FURTHER OBSERVATIONS ON THE THERMAL STABILITY OF N-HYDROXY-2-THIOPYRIDONE ESTERS: IMPROVED DECARBOXYLATIVE RADICAL ADDITIONS TO OLEFINS

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Abstract: Decarboxylative radical addition onto olefins via thiohydroxamate esters can be considerably improved by heating and irradiating the reaction mixture; compound 10 can thus be obtained in 64% yield in one operation from acid chloride 6.

Carboxylic esters 2 derived from N-hydroxy-2-pyridinethione 1 undergo, on heating or on irradiation with visible light, a decarboxylative rearrangement to give sulphides 3 proceeding through a radical chain mechanism as pictured in Scheme 1 (path A). This reaction, discovered and developed by Barton and co-workers over the past few years, has allowed a facile and efficient access to a tremendous variety of functionalised molecules¹. The strength of this method lies in the possibility of capturing the intermediate carbon radical with a radical trap such as, for example, an activated olefin (pathway B). For such a variant to be synthetically useful, route B must prevail over route A otherwise mixtures are obtained. In this Letter, we wish to report a simple experimental modification which improves the control over the usually unwanted decarboxylative rearrangement leading to 3 and therefore extends significantly the scope of the method.



Scheme 1

In most of the initial procedures 1,2, the ester 2 was generated in situ by adding the required acid chloride dropwise to a suspension of the sodium salt of 1 in a refluxing of the appropriate trap in benzene or toluene. The concentration of the ester in the medium remains therefore low in comparison

to that of the trap. Later, it was found that the addition of carbon radicals onto the thiocarbonyl group of esters 2 was, in general, a reversible process³ and, consequently, the importance of path A could be diminished significantly by simply carrying out the reaction at low temperature (ca 0°C) using visible light to initiate the radical chain process. This latter modification has resulted in a considerable improvement in the yield of decarboxylative radical addition to dichalcogenides, quinones, and various other olefins^{1,3,4}.



Scheme 2

If the radical addition onto the olefin is intrinsically slow, as in the case of an unactivated alkene or an unfavorable cyclisation, neither of these procedures works well. Thus, in connection with a project related to the synthesis of ring A of nogalamycin type anthracyclinone antibiotics, we attempted to accomplish the radical addition-cyclisation starting from acid 5, which was prepared from angelica lactone in low but unoptimised overall yield $(16\%)^5$, and phenyl vinyl sulphone as the olefinic trap as depicted in scheme 2. The sequential radical decarboxylation, addition, and cyclisation process was carried out at room temperature and irradiation with visible light from preformed but not isolated thiohydroxamate ester. We had earlier found that these conditions were well-suited for additioncyclisations involving 5-membered ring formation⁶. Indeed the desired adduct 10 was produced but only as the minor component in 18% yield. The major product (36% yield) was compound 11, resulting from simple addition to the phenyl vinyl sulphone. Interestingly, adduct 10 was obtained as a single diasteriomer to which we tentatively assigned the relative stereochemistry indicated on the basis of its NMR spectrum⁷. To improve the cyclisation step, we next attempted to perform the reaction thermally by adding dropwise the corresponding acid chloride of 5 to a suspension of the sodium salt of 1 in refluxing toluene containing the phenyl vinyl sulphone. The ratio of 6 to 7 improved but only very slightly.

Clearly, the formation of the six-membered ring is particularly sluggish as it also involves an *a* priori unfavourable 6-exo cyclisation of an electrophilic radical 8 onto an electrophilic olefin. The intermediate radical 9 arising from the cyclisation is electrophilic in character and does not therefore add again to phenyl vinyl sulphone. In this case a double addition to the external olefin was not a desired process, unlike the examples in our previous work 6 ; whence the need for an unsaturated lactone as an internal trap.

We noticed however that even in refluxing toluene, the solution acquired a yellow colour characteristic of the intermediate thiohydroxamate ester 7. If the latter was accumulating in the medium and quenching prematurely the intermediate radical 8 to give compound 11, then the thermal initiation must not be as efficient as hitherto presumed. This possibility was further supported by a recent incidental observation by Maillard and co-workers⁸ who reported that in a differential microcalorimetric study, ester 2a decomposed relatively slowly at 80°C. To confirm that such esters were indeed not so sensitive to moderate temperatures we carried out the following set of blank experiments. A degassed solution of palmitoyl ester 2b in deuterobenzene was divided into two NMR tubes, one of which was *completely* wrapped with aluminum foil, and both tubes were placed in the same oil bath at 80°C in a normally lit fume cupboard. A similar solution in deuterotoluene was heated to 105°C. The evolution of the reaction in the various tubes was followed by NMR; the results are summarised in the table. It is clear that at 80°C, light is necessary for initiation, and even at 105°C, thermal initiation is not very efficient.

Table. Thermal stability of ester 2b (30mg in 0.5ml degassed solvent) at 80 $^{\circ}$ C (deuterobenzene) and 105 $^{\circ}$ C (deterotoluene) under normal laboratory lighting (entry 1) and in the dark (entry 2).

Entry	solvent	After 2 hrs % 2b : % 3b	After 5 hrs % 2b : % 3b	solvent	After 1 hr % 2b : % 3b	After 2 hrs % 2b : % 3b
1	C ₆ D ₆	20 : 80	0 : 100	C ₇ D ₈	30 : 70	0 : 100
2	C6D6	100 : 0	100 : 0	C_7D_8	80 : 20	45 : 55

It seemed from these observations that increasing the temperature in order to favour the unimolecular cycliation of 8 to 9 must be coupled with a better initiation step if accumulation of the ester is to be avoided. We therefore repeated the above experiment leading to 10 except that this time the reaction mixture was *simultaneously heated to reflux and irradiated* (500W tungsten lamp) while slowly adding the acid chloride derived from acid 5. Under these new conditions, the yield of 10 jumped to 64% and only very small amounts of unwanted 11 were produced.

Considerable improvement in other sluggish additions to olefins can also be gained using these new conditions. For example, the decarboxylative allylation of the palmitoyl ester 2b, generated *in situ* by slow addition of palmitoyl chloride to a suspension of the sodium salt of 1 in refluxing benzene containing a large (seven-fold) excess of allyl phenyl sulphide (scheme 2) has been reported⁹ to give the desired 1-nonadecene 12 in only 20% along with sulphide 3b (20%).



In our hands, this experiment gave under similar conditions (normal laboratory lighting) a non polar fraction consisting of an inseparable mixture of 1-nonadecene 12 (9%) and pentadecane 13 (10%) as determined by nmr spectroscopy and comparison with authentic specimens using capillary gas chromatography. Sulphide 3b was isolated in 48% yield. Pentadecane arises presumably from abstraction of an allylic hydrogen from the allylating reagent¹⁰. These poor results are not surprising in view of the unactivated nature of the olefinic trap. However, when the same experiment was repeated under strong irradiaton (500W tungsten lamp), an almost four-fold increase in yield was observed. The combined yield of 1-nonadecene 12 and pentadecane 13 (ratio ca 1:1) leaped to 74% and only traces of unwanted sulphide 3b were formed.

In addition to shedding some light on the initiation aspect of the decarboxylation reaction, this experimental modification significantly increases its scope by allowing the use of somewhat unreactive olefinic traps as well as opening the way to highly functionalised six-membered ring systems through complex multiple radical addition cascades.

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7. For compound 10: m.p. 178.5 - 180.5 °C (from cyclohexane); v_{max} (nujol) 1760, 1570, 1410, 1300, 1255,

1140, 1080 cm⁻¹; ¹H NMR (200 MHz) δ 8.22 (1H, d, J= 4.8 Hz), 7.72 (2H, d, J= 6.7 Hz), 7.2-7.5 (4H, m), 6.9-7.0 (2H, m), 4.44 (1H, d, J= 12.4 Hz), 3.53 (1H, d, J= 5.7 Hz), 3.06 (1H, d, J= 12.4 Hz), 2.49 (1H, d, J= 14.2 Hz), 1.6-2.2 (9H, m) ppm; ¹³C NMR δ 172.3, 155.01, 149.41, 137.37, 137.09, 134.36, 129.52, 129.08, 122.84, 121.00, 83.91, 60.75, 47.12, 43.77, 35.83, 26.68, 20.18, 19.45 ppm. Found: C, 59.75; H, 5.19; N, 3.48. Calc. for C₂₀H₂₁NO₄S₂: C, 59.53; H, 5.25; N, 3.47.

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10. Hydrogen abstraction from toluene can also be partly responsible for the formation of pentadecane. As our purpose was simply to compare our results with the previous allylation experiment described in ref. 9 under as similar conditions as possible, we did not attempt to improve the ratio of 12 to 13 by changing the solvent.

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