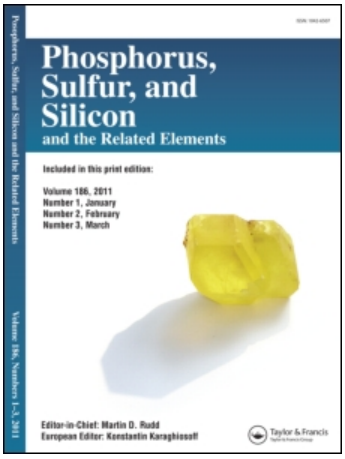

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CHLOROSULFONATION OF N-PHENYLMORPHOLINE, BENZOTHIAZOLE, 2-METHYL BENZOTHIAZOLE AND TRIPHENYLOXAZOLE

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CHLOROSULFONATION OF N-PHENYLMORPHOLINE, BENZOTHIAZOLE, 2-METHYL BENZOTHIAZOLE AND TRIPHENYLOXAZOLE

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N-Phenylmorpholine (1) reacted with chlorosulfonic acid to give the *p*-sulfonyl chloride (2), which was characterized as the sulfonamides (3–5). Benzothiazole (6) was converted into the sulfonyl chloride (7) by sequential treatment with hot chlorosulfonic acid and thionyl chloride. Reaction of (7) with amines afforded the derivatives (8–10); NMR spectral analysis of the dimethylamide (8) indicated that it was a mixture of the 4- and 7-isomers. Chlorosulfonation of 2-methylbenzothiazole (11) was achieved by heating with chlorosulfonic acid with or without thionyl chloride. The chloride (12) was converted into amides (13–19). Study of the NMR spectra indicated that mixtures of the 5- and 6-isomers were formed. 2,4,5-Triphenyloxazole (20) reacted with chlorosulfonic acid to give either the mono-(21), *bis* (23) or *bis-tris* sulfonylchlorides (23, 34); these were converted into 14 sulfonamides. 2-(*p*-Nitrophenyl)-4,5-diphenyloxazole (41) reacted with hot chlorosulfonic acid to give the bis-sulfonyl chloride (42), characterized as the dimethylsulfonamide (43). Attempts to form the pure monosulfonyl chloride and to mono nitrate 2,4,5-triphenyloxazole (20) were unsuccessful.

Key words: N-Phenylmorpholine; benzothiazole; 2-methylbenzothiazole; triphenyloxazole; chlorosulfonation.

INTRODUCTION

The work described in this paper forms part of our general research programme concerned with the synthesis and biological properties of arylsulfonyl derivatives.[1–3] In particular, it extends our previous work on the chlorosulfonation of heterocyclic compounds; for instance thiophen,[4] isoxazole,[5] thiophen and furan-carboxanilides,[6] benzylidenehydantoins,[7] coumarin[8] and diphenylfurazan.[9]

The chlorosulfonation of aromatic tertiary amines occurs preferentially in the *para*-position with respect to the tertiary amino group. The orientation of sulfonation is governed by the combination of the electron-donating properties and the relatively large size of the tertiary amino moiety. Thus, the reaction of N-methyl N-phenylformamide with chlorosulfonic acid is reported[10] to yield the *para*-sulfonyl chloride.

RESULTS AND DISCUSSION

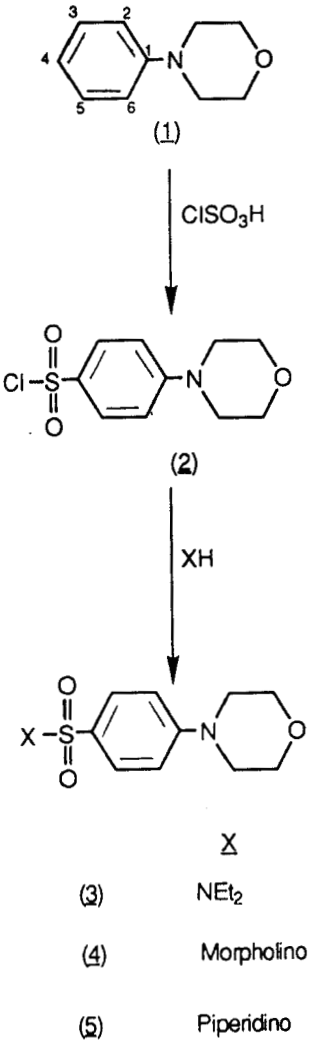
The reaction of N-phenylmorpholine (1), with chlorosulfonic acid was examined under various conditions. It was expected that selective *p*-sulfonation should be

possible with this molecule; the optimum conditions for conversion of (1) into the *para*-sulfonyl chloride (2) (35%) involved treatment with chlorosulfonic acid (6 molar equivalents) for 1 week at room temperature followed by warming at 60°C. Reaction at room temperature afforded largely unchanged N-phenylmorpholine, while prolonged heating at 100°C and above resulted in extensive decomposition. The use of excess chlorosulfonic acid (5 molar equivalents) in boiling thionyl chloride gave a complex mixture of products (multiple spots on TLC). This appeared to contain some of the sulfonic acid (IR spectrum showed a band for the OH group at 3400 cm^{-1}) and the 2,4-bis-sulfonyl chloride since the mass spectrum exhibited an ion cluster at M/Z 364 and the NMR spectrum showed the aromatic proton resonances as a complex multiplet (ABC pattern) indicative of a 1,2,4-trisubstituted benzene ring). The disulfonyl chloride probably results from initial *para*-sulfonation followed by N-sulfonation and rearrangement of the N-sulfonic acid group into the *ortho*-position as has been suggested in the sulfonation of diphenylamine.[11] The chlorosulfonation of (1) proved difficult and very sensitive to the reaction conditions; the crude sulfonyl chloride (2) was unstable and was therefore characterized as the diethylsulfonamide derivative (3). The NMR spectra of (2) and (3) both showed the aromatic proton resonances (δ 7.9–6.9) as a well-defined AA′ BB′ pattern confirming *para*-sulfonation. The sulfonyl chloride (2) was also condensed with morpholine and piperidine to give the sulfonamides (4 and 5). The NMR spectra of these derivatives showed the same AA′ BB′ aromatic proton resonance pattern.

The mass spectra of the compounds (2–5) (Chart 1) showed the relevant molecular ions (M^+) and subsequent fragmentation involving sequential loss of chlorine from the sulfonyl chloride (2) or of the amino moieties from the sulfonamides (3–5) and sulfur dioxide. Attempted condensation of (2) with hydrazine hydrate in methanol failed to give a pure product (multiple spots on TLC) and subsequent condensation with acetone was also unsuccessful.

The sulfonation of benzothiazole (6) by oleum is reported[12] to yield a mixture of the 4-, 6- and 7-sulfonic acids in the ratio of 70, 25 and 5% respectively. However, reaction of (6) with chlorosulfonic acid is claimed[13] to only yield a salt; repetition of the reaction both at room temperature and at 100°C confirmed this observation. On the other hand, when benzothiazole (6) was heated with excess chlorosulfonic acid followed by treatment with thionyl chloride, the sulfonyl chloride (7) was obtained as a gummy solid.

The product was characterized by reaction with amines to give the sulfonamides (8, 10) (Chart 2). Examination of the NMR spectra suggested that the products were generally mainly the 4-sulfonamides together with varying amounts of the 7-isomer. The failure of the reaction of chlorosulfonic acid alone on benzothiazole (6) to give the sulfonyl chloride (7) could be explained by the 4-sulfonic acid existing as the stabilized hydrogen-bonded structure (7a) (Chart 2) which requires the use of the stronger chlorinating agent (thionyl chloride) to convert it to (7); this is analogous to the situation previously observed in chlorosulfonation of diarylureas.[14] The NMR spectrum of the dimethylamide derivative (8) indicated that it was mainly the 4-sulfonamide with approximately 20% of the 7-isomer. There were two singlets (δ, 9.65, 9.58) representing the 2-hydrogen atom. The 5- and 7-protons appeared downfield as two sets of double doublets (δ 8.55, 8.04 respectively) due to the deshielding effect of the dimethylsulfamoyl moiety. The resonances showed both



X	
(3)	NEt_2
(4)	Morpholino
(5)	Piperidino

CHART 1 N-Phenylmorpholine (1) and its sulfonyl derivatives.

ortho-(6Hz) and *meta*- (1Hz) coupling constants. The 6-proton appeared as a doublet (δ, 7.51) with *ortho* coupling. The spectrum also showed another similar pattern of aromatic resonances indicative of the presence of the isomeric 7-sulfonamide. The NMR spectra of the morpholino (9) and the piperidino (10) derivatives exhibited a similar aromatic resonance pattern. The mass spectra of the derivatives showed the molecular ions (M^+) and fragments corresponding to successive loss of the amino and sulfonyl moieties.

Previous workers[15a,15b] reported that 2-methylbenzothiazole (11) reacts with chlorosulfonic acid (4 molar equivalents) at 140°C to give the 6-sulfonyl chloride. We found that under these conditions, the yield of product was low (approximately

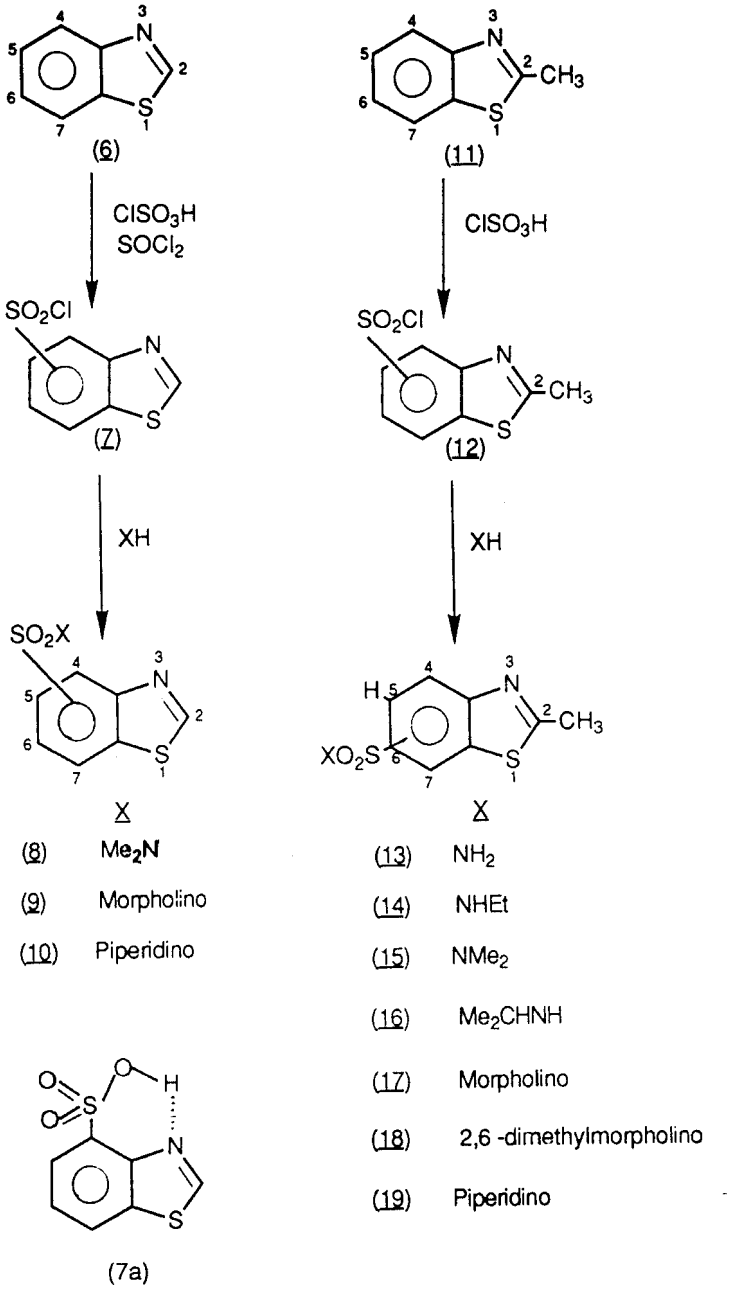


CHART 2 Sulfonyl derivatives of benzothiazole (6) and 2-methylbenzothiazole (11).

20%), however in the presence of thionyl chloride the yield was increased (45%). The difference in the orientation of chlorosulfonation of benzothiazole (6) and the 2-methyl derivative (11) is interesting; the former appears to give the 4-sulfonic acid as the major product, this may arise from breakdown of the initially formed salt. On the other hand, with 2-methylbenzothiazole (11) no salt formation ap-

parently occurs possibly this is inhibited by the steric effect of the methyl group and the orientation is now governed by electron-donation from the nitrogen lone pair of electrons leading to preferential 6-sulfonation. 2-Methylbenzothiazolesulfonyl chloride (12) was reacted with various amines to give the sulfonamides (13–19) (Chart 2 and Table I).

The sulfonamides obtained were mixtures of isomers (2 spots on TLC) and are probably the 5- and 6-sulfonamides with the latter predominating due to the pow-

TABLE I

Physical data for the benzothiazole and 2-methylbenzothiazole sulfonyl derivatives

Comp No	Yield (%)	m.p. (°C)	molecular formula	Analysis Found (calc.) % C	H	N	MS (M^+)
8	50	103-104	$C_9H_{10}N_2O_2S_2$	44.8 (44.6)	4.6 (4.2)	11.3 (11.6)	242
9	65	227	$C_{11}H_{12}N_2O_3S_2$	46.8 (46.5)	4.3 (4.2)	9.8 (9.8)	284
10	45	120	$C_{12}H_{14}N_2O_2S_2$	51.4 (51.1)	5.0 (5.0)	9.8 (9.9)	282
13	50	182-184 (Lit[15] 184-185)	$C_8H_8N_2O_2S_2$	42.0 (42.1)	3.3 (3.5)	12.1 (12.3)	228
14	65	132	$C_{10}H_{12}N_2O_2S_2$	46.5 (46.9)	5.0 (4.7)	11.1 (10.9)	256
15	72	122-123	$C_{10}H_{12}N_2O_2S_2$	46.6 (46.9)	4.9 (4.7)	11.0 (10.9)	256
16	60	165	$C_{11}H_{13}N_2O_2S_2$	55.4 (55.7)	5.8 (5.5)	12.0 (11.8)	237
17	58	150	$C_{12}H_{14}N_2O_3S_2$	48.0 (48.3)	5.0 (4.7)	9.6 (9.4)	298
18	62	138-140	$C_{14}H_{18}N_2O_3S_2$	51.3 (51.5)	5.6 (5.5)	8.9 (9.4)	326
19	60	175-176	$C_{13}H_{16}N_2O_2S_2$	52.6 (52.7)	5.4 (5.4)	9.4 (9.5)	296

erful electron-releasing property of the nitrogen atom enhanced by the (+I) inductive effect of the attached methyl group. Recrystallization of the piperidino derivative (19) from ethanol afforded a pure compound m.p. 175–176°C (one spot on TLC) which is probably the 6-derivative. (Chart 2); the orientation of sulfonation has now been confirmed by X-ray crystallography of (19).[15c]

The NMR spectrum of (19) showed the aromatic 7-H proton resonance as a doublet δ 8.29 (with *meta* coupling $J \simeq 1$ Hz) this was the lowest field signal due to the deshielding effect of the adjacent sulfomoyl moiety. The 4-H proton appeared as a doublet (δ 8.06, with *ortho* coupling $J \simeq 8$ Hz) and the 5-H proton was a double doublet δ 7.84 and δ 7.79 showing both *ortho* and *meta* coupling. This aromatic resonance pattern is consistent with either 5- or 6-sulfonation, but the latter is favoured on electronic grounds.

We have previously reported[16] the chlorosulfonation of 2-methyl-4,5-diphenyloxazole, as an extension to this work, the reaction of chlorosulfonic acid on 2,4,5-triphenyloxazole (20) was studied.

2,4,5-Triphenyloxazole was prepared from benzoin as described by Davidson *et al.*[17] The reaction of the triphenyloxazole (20) with chlorosulfonic acid has been examined under a variety of conditions. Treatment of (20) with chlorosulfonic acid (1.2 molar equivalents) in thionyl chloride at room temperature afforded the monosulfonyl chloride (21), characterized as the dimethylsufonamide (22) (Chart 3). The NMR spectrum of 22 showed some of the aromatic proton resonances (δ 8.30–8.10) as a well-defined AA′ BB′ pattern; the correct aliphatic/aromatic proton ratio of 3:7, and the mass spectrum exhibited the molecular ion (M^+, 404). However, repetition of the chlorosulfonation of (20) afforded mixtures of the sulfonyl chloride (21) and unchanged triphenyloxazole (20). Subsequent reaction with dimethylamine afforded a product from which the desired dimethylsulfonamide (22) was isolated by column chromatography.

When triphenyloxazole (20) was treated with a large excess of chlorosulfonic acid (20 molar equivalents) at room temperature, the 4,4′-bis-sulfonylchloride (23) was formed; the latter compound was also obtained using less reagent (5 molar or 2.5 molar equivalents in thionyl chloride). The reaction of 20 with excess chlorosulfonic acid at room temperature appeared comparatively fast since TLC indicated that the bis-sulfonyl chloride (23) (R_F 0.85) was formed after 1 hour; the same product was obtained after 1 week. The chloride was condensed with a range of amines to give the sulfonamides (24–28, 32, 33); reaction with hydrazine afforded the hydrazine (29) which was characterized as the hydrazones (30, 31) (Chart 3 and Table II). The NMR spectrum of the dimethylsulfonamide derivative (24) showed the aromatic proton resonances (δ 8.5–7.9) containing an AA′ BB′ splitting pattern (δ 8.3–8.1) indicative of *p*-disubstitution and an aromatic-aliphatic proton ratio of approximately one. The mass spectrum also showed the molecular ion (M^+, 511) confirming that the bis-dimethylsulfonamide (24) had been formed.

Triphenyloxazole (20) possesses three phenyl groups, we consider that the 4- and 5-phenyl groups will be activated towards electrophilic substitution by the attached alkenic double bond whereas the 2-phenyl moiety will be relatively deactivated by the adjacent C=N bond. It is therefore predicted that the disulfonyl chloride (23) is the 4,4′-derivative (Chart 3). With regard to the relative reactivity of the 4- and 5-phenyl groups, the lone electron pair on the N-3 nitrogen atom should feed electrons more effectively into the 4-position of the phenyl nucleus as

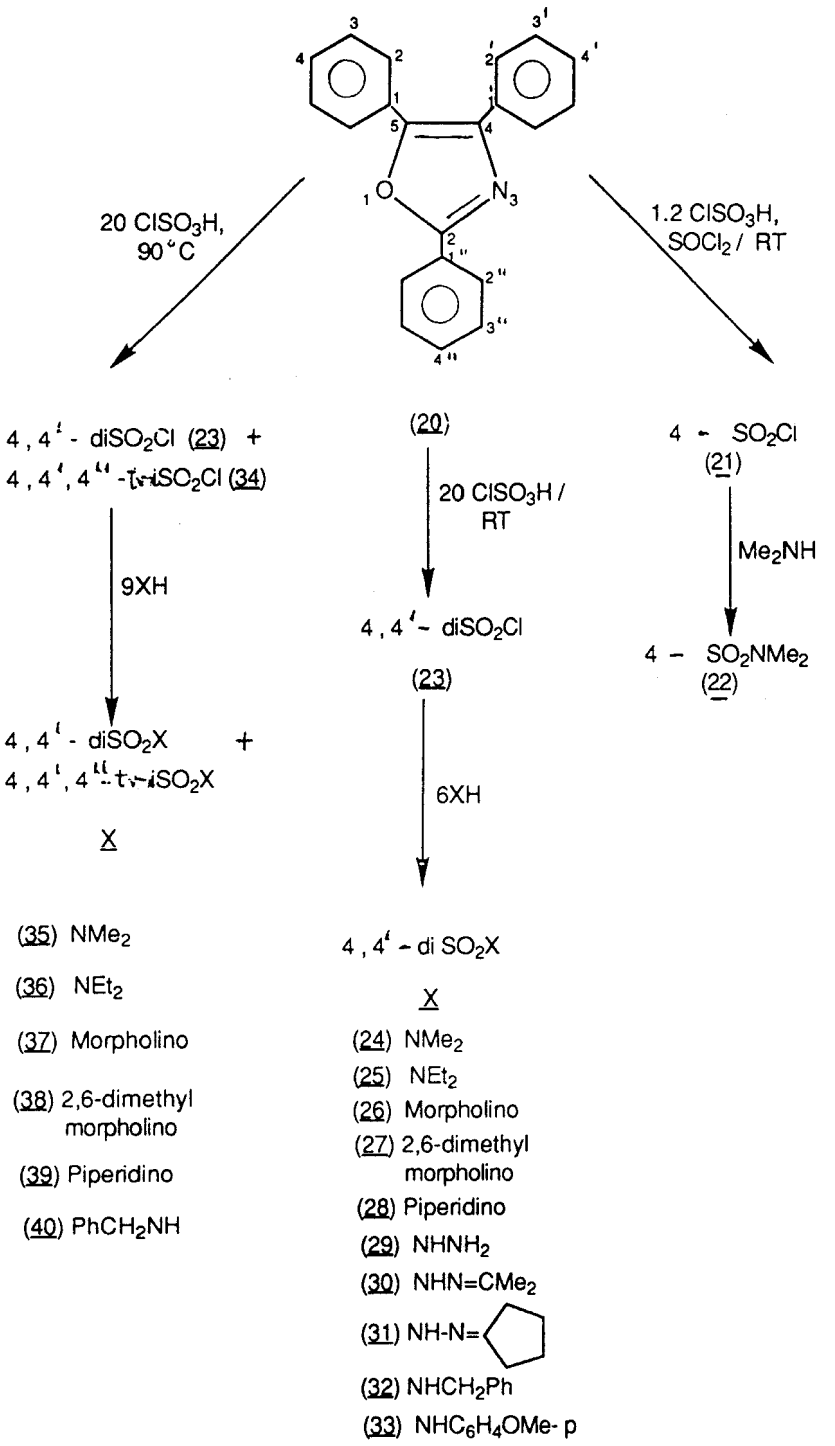


CHART 3 Chlorosulfonation of 2,4,5-triphenyloxazole (20) and its sulfonyl derivatives.

TABLE II

Physical data for the sulfonyl derivatives of 2,4,5-triphenyloxazole (20)

Comp No	Yield (%)	m.p. (°C)	molecular formula	Analysis found (calc.) % C	H	N	MS (M^+)	R_F
22	55	228-230	$C_{23}H_{20}N_2O_3S$	68.0 (68.3)	5.1 (4.9)	6.7 (6.9)	404	0.44
24	61	240-242	$C_{25}H_{25N3}O_5S_2$	58.5 (58.7)	5.2 (4.9)	8.0 (8.2)	511	0.74
25	64	237-238	$C_{29}H_{33}N_3O_5S_2$	61.6 (61.4)	5.6 (5.8)	7.3 (7.4)	567	0.74
26	87	241-242	$C_{29}H_{29}N_3O_7S_2$	58.2 (58.5)	5.1 (4.9)	6.9 (7.0)	595	0.68
27	50	204-205	$C_{33}H_{37}N_3O_7S_2$	61.1 (60.8)	6.1 (5.7)	6.6 (6.4)	652*	0.72
28	37	282	$C_{31}H_{33}N_3O_5S_2$	62.6 (62.9)	5.8 (5.6)	6.8 (7.1)	591	0.78
29	73	137	$C_{21}H_{19}N_5O_5S_2$	51.5 (51.9)	4.3 (3.9)	14.0 (14.4)	-	0.80
30	61	175-176	$C_{27}H_{27}N_5O_5S_2$	57.0 (57.3)	5.0 (4.8)	12.1 (12.4)	-	0.63
31	31	154	$C_{31}H_{31}N_5O_5S_2$	60.0 (60.3)	5.2 (5.0)	11.0 (11.3)	-	0.75
32	58	163	$C_{35}H_{29}N_3O_5S_2$	66.1 (66.1)	5.0 (4.6)	6.4 (6.6)	635	0.40
33	27	265	$C_{35}H_{29}N_3O_7S_2$	54.3 (54.7)	4.1 (3.8)	5.8 (5.5)	668	0.45
35	43	163-166	$C_{27}H_{30}N_4O_7S_3$	54.5 (52.4)	4.5 (4.8)	8.5 (9.1)	618	0.85, 0.74
36	44	115-118	$C_{33}H_{42}N_4O_7S_3$	58.7 (56.4)	5.8 (5.9)	7.6 (8.0)	702*	0.85 0.75
37	55	165-166	$C_{33}H_{36}N_4O_{10}S_3$	55.4 (53.2)	4.9 (4.8)	7.2 (7.5)	744*	0.65 0.60
38	46	141-144	$C_{39}H_{48}N_4O_{10}S_3$	56.0 (51.7)	5.7 (5.8)	6.5 (6.8)	828*	0.83 0.73
39	50	150-152	$C_{36}H_{42}N_4O_7S_3$	60.1 (58.5)	5.7 (5.7)	7.4 (7.6)	738*	0.80 0.74
40	62	85-87	$C_{42}H_{36}N_4O_7S_3$	64.6 (62.7)	4.5 (4.5)	6.8 (7.0)	804*	0.58 0.43

* These represent the $M^+ + 1$ ions, since these mass spectra were determined by FAB method.

compared with the oxygen atom. Hence the latter position would be the favoured site for mono-sulfonation rather than the 4′-position, so accounting for the assigned structure of the 4-sulfonyl chloride (21) (Chart 3).

When 2,4,5-triphenyloxazole (20) was heated with excess chlorosulfonic acid at 90° or 150°C, a mixture of the 4,4′-disulfonyl chloride (23) and the 4,4′,4″-trisulfonyl chloride (34) was obtained. This conclusion was in agreement with the microanalytical data; the product showed two spots (R_F 0.85, 0.74) on TLC, and the mass spectrum displayed the molecular ion for (34) (M^+, 592). All efforts to force the reaction to the pure trisulfonated product were unsuccessful, e.g. use of boiling excess chlorosulfonic acid (20 molar equivalents, 5 days) in the presence of phos-

phorus pentachloride. It is therefore concluded that the formation of the tri-sulfonyl chloride (34) is unfavourable in comparison with the di-sulfonyl chloride (23) and that the reversibility of sulfonation allows the formation of a favoured equilibrium mixture of (23) and (34). This hypothesis is supported by the reported synthesis[18] of the tri-nitro derivative of (20) since nitration unlike sulfonation, is irreversible. The mixture of the sulfonyl chlorides (23, 34) was condensed with amines to give the derivatives (35–40) (Chart 3). Attempted separation of the bis/tris mixture of the dimethylsulfonamides (24, 35) by preparative TLC was unsuccessful.

Study of the NMR spectrum of the mixture of the dimethylamides (24, 35) showed that the aromatic protons resonated as a complex multiplet (δ 8.5–7.8) with no clear AA′ BB′ pattern. This possibly indicates that sulfonation of the least reactive 2-phenyl nucleus has occurred in the *meta*-position. The major product in the mixture appears to be the trisulfonamide (35) since the observed aliphatic-aromatic proton ratio (1:3) is much closer to that of 35 (1:5), as compared with the ratio of 0.9 required for the bis-derivative (24).

2-(*p*-Nitrophenyl)-4,5-diphenyloxazole (41) was prepared from benzoin and *p*-nitrobenzoyl chloride following the method previously described[17a–c] for the synthesis of 2,4,5-triphenyloxazole. Treatment of 41 with excess chlorosulfonic acid (12 molar equivalents) at room temperature gave a mixture of mono- and bis-sulfonyl chlorides (2 spots on TLC); however when the reaction was carried out at 90°C, the bis-sulfonyl chloride (42) was obtained (48%).

The latter compound was characterized as the dimethylsulfonamide derivative (43) (Chart 4). The NMR spectrum showed a complex multiplet for the aromatic proton resonances (δ 8.4–7.2) due to the presence of three overlapping AA′ BB′ patterns. The methyl protons appeared as a singlet (δ 2.8) and the observed aliphatic-aromatic proton ratio of 1:1 was in agreement with the structure (43). The 2-phenyl ring is now strongly deactivated towards electrophilic substitution by the electron-withdrawing nitro substituent consequently no trisulfonation occurs with this substrate. The observed *para*-disulfonation is in agreement with previous results[16] on the chlorosulfonation of 2-methyl-4,5-diphenyloxazole.

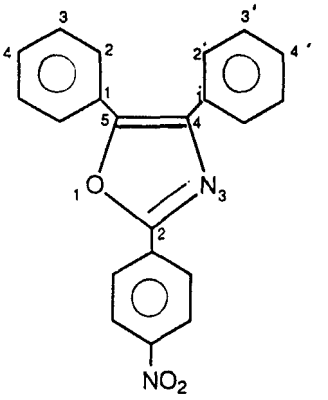
Attempts to prepare the mono-sulfonyl chloride of (41) by reaction with chlorosulfonic acid (1.2 molar equivalents) in thionyl chloride afforded mixtures of the desired product and the starting material (41) as occurred in the analogous reaction with 2,4,5-triphenyloxazole (20) which agrees with our postulate of a similar orientation of sulfonation in both substrates (20, 41).

Previous workers[19] claimed that 2,4,5-triphenyloxazole (20) reacts with concentrated nitric acid at 15°C to give a mono-nitro derivative (m.p. 194°C). We would expect that this product would be 5-(*p*-nitrophenyl)-2,4-diphenyloxazole. It therefore appeared of interest to obtain this compound and examine its chlorosulfonation to determine whether selective mono- and di-sulfonation would occur.

However in our hands, attempted repetition of the nitration of 2,4,5-triphenyloxazole was unsuccessful; the only isolated product was benzil.

EXPERIMENTAL

Melting points were determined using a Gallenkamp electric apparatus and are uncorrected. The NMR spectra were recorded with a Bruker AC250 spectrometer using tetramethylsilane as internal standard and deuterochloroform as solvent unless otherwise stated. Resonances marked by an asterisk were



(41)

12 $ClSO_3H$ / 90°C

4 , 4' - diSO_2Cl

(42)

Me_2NH

4 , 4' - di SO_2NMe_2

(43)

CHART 4 Sulfonation of 2-(*p*-nitrophenyl)-4,5-diphenyloxazole (41).

reduced by D_2O treatment. IR spectra were recorded as Nujol mulls using a Perkin-Elmer 237 spectrometer. Mass spectra were obtained with a VG micromass V15 spectrometer operating at 70 ev. TLC was carried out using Camlab silica gel plates sensitized to UV 254 nm using cyclohexane-ethyl acetate (1:1) as eluant unless otherwise stated.

N-Phenylmorpholine-p-sulfonyl chloride (2). Chlorosulfonic acid (25 ml, 0.38 mole) was gradually added to N-phenylmorpholine (1) (10 g, 0.061 mole) with agitation at 0°C. The dark reddish-brown solution was left for 1 week at room temperature and then heated at 50–60°C for 2 hours. The solution was slowly added to crushed ice with stirring; the precipitate was filtered off, washed with cold water and dried in a vacuum desiccator to give (2) (5.6 g, 35%), m.p. 154–157°C (decomp). TLC showed one spot, R_F 0.58. IR: ν_{max} 1590 (ArC=C), 1360, 1160 (SO_2) cm^{-1}. MS: 263,261 (M^+), 226 (M^+—Cl), 162 (M^+—SO_2Cl). NMR: δ 7.9–6.9 (m, 4 H, ArH AA' BB' pattern), 3.9 (t, 4 H, morpholino O—CH_2), 3.4 (t, 4 H, morpholino N—CH_2).

The diethylsulfonamide derivative (3). The sulfonyl chloride (2 g, 0.0076 mole) was stirred with diethylamine (2 ml, 0.031 mole) in ethanol (30 ml) at room temperature for 2 hours. The mixture was diluted with water and neutralized with dilute hydrochloric acid. The solid was filtered off, washed with water and recrystallized from ethanol to give (3) as gold-coloured plates (1.95 g, 86%), m.p. 125°C. TLC showed one spot, R_F 0.44 (Found: C, 56.5; H, 7.4; N, 9.6. $C_{14}H_{22}N_2O_3S$ requires C, 56.4; H, 7.4; N, 9.4%). IR: ν_{max} 1600 (ArC=C), 1330, 1140 (SO_2) cm^{-1}. NMR: δ 7.7–6.9 (m, 4 H, ArH, AA′ BB′ pattern), 3.9 (t, 4 H, morpholino-O$\underline{CH_2}$), 3.4 (t, 4 H, morpholino N-$\underline{CH_2}$), 3.2 (q, 4 H, N$\underline{CH_2}CH_3$), 1.05 (t, 6 H, $NCH_2\underline{CH_3}$). MS: 298 (M^+), 226 (M^+—NEt_2).

The morpholidate derivative (4). The sulfonyl chloride (2) (2 g) was similarly reacted with morpholine (3.3 g, 4 molar equivalents) to give (4) as a fawn powder (1.6 g, 67%), m.p. 205–206°C. TLC showed one spot, R_F 0.21. (Found: C, 53.6; H, 6.6; N 9.1. $C_{14}H_{20}N_2O_4S$ requires C, 53.8; H, 6.4; N, 9.0%). IR: ν_{max} 1595 (ArC=C), 1330, 1150 (SO_2) cm^{-1}. MS: 312 (M^+), 226 (M^+—C_4H_8NO), 162 (M^+—$SO_2C_4H_8NO$), 86 (C_4H_8NO), 56. NMR: δ 7.70–7.0 (m, 4 H, ArH), 3.9–3.0 (m, 16 H, morpholino H).

The piperidino derivative (5). The sulfonyl chloride (2) (2 g) by reaction with piperidine (2.5 g) afforded (5) as a fawn solid (1 g, 56%), m.p. 224–226°C. TLC showed one spot, R_F 0.30. (Found: C, 58.0, H, 6.8; N 8.8. $C_{15}H_{22}N_2O_3S$ requires C, 58.1; H, 7.1; N, 9.0%). IR: ν_{max} 1590 (ArC=C), 1345, 1140 (SO_2) cm^{-1}. NMR: δ 7.7–6.9. (m, 4 H, ArH), 3.9 (t, 4 H, morpholino O$\underline{CH_2}$), 3.3 (t, 8 H, morpholino and piperidino N—$\underline{CH_2}$), 3.0 (t, 4 H, $SO_2N\underline{CH_2}$), 1.6–1.4 (m, 6 H, piperidino CH_2) MS: 310 (M^+), 226 (M^+—$C_5H_{10}N$), 162 (M^+—$SO_2C_5H_{10}N$).

Chlorosulfonation of benzothiazole (6). Benzothiazole (20 g, 0.15 mole) was gradually added to chlorosulfonic acid (60 ml, 0.90 mole) and the dark solution was refluxed at 150°C for 4½ hours. The cooled solution was treated with thionyl chloride and refluxed for 2 hours. The mixture was added to crushed ice, and the suspension extracted with ether (200 ml) to give the sulfonyl chloride (7) as a gummy solid (14.06 g). The mass spectrum showed the molecular ion (M^+, 235). The product was dissolved in ethanol (50 ml) and directly converted to the sulfonamide derivatives (8–12) by reaction with the appropriate amine (4 molar equivalents) at room temperature (6 hours).

The dimethylsulfonamide (8) (*mainly the 4-isomer*). TLC showed one spot, R_F 0.79. ^{1}H NMR (DMSO-d_6); δ 9.65 (s, 1 H, 2-H), 8.56 (dd, 1 H, 5-H), 8.54 (dd, 1 H, 7-H), 8.46 (dd, 1 H, 6-H), 2.7 (s, 6 H, NMe_2).

The morpholidate (9). TLC showed one spot, R_F 0.79. ^{1}H NMR: δ 9.1 (s, 1 H, 2-H), 8.23 (dd, 1 H, 5-H), 8.18 (dd, 1 H, 7-H), 7.6 (dd, 1 H, 6-H), 3.75–2.0 (m, 8 H, morpholino H).

The piperidino derivative (10). TLC showed one spot, R_F 0.88. ^{1}H NMR: δ 9.2 (s, 1 H, 2 H), 8.3 (dd, H, 5 H), 8.1 (dd, 1 H, 7 H), 7.6 (dd, 1 H, 6-H), 3.4–3.2 (m, 10 H, piperidino H). MS: 282 (M^+), 218 (M^+—SO_2), 198 (M^+—$C_5H_{10}N$), 134 (M^+—$SO_2C_5H_{10}N$), 84 ($C_5H_{10}N$).

Chlorosulfonation of 2-methylbenzothiazole (11). 2-Methylbenzothiazole (20 g, 0.13 mole) was refluxed with chlorosulfonic acid (100 ml, 1.5 moles) for 4 hours, the mixture was allowed to cool and was refluxed with thionyl chloride (50 ml) for 2 hours. The solution was added to crushed ice (1.5 l) and extracted with ether (300 ml) to give a brown oily solid (28 g). Trituration with ethanol at 0°C afforded the sulfonyl chloride (12) as fawn crystals (15.3 g, 45%), m.p. 80–82°C (lit.[15] 68°C). (Found: C 38.5; H, 2.2; N, 5.8. $C_8H_6ClNO_2S_2$ requires C, 38.8; H, 2.4; N, 5.6%). MS showed the molecular ion (M^+ 249, 247), 212 (M^+—Cl), 149 (M^+—SO_2Cl).

The preparation of the sulfonamides (13–19). The sulfonyl chloride (12) (0.01 mole) was stirred with the appropriate amine (0.04 mole) in ethanol (30 ml) at room temperature (3 hours). The mixture was diluted with cold water (100 ml), the product was filtered off and purified by recrystallization from ethanol to give the sulfonamide.

The dimethylamide (15). ^{1}H NMR: δ 8.30 (d, 1 H, 7-H, J1.1 H_z), 8.06 (d, 1 H, 4-H, J7 H_z), 7.85 (dd, 1 H, 5-H, J, 1 H_z and 7 Hz), 2.90 (s, 3 H, CH_3). MS: 256 (M^+), 212 (M^+—NMe_2), 149 (M^+—SO_2NMe_2), 107, 63, 45 (Me_2NH).

The morpholidate (17). ^{1}H NMR: δ 8.28 (d, 1 H, 7-H), 8.05 (d, 1 H, 4-H), 7.83–7.78 (dd, 1 H, 5-H), 2.85 (s, 3 H, CH_3).

The piperidino derivative (19). By recrystallization from ethanol, the first product was prisms (1.5 g), m.p. 135–136°C. TLC showed two spots R_F 0.60, 0.37. A further recrystallization afforded pure (19) as needles (1.1 g), m.p. 174–175°C, TLC showed one spot R_F 0.60. ^{1}H NMR: δ 8.29 (d, 1 H, 7-H), 8.06 (d, 1 H, 4-H), 7.84–7.79 (dd, 1 H, 5-H, J 1.2, J 8.3 Hz). MS: 296 (M^+), 232 (M^+—SO_2), 212 (M^+—$C_5H_{10}N$), 148 (M^+—$SO_2C_5H_{10}N$), 107, 84 ($C_5H_{10}N$).

Chlorosulfonation of 2,4,5-triphenyloxazole (20). a) *Formation of the mono-sulfonyl chloride* (21). A solution of chlorosulfonic acid (2.6 ml, 0.041 mole) in thionyl chloride (20 ml, 0.272 mole) was gradually added to 2,4,5-triphenyloxazole (20) (10 g, 0.034 mole) at 0°C. The solution was left at room temperature for 3 hours and poured onto crushed ice. The precipitate was collected, washed with water and dried to give the mono-sulfonyl chloride (21) (45%), m.p. 135–136°C. TLC (ethyl acetate-cyclohexane 2:3) showed one spot, R_F 0.45. (Found: C 63.4; H, 3.3; N, 3.4. $C_{21}H_{14}ClNO_3S$ requires C 63.7; H, 3.5; 3.5%). IR: ν_{max} 1600 (ArC=C), 1380, 1162 (SO_2) cm^{-1}. MS: 397, 395 (M^+), 360 (M^+—Cl), 296 (M^+—SO_2Cl).

Repetition of this experiment using various amounts of thionyl chloride (5, 8, or 10 molar equivalents) afforded a mixture of the mono-sulfonyl chloride (21) and the starting material (20) (70% yield). TLC (ethyl acetate-cyclohexane 2:3) showed two spots R_F 0.68 (20) and 0.45 (21). The product was reacted with excess dimethylamine and purified by column chromatography on silica gel and elution with ethyl acetate-cyclohexane (2:3) to give the pure dimethylsulfonamide (22) (37%). TLC (ethyl acetate-cyclohexane 2:3) showed one spot, R_F 0.44. IR: ν_{max} 1600 (ArC=C), 1340, 1160 (SO_2) cm^{-1}. NMR (DMSO-d_6): δ 8.50–7.80 (m, 14 H, ArH; AA′ BB′ pattern at δ 8.3–8.1), 2.90 (s, 6 H, NMe_2).

b) *Formation of the bis-sulfonyl chloride* (23). 2,4,5-Triphenyloxazole (20) (10 g, 0.034 mole) was gradually added to chlorosulfonic acid (42 ml, 0.68 mole) at 0°C. The mixture was left for one week at room temperature and added to crushed ice. The solid precipitate was filtered off, washed with water and dried in a vacuum desiccator to give (23) (12.3 g, 83%), m.p. 300–302°. TLC showed one spot, R_F 0.85. (Found: C, 50.5; H, 2.9; N, 2.6. $C_{21}H_{13}Cl_2N_5S_2$ requires C 50.9; H, 2.6; N, 2.8%). IR: ν_{max} 1600 (ArC=C), 1380, 1160 (SO_2) cm^{-1}. MS: 497, 495, 493 (M^+), 393 (M^+—SO_2Cl), 295 (M^+—2xSO_2Cl).

c) *Formation of the bis/tris-sulfonyl chlorides* (23, 34). 2,4,5-Triphenyloxazole (20) (10 g, 0.034 mole) was heated with chlorosulfonic acid (42 ml, 0.68 mole) at 90°C for 5 hours to give mixture of 23 and 24 (15.6 g, 87%), m.p. 143–146°C. TLC showed two spots R_F 0.85 (23) and 0.74 (34). (Found: C, 45.2; H, 2.3; N, 2.4. The bis-sulfonyl chloride (23) requires C, 50.9; H, 2.6; N, 2.8; the tris-sulfonyl chloride (34) requires C, 42.5; H, 2.0; N, 2.4%). IR: ν_{max} 1600 (ArC=C), 1380, 1162 (SO_2) cm^{-1}. MS: 595, 593, 591 (M^+ for 34), 492 (M^+ for 23), 295 (M^+—SO_2Cl).

Repetition of the experiment at 150°C for 5 and 18 hours again afforded a mixture of 23, 34 (64%), m.p. 107–112°C TLC showed two spots R_F 0.85, 0.74.

General procedure for the preparation of the 2,4,5-triphenyloxazole sulfonamides (22, 24–28, 33, 35–40). The sulfonyl chloride (21, 23 or 34) (0.005 mole) was reacted with the appropriate amine (0.015, 0.3 or 0.5 mole respectively) in methanol (20 ml) at room temperature for 6 hours. The mixture was poured onto ice-water (100 ml), and recrystallized from methanol to give the sulfonamide.

The dimethylsulfonamide (22). IR: ν_{max} 1600 (ArC=C), 1350, 1160 (SO_2) cm^{-1}. MS: 404 (M^+), 360 M^+—NMe_2), 297 (M^+—SO_2NMe_2, 165, 77, (C_6H_5). NMR (DMSO-d_6): δ 8.5–7.8 (*m*, 14 H, ArH, AA′ BB′), 2.9 (s, 6 H, NMe_2).

The bis-dimethylsulfonamide (24). IR: ν_{max} 1600 (ArC=C), 1340, 1160 (SO_2) cm^{-1}. MS: 511 (M^+), 403 (M^+—SO_2NMe_2), 354, 295 (M^+—2xSO_2NMe_2), 165, 149, 57, 43. NMR (DMSO-d_6): δ 8.5–7.9 (m, 13 H, ArH), 2.9 (s, 12 H, NMe_2).

The bis-morpholidate (26). IR: ν_{max} 1610 (ArC=C), 1340, 1160 (SO_2) cm^{-1}. NMR (DMSO-d_6): δ 8,3–7.6 (m, 13 H, ArH, AA′ BB′ pattern 8.05, 7.87) 3.8–3.4 (m, 8 H, morpholino $\underline{CH_2}$—O), 2.6–2.6 (m, 8 H, morpholino $\underline{CH_2}$—N).

The piperidino derivative (28). IR: ν_{max} 1610 (ArC=C), 1340, 1160 (SO_2) cm^{-1}. MS: 591 (M^+), 443 (M^+—$SO_2NC_5H_{10}$), 295 (M^+—2x$SO_2NC_5H_{10}$). NMR (DMSO-d_6): δ 8.5–7.9 (m, 13 H, ArH), 3.2–2.9 (m, 8 H, piperidino N—$\underline{CH_2}$), 1.8–1.2 (m, 12 H, piperidino H).

The bis/tris-dimethylsulfonamide (35). IR: ν_{max} 1600 (ArC=C), 1380, 1162 (SO_2) cm^{-1}. MS: 619 (M^+), 511 (M^+—SO_2NMe_2), 403 (M^+—2xSO_2NMe_2) 295 (M^+—3xSO_2NMe_2), 212, 165, 149, 77. NMR (DMSO-d_6): δ 8.5–7.8 (m, ArH), 2.8 (s, NMe_2). The observed aliphatic-aromatic ratio = 1.3. [The tris-derivative (35) requires a ratio of 1.5; the bis-compound (24) requires 0.9].

The bis/tris-piperidino derivative (39). IR: ν_{max} 1610 (ArC=C), 1340, 1160 (SO_2) cm^{-1}. MS: 739 (M^+), 591 (M^+—$SO_2NC_5H_{10}$), 443 (M^+—2x$SO_2NC_5H_{10}$), 295 (M^+—3x$SO_2NC_5H_{10}$). NMR (DMSO-d_6): δ 8.5–7.8 (m, ArH), 3.2–2.9 (m, piperidino N—$\underline{CH_2}$), 1.6–1.2 (m, piperidino H). [The observed aliphatic-aromatic ratio = 3; tris derivative (39) requires 2.5 and the bis compound (28) requires 1.7].

The bis-sulfonylhydrazide (29). The bis-sulfonyl chloride (23) (3 g, 0.006 mole) was added to a solution of hydrazine hydrate (2.4 g of 98%, 0.047 mole) in methanol (15 ml) at 0°C. After 3 hours, the mixture was diluted with ice-water (60 ml), the precipitate collected, washed with water (2 × 15 ml) and dried in a vacuum desiccator. The product was recrystallized from methanol to give (29). IR: ν_{max} 3300, 3250 (NH), 1600 (ArC=C), 1360, 1160 (SO_2) cm^{-1}.

The acetone hydrazone (30). The hydrazide (29) (2 g, 0.004 mole) was added to acetone (15 ml) at

0°C and left at room temperature (30 minutes). The solution was cooled (0°C) when the hydrazone (30) crystallized out as plates. IR; ν_{max} 3250 (NH), 1360, 1160 (SO_2) cm^{-1}. NMR (DMSO-d_6): δ 10.2* (s, 2 H, NH) 8.2–7.6 (m, 13 H, ArH), 2.5 (s, 12 H, $Me_2C{=}N$).

2-(p-Nitrophenyl-4,5-diphenyloxazole (41). A solution of benzoin (5.3 g, 0.025 mole) in pyridine (30 ml) was gradually added to *p*-nitrobenzoyl chloride (5.2 g, 0.028 mole). The mixture was heated on a steam bath for 15 minutes and finally on an electric hot plate to obtain a clear solution. The solution was poured with stirring, into cold water (100 ml); the solid was collected, washed with water and recrystallized from ethanol to give *p*-nitrobenzoylbenzoin (5.6 g, 62%), m.p. 122–125°C. TLC (ethyl acetate-cyclohexane 2:3) showed one spot R_F 0.63.

The above product (8.2 g, 0.023 mole) was refluxed with a solution of ammonium acetate (2 g) in glacial acetic acid (30 ml) for 1 hour. The cold solution was added to water and the precipitate recrystallized from ethanol to give (41) as prisms (5.75 g, 74%), m.p. 157–158°C (Found: C, 73.4; H, 4.4; N, 8.0. $C_{21}H_{14}N_2O_3$ requires C, 73.7; H, 4.1; N, 8.1%). TLC (ethyl acetate-cyclohexane-petroleum ether 1:1:1) showed one spot, R_F 0.57. NMR (DMSO-d_6): δ 8.4–7.4 (m, 14 H, ArH; AA′ BB′ pattern at δ 8.4–8.3). MS showed the molecular ion (M^+, 342).

Chlorosulfonation of 2-(p-nitrophenyl)-4,5-diphenyloxazole (41). The oxazole (41) (2 g, 0.006 mole) was heated with chlorosulfonic acid (5 ml, 0.072 mol) at 90°C for 3 hours. The solution was added to crushed ice; the solid precipitate was filtered off, washed with water and dried in a vacuum desiccator to give the bis-sulfonyl chloride 42 (1.5 g, 48%), m.p. 165–168°C. TLC (ethyl acetate-cyclohexane-petroleum ether 1:1:1) showed one spot, R_F 0.55. The Beilstein test was positive. MS showed the molecular ion (M^+, 538).

The product was characterized as the bis-dimethylsulfonamide derivative (43) (34% from methanol), m.p. 136–139°C. (Found: C, 53.6; H, 4.2; N, 9.8. $C_{25}H_{24}N_4O_7S_2$ requires C, 53.9; H, 4.3; N, 10.0%). TLC (ethyl acetate-cyclohexane-petroleum ether 1:1:1) showed one spot, R_F 0.63. NMR (DMSO-d_6): 8.4–7.2 (m, 12 H, ArH), 2.8 (s, 12 H, NMe_2). MS showed the molecular ion (M^+, 556).

Attempted nitration of 2,4,5-triphenyloxazole (20). 2,4,5-Triphenyloxazole (2 g) was added portionwise to concentrated nitric acid (10 ml) at 0°. The mixture was stirred at room temperature (24 hours) and poured onto ice-water (50 ml). The precipitate was collected, washed with water (3 × 10 ml) and dried. Recrystallization from methanol gave benzil (0.6 g, 42%), m.p. 90–92° (lit.[20], 95°C). TLC (ethyl acetate-cyclohexane-petroleum ether) showed one spot R_F 0.53 (benzil showed one spot, R_F 0.50). (Found: C, 79.7; H, 4.8. $C_{14}H_{10}O_2$ requires C, 80.0; H, 4.7%).

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