Tetrahedron Letters,Vol.31,No.1,pp 123-126,1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

# 1,3-DIPOLAR CYCLOADDITIONS OF 2-ETHOXY- AND 2-(ETHYLTHIO)-1-AZETINES WITH NITRILE OXIDES AND NITRILE YLIDES

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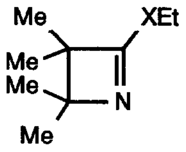
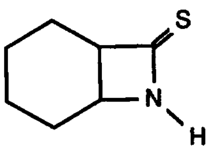
Summary *The first examples of 1,3-dipolar cycloadducts of 1-azetines are reported.*

Diels-Alder [4 + 2][1] and 1,3-dipolar[2a,b] cycloadditions to a variety of cyclic and acyclic imines have been reported. Surprisingly, however, apart from a few examples of 1,3-dipolar cycloadditions to benzazete,[3] and recent reports[4] concerning the trapping of transient azetinones by Lewis-acid catalysed Diels-Alder cycloadditions with silyloxy-1,3-butadienes, there appear to be no instances of cycloadditions to azetines.[5] In this, and the following letter, we report on some successful 1,3-dipolar cycloadditions of nitrile-oxides, -ylides, and -imines, to the 2-ethoxy- (1b) and 2-(ethylthio)-1-azetines (1a and 3).

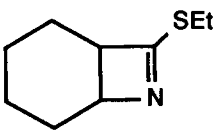
Ethoxy-azetine[6] (1b) was obtained by O-ethylation (using Meerwein's reagent) of 3,3,4,4-tetramethyl-azetidin-2-one.[7] Similarly, S-ethylation of the tetramethyl-, and the cyclohexyl-fused (2), azetidin-2-thiones,[8] prepared in good yield by thionation of the corresponding azetidin-2-ones[7,9] with Lawessons reagent in dry THF, yielded the ethylthio-derivatives[8] (1a) and (3) respectively.



(1) a X = S
b X = O

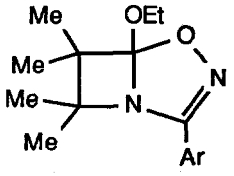


(2)



(3)

Addition of triethylamine to an equimolar solution of aroylhydroximoyl chloride [ArC(Cl)=NOH; Ar = 4-MeOC$_6$H$_4$-, Ph, and 2-NO$_2$C$_6$H$_4$-), prepared in the standard manner by α-chlorination (N-chlorosuccinimide) of the corresponding aldoximes, and 2-ethoxyazetine (1b) in dry benzene resulted in the immediate precipitation of $Et_3N{\cdot}HCl$. T.l.c. ($SiO_2$) examination of the reaction mixture showed complete reaction after ca. 2 hours. The 5-ethoxy-4-oxa-1,3-diazabicyclo[3.2.0]hept-2-enes (4a-c) were readily isolated and purified (flash chromatography on $SiO_2$) without decomposition. Cycloadducts (5 and 6) with the 2-(ethylthio)azetines (1a and 3) were obtained similarly (Table 1).



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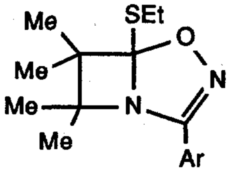

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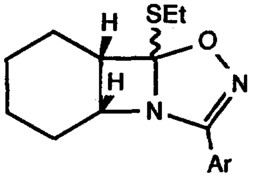


(6)

a) Ar = 4-$MeOC_6H_4$; b) Ar = Ph; c) Ar = 2-$O_2NC_6H_4$.

Table 1

5-Ethoxy- (4a-c) and 5-(ethylthio)- (5a-c) 4-oxa-1,3-diazabicyclo[3.2.0]hept-2-enes and 6-(ethylthio)-5-oxa-2,4-diazatricyclo[5.4.0.0$^{2,6}$]undec-3-enes (6a-c).[8]

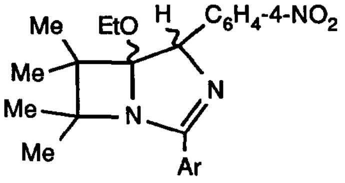
| Adduct | Yield (%) | m.p. (°C) | Adduct | Yield (%) | m.p. (°C) |
|---|---|---|---|---|---|
| 4a | 72 | 109 | 5c | 42 | 91 |
| 4b | 60 | 108 | 6a | 95 | 71 |
| 4c | 34 | 104 | 6b | 54 | semi solid |
| 5a | 80 | 108 | 6c | 43 | semi solid |
| 5b | 62 | 134 | | | |

Tricyclic adducts (6a-c) were isolated as mixtures of diastereoisomers which could be distinguished on t.l.c. and in their 300 MHz p.m.r. spectra. So far, however, all attempts to separate the diastereoisomers by h.p.l.c. have resulted in decomposition of the cycloadducts.

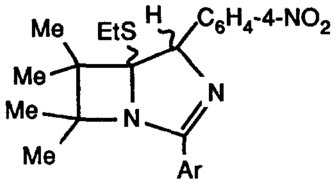
A single-crystal X-ray structure determination on the (ethylthio)-cycloadduct (5a) has confirmed its structure and the expected regiochemistry of the cycloaddition.

The HOMO's for nitrile ylides are of significantly higher energy than those of nitrile oxides.[2a] It is not surprising, therefore, that nitrile ylides fail to react with electron-rich enol ethers,[2a] and, as far as we are aware, there are no examples of addition to imino-ethers.[10] However, we find that nitrile ylides ($4\text{-}NO_2C_6H_4\overset{-}{C}H$-

$\overset{+}{N}\equiv CAr$), generated by dehydrodehalogenation of the corresponding imidoyl chlorides with $Et_3N$ in benzene at room temperature reacted, albeit slowly (12 hours) with azetines (1a, b) to give cycloadducts (7) and (8) (Table 2). Presumably, cycloaddition, as with azirines, is facilitated by the strained nature of the imine bond.



(7)



(8)

a) Ar = Ph; b) Ar = 4-$O_2NC_6H_4$; c) Ar = 4-$MeC_6H_4$

Table 2

5-Ethoxy- (7a-c) and 5-(ethylthio)- (8a-c) 1,3-diazabicyclo[3.2.0]hept-2-enes.[8]

| Adduct | Yield (%) | m.p. (°C) | Adduct | Yield (%) | m.p. (°C) |
|---|---|---|---|---|---|
| 7a | 46 | 167 | 8a | 68 | 149 |
| 7b | 42 | 175 | 8b | 45 | 166 |
| 7c | 53 | 168 | 8c | 61 | 184 |

300 MHz p.m.r. spectra of the products were consistent with (7) and (8), and revealed clearly the diastereotopic character of the $-OCH_2-$ and $-S-CH_2-$ protons. However, a close examination of the high field p.m.r. spectrum of cycloadduct (7a) indicated the presence of only one set of diastereoisomers. An X-ray crystallographic study revealed that the 4-nitrophenyl and -OEt groups adopt a *trans*-configuration. It seems likely that the other cycloadducts are also formed as single '*trans*' diastereoisomeric pairs. This has yet, however, to be confirmed.

Curiously, no 1,3-dipolar cycloadducts were obtained between the azetines and nitrile sulphides, azomethine ylides (generated by thermal ring-opening of aziridines, or by prototropic shifts in anils), nitrones, or aryl azides. In addition, all attempts so far to effect Diels-Alder [4 + 2] cycloadditions with both electron-rich and electron-deficient dienes, have failed. 1,3-Dipolar cycloadditions to nitrile-imines are reported in the following letter.

We thank Roussel Laboratories Ltd., Swindon, for their generosity and a research studentship to (A-B.N.L.), and Dr. Alan Redhouse and Mr. Robin Thompson, Department of Chemistry, University of Salford, for X-ray crystallographic data, details of which will be published elsewhere.

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(Received in UK 10 November 1989)