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Thioepoxide formation by ring closure of allylthiyl radicals—a novel rearrangement of allylic thionitrites

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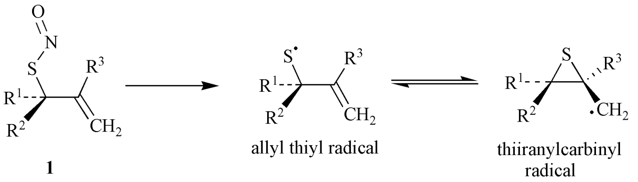
Tertiary allylic thionitrites undergo thermal rearrangement to α,β-episulfide nitroso dimers *via* ring closure of allylthiyl radicals.

Within the last decade, the endogenously generated free radical, nitric oxide, has been implicated in an increasing number of fundamentally important biological processes, including control of blood pressure, cytotoxicity, and neurotransmission.[1] As a direct consequence, the chemistry of nitric oxide derivatives, and in particular of thionitrites (*S*-nitrosothiols) has become an area of considerable current research interest.[2] The vital role played by these intermediates for the storage, transport and release of nitric oxide *in vivo* has been clearly recognised[3] and, to some extent, effectively mirrors their simple thermal decomposition to give disulfide with concomitant liberation of nitric oxide. This latter reaction is generally considered to involve the intermediacy of thiyl radicals and can also be brought about by irradiation or in the presence of certain metal salts.[2]

As part of our ongoing interest in the homolytic reactivity of thionitrites,[4] we have previously shown that the capture of nitric oxide from a thionitrite by a carbon centered radical can be a very effective step in a free radical chain reaction, presumably *via* a propagative addition–elimination mechanism. With this observation in mind, and also given the rapid and reversible addition of thiyl radicals to alkenes, we were especially intrigued by the potential behaviour of tertiary allylic thionitrites (**1**) since the location of the internal alkene trap would then allow us, in principle, to access the thiyl analogue of the well known oxiranyl carbinyl–allyloxy radical rearrangement[5] as implied in Scheme 1. We now wish to report the results of our preliminary study in this area.

The required tertiary allylic thionitrites were readily prepared by the general route shown in Scheme 2. Thus, two carbon homologation of commercially available lactones *via* Wadsworth–Horner–Emmons olefination to their α,β-unsaturated esters and subsequent lithium aluminium hydride reduction gave allylic alcohols which were then transformed into dithiocarbonates using the well established [3,3] sigmatropic shift[6] of the corresponding allylic xanthates. Aminolysis of the dithiocarbonates was most effectively achieved using neat 2-aminoethanol and the resultant tertiary allylic thiols were then nitrosated with sodium nitrite in acetic acid. The desired tertiary allylic thionitrites prepared by this sequence are shown in Scheme 2 and were isolated as green oils. They proved to be sufficiently stable to allow purification by filtration through silica gel and full characterisation by ^{1}H and ^{13}C NMR, IR, UV and mass spectrometry but decomposed slowly if allowed to stand at room temperature for prolonged periods.



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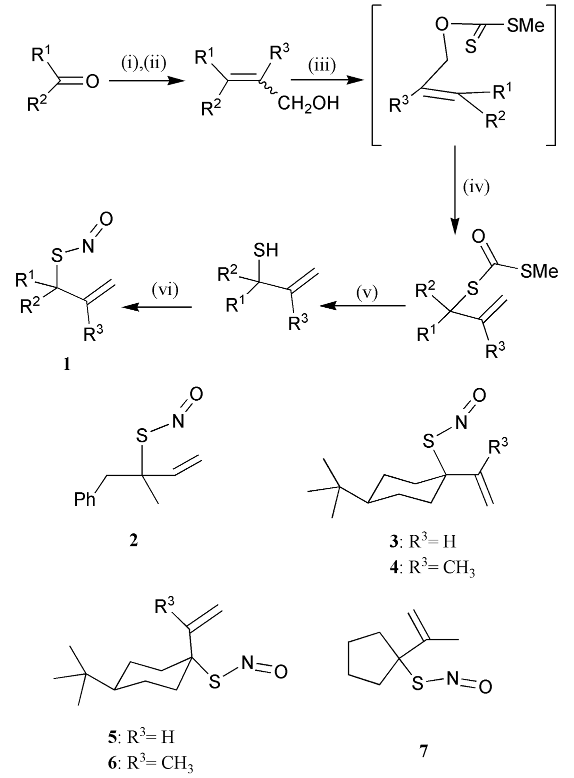
Scheme 1

In order to study their thermal behaviour, thionitrites were simply dissolved in benzene or dichloromethane and the resulting solutions were then heated at 40 °C until total disappearance of their characteristic green colour (usually after 6–7 h). Separation of the reaction mixtures by flash chromatography allowed isolation and characterisation of the major products as the unusual episulfide nitroso dimers of general formula **8** which were accompanied in some instances by a second minor product **9**, which formally resulted from thermodynamically favourable allylic transposition and dimerisation to the corresponding disulfide (Scheme 3). The yields of the products obtained are shown in Table 1.

From a stereochemical viewpoint it was of particular interest to note that the nitroso dimers **8** isolated from thionitrites **3**–**6** were formed as single diastereoisomers in each case whilst those from thionitrites **2** and **7** were formed as mixtures. The centrosymmetric structure of the dimer from thionitrite **3** was unequivocally revealed by an X-ray crystallographic analysis (Fig. 1). However, because of crystal decomposition, refine-



Scheme 2 Reagents and conditions: (i) $(EtO)_2POCH_2CO_2Et$ (for R^3 = H) or $(EtO)_2PO(CH_3)CO_2Et$ (for R^3 = CH_3), NaH, THF, 0 °C to r.t., 2 h, 95–99%; (ii) $LiAlH_4$, Et_2O, 0 °C, 45 min, r.t., 1 h, 70–92%; (iii) a) NaH, THF, 0 °C to r.t., 1 h; b) CS_2, reflux, 1 h; c) MeI; (iv) reflux, 7 h, 45–60%; (v) 2-aminoethanol, r.t., 2 h, 55–85%; (vi) $NaNO_2$, AcOH, r.t., 2 h, 45–85%.

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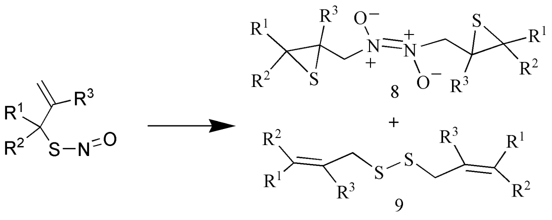

Scheme 3

Table 1 Thermal rearrangement of thionitrites

Thionitrite	Solvent[a]	Product yield (%)	
		Disulfide **9**	Nitroso dimer **8**
2	A	21	52[b]
3	A (B)	16 (18)	39 ,(65)
4	A (B)	0 (0)	43 (73)
5	A (B)	30 (17)	30 (65)
6	A (B)	0 (0)	65 (72)
7	A	0	58

[a] Solvents: A = benzene, B = dichloromethane. [b] For further characterisation, the complex mixture of diastereoisomers was transformed into the corresponding oximes by heating in isopropanol at reflux for 24 h.

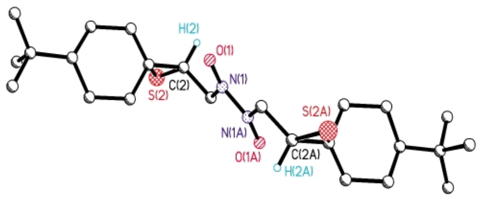

Fig. 1

ment of the structure determination was not possible and the results could only be used as proof of structure. In terms of molecular recognition, it is of interest to note that the single diastereomer corresponds to the (*R*,*S*) or *meso* form implying that the favoured low energy pathway for dimerisation of the nitroso monomer involves exclusive combination of the two different enantiomers.

From a mechanistic standpoint, the above rearrangement could, in principle, be rationalised in terms of an initial electrophilic addition of a nitrosonium cation to the double bond followed by neighbouring group participation from the lone pair of the sulfur atom. However, efforts to trigger such a pathway through the addition of a catalytic quantity of nitrosonium tetrafluoroborate to thionitrite led to extensive decomposition. In similar fashion, even although a formal analogy exists for intramolecular homolytic displacement leading to epoxide formation from allylic peroxy derivatives,[7] the well known lack of reactivity of nitric oxide with alkenes[8] renders such a mechanism unlikely. We therefore consider that the most plausible reaction pathway involves ring closure of an initially formed allylic thiyl radical and that the overall reaction is thermodynamically driven by the highly efficient capture of the carbon centered radical, either by cage recombination with nitric oxide or in a chain process by reaction with the thionitrite. Although extensive mechanistic,[9] computational[10] and synthetic[11,12] work has been carried out on the oxiranyl–carbinyl allyloxy radical equilibrium, primarily for epoxide ring opening[11] but also for reclosure reactions,[12] the rearrangement described herein represents, to the best of our knowledge, the first preparative example involving the sulfur congener.

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