1,3-Dipolar Cycloadditions with Alkynyl Phenyl Sulphones

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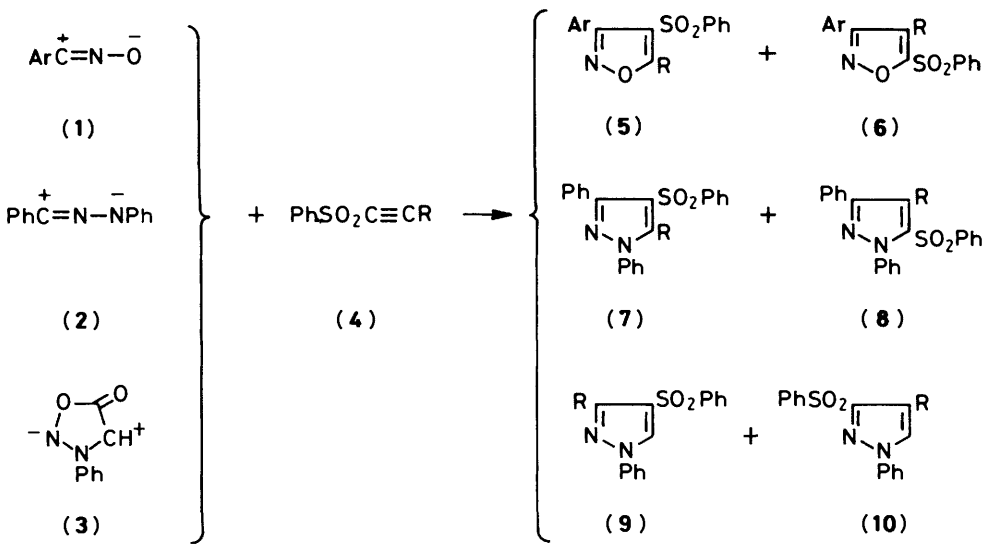
Alkynyl phenyl sulphones (**4**) react with the nitrile oxide (**1**), the nitrile imine (**2**), and sydnone (**3**) to afford predominantly or exclusively 4-phenylsulphonyl substituted cycloadducts (**5**), (**7**), and (**9**). The observed regioselectivity is discussed.

Substituent effects on rate and regioselectivity in 1,3- dipolar cycloadditions represent an intriguing problem which has been the object of a large number of experimental and theoretical studies. In the last years, an increasing interest has been devoted to the influence of the sulphonyl group on the dipolarophilic behaviour of carbon-carbon multiple bonds. However, while several reports have appeared dealing with 1,3-dipolar cycloadditions to open-chain and cyclic α,β-ethylenic sulphones,[1-12] very little is known about the dipolarophilicity of sulphonyl substituted acetylenes.[13] This present research examines the cycloadditions of a number of 1,3-dipoles with the alkynyl phenyl sulphones (**4a—c**) (see Scheme 1).



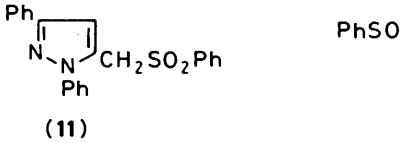
Ar = 2,4,6-Me_3-3,5-Cl_2C_6
a; R = H; b; R = Me; c; R = Ph

Scheme 1.

Results

Reaction of the Nitrile Oxide (**1**) *with Compounds* (**4**).—This reaction was carried out in boiling benzene by using equimolar amounts of the reactants. Times, products, and yields are reported in Table 1. The structures (**5a**) and (**6a**) were assigned unequivocally by the chemical shifts of the isoxazole protons (see Table 2). The regioisomers (**5b,c**) and (**6b,c**) were identified by a comparison of their spectral data with those of authentic samples of (**5b**)[14] and (**5c**) prepared by the reaction of (**1**) with phenylsulphonylacetone and α-phenylsulphonylacetophenone, respectively.

Reaction of the Nitrile Imine (**2**) *with Compounds* (**4**).—The nitrile imine (**2**) was generated *in situ* following two alternative procedures. First, compounds (**4**) were treated with an equimolar amount of 1-(α-chlorobenzylidene)-2-phenylhydrazine in the presence of triethylamine in acetonitrile at room temperature. In the case of (**4a**) and (**4c**), a clean reaction was observed leading to cycloaddition products in good yields (Table 1). However, compound (**4b**) underwent the concomitant base-promoted isomerisation to allenyl phenyl sulphone, which was readily isolated from the reaction mixture along with side-products derived from it, namely (**11**) and (**12**).[15] To avoid this drawback, a different procedure was adopted for generating *in situ* the nitrile imine (**2**), *i.e.* thermolysis of 2,5-diphenyltetrazole in refluxing anisole. Under these conditions, the overall yield of



cycloadducts was satisfactory in the case of (**4a**) and (**4b**), but was modest in the case of (**4c**) owing to the thermal lability of the latter substrate. It is noteworthy that the regiochemical course of the observed cycloadditions was practically independent of the mode of generation of (**2**).

While the isomeric pyrazoles (**7a**) and (**8a**) were readily recognised on the basis of their n.m.r. signals, compounds (**7b**)

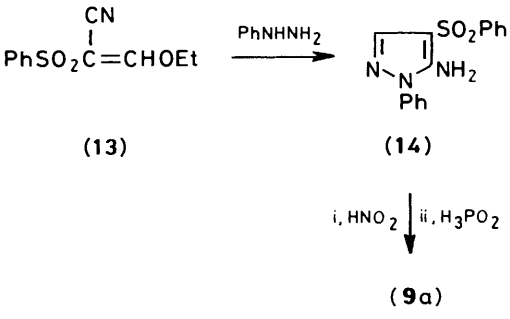
Table 1. Reaction of 1,3-dipoles (**1**)—(**3**) with alkynes (**4**)

Dipole	Dipolarophile	Time (h)	Cycloadducts	Overall yield (%)	Regioisomeric ratio[a]
(**1**)	(**4a**)	5	(**5a**) + (**6a**)	82	80:20
	(**4b**)	24	(**5b**)	84	100:0
	(**4c**)	5	(**5c**)	72	100:0
(**2**)[b]	(**4a**)	20	(**7a**) + (**8a**)	54	70:30
	(**4b**)	40	(**7b**)[c]	15	100:0
	(**4c**)	23	(**7c**)	71	100:0
(**2**)[d]	(**4a**)	16	(**7a**) + (**8a**)	71	76:24
	(**4b**)	30	(**7b**)	60	100:0
	(**4c**)	20	(**7c**)	18	100:0
(**3**)	(**4a**)	24	(**9a**) + (**10a**)	56	75:25
	(**4b**)	24	(**9b**)	58	100:0
	(**4c**)	24	(**9c**)[e]	73	100:0

[a] The cycloadduct having the $PhSO_2$ group in position 4 is the predominant or exclusive regioisomer. [b] From 1-(α-chlorobenzylidene)-2-phenylhydrazine. [c] Side-products were (**11**) (14%), (**12**) (2%) and allenyl phenyl sulphone (7%). [d] From 2,5-diphenyltetrazole. [e] Formula (**9c**) ≡ (**7a**).

and (**7c**) were identified by comparison with authentic samples prepared unambiguously by reaction of (α-chlorobenzylidene)-2-phenylhydrazine with the sodium salts of phenylsulphonylacetone and α-phenylsulphonylacetophenone, respectively.

Reaction of Sydnone (**3**) *with Compounds* (**4**).—All the reactions were carried out by heating to 100 °C a toluene solution of 3-phenylsydnone with an equimolar amount of the appropriate alkynyl phenyl sulphone. Reaction times, yields, and the ratio of regioisomers are reported in Table 1. The structures of the pyrazoles (**9a**) and (**10a**) were assigned on the basis of the chemical shifts of pyrazole protons (Table 2) and for one, (**9a**), of the regioisomers also by independent synthesis according to Scheme 2. Structure (**9b**) was correlated to (**9a**) by oxidative decarboxylation of the 3-methyl group.



(**13**) (**14**) (**9a**)

Scheme 2.

Discussion

The results summarised in Table 1 reveal that the alkynyl phenyl sulphones (**4a–c**) undergo 1,3-dipolar cycloadditions with high regioselectivity or even (within the experimental error limits) with complete regiospecificity. The prevailing, or exclusive, orientation is that which places the sulphonyl group in the 4-position of the resulting heterocyclic system, which corresponds to bond formation between the carbon of the 1,3-dipole and the α-carbon of the sulphone.

The literature data show that the cycloadditions of nitrile oxides,[6,16,17] nitrile imines,[16,17] and sydnones[18–20] with electron-poor alkynes (α,β-acetylenic esters, ketones, and nitriles) lead to regioisomeric mixtures where the cycloadduct having the electron-withdrawing substituent in the 4-position predominates in the case of disubstituted dipolarophiles. However, a preference for the latter cycloadduct as pronounced as that found in the present study is unprecedented. The improvement in formation of the so-called 'reversed' cycloadduct in the case of the monosubstituted compound (**4a**) is particularly remarkable.

For the dipoles (**1**),[21] (**2**),[22,23] and (**3**),[22] it has been either calculated or estimated on the basis of the values determined for simpler molecules, that the larger orbital coefficients are at the carbon in the LUMO and at the external heteroatom in the HOMO. Although quantitative values are not available for the sulphones (**4a–c**), it is plausible that the strong electron-withdrawing effect of the sulphonyl group lowers the orbital energies and determines a large LUMO coefficient at the β-carbon. Consequently, in the reactions investigated here, the HOMO (dipole)–LUMO (dipolarophile) interaction should be important, thus dictating attack of the carbon of the 1,3-dipoles by the α-carbon of the sulphones. Also, electrostatic interaction may affect the regioselectivity, to favour the phenylsulphonyl substituted cycloadducts (**5**), (**7**), and (**9**). This view seems reasonable in the case of sydnone (**3**) owing to the high local charge densities of the mesoionic compounds. On the other hand, the importance of the polar term of the interaction energy has been recently shown for the cycloadditions of (**1**) and (**2**) with alkenyl sulphones.[11]

A further point worthy of attention, is that the propensity for the reversed orientation in 1,3-dipolar cycloadditions is greater for acetylenes than for ethylenes having the same substituents.[4,6,16,17,24] This trend is confirmed if the present results are compared with those obtained for the reactions of (**1**) and (**2**) with the alkene derivatives $PhSO_2CH{=}CHR$.[11] For instance, in the cycloaddition between the latter dipolarophiles and the nitrile oxide (**1**), the regioisomeric ratio (as defined in Table 1) was 9:91 for R = H and 60:40 for R = Ph. As already argued by Houk and co-workers,[4,6] the change of regioselectivity on going from alkenes to alkynes cannot be due to the frequently small difference between their LUMO energies. However, alkynes have lower HOMO energies than alkenes, thus diminishing the importance of the HOMO (dipolarophile)–LUMO (dipole) interaction and increasing the regioselectivity as experimentally observed. Other authors[24] have ascribed the different regioisomeric distribution between acrilonitrile and propiolonitrile to the intervention of secondary orbital interactions in the case of linear alkyne dipolarophiles. Such an attractive interaction between the carbon of the 1,3-dipole and the sulphur could intervene in the present case, thus providing an additional contribution in favour of the 4-phenylsulphonyl substituted cycloadducts. This hypothesis is consistent with the larger value of the carbon–sulphur resonance integral with respect to that of the oxygen–sulphur,[25] particularly at the long distances at which secondary orbital interactions are operative.

Experimental

M.p.s were determined on a Büchi apparatus and are uncorrected. N.m.r. spectra were recorded on a Varian EM-390 instrument; chemical shifts are given in p.p.m. from internal $SiMe_4$.

3,5-Dichloro-2,4,6-trimethylbenzonitrile oxide (**1**),[26] 1-(α-chlorobenzylidene)-2-phenylhydrazine,[27] 2,5-diphenyltetrazole,[28] 3-phenylsydnone (**3**),[29] and the sulphones (**4a**),[30] (**4b**),[15] and (**4c**)[31] were prepared according to literature methods.

Reaction of the Oxide (**1**) *with Compounds* (**4a–c**).—A solution of (**1**) (4.3 mmol) and (**4**) (4.3 mmol) in benzene (43 ml)

Table 2. Physical, spectral, and analytical data of new compounds.[a]

Compd.	M.p. (°C) (Recrystallisation solvent)	δ($CDCl_3$)	Elemental analysis (%) Found (requires) C	H	N
(**5a**)	248 (Toluene)	1.72 (6 H, s), 2.63 (3 H, s), 7.3—7.8 (5 H, m), 9.22 (1 H, s)	54.7 (54.6)	3.6 (3.8)	3.5 (3.5)
(**5c**)	213 (Benzene)	1.88 (6 H, s), 2.61 (3 H, s), 7.2—7.7 (8 H, m), 7.9—8.2 (2 H, m)	60.8 (61.0)	4.2 (4.1)	2.8 (3.0)
(**6a**)	183 (Cyclohexane)	2.15 (6 H, s), 2.60 (3 H, s), 6.85 (1 H, s), 7.5—7.9 (3 H, m), 8.1—8.3 (2 H, m)	54.8 (54.6)	3.8 (3.8)	3.4 (3.5)
(**7a**)/(**9c**)	151 (Pr^i_2O EtOH)	7.2—7.8 (15 H, m), 8.64 (1 H, s)	69.9 (70.0)	4.4 (4.5)	7.9 (7.8)
(**7b**)	154 (Hexane–benzene)	2.73 (3 H, s), 7.2—7.8 (15 H, m)	70.4 (70.6)	4.8 (4.8)	7.6 (7.5)
(**7c**)	243 (Hexane–benzene)	7.1—7.6 (18 H, m), 7.65—7.85 (2 H, m)	74.3 (74.3)	4.8 (4.6)	6.3 (6.4)
(**8a**)	130 (Pr^i_2O–EtOH)	7.2—7.6 (14 H, m), 7.75—7.95 (2 H, m)	70.1 (70.0)	4.4 (4.5)	7.7 (7.8)
(**9a**)	152 (Pr^iOH)	7.3—8.2 (10 H, m), 7.70 (1 H, s), 8.40 (1 H, s)	63.3 (63.4)	4.3 (4.3)	9.9 (9.9)
(**9b**)	182 (Pr^iOH)	2.40 (3 H, s), 7.4—8.2 (10 H, m), 8.85 (1 H, s)	64.6 (64.4)	4.6 (4.7)	9.3 (9.4)
(**10a**)	70 (Pr^iOH–Pr^i_2O)	6.90 (1 H, d, *J* 4.5 Hz), 7.2—7.8 (10 H, m), 7.85 (1 H, d, *J* 4.5 Hz)	63.3 (63.4)	4.2 (4.3)	9.9 (9.9)
(**11**)	139 (Hexane–benzene)	4.50 (2 H, s), 6.71 (1 H, s), 7.1—7.9 (15 H, m)	70.8 (70.6)	4.9 (4.8)	7.5 (7.5)
(**14**)	147 (Pr^iOH)	5.0 (2 H, br s), 7.0—8.0 (10 H, m), 7.71 (1 H, s)	60.2 (60.2)	4.3 (4.4)	14.0 (14.0)

[a] Mass spectra are in agreement with the assigned structures.

was refluxed for the time indicated in Table 1. The solvent was removed and the residue was chromatographed on a silica gel column with light petroleum–diethyl ether (2:1) as the eluant. Products and yields are given in Table 1.

Reaction of the Oxide (**1**) *with α-Phenylsulphonylacetophenone.*—A solution of (**1**) (1.0 mmol) and α-phenylsulphonylacetophenone[32] (1.0 mmol) in absolute ethanol (50 ml) was treated with 0.1M-ethanolic sodium hydroxide (3 ml) and refluxed for 3 h. The solvent was removed under reduced pressure and the residue was taken up with ether and water. The organic solution was dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column with light petroleum–diethyl ether (2:1) as the eluant to afford the isoxazole (**5c**) (28%).

Reaction of the Imine (**2**) *with Compounds* (**4a–c**).—(*a*) A solution of 1-(α-chlorobenzylidene)-2-phenylhydrazine (5 mmol) and (**4**) (5 mmol) in acetonitrile (50 ml) was treated with triethylamine (7.5 mmol) and left at room temperature for the time reported in Table 1. The solvent was removed under reduced pressure and the residue was taken up with diethyl ether and water. The organic solution was dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column with toluene–ethyl acetate (9:1) as the eluant to give the products listed in Table 1.

(*b*) A solution of 2,5-diphenyltetrazole (2.8 mmol) and (**4**) (2.8 mmol) in anisole (10 ml) was refluxed as indicated in Table 1. After removal of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with toluene–ethyl acetate (9:1) as the eluant (Table 1).

Reaction of 1-(α-Chlorobenzylidene)-2-phenylhydrazine with Phenylsulphonylacetone.—A solution of the title hydrazonyl chloride (2.5 mmol) and phenylsulphonylacetone[33] (2.5 mmol) in methanol (25 ml) was treated with 0.25M-sodium methoxide in methanol (10 ml) and refluxed for 1 h. The solvent was removed under reduced pressure and the residue was taken up with diethyl ether and water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on a silica gel column with light petroleum–diethyl ether (1:1) as the eluant to afford pyrazole (**7b**) (29%).

Reaction of 1-(α-Chlorobenzylidene)-2-phenylhydrazine with α-Phenylsulphonylacetophenone.—The reaction was carried out following the procedure described in the preceding preparation (6 h) to give pyrazole (**7c**) (23%).

Reaction of Sydnone (**3**) *with Compounds* (**4a–c**).—A mixture of (**3**) (10 mmol) and (**4**) (10 mmol) in toluene (50 ml) was heated at 100 °C for 24 h. The solvent was evaporated and the residue was chromatographed on a silica gel. column. Elution with toluene gave the products listed in Table 1.

5-Amino-1-phenyl-4-phenylsulphonylpyrazole (**14**).—A mixture of (**13**)[34] (2 g, 8.4 mmol) and phenylhydrazine (0.83 g; 8.4 mmol) in ethanol (50 ml) was heated at 60 °C for 5 h. The solvent was evaporated off and the residue was recrystallised from propan-2-ol to give (**14**) (60%) (Table 2).

Conversion of (**14**) *into* (**9a**).—To a stirred solution of (**14**) (0.5 g, 1.67 mmol) in 20% aqueous hydrochloric acid (15 ml), sodium nitrite (0.13 g; 1.9 mmol) was added in portions with cooling at 5 °C. After 15 min, hypophosphorous acid (3 ml) was added and the solution was kept at room temperature for 12 h. The reaction mixture was extracted twice with dichloromethane (20 ml), the organic solution was dried (Na_2SO_4) and evaporated, and the residue was chromatographed on a silica gel column. Elution with toluene gave (**9a**) (52%).

Conversion of (**9b**) *into* (**9a**).—A solution of (**9b**) (0.5 g, 1.67 mmol) in acetone (50 ml) was treated with potassium permanganate (0.53 g, 3.34 mmol) and stirred at room temperature for 24 h. The solid material was filtered off, the solvent was evaporated, and the crude residue was heated at 200 °C for 30 min. The resulting dark product was chromatographed on a silica gel column with toluene as the eluant to give (**9a**) (30%).

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