Thiations with Sulphur in Dimethylformamide

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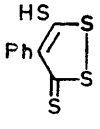
A solution of sulphur in boiling dimethylformamide is a convenient thiation agent. Activated hydrogen and halogen atoms are replaced by thiol groups and further reactions may then occur, often involving dimethylamine liberated from the solvent. However, since the amine is present only in low concentrations, products are sometimes isolated which are formed only in small quantity in the presence of an excess of amine.

THE observation [1] that use of dimethylformamide instead of a hydrocarbon solvent in the reaction of 2-phenylpropene with sulphur led to the isolation of the thiol (**1**) instead of the expected product (**2**) suggested that sulphur–dimethylformamide might have wide application as a thiation agent. Wegler and his co-workers had already used the reagent for the conversion of α- and γ-methylpyridines into the corresponding pyridyldimethylthioacetamides and in the Willgerodt–Kindler reaction, where the products were those obtainable from treatment with dimethylamine.[2] We believe that the reagent operates by liberation of dimethylamine from dimethylformamide by traces of hydrogen sulphide. The amine then opens the eight-membered ring of elemental sulphur, and the resultant polysulphide anions are able to replace suitably activated hydrogen or halogen atoms at relatively low temperatures.[3]



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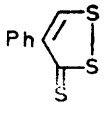

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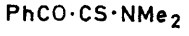


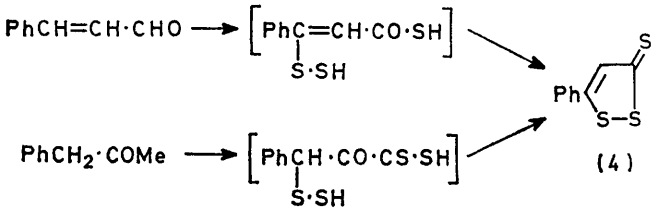
(3)

The refluxing solvent from these reactions is usually bright blue ($\lambda_{max.}$ 620 nm).[4] The reaction can be accelerated by passing an excess of hydrogen sulphide through the mixture.[5] However, we find that the low concentrations of hydrogen sulphide prevailing when dimethylformamide is boiled in an open vessel are advantageous for the preparation of the unreduced thioglyoxylamide (**3**) from acetophenone. This type of compound has previously been prepared by the addition of nitrobenzene to the Willgerodt–Kindler reaction mixture [6] and is also isolated from hindered acetophenones.[7] We find that dimethylamine itself is slowly attacked by the reagent, giving trimethylthiourea. *N*-Methyldithiocarbamic acid is evidently an intermediate and this compound can lose the elements of carbon disulphide to form methylamine, which, like dimethylamine, can react with the primary thiation products. Here again, however, the use of high-boiling solvent in open vessels reduces the amount of such secondary products, as compared with reactions in which the amines themselves are starting materials. Specific examples of the use of the reagent follow.

Cinnamaldehyde reacts not only at the β-hydrogen atom [corresponding to the 5-position in the dithiolethione (**2**)] but also at the hydrogen atom of the aldehyde group. Cyclisation, with loss of the elements of water, then leads to 5-phenyl-1,2-dithiole-3-thione (**4**) (the intermediates shown are merely typical), the same

[1] J. P. Brown, *J. Chem. Soc.* (*C*), **1970**, 1077.
[2] R. Wegler, E. Kühle, and W. Schäfer, *Angew. Chem.*, 1958, **70**, 351; 'Newer Methods of Preparative Organic Chemistry,' Academic Press, New York and London, 1964, vol. III, p. 1; W. Schäfer and R. Wegler, G.P. 1,149,356.
[3] F. Becke, *Internat. J. Sulphur Chem.* (*B*), 1971, **6**, 77; F. Becke and H. Hagen, *Chem.-Ztg.*, 1969, **93**, 474.
[4] T. Chivers and I. Drummond, *Chem. Comm.*, 1971, 1623; R. Bonnaterre and G. Cauquis, *J.C.S. Chem. Comm.*, 1972, 293.
[5] J. P. Brown and T. B. Gay, following paper.
[6] P. A. Barrett, *J. Chem. Soc.*, 1957, 2056.
[7] W. G. Dauben and J. B. Rogan, *J. Amer. Chem. Soc.*, 1956, **78**, 4135.

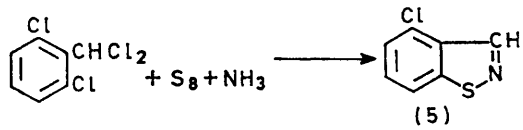
product being isolated from phenylpropan-2-one. Propiophenone is unreactive under these conditions.

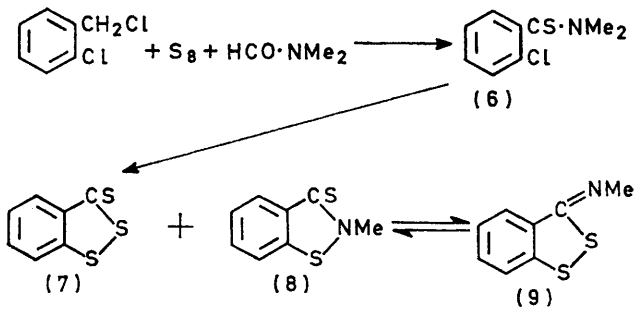


Wegler [2] reports, without details, that unsaturated aldehydes and sulphur may yield dithiolethiones, and Purrello obtained compound (4) as a by-product of the Willgerodt–Kindler reaction with either phenyl vinyl ketone or β-morpholinopropiophenone and showed that it reacted with an excess of morpholine with fission of the dithiole ring.[8] We found that cinnamaldehyde and sulphur did not interact in boiling xylene.

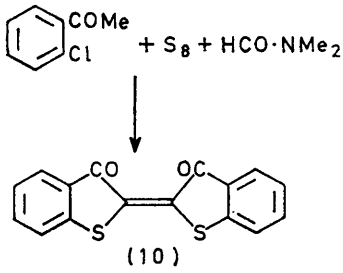
Aromatic aldehydes give thiobenzomorpholides in the Willgerodt–Kindler reaction.[9] The corresponding dimethylthiobenzamides were isolated from reactions of vanillin, piperonal, and *p*-dimethylaminobenzaldehyde with sulphur–dimethylformamide, but the product from benzaldehyde was found to consist of approximately equal amounts of amide and thioamide. The first-formed thiobenzoic acid can evidently react with dimethylamine with loss of either water or hydrogen sulphide. Since thiation, in contrast to most methods of oxidation, does not require the protection of aromatic amino- and hydroxy-groups, it may be of use in synthesis. The α-hydrogen atoms of benzylamines also undergo thiation.[10] The Mannich base from phenol, formaldehyde, and dimethylamine is converted into the tristhioamide with sulphur–dimethylformamide and alkaline hydrolysis then yields hydroxytrimesic acid. Benzylamines may well be intermediates in Becke's synthesis of thioamides from benzyl halides, sulphur, and amines,[3,11] which also proceeds with sulphur–dimethylformamide giving dimethylthiobenzamide from benzyl chloride. The preparation of 5-mercapto-4-phenyl-1,2-dithiole-3-thione (1) from 2-phenylpropyl bromide is a further application of the reagent.

Becke's novel synthesis [12] of chlorobenzoisothiazoles (5) presumably depends upon the activation by the thiocarbonyl group (formed from the dichloroalkyl group) of an *o*-chloro-atom. When we heated *o*-chlorobenzyl chloride with sulphur–dimethylformamide, a little of the *o*-chloro-thioamide (6), which is presumably an intermediate in the synthesis of the main isolated product, 1,2-benzodithiole-3-thione (7), was isolated. This thione, which we obtained in low yield from *o*-chlorobenzaldehyde, did not react with dimethylamine without ring opening (this would no doubt be reversed because of the low concentrations of secondary amine), but it does react with methylamine (see above) to give the isothiazole derivative (8) as a by-product. Compound (8) is known [13] to be interconvertible with the dithiole (9) and g.l.c. evidence suggests that both isomers are present in the reaction mixture. Thiation





followed by cyclisation might also be expected for *o*-chloroacetophenone. Some thioindigo (10), arising from oxidative dimerisation of a cyclised product, was in fact obtained.



A surprising finding was the rapid formation of infusible black solids from sulphur–dimethylformamide and nonan-2-one or undecan-2-one. Similar materials were obtained more slowly and in lower yield from butan-2-one and from acetone. Cyclohexanone, on the other hand, gave a light coloured amorphous solid. Black infusible solid was also obtained as a major product from *o*-xylylene dichloride, in high yield from thiophen-2-carbaldehyde, and in very high yield from cyclopentadiene. The following reacted very slowly (if at all) with sulphur in boiling dimethylformamide: toluene, *o*-chlorotoluene, *o*-chlorobenzonitrile, 1,1,2,2-tetrachloroethane, hexachloroethane and, surprisingly, ethyl benzoylacetate.

EXPERIMENTAL

Formation of Trimethylthiourea.—An excess of isobutene was passed into a boiling mixture of sulphur (96 g) and

[8] F. Bottino and G. Purrello, *Gazzetta*, 1965, **95**, 693; G. Purrello, *ibid.*, p. 1078.
[9] D. A. Peak and F. Stansfield, *J. Chem. Soc.*, 1952, 4067.
[10] F. H. McMillan, *J. Amer. Chem. Soc.*, 1948, **70**, 868.
[11] F. Becke and H. Hagen, G.P. 1,272,286.
[12] F. Becke and H. Hagen, *Annalen*, 1969, **729**, 146.
[13] H. Bõshagen, H. Feltkamp, and W. Geiger, *Ber.*, 1967, **100**, 2435.

dimethylformamide (480 ml) for 15 h. Boiling was continued for 30 h and the solvent was then distilled off under reduced pressure. Toluene (30 ml) was added. A solid separated and was filtered off 3 days later. Recrystallisation from water, with a little added dimethylamine, gave material (10·4 g), m.p. 80—82°, which afforded pale yellow plates, m.p. 87—88° (from benzene) (Found: C, 40·6; H, 8·5; N, 23·8; S, 27·1. Calc. for $C_4H_{10}N_2S$: C, 40·7; H, 8·5; N, 23·7; S, 27·1%). Similar results were obtained with sulphur–dimethylformamide and other starting materials.

Thioglyoxylamides from Ketones.—Acetophenone. A mixture of acetophenone (24 g), sulphur (12·8 g), and dimethylformamide (200 ml) was boiled for 24 h. Solvent was removed and the residue was fractionally distilled. From the fraction of b.p. 104—152° at 0·2 mmHg (10·5 g), NN-*dimethylphenylthioglyoxylamide* (5·05 g), m.p. 78—81°, separated. Recrystallisation from methanol gave yellow prisms, m.p. 81—82° (Found: C, 61·6; H, 5·6; N, 7·2; S, 16·6. $C_{10}H_{11}NOS$ requires C, 62·1; H, 5·7; N, 7·2; S, 16·6%).

o-*Hydroxyacetophenone*. This ketone (27·2 g) similarly yielded a fraction of b.p. 148—168° at 0·5 mmHg (12·1 g), which largely solidified. Recrystallisation from methanol gave o-*hydroxyphenyl*-NN-*dimethylthioglyoxylamide* (6·2 g), m.p. 83—86° (Found: C, 57·1; H, 5·3; N, 6·6; S, 16·2. $C_{10}H_{11}NO_2S$ requires C, 57·4; H, 5·2; N, 6·7; S, 15·3%).

5-*Phenyl*-1,2-*dithiole*-3-*thione*.—(*a*) A mixture of cinnamaldehyde (7·1 g), sulphur (9 g), and dimethylformamide (100 ml) was boiled for 9 h. Solvent was removed, toluene (20 ml) was added to the residue, and the crude dithiolethione (4·15 g), m.p. 99—105°, was filtered off. Recrystallisation from ethanol gave brown-yellow plates, m.p. 120—123°, identical (i.r. spectrum) with an authentic specimen of the dithiolethione. Ethyl cinnamate was unchanged under the same conditions. Cinnamaldehyde did not react with sulphur when xylene replaced dimethylformamide as solvent.

(*b*) A mixture of phenylpropan-2-one (26·8 g), sulphur (26 g), and dimethylformamide (300 ml) was boiled for 16 h. After removal of solvent, the mixture solidified and plates (13·4 g), m.p. 118—121°, were filtered off after adding ethanol. Recrystallisation from ethanol gave bronze-yellow plates, m.p. 123—126° (Found: C, 50·8; H, 2·7; S, 45·8. Calc. for $C_9H_6S_3$: C, 51·4; H, 2·9; S, 45·7%). The i.r. spectrum confirmed the identity. Propiophenone, butyrophenone, and isobutyrophenone were inactive under the same conditions.

Use of Aromatic Aldehydes to Prepare NN-*Dimethylthiobenzamides.—Benzaldehyde.* Redistilled benzaldehyde (21·2 g) was boiled for 40 h with sulphur (19·2 g) and dimethylformamide (200 ml). After removal of the solvent, distillation fractions were collected as follows: (i) yellow oil (9·0 g), b.p. 108—120° at 0·5 mmHg; (ii) yellow oil (18·0 g), b.p. 120—122° at 0·5 mmHg. Fraction (ii) was shown (i.r. spectrum and g.l.c.) to be a mixture (*ca.* 1 : 1) of dimethylbenzamide and dimethylthiobenzamide.

p-*Tolualdehyde*. This aldehyde (24 g) similarly yielded, after 24 h, a fraction of b.p. 140—154° at 0·8 mmHg (23 g), which appeared to be essentially a mixture of the p-*methylthioamide* and amide (3 : 1). Some of the former, m.p. 51°, was isolated and recrystallised from methanol (Found: C, 67·3; H, 7·2; N, 7·8; S, 18·3. $C_{10}H_{13}NS$ requires C, 67·0; H, 7·3; N, 7·8; S, 17·8%). Traces of a high-melting solid, m.p. 184°, believed to be 4,4′-dimethylstilbene (lit.,[14] m.p. 181°) were also isolated (Found: C, 92·4; H, 7·1. Calc. for $C_{16}H_{16}$: C, 92·3; H, 7·7%).

Vanillin. This aldehyde (15·2 g) yielded, after 12 h boiling, removal of solvent, and addition of ethanol, the 4-*hydroxy*-3-*methoxy-thioamide* (10·2 g), m.p. 139—142°. Recrystallisation from ethanol gave red prisms, m.p. 140—143° (Found: C, 56·3; H, 6·1; N, 6·4; S, 15·7. $C_{10}H_{13}NO_2S$ requires C, 56·9; H, 6·2; N, 6·6; S, 15·2%).

Piperonal. Piperonal (15·2 g) similarly yielded the 3,4-*methylenedioxy-thioamide* as greenish-yellow prisms (12·5 g), m.p. 127—130° (from ethanol) (Found: C, 58·0; H, 5·1; N, 6·7; S, 15·1. $C_{10}N_{11}NO_2S$ requires C, 57·4; H, 5·2; N, 6·7; S, 15·3%).

p-*Dimethylaminobenzaldehyde*. The amino-aldehyde (14·9 g) yielded after 24 h yellow needles of the p-*dimethylaminothioamide* (7·8 g), m.p. 98—103°. Recrystallisation from toluene gave a specimen of m.p. 106—108° (Found: C, 63·7; H, 7·9; N, 13·4. $C_{11}H_{16}N_2S$ requires C, 63·5; H, 7·7; N, 13·5%).

Other aromatic aldehydes. *m*-Chlorobenzaldehyde gave a mixed product, believed to contain more amide than thioamide. *p*-Chlorobenzaldehyde (14 g) underwent extensive dehalogenation, although a little p-*chloro-thioamide*, m.p. 77° (Found: C, 54·2; H, 5·2; N, 7·0; S, 16·1. $C_9H_{10}ClNS$ requires C, 54·1; H, 5·0; N, 7·0; S, 16·0%), was isolated. *p*-Nitrobenzaldehyde gave an intractable gum.

Use of Benzyldimethylamines to prepare NN-*Dimethylthioamides*.—A mixture of 2,4,6-tris(dimethylaminomethyl)-phenol (13·3 g), sulphur (14·4 g), and dimethylformamide (150 ml) was boiled for 24 h. Solvent was removed and the residue was boiled with toluene (150 ml), leaving undissolved *tristhioamide* (15·2 g), m.p. 273—276°. A sample was recrystallised from methyl ethyl ketone (Found: C, 51·8; H, 6·3; N, 11·9; S, 25·7. $C_{15}H_{21}N_3OS_3$ requires C, 50·7; H, 5·9; N, 11·8; S, 27·0%). Hydrolysis of the thioamide (8 g) by boiling with 10% aqueous sodium hydroxide (100 ml) for 16 h gave hydroxytrimesic acid (3·7 g) (i.r. spectrum). 6-Dimethylaminomethyl-2,4-dimethylphenol (17·9 g) similarly yielded 2-*hydroxy*-N,N,3,5-*tetramethylthiobenzamide* (9·3 g), m.p. 85—89° (Found: C, 63·8; H, 7·2; N, 7·0. $C_{11}H_{15}NOS$ requires C, 63·2; H, 7·2; N, 6·7%).

Use of Halogenomethyl Compounds to Prepare NN-*Dimethylthioamides.—Benzyl chloride*. A mixture of benzyl chloride (25·3 g), sulphur (13 g), and dimethylformamide (150 ml) was boiled for 24 h. Solvent was removed, the residue was diluted with ether, and *NN*-dimethylthiobenzamide (18·3 g) was filtered off. Recrystallisation from ethanol formed yellow prisms, m.p. 67° (Found: C, 65·1; H, 6·7; N, 8·3; S, 19·1. Calc. for $C_9H_{11}NS$: C, 64·9; H, 6·7; N, 8·5; S, 19·4%).

p-*Xylylene dichloride*. A mixture of the dichloride (17·5 g), sulphur (16 g), and dimethylformamide (200 ml) was boiled for 24 h. After removal of solvent and addition of ethanol, crude *bisthioamide* (8·8 g), m.p. 228—234°, was filtered off. Recrystallisation from methyl ethyl ketone (400 ml) gave light yellow prisms (4·7 g), m.p. 248—251° (Found: C, 58·0; H, 6·6; N, 11·0; S, 24·6. $C_{12}H_{16}N_2S_2$ requires C, 57·1; H, 6·4; N, 11·1; S, 25·2%).

2-*Phenylethyl bromide*. The bromide (18·5 g), sulphur (12·8 g), and dimethylformamide (150 ml), boiled for 32 h, gave crude NN-*dimethylphenyl*(*thioacetamide*) (2·8 g), m.p. 70—73°. Recrystallisation from ethanol and then

[14] P. Pascal and L. Normand, *Bull. Soc. chim. France*, 1911, **9**, 1029.

from toluene gave light yellow prisms, m.p. 79° (Found: C, 66·9; H, 7·5; N, 7·8. $C_{10}H_{13}NS$ requires C, 67·0; H, 7·3; N, 7·8%).

5-*Mercapto*-4-*phenyl*-1,2-*dithiole*-3-*thione*.—A mixture of 2-phenylpropyl bromide (19·9 g), sulphur (16 g), and dimethylformamide (150 ml) was boiled for 30 h. The solvent was removed and replaced by toluene, leaving the dimethylammonium salt of the thiol (19·7 g) undissolved. A sample formed orange prisms, m.p. 183—185° (from ethanol) (Found: C, 45·3; H, 4·7; N, 4·9; S, 43·2. Calc. for $C_{11}H_{13}NS_4$: C, 46·0; H, 4·5; N, 4·9; S, 44·6%).

1,2-*Benzodithiole*-3-*thione*.—(a) *From o-chlorobenzyl chloride*. A mixture of the chloride (120·7 g), sulphur (120 g), and dimethylformamide (1·5 l) was boiled for 40 h. After removal of solvent, water (1 l) was added. The aqueous liquors were decanted and methanol (200 ml) was added to the sticky solid. Crude 1,2-benzodithiole-3-thione (75 g) was filtered off. Recrystallisation from carbon tetrachloride (85 ml) gave orange plates (42 g), m.p. 91—94° (Found: C, 45·3; H, 1·9; S, 54·9. Calc. for $C_7H_4S_3$: C, 45·7; H, 2·2; S, 52·2%). By fractional distillation of mother-liquor residues and fractional crystallisation of solids which separated from the first fraction, we obtained a small sample of o-*chloro*-NN-*dimethylthiobenzamide*, m.p. 105—109° (Found: C, 53·8; H, 4·5; Cl, 17·5; N, 7·0; S, 16·4. $C_9H_{10}ClNS$ requires C, 54·1; H, 5·0; Cl, 17·9; N, 7·0; S, 16·0%). A better method of isolation of the thione (17·4 g), m.p. 91—93° [from the chloride (32·2 g) after 28 h boiling], involved chromatography in benzene solution on silica gel. After elution of the thione, a mixture of the thioamide and 2-methylbenzisothiazoline was eluted with ethanol. The isothiazoline formed pale yellow plates (0·6 g), m.p. 138° (from benzene and then ethanol), identical (i.r. spectrum) with an authentic sample [15] (Found: C, 51·9; H, 4·0; N, 7·4; S, 33·5. Calc. for C_8H_7NS: C, 53·0; H, 3·9; N, 7·7; S, 35·4%).

When hydrogen sulphide was passed continuously into the reaction mixture, chromatography of the product from 32·2 g of chloride gave, after 15 h boiling 19·6 g of thione, m.p. 93—94°. Recrystallisation from toluene raised the m.p. to 94—96°.

(b) *From* o-*chlorobenzaldehyde*. A mixture of the aldehyde (14 g), sulphur (6·4 g), and dimethylformamide (100 ml) was boiled for 24 h. Removal of solvent and recrystallisation of the residue from ethanol gave orange prisms, m.p. 92—95° (Found: C, 45·7; H, 2·2; S, 50·2. Calc. for $C_7H_4S_3$: C, 45·7; H, 2·2; S, 52·2%).

Reaction of o-*Chloroacetophenone with Sulphur–Dimethylformamide*.—A mixture of the ketone (15·6 g), sulphur (13 g), and dimethylformamide (150 ml) was boiled for 20 h. After removal of the solvent, ether (200 ml) was added and the dark red solid (4·1 g) was filtered off. Reprecipitation (by water) from dimethylformamide solution gave a deep red solid, m.p. 260°, whose i.r. spectrum was almost identical with that of an authentic specimen of thioindigo (Found: C, 62·2; H, 2·8; S, 23·4. Calc. for $C_{16}H_8O_2S_2$: C, 64·2; H, 2·8; S, 23·4%). The ethereal residues were distilled; a fraction of b.p. 150—175° at 0·3 mmHg gave yellow prisms (0·35 g), m.p. 71—72°, of o-*chlorophenyl*-NN-*dimethylthioglyoxylamide* (Found: C, 52·6; H, 4·4; Cl, 15·8; N, 6·2; S, 14·0. $C_{10}H_{10}ClNOS$ requires C, 52·7; H, 4·4; N, 6·2; Cl, 15·6; S, 14·1%).

[15] A. Baruffini, P. Borgna, and F. Gialdi, *Il Farmaco*, 1968, **23**, 3.

[3/2213 *Received*, 29*th October*, 1973]