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THE INVENTION OF RADICAL REACTIONS. Part XV.[†] SOME MECHANISTIC ASPECTS OF THE DECARBOXYLATIVE REARRANGEMENT OF THIOHYDROXAMIC ESTERS

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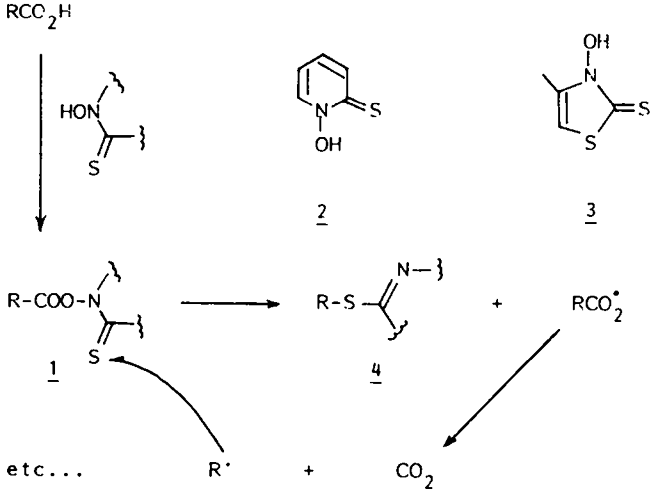
Abstract - Esters (mixed anhydrides) derived from aliphatic or alicyclic carboxylic acids (RCO_2H) and thiohydroxamic acids 2 or 3 undergo a thermally or photochemically induced radical chain reaction to give sulphides 4 with loss of carbon dioxide. On irradiation at low temperature however, the chain reaction is essentially suppressed. Under these conditions moderate to good yields of dimers R-R are obtained from primary acids. The mechanistic and synthetic implications of these observations are discussed.

We have recently described a novel decarboxylation reaction which has proved to be a convenient and mild source of carbon radicals.[1] At the basis of the process is the decarboxylative rearrangement undergone by mixed anhydrides 1 (henceforth called esters for convenience) derived from carboxylic acids and suitable thiohydroxamic acids (e.g. 2 or 3) as outlined in Scheme 1. The reaction follows a simple radical chain mechanism leading ultimately to the sulphide 4 with loss of carbon dioxide.



Scheme 1

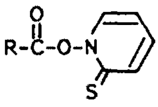
[†] In the light of the results recorded in the present paper we have removed the word "chain" from the title of the series.

The most rewarding aspect of this system is the ease of capture of the intermediate carbon radical with a variety of reagents allowing a multitude of synthetically useful modifications.[1] Although the reaction medium is normally neutral, fairly strong anhydrous acidic conditions are well tolerated. This enables radical additions on base sensitive olefins (e.g. nitroolefins) or on protonated pyridines and other heteroaromatics to be accomplished in good yield.[1]

As implied in Scheme 1, the interception of the radical is in competition with the formation of sulphide 4 (background reaction). The trap must therefore be quite efficient if the desired pathway is to prevail over the background reaction. The presence of this background reaction, however, has a beneficial "disciplinary" effect in preventing any anarchic behaviour of the radical and thus limiting side products to essentially sulphide 4. Nevertheless, if less reactive traps are to be encompassed within the synthetic possibilities offered by this method then a practical way of controlling the efficiency of the background reaction has to be found. We now present a potential solution to this problem which emerged from a better understanding of some aspects of the mechanism. The sequence of events starting with the addition of the carbon radical onto the thiono group of the ester 1 and ending with the extrusion of carbon dioxide was initially viewed to be a series of fast irreversible steps strongly favoured by the aromatisation of the heterocyclic ring.[1,2] We therefore attempted to slow down the formation of sulphide 4 by interfering with the first step, i.e. the addition of the carbon radical to the carbon sulphur double bond. Our conjecture was to incorporate a transition metal salt which could bind to the sulphur atom and thus hinder the approach of the radical.

In a preliminary series of experiments, we examined the effect of various acetylacetonates on the decarboxylative rearrangement itself. Since under thermolytic conditions, a complex mixture was produced, we turned to photolysis at 0-10°C. In the presence of one mole equivalent of chromium^{III} acetylacetonate, irradiation of ester 5a in dichloromethane gave, in addition to the expected 2-pyridylsulphide 6a, significant amounts of triacontane 7a (up to 40%). If oxygen is not rigorously excluded, pentadecanal 8 is also produced. Other acetylacetonates (Fe, Ni, Co) behaved similarly. In the case of the nickel salt, the triketone 9 was concomitantly formed presumably through Ni-catalysed ionic acylation of the acetyl acetone moiety by 5a. Although these results may be construed as a blocking of the thiono group by the metal causing the carbon radical R$^\cdot$ (in this case R = $\underline{n}$-$C_{15}H_{31}$-) to dimerise, further experiments showed this not to be the case. Indeed, the yield of triacontane 7a did not vary much either with the nature or with the amount of metal salt employed. Eventually we irradiated the ester 5a alone at the same temperature and obtained a similar yield of dimer 7a i.e. the metal salt played no role in the radical reaction. This experiment has to be contrasted with the thermal (80°C, refluxing benzene) decomposition of 5a which gives a high yield of the corresponding sulphide 6a and no significant triacontane 7a.

In the course of a parallel study,[3] we came across a similar surprising situation. When ester 10b, derived from diphenylacetic acid, was heated in refluxing benzene (~80°C), large amounts (~40%) of tetraphenylethane 7b and disulphide 12 were isolated in addition to the expected sulphide 11. When the same reaction was run in refluxing toluene (110°C) however, sulphide was produced almost exclusively.



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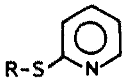


6

R—R

7

5, 6, 7

a, R = $CH_3(CH_2)_{14}$-

b, R = Ph_2CH-

c, R = $PhCH_2$

d, R = Ph_2CHCH_2

e, R = CH_2=$CH(CH_2)_8$-

f, R = 

g, R = $CH_3(CH_2)_7CH$=$CH(CH_2)_7$

h, R = $PhCH_2CH_2$-

i, R = $MeO_2C(CH_2)_4$-

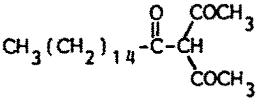
j, R = $CH_3(CH_2)_3\underset{Et}{CH}$-

k, R = 1-adamantyl-

l, R = p-$MeOC_6H_4$-

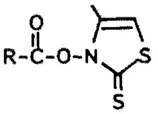
$CH_3(CH_2)_{13}CHO$

8



$CH_3(CH_2)_{14}$-C(=O)-CH($COCH_3$)$_2$

9

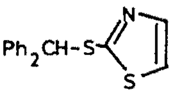


10a R = $CH_3(CH_2)_{14}$-

10b R = Ph_2CH-

10c R = 1-naphthyl

10d R = Ph_2CHCH_2-



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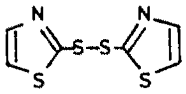


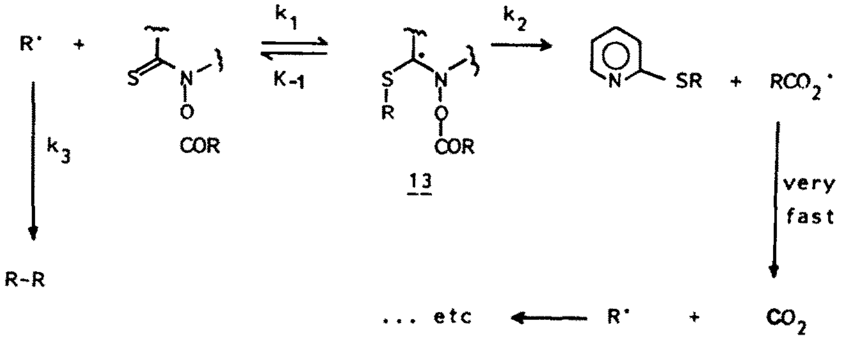
12

The tetraphenyl ethane is clearly produced by combination of two diphenylmethyl radicals. Correspondingly, the disulphide arises by dimerisation of two thiazolylthiyl radicals It appears therefore that at the lower temperature of 80°C, random behaviour of these stabilised radicals competes with (or even supplants) the chain pathway. Yet, increasing the temperature to 110°C is sufficient to simplify the reaction course to the normal radical chain process. Now the chain process plays the major role, leaving little room, if any, for radical-radical interactions. No doubt a similar situation prevails in the case of the palmitic acid derivative described above at the lower temperatures used (0-10°).

This interchange of the order of reactivities is difficult to comprehend in the light of a series of fast irreversible steps for the decarboxylative rearrangement. If this were the case, the key step controlling the fate of the radical R$^\cdot$ would be its addition to the thiono group. Furthermore, this bimolecular step has to be at least as fast as the overall process, the rate constant of which has recently been estimated by Newcomb and Park,[4] using a radical clock, to be ca. 2×10^6 $M^{-1}s^{-1}$ at 50°C for esters of primary acids. From the Arrhenius equation and assumming a normal preexponential factor A ~ 10^8-10^9 $M^{-1}s^{-1}$, it is easily seen that the second order rate constant will vary little (by a factor <5) over a temperature range of 0->85°C.[5] For the sake of comparison, one may consider the recently studied bimolecular reaction of cyclopropyl radicals with carbon tetrachloride. This has a similar rate constant of 7.8×10^5 at ~0°C which increases to only 25×10^5 $M^{-1}s^{-1}$ when the temperature is raised to 68°C.[6]

To explain the dramatic effect of temperature on the course of the reaction, the decarboxylative rearrangement must include, as the rate limiting and product controlling step (at low temperature), a unimolecular fragmentation which is much more sensitive to temperature variation (50-500 fold increase over the same temperature range).[7] In the present system, this can only be the breaking of the N-O bond. Moreover, this further implies that the addition of the carbon radical onto the sulphur atom must be fast and reversible[8] for otherwise the production of dimer R-R would not be controlled by the slow fragmentation step. In other words, those carbon radicals which add onto the thiocarbonyl group in a bimolecular step would be doomed to give sulphide 1 if this step were not reversible.

These possible alterations in our perception of the reaction are delineated in Scheme 2. Reactions of the carbon radical with an ester molecule occurs rapidly to give the stabilised radical 13 which may undergo fission in two directions. Either by scission of the carbon sulphur bond to give back the ester and R• (reverse reaction) or by rupture of the N-O bond with concomitant loss of CO_2. Both of these reactions are unimolecular processes with the former being faster than the latter (i.e. $k_{-1} > k_2$) for ordinary alkyl and cycloalkyl radicals. In the case of tertiary radicals, or when the radical is resonance stabilised, this reverse reaction is especially favoured. This is illustrated by the case of the diphenylacetic acid derivative 10b which, as noted above, gave tetraphenylethane 7b even at 80°C.



Scheme 2

At low temperatures, N-O bond breaking is comparatively slow bringing the chain process almost to a standstill. This is evidenced by the generally long irradiation times neccessary to decompose the thiohydroxamic esters. The consequence is a build up in the concentration of R• which then dimerises. At high temperatures, both fragmentations are rapid, but the fast chain reaction which ensues keeps the concentration of radicals low so that hardly any radical-radical interactions take place.

Finally, in support of the reversibility of the radical addition on the thiono group we have made the following observation. When a mixture of the esters 10c and 10d derived from naphthoic and diphenylpropionic acids was exposed to an excess of triphenylthioantimony $(PhS)_3Sb$ and air, 2,2-diphenylethanol was produced from 10d whereas ester 10c was recovered essentially unchanged in 60-70% yield.[1f]

It is difficult to imagine the phenylthiyl radical, which is the chain propagating species in this instance,[1f] distinguishing, a priori, between the two thiono groups of esters 10c and 10d respectively. Again the only reasonable explanation is a reversible addition which leads to products only in the case of aliphatic ester 10d (aliphatic acids decarboxylate much more readily than aromatic or α,β-unsaturated acids, vide infra).

These findings have a profound bearing on the synthetic utility of the decarboxylation reaction. The impressive sensitivity to temperature allows considerable control of the whole process. We have exploited these results a) to develop a useful synthesis of dimers R-R under extremely mild conditions[9] and b) to improve addition reactions which have heretofore remained unsatisfactory.

To obtain preparatively useful yields of R-R, we simply carried out the irradiations at -64°C. Indeed, in the case of the palmitic derivative 5a, a relatively good yield (75%) of triacontane 7a could be secured (Table, entry 1). However, as shown in the table, other acids afforded only moderate yields of R-R. The poorest result was with secondary acids (for example, entry 10) whereas tertiary acids (for example, 1-adamantanoic and 1-Me-1-cyclohexyl carboxylic acid) gave complex mixtures, presumably the result of other undesired radical interactions such as disproportionation.

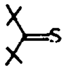
Table

Entry	Ester 5	Irradiation Time (min) in THF at -64°C	R-R[a)] 7 (%)	R-S  6
1	5a	90	7a (75)	6a (20)
2	5b	60	7b (69)	6b (25)
3	5c	30	7c (57)	6c (26)
4	5d	15	7d (22)[12]	6d (39)
5	5e	20	7e (42)	6e (45)
6	5f	10	7f (42)[13]	6f[b)]
7	5g	20	7g (28)	6g (42)
8	5h	50	7h (38)[14]	6h (41)
9	5i	120	7i (24)	6i (35)
10	5j	30	7j (15)[15]	6j (22)

a) The absence of a reference indicates that the compound is described in "Dictionary of Organic Compounds", I. Heibron Ed., Eyre and Spottiswoode, London, 1965. b) not determined.

In an effort to improve the yield of R-R, we attempted to influence the relative concentration of the various radicals by incorporating thiones and thioamides into the system. Since, at low temperatures, k_1 is greater than either k_{-1}, or k_2, the stabilised adduct 13 is expected to be the dominant radical species present. It therefore could act as a storage for the more reactive radicals. We conceived that the addition of other compounds capable of reacting rapidly but reversibly with radicals ("radical accumulators") would have an ameliorating effect on the yield of dimer. We therefore examined a variety of substances such as

14, triphenylphosphine sulphide 15, selenide 16, tetramethylthiourea 17 and thioamide 18. On the whole, the results were worse so this approach was abandoned. It is likely that the formation of sulphides 6 also occurs by the S_H2 pathway : R˙ + PySSPy -> RSPy + PyS˙ since at low temperatures, the concentration of PySSPy becomes significant. Such a reaction would not be expected to be influenced by the presence of "radical accumulators".



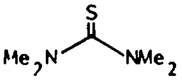
14

$Ph_3P=S$

15

$Ph_3P=Se$

16



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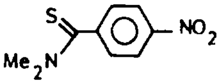


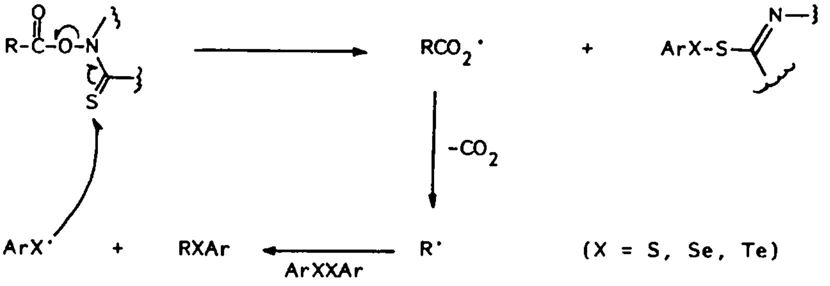
18

$CH_3(CH_2)_{14}$-S-Ph

19

An alternative possibility we are now considering is to scavange selectively the sulphur radicals with metallic ions. This should give the formation of dimer a better chance. Nevertheless, despite the various shortcomings, this method for coupling carbon radicals offers the advantages of simplicity and neutral, non-oxidising conditions.

Lowering the temperature has also allowed us to improve considerably several additions reactions that occured poorly under thermolytic conditions. For example, if the carbon radical is to be captured efficiently by diphenyldisulphide under thermolytic conditions (Scheme 3) a vast excess of the trap has to be used.



Scheme 3

Thus, in the case of ester 10b, the reaction had to be conducted in 30 equivalents of molten diphenyldisulphide to afford a good yield (74% after a very tedious purification !) of the desired sulphide 19.[10a] Clearly, the S_H2 substitution in this case does not compete well with the decarboxylative rearrangement. If, however, the reaction is carried out at 0°C photochemically using ester 5a for example, only 2 equivalents of diphenyldisulphide are necessary to furnish an 82% yield of the same phenylsulphide 19[10b]. These results have caused us to favour the use of esters derived from N-hydroxy-2-pyridine thione 2 since they can be conveniently decomposed by visible light from a tungsten lamp unlike those derived from 3 which require U.V. irradiation.

This modification was easily extended to diselenides and ditellurides with excellent results.[10b] Essentially quantitative yields of selenides and tellurides were obtained with only a modest excess of the trap. It is evident from these first results that the sensitivity of the reaction to temperature provides a simple yet powerful tool for the control of the decarboxylation. We are presently examining the generality of these findings as well as their importance, with respect to other systems. Professor Newcomb has independently arrived at the same conclusion.[4]

The discussion in this paper, as well as in all our preceding articles,[1] has always assumed that carboxylate radicals loose carbon dioxide very fast at room temperature if alkyl or cycloalkyl radicals are produced.[10] However, with the mechanism now proposed (Scheme 2) one can question the two-step fragmentation of 13 into carboxyl radical and then into carbon radical. It is conceivable that the first step to 13 is reversible and that the two following steps are concerted. We examined this possibility first by a study of the photolysis of the ester 5k at -80° in the presence of a large excess of thiophenol. The only product from the photolysis was the adamantane and no trace of adamantanoic acid could be detected. In blank experiments it was shown that as low as 3% of acid could have been isolated and characterised. In contrast when the aromatic ester 5l was photolysed under similar circumstances the acid was produced in 80% yield.

In the Experimental Section attention is drawn to an inexpensive source of N-hydroxy-2-thiopyridone 2.

Experimental

Melting points are uncorrected. Unless otherwise stated, NMR data are for deuterochloroform solutions with tetramethylsilane as internal standard. I.R. spectra are of dichloromethane solutions unless stated to the contrary. N-Hydroxypyridine-2-thione 2 and its sodium salt are available commercially. Both, however may be obtained more cheaply starting from the 40% aqueous solution of the sodium salt (trade name : sodium omadine from Olin Corp.) as described below. Both compounds should be stored away from light in dark bottles.

N-Hydroxypyridine-2-thione 2.- The 40% aqueous solution of the sodium salt (100 g) was diluted with water (40 ml). Dropwise addition of concentrated HCl (30 ml) caused the precipitation of the free acid, which was filtered and recrystallised from ethanol to give a white crystalline solid (38 g, 95%), m.p. 170-172°C.

N-Hydroxypyridine-2-thione sodium salt.- The 40% aqueous solution (400 g) was concentrated in a rotary evaporator under vacuum (2-3 mmHg) keeping the temperature below 50°C. To the residue was added 95% ethanol (150 ml) and the mixture stirred until all was dissolved. Slow crystallisation at 4°C gave 144 g (89%) of the pure sodium salt as white crystals, which were dried at 50°C under vacuum, m.p. 285-290°C.

General Procedure for the Preparation of Esters 5.- (Note : These compounds are sensitive to light and moisture. The reaction vessel, chromatography column etc... should therefore be covered with aluminium foil). To a solution of the carboxylic acid chloride (100 mmole; prepared from the corresponding acid and oxalyl chloride using standard methods) in dry, degassed dichloromethane (50 ml) was added the sodium salt of N-hydroxypyridine-2-thione 2 (10.5 mmole). After stirring for 1-2 hours at room temperature under an inert atmosphere, the reaction mixture was rapidly filtered and the solvent evaporated under vacuum without heating. The yellow residue may be used as such or further purified by filtration through a short silica column.

*General Procedure for the Obtention of Dimers **7**.*- The crude ester (0.5 mmole) was dissolved in dry, degassed tetrahydrofuran (20 ml) in the dark and cooled to -64°C under an argon atmosphere. The yellow solution was then irradiated using a 300 W projector lamp until the colour faded completely. Evaporation of the solvent and purification of the residue by chromatography on silica (pentane-dichloromethane mixtures) gave the known dimers **7** (for irradiation times, yields and references see Table).

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