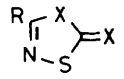
Cycloaddition Reactions of 1,4,2-Dithiazole-5-thiones

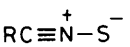
Derek J. Greig, Michael McPherson, and R. Michael Paton*
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ
John Crosby*
Imperial Chemical Industries plc, Organics Division, P.O. Box 42, Blackley, Manchester M9 3DA

1,4,2-Dithiazole-5-thiones can act either as the 2-atom or the 3-atom component in 2 + 3-cycloadditions. Benzonitrile *N*-phenylimine, generated *in situ* by dehydrochlorination of *N*-phenylbenzohydrazonoyl chloride, reacts at the exocyclic C=S double bond forming the thiadiazolethione (**17**) and the spiro compound (**18**) by collapse of the initial cycloadduct (**19**) and further 1,3-dipolar cycloaddition. The corresponding reaction with ethyl azidoformate yields a 5-ethoxycarbonylimino-1,4,2-dithiazole. On treatment with dimethyl acetylenedicarboxylate and ethyl cyanoformate the dithiazolethione itself acts as a 1,3-dipole forming 1,3-dithiole and 1,4,2-dithiazole thiones with expulsion of a nitrile fragment.

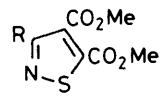
The thermal decarboxylation of 1,3,4-oxathiazol-2-ones (**1**) is the most commonly used method[1,2] for the generation of nitrile sulphides (**2**). The synthesis and thermal stability of (**1**) have therefore been the subject of detailed examination. In contrast, the analogous 1,4,2-dithiazole-5-thiones (**3**), which on extrusion of carbon disulphide would also afford nitrile



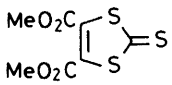
(**1**) X = O
(**3**) X = S



(**2**)



(**4**)

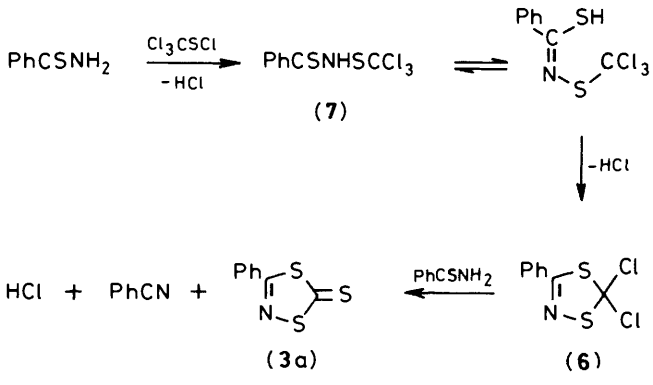


(**5**)

sulphides, have received much less attention. Photolysis of (**3**) in the presence of dimethyl acetylenedicarboxylate (DMAD) does give the isothiazole (**4**) in low yield,[3] presumably *via* (**2**). On the other hand Noel and Vialle[4] have reported that the thermal reaction follows a different pathway yielding the dithiolethione (**5**), although some subsequent work[5] failed to reproduce these results. We now describe some 2 + 3-cycloaddition reactions of (**3**) in which it can act either as the 3-atom or the 2-atom component.

Results and Discussion

Synthesis of Dithiazolethiones (**3**).—These were first prepared[5] in low yield (9—14%) by reaction of the appropriate thiobenzamide with thiophosgene in carbon disulphide. There is also a brief report[4] of their formation (15—25%) from trichloromethanesulphenyl chloride and thiobenzamides, and this approach was adopted for the present work in view of the yields reported. Treatment of thiobenzamide with Cl_3CSCl in chloroform afforded a mixture of (**3a**) and 3,5-diphenyl-1,2,4-thiadiazole, together with HCl and benzonitrile. The yield † of (**3a**) proved to be dependent on the ratio of reactants, varying from 29% at a molar ratio of 2:1 to a trace at 1:5. These results are consistent with the mechanism outlined in Scheme 1, in which an intermediate dichlorodithiazole (**6**), formed from equimolar amounts of thioamide and the sulphenyl chloride, is subsequently attacked at C-5 by further thioamide. An intermediate similar to (**6**), 2,2-dichloro-1,3,4-oxathiazole, is believed[6] to be involved in the conversion of benzamide into (**1**, R = Ph) using Cl_3CSCl. The detection of HCl and benzonitrile as by-products gives further support to the above hypothesis. The thiadiazole may result from a side reaction of thiobenzamide with (**6**) or the thioamide derivative (**7**).



Scheme 1.

Using the 2:1 ratio of thioamide to sulphenyl chloride the corresponding *p*-methoxyphenyl (**3b**) (28%), *p*-tolyl (**3c**) (25%), and *p*-chlorophenyl (**3d**) (21%) derivatives were similarly prepared.

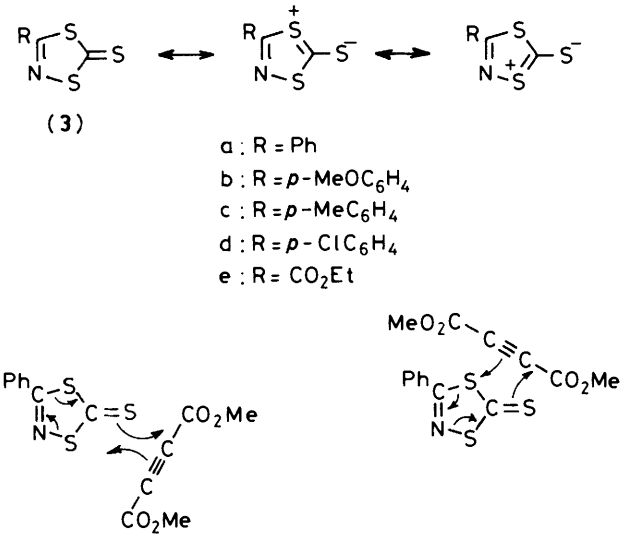
Reactions of Dithiazolethiones (**3**) *with Dipolarophiles*.—In contrast to the oxathiazolones (**1**), which undergo thermal fragmentation at 110—140 °C, the compounds (**3**) are much more stable. Even after 50 h under reflux in xylene >90% of compound (**3a**) could be recovered unchanged. However, in the presence of DMAD (1:3 molar ratio) a rapid reaction took place, no starting material being detectable after 10 min. Removal of the solvent and excess of DMAD afforded the dithiolethione (**5**) (85%) as reported by Noel and Vialle.[4]

Having established that (**3**) would indeed add to an electron-deficient alkyne, the corresponding reaction with ethyl cyanoformate (ECF), an electron-deficient nitrile, was examined. After 40 h under reflux in xylene (**3a**) and ECF (1:3) yielded benzonitrile and 3-ethoxycarbonyl-1,4,2-dithiazole-5-thione

† As 2 mol of thioamide are required to produce each mol of (**3**) the maximum yield is 50%.

(**3e**) (56%). In the absence of solvent the yield rose to 83%; (**3b**) reacted similarly forming (**3e**) (76%). In contrast, no reaction was observed between (**3a**) and dimethyl fumarate.

The formation of (**5**) and (**3e**) involves cycloaddition of the alkyne (or nitrile) to the exocyclic sulphur and one of the ring sulphurs and is accompanied by expulsion of a nitrile fragment. The mechanism may be concerted (Scheme 2), a process designated[7] [2′ + (1,2,3)]-cyclodismutation or cyclosubstitution.

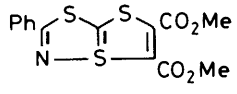


(**3**)

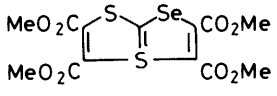
a : R = Ph
b : R = *p*-$MeOC_6H_4$
c : R = *p*-MeC_6H_4
d : R = *p*-ClC_6H_4
e : R = CO_2Et

Scheme 2.

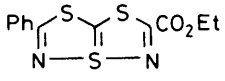
Alternatively, the reaction may proceed in two steps, cycloaddition followed by cyclofragmentation, *via* a bicyclic intermediate (**8**) involving a hypervalent sulphur at one of the bridgeheads. A similar intermediate (**9**) has been proposed[8] to explain the interconversion of 4,5-dimethoxycarbonyl-1,3-dithiole-3-selone and 4,5-dimethoxycarbonyl-1,3-thiaselenole-3-thione in the presence of DMAD. The corresponding intermediate for the reaction of (**3a**) with ECF would be (**10**). The



(**8**)

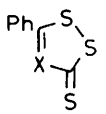


(**9**)

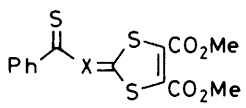


(**10**)

present work does not allow a choice to be made between the two reaction pathways, nor can a stepwise mechanism *via* a zwitterionic intermediate be ruled out.



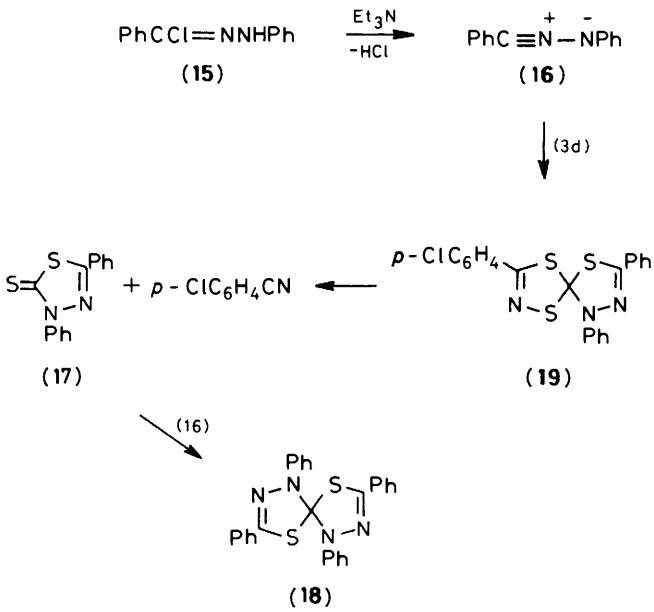
(**11**) X = N
(**12**) X = CH



(**13**) X = N
(**14**) X = CH

The behaviour of 1,4,2-dithiazole-5-thiones parallels that of other 5-membered heterocycles[7] incorporating –S–C(=S)–, particularly 1,3-dithiole-2-thiones,[9] which with DMAD also yield (**5**). The reaction of 5-phenyl-1,2,4-dithiazole-3-thione (**11**), an isomer of (**3a**), with DMAD has also been reported[10] to closely follow that of its carba analogues, *e.g.* (**12**), the respective products being (**13**) and (**14**).

Reactions of Dithiazolethiones (**3**) *with* 1,3-*Dipoles*.—Having established that 1,4,2-dithiazole-5-thiones can act as the 3-atom component in 2 + 3-cycloadditions their reactivity towards 1,3-dipoles was examined. Dehydrochlorination of hydrazonoyl chlorides is an established means of generating nitrile imines.[11] A typical dithiazolethione (**3d**) was therefore heated with a mixture of triethylamine and *N*-phenylbenzohydrazonoyl chloride (**15**), a source of benzonitrile *N*-phenylimine (**16**). After removal of triethylamine hydrochloride, chromatography of the reaction mixture afforded sulphur, some unchanged (**3d**), *p*-chlorobenzonitrile [97%, based on consumed (**3d**)], the diphenylthiadiazole (**17**) (61%), and the spirothiadiazole (**18**) (25%). (**17**) and (**18**) were characterised by comparison with authentic samples prepared[12] by reaction of (**15**) with carbon disulphide and Et_3N. The formation of these products is consistent with the reaction sequence outlined in Scheme 3,

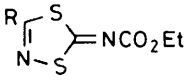


Scheme 3.

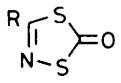
involving 1,3-dipolar cycloaddition of the nitrile imine to the thiocarbonyl group of (**3d**), followed by collapse of the resulting spiro-adduct (**19**) to (**17**) with concomitant formation of *p*-chlorobenzonitrile. Further cycloaddition of (**16**) to the C=S of (**17**) accounts for the spiro product (**18**). Under similar conditions (**3a**) gave the same heterocyclic products, albeit in different proportions, together with benzonitrile. The relative amounts depend on the extent of conversion of (**17**) to (**18**). No evidence was found for the spiro-dithiazole-thiadiazole (**19**), but the formation of (**17**) and (**18**) together with the appropriate nitrile is taken as evidence for its involvement.

Treatment of (**3a**) with an excess of ethyl azidoformate (*ca.* 1:8) in carbon tetrachloride under reflux yielded the 5-iminodithiazole (**20**) (46%); likewise (**3c**) gave (**21**) (30%). Such products could be formed either by 3 + 2-cycloaddition of the azide to the thiocarbonyl group and decomposition of the

resulting spiro-adduct with loss of nitrogen and sulphur,[13] or *via* ethoxycarbonylnitrene and thiaziridine intermediates.[14] Similar behaviour is shown by 1,2-dithiole-3-thiones which with the same azide yield 3-ethoxycarbonylimino-1,2-dithiole.[14]



(20) R = Ph
(21) R = *p*-MeC_6H_4



(22)

Benzonitrile oxide has also been reported[4] to react with (3). In this case the spiro-adduct was isolated at low temperature. When heated it decomposed to 1,4,2-dithiazole-2-ones (22) thus providing an alternative to mercuric acetate[4] or potassium permanganate in acetone[14] for the thiocarbonyl to carbonyl conversion.

Although nitrile imines, azides, and nitrile oxides undergo cycloaddition to the C=S double bond of (3), no such reaction was observed with a typical nitrile sulphide. Treatment with *p*-toluonitrile sulphide of (3a), generated *in situ* by thermal decarboxylation of the corresponding oxathiazolone (1; R = *p*-MeC_6H_4), gave only unchanged (3a) together with *p*-toluonitrile and sulphur, the expected nitrile sulphide decomposition products.[1]

Experimental

Mass spectra (70 eV ionisation potential) were measured using an AEI MS 902 instrument. Varian HA 100 and Brucker WP 80, and Brucker WP 200 and Varian CFT 20 spectrometers were used to record ^1H and ^{13}C n.m.r. spectra respectively. All samples were run as solutions in $CDCl_3$ unless otherwise stated, and chemical shifts are recorded with respect to Me_4Si. I.r. spectra were recorded using a Perkin-Elmer model 257 spectrophotometer. H.p.l.c. analyses were performed as previously described.[2] Thioamides were prepared by the method of Fairfull *et al.*[15]

Synthesis of the 1,4,2-*Dithiazole*-5-*thiones* (3).—The general method was to heat under reflux a solution of the thioamide and trichloromethanesulphenyl chloride (0.5 mol per mol of thioamide) in chloroform as described below for 3-phenyl-1,4,2-dithiazole-5-thione. The reactions were continued until evolution of HCl had ceased. After removal of the solvent the dithiazolethiones were separated from nitrile and thiadiazole by-products by chromatography.

3-*Phenyl*-1,4,2-*dithiazole*-5-*thione* (3a).—Trichloromethanesulphenyl chloride (14.0 g, 75 mmol) in dry chloroform (20 ml) was added dropwise to a solution of thiobenzamide (20.5 g, 150 mmol) in chloroform (800 ml) at 40—45 °C, and the mixture heated under reflux until evolution of HCl had ceased (4 h). The solvent and unchanged sulphenyl chloride were removed under reduced pressure and the yellow residue chromatographed on silica (6% deactivated). Elution with light petroleum–CH_2Cl_2 (4:1) yielded 3-phenyl-1,4,2-dithiazole-5-thione (9.2 g, 43 mmol, 29%) as yellow crystals, m.p. 118 °C (from ethanol) (lit.,[4] 118 °C); δ_C (20 MHz) 218.7 (C-5), 172.4 (C-3), 132.1, 129.1 and 127.4 (5 PhCH), and 131.5 (PhC); *m/z* 211 (M^+), 135 ($PhCNS^+$), 103 ($PhCN^+$), and 76 (CS_2^+). Further elution with dichloromethane afforded benzonitrile ($\nu_{max.}$ 2 225 cm^{-1}) and 3,5-diphenyl-1,2,4-thiadiazole, m.p. and mixed m.p. 91 °C (lit.,[16] 90 °C).

In a repeat experiment with 1:1 molar ratio of reactants the yield of (3a) was 13%. Using Cl_3CSCl–thiobenzamide (5:1), only a trace of (3a) could be detected (h.p.l.c.).

The following 3-substituted-1,4,2-dithiazole-5-thiones were prepared similarly.

3-(*p*-Methoxyphenyl)-1,4,2-dithiazole-5-thione (3b) (28%), m.p. 118 °C (from ethanol) (lit.,[4] 118 °C); δ_C (20 MHz) 219.0 (C-5), 172.0 (C-3), 162.6 and 124.4 (ArC), 129.2 and 114.5 (4 ArCH), and 55.3 (OMe); *m/z* 241 (M^+), 165 ($MeOC_6H_4CNS^+$), 133 ($MeOC_6H_4CH^+$), and 76 (CS_2^+).

3-(p-*Tolyl*)-1,4,2-*dithiazole*-5-*thione* (3c) (25%), m.p. 126—126.5 °C (from ethanol) (Found: C, 48.1; H, 3.1; N, 6.1. $C_9H_7NS_3$ requires C, 48.0; H, 3.1; N, 6.2%); δ_C (20 MHz) 218.9 (C-5), 172.5 (C-3), 142.9 and 129.0 (ArC), 129.8 and 127.4 (4 ArCH), and 20.8 (Me); *m/z* 225 (M^+), 149 ($MeC_6H_4CNS^+$), 117 ($MeC_6H_4CN^+$), and 76 (CS_2^+).

3-(*p*-Chlorophenyl)-1,4,2-dithiazole-5-thione (3d) (21%), m.p. 108 °C (from ethanol) (lit.,[4] 108 °C); δ_C (20 MHz) 218.0 (C-5), 170.8 (C-3), 138.4 and 129.9 (ArC), and 129.4 and 128.6 (4 ArCH); *m/z* 247 and 245 (M^+), 171 and 169 ($ClC_6H_4CNS^+$), 139 and 137 ($ClC_6H_4CN^+$), and 76 (CS_2^+).

Reaction of 1,4,2-*Dithiazole*-5-*thiones with Dipolarophiles.*—*Dimethyl acetylenedicarboxylate* (DMAD). DMAD (4.0 g, 28.2 mmol) was added to a solution of (3a) (2.0 g, 9.5 mmol) in dry xylene (50 ml) and the mixture heated under reflux for 10 min, by which time h.p.l.c. analysis indicated complete consumption of the dithiazolethione. Concentration of the reaction mixture gave an amber oil, which was treated with cold methanol to afford 4,5-dimethoxycarbonyl-1,3-dithiole-2-thione (5) (2.0 g, 85%) as yellow needles, m.p. 87 °C (from ethanol) (lit.,[9] 86—87 °C); $\nu_{max.}$(Nujol) 1 750 and 1 725 cm^{-1} (C=O); δ_C (20 MHz) 207.2 (C-2), 157.9 (2 C=O), 130.8 (C_4 and C_5), and 53.7 (2 Me); *m/z* 250 (M^+).

In the absence of DMAD, (3a) (>90%) remained unchanged after 50 h under reflux, and no products were detectable (h.p.l.c.).

Ethyl cyanoformate. A solution of (3a) (2.0 g, 9.5 mmol) and ethyl cyanoformate (2.8 g, 28.3 mmol) in dry xylene (40 ml) was heated under reflux for 40 h. The solvent and excess of dipolarophile were removed under reduced pressure to leave an oil from which benzonitrile was isolated by vacuum distillation (Kugelrohr). Chromatography on silica yielded unchanged (3a) (0.25 g, 1.2 mmol, 12% recovery) and 3-ethoxycarbonyl-1,4,2-dithiazole-5-thione (3e) [0.96 g, 49%; 56% based on consumed (3a)] as yellow needles, m.p. 44 °C (Found: C, 28.8; H, 2.4; N, 6.6. $C_5H_5NO_2S_3$ requires C, 29.0; H, 2.4; N, 6.8%); δ_C (20 MHz) 217.2 (C-5), 163.6 and 155.7 (C=O and C-3), 63.8 (CH_2), and 13.7 (CH_3); *m/z* 207 (M^+), 131 (EtO_2CCNS^+), and 76 (CS_2^+).

Under similar conditions, (3b) yielded (3e) [76%, based on consumed (3b)], together with *p*-methoxybenzonitrile.

In a repeat experiment (3a) (14.2 mmol) was heated with ethyl cyanoformate (35.5 mmol) under reflux in the absence of solvent for 52 h to yield (3e) in 83% yield.

Dimethyl fumarate. A solution of (3a) (2.0 g, 9.5 mmol) and dimethyl fumarate (4.1 g, 28.5 mmol) in dry xylene (40 ml) was heated under reflux for 40 h. After removal of the solvent under reduced pressure Kugelrohr distillation yielded benzonitrile (76 mg, 8%). Chromatography (silica, light petroleum–CH_2Cl_2) of the residue gave unchanged (3a) (1.88 g, 94% recovery) and dimethyl fumarate (3.9 g, 95% recovery).

Reaction of 1,4,2-*Dithiazole*-5-*thiones with Ethyl Azidoformate.*—A solution of (3a) (1.00 g, 4.74 mmol) and ethyl azidoformate (4.0 g, 34.8 mmol) in dry carbon tetrachloride (60 ml) was heated under reflux for 48 h. Removal of the solvent and chromatography (silica, light petroleum–ethyl acetate 6:1) gave an off-white solid, which on treatment with charcoal and recrystallisation from ethanol yielded 5-*ethoxycarbonylimino*-3-*phenyl*-1,4,2-*dithiazole* (20) (0.58 g, 46%) as white needles, m.p. 135—136 °C (Found: C, 49.8; H, 3.9; N, 10.2. $C_{11}H_{10}N_2O_2S_2$ requires C, 49.6; H, 3.8; N, 10.5%); $\nu_{max.}$ 1 655 (C=O), 1 605 cm^{-1}

(CO); δ_C (20 MHz) 198.2 (C-5), 161.6 and 160.7 (C-3 and CO), 131.7, 129.0, and 127.5 (5 PhCH), 128.4 (PhC), 63.2 (CH_2), and 14.0 (CH_3); *m/z* 266 (M^+), 194 [$(M - CO_2Et)^+$], 135 ($PhCNS^+$), and 103 ($PhCN^+$).

Under similar conditions (**3c**) with ethyl azidoformate yielded 5-*ethoxycarbonylimino*-3-(p-*tolyl*)-1,4,2-*dithiazole* (**21**) (30%), m.p. 155—157 °C (from ethanol) (Found: C, 51.3; H, 4.5; N, 9.7. $C_{12}H_{12}N_2O_2S_2$ requires C, 51.4; H, 4.3; N, 10.0%); $\nu_{max.}$ 1 655 (CO), 1 610 cm^{-1} (CN); δ_C (50 MHz) 198.4 (C-5), 161.6 and 160.7 (C-3 and CO), 142.4 and 129.4 (ArC), 129.7 and 127.3 (4 ArCH), 63.1 (CH_2), 21.3 and 14.1 (CH_3); *m/z* 280 (M^+), 208 ([$M - CO_2Et$]$^+$), 149 ($MeC_6H_4CNS^+$), and 117 ($MeC_6H_4CN^+$).

Reaction of 1,4,2-*Dithiazole*-5-*thiones with* N-*Phenylbenzohydrazonoyl Chloride*.—A solution of (**3d**) (1.00 g, 4.07 mmol), *N*-phenylbenzohydrazonoyl chloride (0.94 g, 4.08 mmol), and triethylamine (3 ml) in dry toluene (10 ml) was heated under reflux for 30 min. Removal of triethylamine hydrochloride by filtration and the solvent under reduced pressure left a solid which was chromatographed on silica. Elution with light petroleum–CH_2Cl_2 afforded sulphur (0.11 g), unchanged (**3d**) (260 mg, 1.06 mmol), *p*-chlorobenzonitrile (0.40 g, 2.91 mmol), 3,3′,5,5′-tetraphenyl-2(3*H*),2′(3′*H*)-spirobi-1,3,4-thiadiazole (**18**) (0.35 g, 0.75 mmol) (m.p. and mixed m.p. 147—149 °C), and 3,5-diphenyl-1,3,4-thiadiazole-2-thione (**17**) (0.50 g, 1.85 mmol) (m.p. and mixed m.p. 149—152 °C). The i.r. and ^{13}C n.m.r. spectra of (**17**) and (**18**) were indistinguishable from authentic samples prepared as previously described.[12]

Under similar conditions (**3a**) (1.00 g, 4.74 mmol) and *N*-phenylbenzohydrazonoyl chloride (1.09 g, 4.73 mmol) yielded sulphur (0.70 g), unchanged (**3a**) (0.35 g, 1.66 mmol), benzonitrile, (**18**) (0.53 g, 1.14 mmol), and (**17**) (0.49 g, 1.81 mmol).

Reaction of 3-*Phenyl*-1,4,2-*dithiazole*-5-*thione with* 5-(p-*Tolyl*)-1,3,4-*oxathiazol*-2-*one*.—A solution of (**3a**) (1.00 g, 4.74 mmol) and 5-(*p*-tolyl)-1,3,4-oxathiazole-2-one[17] (0.91 g, 4.72 mmol) in dry xylene (30 ml) was heated under reflux for 16 h. Removal of the solvent under reduced pressure and chromatography of the residue (silica, light petroleum–CH_2Cl_2) afforded sulphur (0.14 g), unchanged (**3a**) (0.52 g, 2.46 mmol), and *p*-toluonitrile (0.475 g, 4.06 mmol). Compound (**3c**) was not detectable (h.p.l.c.).

References

1 R. K. Howe and B. R. Shelton, *J. Org. Chem.*, 1981, **46**, 771.
2 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, and references therein.
3 A. Holm and N. H. Toubro, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1445.
4 D. Noel and J. Vialle, *Bull. Soc. Chim. Fr.*, 1967, 2239.
5 H. Behringer and D. Deichmann, *Tetrahedron Lett.*, 1967, 1013.
6 A. Senning and P. Kelly, *Acta Chem. Scand.*, 1967, **21**, 1871.
7 V. N. Drozd and N. S. Zefirov, *Sulfur Reports*, 1981, **1**, 271, and references therein.
8 M. V. Lakshmikantham and M. P. Cava, *J. Org. Chem.*, 1976, **41**, 879.
9 D. B. J. Easton, D. Leaver, and T. J. Rawlings, *J. Chem. Soc., Perkin Trans. 1*, 1972, 41.
10 G. Lang and J. Vialle, *Bull. Soc. Chim. Fr.*, 1967, 2865.
11 R. Huisgen, K. Adelsberger, E. Aufderhaar, H. Knupfer, and G. Wallbillich, *Monatsh. Chem.*, 1967, **98**, 1618.
12 R. Huisgen, R. Gashey, M. Seidel, H. Knupfer, and R. Schmidt, *Justus Liebigs Ann. Chem.*, 1962, **658**, 169.
13 M. S. Raasch, *J. Org. Chem.*, 1978, **43**, 2500.
14 M. S. Chauhan and D. M. McKinnon, *Can. J. Chem.*, 1976, **54**, 3879.
15 A. E. S. Fairfull, J. L. Lowe, and D. A. Peak, *J. Chem. Soc.*, 1952, 742.
16 A. W. Hofmann, *Chem. Ber.*, 1869, **2**, 645.
17 B.P. 1 079 348 (1966).

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