.COMe$, and azobisisobutyronitrile (ABIBN) $Me_2C(CN){-}N{=}N{-}C(CN)Me_2$ having half lives of 6.4 h at 130 °C, 8.1 h at 70 °C, 7.3 h at 70 °C, 12.5 h at 100 °C, and 4.8 h at 70 °C respectively. These compounds, and others such as chlorine, bromine, alkyl bromides and iodides, thiols, and sulfonyl halides also readily produce radicals on irradiation with ultraviolet light. High energy radiation [10] (X-rays, γ-rays, and electron beams) when absorbed by many compounds will also cause them to break down to afford free radicals. Thus a wide variety of free radical sources is available to initiate reactions in solution at ambient pressures, and temperatures in the 0–200 °C range.

A dialkyl peroxide such as di-*t*-butyl peroxide [11] affords two *t*-butoxyl radicals, which may fragment to give acetone and methyl radicals. Benzoyl peroxide decomposes

$$Me_3CO{-}OCMe_3 \rightarrow 2Me_3CO\cdot$$

$$Me_3CO\cdot \rightarrow MeCOMe + Me\cdot$$

with the formation of benzoyloxy radicals, which may subsequently decarboxylate to afford phenyl radicals. Peroxides can be used as sources of radicals to be incorporated in

$$PhCO.O{-}O.COPh \rightarrow 2PhCO.O\cdot$$

$$PhCO.O\cdot \rightarrow Ph\cdot + CO_2$$

a product as a result of reaction with a substrate e.g. the formation of a biaryl by reaction of phenyl radicals with an aromatic compound. Alternatively they are used in small quantity (< 1% compared with reactants) to provide a source of radicals to initiate a chain reaction e.g. a free radical addition to a multiple bond.

$$Rad\cdot \text{ (from peroxide)} + AB \rightarrow RadB + A\cdot$$

$$\left.\begin{array}{l} A\cdot + X{=}Y \rightarrow AXY\cdot \\ AXY\cdot + AB \rightarrow AXYB + A\cdot \end{array}\right\} \text{Chain Reaction}$$

Free radicals may also be produced in redox reactions as typified by the reaction of an alkyl hydroperoxide with a metal ion [12, 13]. Redox reactions can also occur with

$$ROOH + M^{n+} \rightarrow RO\cdot + OH^- + M^{(n+1)+}$$

symmetric peroxides [14], and with peresters [15]. As with the thermal and photochemical fission of peroxides and azo compounds to produce free radicals, redox reac-

tions can also be used to produce radicals either to be involved directly in the product or to initiate a chain reaction.

Occasionally molecule-induced homolysis appears to occur when radicals are formed at an anomalously rapid rate from the interaction of non-radical species. For example iodine and styrene interact at 25 °C to produce radicals at a rate 10^6 greater than can be explained either by homolysis of iodine or by thermal initiation by the styrene [16]. This interaction mechanism is second order in styrene and first order in iodine and a possible reaction leading to a resonance stabilised benzyl-type radical is as follows:

$$PhCH{=}CH_2 + I_2 \rightarrow 2Ph\dot{C}HCH_2I$$

1.3 Radical-Radical Reactions

One reaction that can occur when two radicals meet involves their combination to give a neutral molecule. An example is the dimerisation of ethyl radicals to give *n*-butane. Alternatively one radical may abstract an atom from another radical so that reaction between

$$C_2H_5\cdot + C_2H_5\cdot \rightarrow C_4H_{10}$$

the two radicals affords a saturated and an unsaturated molecule. Thus instead of two ethyl radicals combining to give butane, they may give one molecule each of ethane and ethylene. For radicals such as methyl and benzyl, which lack an abstractable atom β to

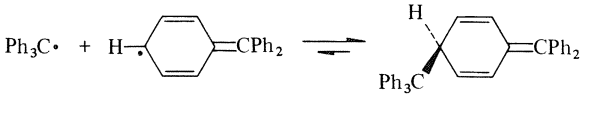
$$C_2H_5\cdot + C_2H_5\cdot \rightarrow C_2H_6 + C_2H_4$$

the radical centre, this type of disproportionation cannot occur.

Combination and disproportionation reactions are frequently observed in gas phase reactions where the chances of radicals colliding is relatively high. However, in solution, radicals are more likely to first encounter a solvent molecule as a substrate for reaction. Therefore to maximise product formation from radical radical reactions, relatively "inert" solvents are required. Resonance stabilisation and steric factors may affect the reactions of radicals. Thus diphenylmethyl radicals readily undergo "head to head" dimerisation

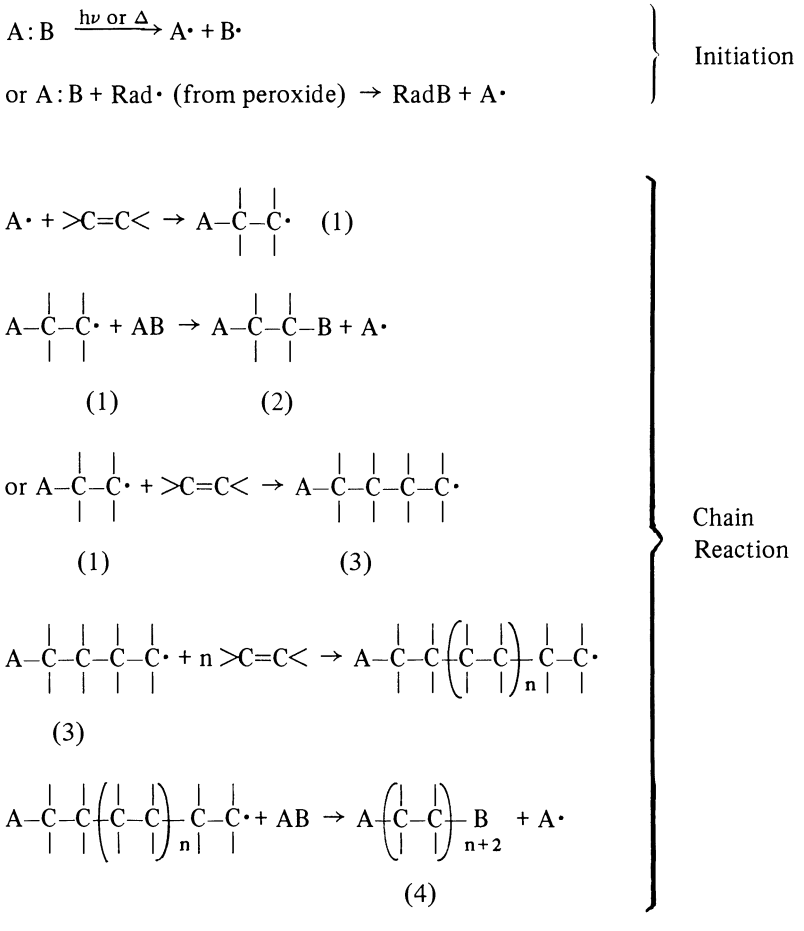
$$2Ph_2\dot{C}H \rightarrow Ph_2CHCHPh_2$$

whereas triphenylmethyl radicals undergo "head to tail" dimerisation in a reaction which is reversible at room temperature [17].



1.4 Addition Reactions

The addition of a compound AB to a double bond may be considered to involve the following steps:



The chain reaction is usually terminated by the combination or disproportionation of radicals.

If the olefin and AB are present in comparable quantities, and both the addition of A· to the olefin and the abstraction of B from AB by the intermediate radical (1) to afford the 1 : 1-adduct (2) are favourable, then (2) is produced in good yield. If (1) is a resonance stabilised radical then it may prefer to react with another molecule of olefin to give a similarly stabilised intermediate (3) so that ultimately telomer, or polymer (4) results. Formation of polymer is also favoured by a vast excess of olefin compared with AB. The free radical addition of carbon tetrachloride to styrene [18] leads to polymer since the benzyl-type radical (5) from addition of trichloromethyl radicals to styrene is

$$Cl_3C\cdot + PhCH{=}CH_2 \rightarrow Ph\dot{C}HCH_2CCl_3$$

(5)

$$Ph\dot{C}HCH_2CCl_3 + PhCH{=}CH_2 \rightarrow Ph\dot{C}HCH_2CH(Ph)CH_2CCl_3$$

(5) (6)

resonance stabilised, and hence prefers to react with another molecule of styrene. This gives the similarly resonance stabilised radical (6). The abstraction of chlorine from car-

$$Ph\dot{C}HCH_2CCl_3 + CCl_4 \rightarrow PhCHClCH_2CCl_3 + Cl_3C\cdot$$

(5) (7)

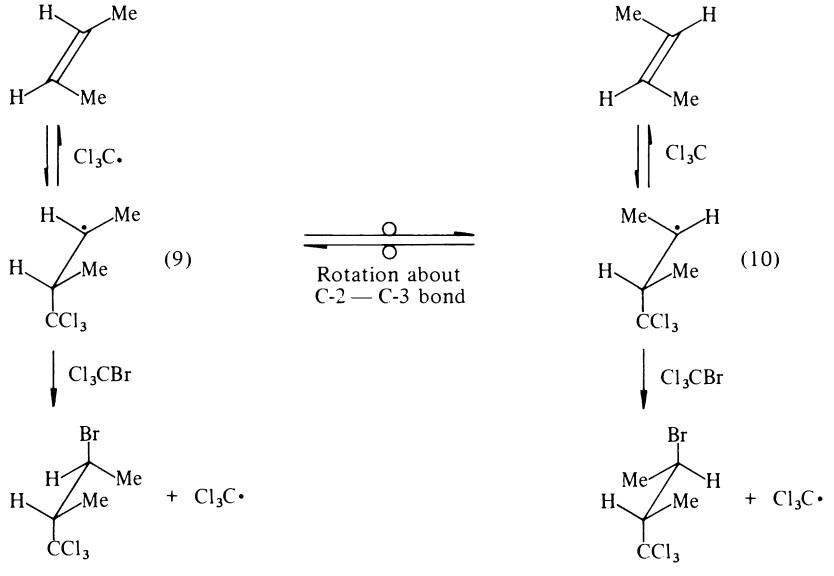
bon tetrachloride to afford the 1 : 1-adduct (7) and trichloromethyl radicals is energetically less favoured. In contrast, the addition of carbon tetrachloride to oct-1-ene [19] affords the 1 : 1-adduct (8) in 85% yield; the radicals in the two stages of the chain reaction being

$$CH_2{=}CH(CH_2)_5CH_3 + Cl_3C\cdot \rightarrow Cl_3CCH_2\dot{C}H(CH_2)_5CH_3$$

$$Cl_3CCH_2\dot{C}H(CH_2)_5CH_3 + CCl_4 \rightarrow Cl_3CCH_2CHCl(CH_2)_5CH_3 + Cl_3C\cdot$$

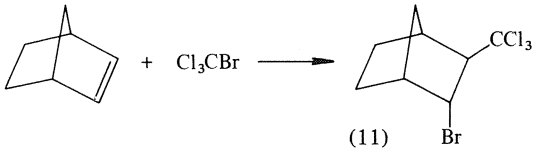
(8)

of comparable reactivity. Additions to carbon-carbon unsaturated systems have been extensively reviewed [4–7, 20–24]; in many cases useful yields of 1 : 1-adducts result. The reactions can however be complicated when the addition of a radical to the double bond is reversible as commonly occurs with alkanethiyl radicals, trichloromethyl radi-



cals, and bromine atoms. This reversibility may have the effect of causing geometric isomerism of the alkene [25]. For example in the photochemically induced addition of bromotrichloromethane to *cis*- and *trans*-but-2-ene [26] there is a lack of stereospecificity since radicals (9) and (10) formed by the initial addition of trichloromethyl radicals to the double bond system undergo rotational isomerism faster than chain transfer to afford products.

Steric factors can have a pronounced effect on the stereochemistry of free radical addition to a double bond. For cyclic olefins, in which bond rotation cannot occur in the intermediate radical, stereospecific addition may be approached. In the addition of bromotrichloromethane to norbornene in which electronic effects and torsional strain are important, in addition to steric factors, the *trans* adduct (11) is produced in yields of 95% [27].



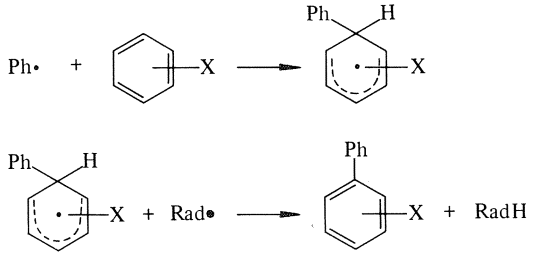
(11)

Intramolecular free radical additions can also occur with suitable disposition of double bond and radical centre. By far the most common example is found when a five-membered ring with an exocyclic radical centre can be formed.

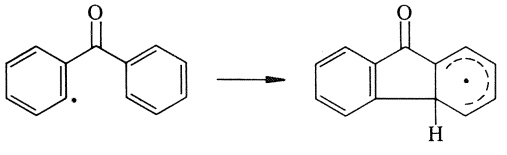
Formation of six-membered rings can also occur, especially where the addition reaction becomes reversible and thermodynamic control favours the six-membered ring [28].

1.5 Substitution

The most fully investigated reaction is that of homolytic aromatic substitution [29] in which a radical substitutes for an atom or group (usually hydrogen) attached to an aromatic ring as generalised below:



The reaction is considered to involve radical addition followed by radical abstraction, and certain examples are of synthetic importance. Intramolecular aromatic substitution may also be useful when the radical centre and aromatic system are conveniently juxtaposed as in the benzoylphenyl radical (12) [30].

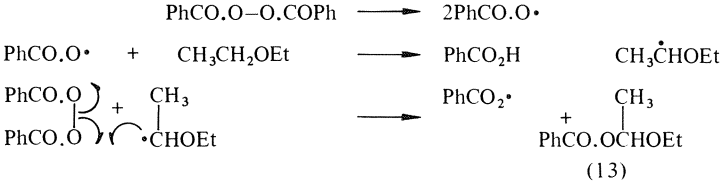


(12)

Bimolecular homolytic substitution S_H2 reactions (c.f. S_N2) occur when a radical

$$R\cdot + AB \rightarrow RA + B\cdot$$

attacks a fully saturated atom [31, 32]. Such a process is a pathway to the formation of 1-ethoxyethyl benzoate (13) 95% from the reaction between benzoyl peroxide and diethyl ether [33]. The combination of 1-ethoxyethyl radicals with benzoyloxy radicals



(13)

could, in principle, also lead to the formation of (13), but the relatively low concentration of benzoyloxy radicals compared with molecules of benzoyl peroxide makes product formation by this route unlikely. Such kinetic considerations need to be borne in mind when attempting to predict the outcome of a reaction, and an appreciation of radical rate processes is most useful [34, 35].

The product-forming propagation steps of chain reactions can often be considered as being substitution reactions. For example, in the photolytic bromination of toluene bromine atoms are initially formed. These atoms displace benzyl radicals from toluene

$$Br_2 \xrightarrow{h\nu} 2Br\cdot$$

$$PhCH_3 + Br\cdot \rightarrow Ph\dot{C}H_2 + HBr$$

$$Ph\dot{C}H_2 + Br_2 \rightarrow PhCH_2Br + Br\cdot$$

via an S_H2 at hydrogen to form one of the products, hydrogen bromide; a further S_H2 between benzyl radicals and bromine affords the product benzyl bromide. Although both the above stages are clearly substitution reactions, they are often referred to as abstraction reactions.

1.6 Fragmentation

$$ABC^{\cdot} \rightarrow AB + C^{\cdot} \text{ or } A^{\cdot} + BC^{\cdot}$$

Radicals can fragment to form a new radical and a neutral molecule. This process is also referred to as elimination [36]. Such a process is the key step in displacement reactions at colligatively unsaturated centres. Thus in the reaction of *n*-butanethiol with triethyl-

$$Et_3SnCH{=}CH_2 + BuS^{\cdot} \rightarrow Et_3SnC(SBu)\dot{C}H_2 \quad (14)$$

$$Et_3SnC(SBu)\dot{C}H_2 \rightarrow Et_3Sn^{\cdot} + CH(SBu){=}CH_2$$

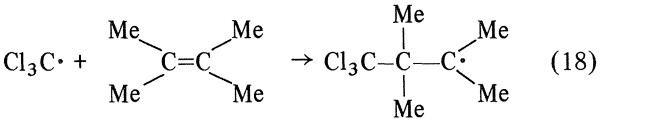
vinylstannane [37], the radical (14) fragments to afford triethylstannyl radicals and butyl vinyl sulphide. This fragmentation or elimination process involves homolysis of a covalent bond β to the radical centre, and is hence referred to as β-scission. β-Bromoalkyl radicals and β-alkanethiylalkyl radicals can also undergo β-scission. In the reaction of butanal with 1,1-dimethylprop-2-en-1-yl phenyl sulfide the radical (15) formed by addition of butyroyl radicals to the olefinic double bond undergoes β-scission to afford (16) rather than abstract hydrogen from butanal to give the 1 : 1-adduct (17) [38].

$$PhSC(Me)_2CH{=}CH_2 + Pr\dot{C}O \rightarrow PhSC(Me)_2\dot{C}HCH_2COPr \quad (15)$$

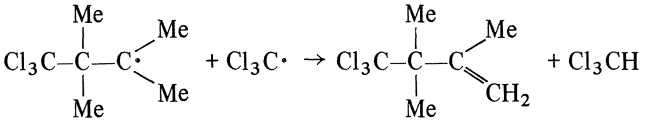
$$PhSC(Me_2)\dot{C}HCH_2COPr \rightarrow PhS^{\cdot} + Me_2C{=}CHCH_2COPr \quad (16)$$

$$\left[PrCHO + PhSC(Me_2)\dot{C}HCH_2COPr \rightarrow Pr\dot{C}O + PhSC(Me_2)CH_2CH_2COPr \quad (17) \right]$$

The loss of an atom β to a radical centre sometimes involves the intermediacy of another radical. For example the addition of trichloromethyl radicals to 2,3-dimethylbut-2-ene affords radical (18) [39]. Loss of the methyl hydrogen to the trichloromethyl radi-



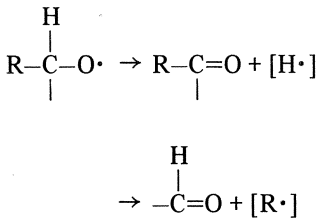
(18)



(19)

cal results in the formation of chloroform and the product of the apparent β-scission 4,4,4-trichloro-2,3,3-trimethylbut-1-ene (19).

β-Scission reactions can also involve the formation of carbonyl functions as well as of carbon-carbon double bonds. An alkoxyl radical can afford a carbonyl function by



fission of a bond β to the radical centre. This is illustrated by the thermolytic decomposition of *t*-amyl hypochlorite to afford acetone and ethyl chloride in a chain reaction [40]. The formation of a carbonyl group by β-scission of a carbon-oxygen bond is also common.

$$Me_2(Et)COCl \rightarrow Me_2(Et)CO\cdot + Cl\cdot$$

$$Me_2(Et)CO\cdot \rightarrow Me_2CO + Et\cdot$$

$$Et\cdot + Me_2(Et)COCl \rightarrow EtCl + Me_2(Et)CO\cdot$$

When an ether is heated with a peroxide the intermediate β-alkoxyl radical (20) undergoes β-scission.

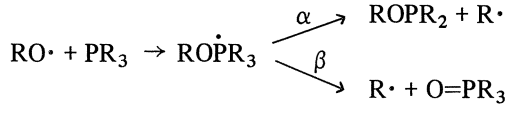
$$RCH_2OR' + Rad\cdot \text{ (from peroxide)} \rightarrow \dot{R}CHOR' + RadH$$

(20)

$$\dot{R}CHOR' \rightarrow RCHO + R'\cdot$$

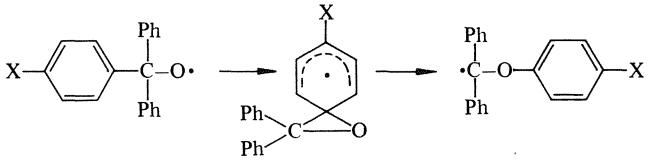
(20)

As well as β-scission processes a few radicals undergo α-scission processes. The autoxidation of trialkylphosphines yields both trialkylphosphine oxides and alkyl dialkylphosphinates [41]. Competitive α- and β-scission processes in an intermediate phosphoranyl radical account for these products.

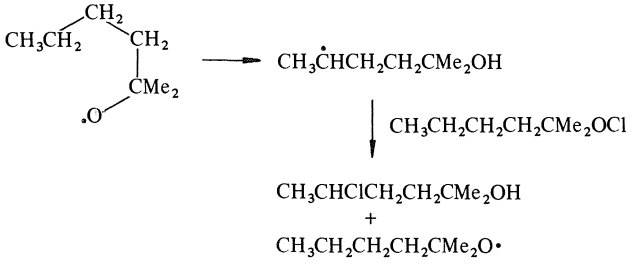


1.7 Rearrangement

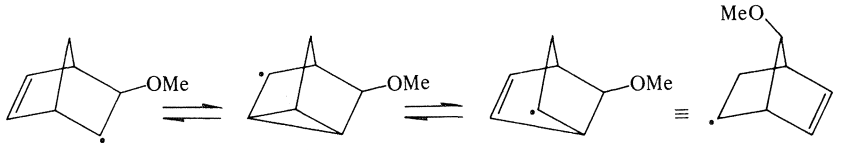
Several modes of rearrangement of radicals have been found [25, 36, 42], although many involve two step processes. Some β-substituents to radical centres do however appear to undergo 1,2-shifts. Such substituents have included chloro, phenyl and acetoxy functions. Aryl groups, particularly those having electron-withdrawing groups, have occasionally been shown to migrate e.g. [43].



Apparent shifts of hydrogen atoms are in reality intramolecular or even intermolecular hydrogen abstraction reactions. Intramolecular abstractions occur only over a suitable selective distance between the reacting centres [44] and hence when the juxtaposition of such centres is dictated by the stereochemistry of semi-rigid compounds, the reaction may be valuable. The Barton reaction [45] in its many variations well illustrates this phenomenon. The hydrogen abstraction usually proceeds *via* a six-membered cyclic transition state. Thus alkoxyl radicals generated from suitable hypochlorites afford δ-chloroalcohols [46], as well as carbonyl compounds derived from β-scission processes.



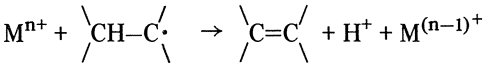
Allylic and homoallylic rearrangements of radicals probably all proceed *via* addition/elimination pathways. Homoallylic rearrangement is often observed in radicals derived from addition to norbornadienes. The importance of the two step process is illustrated by the interconversion of radicals (21–23) [47].



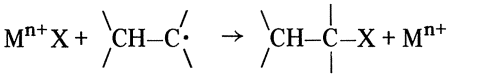
(21) (22) (23)

1.8 Oxidation

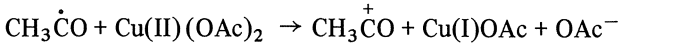
Certain transition metal ions oxidise radicals [12–15, 48]. For alkyl radicals there exist a variety of mechanistic pathways leading overall to oxidative elimination, or oxidative



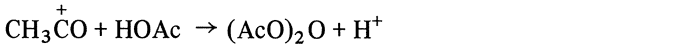
substitution.



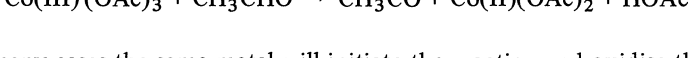
These reactions can, broadly speaking, proceed *via* carbonium ion formation or *via* synchronous processes. Generally the relative rates of oxidative elimination and substitution do not vary much with the metal [Pb(IV), Co(III), Mn(III), Ce(IV), Ag(II)] although with copper elimination is often favoured [47]. Radicals other than alkyls can of course be oxidised. For example acyl radicals are oxidised by Cu(II) acetate in the conversion of acetaldehyde to acetic anhydride using a mixture of Cu(II) and Co(III) acetates in acetic acid [49].



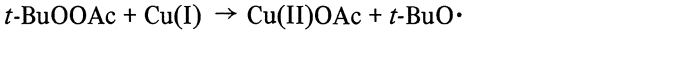
then

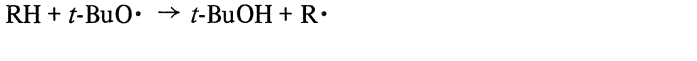


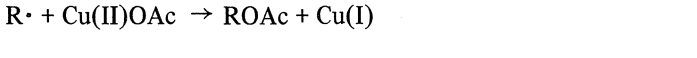
The reaction is initiated by Co(III) as follows:



In many cases the same metal will initiate the reaction and oxidise the radicals. For example the oxidation of an alkane RH by *t*-butyl peracetate and Cu(I) salts involves the following steps [50, 51]:







The potential of a metal to oxidise radicals and to initiate radical reactions can alter the course of a reaction. The photochemical addition of chloroform to alkenes is propagated by the reactions:

$$Cl_3C\cdot + CH_2{=}CHR \rightarrow Cl_3CCH_2\dot{C}HR$$

$$Cl_3CCH_2\dot{C}HR + Cl_3CH \rightarrow Cl_3CCH_2CH_2R + Cl_3C\cdot$$

and initiated by the reaction:

$$Cl_3CH + Rad\cdot \rightarrow Cl_3C\cdot + RadH$$

However in the presence of Fe(II) the initiation reaction is

$$Fe(II) + Cl_3CH \rightarrow Fe(III)Cl + Cl_2\dot{C}H$$

and the competing propagation reactions are [52]:

$$Cl_2CHCH_2\dot{C}HR + Fe(III)Cl \rightarrow Cl_2CHCH_2CHClR + Fe(II)$$

$$Cl_2CHCH_2\dot{C}HR + Cl_3CH \rightarrow Cl_2CHCH_2CH_2R + Cl_3C\cdot$$

Many organic compounds are subject to anodic oxidation in an electrochemical cell. In the case of hydrocarbons an initial electron transfer gives a cation radical, which may then transfer a second electron forming a dication.

$$RH \xrightarrow{-e} RH^{\ddagger} \xrightarrow{-e} RH^{++}$$

An alternative pathway is for the cation radical to transfer a proton to a suitable base in the system affording a radical which could lose an electron at the anode giving a monocation. The various species can lead to products by a variety of different pathways so

$$RH^{\ddagger} \xrightarrow{-H^+} R\cdot \xrightarrow{-e} R^+$$

that a number of different products will often be produced as a result of the electrochemical oxidation of an organic compound [53].

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2. Alkanes and Alkenes

In 1849 [1] Kolbe attempted to isolate the methyl radical *via* the electrolysis of an aqueous solution of potassium acetate. The hydrocarbon he obtained is now known to be ethane, but further investigations into the electrolysis of the alkali metal salts of aliphatic carboxylic acids have shown the reaction to have considerable utility for the synthesis of dimeric hydrocarbon products.

$$RCO_2^- \xrightarrow{-1e} RCO_2\cdot \rightarrow R\cdot + CO_2$$

$$2R\cdot \rightarrow R{-}R$$

The products obtained in these electrolysis reactions are very dependent on conditions, and the formation of dimeric hydrocarbon products is favoured by using platinum electrodes with methanol as solvent [2]. The reaction works particularly well for the synthesis of straight-chain hydrocarbons containing six or more carbon atoms (yields of the order of 75%) as is exemplified by the formation of *n*-triacontane from hexadecanoic acid [3].

$$CH_3(CH_2)_{14}CO_2H \rightarrow CH_3(CH_2)_{28}CH_3 \quad (88\%)$$

It has been observed that alkyl, aryl, alkoxyl, hydroxyl and halogen substituents α- to the carboxyl group promote carbonium ion reactions and hence lead to a reduction in the yield of the radical coupling product. The utility and scope of the electrolysis of metal salts of carboxylic acids in the synthesis of hydrocarbons, together with tabulated summaries of reactions, is given in a recent review [4] and in texts on electrochemistry [5]. The presence of double bonds in the aliphatic carboxylic acid may allow intramolecular radical cyclisation to compete with radical dimerisation. The electrolysis of β, γ-unsaturated acids gives rise to allyl radicals, which can dimerise in several different ways resulting in product mixtures [6].

Radicals R· may also be derived from carboxylic acids RCO_2H on oxidation with lead tetraacetate. By using a solvent SH which can easily donate a hydrogen atom to the radical, alkanes may result. The reaction competes with the oxidation of radicals to carbonium ions. Alkanes (70–80% based on the carboxylic acid) have been obtained from

$$Pb(IV)(OAc)_4 + RCO_2H \rightarrow Pb(IV)(OAc)_3O_2CR + AcOH$$

$$(AcO)_3Pb(IV)O_2CR \xrightarrow{\text{heat or uv}} (AcO)_3Pb(III) + R\cdot + CO_2$$

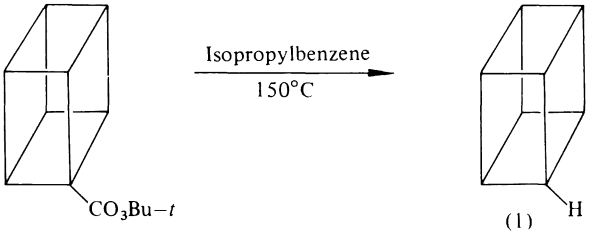
$$R\cdot \xrightarrow{Pb(IV)} [R^+] + Pb(III)$$

$$R\cdot \xrightarrow{Pb(III)} [R^+] + Pb(II)$$

$$R\cdot \xrightarrow{SH} RH + S\cdot$$

the photochemical decarboxylation of primary carboxylic acids with lead tetraacetate in chloroform at room temperature [7]. With secondary carboxylic acids the yields are lower (50–60%). However this may well be considered a convenient procedure, in the absence of electrolysis equipment, for converting primary and secondary carboxylic acids into alkanes in a single step. The main problem is that the alkane is formed together with varying amounts of alkene and acetate, and that most reactions investigated to date are of only marginal preparative value [8]. Product ratios are very solvent dependent although conditions have been developed under which good yields of cyclohexene and cyclobutene are obtained from cyclohexane carboxylic acid and cyclobutane carboxylic acid. The decarboxylation of acids with copper in quinoline can also be useful [9].

The thermal decomposition of *t*-butyl peroxyesters also gives rise to radicals, which can afford hydrocarbons by abstraction of hydrogen from solvent. Peroxyesters have been successfully utilised to remove carboxyl functions in the final step of the synthesis of cubane (1) [10], and norlongicyclene [11].



(1)

A two stage reaction procedure is available for the conversion of carboxylic acids to hydrocarbons. It involves an initial conversion of the acid to the bromide *via* the Cristol Firth reaction (discussed in chapter 4) followed by the reduction of the bromide to the hydrocarbon with tri-*n*-butyltin hydride. Application of this method to the decarboxylation of bridged acids has afforded hydrocarbons in overall yields of 80–90% [12]. The

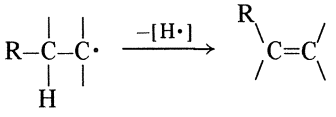
$$RCO_2H \xrightarrow{Br_2/HgO} RBr \xrightarrow{Bu_3SnH} RH$$

decarbonylation of aldehydes to afford hydrocarbons on heating with di-*t*-butyl peroxide at 130 °C has some merit. The yield is dependent on the structure of the alkyl group, and

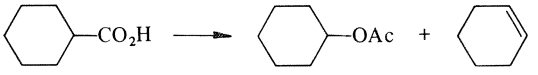
ketones and esters may also be formed. In addition rearrangements of the intermediate free radical have also been observed [13].

e.g. $PhCH_2CH(Me)CHO \rightarrow PhCH_2CH_2Me$ (98%)

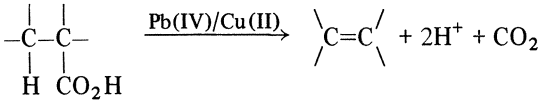
An alternative reaction to the abstraction of a hydrogen atom by an alkyl radical to give an alkane is for the radical to lose a hydrogen atom to afford an alkene. Alkenes are



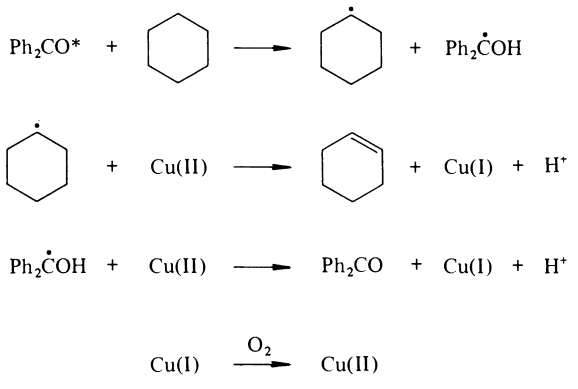
therefore possible products from the oxidation of carboxylic acids. The lead tetraacetate oxidation of cyclohexanecarboxylic acid in benzene affords cyclohexyl acetate (13%) and cyclohexene (4.7%). In dimethylformamide as solvent, cyclohexene is the major



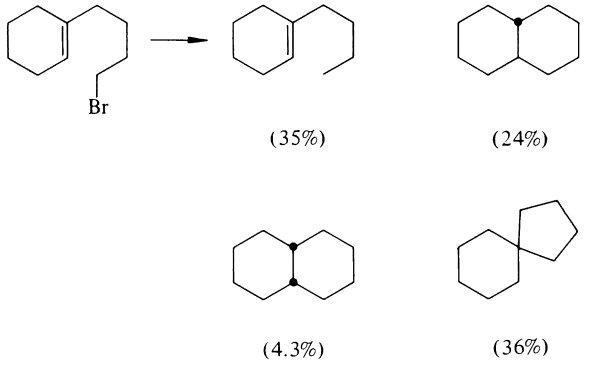
product [14]. Electron transfer oxidation of alkyl radicals by Cu(II) is much more facile than oxidation by Pb(IV) [15]. Cu(II) alone does not usually affect decarboxylation under mild conditions, but the combination of $Pb(IV)(OAc)_4$ and $Cu(II)(OAc)_2$ is effective for the smooth conversion of carboxylic acids to alkenes [16]. Primary car-



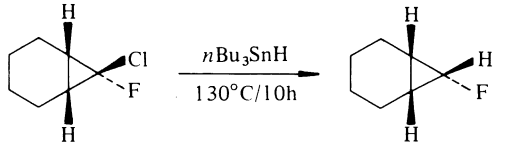
boxylic acids give exclusively terminal alkenes e.g. oct-1-ene (87%) and no oct-2-ene is produced from nonanoic acid. For unsymmetrical secondary alkyl radicals derived from secondary carboxylic acids, oxidative elimination can occur in more than one direction. The procedure has been used to afford cyclobutene (78%) from cyclobutane carboxylic acid. Δ^{22}-24-Norcholene has been successfully produced from cholanic acid [17]. A very recent procedure for converting cyclohexane to cyclohexene is to photolyse benzophenone and Cu(II) pivalate in cyclohexane until the blue colour is discharged. By reoxidising Cu(I) to Cu(II) with air the procedure can be repeated up to ten times with up to 100% conversion of cyclohexane to cyclohexene based on copper consumed [18]. The reaction is catalytic in benzophenone and Cu(II), and may be applicable for the synthesis of other unsaturated hydrocarbons.



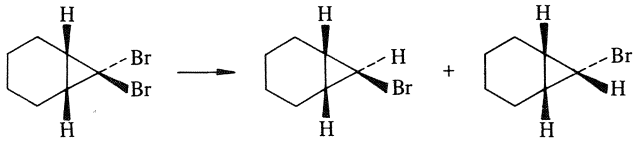
Alkyl halides may be reduced to alkanes on reaction with trialkyltin hydrides [19]. For example tri-*n*-butyltin hydride will reduce 1-bromooctane to octane (80%) during one hour [20]. The reaction gives good yields with primary and secondary halides and also with benzylic halides. Alkenyl [21] and alkynyl [22] halides afford radicals, which can give rise to rearrangement or intramolecular reaction resulting in mixtures of products, e.g. [21].



Simple carbon radicals produced in these reactions tend to lose their stereochemical identity, but this does not appear to be the case with the α-fluorocyclopropyl radical in the norcarane series, where configuration is completely retained on the time scale for the reductions [23].



The adducts of dihalocarbenes to olefins afford geminal dihalocyclopropanes. There is usually some selectivity, dependent upon steric factors in the hydrogen transfer reaction, in the reduction to monohalides [24].



(23.5%) (58.5%)

A simplified procedure for the reduction of alkyl halides to alkanes utilises lithium aluminium hydride plus about 10 mole % of tin halide as reducing agent. This has the advantage of obviating the necessity of preparing a trialkyltin hydride [25].

The reduction of esters, particularly benzoates, with tri-*n*-butyltin hydride can also afford hydrocarbons. The reaction is much slower than with the halide, but may have some potential in the synthesis of benzylic-type hydrocarbons [26]. Toluene (75%) for example was obtained from benzyl benzoate.

$$ROCOR^2 + (R^1)_3SnH \rightarrow RH + (R^1)_3SnOCOR^2$$

Brown [27] has devised procedures for the production of dimeric hydrocarbons by the air-induced coupling of benzylic and allylic iodides using triethylborane. An excess

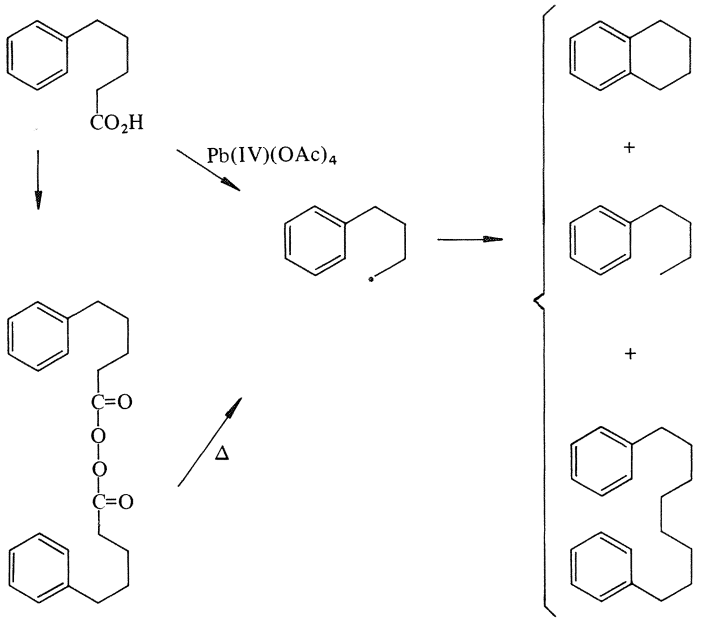
$$R_3B + O_2 \rightarrow R_2BO_2\cdot + R\cdot$$

$$R\cdot + R'I \rightarrow RI + R'\cdot$$

$$2R'\cdot \rightarrow R'-R'$$

(100%) of the organoborane is used to prevent addition of oxygen to the radicals derived from the iodide. Biallyl (97%) for example could be obtained from allyl bromide. An approximately statistical distribution of products resulted from using mixed allylic and benzylic iodides. If it is necessary to couple an expensive iodide with a less expensive iodide, an excess of the less expensive iodide may be used to increase the conversion of the more valuable material. By this method 4-phenylbut-1-ene could be obtained using allyl iodide in four-fold excess. The coupling of allylic and benzylic halides can also be carried out using $TiCl_3$ or $TiCl_4/LiAlH_4$ in what is said to be an efficient preparative procedure involving a radical mechanism [28].

4-Arylbut-1-yl radicals are produced by the thermal decomposition of the diacyl peroxide derived from 4-arylpentanoic acid [29] or by lead tetraacetate oxidation of 4-arylpentanoic acid [30]. Cyclisation of the 4-phenylbut-1-yl radicals can occur to give tetralin with varying degrees of success, but from the synthetic standpoint the reaction is complicated by the concomitant formation of 1-phenylbutane and/or 1,8-diphenyloctane. The electrolysis of 4-phenylpentanoic acid is similarly unsatisfactory from the synthetic standpoint [31].

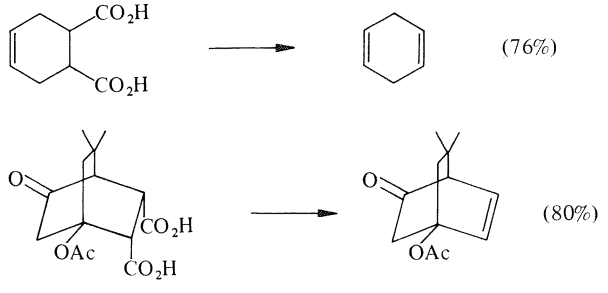


Vicinal dibromides formed by the addition of bromine to ethylene, propene, isobutene, *trans*-stilbene, and *cis*- and *trans*-but-2-ene undergo dehalogenation, on treatment with tri-*n*-butyltin hydride, to give alkenes in accordance with the following equation.

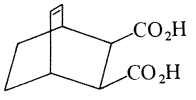
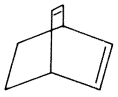
$$\mathrm{Br{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}Br} + 2\ n\mathrm{Bu_3SnH} \rightarrow 2\ n\mathrm{Bu_3SnBr} + \mathrm{H_2} + \mathrm{>C{=}C<}$$

The reaction is particularly useful in regenerating an olefinic double bond that has been protected by the addition of bromine. Styrene (99%) was obtained from 1,2-dibromoethylbenzene. In the reaction of (±)- and *meso*-2,3-dibromobutanes, but-2-enes were obtained in a reaction in which *anti*-elimination predominated [32]. The stereospecificity increases with increased organotin hydride concentration and with decreasing temperature. The isomeric 2,3-dichlorobutanes tend to afford butane as the major product.

The formation of alkenes from 1,2-dicarboxylic acids *via* oxidation with lead tetraacetate leads to low and variable yields [33, 34]. However the bisdecarboxylation of certain bicycloalkane dicarboxylic acids with lead tetraacetate utilizing an oxygen atmosphere has sometimes been accomplished with moderate success [35]. Diacids are smoothly

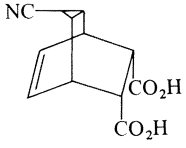
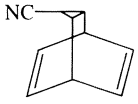


decarboxylated upon electrolysis to give consistently higher yields of alkenes than are formed on lead tetraacetate oxidation. More importantly the reactions are much less adversely affected by the presence of a proximate double bond in the starting material [36]. Yields are usually in the range 24–63%, e.g.

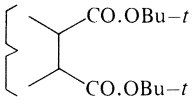
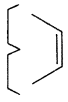



(48%) [36]
(40%) [37]

In the following more complex system the yield was 48% [37].

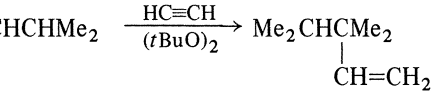
An alternative to the oxidation of 1,2-dicarboxylic acids is to treat the corresponding diacyl chlorides with *t*-butyl hydroperoxide affording the di-*t*-butyl peresters, which are then decomposed either thermally or photochemically to provide the alkene [38]. For

+ CO_2

example cyclohexene (38%) and norbornene (34%) were obtained from the corresponding 1,2-dicarboxylic acids.

Alk-1-enes (~8%) are produced when secondary alkanes or cycloalkanes add to ethyne in a free radical reaction initiated by di-*t*-butyl peroxide and carried out at 100–200 p.s.i. in a high pressure autoclave at 140 °C [39].



e.g. $Me_2CHCHMe_2 \xrightarrow[(tBuO)_2]{HC\equiv CH} Me_2CHCMe_2$ (with $CH=CH_2$ on the second carbon)

Cyclohexane affords vinylcyclohexane. In a similar way α-substituted allyl alcohols, amines, esters and ketones may be produced when the appropriate substrate is added to ethyne.

$$RCH_2X + HC\equiv CH \rightarrow RCHXCH=CH_2$$

R = OH, OR, NR_2, CO_2R, COR

2-Bromoalkenes are best prepared via the addition of hydrogen bromide to 1-trialkylsilylalkynes. The reaction probably proceeds *via* two addition steps followed by an elimination [40].

$$RC{\equiv}CSiMe_3 + HBr \rightarrow RCBr{=}CHSiMe_3$$

$$RCBr{=}CHSiMe_3 + HBr \rightarrow RCBr_2CH_2SiMe_3$$

$$RCBr_2CH_2SiMe_3 \rightarrow RCBr{=}CH_2 + Me_3SiBr$$

A valuable method of forming alkenes involves the reductive coupling of carbonyl compounds using low valency titanium species [41, 42]. The reaction is envisaged as occuring *via* initial electron transfer to form ketyl radicals which dimerise. Further reduction affords products in yields of 40–95%.

$$R^1R^2CO \xrightarrow[\text{or } Ti(III)Cl_3/K/THF]{Ti(III)Cl_3/LiAlH_4} R^1R^2\dot{C}O^-$$

$$2\,R^1R^2\dot{C}O^- \rightarrow R^1R^2\overset{\overline{O}}{C}\!-\!\overset{\overline{O}}{C}R^1R^2 \rightarrow R^1R^2C{=}CR^1R^2$$

Assymetric alkenes may be formed by coupling two different ketones, if one of the ketones can be used in excess and its self coupling product is volatile and easily removed [43]. Mixed coupling between diaryl ketones and dialkyl ketones also affords only one major product, possibly because either the dianion or the radical anion formed from the diaryl ketone undergoes addition to the dialkyl ketone.

The reaction has been extended to afford cycloalkenes of ring size 4–16 in yields of 50–95% by using dicarbonyl compounds; both ketones and aldehydes are useful starting materials [44].

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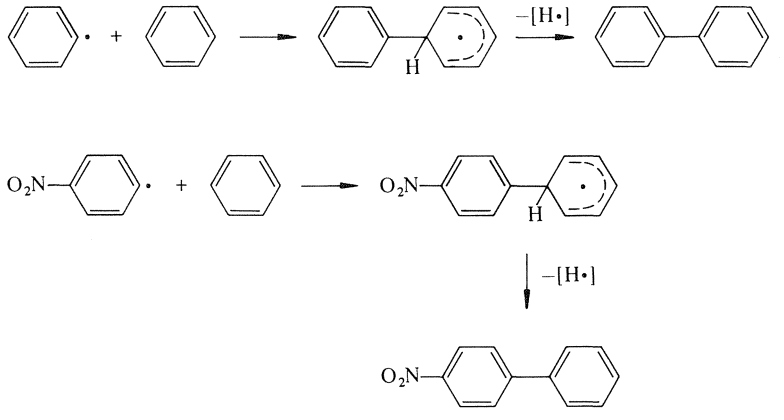
3. Aromatic, Heteroaromatic, and Fluoroaromatic Compounds

A variety of aromatic compounds have been prepared by various procedures in which an aryl radical substitutes in another aromatic nucleus. Usually a mixture of positional isomers results, the separation of which is often difficult. The field of study is known as homolytic aromatic substitution, and several comprehensive reviews on the subject are available [1–7]. For this reason the chapter will concentrate on the general features of the reactions that have proved to be of synthetic value.

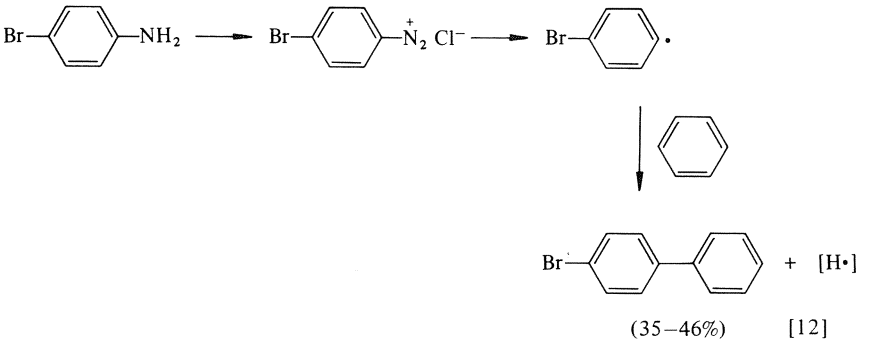
A phenyl radical can afford biphenyl *via* substitution in benzene, and similarly a substituted phenyl radical can give rise to a substituted biphenyl. If a phenyl radical reacts



with a monosubstituted benzene as solvent, a mixture of *o*-, *m*-, and *p*-substituted biphenyls results. The synthetic value of such schemes is dependent on the ease of separation of the individual isomers. The *ortho*-isomer usually predominates in the product mixture, but the early workers in the field found that in many reactions the *para*-isomer was sufficiently insoluble for it to be crystallised from the reaction mixture in a pure form, albeit in low yield (5%), so that in the 1930's this was a useful procedure by which *p*-substituted biphenyls could be prepared [1, 8].

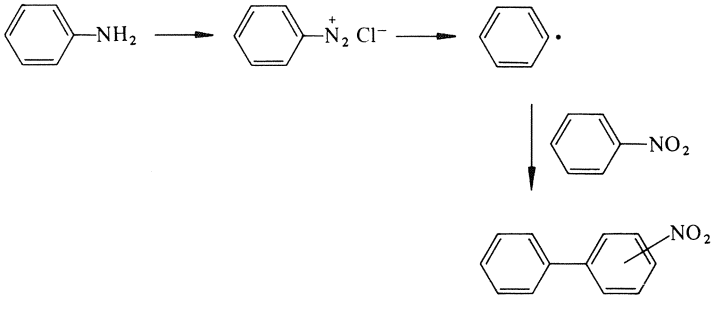
The synthetic value of homolytic aromatic substitution reactions in the synthesis of aromatic compounds depends on the source of aryl or phenyl radicals employed, the ease of the experimental procedures, and the yield of the substitution step.

In the Gomberg reaction [2, 3, 9, 10] an aqueous solution of a diazonium salt is vigorously stirred with an aromatic solvent and sodium hydroxide or sodium acetate [11] is slowly added. The reaction leads to a very tarry product, and the biaryl can best be isolated by steam distillation in yields which are usually in the region of 10–20%.



(35–46%) [12]

From the synthetic standpoint the Gomberg reaction is quite useful for making monosubstituted biphenyls by the substitution of monosubstituted phenyl radicals in benzene as illustrated in the reaction above. In the following example phenyl radicals substitute in nitrobenzene to form a mixture of *ortho, meta,* and *para* nitrobiphenyls.



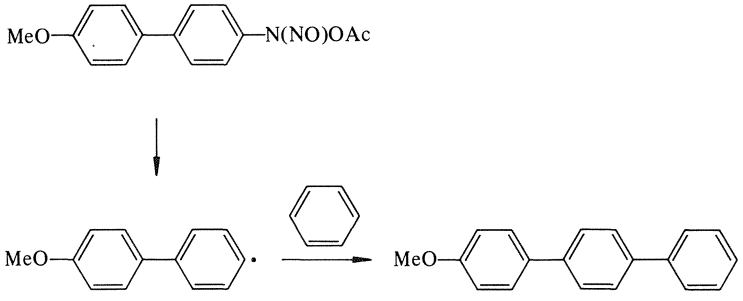
ortho : *meta* : *para*
60 : 10 : 30

[13, 14]

It is synthetically useful since *p*-nitrobiphenyl can be readily crystallised from the reaction mixture in a relatively pure form. In related reactions it has occasionally been possible for the three isomers to be isolated. For example in the phenylation of pyridine, 2-, 3-, and 4-phenylpyridine have all been isolated *via* fractional crystallisation of the picrates [15], and the 2-, 3-, and 4-methyl-*p*-terphenyls from the reaction between 4-nitrosoacetamidobiphenyl and toluene isolated by fractional crystallisation of the product mixture [16]. A useful tabular summary of preparative arylation reactions in the earlier literature, and the isomers obtained, has been drawn up by Augood and Williams [2]. Many of these reactions were carried out before the widespread availability

of column, plate, and gas-liquid chromatography as means for the separation of isomers, and compounds were isolated by fractional distillation or crystallisation. For the arylation of a solid aromatic compound Grieve and Hey [8] used chloroform or carbon tetrachloride as solvent. Although these solvents also react with aryl radicals the by-products so formed could be readily separated from the required biaryls.

In a useful alternative to the Gomberg reaction Cadogan [17] employed the diazonium fluoroborate with copper powder in a moist acetone solution of the aromatic compound as a means of generating aryl radicals to react with the aromatic compound. Some of the disadvantages of the Gomberg reaction were overcome by Hey [18, 19] who used the *N*-nitrosoderivatives of aromatic amines, which are soluble in aromatic solvents and decompose thermally at about 50 °C to afford aryl radicals. The details of the reaction mechanism have only recently been clarified [20]. The yield of biaryl formed is often in the region of 50%, e.g.

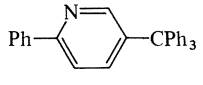


(58%) [21]

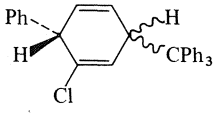
Preparatively useful examples of these reactions have been tabulated [2, 9].

1-Aryl-3,3-dialkyltriazenes ArN=NNR$_2$ [22] also afford aryl radicals, which can substitute in an aromatic solvent leading to biaryl formation. The reaction is conventionally carried out in acid solution; hydrogen chloride gas being passed into a solution of the triazene in the aromatic solvent and yields of biaryls of the order of 40% may be obtained.

Phenylazotriphenylmethane PhN=NCPh$_3$[23, 24] is a useful source of phenyl radicals on account of its ease of handling and preparation. The ratio of product monosubstituted biphenyls formed from reaction with a monosubstituted aromatic solvent is, however, sometimes changed due to intervention by triphenylmethyl radicals. For example (1) and (2) result from the *ortho* isomers produced in the phenylation of pyridine [25] and chlorobenzene [26] respectively. Phenylhydrazine [27] has been used as a reagent for the production of phenyl radicals *via* oxidation with silver oxide, but the reaction does not appear to have any synthetic advantage.



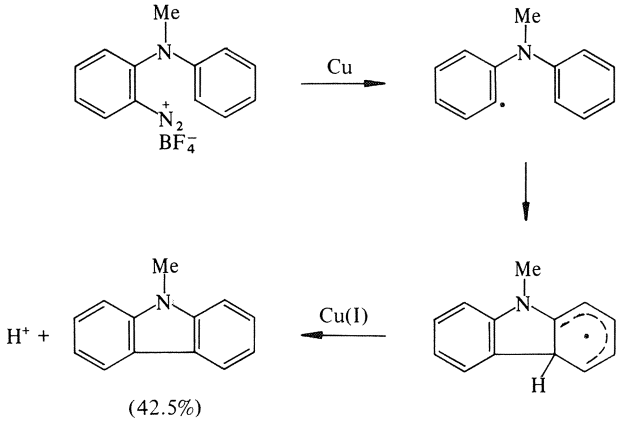
(1)



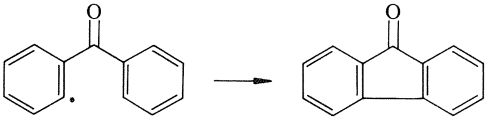
(2)

Benzoyl peroxide is an excellent source of phenyl radicals when it is allowed to decompose at 80 °C in an aromatic solvent. Its reactions to afford biaryls (yields up to 50%) in this procedure have been extensively reviewed [1–7]. The biaryls can be readily separated from benzoic acid and benzoate esters, and any synthetic problem would usually be concerned with the separation of the biaryl isomeric mixture. At 80 °C biphenyl (0.32 mole) results from the decomposition of benzoyl peroxide (1 mole) in dilute benzene solution. Certain additives, of which nitrosobenzene is possibly one of the more effective, produce an increase in the yield of biphenyl to (0.86 mole) [28–30]. In reactions between benzoyl peroxide and monosubstituted aromatics to afford biaryls the addition of molecular oxygen has often doubled the yield of biaryl, sometimes up to one mole per mole of peroxide, without affecting the isomer ratio [31]. Transition metal salts have proved to be similarly useful in improving the yield [32].

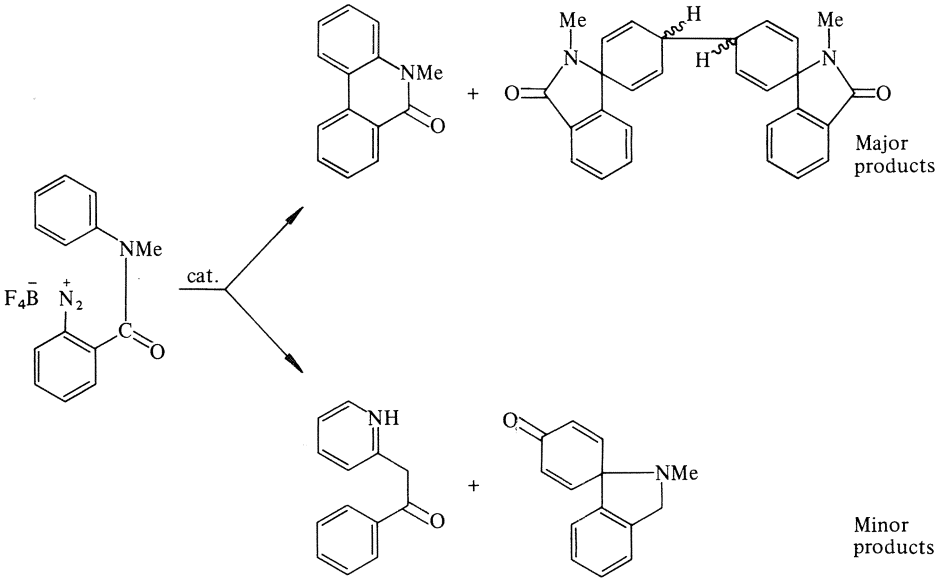
Intramolecular free radical aromatic substitution [33] is a synthetically useful reaction. A suspension of a suitable dry diazonium salt, of which the tetrafluoroborate is particularly favoured, treated in acetone solvent with copper powder, evolves nitrogen and affords the cyclised product in yields which are usually in the region of 20–50%. A typical example [34] is set out below:



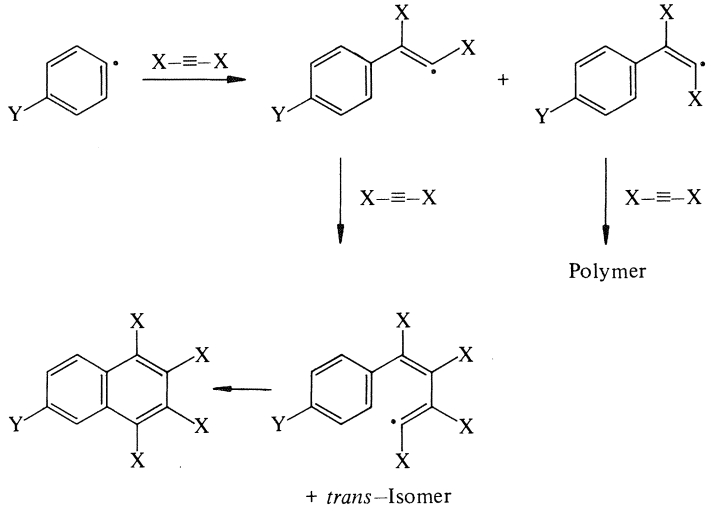
The *o*-benzoylphenyl radical has been prepared by a variety of routes and on cyclisation affords fluorenone in good yield [35–39]. Phenanthridines and related compounds



may also be prepared by routes involving intramolecular internuclear homolytic cyclisation [40], but the reactions, as illustrated by the example below [41], are often complicated by the formation of mixtures of products.

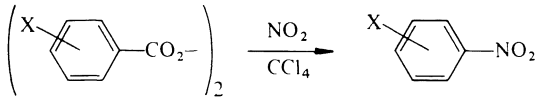


Aromatic annelation reactions are rare, but in the following example, due to Cadogan [42], aryl radicals generated in the presence of dimethyl acetylenedicarboxylate gave the corresponding 1,2,3,4-tetramethoxycarbonylnaphthalenes (50%).



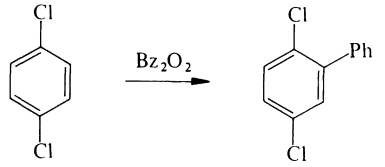
X = CO_2Me; Y = H, Br, or Me

Nitrogen dioxide NO_2 is a fairly stable free radical and the decomposition of aroyl peroxides in its presence results in its combination with the derived aryl radicals giving nitro compounds [43, 44]. This method is useful for preparing compounds not readily

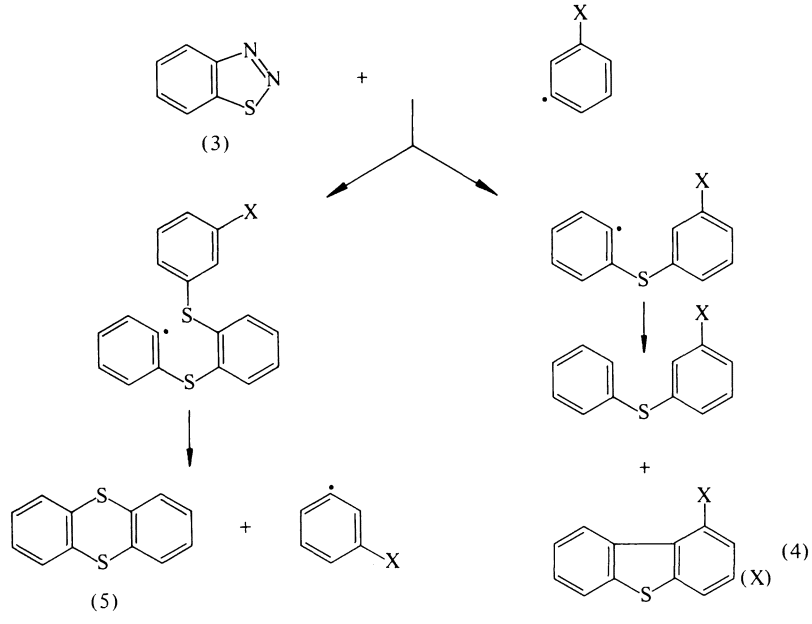


available from substitution reactions involving the nitronium ion NO_2^+ and related species. For example *p*-nitrobenzoyl peroxide affords *p*-dinitrobenzene (34%) when allowed to decompose in the presence of NO_2 gas [44].

The reaction of *p*-disubstituted benzenes with benzoyl peroxide affords 2,5-disubstituted biphenyls. The reaction can be useful when both substituents are the same; otherwise the problem of mixture separation occurs [45].



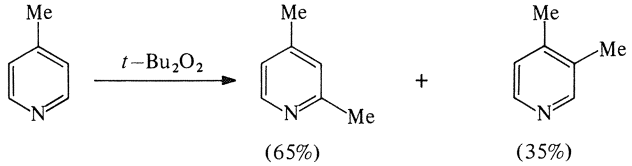
The arylation of heterocyclic compounds has been reviewed by Norman and Radda [46], and by Bass and Nababsing [47]. The Gomberg reaction, [12, 48–50] the thermal decomposition of *N*-nitrosoacetanilides [50–51] and of diaroyl peroxides [50] have all been used to achieve successful syntheses of 2-arylthiophenes by the substitution of the derived aryl radicals in thiophen. Most sources of phenyl radicals afford 2- and 3-phenylthiophen in an ~10:1 ratio; with phenylazotriphenylmethane there is a smaller proportion of the 2-isomer [52]. The arylation of 2- and 3-substituted thiophenes [53, 54], and of condensed thiophenes has been the subject of detailed study, but due to the formation of mixtures



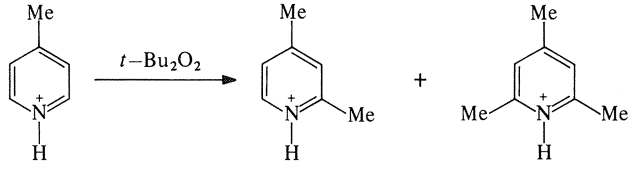
of isomeric products the reactions are of reduced synthetic significance. The whole field of free radical substitution in thiophenes has been reviewed by Tiecco and Tundo [55].

With furan, arylation is very specific and affords 2-arylfurans (35%) as the sole arylation products [56]. The arylation of pyridine affords mixtures of the three arylpyridines [15, 57, 58]. This subject and the arylation of other nitrogen heterocycles has been discussed by Norman and Radda [46]. The phenylation of isothiazole gives mixtures of 3-, 4-, and 5-phenylisothiazole with the 3- and 5-isomers predominating [59]. Phenylation of thiazole gives a 47 : 11.5 : 41.5 mixture of the 2-, 4-, and 5-phenylthiazoles; however the reaction is more specific with the conjugate acid of thiazole when the ratio of the phenylthiazoles becomes 83 : 4 : 13 [60]. The phenylation of benzo[b]thiophen and benzo[b]furan gives mixtures [61]. In the case of 1,2,3-benzothiadiazole (3), radical attack occurs at the sulfur atom. Among the important products are two isomeric dibenzothiophenes (4) and thianthrene (5) as shown in the scheme at the foot of page 29 [62].

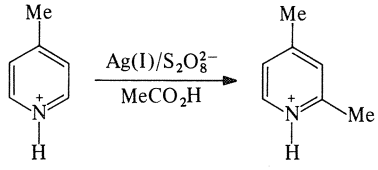
Homolytic substitution reactions of protonated heteroaromatic compounds have been reviewed by Minisci [63, 64]. He has been to the forefront in developing this synthetically important field of study since these homolytic substitution reactions are very much more specific than those carried out in neutral media. For example 4-substituted pyridines are substituted almost exclusively in the 2-position, whereas in neutral solution both the 2- and 3-positions are substituted e.g.



(65%) (35%) [65]



(98%) (2%) [66]



(100%) [67]

The silver ion catalysed decarboxylation of carboxylic acids by peroxydisulfate is the simplest and most convenient method for the alkylation of protonated heteroaromatic bases.

$$S_2O_8^{2-} + Ag^+ \rightarrow SO_4^{\cdot-} + SO_4^{2-} + Ag^{2+}$$

$$SO_4^{\cdot-} + Ag^+ \rightarrow SO_4^{2-} + Ag^{2+}$$

$$RCOOH + Ag^{2+} \rightarrow RCOO\cdot + Ag^+ + H^+$$

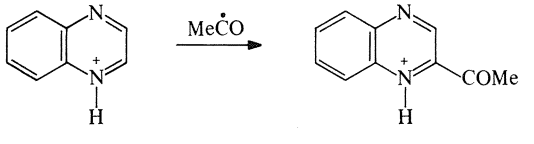
$$RCOO\cdot \rightarrow R\cdot + CO_2$$

The acylation of heteroaromatic bases *via* oxidation of aldehydes and the oxidative decarboxylation of α-ketoacids are particularly useful synthetic procedures since electrophilic acylation is not practicable in these systems.

$$t\text{-BuOOH} + Fe^{2+} \longrightarrow t\text{-BuO}\cdot + FeOH^{2+}$$

$$t\text{-BuO}\cdot + RCHO \longrightarrow t\text{-BuOH} + R\dot{C}O$$

$$RCO.COOH + Ag^{2+} \longrightarrow R\dot{C}O + CO_2 + Ag^+ + H^+$$



[68]

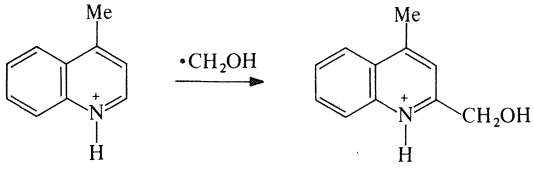
The oxidation of alcohols with a variety of oxidising agents leads to α-hydroxyalkyl radicals. These will attack protonated heteroaromatic bases only when obtained from methanol or from primary alcohols [69, 70].

$$CH_3OH + SO_4^{\cdot-} \longrightarrow CH_3\dot{O}H^+ + SO_4^{2-}$$

$$CH_3\dot{O}H^+ \longrightarrow CH_3O\cdot + H^+$$

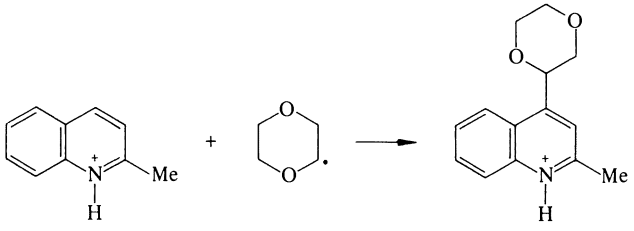
$$CH_3O\cdot + CH_3OH \longrightarrow CH_3OH + \dot{C}H_2OH$$

e.g.



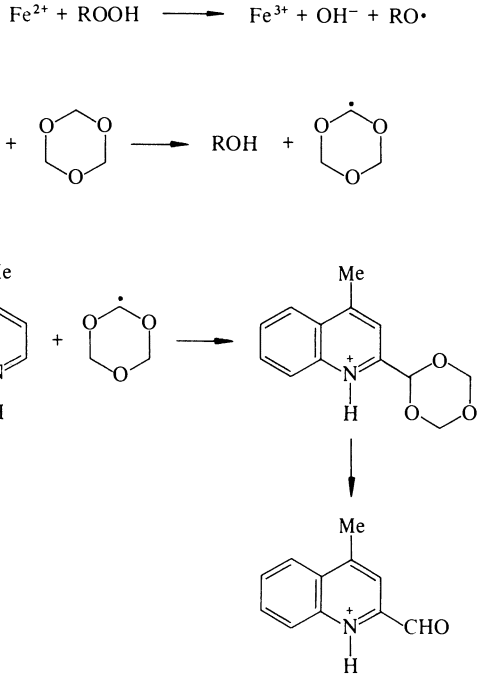
(47%) [69]

Hydrogen peroxide, *t*-butyl hydroperoxide, and ammonium peroxydisulfate have all been used to produce radicals from the ethers dioxane, tetrahydrofuran, 1,3-dioxolan, and



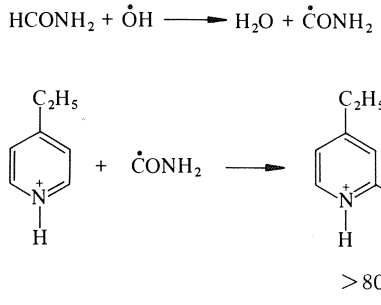
(74%) [69]

diethyl ether for the oxyalkylation of protonated heteroaromatic bases [69, 70]. If trioxan is used, one is introducing a potential source of an aldehyde group [71]. α-Oxyalkyl radi-

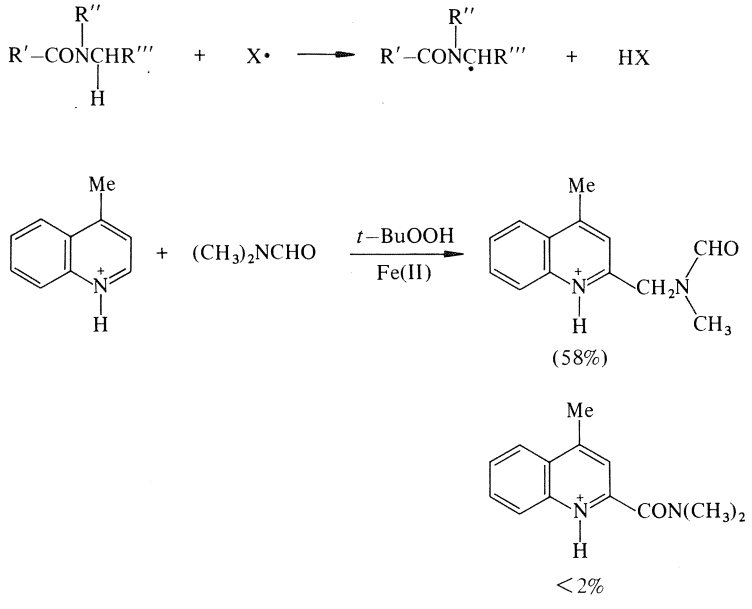


cals are readily obtained by the silver-catalysed decarboxylation of α-hydroxy-, alkoxy-, or phenoxy-carboxylic acids, and have been utilised for the oxyalkylation of protonated heteroaromatic bases. A quantitative yield of phenoxymethyl derivatives of quinoline have been obtained using phenoxyacetic acid [72].

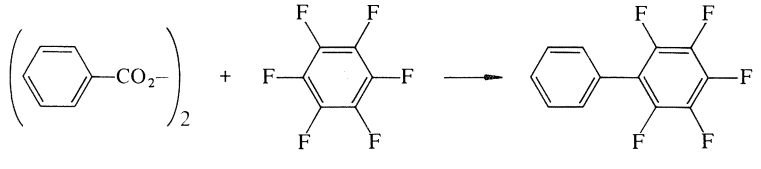
Carbamoyl radicals are easily obtained by hydrogen abstraction from formamide, and similarly undergo substitution reactions [73]. Similarly α-*N*-amidoalkyl radicals are



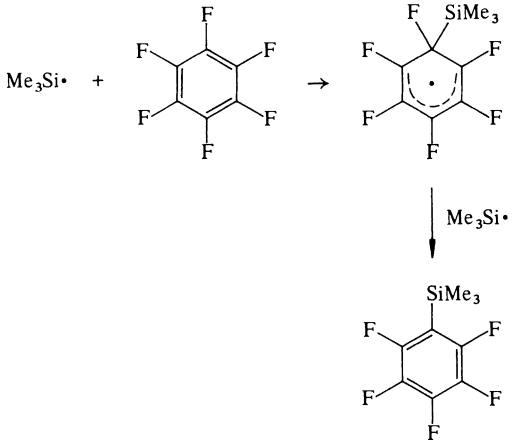
obtained by hydrogen abstraction from *N*-alkylamides and can be used to substitute in protonated heteroaromatic bases.



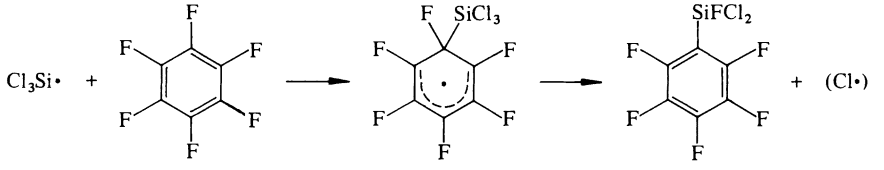
Homolytic substitution of polyfluoroaromatic compounds [75] has led to a number of reactions that have proved to be of synthetic value. In hexafluorobenzene the decomposition of aroyl peroxides proceeds smoothly to give good yields of products in which the aryl group has effectively substituted for a fluorine atom in the hexafluorobenzene. e.g. 2,3,4,5,6-pentafluorobiphenyl (1.43 moles) results from the decomposition of benzoyl peroxide (1 mole) in hexafluorobenzene [76]. Less useful is the pentafluorophenylation



of fluoro-, chloro-, bromo-, and nitro-benzene which leads to mixtures of *ortho, meta,* and *para* isomers as a result of substitution for aromatic hydrogen [77, 78]. Similarly disadvantageous is the phenylation of chloro- and bromo-pentafluorobenzene, which affords similar mixtures of *ortho, meta,* and *para* isomers in reactions involving displacement of fluorine rather than the other halogen [6]. Trimethylsilylation of hexafluorobenzene to give 2,3,4,5,6-pentafluorophenylsilane occurs when a mixture of trimethylsilane and hexafluorobenzene is irradiated with uv light. The analogous reaction with trichlorosilyl radi-

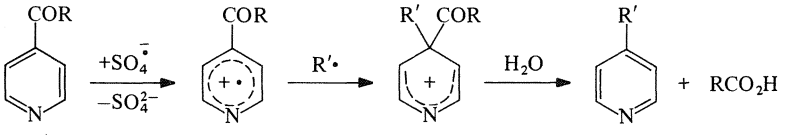


cals is complicated by halogen exchange and the products of direct substitution are not formed [79].



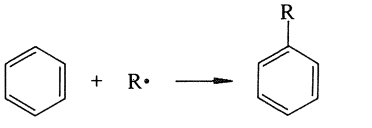
The Friedel-Crafts alkylation reaction requires quite severe conditions and employs powerful Lewis Acid catalysts. The number of functional groups inert to such catalysts are few. The free radical alkylation of aromatic compounds is a milder complementary procedure [3]. The reaction affords mixtures of products formed as a result of both nuclear and side-chain attack as well as by the dimerisation of intermediate σ-complexes. Simple alkyl radicals are probably best generated by the photolysis of alkylmercuric iodides [80]. However cyclohex-1-enyl radicals have been successfully generated from cyclohex-1-enoyl peroxide [81] and phenylethynyl radicals by the photolysis of the iodide [82]. Early experiments by Waters [83, 84] involved methyl radicals, derived from the thermal decomposition of di-*t*-butyl peroxide, reacting with monosubstituted aromatic compounds and also with polycyclic compounds [85]. Cyano radicals from cyanogen iodide also effect aromatic substitution reactions [86].

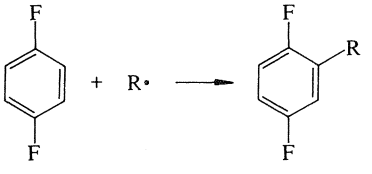
1-Adamantyl and other alkyl radicals produced in the Ag(I) catalysed decarboxylation of carboxylic acids by $(NH_4)_2S_2O_8$, react with acyl-heteroaromatic bases affecting the displacement of the acyl group; a mechanism has been proposed in which the reacting species is the radical cation of the heteroaromatic compound [87].



A similar substitution was found in the reaction of alkyl radicals with the acyl derivatives of protonated quinoline and benzothiazole derivatives [88].

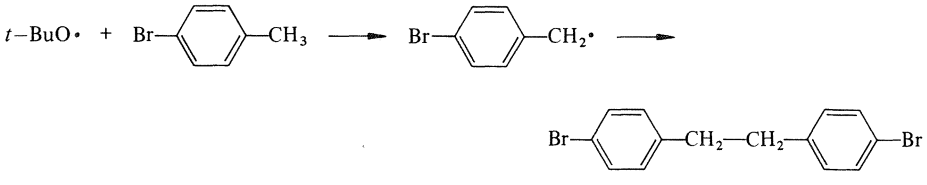
Bridgehead free radicals may be produced by the thermal decomposition of the *t*-butyl peroxyesters of adamant-1-yl, bicyclo[2,2,2]oct-1-yl and norborn-1-yl carboxylic acids. Single substitution products for aromatic hydrogen occur with benzene and



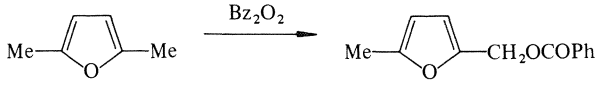


p-difluorobenzene [89]. Substitution for fluorine instead of hydrogen was of minor importance in the latter example. Similar substitutions in benzene have been affected by apocamph-1-yl [90] and perchlorohomocubyl radicals [91].

In any reaction of an alkylbenzene with free radicals, abstraction of an α-hydrogen atom from the side chain, leading to benzylic radicals, which may then dimerise, occurs to varying degrees. Particularly good yields of dimer result from the reaction of di-*t*-butyl peroxide with aromatic and heterocyclic compounds containing alkyl side-chains [92], e.g.



In the reaction of benzoyl peroxide with aromatic compounds, esters (benzoates) are usually formed as relatively minor products in comparison with the biaryls. The extent of benzoyloxylation with anisole and other methoxybenzenes is however much greater and in the reaction of benzoyl peroxide with *p*-methylanisole, the major product is 2-methoxy-5-methylphenyl benzoate [93]. Acyloxylation of anisole also takes place on reaction with lead tetraacetate and lead tetrabenzoate [94]. 2,5-Dimethylfuran reacts with benzoyl peroxide to give the product formally derived by substitution in the methyl group by a benzoyloxy radical [95]. Esters are also formed when 2-thenoyl peroxide

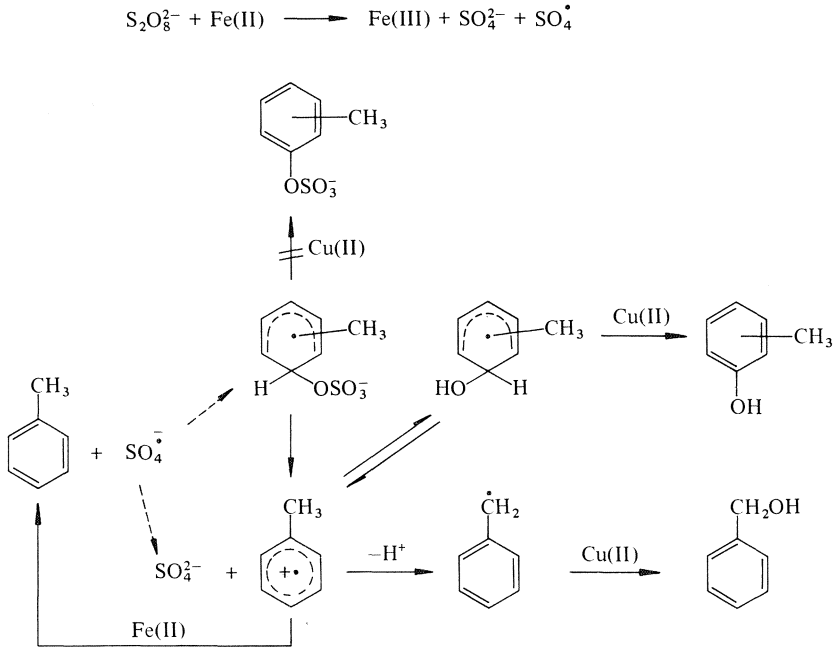


decomposes in aromatic solvents. Aryl 2-thenoates are formed in small yield by nuclear attack; in the halogenobenzenes phenyl 2-thenoate resulted from displacement of the halogen [96].

Hydroxyl radicals may be produced from hydrogen peroxide by reduction with Fe(II). This so-called Fenton's reagent can be used to produce phenols as a result of substitution

$$H_2O_2 + Fe(II) \rightarrow Fe(III) + OH^- + OH^{\bullet}$$

in aromatic systems. However reactions are not particularly useful from the synthetic standpoint due to the mixtures of isomers formed together with products resulting from side chain reaction [97–99]. The pH of solution and the various metal ions present control the relative amounts of products formed [100]. Heterocyclic compounds similarly

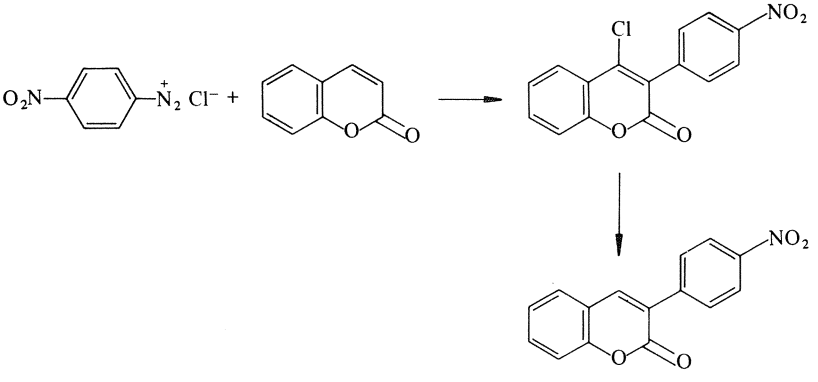


produce mixtures of products on hydroxylation [46] and yields are low. When there is a side chain attached to the aromatic ring, oxidation by Fenton's reagent appears to occur solely at the side chain. However phenols can be made the major products by carrying out the reactions in the presence of Cu(II) ions. Oxidation of a variety of aromatic molecules by $S_2O_8^{2-}$/Fe(II) in the presence of Cu(II) also gives phenolic products in good yield. This may be of synthetic value. Toluene for example gives 21% of cresols (*o*:*m*:*p*; 62:5:33) and 15% of benzyl alcohol as shown in the scheme at the foot of page 36 [101].

In the Meerwein reaction [102], unsaturated compounds may be arylated on reaction with diazonium salts.

$$ArN_2Cl + RCH{=}CRZ \xrightarrow{\text{Copper salt}} ArCR{=}CRZ + ArCHR \cdot C(R)ClZ$$

The group Z is usually electron withdrawing. Yields are low (20–40%) but this is offset by the availability at low cost of a wide variety of aromatic amines and unsaturated compounds. The addition product usually predominates.



(35–45%)

The reaction of phenylhydrazones with oxygen gives Busch's hydroperoxides. If the metal ion catalysed decomposition of hydroperoxides is carried out in the presence of

$$PhNHN{=}CRR' + O_2 \rightarrow PhN{=}\underset{\displaystyle OOH}{\underset{|}{N}}CRR'$$

an alkene and halide ions, the products that are obtained are identical with those of the Meerwein reaction. The reaction works best on α,β-unsaturated carbonyl compounds as set out below for methacrylic acid [103, 104].

$$PhN{=}\underset{\displaystyle OOH}{\underset{|}{N}}CMe_2 + Fe(II) \rightarrow PhN{=}\underset{\displaystyle \dot{O}}{\underset{|}{N}}CMe_2 + Fe(II)OH$$

$$PhN{=}N\underset{\substack{|\\ \dot{O}}}{C}Me_2 \rightarrow Ph\cdot + N_2 + Me_2CO$$

$$CH_2{=}C(Me)COOH + Ph\cdot \rightarrow PhCH_2\dot{C}(Me)COOH$$

$$PhCH_2\dot{C}(Me)COOH + X^- + Fe(III) \rightarrow PhCH_2\underset{\substack{|\\ X}}{C}(Me)COOH$$

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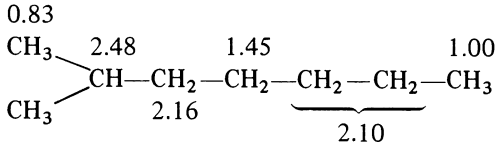
4. Halogen Compounds

Homolytic halogenation [1] is an important procedure for the introduction of halogen groups into organic molecules. All four halogens can be introduced although examples involving the introduction of a fluorine atom in a free radical procedure are not common [2].

Free radical chlorination of organic molecules has been reviewed by Poutsma [3, 4] and is also discussed by Sosnovsky in his book [5]. Chlorination of hydrocarbons with molecular chlorine leads to mixtures of products, although there is some selectivity in the site of attack ($3° > 2° > 1°$) for the hydrogen to be replaced by chlorine [6, 7]. Rearrangements involving 1,2-hydrogen or 1,2-alkyl shifts do not occur during halogenation. The relative selectivities of the various hydrogen atoms in 2-methylheptane towards a chlorine atom are set out below and serve to indicate that this is not a particularly useful



synthetic reaction [6]. Kharasch and Brown [8] discovered that hydrocarbons could be chlorinated with sulfuryl chloride, and they obtained chlorides (80–100%) from compounds such as cyclohexane, *n*-heptane, *n*-butyl chloride, and toluene.

$$RH + SO_2Cl_2 \xrightarrow[\text{peroxide}]{\Delta} RCl + HCl + SO_2$$

This is slightly more selective than molecular chlorine [6, 9]. A comparison of radical chlorinating agents has been drawn up by Poutsma [3]. The greatest selectivity is shown by trichloromethanesulfenyl chloride [10].

$$RH + 2CCl_3SCl \xrightarrow{h\nu} RCl + HCl + Cl_3CSSCCl_3$$

A quantitative reaction was found with cyclohexane at 0° in sunlight. In the chlorination of *n*-pentane the relative selectivity of secondary to primary hydrogens was 33 : 1.

Iodobenzene dichloride is also a selective chlorinating agent [11] and with *n*-butane the relative selectivity of secondary to primary hydrogens is 21 : 1 [12].

$$RH + C_6H_5ICl_2 \xrightarrow{h\nu} RCl + C_6H_5I + HCl$$

Trichloromethanesulfonyl chloride [13] can also be employed in the chlorination of hydrocarbons.

$$RH + Cl_3CSO_2Cl \xrightarrow[\text{peroxide}]{\Delta} RCl + Cl_3CH + SO_2$$

There is a very high preference for secondary over primary hydrogen substitution. Unfortunately the chain length of the reaction is small, and the appreciable quantity of initiator needed is a considerable drawback to the use of this reagent.

Phosphorus pentachloride is a potentially valuable chlorinating agent [14], and relative selectivities of *ca.* 30:1 for secondary and primary hydrogens in *n*-alkanes have been reported [15, 16].

$$RH + PCl_5 \rightarrow RCl + PCl_3 + HCl$$

With metal ion catalysed halogenation using readily available *N*-haloamines high selectivity occurs [17, 18]. This method of halogenation is an important new synthetic procedure.

$$(R^1)_2\overset{+}{N}HX \xrightarrow{Fe(II)} (R^1)_2\overset{\ddagger}{N}H + X^- + Fe(III)$$

$$(R^1)_2\overset{\ddagger}{N}H + R^2H \rightarrow (R^1)_2\overset{+}{N}H_2 + R^2\cdot$$

$$R^2\cdot + (R^1)_2\overset{+}{N}HX \rightarrow R^2X + (R^1)_2\overset{\ddagger}{N}H$$

Most experiments have involved straight chain saturated compounds containing polar moieties such as halogen, ester, or ether groups. Halogenations occur preferentially at the ω-1 position, e.g. the chlorination of methyl hexanoate with *N*-chlorodi-isobutylamine leads to the following isomer distribution [19],

$$\underset{(7.1)}{CH_3}—\underset{(3.0)}{CH_2}—CH_2—CH_2—CH_2—CO_2CH_3$$
$$\underset{(89.9)}{\quad}$$

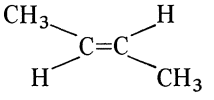
and of *n*-hexanol with *N*-chlorodi-isopropylamine the distribution is as follows [20].

$$\underset{(6)}{CH_3}—\underset{(90)}{CH_2}—\underset{(2)}{CH_2}—\underset{(2)}{CH_2}—CH_2—CH_2OH$$

Even unsubstituted hydrocarbons give high yields of ω-1 isomers. Chlorination of *n*-heptane with *N*-chlorodi-isobutylamine gave the following isomer distribution [21].

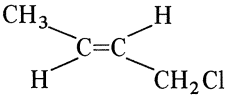
$$\underset{(1.3)}{CH_3}\text{—}\underset{(64.4)}{CH_2}\text{—}\underset{(11.3)}{CH_2}\text{—}\underset{(22.9)}{CH_2}\text{—}CH_2\text{—}CH_2\text{—}CH_3$$

Recently it has been shown that a spontaneous radical-forming process occurs between many olefins and chlorine in the liquid phase in the dark and that many of the supposed polar reactions in non-polar solvents are really radical reactions. Hydrogen abstraction competes with addition so that product mixtures result [22].



$\xrightarrow[-90\ °C]{Cl_2}$ $CH_3CHClCHClCH_3$

meso + *dl* (82%)



(14%)

$CH_3CHClCH{=}CH_2$ (4%)

Kharasch and Brown [23] reported that the peroxide initiated chlorination of cyclohexene, allyl chloride, 1,2-dichloroethylene, stilbene, and tetraphenylethylene with sulfuryl chloride afforded good yields of dichlorides although with linear olefins Kharasch and Zavist [24] found that β-chlorosulfones are also formed as by-products.

$$Rad\cdot + SO_2Cl_2 \rightarrow RadCl + \cdot SO_2Cl$$

$$\cdot SO_2Cl \rightarrow SO_2 + Cl\cdot$$

$$Cl\cdot + RCH{=}CH_2 \rightarrow R\dot{C}HCH_2Cl$$

$$R\dot{C}HCH_2Cl + SO_2Cl_2 \rightarrow RCHClCH_2Cl + \cdot SO_2Cl$$

$$\cdot SO_2Cl + RCH{=}CH_2 \rightarrow R\dot{C}HCH_2SO_2Cl$$

$$R\dot{C}HCH_2SO_2Cl \rightarrow RCHClCH_2SO_2\cdot$$

$$RCHClCH_2SO_2\cdot + RCH{=}CH_2 \rightarrow RCHClCH_2SO_2CH_2\dot{C}HR$$

$$RCHClCH_2SO_2CH_2\dot{C}HR + SO_2Cl_2 \rightarrow RCHClCH_2SO_2CH_2CHClR + \cdot SO_2Cl$$

The reaction of iodobenzene dichloride with alkenes in non-polar solvents gives dichlorides, often with stereochemistry different from the product obtained with molecular chlorine [25–27]. A preliminary investigation [28] into the reactions with 2-methylbut-1-ene and 2-methylbut-2-ene showed that the corresponding dichlorides were predominantly formed whereas with molecular chlorine a polar reaction would have afforded

allylic chlorides [29]. The reagent may be particularly useful for converting branched alkenes to dichlorides without rearrangement.

Free radical bromination has been reviewed by Thaler [30] and by Poutsma [4]; it was also considered by Sosnovsky [5]. A comparison of bromination and chlorination of substituted butanes has been made by Tedder [31, 32]. Bromination is very much more rapid than chlorination but mixtures still result. There is always high reactivity at position 3, but that at 1 and 2 is very substituent dependent. Bromotrichloromethane is particularly useful as a benzylic brominating agent [33] with a selectivity somewhat greater than that for bromine [34].

$$RH + BrCCl_3 \rightarrow RBr + HCCl_3$$

By this means toluene readily affords benzyl bromide and diphenylmethane gives diphenylmethyl bromide.

Walling and Padwa [35] prepared and characterised *t*-butyl hypobromite. It smoothly brominated hydrocarbons. Halogenation with *t*-butyl hypochlorite in the presence of bromotrichloromethane also produced alkyl bromides in some systems and the technique could be of value in the bromination of otherwise unreactive hydrocarbons.

Protonated *N*-bromoamines, like the corresponding *N*-chloroamines, are much more selective than the parent halogen in the halogenation of straight chain hydrocarbons and their derivatives [17]. Bromination of methyl heptanoate with *N*-bromodimethylamine affords the following isomer distribution [36].

$$\begin{array}{cccccccc} & & & & (1.0) & & & \\ CH_3 & -CH_2- & CH_2 & -CH_2- & CH_2 & -CH_2CO_2CH_3 & & \\ (3.5) & (82.2) & (13.4) & & & & & \end{array}$$

The addition of hydrogen bromide to olefins can occur in two ways.

$$RCH{=}CH_2 + HBr \begin{cases} \rightarrow RCHBrCH_3 & \text{normal} \\ \rightarrow RCH_2CH_2Br & \text{abnormal} \end{cases}$$

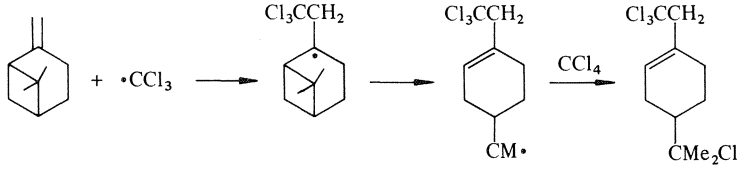
When reaction conditions favour a radical mechanism, addition occurs contrary to Markovnikoff's rule, and the "abnormal" product is obtained; the halogen atom attaches itself to that unsaturated carbon atom which carries the most hydrogen atoms [5, 37]. Free radical initiators, non-polar solvents, and higher temperatures (up to 100 °C) promote the abnormal addition. The synthetic value of the abnormal addition is evidenced by the conversion of pent-1-ene into 1-bromopentane [38].

Polyhalides are formed by the addition of alkyl polyhalides to olefins [5].

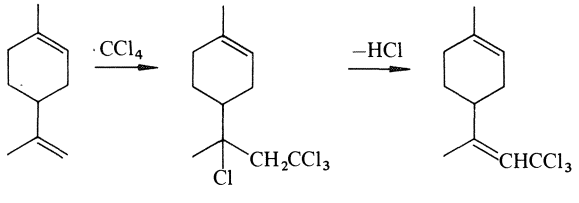
$$RCH{=}CH_2 + XCY_3 \rightarrow RCHXCH_2CY_3$$

X = Cl or Br
Y = Cl or Br

Oct-1-ene affords $Cl_3CCH_2CHBrC_6H_{13}$ (88%) with bromotrichloromethane [39] and $Cl_3CCH_2CHClC_6H_{13}$ (85%) with carbon tetrachloride [40]. Reactions, particularly with monoterpenes, can be complicated by rearrangement and/or elimination of hydrogen halides. For example



[41] (97%)



[42]

$$Cl_3CCH{=}CH_2 + HBr \longrightarrow Cl_2CHCHClCH_2Br$$

[43]

Rearrangements of the above type involving halogen shift have been reviewed by Freidlina [44].

The addition of 1,1,1,3-tetrachloropropane to vinylidene chloride in the presence of coordination metal catalysts gives the adduct $ClCH_2CH_2CCl_2CH_2CCl_3$ and higher telomers along with an appreciable amount of $ClCH_2CH_2CCl_2CH_2CHCl_2$ formed by 1,5-hydrogen shift in the intermediate radical [45].

$$ClCH_2CH_2CCl_3 \xrightarrow[a]{} ClCH_2CH_2\dot{C}Cl_2 \xrightarrow[b]{CH_2=CCl_2} ClCH_2CH_2CCl_2CH_2\dot{C}Cl_2$$

(I)

$$(I) \xrightarrow[c]{n CH_2=CCl_2} ClCH_2CH_2CCl_2(CH_2CCl_2)_n\cdot \xrightarrow[d]{RCl} ClCH_2(CH_2CCl_2)_{n+1}Cl$$

$$(I) \xrightarrow[e]{1,5\text{-H shift}} Cl\dot{C}HCH_2CCl_2CH_2CHCl_2 \xrightarrow[f]{RCl} CHCl_2CH_2CCl_2CH_2CHCl_2$$

(2) (3)

It is suggested that the intermediate radical (I) (steps a, b) undergoes, alongside propagation (c) and chain transfer (d) reactions, a 1,5-hydrogen shift (e) to give a more reactive though less stable radical (2) which is converted into (3) in a chain transfer reaction (f). Similar rearrangements have been suggested for the $Cl(CH_2)_3CH(CCl_2)\dot{C}Cl_2$ radical in the addition of carbon tetrachloride to 1,1,5-trichloropent-1-ene [46].

The addition reactions of bromofluoromethane and other mixed alkyl halides is considered by Sosnovsky [5], and may be exemplified as follows.

$$CH_3CH{=}CH_2 + BrCBrF_2 \rightarrow CH_3CHBrCH_2CBrF_2 \quad (67\%) \qquad [47]$$

$$CH_3CH{=}CH_2 + CClF_2Br \rightarrow CH_3CHBrCH_2CCl_2F \quad (42\%) \qquad [48]$$

$$CF_2{=}CH_2 + Cl_2CFI \rightarrow CF_2ICH_2CFCl_2 \quad (78\%) \qquad [49]$$

$$CF_2{=}CH_2 + C_2F_5I \rightarrow ICF_2CH_2C_2F_5 \quad (91\%) \qquad [50]$$

Chloroform, bromoform, and iodoform react with terminal olefins. Because the chain transfer step is slow the reactions tend to produce telomers and yields of 1 : 1 adducts tend to be low [5]. Kharasch [40] found that 1,1,1-trichlorononane (22%) could be obtained by addition of chloroform to oct-1-ene, and Davies [51] obtained the adducts of chloroform with 6-chloroaldrin and 6-bromoaldrin in yields of 28.5 and 21% respectively.

Derivatives of α-halogenated acids may also add to alkenes by a free radical process [5].

$$RCH{=}CH_2 + XCH_2COY \rightarrow RCHXCH_2CH_2COY$$

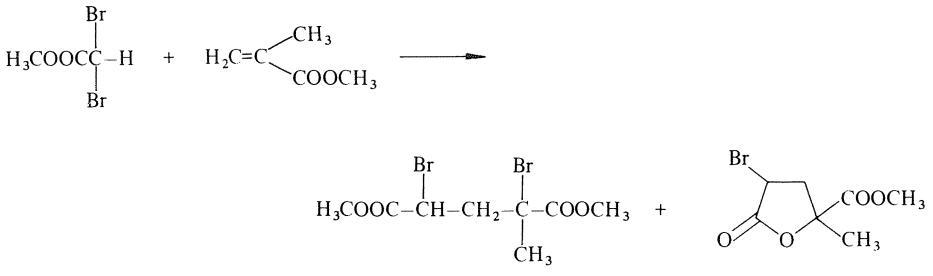
X = Br
Y = OR, Cl

for example [52]

$$Me_2C{=}CH_2 + CH_3CHBrCO_2Et \rightarrow Me_2CBrCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}HCO_2Et$$

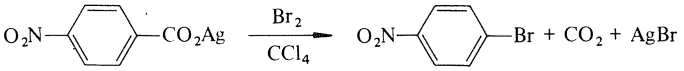
Ethyl bromoacetate, like carbon tetrachloride, forms a 1 : 1 adduct with β-pinene in which ring opening has occured [53].

A review by Freidlina [54] discusses the synthetic applications of homolytic addition and telomerisation reactions of bromine-containing addends with unsaturated compounds containing electron-withdrawing substituents. For example, in the presence of iron pentacarbonyl or iron(III) chloride, methyl dibromoacetate undergoes addition to methyl 2-methylpropenoate almost exclusively *via* homolytic cleavage of the carbon-bromine bond.

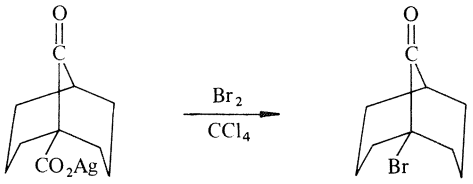


The product proportions are dependent on the initiator and on the presence of dimethylaniline or acetonitrile.

The Hunsdiecker reaction [55] is an excellent procedure for the conversion of carboxylic acids to halides by the action of halogens on dry silver carboxylates.



(79%) [56]



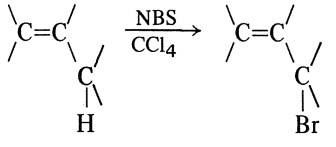
(70%) [57]

The Cristol-Firth reaction [58] is a modification of the Hunsdiecker reaction and employs the addition of halogen to a boiling carbon tetrachloride solution of a carboxylic acid in the presence of red mercuric oxide (it obviates the necessity of preparing anhydrous silver salts) and has been well utilized [59].

The formation of alkyl halides from acids by decarboxylation with lead(IV) acetate in the presence of halide salts has been investigated by Kochi [60]. Usually an excess of acid is employed with an approximately 1 : 1 mixture of lithium halide and lead(IV) acetate in benzene at 80 °C. Yields of chlorides obtained are usually in the region of 75–100% based on lead(IV) acetate. For example, β,β-dimethylbutyric acid affords neopentyl chloride. Decarboxylation of acids to afford alkyl bromides and iodides can also be effected with bromide and iodide salts. Isobutyric acid and lithium bromide afford isobutyl bromide (50–60%). There are two major drawbacks in the preparation of tertiary chlorides by Kochi's procedure. Yields are lowered substantially in large scale work probably due to the low solubility of lithium chloride in benzene. Also, heat sensitive chlorides obtained by Kochi's procedure are contaminated with appreciable amounts of acetates and alkenes. These drawbacks can be overcome, and yields improved, if a 5 : 1 mixture of dimethylformamide and glacial acetic acid is used as solvent and *N*-chlorosuccinimide as chlorine donor. Yields of tertiary chlorides up to 95% have been obtained [61].

The photolysis of lead(IV) carboxylates in carbon tetrachloride gives good yields (25–68%) of chlorides. For example, 42% of 1-chloroundecane was obtained from the photolysis of the lead(IV) salt of lauric acid [62]. The photolysis of acids in the presence of lead(IV) acetate and iodine usually affords very high yields of iodides [63].

Allylic halides may be prepared in high yield by procedures involving free radicals [3, 64, 65]. The best known reaction is that of alkenes with *N*-bromosuccinimide in carbon tetrachloride to afford allylic bromides.



Cyclohexene, for example, gives a good yield of 3-bromocyclohexene but in many cases double bond migration occurs. It is said that product proportions depend on the various canonical species that go to make up the intermediate allylic radical.

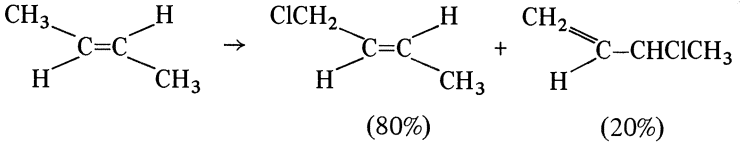
$$CH_2{=}CHCH_2CH_2CH{=}CH_2 \rightarrow BrCH_2CH{=}CHCH_2CH{=}CH_2 \quad (90\%)$$

$$+$$

$$CH_2{=}CHCHBrCH_2CH{=}CH_2 \quad (10\%)$$

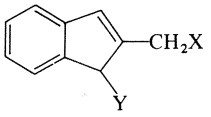
For *cis* and *trans* double bond isomers an equilibrium mixture of *cis* and *trans*-allylic bromides may result [66]. Side chain bromination is also readily achieved with *N*-bromosuccinimide; toluene affording benzylbromide (93%) [67]. 3-Ethyl-4-methyl-7-methoxycoumarin affords 60% of 3-α-bromoethyl-4-methyl-7-methoxycoumarin [68].

This latter example indicates the greater reactivity of secondary over primary hydrogens. Allylic chlorination is probably best effected with *t*-butyl hypochlorite. As with *N*-bromosuccinimide there is the possibility of double bond migration, evidenced by the following example [69].



(80%) (20%)

The reaction of 2-methylindene (4) with *N*-bromosuccinimide afforded a mixture of the monobromide derivatives (5) and (6) with the former predominating. This reaction was used as an essential step in a synthesis of isobenzofulvene [70].



(4) X = Y = H

(5) X = H, Y = Br

(6) X = Br, Y = H

The conversion of primary and secondary alcohols into the corresponding halides can be difficult and sometimes involves rearrangement when heterolytic reactions are used. These problems may be circumvented by converting the alcohol to the alkyl *t*-butyl peroxyglyoxalate and thermally decomposing this in the presence of a halogen donor [71].

$$ROH + ClCOCOCl \rightarrow ROCOCOCl + HCl$$

$$ROCOCOCl + t\text{-}BuOOH \xrightarrow[CCl_3X]{\text{pyridine}} ROCOCOOOBu\text{-}t$$

$$ROCOCOOOBu\text{-}t \xrightarrow{CCl_3X} R\cdot + 2CO_2 + t\text{-}BuO\cdot$$

$$R\cdot + CCl_3X \rightarrow RX + \cdot CCl_3 \ (X = Cl, Br)$$

The likely contaminants are carbonates, haloformates, and alkanes.

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5. Alcohols

The substitution of a hydroxyl group for a hydrogen atom of an alkane in an effective manner is not usually feasible. Tertiary hydrogens may be oxidised with chromate or permanganate to afford the corresponding alcohol [1, 2], but this is of limited synthetic utility. One of the best examples of this reaction is the permanganate oxidation of a dihydro-α-terpineol (1) to afford the diol (2) [3].

(1) (2)
(40%)

The corresponding *trans* isomer of (1) gives a 12% yield of the corresponding diol.

Autoxidation of suitable alkanes affords alcohols in good yields after reduction of the initially formed peroxides and hydroperoxides [4, 5], but again this reaction is of limited synthetic use.

$$RH \xrightarrow{O_2/M^{n+}} ROOH \rightarrow ROH$$

Unfortunately, the reaction between alkanes and hydrogen peroxide in the presence of metal ions, a reaction which might be considered potentially useful to effect substitution of a hydrogen atom by a hydroxyl group generally produces no useful products [6]. Aralkanes do produce products derived from side-chain reaction with hydrogen peroxide and metal ions, but any alcohol formed is usually oxidised further under the reaction conditions. Thus ethylbenzene yields acetophenone rather than 1-phenylethanol [7].

Alcohols on oxidation with hydrogen peroxide and metal ions tend to afford aldehydes or ketones as the major products [6], although oxidation of cyclohexanol with iron(II) perchlorate and hydrogen peroxide in acetonitrile as solvent can afford diols quite stereospecifically [8]. Thus cyclohexanol gives 70% of the *cis*-1,3-diol together with smaller amounts of the *trans*-1,3-, and the *cis*- and *trans*- 1,2- and 1,4-diols. Tertiary alcohols afford products derived from dimerisation of the intermediate radicals [9].

$$R^1R^2C(Me)OH \rightarrow R^1R^2C(\dot{C}H_2)OH \rightarrow R^1R^2C(OH)CH_2CH_2C(OH)R^1R^2$$

However, if copper(II) salts are present the first formed radical may be hydroxylated prior to dimerisation [10].

$$R^1R^2C(OH)\dot{C}H_2 \xrightarrow{Cu(II)(OH)} R^1R^2C(OH)CH_2OH$$

This is probably an example of ligand transfer, as formulated in the equation. Presumably the reaction could be extended and its synthetic value increased if other functional groups were introduced, in place of the second hydroxyl, by the use of appropriate copper salts.

The reaction between alkenes and hydrogen peroxide in the presence of metal ions affords a variety of products. Carbon-carbon bond cleavage is often involved and reaction leads to highly oxidised products [6]. However, when suitable conditions exist, the products derived from radicals early in the reaction sequence may be trapped in some way and treated to produce useful products. For example, treatment of butadiene with hydrogen peroxide in the presence of iron(II) yields dimers containing terminal hydroxyl groups. If the products are then hydrogenated a 30% yield of 1,8-octanediol is obtained [11]. Allyl alcohol is oxidised by hydrogen peroxide in the presence of both iron(II) and copper(II) ions to afford a 43% yield of glycerol [12]. Presumably the copper prevents the further oxidation of glycerol which readily occurs with Fenton's reagent.

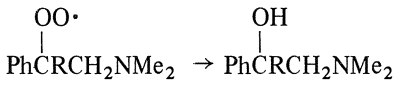
The addition of water or of alcohols to an alkene in a free radical reaction promises great utility as a general method of alkylating alcohols (or water).

$$RCH{=}CH_2 + R'CH_2OH \rightarrow R'CH(OH)CH_2CH_2R$$

These reactions have been well reviewed up to 1964 by Sosnovsky [13] but unfortunately telomerisation is a serious competing reaction, and only moderate yields are obtained. Little recent work has been done on these reactions. Higher yields are expected from those alcohols containing tertiary and secondary α-hydrogen atoms. Yields are optimised by using high alcohol to alkene ratios and efficient initiators. The addition to highly fluorinated alkenes appears to proceed more readily with increased yield of 1 : 1 adduct.

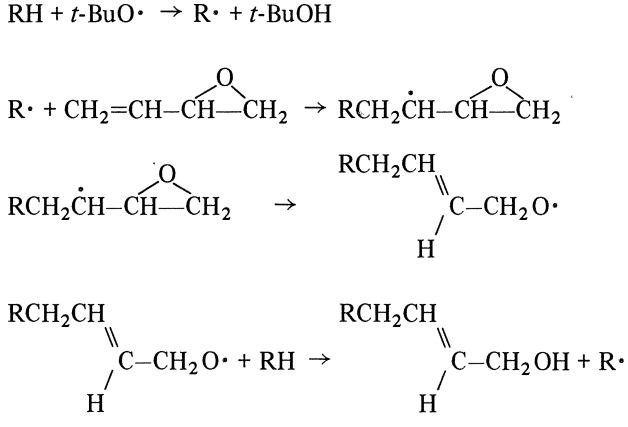
A more promising approach appears to be that adopted by Minisci [14], who has studied the addition of amino radicals to alkenes in the presence of oxygen leading to the formation of peroxyl radicals. These, in the presence of a hydrogen donor and the transition metal used to initiate the reaction, afford some substituted alcohols although the corresponding ketone is generally the major product. The sequence which leads to useful products may be written as

$$PhCR{=}CH_2 + Me_2N\cdot \xrightarrow{O_2} PhC(OO\cdot)RCH_2NMe_2$$



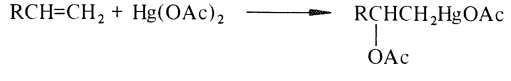
The amino radicals are formed by reaction between N-chloroamines and iron(II) or copper(I) salts. The mechanistic details of this reaction have been challenged [15].

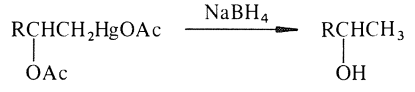
Allylic alcohols have been prepared by the addition of alkyl radicals derived from alkanes to vinyloxiranes [16]. For example the di-*t*-butyl peroxide catalysed addition of cyclopentane, cyclohexane, and cycloheptane to vinyloxirane at 130° affords 6–43% of *trans*-products.



Isopropanol also affords 11% of addition product.

The reductive demercuration of alkylmercury bromides by metal hydrides is a free radical chain process [17]. Radical processes are probably involved in the demercuration of other mercurials formed in versatile synthetic procedures for the conversion of alkenes [18, 19] and cyclopropanes [20] to alcohols [21].





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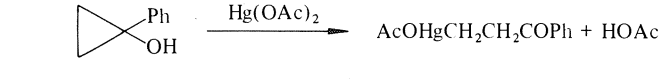
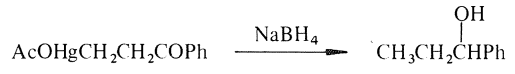
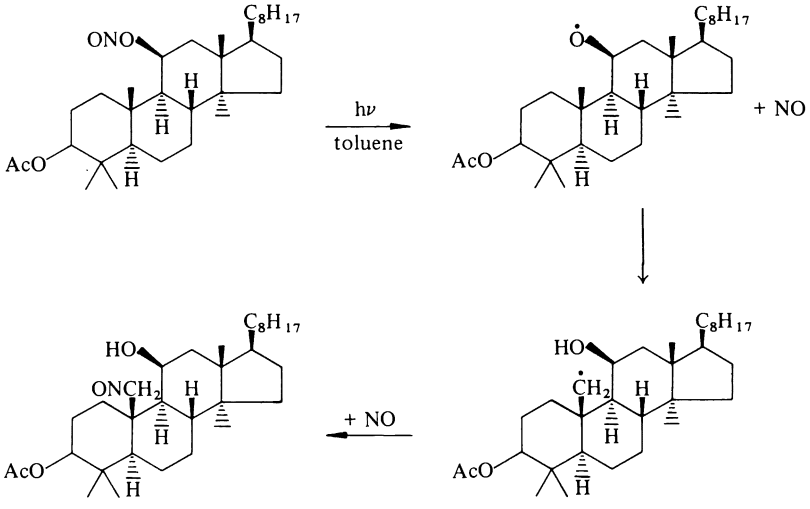




Perhaps the most useful reactions affording the hydroxyl group are the intramolecular hydrogen abstraction reactions, invariably involving hypohalites or nitrites. These have been most exploited in those systems of fixed geometry where the juxtaposition of parent and daughter radical centres are those required to provide regioselectivity. This is most true of the steroidal systems, and the geometrical requirements seem well understood [22–24]. Most simply, reaction takes place *via* a six-membered transition state in a chain reaction in the case of hypohalites, and in a non-chain reaction in the case of nitrites. Photochemical initiation is usually the method of choice, particularly in the Barton reaction (nitrite) one example of which is given here [25].



(66% as oxime)

Attention has recently been given to other means of using radicals in regioselective reactions. For example, a selective oxidative demethylation has been accomplished using a photolytically excited nitroxide to afford a mixture of lactol and ketone products [26].

It has been suggested that there would be an advantage in these regioselective reactions if the parent functional group migrated during the course of the reaction [27]. This idea, still in its infancy, is further discussed in chapter 7.

The use of intermolecular abstraction reactions is preparatively limited. Tertiary hypochlorites afford products derived from intramolecular abstraction of tertiary or secondary atoms in the expected δ-position [28, 29].

$$CH_3CH_2CH_2CH_2CMe_2OCl \xrightarrow{h\nu} CH_3CHClCH_2CH_2CMe_2OH$$

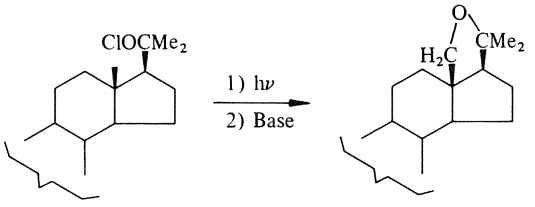
(55%)

If the δ-hydrogen is primary, fragmentation reactions occur extensively [30].

$$CH_3CH_2CH_2CMe_2OCl \xrightarrow{h\nu} Me_2CO + CH_3CH_2CH_2Cl$$

(59%)

The reaction is most used in the steroid systems where δ-halogenoalcohols are cyclised to afford substituted tetrahydrofurans [22].



The reduction of ketones to secondary alcohols using as reducing agent dissolving metals in proton sources is a well-known reaction [31, 32]. With sodium and alcohol the reaction affords the sodium alkoxide [33].

$$R_1R_2CO + e \rightarrow R_1R_2\dot{C}{-}O^-$$

$$R_1R_2\dot{C}{-}O^- + H^+ \rightarrow R_1R_2CHO\cdot$$

$$R_1R_2CHO\cdot + Na \rightarrow R_1R_2CHO^-Na^+$$

The use of Grignard reagents to effect electron transfer allows the formation of dimers to occur extensively, yielding after work up, pinacols [34]. The reaction is apparently catalysed by iron and other transition metals and affords pinacols in yields of up to 70%.

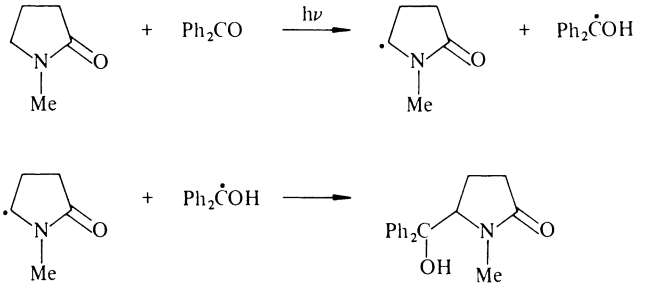
$$Ar_2CO + MeMgBr \rightarrow Ar_2\dot{C}OMgBr$$

$$2\,Ar_2\dot{C}OMgBr \rightarrow \begin{matrix} Ar_2COMgBr \\ | \\ Ar_2COMgBr \end{matrix} \xrightarrow{H^+/H_2O} \begin{matrix} Ar_2COH \\ | \\ Ar_2COH \end{matrix}$$

Pinacols are also obtained in high yield by the photoreduction of aryl ketones in the presence of a suitable hydrogen donor [35]. This reaction is of limited use, however, since to obtain the highest yields it is necessary to use ketones to provide the abstracting triplet, and secondary alcohols to act as hydrogen donors; both of which should have the same substituents if multi-component mixtures are to be avoided.

$$RCOAr + R'CHAr'OH \rightarrow \begin{matrix} Ar \\ | \\ RCOH \\ | \\ R'COH \\ | \\ Ar' \end{matrix} + \begin{matrix} Ar \\ | \\ RCOH \\ | \\ RCOH \\ | \\ Ar \end{matrix} + \begin{matrix} Ar' \\ | \\ R'COH \\ | \\ R'COH \\ | \\ Ar' \end{matrix}$$

A preparatively more effective use of the protonated ketyl radicals formed from ketone triplets by hydrogen abstraction is made by allowing them to couple with other radicals. For example the photolysis of benzophenone in the presence of *N*-methylpyrrolidone affords diphenyl-*N*-methyl-5-pyrrolidinocarbinol [36].



Similarly, α-hydroxyalkyl radicals formed from an alcohol and di-*t*-butyl peroxide under photolysis will effect substitution at C-8 of a purine or purine nucleoside [37–40] (See Chapter 13).

The reductive coupling of aldehydes at a cathode has been investigated, and appears to be a preparatively useful reaction [41]. The cathodic reduction of carbonyl compounds may be modified by carrying out the reaction in the presence of an alkene. The first formed ketyl may then undergo addition to the alkene, followed by reduction of the resultant product radical [42, 43], e.g.

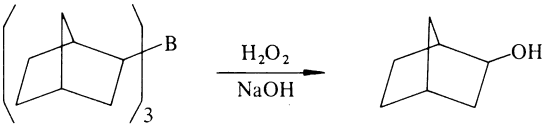
$$Me_2CO + e \xrightarrow{H^+} Me_2\dot{C}OH$$

$$Me_2\dot{C}OH + CF_2{=}CFCl \rightarrow Me_2C(OH)CF_2\dot{C}FCl$$

$$Me_2C(OH)CF_2\dot{C}FCl + e + H^+ \rightarrow Me_2C(OH)CF_2CFHCl$$

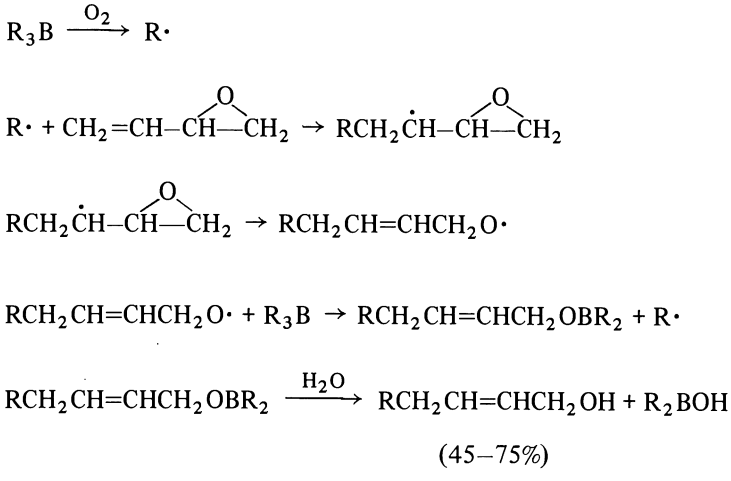
(43%)

The controlled oxidation of organoboranes followed by treatment with aqueous alkali affords a nearly quantitative yield of alcohol [44]. However, the free radical nature of this reaction results in a loss of stereospecificity compared with the alternative work up using alkaline hydrogen peroxide [45, 46]. For example, the conversion of norbornene to norborneol *via* alkaline hydrogen peroxide work up of the intermediate borane affords 100% of the *exo*-isomer.

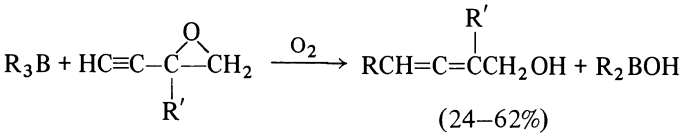


Whereas oxidation followed by aqueous alkali affords a mixture of 86% *exo*- and 14% *endo*-norborneol [47].

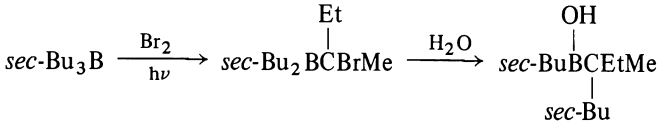
Allylic [48] and allenic [49] alcohols are prepared by the oxygen induced 1,4-addition of organoboranes to ethenyl- and ethynyl-oxiranes respectively.



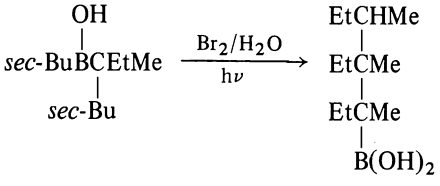
similarly,



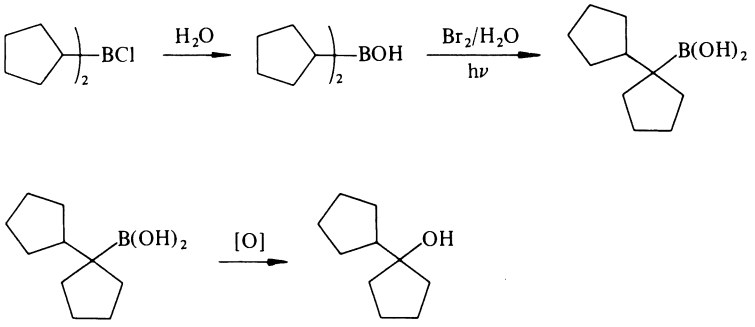
A useful synthesis of tertiary alcohols involves the photobromination of organoboranes in the presence of water [50]. The alkyl group is brominated at the α-position and migrates, e.g. when one mole of bromine is used



Further bromination with an additional mole of bromine effects a second migration.

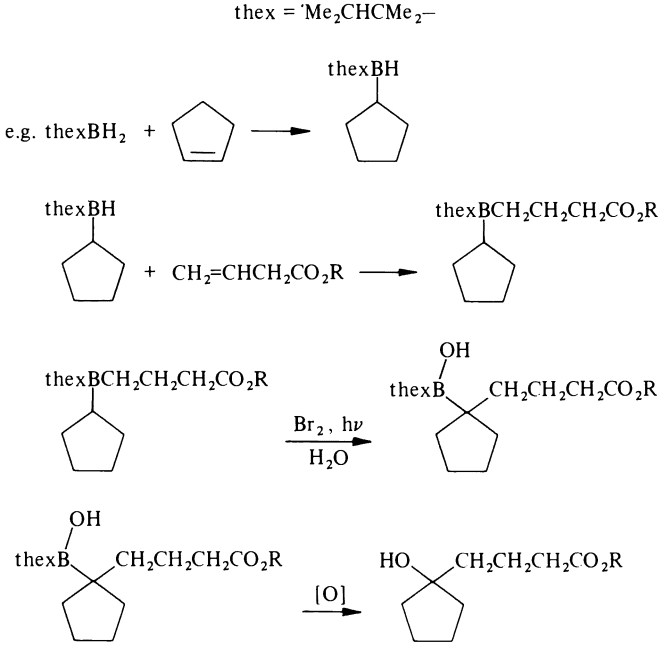


Either intermediate on oxidation affords the corresponding tertiary alcohol in high yield. Hydroboration with monochloroborane followed by hydrolysis and photochemical bromination in the presence of water leads directly to the alkylboronic acid [51], e.g.

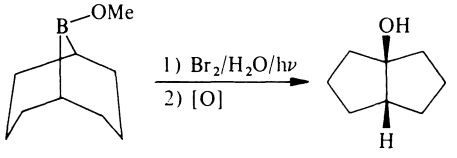


(97%)

A modification of the reaction is to prepare a thexyldialkylborane, then the bromination-hydrolysis links the two alkyl groups [52]. At least one of the groups needs a tertiary α-hydrogen atom for the best yields.



Bridged polycyclic alcohols have also been formed using these procedures [53], e.g.

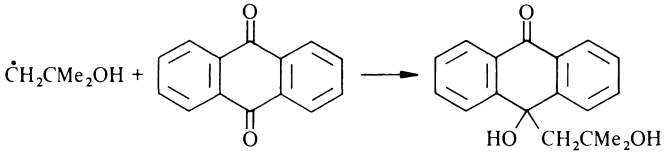


(65%)

An effective addition of alkyl radicals to a quinone has been recently accomplished. Photolysis of anthraquinone and ammonia in *t*-butyl alcohol afforded 74% of the mono adduct. H-abstraction was suggested to occur *via* an exciplex but the amminium radical cation could be involved [54].

$$^3AQ + NH_3 \xrightarrow{h\nu} [AQ^{\cdot-}\ NH_3^{+\cdot}]\ \text{exciplex}$$

$$\text{exciplex} + CH_3CMe_2OH \longrightarrow \dot{C}H_2CMe_2OH + NH_4^+ + AQ^{\cdot-}$$



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6. Ethers, Peroxides, and Hydroperoxides

The α-alkylation of ethers *via* the addition of alkoxyalkyl radicals to alkenes, although seemingly an attractive method for preparing more highly branched ethers, has received little attention. Apparently telomerisation is extensive and the product mixture is ill-defined [1, 2].

$$RCH_2OR^1 + Rad\cdot \rightarrow R\dot{C}HOR^1 + RadH$$

$$R\dot{C}HOR^1 + CH_2{=}CHR^2 \rightarrow R(R^1O)CHCH_2\dot{C}HR^2 \text{ etc.}$$

A synthetically somewhat limited method of ether production involves the addition of tertiary alkoxyl radicals to conjugated dienes such as butadiene or isoprene. The alkoxyl radicals are generated from hydroperoxides using iron(II), and in the absence of other reactive species dimeric products are generally obtained [3–6]. For example

$$Me_2RCOOH \xrightarrow{Fe(II)} Me_2RCO\cdot$$

$$Me_2RCO\cdot + CH_2{=}CHCH{=}CH_2 \rightarrow Me_2RCOCH_2\dot{C}HCH{=}CH_2$$

(1)

$$2\,Me_2RCOCH_2\dot{C}HCH{=}CH_2 \rightarrow Me_2RCOCH_2CH{=}CHCH_2CH_2CH{=}CHCH_2OCRMe_2 + \text{isomers}$$

(1) (80–95%)

In the presence of thiols, thiyl radicals are produced and couple with the first formed allylic radicals (1) [7].

$$R'SH + Fe(III) \rightarrow R'S\cdot + H^+ + Fe(II)$$

$$Me_2RCOCH_2\dot{C}HCH{=}CH_2 + R'S\cdot \rightarrow Me_2RCOC_4H_6SR' \quad (\text{ca. } 75\%)$$

(1)

(R = Me; R′ = Ph, n-C_3H_7, t-Bu)

In the presence of a suitable anionic reagent and an oxidising agent, the radical (1) can be oxidised and trapped to yield a variety of unsaturated ethers. Thus nitrato- [8], chloro- [9, 10], azido- [11], and thiocyanato- [12] ethers have been prepared in this way. Other alkadienes such as cyclopentadiene and furan [13], and also styrene [8], have been used in place of butadiene in similar reactions. When triphenylmethyl hydroperoxide is the hydroperoxide used the products contain a rearranged moiety [14].

$$Ph_3CO\cdot \rightarrow Ph_2\dot{C}OPh$$

Allylic peroxides result from the reaction of hydroperoxides with alkenes in the presence of copper(I) or cobalt(II) [15, 16].

$$t\text{-BuOOH} + Co(II) \rightarrow t\text{-BuO}\cdot + OH^- + Co(III)$$

$$t\text{-BuOOH} + t\text{-BuO}\cdot \rightarrow t\text{-BuOO}\cdot + t\text{-BuOH}$$

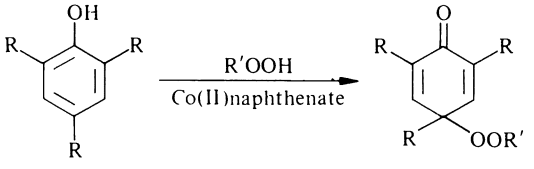
$$t\text{-BuOOH} + Co(III) \rightarrow t\text{-BuOO}\cdot + H^+ + Co(II)$$

$$t\text{-BuOO}\cdot + CH_2{=}CHCH_2R \rightarrow t\text{-BuOOCH}_2\dot{C}HCH_2R$$

$$t\text{-BuOOCH}_2\dot{C}HCH_2R + Co(III) \rightarrow t\text{-BuOOCH}_2CH{=}CHR + H^+ + Co(II)$$

$$t\text{-BuOOCH}_2\dot{C}HCH_2R + t\text{-BuO}\cdot \rightarrow t\text{-BuOOCH}_2CH{=}CHR + t\text{-BuOH}$$

Cyclohexene affords ca. 7% of 3-*t*-butylperoxycyclohexene [15]. The peroxides are mixed with products of their decomposition. Other alkenes [17, 18] and substituted phenols [19] have been similarly treated. Phenols usually react as follows.



(10–85%)

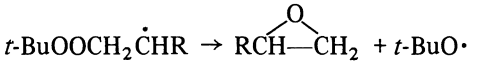
R = Me, *t*-Bu
R′ = *t*-Bu, tetralyl, $PhMe_2C$, Ph_2MeC, Ph_3C

With dienes, diperoxides result [15].

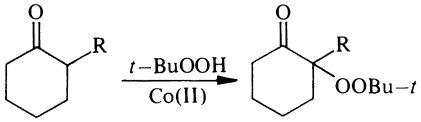
In the presence of the acetylacetonates of vanadium, molybdenum, manganese, and chromium a different reaction occurs between hydroperoxides and alkenes and oxiranes are obtained [20–22].

$$t\text{-BuOOH} + M^{n+1} \rightarrow t\text{-BuOO}\cdot + M^n + H^+$$

$$t\text{-BuOO}\cdot + CH_2{=}CHR \rightarrow t\text{-BuOOCH}_2\dot{C}HR$$



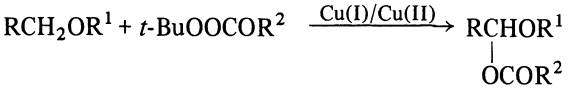
Other compounds besides alkenes contain active hydrogen atoms which may be substituted by peroxy groups, for example cyclohexanone gives a β-ketoperoxide [23, 24].



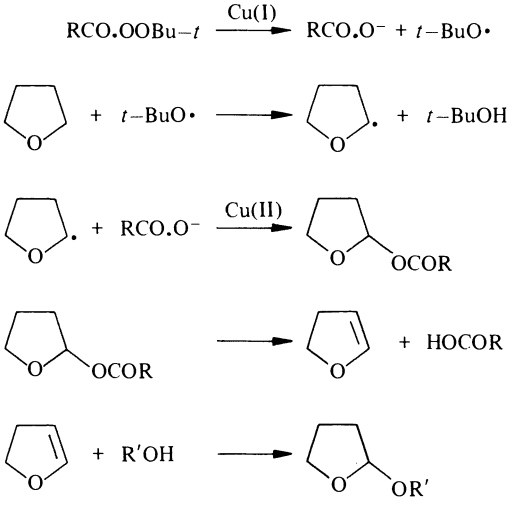
(95%)

In a similar reaction with *t*-butyl hydroperoxide and metal ions benzaldehyde yields *t*-butyl peroxybenzoate (18%) [25], dimethylaniline yields *N*-methyl-*N*-*t*-butylperoxymethylaniline (95%) [24], and various secondary alkyl nitriles are substituted by *t*-butylperoxyl groups (ca. 90%) [25].

Ethers afford α-acyloxy derivatives on treatment with *t*-butyl peresters [26–32].



When the α-hydrogen of the ether is tertiary the products are unstable [30]. In contrast cyclic ethers react with *t*-butyl peresters to yield mainly 2-*t*-butoxy-substituted ethers [26, 27, 29]. If the reaction is carried out in the presence of excess alcohol, the corresponding 2-alkoxyether is obtained [27, 33], e.g.

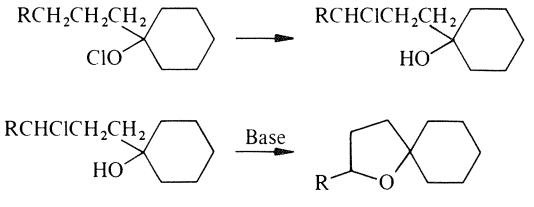


The 2-acyloxy derivatives of cyclic ethers can however be obtained when the reaction mixture is photolysed [34, 35].

Chlorination and bromination of ethers is effected with chlorine, sulphuryl chloride, bromine, and *N*-bromosuccinimide [36]. When molecular chlorine is used the degree of chlorination depends on the temperature and the amount of chlorine used. As would be expected mono-chlorination is favoured by low temperatures. Chorine-substituted ethers [37] are frequently the products of the chlorination of alcohols, e.g. [38].

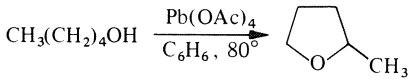
$$MeCH_2CH_2OH \xrightarrow[h\nu]{Cl_2} MeCH_2CHClOCH_2CH_2Me + MeCHClCHClOCH_2CH_2Me + MeCCl_2CHClOCH_2CH_2Me$$

Cyclic ethers may be prepared in a Barton-type reaction by the photolysis of tertiary hypochlorites containing non-primary δ-hydrogen atoms, followed by treatment with base [39], e.g. [40]

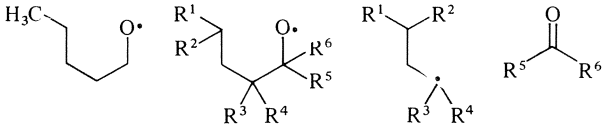


(63%)

Cyclic ethers are also prepared in a convenient and useful procedure by the intramolecular oxidative cyclisation of alcohols with lead(IV) acetate in non-polar solvents [41–45]. For example pentan-1-ol affords 2-methyltetrahydrofuran (43–45%) [44].

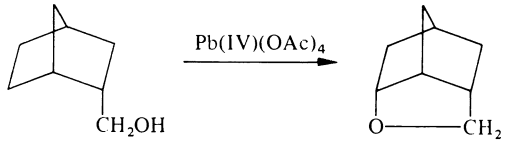


The intermediate radical (1) may be involved.

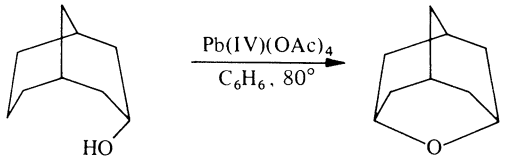


(1) (2) (3) (4)

When substituents are present as in the intermediate radical (2), products derived from the fragmentation (2) → (3) + (4) may also become important. Examples of the cyclisation of alcohols have also been found in polycyclic systems.

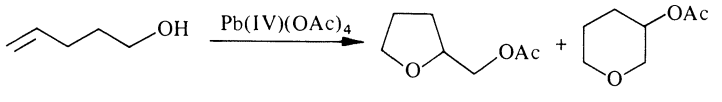


(38%) [45]



(89%) [43]

The latter conversion is also effected in 60% yield by the photolysis of the alcohol in the presence of mercury(II) oxide and bromine [43]. The oxidative cyclisation of unsaturated alcohols can also be carried out but product mixtures often result [46].



(14%) (26%)

Organoboranes are easily prepared by the addition of a borane to an alkene [47]. The low temperature autoxidation of organoboranes leads to a bis(alkylperoxy)borate [48].

$$R_3B + O_2 \rightarrow R\cdot + R_2BO_2\cdot \qquad \text{initiation}$$

$$\left.\begin{array}{l} R\cdot + O_2 \rightarrow RO_2\cdot \\ RO_2\cdot + R_3B \rightarrow RO_2BR_2 + R\cdot \end{array}\right\} \text{chain reaction}$$

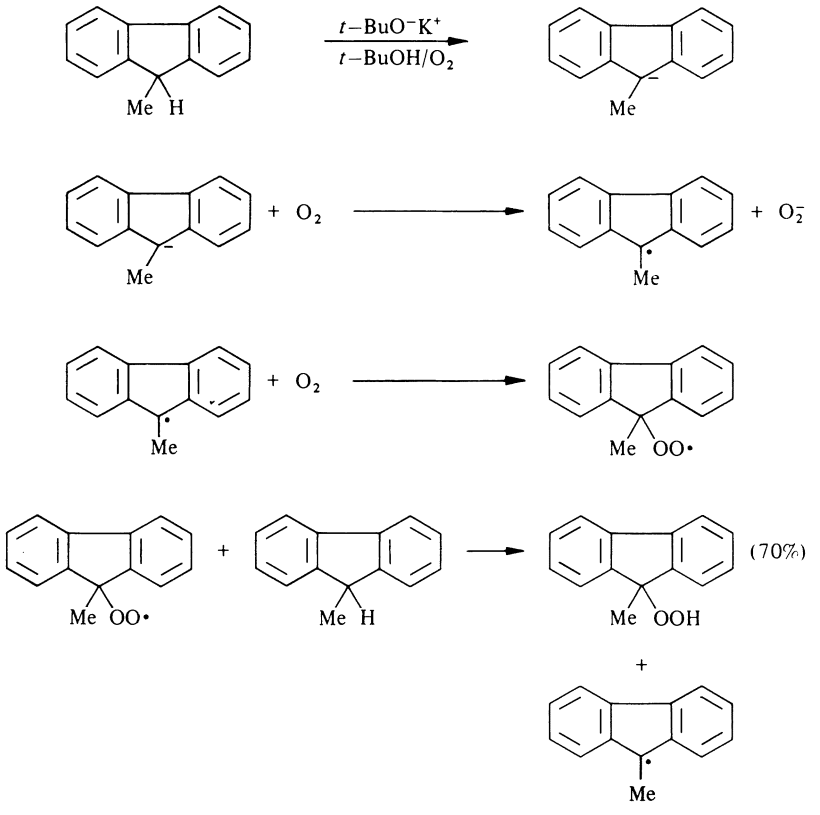
$$RO_2BR_2 + O_2 \rightarrow (RO_2)_2BR$$

Addition of a 30% aqueous solution of hydrogen peroxide to the reaction mixture at 0 °C liberates an alkyl hydroperoxide with concurrent oxidation of the remaining boron-carbon bond.

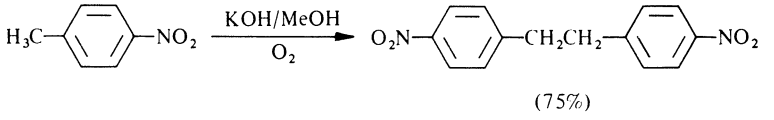
$$RB(O_2R)_2 + H_2O_2 + 2H_2O \rightarrow ROH + 2RO_2H + B(OH)_3$$

When the alkene is valuable the hydroboration step may be carried out with the diethyl-etherate of dichloroborane and oxidised as above [47].

Autoxidation of alkanes, alkenes, aralkanes, ethers, alcohols, and ketones affords hydroperoxides [49–52]. Carbanions also undergo autoxidation to afford hydroperoxides or the corresponding alcohol [53], e.g.



However, compounds containing less reactive hydrogen atoms may afford products derived from coupling reactions [54].



Many organometallic compounds yield organometallic peroxides on autoxidation [55]. Recent reviews of mechanistic details have been published [56, 57].

The major drawback with autoxidation as a means of preparing hydroperoxides is that the isolation and subsequent purification of the product is difficult. Therefore, at least for simple primary, secondary, and tertiary hydroperoxides and also peroxides, the heterolytic methods recently developed using silver trifluoroacetate are to be preferred [58]. Secondary alkyl *t*-butyl peroxides may be prepared by the peroxy-mercuration of an alkene [59] followed by sodium borohydride work up [60], a reaction which is probably radical in nature [61]. Heterolytic methods involving hydroperoxide complexes of diazabicyclooctane are probably the preferred method for preparation of some organometallic peroxides and hydroperoxides [62].

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7. Aldehydes and Ketones

The addition of radicals to carbon monoxide apparently proceeds well to afford low to moderate yields of addition products when a good transfer agent is present.

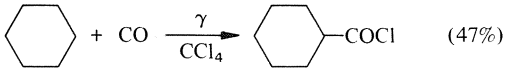
$$R\cdot + CO \rightarrow R\dot{C}O$$

$$R\dot{C}O + XS \rightarrow RCOX + S\cdot$$

For example a thiol mixed with acetylene and carbon monoxide under pressure, with initiation, affords a β-thioalkoxy unsaturated aldehyde [1].

$$RSH + HC{\equiv}CH + CO \rightarrow RSCH{=}CHCHO \quad (17\%)$$

When carbon tetrachloride is used as the transfer agent, acyl chlorides are formed in good yield [2, 3].



(47%)

Probably more useful from the preparative standpoint are the various radical additions of carbonyl compounds to alkenes and alkynes. For example, the addition of aldehydes to alkenes affords ketones in moderate to good yields.

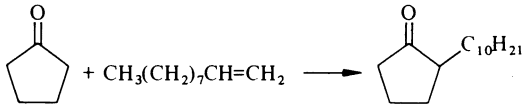
$$RCHO + CH_2{=}CHR' \rightarrow RCOCH_2CH_2R'$$

Such addition reactions are however prone to telomerisation and steric inhibition to addition, and in this connection aromatic aldehydes appear to undergo addition less readily than aliphatic aldehydes. These addition reactions in which acyl radicals are the adding species have been reviewed [4, 5], and the chain mechanism discussed [6].
Aldehydes also undergo oxidative addition reactions with alkenes, usually when initiation is accomplished using metal salts [7]. Often the two modes of addition can occur together, the acyl radical addition being favoured by low metal salt concentration. Thus using manganese(III) acetate the two possible modes of addition are [8]

$$RCH_2CHO \xrightarrow[Mn(III)(OAc)_3]{CH_2=CHR'} \begin{cases} RCH_2COCH_2CH_2R' + RCH_2COCHR'CH_3 \\ RCH(CHO)CH_2CH_2R' \end{cases}$$

Products may also be formed by the oxidation of intermediate radicals to cations followed by acetate ion trapping.

Ketones also undergo addition reactions with alkenes [4], but in order to obtain good yields of 1 : 1 adducts the reactions must be initiated, usually with di-*t*-butyl peroxide [9–11]. For example [10],



(71%)

It has been stated that the presence of certain transition metal oxides increases yields [12]. Such reactions may also be initiated with metal salts; thus without solvent, acetone and a terminal alkene in the presence of manganese(III) acetate afford mainly 1 : 1 adduct [13]. In contrast, with acetic acid as solvent oxidation of the intermediate radicals results in the formation of acetoxy-substituted and unsaturated products.

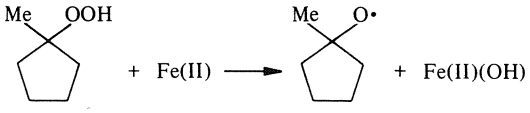
The manganese(III) acetate initiated addition of ketones to isopropenyl acetate in acetic acid as solvent affords 1,4-diketones in yields of 20–40% [14].

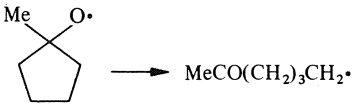
$$R^1COCH_2R^2 + Rad\cdot \rightarrow R^1COCHR^2 + RadH$$

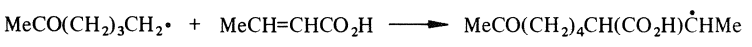
$$R^1COCHR^2 + CH_2=C(OAc)Me \rightarrow R^1COCHR^2CH_2C(OAc)(Me)\cdot$$

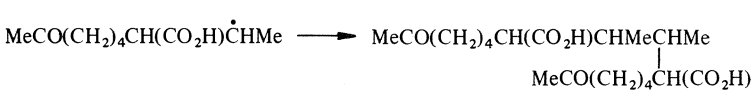
$$R^1COCHR^2CH_2C(OAc)(Me)\cdot \rightarrow R^1COCHR^2CH_2CO.Me + Ac\cdot$$

These addition reactions may be extended to produce longer chain diketones *via* dimerisation of intermediate radicals; such reactions have been accomplished using selected aldehydes and ketones mixed with alkene, hydrogen peroxide, and a metal salt [15]. A further extension of such reactions is provided by the metal salt catalysed decomposition of cyclic alkyl hydroperoxides in the presence of unsaturated compounds. For example [16],

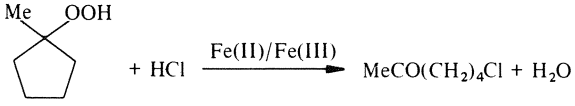






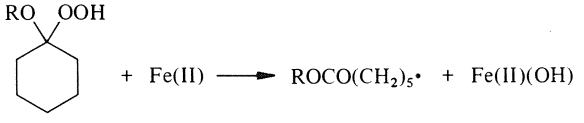


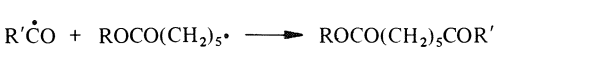
With butadiene dimeric diketones may be formed [17]. Instead of incorporating an unsaturated compound in the product, the first formed radical from the hydroperoxide can afford a chloro-ketone by reaction with hydrogen chloride as in the example below [18]:



In the presence of cyanide a ketonitrile [19] results and in the presence of a thiol a keto-sulfide [20] is formed.
In the absence of a reactive substrate the first formed radicals dimerise affording the diketone $MeCO(CH_2)_8COMe$ [21].

The complexes formed between cyclic ketones and hydroperoxides afford useful products on catalytic decomposition [22]. For example [23], the iron(II) sulfate catalysed decomposition of 1-alkoxycyclohexyl hydroperoxides in the presence of an aldehyde dissolved in sulfuric acid/methanol affords moderate yields of keto ester.





Hydroxyl radicals generated from hydrogen peroxide and iron(II) undergo addition to ethyne affording acetaldehyde [24]. In the presence of copper(II) the intermediate radicals undergo oxidation to afford glycolaldehyde.

$$HOOH + Fe(II) \rightarrow HO\cdot + Fe(II)(OH)$$

$$HO\cdot + HC{\equiv}CH \rightarrow HOCH{=}\dot{C}H$$

$$HOCH{=}\dot{C}H \xrightarrow{Fe(II)/H_2O_2} HOCH{=}CH_2 \rightleftharpoons OCHCH_3$$

$$HOCH{=}\dot{C}H \xrightarrow{Cu(II)/H_2O_2} HOCH_2CHO$$

The radical 1,4-addition of organoboranes to an α,β-unsaturated ketone or aldehyde followed by hydrolysis yields a longer chain ketone or aldehyde [25–27].

$$R_3B \xrightarrow{O_2} R\cdot$$

$$R\cdot + CH_2{=}CHCOR' \rightarrow RCH_2\dot{C}HCOR' \rightleftharpoons RCH_2CH{=}CR'O\cdot$$

$$RCH_2CH{=}CR'O\cdot + R_3B \rightarrow RCH_2CH{=}CR'OBR_2 + R\cdot$$

$$RCH_2CH{=}CR'OBR_2 \xrightarrow{H_2O} RCH_2CH_2COR'$$

The most efficient use of the alkene used to generate the organoborane is accomplished using 3,5-dimethylborinane derivatives [27, 28] or alkyldiphenylboranes [27]. α-Bromoaldehydes may be synthesised using 2-bromoacrolein [29]. α,β-Unsaturated ketones are produced by the 1,4-addition of organoboranes to acetylacetylene [30].

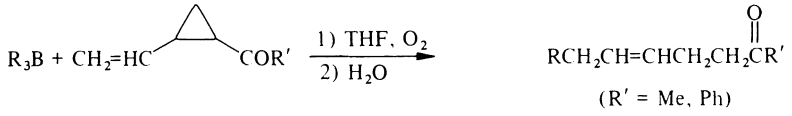
$$R_3B \xrightarrow{O_2} R\cdot$$

$$R\cdot + HC{\equiv}CCOCH_3 \rightarrow RCH{=}\dot{C}COCH_3 \rightleftharpoons RCH{=}C{=}C(CH_3)O\cdot$$

$$RCH{=}C{=}C(CH_3)O\cdot + R_3B \rightarrow RCH{=}C{=}C(CH_3)OBR_2 + R\cdot$$

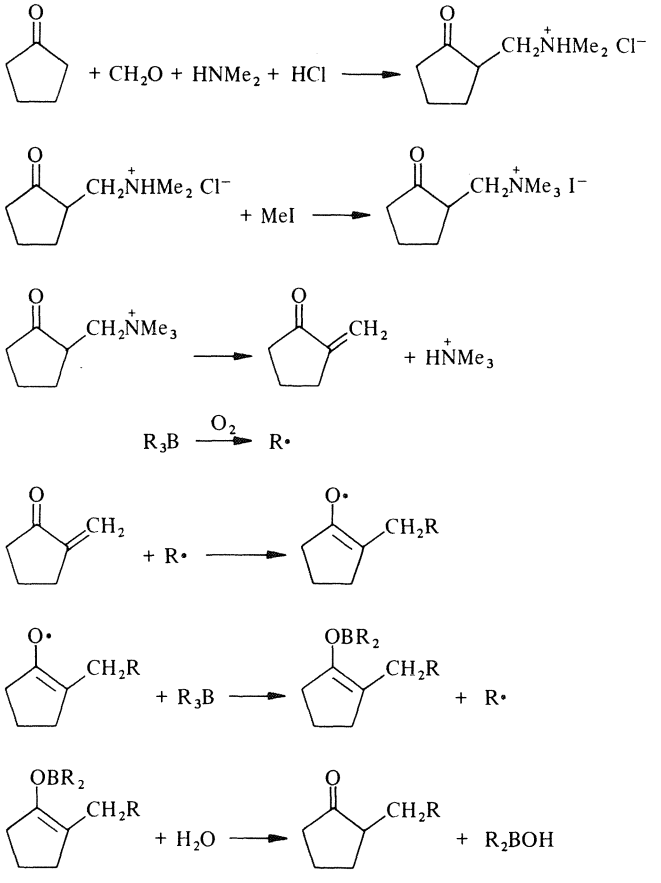
$$RCH{=}C{=}C(CH_3)OBR_2 \xrightarrow{H_2O} RCH{=}CHCOCH_3$$

This last reaction has been extended to afford γ,δ-unsaturated ketones utilising effectively a 1,6-addition of the borane to l-acetyl-2-vinylcyclopropane or 1-benzoyl-2-vinylcyclopropane [31].

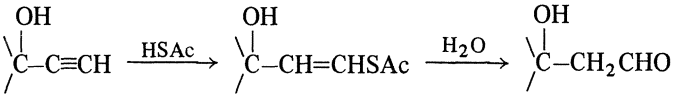


However, to obtain reasonable yields it is necessary to use lithium dialkylcuprates in place of the borane.

Cyclic ketones may be α-alkylated by converting them to Mannich bases, quaternising in situ, and treating with borane in alkaline solution [32].



The free radical addition of thioacetic acid to alkynylcarbinols gives γ-hydroxy-α,β-unsaturated thioesters. These products afford aldols (β-hydroxyaldehydes) on hydrolysis [33].



The aldols are dehydrated to afford α,β-unsaturated aldehydes. Alternatively the first formed adduct may be dehydrated and then hydrolysed.

The β-scission, carbon-carbon bond cleavage of alkoxyl radicals affords a carbonyl group and the pattern of fragmentation can generally be predicted;

$$R^1R^2R^3CO\cdot \rightarrow R^1\cdot + R^2R^3CO$$

the more substituted an alkyl radical, the more likely it is to cleave [34]. Alkoxyl radicals are formed from hypochlorites by thermal or photochemical decomposition and also by the metal salt catalysed decomposition of hydroperoxides. For example, *n*-butyl hydroperoxide with iron(II) sulfate affords 45–55% butyraldehyde, 10–15% formaldehyde and 10% propane [35].

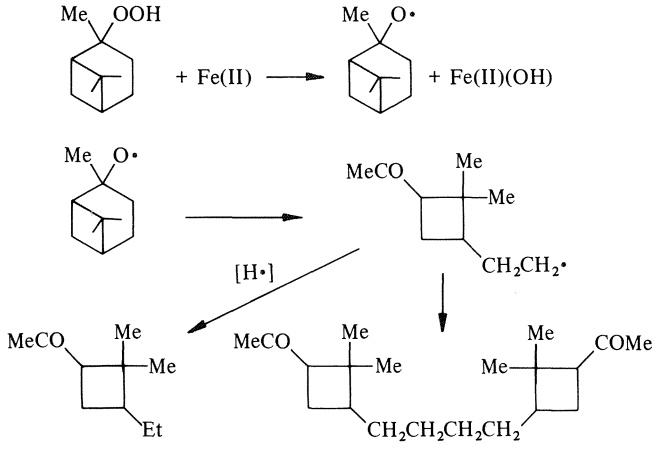
$$CH_3CH_2CH_2CH_2OOH + Fe(II) \rightarrow CH_3CH_2CH_2CH_2O\cdot + Fe(II)(OH)$$

$$CH_3CH_2CH_2CH_2O\cdot \xrightarrow{Fe(II)(OH)} CH_3CH_2CH_2CHO + H_2O$$

$$CH_3CH_2CH_2CH_2O\cdot \rightarrow CH_3CH_2CH_2\cdot + CH_2O$$

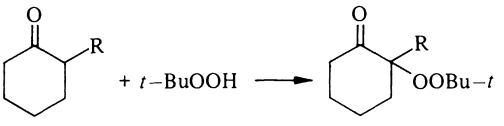
$$CH_3CH_2CH_2\cdot + n\text{-}BuOOH \rightarrow CH_3CH_2CH_3 + n\text{-}BuOO\cdot$$

Apparently the presence of the metal ion affects the formal cleavage pattern. The use of cyclic hydroperoxides has already been mentioned; another example is the use of pinane hydroperoxide to afford bis-cyclobutyl-substituted butanes [36, 37], or a substituted cyclobutane [38].



The formation of carbonyl functions is a reaction discussed, along with other reactions, in general reviews on the metal salt catalysed decomposition of hydroperoxides [22], and peroxides [39]. The fragmentation of oxy-radicals has also been reviewed [40].

Alkenes on treatment with *t*-butyl hydroperoxide and cobalt(II) salts yield allylic peroxides which may be decomposed *in situ* affording aldehydes and ketones [41]. For example, cyclohexene affords cyclohexen-3-yl *t*-butyl peroxide; some of which decomposes to form cyclohex-2-enone. In a similar reaction cyclic ketones may be α-substituted with a *t*-butylperoxy function [42, 43].



(90%)

(A preparative study of the decomposition of such peroxides could be useful).

Alcohols may be oxidised to carbonyl compounds using hydrogen peroxide and iron(II) salts or peroxydisulfate and silver(I) nitrate [44]. More useful perhaps is the peroxydisulfate/silver(I) oxidation of primary amines to yield aldimines, which can be hydrolysed to aldehydes in acid solution with varying yields (15–95%). Primary amines with secondary alkyl groups yield ketones [45]. Secondary amines also react but yields are lower [46].

$$^{-}O_3SOSO_3^{-} + Ag(I) \rightarrow {}^{-}O_3SO\cdot + SO_4^{2-} + Ag(II)$$

$$RCH_2NH_2 + {}^{-}O_3SO\cdot \rightarrow R\dot{C}HNH_2 + {}^{-}O_3SOH$$

$$R\dot{C}HNH_2 + SO_4^{2-} + Ag(II) \rightarrow \underset{\displaystyle OSO_3^-}{\overset{|}{RCH}}NH_2 + Ag(I)$$

$$\underset{\displaystyle OSO_3^-}{\overset{|}{RCH}}NH_2 \rightarrow RCH{=}NH + HOSO_3^-$$

$$RCH{=}NH + H_2O \rightarrow RCHO + NH_3$$

$$RCHO + RCH_2NH_2 \rightarrow RCH{=}NCH_2R \text{ (isolable)}$$

The metal ion catalysed reaction of hydroperoxides with benzyl methyl ethers affords acetals [47], but whether the reaction is of general utility for other ethers is not known.

$$ArCH_2OMe + t\text{-BuOOH} \xrightarrow{M^+} ArCH\begin{matrix}\diagup OBu\text{-}t\\ \diagdown OMe\end{matrix} + H_2O$$

The reaction of ethers with *t*-butyl peroxyesters affords alkyl acyloxyalkyl ethers which yield acetals on treatment with excess alcohol [48, 49].

$$RCO.OOBu\text{-}t \xrightarrow{Cu(I)/Cu(II)} RCO.O^{-} + t\text{-BuO}\cdot$$

$$R'CH_2OCH_2R' + t\text{-BuO}\cdot \rightarrow R'\dot{C}HOCH_2R' + t\text{-BuOH}$$

$$R^1\dot{C}HOCH_2R^1 + RCO.O^- + Cu(II) \rightarrow R^1\underset{\underset{OCOR}{|}}{C}HOCH_2R^1 + Cu(I)$$

then

$$R^1\underset{\underset{OCOR}{|}}{C}HOCH_2R^1 \xrightarrow{\text{excess } R^2OH} R^1CH(OR^2)_2$$

Mixed acetals may sometimes be formed [48–51].

$$R^1CH_2\underset{\underset{OCOPh}{|}}{O}CHR^1 + t\text{-BuOH} \rightarrow R^1CH_2\underset{\underset{OBu\text{-}t}{|}}{O}CHR^1 + PhCO_2H$$

Ketals can be similarly prepared from ethers with tertiary hydrogen atoms [48, 49].

The acyloin condensation of alkyl esters [52–54] is probably a radical process. The copper(II) acetate oxidation of acyloins affords α-dicarbonyls [55].

Aldehydes have been prepared by the iron(II) catalysed decomposition of tertiary amine oxides [56–58]. Secondary and tertiary amines also result in peroxides. The reaction is carried out in an acidic medium but the selectivity of aldehyde formation from a mixed tertiary amine oxide decreases with increasing pH [58]. The ease of aldehyde formation is $PhCH_2 > Me > RCH_2 \sim R_2CH$ [58].

$$R_2\overset{\uparrow}{O}NCH_2R' + H^+ \rightarrow R_2\underset{\underset{+}{|}}{\overset{OH}{\overset{|}{N}}}CH_2R'$$

$$R_2\underset{\underset{+}{|}}{\overset{OH}{\overset{|}{N}}}CH_2R' + Fe(II) + H^+ \rightarrow R_2\overset{+}{\dot{N}}CH_2R' + H_2O + Fe(III)$$

$$R_2\overset{+}{\dot{N}}CH_2R' \rightarrow R_2N\dot{C}HR' + H^+$$

$$R_2N\dot{C}HR' + Fe(III) \rightarrow R_2\overset{+}{N}{=}CHR' + Fe(II)$$

$$R_2\overset{+}{N}{=}CHR' + H_2O \rightarrow R_2\overset{+}{N}H_2 + R'CHO$$

also

$$R_2\overset{+}{\dot{N}}CH_2R' + Fe(II) \rightarrow R_2NCH_2R' + Fe(III)$$

and

$$R_2N\dot{C}HR' + H^+ + Fe(II) \rightarrow R_2NCH_2R' + Fe(III)$$

The free radical halogenation of ketones, aldehydes, and the bromination of acetals has been reviewed by Sosnovsky [4]. More recently aliphatic aldehydes have been converted to 2,2-dihalogenated derivatives by protecting the aldehydic function as its Schiff base using *t*-butylamine, and brominating with two moles of *N*-bromosuccinimide. Hydrolysis reforms the aldehydic product [59].

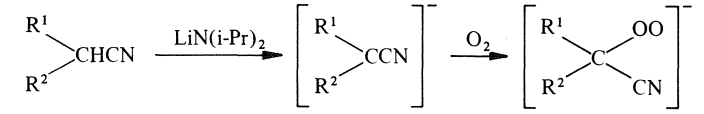
$$RCH_2CHO \xrightarrow{t\text{-}BuNH_2} RCH_2CH{=}NBu\text{-}t$$

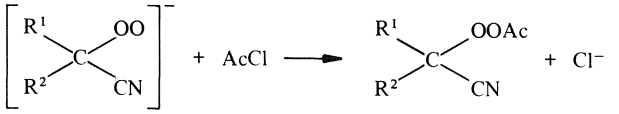
$$RCH_2CH{=}NBu\text{-}t \xrightarrow{NBS} RCBr_2CH{=}NBu\text{-}t$$

$$RCBr_2CH{=}NBu\text{-}t \xrightarrow{H_2O/H^+} RCBr_2CHO$$

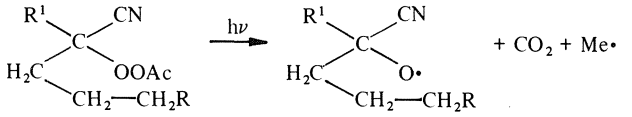
The monobromination of ketones at the α-carbon has been accomplished using 2-bromo-2-cyano-*N*,*N*-dimethylacetamide [60]. The reaction shows high selectivity, also afforded by the use of pyrrolidone hydrotribromide [61].

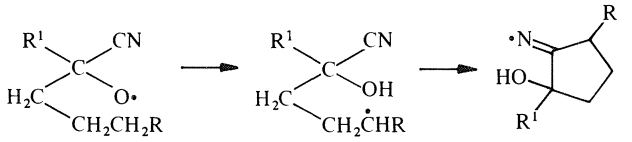
δ-Ketonitriles have been produced in good yield *via* the decomposition of α-peracetoxynitriles [62]. (The latter have been prepared by oxidation of nitrile anions in the presence of acetyl chloride.)

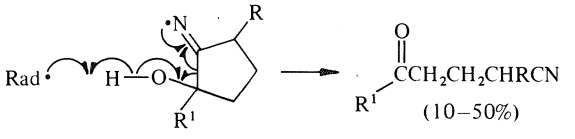




(60–80%)

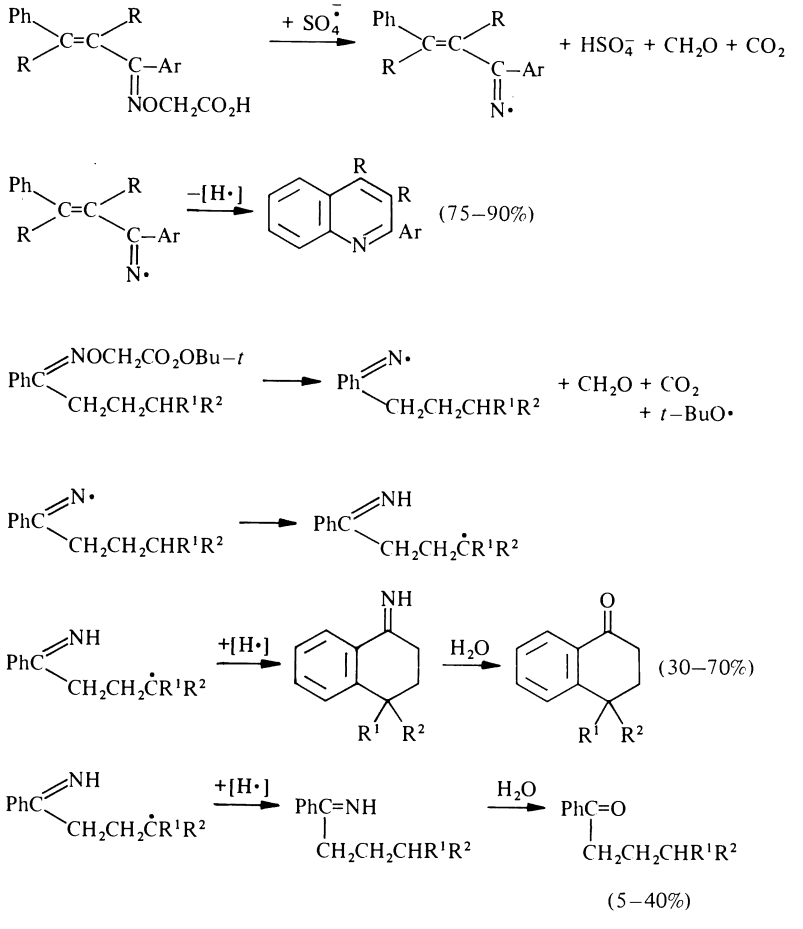






This decomposition reaction involves migration of the parent functional group, whilst the daughter function stays in its original site. It has been suggested that this could be of great advantage when combined with the efficiency and regioselectivity of intramolecular radical reactions often used to introduce functionality at a carbon-hydrogen bond; further developments are awaited with interest.

The persulfate oxidation of oximinoacetic acids has been shown to be synthetically useful, affording substituted quinolines or imines [63]. Decomposition of the *t*-butyl peresters of the oximinoacetic acids affords similar products. Hydrolysis of the imines forms tetralones.



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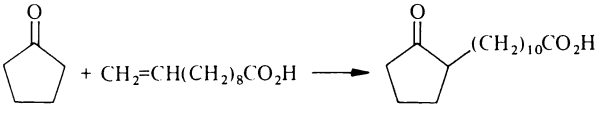
8. Carboxylic Acids and Their Derivatives

Radical additions to unsaturated compounds are attractive methods for preparing carboxylic acids and their derivatives (ester, halide, lactone, amide, anhydride). The carboxylic acid function may be in the unsaturated compound, for example cyclopentanone adds to undecylenic acid affording a 70% yield of product [1].



More often, however, a carboxylic acid function is on the addendum. Telomerisation tends to occur with the smaller alkenes so that the addition of acetic acid to ethene affords a mixture of straight chain carboxylic acids [2]. With larger alkenes, however, telomerisation is less extensive, and yields of up to 70% of 1 : 1 adducts have been obtained with a variety of acids and esters [3]. Dicarboxylic acids may be produced by the bis-addition of carboxylic acids to α,ω-dialkenes [4]. Generally esters have been predominantly alkylated at the α-position of the acid moiety, (not at the α-position of the alcohol derived moiety [3]) as is exemplified in the following example utilising a methyl ester, e.g. [3]

$$n\text{-}C_6H_{13}CO_2Me + CH_2{=}CH(CH_2)_5CH_3 \rightarrow n\text{-}C_8H_{17}CH(C_5H_{11})CO_2Me \quad (55\%)$$

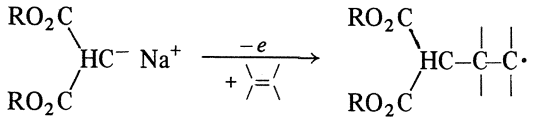
but also [5]

$$CH_2(CO_2Et)_2 + C_6H_{13}CH{=}CH_2 \rightarrow C_8H_{17}CH(CO_2Et)_2 \quad (79\%)$$

in the latter example 2–14% of the 2 : 1 adduct $C_8H_{17}CH(C_6H_{13})CH_2CH(CO_2Et)_2$ is also formed. However, with polyhalogenoalkenes diethyl malonate undergoes addition reactions *via* the α-position of the alcohol derived moiety [6].

$$EtO_2CCH_2CO_2CH_2CH_3 + CF_2{=}CFCF_3 \rightarrow EtO_2CCH_2CO_2CH(CH_3)CF_2CFHCF_3 \quad (40\%)$$

This is not particularly useful since hydrolysis merely reforms the di-acid of the original ester. Esters such as dialkyl malonates may also be alkylated at the methylene group of the acid function by anodic oxidation of the sodio derivative in the presence of an alkene [7].



Examples of radical addition reactions involving carboxylic acids and their derivatives and various unsaturated compounds are scattered throughout the review literature [8–14]. Esters may also be formed by the addition of aldehydes to selected ketones, e.g. [15].

$$PhCHO + (CF_3)_2CO \rightarrow PhCO_2CH(CF_3)_2 \quad (50\%)$$

Acid chlorides add to ketones resulting in ester formation, in a radical chain reaction involving triphenyltin hydride [16, 17].

$$RCOCl + Ph_3Sn\cdot \rightarrow Ph_3SnCl + R\dot{C}O$$

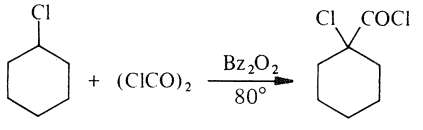
$$R\dot{C}O + R^1COR^2 \rightarrow RCO_2\dot{C}R^1R^2$$

$$RCO_2\dot{C}R^1R^2 + Ph_3SnH \rightarrow RCO_2CHR^1R^2 + Ph_3Sn\cdot$$

Acid chlorides may be prepared *via* the addition of alkyl radicals to carbon monoxide in carbon tetrachloride [18, 19].

$$R\cdot + CO \rightarrow R\dot{C}O \xrightarrow{CCl_4} RCOCl + \dot{C}Cl_3$$

They are also prepared *via* the chloroformylation reaction using oxalyl chloride or phosgene [20, 21]. For example



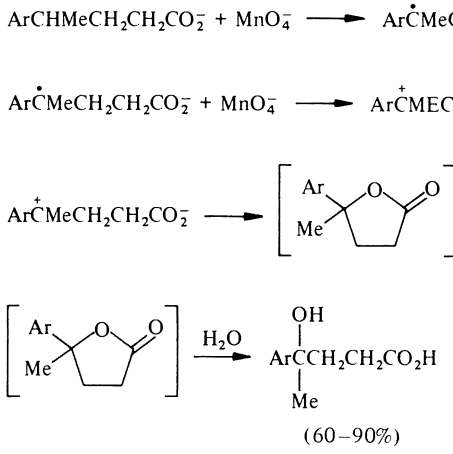
(60%)

Mixed anhydrides have been prepared by the addition of acetic anhydride to terminal alkenes [22, 23], for example

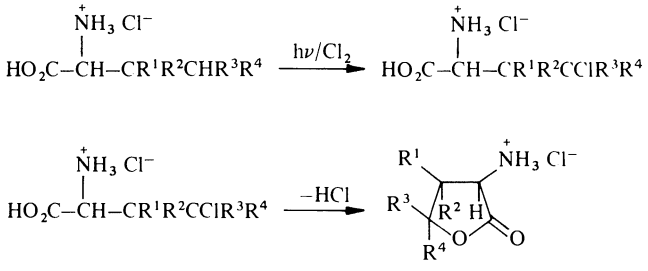
$$CH_3(CH_2)_5CH{=}CH_2 + CH_3CO.O.COCH_3 \rightarrow n\text{-}C_9H_{19}CO.O.COCH_3$$

Unfortunately, distillation cannot be used to work up the reaction mixture as mixed anhydrides tend to decompose when so treated [24].

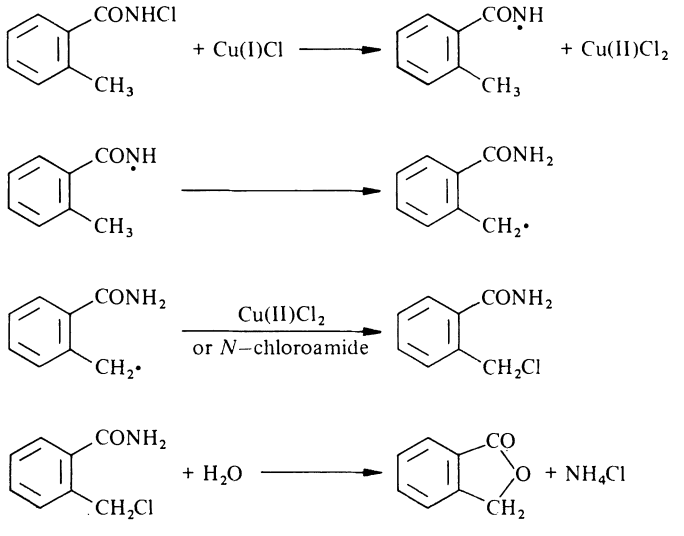
The permanganate or chromate oxidation of carboxylic acids containing a tertiary hydrogen atom affords γ-hydroxy acids [25, 26] in a free radical reaction [27].



The radical addition of alcohols to acrylic acid or alkyl acrylate affords lactones [28], as does the manganese(III) acetate initiated addition of acids to alkenes [29]. The photochlorination of α-aminocarboxylic acids dissolved in dilute hydrochloric acid affords chloro-amino acids, which on hydrolysis produce α-amino-γ-hydroxycarboxylic acid lactones [30].

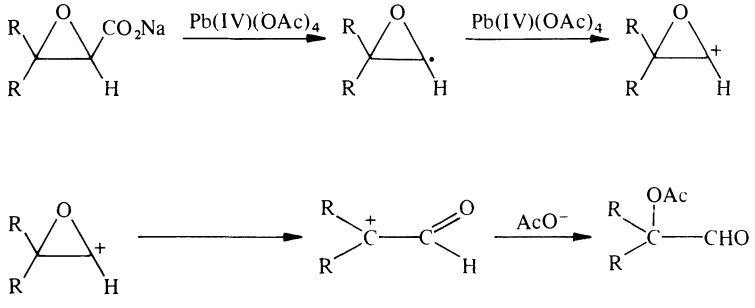


Irradiation of amides in the presence of iodine and lead(IV) acetate affords *N*-iodoamides but it is preferable to use *t*-butyl hypochlorite and iodine in an electrophilic reaction. Rather than isolate any *N*-iodoamide it is usual to form them *in situ* and they are then photolytically converted to iminolactones. These may then be hydrolysed and acidified to afford γ-lactones [31, 32]. The photolytic decomposition of *N*-chloroamides also affords γ-lactones [33]. In these reactions the juxtaposition of reactive centres must be such that a six-membered cyclic transition state can form; however, a small amount of δ-lactone is also produced. *N*-chloroamides may also be decomposed using copper(I) chloride [33].



N-Alkyliminolactones are most readily prepared using the corresponding *N*-alkyl-*N*-bromoamide (from *N*-alkylamide, Br_2, *t*-BuOCl) in carbon tetrachloride and irradiation [34]. Apparently the product readily comes out of solution as the hydrogen bromide complex.

Alkyl ω-alkenoates (25–50%) are prepared by the oxidative decarboxylation of ω-alkoxycarbonylalkanoic acids in the presence of copper [35], a reaction originally due to Kochi [36]. There are many versatile and potentially very useful reactions producing carboxylic acids or their derivatives *via* the use of transition metal ions to oxidise radicals or to effect ligand transfer mechanisms [37, 38]. For example, α-acetoxyaldehydes can be easily obtained from glycidic esters in yields of 35–55% [39]. The glycidates are first converted to sodium glycidates [40], and these are decarboxylated with lead(IV) acetate. The following scheme, although not necessarily the true mechanism of the reaction, rationalises the formation of products.



The metal ion induced decomposition of hydroperoxides and peroxyacids [41], of hydrogen peroxide and peroxydisulfate [42], of dialkyl peroxides, diacyl peroxides, and peroxydicarbonates [43], and of peroxyesters [44] in the presence of reactive substrates can

lead to carboxylic acids or their derivatives. Some of the more important examples of these reactions are given below.

The iron(II) sulphate induced decomposition of α-hydroperoxyethers affords esters which are likely to be contaminated with varying proportions of other producst such as formates, aldehydes, alkanes etc. These are formed from cleavage reactions of intermediate alkoxyl radicals [45].

$$R^1CH(OR^2)OOH + Fe(II) \rightarrow R^1CH(OR^2)O\cdot + Fe(II)(OH)$$

$$R^1CH(OR^2)O\cdot + Fe(II)(OH) \rightarrow R^1COOR^2 + H_2O + Fe(II)$$

(27%)

$$R^1CH(OR^2)O\cdot \rightarrow R^1CHO + \cdot OR^2$$

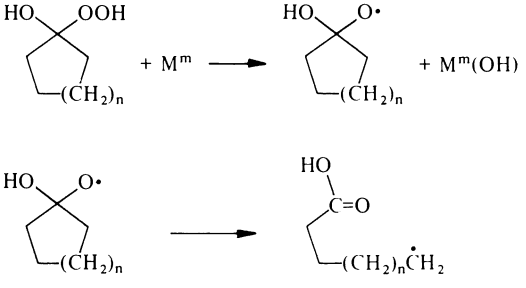
(38%)

$$R^1CH(OR^2)O\cdot \rightarrow HCOOR^2 + R^1\cdot$$

(30%)

$$R^1\cdot + R^1\cdot \rightarrow R^1R^1 \quad (18\%)$$

The metal ion induced decomposition of the complexes of hydrogen peroxide and cyclic ketones to afford acids is perhaps more useful. The product depends on conditions. The first step may be envisaged as a ring opening.



Dimerisation of these radicals then affords dicarboxylic acids, although if a hydrogen donor is present the mono-carboxylic acid is formed [46–49].

$$HO_2C(CH_2)_{n+2}\dot{C}H_2 \xrightarrow{Fe(II)SO_4} HO_2C(CH_2)_{2n+6}CO_2H$$

(ca. 60%)

$$HO_2C(CH_2)_{n+2}\dot{C}H_2 \xrightarrow[+[H\cdot]]{Fe(II)SO_4/Cu(II)SO_4} HO_2C(CH_2)_{n+2}CH_3 \quad (ca.\ 75\%)$$

If large amounts of copper(II) ions are present the unsaturated acid is formed [49, 50].

$$HO_2C(CH_2)_{n+2}\dot{C}H_2 \rightarrow HO_2C(CH_2)_{n+1}CH{=}CH_2 \quad \text{(ca. 25\%)}$$
$$+$$
$$HO_2C(CH_2)_nCH{=}CHCH_3 \quad \text{(ca. 20\%)}$$

Groups derived from an alkene or from a metal halide etc. can be incorporated into the acid product, e.g. [51]

$$HO_2C(CH_2)_{n+2}\dot{C}H_2 + CH_2{=}CHR + X^- \xrightarrow{Cu(II)} HO_2C(CH_2)_{n+4}CHXR \quad (10\text{–}50\%)$$

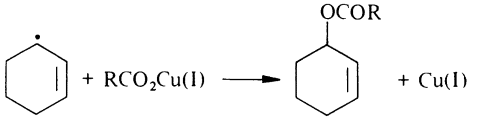
or [49–51]

$$HO_2C(CH_2)_{n+2}\dot{C}H_2 + X^- + M^{m+1} \rightarrow HO_2C(CH_2)_{n+3}X + M^m \quad \text{(ca. 55\%)}$$

Esters may be formed by the metal ion induced decomposition of *t*-butyl peresters [52] or *t*-butyl hydroperoxide [53, 54] in the presence of acid (metal salts of the acid may also be used) and a suitable alkane (aralkane) or alkene, e.g.

$$t\text{–BuOOH} + Cu(I) \longrightarrow t\text{–BuO}\cdot + Cu(I)(OH)$$

$$RCO_2H + Cu(I)(OH) \longrightarrow RCO_2Cu(I) + H_2O$$



(90%)

In the presence of an acid anhydride the cobalt induced decomposition of *t*-butyl hydroperoxide affords perester [55].

The production of radicals from a reactive substrate in the presence of carbon monoxide using hydrogen peroxide and iron(II) salts affords a poor yield (10–25%) of acid [56]. Effective substrates include alcohols, nitriles, and amines. e.g.

$$H_2O_2 + Fe(II) \rightarrow HO\cdot + Fe(II)(OH)$$

$$Me_2XCCH_3 + \cdot OH \rightarrow Me_2XC\dot{C}H_2 + H_2O$$

$$Me_2XC\dot{C}H_2 + CO \rightarrow Me_2XCCH_2\dot{C}O$$

$$Me_2XCCH_2\dot{C}O + Fe(II)(OH) \rightarrow Me_2XCCH_2CO_2H + Fe(II) \quad [X = OH, CN, NH_2]$$

The decomposition of dialkyl peroxides in the presence of an aldehyde may lead to ester formation [57, 58].

$$t\text{-BuOOBu-}t \xrightarrow{Cu(I)} t\text{-BuO}\cdot + t\text{-BuO}^-$$

$$PhCHO + t\text{-BuO}\cdot \rightarrow Ph\dot{C}O + t\text{-BuOH}$$

$$Ph\dot{C}O + {}^-OBu\text{-}t \xrightarrow{Cu(II)} PhCO_2Bu\text{-}t \quad (ca.\ 85\%)$$

In the absence of copper(II) salt the thermal decomposition of di-*t*-butyl peroxide in benzaldehyde affords 1,2-diphenylethylene glycol dibenzoate (90%), probably as a result of the dimerisation of the initial radical addition product [59].

$$Ph\dot{C}O + PhCHO \rightarrow Ph\dot{C}HOCOPh$$

$$2\,Ph\dot{C}HOCOPh \rightarrow \begin{matrix} PhCHOCOPh \\ | \\ PhCHOCOPh \end{matrix}$$

Aroyloxyl radicals have a finite lifetime and undergo addition to double bonds. If the radicals are produced from aroyl peroxides in the presence of iron(II) chloride with added lithium chloride a low yield of chloro-substituted alkyl benzoates is formed [60, 61], as for example with styrene:

$$ArCO_2\cdot + CH_2{=}CHPh \rightarrow ArCO_2CH_2\dot{C}HPh$$

$$ArCO_2CH_2\dot{C}HPh + Fe(III) + Cl^- \rightarrow ArCO_2CH_2CHClPh + Fe(II)$$

The other products include α-chlorobibenzyl and benzoic acids.

From the foregoing it can be seen that many compounds containing hydrogen atoms active towards abstraction by alkoxyl radicals may be oxidised by suitable metal ions and formally trapped by available nucleophilic species. Such reactions afford a variety of pro-

ducts and are often conveniently carried out using the readily available peroxyesters. For example, with an ether the following occurs [62–64]

$$t\text{-BuOOCOR}^1 + \text{Cu(I)} \rightarrow t\text{-BuO}\cdot + \text{R}^1\text{CO}_2\text{Cu(I)}$$

$$t\text{-BuO}\cdot + \text{R}^2\text{CH}_2\text{OR}^3 \rightarrow t\text{-BuOH} + \text{R}^2\dot{\text{C}}\text{HOR}^3$$

$$\text{R}^2\dot{\text{C}}\text{HOR}^3 + \text{R}^1\text{CO}_2\text{Cu(I)} \rightarrow \text{R}^1\text{CO}_2\text{CHR}^2\text{OR}^3 + \text{Cu(I)}$$

(40–50%)

With alkenes allylic substitution occurs [65].

$$t\text{-BuOOCOR} + \text{Cu(I)} \rightarrow t\text{-BuO}\cdot + \text{Cu(I)OCOR}$$

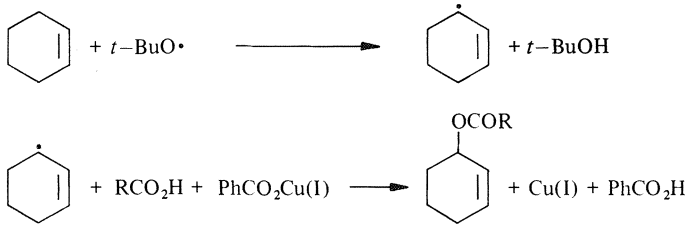
$$t\text{-BuO}\cdot + \text{CH}_2{=}\text{CHCH}_2\text{R}' \rightarrow t\text{-BuOH} + \text{CH}_2{=}\text{C}\dot{\text{H}}\text{R}'$$

$$\text{CH}_2{=}\text{C}\dot{\text{H}}\text{R}' + \text{Cu(I)OCOR} \rightarrow \text{CH}_2{=}\text{CHCH(R}')\text{OCOR} + \text{Cu(I)}$$

(35–61%)

If the reaction is carried out in a carboxylic acid as solvent then the allylic ester of that acid is obtained [65], e.g.

$$t\text{-BuOOCOPh} + \text{Cu(I)} \longrightarrow t\text{-BuO}\cdot + \text{Cu(I)OCOPh}$$



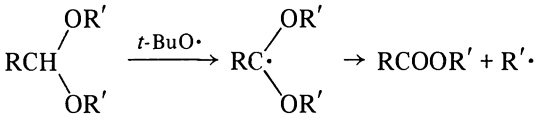
(50–73%)

Aldehydes react with *t*-butyl peroxybenzoate in the presence of copper(I), and this affords a method of preparing mixed aromatic acid anhydrides [58, 66]; the reaction is not applicable to aliphatic aldehydes.

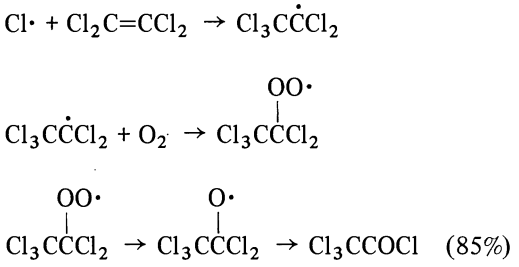
$$t\text{-BuOOCOAr} + \text{Ar}'\text{CHO} \xrightarrow{\text{Cu(I)}} \text{ArCOOCOAr}'$$

There are other radical reactions affording carboxylic acids or their derivatives, but they are of limited appeal as synthetic methods. For example, the autoxidation of an

aldehyde to afford a carboxylic acid is a well known but preparatively limited reaction; it is catalysed by silver(I) and copper(I) [67]. Acetals in the presence of peroxides are oxidised *via* cleavage reactions to afford esters [68–71].

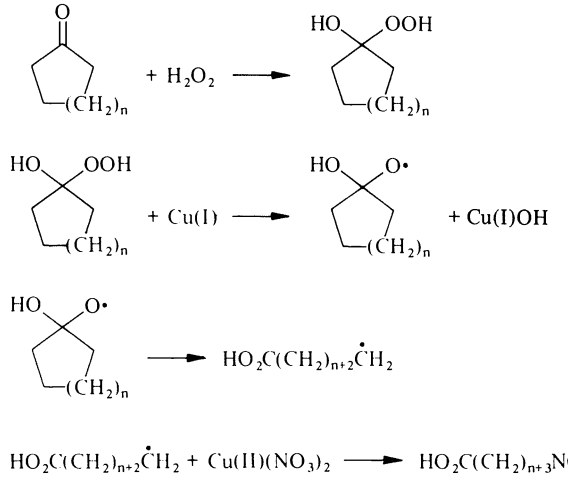


There is a relatively unexplored method of forming acid chlorides by carrying out addition reactions to an alkene in the presence of oxygen, e.g. [72, 73]



Iodine triacylates are converted to esters by treatment with mercuric oxide [74]. Esters are also formed by the reaction of 1 mole of iodine with 2 moles of the silver salt of a carboxylic acid [75]. The reaction is related to the Hunsdiecker reaction (see chapter 4) and alkyl iodides may also be formed.

Cyclic ketones are oxidised by ammonium hexanitratocerate to afford nitratocarboxylic acids [76, 77] which may also be formed from cyclic ketones using hydrogen peroxide and copper(II) nitrate [78].



Amides are usefully prepared by the metal ion induced decomposition of oxaziridines [79]. These reactions are mentioned more fully in Chap. 9.

N-Bromoamides undergo addition reactions with alkenes in the presence of chromium(II) chloride [80, 81]. Using an excess of *N*-bromoamide affords 1 : 1 adducts in yields better than 90%. *N*-Halocarbamates undergo similar addition reactions [80, 81].

$$ZCONHX + CH_2{=}CHR \xrightarrow{Cr(II)Cl_2} ZCONHCH_2CHRX$$

X = Cl, Br; Z = alkyl, alkoxyl

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9. Nitrogen-containing Compounds

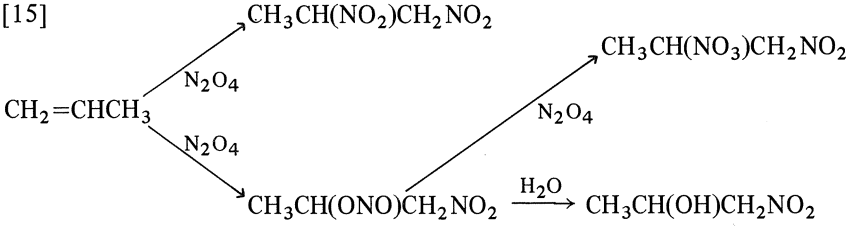
The paramagnetic oxides of nitrogen, NO, $2NO_2 \rightleftharpoons N_2O_4$, and the compounds such as NOCl, NO_2Cl, and nitric acid which can give rise to these species, undergo typical radical reactions. These have often been reviewed [1] and attention is drawn only to representative reactions. Aliphatic nitro compounds are obtained by the liquid phase nitration [1–3] or vapour phase nitration [1, 3–5] of saturated hydrocarbons. The side-chains of aromatic compounds may also be nitrated.

$$PhCH_3 \xrightarrow{HNO_3} PhCH_2NO_2 \quad (55\%) \qquad [6]$$

When nitric acid is used the reaction is catalysed by nitrogen dioxide [7]. In the liquid phase the ease of substitution of hydrogen atoms is the expected tertiary > secondary > primary [8].

The addition of nitrogen dioxide (nitrogen tetroxide) to alkenes [1, 3, 9–13] fluoroalkenes [14] and alkynes [12] can yield α,β-dinitro compounds or the β-nitronitrite. Further oxidation can occur so that the nitronitrite affords nitronitrate; hydrolysis of the nitronitrite affords nitro-alcohol.

[15]



The addition reactions of dinitrogen trioxide [1, 3, 12, 13] and of dinitrogen oxide [16] have been less well investigated and give mixtures of products. In place of dinitrogen trioxide a mixture of nitric oxide and nitrogen dioxide will afford a similar product.

$$PhCH{=}CH_2 \xrightarrow{NO,\ NO_2} PhCH(NO)CH_2NO_2 \qquad [17]$$

(60%)

Nitryl chloride [1, 3] nitrosyl chloride [1, 3, 16], and nitrosyl bromide [1] undergo addition reactions. For example,

$$BrCH{=}CH_2 + NO_2Cl \rightarrow CHBrClCH_2NO_2 \quad [18]$$

(85%)

$$ClCH{=}CH_2 + NOCl \xrightarrow[\text{oxid.}]{NOCl} CHCl_2CH_2NO_2 \quad [19]$$

(20%)

With the nitrosyl halides oxidation can occur and the products of halogen addition may also be found.

$$CF_2{=}CF_2 + NOBr \rightarrow CF_2BrCF_2NO \xrightarrow{NOBr} CF_2BrCF_2NO_2 \quad (37\%) \quad [20]$$

$$\downarrow$$

$$CF_2BrCF_2Br \quad (10\%)$$

Addition reactions are catalysed by the addition of iron(III) chloride [21].

$$CF_2{=}CF_2 + NOCl \xrightarrow{Fe(III)Cl_3} CF_2ClCF_2NO$$

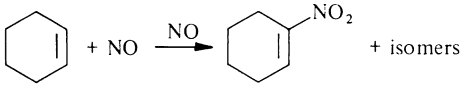
(79%)

β-Chloronitroso compounds are also obtained in good yield by the reaction of nitric oxide with fluoroalkenes in a flow apparatus in the presence of iron(III) chloride [22]. β-Halogenonitro compounds are obtained by the addition of dinitrogen tetroxide to alkenes in the presence of halogen [23, 24]. For example [23],

$$CH_2{=}CHCO_2Me \xrightarrow[I_2]{N_2O_4} O_2NCH_2CHICO_2Me$$

(75%)

Nitric oxide often reacts with alkenes to yield nitroalkene as the major product [25, 26]. For example [25],



However, addition can also occur [22, 27].

$$CF_2{=}CF_2 \xrightarrow[\text{oxid.}]{NO} CF_2NOCF_2NO_2 \quad (90\%)$$

In these reactions the initial nitroso products are oxidised either by disproportionation reactions or by oxygen to afford the above products [27]. Alkenes, with nitric acid, also undergo substitution reactions [1, 28], usually with migration of the double bond. For example [29],

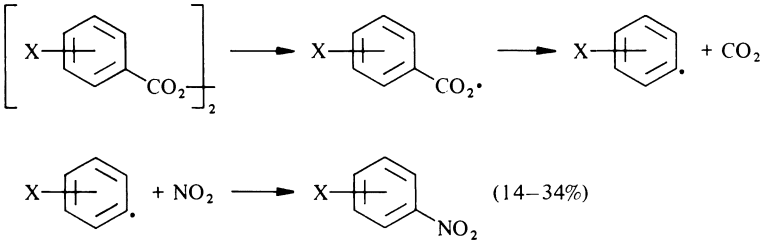
$$CH_3(CH_2)_5CH{=}CH_2 \xrightarrow{HNO_3} CH_3(CH_2)_4CH{=}CHCH_2NO_2 \quad (83\%)$$

Nitric oxide and nitrogen dioxide couple with organic radicals in solution affording nitroso and nitro compounds [2, 30]. Nitrites and nitrates may also be formed [2]. Decomposition of diethyl peroxide in the presence of nitric oxide yields ethyl nitrite [31].

$$EtOOEt \rightarrow 2\,EtO\cdot$$

$$EtO\cdot + NO \rightarrow EtONO \quad (50\text{–}60\%)$$

Although these coupling reactions have been little used for preparative purposes they have merit as routes to some otherwise inaccessible nitroaromatics. Of particular note is the formation of nitro compounds from the decomposition of diaroyl peroxides in the presence of nitrogen dioxide [32, 33].



X = H, *m*–Cl, m–Br, *o*–NO_2, p–NO_2, *m*–Me, *m*–MeO, *o*–$MeOCO_2$

Nitrites decompose under photolysis; for example *t*-butyl nitrite yields nitrosomethane dimer [34].

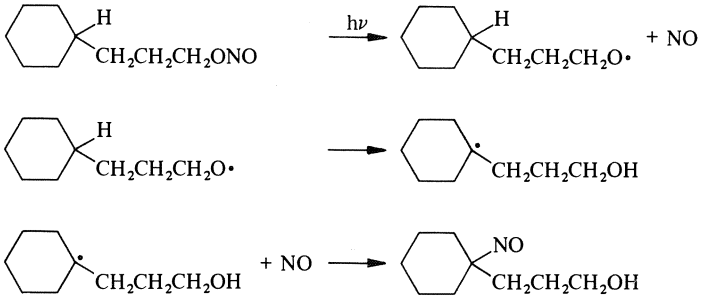
$$t\text{-}BuONO \xrightarrow{h\nu} t\text{-}BuO\cdot + NO$$

$$t\text{-}BuO\cdot \rightarrow Me\cdot + Me_2CO$$

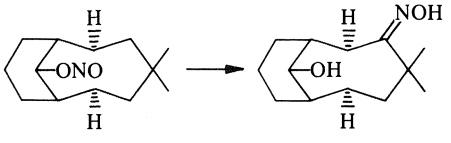
$$Me\cdot + NO \rightarrow MeNO$$

$$2\,MeNO \rightarrow (MeNO)_2$$

The formation of nitroso compounds (or oximes) *via* the photolysis of nitrites is preparatively most useful when the juxtaposition of reactive centres is such that abstraction reactions occur *via* a six-membered cyclic transition state [35–41]. For example 3-cyclohexyl-1-propyl nitrite affords a 31% yield of a tertiary *C*-nitroso product [37].

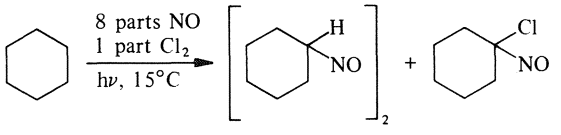


In the steroid system where the stereochemistry is fixed the reaction is known as the Barton reaction [42, 43]. A *C*-nitroso compound or a dimer may be isolated and readily converted to the mono-oxime, and such mono-oximes are often the isolated products. One example of the Barton reaction is given in Chap. 5, another yielding an oxime is shown below [44].



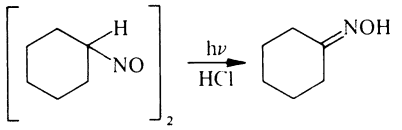
(50–60%)

Photolysis of hydrocarbons in the presence of nitric oxide and chlorine affords chloronitrosoalkanes and bis-nitrosoalkanes [45–48]. The relative yields depend on the ratio of nitric oxide to chlorine. For example [45, 47],



(60%) (20%)

Heating the bis-nitrosoalkanes [47] or photolysis of bis-nitrosoalkanes in the presence of hydrogen chloride [49, 50] affords the mono-oxime.



(93%)

Recently the chemistry of nitrogen-centred radicals has received more attention and been reviewed [51–53]. Perfluoroalkylamino radicals formed by the photolysis of *N*-halogenoperfluoroalkylamines undergo addition to alkenes [54–56], for example

$$(CF_3)_2NCl + CF_3CF{=}CF_2 \rightarrow (CF_3)_2NCF_2CFClCF_3 \quad (96\%)$$

$$+$$

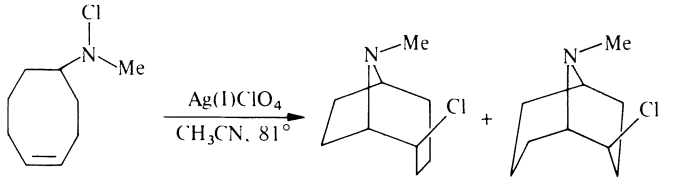
$$(CF_3)_2NCF(CF_3)CF_2Cl \quad (4\%)$$

(yield 76%)

$$(CF_3)_2NCl + \textit{cis}\text{-}CH_3CH{=}CHCH_3 \rightarrow \begin{matrix}(CF_3)_2N\\ \diagdown\\ \quad CHCHClCH_3\\ \diagup\\ CH_3\end{matrix} \quad (99\%)$$

(*erythro* : *threo* = 1 : 9)

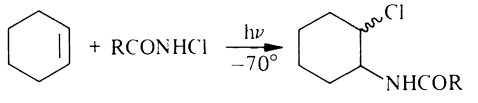
and intramolecular addition of amino radicals to alkenes may be effected [57], but dialkyl-



(32%) (8%)

amino radicals normally show little tendency to add to alkenes.

Amido radicals generated by photolysis of *N*-chloroamides add to cyclohexene at low temperatures (to minimise hydrogen abstraction reactions) [58].



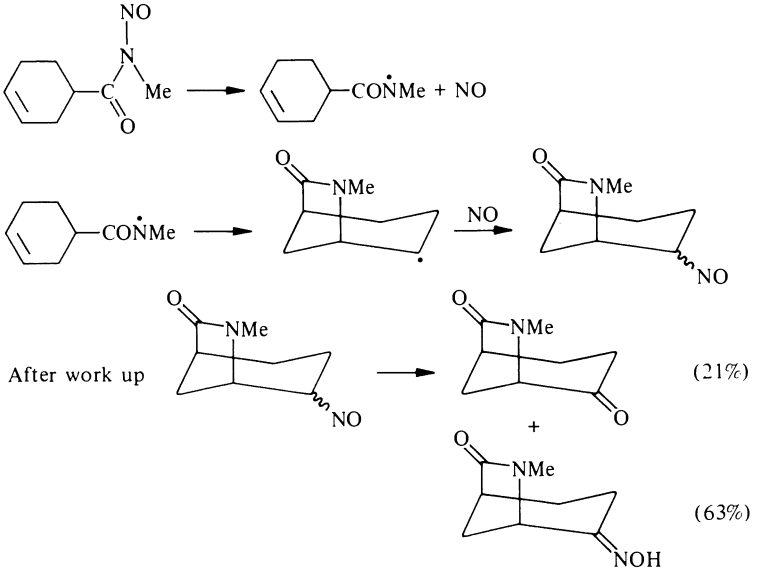
(90%)

N-Bromoamides undergo addition reactions with a variety of alkenes in the presence of chromium(II) chloride [59, 60]. Similar addition reactions occur with *N*-halocarbamates.

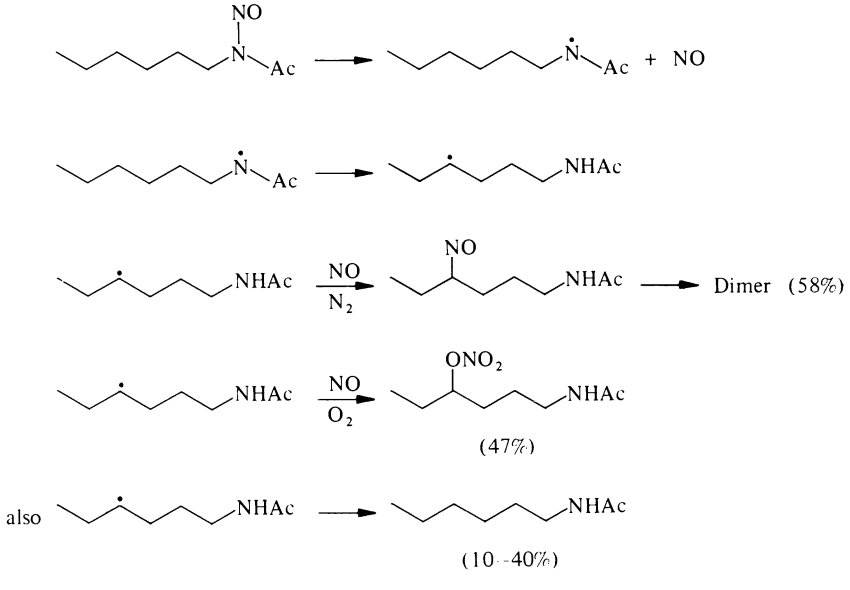
$$ZCONHX + CH_2{=}CHR \xrightarrow{Cr(II)Cl_2} ZCONHCH_2CHRX \quad (60–95\%)$$

Z = alkyl; X = Br Z = alkoxy; X = Cl, Br

Intramolecular addition reactions can also occur with amido radicals affording five-membered lactams, e.g. [61, 62]



Photolysis of saturated *N*-nitrosoamides can lead to 4-nitroso, or in the presence of oxygen, 4-nitrato substituted amides *via* hydrogen abstraction reactions involving six-membered cyclic transition states [63].



The photolysis of *N*-nitrosoamines affords amino radicals which are protonated under acidic conditions and enter into a variety of reactions [64]. In synthetic reactions, amino radicals (usually protonated) have been most commonly formed by the metal ion induced decomposition of hydroxylamines and *N*-halogenoamines [65–67].
Such formed amino radicals may participate in homolytic aromatic substitution reactions [68] (see Chap. 3) or in addition reactions with alkenes [65, 66].
The fate of the carbon-centred radicals so produced depends on the reaction conditions. Using titanium(III), reduction occurs to afford an amine as product [69, 70].

$$R_2NOH + Ti(III) \rightarrow R_2N\cdot + Ti(III)(OH)$$

$$R_2N\cdot + CH_2{=}CHR' \rightarrow R_2NCH_2\dot{C}HR'$$

$$R_2NCH_2\dot{C}HR' + Ti(III)(H_2O) \rightarrow R_2NCH_2CH_2R' + Ti(III)(OH)$$

(ca. 10%)

Oxidation of the radical by molecular oxygen affords α-aminoketones [71].

$$R_2NCH_2\dot{C}HR' + O_2 \rightarrow R_2NCH_2\underset{\displaystyle OO\cdot}{\underset{|}{C}}HR'$$

$$R_2NCH_2\underset{\displaystyle OO\cdot}{\underset{|}{C}}HR' + Fe(II) \rightarrow R_2NCH_2COR' + Fe(II)(OH)$$

(40–75%)

The mechanism of this reaction has recently been investigated and may well involve a complex formed between amino radicals, oxygen, and the metal ion [72].
A ligand transfer process affords a substituted amine [70, 73–75].

$$R_2NCH_2\dot{C}HR' + M^nX \rightarrow R_2NCH_2CHXR' + M^n$$

(15–40%)

X = Cl, OH, OMe, N_3, NR_2

Production of a β-chloroalkylamine followed by treatment with base affords an aziridine [74].
Addition to butadiene tends to afford mixtures of products resulting from reduction, dimerisation, and ligand transfer processes [70, 76–78]. However, when the amino radicals are produced from *N*-haloamines in the presence of butadiene the reactions tend to be cleaner. With halide ion present the ligand transfer process occurs well [79–81].

$$R_2N\cdot + CH_2{=}CHCH{=}CH_2 \rightarrow R_2NCH_2CH{=}C\dot{H}CH_2$$

$$R_2NCH_2CH{=}C\dot{H}CH_2 + M^nX \rightarrow R_2NCH_2CH{=}CHCH_2X + M^n$$

(70–80%)

Without halide ion dimerisation occurs but the product is mixed with branched isomers and the products of chloroamination [80, 82]. It should be noted that unprotonated amino radicals produced by metal ion induced decomposition of *N*-chloroamines afford mainly *cis* adducts with alkenes, whereas the protonated radicals afford both *cis* and *trans* adducts [74, 83]. Furthermore, alkenes substituted with strongly electron-withdrawing groups give poor yields of products [71, 82, 84].

The copper(I) ion induced decomposition of *N,N*-dichloro compounds in the presence of nitrosobenzene affords good yields of azoxy compounds substituted with alkyl, aryl, ester, acyl, and amide groups [85].

$$RNCl_2 + Cu(I) \rightarrow R\dot{N}Cl + Cu(I)Cl$$

$$ArNO + R\dot{N}Cl \rightarrow Ar\overset{O\cdot}{\underset{|}{N}}—\overset{Cl}{\underset{|}{N}}–R$$

$$Ar\overset{O\cdot}{\underset{|}{N}}—\overset{Cl}{\underset{|}{N}}–R + Cu(I) \rightarrow ArN(O)=NR + Cu(I)Cl \quad (51–83\%)$$

In the absence of reactive substrates dialkylamino radicals produced from *N*-chloroamines and metal ions attack the solvent, abstracting hydrogen and affording the products of chlorination of the solvent in a regioselective reaction, particularly when the amino radicals are protonated [65, 66] (see Chap. 4).

When no solvent is used intramolecular hydrogen abstraction occurs leading to products of cyclisation [86, 87].

$$Me(CH_2)_3\overset{+}{N}H_2Cl \xrightarrow[H_2SO_4]{Fe(II)} \underset{H}{\overset{N}{\langle\!\rangle}} \quad (72\%)$$

The same cyclisation reactions are more usually induced thermally or photolytically when the reaction is known as the Hofmann-Löffler-Freytag reaction [67, 88]. The reaction generally occurs *via* cyclic six-membered transition states although seven-membered cyclic transition states also readily occur [86]. A modification of the reaction is to use *N*-chlorodimethylamine to produce the chain-carrying amino radicals in the presence of an amine which will afford the desired cyclic product [86, 89], on treatment with sodium hydroxide.

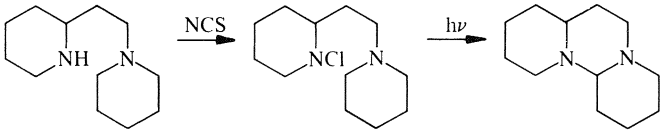
$$Me_2\overset{+}{N}HCl + Fe(II) \xrightarrow{H_2SO_4} Me_2\overset{+}{\dot{N}}H + Cl^- + Fe(III)$$

$$MeCH_2(CH_2)_4\overset{+}{N}H_2R + Me_2\overset{+}{\dot{N}}H \longrightarrow Me\dot{C}H(CH_2)_4\overset{+}{N}H_2R + Me_2\overset{+}{N}H_2$$

$$Me\dot{C}H(CH_2)_4\overset{+}{N}H_2 + Me_2\overset{+}{N}HCl \longrightarrow MeCHCl(CH_2)_4\overset{+}{N}H_2R + Me_2\overset{+}{\dot{N}}H$$

$$MeCHCl(CH_2)_4\overset{+}{N}H_2R \xrightarrow{OH^-} \underset{R}{\overset{N}{\langle\!\rangle}}Me$$

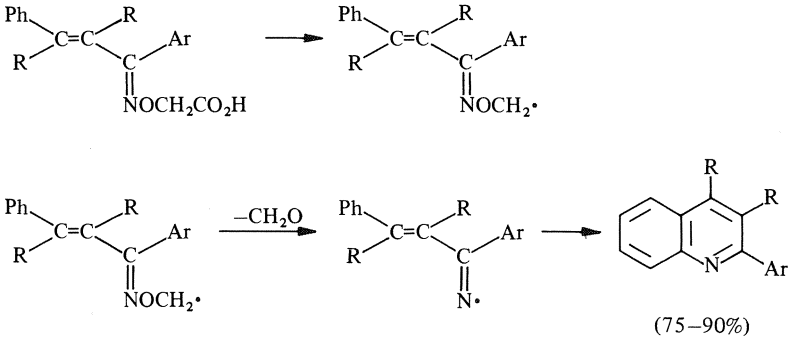
Another modification avoiding the use of strongly acid conditions is to produce the intermediate chloro compound using *N*-chlorosuccinimide [90]. Photolysis affords the product of cyclisation; the addition of triethylamine is recommended to increase the yield. For example,



(50%)

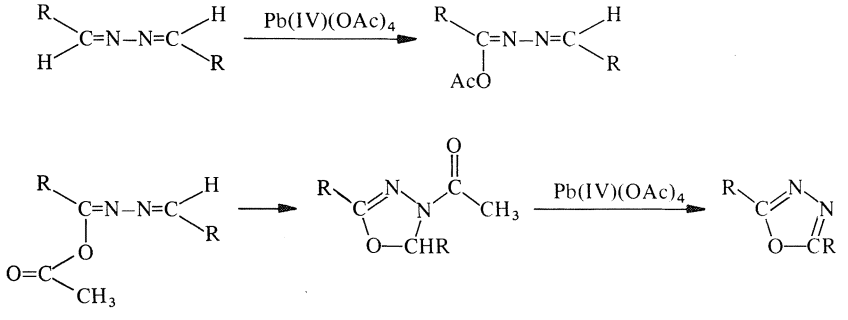
The chemistry of *N*-chloro- and *N*-bromoamines has been reviewed [91].

Other nitrogen-centred radicals have been produced and used in synthetically useful reactions, for example the persulphate oxidation of oximinoacetic acids affords iminyl radicals, which can undergo successive intramolecular addition and aromatic substitution reactions [92].

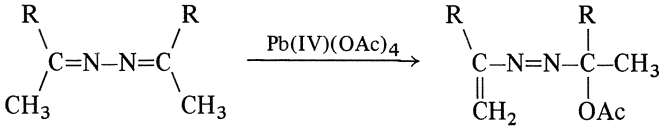


(75–90%)

The oxidative cyclisation reactions of oximes, semicarbazones, hydrazones, and azines using lead(IV) acetate may involve radical species [93, 94]. For example [95, 96] aldazines cyclise to 1,3,4-oxadiazoles, *via* acetoxyazines.

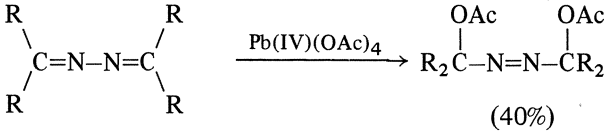


Ketazines with reactive hydrogens in the alkyl groups form α,β-unsaturated azo-acetates.



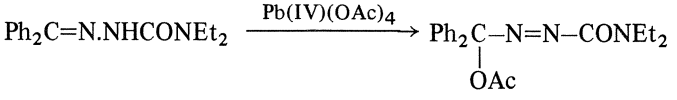
(40–70%)

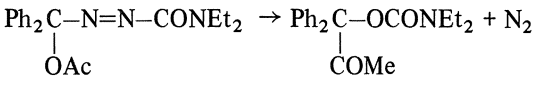
Ketazines without such hydrogens form bis-acetoxyazo compounds [95, 96].



(40%)

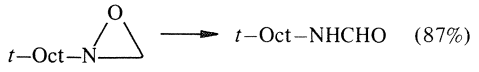
The diethyl semicarbazone of benzophenone is oxidised with lead(IV) acetate to a carbamate [97].



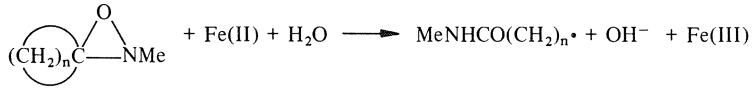


(63%)

Oxaziridines undergo ring-opening reactions in the presence of metal ions [65, 98] for example [99],



Oxaziridines substituted in the 3-position with alkyl groups lead to a mixture of products [99], but the reaction is synthetically very useful when a spiro-bicyclic oxaziridine is used since the carbon ring undergoes opening to afford an amido substituted alkyl radical [100].



The fate of the radical depends on the reaction conditions. Generally dimeric products are obtained [100] but in the presence of anions ligand transfer can occur [101, 102].

$$MeNHCO(CH_2)_n^{\bullet} + Fe(II)X \rightarrow MeNHCO(CH_2)_nX + Fe(II)$$

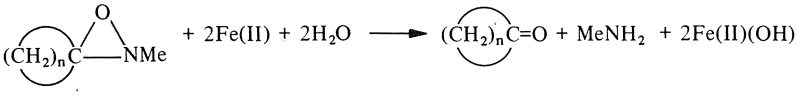
Alternatively the radical is oxidised with copper(II) ions [102],

$$MeNHCO(CH_2)_n^{\bullet} + Cu(II) \rightarrow MeNHCO(CH_2)_{n-2}CH{=}CH_2 + H^+ + Cu(I)$$

or reduced with titanium(III) ions [102].

$$MeNHCO(CH_2)_n^{\bullet} + H_2O + Ti(III) \rightarrow MeNHCO(CH_2)_{n-1}CH_3 + Ti(III)(OH)$$

In these reactions the usual contaminating products are the corresponding ketone and amine [102].



The amido substituted radical will undergo addition to butadiene; the new amido substituted radical can dimerise to yield products [103], or the amido-alkyl radical will undergo addition to an alkene containing an electron withdrawing group or one such as styrene and the resultant radical will dimerise to afford products [103]. Ligand transfer processes will also afford products [103]. The resultant radical can also substitute in heteroaromatic bases [103, 104], and undergoes addition to benzoquinone [103].

Hydrogen abstraction from the alkyl groups of amines occurs when they are treated with hydrogen peroxide and iron(II) ions [105]. The main products are diamines obtained by dimerisation of the first formed radicals. In the following example the radicals are derived by abstraction of hydrogen from the γ-position in the alkyl side chain.

$$n\text{-}PrNH_2 \xrightarrow[Fe(II)]{H_2O_2} H_2N(CH_2)_6NH_2$$

Nitriles will similarly lead to dimerised products (18–60%). Longer chain diamines are produced by allowing the first formed aminoalkyl radicals to undergo addition to butadiene. Usually one butadiene group is incorporated into the product [106]. Thus

$$t\text{-}BuNH_2 + C_4H_{10} \xrightarrow[Fe(II)]{H_2O_2} Me_2\underset{\displaystyle NH_2}{\underset{|}{C}}CH_2(C_4H_{10})CH_2\underset{\displaystyle NH_2}{\underset{|}{C}}Me_2$$

(38%)

Primary amines react with aqueous alkaline peroxydisulfate solution when catalytically decomposed by silver(I) ions to afford aldimines [107]. The reaction scheme is given in Chap. 7, p. 75.

Primary amines with secondary alkyl groups similarly afford ketimines. Secondary amines are obtained by hydrogenation of the imines. Secondary amines may be used as starting material, but the yields are lower [108].

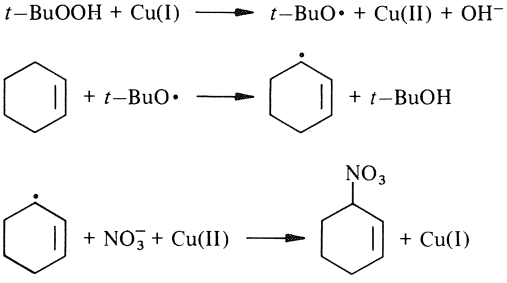
Amino substituted peroxides are made in high yield by the catalytic decomposition of *t*-butyl hydroperoxide induced by copper(I) ions in the presence of an amine [109], e.g.

$$t\text{-BuOOH} + Me_2NPh \xrightarrow{Cu(I)} PhMeNCH_2OOBu\text{-}t$$

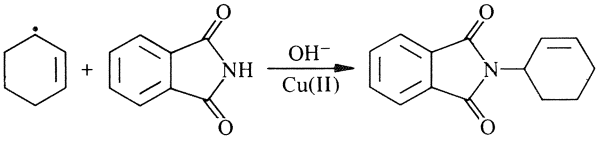
(90%)

Secondary nitriles may be similarly substituted although the primary analogues do not react well [110].

The catalytic decomposition of *t*-butyl hydroperoxide in cyclohexene with copper(I) chloride in the presence of copper(I) nitrate affords cyclohexenyl nitrate [111].

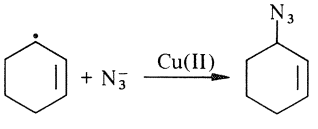


In the presence of phthalimide *N*-cyclohexenylphthalimide is formed [112],

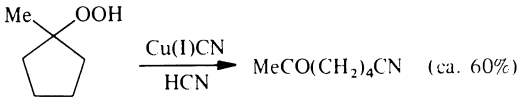


(14%)

and with sodium azide 3-azidocyclohexene is formed [113].

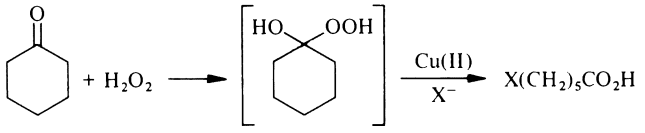


The induced decomposition of cyclic hydroperoxides allows the formation of substituted ketones, e.g. [114]

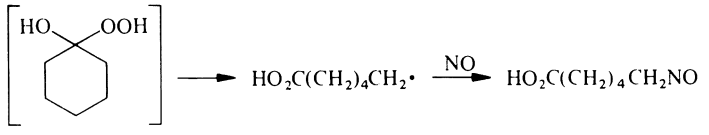


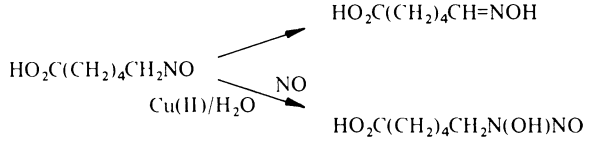
Ketonitriles have also been prepared by the decomposition of α-peracetoxynitriles which is followed by a regioselective rearrangement reaction [115] (see Chap. 7).

The complexes of cyclic ketones with hydrogen peroxide may also be decomposed catalytically to afford useful products. For example with copper(II) nitrate, or with copper(II) sulfate and sodium nitrite, nitrato and nitro carboxylic acids may be formed [111].



In the presence of nitric oxide, an oxime and an *N*-nitrosohydroxylamine are formed. These can be reduced to the corresponding ω-amino acid [116].





It is useful to note that recently a convenient method for reducing azides to amines has been developed [117].

Interestingly nitroxides have not figured greatly in synthetic techniques although their use is now becoming more frequent. *N*-Alkylhydroxylamines are oxidised to the corresponding nitroso compound *via* the nitroxide, using lead(IV) acetate [118], *t*-butyl hydroperoxide [119], or DPPH [120].

$$RNHOH \xrightarrow{-[H\cdot]} RN(O\cdot)H \xrightarrow{-[H\cdot]} RNO$$

N,N-Dialkylhydroxylamines afford the corresponding nitrone unless both alkyl groups are tertiary when the *t*-alkyl-*C*-nitroso compound is formed.

$$RCH_2NR'OH \xrightarrow{-[H\cdot]} RCH_2N(O\cdot)R' \xrightarrow{-[H\cdot]} RCH{=}N(O)R'$$

$$t\text{-}R_2NOH \xrightarrow{-[H\cdot]} t\text{-}R_2NO\cdot \xrightarrow{-[t\text{-}R\cdot]} t\text{-}RNO$$

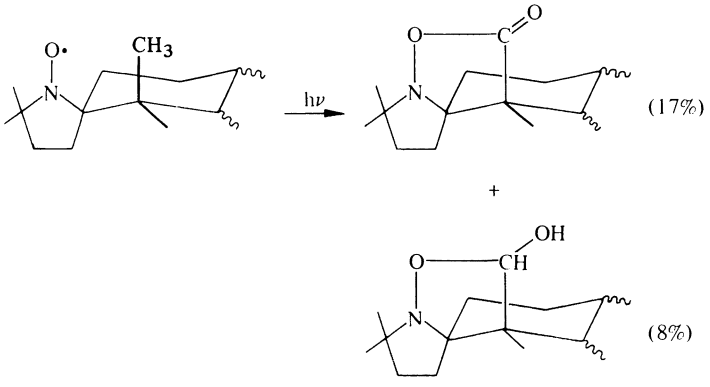
Bis-trifluoromethyl nitroxide couples with other radicals to afford a variety of products. Thus with the trifluoromethyl radical produced photolytically from trifluoromethyl iodide there is a high yield of *N*-trifluoromethoxy-bis-trifluoromethylamine [121]. The radicals which couple may be formed *in situ* by hydrogen abstraction, e.g. with aldehydes [122],

$$(CF_3)_2NO\cdot + RCHO \rightarrow (CF_3)_2NOH + R\dot{C}O$$

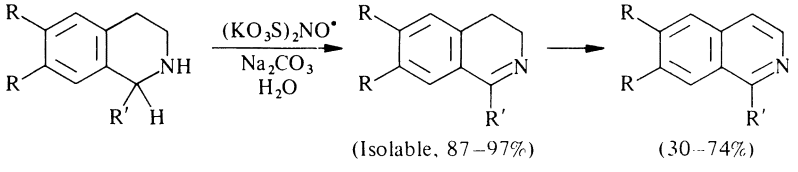
$$(CF_3)_2NO\cdot + R\dot{C}O \rightarrow RCOON(CF_3)_2 \quad (98\%)$$

or they may be formed *via* addition reactions of the nitroxide [123, 124].

A photolytically excited nitroxide has been used to effect selective oxidative demethylation [125].

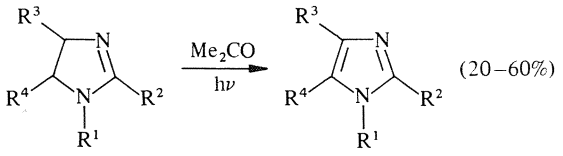


Fremy's salt [$(KO_3S)_2NO\cdot$] has been used to oxidise tetrahydroisoquinolines to isoquinolines [126].



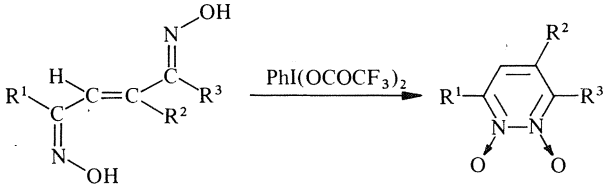
Benzylic hydrogens are also oxidised, thus tetrahydropapaverine afforded 57% of 3,4-dihydroketopapaverine (see Chap. 13).

Other nitrogen heterocycles have been oxidised *via* hydrogen atom abstraction reactions. For example, irradiation of 4,5-dihydroimidazoles in acetone affords imidazoles [127].



In this reaction a small amount of product deriving from substitution by the dimethylcarbinyl radical was also observed. In a similar reaction C-8 of a purine system may be alkylated, e.g. with isopropanol, di-*t*-butyl peroxide, and uv-light [128–131] (see Chap. 13).

Pyridazine 1,2-dioxides have been prepared in good yield by oxidation of the oximes of 1,4-diketones using phenyliodine bis-trifluoroacetate [132].



It has been suggested that the reaction occurs *via* iminoxyl radicals; a similar route was suggested for the silver oxide oxidation of benzaldoxime to benzaldazine-bis-*N*-oxide [133].

Nitriles may be made by treating an oxime with thiochloroformate [134], the reaction is said to form the oxime thiocarbamate, which is dehydrated in a caged radical reaction [135]. Isonitriles may be isomerised to nitriles by a radical addition-elimination sequence [136].

$$R\text{–}\overset{+}{N}\equiv\overset{-}{C} + R'\cdot \rightarrow R\text{–}N{=}\dot{C}R' \rightarrow R'CN + R\cdot$$

If the radical involved is oxygen-centred an isocyanate is formed [123, 136], and if sulfur-centred an isothiocyanate is formed [137].

$$R\text{–}\overset{+}{N}\equiv\overset{-}{C} + \cdot OR' \rightarrow R\text{–}N{=}\dot{C}OR' \rightarrow RNCO + R'\cdot$$

Benzaldimines afford nitriles *via* abstraction reactions [138].

Organoboranes can be converted into azidoalkanes by treatment of the borane with hydrogen peroxide catalytically decomposed with iron(III) azide [139].

$$HO\cdot + R_3B \rightarrow HOBR_2 + R\cdot$$

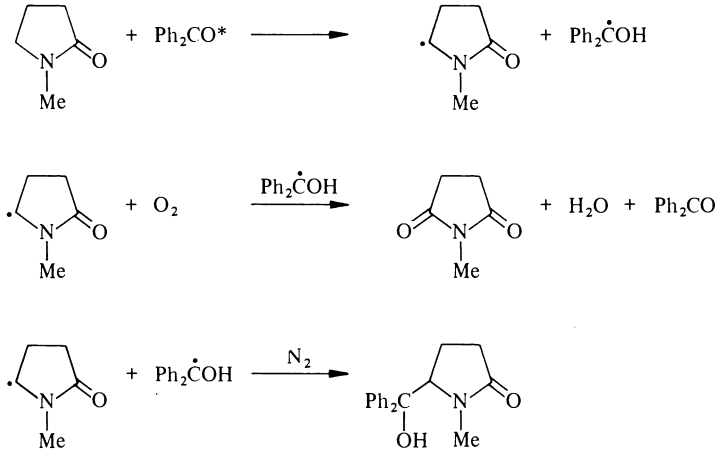
$$^{-}N_3 + R\cdot + Fe(III) \rightarrow RN_3 + Fe(II)$$

(60–100%)

The value of this reaction is that the azidoalkane can be readily reduced to the amine [117].

Lactams are transformed into imides *via* a hydrogen atom abstraction reaction of photoexcited benzophenone in the presence of oxygen [140]. For example, *N*-methyl-

pyrrolidone afforded *N*-methylsuccinimide in 60% yield. If the reaction is carried out under an inert atmosphere of nitrogen the substituted pyrrolidone is obtained.



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10. Sulfur-containing Compounds

The weak sulfur-sulfur bond in elemental sulfur allows carbon-centred radicals and thiyl radicals to effect S_H2 reactions at such sulfur atoms leading to the formation of polysulfides. For example [1],

$$Me_2\dot{C}CN + S_8 \rightarrow Me_2(CN)CS_nC(CN)Me_2$$

and [2]

$$MeSSMe \xrightarrow{120\,^\circ C} 2\,MeS\cdot$$

$$MeS\cdot + S_8 \xrightarrow{MeS\cdot/MeSSMe} MeS_nMe$$

There are comprehensive accounts of these and other analogous reactions [3–5]. Polysulfides are reduced with lithium aluminium hydride to thiols, which offers a route to thiols of limited preparative value [6]. Sulfur monochloride reacts with alkanes *via* displacement reactions at sulfur affording a mixture of disulfides, polysulfides, and alkyl chlorides [6].

The displacement reactions at sulfur may be modified by steric effects. The reaction between trifluoromethylsulfenyl chloride and alkanes can yield both sulfides and chlorides as products [7]. The larger attacking radicals tend to react at the more accessible terminal chlorine atom, whereas smaller (usually primary and secondary) radicals can react at the sulfur atom.

$$R_3C\cdot + ClSCF_3 \rightarrow R_3CCl + \cdot SCF_3$$

$$RCH_2\cdot + ClSCF_3 \rightarrow RCH_2SCF_3 + Cl\cdot$$

The net result is that primary sites generally lead to sulfides whereas tertiary sites lead to chlorides. Secondary sites lead to both sulfide and chloride as product.

Trialkylboranes undergo facile photochemical reactions with disulfides effecting the production of monosulfides [8, 9]. The reaction may also be initiated with oxygen.

$$R'SSR' \rightarrow 2\,R'S\cdot$$

$$R'S\cdot + R_3B \rightarrow R'SBR_2 + R\cdot$$

$$R\cdot + R'SSR' \rightarrow RSR' + \cdot SR'$$

In effecting the conversion of a valuable alkene to a sulfide the use of 3,5-dimethylborinane derivatives is recommended [10]. Although a detailed study of the reaction has not been made, it would appear to be of general applicability and of particular use in preparing monosulfides inaccessible through addition reactions or S_N2 reactions.

Monosulfides are readily obtained by the addition of thiols and hydrogen sulfide to alkenes and alkynes.

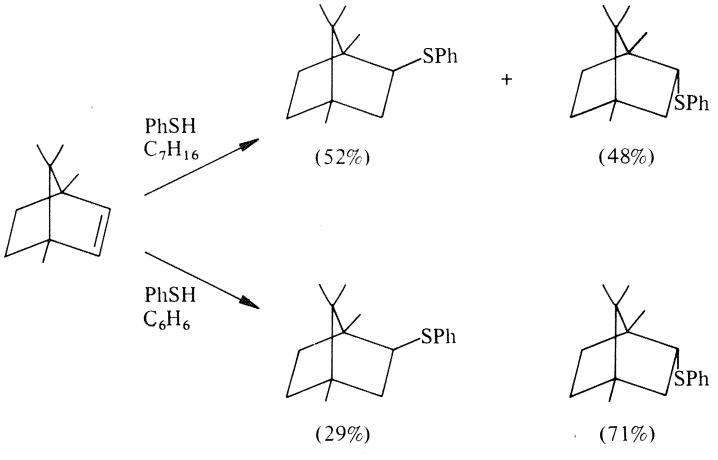
$$RSH + CH_2{=}CHR' \rightarrow RSCH_2CH_2R'$$

Thioacids (RCO.SH) and thiolcarboxylic acids [$HS(CR_2)_nCO_2H$] also undergo addition reactions. The chemistry and mechanism of thiyl radical addition have been much discussed [11–14], and there are reviews pertinent to the preparative uses [15–17]. Rather than list examples of thiyl radical addition products, some points not always widely recognised will be considered. Firstly, the addition reactions of thiyl radicals are often, but not always, reversible. One effect of this reversibility is that the overall rate of addition may well drop as the temperature of a reaction is increased [18]. Related to the reversibility of addition, it is sometimes observed that β-thio-substituted radicals undergo elimination of thiyl radical to afford an alkene or products derived from the alkene rather than the expected sulfide product. For example, in the addition of *n*-butyraldehyde to 2-methylbut-3-en-2-yl phenyl sulfide, initiated by *t*-butyl hydroperoxide, no 1 : 1 adduct was formed. The major product was 7-methyl-6-octen-4-one [19].

$$Me_2C(SPh)CH{=}CH_2 + C_3H_7\dot{C}O \rightarrow Me_2C(SPh)\dot{C}HCH_2COC_3H_7$$

$$Me_2C(SPh)\dot{C}HCH_2COC_3H_7 \rightarrow Me_2C{=}CHCH_2COC_3H_7 + \cdot SPh$$

Secondly, the presence of acid [20], or sulfur [21], or sulfur dioxide [22] promotes ionic, Markovnikoff addition. Transition metals can increase the yield of anti-Markovnikoff products [15]. Thirdly, solvent effects are possible; in the addition of thiols to various methyl-substituted norbornenes an increase of *endo* sulfide over *exo* sulfide ratio was noted when the solvent was changed from hexane to benzene [20]. For example,



Disulfides undergo radical additions to double bonds [15]. The products are the 1,2-bis-monosulfides, usually in good yield, although some telomerisation can occur.

$$RSSR \rightarrow 2\ RS\cdot \qquad \text{initiation}$$

$$RS\cdot + CH_2{=}CHR' \rightarrow RSCH_2\dot{C}HR'$$

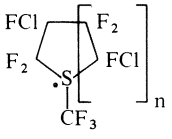
$$RSCH_2\dot{C}HR' + RSSR \rightarrow RSCH_2CH(SR)R' + RS\cdot \qquad \Big\} \text{ chain reaction}$$

For example bis-trifluoromethyl disulfide adds to ethylene and propene to afford respectively $CF_3SCH_2CH_2SCF_3$ (100%) and $CF_3SCH_2CH(Me)SCF_3$ (100%) [23]. With halogenated alkenes telomers tend to predominate; however, trifluorochloroethene also affords a substituted thiacyclopentane.

$$CF_3S\cdot + CF_2 = CFCl \longrightarrow CF_3SCF_2\dot{C}FCl$$

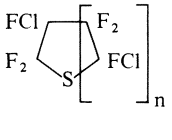
$$CF_3SCF_2\dot{C}FCl + (CF_2 = CFCl) \xrightarrow{n \text{ times}} CF_3SCF_2CFCl(CF_2CFCl)_{n-1}CF_2\dot{C}FCl$$

$$CF_3SCF_2CFCl(CF_2CFCl)_{n-1}CF_2\dot{C}FCl \longrightarrow$$



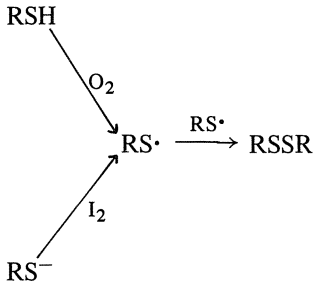
Yields

n = 1	ca. 20%
n = 2	24.8%
n = 3	22.2%
n = 4	19.9%



Clearly a combination of suitable rates of addition and chain transfer coupled with the presence of an element capable of increasing its valency allows some scope in preparative procedures.

Disulfides are readily prepared *via* the oxidation of thiols [24] or by the iodine oxidation of aqueous solutions of sodium thioalkoxides [25].



The addition of a thiol to an unsaturated compound in the presence of carbon monoxide, under pressure, affords alkanethio-substituted aldehydes in low yields.
Presumably intermediate adduct radicals undergo addition to carbon monoxide [26].

$$n\text{-BuSH} + HC{\equiv}CH + CO \rightarrow n\text{-BuSCH=CHCHO}$$

(17%)

1,2-Bis-(*n*-butanethio)ethane is also formed.

The addition of a thiol to an unsaturated compound in the presence of oxygen sometimes affords β-hydroxysulfoxides [27].

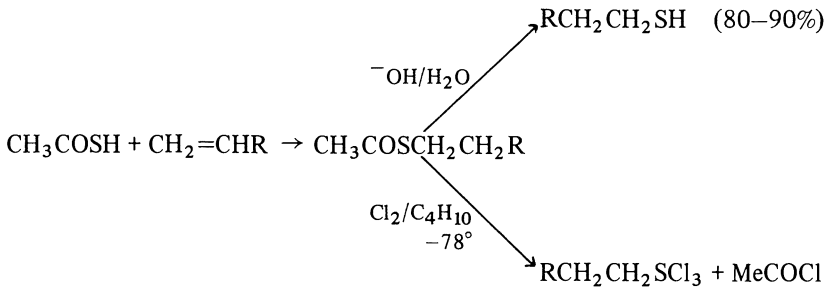
$$RS\cdot + CH_2{=}CHPh \rightarrow RSCH_2\dot{C}HPh$$

$$RSCH_2\dot{C}HPh + O_2 \rightarrow RSCH_2\underset{\displaystyle OO\cdot}{\underset{|}{C}}HPh$$

$$RSCH_2\underset{\displaystyle OO\cdot}{\underset{|}{C}}HPh \xrightarrow{RSH} RSOCH_2\underset{\displaystyle OH}{\underset{|}{C}}HPh \quad (87\%)$$

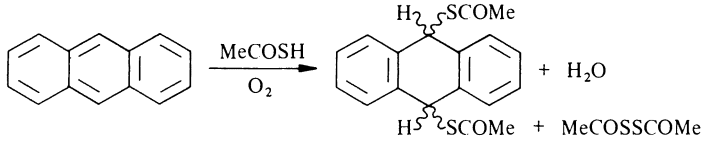
It has been noted that peroxyl radicals can oxidise sulfides to sulfoxides [28], although hydroperoxides are implicated [29].

Addition of thioacetic acid to an alkene affords a good yield of thioester which can readily be hydrolysed to afford a thiol [30], or it can be converted to alkylsulfur trichloride [31].



It may also be possible to convert the thioester to an alkanesulfonyl halide [32–34].

The 9,10 positions of anthracene undergo addition reactions with *S*-thioacetoxyl radicals in a reaction initiated with oxygen [22]



cis and trans (68%)

In ethereal solution, the monosubstituted analogue 9-*S*-thioacetoxy-9,10-dihydroanthracene is formed in 18% yield [22]. A similar reaction carried out in the presence of ferrocene and initiated with *t*-butyl hydroperoxide affords the substitution product 9-*S*-thioacetoxyanthracene [35]. Thiols add to other unsaturated systems, possibly *via* radical reactions, affording useful products. Ketens afford thioesters [36, 37],

$$R_2C{=}C{=}O + R'SH \rightarrow R_2CHCOSR'$$

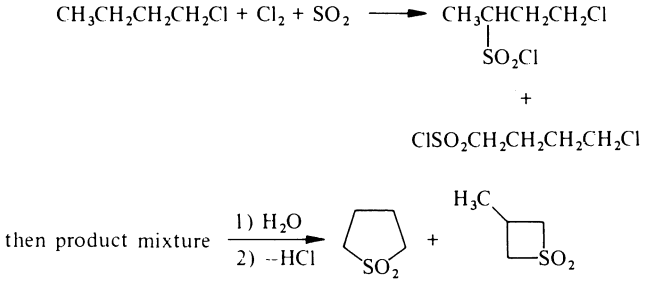
and ketenimines afford thioimidates, although the use of sodium thioalkoxide affords the same products in similar yields [38].

$$Ph_2C{=}C{=}NAr \xrightarrow[h\nu,\ \text{or}\ 80^\circ]{RSH} Ph_2CHC(SR){=}NAr$$

Carbonyl cyanide undergoes addition reactions with thiols. The first formed products are unstable and spontaneously (or with a little warming) lose hydrogen cyanide to afford cyanothioformates [39].

$$RSH + (NC)_2C{=}O \rightarrow RSC(CN)_2OH \rightarrow RSCO.CN + HCN \quad (65–85\%)$$

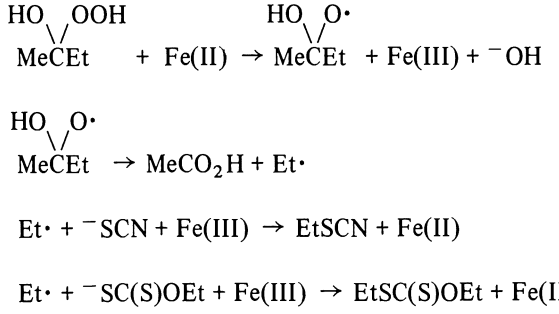
Sulfur-halogen bonds are also suitable for homolytic reactions. At room temperature and slightly above sulfuryl chloride undergoes addition to alkenes affording β-chlorosulfonyl chlorides in radical reactions, usually catalysed by light or benzoyl peroxide at 60 °C [40, 41]. The elements of chlorine are also added (c.f. Chap. 4) in a free radical reaction favoured by higher temperatures. Similarly at higher temperatures alkanes and substituted alkanes are substituted by chlorine using sulfuryl chloride [42] or a mixture of sulfur dioxide and chlorine [44], but lower temperatures favour chlorosulfonation [42–45]. Most of the preparative studies made on these reactions have been tabulated [15]. Work up of the product mixture obtained from chlorosulfonation of *n*-butyl chloride leads to sultones as outlined below [46].



Treatment of the chloroalkylsulfonyl chlorides with ammonia affords sultams [46].

Sulfonyl chlorides also react with alkenes [15]. Addition reactions have been initiated with light, benzoyl peroxide, or copper(I) chloride, and product formation is favoured by lower temperatures. Trichloromethanesulfonyl chloride loses sulfur dioxide and effectively the elements of carbon tetrachloride are added conveniently to a double bond [15]. Sulfonyl bromides and iodides but not apparently fluorides also readily undergo free radical addition reactions.

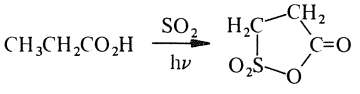
Substituted thiocyanates have been prepared by free radical substitution reactions on hydrocarbons using thiocyanogen and thiocyanogen chloride, in some cases isothiocyanates are preferentially formed. Such reactions have not been widely studied and most have been tabulated [15]. Radical addition of thiocyanic acid to alkenes apparently occurs but has been almost ignored [47]. Radicals formed by the transition metal ion catalysed decomposition of peroxides may be formally oxidised and trapped by thiocyanate ion or xanthogenate. For example [48–50],



The radical addition of bisulfite ion to alkenes in aqueous solution, initiated by peroxides, yields sulfonates in good yields. Most results have been tabulated [15].

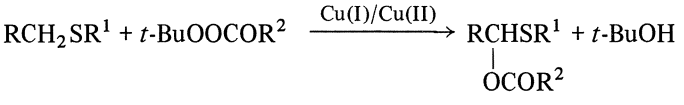
$$RCH{=}CH_2 + HSO_3^- \rightarrow RCH_2CH_2SO_3^-$$

When initiated with peroxides the reaction between sulfuryl chloride and aliphatic acids affords chlorinated acids [43, 45], however, with uv light cyclic mixed anhydrides are also formed *via* reaction at the β or γ-positions of the acid [45], in yields of 40–60% with the lower acids.



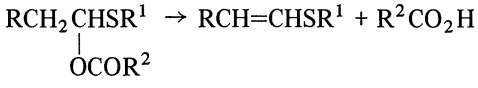
These anhydrides may react further with an alcohol or an amine to afford alkoxycarbonyl- and amidyl-substituted sulfonic acids. This apparently useful series of reactions does not appear to have been widely used in preparative chemistry.

Hydroperoxides oxidise sulfides to sulfoxides as mentioned above. Interestingly an excess of hydroperoxide does not lead *via* further oxidation to sulfone [51], unless transition metal ions are present and then good yields are obtained. Perhaps the easiest method of oxidising sulfides to sulfones in excellent yield is to use hydrogen peroxide catalysed by ammonium molybdate [52]. It is safer to use methanol as solvent rather than acetone. The reaction of dialkyl peroxides and diacyl peroxides with sulfides does not appear to have been studied but the transition metal ion catalysed reaction of peroxyesters with alkyl sulfides has been shown to afford α-acyloxyalkyl sulfides [53–55], without oxi-

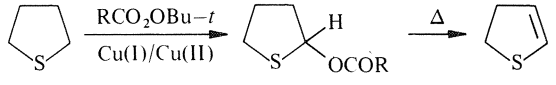


R = H, Me, Et, *n*-Pr, *n*-Bu, Ph (40–80%)
R^1 = Me, Et, *n*-Pr, *n*-Bu, *i*-Pr, *i*-Bu, *t*-Bu, Ph
R^2 = Me, Ph

dation of the sulfur atom. Prolonged heating of these reaction mixtures affords dialkyl-mercaptals [55]. Pyrolysis of the α-acyloxy-substituted sulfides affords alkenyl sulfides [56, 57].



Cyclic sulfides such as tetrahydrothiophene may also be α-acyloxy substituted [55] and pyrolysis of the product affords 2,3-dihydrothiophene in 60% yield.



Interestingly 1,4-thioxane reacts with *t*-butyl peroxybenzoate in the presence of copper(I) chloride to afford 3-benzoyloxy-1,4-thioxane [58] although reaction at the carbon α to oxygen in 1,4-dioxane is also fast.

There are other radical reactions of sulfur compounds of limited synthetic utility. Pentafluorosulfur chloride undergoes free radical additions to alkenes and alkynes.

$$F_5SCl + CH_2{=}CHR \rightarrow F_5SCH_2CHClR$$

In photochemical reactions dichloro products may also be formed. Some results have been tabulated [15, 59].

The photochemical reaction of aliphatic hydrocarbons with liquid sulphur dioxide affords sulfinic acids [60, 61].

$$RH + SO_2 \xrightarrow{h\nu} RSO_2H$$

In the presence of oxygen sulfonic acids are formed [15, 62], mainly by reaction at the expected secondary positions; for example *n*-heptane affords mainly heptane-2-sulfonic acid [63]. If the reaction is carried out in acetic acid or acetic anhydride the mixed peranhydride may be formed [64],

$$RH + SO_2 + (MeCO)_2O \xrightarrow{O_2} RSO_2OOCOMe$$

but if carried out in phosphorus trichloride the symmetrical anhydride results.

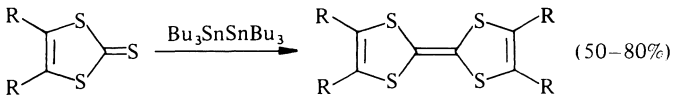
$$RH + SO_2 \xrightarrow[PCl_3]{O_2} (RSO_2)_2O$$

Sulfur dioxide reacts with alkenes in the presence of peroxides or uv light to afford polysulfones [12, 65]. When bromotrichloromethane is included in the reaction mixture halogenated sulfones are formed in low yield [65], for example oct-1-ene affords 1,1,1-trichloro-3-nonyl 2-bromooctyl sulfone.

$$2\,CH_2{=}CH(CH_2)_5CH_3 + BrCCl_3 \xrightarrow[h\nu]{SO_2} Cl_3CCH_2\underset{\displaystyle SO_2\atop\displaystyle CH_2CHBr(CH_2)_5CH_3}{CH(CH_2)_5CH_3}$$

(15%)

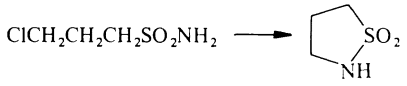
o-Quinones react with sulfur dioxide in the presence of uv light to afford cyclic esters of sulfuric acid [66]. The photolysis of a mixture of 1,3-dithiole-2-thione and hexabutylditin in hexane solution affords tetrathiofulvalene, in a reaction which may proceed *via* radical pathways [67].



N-Chlorosulfonamides under photolysis or on heating afford γ and δ-chlorosulfonamides with the γ-isomer predominating [68], for example

$$CH_3CH_2CH_2CH_2SO_2NBu\text{-}t \xrightarrow{h\nu} CH_3CHClCH_2CH_2SO_2NHBu\text{-}t \quad (45–50\%)$$
$$\begin{matrix} | \\ Cl \end{matrix}$$
$$+$$
$$Cl(CH_2)_4SO_2NHBu\text{-}t + C_4H_9SO_2NHBu\text{-}t$$
$$(4–12\%) \qquad (20–45\%)$$

The resulting γ-chlorosulfonamides, on treatment with base, cyclise, affording a convenient route to sultams, e.g.



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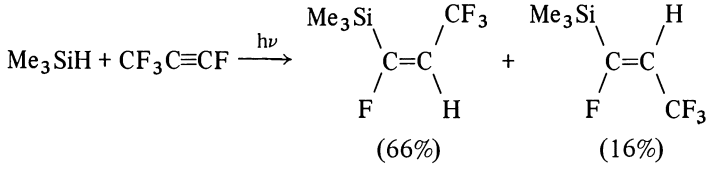
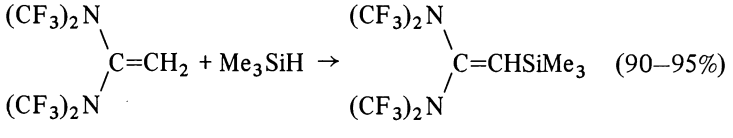
11. Organometallic Compounds

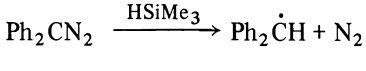
Free radical addition and substitution reactions which have proved so useful in organic synthesis have received less attention in the synthesis of organometallic compounds. The majority of these studies have involved the main group elements and have concentrated on addition reactions. Initially particular reference was made to the addition of silanes, germanes, and various phosphorus compounds to carbon-carbon double and triple bonds [1]. More recently, reactions with more varied substrates have been studied. These include the addition of silanes to halogenated alkenes and alkynes [2, 3], e.g.

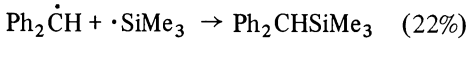


the substitution of unsaturated amines by subsequent addition, elimination reactions, e. g. [4]

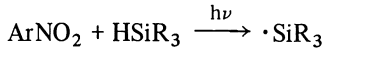


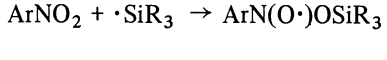
addition to diphenyldiazomethane [5] with loss of nitrogen,





and the reaction of silanes with nitroarenes to afford nitroxides, e.g. [6]





Addition reactions appear to be generally best initiated by peroxides [7], but uv light, iron salts, and azo compounds have also been used [1]. The additions to terminal double bonds usually afford *anti*-Markovnikoff products,

$$R_3Si\cdot + CH_2{=}CHR' \xrightarrow{R_3SiH} R_3SiCH_2CH_2R'$$

whereas additions to non-terminal double bonds lead to a mixture of products in which product formation is dominated by steric effects.

$$R_3SiH + R^1CH{=}CHR^2 \begin{cases} \rightarrow R^1CH(SiR_3)CH_2R^2 \\ \rightarrow R^1CH_2CH(SiR_3)R^2 \end{cases}$$

Silanes also undergo addition reactions to carbonyl compounds although such reactions have not been preparatively exploited. For example, the photolysis of acetone and trichlorosilane affords 2-trichlorosiloxypropane [8].

$$Cl_3SiH + Me_2CO \xrightarrow{h\nu} Me_2HCOSiCl_3$$

With methyl acetate reduction occurs on γ-irradiation [9].

$$Cl_3SiH + MeCOOMe \xrightarrow{\gamma} MeCH_2OMe$$

Silanes add to azo compounds [10].

$$R_3SiH + R^1N{=}NR^2 \rightarrow \begin{array}{ccc} & R^1 \quad R^2 & \\ & \backslash \quad / & \\ & N{-}N & \\ / & & \backslash \\ R_3Si & & H \end{array}$$

Silyl radicals need not be derived from homolysis of a silicon-hydrogen bond. Photolysis of phenylacetyltriphenylsilane affords silyl radicals which add to the carbonyl group of the starting compound [11].

$$Ph_3SiCOCH_2Ph \xrightarrow{h\nu} Ph_3Si\cdot + PhCH_2\dot{C}O$$

$$Ph_3Si\cdot + Ph_3SiCOCH_2Ph \rightarrow Ph_3Si\dot{C}(OSiPh_3)CH_2Ph$$

$$PhCH_2\dot{C}O \rightarrow Ph\dot{C}H_2 + CO$$

$$Ph_3SiC(OSiPh_3)CH_2Ph + PhCH_2 \rightarrow Ph_3SiC(OSiPh_3)(CH_2Ph)_2$$

(40%)

$$Ph_3SiC(OSiPh_3)CH_2Ph \xrightarrow{-[H\cdot]} \begin{matrix} Ph_3Si \\ \diagdown \\ \quad C{=}CHPh \\ \diagup \\ Ph_3SiO \end{matrix} \quad (8\text{–}12\%)$$

$$Ph_3Si\cdot + \cdot CH_2Ph \rightarrow Ph_3SiCH_2Ph \quad (30\text{–}35\%)$$

Free radical additions to organosilanes containing unsaturated alkyl groups have proved synthetically useful. Hydrogen bromide undergoes addition to trimethylsilylacetylene [12].

$$Me_3SiC{\equiv}CH + HBr \rightarrow Me_3SiCH{=}CHBr \quad (70\%)$$

However, 1-trialkylsilylalkynes undergo a two step addition of hydrogen bromide followed by an elimination of silyl bromide to afford 2-bromoalkenes (see Chap. 2). Hydrogen sulfide and diallyldimethylsilane afford 1,1-dimethyl-1-sila-5-thiacyclooctane [13].

$$CH_2{=}CHCH_2SiMe_2CH_2CH{=}CH_2 + H_2S \longrightarrow HS(CH_2)_3SiMe_2CH_2CH{=}CH_2$$

$$HS(CH_2)_3SiMe_2CH_2CH{=}CH_2 \longrightarrow \text{(SiMe}_2\text{, S)} \quad (25\%)$$

Photobromination of vinylsilane and vinylgermane affords the corresponding dibromides [14], e.g.

$$Ph_3SiCX{=}CH_2 + Br_2 \xrightarrow[h\nu]{CCl_4} Ph_3SiCXBrCH_2Br$$

(78–95%)

Highly branched polysilanes have been prepared by allowing silyl radicals to couple in benzene solution [15], e.g.

$$2\,(Me_3Si)_3SiH \xrightarrow[130\,^\circ C,\ C_6H_6]{t\text{-BuOOBu-}t} (Me_3Si)_3SiSi(SiMe_3)_3$$

(92%)

However, with less substituted silanes, dimers are not formed and the only products obtained were those derived from aromatic substitution reactions (14–19%) together with polymers of unknown structure (40–55%), e.g.

$$Me_3SiSiMe_2H \xrightarrow[130\,^\circ C,\ C_6H_6]{t\text{-BuOOBu-}t} Me_3SiSiMe_2Ph$$

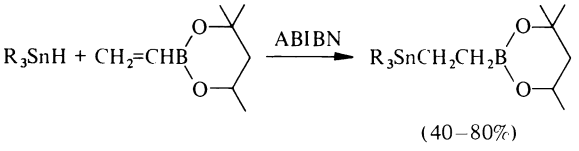
The addition of germanes to unsaturated compounds has received less study, but appears to take place under milder conditions than those required for the analogous additions of silanes [1]. Germanyl radicals add preferentially to carbon-carbon double bonds rather than to carbonyl functions [16], e.g.

$$Ph_3GeH + CH_2{=}CH(CH_2)_8CHO \xrightarrow{ABIBN} Ph_3Ge(CH_2)_{10}CHO \quad (80\%)$$
$$+$$
$$Ph_3Ge(CH_2)_{11}OGePh_3 \quad (20\%)$$

The addition of stannanes to carbon-carbon double bonds is reversible [17, 18], but affords useful products [19–21]. For example, in the course of synthesising organotin substituted barbituric acids [22, 23] diethyl propenylmalonate was found to react with triphenyltin hydride.

$$Ph_3SnH + CH_2{=}CHCH_2CH(CO_2Et)_2 \xrightarrow[80\,^\circ C]{ABIBN} Ph_3Sn(CH_2)_3CH(CO_2Et)_2$$
$$(90\%)$$

Another recent example of hydrostannation is the addition to 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane [24].



(40–80%)

Homolytic additions to alkenyltin compounds are preparatively useful [25]. Some examples are

[26] $CH_2{=}CHSnPh_3 + p\text{-}MeC_6H_4SH \xrightarrow{ABIBN} p\text{-}MeC_6H_4SCH_2CH_2SnPh_3$
(60%)

[27] $CH_2{=}CHCH_2SnBu_3 + MeCOSH \rightarrow MeCOS(CH_2)_3SnBu_3$
(87%)

[28] $CH_2{=}CHSnR_3 + R_3SnH \xrightarrow{ABIBN} R_3Sn(CH_2)_2SnR_3 \quad (60\%)$
$+$
$(R_3Sn)_2CHCH_3 \quad (40\%)$

Homolytic additions to allyltin compounds do not always lead to the expected addition products. For example, allyltrimethylstannane on reaction with carbon tetrachloride, chloroform, methyl chloroacetate, and 1,1,1-trichloroethane undergoes an addition-elimination reaction (known as an S_H2' reaction) to afford trimethyltin chloride [29, 30].

$$RCl \rightarrow R\cdot + Cl\cdot$$

$$R\cdot + CH_2{=}CHCH_2SnMe_3 \rightarrow RCH_2CH{=}CH_2 + Me_3Sn\cdot$$

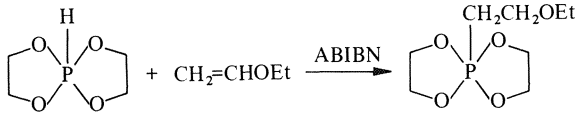
$$Me_3Sn\cdot + RCl \rightarrow Me_3SnCl + R\cdot$$

Most phosphorus compounds with a phosphorus-hydrogen bond will undergo addition to alkenes [1]. Thus phosphine, and primary and secondary phosphines undergo ready addition reactions to alkenes, usually initiated with di-*t*-butyl peroxide [31]. Phosphorous acid [32, 33], its esters [34–36], and salts [37] undergo addition reactions in good yield as does hypophosphorous acid [38] and sodium hypophosphite [39]. Many of the products have been listed by Kosolopoff [40, 41]. More recently attention has been drawn to the addition of diphosphines such as tetrafluoro [42] and tetramethyl [43, 44] diphosphine to alkenes to afford 1,2-bis-phosphino adducts, e.g.

$$F_2PPF_2 + CH_2{=}CHR \xrightarrow{h\nu} F_2PCH_2CH(R)PF_2 \quad (25–50\%)$$

$$Me_2PPMe_2 + CH_2{=}CH_2 \xrightarrow{h\nu} Me_2PCH_2CH_2PMe_2 \quad (68\%)$$

Tetraoxaphosphaspirononane undergoes homolytic addition to ethyl vinyl ether [45].



(65%)

Free radical substitution reactions of organometallic compounds appear less frequently in the literature than do addition reactions, although autoxidation studies of organometallics abound. Examples of radical substitution reactions of organic side chains are rare, but probably there is some scope here for the development of preparative routes. For example, the chlorination of alkyltrichlorosilanes [1, 46, 47] proceeds readily as does the free radical halogenation of transition metal substituted silicon hydrides when carbon tetrachloride or carbon tetrabromide are used as halogenating agents [48]. However, the photolytic halogenation of arylstannanes leads only to tin halides *via* tin-carbon bond cleavage [49], although electrophilic substitution occurred along the expected pathway. 1-Triphenylsilyl-2-phenylethane was mono-, di-, or tri-brominated using *N*-bromosuccinimide in 1, 2, or 3 mole equivalents [14].

$$Ph_3SiCH_2CH_2Ph \xrightarrow{NBS} Ph_3SiCH_2CHBrPh \quad (81\%)$$

$$Ph_3SiCH_2CH_2Ph \xrightarrow{2\times NBS} Ph_3SiCHBrCHBrPh \quad \text{(isolated } \textit{threo}\ 18\%, \textit{erythro}\ 9\%)$$

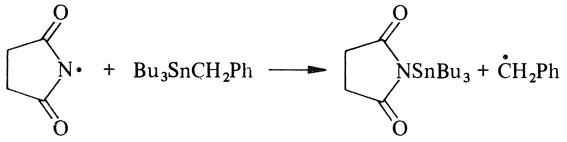
$$Ph_3SiCH_2CH_2Ph \xrightarrow{3\times NBS} Ph_3SiCBr_2CHBrPh \quad (44\%)$$

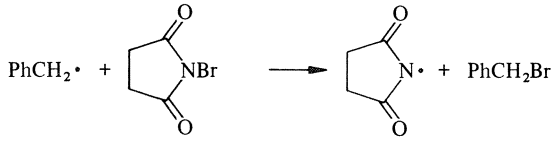
Radical substitution reactions at a metal centre are more frequently encountered and have been more studied [50]. Autoxidation at the metal to produce metal peroxides, or products derived from these, has been studied and reviewed [51–53], and is now recognised [54] to occur *via* bimolecular homolytic substitution S_H2 at the metal centre [50].

$$RM \xrightarrow{O_2} R\cdot \qquad \text{initiation}$$

$$\left.\begin{array}{l} R\cdot + O_2 \rightarrow RO_2\cdot \\ RO_2\cdot + RM \rightarrow RO_2M + R\cdot \end{array}\right\} \text{chain reaction}$$

Such reactions, be they synchronous or stepwise, offer great scope as preparative routes usually occurring at a multivalent metallic centre with an accessible low-lying unfilled orbital. The attacking radicals usually involve an electronegative atom such as in RO·, ROO·, RS·, $R_2N\cdot$, Cl·, Br·, and triplet state ketones R_2CO^*. For example, tetrabutyltin and benzylbutyltin react with *N*-bromosuccinimide on initiation with *t*-butyl hyponitrite affording *N*-tributylstannylsuccinimide [55, 56]. The benzyl radical is displaced, as would be expected, rather than the *n*-butyl.





However, the reaction is not always so simple and steric constraints in the intermediate stages may affect the course of the reaction, since di-*n*-butyl-*t*-butyltin chloride undergoes preferential displacement of an *n*-butyl radical in a reaction with *t*-butoxyl radicals [57].

$$(n\text{-Bu})_2\overset{t\text{-Bu}}{\underset{|}{\text{Sn}}}\text{Cl} + t\text{-BuO}\cdot \rightarrow n\text{-Bu}\overset{t\text{-Bu}}{\underset{t\text{-BuO}}{\overset{|}{\underset{|}{\text{Sn}}}}}\text{Cl} + n\text{-Bu}\cdot$$

Phosphorus(III) compounds are converted to phosphorus(V) oxides and sulphides *via* addition of a radical (RO· or RS·) followed by a scission reaction [58], e.g.

$$t\text{-BuSSBu-}t \rightarrow 2\,t\text{-BuS}\cdot$$

$$t\text{-BuS}\cdot + (\text{RO})_3\text{P} \rightarrow (\text{RO})_3\text{PS} + t\text{-Bu}\cdot$$

Oxidation may also be accomplished using nitric oxide [59, 60] as a mild radical reagent or nitrogen dioxide, although there may be complications [61]. There are reviews of phosphorus-centred radical reactions [19, 20, 62] and of the radical reactions undergone by phosphorus compounds [63]. Oxidation has also been effected with bis-trifluoromethyl nitroxide [64], e.g.

$$2\,(\text{CF}_3)_2\text{NO}\cdot + \text{P}(\text{C}_6\text{F}_5)_3 \rightarrow \text{OP}(\text{C}_6\text{F}_5)_3 + (\text{CF}_3)_2\text{NON}(\text{CF}_3)_2$$

However, with the corresponding arsenic and antimony compounds [64], and with other phosphines and stibines [65, 66] the addition products are formed, e.g.

$$(\text{CF}_3)_2\text{PX} + 2\,(\text{CF}_3)_2\text{NO}\cdot \rightarrow [(\text{CF}_3)_2\text{NO}]_2\text{PX}(\text{CF}_3)_2$$

$\text{X} = \text{F, Cl, Br, CN, CF}_3$

Substitution can also occur [66].

$$(\text{CF}_3)_2\text{NO}\cdot + (\text{CF}_3)_2\text{PI} \rightarrow (\text{CF}_3)_2\text{PON}(\text{CF}_3)_2 + \text{I}\cdot$$

Other similar reactions have been briefly reviewed [67].

Phosphorus trichloride and dichlorophosphines undergo reaction with alkanes in the presence of oxygen to afford alkylphosphonyl dichlorides and dialkylphosphonyl chloride respectively [1, 63].

$$\text{RH} + 2\,\text{PCl}_3 + \text{O}_2 \rightarrow \text{RP(O)Cl}_2 + \text{POCl}_3 + \text{HCl}$$

$$\text{RH} + 2\,\text{R'PCl}_2 + \text{O}_2 \rightarrow \text{RR'P(O)Cl} + \text{R'P(O)Cl}_2 + \text{HCl}$$

Phosphites react with alkyl halides to afford dialkyl alkylphosphonates [1], possibly by mixed pathways.

$$(\text{RO})_3\text{P} + \text{R'Cl} \rightarrow (\text{RO})_2\text{P(O)R'} + \text{RCl}$$

Such reactions may be catalysed by metal ions [68],

$$\text{MeOCHClCO}_2\text{Me} + \text{R'OPR}_2 \xrightarrow[50-75^\circ]{\text{Fe(III)Cl}_3} \text{R}_2\text{P(O)CH(OMe)CO}_2\text{Me} + \text{R'Cl}$$

although other reaction pathways may be followed [69].

$$2P(OR)_3 + 2\,PhCCl_3 \xrightarrow[Cu(I)Cl]{C_6H_6} PhCl_2C.CCl_2Ph + RCl + (RO)_3PO + (RO)_2PCl$$
(70–77%)

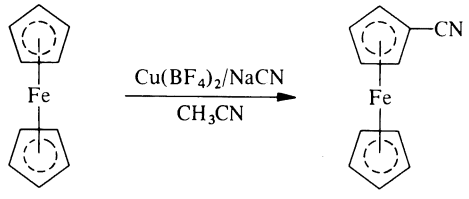
Free radicals have been implicated in the formation of Grignard reagents [70, 71] and in various 1,4-addition reactions of boranes [72]. The reactions of these reagents also may involve free radicals [72–77]. However, since these particular organometallics tend to be formed and allowed to react *in situ*, and furthermore since their reactions are so well documented, they will not be considered further. For similar reasons no consideration will be given to the organometallic compounds generally used in synthetic radical reactions to afford organic products, such as in the homolytic displacement reaction shown by allyl-bis(dimethylglyoximato)pyridinecobalt(III) with bromotrichloromethane in the preparation of 4,4,4-trichlorobut-1-ene [78].

$$CH_2{=}CHCH_2Co(dmgH)_2py + BrCCl_3 \xrightarrow[(BzO_2)_2]{CHCl_3} Cl_3CCH_2CH_2CH{=}CH_2$$
(95%)

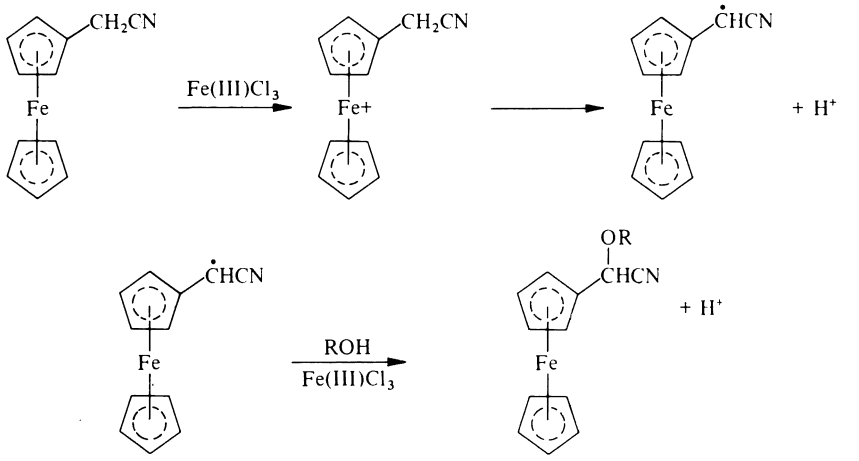
Recently it has been suggested that some reactions previously thought of as being heterolytic in nature are in fact homolytic. However, the evidence is not completely convincing and many of these reactions are in a state of continuous assessment. Several examples of oxidative addition to platinum group metals such as the addition of methyl iodide to tris(triphenylphosphine)platinum(0) are said to involve radicals [79]. There are related reactions such as the oxidative addition of alkyl and aryl halides to tin(II) alkyls and amides [80]. There are also substitution reactions such as those involved in the reaction between thiols and methylgold(I) and methylplatinum(II) [81], and the reaction between alkenes and platinum(II) complexes [82]. However, more recently a reinvestigation of the oxidative addition of alkyl halides to palladium(0) complexes suggests that there are probably no free radical intermediates [83].

Electron transfer, from d^{10} species, as a possible initiation of free radical pathways in oxidative additions, has been investigated [84] and there is a general review of free radicals in organometallic chemistry [85] and of electron transfer in organometallic catalytic reactions [86].

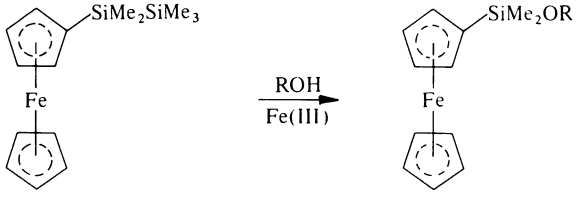
Substituted ferrocenes have been prepared from the ferrocene radical cation by treatment with suitable reagents [87], thus $Cu(BF_4)_2$ in acetonitrile containing sodium cyanide affords 40% of cyanoferrocene.



Other groups have been introduced, such as SO_2Ph, SC_6H_4Me-*p*, CMe_2CN, Ph. Side chains may be oxidised, for example with alcohol and iron(III) chloride [88].



or [89]



Other reactions have been observed [90–96]. Ferrocenylketones are photoreduced with tin(IV) hydrides [97], albeit in low yield.

Dialkylmercurials undergo a free radical reductive elimination in carbon tetrachloride [98–100], e.g.

$$CCl_4 \xrightarrow{h\nu} \cdot CCl_3 + Cl\cdot$$

$$\cdot CCl_3 + HCMe_2CH_2HgR \rightarrow CHCl_3 + \cdot CMe_2CH_2HgR$$

$$\cdot CMe_2CH_2HgR \rightarrow Me_2C{=}CH_2 + \cdot HgR$$

$$\cdot HgR \rightarrow Hg + R\cdot$$

$$R\cdot + CCl_4 \rightarrow \cdot CCl_3 + RCl$$

However, alkylmercuric salts are formed in good yield by treating mercuric alkoxides with trialkylboranes [101].

$$Hg(OMe)_2 \rightarrow 2\,MeO\cdot + Hg$$

$$MeO\cdot + R_3B \rightarrow MeOBR_2 + R\cdot$$

$$R\cdot + Hg(OMe)_2 \rightarrow RHg(OMe) + \cdot OMe$$

Similarly mercuric carboxylates may be converted to alkylmercuric carboxylates [102].

$$Hg(OCOR)_2 \rightarrow (RCO_2)Hg\cdot + R\cdot + CO_2$$

$$R\cdot + Hg(OOCR)_2 \rightarrow RHg(OOCR) + R\cdot + CO_2$$

At least one nitroxide reacts with metallic mercury to afford products [103].

$$2\,(CF_3)_2NO\cdot + Hg \rightarrow [(CF_3)_2NO]_2Hg$$

Some organometallic species may be thought of as radicals (or radical precursors). Thus thermal homolysis of $L_2Mn(CO)_8$ in the presence of 2-methyl-2-nitrosopropane affords the nitroxide *t*-BuN(O·)Mn(CO)$_4$L [104].
Pentacarbonylmanganese will effect substitution reactions with polysilanes [105, 106].

$$2\,R_3SiH + Mn_2(CO)_{10} \xrightarrow[36\,hr]{130^\circ} 2\,R_3SiMn(CO)_5$$

It has been suggested that radicals are important in other miscellaneous reactions, often involving electron transfer. The mechanism for the oxidation of titanium(III) chloride is considered to be [107]:

$$Ti(III)Cl_3 + O_2 \xrightarrow{\text{pyridine}} Cl_3Ti(IV)(O_2^{\cdot-})$$

$$Cl_3Ti(IV)(O_2^{\cdot-}) + Ti(III)Cl_3 \rightarrow 2\,TiCl_3O\cdot$$

$$TiCl_3O\cdot + TiCl_3 \xrightarrow{\text{pyridine}} Ti_2Cl_6O(C_5H_5N)_4$$

Triphenylmethyl radicals complex with titanium chlorides [108].

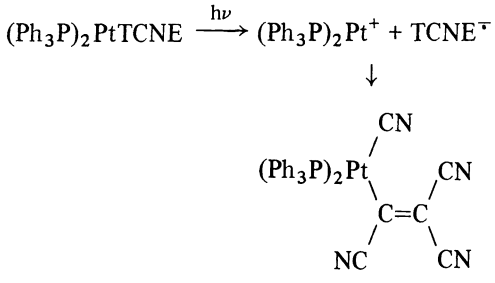
e.g. $Ph_3C\cdot + Ti(II)Cl_2 \rightarrow Ph_3CTiCl_2$

Perfluoroalkyl iodides it is suggested undergo electron transfer with $(Co(I)salphen)^-$ to afford perfluoroalkyl radicals, which are then involved in an oxidative addition [109]; similarly Co(II) complexes react with benzyl halides [110, 111].

Nitrogen dioxide has been used as a single electron oxidant [112].

$$cis\ Mo(CO)_2(DPE)_2 \xrightarrow[CHCl_3]{NO_2} (trans\ Mo(CO)_2(DPE)_2)^+$$

Ligands have been observed to undergo rearrangement under photolysis, possibly *via* radical mechanisms, for example [113],



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12. Stable Free Radicals

As discussed in chapter 1 radicals can be removed from a system by reaction with a substrate, for example as, a result of the abstraction of a hydrogen atom from a solvent or by addition reactions with atmospheric oxygen.

$$R\cdot + SH \rightarrow RH + S\cdot \quad (SH = \text{solvent})$$

$$R\cdot + O_2 \rightarrow RO_2\cdot$$

Alternatively radicals may undergo rearrangement or elimination reactions, or they may dimerise or disproportionate leading to non-radical products.

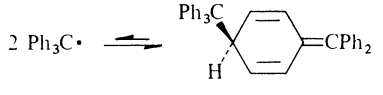
$$R\cdot + R'\cdot \rightarrow RR'$$

$$RCH_2\dot{C}H_2 + R'CH_2\dot{C}H_2 \rightarrow RCH{=}CH_2 + R'CH_2CH_3$$

If the above reactions do not occur, or occur slowly, the radical lifetime is extended, and the radicals are called stable [1, 2]. The thermal and chemical stabilities of radicals are governed by two main factors, resonance and steric hindrance [3–5].

Most simple alkyl radicals undergo bimolecular self reaction at the diffusion controlled limit [4–6] in solution, so that their lifetimes are usually only of the order of milliseconds or less (dependent on concentration). Increasing substitution extends the lifetime of the radical so that at ambient temperatures di-*t*-butylmethyl has a lifetime of ca. 50 sec, tri-*t*-butylmethyl ca. 9 min, and tris(trimethylsilyl)methyl ca. 2 days when prepared under suitable conditions [7–9]. The longevity of radicals with central atoms other than carbon may be similarly increased, and thus long-lived silyl [10], tin- [10–12] and nitrogen- [13] centred radicals have been observed. Information on preparative methods is given in a number of accounts of stable free radicals [1, 14].

The triphenylmethyl radical (1) [15, 16] is known to exist in solution in equilibrium with its head-to-tail dimer (2) [17]. For general preparative purposes Gomberg's initial

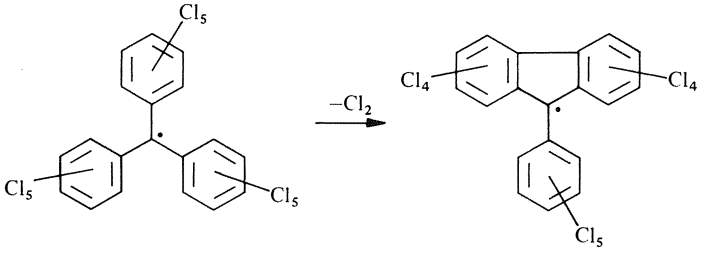


(1) (2)

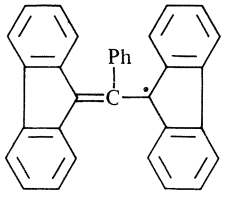
method [18] is still the most suitable, and involves the reaction of triphenylmethyl chloride in solution with a metal e.g. silver [19].

$$Ph_3CCl + M\cdot \rightarrow Ph_3C\cdot + M^+Cl^-$$

Various other triarylmethyl-type free radicals can be prepared in solution, in equilibrium with dimer, by similar procedures. The degree of dissociation of dimer depends on the stability of the triarylmethyl radical, which if it contains substituents which can aid delocalisation of the radical centre, results in the equilibrium moving in its direction. The degree of dissociation of "hexa-*p*-tolylethane" is given as 16% in 0.1 M benzene solution at 25 °C [20], but tri-(*p*-nitrophenyl)methyl [21, 22] and tri-(*p*-phenylphenyl)methyl [23] radicals can be obtained as dark green crystals which even in the solid state are apparently entirely monomeric. Perchlorotriphenylmethyl, perchlorodiphenylmethyl, and some higher perchloro homologues are also completely dissociated in solution and in the solid state [24]. They are prepared by the oxygen or iodine oxidation of the corresponding anion. Perchlorotriphenylmethyl and its homologues can be converted to another long-lived radical, perchloro-9-phenylfluorenyl, on thermolysis [25].

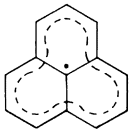


An interesting example of the difficulty that early workers had in convincing the chemical world of the possibility of stable free radicals as discrete species, is the work of Koelsch. In 1932 he discovered that treatment of α,γ-bisdiphenylene-β-phenylallyl chloride with mercury gave the red-brown radical α,γ-bisdiphenylene-β-phenylallyl.



The report of this work was rejected for publication in the "Journal of the American Chemical Society" on the basis that the properties of the product reported were not consistent with a radical structure. In 1957 the paper was resubmitted (and accepted) following the demonstration by e.s.r. measurements that the radical had survived unchanged during the intervening twenty five years [26].

The perinaphthyl radical is readily prepared by treating perinaphthalene with methoxide ion and then shaking the resulting perinaphthenide anion in oxygen [27, 28].



It may be thought of as an allyl-type radical enjoying a high degree of symmetry [29] and the extensive delocalisation leads to the structural representation above.

Diarylamino radicals are similar to triarylmethyl radicals in that they can be prepared in solution in equilibrium with their tetraarylhydrazine dimer.

$$Ar_2N{-}NAr_2 \rightleftharpoons 2\ Ar_2N\cdot$$

The radicals are best prepared by oxidation of the corresponding secondary amines with a suitable oxidant [30].

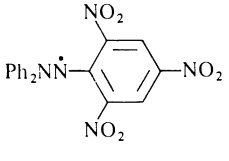
$$Ar_2NH \rightarrow Ar_2N\cdot$$

The proportion of diarylamino radical present in equilibrium with its dimer depends on the ability of substituent groups in the aromatic rings to stabilise the radical centre by delocalisation [31] and by steric hindrance to dimerisation [1].

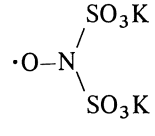
Hydrazyl radicals are produced by oxidation of triarylhydrazines. In solution they may exist in equilibrium with hexaaryltetrazenes [32, 33].

$$2\ Ar_2NNHAr \rightarrow 2\ Ar_2N\dot{N}Ar \rightleftharpoons \begin{matrix} Ar_2NNAr \\ | \\ Ar_2NNAr \end{matrix}$$

2,2-Diphenyl-1-picrylhydrazyl [34] (DPPH), a violet solid, is a remarkably long-lived radical, which shows no tendency to dimerise in the solid state or in solution. It is valuable as a radical scavenger.



The inorganic nitroxide Fremy's salt [35] has a long history and can be prepared as



an orange solid [36]. Organic nitroxides are often prepared by oxidation of *N,N*-disubstituted hydroxylamines with a suitable reagent [1, 37, 38].

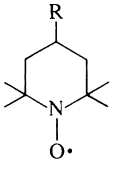
$$R_2NOH \rightarrow R_2NO\cdot$$

Nitroxides are also obtained by the oxidation of secondary amines [1, 38, 39], and by the addition of radicals to tertiary *C*-nitroso compounds. For example [40, 41],

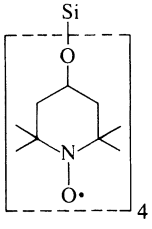
$$t\text{-BuNO} + Me_2\dot{C}CN \rightarrow t\text{-Bu}\overset{\overset{O\cdot}{|}}{N}CMe_2CN$$

Other nitroxides include perfluoromorpholino nitroxide [42], 2,5-diazadecafluorohexan-bis-*N*-oxyl [43], and bis-trifluoromethyl nitroxide [44]. The preparation of many nitroxides has been listed by Rozantsev [38]. A variety of nitroxides have been produced containing *t*-alkyl substituents, which include di-*t*-butyl nitroxide [45, 46], various 4-substituted 2,2,6,6-tetramethylpiperidinyl nitroxides such as (3) [47, 48], and exotic polynitroxides such as (4) [38], and acyl *t*-butyl nitroxides [49].

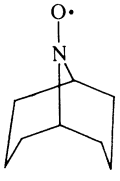
ref. [47] R = CHO
ref. [48] R = CN



(3)



(4)



(5)

The longer lived and therefore isolable nitroxides are those which cannot undergo disproportionation reactions. Nitroxides containing primary and secondary alkyl groups do undergo such reactions and have considerably shorter lifetimes. For example diethyl nitroxide [50–52] decays relatively rapidly with the overall reaction being:

$$2\,CH_3CH_2\overset{\overset{O\cdot}{|}}{N}CH_2CH_3 \rightarrow (CH_3CH_2)_2NOH + CH_3CH{=}\overset{\overset{O^-}{|}}{\underset{+}{N}}CH_2CH_3$$

However, bicyclic nitroxides [53, 54] such as (5), although containing a C–H group α to the nitroxide group do not undergo disproportionation reactions because in accordance

with Bredt's rule [55] the formation of a nitrone with a double bond at the bridgehead cannot occur. This increases the longevity of the radical (5) which has been isolated as a solid. Analogous nitroxides have also been isolated [53, 54, 56].

Most nitroxides have not proved to be sufficiently long-lived to allow isolation and so have been formed and studied in the cavity of e.s.r. spectrometers [1, 39, 57–60]. The usual system involves generating a radical in the presence of a *C*-nitroso compound or a nitrone to which addition occurs affording the nitroxide.

$$R\cdot + R'NO \rightarrow R\overset{O\cdot}{\underset{|}{N}}R'$$

$$R\cdot + R^1\overset{O^-}{\underset{|}{\overset{|}{\underset{+}{N}}}}{=}CHR^2 \rightarrow R^1\overset{O\cdot}{\underset{|}{N}}CHRR^2$$

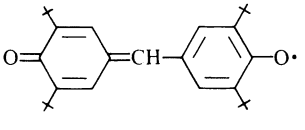
The addendum is generated directly from a suitable radical precursor (e.g. ABIBN [40, 41] or *t*-butyl hyponitrite [61]) or is generated from a suitable substrate by hydrogen abstraction. For example [61, 62]

$$t\text{-BuCHO} + t\text{-BuO}\cdot \rightarrow t\text{-Bu}\dot{C}O + t\text{-BuOH}$$

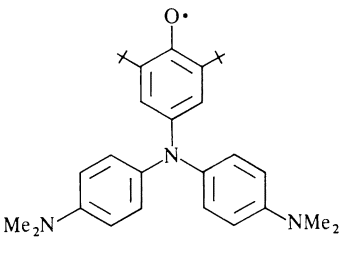
$$t\text{-Bu}\dot{C}O + t\text{-BuNO} \rightarrow t\text{-Bu}\overset{O\cdot}{\underset{|}{N}}COBu\text{-}t$$

Other means of radical generation have been used and the technique of forming a radical, allowing it to add to a *C*-nitroso compound or a related nitrone to form a relatively longer lived nitroxide radical, is known as "spin-trapping". Indeed this technique has been used to study the reactions of radicals [61, 62] and even to "prove" the existence of radicals in a system. However, many cautionary notes [58–60] have been published in this respect. Organic compounds may be "spin-labelled" by substituting them with suitable nitroxide groups and the sensitivity of the e.s.r. technique may then be used to probe the properties of solvents and liquids [63].

Aroxyl radicals are produced by oxidation of phenols [64] and are stable, towards dimerisation, if highly substituted in the *ortho* and *para* positions, because delocalisation of the radical centre over the aromatic ring otherwise allows head-to-tail reactions to



(6)



(7)

occur. Galvinoxyl (6) [65, 66] and the aminoaroxyl radicals like (7) [67] are particularly stable towards dimerisation.

The life-times of radicals may be prolonged by physically preventing bimolecular reactions. Thus radicals are commonly trapped and studied in matrices [60, 68].

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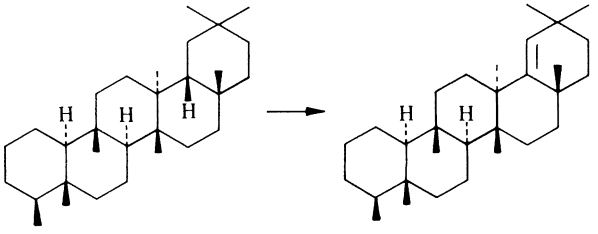
13. Naturally Ocurring and Related Compounds

The effectiveness of a synthetic reaction depends very much upon its selectivity. A good test is to examine such reactions on polyfunctional molecules of which naturally occurring compounds, because of their diversity of structure, provide excellent examples. In this chapter are provided examples of free radical reactions being used at essential stages in the synthesis of, and also in the modification of functional groups in, such molecules.

The selective dehydrogenation of the hydrocarbon friedlane (1) to friedel-18-ene (2) is accomplished in 45% yield when (1) is oxidised using *N*-bromosuccinimide. Similar results are obtained using a dilute solution of bromine in carbon tetrachloride [1].

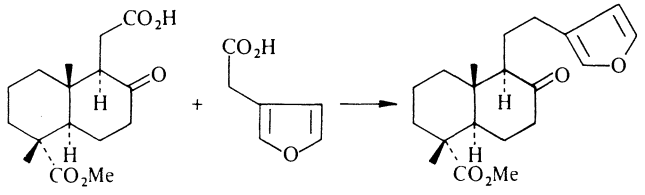


(1) (2)

The electrolysis of a mixture of two carboxylic acids can, in principle, lead to the three possible combination products of the derived radicals.

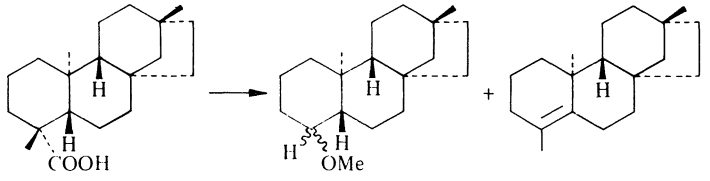
$$RCO_2H + R'CO_2H \rightarrow R\cdot + R'\cdot$$
$$\downarrow$$
$$RR + R'R' + RR'$$

Under carefully controlled conditions, particularly if one of the acids is used in considerable excess, the reaction can be exploited to give the crossed product. In a synthesis of the antipodal polyalthic acid from levopimaric acid, the electrolysis of a mixture of the keto-acid ester (3) and 3-furylacetic acid (4) gave the keto-ester (5) [2]. Similarly the electrolysis of a mixture of (+)-cyclopent-2-ene-1-acetic acid and ethyl hydrogen brassylate



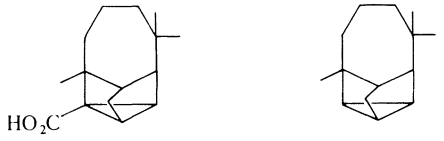
(3) (4) (5)

afforded, after saponification of the product mixture, chaulmoogric acid identical with the natural material [3]. The electrochemical oxidative decarboxylation of a carboxylic acid can be utilised to give olefins. Doubt had been expressed as to whether the carboxyl group in the steviol-isosteviol system was located at position 4 or 10. A key experiment in locating the carboxyl group at 4 was the anodic reaction of isostevic acid (6) in methanol to afford (7) and (8) in yields of 65 and 25% respectively [4].



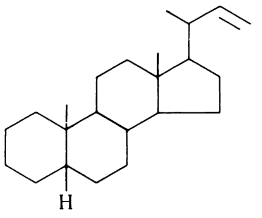
(6) (7) (8)

Pseudolongifolic acid (9) is inert to treatment with Pb(IV) in solution. However (9) could be converted to the corresponding hydrocarbon norlongicyclene (10) as a result of the thermal decomposition of the perester of (9) [5].



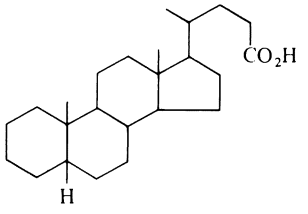
(9) (10)

Free radicals are also involved in the oxidative procedures set out below for the conversion of cholanic acid (11) into Δ^{22}-24-norcholene (12) and 20,24-oxidocholane (13) [6].



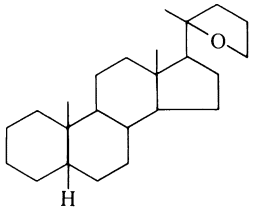
(12)

$Pb(IV)(OAc)_4$
$Cu(II)/C_6H_5N$



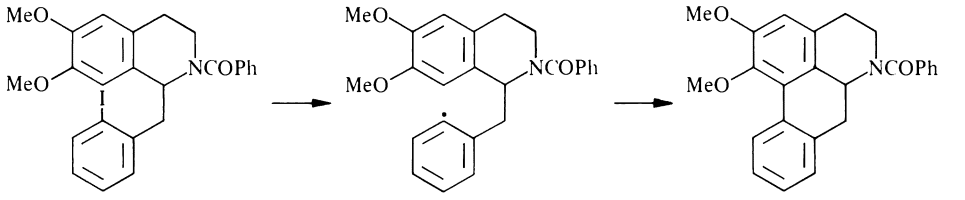
(11)

(i) CH_2N_2
(ii) $LiAlH_4$
(iii) $Pb(IV)(OAc)_4$



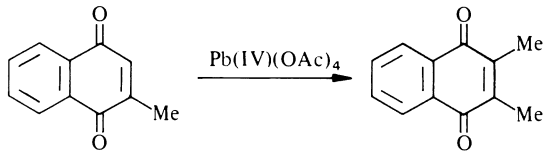
(13)

Intramolecular homolytic aromatic substitution can be a useful method of ring closure. It was involved in the key step of the photolysis of the iodide (14) in the synthesis of *N*-benzoyl-nor-nuciferine (15) [7].



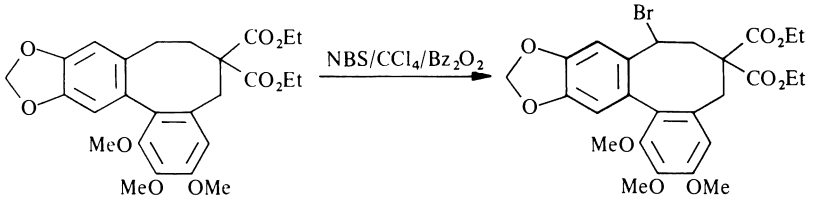
(14) (15)

The alkylation of quinones can be accomplished with Pb(IV) carboxylates. This is exemplified by the conversion of 2-methyl-1,4-naphthoquinone (16) to 2,3-dimethyl-1,4-naphthoquinone (17) on treatment with Pb(IV) acetate [8].



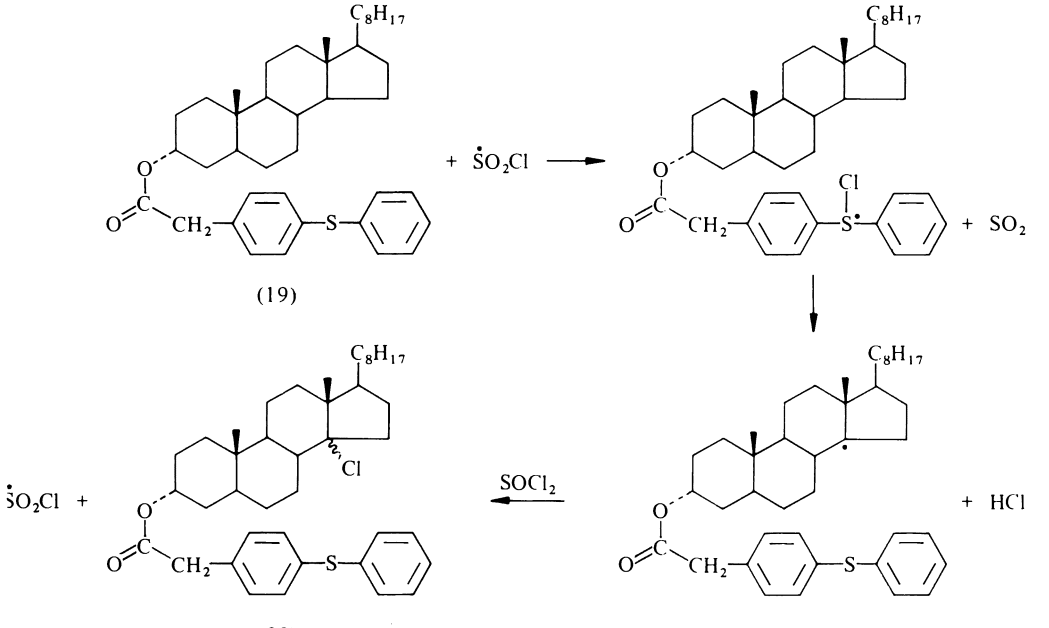
(16) (17)

Allylic bromination is readily accomplished with *N*-bromosuccinimide. This reaction has been used to obtain the bromide (18) in a key stage in the synthesis of (±)-steganacin [9].



(18)

In his classic work on free radical chlorination modified by aromatic solvents, Russell [10] showed that complexation of chlorine atoms to iodobenzene and to diphenyl sulphide was unusually strong and apparently involved direct bonding to the heteroatom rather than to the aromatic ring. This concept has been utilised by Breslow [11] who attached an iodophenyl group as a template on to a steroid in order to direct the site of free radical chlori-



(19) (20)

nation. More recently he has found the use of a diphenyl sulfide group as a template to be preferable. In the example below, chlorination of the derivative (19) of cholestan-3α-ol with sulfuryl chloride proceded by a radical relay process. Hydrolysis and dehydrochlorination of product (20) followed by acetylation afforded Δ^{14}-cholesten-3α-yl acetate [12].

Photofluorination by trifluoromethyl hypofluorite has been suggested as involving the following mechanism:

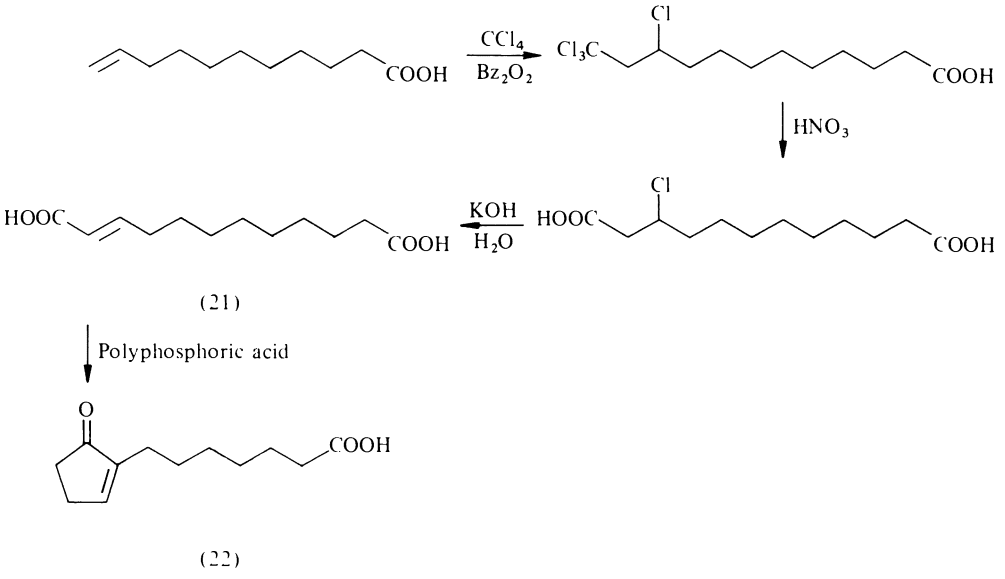
$$CF_3OF \rightarrow CF_3O\cdot + F\cdot$$

$$RH + F\cdot \rightarrow R\cdot + HF$$

$$R\cdot + CF_3OF \rightarrow RF + CF_3O\cdot$$

$$CF_3O\cdot + RH \rightarrow R\cdot + COF_2 + HF$$

Procedures have been designed to utilise this process for the conversion of D-alanine, L-alanine and D-alanine-2-*d* into the novel antibacterials 3-fluoro-D-alanine, 3-fluoro-L-alanine and 3-fluoro-D-alanine-2-*d* respectively with yields of 20, 54 and 59% [13]. Trichloromethyl groups can be converted to carboxyl groups. In a synthesis of the plant hormone *trans*-2-dodecendioic acid (21) the first stage was the peroxide catalysed addition of carbon tetrachloride to undec-10-enoic acid [14]. The dioic acid (21) can be converted *via* a one-step cyclization with polyphosphoric acid into the versatile prostanoid synthon (22)



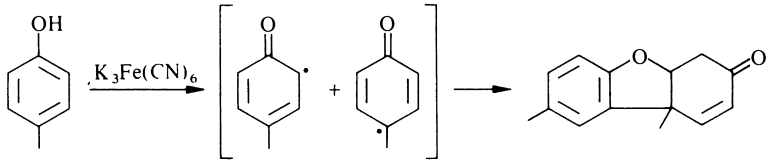
(21)

(22)

(an alternative synthesis of an ester of (22) is given at the end of this chapter).

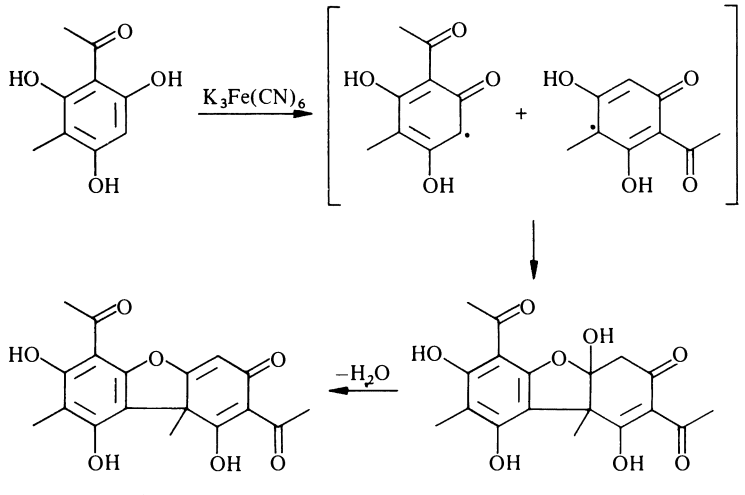
The oxidative coupling of phenols is important in synthetic and biosynthetic studies, and has been reviewed in detail by Taylor and Battersby [15]. The classic example is the

one-electron oxidation of *p*-cresol (23) to give Pummerer's ketone (24) first reported by Pummerer in 1922 [16] although it was not until much later that Barton [17] established



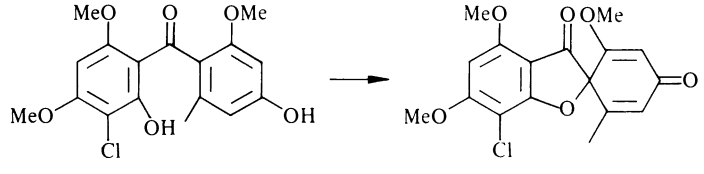
(23) (24)

the correct structure (24), pictured above as formed by the dimerisation of two canonical forms of the intermediate phenoxyl radical. He then used this knowledge to synthesise usnic acid (25).



(25)

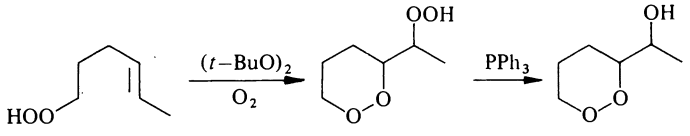
Intramolecular phenol coupling has also been observed, and the facile coupling of Griseophenone A (26) using ferricyanide led to dehydrogriseofulvin (27) in 60–70% yield [18].



(26) (27)

This biogenetic synthesis has been adopted in the preparation of analogues [19]. Phenol oxidation in the alkaloid field although of great biogenetic significance tends in the laboratory to give very low yields of products [20, 21]. However in the synthesis of dimeric fungal metabolites such as ustilaginoidin and related compounds phenol oxidative coupling has proved to be of particular value [22]. The stereospecific oxidative dimerisation of (S)-(+)-7-hydroxy-1,5,6-trimethyl-1,2,3,4-tetrahydronaphthalene by potassium ferricycanide in ethereal solution was reported to give one pure isomer, the (SS)-trans-IIa-enantiomer [23].

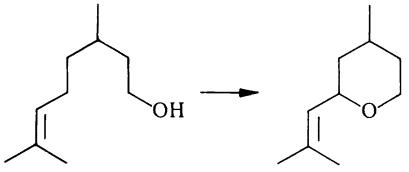
As part of the intensive effort devoted to prostaglandin synthesis it has been suggested that the formation of cyclic peroxides from unsaturated hydroperoxides may be useful models for prostaglandin biosynthesis [24]. The *t*-butoxyl radical (from di-*t*-butyl



(28) (29) (30)

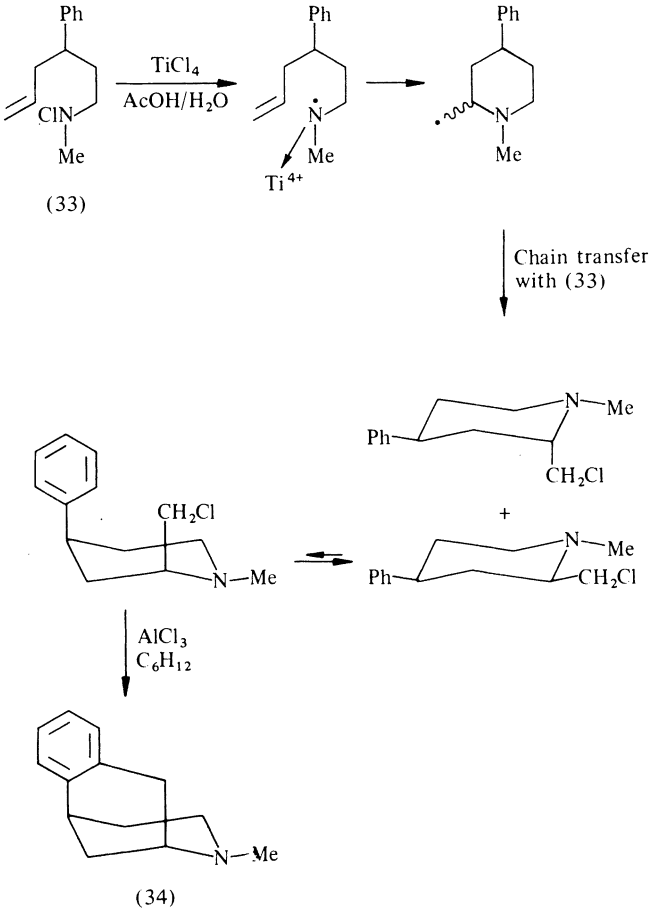
peroxide) induced decomposition of the hydroperoxide (28) in the presence of oxygen gave the almost pure cyclised hydroperoxide (29). This was reduced to the alcohol (30) using triphenylphosphine.

The electrolysis of alcohols affords alkoxyl radicals which are capable of intramolecular cyclisation to afford cyclic ethers. The electrolysis of citronellol (31) in acetonitrile containing tetraethylammonium *p*-toluenesulfonate afforded rose oxide (32) in 26% yield [25], although there is some doubt about the precise mechanistic details. Free radical cyclisations involving ring closure by addition of a free radical centre on to a double

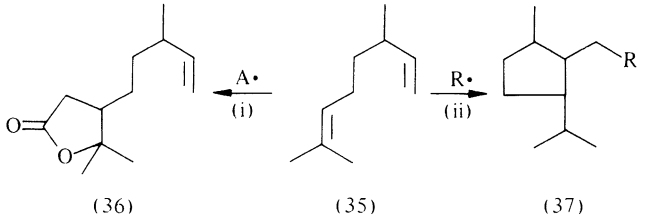


(31) (32)

bond have been extensively studied by Julia [26]. An elegant synthesis of 2-methyl-6,7-benzomorphane (34), involving in a key step the radical cyclisation of the unsaturated *N*-chloroamine (33), has been developed by Surzur, and is set out overleaf [27].



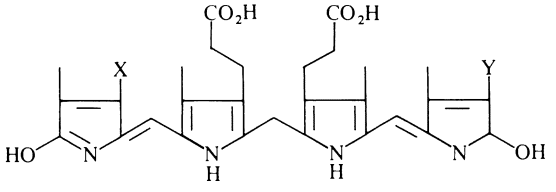
The addition to 3,7-dimethylocta-1,6-diene (35) of carbon-centred radicals generated *in situ* by manganese(III) acetate oxidation shows discrimination between two pathways (i)



and (ii) depending on the nature of the radical. Radicals (A•): $\dot{C}H_2CO_2H$, $\dot{C}H(COMe)CO_2Et$ and $\dot{C}H(COMe)_2$ lead to products of type (36). Radicals (R•): $\dot{C}H_2COMe$, $\dot{C}H(CO_2Me)_2$, $\dot{C}H_2COPh$, oxocyclopentyl, oxocyclohexyl on the other hand yield products of type (37).

Radicals $\dot{C}H_2CO_2H$ and $\dot{C}H(COMe)_2$ also gave some product of type (37) but $\dot{C}H(CO_2Me)_2$ and the ketone-substituted radicals gave no evidence of addition at the 6,7-alkene centre. It is suggested that addition to the 6,7-bond is reversible; if the tertiary radical formed can react it is trapped and closure occurs. Ring closure is likely to be facilitated by co-ordination with manganese ions [28].

The addition of the elements of methyl thioglycollate to 2-vinylbiladiene-*a,c* (38) has been accomplished by the irradiation of (38) in the presence of dimethyl dithioglycollate

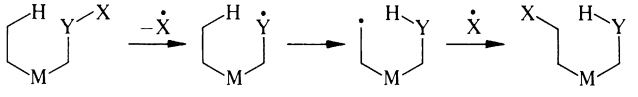


(38) X = $-CH{=}CH_2$; Y = $-CH(Me)SCH_2CO_2Me$
(39) X = $-CH_2CH_2SCH_2CO_2Me$; Y = $-CH(Me)SCH_2CO_2Me$

and methyl thioglycollate. Product (39) is said to be formed in an S_{H2} reaction by excited (38) on the sulfur-sulfur bond of dimethyl dithioglycollate followed by rapid chain transfer with the thiol hydrogen of methyl thioglycollate [29]. No reaction occurs between (38) and methyl thioglycollate on its own.

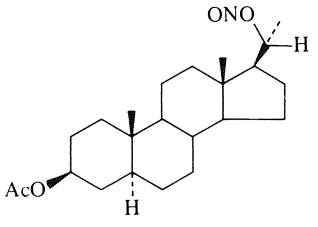
Free radical reduction of ketones by tin hydrides can be very selective. In pregnenolone the carbonyl at C-3, in preference to that at C-20, was reduced to hydroxyl by diphenyltin dihydride in a ratio of about 6.5 : 1. This result stands in marked contrast to the fact that sodium borohydride reduces the keto group at C-20 preferentially when there is a double bond in the 4,5- position [30].

The Barton reaction [31–33] has proved particularly useful for the functionalisation of methyl, methylene and methine groups in natural products. The transformation begins

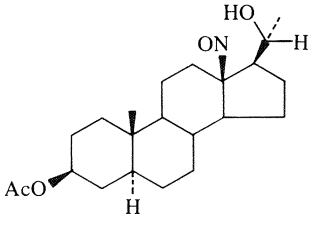


(40) (41) (42) (43)

with the homolysis of the X–Y bond in a suitable substrate (40) to give a radical (41). This radical, if it has sufficient energy, may abstract a hydrogen atom from a conformationally adjacent carbon to afford the rearranged radical (42) which affords (43) on recombination. For example the nitrite (44) rearranged to the nitroso compound (45) [34]. Hypoiodites and hypochlorites behave similarly, although a chain mechanism is indicated.

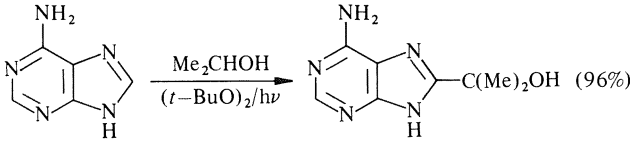


(44)

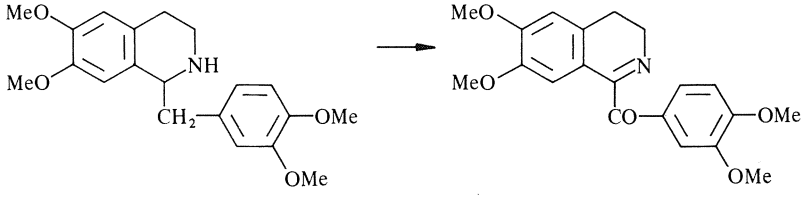


(45)
(Isolated as oxime)

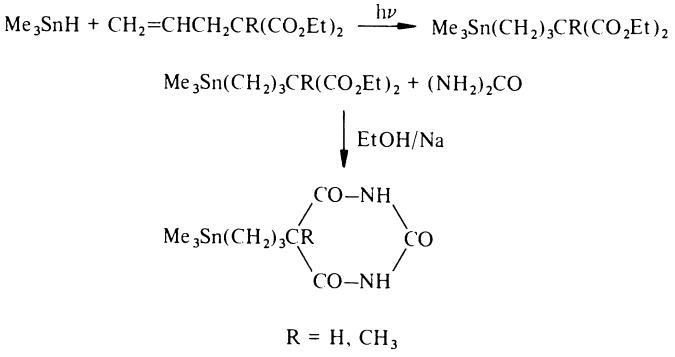
The photolysis of alcohols and di-*t*-butyl peroxide affords α-hydroxyalkyl radicals which can be used to effect substitution at C-8 of a purine or purine nucleoside [35], e.g.



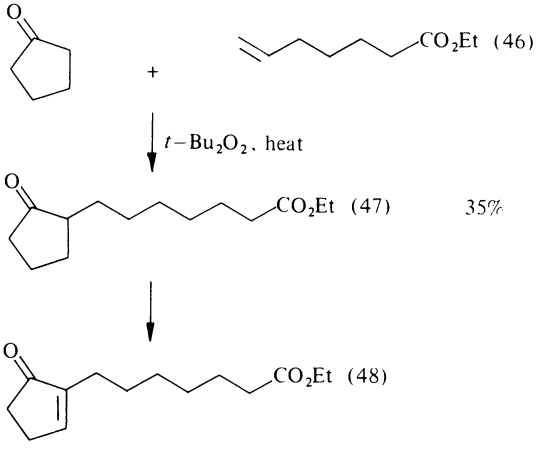
Oxidation of tetrahydroisoquinolines with Fremy's salt leads to isoquinolines. Benzylic hydrogens in related systems can also be oxidised as exemplified by the oxidation of tetrahydropapaverine to afford 3,4-dihydroketopapaverine (57%) [36].



A free radical addition reaction is involved in a stage in the synthesis of organotin substituted barbituric acids [37]. Triphenyl- and tributyl-tin hydrides were found to add to the terminal double bond of unsaturated ethyl malonates to give organotin substituted ethyl malonates but they could not be cyclised to give barbituric compounds. Trimethyl-tin hydride was found to add in a photochemical reaction to the terminal double bond of diethyl allyl malonate and allyl methyl malonate giving respectively diethyl-(3-trimethyl-stannylpropyl)- and diethyl-(3-trimethylstannylpropyl) methyl-malonates. Treatment with urea gave the organostannyl barbituric acids.



Radical addition of cyclopentanone to the unsaturated heptanoic acid derivative (46) afforded the cyclopentane-2-oxoheptanoate derivative (47) [38] which can be used as a starting material for the synthesis of the prostanoid synthon (48) [39].



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