

Cycloaddition Reactions of Sulphines with Benzonitrile Oxide †

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Diarylsulphines (diaryl thioketone *S*-oxides) undergo cycloadditions with benzonitrile oxide to yield 1,4,2-oxathiazole 4-oxides, with the exception of thiofluorenone *S*-oxide which gives a 1,5,2-oxathiazole 5-oxide as the dominant product. From the nature of the products obtained from geometrically isomeric sulphines, the cycloaddition was shown to be stereospecific.

NITRILE oxides show a well documented² propensity to undergo 1,3-dipolar cycloaddition reactions with a variety of carbon-carbon unsaturated dipolarophiles and heterodipolarophiles like ketones, thiocarbonyl deriv-

atives, and imino-compounds. Sulphines (thione *S*-oxides) ($\text{XYC}=\text{S}=\text{O}$) act as dipolarophiles in cycloaddition reactions with diazoalkanes,³ nitrile imides,⁴ and nitrilium ylides.¹ Because of the bent structure⁵ of the CSO system, sulphines exist, if appropriately substituted ($\text{X} \neq \text{Y}$), as stable geometric isomers.⁵ They are therefore particularly attractive as dipolarophiles, because the

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¹ B. F. Bonini, G. Maccagnani, G. Mazzanti, and B. Zwanenburg, *Gazzetta*, in the press.

² C. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer Verlag, Berlin, 1971.

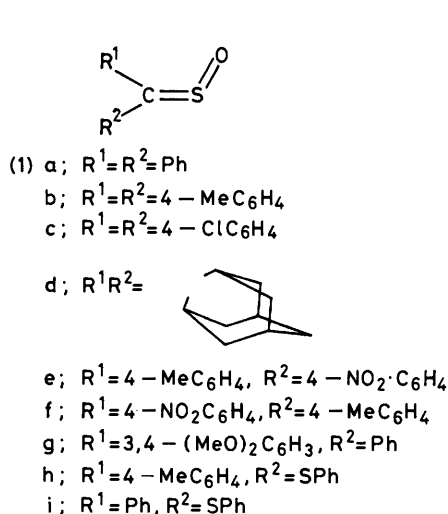
³ B. F. Bonini, G. Maccagnani, A. Wagenaar, L. Thijs, and B. Zwanenburg, *J.C.S. Perkin I*, 1972, 2490; C. G. Venier, and C. G. Gibbs, *Tetrahedron Letters*, 1972, 2293; B. Zwanenburg, A. Wagenaar, L. Thijs, and J. Strating, *J.C.S. Perkin I*, 1973, 73; L. Thijs, A. Wagenaar, E. M. M. van Rens, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3589.

⁴ B. F. Bonini, G. Maccagnani, L. Thijs, and B. Zwanenburg, *Tetrahedron Letters*, 1973, 3569.

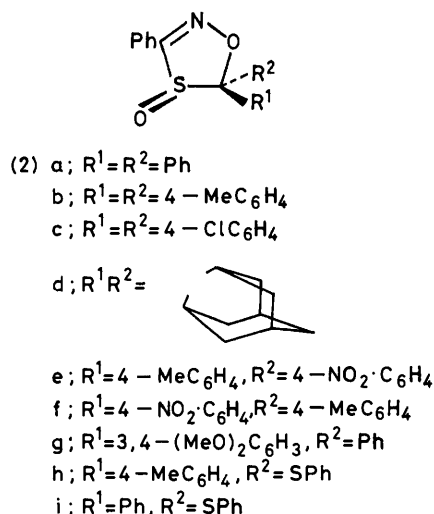
⁵ J. F. King and T. Durst, *J. Amer. Chem. Soc.*, 1963, **85**, 2676; *Canad. J. Chem.*, 1966, **44**, 819; B. Zwanenburg, L. Thijs, and J. Strating, *Tetrahedron Letters*, 1967, 3453; B. Zwanenburg and J. Strating, *Quart. Reports Sulfur Chem.*, 1970, **5**, 79; B. F. Bonini, L. Lunazzi, G. Maccagnani, and G. Mazzanti, *J.C.S. Perkin I*, 1973, 2314; A. Tangerman and B. Zwanenburg, *Tetrahedron Letters*, 1973, 79; Th. W. Hummelink, *J. Cryst. Mol. Struct.*, 1974, **4**, 87, 373.

regiospecificity as well as the stereospecificity of their cycloaddition reactions can be investigated. We report here the cycloaddition reactions of benzonitrile oxide with sulphines.

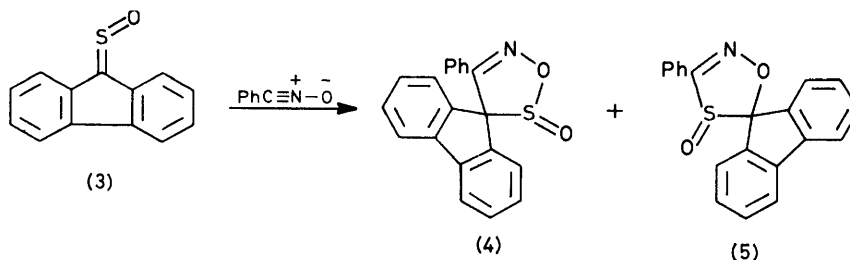
Diphenylsulphine (1a) with benzonitrile oxide



regiospecific. The orientation in cycloadditions with heterodipolarophiles usually obeys the principle of maximum gain in σ -bond energy,^{7,8} viz. the reactants join in the direction that gives the better compensation for the π -bond energy in the combined energy of the two



(generated ² *in situ* from benzohydroximoyl chloride and triethylamine in ether) smoothly afforded the cycloadduct (2a) in 75% yield. The product was identified unambiguously by an independent synthesis as follows. Cycloaddition of thiobenzophenone and benzonitrile oxide gave 3,5,5-triphenyl-1,4,2-oxathiazole, the structure of which was firmly established by Huisgen *et al.*⁶



Subsequent oxidation with peroxy-acid gave the 4-oxide (2a').

The sulphines (1b—d) with benzonitrile oxide similarly gave the cycloadducts (2b) (67%), (2c) (50%), and (2d) (88%), respectively. I.r. absorptions at 1085—1090 cm^{-1} [also observed for (2a)] are indicative of structure (2). In all four cases none of the other regioisomer was detected; besides the adduct (2) only starting sulphine, some ketone (R^1R^2CO), and furoxan were isolated (for material balance see Experimental section). From bis-(4-methoxyphenyl)sulphine no cycloadduct was obtained.

The foregoing results show that the cycloaddition is

new σ -bonds. This rule predicts the observed regiochemistry. The orientation in cycloadditions of thio-ketones⁶ and their S-oxides is thus the same, in spite of the difference in charge distribution^{9,10} between C=S and C=S=O. Also in terms of the frontier orbital perturbation approach¹¹ the HOMO and LUMO coefficients and energies¹⁰ of the C=S and C=S=O groups are different.

An unexpected result was obtained when thiofluorenone S-oxide (3) reacted with benzonitrile oxide. The predominant product showed i.r. absorption at 1155 cm^{-1} indicative of structure (4) (a cyclic sulphinic ester). The minor product (yield 6.5%) showed i.r. absorption at 1080 cm^{-1} , in agreement with the sulphoxide structure (5). Additional evidence for the structures of (4) and (5) was obtained from mass spectra. The minor product (5) showed its molecular ion at m/e 331 (ca. 10%), prominent peaks at m/e 228 ($M^+ - PhCN$) and 212 ($M^+ - PhCNO$),

⁹ J. P. Snyder and D. N. Harpp, *J.C.S. Chem. Comm.*, 1972, 1305; F. Bernardi, G. Maccagnani, and A. Mangini, *Anales de Quim.*, 1974, **70**, 1199; J. van Lierop, A. van der Avoird, and B. Zwanenburg, *Tetrahedron*, 1977, **33**, 359.

¹⁰ J. P. Snyder, *J. Org. Chem.*, 1973, **38**, 3965.

¹¹ K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Amer. Chem. Soc.*, 1973, **95**, 7301.

⁶ R. Huisgen and W. Mack, *Chem. Ber.*, 1972, **105**, 2815.

⁷ R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 633.

⁸ Ref. 2, ch. 5, p. 95.

and fragments at m/e 180 ($M^+ - \text{PhCNSO}$), 179 ($M^+ - \text{C}_{12}\text{H}_8$), 152 (C_{12}H_8), 151 (PhCNSO), and 119 (PhCNO). This fragmentation pattern is basically the same as that observed for (2b) (see Experimental section). The major product (4) showed no molecular ion; strong peaks were found at m/e 267 ($M^+ - \text{SO}_2$), 190 ($M^+ - \text{Ph} - \text{SO}_2$), and 164 ($M^+ - \text{Ph} - \text{CN} - \text{SO}_2$), of which the first in particular confirms the cyclic sulphinate structure. This deviant behaviour of thiofluorenone *S*-oxide shows that the regioselectivity also depends on the nature of the substituents at the sulphine carbon atom. Other fused aromatic sulphines (xanthenthione *S*-oxide and thioxanthenthione *S*-oxide) did not react with benzonitrile oxide.

The stereospecificity of the cycloaddition was studied with the geometrical isomers (1e and f). The *E*-isomer (1e) reacted slowly with the 1,3-dipole. After 20 h at 20 °C only 30% of the adduct (2e) (m.p. 136.5–137°) was isolated, and 60% of the sulphine could be recovered. The *Z*-isomer (1f) gave under the same conditions a different adduct (2f) (m.p. 114–115°) in 41% yield. Although these results point to a stereospecific cycloaddition, a more convincing experiment is the following. A mixture of (1e and f) in the ratio of 34 : 66 was treated with benzonitrile oxide for 20 h at 20 °C. The adducts (2e and f) were isolated as a mixture in the ratio 24 : 76. From the ratio of recovered sulphine isomers (43 : 57) it can be calculated that isomeric composition of the sulphine mixture that had reacted in the cycloaddition was 24 : 76, in excellent agreement with the adduct ratio obtained.

This stereospecificity points to simultaneous bond formation during the cycloaddition. The loss of stereochemistry encountered in the cycloaddition of sulphines with benzonitrile *N*-phenylimide (stereomutation of the cycloadducts *via* a ring-opening–ring-closure reaction)⁴ is not observed here.

The *E*- and *Z*-isomers of phenyl-*o*-tolylsulphine, as well as those of phenyl-(2,4,6-trimethylphenyl)sulphine did not react with benzonitrile oxide, indicating that the cycloaddition is sensitive to steric hindrance. In the search for *E*- and *Z*-pairs of substituted diarylsulphines we were faced with the problem that the kinetically controlled¹² oxidation of thioketones to sulphines produces either only one isomer or results in a mixture of isomers which cannot be separated. Oxidation of 3,4-dimethoxythiobenzophenone gave only isomer (1g), and 3-chloro-4'-methoxy-, 3-chloro-4'-methyl-, and 4-chloro-4'-methoxy-thiobenzophenone and 2-methoxythiofluorenone all gave inseparable mixtures of isomeric sulphines. The sulphine (1g) gave the cycloadduct (2g) in 56% yield.

Isomeric sulphines derived from dithioesters by oxidation with 1 equiv. of peroxy-acid usually can be separated easily, e.g. *E*- and *Z*-phenylthio-*p*-tolylsul-

phine. The latter substrates were both subjected to cycloaddition; only the *E*-isomer (1h) gave the desired adduct (yield 29%; recovered sulphine 70%). The *E*- and *Z*-isomers of both ethylthio-*p*-tolylsulphine and ethylthio-*p*-methoxyphenylsulphine did not react with benzonitrile oxide.

The generation of the 1,3-dipole was also performed in a different manner, from α -nitrotoluene and phenyl isocyanate (dehydrating agent) in the presence of a catalytic amount of triethylamine.¹³ The sulphine (1b) gave the adduct (2b) in 40% yield. From the sulphine (3) only the adduct (4) was isolated (78%); the presence of a small amount of the adduct (5) was deduced from the i.r. spectrum of the crude product. The sulphine (1i) gave (2i) in 47% yield. These results show that this method gives lower yields than the one *via* benzohydroximoyl chloride.

The cycloadducts (2) are thermally unstable. A solution of (2a) in refluxing xylene evolved sulphur dioxide (50%), giving benzophenone, benzonitrile, and small amounts of phenyl isocyanate, phenyl isothiocyanate, and the sulphine (1a), all identified by g.l.c. The predominant thermal fragmentation therefore is extrusion of sulphur monoxide (which disproportionates to sulphur and sulphur dioxide) to give benzophenone and benzonitrile.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 257 spectrometer. N.m.r. spectra were obtained with a JEOL C-60 HL or Varian T-60 spectrometer (Me_4Si as internal standard). Mass spectra were recorded with a JEOL JMS D100 spectrometer.

All experiments were carried out under nitrogen and with dry solvents. Benzohydroximoyl chloride was prepared as described in ref. 14. Sulphines were prepared as reported previously¹⁵ by oxidation of the corresponding thiocarbonyl compounds with *m*-chloroperbenzoic acid.

3,5,5-Triphenyl-1,4,2-oxathiazole 4-Oxide (2a).—A solution of triethylamine (0.505 g, 5 mmol) in ether (10 ml) was added slowly at 20 °C to a stirred solution of diphenylsulphine (1a) (1.07 g, 5 mmol) and benzohydroximoyl chloride (0.77 g, 5 mmol) in ether (40 ml). After stirring for 30 min the precipitated Et_3NHCl was filtered off and the filtrate concentrated *in vacuo*. The residue gave, after washing with cold ethanol, the adduct (2a) (1.25 g, 75%), m.p. 137–138° (from ethanol) (lit.,⁶ 136°). The alcoholic washings gave, after concentration and chromatography on silica gel plates (benzene), starting sulphine (0.27 g) contaminated with a little benzophenone. The adduct (2a) was identical with that prepared by cycloaddition of benzonitrile oxide with thiobenzophenone and subsequent oxidation according to the procedure of Huisgen *et al.*⁶

3-Phenyl-5,5-bis-(*p*-tolyl)-1,4,2-oxathiazole 4-Oxide (2b).—As described for (2a), bis-(*p*-tolyl)sulphine (1b) (5 mmol) gave the adduct (2b) (1.2 g, 67%), m.p. 133–133.5° (from

¹² A. Battaglia, A. Dondoni, P. Giorgianni, G. Maccagnani, and G. Mazzanti, *J. Chem. Soc. (B)*, 1971, 1547.

¹³ T. Mukaiyama and T. Hoshino, *J. Amer. Chem. Soc.*, 1960, **82**, 5339; ref. 2, p. 52.

¹⁴ P. Rajagopalan, B. G. Advani, C. N. Talaty, *Org. Synth.*, 1969, **49**, 70.

¹⁵ B. Zwanenburg, L. Thijs, and J. Strating, *Rec. Trav. chim.*, 1967, **86**, 577; B. F. Bonini, S. Gheretti, G. Maccagnani, and G. Mazzanti, *Boll. sci. Fac. Chim. ind. Bologna*, 1969, **27**, 419; B. Zwanenburg, L. Thijs, and J. Strating, *Rec. Trav. chim.*, 1971, **90**, 614; B. Zwanenburg, L. Thijs, and A. Tangerman, *Tetrahedron*, 1971, **27**, 1731; A. Tangerman and B. Zwanenburg, *J.C.S. Perkin II*, 1974, 1413.

ethanol) (Found: C, 73.3; H, 5.3; N, 3.85; S, 8.65. $C_{22}H_{19}NO_2S$ requires C, 73.1; H, 5.3; N, 3.9; S, 8.85%), ν_{\max} (CCl_4) 1 085 cm^{-1} (SO), δ ($CDCl_3$) 2.28 (6 H, s, Me) and 6.9—7.9 (13 H, m, ArH), m/e 361 (M^+ , ca. 10%); strong peaks at 258 (M^+ — PhCN) and 242 (M^+ — PhCNO); other fragments at 210 (M^+ — PhCNSO), 179 [M^+ — (PhMe) $_2$], 151 (PhCNSO), and 119 (PhCNO). In addition the sulphine (1b) (0.25 g, 20%) contaminated with some ketone and diphenylfuroxan (0.15 g) were obtained.

5,5-Bis-(p-chlorophenyl)-3-phenyl-1,4,2-oxathiazole 4-Oxide (2c).—As described for (2a), the sulphine (1c) (5 mmol) gave after stirring for 1 h, filtration, concentration of the filtrate, and washing the residue with hexane, the white crystalline adduct (2c) (1.0 g, 50%), m.p. 141—141.5° (from ethanol) (Found: C, 59.9; H, 3.25; N, 3.45; S, 7.75. $C_{20}H_{13}Cl_2NO_2S$ requires C, 59.7; H, 3.25; N, 3.50; S, 7.95%), ν_{\max} (CCl_4) 1 090 cm^{-1} (SO). The hexane washings gave, after concentration and chromatography on silica plates (benzene), *pp'*-dichlorobenzophenone (0.5 g, 40%) and diphenylfuroxan (0.2 g).

3'-Phenyladamantane-2-spiro-5'-1',4',2'-oxathiazole 4'-Oxide (2d).—Triethylamine (0.48 g, 4.8 mmol) dissolved in benzene (10 ml) was added gradually at 20 °C to a stirred solution of adamantane-2-thione S-oxide (1d) (0.87 g, 4.8 mmol) in benzene (50 ml). After stirring for 2 h the mixture was filtered, the filtrate concentrated, and the residue extracted with boiling methanol (20 ml). Concentration of the methanolic solution afforded the adduct (2d) (1.27 g, 88%), m.p. 166—168° (from methanol) (Found: C, 67.7; H, 6.45; N, 4.45; S, 10.95. $C_{17}H_{19}NO_2S$ requires C, 67.75; H, 6.35; N, 4.65; S, 10.65%), ν_{\max} (KBr) 1 040—1 055 cm^{-1} (SO), δ (CS_2) 1.6—2.8 (14 H, m) and 7.2—8.2 (5 H, m).

Cycloaddition with Thiofluorenone S-Oxide (3).—Triethylamine (0.33 g, 3.3 mmol) in ether (10 ml) was added to a stirred solution of (3) (0.70 g, 3.3 mmol) and benzohydroximoyl chloride (0.51 g, 3.3 mmol) in ether (90 ml). After stirring for 4 h, filtration (to remove Et_3NHCl), concentration of the filtrate, and washing of the residue with cold ethanol (10 ml) gave 3'-phenylfluorene-9-spiro-4'-1',5',2'-oxathiazole 5'-oxide (4) (0.75 g, 69%), m.p. 99—101° (from dichloromethane-hexane) (Found: C, 72.1; H, 3.8; N, 4.3; S, 9.8. $C_{20}H_{13}NO_2S$ requires C, 72.5; H, 3.95; N, 4.25; S, 9.7%), ν_{\max} (KBr) 1 155 cm^{-1} (sulphinic ester), m/e 267 (M — SO_2), 190, and 164.

The ethanolic washing gave, after concentration and chromatography on silica gel plates (benzene-light petroleum, 1 : 1) 3'-phenylfluorene-9-spiro-5'-1',4',2'-oxathiazole 4'-oxide (5), (70 mg, 6.4%), m.p. 131—133° (from ethanol) (Found: C, 72.0; H, 3.8; N, 4.3; S, 9.7%), ν_{\max} (CS_2) 1 080 cm^{-1} (SO).

Cycloadditions with the Sulphines (1e and f).—The reaction with the *E*-sulphine (1e) (1.1 mmol) was carried out in benzene as described for (1d). After stirring for 20 h, filtration, and concentration of the filtrate, the product was chromatographed on silica gel plates (benzene; three times). Four products were isolated: (i) the adduct (2e) (0.13 g, 30%), m.p. 136.5—137° (from ethanol) (Found: C, 64.6;

H, 4.05; N, 7.05. $C_{21}H_{16}N_2O_4S$ requires C, 64.3; H, 4.1; N, 7.1%), ν_{\max} (CCl_4) 1 085 cm^{-1} (SO), δ (C_6D_6) 2.00 (3 H, s, Me) and 6.9—7.9 (13 H, m, ArH); (ii) the starting sulphine (1e) (0.18 g, 60%), (iii) 4-methyl-4'-nitrobenzophenone (15 mg 6%), m.p. 119—121°; and (iv) diphenylfuroxan (20 mg).

The reaction with the *Z*-isomer (1f) (1.83 mmol; contaminated with 15% of the *E*-isomer) was performed in the same manner (reaction time 20 h). After work-up and chromatography, four products were obtained: (i) the adduct (2f) (0.30 g, 42%), m.p. 114—115° (from ethanol) (Found: C, 64.75; H, 4.05; N, 7.2%), ν_{\max} (CCl_4) 1 080 cm^{-1} (SO), δ (C_6D_6) 1.93 (3 H, s, Me) and 6.8—7.9 (13 H, m, ArH); (ii) the starting sulphine (0.10 g, 22%); (iii) 4-methyl-4'-nitrobenzophenone (0.10 g, 20%); and (iv) diphenylfuroxan (56 mg). No *E*-product (2e) was found.

The reaction with a mixture of (1e and f) (2.0 mmol, *E* : *Z* 34 : 66 according to the integrated Me n.m.r. signals) was conducted in the same manner. Work-up and chromatography gave: (i) a mixture of *E*-adduct (2e) and *Z*-adduct (2f) (0.258 g, 33%) in the ratio 24 : 76 [from the integrated n.m.r. spectrum; δ_{Me} 2.00 (*E*) and 1.93 (*Z*)]; (ii) a mixture of *E*- and *Z*-sulphines (0.274 g, 50%) in the ratio 43 : 57; (iii) 4-methyl-4'-nitrobenzophenone (30 mg, 6%); and (iv) diphenylfuroxan (28 mg).

Reaction with the Sulphine (1g).—The *Z*-sulphine (1g) (1.82 mmol) was treated as described for (1d). After 20 h the mixture was worked up. The semisolid crude product was washed with a little ether, yielding the adduct (2g) (0.407 g, 56%), m.p. 120° (decomp.) (from benzene-petroleum) (Found: C, 67.1; H, 4.9; N, 3.95; S, 7.5. $C_{22}H_{19}NO_4S$ requires C, 67.15; H, 4.9; N, 3.55; S, 8.15%).

Reaction with the Sulphine (1h).—The *E*-sulphine (1h) was treated as described for (1g). Work-up and chromatography on silica gel plates (CH_2Cl_2 - CCl_4 , 1 : 2) gave the adduct (2h) (29%), m.p. 94—96° (from benzene-petroleum) (Found: C, 66.6; H, 4.5; N, 3.6. $C_{21}H_{17}NO_2S$ requires C, 66.5; H, 4.5; N, 3.7%), ν_{\max} (KBr) 1 080 cm^{-1} (SO), and the starting sulphine (50%). The *Z*-isomer did not react.

Generation of Benzonitrile Oxide from α -Nitrotoluene.—To a solution of the sulphine (3) (1.00 g, 4.71 mmol), α -nitrotoluene (0.64 g, 4.67 mmol), and phenyl isocyanate (1.20 g, 10.1 mmol) in ether (35 ml), five drops of triethylamine were added. The mixture was gently refluxed; *NN'*-diphenylurea was slowly precipitated. After 3 h the mixture was filtered, the filtrate concentrated, and the residue crystallized (CH_2Cl_2 - Et_2O , 1 : 1) to give the adduct (4) (1.22 g, 78%), m.p. 97—99°. The crude product showed i.r. absorption at 1 080 cm^{-1} attributable to a small amount of the adduct (5).

The cycloaddition of di-*p*-tolylsulphine (1b) was performed in the same manner; yield 40% of the adduct (2b).

The *E*-sulphine (1j) in the same manner gave 47% of the adduct (2j), m.p. 112—115° (from CH_2Cl_2 - Et_2O , 1 : 1), ν_{\max} 1 085 cm^{-1} (SO).