Tetrahedron Letters,Vol.27,No.12,pp 1327-1330,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

RADICAL DECARBOXYLATIVE ADDITION ONTO PROTONATED HETEROAROMATIC (and RELATED) COMPOUNDS

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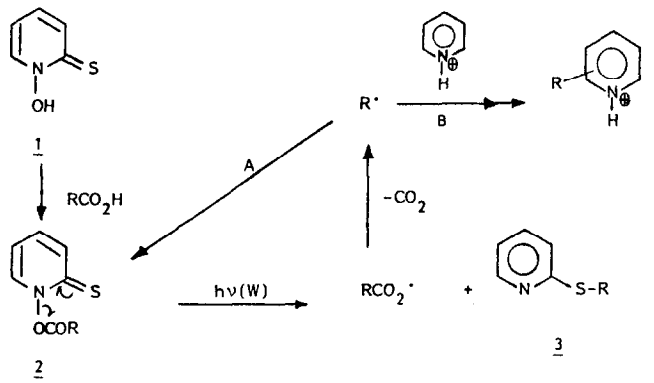
Radicals generated by irradiation of the esters of N-hydroxy-2-thiopyridone with tungsten light add efficiently to protonated heteroaromatic compounds containing a basic methine nitrogen. Other compounds with a similar functionality also show radicophilicity under the same conditions.

In the course of our study of the radical decarboxylation of carboxylic acids via their esters 2[1] (mixed anhydrides) with thiohydroxamic acid 1, we found that the reaction was not affected by the presence of a strong anhydrous acid. This observation allowed us to capture efficiently the intermediate carbon radical R· by highly electrophilic, but base sensitive, nitroalkenes.[2a] Further work[2b] showed that other strongly electrophilic olefins such as vinylsulphones were also very radicophilic giving excellent yields of addition products.

The compatibility of this radical generating system with an acidic medium prompted us to attempt the trapping of the radical by protonated pyridines and related species (Scheme 1, path B).



Scheme 1

Radical additions to positively charged heteroaromatics have been extensively studied, especially by the group of Minisci,[3] who found the reaction to be very fast for common nucleophilic carbon centered radicals. Indeed, when ester 2a derived from adamantanoic acid was irradiated with a tungsten lamp in the presence of lepidinium camphorsulphonate 4 in dichloromethane at room temperature, a smooth reaction occured to give the expected 2-substituted lepidine 5 in almost quantitative yield. Generally high yields were observed with primary, secondary and tertiary aliphatic and alicyclic radicals as well as with other substituted pyridinium salts (Table). These reactions take place under very mild conditions without recourse to electrolysis, or to metal salts and strong oxidants, for the generation of carbon radicals from carboxylic acids.[3]

Table

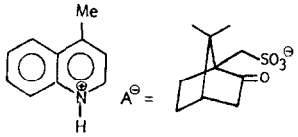
Entry	Ester	Heteroaromatic Salt (eq.)	Product (Yield %)
1	2a	4 (6.5)	5a (97)
2	2b	4 (6.5)	5b (81)
3	2c	4 (7)	5c (70)
4	2d	4 (2)	5d (77)
5	2a	6 (6)	11 (43); 12 (41)
6	2a	7 (7)	13 (65)
7	2a	8 (6)	14 (81)
8	2a	9 (6)	15 (87)
9	2c	9 (8.8)	16 (44)
10	2a	10 (6)	17 (72)
11	2a	22 (5)	23 (52)
12	2a	24 (6)	25 (37)

Camphorsulphonates were used throughout since they are easy to obtain dry and are nicely soluble in dichloromethane. In the absence of acid yields were much lower and the formation of the rearranged sulphide 3 dominated. For example methyl nicotinate alone gave only 22% of adduct 14 and 30% of the corresponding sulphide 3a, as compared with 79% of 14 under the usual acidic conditions (Table, entry 7). Pyridine itself, even when used as solvent, did not undergo radical addition. In contrast the pyridinium salt 6, afforded almost equal amounts of 2- and 4-substituted derivatives 11 and 12. N-Methylpyridinium salts were less satisfactory than the protonated analogues (Table, Entry 5).

The heterocyclic part of the esters 2 is isolated as 2-thiopyridone 18 mixed with varying amounts of 2,2'-dipyridyl disulphide. The formation of 18 may be rationalised by the mechanism depicted in Scheme 2. Addition of the carbon radical to the pyridine ring produces a protonated nitrogen radical 20 which suffers the loss of a proton to form a neutral carbon radical[3] 21 capable of carrying the chain. Finally, elimination of 2-thiopyridone 18 and concomitant aromatisation lead to the observed products. The fact that the tautomeric equilibrium 18 $\rightleftharpoons$ 19 lies strongly in favour of the thioamide[4] 18 is of importance to the success of the reaction. Had the mercapto form 19 predominated, extensive formation of alkane RH would surely be observed, given the excellent hydrogen atom transfer ability of thiols.

2, 3, 5

a) R = 1-adamantyl
b) R = cyclohexyl
c) R = $CH_3(CH_2)_{14}$-
d) R = $(CH_3)_3C$-



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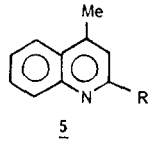

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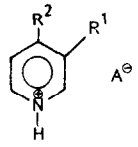
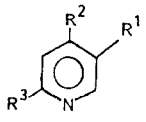
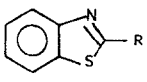


6, R^1=R^2=H
7, R^1=H; R^2=Me
8, R^1=CO_2Me; R^2= H
9, R^1=H; R^2=Ph
10, R^1=H; R^2=CN

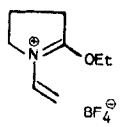


11, R^1=R^2=H; R^3=1-adamantyl
12, R^1=R^3=H; R^2=1-adamantyl
13, R^1=H; R^2=Me; R^3=1-adamantyl
14, R^1=CO_2Me; R^2=H; R^3=1-adamantyl
15, R^1=H; R^2=Ph; R^3=1-adamantyl
16, R^1=H; R^2=Ph; R^3=$CH_3(CH_2)_{14}$-
17, R^1=H; R^2=CN; R^3=1-adamantyl



22, R=H
23, R=1-adamantyl

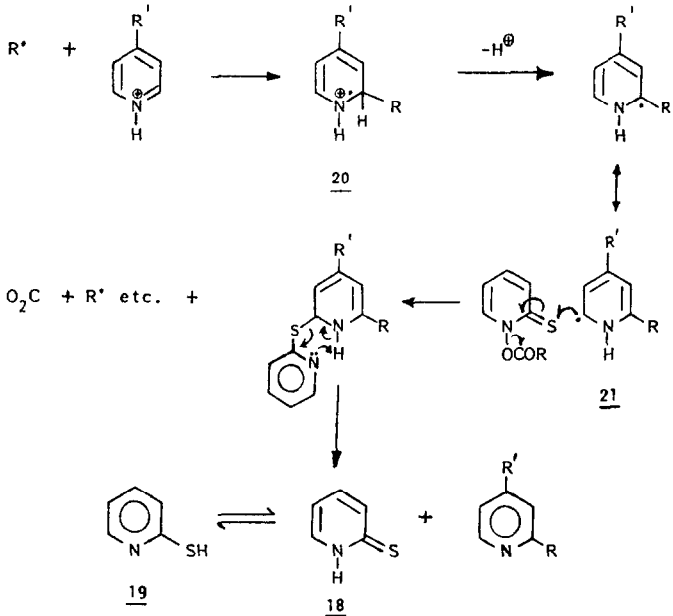
24, R=H
25, R=1-adamantyl



26

Ad-(1)-CH_2CHO

27

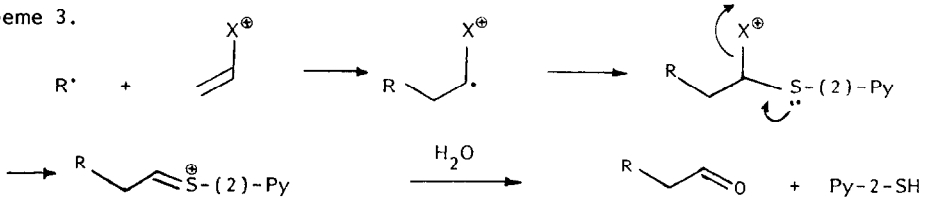


Scheme 2

The masterly work of Minisci and his colleagues[3] on the radical substitution of protonated pyridines also proposes the same radical cation intermediate which is then stabilised by electron transfer and proton loss. We do not think that this step applies to our system because the addition of the electron acceptors 1,3-dinitrobenzene (1 equiv.) or of 2,6-di-t-butylquinone (0.5 equiv.) have very little effect on the reaction. Also when the adamantyl ester 2a is reduced with magnesium or zinc in acetic acid (conditions under which 2a is not hydrolysed) adamantoic acid is recovered in high yield and the reduction product 2-thiopyridone is formed. Thus reduction of esters like 2a by electron transfer does not lead to radical fragmentation.

We have briefly examined radical additions to other heterocyclic systems with encouraging preliminary results. Thus irradiation of ester 2a and the protonated benzothiazole 22 gave the 2-substituted derivative 23 in 52% yield. The simple thiazoline 24 similarly gave the corresponding adduct 25 (37%). This adduct could be converted back to adamantanoic acid in quantitative yield by exposure to sodium nitrite in aqueous acetic acid. If the starting thiazoline 24 was labelled in the 2-position the overall sequence would have led to labelled adamantanoic acid, a transformation which is otherwise difficult to perform under such mild conditions.

Preliminary experiments on the addition of the adamantyl radical to dimethylvinylsulphonium tetrafluoroborate and to the N-vinyl-iminium salt[5] 26 gave on work up the corresponding homo-aldehyde 27 in yields which have not yet been optimised. The mechanism of aldehyde formation is presumed to be that shown in Scheme 3.



Scheme 3

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(Received in France 30 January 1986)