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Invention of new reactions useful in the chemistry of natural products

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Abstract - The design of new Radical chain reactions useful in the synthesis or modification of Natural Products is discussed. Such reactions can give good yields, and show a selectivity which complements perfectly the ionic reactions in more general use. A flexible system for the production of many kinds of carbon radicals has been invented. It should be applicable for the generation of other kinds of radicals based on elements other than carbon. In the design of these reactions a vital role is played by a disciplinary group (usually the thiocarbonyl group), an idea which is of general application in the invention of radical chain reactions.
In a final section a new synthesis of pyrroles is described which is specially designed (by S.Z.Z) for intermediates in the preparation of porphyrins.

New reactions useful in synthesis are usually discovered by accident. It is, however, possible to invent reactions by conception (ref. 1). Most of this article is devoted to the invention of new radical chain reactions to give good yields of products. This can be done with the aid of the disciplinary group concept (vide infra).

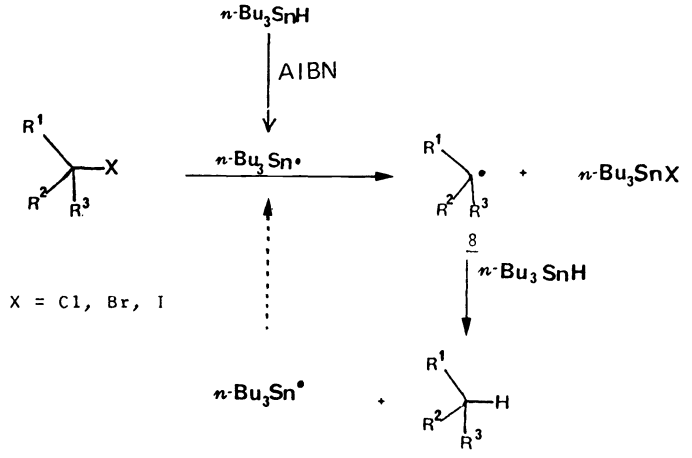
Radical reactions have, of course, an enormous importance in the synthesis of polymers. However, we are concerned here with their use in the chemical synthesis of homogeneous, low molecular weight molecules. In this area of scientific research, radical reactions are not often used, because they are considered 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.

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 etc... one can devise a system capable of effecting a highly selective transformation. Radical-radical interactions however (coupling, disproportionation etc...) 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; tolerance of many functional groups that have to be protected in ionic chemistry. In ionic reactions β-elimination is a serious problem in the carbohydrate and amino-glycoside antibiotic fields. These important compounds are heavily functionalised and selective deoxygenation or deamination presented a challenging problem. We shall first consider the problem of deoxygenation.

Many years ago, Van der Kerk (ref. 2) 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 (e.g. azoisobutyronitrile - A.I.B.N.) abstract the halogen to give a carbon radical. This latter abstracts a hydrogen atom from the hydride to give the alkane and a stannyl radical, thus propagating the chain (Scheme 1). This reaction has developed

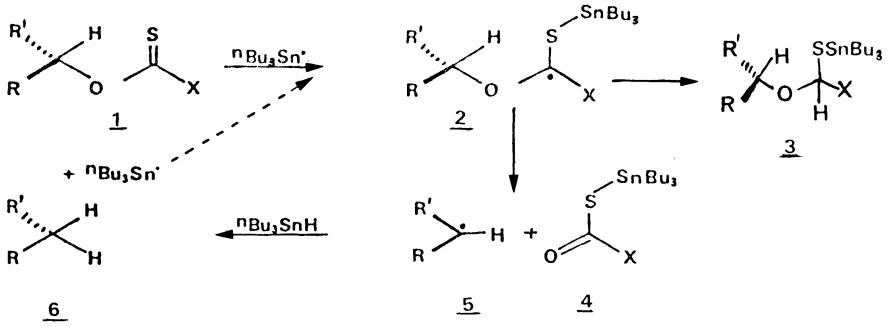
into a useful synthetic tool, not only for reducing halides but also for making carbon-carbon bonds by interception of the intermediate carbon radical.

Scheme 1



Our conception for the radical deoxygenation of secondary alcohols is summarised in Scheme 2. In the presence of stannyl radicals, thionoester derivatives of the alcohol such as 1 would react to give a carbon radical 2. This radical can, of course, react with the stannane to give 3. If, however, the temperature is sufficiently high, fragmentation of 2 may take place to form a carbonyl derivative 4 and another carbon radical 5. This latter can now be reduced by the stannane to give the desired alkane 6. The chain is propagated by the stannyl radical 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. In this, and all other reactions where tin hydrides are involved, it is the weakness of the tin-hydrogen bond which produces the disciplinary effect on the radicals and thus prevents random reactivity.

Scheme 2

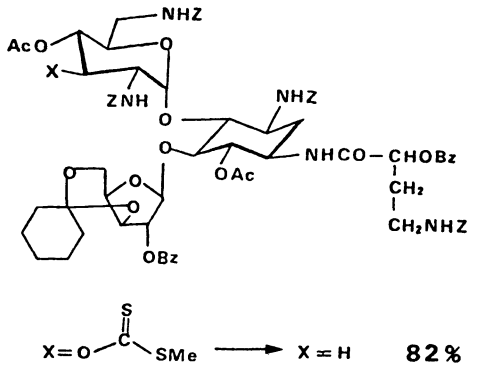


7 X = Ph 8 X = Imidazole 9 X = SMe

After some experimentation, we found that thionobenzoates 7, thionoimidazolides 8 and especially xanthates 9 were suitable substrates (ref. 3). For secondary alcohols, moderate temperatures (80-110°C) are sufficient to cause the fragmentation of the intermediate radical 2 and yields are generally excellent. In the case of primary alcohols, higher temperatures are required and yields are moderate to good (ref. 4). With tertiary alcohols problems were encountered in the preparation of the various thionoesters. 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 (ref. 5).

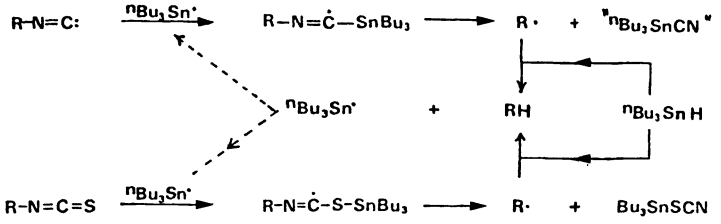
Despite these various limitations, this deoxygenation reaction has found widespread use especially, as originally intended, in the carbohydrate and aminoglycoside field, where most hydroxy groups belong to the secondary type. The example shown in Scheme 3 illustrates the exceptional tolerance of other functional groups and absence of β-elimination (ref. 6).

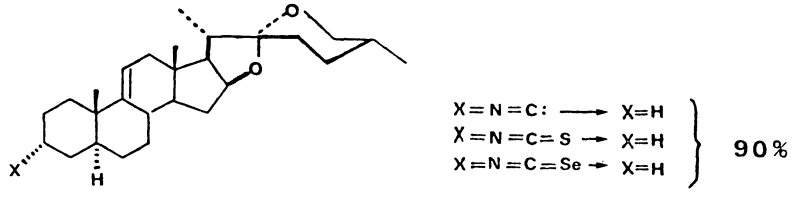
Scheme 3



In a conceptually similar approach, we developped 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 4) (ref. 7). As in the case of thionoesters, the carbon radical formed is reduced to the alkane. Although this reaction was independently discovered by Saegusa (ref. 8), the yields reported were only moderate and the synthetic potential underestimated. Isothiocyanates and isoselenocyanates also undergo a similar reduction. This deamination reaction was successfully tested on a variety of substrates including a dipeptide pointing to possible applications in the peptide field. Even the 6-amino group in penicillins could be removed without harm to the sensitive β-lactam moiety (ref. 9). 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 (ref. 10).

Scheme 4

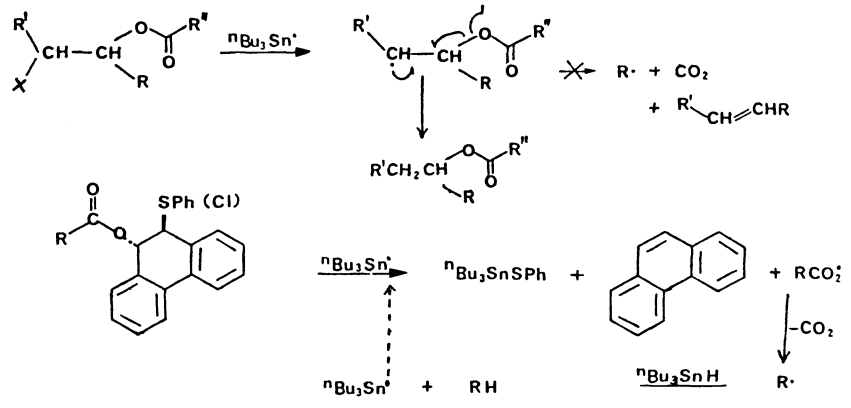




Another important problem that attracted our attention is the radical decarboxylation of carboxylic acids. Existing methods lack mildness and generality and hence are ill-suited for complex and often fragile natural products. We were aware that a carboxylic radical would not be formed by β-elimination from an alicyclic or aliphatic radical.

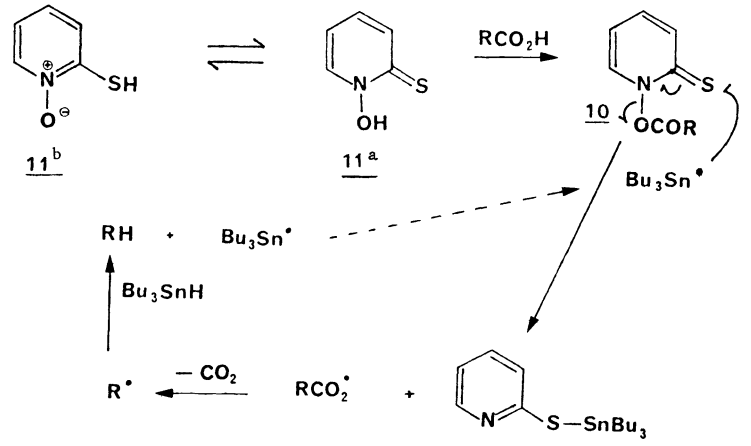
We, therefore, designed a molecule where the double bond formed is incorporated in an aromatic array, as in the case of dihydrophenanthrene derivatives (Scheme 5). With this aromatisation driving force, good yields of nor-alkanes are obtained by β-elimination (ref. 11).

Scheme 5



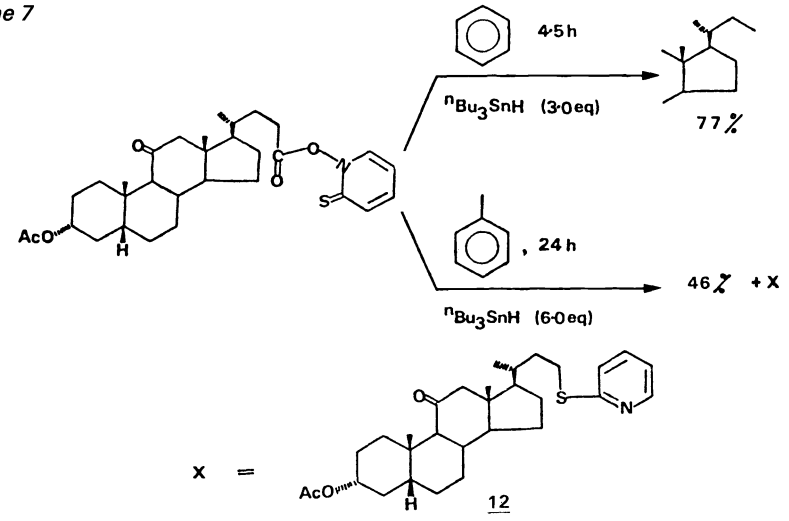
The difficulty in preparing the various ester intermediates, especially when hindered, was however a drawback to this method. We conceived that the esters (mixed anhydrides) of thiohydroxamic acids of type $-\overset{S}{\overset{\|}{C}}-N-O-CO-R$ should show a facile radical fragmentation based on the same considerations that had been taken into account in the design of the deoxygenation reaction (see above). Thus these esters have a relatively weak (N-O)β-bond making, in principle, 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 10 derived from N-hydroxy thiopyridone 11a. This compound exists in equilibrium with its tautomer, 2-thiopyridine-N-oxide 11b, but the derived esters are entirely in the form shown in 10. These derivatives 10 are easily accessible from acids or from acid chlorides (Scheme 6). A non-negligible advantage is the commercial availability of 11 and of its sodium salt. The reaction with tributylstannane occured smoothly to give, in high yield, the corresponding nor-alkane from a variety of aliphatic and alicyclic acids (Scheme 6) (ref. 12).

Scheme 6



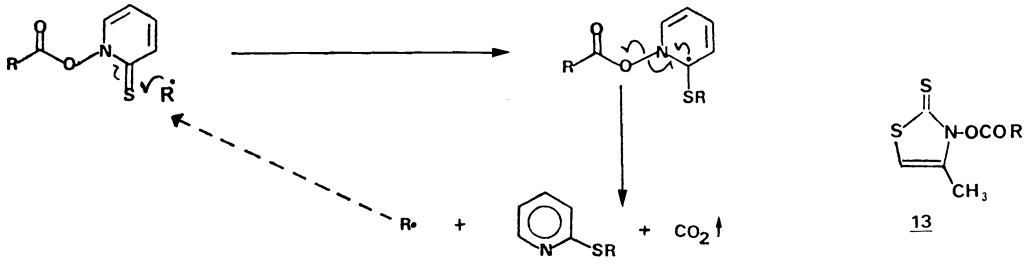
In the case of primary acids, however, we were surprised to find that reactions were faster and gave a higher yield in benzene at 80°C than in toluene at 110°C. Examination of the reaction mixture in a particular case showed the presence of another compound, identified as the sulphide 12. This is slowly reduced by the stannane to the same nor-alkane (Scheme 7). Apparently, at the higher temperature of refluxing toluene the formation of sulphide can compete with the "normal" reduction. Indeed, in the absence of

Scheme 7



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 8. The reaction occurs with other thiohydroxamic esters having an appropriate structure such as 13 (Ref. 13). Furthermore, the decarboxylation may be promoted thermally or photochemically at room temperature or lower.

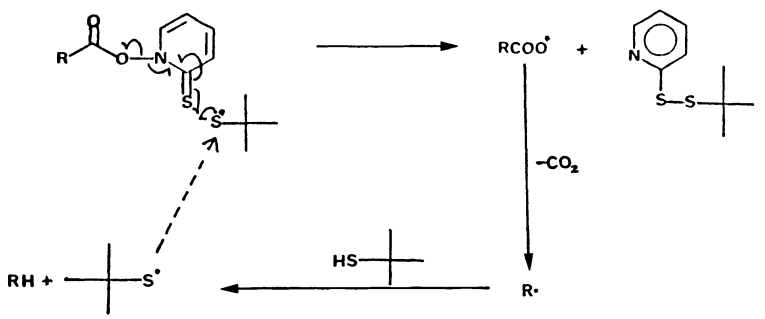
Scheme 8



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

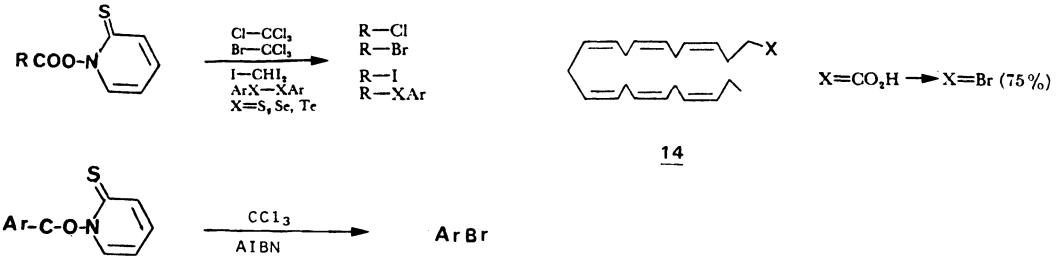
To illustrate this conception, let us consider performing the decarboxylation in the presence of a thiol. Being an excellent hydrogen atom donor, the thiol reduces the radical to the alkane with formation of a thiyl radical which propagates the chain (Scheme 9). In practice, the reaction proceeds as predicted. High yields of nor-alkane are obtained without the purification problems usually encountered in stannane reductions (ref. 12).

Scheme 9



As a consequene 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 10) (ref. 14). In terms of mildness of conditions, generality and yields this method is far superior to the classical Hunsdiecker reaction and its variants, practically all based on the use of heavy metal salts. Furthermore, by incorporating an initiator (AIBN) we have been able to extend the reaction to the more difficult case of aromatic and α,β unsaturated acids (ref. 15), even those with electron releasing substituents, which usually undergo ring bromination when subjected to Hunsdiecker conditions. As a demonstration of the mildness of our conditions, we can note the successful decarboxylative bromination of the heavily functionalised acid 14 by Prof. Ikegami using our method (ref. 16). All other classical methods failed in this case.

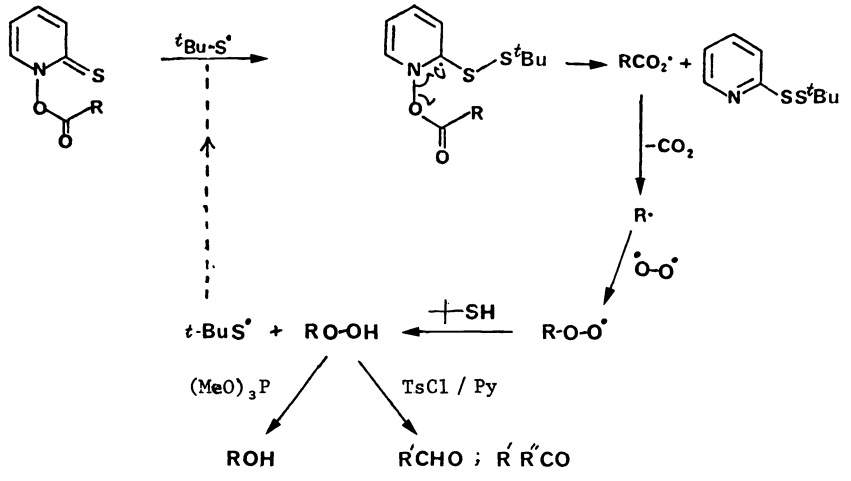
Scheme 10



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 10) (ref. 17).

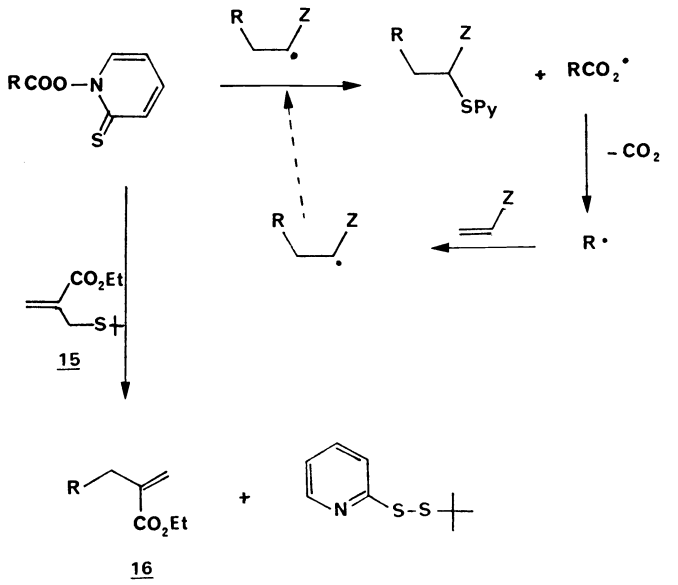
We have also found it possible to intercept the carbon radical with oxygen. The reaction has to be performed in the presence of a thiol to reduce the intermediate hydroperoxy radical to the hydroperoxide and to furnish the thiyl (propagating) radical. The hydroperoxide can be reduced further to the corresponding alcohol by a phosphite or transformed into an aldehyde or a ketone depending on whether the starting acid is primary or secondary (Scheme 11) (ref. 18).

Scheme 11



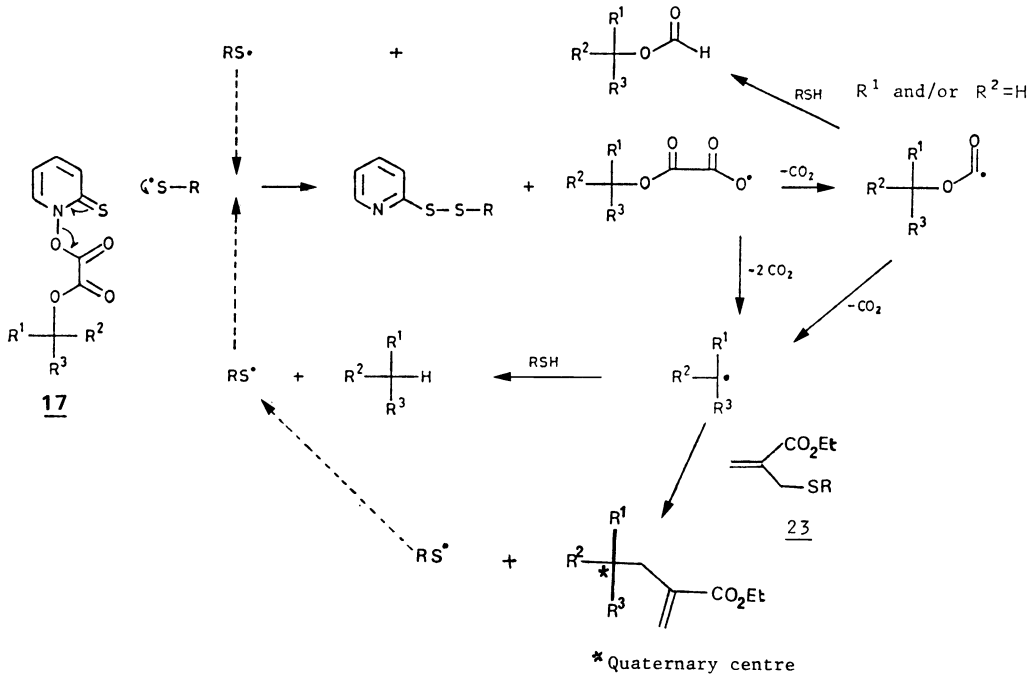
We next examined a transformation of crucial importance to organic synthesis : the formation of carbon-carbon bonds. We were encouraged in this respect by the work of Giese (ref. 19) and others on the addition of carbon radicals to electron deficient double bonds. We found that similar addition could be achieved with our system if the olefin was sufficiently activated for the addition to compete successfully against the background decarboxylative rearrangement (Scheme 12) (ref. 20). Yields were variable being highest for reactive, not easily polymerised olefins. An interesting reagent is the acrylic ester derivative 15. The sulphur moiety, by acting as a leaving group, prevents polymerisation and efficiently propagates the chain. The products 16 have furthermore considerable synthetic potential (ref. 21).

Scheme 12



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 17 can be produced it will, by loss of two molecules of carbon dioxide, give a tertiary carbon radical which can be reduced as before by a thiol (Scheme 13). This conception was readily reduced to practice and a variety of tertiary alcohols were deoxygenated in good yield (ref. 22).

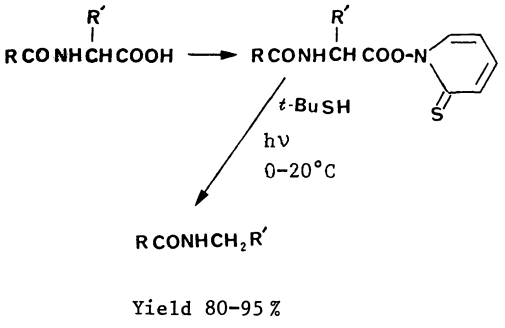
Scheme 13



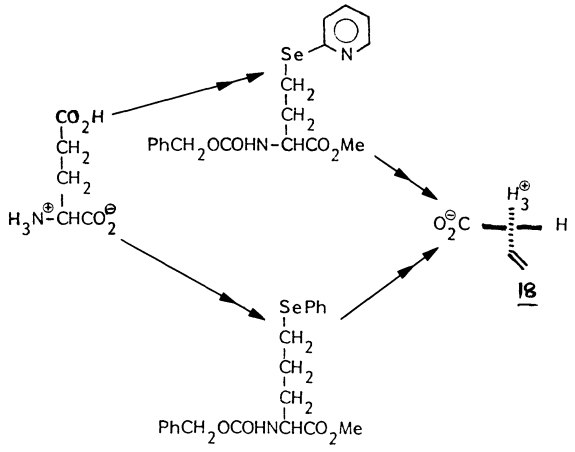
Interception of the tertiary radical with the acrylate reagent 23 results in the formation of a quaternary centre directly from an alcohol (Scheme 13) (ref. 23). The synthetic potential of this transformation is considerable given the difficulties usually encountered in creating quaternary centres.

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 synthesised and decarboxylated in very high yield (Scheme 14) using a thiol as hydrogen atom transfer reagent. Alcoholic, phenolic and even 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 (ref. 25). As an example, we carried out the synthesis of optically active vinylglycine 18, an important amino acid, from glutamic acid (Scheme 15) (ref. 25).

Scheme 14

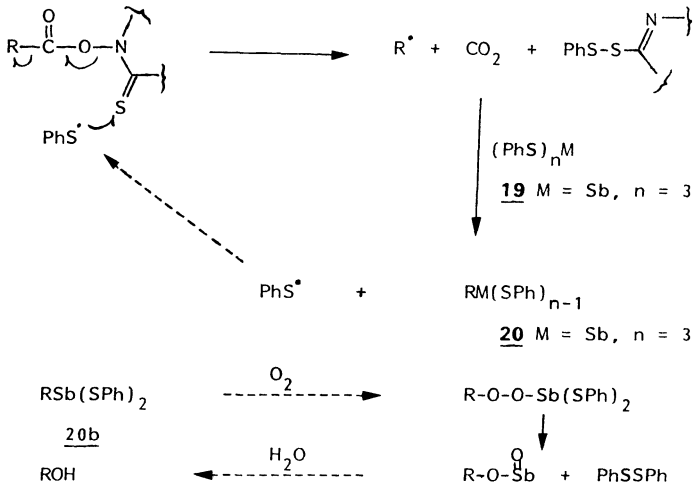


Scheme 15



In the reactions that we have described above, based on the esters of thiohydroxamic esters (mixed anhydrides), the disciplinary group, which prevents random reactions, is the thione function. Another feature is the elevated yields which are seen when a thiyl radical as propagating radical reacts (soft-soft) with the thione function. We conceived that we could exploit this reactivity of thiyl radical to induce carbon radical reactions with other elements such as metalloids and transition metal elements. The following examples illustrate that this idea opens up a new chapter in the preparation of M-R (M = metal or metalloid) bonds. Thus (Scheme 16) one can conceive that a radical generated in the usual way could react with a species $(PhS)_n M$ 19 to give with elimination of a PhS$^\bullet$ radical a derivative $R\text{-}M(SPh)_{n-1}$ 20. The chain would then be propagated.

Scheme 16



In fact, in the case where M = antimony and n is 3 we have been able to develop a high yielding reaction which converts an acid into the corresponding nor-alcohol. The reaction works so well because 19 and its congeners are sensitive to oxygen and produce

spontaneously thiyl radicals. After hydrolysis excellent yields of nor-alcohol are obtained. This is surely the best method available for the change $R-CO_2H \rightarrow R-OH$ under very mild conditions. It works equally well with primary, secondary and tertiary acids in the aliphatic and alicyclic series. Simply stirring a mixture of the ester and $(PhS)_3Sb$ under air at room temperature is sufficient to bring about the desired conversion (ref. 26).

We have so far endeavoured to demonstrate the great synthetic potential of well designed radical chain reactions by highlighting some of our recent contributions to that area.

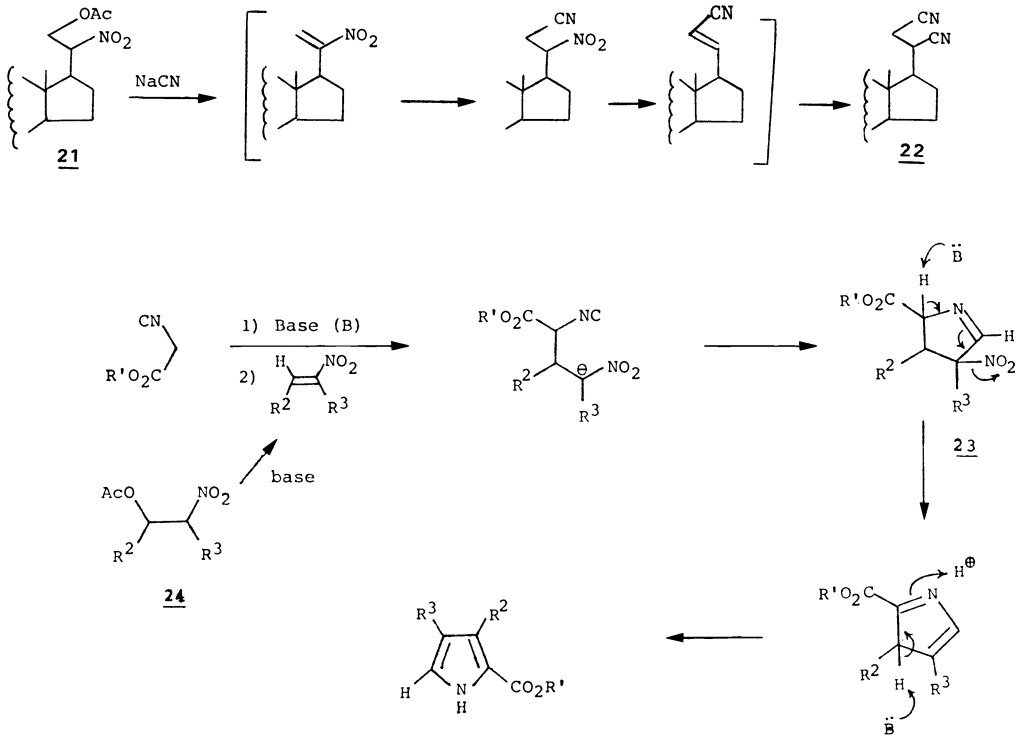
The quest for new ionic processes which occur under very mild conditions is also a worthwhile undertaking, despite the various possible complications enumerated in the introduction of this article. One reaction we have recently developed provides an expedient entry into a variety of important pyrroles only tediously obtained by conventional methods.

In an earlier work on the construction of the corticoid side chain, we observed a rather facile elimination of the nitro group (as nitrite) when the nitro acetate 21 was treated with sodium cyanide leading ultimately to the dinitrile 22 (Scheme 17) (ref. 27).

One of us (S.Z.Z.) proposed that a pyrroline intermediate 23, obtained by addition of an α-isocyanoacetate onto a nitro-olefin followed by cyclisation would undergo loss of nitrite and double bond shift to give the pyrrole (Scheme 17). This is indeed the case. In practice, the nitroolefin is best generated in situ from the more accessible β-nitroacetate 24. Using this method, a number of pyrroles with methyl, ethyl and propionate side chains were easily prepared. These are basic building blocks for porphyrins and bile pigments (ref. 28).

Although this new synthesis is ionic the conditions used are as mild as our radical chemistry. The β-nitroacetates 24 are made from the condensation of nitro-alkane with an aldehyde (the Henry reaction) followed by acetylation. Only mild base is needed for this condensation (e.g. guanidine bases) (ref. 29). The same base served to eliminate acetate to give the nitro-olefin and complete all the other steps in this "one pot" reaction.

Scheme 17



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