Bull. Chem. Soc. Ethiop. **2003**, 17(1), 53-60. ISSN 1011-3924
Printed in Ethiopia

SYNTHESIS AND FUNGICIDAL ACTIVITY OF ACETYL SUBSTITUTED BENZYL DISULFIDES

E.T. Ayodele*, A.A. Olajire, O.S. Amuda and S.O. Oladoye

Department of Pure and Applied Chemistry, Ladoke Akintola University of Technology, Ogbomoso, Nigeria

(Received February 11, 2002; revised November 22, 2002)

ABSTRACT. The synthesis and fungicidal activity of acetyl substituted benzyl disulfides **1(a – g)** are reported. The compounds were characterized by elemental analysis, nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) and mass spectrometric techniques. The results of the biological screening showed that the synthesized compound possess very high fungicidal activity.

KEY WORDS: Acetyl substituted benzyl disulfides, Fungicidal activity

INTRODUCTION

Unsymmetrical disulfides are sulfides of the general formula RSSR' where R and R' are different groups. Nucleophilic displacement of a sulphinic acid form thiosulfonates by thiols had been exploited to produce a wide variety of unsymmetrical disulfides [1]. While the reactions proceed readily and completely in most cases, even at –86 °C, subsequent disproportionation of both products is a complication whose importance varies greatly with structure. The reaction proceeds according to Scheme 1

$$RSH + R'SO_2SR' \longrightarrow RSSR' + R'SO_2H$$

Scheme 1

The relative stabilities of some disulfides towards disproportionation have been studied in detail [2-4]. The treatment of two mercaptans with bromine has been reported to give a mixture of three disulfides, one of which is unsymmetrical (Scheme 2) [5].

$$3RSH + 3\ R'SH \xrightarrow{Br_2} RSSR + RSSR' + R'SSR'$$

Scheme 2

These disulfides may be separated by fractional distillation. Other oxidizing agents have been reportedly used for this reaction [6].

The reaction of a mercaptide with Bunte salt has been reported to give an unsymmetrical disulfide [7] as shown in Scheme 3.

$$RSSO_3^-Na^+ + R'S^-Na^+ \longrightarrow RSSR' + Na_2SO_4$$

Scheme 3

*Corresponding author. E-mail: ayodele@esscon.skannet.com

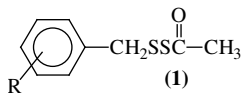
A neat way of preparing a pure unsymmetrical disulfide is by the reaction of a sulphenyl halide with a mercaptide [8, 9].

A reaction of S–alkylthioisothiouronium chloride with a mercaptan, in the presence of a base, also gives pure unsymmetrical disulfide [10].

Methods for the synthesis of organic disulfides had been reviewed [11-13]. Sulfur and its compounds particularly disulfides continue to have application in agro-chemicals, as shown by large varieties of new sulfur based crop protection chemicals in development around the world [14, 15].

Methods for the synthesis of compound **1** had been reported [16, 17]. However, the method used in the present work had the advantage over these reported methods in that reactions are carried out under mild conditions and the reaction products are easily isolated and purification by recrystallisation from petroleum is less cumbersome. The yields are higher in the present method.

In the present investigation, the synthesis and fungicidal activity of acetyl substituted benzyl disulfides (R = *o*–CH_3, *p*–CH_3, *o*–Cl, *p*–Cl, *p*–CH_3O, H, F) are reported. The synthsised compounds were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometric techniques. To our knowledge, no detailed study of the synthesis and fungicidal activity of this class of compounds have been reported in the literature.

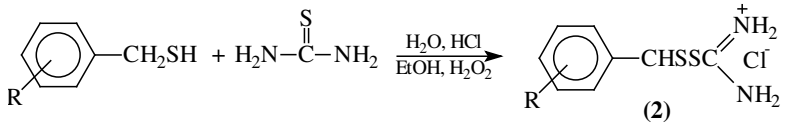


(1)

R = *o*–CH_3 (**1a**); *p*– CH_3 (**1b**); *o*– Cl (**1c**); *p*–Cl (**1d**); *p*–CH_3O (**1e**); H (**1f**) and *p*–F (**1g**)

DISCUSSION

Compounds **1**(**a** – **g**) were prepared by the reaction of substituted S–benzylthioisothiouronium chloride with thioacetic acid. Various substituted benzylthioisothiouronium chloride (**2**) were prepared in good yield as reported [18]. The reaction proceeds according to Scheme 4 below.



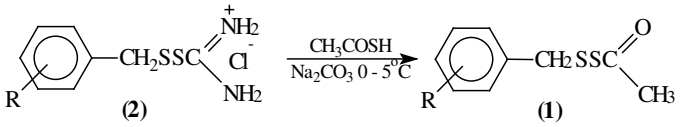
(2)

R = *o*–CH_3 (**2a**), *p*–CH_3 (**2b**), *o*–Cl (**2c**), *p*–Cl (**2d**), *p*–CH_3O (**2e**), H (**2f**) and *p*–F (**2g**)

Scheme 4

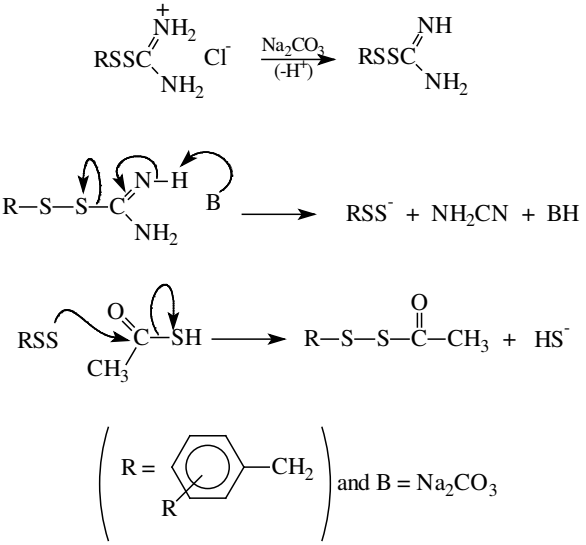
A mechanism proposed for this reaction had been explained elsewhere [18].

The substituted benzyl acetyl compounds **1**(**a**–**g**) were prepared by treating the corresponding S–benzylthioisothiouronium chloride (**2a**–**g**) with thioacetic acid in the presence of potassium carbonate as a base and at low temperature 0-5 °C (Scheme 5)



Scheme 5

A mechanism that we proposed for this reaction is depicted in Scheme 6.



Scheme 6

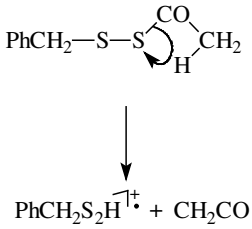
The analytical and spectral results showed that all the synthesized compounds were pure (Experimental).

Mass spectrometry

Molecular ions were generally strong under the conditions of our measurements with relative intensities of about 50% in most of the compounds.

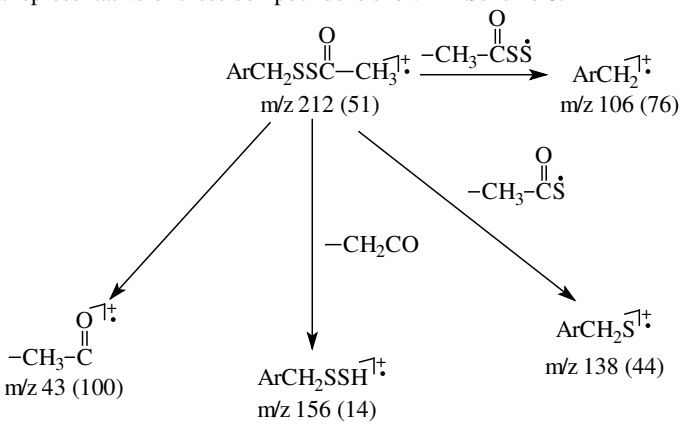
The most abundant ions in the spectra of all compounds were those derived form carbon–sulfur fission viz, the resonance – stabilized benzyl (or isomeric tropylium) cation [19]. The elimination of S_2 in the mass spectrometry of aromatic disulfides has been recognized [20].

Benzyl acetyl disulfide (**1f**) gives the radical cation $[PhCH_2S_2H]^{\ddagger}$, *m/z* 156, most probably by direct elimination of the stable ketene molecule (Scheme 7).



Scheme 7

All the compounds gave peak corresponding to $ArCH_2S^{>}$ and the base peak for all compounds was the acetyl cation $CH_3{-}\overset{O}{\overset{\|}{C}}{}^{+\cdot}$. The fragmentation pattern of acetyl *p*-methylbenzyl disulfide as a representative of these compounds is shown in Scheme 8.



Scheme 8

Fungicidal screening

Compounds (**1a** – **g**) were tested for fungicidal activity as described in the experimental section. Also tested for fungicidal activity were guazatine/imazalil and phenyl mercury acetate which are two well – established fungicides so as to compare their activities with those of compounds **1**(**a** – **d**). The fungal organisms against which the synthesized compounds were tested are *Fusarium culmorum* (F1), *Fusarium oxysporum* (F2) and *Gaeumannomyces graminis* (F3). Germinaiton of spores was assessed by measuring the diameter of growth of each plate and comparing it with the control. The percentage of inhibition (% I) of growth was calculated by the following equation.

$$\% I = \frac{d_c - d}{d_c} \times 100$$

where d = diameter of growth for the plate treated with chemical and d_c = diameter of growth for the control plate.

The percentage inhibition (% I) of growth was then ranked as given in Table 1. The results of *in vitro* test are given in Table 2.

Table 1. Ranking of the percentage inhibition (% I) of growth.

Rank	0	1	2	3	4
% I	10	11-20	21-49	50-79	≥ 80

Table 2. *In vitro* test results for compound **1** (**a** – **g**), guazatine/imazalil and phenyl mercury acetate $^{a}C_{F_1}$ (ppm).

Compound	$^{a}C_{F_1}$ (ppm)			$^{a}C_{F_2}$ (ppm)			$^{a}C_{F_3}$ (ppm)		
	10	100	1000	10	100	1000	10	100	1000
1_a	2[b]	3	4	3	3	4	2	3	4
1_b	3	3	4	2	3	4	3	3	4
1_c	3	3	4	3	3	4	3	4	4
1_d	3	3	4	3	4	4	3	3	4
1_e	3	3	4	3	3	4	2	3	4
1_f	2	3	4	2	3	4	3	3	4
1_g	3	4	4	3	4	4	3	4	4
Guazatine/imazalil	3	4	4	3	3	4	3	3	4
Phenyl mercury acetate	3	4	4	3	3	4	3	3	4

[a]Concentration (ppm) of fungal organism. [b]Rank for percentage inhibition of growth (Table 1).

From Table 2, it can be seen that all compounds gave 80-100% control of the organism tested against at 1000 ppm. At lower concentrations (100 and 10 ppm) there are generally decreases in activity. The activity results for these compounds were comparable with those of guazatine/imazalil and phenyl mercury acetate, which are two well-established fungicides. The moderately good fungicidal activity of these compounds establishes their potential usefulness as good fungicides.

EXPERIMENTAL

Starting materials, solvents and reagents

Most reagents were supplied by Aldrich chemical company or Lancaster synthesis and were used directly. Diethyl ether was dried over sodium wire.

The following starting materials were prepared as described.

*S–(o–Methylbenzylthio)isothiouronium chloride (**2a**)*. M.p. 158-159 °C (lit [16] m.p. 157-159 °C); found: C, 43.54; H, 5. 49; N, 11.25; S, 25.80%; calc. for $C_9H_{13}ClN_2S_2$: C, 43.44; H, 5.28; N, 11.26; S, 25.77%.

*S–(p–Chlorobenzylthio)isothiouronium chloride (**2d**)*. M.p. 153-154 °C (lit [16] m.p. 150-152 °C); found: C, 35.56; H, 3.62; N, 10.56; S, 23.72%; calc. for $C_8H_{10}Cl_2N_2S_2$: C, 35.67; H, 3.75; N, 10.40; S, 23.81%.

*S–(o–Chlorobenzylthio)isothiouronium chloride (**2c**)*. M.p. 154-155 °C (lit [16] m.p. 155-156 °C); found: C, 35.84; H, 3.61; N, 10.52; S, 23.69%; calc. for $C_8H_{10}Cl_2N_2S_2$: C, 35.67; H, 3.75; N, 10.40 S, 23.81%.

*S–(p–Fluorobenzylthio)isothiouronium chloride (**2g**)*. M.p. 163-164 °C (lit [16] m.p. 162-163 °C); found: C, 37.89; H, 3.93; N, 11.05; S, 25.29%; calc. for $C_8H_{10}FClN_2S_2$: C, 38.02; H, 3.96; N, 11.09; S, 25.38 %.

*S–(p–Methoxybenzylthio)isothiouronium chloride (**2e**)*. M.p. 155-156 °C (lit [16] m.p. 153-155 °C); found: C, 40.05; H, 4.65; N, 10.53; S, 24.13%; calc. for $C_9H_{12}ClN_2OS_2$: C, 40.81; H, 4.96; N, 10.58; S, 24.21%.

*S–Benzylthioisothiouronium chloride (**2f**)*. M.p. 147-149 °C (lit. m.p. [16] 145-148 °C); found: C, 40.98; H, 4.83; N, 11.96; S, 27.10%; calc. for $C_9H_{11}ClN_2S_2$: C, 40.91; H, 4.73; N, 11.94; S, 27.27%.

Analytical methods

Elemental analysis. All analyses for carbon, hydrogen, nitrogen and sulfur were carried out in the Department of Applied Chemistry, University of North London using a Carlo Erba 1106 elemental analyzer.

Nuclear magnetic resonance spectroscopy. Routine ^{1}H NMR spectra were obtained using a Perkin Elmer R 12B continuous wave spectrometer at a field of 60 MHz and on a Bruker WP 80 instrument at 80 MHz. Higher fields ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AM 250 Fourier transform spectrometer at 250.13 MHz and 62.89 MHz, respectively. Chemical shifts for ^{1}H NMR and ^{13}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 KRATUS "PROFILE" high resolution double – focusing field instrument.

*Synthesis of acetyl p-methoxybenzyl disulphide (**1e**)*

S–(*p*–Methoxybenzylthio)isothiouronium chloride (**2e**) (2.11 g, 0.008 mol) in water (40 cm^3) was added to an ice cold solution of thioacetic acid (0.71 cm^3, 0.008 mol) in aqueous potassium carbonate (30 cm^3, 4%) with vigorous stirring. Stirring was continued for an additional 20 minutes after which a white solid separated, which was collected, washed with several portions of water and left to dry overnight. Recrystalization of this solid from petroleum ether, b.p. 40-60 °C, gave acetyl *p*–methoxybenzyl disulfide (1.68 g, 92%) as a white crystalline solid, m.p. 60-61 °C. Found: C, 52.61; H, 5.26; S, 28.06%; calc. for $C_{10}H_{12}O_2S_2$: C, 52.49; H, 5.28; S, 28.02%; ^{1}H NMR ($CDCl_3$) δ: 2.30 (CH_3, s, 3H), 3.21 (CH_3O, s, 3H), 4.31 ($ArCH_2$, s, 2H), 7.31 (Ar–H, m, 4H); ^{13}C NMR ($CDCl_3$) δ: 28.91 (CH_3), 35.48 (CH_3O), 43.02 ($ArCH_2$), 127.75 (ArC–1), 128.54 (ArC–3, 5), 129.32 (ArC–2, 6), 136.02 (ArC–4); MS: *m/z* (%), M (228, 54), 196 (8), 121 (62), 75 (60), 43 (100).

Similar procedures were used to prepare the following compounds:

*Acetyl o–methylbenzyl disulfide (**1a**)*. S–(*o*–Methylbenzylthio)isothiouronium chloride (**2a**) (1.99 g, 0.008 mol) in water (45.0 cm^3), thioacetic acid (0.71 cm^3, 0.008 mol) and potassium

carbonate (30 cm^3, 4%) gave acetyl *o*–methylbenzyl disulfide (1.70 g, 90%) as a white solid, m.p. 62-63 °C. Found: C, 56.84; H, 5.61; S, 30.09%; $C_{10}H_{12}OS_2$ requires C, 56.60; H, 5.66; S, 30.19%; ^{1}H NMR ($CDCl_3$) δ: 2.21 (CH_3, s, 3H); 4.28 (ArC$\underline{H}_2$, s, 2H), 7.28 (Ar–H, m, 4H); ^{13}C NMR ($CDCl_3$)) δ: 28.76 (CH_3), 29.21 (CH_3), 42.95 ($ArCH_2$), 126.15 (ArC–1), 127.89 (ArC–3), 130.62 (ArC–2), 134.03 (ArC–1), 127.89 (ArC–3), 130.62 (ArC–2), 134.03 (ArC–5), 136.95 (ArC–4); MS: *m/z* (%), M (212, 48), 156 (12), 138 (43), 106 (80), 43 (100).

*Acetyl p–methylbenzyl disulfide (**1b**).* S–(*p*–Methylbenzylthio)isothiouronium chloride (**2b**) (1.98 g, 0.008 mol) in water (45.0 cm^3) thioacetic acid (0.71 cm^3, 0.008 mol) and potassium carbonate (30 cm^3, 4%) gave acetyl *p*–methylbenzyl disulfide (1.70 g, 92%) as a white solid m.p. 59-60 °C. Found: C, 56.59; H, 5.64; S, 30.21%; $C_{10}H_{12}OS_2$ requires: C, 56.60; H, 5.66; S, 30.19%; ^{1}H NMR ($CDCl_3$) δ: 2.31 ($C\underline{H}_3$, s, 3H), 2.34 ($C\underline{H}_3$, s, 3H), 4.03 ($ArC\underline{H}_2$, s, 4H), 7.34 (Ar–H, m, 4H); ^{13}C NMR ($CDCl_3$) δ: 27.86 ($\underline{C}H_3$), 29.36 (CH_3), 43.45 ($Ar\underline{C}H_2$), 129.18 (ArC–1), 128.47 (ArC–3, 4), 134.02 (ArC–2, 6), 137.43 (Ar$\underline{C}$–4); MS: *m/z* (%) M (212, 51), 156 (14), 138 (44), 106 (76), 43 (100).

*Acetyl o–chlorobenzyl disulfide (**1c**).* S–(*o*–Chlorobenzylthio)isothiouronium chloride (**2c**) (2.15 g, 0.008 mol) in water (45.0 cm^3), thioacetic acid (0.71 cm^3, 0.008 mol) and potassium carbonate (30 cm^3, 4%) gave acetyl *o*–chlorobenzyl disulfide (1.86 g, 92%) as a white crystalline solid, m.p. 67-68 °C; found: C, 46.39, H, 3.90; S, 27.41%; $C_9H_9ClOS_2$ requires C, 46.45; H, 3.87; S, 27.53%. ^{1}H NMR ($CDCl_3$) δ: 2.35 ($C\underline{H}_3$, s, 3H); 4.08 ($Ar\underline{C}H_2$, s, 2H); 7.31 (Ar–$\underline{H}$, m, 4H); ^{13}C NMR ($CDCl_3$) δ: 23.20 ($\underline{C}H_3$), 42.31 ($Ar\underline{C}H_2$, s 2H); 126.73 (ArC–1); 128.97 (ArC–3), 129.79 (Ar$\underline{C}$–5), 131.70 (Ar$\underline{C}$–2), 133.87 (Ar$\underline{C}$–6), 134.32 (ArC–4); MS: *m/z* M (232, 47), 158 (38), 156 (15), 126 (73), 43 (100).

*Acetyl p–chlorobenzyl disulfide (**1d**).* S–(*p*–Chlorobenzylthio)isothiouronium chloride (**2d**) (2.15 g, 0.008 mol) in water (45.0 cm^3), thioacetic acid (0.71 cm^3, 0.008 mol) and potassium carbonate (30 cm^3, 4%) gave acetyl *p*–chlorobenzyl disulfide (1.86 g, 87%) as a white crystalline solid, m.p. 60-61 °C. Found: C, 46.38; H, 3.83; S, 27.38%; $C_9H_9ClOS_2$ requires: C, 46.45; H, 3.87; S, 27.53%; ^{1}H NMR ($CDCl_3$) δ: 2.33 ($C\underline{H}_3$, s, 3H), 4.03 ($ArC\underline{H}_2$, s, 2H), 7.40 (Ar$\underline{H}$, m, 4H); ^{13}C NMR ($CDCl_3$) δ: 22($\underline{C}H_3$), 42.45 ($Ar\underline{C}H_2$), 128.82 (ArC–1), 131.02 (Ar$\underline{C}$–3, 5), 133.28 (Ar$\underline{C}$–2, 6), 134.87 (Ar$\underline{C}$–4); MS: *m/z* (%) M (232, 50), 158 (41), 156 (18), 126 (76), 43 (100).

*Acetyl p–fluorobenzyl disulfide (**1g**).* S–(*p*–Fluorobenzylthio)isothiouronium chloride (**2g**) (2.02 g, 0.008 mol) in water (45 cm^3), thioacetic acid (0.71 cm^3, 0.008 mol) and potassium carbonate (30 cm^3, 4%) gave acetyl *p*–fluorobenzyl disulfide (1.73 g, 87%) as a white crystalline solid, m.p. 56-57 °C. Found: 49.89; H, 4.23; S, 29.48%; $C_9H_9FOS_2$ requires: C, 50.00; H, 4.17; S, 29.63%; ^{1}H NMR ($CDCl_3$) δ: 2.32 (CH_3, s, 3H), 4.08 (ArH_2, s, 2H), 7.29 (ArC–$\underline{H}$, m, 4H); ^{13}C NMR ($CDCl_3$) δ: 23.19 ($\underline{C}H_3$), 42.10 ($Ar\underline{C}H_2$), 127.31 (Ar$\underline{C}$–1), 129.12 (Ar$\underline{C}$–3, 5), 134.26 (Ar$\underline{C}$–2, 6), 135.12 (Ar$\underline{C}$–4); MS: *m/z* (%), M (216, 45), 156 (18), 142 (47), 110 (81), 43 (100).

*Acetyl benzyl disulfide (**1f**).* S–(Benzylthio)isothiouronium chloride (**2f**) (1.88 g, 0.008 mol) in water (45.0 cm^3), thioacetic acid (0.71 cm^3, 0.008 mol) and potassium carbonate (30 cm^3, 4%) gave acetyl benzyl disulfide (1.58 g, 90%) as a white crystalline solid, m.p. 56-57 °C. Found: C, 54.52, H, 5.01; S, 32.50%; $C_9H_{10}OS_2$ requoires: C, 54.55; H, 5.05; S, 32.32%; ^{1}H NMR ($CDCl_3$) δ: 2.35 ($C\underline{H}_3$, s, 3H), 4.01 ($ArC\underline{H}_2$, s, 2H), 7.31 (ArC–$\underline{H}$, m, 5H); ^{13}C NMR ($CDCl_3$) δ: 23.20 ($\underline{C}H_3$), 43.13 ($Ar\underline{C}H_2$), 126.93 (ArC–1), 128.62 (ArC–3, 5), 129.54 (ArC–2, 6), 135.21 (ArC–4); MS: *m/z* (%), M (198, 50), 156 (12), 123 (43), 91 (80), 43 (100).

Biological screening

In vitro activity. Fungicidal tests *in vitro* were carried out by standard techniques in Suboround Dextrose Agar (SDA) as nutrient. For *Fusarium culmorum, Fusarium oxysporum* and *Ganenomyceles graminis*, sample concentrations of 1000, 100, and 10 ppm were used. A control solution containing SDA (13 g) in water (200 mL) was prepared. Also, solutions containing (a) guazatine/imazalil, and (b) phenylmercury acetate at various concentrations of active ingredient (1000, 100, 10 ppm) were prepared as standards. The solutions were poured into petri dishes and allowed to cool. Each plate was then inoculated with a 5 mm agar plug containing actively growing fungus. All plates were kept in a sterilized incubator and maintained at 25 °C. The growth diameter of fungal spore was measured every three days until there was complete growth on the control dish, *i.e.* until all the surface of the plate was covered with fungal spore (approximate diameter, 86 cm).

REFERENCES

1. Parsons, T.F.; Buckman, J.D.; Pearson, D.E.; Field, L. *J. Org. Chem.* **1965**, 30, 1923.
2. Crenshaw, R.R.; Field, L. *J. Org. Chem.* **1965**, 30, 175.
3. Bellas, M.; Tuleen, D.L.; Field, L. *J. Org. Chem.* **1967**, 32, 2591.
4. Field, L.; Buckman, J.D. *J. Org. Chem.* **1967**, 32, 3467.
5. Otto, R.; Rössing. A. *Chem. Ber.* **1886**, 19, 3132.
6. McAllan, D.T.; Cullum, T.V.; Dean, R.A.; Fidler, F.A. *J. Am. Chem. Soc.* **1951**, 73, 3627.
7. Footner, H.B.; Smiles, S. *J. Org. Chem.* **1937**, 1, 2887.
8. Brintzinger, H.; Langheck, M.; Eeewanger, H. *Chem. Ber*. **1954**, 87, 300; *Chem. Abstr.* **1955**, 49, 4544.
9. Brintzinger, H.; Schmahe, H. *Chem. Ber*. **1954**, 87, 314; *Chem. Abstr.* **1955**, 49, 4545.
10. Matsukawa, T. *Yagugaku Zasshi* **1953**, 73, 216.
11. Kharasch, N. *Organic Sulfur Compounds* **1961**, 1, 125.
12. Cavallini, C.B. *Enzymologia* **1960**, 22, 221.
13. Field, L. *Organic Chemistry of Sulfur*, Oae, S. (Ed.); Plenum: London; **1977**; p 205.
14. Horpkins, W.L. *G. Chem. New Product Review* **1990**, 8.
15. Anon, E. *Agrichem Age* **1989**, 33, 20.
16. Fujisawa, T.; Kobayashi, N.; *J. Org. Chem.* **1971**, 36,3546.
17. Freeman, F.; Huang, B.G.; Lin, R.I.S. *Synthesis* **1994**, 7, 699.
18. Sirakawa, K.; Aki, O.; Tsujikawa, T.; Tsuda, T. *Chem. Pharm. Bull.* **1970**, 18, 235.
19. McLafferty, F.W.; Tureckck, F. *Interpretation of Mass Spectra*, 4th ed., University Books: Mill Valley, California; **1993**; p 238.
20. Ref. 11, p 269.