SOME RECENT PROGRESS IN NATURAL PRODUCT CHEMISTRY

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Abstract —— It is only in recent years that radical reactions have become part of the general practise of Organic Synthesis. Dehalogenation, deoxygenation and deamination are three processes advantageously carried out under radical conditions. In studying the radical decarboxylation of acids a new and convenient method of formation of carbon radicals has been developed. The application of this new radical reaction in Natural Product Chemistry will be discussed.

Radical chain reactions can be used in the synthesis of organic compounds and have advantages over ionic reactions (Scheme 1)[1]. The reduction of organic halides by tin hydrides is a well known radical chain reaction which usually gives high yields[2,3].

THE ADVANTAGES OF RADICAL CHAIN REACTIONS

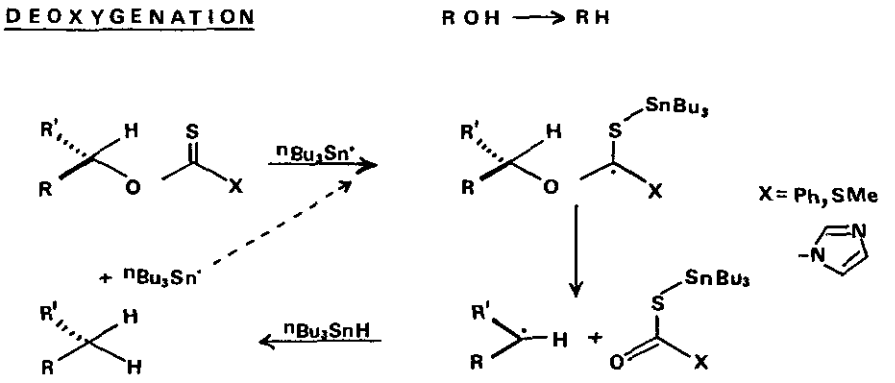
(1) PROCEED UNDER NEUTRAL CONDITIONS.

(2) ARE LESS SUBJECT TO INTERFERENCE FROM :-

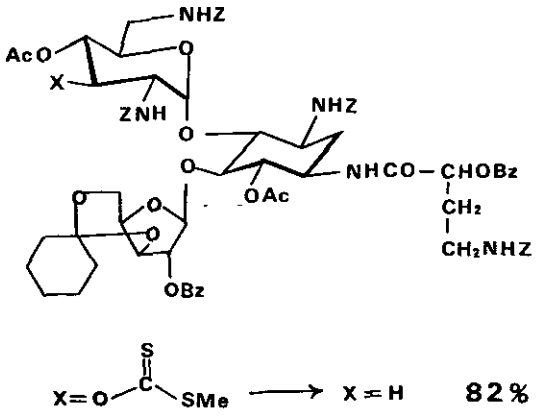
- (A) STERIC EFFECTS
- (B) POLAR EFFECTS
- (C) COMPETING CARBOCATIONIC REARRANGEMENT OR CARBANIONIC ELIMINATION REACTIONS.

SCHEME 1

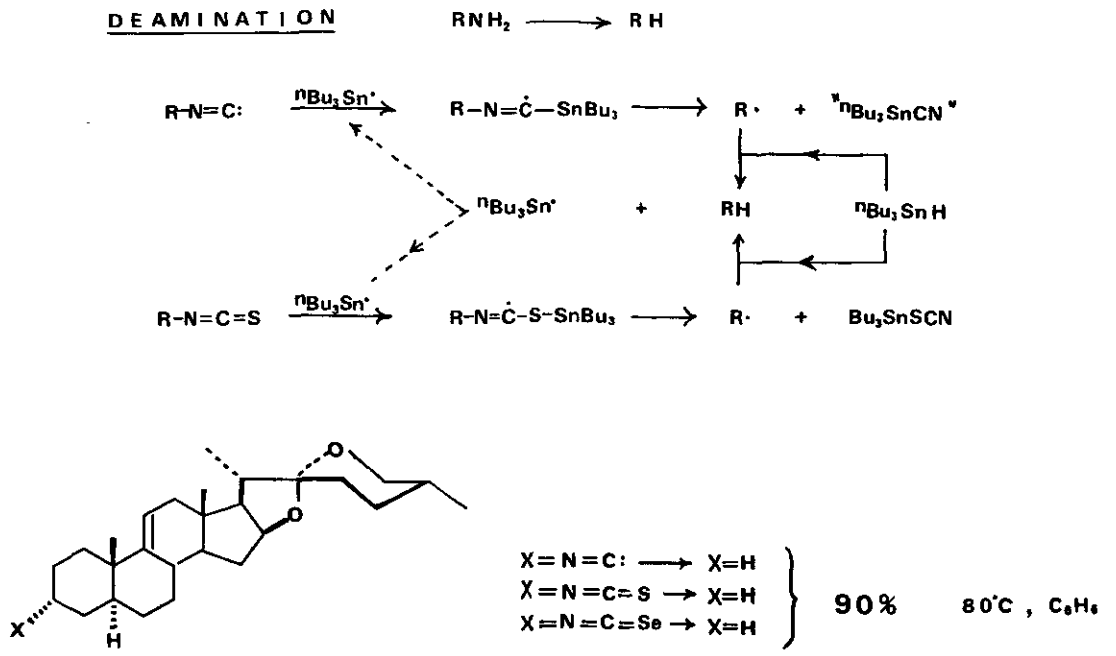
We invented the radical chain reaction shown in Scheme 2[4] in order to deoxygenate hindered secondary alcohols in carbohydrates. Of the many examples of this reaction we show a typical case from the Japanese literature in Scheme 3[5]. In a similar way we adapted (Scheme 4) a reaction originally described by Saegusa[6] for the deamination of primary amines by reduction of their derived isonitriles with tributyltin hydride[7]. The corresponding reduction of isothiocyanates and of isoselenocyanates also affords the deaminated products[7].



SCHEME 2



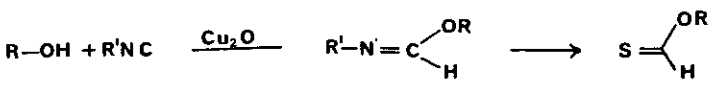
SCHEME 3



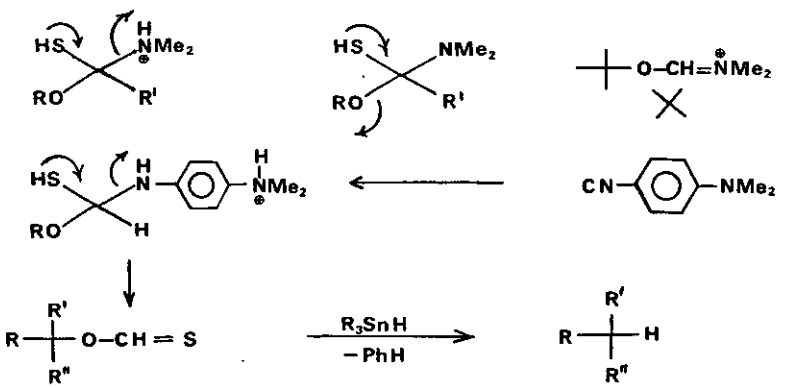
SCHEME 4

When we had solved the problem of radical deoxygenation of secondary alcohols[4], we had no difficulty in finding a similar solution for primary alcohols, such as complex pivaloyl alcohols of the triterpenoid series. It was necessary simply to work in a higher boiling aromatic hydrocarbon and thus raise the temperature[8]. The problem of the radical deoxygenation of tertiary alcohols was much more difficult. In general thionoformates of primary and secondary alcohols cannot be reduced to hydrocarbon by tin hydrides. The carbon-oxygen bond is too strong. We conceived, however, that the thionoformates of tertiary alcohols would be reducable. However, tertiary thionoformates cannot be synthesised by the Vilsmeir route which works so well for primary and secondary alcohols because the intermediates eliminate. We therefore adapted a method due to Saegusa[9] for the synthesis of imino-ethers from isonitriles. By the choice of 4-N-dimethyl-aminophenylisonitrile as starting material we were able to make thionoformates in very good yield (Scheme 5). Reduction with tributyltin hydride at 80° gave excellent yields of hydrocarbon[10]. A method based on the radical reduction of the phenyl-selenocarbonates of tertiary alcohols also seems promising[11].

THE TERTIARY ALCOHOL PROBLEM



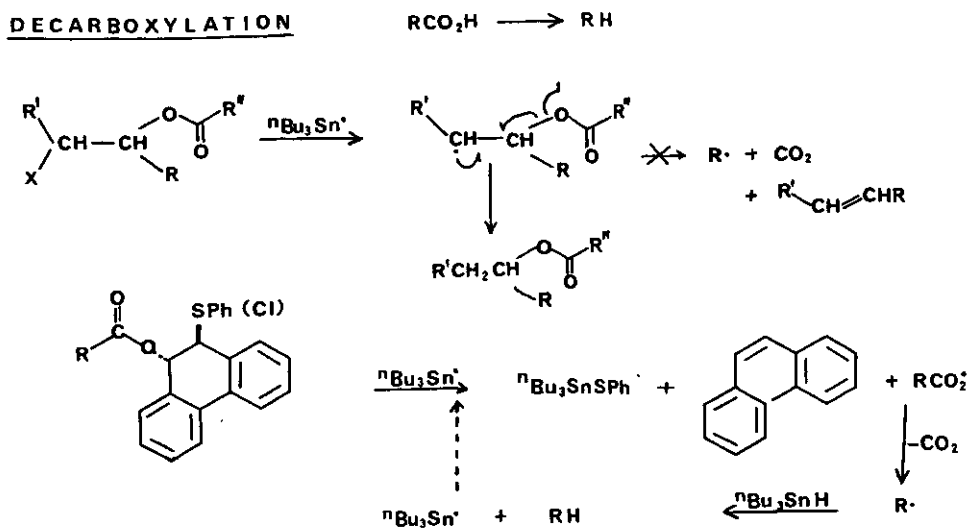
T. SAEGUSA 1967



SCHEME 5

The decarboxylation of carboxylic acid by a radical reaction still remains an interesting problem in organic synthesis. Our first solution was to induce radical formation by β-elimination. Normally halohydrin esters do not fragment when reduced by tin hydrides. We conceived (Scheme 6) that aromatisation might provide the additional driving force for β-elimination. In the event reduction of dihydrophenanthrene derivatives where one substituent had a high affinity for tin radicals (PhS or Cl) and the other was an ester residue set up the required radical chain reaction and gave good yields of hydrocarbon[12].

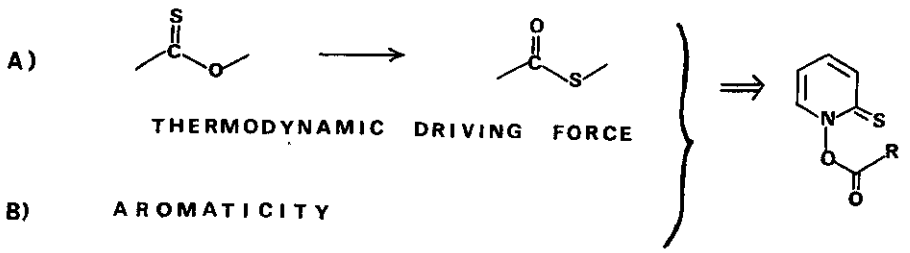
This method has the disadvantage that the intermediate esters are not very easy to synthesise since the secondary hydroxyl group is somewhat hindered. For this reason we have developed another procedure which has led (and is leading) to a new chapter in radical chemistry.

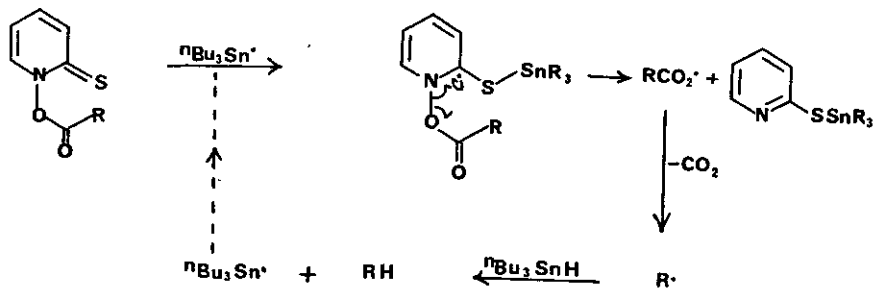


SCHEME 6

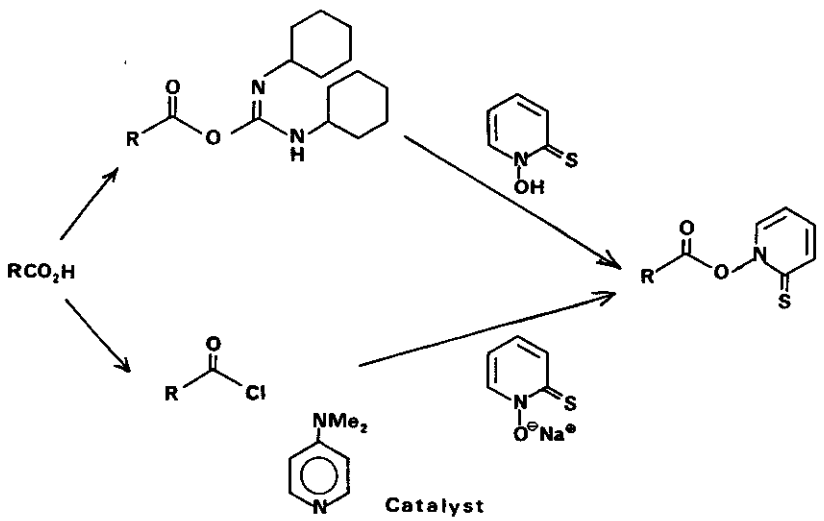
We conceived (Scheme 7) that we needed to add the driving force of thiocarbonyl reduction to that of aromatisation to give a reinforced radical elimination reaction. We selected the esters of N-hydroxy-2-thiopyridone as promising and imagined the radical chain reaction shown in Scheme 7. In the event[13] it proved easy to prepare these esters from commercially available material using carbodiimide (for primary acids) or better the acid chloride and the appropriate sodium salt for all types of acid (Scheme 8). We also prepared a cyclic anhydride with phosgene (Scheme 8) which reacted readily with acids with loss of CO_2 to give the thiono-esters required. As shown in Schemes 9, 10 and 11 primary, secondary and tertiary acids were all cleanly reduced to hydrocarbon in benzene under reflux using tributyltin hydride as reductant.

CONCEPTION





SCHEME 7



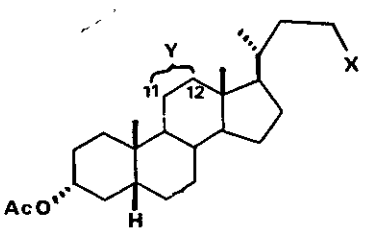
SCHEME 8

PRIMARY ACIDS

$CH_3(CH_2)_n X$

n = 16 $X = CO_2H \xrightarrow[C_6H_6]{80^\circ} X = H$ 95%

n = 14 $X = CO_2H \xrightarrow[C_6H_6]{80^\circ} X = H$ 72%

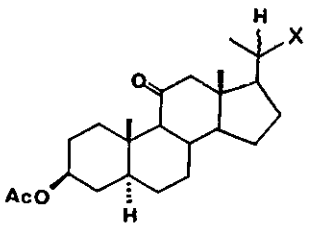


Y = 11-keto $X = CO_2H \xrightarrow[C_6H_6]{80^\circ} X = H$ 91%

Y = 12-keto $X = CO_2H \xrightarrow[C_6H_6]{80^\circ} X = H$ 77%

SCHEME 9

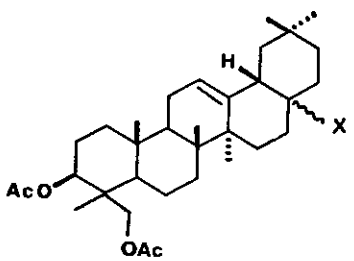
SECONDARY

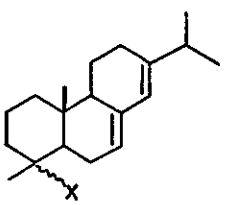


$X = CO_2H \xrightarrow[C_6H_6]{40^\circ} X = H$ 72%

SCHEME 10

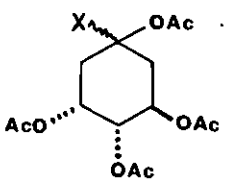
TERTIARY ACIDS





$X = \beta CO_2H \xrightarrow[C_6H_6]{80^\circ} X = H$ 86%

$X = \alpha CO_2H \xrightarrow[C_6H_6]{80^\circ} X = H$ 65%

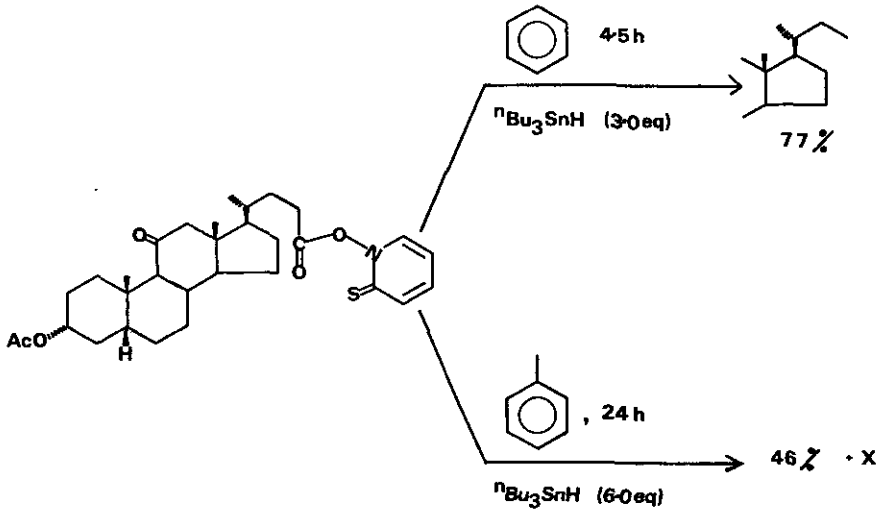


$X = \beta CO_2H \xrightarrow[C_6H_5CH_3]{110^\circ} X = H$ 73%

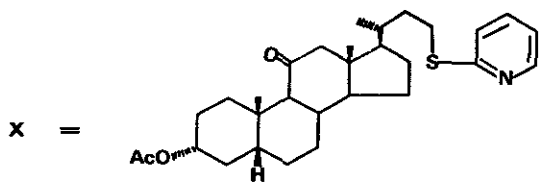
SCHEME 11

However, as shown in Scheme 12, we found that the reduction of a primary acid derivative gave a higher yield in a faster reaction at 80° in benzene than it did at 110° in toluene. Moreover, in the second reaction another product (X) was formed at the expense of the desired reduction product. The structure of (X) was readily determined (Scheme 13) and suggested the existance of a second mode of radical decomposition for the thiopyridone esters.

AN APPARENT ANOMALY

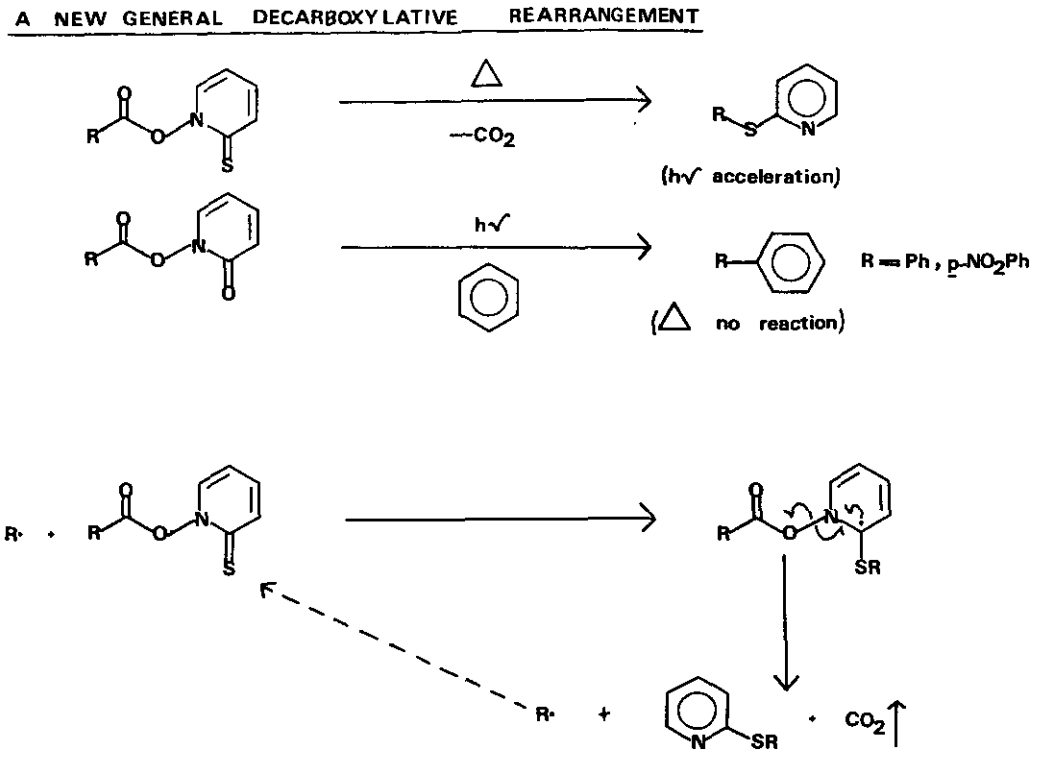


SCHEME 12



SCHEME 13

As shown in Scheme 14 all the thiopyridone esters that we have prepared lose CO_2 on heating to give thiopyridine derivatives. This is a new radical chain reaction which is accelerated by day light. The propagation steps are shown in Scheme 14. We note that the corresponding pyridone esters can be photolysed in benzene to give radicals which then attack the solvent[14] as indicated in Scheme 14. However, these pyridone esters are stable thermally up to 140°.

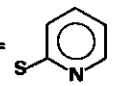


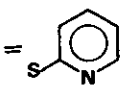
SCHEME 14

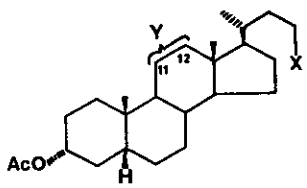
Without the tributyltin hydride the thiopyridone esters of primary and secondary acids on heating in toluene, or more slowly in benzene, give good yields of product as exemplified in Scheme 15. The derivatives of tertiary acids rearrange so easily (Scheme 16) that the tributyltin hydride reductions previously reported (Scheme 11) are in reality mostly the reduction of the tertiary thiopyridine derivative. As an exception the derivative of adamantane-1-carboxylic acid requires to be heated under reflux in chlorobenzene (Scheme 16). This observation justifies in the future a more detailed study.

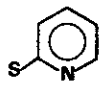
PRIMARY ACIDS :—

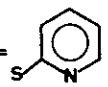
$CH_3(CH_2)_nX$

n = 16 X = CO_2H $\xrightarrow{110^\circ}$ X=  74%

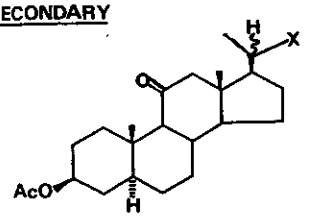
n = 14 X = CO_2H $\xrightarrow{80^\circ}$ X=  92%

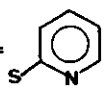


Y= 12-α-Acetoxy X= CO_2H $\xrightarrow{110^\circ}$ X=  74%

Y= 11-keto X= CO_2H $\xrightarrow{80^\circ}$ X=  77%

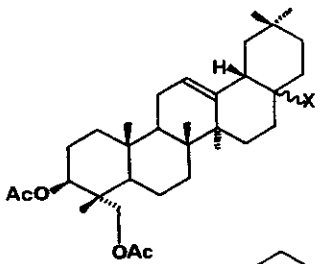
SECONDARY

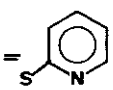


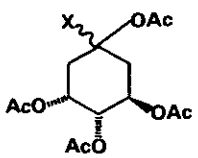
X= CO_2H $\xrightarrow{110^\circ}$ X =  98%

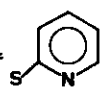
SCHEME 15

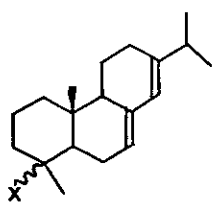
TERTIARY ACIDS

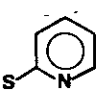


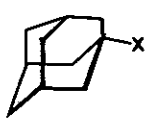
X= β-CO_2H $\xrightarrow{80^\circ}$ X=  74%

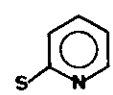


X= β-CO_2H $\xrightarrow{110^\circ}$ X =  72%



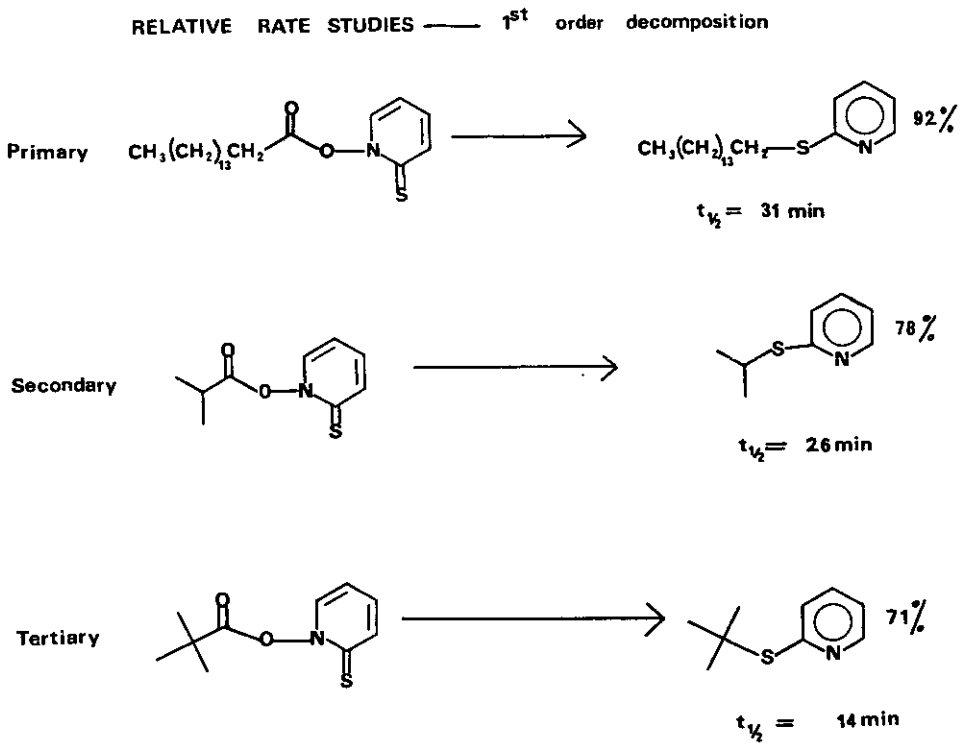
X= α-CO_2H $\xrightarrow{80^\circ}$ X=  71%



X= CO_2H $\xrightarrow[\text{PhCl reflux}]{}$ X =  55%

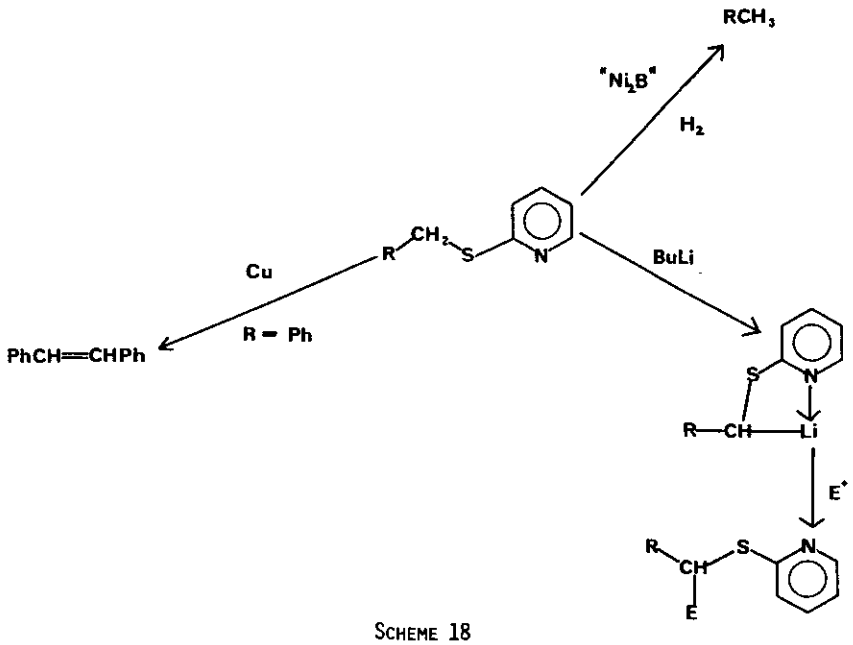
SCHEME 16

Scheme 17 shows some preliminary kinetic data all obtained at 81° (cyclohexane under reflux) with constant laboratory lighting. For simple esters the rates are in the order expected but it is surprising that the rate differences are not greater. This may imply that the addition of radicals to the thione function is not completely concerted with the fragmentation process.



SCHEME 17

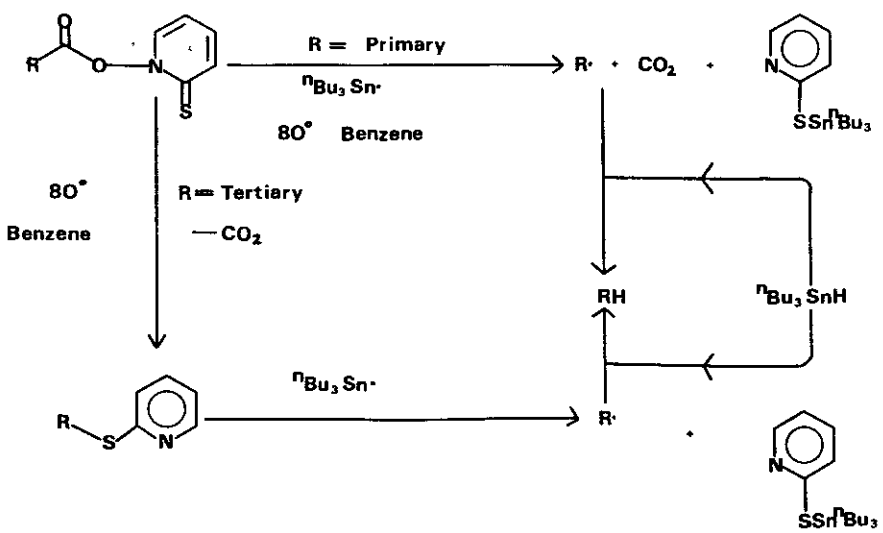
Derivatives of 2-thiopyridine have already been shown to be useful intermediates in Organic Synthesis (Scheme 18) by Mukaiyama and his colleagues[15].



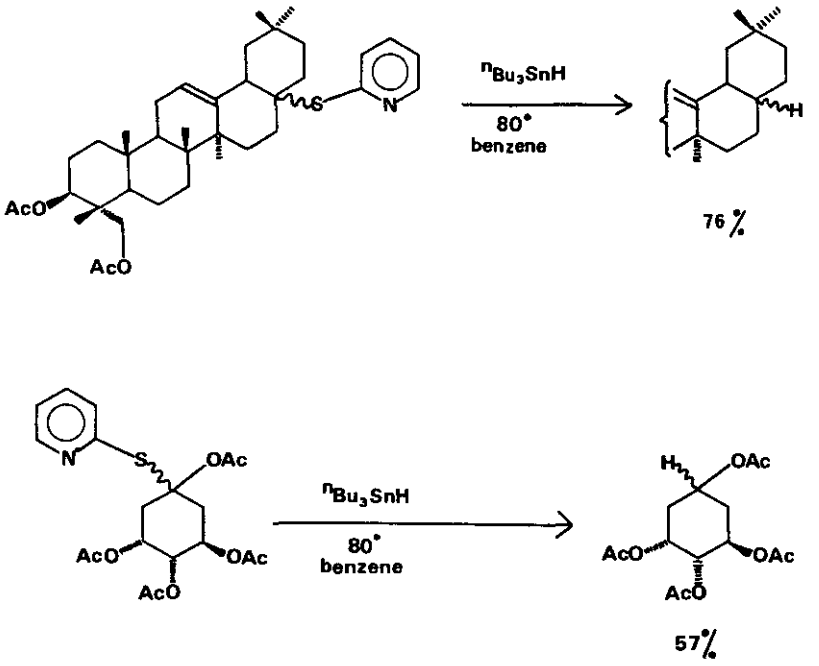
SCHEME 18

To summarise our resultants, we can state (Scheme 19) that primary acids are decarboxylated at 80° by attack of tin radicals upon the thione sulphur. Tertiary acids lose CO_2 so fast that it is the thiopyridine function which is reduced by the tin radicals. Primary and secondary acids at 110° show both types of reaction. Examples of tertiary thiopyridine reduction are given in Scheme 20.

THE STANNANE DECARBOXYLATION



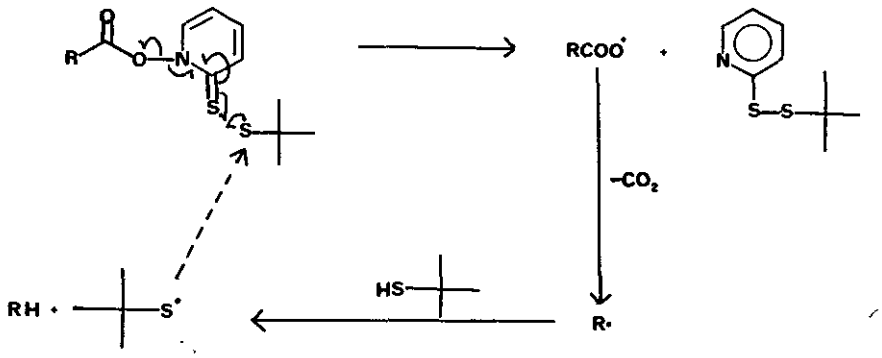
SCHEME 19



SCHEME 20

The 2-thiopyridone esters that we have synthesised are an axcellent source of carbon radicals which can be intercepted and used in practical Organic Synthesis. We conceived that these carbon radicals could be quenched by hydrogen atom transfer from, for example, thiols[16]. This idea (Scheme 21) implies that carbon radicals will react faster with thiols (hydrogen atom transfer) than with the thiopyridone grouping. In the event (Scheme 22) excellent yields of hydrocarbon were obtained with either preformation of the thiopyridone ester followed by addition of thiol or by adding the acid chloride to a mixture of the sodium salt of the N-hydrothiopyridone and the thiol.

t-BUTYLMERCAPTAN Hydrogen atom donor and source of chain carrying t-butylthiyl radical

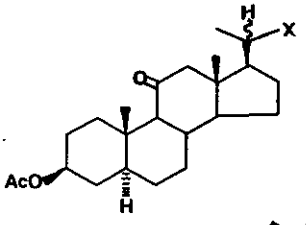


comparable yields of noralkane and mixed disulphide are isolated

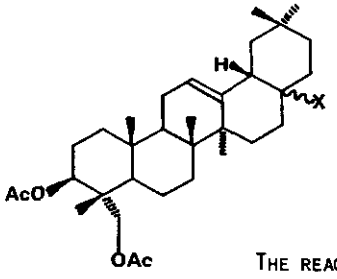
SCHEME 21

RCOOH ⟶ RH

$CH_3(CH_2)_{14}COOH \longrightarrow CH_3(CH_2)_{13}CH_3$ 72%



X= COOH ⟶ X= H 82%



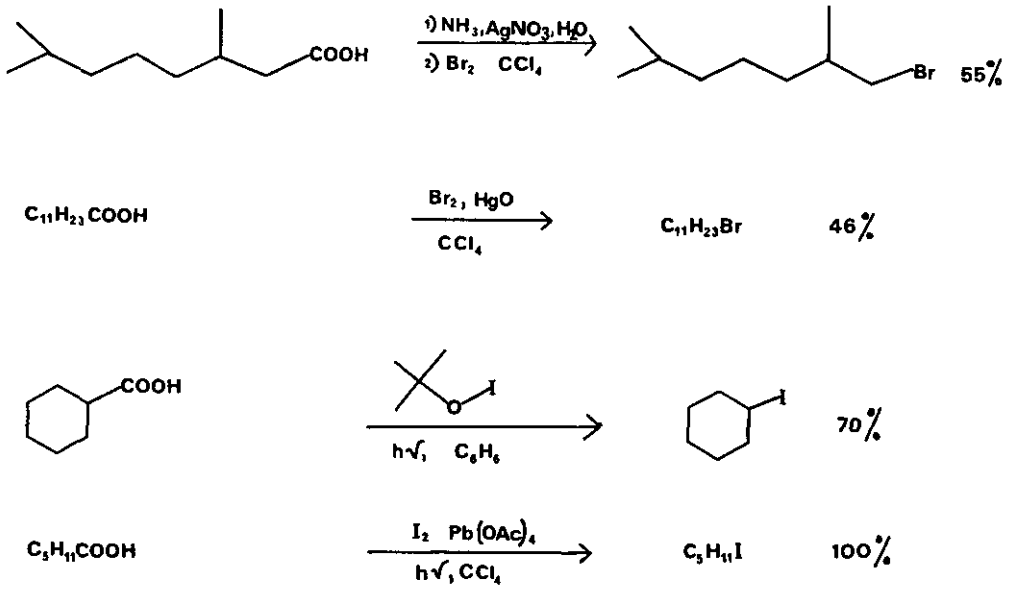
X= COOH ⟶ X = H 85%

SCHEME 22

THE REACTION IS PERFORMED EITHER BY PREFORMING THE ESTER AS BEFORE OR BY ADDITION OF THE DERIVED ACID CHLORIDE TO A REFLUXING BENZENE SOLUTION OF t-BUTYLMERCAPTAN, DMAP AND THE SODIUM SALT OF THE THIONOHYDROXAMIC ACID.

Encouraged by this success, we examined the possibility of effecting a modified Hunsdiecker reaction using the same kind of radical chain reaction. There are already several ways in which this reaction can be carried out (Scheme 23). The original procedure involves the silver salt[17] and is no longer much utilised. The variant involving the mercury salt of the acid[18] is often preferred. For the preparation of iodides the use of t-butylhypoiodite with tungsten lamp illumination, or of lead tetra-acetate-iodine with similar illumination, gives excellent yields[19].

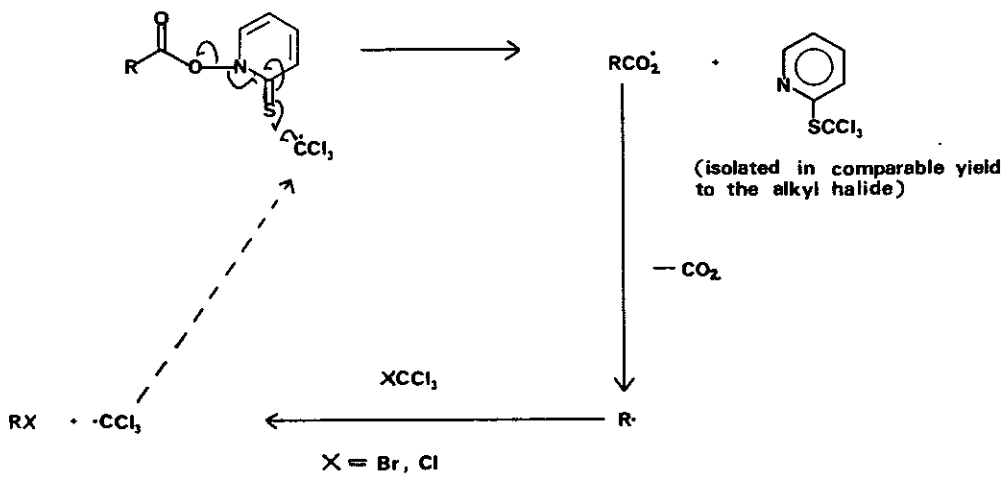
HUNSDIECKER REACTION



SCHEME 23

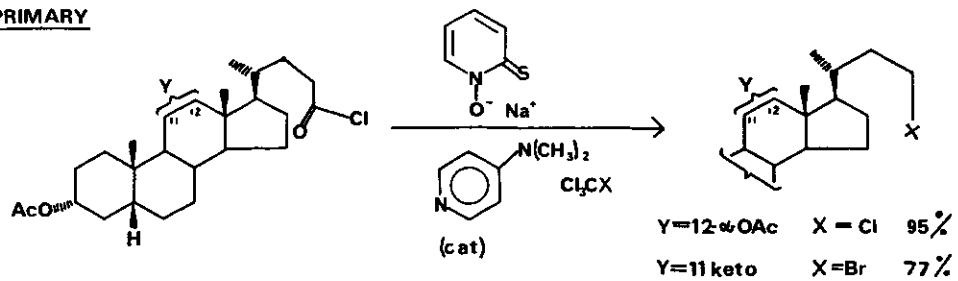
We conceived that carbon tetrachloride should permit the synthesis of chlorides with the trichloromethyl radical acting as chain carrier (Scheme 24). A similar reaction should work for bromotrichloromethane permitting the synthesis of bromides. In the event primary, second and tertiary acids gave excellent yields of chlorides and bromides (Schemes 25 and 26). For the synthesis of iodides we used iodoform as source of iodine with good results (Shceme 26). In appropriate cases we confirmed that the trichloromethyl radical did indeed add to the thiocarbonyl group to give 2-trichloromethylthiopyridine (Scheme 24).

THE TRICHLOROMETHYL RADICAL AS CHAIN CARRIER

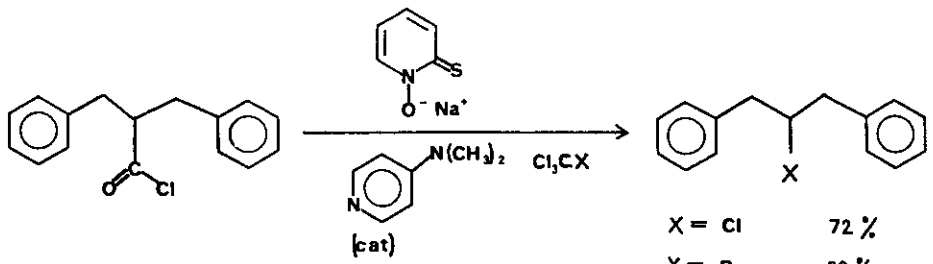


SCHEME 24

PRIMARY

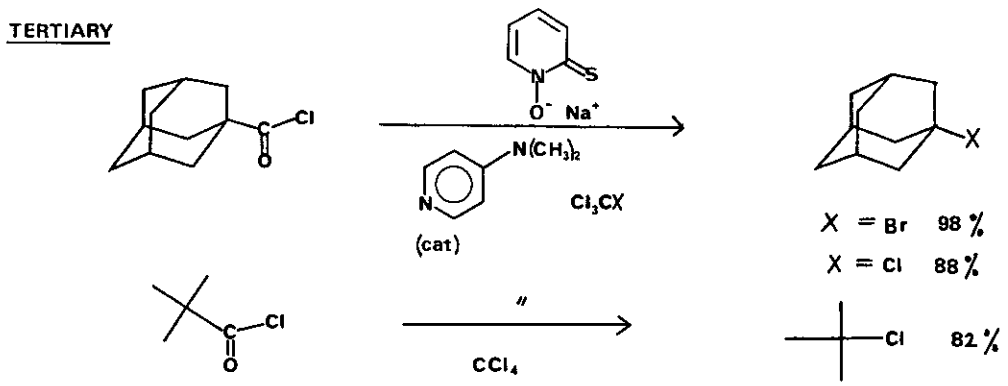


SECONDARY

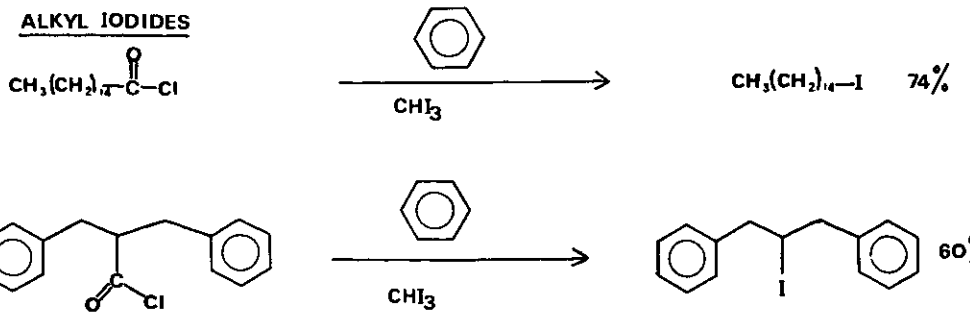


SCHEME 25

TERTIARY



ALKYL IODIDES



SCHEME 26

We are convinced that this new way of making carbon radicals will be of value in Organic Synthesis. Two preliminary accounts of this work will appear shortly[13,20]. We thank particularly Mr. David Crich who is responsable for all the work on the decarboxylation of the esters of N-hydroxylthiopyridone.

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