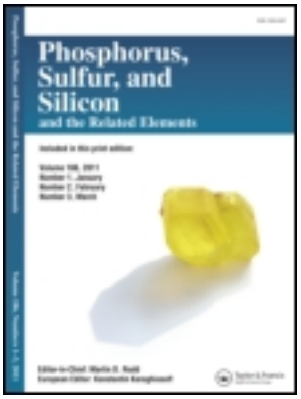

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Characterization and Comparative Studies on Conventional and Microwave Synthesis of Some Disulfides

Nalan Turkoz Karakullukcu [a], Hasan Yakan [a], Seyhan Ozturk [a] & Halil Kutuk [a]

[a] Chemistry Department, Faculty of Arts and Sciences, Ondokuz Mayis University, Atakum, Samsun, Turkey

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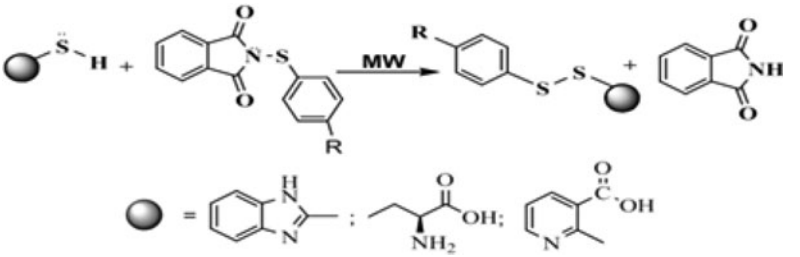
CHARACTERIZATION AND COMPARATIVE STUDIES ON CONVENTIONAL AND MICROWAVE SYNTHESIS OF SOME DISULFIDES

Nalan Turkoz Karakullukcu, Hasan Yakan, Seyhan Ozturk, and Halil Kutuk

Chemistry Department, Faculty of Arts and Sciences, Ondokuz Mayis University, Atakum, Samsun, Turkey

GRAPHICAL ABSTRACT



Abstract *Some disulfide derivatives have been prepared by microwave assisted synthesis methodology from thiophthalimides(sulfenimides) and thiols in a modified microwave oven under reflux at 600 Watt in ethanol. Elucidation of the structures of the synthesized compounds has been performed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic methods.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental files: Additional figures]*

Keywords Disulfides; cysteine; 2-mercaptobenzimidazole; 2-mercaptonicotinic acid; microwave heating

INTRODUCTION

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions.[1] High-speed microwave-assisted chemistry has attracted a considerable amount of attention in recent years.[2] Since the pioneering work of Gedye[3] and Giguere/Majetich[4] in 1986, microwave irradiation has frequently been employed to accelerate organic chemical transformations for many organic reactions.

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Address correspondence to Prof. Dr. Halil Kutuk, OMU Fen-Ed. Fakultesi, Kimya Bolumu, 55139 Atakum, Samsun, Turkey. E-mail: hkutuk@omu.edu.tr

The microwave-assisted synthesis offers considerable advantages over conventional heating because of rapid heating and substantial rate enhancements of a wide range of organic reactions.[5] The increasing demand of clean and efficient chemical synthesis makes solvent-free reactions requisite which give a more eco-friendly approach required from both economic and environmental standpoints.[6] Microwave heating has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional heating methods.[5,7]

Recently, in the literature many studies have been reported for microwave assisted synthesis of disulfides,[8] *N*-arylsulfonyl imines,[9] 1,2,4-triazol-5-one derivatives,[10] bicyclic thiazolo-pyrimidine and pyrimido-thiazine derivatives,[11] *N*-bromosulfonamides,[12] 1,2,4-benzothiadiazines,[13] benzothiazole,[14] and tetrathiomolybdate.[15]

Disulfides are found in numerous natural products and biologically significant functional materials. For example, diallyl disulfide is the active constituent of garlic and the antibacterial disulfide monoxide is also present in alicin.[16] Some disulfides have antitumor activity.[17] Similarly, compounds having disulfide bonds play a vital role in living organisms.[18]

Disulfides are also key intermediates in a wide variety of organic synthetic processes. Industrially, disulfides find wide application as vulcanizing agents for rubbers and elastomers, giving them excellent tensile strength.[19] We now report that some disulfide derivates are obtained with microwave heating.

RESULTS AND DISCUSSION

Disulfide derivatives were synthesized by treating thiophthalimides **1** with thiols **2–4** by using microwave irradiation, as described in Scheme 1. Microwave reactions were carried out under reflux in ethanol as solvent at 600 Watt power output. Thiophthalimides were prepared according to the literature.[20]

By using 600 W (2450 MHz, a wavelength of 12.2 cm and an energy of 0.94 J/mol) microwave irradiation, **5–7a, b** were obtained under reflux in ethanol. In fact, these products could not be obtained under classical heating, even after prolonged heating session.

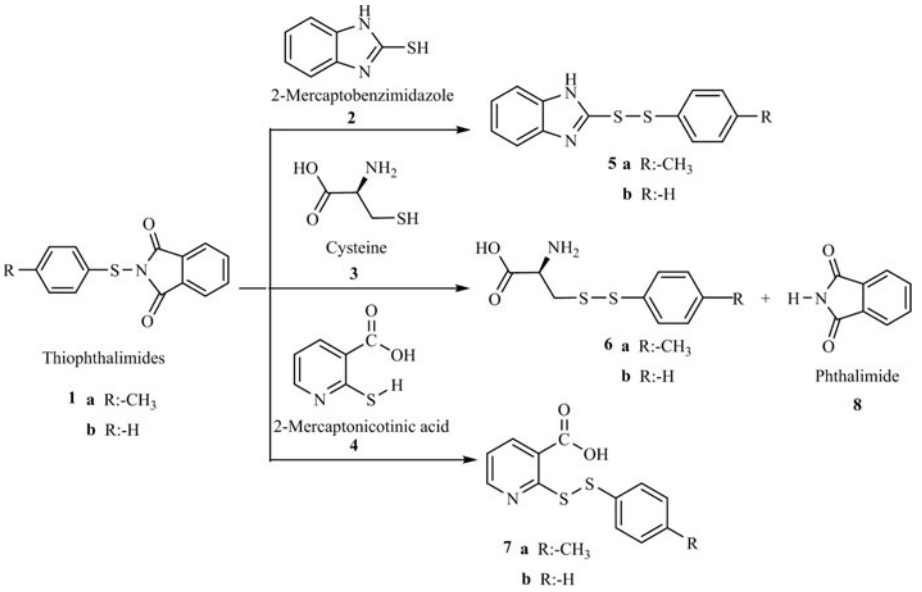
Elucidation of the structures of the synthesized compounds was in accordance with the proposed structures. Comparison of the IR spectra at each step clearly indicated the formation of disulfides, generally by the disappearance of the C=O stretching band at about 1741 cm^{-1} and the S−N stretching band at about 1071 cm^{-1} in sulfenimides, and the appearance of a new S−S band at about 525 cm^{-1} in disulfides. The current experimental results for reaction times, yields, decomposition points, and R_f values are summarized in Table 1.

The characteristic IR vibrations, and ^{1}H NMR, and ^{13}C NMR chemical shifts are given in Tables 2, and 3, respectively. The spectra are in agreement with the structures of the synthesized disulfides. Related experimental results are collated in Table 4.

The conventional mechanism for the synthesis of disulfides is shown in Scheme 2.[22]

CONCLUSIONS

In this study, the microwave-assisted synthesis method has been compared with the classical method. The synthesis of some disulfides which is not possible by classical heating methods may be obtained only by using 600 W microwave irradiation with reflux in ethanol. The notable advantages of this method are easy and quick work-up, no undesirable



Scheme 1

by-products occur. This study describes a successful approach for the synthesis of some disulfides using a modified microwave oven. Discovered advantages of using microwaves over traditional heating methods for performing an organic reaction included better yields, shorter reaction times, reduction of by-products, and no thermal decomposition of products.[7]

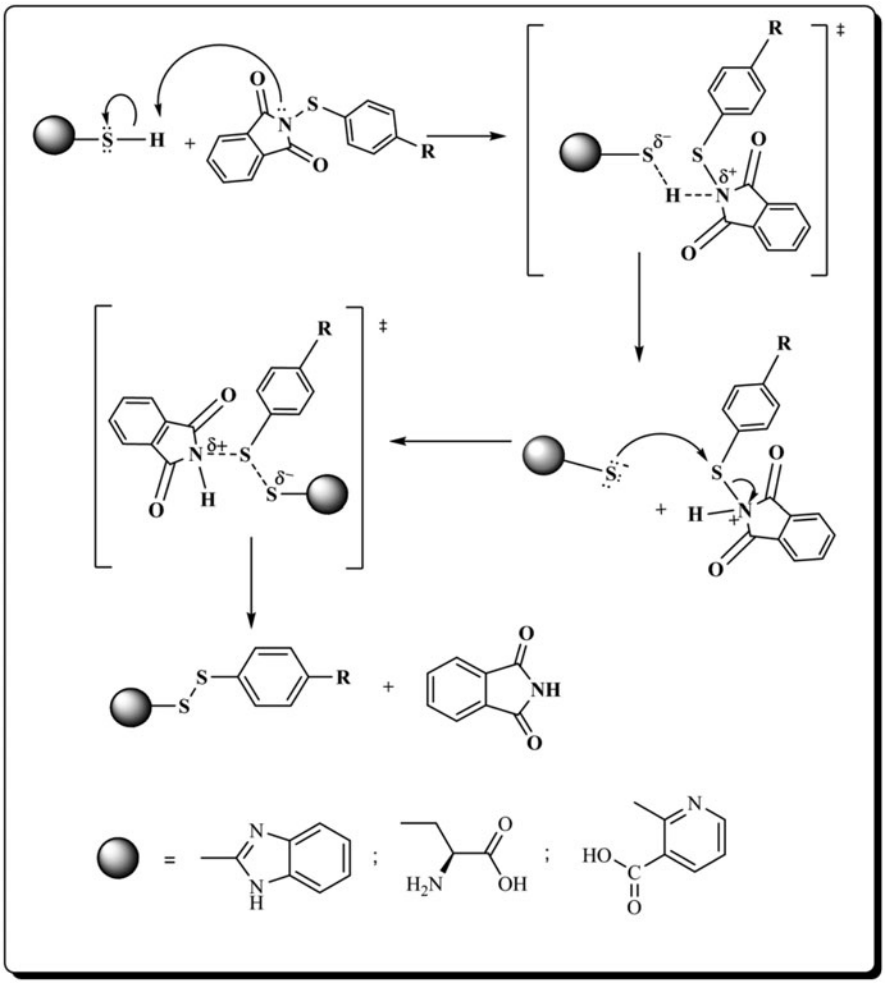
EXPERIMENTAL

All raw materials and solvents were purchased from Aldrich and Merck Chemical Company and were used without further purification. IR spectra were recorded on a Bruker Vertex 80v spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 at 400 MHz in an Avence II NMR spectrometer and in $CDCl_3$ at 200 MHz in a BRUKER AC 200NMR spectrometer using TMS as the internal standard. Melting points were measured with a Gallenkamp electrothermal apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on Merck plates. The disulfide derivatives

Table 1 The reaction time, yields, decomposition points, and R_f values for the synthesized disulfides under microwave irradiation (600 W)

Compounds	Time (min.)	Yield (%)	°C	*R_f
5a	120	63	222	0.33
5b	145	58	220	0.35
6a	70	43	Oil	0.31
6b	90	48	172	0.30
7a	220	45	177	0.29
7b	245	55	148	0.28

*Solvent conditions: mixture of *n*-butanol, acetic acid, and water (4:1:1).



Scheme 2

5–7a, b were synthesized under microwave irradiation (600 W) by using a domestic microwave (BOSCH HMT 812 C) oven that was modified by fitting a reflux system and an internal camera was used for all synthesis as shown in Figure 1.[23]

Table 2 The characteristic IR vibrations (cm^{-1}) data for the synthesized compounds

Compounds	υ_{C-H} (Arom.)	υ_{S-S}	υ_{C-H}	υ_{-NH}	$\upsilon_{C=N}$	$\upsilon_{=OH}$	$\upsilon_{C=O}$
5a	3033	625	2950—2870	3200	1509	—	—
5b	3030	620	—	3220	1505	—	—
6a	3019	618	2915–2860	*	—	3300–2710	1590
6b	3050	684	—	*	—	3420–2550	1582
7a	3055	643	2919–2863	—	1552	3155	1675
7b	3057	684	—	—	1551	3151	1596

*NH band was under the OH band.

Table 3 ^{1}H NMR and ^{13}C NMR chemical shifts spectral data for synthesized compounds

Chemical Shifts (δ), ppm
s: singlet d: doublet t: triplet dd: doublet of doublets
DMSO-d_6 and $CDCl_3$ signals are shown at 2.54 and 7.26 ppm for ^{1}H NMR and 39.50 and 77.2 ppm in ^{13}C *NMR*, respectively.[21]

Compounds	^{1}H NMR	^{13}C-NMR
5a	2.06 (3H, s, –CH_3); 5.00 (1H, s, –NH); 7.26–7.29 (2H, d); 7.36–7.38 (2H, d); 7.51–7.58 (2H; dd, J = 7.46 Hz); 7.75–7.84 (2H, dd, J = 9.14 Hz)	21.0, 124.8, 125.0, 128.5, 129.1, 130.5, 130.7, 137.9, 138.7
5b	5,02 (1H, s, -NH); 7,14–7,19 (1H, dd, J = 6.58 Hz); 7,28–7,31 (2H; dd, J = 6.12 Hz); 7,35–7,38 (2H; dd, J = 6.26 Hz); 7,50–7,61 (2H; dd, J = 8.98 Hz); 7,77–7,87 (2H, dd, 8.76 Hz)	114.5, 123.3, 125.6, 129.1, 129.4, 135.4, 138.1, 140.5
6a	2.06 (2H, s, –NH_2); 2.42 (3H, s, –CH_3); 2.81–2.91 (2H, d); 3.33–3.51 (1H, t); 7.71–7.79 (2H, d); 8.11–8.18 (2H, d); 11.33 (1H, s, -OH)	22.2, 46.8, 56.9, 127.7, 128.0, 129.9, 136.2, 176.3
6b	2.00 (2H, s, –NH_2); 3.17–3.21 (2H, d); 3.78–3.83 (1H, t); 7.04–7.08 (1H, dd, J = 7.67 Hz); 7.10–7.15 (2H, dd, J = 7.83 Hz); 7.18–7.24 (2H, dd, J = 9.45 Hz); 11.30 (1H, s, –OH)	45.6, 56.9, 126.5, 129.3, 129.4, 133.2, 176.3
7a	2.06 (3H, s, -CH_3); 7.09–7.15 (2H, d); 7.33–7.37 (2H, d); 7.71–7.88 (1H, dd, J = 9.64 Hz); 8.26–8.28 (1H, dd, J = 6.47 Hz); 8.50–8.64 (1H, dd, J = 8.66 Hz); 13.89 (1H, s, –OH)	21.1, 121.7, 123.3, 128.8, 130.0, 133.0, 137.2, 139.8, 153.0, 167.1, 180.3
7b	7.02–7.05 (1H, dd, J = 6.62 Hz); 7.12–7.17 (2H, dd, J = 7.78 Hz); 7.19–7.22 (2H, dd, J = 7.82 Hz); 7.43–7.45 (1H, dd, J = 6.22 Hz); 8.22–8.25 (1H, dd, J = 7.34 Hz); 8.69–8.71 (1H, dd, J = 6.12 Hz); 11.80 (1H, s, –OH)	122.1, 123.5, 125.6, 129.1, 129.4, 135.2, 138.4, 151.2, 170.8, 179.7

Synthesis of Substituted Thiophthalimides

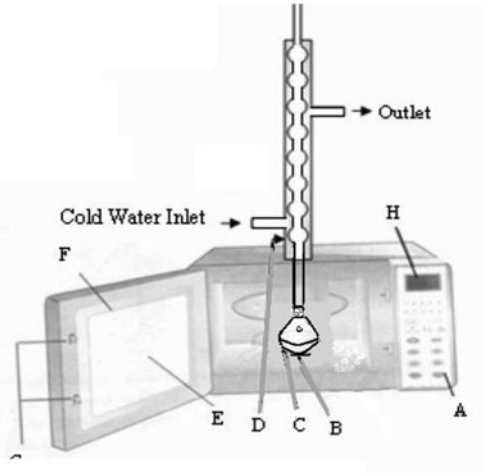
N-(p-Methylphenylthio)phthalimide 1a, *p*-Methylthiophenol (2.60 g, 21 mmol), and phthalimide (2.94 g, 20 mmol) were dissolved in hot pyridine-acetonitrile (18 mL, 4:5 mixture), and the resulting solution was cooled to room temperature with continuous stirring. A solution of bromine (3.79 g, 1.22 mL, 24 mmol) in acetonitrile (10 mL) was then added dropwise over 30 min. After a further period of 2 h, methanol (40 mL) was added dropwise over 30 min. The products were cooled in an ice-water bath for 30 min, and then the product **1a** was filtered as a pale yellow powder. The product was recrystallized from methanol. Yield: 81%, m.p. 202–204°C (lit.[24] 204–205°C); found C, 67.60; H, 4.28; N, 5.28; S, 11.88; calc. for $C_{15}H_{11}NO_2S$ C, 66.89; H, 4.12; N, 5.20; S, 11.91%; ^{1}H NMR ($CDCl_3$): δ = 2.32 (CH_3, 3H, s), 7.11–7.16 (2H, d), 7.57–7.62 (2H, d), 7.73–7.80 (2H, dd J = 7.86 Hz), 7.87–7.93 (2H, dd J = 8.24 Hz); and ^{13}C NMR ($CDCl_3$): δ = 21.2, 123.9, 129.9, 131.3, 131.9, 132.6, 134.5, 140.3, and 167.7.

N-(Phenylthio)phthalimide 1b, Thiophenol (2.31 g, 21 mmol), and phthalimide (2.94 g, 20 mmol) were dissolved in hot pyridine-acetonitrile (18 mL, 4:5 mixture) and the resulting solution was cooled to room temperature with continuous stirring. A solution of bromine (3.79 g, 1.22 mL, 24 mmol) in acetonitrile (10 mL) was then added dropwise over 30 min. After a further period of 2 h, methanol (40 mL) was added dropwise over 30 min. The products were cooled in an ice-water bath for 30 min, and then the product **1b**

Table 4 Comparison of microwave and classical heating for synthesized compounds

	Classical heating			Microwave heating		
Compounds	Time (min.)	Yield (%)	React. cond.	Time (min.)	Yield (%)	React. cond.
5a	—	—	a	—	—	b, c, d
				120	63	e
5b	—	—	a	—	—	b, c, d
				145	58	e
6a	—	—	a	—	—	b, c, d
				70	43	e
6b	—	—	a	—	—	b, c, d
				90	48	e
7a	—	—	a	—	—	b, c, d
				220	45	e
7b	—	—	a	—	—	b, c, d
				245	55	e

[a]Reflux in EtOH.
[b]With ethanol (neat) at 360 W.
[c]With reflux in ethanol at 360 W.
[d]With ethanol (neat) at 600 W.
[e]With reflux in ethanol at 600 W.
Note. "-" indicates the reactions could not synthesized by both conventional and microwave methods.



A. Power and time control panel
B. Glass Flask
C. Magnetic stirrer
D. Refluxing condenser unit
E. Observations window
F. Door assembly
G. Safety interlock system
H. Display unit

Figure 1 A modified domestic microwave oven[23].

was filtered as white crystals. Yield: 84%, m.p. 161–163°C (lit.[25] 160–161°C); ^{1}H NMR ($CDCl_3$): δ = 7.23–7.93 (arom-H, 9H,m); ^{13}C NMR ($CDCl_3$): δ = 124.0, 129.3, 130.9, 131.9, 134.7, 134.9, and 167.7.

Synthesis of Substituted Disulfides

General process–microwave method. A mixture of thiophthalimide (5.00 mmol) and thiol (5.00 mmol) were ground thoroughly and then transferred to a flask. The mixture was refluxed in ethanol (15 mL) and was irradiated in a microwave oven at 600 W. The reaction mixture was monitored throughout the experiment with a TLC on silica gel with a mixture of *n*-butanol, acetic acid, and water (4:1:1) as eluents, to determine whether or not the reaction had terminated. When the reaction was finished, hot water added, stirred, and filtered. Since phthalimide dissolves in hot water, disulfide was separated from phthalimide and recrystallized by using ethanol or acetone.

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