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Reverse-Cope Cyclisations of Thiahydroxylamines Derived from the Addition of Allylic Thiols to Nitrones : Syntheses of 1,3-Thiazolidine-*N*-oxides and 1,5,2-Oxathiazinanes

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Abstract:- *Allylthiols 7 react as nucleophiles with nitrones 8 to give intermediate thiahydroxylamines which undergo reverse-Cope cyclisations to provide 1,3-thiazolidine-N-oxides 9; in the case of derivatives of C-phenyl nitrone, thermolysis results in smooth Meisenheimer rearrangement leading to the 1,5,2-oxathiazinane 14.*
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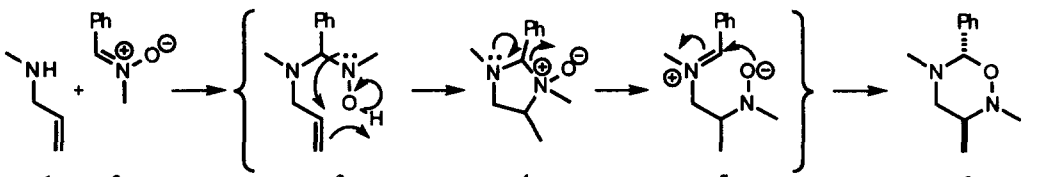
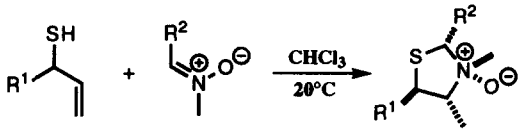
We have recently reported[1] that reaction between *N*-methylallylamine **1** and nitrones **2** leads to the oxadiazines **6**, presumably *via* an initial nucleophilic attack by the amine onto the nitrone followed by reverse-Cope cyclisation[2,3] and Meisenheimer rearrangement (Scheme 1). Overall, this sequence represents a method for the amination of an "unactivated" alkene function and is useful for the stereoselective elaboration of *syn*-vicinal diamines. In view of this and of the uncertainty surrounding the proposed mechanism, we were intrigued by the prospect that other nucleophiles could be used to trigger the reaction sequence to provide other heterocyclic systems as well as other, potentially useful, amine derivatives. Herein, we report that allylthiols can also participate in this Scheme and define some of the scope and limitations of this chemistry, which has led to two unprecedented heterocyclic ring systems.



Scheme 1

Our first experiment was to follow the reaction between allylthiol **7a** and the *C*-phenyl nitrone **8a** by ^{1}H NMR in deuteriochloroform. A product was clearly visible after 3.5h at ambient temperature, identified by the appearance of a characteristic doublet at δ_H 1.49 (J 6.3Hz), and was present at its maximum amount after

approximately 4 days. Very rapid chromatography over silica gel eluted first with petrol:ethyl acetate [2:1] and then with methanol gave, in *ca.* 80% yield, what proved to be the thiazolidine-*N*-oxide **9a**, according to its high polarity,[3] spectroscopic and analytical data and subsequent chemistry. As reported in the preceding paper,[1] the *C*-aryl nitrones [**8**; R^2 = aryl] are amongst the least reactive in this type of chemistry. We therefore examined similar reactions of some *C*-alkyl nitrones and were delighted to observe that the related thiazolidine-*N*-oxides **9b** and **9c** were formed much more rapidly at ambient temperature in chloroform (Scheme 2). Incorporation of a



a) R^1 = H; R^2 = Ph; 120h; 80% [91%]
b) R^1 = H; R^2 = c-C_3H_5; 2h; 86% [>95%]
c) R^1 = H; R^2 = n-C_5H_{11}; 16h; - [>90%]
d) R^1 = Ph; R^2 = c-C_3H_5; 16h; 79% [>95%]
e) R^1 = Ph; R^2 = n-C_5H_{11}; 16h; 82% [>90%]

7a) R^1 = H
b) R^1 = Ph

8a) R^2 = Ph
b) R^2 = c-C_3H_5
c) R^2 = n-C_5H_{11}

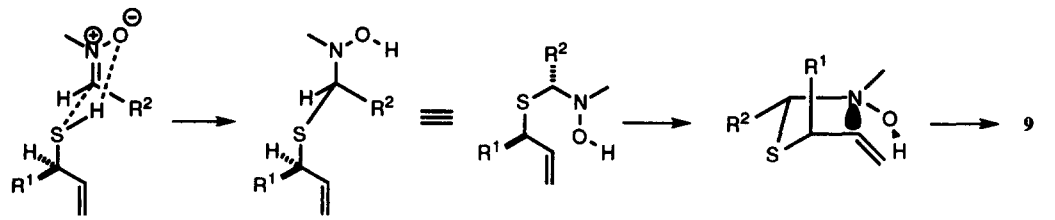
9

10

Scheme 2

further substituent adjacent to the thiol group had little effect on the rate as the trisubstituted thiazolidine-*N*-oxides **9d** and **9e** were formed at a similar rate from 1-phenyl-2-propen-1-thiol **7b**.[4]

These results merit several comments. In all cases except the 2-pentyl example **9c**, the products could be purified by rapid chromatography over silica gel but were usually formed in excellent yields (the yields quoted in square brackets were deduced from ^{1}H NMR spectra) and of sufficient purity for most subsequent synthetic purposes. The products were stable if stored under nitrogen neat for a few months. The isolation of the thiazolidine-*N*-oxides **9** provides good evidence for the mechanism proposed in Scheme 1 for the corresponding allylamine reactions and also represents, to the best of our knowledge, the first synthetic route to such derivatives, as oxidation of thiazolidines in general gives the corresponding *S*-oxides.[5] The subsequent Meisenheimer rearrangement, assumed to occur in the case of the allylamine reactions shown in Scheme 1, does not occur rapidly in these cases (see below) at ambient temperature, due to the lower basicity of the sulfur atom. Despite the greater reactivity of the *C*-alkyl nitrones **8b** and **8c**, these showed no reaction with distally substituted allylic thiols **10** [R = Me or Ph], a common feature of this type of reverse-Cope chemistry.[1,2]



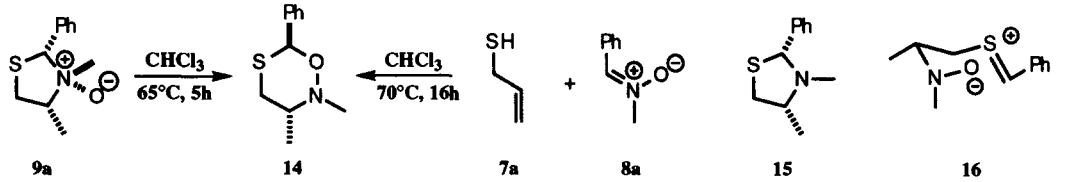
11 **12** **13**

Scheme 3

The thiazolidine-*N*-oxides **9** were all formed with >95% stereoselectivities and their detailed structures were secured by NMR spectroscopy, in particular nOe measurements, and were substantiated by an X-ray crystallographic structure determination of the cyclopropyl derivative **9b**.[6] Mechanistic considerations also aided the determination of the stereochemistry: in order that the hydroxylamine and alkene orbitals can achieve

reasonable overlap, it is necessary for these to be positioned *syn* to each other and hence give products in which the 4-methyl and *N*-oxide oxygen are also *syn* to each other. An explanation of these stereochemical features is outlined in Scheme 3. The initial approach of the thiol to the nitrone obeys Cram's rule, with the two substituents R^1 and R^2 positioned *anti*; the resulting thiahydroxylamine **11** could then adopt conformation **12** and thence the boat-like transition state **13**, allowing the required *syn* arrangement of the hydroxylamine and alkene functions.

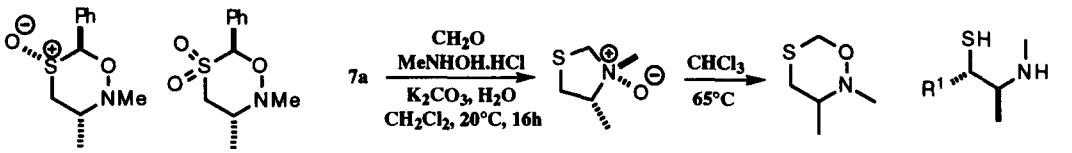
The lack of subsequent and rapid Meisenheimer rearrangement of the thiazolidine-*N*-oxides **9** at ambient temperature, as observed in the allylamine examples (Scheme 1), led us to examine their thermal behaviour. We were pleased to find that upon heating to reflux in chloroform, the phenyl derivative **9a** underwent smooth rearrangement to the *trans*-1,5,2-oxathiazinane **14** in >90% isolated yield (Scheme 4).[7] The same high yield was obtainable if the starting materials **7a** and **8a** were heated together; the best conditions found were thermolysis in $CHCl_3$ at 70°C (sealed tube). In refluxing toluene, a second product, the deoxygenated thiazolidine **15**, was formed in *ca* 10% yield along with the oxathiazinane **14** (62%). Under these conditions, it seems likely that the deoxygenation occurs *via* proton exchange between the *N*-oxide **9a** and allylthiol followed by deoxygenation by attack of the thiolate on the oxygen of the resulting hydroxyammonium species.[8] To the best of our knowledge, this represents the first synthesis of the 1,5,2-oxathiazinane ring system.[9]



9a **14** **7a** **8a** **15** **16**

Scheme 4

The structure **14** was established by NMR, microanalysis and X-ray analysis,[6] which showed that the heterocyclic ring adopts a chair conformation, reflected in the NMR coupling constants which display typical equatorial-axial and axial-axial values. The origin of the observed stereochemistry is presumably in the final step of the Meisenheimer rearrangement (Scheme 1), which proceeds *via* a chair-like transition state **16**.



17 **18** **19** **20** **21**

Oxidation of the initial oxathiazinane **14** could be achieved using a variety of reagents typically used for such transformations [*m*CPBA, H_2O_2, $NaIO_4$] and gave a single sulfoxide **17** in 77-86% isolated yields. Further oxidation of this derivative **17** or of the parent **14** with ruthenium tetroxide [$RuCl_3$ (cat.), $NaIO_4$, aq. MeOH] led to the corresponding sulfone **18**, also in excellent isolated yield [80-85%].

Attempts to effect Meisenheimer rearrangements of the 2-alkylthiazolidine-*N*-oxides **9b-e** were much less successful and led to mixtures which, while containing the corresponding oxathiazinane, also contained similar amounts of the related thiazolidine- and oxathiazinane-*S*-oxides,[7] along with unidentified elimination products,[3]

thus rendering this an impractical method for preparing these novel heterocycles. Presumably, the Meisenheimer process is faster in the case of the 2-phenyl derivative **9a** as the new double bond [*cf.* **16**] is in conjugation with the phenyl ring. The premix method for the *in situ* generation of formaldehyde nitrone[1] could also be applied to allylthiol **7a** and led to a excellent yield of the sensitive thiazolidine-*N*-oxide **19**, thermolysis of which led to the oxathiazinane **20**. Unfortunately, and despite the much greater reactivity of the formaldehyde nitrone, more highly substituted unsaturated thiols **10** did not afford useful yields of the expected thiazolidine-*N*-oxides. Finally, reduction of both the thiazolidine-*N*-oxides **9** and the oxathiazine **14** using titanium(III) chloride gave the amino-thiols **21** in 60-70% isolated yields, thus defining an approach of some generality to these ligands.

Acknowledgements

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4. Hacklert, R.E.; Balko, T.W. *J. Org. Chem.*, **1973**, *38*, 2106. It was fortunate that this thiol reacted at ambient temperature as heating causes rapid rearrangement to the corresponding cinnamylthiol.
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6. We are very grateful to Professor M.B. Hursthouse and Mr D.E. Hibbs, Cardiff University, for these data, full details of which will be reported separately.
7. At ambient temperature in chloroform, the thiazolidine-*N*-oxide **9a** slowly (>15 days) underwent Meisenheimer rearrangement to the oxathiazinane **14** but this was accompanied by similar amounts of the two possible *S*-oxides derived from these ring systems, presumably formed by *N*- to *S*-oxygen transfer.
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