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INTRAMOLECULAR CYCLOADDITION REACTIONS INVOLVING NITRILE SULPHIDES

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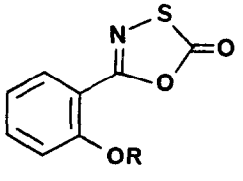
Summary: *ortho*-(Phenylpropioloxy)benzonitrile sulphide, generated *in situ* by thermal decarboxylation of the oxathiazolone (**1**), undergoes intramolecular 1,3-dipolar cycloaddition forming the chromenoisothiazole (**4a**); *ortho*-cinnamoylbenzonitrile sulphides also yield (**4**), together with nitrile, chromenoquinoline and aminochromene by-products.

The utility of 1,3-dipolar cycloaddition reactions for the preparation of 5-membered heterocycles has been appreciated[1] for more than 20 years. Recently the synthetic scope has been extended to include polycyclic systems formed *via* intramolecular cycloadditions.[2] Examples have been described for most 1,3-dipoles including the nitrilium betaines: nitrile ylides, nitrile imines, and nitrile oxides. We now report the first cases involving nitrile sulphides.

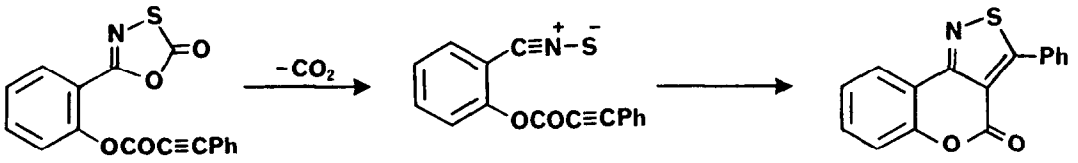
To establish the feasibility of such a process we examined the thermolysis of the *ortho*-(acyloxyphenyl)oxathiazolones, (**1**) and (**2**), which incorporate both an established source[3] of nitrile sulphides - the oxathiazolone - and an activated dipolarophile.



(**1**) R = COC≡CPh
(**2**) R = E-COCH=CHAr
(**3**) R = H

The acetylenic oxathiazolone (**1**) was prepared from salicylamide by treatment with chlorocarbonylsulphenyl chloride to give 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one (**3**), which was then acylated with phenylpropiolyl chloride. A solution of (**1**) in xylene was heated under reflux for 16 h. Removal of the solvent and chromatography of the residue (silica/hexane-diethyl ether) afforded 4-oxo-3-phenyl-4*H*-chromeno[4,3-*c*]isothiazole (**4a**)[4] (70%), consistent with initial decarboxylation of the oxathiazolone followed by intramolecular 1,3-dipolar cycloaddition of the resulting nitrile sulphide to the adjacent alkyne

(Scheme 1). The analogous intermolecular reaction between benzonitrile sulphide and ethyl phenylpropiolate is reported[3] to give a regio isomeric mixture of isothiazoles. In the intramolecular reaction steric constraints ensure that only one isomer is formed. Normally cycloadducts are accompanied by nitriles as by-products, often in substantial quantities, resulting from a competing fragmentation process.[5] In the present case, however, only a trace (<1%) of *o*-cyanophenyl phenylpropiolate could be detected by hplc.



(1) (4a)

Scheme 1

Having established that intramolecular cycloaddition could take place to an activated alkyne, the corresponding alkenes were studied. The olefinic oxathiazolones (**2**) were prepared, either from (**3**) and the appropriate cinnamoyl chloride, or by reaction of the 2-cinnamoyloxybenzamide with chlorocarbonylsulphenyl chloride. Thermolysis of (**2b**) in xylene (18 h) yielded a mixture of products: *o*-cyanophenyl *p*-methylcinnamate(**5b**) (35%), 4-oxo-3-(*p*-tolyl)-4*H*-chromeno[4,3-*c*]isothiazole (**4b**) (30%), 10-methyl-6-oxo-6*H*-chromeno-[4,3-*b*]quinoline (**6b**) (3%)[6], and 4-amino-3-(*p*-methylbenzyl)-2-oxochromene (**7b**) (15%)[7], which were separated by chromatography and crystallisation. The *para*-substituted cinnamate esters (**2a**), (**2c**) and (**2d**) each yielded a similar mixture of products (Table and Scheme 2).

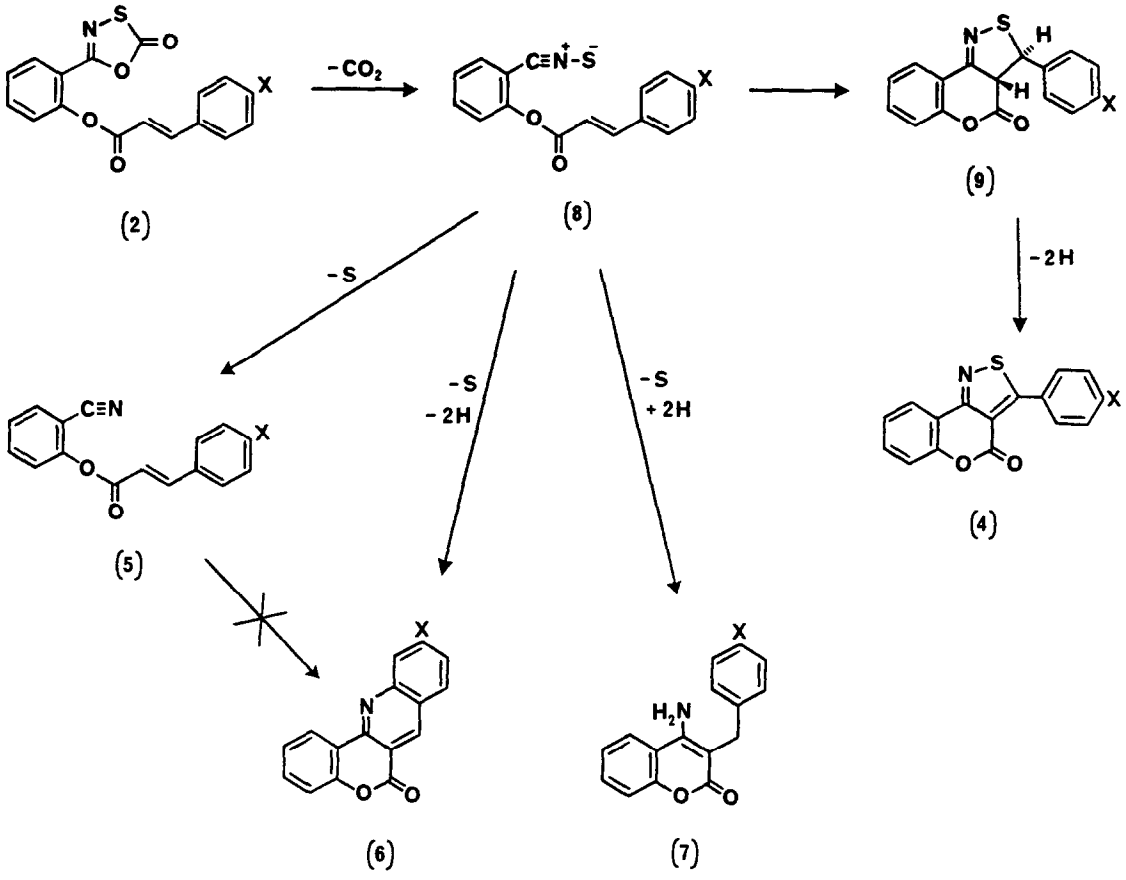
Table Products from the thermolysis of (2)

Reactant	Yields(%) of Products (4)[a]	(5)[a]	(6)[a]	(7)[b]
(**2a**)	14	27	13	-[c]
(**2b**)	30	35	3	15
(**2c**)	21	33	8	28
(**2d**)	14	35	14	12

[a] Yields determined by hplc (silica/hexane-diethyl ether or dioxan)

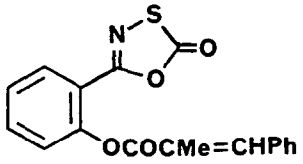
[b] Isolated yield

[c] Not determined

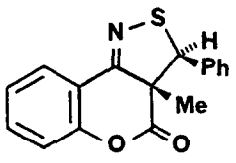


Scheme 2 (2),(4)-(9) a X=H; b, X=Me; c, X=Cl; d X=OMe

The formation of (5) and (4) can readily be explained in terms of competing fragmentation and cycloaddition of the intermediate nitrile sulphide (8), followed by rapid dehydrogenation of first-formed Δ^2-isothiazoline adduct (9). Isolation of (4) rather than (9) is not unexpected. Facile oxidation of Δ^2-isothiazolines has been observed previously.[8] To confirm that isothiazolines are the first-formed products the α-methylcinnamate derivative (10) was prepared and its thermolysis studied. In this case dehydrogenatioan is blocked and the isolated products are the methylisothiazoline (11) (5%)[9] and *o*-cyanophenyl α-methylcinnamate (81%). The modes of formation of the amino compound and the quinoline are not known. The latter is formally a 2 + 4-cycloadduct (with dehydrogenation) between the nitrile and the diene comprising the exocyclic and one of the endocyclic double bonds of the styrene group. However, failure to detect (6a) on heating a solution of *o*-cyanophenyl cinnamate (5a) in xylene for up to 6 weeks under reflux precludes its formation from this source. The mechanisms of these reactions are currently under investigation.



(10)



(11)

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References and Footnotes

1. R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **2**, 565.
2. A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123.
3. R.K. Howe, T.A. Gruner, L.G. Carter, L.L. Black and J.E. Franz, *J. Org. Chem.*, 1978, **43**, 3736.
4. M.p. 166.5-168.5°C. Found: C, 68.8; H, 3.2; N, 4.9. $C_{16}H_9NO_2S$ requires C, 68.8; H, 3.2; N, 5.0%; ν_{max} 1730 cm $^{-1}$ (C=O); δ_C($CDCl_3$, 50 MHz) 177.9 (C-3), 162.4 (C-9b), 156.2 (C-4), 152.3 (C-5a), 131.8, 124.6, 124.0, 116.9 (CH-6,7,8,9), 130.8, 129.2, 128.6 (5 PhCH), 128.0 (PhC), 117.1 (C-3b), and 116.7 (C-9a); *m/z* 279 (M^+).
5. R.K. Howe and J.E. Franz, *J. Org. Chem.*, 1974, **39**, 962.
6. M.p. 205-207°C. Found: C, 78.0; H, 4.3; N, 5.3. $C_{17}H_{11}NO_2$ requires C, 78.2; H, 4.2; N, 5.4%; δ_C ($CDCl_3$, 50 MHz) 161.3, 152.7, 151.3, 149.6, 144.4, 125.5, 119.8, 115.0 (ArC), 140.4, 132.1, 129.7, 128.9, 128.4, 125.1, 124.7, 117.2 (ArCH), and 22.2 (CH_3); *m/z* 261 (M^+).
7. M.p. 203-206°C. Found: C, 76.8. H, 5.8; N, 5.2. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%; ν_{max} 3475, 3350, 3240 (NH_2), 1670, 1640 (C=O); δ_C (DMSO-d_6, 50 MHz) 162.2, 152.3, 150.7, 137.1, 134.5, 114.8, 95.6 (ArC) 131.2, 128.6, 127.9, 123.2, 123.0, 116.5 (ArCH), 29.1 (CH_2), and 20.5 (CH_3); *m/z* 265 (M^+).
8. R.K. Howe and J.E. Franz, *J Org. Chem.*, 1978, **43**, 3742; R.M. Paton, J.F. Ross and J. Crosby, *J. Chem. Soc., Chem. Commun.*, 1980, 1194.
9. M.p. 149-151°C. Found: C, 69.0; H, 4.2; N, 4.7. $C_{17}H_{13}NO_2S$ requires C, 69.1; H, 4.4; N, 4.7%; δ_H (DMSO-d_6, 200 MHz) 7.2-7.9 (m, 9H, ArH), 5.93 (s, 1H, isothiazoline ring CH), and 1.15 (s, 3H, CH_3); δ_C (DMSO-d_6, 50 MHz) 168.3 (C-4), 161.2 (C-9b), 151.8 (C-5A), 133.0, 125.5, 125.1, 116.9 (CH-6,7,8,9), 132.2 (PhC), 130.4, 128.5, 128.3 (PhCH), 117.2 (C-9a), 61.1 (C-3a), 59.7 (CH-3), and 17.6 (CH_3); *m/z* 295 (M^+).

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