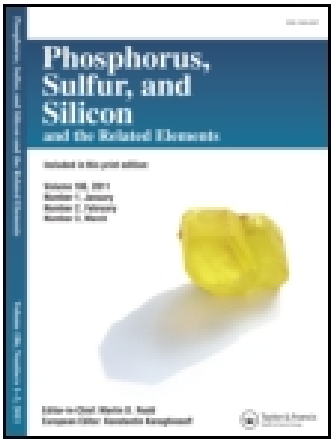


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Microwave-Assisted Synthesis of Disulfides

Halil Kutuk [a] & Nalan Turkoz [a]
[a] Ondokuz Mayıs Üniversitesi, Fen-Edebiyat Fakültesi, Kimya Bölümü , Samsun , Atakum , Turkey
Published online: 04 Aug 2011.

To cite this article: Halil Kutuk & Nalan Turkoz (2011) Microwave-Assisted Synthesis of Disulfides, Phosphorus, Sulfur, and Silicon and the Related Elements, 186:7, 1515-1522, DOI: 10.1080/10426507.2010.520174

To link to this article: http://dx.doi.org/10.1080/10426507.2010.520174

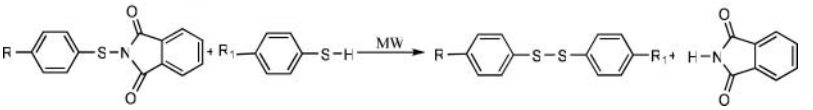
Phosphorus, Sulfur, and Silicon, 186:1515–1522, 2011

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2010.520174

MICROWAVE-ASSISTED SYNTHESIS OF DISULFIDES

Halil Kutuk and Nalan Turkoz
Ondokuz Mayıs Üniversitesi, Fen-Edebiyat Fakültesi, Kimya Bölümü, Samsun, Atakum, Turkey

GRAPHICAL ABSTRACT



Abstract *A new microwave-assisted synthesis methodology for the preparation of substituted disulfide derivatives is presented. 4-Substituted sulfenimides were reacted with 4-substituted thiols under neat (to right doughy consistency) conditions in chloroform, with both microwave heating and conventional methods. The resulting 4-substituted disulfide derivatives were obtained at higher yields and in shorter reaction times with microwave heating. Their chemistry was confirmed by ^{1}H-NMR, ^{13}C-NMR, infrared (IR), and elemental analysis.*

Keywords Disulfides; microwave; microwave effect; synthesis

INTRODUCTION

The high-speed synthesis of many organic compounds with the assistance of microwave irradiation has attracted a considerable amount of attention in recent years.[1] Microwave-promoted organic reactions, as well as environmentally benign methods, can accelerate a great number of chemical processes. In particular, reaction times and energy inputs are reduced in normally long running reactions at high temperatures when compared to conventional conditions,[2] which is a comparatively slow and inefficient method

Received 25 June 2010; accepted 23 August 2010.
We thank the Ondokuz Mayis University (Grant No. F-391) for financial support of this work.
Address correspondence to H. Kutuk, Ondokuz Mayıs Üniversitesi, Fen-Edebiyat Fakültesi, Kimya Bölümü, Samsun, Atakum 55139, Turkey. E-mail: hkutuk@omu.edu.tr

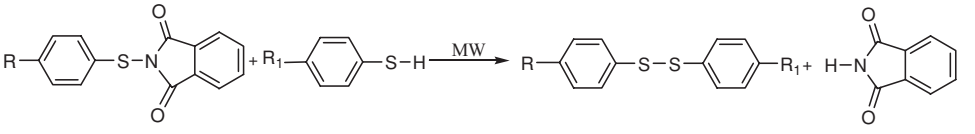
for transferring energy into the system. In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with molecules that are present in the reaction mixture, so the microwave heating technique is slowly moving from laboratory curiosity to an established technique that is widely used in both the academic and industrial environments. Microwave irradiation frequently leads to dramatically reduced reaction times, from days and hours down to minutes and seconds; higher yields; and cleaner reaction profiles and improved reproducibility.[3]

Recently, many studies have been reported in the literature on microwave-assisted synthesis of N-arylsulfonyl imines,[4] *N,N*-dialkyl-*p*-alkylphosphonamidic anhydrides,[5] bicyclic thiazolo-pyrimidine and pyrimido-thiazine derivatives,[6] and alkyl and arenesulfonamides,[7] quinolines using *N*-bromosulfonamides.[8]

The previously stated benefits of microwave irradiation have direct application, because disulfides are important organic sulfide compounds possessing a unique and rich chemistry in the synthetic and biochemical areas. For example, large disulfide-linked aggregates are prevalent in proteins and many other bioactive molecules.[9] Industrially, disulfides find wide application as vulcanizing agents for rubbers and elastomers, giving them excellent tensile strength.[10] In the field of human health they have exciting potential. Diallyl sulfide (DAS), diallyl disulfide (DADS), and diallyl trisulfide (DATS), which are the major organosulfide compounds (OSCs) of garlic, have been shown to inhibit chemically induced cancers of the skin, fore-stomach, lung, breast, colon, and esophagus,[11] as well as to suppress the proliferation of cancer cells in culture and inhibit the growth of transplanted tumor xenographs in vivo.[12]

RESULTS AND DISCUSSION

Substituted disulfide derivatives **2** were synthesized by treating 4-substituted thiols with 4-substituted sulfenimides **1** by using microwave irradiation, as described in Scheme 1. 4-Substituted sulfenimides were prepared according to the literature.[13] Microwave reactions were carried out using chloroform as a neat solvent.



1 **2**

	R and R_1
a	-H
b	$-CH_3$
c	$-NO_2$
d	$-OCH_3$
e	-Cl
f	-Br

Scheme 1

Table 1 IR, ^{1}H-NMR, and ^{13}C-NMR data for the synthesized compounds

Compound no.	IR (υ, cm^{-1})	^{1}H-NMR (DMSO-d_6, δ, ppm)	^{13}C-NMR (DMSO-d_6, δ, ppm)
2aa	3080 (C−H); 1600–1446 (C=C); 476 (S−S)	7.62–7.52 (4H, dd, $J = 8.0$ Hz); 7.43–7.37 (4H, dd, $J = 8.0$ Hz); 7.33–7.24 (2H, dd, $J = 8.0$ Hz)	136.22, 129.93, 128.04, 127.63
2ab	3050 (C−H); 2948–2821 ($-CH_3$); 1628–1439 (C=C); 523 (S−S)	7.80–7.70 (2H, dd, $J = 8.0$ Hz); 7.68–7.65 (2H, d); 7.62–7.53 (2H, dd, $J = 8.5$ Hz); 7.25–7.20 (H, dd, $J = 8.2$ Hz); 7.15–7.10 (2H, d); 2.35 (3H, s, $-CH_3$)	, 134.68, 134.26, 131.88, 130.85, 129.28, 124.03, 123.54, 25.00
2ac	3100 (C−H); 1618–1456 (C=C); 1550–1345 ($-NO_2$); 1048 (C−N); 540 (S−S)	8.90–8.20 (2H, d); 7.88–7.80 (2H, d); 7.70–7.63 (2H, dd, $J = 8.0$ Hz); 7.55–7.51 (2H, dd, $J = 8.2$ Hz); 7.40–7.35 (H, dd, $J = 8.6$ Hz)	146.57, 143.63, 129.74, 127.79, 126.75, 126.28, 124.61, 123.00
2ad	3050 (C−H); 2945–2833 ($-OCH_3$); 1613–1412 (C=C); 1197–1062 (C−O−C); 550 (S−S)	7.90–7.85 (2H, dd, $J = 7.8$ Hz); 7.80–7.77 (2H, d); 7.50–7.41 (2H, dd, $J = 8.2$ Hz); 7.33–7.27 (H, dd, $J = 8.1$ Hz); 6.10–5.84 (2H, d); 3.79 (3H, s, $-OCH_3$)	134.33, 132.66, 131.72, 128.97, 128.14, 123.60, 114.56, 55.34
2ae	3070 (C−H); 1618–1432 (C=C); 1054 (C−Cl); 542 (S−S)	7.50–7.48 (2H, dd, $J = 8.0$ Hz); 7.44–7.42 (2H, dd, $J = 8.1$ Hz); 7.28–7.26 (2H, dd, $J = 8.1$ Hz); 7.24–7.20 (H, dd, $J = 8.0$ Hz); 7.31–7.29 (2H, d)	139.64, 134.20, 132.60, 129.36, 127.59, 127.04, 126.09, 122.81
2bb	3056 (C−H); 2921–2868 (C−H); 1601–1466 (C=C); 520 (S−S)	7.38–7.34 (4H, d); 7.17–7.13 (4H, d); 2.24 (6H, s, $-CH_3$)	137.63, 132.72, 130.15, 128.22, 20.68
2bc	3083 (C−H); 2920–2841 (C−H); 1574–1530 (C=C); 1460–1330 (Ar-NO_2); 1085 (C−N); 496 (S−S)	8.22–8.16 (2H, d); 7.77–7.58 (2H, d); 7.43–7.33 (2H, d); 7.18–7.12 (2H, d); 2.43 (3H, s, $-CH_3$)	146.29, 145.27, 137.87, 130.26, 128.70, 128.11, 126.25, 124.36, 20.58
2bd	3110 (C−H); 2956–2863 (C−H); 1513–1460 (C=C); 1180–1053 (C−O−C); 496 (S−S)	7.37–7.35 (2H, d); 7.32–7.20 (2H, d); 7.10–7.01 (2H, d); 6.83–6.76 (2H, d); 3.76 (3H, s, $-OCH_3$); 2.30 (3H, s, $-CH_3$)	159.83, 134.25, 132.64, 132.56, 129.71, 129.30, 127.36, 114.55, 55.30, 21.02
2be	3057 (C−H); 2921–2868 (C−H); 1655–1574 (C=C); 1089 (C−Cl); 496 (S−S)	7.63–7.58 (2H, d); 7.48–7.44 (2H, d); 7.42–7.37 (2H, d); 7.21–7.12 (2H, d); 2.26 (3H, s, $-CH_3$)	137.80, 135.09, 134.48, 132.53, 131.95, 130.11, 129.16, 128.27, 20.54
2bf	3057 (C−H); 2921–2868 (C−H); 1655–1574 (C=C); 654 (C−Br); 496 (S−S)	7.37–7.36 (2H, d); 7.35–7.24 (2H, d); 7.12–7.08 (2H, d); 6.90–6.73 (2H, d); 2.31 (3H, s, $-CH_3$)	137.87, 134.55, 132.71, 132.03, 130.04, 129.35, 128.62, 121.06, 21.00
2cd	3101 (C−H); 2968–2840 (C−H); 1655–1593 (C=C); 1520–1350 (Ar-NO_2); 1114–1038	8.24–8.20 (2H, d); 7.83–7.80 (2H, d); 7.60–7.50 (2H, d); 6.98–6.96 (2H, d); 3.50 (3H, s, $-OCH_3$)	158.17, 145.80, 145.01, 131.16, 130.07, 127.60, 121.50, 115.30, 55.50

(Continued on next page)

Table 1 IR, ^{1}H-NMR, and ^{13}C-NMR data for the synthesized compounds *(Continued)*

Compound no.	IR (υ, cm^{-1})	^{1}H-NMR (DMSO-d_6, δ, ppm)	^{13}C-NMR (DMSO-d_6, δ, ppm)
	(C−O−C); 1078 (C−N); 519 (S−S)		
2ce	3188 (C−H); 1650–1599 (C=C);1538–1320 (Ar-NO_2); 1111 (C−N); 1090 (C−Cl); 510 (S−S)	8.20–8.18 (2H, d); 7.79–7.74 (2H, d); 7.52–7.48 (2H, d); 7.42–7.21 (2H, d)	146.97, 144.99, 144.03, 134.14, 133.00, 130.02, 127.17, 124.88
2de	3029 (C−H); 2953–2840 (C−H); 1450–1375 (C=C); 502 (S−S); 1114–1050 (C−O−C); 1038 (C−Cl)	8.23–8.21 (2H, d); 7.77–7.72 (2H, d); 7.43–7.41 (2H, d); 7.20–7.18 (2H, d); 3.61 (3H, s, -OCH_3)	159.80, 136.04, 135.06, 132.50, 132.00, 129.66, 129.20, 114.70, 55.24
2df	3029 (C−H); 2953–2840 (C−H); 1450–1375 (C=C);1114–1038 (C−O−C); 818 (C−Br); 502 (S−S)	7.54–7.46 (2H, d); 7.40–7.37 (4H, d); 7.10–6.90 (2H, d); 3.73 (3H, s, -OCH_3)	159.82, 135.89, 135.00, 132.03, 129.20, 126.97, 120.89, 115.08, 55.27
2ee	3130 (C−H); 1548–1395 (C=C); 1012 (C−Cl); 476 (S−S)	7.54–7.51 (4H, d); 7.46–7.43 (4H, d)	134.76, 133.01, 130.10, 129.93
2ef	3130 (C−H); 1550–1450 (C=C); 1012 (C−Cl); 757 (C−Br); 476 (S−S)	7.48–7.45 (2H, d); 7.43–7.41 (2H, d); 7.39–7.37 (2H, d); 7.33–7.30 (2H, d)	136.00, 133.20, 132.50, 131.20, 130.72, 129.20, 120.30
2ff	3106 (C−H); 1548–1395 (C=C); 757 (C−Br); 476 (S−S)	7.54–7.51 (4H, d); 7.43–7.41 (4H, d)	134.92, 133.20, 132.50, 131.20, 130.72, 129.20, 120.30

By using 360-W (2450 MHz, a wavelength of 12.2 cm, and an energy of 0.23 cal/mol) microwave irradiation, **2a–f** were obtained at higher yields and with lower reaction times than by classical heating methods. For example, under classical conditions, 4-bromodiphenyldisulfide **af** was produced with 25% yield in 1920 min; under microwave conditions, the reaction proceeded 640 times faster and reaction yield increased to 69% in just 3 min. 4-Chlorodiphenyldisulfide **ae**, under the conventional method, was obtained with 40% yield in 1440 min, whereas under microwave conditions it was synthesized with 77% yield in 2 min, an approximately 720 times shorter period.

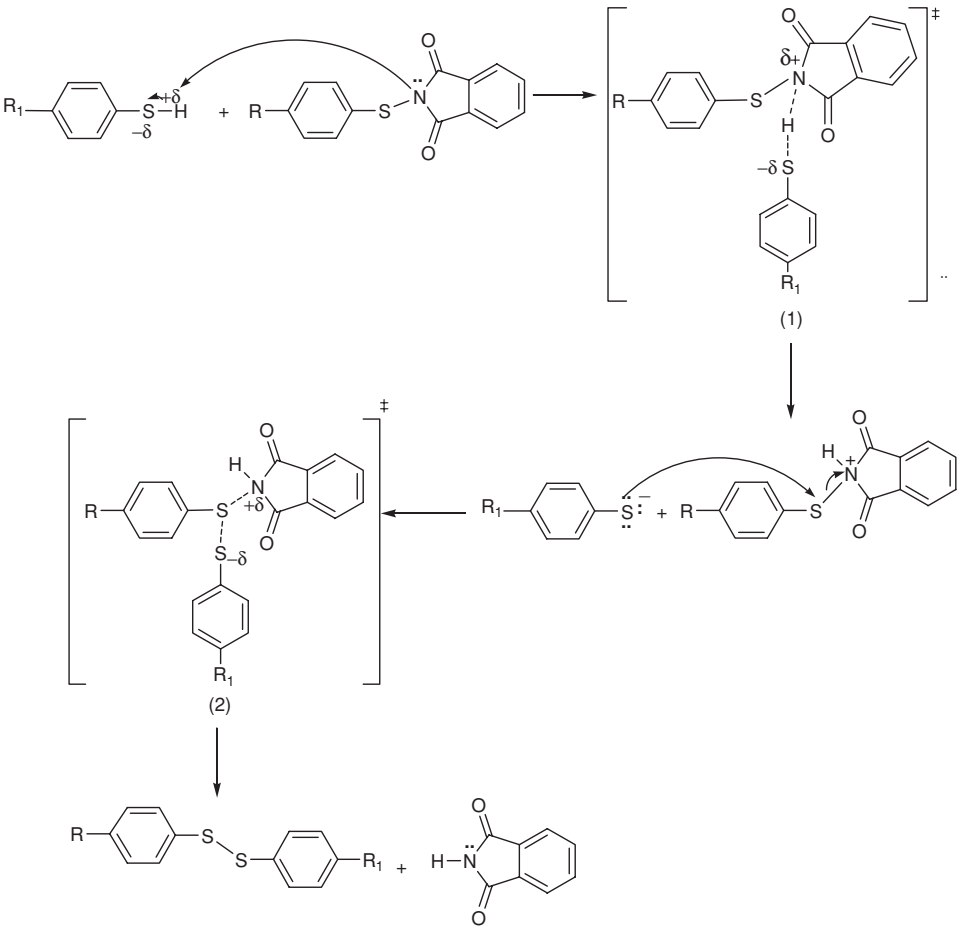
Spectral investigations of the newly synthesized intermediates and sulfenimides were in accordance with the proposed structures. Comparison of the infrared (IR) spectra at each step clearly indicated the formation of disulfides, generally by the disappearance of the C=O band at about 1748 cm^{-1}, the S-N band at about 1079 cm^{-1} in sulfenimides, and the appearance of a new S−S band at about 520 cm^{-1} in disulfides. The IR, ^{1}H-NMR, and ^{13}C-NMR values in Table 1 are in agreement with the structures of synthesized disulfides.

The current experimental results are summarized in Table 2. All of the products were produced in a very short time, and their yields were very high. The experimental procedure is simple and there were no undesirable by-products. Finally, some advantages of microwaves over traditional heating (hot plates, Bunsen burner, etc.) for performing an organic reaction are better yields, shorter reaction time (usually 1/1000), reduction of by-products, and no thermal decomposition of products.[3]

The products' structures were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis and are given in Tables 1 and 3, respectively.

In comparing the microwave-assisted synthesis method with the classical method from the literature,[14] it is clear that the synthesized compounds were obtained in a much shorter time and at higher yields under microwave irradiation than by classical heating. Related experimental results are collated in Table 4.

The conventional mechanism for the synthesis of disulfides is shown in Scheme 2.[15]



Scheme 2

EXPERIMENTAL

The substituted disulfide derivatives **2a–f** were synthesized under microwave irradiation (360 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 syntheses. Microwaves

Table 2 Physical data and reaction times for the synthesized disulfides under microwave irradiation (360 W)

	Microwave Conditions				Classical Heating			
Compound no.	m.p. (°C)	Reaction time (min)	Yield (%)	m.p. °C (Lit.[17])	Reaction time (h)	Yield (%)	Reaction cond.	R_f TLC
2aa	56–58	7	72	62	19	70	a	0.28
2ab	153–155	12	88					0.31
2ac	170–173	10	98					0.36
2ad	226–228	15	83					0.41
2ae	150–153	2	77					0.22
2af	219–223	3	69					0.25
2ba	154–156	15	73					0.31
2bb	41–43	17	93	47.5	19	73	a	0.32
2bc	46–49	14	55					0.33
2bd	Liquid	20	75	46–47	0.5	59	b	0.26
2be	48–50	5	94					0.29
2bf	61–64	8	91					0.30
2ca	169–172	27	55					0.36
2cb	47–50	38	46					0.33
2cc	155–158	20	70					0.27
2cd	64–66	33	58					0.38
2ce	117–121	16	82					0.35
2cf	145–148	19	78					0.29
2da	227–229	16	71					0.41
2db	Liquid	18	67		0.5	58	b	0.26
2dc	63–66	15	54					0.38
2dd	Liquid	21	58		19	70	a	0.35
2de	Liquid	7	78					0.25
2df	Liquid	10	83					0.24
2ea	151–155	6	73					0.22
2eb	48–50	15	72		19	80	a	0.29
2ec	117–120	13	55					0.34
2ed	Liquid	18	54					0.25
2ee	60–62	3	85	72.8	1	35	c	0.34
2ef	75–78	4	80					0.33
2fa	220–223	9	70					0.25
2fb	61–63	16	65					0.30
2fc	146–150	14	60					0.28
2fd	Liquid	20	67					0.24
2fe	76–78	4	84					0.34
2ff	90–93	3	92					0.29

[a]Reflux in CH_2Cl_2.[18]
[b]−20 °C in CH_2Cl_2.[19]
[c]Catalytic amount of nitric oxide in air and CD_3CN.[20]

at 2450 MHz were used in the microwave oven. This frequency corresponds to a wavelength of 12.2 cm and an energy of 0.23 cal/mol (=0.94 J/mol). This frequency can only cause rotation of molecules.[16] All raw materials and solvents were purchased from Aldrich Chemical Company and were used without further purification. IR spectra were recorded on a Bruker Vertex 80v spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were determined in DMSO-d_6 at 400 MHz in an Avance II NMR spectrometer using tetramethylsilane (TMS) as the internal standard. Elemental analyses were performed by the Central Laboratory

Table 3 Analytical data for some of the synthesized disulfides

Comp. no.	Formula (m.wt)	Analytical data found/(calcd.) (%)			
		C	H	N	S
2aa	$C_{12}H_{10}S_2$ (218)	65.83 (66.05)	4.69 (4.58)		29.16 (29.35)
2bb	$C_{14}H_{14}S_2$ (246)	68.71 (68.29)	5.76 (5.69)		25.84 (26.01)
2bc	$C_{13}H_{11}NO_2S_2$ (277)	56.97 (56.31)	4.22 (3.97)	5.29 (5.05)	22.76 (23.10)
2be	$C_{13}H_{11}S_2Cl$ (266.5)	59.25 (58.54)	4.58 (4.13)		23.32 (24.01)
2bf	$C_{13}H_{11}S_2Br$ (311)	50.47 (50.16)	3.88 (3.53)		20.10 (20.57)
2cc	$C_{12}H_8N_2O_4S_2$ (308)	46.85 (46.75)	3.04 (2.59)	9.20 (9.09)	20.45 (20.78)
2cf	$C_{12}H_8NO_2S_2Br$ (342)	41.89 (42.10)	2.64 (2.33)	4.58 (4.09)	17.75 (18.71)
2ec	$C_{12}H_8NO_2S_2Cl$ (297.5)	48.87 (48.40)	2.88 (2.68)	4.80 (4.70)	21.19 (21.51)
2ee	$C_{12}H_8S_2Cl_2$ (287)	50.73 (50.17)	2.98 (2.78)		21.40 (22.29)
2ff	$C_{12}H_8S_2Br_2$ (376)	37.28 (38.29)	2.70 (2.12)		17.47 (17.02)

of the Middle East Technical University (METU) in Ankara, Turkey. Melting points were measured with a Gallenkamp electrothermal apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on Merck plates.

Synthesis of Substituted Disulfides

General Process—Conventional Method. A mixture of 4-substituted sulfenimide (5.00 mmol) and 4-substituted thiol (5.00 mmol) was ground thoroughly and then transferred to a round-base flask. The mixture was refluxed in ethanol (50 mL). The reaction mixture was controlled by TLC at regular intervals on silica gel with a mixture of hexane and ethyl acetate (5:1) as the eluent. When the reaction was finished, hot water was added, and it was stirred and filtered. Because phthalimide dissolves in hot water, the disulfide was separated from the phthalimide. Then the disulfide was recrystallized using ethanol or acetone.

General Process—Microwave Method. A mixture of 4-substituted sulfenimide (5.00 mmol) and 4-substituted thiol (5.00 mmol) was ground thoroughly and then transferred to a flask and chloroform was added. The mixture was irradiated in a microwave oven at 360 W. The reaction mixture was monitored throughout the experiment with TLC

Table 4 Comparison of microwave and classical heating for production of some disulfides

Comp. no.	Classical heating			Microwave conditions		
	Reaction time (min)	Yield (%)	Reaction cond.	Reaction time (min)	Yield (%)	Reaction cond.
1aa	2700	23	a	7	72	b
1ab	3600	35	a	12	88	b
1ac	3180	40	a	10	98	b
1ad	5760	30	a	15	83	b
1ae	1440	40	a	2	77	b
1af	1920	25	a	3	69	b

[a]Reflux in EtOH.
[b]With chloroform under microwave irradiation (360 W).

on silica gel with a mixture of hexane and ethyl acetate (5:1) as the eluent, to determine whether the reaction had terminated. When the reaction was finished, the product was purified as mentioned above.

REFERENCES

1. Adam, D. *Nature* **2003,** *421*, 571–572.
2. Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.
3. Kappe, C. O. *Angew. Chem. Int. Ed.* **2004,** *43*, 6250–6284.
4. Hasaninejad, A.; Zare, A.; Zare, A. R. M.; Parhami, A.; Sharghi, A.; Khalafi-Nezhad, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008,** *183*, 2769–2776.
5. Kumar, R.; Gupta, A. K.; Kaushik, M. P. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010,** *185*, 765–775.
6. Virsodiaa, V. R.; Vekariyaa, N. R.; Manvarb, A. T.; Khuntb, R. C.; Marvaniab, B. R.; Savaliab, B. S.; Shahb, A. K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2009,** *184*, 34–44.
7. Malik, S.; Nadir, U. K.; Pandey, P. S. *Synth. Commun.* **2008,** *38*, 3074–3081.
8. Ghorbani-Vaghei, R.; Akbari-Dadamahaleh, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2010,** *185*, 319–324.
9. Bodzansky, M. *Principles of Peptide Synthesis*; Springer-Verlag: Berlin, 1984.
10. Wang, J. X.; Gao, L.; Huang, D. *Synth. Commun.* **2002,** *32*, 963–969.
11. Khanum, F.; Anilakumar, K. R.; Viswanathan, K. R. *Food Sci. Nutr.* **2004,** *44*, 479–488.
12. Herman-Antosiewicz, A.; Singh, S. V. *Mutat. Res.* **2004,** *555*, 121–131.
13. Behforouz, M.; Kerwood, J. E. *J. Org. Chem.* **1968,** *34*, 51–55.
14. Harpp, D. N.; Ash, D. K.; Back, T. G.; Gleason, J. G.; Orwig, B. A.; VanHorn, W. F. *Tetrahedron Lett*. **1970,** *41*, 3551–3554.
15. Suwa, S.; Sakamoto, T.; Kikugawa, Y. *Chem Pharm. Bull.* **1999,** *47*, 980–982.
16. Letellier, M.; Budzinski, H. *Analusis* **1999,** *27*, 259–271.
17. Lide, D. R. *CRC Handbook of Chemistry and Physics*, 85th ed.; CRC Press: Boca Raton, FL, 2003.
18. Oae, S.; Togo, H.; Numata, T.; Fujimori, K. *Chem. Lett.* **1980,** 1193–1196.
19. Stellenboom, N.; Hunter, R.; Caira, M. R. *Tetrahedron* **2010,** *66*, 3228–3241.
20. Tsutsumi, N.; Itoh, T.; Ohsawa, A. *Chem. Pharm. Bull.* **2000,** *48*(10), 1524–1528.