New and Improved Methods for the Radical Decarboxylation of Acids

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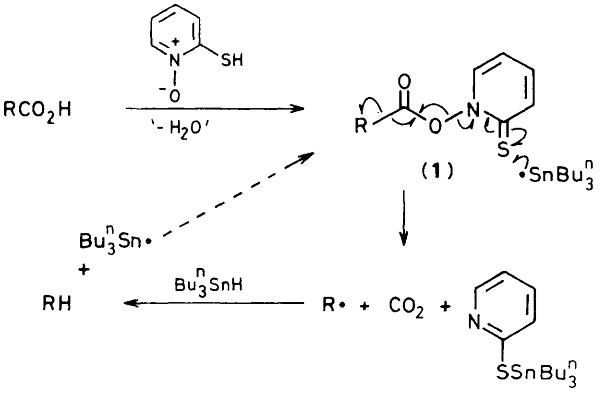
Carboxylic acid esters derived from *N*-hydroxypyridine-2-thione undergo efficient radical chain decarboxylation to the corresponding nor-alkane on treatment with either tri-n-butylstannane or t-butylmercaptan; in the absence of these hydrogen atom donors a smooth decarboxylative rearrangement giving noralkyl 2-pyridyl sulphides is observed.

The decarboxylation of organic acids with[1] or without[2] concomitant replacement by a functional group is a useful synthetic transformation. We have recently shown[3] that the esters prepared from *trans*-9-hydroxy-10-phenylthio (or chloro)-9,10-dihydrophenanthrene suffer smooth reductive decarboxylation on treatment with tri-n-butylstannane. Nevertheless, variable yields in the esterification step prompted us to search for an alternative method. We conceived that the *O*-esters of thiohydroxamic acids should be reduced in a radical chain reaction by tin hydride reagents. Since the sodium salt of *N*-hydroxypyridine-2-thione is commercially available we have used it for the first part of our work (see Scheme 1). In this system we have not only retained the concept of thiocarbonyl reduction[4] as a driving force for expulsion of the carboxylate radical, but have also incorporated the idea of aromatisation[3] as an additional aid for smooth fragmentation.

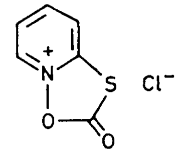


Scheme 1

Table 1. Reaction of acyloxypyridine-2-thiones with tri-n-butylstannane.

Acid	Esterification method[a]	Temp./°C (benzene or toluene as solvent)	Time/ h	Products[b] (yield %)[c]	
(3)	A	80	6	**(4)**	(95)
(3)	B	80	3	**(4)**	(70)
(6)	C	80[d]	0.5	**(7)**	(72)
(9)	C	80	6	**(10)**	(91
(11)	C	80	6	**(12)** **(13)**	(77); (20)
(14)	C	80	6	**(15)**	(92)
(17)	C	60	3	**(19)** **(20)**	(48); (39)
(17)	C	40	6	**(19)** **(20)**	(72); (15)
(21)	C	80	3	**(22)**	(86)
(24)	C	80	3	**(25)**	(65)
(27)	C	110	0.33	**(28)**	(73)

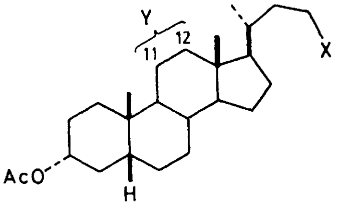
[a] A: Acid + DCC + 4-dimethylaminopyridine. B: Use of reagent **(2)**. C: Acid chloride prepared from oxalyl chloride. [b] All new compounds gave satisfactory spectroscopic and microanalytical data. [c] Isolated yields are based on the free carboxylic acid. [d] An inverse addition of the ester to the stannane was used in this case.



(2)

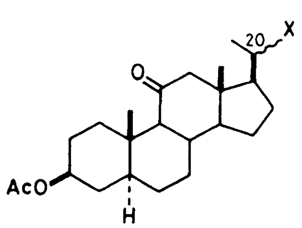
$Me[CH_2]_nX$

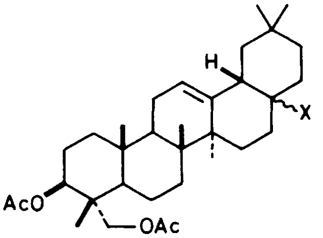
(3) $n = 16, X = CO_2H$
(4) $n = 16, X = H$
(5) $n = 16$, X = 2-pyridylthio
(6) $n = 14, X = CO_2H$
(7) $n = 14, X = H$
(8) $n = 14$, X = 2-pyridylthio



(9) $X = CO_2H$, Y = 12-oxo
(10) X = H, Y = 12-oxo
(11) $X = CO_2H$, Y = 11-oxo
(12) X = H, Y = 11-oxo
(13) X = 2-pyridylthio, Y = 11-oxo
(14) $X = CO_2H$, Y = 12α-OAc
(15) X = H, Y = 12α-OAc
(16) X = 2-pyridylthio, Y = 12α-OAc

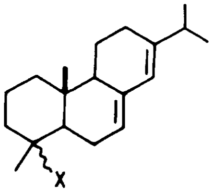
The results presented in Table 1 confirm this idea demonstrating that high yields of nor-alkanes can be prepared from a variety of primary, secondary, and tertiary acids in a reaction which is compatible with ester, ketonic, and olefinic functionality. Esters were routinely prepared from either the sodium salt of the thiohydroxamic *O*-acid or the free mercaptan using either the derived acid chloride or the mixed anhydride formed with dicyclohexylcarbodiimide (DCC).[5] In all cases, 4-dimethylaminopyridine served as an efficient catalyst. Although it was possible to achieve a high yield 'one pot' decarboxylation of stearic acid **(3)** by use of DCC, we note that application of this method in the case of the secondary steroidal acid **(17)** led to appreciable amounts of the intramolecularly rearranged[6] *N*-acylurea **(18)**. We have also shown that the reagent **(2)**, prepared by treatment of the thiohydroxamic acid with phosgene, may be used for direct reaction with a carboxylic acid.

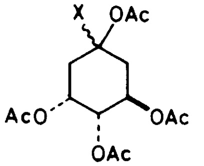




(17) X = CO$_2$H
(18) X = CO–N(C$_6$H$_{11}$)–CONH(C$_6$H$_{11}$)
(19) X = H
(20) X = 2-pyridylthio
(3:1 mixture at C-20)

(21) X = β-CO$_2$H
(22) X = H
(23) X = 2-pyridylthio





(24) X = α-CO$_2$H
(25) X = H
(26) X = 2-pyridylthio

(27) X = β-CO$_2$H
(28) X = H
(29) X = 2-pyridylthio

$R^1R^2R^3CX$

(30) X = CO$_2$H, R^1 = R^3 = H, R^2 = Bu^t
(31) X = 2-pyridylthio, R^1 = R^3 = H, R^2 = Bu^t
(32) X = CO$_2$H, R^1 = H, R^2 = R^3 = Me
(33) X = 2-pyridylthio, R^1 = H, R^2 = R^3 = Me
(34) X = CO$_2$H, R^1 = R^2 = R^3 = Me
(35) X = 2-pyridylthio, R^1 = R^2 = R^3 = Me

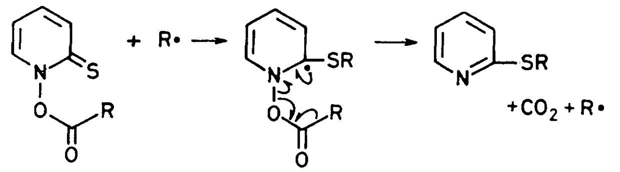
In the course of yield optimisation studies we observed that the steroidal sulphides **(13)** and **(20)** were isolated as by-products of attempted stannane reduction. We therefore examined the thermal behaviour of esters **(1)** in the absence of the hydride and found that this decarboxylative rearrangement is a high yielding radical chain reaction for the preparation of noralkyl pyridyl sulphides (Scheme 2 and Table 2).

Such compounds have been shown to be valuable intermediates for organic synthesis by virtue of their facile formation of a chelated lithio anion,[7] and have also been used for thiiran[8] and olefin syntheses.[9] It is clear that the reductions reported in Table 1 involve two different radical chain reactions. Tertiary acid derivatives lose CO$_2$ and rearrange so easily (Scheme 2) that the reduction is in reality a reduction of the tertiary pyridyl sulphide. In agreement **(23)** and **(29)** were rapidly reduced by tributyltin hydride to give the alkanes **(22)** and **(28)** (76% and 57% respectively). For the derivatives of primary and secondary acids heating at 80 °C gave the radical chain reaction originally conceived (Scheme 1), but heating at 110 °C provoked a competition between reduction (Scheme 1) and rearrangement (Scheme 2). Nor-alkanes can always be obtained by reduction of the pyridyl sulphides with Raney nickel or with 'nickel boride'. However, by lowering the temperature of the hydride reduction for primary and secondary derivatives, it was possible to isolate higher yields of nor-alkane after a shorter reaction time [*e.g.* **(19)** from **(17)**, Table 1] by reduction of the ester instead of passing through the pyridyl sulphide.

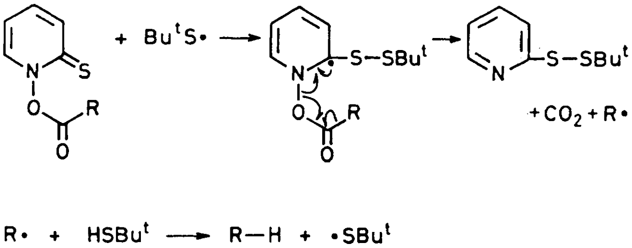
Table 2. Thermal decarboxylative rearrangement of *N*-acyloxypyridine-2-thiones.

Acid	Temp. /°C	Time /h	Product[b]	(yield %)[c]
(3)	110	2	**(5)**	(74)
(6)	80	2	**(8)**	(92)
(11)	110	2.0	**(13)**	(77)
(14)	110	2.5	**(16)**	(74)
(17)	110	1.5	**(20)**	(98)
(21)	80	1	**(23)**	(74)
(24)	80	3	**(26)**	(71)
(27)	110	2	**(29)**	(72)
(30)	130	1.5	**(31)**	(78)
(32)	80	2.5	**(33)**	(78)
(34)	80	1.5	**(35)**	(71)

[b, c] See Table 1.



Scheme 2



Scheme 3

Although the decarboxylative rearrangement to pyridyl sulphides proceeds purely thermally in the dark, we have demonstrated that the reaction is considerably accelerated by irradiation with a tungsten lamp. This behaviour stands in contrast to the thermally stable oxygen analogues, *N*-acyloxy-2-pyridones, which undergo N–O bond cleavage and decarboxylation but without formation of rearranged products on photolysis (u.v.) in benzene.[10]

Finally, we have investigated the use of non-nucleophilic t-butyl mercaptan as the hydrogen atom donor[11] in the decarboxylation reaction. Once again, high yields of the derived nor-alkane were isolated (Table 3). The experiment was conveniently performed by dropwise addition of the acid chloride to

Table 3. Reaction of *N*-acyloxypyridine-2-thiones with t-butyl mercaptan.

Acid	Product[b]	(Yield %)[c]
(6)	**(7)**	(72)
(17)	**(19)**	(82)
(14)	**(15)**	(74)
(11)	**(12)**	(62)
(21)[d]	**(22)**	(85)

[b, c] See Table 1. [d] In this case the ester was preformed using method C.

a dry refluxing benzene solution of the thiol containing 4-dimethylaminopyridine and the salt of the thiohydroxamic acid. The isolation of t-butyl pyridyl disulphide in comparable yield to the nor-alkane supports the argument for the existence of an efficient radical chain reaction (as in Scheme 3) involving the t-butylthiyl radical as carrier.

We consider that the decarboxylation reactions described herein use readily available reagents and proceed under very mild conditions. In addition, we can now replace stannanes by thiols for the hydrogen atom transfer reaction. Such reactions should find applications in organic synthesis.

We thank Roussel-Uclaf for generous financial support and Dr. D. Villemin for a preliminary experiment.

Received, 27th May 1983; Com. 679

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