1,3-DIPOLAR CYCLOADDITIONS OF 2-ETHOXY- AND 2-(ETHYLTHIO)-1-AZETINES WITH NITRILIMINES

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<u>Summary</u>: 1,3-Dipolar cycloadditions of diphenylnitrilimines with 2EtO- and 2EtS-tetramethyl-1-azetines (1a,b) are accompanied by ring-opening and loss of EtXH (X = O or S) to give 1,2,4-triazoles (3), whereas with N-(4-nitrophenyl) nitrilimines the expected cycloadducts and/or ring-opened products are formed.

In the preceding letter, the 1,3-dipolar cycloadditions of 1-azetines (1a,b) and (2) with nitrile oxides and nitrile ylides were described. We now report that 1,3-dipolar cycloadditions of these azetines with nitrilimines are, in some cases, accompanied by unexpected loss of the ethoxy- or ethylthio-substituent and ring-opening of the primary adduct to yield 1,2,4-triazoles.

The reaction of diphenylnitrilimine (Ph \vec{N} - \vec{N} =CPh), generated *in situ* by dehydrohalogenation of the hydrazonyl halide [PhC(X)=NNHPh; X = Cl or Br]¹ with Et₃N in boiling benzene, with ethoxyazetine (1b) was complete (by t.l.c.) after 2 hours. Removal of solvent and Et₃N.HCl and then purification of the solid residue by flash chromatography (SiO₂) furnished a single crystalline product in 57% yield. It was apparent immediately from the ¹H p.m.r. spectrum that this was not the expected 1:1 cycloadduct (4; X = O) since the EtO- resonances were missing and only 3, rather than 4, methyl signals were present. In addition the two one-proton singlets at 4.5 and 4.65 δ were suggestive of a methylene unit (=CH₂), a feature which was confirmed by the ¹³C n.m.r. spectrum. Also in accord was the mass spectrum which indicated M⁺ 303 mass units, i.e. the expected 1:1 adduct (M⁺ 349) minus EtOH.

Addition of diphenylnitrilimine to the (ethylthio) azetine (1a) under similar conditions gave the same cycloadduct (60%). Initially, this common cycloadduct was thought to have a bicyclic structure.² However, single crystal X-ray crystallographic studies revealed that it was in fact the 1,2,4-triazole derivative (3a).³



a) Ar = R = Ph;
b) Ar = 4-NO₂-phenyl, R = Ph;
c) Ar = 4-NO₂-phenyl, R = 4-Cl-phenyl;
d) Ar = R = 4-NO₂ phenyl;
e) Ar = 4-NO₂-phenyl, R = CO₂Me

A mechanistic rationale for this unexpected ring-opened product is outlined in the Scheme. Loss of EtX^{-} from the initial cycloadduct (4) yields a resonance stabilised triazolium species (5 <----> 5a), which by opening of the four-membered ring and loss of a proton, furnishes the aromatic 1,2,4-triazole system (3a).⁴



Interestingly, reaction of the 4-nitrophenyl-nitrilimine $4-NO_2C_6H_4N-N=CR$ (8; R = Ph) with ethoxy-(1b) and with ethyl thio-azetine (1a) gave only unrearranged adducts (6b) and (7b)⁵ in excellent yields (Table). Presumably, replacement of the phenyl group at N-1 of the nitrilimine by 4-nitrophenyl, in which the lone-pair on nitrogen are less available for triazolium ion (5) stabilisation, allows isolation of the primary cycloadducts.⁶

On this basis, and as anticipated, the ethylthio adduct (7b) on heating at 180°C in boiling 1,2dichlorobenzene lost EtSH and underwent quantitative rearrangement to the 1,2,4-triazole (3b).

Whereas 4-nitrophenylnitrilimines (8; $R = 4-ClC_6H_4$, $4-NO_2C_6H_4$, and CO_2M_6) with ethoxy-azetine (1b), gave only normal adducts (6c-e) (Table), mixtures of expected (7c-e) and rearranged (3c-e) adducts were obtained with the (ethylthio) azetine (1a) (Table). These latter results may reflect the greater nucleofugacity of the SEt group over that of OEt.

tetramethyl-5-ethylthio- (7b-e) 1.3.4-triazabicyclo[3.2.0]hept-2-enes.7					
Adduct	Yield	m.p.	Adduct	Yield	m.p.
	(%)	(°C)		(%)	(*C)
3a	57-60	95	6d	57	213
3ь	98	133	6e	43	126
3c	37	oil ^a	75	88	154
3d	39	oil ^a	7c	18	oila
3e	15	oil ^a	7d	21	oila
6b	89	143	7e	34	oila
6с	55	191			

Table 1-Aryl-5-(butenyl)-1,2,4-triazoles (3a-e). 6.6.7.7-tetramethyl-5-ethoxy- (6b-e). and 6.6.7.7-

^aYields estimated from 300 MHz p.m.r. spectra of the mixtures.

Diphenylnitrilimine addition to the bicyclic azetine (2) was also accompanied by loss of EtSH. In addition, the mass spectrum of the product clearly showed (confirmed by elemental analysis) the presence of chlorine (M⁺ 337, 339; 3:1). We are not yet certain of the structure of this chloro-derivative, which is produced in 73% yield as a semi-solid mixture (as yet unseparated) of diastereoisomers. However, the significant downfield proton shift, [from ca. 4.0 δ in the nitrile-oxide cycloadducts of (2), to 4.4 δ in the chloro-product], of one of the 1H complex multiplets of the cyclohexyl ring is consistent with a ring-opened structure such as (9).

Further work is underway to explore the differences in behaviour of the tetramethyl - and cyclohexyl -

derivatives and to extend the scope of these cycloadditions.

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References

- P. Caramella and P. Grünanger in '1,3-Dipolar Cycloaddition Chemistry', ed. A. Padwa, John Wiley and Sons, New York, 1984, Vol. 1, p. 291.
- 2. We thank a referee for prompting us to consider alternative structures.
- Triazole formation is in contrast to the ring-opening and rearrangement to 1,3,5-benzotriazepines, undergone by nitrilimine-2-phenylbenzazete 1,3-dipolar cycloadducts. P.W. Manley, R. Somanathan, D.L.R. Reeves, and R.C. Storr, J. Chem. Soc., Chem. Comm., 1978, 396.
- Aromatisation (by loss of EtOH) of 1,2,4-triazolines to 1,2,4-triazoles has been noted during the related cycloaddition of diphenylnitrilimine to ethyl acetimidate [MeC(OEt)=NH] R. Huisgen, R. Grashey,
 E. Aufderhaar, and R. Kunz, Chem. Ber., 1965, 98, 642.
- 5. Structures (3b) and (7b) were determined unequivocally by single-crystal X-ray crystallography.
- A similar argument may account for the stability of the nitrile oxide-azetine cycloadducts reported in the preceding letter.
- 7. All cycloadducts were characterised satisfactorily by 300 MHz p.m.r. spectroscopy and, in most cases, by elemental analysis.

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