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The invention of chemical reactions of relevance to the chemistry of natural products

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Abstract
New reagents and reactions for use in the chemistry of Natural Products can be invented and not just discovered by hazard. First, we must recognize a reaction that would be important synthetically, but which does not yet exist in a satisfactory form. Thus, the reaction proposed either does not exist, or if it does, it is carried out under harsh conditions and is non-selective. Poor yields, uneconomic reagents and lack of stereoselectivity are other factors that spur invention. Thus, one has only to read the great syntheses of the day and ask for the yield, the conditions, the cost and the stereoselectivity at each step. It is a rare academic synthesis that does not have a weak step. It is even more unusual that new reagents or reactions are presented to alleviate the defects. Some modest efforts to help will be presented.

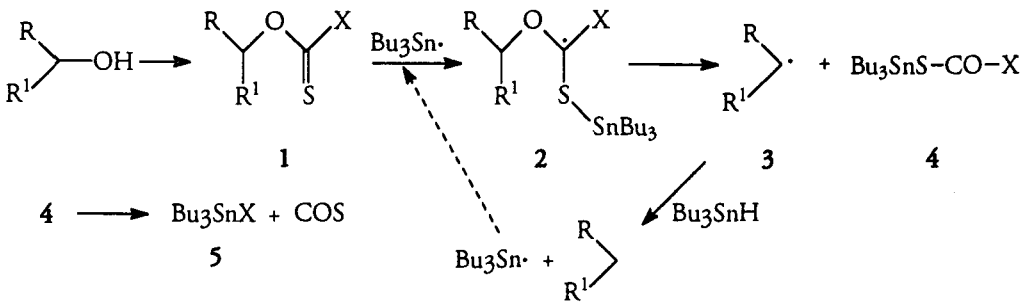
The Invention of chemical reaction is not a subject that interests many chemists. Indeed, most of the reactions that we use in synthesis today were not invented, but discovered by accident. Typical examples, which have revolutionized synthesis since 1940, are the Birch reduction, the Wittig reaction, Brown's hydroboration and derived borane chemistry and Ziegler-Natta olefin polymerization.

Important reactions where the intent was clearly invention are the Sharpless epoxidation and 1,2-dihydroxylation reactions and Noyori's selective hydrogenation catalysts. In both cases, very important problems of stereoselectivity were solved.

Let us now consider the invention of the ideal new chemical reaction. It should give 100% yield of a single product at room temperature and (preferably) under neutral conditions. It should be run at atmospheric pressure. If any reagents are used, they should be of low molecular weight. All constituents of the system should be non-toxic and environmentally friendly. Finally, all constituents of the system, except the desired product, should be cheap. The value added by the reaction should be maximal.

In 1975, Barton and McCombie[1] described a new radical chain reaction for the deoxygenation of alcohols, especially secondary alcohols. This reaction was invented for use in the field of aminoglycoside antibiotics. The radical mechanism avoids many problems of steric hindrance, rearrangement, elimination and neighboring group participation that are found in ionic reactions.

During the last five years, we have continued to improve the deoxygenation reaction. This reaction is traditionally based on a thiocarbonyl group **1** (Scheme 1) which is attacked by a tributyl



Scheme 1

tin radical to give an intermediate radical **2** which collapses to a secondary radical **3** and a tin intermediate **4**. The radical **3** is reduced with concomitant reformation of the tin radical. Alternative suggestions[2] of a different mechanism for the reduction of the xanthate function have been refuted[3] using ^{119}Sn N.M.R. spectroscopy. Taking advantage[4] of the ability of Et_3B-O_2 to generate radicals over a wide temperature range from -80° upwards, it was possible to initiate tributyl tin hydride reduction of xanthates **1** (X=SMe) at -20 where intermediate **4** was stable and gave a clear N.M.R. signal. After the reaction was complete, the temperature of the probe was raised to 20°. Intermediate **4** (X=SMe) then fragmented to **5** (X=SMe), identical with an authentic specimen, and COS. Other synthetic transformations have also appeared in the literature which give strong support to the original mechanism.[5]

In the original studies,[1] X in **1** was Ph, SMe and imidazoyl. Later,[6] Robins added X=PhO, which makes the thioacylation of the alcohol easier. We added[7] to the list X=2,4,6-trichlorophenyloxy and X=pentafluorophenyloxy. These derivative also give facile deoxygenation.

Although tributyl- and triphenyl- tin hydrides have been used for thirty years in the dehalogenation and deoxygenation of many types of organic compounds by a radical mechanism, they have, in fact, disadvantages for synthesis on a large scale. Tin residues are always formed and are difficult to remove. Organotin compounds are toxic and a step involving tin hydride would not be easily undertaken on a large scale in (say) the pharmaceutical industry. We have, since 1987, begun a search for other elements in the Periodic Table which would have weak M-H bonds, but strong M-O and M-halogen bonds. The obvious choice was silicon and we started with Ph_2SiH_2 which is commercially available. However, Chatgilialoglu, Griller and their colleagues[8] anticipated our research with the use of tristrimethylsilylsilane $(Me_3Si)_3SiH$ with a Si-H bond strength of 79 kilocals, comparable with the Sn-H bond strength of 74±2 kilocals. Tristrimethylsilylsilane substitutes very well for tin hydrides in many reactions.[9] However, it is of high molecular weight and, at present, is very expensive. Diphenylsilane also served[10] very well for the deoxygenation of secondary alcohols at room temperature using the xanthate or the 4-fluorophenyloxy derivative with initiation by triethylboron-air. Primary alcohols at room temperature gave mainly thioformates, but at 80° deoxygenation proceeded smoothly.

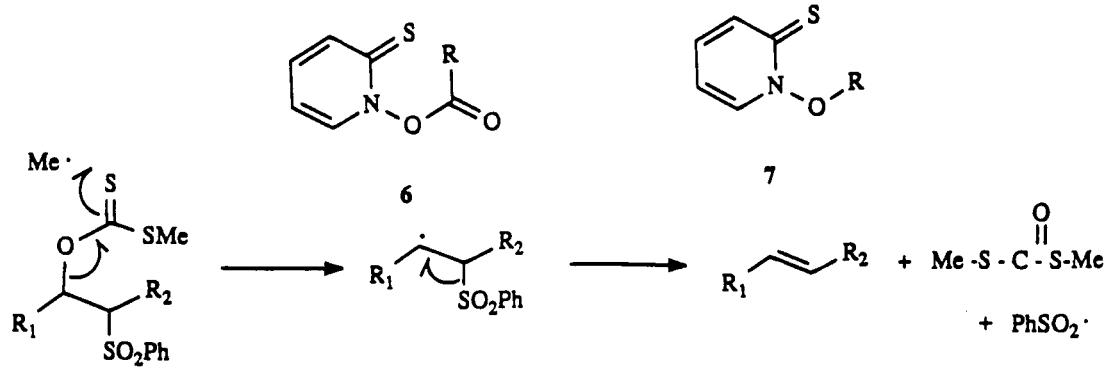
Some time ago, we reported[11] that 1,2-dixanthates of any geometry could be smoothly reduced to the corresponding olefins with tributyl tin hydride under the same conditions then in use for xanthate reduction. This reaction has taken on a new importance because of the need to synthesize dideoxynucleosides for treatment of A.I.D.S. The conversion of a nucleoside, after protection of the primary alcohol by (say) the t-butyldimethylsilyl group, to the 2′,3′-dixanthate is easily carried out. Tin hydride reduction[12] then affords in good yield the desired olefin, easily hydrogenated to the

dideoxynucleoside. We have been able to effect the same transformation in good yield using diphenylsilane as the reductant.[13] For larger scale working Et_3B-air is not easy to use as an initiator. We found that toluene under reflux with A.I.B.N. or dibenzoyl peroxide as initiator gave very satisfactory results.

Although the bond strength of the Si-H bond in phenylsilane is 88 kilocals, it can also be used in the deoxygenation of secondary and primary alcohols under the same conditions as used with diphenylsilane.[14] Since relatively large amounts of dibenzoyl peroxide were used, we showed, by using deuterotoluene and in a separate experiment, deuterated phenylsilane, that the hydrogen transferred did indeed come from the silane and not from the toluene. Phenylsilane can also be used in the efficient conversion of 1,2-dixanthates into olefins.[15]

Triethylsilane has an Si-H bond strength of 90 kilocals. However, it can be used as a solvent for the deoxygenation process and at the same time as a source of silyl radicals. Both the deoxygenation of secondary alcohols and the formation of olefins from 1,2-dixanthates are essentially quantitative reactions.[15] The excess triethylsilane is readily recovered and it has just the right boiling point (107-108°C).

The Julia olefin synthesis[16] is frequently used as a key step in the construction of complex, biologically important, natural products. In general, it consists of the addition of a sulfone anion to a carbonyl group, usually an aldehyde. This step goes in good yield. The second step is acetylation and sodium amalgam reduction to produce olefin. This step proceeds in variable, often bad, yield. Lythgoe and Waterhouse[17] were the first to convert the alcohol to xanthate and to make the corresponding radical by the Barton-McCombie reaction. Then β-elimination of the sulfonyl radical afforded the olefin in good yield. The reaction was later used effectively in synthesis, particularly by D.R. Williams.[18] We have recently studied this reaction[19] with the objective of avoiding tin hydride reagents. The photolysis or pyrolysis of acyl derivatives *N*-hydroxy-2-thiopyridone **6** is an excellent source of disciplined carbon radicals.[20] We have used **6** (R=Me) as a convenient source of the methyl radical, which can attack the thionocarbonyl group of a xanthate (Scheme 2) to give fragmentation to dimethyldithiocarbonate, the desired olefin and a phenylsulfonyl radical which will carry the chain. This method gives largely the *trans* olefin in about 80% yield. Alternatively, diphenylsilane and an initiator can be used in toluene under reflux.

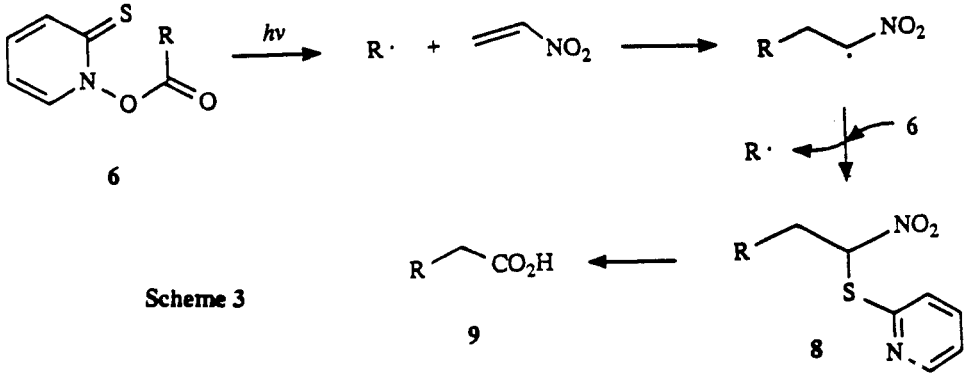


Scheme 2

Acyl derivatives of type **6** give carbon radicals when R is alkyl or cycloalkyl. If R is aryl, the corresponding arylcarboxy radicals ($R\text{-}CO_2\cdot$) do not give aryl radicals at less than 100° or more. At room temperature, arylcarboxy radicals are stable and can be trapped by electron rich olefins like vinyl ethers.[21,22] The photolysis of any derivative **7** of *N*-hydroxy-2-thiopyridone affords the corresponding

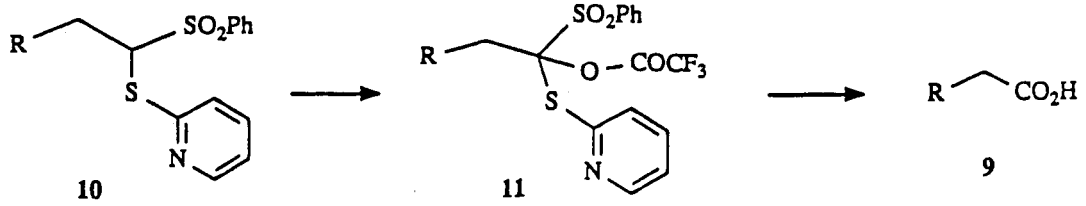
oxygen centered radical.[22] The parent compound **7** (R=H) affords a convenient source of hydroxyl radicals.[22,23] Deoxygenation of benzoyloxy radicals with P^{III} compounds affords quantitatively benzoyl radicals. Photolysis of **7** (R=alkyl) provides a convenient source of alkoxy radicals.[24]

The homologation of carboxylic acids is a reaction frequently needed in synthetic chemistry. The aesthetically pleasing Arndt-Eistert reaction is no longer acceptable, since diazomethane is involved. We provided[25] a solution to this problem by the addition of carbon radicals, generated from compounds

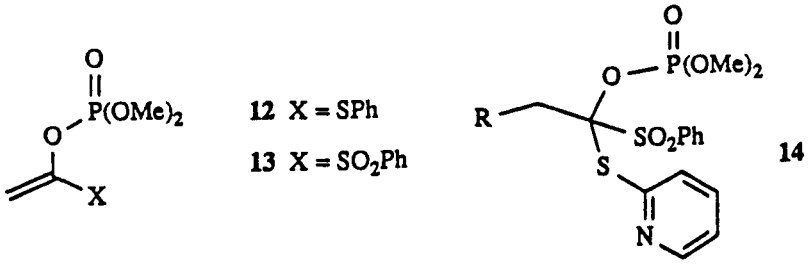


Scheme 3

of type **6**, to nitroethylene (Scheme 3). The adducts **8** were converted in high yield to the homocarboxylic acids **9** with H_2O_2 under mild basic conditions (K_2CO_3: 40°). However, it is not easy to make nitroethylene on a large scale. We have, therefore, looked for another solution to the

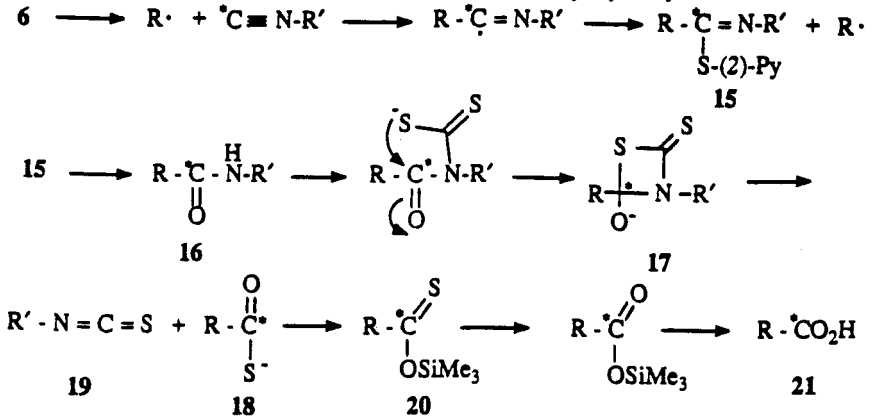


problem.[26] Addition of radicals from **6** to phenylvinylsulfone is a very efficient, known reaction to give **10**. Oxidation to sulfoxide followed by Pummerer rearrangement with trifluoroacetic anhydride affords derivatives **11**. Mild alkaline hydrolysis affords **9**. The Perkow reaction[27] on phenylthiochloroacetate gave derivative **12** (X=SPh), easily oxidized to the sulfone **12** (X=SO_2Ph). Addition of the radical to the latter afforded **14** which was smoothly hydrolysed to acid **9** with 1 M KOH. Several other less suitable alternatives were also examined.[26]



The conversion of a carboxylic acid back to a carboxylic acid might seem a useless synthetic reaction. However, if this enables the carboxyl to become labeled with ^{13}C or ^{14}C, then it provides a convenient method for the synthesis of specifically labeled prostaglandins, leucotrienes and other compounds of the arachidonic acid cascade, as well of course, of the side chain carboxyls in peptides. Our first solution to

the problem[28] was to use radical generators of type **6**, reacting the radical with a suitably activated isonitrile (Scheme 4) to give derivative **15**, which was readily hydrolysed with water to give **16**. An

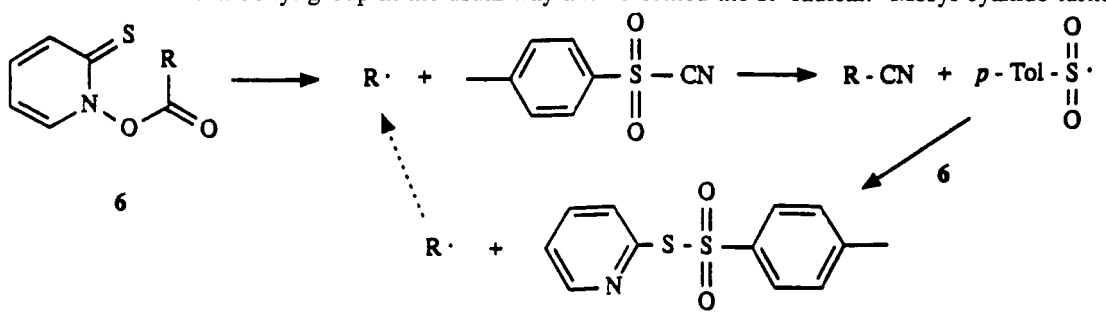


Scheme 4

ingenious procedure[29] for the conversion of secondary amides to thioacids and isothiocyanates was adapted to our problem. Normally,[29] the anion, generated with sodium hydride reacts with CS_2 to give via **17** the thioacid anion **18** and isothiocyanate **19**. We conceived that if hexamethyldisilazane anion was used as base, the thioacid anion **18** would be silylated[30] on oxygen *in situ* to give the thiocarbonyl derivative **20**. So addition of phenylseleninic acid[31] would then convert the thiocarbonyl to carbonyl, also *in situ*, and give, on addition of water, the desired labeled carboxylic acid **21**. This idea worked well and should find other applications. The weak step in this synthesis is the radical addition to the isonitrile. Isonitriles that are sufficiently radicophilic are also easily polymerized. So we decided to develop a better procedure.

The sulfonylcyanide function shows some radical behavior.[32] We decided to compare the well-known p-toluenesulfonyl cyanide with mesyl cyanide, a reagent that had not been used in radical reactions before. Neither reagent had been studied in our thiocarbonyl mediated radical chemistry.

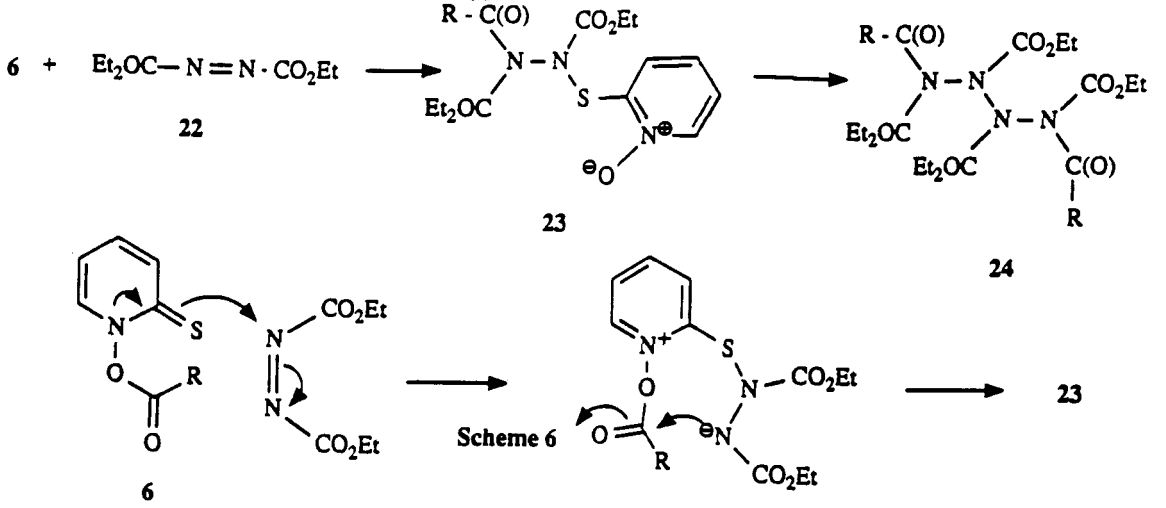
Radicals generated by the photolysis (W light) of **6** readily reacted with the cyanide function of *p*-toluenesulfonyl cyanide to furnish (Scheme 5) the appropriate nitrile and the sulfonyl radical. This reacted with the thiocarbonyl group in the usual way and reformed the R· radical. Mesyl cyanide turned



Scheme 5

out to be even more reactive towards carbon radicals and furnished excellent yields of R-CN.[33] Conditions for alkaline hydrolysis, which did not conjugate skipped dienes like linoleic acid, were developed.

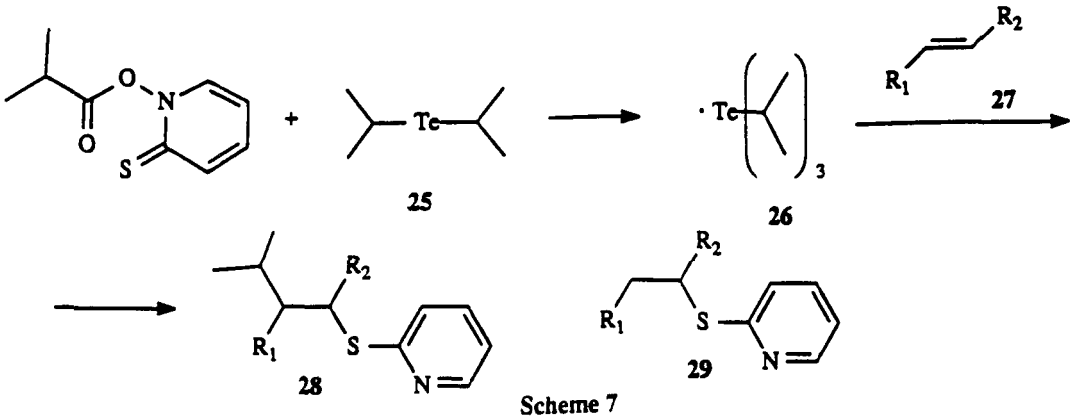
One of our research projects has been to find a reagent which would react with carbon radicals in such a way as to introduce the amine function. During this work, we decided to examine the possibility of adding carbon radicals to diethylazodicarboxylate **22**. When **6** and **22** in CH_2Cl_2 were left at room with tungsten lamp irradiation, or in the dark, they rapidly reacted to give compounds of type **23**, a class of substances never seen before.[34] On photolysis unusual dimers **24** were produced with four linked nitrogen atoms. The formation of **23** is suggested to be as in Scheme 6.



Scheme 6

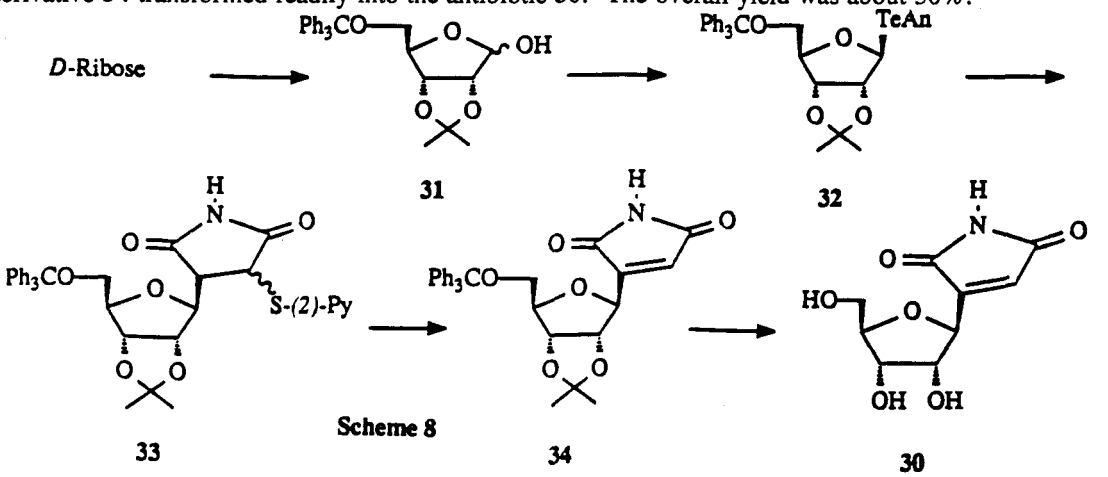
Another idea was the concept of a radical accumulator whose presence might facilitate addition to β-mono and β,β-di-substituted olefins. We conceived that alkylaryl or dialkyl tellurides should react with alkyl radicals and give an intermediate radical of type $R^1R^2R^3Te\cdot$ which might have a long life on the radical time scale. A secondary objective would be the exchange of one radical against another. In this way, the special nucleophilic properties of (say) the aryl telluride anion could be exploited to make complex natural product derived radicals.

The photolysis of **6** (R=$CHMe_2$) in the presence of di-isopropyl telluride **25** gave the postulated radical **26**, whose interaction with activated olefins **27** was studied[35] (Scheme 7). With phenyl vinyl sulfone **27** (R^1=H, R^2=SO_2Ph) the adduct **28** (R^1=H, R^2=SO_2Ph) was formed in good yield. However in comparable experiments with **6** (R=$CHMe_2$ and other radicals) without **25**, there was no significant change in yield. However when a primary radical was generated from **6** (R=Me, $PhCH_2CH_2$ etc.) in the presence of **25**, a clean radical exchange occurred to give $MeTeCHMe_2$ or $PhCH_2CH_2TeCHMe_2$ and adduct **28** (R^1=H, R^2=$PhSO_2$) in satisfactory yield.



Scheme 7

So the exchange process does exist, but there is no observable accumulator effect. The exchange process is useful in the preparation of carbon radicals from complex natural products like carbohydrates.[36] Since dianisyl ditelluride is easy to prepare, we have used the derived ($NaBH_4$)anisyl telluride anion as a nucleophile at primary and secondary positions, including especially the glycosidic carbon, to displace tosylates or bromides to give the appropriate anisyl tellurides. Photolysis of **6** (R=Me) affords a controlled supply of methyl radicals which exchange with tellurides to give AnTeMe (An=anisyl) and the desired carbohydrate radical. In the presence of a suitable radical trap like **27** (R^1=H, R^2=$PhSO_2$, COMe, CO_2Me etc.) adducts **29** (R^1=carbohydrate residue, R^2=$PhSO_2$, COMe, CO_2Me etc.) were formed in good yield. A short synthesis of showdomycin **30** (Scheme 8) illustrated the utility of the method. D-ribose was converted to the known derivative **31** which on mesylation and displacement with anisyltelluride anion gave **32**. Methyl radical exchange on **32** in the presence maleimide gave **33** which on oxidation to sulfoxide and elimination afforded the showdomycin derivative **34** transformed readily into the antibiotic **30**. The overall yield was about 30%.



31 **32** **33** **34** **30**

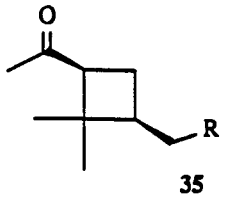
Scheme 8

We consider that the preparative chemistry associated with the acyl derivatives of thiohydroxamic acids is soundly based on experiment. Any reaction that does not give the planned product needs investigation. Following a report[37] that *cis*-pinonic acid **35** (R=CO_2H) did not afford the desired bromide **35** under reflux in CCl_4, we investigated the system. Irradiation of the *N*-hydroxy-2-thiopyridone derivative of **35** at room temperature with $BrCCl_3$ gave, in fact, an excellent yield of the bromide **35** (R=Br) (84%). With diphenyldiselenide, the radical was trapped even better (98%). The problem with the earlier work was shown to be due to the opening of the radical **36** to give the more stable radical **37** with relief of ring strain.[38]

With so much good radical chemistry based on acyl derivatives of thiohydroxamic acids, we naturally wondered if the corresponding derivatives of ordinary hydroxamic acids would show similar reactivity. Of the hydroxamic acids studied, only the dihydrocinnamoyl derivative of **38** showed, with an initiated tin hydride reduction, a good yield of the hydrocarbon (97%). The next best was the derivative of *N*-hydroxy-2-pyridone which gave 73% of hydrocarbon. These results,[39] as well as those in the literature,[40] serve to confirm the superiority of thiohydroxamic acids as radical generators. We were not able to trap any radical produced from **38** to make a carbon-carbon bond.

The reactions based on *N*-hydroxy-2-thiopyridone derivatives are clearly radical chain reactions. We have reported[41] quantum yield measurements for a number of reactions based on *N*-hydroxy-2-thiopyridone. Most of the reactions had quantum yields of 10-30. Synthesis of the *N*-hydroxyquinazolin-4-thione **39** (Ar=Ph, An, 1-Naph) by an improved route gave a thiohydroxamic acid

which was more sensitive to light than *N*-hydroxy-2-thiopyridone. The quantum yield for bromination was in the range 30-60. More important, whilst the *N*-hydroxy-2-thiopyridone system makes[42] only radicals, without a chain, at -30°, the derivatives of **39** continue radical chain reactions even at -60°.



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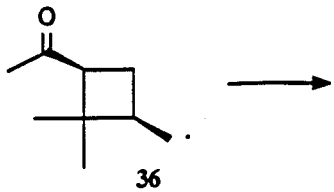

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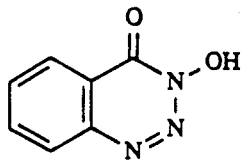

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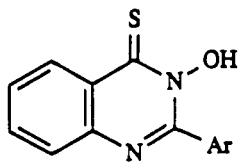

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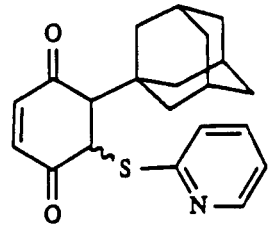

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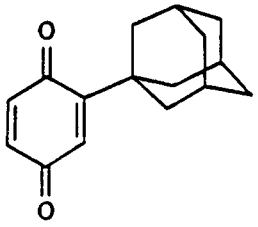

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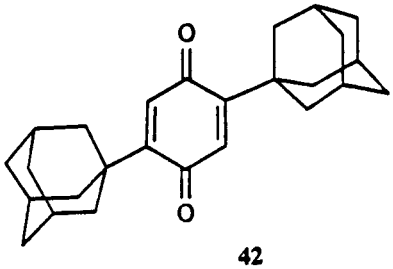

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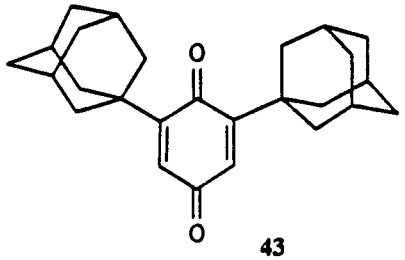

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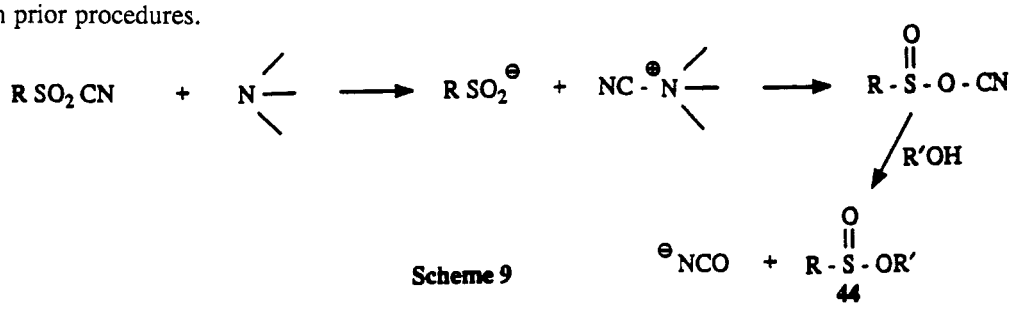
The synthesis of hindered quinones can be accomplished with difficulty using ionic reactions. We decided[43] to explore the limits of radical chemistry by adding *t*-adamantyl radicals to quinone. The photolysis of **6** (R=*t*-adamantyl) in the presence of benzoquinone afforded an adduct **40** which on peracid oxidation readily eliminated to give **41**. Addition of a second *t*-adamantyl group to **41** afforded, after oxidative elimination, the two hindered quinones **42** and **43**, easily distinguished from each other by ^{13}C N.M.R. All attempts to add a third *t*-adamantyl radical to **42** and **43** failed. We carried out similar studies with naphthoquinone where the adducts are of greater biological interest.

Whilst we try to invent new and significant chemical reactions, we still also discover them by accident. Treatment of all kinds of alcohols with mesyl or tosyl cyanides and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) afforded the corresponding mesyl and tosyl sulfinates **44** in very good yield.[44] This is an unexpected ionic reaction; we had expected to make imidates. The mechanism (Scheme 9) is supported by low temperature ^{13}C N.M.R. spectroscopy. This seems to be a better method to prepare sulfinates than prior procedures.



Scheme 9

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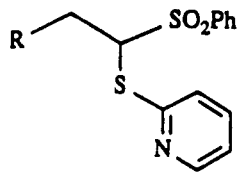
Interaction with Dr. S.Z. Zard of the Ecole Polytechnique, Palaiseau, France, has been fruitful over many years. The main recent results were multiple radical addition, where a second ring is formed with defined stereochemistry,[45] an improved synthesis of pyrroles[46] and work on the manipulation of geminal 2-*S*-pyridyl phenyl sulfones **10** formed from the addition of carbon radicals R to phenyl vinyl sulfone.[47] Thus, reduction with sodium hydrogen telluride removed the 2-*S*-pyridyl function to give **45**. Oxidation of **10** to the sulfoxide **46** and thermal elimination gave the vinyl sulfone **47** which afforded with sodium hydrogen telluride the vinylic olefin **48**. The phenylsulfone group could also be removed selectively. Treatment with trimethylaluminum gave **49**, whilst ethylaluminum dichloride and allyltrimethyl silane afforded the allylated derivative **50**. Oxidation to the sulfoxide and thermal elimination gave **51**. All these reactions proceeded in good yield. Thus the chemistry of this geminal function, based on radical chemistry, has been considerably expanded.



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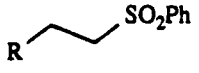

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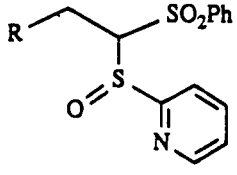

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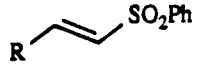

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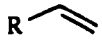

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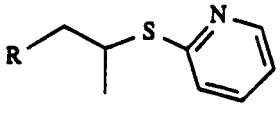

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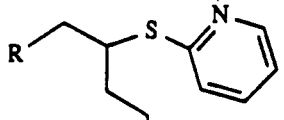

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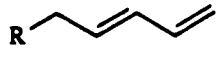
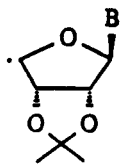


51

In collaboration with Professor Pierre Potier, a full paper[48] on the manipulation of α-amino-acids and peptides by radical chemistry based on acyl derivatives **6** has appeared.

A program on the manipulation of nucleosides using radical chemistry based on **6** has been inaugurated in collaboration with Dr. S.D. Gero and Dr. B. Quiclet-Sire. Particular attention has been given to the stereoselectivity of radical reactions.

Uronic acids, which are easily prepared, can be converted into the 4′ radical **52** by chemistry based on **6**. We postulated that if the hindrance on the α-side of the molecule was great enough, the carbon-carbon bond formed by reaction of **52** with a suitable radicophilic olefin would be the natural β-bond. In fact, even a dimethylketal as in **52** (B=natural base or protected derivative thereof) was sufficient to direct the bond formation very largely to the desired β-face.[49] Even the uronic acid from the *N*-benzoyladenine derivative **53** gave clean β-addition.



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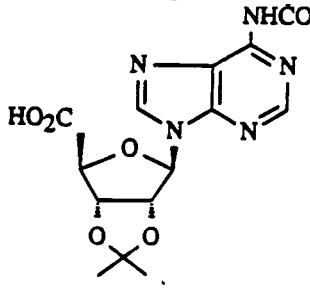
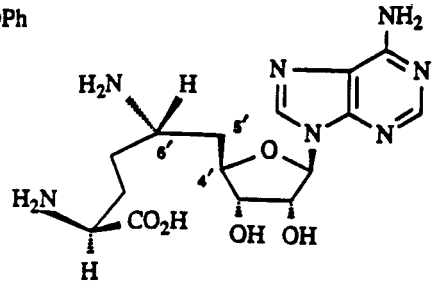


53



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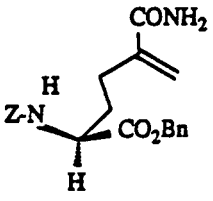
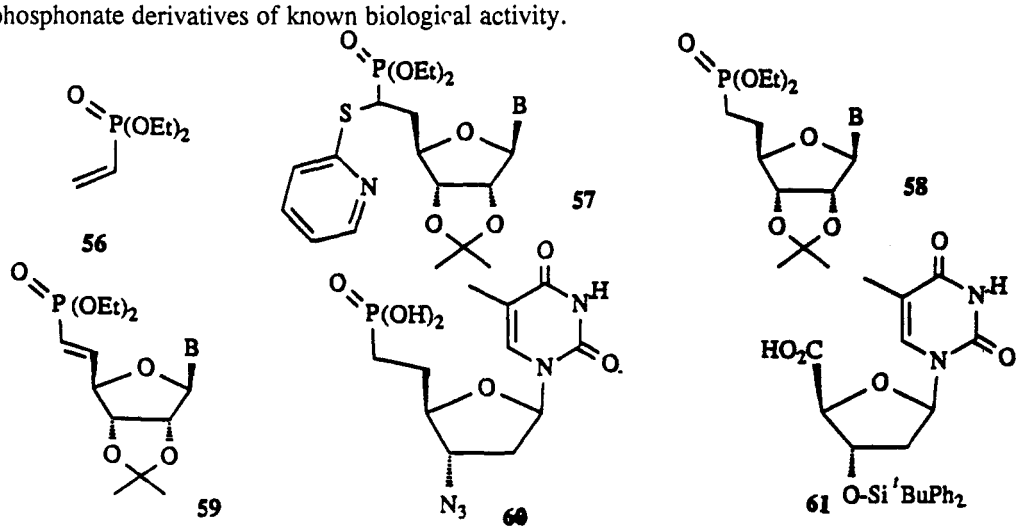


55

Sinefungin **54** is an important antibiotic[50] with anti-fungal, anti-parasite and strong anti-A.I.D.S. activity. It also shows mammalian toxicity. Until recently, this biological activity could not be evaluated properly through lack of the natural product. We decided[51] to make sinefungin by radical chemistry involving the adenosine derivative **53** and an unsaturated amide **55** readily available from aspartic acid again using radical chemistry based on **6** (conventional peptide nomenclature is used: Z=carbobenzyloxy, Bn=benzyl). Using the appropriate derivative **6** of **53**, the entire carbon skeleton was constructed in one step by the addition of the 4'-radical to **55**. Known chemistry converted the amide stereospecifically to amine. Removal of the protecting groups then gave the desired sinefungin as well as its epimer at 6'. The biology of sinefungin was then studied in detail, as well as, that of the uracil analogue which was prepared in the same way starting with uridine.[52] Another ionic-based synthesis of sinefungin was recently reported by Rapoport.[53]

Phosphonates which are isosteric with RNA and DNA derivatives are potentially of great biological interest. It seemed to me[54] that the addition of the radical **52** to diethylvinylphosphonate **56** would afford **57**, easily reducible to **58**, or by oxidation and elimination converted to the vinylphosphonate **59** from which additional interesting analogues can be foreseen. The addition of the radical of type **52** worked satisfactorily (45-70% yield) on both adenosine and uridine. Tributyl tin hydride reduction gave cleanly **58** (70-95%). The reaction could also be applied to aspartic and glutamic acids to give optically active phosphonate derivatives of known biological activity.



We decided to make the phosphonate analogue **60** of AZT in the hope that it would be a powerful anti-AIDS compound. We started with the uronic acid **61** using *t*-butyldiphenylsilyl as a very bulky protecting group to direct the radical reaction to the β-face of the molecule. This worked well in practice. The phosphonate addition reaction (70%) and further manipulation using known ionic chemistry afforded the desired phosphonic acid **60**.[55] At almost the same time,[56] a Japanese communication described the synthesis by a non-radical route of the same compound, which was reported to be very active against the AIDS virus. However, tests in France did not show such biology. The Japanese article does not give any physical constants, whereas we published adequate data to justify our reported structures.

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