Microwave-Assisted Synthesis of Disulfides Using Tetrathiomolybdate: A Step toward Greener Synthesis

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ABSTRACT: An eco-friendly, efficient, and rapid synthetic procedure for disulfides using benzyl triethyl ammonium tetrathiomolybdate through microwave irradiation of solid support adsorbed reactants is reported. © 2012 Wiley Periodicals, Inc. Heteroatom Chem 00:1–4, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21025

INTRODUCTION

The synthesis and chemistry of disulfides continue to be an area of considerable interest among researchers on account of their biological role, industrial applications, and utility in organic synthesis [1–5]. Although a variety of methods have been devised for their synthesis, disulfides are mostly synthesized from the corresponding halides, thiocyanates, and alcohols using tetrathiomolybdate [2,4]. This is due to advantages such as straightforward reaction methodologies and mild reaction conditions that can be tuned green by careful and intelligent modifications in the experimental procedure. An appropriate choice of parameters in these steps is expected to ensure the synthesis of disulfides through solventless and/or use of eco-friendly solvent choices and biphasic catalysis pathways. The disadvantages such as longer reaction times, operational complications, and the use of volatile organic

compounds (VOCs) in this often opted procedure for disulfide synthesis have been a great challenge for environment-conscious synthetic chemists. Such challenges in synthetic organic chemistry are usually overcome through the use of unconventional reactor designs and reaction pathways that require the use of nonhazardous and eco-friendly chemicals to ensure efficient and green synthesis of desired substances. It is in this context that microwave irradiation coupled with solid support is receiving considerable attention in organic synthesis [6-8]. The use of microwave irradiation in organic synthesis has ensured minimal or no use of VOCs, simple workup coupled with higher yields, shorter reaction times, low energy consumption, and selectivity [9-13] in certain reactions. In view of these facts and drawing an inspiration from some recent reports [14,15], we attempted the use of microwave irradiation in the synthesis of disulfides from alkyl halides and thiocyanates using benzyl triethyl ammonium tetrathiomolybdate (BTATM). In the present communication, we report results from our preliminary investigations about the synthesis of disulfides through microwave irradiation of solid-supported reactants. The main finding of the present communication is that the use of microwave irradiation turns the conventional synthetic procedure of disulfides eco-friendly, efficient, and time saving.

RESULTS AND DISCUSSION

Before attempting the microwave-assisted synthesis, we explored the stability of silica-supported as well as water-solubilized BTATM on exposure to

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microwave irradiation. For this purpose, these samples were irradiated at different power levels up to the maximum of 300 s and temperatures were recorded. It was found that the temperature reaches a maximum of 80°C in the case of BTATM in water and 62°C in the case of BTATM on silica gel. This temperature is much less than the decomposition temperature of BTATM (130–150°C). The UV spectra of pre- and postirradiated BTATM were found to be identical, establishing that the BTATM is stable under the microwave irradiation conditions that we attempted in our experiments.

Our most solvent selections for thin-layer chromatography (TLC) analysis of product from the reactions carried out under conventional conditions and microwave irradiation showed the product as a single entity in accordance with earlier reports. Incidentally, with a solvent choice of petroleum ether:chloroform (7:3 v/v) revealed that the product is a combination of two hard to separate entities whose ratio apparently varied with the reaction time. Earlier, Harpp and MacDonald have also reported formation of an inseparable mixture of mono- and disulfides from alkyl halides using a molybdenum-persulfide complex [16]. Similar results using haloesters with BTATM and formation of thiol in addition to disulfides with piperidinium tetrathiomolybdate have been reported by Chandrasekaran and coworkers [4,17]. To confirm the formation of two products in our case, the reaction products were subjected to the gas chromatographymass spectrometry (GC-MS) analysis and we found that the product is indeed a mixture of monosulfide and disulfide of the starting compound wherein the ratio of mono/di analog decreases with an increase in the reaction time. Overall, the yield of each reaction along with the percentage composition of different products as determined by the GC-MS analysis is presented in Table 1.

The GC-MS analysis of the product from the reaction of benzyl chloride with BTATM revealed the presence of two compounds with Kovet's retention indices 2068 and 1817 corresponding to dibenzyl disulfide (DBDS) and dibenzyl monosulfide (DBS). The best yield of approximately 70.1% was observed with an irradiation time of 300 s at the medium-high power level. We observed that the overall yield and proportion of DBDS in the product increases with an increase in time and power levels.

In the reaction of benzyl thiocyanate with BTATM under similar reaction conditions, as mentioned for benzyl chloride, a yield of 98.3% in 300 s at the medium–high power level with 100% fraction of DBDS is formed. Again, in this case, the overall

TABLE 1 Overall Yield for the Reaction of Benzyl Chloride,
Benzyl Thiocyanate, Benzyl Bromide, Hexyl Bromide, Octyl
Bromide at Different Time Durations with Composition of the
Reaction Mixture Based on GC-MS Analysis

			%Composition		
Substrate	Time (s)	Overall Yield (%)	RSSR (disulfide)	RSR (monosulfide)	
Benzyl chloride	60	52.66	51.0	1.66	
-	120	52.8	51.8	1.0	
	180	53.2	52.8	0.4	
	240	56.7	56.3	0.4	
	300	70.1	69.9	0.2	
Benzyl thiocyanate	60	65.03	64.75	0.28	
	120	73.03	72.95	0.08	
	180	79.58	79.5	0.08	
	240	89.93	89.9	0.03	
	300	98.3	98.3		
Benzyl bromide	30	56.3	42.6	13.7	
	60	52.5	43.4	9.1	
	120	50.3	27.4	22.9	
	150	46.62	23.31	23.31	
	180	46.5	23.2	23.3	
	270	46.5	23.2	23.3	
Hexyl bromide	60	63.9	62.5	1.4	
	120	64.24	63.8	0.44	
	180	64.34	63.9	0.39	
	240	68.53	68.24	0.29	
Octyl bromide	60	66	64.5	1.5	
	120	66.80	66.3	0.5	
	180	67.25	67.11	0.14	
	240	68.80	68.55	0.25	

yield and proportion of DBDS was found to increase with an increase in time and power levels.

For benzyl bromide with BTATM, the best yield of 56.3% was observed with an irradiation time of 30 s at the medium–low power level and surprisingly the amount of DBS increases (a decrease in the DBDS:DBS ratio) when we move from the medium– low to medium power level. However, switching to the medium–high power level was found to decrease the overall yield, perhaps on account of overheating, leading to decomposition of the reactant/product. With an increase in temperature from room temperature to the medium–low power level under microwave irradiation, the reaction time is reduced but the overall yield decreases, indicating the instability of the reactant with increasing temperature.

In the reaction of hexyl bromide with BTATM, the GC-MS analysis of the product revealed the presence of two compounds with Kovet's retention indices 1716 and 1465 corresponding to dihexyl disulfide and dihexyl monosulfide. The overall yield and percentage composition of dihexyl disulfide increase with an increase in time and power levels.

For the reaction of octyl bromide with BTATM, the GC-MS analysis of the product revealed the

presence of two compounds with Kovet's retention indices 2113 and 1817 corresponding to dioctyl disulfide (DODS) and dioctyl monosulfide. The overall yield as well as percentage composition of DODS increases with increasing time and power levels.

Interestingly, we found that the relative ratio of disulfide:monosulfide changes with a change in the irradiation time at all power levels.

We also compared the efficiency of the microwave-assisted procedure with the conventional one for the synthesis of disulfides from the abovementioned substrates. A comparative account of the two synthetic procedures is given in Table 2.

From the data, it is evident that for all the five substrates, viz., benzyl chloride, benzyl thiocyanate, benzyl bromide, hexyl bromide, and octyl bromide, the higher percentage yields for their corresponding disulfides were obtained under microwave irradiation and in a much shorter time than under conventional conditions.

From our observations in the present study, we make following inferences:

- 1. The overall yield as well as percentage yield of DBDS is best achieved when benzyl thiocyanate is used as a substrate as compared with benzyl chloride and benzyl bromide. Its irradiation at the medium-high power level for 300 s increases the overall yield to 98.3% comprising 100% dibenzyl disulfide. This can be best explained in terms of inherent dipole of a molecule [18–20], viz., a higher dipole moment leads to efficient microwave heating. In the benzyl series of studied compounds, the dipole moment is in the order SCN⁻ > Cl⁻ > Br⁻, which explains the higher yields in the case of benzyl thiocyanate than benzyl bromide and benzyl chloride, respectively.
- 2. In the case of benzyl bromide, overall yield and percentage composition of DBDS decrease with increasing time and power level, whereas in the

 TABLE 2
 Comparative Data of Conventional and Microwave Reactions

Substrate	Ro Tempo	oom erature	Microwave Irradiation	
	Time (h)	Yield (%)	Time (s)	Yield (%)
Benzyl thiocyanate	6	80	300	98.3
Benzyl chloride	5	60	300	71
Benzyl bromide	1	55	30	57
Hexyl bromide	10	60	240	68.58
Octyl bromide	11	62	240	68.80

case of benzyl chloride and benzyl thiocyanate, the overall yield and percentage composition of DBDS increase progressively with an increase in time and power levels.

3. Microwave-assisted synthesis of disulfides using BTATM is an efficient, less time-consuming, greener synthetic procedure as compared with conventional conditions.

CONCLUSIONS

For the first time through an eco-friendly procedure, disulfides have been conveniently prepared using alkyl halides and thiocyanates using BTATM under solvent-free microwave conditions. With thiocyanate as the substrate, a maximum yield of 98.3% has been obtained under microwave irradiation and hence it is a suitable substrate for the synthesis of disulfides. Because the reactions have been carried out on a solid support with minimal involvement of solvents, the procedure provides a green chemistry approach.

EXPERIMENTAL

Reactions were performed in a Sharp Carousel TM microwave oven (Thailand) (model R-210 B with output power of 800 W). The GC-MS analysis was carried on a Varian GC-3800 capillary column VF-5 ms (60 m \times 0.25 mm film thickness 0.25 µm) coupled with a 4000 series mass detector (Applied Biosystems/MDS Sciex) under the following conditions: injection volume 0.5 µL with a split ratio 1:60; helium as a carrier gas at 1.3 mL/min constant flow mode; injector temperature 280°C; oven temperature 80°–280°C. In a typical synthetic procedure, 1 mmol of the substrate and BTATM (0.66 g, 1.1 mmol) in 1 mL of acetonitrile was adsorbed on silica gel (60-120 mesh) used as solid support. Different reaction mixtures were prepared and irradiated for different time durations at mediumlow, medium, and medium-high power levels. For the reaction of benzyl bromide with BTATM, different mixtures were prepared and irradiated at medium-low, medium, and medium-high power levels for different time periods of 30, 60, 120, 150, 180, and 270 s. Irradiation was carried out in multiple heating cycles of 15 s, and progress of reaction was monitored with TLC. The mixture of benzyl chloride and benzyl thiocyanate with BTATM on solid support was irradiated for 60, 120, 180, 240, and 300 s. In the reaction of hexyl bromide and octyl bromide with BTATM, irradiation was carried out in multiple heating cycles of 30 s. Because the reactions were carried out under solvent-free conditions, irradiation of the same mixture at different time intervals that could have led to a change in the concentration of reactants as well as the products was avoided. To maintain the concentration to be considerably accurate for each substrate, we took several equally concentrated reaction mixtures adsorbed on the same amount of solid support and irradiated them at medium-low, medium, and mediumhigh power levels for various time durations. Reactions were monitored periodically with TLC. After irradiating for specified durations, reaction mixtures were eluted with diethyl ether $(3 \times 20 \text{ mL})$. The concentration of the ethereal layer yielded a white color solid/colorless liquid. Solids were crystallized; melting points recorded, and the percentage yield at different time durations and power levels were obtained.

The analytical data for products are as follows:

BTATM: UV–visible (DMF): λ max: 279, 342, 468. IR (KBr, cm⁻¹): 3036, 2969, 1508, 1473, 1450, 1392, 1373, 1153, 1010, 788, 750, 704, 468 (Mo-S). mp: 130°C

Dibenzyl disulfide: MS (*m*/*z*): 246 (M⁺), 182, 121, 91. ¹H NMR (200 MHz, CDCl₃): 7.28 (s, 10H), 3.60 (s, 4H). IR (KBr, cm⁻¹): 3049, 3025, 2922, 2853, 1597, 1491, 1451, 1382, 1222, 1120, 658. mp: 70°C.

Dibenzyl monosulfide: MS (*m*/*z*): 214 (M⁺), 182, 121, 91. ¹H NMR (200 MHz, CDCl₃): 7.17 (s, 10H), 3.45 (s, 4H). IR (KBr, cm⁻¹): 3110, 3080, 3050, 2940, 1625, 1600, 1505, 1462, 1430, 1232, 1205, 1070, 1030. mp: 49°C.

Dihexyl disulfide: MS (*m*/*z*): 234 (M⁺), 154, 117, 81. ¹H NMR (200 MHz, CDCl₃): 2.5 (t, 4H), 1.26–1.65 (m, 16H), 1.2 (t, 6H). bp: 300°C.

Dihexyl monosulfide: MS (*m*/*z*): 202 (M⁺), 131, 117, 84, 69, 61, 55, 43, 29. ¹H NMR (200 MHz, CDCl₃): 2.4 (t, 4H), 1.29–1.66 (m, 16H), 1.2 (t, 6H). bp: 220°C.

Dioctyl disulfide: MS (*m*/*z*): 290 (M⁺), 178, 145, 112, 87, 71, 57. ¹H NMR (200 MHz, CDCl₃): 2.46 (t, 4H), 1.29–1.59 (m, 24H), 0.96 (t, 6H). bp: 240°C/10 mmHg.

Dioctyl monosulfide: MS (*m*/*z*): 258 (M⁺),159, 145, 112, 83. ¹H NMR (200 MHz, CDCl₃): 2.40 (t, 4H), 1.27–1.59 (m, 24H), 0.96 (t, 6H). bp 180°C/10 mmHg.

REFERENCES

- [1] Witt, D. Synthesis, 2008, 16, 2491.
- [2] Prabhu K. R.; Devan, N; Chandrasekaran, S. Synlett 2000, 11, 1762.
- [3] Sureshkumar, D.; Kothua, S. M.; Chandrasekaran, S. J Am Chem Soc 2005, 127, 12760; (b) Stiefel, E. I. Prog Inorg Chem 1973, 22, 1; (c) Massoth, F. E. Adv Catal 1978, 27, 265.
- [4] Dhar, P.; Chandrasekaran, S. J Org Chem 1989, 54, 2998.
- [5] Prabhu, K. R.; Ramesha, A. R.; Chandrasekaran, S. J Org Chem 1995, 60, 7192.
- [6] Bram, G.; Loupy, A.; Majdoub, M.; Guitrezz, E.; Ruiz Hitzky, E. Tetrahedron 1990, 46, 5167.
- [7] Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B.
 S. J.; Mingos, D. M. P. Chem Soc Rev 1998, 27, 213.
- [8] Varma, R. S. Advances in Green Chemistry: Chemical Synthesis Using Microwave Irradiation; Astra Zeneca Research Foundation, Bangalore, India, 2002.
- [9] Forfar, I.; Cabildo, P.; Claramunt, R. M.; Elguero, J. Chem Lett 1994, 23(11), 2079.
- [10] Herradon, C; Morcuende, A.; Valverde, S. Synlett 1995, 61, 7146.
- [11] Carrillo-Munoz, J. R.; Bouvet, D.; Loupy, A.; Petit, A. J Org Chem 1996, 61, 7146.
- [12] Almena, I.; Diaz Ortiz, A.; Diaz Barra, E.; de la Houz, A.; Loupy, A. Chem Lett 1996, 37, 333.
- [13] Lang, F.; de la Cruz, P.; de la Houz, A.; Diaz Ortiz, A.; Diaz Barra, A. Cont Org Synth 1997, 65, 3659.
- [14] Wang, J. X.; Gao, L.; Huang, D. Synth Commun 2002, 32(7), 963.
- [15] Gormer, K.; Waldmann, H.; Triola, G. J Org Chem 2010, 75, 1811.
- [16] Harpp, D. N.; MacDonald, J. G. Tetrahedron Lett 1984, 25, 703.
- [17] Ramesha, A. R.; Chandrasekaran, S. Synth Commun 1992, 22(22), 3277.
- [18] Reddy, S. R.; Rao, B. R.; Manikyamba, P. Indian J Chem A 2007, 46, 436.
- [19] Schaefer, T.; Sebastian, R.; Penner, G. H. Can J Chem 1986, 64, 1372.
- [20] Furton, K. G.; Pool, C. F.; Kersten, B. R. Anal Chim Acta 1987, 192, 255.