Pergamon

Tetrahedron Letters, Vol. 38, No. 12, pp. 2175-2178, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00275-X

Exploiting the 1,3-Dithiane of 2-Oxopropanenitrile Oxide to Limit Competing Dimerization in 1,3-Dipolar Cycloaddition Reactions

Stuart J. Barrow and Christopher J. Easton*

Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia

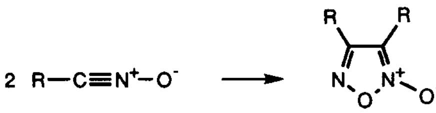
G. Paul Savage and Gregory W. Simpson

CSIRO Division of Chemicals and Polymers, Private Bag 10, Rosebank MDC, Clayton, VIC 3169, Australia

Abstract: The 1,3-dithiane of 2-oxopropanenitrile oxide is less prone to dimerization than the parent compound and, as a consequence, it undergoes more efficient cycloaddition reactions with a range of mono- and 1,1- and 1,2-di-substituted alkenes. © 1997 Elsevier Science Ltd.

INTRODUCTION

1,3-Dipolar cycloaddition reactions of nitrile oxides with alkenes provide ready access to Δ^2-isoxazolines, which are of interest as precursors of β-amino alcohols, β-hydroxy ketones, 1,3-diols and many other classes of compounds.[1] Nitrile oxides also undergo dimerization to give furoxans (Scheme 1), and the extent to which this competing process limits access to the isoxazolines depends on the degree of substitution of the alkene and the nature of the nitrile oxide.[1,2] Alkylnitrile oxides are more prone to dimerization than the more bulky aryl derivatives. While they give modest yields of cycloadducts in reactions with mono- and 1,1-di-substituted alkenes, generally dimerization of alkylnitrile oxides occurs in preference to reaction with 1,2-disubstituted and more highly substituted alkenes, even when the nitrile oxide is generated *in situ* in the presence of an excess of the dipolarophile.



Scheme 1

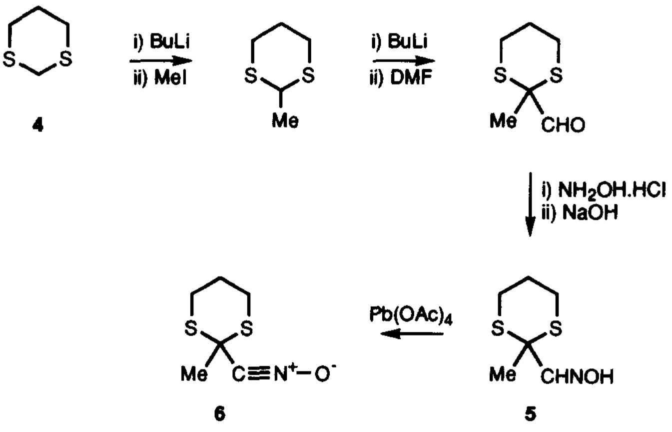
Several methods have been developed to circumvent dimerization of alkylnitrile oxides. The furoxans can react as masked nitrile oxides, undergoing cycloaddition with alkenes.[3] Alternatively, some furoxans undergo thermolytic cycloreversion to nitrile oxides.[2,4] Although these methods are not applicable generally, due to the vigorous reaction conditions that usually must be employed, Curran and Fenk[2] have shown that bis(2-((trimethylsilyl)oxy)prop-2-yl)furoxan affords the corresponding nitrile oxide **1**, on heating in benzene at 165 °C, and the nitrile oxide **1** gives good yields of cycloadducts with mono-, di- and tri-substitituted

$Me_3SiOC(Me_2){-}C{\equiv}N^+{-}O^-$ **1** $\quad$ $t\text{-}Bu{-}C{\equiv}N^+{-}O^-$ **2** $\quad$ $Ac{-}C{\equiv}N^+{-}O^-$ **3**

alkenes under these conditions. The nitrile oxide **1** is also accessible from the corresponding nitroalkane,[5] and it reacts with a variety of alkenes without competing dimerization.[5,6] The tendency of the nitrile oxide **1** and the analogous *tert*-butyl derivative **2** to undergo cycloaddition in preference to dimerization can be attributed to the steric bulk of these species.[2,5] With this in mind, we anticipated that an alternative solution to the problem of dimerization of nitrile oxides would be to temporarily introduce bulky substituents or steric auxiliaries, to affect the reactivity of the nitrile oxides and favour the cycloaddition processes. This hypothesis has now been examined using the dithiane **6** as an analogue of the nitrile oxide **3**.

RESULTS AND DISCUSSION

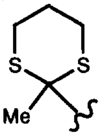
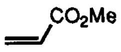
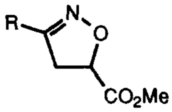
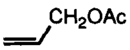
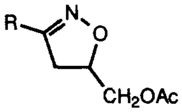
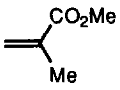
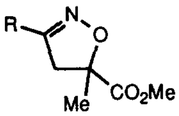
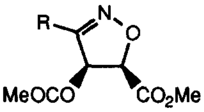
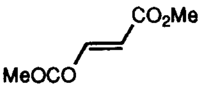
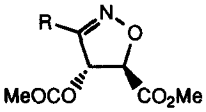
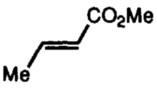
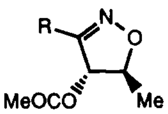
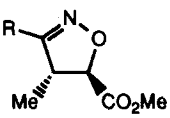
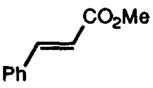
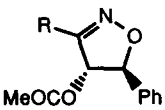
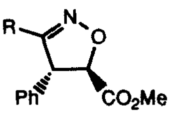
The nitrile oxide **6** was obtained from 1,3-dithiane **4** as shown in Scheme 2. Lead tetraacetate was used for the oxidation of the aldoxime **5**.[7] In order to prevent condensation of the nitrile oxide **6** with the acetic acid formed as a by-product in this reaction, it was necessary to wash the crude reaction mixture with aqueous sodium bicarbonate. The yield of the nitrile oxide **6** was only approximately 40% using this reagent, but the more commonly used method of treatment with *N*-chlorosuccinimide followed by triethylamine[8] resulted in decomposition, presumably as a result of oxidation on sulfur. Reactions of the nitrile oxide **6** were monitored by ^1H NMR spectroscopy, using solutions (*ca.* 0.06 M) in deuteriochloroform, containing methyl benzoate as an internal standard. In the absence of a dipolarophile, less than 30% of the nitrile oxide **6** reacted in solutions stored at room temperature for three days. Under the same conditions, the nitrile oxide **6** reacted with each of the alkenes **7-13** (2 mole equivalents), however, to give the corresponding cycloadducts, in yields ranging from 56-85% (Table 1).



Scheme 2

The nitrile oxide **6** is the 1,3-dithiane of 2-oxopropanenitrile oxide **3**. To examine the effect of the dithiane moiety as a steric auxiliary, reactions of the latter compound were also investigated and compared. The

Table 1. Products and yields of reactions of the nitrile oxides **3** and **6** with the alkenes **7**-**13**.

Alkene	Cycloadduct[9]	Yield (%)	
		R = Ac	R = 
		3	**6**
 **7**		29	83
 **8**		23	85
 **9**		27	80
 **10**		-	73
 **11**		-	78
 **12**	 	-	58 (5:1)
 **13**	 	-	56 (3:1)

nitrile oxide **3** undergoes relatively rapid dimerization, and no starting material remained detectable after 5 minutes in a *ca.* 0.08 M solution prepared in deuteriochloroform. For this reason it was generated *in situ*, by treatment of the corresponding nitrite with *N*-chlorosuccinimide and triethylamine. Otherwise the experimental conditions for the reactions of the nitrile oxide **3** with the alkenes **7-13** were the same as those used for the reactions of the dithiane **6**, although the reactions of the ketone **3** were complete in less than one hour. Under these conditions, 2-oxopropanenitrile oxide **3** gave modest yields of cycloadducts with the monosubstituted alkenes **7** and **8**, and the 1,1-disubstituted alkene **9**, but no cycloadducts were formed from the 1,2-disubstituted alkenes **10-13** (Table 1).

Clearly the results of the experiments with 2-oxopropanenitrile oxide **3** are in marked contrast to those with the dithiane **6** and they show that the protecting group of the dithiane **6** significantly increases the yields of cycloadducts. Presumably this is a result of the dithiane moiety acting as a steric auxiliary to reduce the rate of the competing dimerization reaction by at least three orders of magnitude, as indicated in the preliminary experiments described above. Our present studies have been restricted to a comparison of the reactions of the nitrile oxides **3** and **6**, but it seems likely that steric auxiliaries may provide a general method to ameliorate the problem of dimerization of alkylnitrile oxides, since analogues of the dithiane **6** are readily available and synthetically versatile. Currently we are investigating alternative methods for the preparation of the dithiane **6**, to overcome the limitation of the method due to the modest yield of that compound. We also intend to examine reactions of the corresponding 1,3-dioxane, as a way to avoid complications due to reactions on sulfur.

REFERENCES

1. Grundmann, C.; Grünanger, P. *The Nitrile Oxides*; Springer-Verlag: Berlin, 1971; Caramella, P.; Grünanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Ed., Wiley (Interscience): New York, 1984, vol. 1, p. 291; Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH Publishers: New York, 1988; Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocyclic Chem.*, **1994**, *60*, 261.
2. Curran, D. P.; Fenk, C. J. *J. Am. Chem. Soc.*, **1985**, *107*, 6023.
3. Shimizu, T.; Hayashi, Y.; Teramura, K. *J. Org. Chem.*, **1983**, *48*, 3053; Shimizu, T.; Hayashi, Y.; Taniguchi, T.; Teramura, K. *Tetrahedron*, **1985**, *41*, 727.
4. Chapman, J. A.; Crosby, J.; Cummings, C. A.; Rennie, R. A. C.; Paton, R. M. *J. Chem. Soc., Chem. Commun.*, **1976**, 240; Mitchell, W. R.; Paton, R. M. *Tetrahedron Lett.*, **1979**, 2443; Whitney, R. A.; Nicholas, E. S. *Tetrahedron Lett.*, **1981**, *22*, 3371; Dondoni, A.; Barbaro, G.; Battaglia, A.; Giorgianni, P. *J. Org. Chem.*, **1972**, *37*, 3196; Bianchi, G.; DiMicheli, C.; Gandolfi, R. *Angew. Chem., Int. Ed. Engl.*, **1979**, *18*, 721.
5. Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.*, **1984**, *49*, 3474.
6. Curran, D. P.; Fenk, C. J. *Tetrahedron Lett.*, **1986**, *27*, 4865; Inouye, Y.; Mitsuya, M.; Tokuhisa, K.; Kakisawa, H. *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 3300.
7. Just, G.; Dahl, K. *Tetrahedron*, **1968**, *24*, 5251.
8. Liu, K.-C.; Shelton, B. R.; Howe, R. K., *J. Org. Chem.*, **1980**, *45*, 3916.
9. All new compounds were fully characterized. Stereochemical descriptors show relative stereochemistry only.

(*Received in UK* 23 *January* 1997; *accepted* 7 *February* 1997)