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Studies on the intermolecular free radical addition of thionitrites to alkenes: a convenient method for the preparation of α-tritylthio oximes and related derivatives

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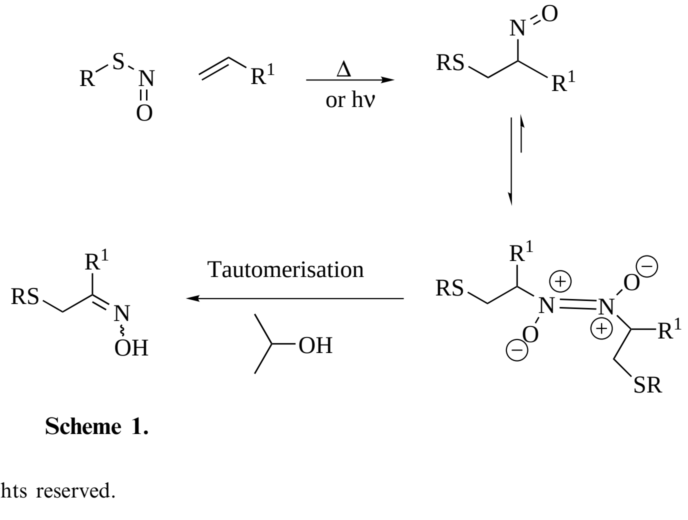
Abstract—The addition of trityl thionitrite to a variety of alkenes is promoted either by heat or by visible light and provides a simple method for the preparation of α-tritylthio oxime building blocks and related derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

The endogenously generated free radical, nitric oxide, has been implicated in an increasing number of fundamental biological events over the last decade, and is now currently considered to be one of the most important molecules in the field of biomedical sciences.[1] As a direct consequence of the exponential growth in this area, it is not surprising that chemists have taken a renewed interest, both in the chemistry of nitric oxide itself, and also in some of its less studied derivatives.[2] In particular, the structure and chemical reactivity of thionitrites (*S*-nitrosothiols) has attracted considerable attention because of their role as potential biocatalysts in the storage, transport and release of nitric oxide.[3,4] Within this framework, we have recently undertaken a programme of research which has centred around the use of thionitrites, both as biological probes,[5] and as reagents for controlled delivery of nitric oxide to carbon centred radicals.[6] Herein, in continuation of this theme, we now wish to report the results of a preliminary study on the factors which influence the intermolecular free radical addition of a thionitrite to an alkene. As encapsulated in Scheme 1, we envisaged that this reaction would afford synthetically versatile α-alkylthio or α-arylthio oximes. To the best of our knowledge, the only isolated report of such a reaction can be found in a pioneering study by Gowenlock[7] who demonstrated that the addition of *tert*-butyl thionitrite or trityl thionitrite across the double bond of styrene furnished a diastereoisomeric mixture of α-nitroso dimers. Although the monomeric nitroso compounds formed in this reaction sequence can in principle act as efficient radical scavengers, ample precedent exists both in the form of the Barton nitrite photolysis[8] and in our decarboxylative nitrosation[6] for facile in situ conversion to nitroso dimers. Our own intention, however, was to achieve in situ tautomerisation of such intermediates to the corresponding oximes as outlined in Scheme 1.

From a mechanistic standpoint, we reasoned that the overall efficiency of the putative propagation sequence shown in Scheme 2 should be influenced, to some extent, by the nature of the alkene acceptor which determines both the rates of the reversible addition of thiyl radicals to alkenes and the subsequent capture of nitric oxide from the thionitrite by the carbon centred radical, most probably via the addition elimination sequence shown.



Scheme 1.

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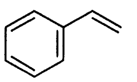
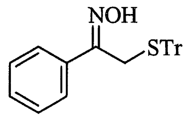
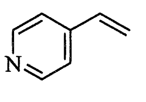
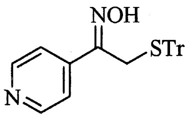
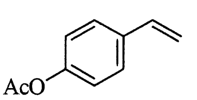
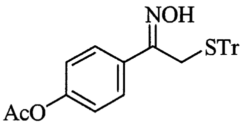
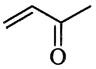
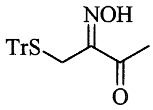
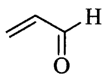
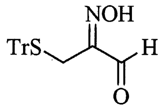
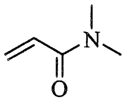
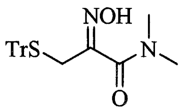
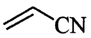
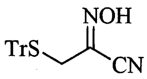
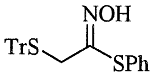
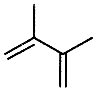
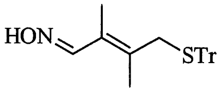
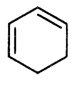
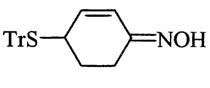
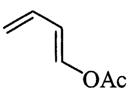
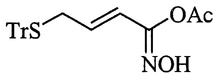
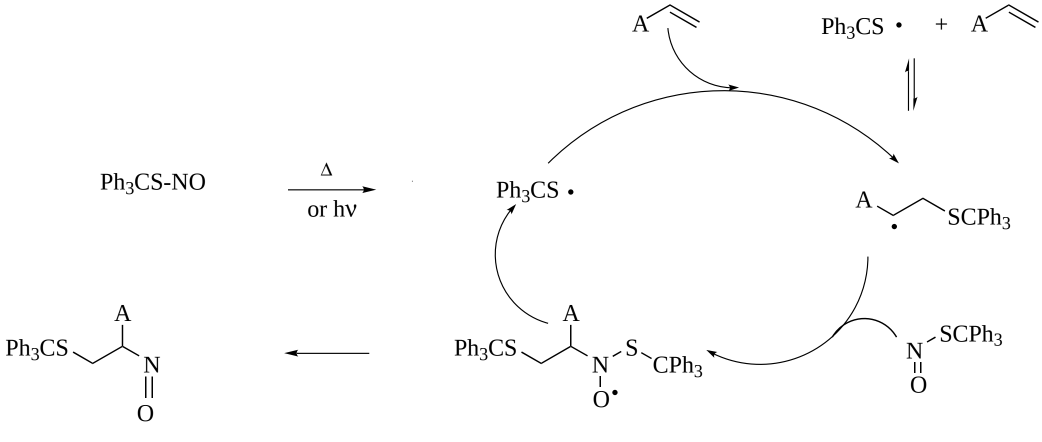
The results for a variety of alkene acceptors using highly crystalline and readily prepared trityl thionitrite[9] are shown in Table 1 and reveal that preparatively useful yields can be obtained under very mild thermal conditions or by simple irradiation at room temperature with a 500 watt tungsten lamp. Reactions were typically performed using a 2:1 mixture by volume of isopropanol and benzene with six equiv. of the alkene acceptor and easily monitored by the disappearance of the characteristic dark green colour of the thionitrite, and for those reactions where photochemical conditions were employed, the crude reaction mixture was subsequently heated to 65°C for a period of 5–6 h to ensure complete tautomerisation to the corresponding oxime isomers.

Table 1. Intermolecular addition of trityl thionitrite onto activated alkenes

Entry	Alkene	Conditions	Addition product	Isolated yield
1		Δ hν		72%[a] 48%[a]
2		Δ		87%[a]
3		Δ		23%[a]
4		Δ hν		55%[a] 57%[a]
5		Δ		42%[a]
6		Δ		42%[a]
7		Δ		40%[b]
8		Δ		29%[b]
9		Δ		75%[a,c]
10		Δ		42%[a]
11		Δ		42%[a,c]

(a) only one isomer of the oxime was formed.
(b) The *Z/E* mixture of the two oximes in a proportion 1:1 was formed.
(c) The isomer of the alkene isolated was that which is drawn and only traces of other isomers were detected.



Scheme 2.

Careful scrutiny of the isolated yields in these reactions reveals several features of interest. Thus, in terms of the polar characteristics of the intermediates involved in the mechanism outlined above, we had initially anticipated that an electron rich alkene would prove to be a more efficient substrate, in as much as it should not only favour addition of the electrophilic thiyl radical but should also lead to a more nucleophilic carbon centred radical for reaction with the thionitrite in the chain propagation step. In the event, however, both the electron rich styrene (entry 3), particularly when viewed in relation to its neutral (entry 1) and electron poor (entry 2) congeners, as well as phenyl vinyl sulphide (entry 8), proved to be the poorest alkene acceptors. A plausible explanation for these observations may lie in the fact that the radicals formed by the addition of the tritylthiyl radical to such electron rich alkenes will have a particularly low ionisation potential, and it is therefore possible that electron transfer to the thionitrite could then effectively compete in such cases and hence lead to termination of the simple propagation sequence. Some tentative support for such a hypothesis comes from the elegant series of studies by Williams[10] who has established that this is the vital role of copper ion in the induced homolysis of thionitrites.

In summary, the mild neutral conditions in this intermolecular free radical chain reaction of easily prepared trityl thionitrite with an extensive range of inexpensive alkenes and dienes offer a highly regiospecific route to richly functionalised α-tritylthio oximes and related derivatives, thereby extending the range of radical functionalisation reactions to oximes using nitrite derivatives.[11]

Acknowledgements

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