Nitrile Sulphides. Part 10.[1,2] Intramolecular 1,3-Dipolar Cycloadditions

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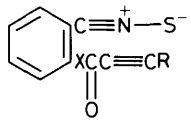
Intramolecular 1,3-dipolar cycloadditions involving acetylenic and olefinic esters of *o*-hydroxybenzonitrile sulphide have been examined. The nitrile sulphides were generated by thermal decarboxylation of the corresponding 1,3,4-oxathiazol-2-one. *o*-Phenylpropiolyloxy and -amido derivatives (**1a**) and (**2a**) afforded chromeno[4,3-*c*]isothiazolone (**7a**) (70%) and isothiazolo[4,3-*c*]quinolinone (**9a**) (81%) respectively. Four products were formed on thermolysis of cinnamate esters (**10**): *o*-cyanophenyl cinnamates resulting from desulphuration of the nitrile sulphide; chromenoisothiazolones (**7**) from intramolecular cycloaddition followed by dehydrogenation of the resulting 4,5-dihydroisothiazole; chromeno[4,3-*b*]quinolinones (**14**); and 4-amino-3-benzylchromenones (**15**). The last two compounds are believed to be formed by a pathway involving the 2,5- dihydroisothiazole tautomer (**17**), extrusion of sulphur, followed by cyclisation or hydrogenation (Scheme 2). α- and β-Methylcinnamate esters (**19**) and (**20**) afforded, in addition to nitrile by-products, dihydroisothiazole (**21**) and 4-amino-3-(α-styryl)chromenone (**23**) respectively.

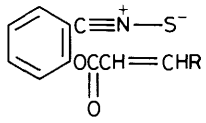
Intramolecular cycloadditions have been reported for most classes of 1,3-dipoles and they find widespread application in the preparation of polycyclic heterocycles.[3] Particular attention has been devoted to nitrile oxides ($RC{\equiv}N^{+}{-}O^{-}$) in view of their utility in natural product synthesis,[4] and to a lesser extent to two other nitrilium betaines: the nitrile ylides and imines ($RC{\equiv}N^{+}{-}X^{-}$; X = CR_2, NR). In this paper we describe the first cases involving nitrile sulphides ($RC{\equiv}N^{+}{-}S^{-}$). Although these have been a rather neglected class of 1,3-dipoles they are proving[5,6] to be well suited for the synthesis of 5-membered heterocycles incorporating the C=N–S unit, most of which are accessible only with difficulty by other means.

Results and Discussion

The highest yielding nitrile sulphide cycloaddition reactions are those involving alkynes and alkenes activated by electron-withdrawing groups. To test the feasibility of the intramolecular process we therefore selected as test cases *ortho*-substituted benzonitrile sulphides (**1**)—(**3**) which incorporate an activated dipolarophile in close proximity to the 1,3-dipole.

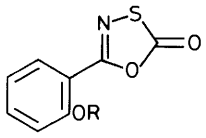


(**1**) X = O
(**2**) X = NH

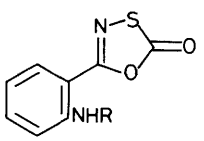


(**3**)

Generation of the Nitrile Sulphides.—Nitrile sulphides are short-lived species prone to rapid fragmentation to sulphur and the corresponding nitrile, and they must, therefore, be generated in the presence of the dipolarophile. The most commonly used sources, and the ones chosen for the present work, are 1,3,4-oxathiazol-2-ones[6] which readily decarboxylate at 100—150 °C. We have previously shown[5] that the *o*-acetoxyphenyl-oxathiazolone (**4a**) can be prepared from salicylamide by two routes either by initial *O*-acetylation followed by treatment with chlorocarbonylsulphenyl chloride, or better, in view of the tendency of *O*-acylsalicylamides to rearrange to their *N*-acyl isomers, by acetylation of the *o*-hydroxyphenyl analogue (**4b**),



(**4**)

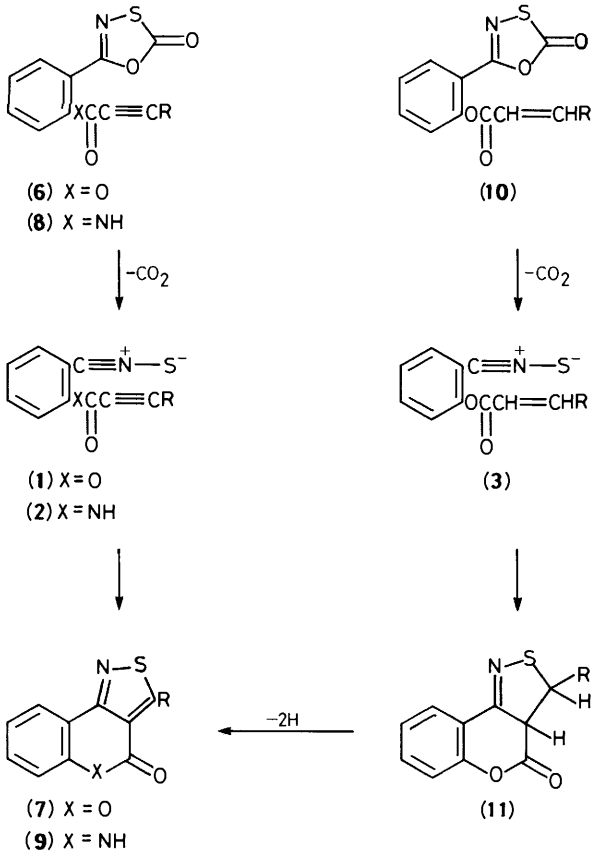


(**5**)

a; R = Ac
b; R = H
c; R = 2-furoyl
d; R = 3-furoyl

which is itself readily prepared in high yield from salicylamide. The latter approach was found to be the more satisfactory in the present work, particularly for derivatives which are liable to polymerise, but both methods were employed. In contrast the corresponding *o*-anilino-oxathiazolone (**5b**) is as yet unknown [anthranilamide affords[5] quinazolinedione rather than (**5b**) on treatment with ClCOSCl] and *ortho*-amido derivatives must be prepared from the appropriate amidobenzamide. Using this route the *o*-(phenylpropiolamido)phenyloxathiazolone (**8a**) was obtained (36% yield) from *o*-(phenylpropiolamido)benzamide.

Cyclisation of o-(*Arylpropiolyloxy*)*benzonitrile Sulphide.*—A solution of the oxathiazolone (**6a**) in xylene was heated under reflux until h.p.l.c. analysis indicated that all the starting material had been consumed (after *ca.* 16 h). Removal of the solvent and chromatography of the residue afforded in 70% yield a white crystalline solid, which was identified from its analytical and spectroscopic properties as 3-phenylchromeno-[4,3-*c*]isothiazol-4-one (**7a**). Traces of *o*-cyanophenyl phenylpropiolate (< 1%), the expected by-product resulting from the competing fragmentation of the nitrile sulphide, were also detected in the reaction mixture by h.p.l.c. Formation of compound (**7a**) is entirely consistent with the reaction pathway illustrated in Scheme 1 involving initial decarboxylation of the oxathiazolone followed by intramolecular 1,3-dipolar cycloaddition of the transient nitrile sulphide (**1a**) to the adjacent alkyne. The *p*-chlorophenyl analogue (**6b**) reacted similarly, albeit in lower yield. The structures of the products were deduced from their analytical and spectral properties. Their ^{13}C n.m.r. spectra (Table 1) show characteristic absorptions for the



Scheme 1.

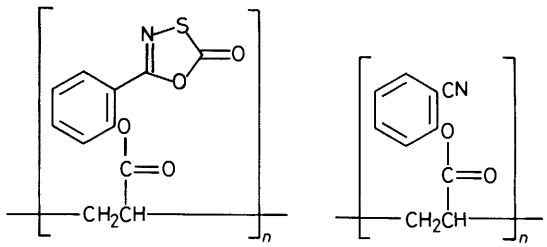
carbons of the heterocyclic rings comparable with those previously reported[5] for the parent compound (**7c**), its 3-alkoxycarbonyl derivatives (**7d, e**), and several other substituted analogues, *vide infra*. The δ_C-values for C-3, and to a lesser extent C-3a and C-4, show expected substituent-dependence; the other peaks are little affected. There is also a distinctive high frequency doublet of doublets in the proton n.m.r. (δ_H 8.3, $J_{9,8}$ 8, $J_{9,7}$ 2 Hz) attributable to 9-H which is proximate to the nitrogen of the isothiazole.

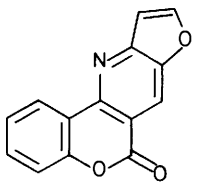
An intermolecular analogue of this reaction has been reported by Howe *et al.*[6] who generated *m*-trifluoromethylbenzonitrile sulphide in the presence of ethyl phenylpropiolate. A regioisomeric mixture of 4- and 5-phenylisothiazole-5- and -4-carboxylates was formed. In the intramolecular reactions described here the isothiazole-5-carboxylate is precluded for steric reasons.

Cyclisation of o-(*Arylpropiolamido*)*benzonitrile Sulphide.*—Thermolysis of oxathiazolone (**8a**) in xylene under reflux for 23 h afforded 3-phenylisothiazolo[4,3-*c*]quinolin-4(5*H*)-one (**9a**) (81%) presumably *via* the nitrile sulphide (**2a**). That the product is the expected quinolinone tautomer, as opposed to a quinolin-2-ol, is evident from i.r. absorption at 3 130 (NH) and 1 675 cm^{-1} (C=O), and from its ^{13}C n.m.r. chemical shifts (Table 1). Compound (**9a**) is only the second example of an isothiazol[4,3-*c*]quinoline, the previous case being the parent heterocycle (**9c**) which was also prepared by a route involving a nitrile sulphide.[5]

Cyclisation of Acrylate, Fumarate, and Cinnamate Esters of 2-*Hydroxybenzonitrile Sulphide.*—In order to investigate intramolecular cycloadditions involving nitrile sulphides and olefinic dipolarophiles a series of acrylate esters of phenolic oxathiazolone (**4b**) were prepared.

Thermal decarboxylation of unsubstituted acrylate derivative (**10c**) afforded the chromenoisothiazolone (**7c**) (24%), which is formally the intramolecular adduct, not of the olefinic nitrile sulphide (**3c**), but of the corresponding propiolate ester (**1c**). The product was identical with that previously prepared[5] by hydrolysis and decarboxylation of the methoxycarbonyl compound (**7d**). It presumably results from rapid dehydrogenation of the 2-isothiazoline (4,5-dihydroisothiazole) (**11c**), the expected cycloadduct of nitrile sulphide (**3c**) as outlined in Scheme 1. Ready oxidation of compound (**11c**) is not unexpected as it is known that simple isothiazolines can be dehydrogenated using quinones,[7] hypochlorite,[8] or by heating in the presence of sulphur and/or oxygen.[8] In the present case formation of the more conjugated chromenoisothiazolone ring system is expected to facilitate the process. The comparatively low yield of product and the failure to isolate *o*-cyanophenyl acrylate, the expected nitrile sulphide-derived by-product, can be attributed to facile polymerisation of both the oxathiazolone precursor and the nitrile. This hypothesis is supported by i.r. detection (2 330 cm^{-1}) of nitriles in the polar 'polymer' residues. Polymeric oxathiazolones and nitriles similar to (**12**) and (**13**) (and their copolymers with styrene and methyl methacrylate) have been prepared and their reactions studied.[9] Under the dilute conditions used there was no indication of products resulting from intermolecular cycloaddition between nitrile sulphide and acrylate moieties.

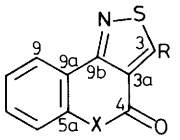




The ethyl fumarate ester (**3e**) behaved similarly. Thermolysis of the precursor oxathiazolone (**10e**) afforded, in modest yield (28%), the isothiazolecarboxylate (**7e**). This compound has previously been synthesised directly from the phenolic oxathiazolone (**4b**) and diethyl fumarate.[5]

Thermal decarboxylation of the cinnamate esters (**10a, b, f, g**) afforded, in addition to sulphur, a mixture of four products: *o*-cyanophenyl cinnamates, 3-arylchromenoisothiazolones (**7**) [identical with those formed from the acetylenic nitrile sulphides (**1**)], chromeno[4,3-*b*]quinolin-6-ones (**14**), and 4-amino-3-benzylchromenones (**15**). Their yields are presented in Table 2. The 3-(2-furyl)acrylate ester (**10h**) afforded a similar array of products; in this case the furopyridine (**16**) is formed rather than a quinoline. In the case of the unsubstituted

Table 1. Selected n.m.r. data[a] for chromenoisothiazolones (**7**) and isothiazoloquinolinones (**9**)



Compd.	X	R	δ_H[b] 9-H	δ_C C-3	C-3a	C-4	C-5a	C-9a	C-9b
(**7a**)	O	C_6H_5	8.27	177.9	117.1	156.2	152.3	116.9	162.4
(**7b**)	O	C_6H_4Cl-*p*	8.30	176.6	117.3	156.4	152.6	117.2	162.8
(**7c**)[c]	O	H	8.26	156.8	123.1	156.2	152.5	116.7	161.2
(**7d**)[c]	O	CO_2Me	8.18	164.0	120.8	154.0	152.5	116.4	162.2
(**7e**)[c]	O	CO_2Et	*d*	164.3	120.4	153.8	152.2	116.1	161.9
(**7f**)	O	C_6H_4OMe-*p*	8.25	178.1	117.4	156.6	152.5	116.1	162.6
(**7g**)	O	C_6H_4Me-*p*	8.25	178.2	117.3	156.3	152.4	116.5	162.5
(**7h**)	O	2-furyl	8.26	164.4	114.0	162.3	152.5	117.1	162.3
(**7i**)	O	mesityl	8.33	176.9	119.6	155.5	152.6	117.3	161.9
(**7j**)	O	$C_6H_3Cl_2$-*o,o*	8.33	170.1	120.8	155.3	152.8	117.3	161.7
(**9a**)	NH	C_6H_5	8.29	173.9	121.6	157.6	137.9	116.2	162.9
(**9c**)[c]	NH	H	8.23	155.2	127.9	157.7	138.1	116.1	161.5

[a] Recorded in $CDCl_3$ [(**9a, c**) in CD_3SOCD_3], ^1H spectra at 80, 200, or 360 MHz, ^{13}C spectra at 20 or 50 MHz; full details published in ref. 13. [b] Doublet of doublets, *J* 2 and 8 Hz. [c] Ref. 5. [d] Not determined.

Table 2. Thermolysis of cinnamate esters (**10a, b, f, g**); product yields

Compd.	R	Yields (%) Nitrile[a]	(**7**)[a]	(**14**)[a]	(**15**)[b]
(**10a**)	Ph	27	14	13	—
(**10b**)	C_6H_4Cl-*p*	33	21	8	28
(**10f**)	C_6H_4OMe-*p*	35	14	14	12
(**10g**)	C_6H_4Me-*p*	34	30	3	25

[a] Determined by h.p.l.c. [b] Isolated.

cinnamate ester (**10a**), compound (**15a**) was not isolated but an additional white solid was precipitated from the refluxing reaction mixture. The likely identity of this compound is discussed later. The fused quinoline (**14a**) was characterised by comparison of its spectroscopic properties and m.p. with those of an authentic sample synthesised from 4-hydroxychromen-2-one, aniline, and paraformaldehyde by an established literature procedure.[10] The 4-aminochromenones, which crystallised from the reaction mixture on cooling, were identified from their analytical and spectroscopic properties. Thus for the *p*-methoxyphenyl derivative (**15f**), i.r. spectroscopy showed the presence of the NH_2 group ($\nu_{max.}$ 3 470, 3 340, and 3 230 cm^{-1}) and an amide-like carbonyl (1 640 cm^{-1}). Its ^1H n.m.r. spectrum contained, in addition to aromatic absorptions, peaks attributable to NH_2 (δ 7.05) and a benzylic CH_2 (δ 3.78). ^{13}C N.m.r. spectroscopy again proved valuable in characterising the chromenone framework (Table 3). Authentic samples of the nitrile by-products were prepared by acylation of *o*-cyanophenol.

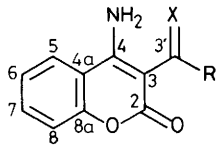
The unexpected formation of the amines and quinolines prompted an investigation of the reaction pathway. Two of the four products are readily explained (Scheme 2). The *o*-cyanophenyl cinnamates are anticipated by-products resulting from fragmentation of the nitrile sulphides (**3**), and the isothiazoles (**7**) presumably result from dehydrogenation of an initial isothiazoline intramolecular adduct (**11**) as described earlier for the acrylate analogue. The quinolines (**14**) are formally dehydrogenated intramolecular hetero-Diels–Alder adducts of the *o*-cyanophenyl cinnamates, the components being the nitrile and the diene comprising the exocyclic and one of the endocyclic double bonds of the styryl moiety. The possibility that they are formed by this route was excluded by an experiment in which *o*-cyanophenyl cinnamate itself was heated under similar conditions. After 6 weeks under reflux in xylene no trace of quinoline (**14a**) could be detected. The involvement of the nitrile sulphide function as an activated nitrilic dipolarophile was also considered. To test this hypothesis 2- and 3-furoate esters (**4c**) and (**4d**) which incoporate adjacent activated dienes were prepared and their thermal decarboxylation examined. However, the only identifiable products were *o*-cyanophenyl 2- and 3-furoates (79% and 92% respectively) resulting from decompositon of the nitrile sulphides.

The proposed mechanism accounting for all the isolated products is presented in Scheme 2. Decarboxylation of the oxathiazolone (**10**) affords the nitrile sulphide (**3**), which either fragments to the corresponding nitrile or, as earlier indicated, undergoes intramolecular cycloaddition yielding the 2-isothiazoline (**11**) and hence isothiazole (**7**) by oxidation. The remaining two products may result from rearrangement of the 2-isothiazoline to a 3-isothiazoline (2,5-dihydroisothiazole) (**17**), and subsequent extrusion of sulphur to form an intermediate, perhaps diradical (**18**), capable of both hydrogenation to the amine and oxidative cyclisation to the quinoline.

Evidence for the formation of 2-isothiazolines as the initial cycloadducts was provided by experiments involving thermolysis of α- and β-methylcinnamate esters (**19**) and (**20**). The α-methyl isomer (**19**) yielded two products only: *o*-cyanophenyl α-methylcinnamate (81%) and the methylisothiazoline adduct (**21**) (5%). The presence of the α-methyl group prevents both dehydrogenation of the isothiazoline and tautomerism; subsequent formation of aminochromenones and cyclised quinolines is also precluded. Compound (**21**) was readily identified from its n.m.r. spectra which show characteristic peaks at δ_H 5.93 (3-H) and 1.15 p.p.m. (Me), and at δ_C 61.1 (C-3a), 59.7 (C-3), and 17.6 p.p.m. (Me).

The β-methyl compound (**20**) also afforded two products: *o*-cyanophenyl β-methylcinnamate (85%) and a second compound (15%), which was *not* the anticipated 2-isothiazoline (**22**) but an

Table 3. Selected n.m.r. data[a] for 4-amino-2-oxochromenes



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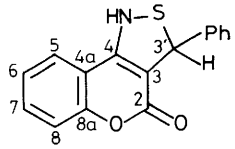


(17a)

Compd.	X	R	δ_H X-H	δ_H 5-H[b]	δ_C C-2	C-3	C-4	C-4a	C-5, 6, 7, 8				C-8a	C-3′
(15b)	H_2	C_5H_4Cl-*p*	3.81	8.08	162.1	94.8	152.2	114.7	131.3	123.2	123.0	116.4	150.9	28.9
(15f)	H_2	C_6H_4OMe-*p*	3.76	8.06	162.2	95.9	152.2	114.8	131.2	123.2	122.9	116.4	150.5	28.6
(15g)	H_2	C_6H_4Me-*p*	3.78	8.06	162.2	95.6	152.3	114.8	131.3	123.2	123.0	116.5	150.7	29.1
(15h)	H_2	2-furyl	3.83	8.06	161.7	92.1	152.3	114.8	131.4	123.2	123.0	116.5	151.1	23.2
(15i)	H_2	mesityl	4.03	—	163.0	97.2	152.5	114.8	130.9	123.3	120.2	117.2	149.5	26.6
(23)	CH_2	C_6H_5	6.00 5.39	7.66	161.2	98.8	152.4	113.5	131.2	123.0	121.9	116.5	150.6	140.0
(17a)			5.89[c]	8.07	161.0	95.1	152.3	114.6	131.8	123.4	123.3	116.5	151.1	53.2

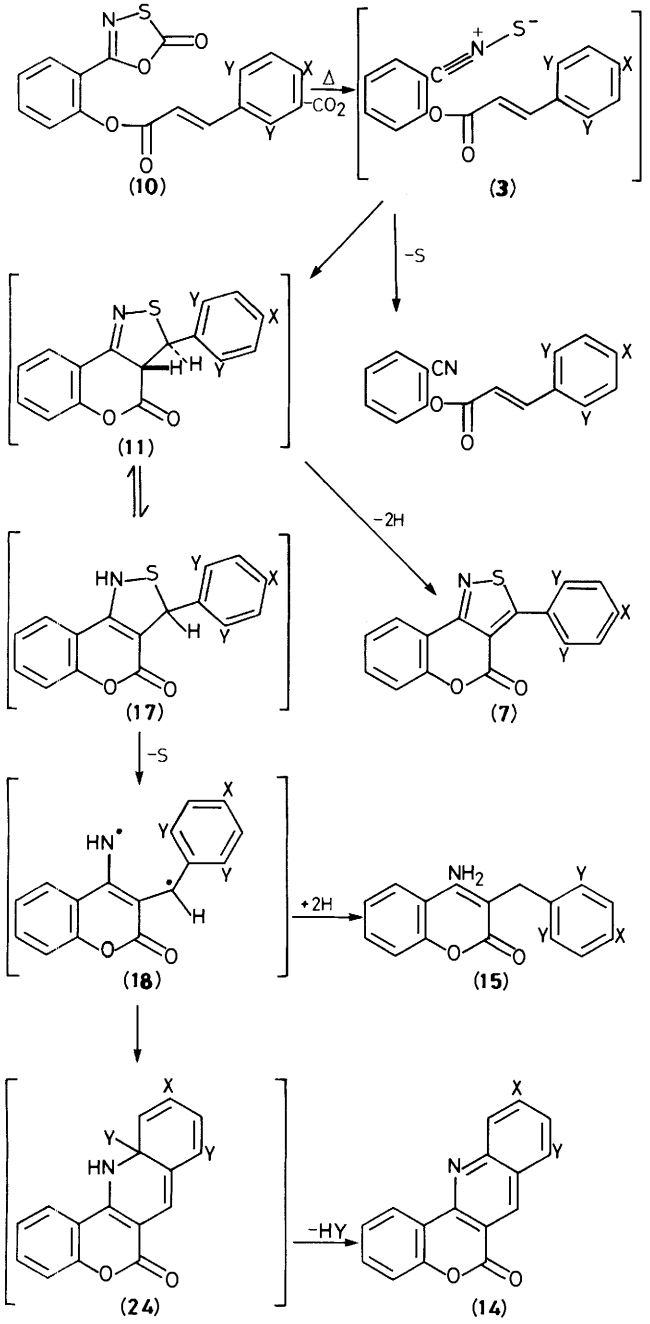
[a] Recorded in CD_3SOCD_3 [(**17a**), (**23**) in $CDCl_3$], ^1H spectra at 80, 200, and 360 MHz, ^{13}C spectra at 50 MHz; full details published in ref. 13. [b] Doublet of doublets, *J* 8 and 2 Hz. [c] 3′-H.

amine which was assigned structure (**23**) on the basis of its analytical and spectroscopic data. The i.r. spectrum [$\nu_{max.}$ 3 430, 3 340, 3 210 (NH_2), and 1 665 cm^{-1} (C=O)] and ^{13}C n.m.r. spectrum (Table 3) clearly demonstrated that it contained both phenyl and aminochromenones moieties. Signals for the remaining carbons (δ_C 140.0 and 118.2 p.p.m.), taken together with ^1H n.m.r. data, indicated a 1,1-disubstituted ethene link between the above units; the methylene protons (δ_H 6.00 and 5.39 p.p.m.) show a small mutual coupling to each other and appear as fine doublets (*J* 1.2 Hz). The n.m.r. data for compound (**23**) is compared with those for related 4-aminochromen-2-ones in Table 3. Further support for structure (**23**) was provided by n.O.e. experiments (Figure). Selective irradiation of the relevant protons established the spatial proximity of the methylene protons to each other, of the pendant phenyl *ortho* protons (H_o) to one methylene proton (H_b), and of the amino protons to the adjacent 5-H of the fused benzo ring (thereby confirming the assignment of this distinctive high frequency doublet of doublets). Neither H_o nor the methylene protons (H_a, H_b) showed detectable interaction with the amino protons suggesting that the styryl until is twisted away from the plane of the chromene.

The proposed mechanism (Scheme 3) is similar to that postulated for the desulphuration of 1-alkyl-3-arylbenz[*c*]isothiazolium tetrafluoroborates by primary amines[11] and the extrusion of selenium from *c*-fused isoselenazoles by carbanions.[12] The failure to isolate the isothiazoline (**22**) from the β-methylcinnamate ester and the formation of olefinic amine (**23**) provides support for the proposed tautomeric pathway. Unlike the α-methylcinnamate-derived methylisothiazoline (**21**), which has position 3a blocked, the 3-methylisothiazoline (**22**) does possess the hydrogen at C-3a necessary for tautomerism to take place. It also suggests that the desulphuration pathway illustrated in Scheme 3, which is only possible with a hydrogen-bearing substituent at C-3 (the 5-position of the 3-isothiazoline ring), is more facile than that *via* the diradical-type intermediate.

Further supporting evidence was obtained by the use of blocking groups affecting the later stages of the reaction pathway. To this end *o*-disubstituted cinnamates (**10i**) and (**10j**) were prepared and their thermolyses studied. The 2,4,6-trimethylcinnamate (**10i**) afforded the chromenoisothiazolone (**7i**) (33%) and the aminochromenone (**15i**) (24%) in addition to the expected nitrile by-product (34%). The *o*-methyl groups apparently inhibit the radical cyclisation step leading to the quinoline. No products derived from the dihydroquinoline (**24i**) were detected. In contrast, the 2,6-dichlorocinnamate derivative (**10j**) yielded nitrile (7%), the isothiazole (**7j**) (31%), and 8-chloro-6*H*-chromeno[4,3-*b*]quinolin-6-one (**14j**) (28%). In this case ring closure with loss of HCl occurs in preference to dehydrogenation.

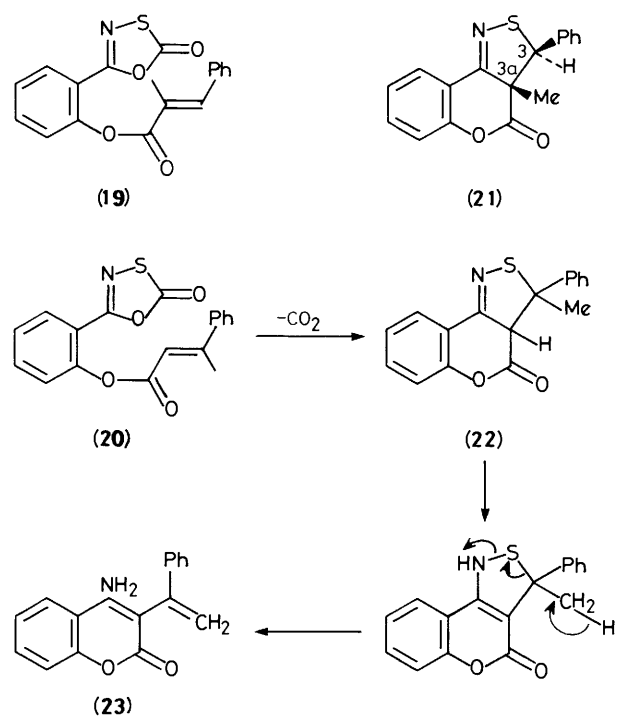
The identity of the insoluble white solid isolated from the thermolysis of the unsubstituted cinnamate ester (**10a**) is now considered. This material proved to have very low solubility in most common solvents, with only DMF and DMSO giving solutions of sufficient strength for n.m.r. spectra to be recorded. In an attempted recrystallisation from benzonitrile at *ca.* 150 °C it was found to decompose at such temperatures in solution; as a solid it melts over a narrow range (228—230 °C). It is tentatively identified as the elusive 3-isothiazoline (**17a**) on the basis of its chemical and spectroscopic properties. Heating for 1 h under reflux in benzonitrile resulted in its complete disappearance. Examination of the resulting solution by h.p.l.c. established the presence of both chromenoisothiazolones (**7a**) and, notably, chromenoquinolinone (**14a**) consistent with the compound being an intermediate on the pathway to this quinoline. Its fairly sharp melting point and clean n.m.r. spectra indicate that it is predominantly a single compound. The mass spectrum shows a strong peak at *m/z* 279 [$(M - 2)^+$] rather than a molecular ion (*m/z* 281). The i.r. data resemble those of 4-aminochromen-2-ones with NH peaks at 3 430, 3 360, and 3 250 cm^{-1} and an amide-like carbonyl absorption at 1 630 cm^{-1}. Further strong support is provided by its ^{13}C n.m.r. spectrum (Table 3) which is entirely compatible with the proposed structure incorporating a methine carbon (53.2 p.p.m., C-3) as well as phenyl and chromen-2-one units. In the proton spectrum there is a distinctive peak (δ 5.89, s, 1 H) assigned to 3-H, comparable to that found for 3-H in the methylisothiazoline (**21**), and a high frequency signal (δ 8.07) similar to that described earlier for 5-H of 4-aminochromen-2-ones (Table 3).



	a	b	f	g	i	j
X:	H	Cl	OMe	Me	Me	H
Y:	H	H	H	H	Me	Cl

Scheme 2.

An example of the corresponding intermolecular reaction of a typical nitrile sulphide and a cinnamate ester was also examined. Thermolysis of the *p*-methoxyphenyloxathiazolone (**25**) with *p*-t-butylphenyl cinnamate (the methoxy and t-butyl substituents were chosen to facilitate recognition of the individual regioisomers) afforded *p*-methoxybenzonitrile as the major product and a low yield (*ca.* 7%) of a regioisomeric mixture (*ca.* 1:1) of isothiazolines (**26**) and (**27**). The lack of regioselectivity is typical of nitrile sulphide cycloadditions to unsymmetrically substituted alkenes and alkynes.[5,6] For the intramolecular case geometric constraints ensure that only one regioisomer is formed.



Scheme 3.

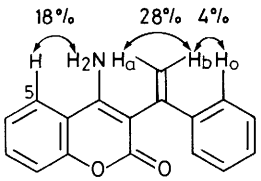
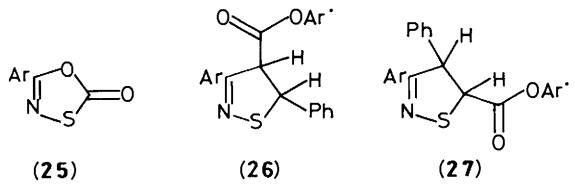


Figure. Selected n.O.e. data for 4-amino-3-styrylchromenone (**23**)



Ar = C_6H_4OMe-*p*, Ar′ = $C_6H_4Bu^t$-*p*

Experimental

The instrumentation for recording i.r., ^1H and ^{13}C n.m.r., and mass spectra, and the analytical methods used for monitoring the reactions were as previously described.[14] N.m.r. spectra were recorded in $CDCl_3$ unless otherwise stated. Authentic samples of the nitrile by-products were obtained by acylation of *o*-cyanophenol.[13] Chromenoquinolinone (**14a**) was synthesised from 4-hydroxychromen-2-one, aniline, and paraformaldehyde by the method of Buu-Hoi *et al.*,[10] m.p. 227—229 °C (lit.,[10] 224—225 °C).

Preparation of 1,3,4-*Oxathiazol*-2-*ones*.—Oxathiazolones (**4b—d**), (**6**), (**8a**), (**10**), (**19**), (**20**), and (**25**) were prepared by established literature procedures[5] involving either treatment of the appropriate carboxamide[13] with chlorocarbonylsulphenyl chloride (method A) or acylation of 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one (method B). The method employed, product yields, and analytical data for new compounds are presented in Table 4. All show ^{13}C n.m.r. peaks characteristic of the

Table 4. Preparation of oxathiazolones

Compound (Formula)	Method[a]	Yield (%)	M.p. (°C)	Solvent	Found (%) (Required) C	H	N
(4c)	A	62	108—110	EtOH	53.7	2.6	4.8
($C_{13}H_7NO_5S$)					(54.0)	(2.4)	(4.8)
(4d)	A	55	104—106	EtOH	54.2	2.6	4.9
($C_{13}H_7NO_5S$)					(54.0)	(2.4)	(4.8)
(6a)	B	85	107.5—108.5	EtOH	62.9	2.9	4.3
($C_{17}H_9NO_4S$)					(63.2)	(2.8)	(4.3)
(6b)	B	46	133—135	EtOH–$CHCl_3$	56.8	1.9	3.8
($C_{17}H_8ClNO_4S$)					(57.1)	(2.2)	(3.9)
(8a)	A	13	163—165	Cyclohexane–EtOAc	63.2	3.0	8.5
($C_{17}H_{10}N_2O_3S$)			(decomp.)		(63.4)	(3.1)	(8.7)
(10a)	A	60	129—131	EtOH	62.6	3.3	4.2
($C_{17}H_{11}NO_4S$)	B	85			(62.8)	(3.4)	(4.3)
(10b)	A	51	139—140	EtOH	56.7	2.7	3.9
($C_{17}H_{10}ClNO_4S$)					(56.8)	(2.8)	(3.9)
(10c)	B	70	74—76	Hexane–EtOAc	53.2	2.8	5.6
($C_{11}H_7NO_4S$)					(53.0)	(2.8)	(5.6)
(10e)	A	41	78—80	EtOH	52.2	3.4	4.5
($C_{14}H_{11}NO_6S$)					(52.3)	(3.4)	(4.4)
(10f)	A	37	143—145	EtOH–$CHCl_3$	60.6	3.8	3.9
($C_{18}H_{13}NO_5S$)					(60.9)	(3.7)	(3.9)
(10g)	A	70	125—127	EtOH	63.9	4.1	4.2
($C_{18}H_{13}NO_4S$)					(63.7)	(3.8)	(4.1)
(10h)	A	61	143.5—145	EtOH	57.0	3.0	4.5
($C_{15}H_9NO_5S$)					(57.1)	(2.9)	(4.4)
(10i)	B	68	142—144	EtOH–$CHCl_3$	65.6	4.6	4.0
($C_{20}H_{17}NO_4S$)					(65.4)	(4.6)	(3.8)
(10j)	B	59	159—161	EtOH–$CHCl_3$	51.6	2.2	3.3
($C_{17}H_9Cl_2NO_4S$)					(51.8)	(2.3)	(3.6)
(19)	B	71	99—101	Hexane–EtOAc	63.5	3.8	4.0
($C_{18}H_{13}NO_4S$)					(63.7)	(3.8)	(4.1)
(20)	B	32	100.5—101.5	Hexane–EtOAc	63.6	3.8	4.3
($C_{18}H_{13}NO_4S$)					(63.7)	(3.8)	(4.1)

[a] Method A, ClCOSCl + *O*-acylsalicylamide or *N*-acylanthranilamide; Method B, acylation of oxathiazolone (**4b**).

oxathiazolone ring[5] at 172—174 p.p.m. for C-2 and 153—155 p.p.m. for C-5. Full details are given in ref. 13.

Thermolysis of Oxathiazolones.—General procedure. A solution of the oxathiazolone (10 mmol) was dissolved in dry xylene (*ca.* 250 ml) and heated under reflux (*ca.* 138 °C) until h.p.l.c. analysis showed that no starting material remained. A portion of the reaction mixture was set aside for h.p.l.c. analysis. After removal of precipitated material by filtration, the residue was concentrated and the products separated by chromatography and/or crystallisation. The products, their yields (by h.p.l.c.), analytical data, and m.p.s are presented in Table 5.

5-(3-*Arylpropiolyloxyphenyl*)-1,3,4-*oxathiazol*-2-*ones* (**6a**, **b**). Oxathiazolone (**6a**) (2.55 g, 7.9 mmol) was heated in xylene (250 ml) for 18 h as described above. Flash chromatography and crystallisation of the residue from cyclohexane afforded 3-*phenylchromeno*[4,3-c]*isothiazol*-4-*one* (**7a**) as colourless needles, m.p. 166.5—168.5 °C; $\nu_{max.}$(Nujol) 1 730 cm^{-1} (C=O); *m*/*z* 279 (M^+). Oxathiazolone (**6b**) reacted similarly.

5-(3-*Phenylpropiolamidophenyl*)-1,3,4-*oxathiazol*-2-*one* (**8a**). A solution of the oxathiazolone (0.334 g, 1.04 mmol) in xylene (25 ml) was thermolysed for 23 h as described above. On cooling 3-*phenylisothiazolo*[4,3-c]*quinolin*-4(5H)-*one* (**9a**) crystallised from the reaction mixture as colourless needles, m.p. 303—304 °C; $\nu_{max.}$(Nujol) 3 130 (NH) and 1 675 cm^{-1} (C=O); *m*/*z* 278 (M^+).

Cinnamate esters (**10a**, **b**, **f**—**j**), (**19**), and (**20**) *of* 5-(o-*hydroxyphenyl*)-1,3,4-*oxathiazol*-2-*one*. The cinnamoyloxy oxathiazolone (**10a**) (6.50 g, 20 mmol) was heated in xylene (500 ml) as described above. From the refluxing solution a solid was precipitated which was assigned structure (**17a**), 1,3-*dihydro*-3-*phenylchromeno*[4,3-c]*isothiazol*-4-*one* (1.29 g, 23%), m.p. 228—230 °C; $\nu_{max.}$(Nujol) 3 430, 3 360, 3 250 (NH), and 1 630 cm^{-1} (C=O); *m*/*z* 279 [$(M - 2)^+$]. Concentration of reaction mixture and repeated flash chromatography afforded the following three products: 3-phenylchromeno[4,3-*c*]isothiazol-4-one (**7a**) (80 mg, 2%), m.p. 166.5—168.5 °C; chromeno[4,3-*b*]quinolin-6-one (**14a**) (192 mg, 4%), m.p. 224—225 °C (lit.,[10] 227—229 °C), mixed m.p. 228—231 °C); and *o*-cyanophenyl cinnamate (183 mg, 4%), m.p. and mixed m.p. 102—103 °C. A solution of *o*-cyanophenyl cinnamate (256 mg, 2.03 mmol) in xylene (25 ml) was heated at reflux for 6 weeks. Although some decomposition had taken place (58% starting material remained), h.p.l.c. analysis showed that no chromenoquinolinone (**14a**) had been formed.

The *p*-methoxycinnamoyloxy oxathiazolone (**10f**) (3.55 g, 10.0 mmol) was heated in xylene (250 ml) for 20 h as described above. On cooling a precipitate was formed, which was separated by filtration and identified as 4-*amino*-3-(p-*methoxybenzyl*)-*chromen*-2-*one* (**15f**) (192 mg, 2%), m.p. 240—243 °C; $\nu_{max.}$(Nujol) 3 470, 3 340, 3 230 (NH), and 1 640 cm^{-1} (C=O); δ_H(80 MHz, CD_3SOCD_3) 8.06 (1 H, dd, *J* 2 and 10 Hz, 5-H), 7.6—7.1 (3 H, m, 6, 7, and 8-H), 7.22 (2 H, d, *J* 9 Hz, *m*-ArH), 7.02 (2 H, br, NH_2), 6.79 (2 H, d, *J* 9 Hz, *o*-ArH), 3.76 (2 H, s, CH_2), and 3.68 (3 H, s, OMe); *m*/*z* 281 (M^+). The residue was concentrated and chromatographed (silica; dichloromethane–

Table 5. Analytical data for reaction products

Compound (Formula)	Method[a]	Yield (%)	M.p. (°C)	Solvent	Found (%) (Required) C	H	N
(7a)	C	70	166.5—168.5	Cyclohexane	68.7	3.1	4.9
($C_{16}H_9NO_2S$)	D	14			(68.8)	(3.2)	(5.0)
(7b)	C	15	216.5—217.5	EtOH–$CHCl_3$	61.2	2.6	4.6
($C_{16}H_8ClNO_2S$)	D	21			(61.2)	(2.6)	(4.5)
(7f)	D	14	175—180	Hexane–EtOAc	65.8	3.8	4.6
($C_{17}H_{11}NO_3S$)			(decomp.)		(66.0)	(3.6)	(4.5)
(7g)	D	30	195—197	EtOAc	69.4	3.9	4.8
($C_{17}H_{11}NO_2S$)					(69.6)	(3.8)	(4.8)
(7h)	D	16	251—254	EtOAc	62.2	2.6	5.1
($C_{14}H_7NO_3S$)					(62.5)	(2.6)	(5.2)
(7i)	D	33	159—160	Hexane–cyclohexane	71.3	4.7	4.6
($C_{19}H_{15}NO_2S$)					(71.0)	(4.7)	(4.4)
(7j)	D	31	177.5—178	EtOAc	55.4	2.0	4.0
($C_{16}H_7Cl_2NO_2S$)					(55.2)	(2.0)	(4.0)
(9a)	C	81	303—304	Xylene	68.8	3.6	10.1
($C_{16}H_{10}N_2OS$)					(69.1)	(3.6)	(10.1)
(14f)	D	14	236—238	EtOAc	73.5	3.9	5.0
($C_{17}H_{11}NO_3$)					(73.7)	(4.0)	(5.1)
(14g)	D	3	205—207	EtOAc	78.0	4.3	5.3
($C_{17}H_{11}NO_2$)					(78.2)	(4.2)	(5.4)
(14j)	D	28	235.5—237	EtOAc	67.9	2.8	5.1
($C_{16}H_8ClNO_2$)					(68.2)	(2.8)	(5.0)
(15f)	D	12	240—243	AcOH	72.7	5.4	4.9
($C_{17}H_{15}NO_3$)					(72.6)	(5.3)	(5.0)
(15g)	D	13	203—206	EtOH	76.8	5.8	5.2
($C_{17}H_{15}NO_2$)					(77.0)	(5.7)	(5.3)
(15h)[b]	D	3	212—215	EtOAc	69.6	4.4	5.7
($C_{14}H_{11}NO_3$)					(69.7)	(4.6)	(5.8)
(15i)	D	15	209—211	EtOAc	77.8	6.5	5.0
($C_{19}H_{19}NO_2$)					(77.8)	(6.5)	(4.8)
(16)	D	16	180—182	MeOH		*m/z* 237.0418	
($C_{14}H_7NO_3$)						(*M*, 237.0426)	
(21)	D	5	149—151	Cyclohexane	69.0	4.2	4.7
($C_{17}H_{13}NO_2S$)					(69.2)	(4.4)	(4.8)
(23)	D	15	175—178	—		*m/z* 263.0946	
($C_{17}H_{13}NO_2$)						(*M*, 263.0946)	

[a] Method C, from acetylenic precursor; Method D, from olefinic precursor. [b] 4-Amino-3-furfurylchromen-2-one.

light petroleum, 1:1) to yield: sulphur (0.21 g, 66%); 3-(p-*methoxyphenyl*)*chromeno*[4,3-c]*isothiazol*-4-*one* (**7f**) (0.234 g, 8%), m.p. (decomp.) 175—180 °C; $\nu_{max.}$(Nujol) 1 750 cm^{-1} (C=O); *m/z* 309 (M^+); and 10-*methoxychromeno*[4,3-b]*quinolin*-6-*one* (**14f**) (314 mg, 11%), m.p. 236—238 °C (Found: C, 73.5; H, 3.9; N, 5.0. $C_{17}H_{11}NO_3$ requires C, 73.7; H, 4.0; N, 5.1%); $\nu_{max.}$(Nujol) 1 737 cm^{-1} (C=O); *m/z* 277 (M^+). *o*-Cyanophenyl *p*-methoxycinnamate was not isolated pure but its presence in the reaction mixture was established by t.l.c. and h.p.l.c. The oxathiazolones (**10b, g**) reacted similarly.

The oxathiazolones (**10h, i, j**) were treated in a similar manner to give the products listed in Table 5.

5-[*o*-(α-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (**19**) (3.39 g, 10.0 mmol) was heated in xylene (250 ml) for 19 h as described above. Flash chromatography of the residue (silica; hexane–diethyl ether, 9:1) afforded sulphur (179 mg, 87%) followed by 3,3a-*dihydro*-3a-*methylchromeno*[4,3-c]*isothiazol*-4-*one* (**21**) (151 mg, 5%), m.p. 149—151 °C; $\nu_{max.}$(Nujol) 1 781 cm^{-1} (C=O); δ_H(200 MHz, CD_3SOCD_3) 7.84 (1 H, dd, *J* 2 and 8 Hz, 9-H), 7.7—7.2 (8 H, m, ArH), 5.93 (1 H, s, 3-H), and 1.15 (3 H, s, Me); *m/z* 295 (M^+); and *o*-cyanophenyl α-methylcinnamate (2.13 g, 81%).

5-[*o*-(β-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (**20**) (5.09 g, 15.0 mmol) was heated in xylene (375 ml) for 8 h as described above. The residue was subjected to flash chromatography eluting first with hexane–ethyl acetate (4:1) and then with chloroform–methanol (24:1). This yielded sulphur (435 mg, 90%), *o*-cyanophenyl β-methylcinnamate (3.35 g, 85%), and 4-*amino*-3-(α-*styryl*)*chromen*-2-*one* (**23**) (610 mg, 15%) m.p. 175—178 °C; $\nu_{max.}$(Nujol) 3 430, 3 340, 3 210 (NH_2), and 1 665 cm^{-1} (C=O); δ_H(360 MHz, $CDCl_3$) 7.66 (1 H, dd, *J* 1 and 8 Hz, 5-H), 7.50 (1 H, dt, *J* 1 and 8 Hz, 6- or 7-H), 7.4—7.1 (6 H, m, 6 or 7-H and 5 × PhH), 7.27 (1 H, dd, *J* 1 and 8 Hz, 8-H), 6.00 (1 H, d, *J* 1.2 Hz, H_a), 5.51 (2 H, br, NH_2), and 5.39 (1 H, d, *J* 1.2 Hz, H_b); *m/z* 263 (M^+).

Acrylate (**10c**), *fumarate* (**10e**), *and furoate* (**4c, d**) *esters of* 5-(o-*hydroxyphenyl*)-1,3,4-*oxathiazol*-2-*one*. Thermolysis of the acrylate ester (**10c**), using the procedure described above for cinnamate esters, afforded chromeno[4,3-*c*]isothiazol-4-one (**7c**) (24%), m.p. and mixed m.p. 168—169 °C (lit.,[5] 168—169 °C). Under similar conditions the fumarate ester (**10e**) yielded ethyl 4-oxo-4*H*-chromeno[4,3-*c*]isothiazole-3-carboxylate (**7e**) (28%), m.p. and mixed m.p. 118—120 °C (lit.,[5] 118—120 °C). From the corresponding thermolyses of the furoate esters (**4a**) and (**4b**) the only products isolated were the corresponding nitriles (58% and 73% respectively, 79% and 92% by h.p.l.c.

Reaction of 5-(p-*methoxyphenyl*)-1,3,4-*oxathiazol*-2-*one* (**25**) *with* p-*t*-*butylphenyl cinnamate*. The oxathiazolone (**25**)[15] (1.78 g, 5.6 mmol) was added in small portions over a period of 5 h to

a solution of *p*-t-butylphenyl cinnamate (7.75 g, 28.0 mmol) in xylene (50 ml) under reflux. After being heated for a further 5 h the solution was allowed to cool and unchanged cinnamate ester removed by filtration. Concentration of the residue and chromatography afforded *p*-methoxybenzonitrile (650 mg, 70%) followed by an inseparable mixture of p-*t-butylphenyl* 4,5-*dihydro*-3-(p-*methoxyphenyl*)-5-*phenylisothiazole*-4-*carboxylate* (**26**) and its -4-*phenylisothiazole*-5-*carboxylate regioisomer* (**27**) (32 mg, 1%) (Found: M^+, 445.1633. $C_{27}H_{27}NO_3S$ requires *M*, 445.1712); $\nu_{max.}$(film) 1 747 cm^{-1} (C=O); δ_H(80 MHz, $CDCl_3$) 7.9—6.7 (26 H, m, ArH), 5.48 (2 H, d, *J* 3 Hz, 2 × 5-H), 4.47 (2 H, d, *J* 3 Hz, 2 × 4-H), 1.31 (9 H, s, Bu^t), 1.29 (9 H, s, Bu^t), 3.86 (3 H, s, OMe), and 3.75 (3 H, s, OMe); *m*/*z* 445 (M^+).

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References

1 Part 9, M. C. McKie and R. M. Paton, *J. Chem. Res.*, 1987, (*S*) 254; (*M*) 2051.
2 Preliminary communication. P. A. Brownsort, R. M. Paton, and A. G. Sutherland, *Tetrahedron Lett.*, 1985, **26**, 3727.
3 A. Padwa in '1,3-Dipolar Cycloadditon Chemistry,' ed. A. Padwa, Wiley, 1984, ch. 12.
4 See for example A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410.
5 P. A. Brownsort and R. M. Paton, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2339 and references therein.
6 R. K. Howe, T. A. Gruner, L. G. Carter, L. L. Black, and J. E. Franz, *J. Org. Chem.*, 1978, **43**, 3736.
7 R. M. Paton, J. F. Ross, and J. Crosby, *J. Chem. Soc., Chem. Commun.*, 1980, 1194.
8 J. F. Ross, PhD Thesis, University of Edinburgh, 1981.
9 C. A. Abrahams, A. N. Aitchison, R. M. Paton, and C. Pearson, unpublished observations.
10 N. P. Buu-Hoi, M. Mangane, and P. Jacquignon, *J. Chem. Soc. C*, 1966, 50.
11 O. Aki, Y. Nakagawa, and K. Sirukawa, *Chem. Pharm. Bull.*, 1972, **20**, 2372.
12 T. Veda and J. Sakakibara, poster presented at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Canada, 1985.
13 P. A. Brownsort, PhD Thesis, University of Edinburgh, 1987.
14 D. J. Greig, M. McPherson, R. M. Paton, and J. Crosby, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1205.
15 A. M. Damas, R. O. Gould, M. M. Harding, R. M. Paton, J. F. Ross, and J. Crosby, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2991.

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