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Radicals: Their Importance in Synthetic Chemistry and Their Relevance to Biology

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Radicals: their importance in synthetic chemistry and their relevance to biology

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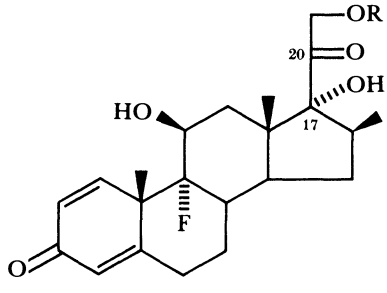
Radical chain reactions are not often used in synthetic chemistry, although in fact such reactions can give good yields and show a selectivity that complements perfectly the ionic reactions that are in more general use. The design of radical chain reactions is discussed as well as a new method for obtaining carbon radicals in good yields under mild conditions.

Radical reactions have, of course, an enormous importance in the synthesis of polymers. However, we are concerned here with their use in the chemical synthesis of homogenous, low molecular mass molecules. In this area of scientific research, radical reactions are not often used because they are considered to be unselective and to give poor yields of products. It is the purpose of this article to show that well designed radical reactions can give high yields of single products and play an important role in organic synthesis. We will concentrate on reactions that give a high yield.

Radicals react with various functional groups at very different rates, which can vary over many powers of ten. By a judicious choice of reagents, solvents and other conditions one can devise a system capable of effecting a highly selective transformation. However, radical–radical interactions (such as coupling, disproportionation) are extremely fast processes and therefore much more difficult to control. If the sequence of radical reactions is conceived so as to constitute a linear chain process where the propagating steps are so fast that the concentration of radical species remains very small, radical–radical interactions can be largely avoided. Under such controlled conditions, clean high-yielding reactions become possible. Moreover, radical and radical chain reactions have several advantages over conventional ionic processes: neutral conditions; lower steric effects; lower polar effects; lower tendancy to unwanted elimination reactions and tolerance of many functional groups that have to be protected in ionic chemistry.

The following reactions will illustrate the scope and utility of well designed radical reactions.

Some years ago, we became interested in the problem of introducing the important 17α-hydroxy group in adrenocortical hormones such as **1**. An unexpected observation during



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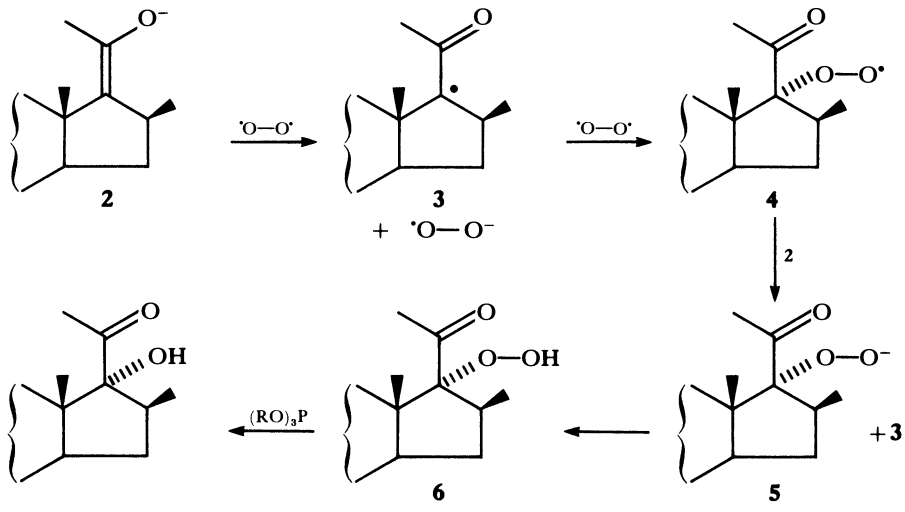
the determination of the structure of limonin (Barton *et al.* 1961) suggested that the enolate of a suitable 20-ketopregnane derivative (**2**) would react with triplet oxygen with electron transfer to give a superoxide anion and a carbon radical (**3**). The latter would then react very rapidly with oxygen to produce a hydroperoxy radical (**4**), which by electron transfer from the enolate would give the hydroperoxide anion **5** and reform the carbon radical to carry the chain (scheme 1) (Barton *et al.* 1960, 1962).



Scheme 1

The 17α-hydroperoxide **6** could be easily reduced to the desired alcohol. However, the high reactivity of hydroperoxide **6** made the reaction difficult to reproduce, especially on a large scale, but operating in the presence of a phosphite to reduce the hydroperoxide as it is formed obviated this problem (Gardner *et al.* 1968). Thus with the use of simple and cheap reagents the desired transformation was achieved in nearly quantitative yield and has become an industrial process.

In the same field of corticosteroids, we were faced by the challenge to debrominate the hydrocortisone precursor **7** without concomitant elimination of the 11-β-hydroxy group. Conventional approaches completely failed, affording only 9(11)-olefin, so we had to devise a new method.

Consideration of the various mechanistic pathways for one-electron reduction by, for example, Cr^{II} led us to postulate that carbon radicals would be involved at least in the initial stages (scheme 2). The carbon radical **8**, produced on debromination, would presumably react to give an organochromium(III) species prone to further one-electron reduction resulting in elimination. We thought that a good hydrogen-atom donor would trap this initial carbon radical before it could give the organochromium complex.

Indeed, addition of a suitable mercaptan completely suppressed the elimination of the hydroxy group and resulted in a spectacular improvement in the yield (Barton *et al.* 1964, 1966). The efficiency of this method was recently demonstrated by Shephard & Van Rheehen (Shephard & Van Rheenen 1979) at the Upjohn Company, in a novel partial synthesis of hydrocortisone that is now part of an important industrial process. Yields exceeding 90% were reported for the removal of the 9α-bromine using our method. This example clearly illustrates the superiority of a radical process in avoiding a β-elimination.

The process of β-elimination is also a serious problem in the carbohydrate and aminoglycoside

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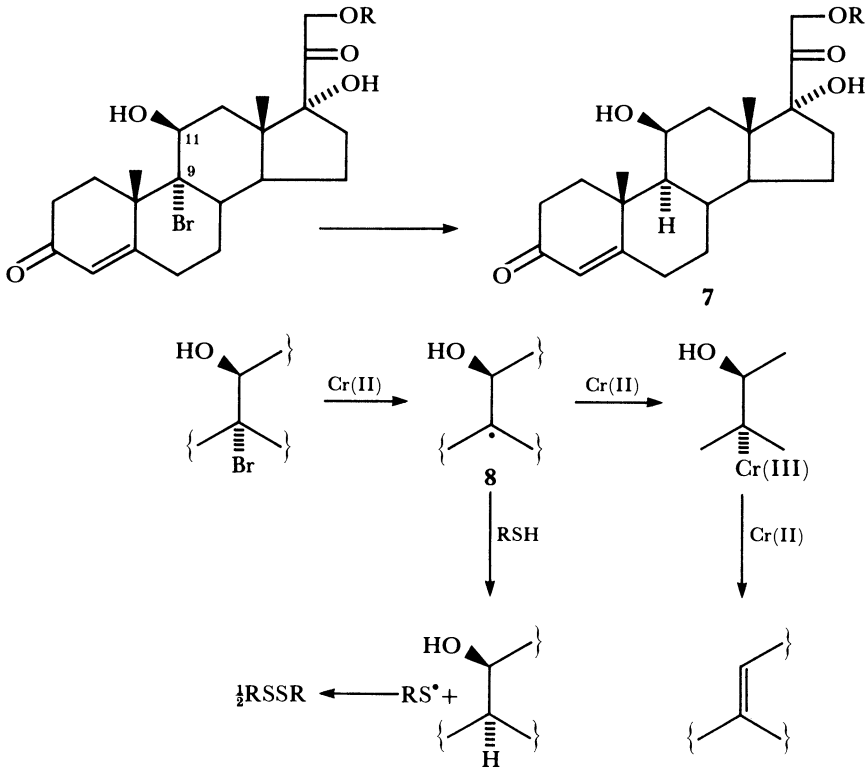
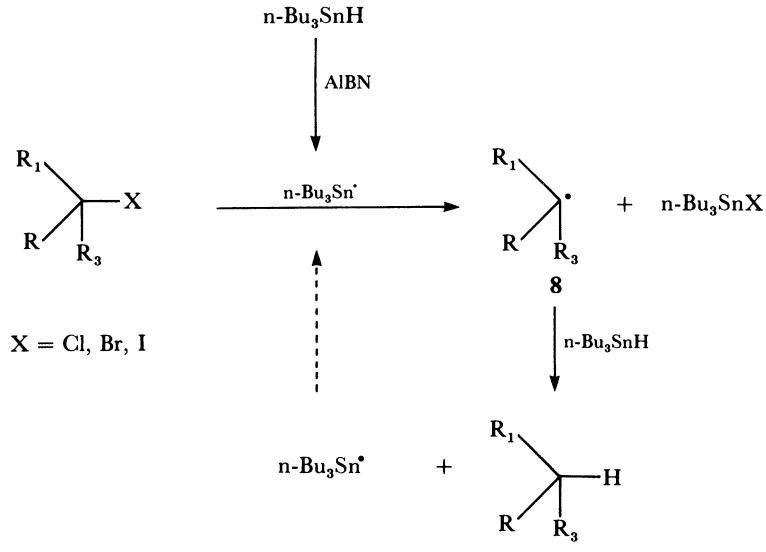


SCHEME 2

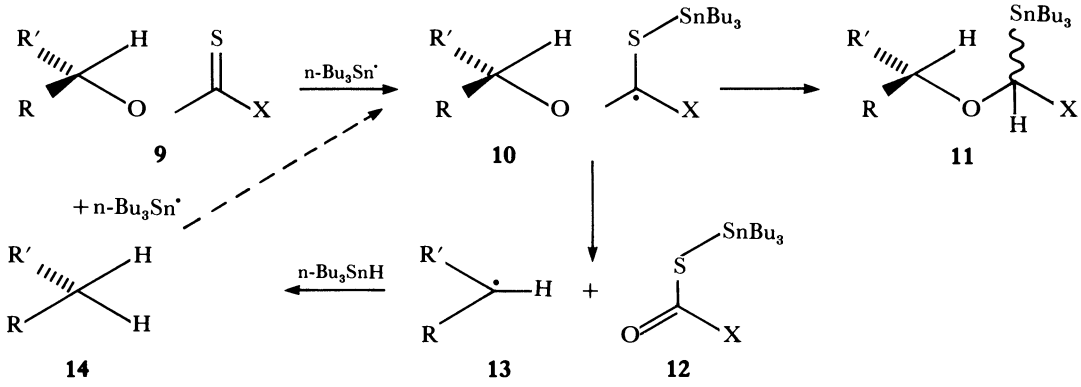
fields. These important substances are usually heavily functionalized and selective deoxygenation or deamination present a formidable challenge.

We shall first consider the problem of deoxygenation. Many years ago, Van der Kerk (Van der Kerk *et al.* 1957) discovered accidentally the facile reduction of alkyl halides by stannanes. The mechanism involved is that of a typical radical chain reaction. The stannyl radicals, generated photochemically, thermally or by a chemical initiator (such as azoisobutyronitrile, AIBN), abstract the halogen to give a carbon radical. This carbon radical abstracts a hydrogen



SCHEME 3

atom from the hydride to give the alkane and a stannyl radical, thus propagating the chain (scheme 3). This reaction has developed into a useful synthetic tool, not only for reducing halides but also for making carbon–carbon bonds by interception of the intermediate carbon radical **8**.



15 X = Ph
16 X = imidazole
17 X = SMe

SCHEME 4

Our conception for the radical deoxygenation of secondary alcohols is summarized in scheme 4. In the presence of stannyl radicals, thionoester derivatives of the alcohol such as **9** would react to give a carbon radical (**10**). This radical can, of course, react with the stannane to give **11**. If, however, the temperature is sufficiently high, fragmentation of **10** may take place to form a carbonyl derivative (**12**) and another radical (**13**). This can be reduced by the stannane to give the desired alkane (**14**). The chain is propagated by the stannyl radical that is also produced. The driving force for the process is the conversion of a thiocarbonyl into a carbonyl and the increase of entropy produced by the fragmentation.

After some experimentation, we found that thionobenzoates (**15**), thionoimidazolides (**16**) and especially xanthates (**17**) were suitable substrates (Barton & McCombie 1975). For secondary alcohols, moderate temperatures (80–110 °C) are sufficient to cause the fragmentation of the intermediate radical (**10**) and yields are generally excellent. For primary alcohols, higher temperatures are required and yields are moderate to good (Barton *et al.* 1981). With tertiary alcohols, problems were encountered in the preparation of the various thionesters. These derivatives underwent Chugaev elimination too readily to survive the reaction conditions. We found, however, that thionoformates were thermally stable enough to allow the deoxygenation to take place in good yields, but these derivatives were relatively inaccessible (Barton *et al.* 1982).

Despite these various limitations, this deoxygenation reaction has found widespread use, especially (as originally intended) in the carbohydrate and aminoglycoside field where most hydroxy groups belong to the secondary type. The example shown in scheme 5 illustrates the exceptional tolerance of other functional groups and absence of β-elimination (Hayashi *et al.* 1978).

In a conceptually similar approach, we developed an efficient radical deamination method based on the reaction of isocyanides with tributylstannane. Isocyanides are easily accessible from the corresponding amine and undergo, on treatment with the stannane, a smooth fission of the carbon–nitrogen bond (scheme 6) (Barton *et al.* 1979). As for thionesters, the carbon radical formed is reduced to the alkane. Although this reaction was independently discovered by

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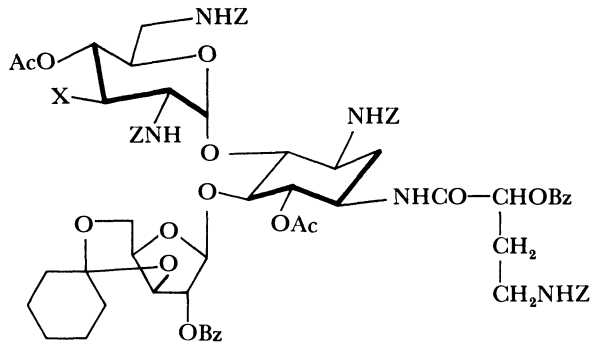
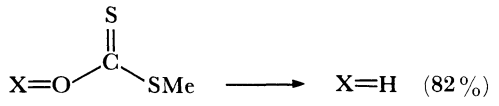
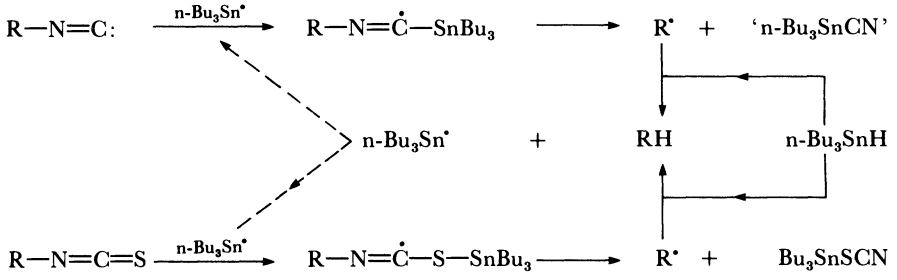
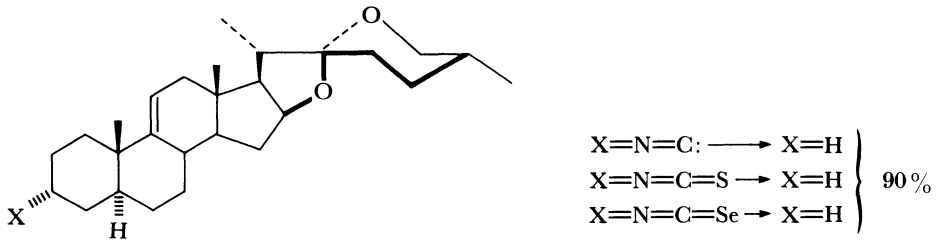




SCHEME 5

Saegusa, the yields reported were only moderate and the synthetic potential somewhat underestimated (Saegusa *et al.* 1968). Isothiocyanates and isoselenocyanates also undergo a similar reduction. This deamination reaction was successfully tested on a variety of substrates, including a dipeptide, which suggested possible applications in the peptide field. Even the 6-amino group in penicillins could be removed without harm to the sensitive β-lactam moiety (Ivor John *et al.* 1979).





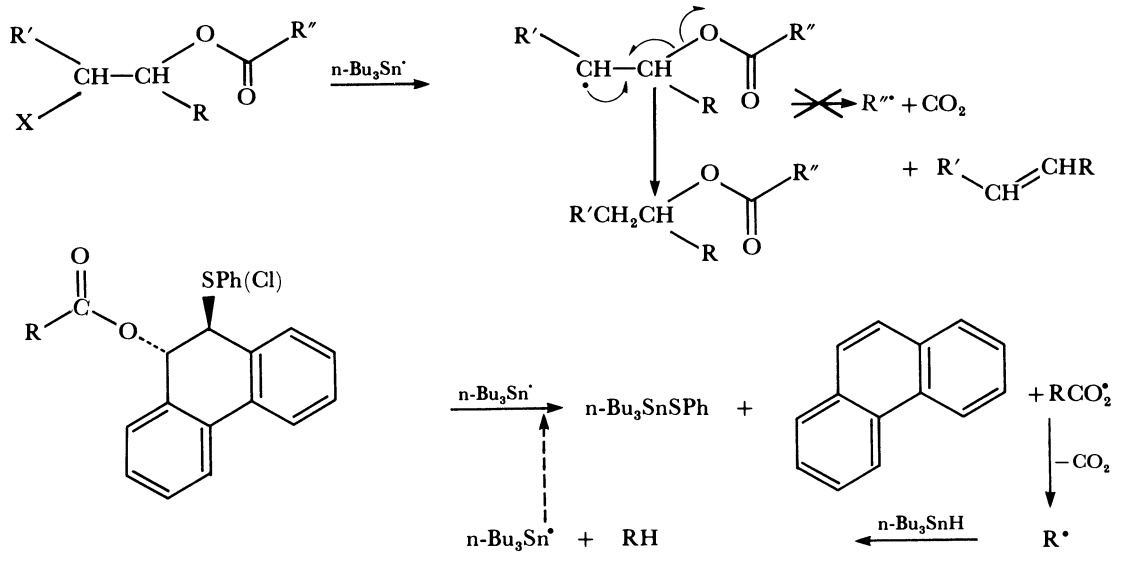
SCHEME 6

As expected, the order of reactivity is tertiary > secondary > primary isocyanide. Consequently, selective deamination is possible by simple adjustment of the reaction temperature. We have thus been able to prepare a number of deaminated neamine derivatives, useful in structure–activity determinations (Barton *et al.* 1980*a*).

Another important problem that attracted our attention is the decarboxylation of carboxylic

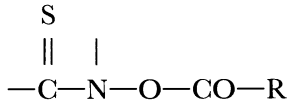
acids by radicals. Existing methods lack mildness and generality and hence are ill-suited for complex and often fragile natural products.

We were aware that a carboxylic radical would not be formed by β-elimination from an alicyclic or aliphatic radical. We therefore designed a molecule where the double bond formed is incorporated in an aromatic array, as for dihydrophenanthrene derivatives (scheme 7). With this aromatization driving force, good yields of noralkanes are obtained by β-elimination (Barton *et al.* 1980*b*).



SCHEME 7

The difficulty in preparing the various ester intermediates, especially when hindered, was a drawback to this method. We conceived that the esters (mixed anhydrides) of thiohydroxamic acids of the type

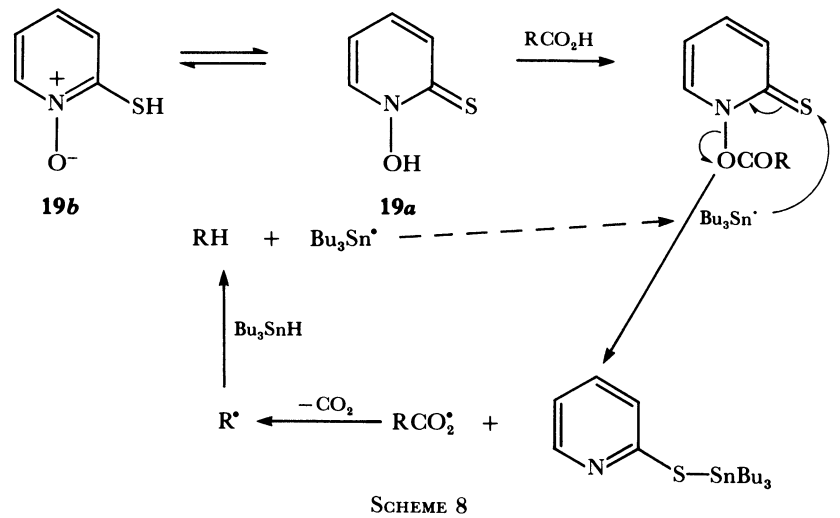


should show a facile radical fragmentation based on the same considerations that had been taken into account in the design of the deoxygenation reaction described earlier. Thus these esters have a relatively weak (N—O) β-bond that, in principle, makes fragmentation easy. Drawing on our previous experience, we incorporated the C=N double bond to be formed by the fragmentation into an aromatic system for additional driving force. Specifically, we examined esters (**18**), derived from *N*-hydroxy thiopyridone (**19*a***). This compound exists in equilibrium with its tautomer, 2-thiopyridine-*N*-oxide (**19*b***), but the derived esters are entirely in the form shown (**18**).

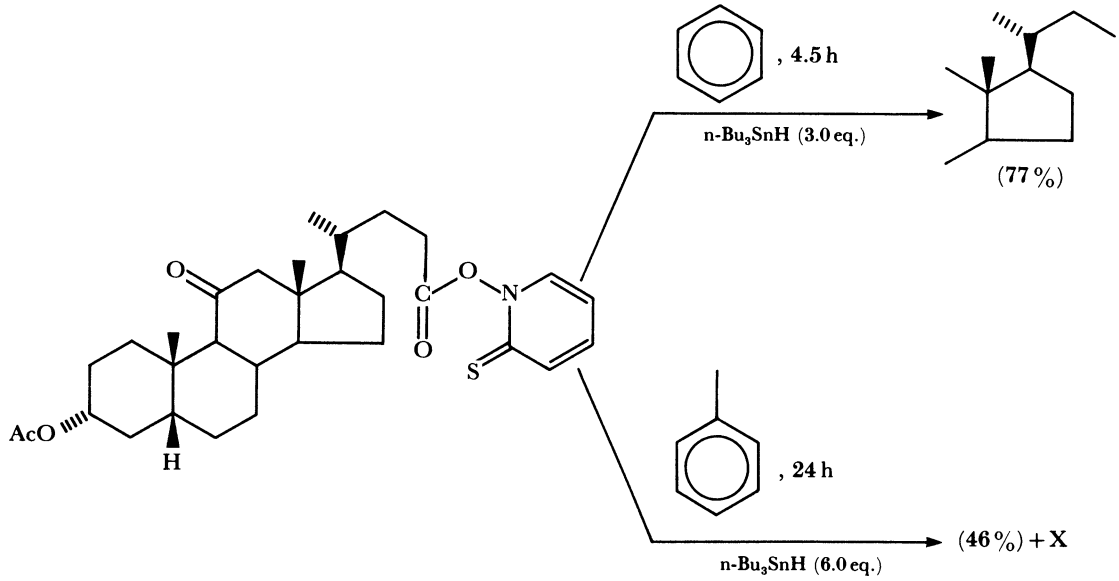
These derivatives (**18**) are easily accessible from acids or from acid chlorides (scheme 8). A non-negligible advantage is the commercial availability of **19** and of its sodium salt.

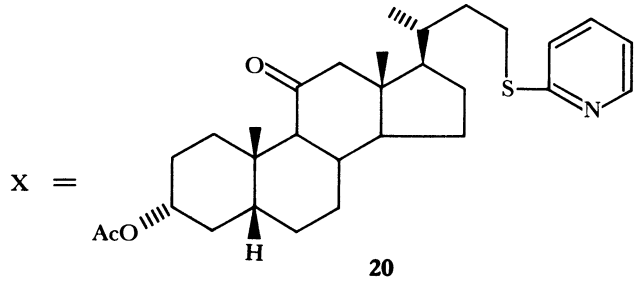
The reaction with tributylstannane occurred smoothly to give, in high yield, the corresponding noralkane from a variety of aliphatic and alicyclic acids (scheme 8) (Barton *et al.* 1983*a*).

For primary acids, however, we were surprised to find that reactions were faster and gave a higher yield in benzene at 80 °C than in toluene at 110 °C. Careful examination of the reaction mixture in a particular case showed the presence of another compound, identified as the sulphide (**20**). This is slowly reduced by the stannane to the same noralkane (scheme 9).



SCHEME 8





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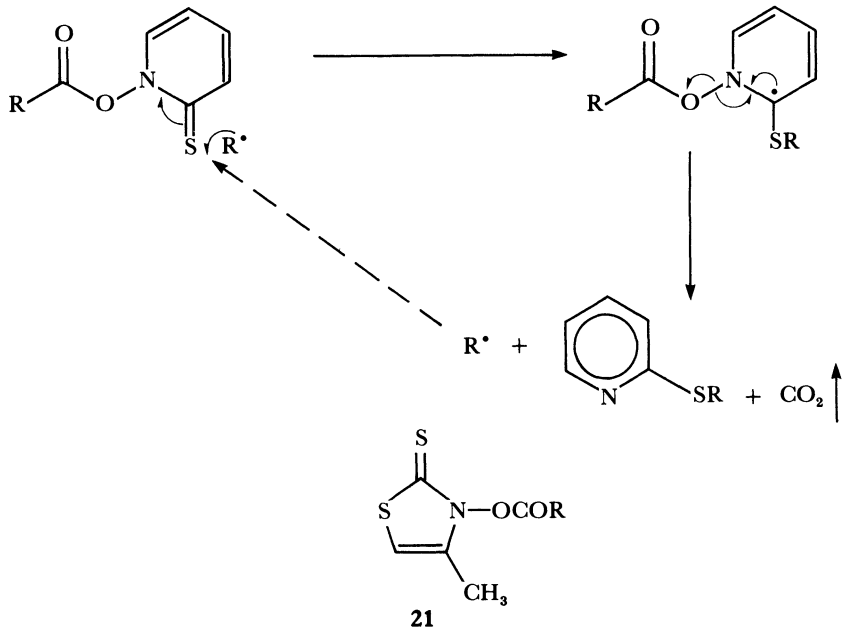
SCHEME 9

Apparently, at the higher temperature of refluxing toluene the formation of sulphide can compete with the 'normal' reduction. Indeed, in the absence of the reducing agent, the sulphide is the exclusive product. We found this novel decarboxylative rearrangement to be a general high-yielding reaction proceeding by the simple radical chain mechanism depicted in scheme 10. We had in essence discovered a new and mild way of generating carbon radicals from



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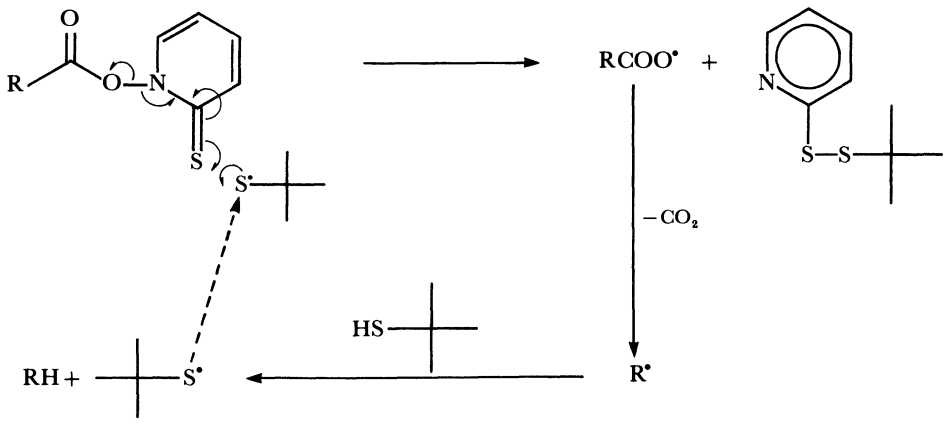
Scheme 10

carboxylic acids. The reaction occurs with other thiohydroxamic esters having an appropriate structure, such as **21** (Barton & Kretzschmar 1983). Furthermore, the decarboxylation may be promoted thermally or photochemically at room temperature or lower.

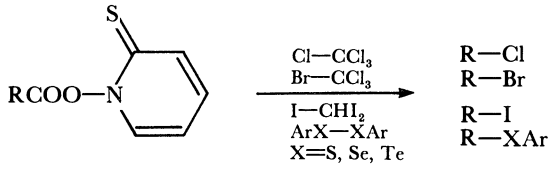
Having at hand a convenient source of carbon radicals, we considered ways of intercepting them by various reagents, thus diverting the reaction from its normal course. However, to retain all the advantages of radical reactions we had to maintain the chain mechanism by using an appropriate propagating (chain-carrying) radical.

To illustrate this conception, let us consider performing the decarboxylation in the presence of a thiol. Being an excellent hydrogen-atom donor, the thiol reduces the radical to the alkane with formation of a thiyl radical which propagates the chain (scheme 11). In practice, the reaction proceeds as predicted. High yields of noralkane are obtained without the purification problems usually encountered in stannane reductions (Barton *et al.* 1983*a*).



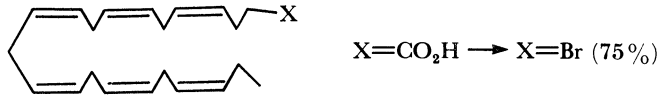
Scheme 11

As a consequence of similar mechanistic considerations, we have succeeded in preparing chlorides, bromides and iodides in excellent yield simply by operating in the presence of carbon tetrachloride, bromotrichloromethane and iodoform respectively (scheme 12) (Barton *et al.* 1983*b*). In terms of mildness of conditions, generality and yields this method is far superior



Scheme 12

to the classical Hunsdiecker reaction and its variants, which are practically all based on the use of toxic or expensive heavy metal salts. As a demonstration of the mildness of the conditions, we can cite the successful decarboxylative bromination of the heavily functionalized acid **22** with the use of our method (S. Ikegami 1984, personal communication). All other classical methods failed in this case.



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Reductive chalcogenation can similarly be achieved, leading to sulphides, selenides and even tellurides. The carbon radical in this case is trapped with a diaryl disulphide, diselenide or a ditelluride respectively (scheme 12) (Barton *et al.* 1984*a*).

We have also found it possible to intercept the carbon radical with oxygen. The reaction has to be performed in the presence of a thiol to reduce the intermediate hydroperoxy radical to the hydroperoxide and to furnish the thiyl (propagating) radical. The hydroperoxide can be reduced further, to the corresponding alcohol, by a phosphite, or transformed into an aldehyde or a ketone depending on whether the starting acid is primary or secondary (scheme 13) (Barton *et al.* 1984*b*).

We next examined a transformation of crucial importance to organic synthesis, the formation of carbon–carbon bonds. We were encouraged in this respect by the work of Giese (Giese 1983) and others on the addition of carbon radicals to electron-deficient double bonds. We found that similar addition could be achieved with our system if the olefin was sufficiently activated for the addition to compete successfully against the background decarboxylative rearrangement (scheme 14) (Barton *et al.* 1984*c*). Yields were variable, being highest for reactive, not easily polymerized, olefins. An interesting reagent is the acrylic ester derivative **23**. The sulphur moiety, by acting as a leaving group, prevents polymerization and efficiently propagates the chain. The products (**24**) have considerable synthetic protential (Barton & Crich 1984*a*).

Somewhat inevitably, our work on the decarboxylation of acids provided us with the key to the so-far inadequately solved problem of radical deoxygenation of tertiary alcohols.

If a carboxyl radical derived from the hemi-ester of oxalic acid such as **25** can be produced it will, by the loss of two molecules of carbon dioxide, give a tertiary carbon radical which can

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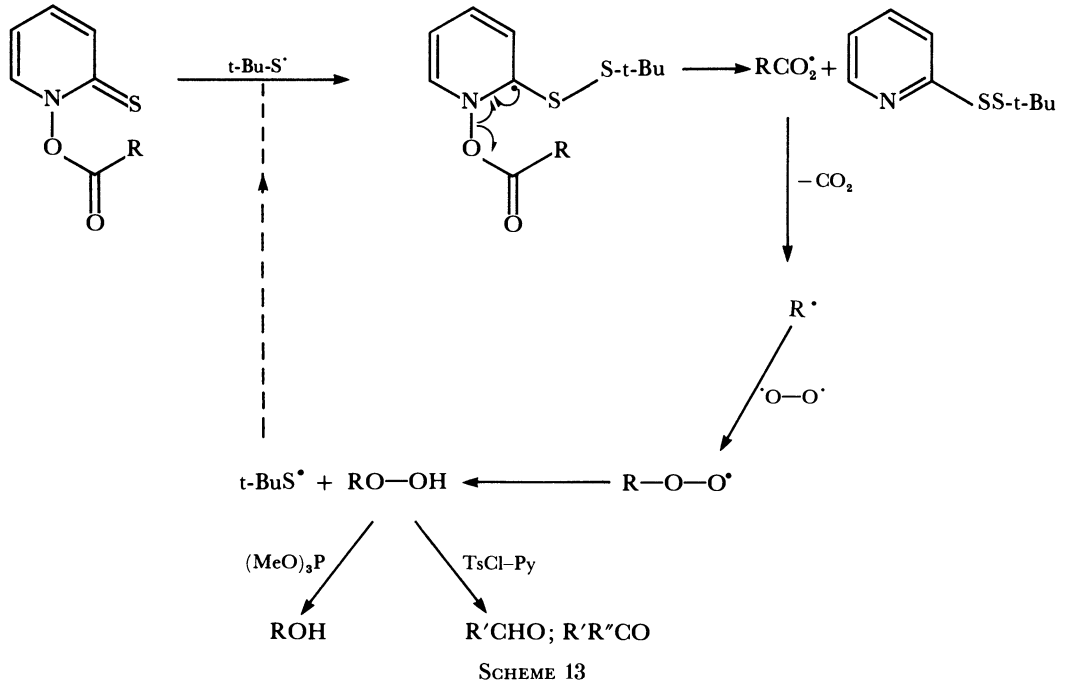
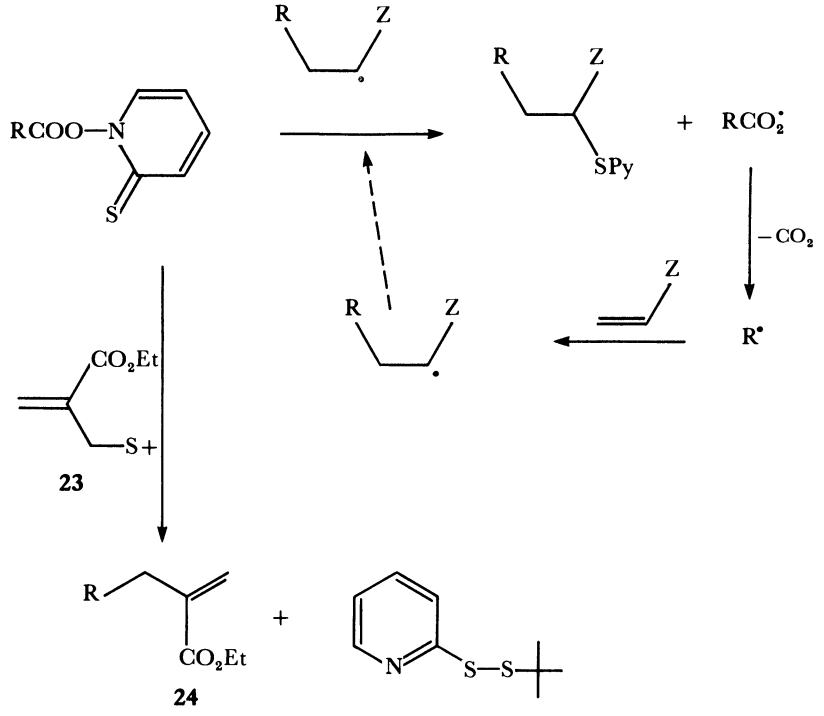


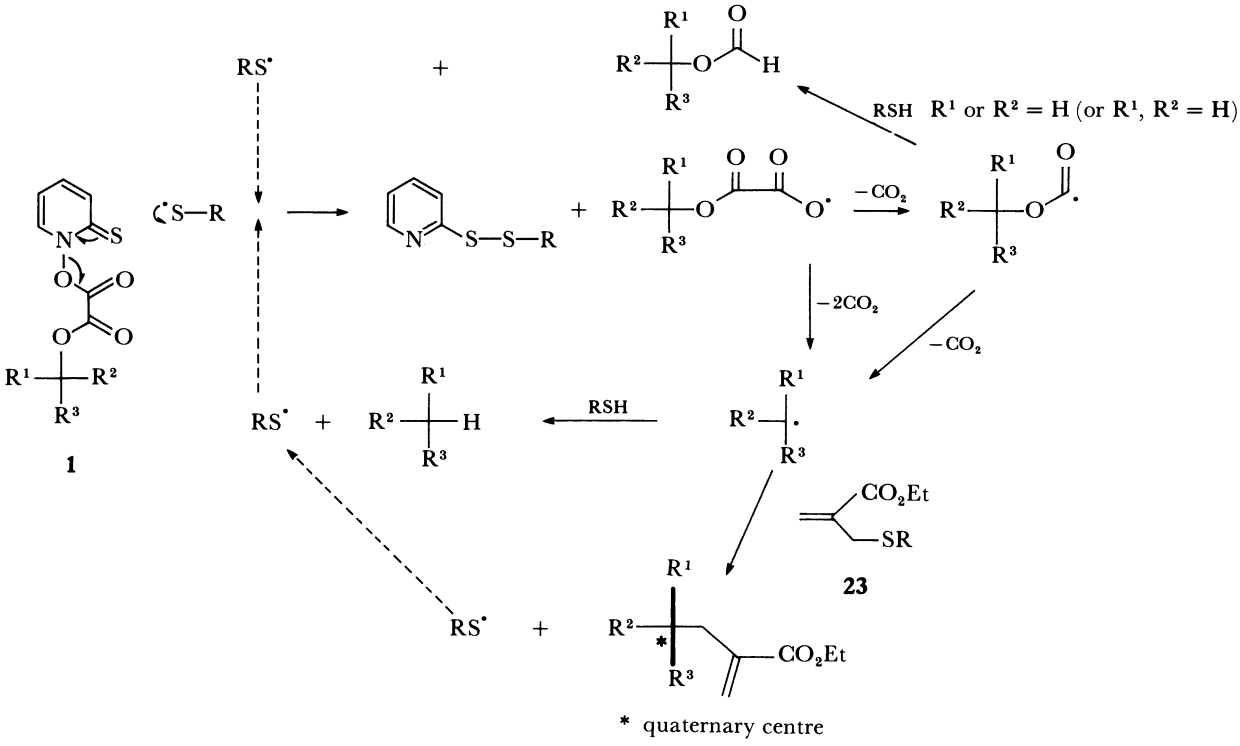
Scheme 13



Scheme 14

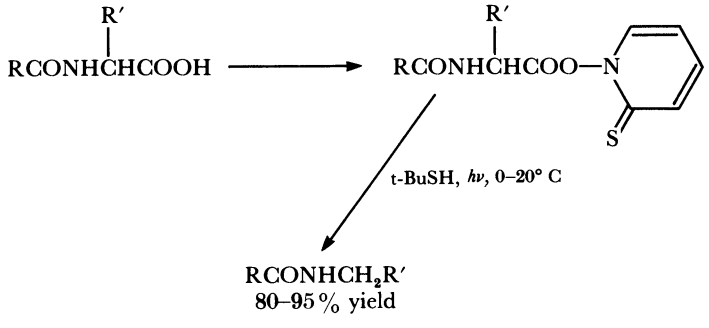
be reduced as before by a thiol (scheme 15). This conception was readily applied in practice and a variety of tertiary alcohols were deoxygenated in good yield (Barton *et al.* 1984*b*).

Interception of the tertiary radical with the acrylate reagent **23** results in the formation of a quaternary centre directly from an alcohol (scheme 15) (D.H.R. Barton & D. Crich 1984, unpublished results). The synthetic potential of this transformation is considerable given the difficulties usually encountered in creating quaternary centres



SCHEME 15

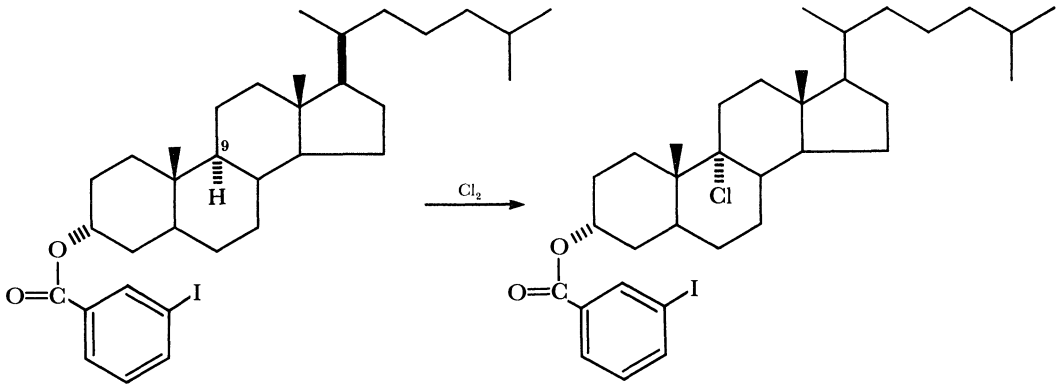
This type of radical chemistry is well suited for the manipulation of amino acids and peptides. By using a mixed anhydride coupling procedure, *N*-hydroxy-2-thiopyridone esters of *N*-protected amino acids or peptides can be synthesized and decarboxylated in very high yield (scheme 16) by using a thiol as hydrogen-atom transfer reagent. Alcoholic, phenolic and even



SCHEME 16

indolic groups do not need protection in this reaction. Equally important is the manipulation of side-chain carboxyl groups, made possible when the α-carboxyl is appropriately protected (Barton *et al.* 1984*d*).

The variety of synthetic possibilities uncovered by the decarboxylation reaction is remarkable and is probably only an indication of what may be in store. Radical reactions can achieve amazingly selective transformations, given proper control of the various parameters. An additional example to the reactions discussed so far is the ingenious device conceived by Breslow (Breslow *et al.* 1977) for remote functionalization of molecules. This has been elegantly applied



Scheme 17

in the selective intramolecular radical chlorination of the important 9α-positions of steroids (scheme 17).

This short review of synthetically useful radical chemistry demonstrates that high-yielding and selective reactions can be effected if the propagation steps are properly designed.

We thank all our colleagues who have participated in this work and whose names are cited in the References. Dr David Crich played the pioneering role in the early work. We thank also Roussel–Uclaf for their generous support.

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