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KETENE-S,S-ACETALS AS 1,3-DIPOLAROPHILES.REACTIVITY TOWARDS ELECTRON-DEFICIENT AZIDES.

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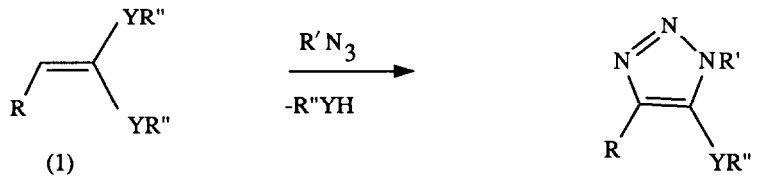
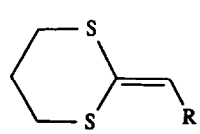
*Summary. The reactivity of a series of ketene-S,S-acetals (**2a-e**) towards p-toluenesulphonyl azide and ethoxycarbonyl azide is determined by the nature of the substituents on both the dipolarophile and the 1,3-dipole. With p-toluenesulphonyl azide rearrangement of the 1,3-dithianyl ring is observed to give (**4**), but with ethoxycarbonyl azide a different pathway is followed leading to β-amino ketene-S,S-acetals (**6**), albeit in low yield.*

Cycloaddition reactions between azides and alkenes have become a powerful tool in heterocyclic synthesis.[1] The initial cycloadducts (Δ^3-1,2,3-triazolines) may rapidly expel nitrogen or, with reactions involving electron-rich dipolarophiles such as ketene-O,O- or N,N-acetals (**1**,Y=O,NR"),may undergo aromatization with loss of R"OH or $R"_2NH$ to give a 1,2,3-triazole as shown below.[2,3]



(1)

Although ketene-S,S-acetals (**1**,Y=S) may also be regarded as electron-rich alkenes, the reactivity of this class of compounds in cycloaddition processes, and towards 1,3-dipoles in particular, is less clearly defined; only very recently the reaction of the simple ketene-S,S-acetal(**2a**) with nitrones and nitrile oxides was reported.[4] Our interest in this aspect of organosulphur chemistry has prompted a study of the reactivity of a series of ketene-S,S-acetals (**2a-e**) towards p-toluenesulphonyl azide (TsN_3) and ethyl azidoformate (EtO_2CN_3) and the results of this investigation are the subject of this communication.

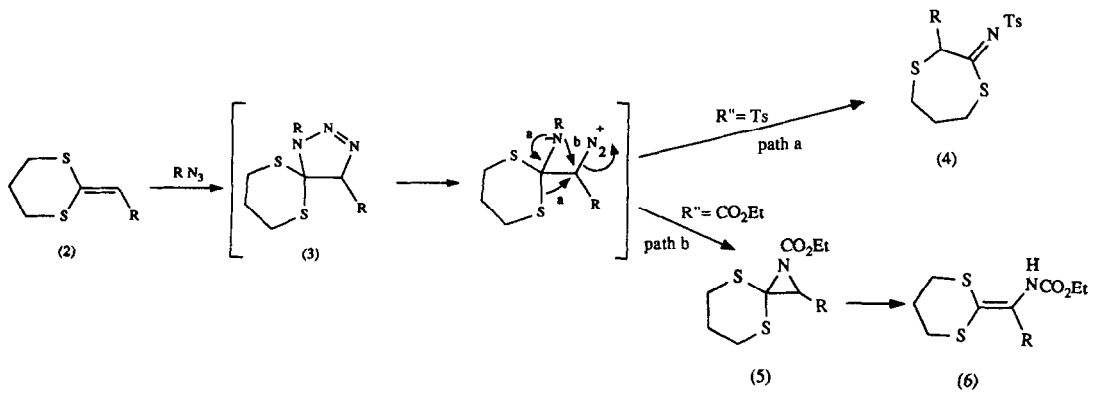


(2a) R= H
(2b) R=Me
(2c) R= Ph
(2d) R= 2-furanyl
(2e) R= CO_2Et

A solution of the ketene-S,S-acetal (**2a-e**), which were all prepared using established procedures[5], and the appropriate azide (TsN_3 or EtO_2CN_3) in cyclohexane was heated at reflux (2-24h) under an atmosphere of nitrogen.The products were isolated by either direct crystallisation from the reaction mixture or following chromatography (Table) and the general pattern of reactivity observed is shown in the Scheme.

TABLE

Ketene-S,S-Acetal (2)	**Reaction with TsN_3 Products, yield**	**Reaction with EtO_2CN_3 Products, yield**
a,R=H	**(4a), 59%**	**(6a), 11%**
b,R=Me	**(4b), 89%**	**(6b), 5%**
c,R=Ph	**(4c), 24%;(7), 18%**	**(6c), 33%**
d,R=2-furanyl	**(8), 33%**	**see text**
e,R=CO_2Et	**no reaction**	**no reaction**

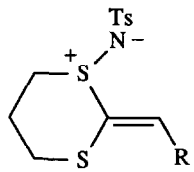


SCHEME

With TsN_3 the major reaction, path (a), involves fragmentation of the putative triazoline cycloadduct (**3**,R'=Ts) followed by loss of nitrogen and migration of sulphur to give the 1,4-dithiepane derivative (**4**); in the case of (**4b**) [m.p.145-145.5°C(methanol)] this assignment has been confirmed by x-ray crystallographic analysis (Figure).[6] Although the ring expansion of 1,3-dithane rings may be triggered by build-up of positive charge on the carbon atom β with respect to sulphur, the N-sulphonyl residue must also play a role in promoting this pathway (see below)[7,8]. Reaction of (**2c**) with TsN_3 gave, in addition to (**4c**) [m.p. 164-165°C(methanol)], the sulphilimine (**7**) [m.p.155-156°C (methanol)] in 18% yield.

In contrast, the reaction of (**2a-c**) with EtO_2CN_3 gave low yields of the β-amino ketene-S,S-acetals (**6**).[9] The formation of these products from triazoline (**3**,R'=CO_2Et) suggests the intermediacy of an unstable aziridine (**5**), [path (b)(Scheme)],with no evidence for a competing migration of sulphur, path(a), being observed.

The reactivity of ketene-S,S-acetals as 1,3-dipolarophiles is also substantially influenced by the nature of any substituents present. The 2-furanyl derivative (**2d**) did not undergo 1,3-dipolar cycloaddition but on prolonged reaction (20h) with TsN_3, the nitrene-derived sulphilimine (**8**)[10] was isolated in 33% yield; reaction of (**2d**) with EtO_2CN_3 produced a complex mixture of products. The presence of the electron-withdrawing ethoxycarbonyl residue in (**2e**) resulted in complete deactivation towards both 1,3- dipolar cycloaddition and sulphilimine formation.



(7) R= Ph
(8) R= 2-furanyl

Since TsN_3 and EtO_2CN_3 are both known to behave, below their decomposition temperatures, as 1,3-dipoles it is puzzling why such a clear-cut separation of the two paths (a) and (b) (Scheme) takes place. These results suggest that it is a relatively subtle difference in the electron-withdrawing nature of the substituent on nitrogen, Ts- or EtO_2C-, that determines the fate of the initial cycloadduct (**3**,R=Ts- or EtO_2C-) leading to (**4**) or (**6**) respectively. Given the low yields and the complex nature of the reaction mixtures usually obtained using EtO_2CN_3, it is difficult to completely exclude the possibility that rearrangement via path (a) does not also take place to a certain extent. With this in mind we are currently studying the effect of solvents and external catalysts in selectively promoting either of these reaction pathways. The intramolecular variant of this type of 1,3-dipolarcycloaddition reaction is also under investigation as an entry to heterocyclic amino acids, such as the polysubstituted prolines.

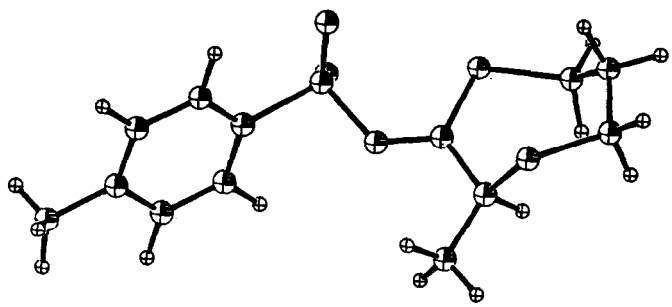


Figure. ORTEP drawing of (4b)

Acknowledgements. We thank Dr.M.McPartlin, The Polytechnic of North London,for performing the x-ray analysis of (**4b**) and SERC and Imperial Chemical Industries PLC for a CASE award (to W.O.M.)

References and Notes.

1. (a) W. Lwowski in "Azides and Nitrenes: Reactivity and Utility" ed. A. Padwa, Academic Press, New York, 1984, ch. 4, p. 205; (b) W.Lwowski in "1,3-Dipolarcycloaddition Chemistry" ed. A.Padwa, Wiley,New York, 1985, ch. 5, p. 559.
2. For a review of the chemistry of Δ^2 -1,2,3-triazolines see P.K.Kadaba, B.Stanovic and M.Tišler, Adv. Heterocycl. Chem.,1984, **37**, 219. Triazolines related to (**3**, R=COOEt) have been isolated from the reaction of ketene-O,O-acetals with $EtOOCN_3$, but these are unstable above 30°C and all efforts to isolate the corresponding N-sulphonyl triazolines have failed (M.L.Graziano and R.Scarpati, J. Heterocycl. Chem., 1976,**13**,205).
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5. E.J.Corey and A.P.Kozikowski, Tetrahedron Lett.,**1975**, 925; B.-Th.Gröbel and D. Seebach, Synthesis, **1977**,391; R.K.Dieter, J. Org. Chem., **1981**,46,5031.
6. *Crystal data for* $C_{13}H_{17}O_2S_3$: Monoclinic, space group $P2_1/c$. a=12.651(3), b=6.363(2), c=20.000(4)Å, β= 106.86(2), U=1540.8Å^3, Z=4, Mo-Kα radiation, R=0.0470 and Rw=0.0459 for 2431 reflections recorded of which 1458 were observed with I/α(I)>2.0. The structure was solved using direct methods . In the final stages of full matrix refinement, all non-hydrogens were assigned anisotropic thermal parameters. Hydrogen atoms were included at calculated positions. Atomic co-ordinates, bond lengths and angles , and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
7. For the ring expansion of 1,3-dithianes see B.M.Trost, K.Hiroi and L.N. Jungheim, J. Org. Chem.,1980,**45**,1839; K.Hiroi, S.Sato, and K.Matsuo, Chem. Pharm. Bull.,1980,**28**,558 and references therein.
8. Alkyl group migrations have been observed in the decomposition of Δ^2-triazolines. See J.E.McMurray, J.Am. Chem.Soc., 1969,**91**,3676; J.E.McMurray and A.P.Coppolino, J.Org. Chem.,1973,**38**,2821;R.A.Wohl, J.Org.Chem., 1973,**38**,3862; Y.Sato, H.Kojima and H.Shirai, J. Org. Chem., 1976,**41**,3325; L.Fitjer, Angew.Chem.Int.Ed.Engl.,1976,**15**,763; S.P.McManus, M.Ortiz and R.A.Abramovitch, J.Org. Chem.,1981,**46**,336.
9. Although we have not been able to prove that (**3**, R= CO_2Et) is involved in the formation of (**6**), the regiochemistry shown in the Scheme is consistent with that reported for ketene-O,O-acetals.[2] Alternative syntheses of (**6a**) and (**6b**) have been developed starting from glycine and alanine respectively and details will be published in due course. The phenyl derivative (**6c**) was prepared by reaction of α-(1,3-dithian-2-ylidene)benzylamine[P.C.B. Page, M.B.Van Niel and D.Westwood, J.Chem.Soc.,Perkin Trans. 1,1988,296] with EtOOCCl.
10. Sulphilimines(**7**) and (**8**) are also available by reaction of the appropriate ketene-S,S-acetal (**2**) with chloramine-T. Using this reagent, sulphimines were also prepared from (**2a**) and(**2b**), although these were not detected in the reaction of (**2a**) or (**2b**) with TsN_3; (**2e**) was unreactive towards chloramine-T. Although (**7**) and (**8**) are formally nitrene-derived products, their formation by rearrangement of (**3**) cannot be excluded at this stage.

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