

Observations on the Reaction of *O*-Acylthiohydroxamates with Thionitrite Esters: a Novel Free Radical Chain Reaction for Decarboxylative Amination

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Treatment of primary and secondary *O*-acyl derivatives of *N*-hydroxy-2-thiopyridone with thionitrite esters gives *trans* nitroso dimers in a free radical chain reaction.

The proven versatility of *O*-acylthiohydroxamate derivatives **1** of carboxylic acids in acting as mild and 'well disciplined' precursors of carbon centred radicals (R·) (Scheme 1) has led to the invention of a variety of extremely useful decarboxylative free radical chain reactions.¹ More recently, such derivatives, in conjunction with 3-phenyl-3-(trifluoromethyl)diazirine as a radical trap, have been used in a non-chain decarboxylative amination sequence² which provides an elegant solution to the important problem of creating a new carbon-nitrogen bond under free radical conditions.³

As part of a more extensive study on the chemistry of thionitrite esters as biocatalysts⁴ and reagents for the storage, transport and release of biologically fundamental nitric oxide,⁵ we conceived that the radicophilic nature of the thiocarbonyl group in compound **1** could be combined with the facile induced homolysis of thionitrites to set up the propagation sequence shown in Scheme 1. Although such a decarboxylative reaction leads in the first instance to the formation of a monomeric nitroso compound **2** which can function as a radical scavenger, examination of the Barton nitrite photolysis⁶ provides a good but somewhat surprising literature precedent that dimerisation to give **3** is a favoured low energy pathway and even takes precedence over the simple tautomerisation to an oxime which might also have been initially anticipated as the primary product.

A preliminary study using the *O*-acylthiohydroxamate derivative of octadecanoic acid **4** served to confirm the above hypothesis, (Scheme 2 and Table 1) inasmuch as the *trans*-nitroso dimer **5** was isolated as the primary product. Examination of the results in Table 1 also reveals several features of preparative and mechanistic interest. Thus, of the three thionitrite esters examined, readily prepared and crystalline

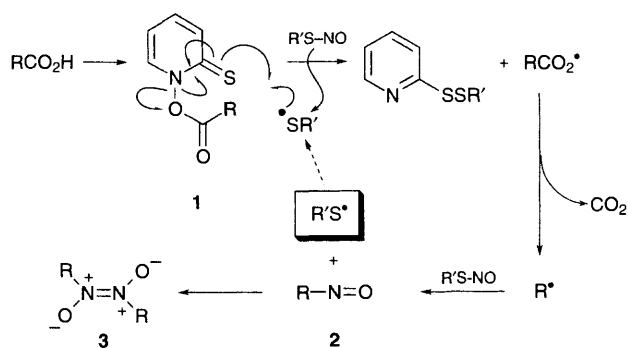
trityl thionitrite⁷ proved to be the most practical reagent of choice. As in other areas of *O*-acylthiohydroxamate chemistry, reactions may be conducted either thermally or by simple irradiation at room temperature using the light from a 250 W tungsten lamp. However, in terms of the stoichiometry of the reaction, the use of essentially equimolar quantities of the two reagents proved to be vital, and an experiment conducted in the presence of 2 equiv. of trityl thionitrite led to a dramatic decrease in the isolated yield of *trans*-nitroso dimer **5**. This was accompanied by a significant increase in the production of the nitrate ester byproduct **6** whose formation may be formally rationalised as shown in Scheme 3 via the known reaction of a nitroso compound with two molecules of nitric oxide to give a diazonium nitrate followed by loss of nitrogen.⁸

The scope of the photochemical reaction using trityl thionitrite was then examined using the series of primary and secondary carboxylic acid derivatives shown. The results are summarised under the formulae **7–9**, and the steroidal examples further indicate that the reaction is tolerant of ester and ketonic functionality.

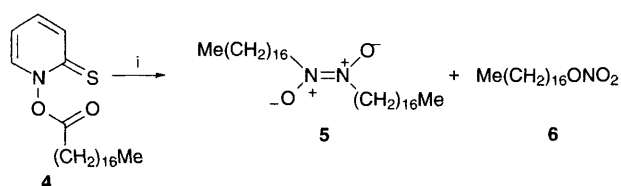
The product nitroso dimers derived from primary and secondary carboxylic acids are versatile intermediates. Thus, as in the case of the nitrite ester photolysis,⁶ the products from **7** and **9** could be usefully transformed in quantitative yield into their derived oximes **10** and **11** respectively, by the simple expedient of refluxing them in isopropanol. Alternatively, as demonstrated for the dimer **5**, catalytic hydrogenation over a platinum oxide catalyst furnished heptadecylamine (75%), thereby providing a mild and neutral alternative route from a carboxylic acid to the corresponding nor amine.

Unfortunately however, in contrast to the diazine method developed by Barton and coworkers,² the present strategy cannot be applied to derivatives of tertiary carboxylic acids. Thus, an attempted reaction using the tertiary aliphatic acid derivatives **12** led only to the isolation of an isomeric mixture of the alkenes **13** and **14** (13:14, 1:3) in 29.5% yield. In this instance, the known reluctance of tertiary aliphatic nitroso compounds to undergo dimerisation possibly encourages formation of their corresponding nitrate esters (*cf* Scheme 3) which can then eliminate to give the olefins.

Finally, in view of the known propensity of *O*-alkylthiohydroxamates to act as efficient precursors for the generation of

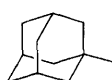


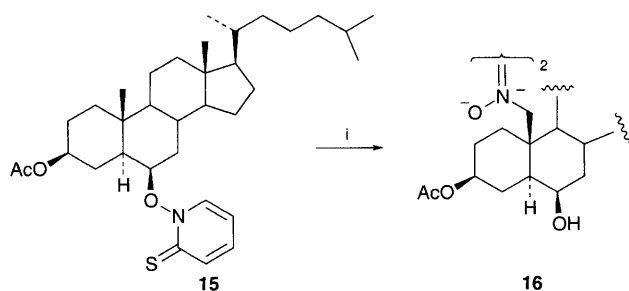
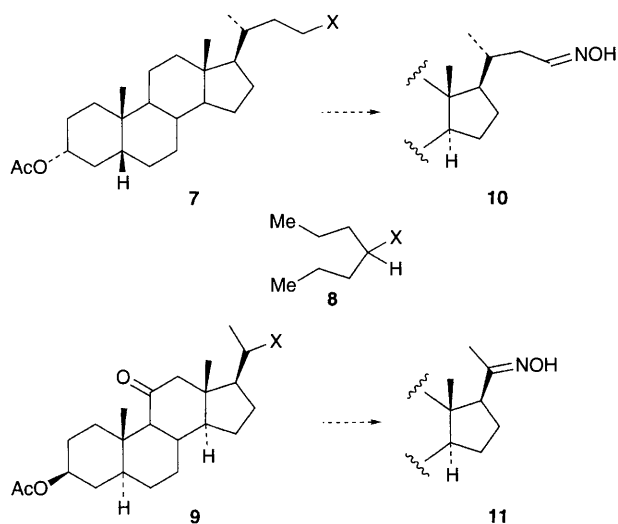
Scheme 1



Scheme 2 Reagents and conditions: (i) R'SNO, degassed benzene, N₂. Method A: Thermal 60–65 °C; method B: visible light (250 W tungsten lamp).

Table 1 The reaction of acylthiohydroxamate **4** with thionitrite esters R'SNO

R'	Equiv. of R'SNO	Method	Yield 5 (%)	Yield 6 (%)
Ph ₃ C	1.0	B	54.7	3.7
Ph ₃ C	1.03	A	47.3	4.4
Ph ₃ C	2.2	B	15.7	15.8
	0.91	B	52.5	5.4
<i>tert</i> -dodecyl	1.03	B	41.6	8.8

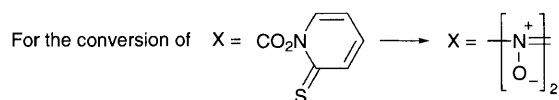


Scheme 4 Reagents and conditions: i, Ph_3CSNO , (1 equiv), method B, 2 h

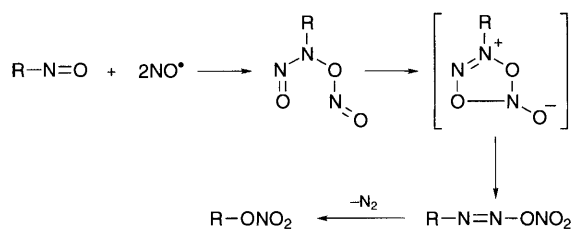
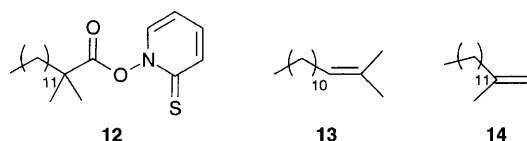
Thus, as shown in Scheme 4, simple irradiation of a degassed benzene solution of equimolar amounts of the steroidal derivative **15** and trityl thionitrite with a 250 W tungsten lamp for 2 h, led, after filtration of the precipitated product and further chromatography of the filtrate to an isolated yield of 41% of the nitroso dimer **16** which is also the primary product of classical nitrite photolysis.

Since the free radical chain reactions described herein using thionitrite ester reagents occur under particularly mild, neutral conditions and use only inexpensive reagents the present methods therefore show some promise for the selective introduction of a new carbon nitrogen bond under non-ionic conditions.

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Compound	Method	Yield (%)
7	A	62
	B	60
8	B	33
9	B	48



Scheme 3

alkoxy radicals,⁹ we have also been able to carry out the equivalent of the Barton nitrite photolysis without the necessity of using a high pressure mercury lamp as an ultraviolet source.

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