

## SYNTHESIS OF SUBSTITUTED BENZYL PHTHALIMIDO DISULPHIDES

E.T. Ayodele and A.A. Olajire\*

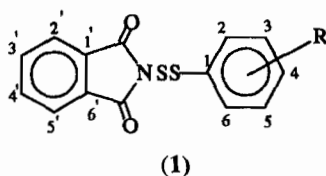
Department of Pure and Applied Chemistry, Ladoko Akintola University of Technology,  
Ogbomosho, Nigeria

(Received December 22, 1998; revised June 9, 1999)

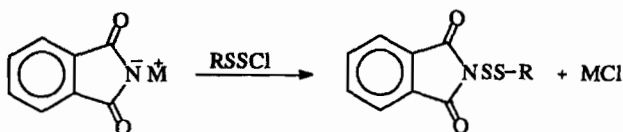
**ABSTRACT.** Substituted benzyl phthalimido disulphides were synthesized by the reaction of *N,N'*-thiobisphthalimide with various substituted benzyl mercaptans. All the compounds are new. The various compounds were characterized by elemental analysis, nuclear magnetic resonance (<sup>1</sup>H NMR and <sup>13</sup>C NMR) and mass spectrometric techniques.

### INTRODUCTION

Unsymmetrical organosulphur compounds are known to be of biological importance and several of them have been isolated from natural sources [1,2]. The first three related examples of compounds (**1**) reported in the literature [3] were prepared by the reaction of an alkali metal derivatives of phthalimide with thiosulphenyl chloride (Scheme 1).



R = *o*-Cl (**1a**), *p*-Cl (**1b**), *o*-Me (**1c**), *p*-Me (**1d**), *p*-MeO (**1e**)



R = CCl<sub>3</sub> (**2a**), CBrCl<sub>2</sub> (**2b**), CCl<sub>2</sub>CCl<sub>3</sub> (**2c**)

Scheme 1

Due to the unavailability and instability of thiosulphenyl chlorides, this method (Scheme 1) was not considered to be suitable [4,5].

Compounds containing the sulphur-nitrogen bond are important from practical as well as theoretical points of view. They have found many applications in synthesis [6] and as herbicides [7], fungicides [8,9], and as accelerators in the vulcanization of rubber [10].

Also, compounds containing the sulphur-nitrogen bond are important in agrochemicals, as shown by the large variety of new sulphur-based crop protection chemicals in current development around the world [11,12]. For instance, the sulphonylurea herbicides [13] are

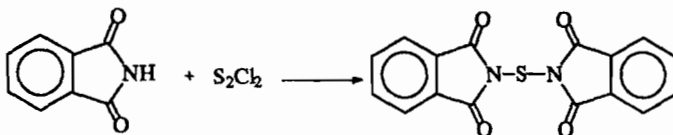
about one to two orders of magnitude more active than standard herbicides used for controlling of weeds in agriculture.

In the present investigation, a method for the preparation of substituted benzyl phthalimido disulphides is described.  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectral data of the synthesized compounds are discussed. To our knowledge, no detailed study of the synthesized compounds have been reported in the literature.

## RESULTS AND DISCUSSION

The method used for the synthesis of these compounds consisted of two steps, which are described, in detail below [14].

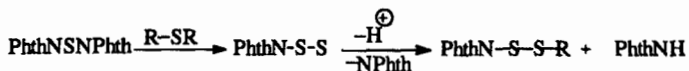
*Step 1.* *N,N'*-Thiobisphthalimide was prepared readily by the reaction of phthalimide with freshly distilled sulphur monochloride (Scheme 2) [15]. On dropwise addition of sulphur monochloride to a vigorously stirred solution of phthalimide in anhydrous *N,N'*-dimethyl formamide, a yellow precipitate appeared after 25 minutes and the mixture was then stirred at 28 °C for a further 20 hours. The product was isolated by filtration and recrystallization and the product exhibited no =NH; -NH<sub>2</sub>, or -COOH bands in its infrared spectrum.



Scheme 2

*Step 2.* The desired substituted benzyl phthalimido disulphide was prepared by the reaction of *N,N'*-thiobisphthalimide with substituted benzyl mercaptans. An advantage of this method is that the precipitation of phthalimide from the cold reaction mixture is a good indication that the reaction has taken place and may be used quantitatively to monitor the extent of reaction. The products obtained were all crystalline white solids and were well characterized.

It is proposed that a phthalimido group is displaced from *N,N'*-thiobisphthalimide by nucleophilic attack on the sulphur atom by the mercaptan. The phthalimido group is known [14] to be a very good leaving group, and the formation of phthalimide in the cold reaction mixture support this mechanism (Scheme 3).



(Phth = phthaloyl)

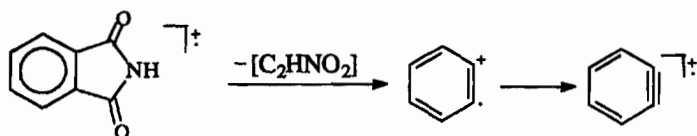
Scheme 3

$^1\text{H}$  NMR. For compounds in this class, the peaks at  $\delta$  7.84-7.85 were assigned to the protons of the benzene ring of the phthalimido group; they are shifted downfield because of the effect of the oxygen of the carbonyl group. Next to these peaks, but well distinguishable from them, are peak at  $\delta$  7.23-7.35 which are assigned to the protons of the other benzene ring present in the molecule. Further evidence for this assignment lies in the fact that the protons of the benzene ring in compounds in which no phthalimido group is present gave peaks at  $\delta$  7.19-

7.35 [16]. The spectra for this class of compound are quite simple and the protons are easily assigned to their respective peaks.

$^{13}\text{C}$  NMR. The carbonyl carbon atoms absorb well downfield at  $\delta$  167-169 and this range was constant for all the compounds synthesized. The methylene carbon of the benzyl group ( $\text{ArCH}_2$ ) gave a signal at  $\delta$  42.6-45.7. The absorptions of the phthalimido aromatic carbons  $\text{ArC-1',6'}$ ;  $\text{ArC-2',5'}$  and  $\text{ArC-3',4'}$  were shifted downfield when compared with carbons of  $\text{ArC-1}$  and  $\text{ArC-4}$  of the benzyl group because of their proximity to the oxygen of the carbonyl group. Also, the carbon of the methoxy group absorbed downfield when compared with that of the methyl group.

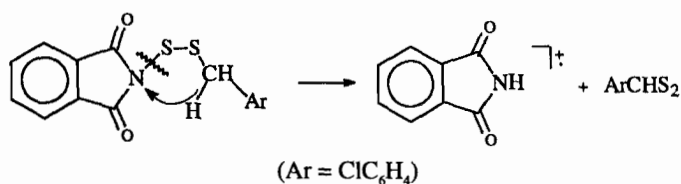
*Mass spectrometry.* All the synthesized compounds gave relatively weak molecular ions under electron impact conditions except 2-chlorobenzyl phthalimido disulphide which gave a peak at  $[\text{M}-1]^+$ . All the compounds synthesized gave a fragment at  $m/z$  76, which is due to the ion  $\text{C}_6\text{H}_4^+$ . This may possibly be formed as a result of intermolecular rearrangement involving the phthalimide cation radical ( $m/z$  147) as shown in Scheme 4 below.



Scheme 4

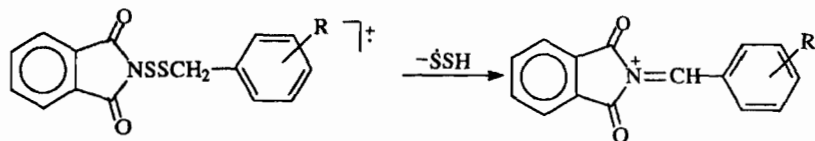
The elimination of  $\text{C}_2\text{HNO}_2$  is equivalent to the loss of a molecule each of  $\text{CO}$  and  $\text{HNCO}$ .

The phthalimide cation radical may be formed by N-S cleavage as shown in Scheme 5.



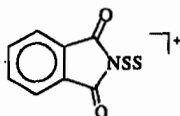
Scheme 5

The compounds gave fragment ions at  $m/z$  250 (**1c** and **1d**), 266 (**1e**), and 270 (**1a** and **1b**) which are characteristic of the molecular ion having lost  $\text{SSH}$  (Scheme 6).

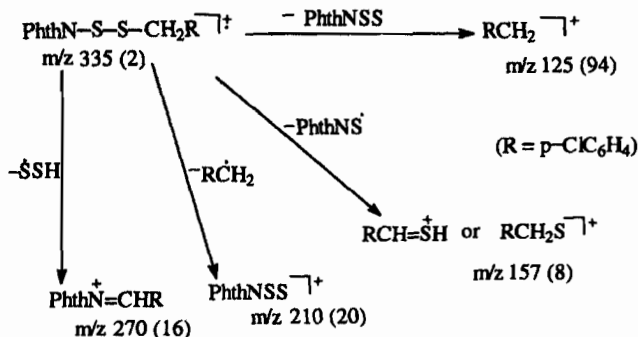


Scheme 6

All the compounds gave a fragment ion at  $m/z$  210 which is characteristic of the ion:



The ion above may be formed as a result of the loss of  $\text{ArCH}_2$  from the molecular ion. The possible fragmentation pattern of 4-chlorobenzyl phthalimido disulphide as a representative of this class of compound is given in Scheme 7 below.



Scheme 7

## EXPERIMENT

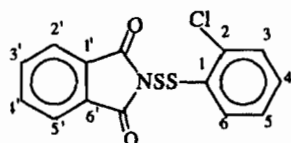
**Reagents.** Most reagents (e.g. mercaptans) involved in this synthetic work were used without further purification; however sulphur monochloride was purified by distillation prior to use. It was distilled over sulphur and the fraction was collected at the boiling range of 138-139 °C at atmospheric pressure. Dimethyl formamide was dried over molecular sieves (E. Merck type 4A), toluene and diethylether were dried over sodium wire.

**Elemental Analysis.** All analyses for carbon, hydrogen, nitrogen, and sulphur were carried out in the Department of Applied Chemistry, University of North London; using a Carlo Erba 1106 elemental analyser.

**Nuclear magnetic resonance spectroscopy.** Routine  $^1\text{H}$  NMR spectra were obtained using Perkin-Elmer R 12B continuous wave spectrometer at 60 MHz and on a Bruker WP 80 instrument at 80 MHz. Higher field  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were recorded on a Bruker AM 250 FT spectrometer at 250.13 MHz and 62.89 MHz, respectively. Chemical shifts for  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are given relative to internal standard tetramethylsilane (TMS).

**Mass Spectrometry.** Electron impact (EI) mass spectra were recorded in the Department of Applied Chemistry, University of North London, using a KRATOS 'PROFILE' high resolution mass spectrometer which is a double-focusing field instrument.

**Synthesis of 2-chlorobenzyl phthalimido disulphide (1a).** A mixture of *N,N'*-thiobisphthalimide (11.49 g, 0.035 mol) and 2-chlorobenzyl mercaptan (4.6 cm<sup>3</sup>, 0.035 mol) was refluxed in toluene (150 cm<sup>3</sup>) for 4 h. On cooling to room temperature, phthalimide separated out as a solid and was filtered off. The filtrate was evaporated under reduced pressure to give a solid product which was filtered and allowed to dry in air overnight. Double recrystallization of this material from ethanol afforded 2-chlorobenzyl phthalimido disulphide (10.55 g, 90%) as a needle-like white crystalline solid;



(1a)

(found: C, 53.71; H, 2.96; N, 4.18; S, 19.10; C<sub>15</sub>H<sub>10</sub>ClNO<sub>2</sub>S<sub>2</sub> requires: C, 53.65; H, 3.01; N, 4.17; S, 19.08%); m.p. 148-149 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.32 (ArCH<sub>2</sub>, s, 2H); 7.23 (Ar-H, m, 4H); 7.84 (Ar-H, m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 43.13 (Ar-CH<sub>2</sub>S); 124.07 (ArC-1); 126.82 (ArC-3); 129.70 (ArC-2); 126.7 (ArC-5); 129.6 (ArC-6); 131.9 (ArC-4); 132.21 (ArC-3',4'); 134.09 (ArC-2',5'); 134.83 (ArC-1',6'); 167.82 (C=O); MS: m/z (%), 334 (M<sup>+</sup>, 1), 270 (19), 210 (18), 178 (16), 157 (8), 147 (37), 125 (92), 76 (21).

Similar procedures were used to synthesize the following compounds.

**4-Chlorobenzyl phthalimido disulphide (1b).** *N,N'*-Thiobisphthalimide (16.24 g, 0.05 mol) and 4-chlorobenzyl mercaptan (6.6 cm<sup>3</sup>, 0.05 mol) gave 4-chlorobenzyl phthalimido disulphide (15.95%) as needle-like white crystals; (found: C, 53.69; H, 2.99; N, 4.17; S, 19.20; C<sub>15</sub>H<sub>10</sub>ClNO<sub>2</sub>S<sub>2</sub> requires: C, 53.65; H, 3.01; N, 4.17; S, 19.08%); m.p. 153-154 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.38 (Ar-CH<sub>2</sub>S, s, 2H); 7.25 (Ar-H, m, 4H); 7.85 (Ar-H, m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 43.48 (Ar-CH<sub>2</sub>S); 124.21 (ArC-1); 126.79 (ArC-3,5); 129.67 (ArC-2,6); 131.26 (ArC-4); 132.18 (ArC-3',4'); 134.48 (ArC-2',5'); 135.08 (ArC-1',6'); 169.57 (C=O); MS: m/z (%), 335 (M<sup>+</sup>, 2), 270 (16); 210 (20); 178 (18); 157 (12); 147 (36); 125 (94); 76 (18).

**2-Methylbenzyl phthalimido disulphide (1c).** *N,N'*-Thiobisphthalimide (12.98 g, 0.04 mol) and 2-methylbenzyl mercaptan (5.53 g, 0.04 mol) gave 2-methylbenzyl phthalimido disulphide (10.89 g, 85%) as needle-like white crystals; (found: C, 60.76; H, 4.21; N, 8.89; S, 20.21; C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>S<sub>2</sub> requires: C, 60.94; H, 4.16; N, 8.89; S, 20.33%); m.p. 147-148 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.33 (CH<sub>3</sub>, s, 3H), 4.37 (ArCH<sub>2</sub>S, s, 2H); 7.25 (Ar-H, m, 4H); 7.85 (Ar-H, m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 20.98 (CH<sub>3</sub>); 45.67 (ArCH<sub>2</sub>S); 124.47 (ArC-1); 129.12 (ArC-3); 128.90 (ArC-5), 129.46 (ArC-6); 130.11 (ArC-2); 132.36 (ArC-1); 133.37 (ArC-3',4'); 134.68 (ArC-2',5'); 138.01 (ArC-1',6'); 167.98 (C=O); MS: m/z (%) 315 (M<sup>+</sup>, 10); 250 (13), 194 (25), 178 (12), 147 (21), 137 (26), 105 (100), 76 (16).

**4-Methylbenzyl phthalimido disulphide (1d).** *N,N'*-Thiobisphthalimide (12.98 g, 0.04 mol) and 4-methylbenzyl mercaptan (5.53 g, 0.04 mol) gave 4-methyl benzyl phthalimido disulphide (11.22 g, 89%) as needle-like white crystals; (found: C, 60.89; H, 4.25; N, 8.67; S, 20.21; C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>S<sub>2</sub> requires: C, 60.94; H, 4.16; N, 8.89; S, 20.3); m.p. 131-132 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 2.30 (CH<sub>3</sub>, s, 3H); 4.30 (ArCH<sub>2</sub>S, s, 2H); 7.25 (Ar-H, m, 4H); 7.85 (Ar-H, m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 21.17 (CH<sub>3</sub>); 45.21 (Ar-CH<sub>2</sub>S); 124.03 (ArC-3,5); 129.32 (ArC-2,6); 129.35 (ArC-1); 132.25

(ArC-4); 133.35 (ArC-3',4'); 134.77 (ArC-2',5'); 137.43 (ArC-1',6'); 169.06 (C=O); MS: m/z (%), 315 (M<sup>+</sup>, 13); 250 (12), 194 (4), 178 (2), 147 (21), 137 (21), 105 (100), 76 (23).

*4-Methoxybenzyl phthalimido disulphide (Ie)*. *N,N'*-Thiobisphthalimide (16.24 g, 0.05 mol) and 4-methoxybenzyl mercaptan (7.7 g, 0.05 mol) gave 4-methoxybenzyl phthalimido disulphide (14.08 g, 85%) as a crystalline white solid; (found: C, 58.06; H, 3.97; N, 4.26; S, 19.40; C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>S<sub>2</sub> requires: C, 58.00; H, 3.96; N, 4.23; S, 19.36%); m.p. 148-149 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.78 (CH<sub>3</sub>O, s, 3H), 4.30 (ArCH<sub>2</sub>S, s, 2H); 6.85 (Ar-H, m, 2H); 7.35 (Ar-H, m, 2H); 7.85 (Ar-H, m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 45.29 (Ar-CH<sub>2</sub>S); 55.20 (CH<sub>3</sub>O); 125.75 (ArC-3,5); 130.32 (ArC-2,6), 113.72 (ArC-1); 158.34 (ArC-4); 134.37 (ArC-3',4'); 135.03 (ArC-2',5'); 138.58 (ArC-1',6'); 167.64 (C=O); MS: m/z (%) 331 (M<sup>+</sup>, 12); 266 (14), 210 (24), 178 (13), 153 (27), 147 (16); 121 (100); 76 (28).

### ACKNOWLEDGEMENT

The authors are grateful to Prof. Harry Hudson for his useful suggestions.

### REFERENCE

1. Sandy, J.D., Davies; C.R.; Neubergers, A. *Biochem. J.* **1975**, 150, 245.
2. Kobayashi, S.; Morita, K. *Tetrahedron Lett.* **1966**, 573.
3. Wolf, F.; Dietz, H.J.; Haase H.J.; Nusch, D. *J. Pract. Chem.* **1967**, 35, 186.
4. Harpp, D.N.; Ash, D.K. *Int. J. Sulphur Chem.* **1971**, A1, 597.
5. Harpp, D.N.; Back, T.G.; Gleason, T.; Orwig, B.A.; Van Horn, W.F.; Synder, J.P. *Tetrahedron Lett.* **1970**, 3351.
5. Boustany, K.; Vander Kooi, J.P. *Tetrahedron Lett.*, **1970**, 4983.
7. Anon, E. *Agrichem. Age* **1989**, 33, 20.
8. Tisdale, W.H.; Williams, L. *U.S. Pat.* **1934**, 1972961.
9. Hester, W.F. *U.S. Pat.* **1943**, 2317765.
10. Brodnitz, M.H.; Gardens, J.V.P.A. *Ger. Offen.* **1972**, 2020051.
11. Horpkins, W.L. *Ag. Chem. New Product Review*, **1990**, 8.
12. Cullen, T.G. *Abstr. Div. Agrochem.*, ACS 199th National Meeting Boston, April 22-27, 1990, paper 10-12.
13. Hackler, R.E. *Abstr. Div. Agrochem.*, ACS 199th National Meeting Boston, April 22-27, 1990, paper 31.
14. Harpp, D.N.; Ash, D.K. *Int. J. Sulphur Chem.* **1971**, A1, 211.
15. Kalnins, V.M. *Can. J. Chem.* **1966**, 44, 2111.
16. Ayodele, E.T. *Ph.D. Thesis*, University of North London, U.K., 1994; p 78.
17. Wehrli, F.W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*, Heyden: London; 1978; pp 46-47.