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PAPER

Microwave-Assisted Synthesis of Asymmetric Disulfides

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Thiourea is very useful in the synthesis of asymmetric and symmetric disulfides. In this paper, we report an efficient, odorless, and one-pot procedure for the synthesis of benzyl alkyl disulfides by using the mixtures of thiourea, alkyl halides, and benzyl thiocyanates. The reaction was carried out in water with the assistance of microwave, enabling a time-saving process. Optimal conditions were obtained as follows: benzyl thiocyanate (1.0 equiv), thiourea (2.0 equiv), and alkyl halide (1.2 equiv) were reacted under microwave irradiation using K_3PO_4 as the base in water at 90 °C for 15 min. In most cases, the yields are higher than 80%. In this protocol, the substrates are readily available and their synthesis is much easier than the corresponding thiols. Moreover, it is environmentally and economically friendly.

Introduction

Disulfide compounds are important in chemistry, biochemistry, and materials science.[1-8] Particularly, disulfide bonds exist in a vast number of proteins, playing an extremely vital role in stabilizing the structures of proteins.[9] There are also a wide variety of biologically active target molecules that contain disulfide moieties, which possess properties such as anticancer activity.[10] Therefore, it is interesting to develop protocols for the formation of asymmetric disulfide bonds toward the synthesis of biologically active peptides and peptide mimetics.[11]

There have been many different protocols for the synthesis of symmetric disulfides. However, most of them cannot be applied to the synthesis of asymmetric disulfides because of the fast thiol-disufide exchange reaction. Recently, the synthesis of asymmetric disulfides has attracted great attention from several research groups, and some methodologies have been proposed.[12] The most popular approach involves substitution of a sulfenyl derivative with a thiol or its derivative. Asymmetric disulfides have been obtained from the corresponding thiols and 5, 5-dimethyl-2-thioxo-1, 3, 2-dioxaphosphorinane-2-disulfanyl derivatives under mild conditions with good to excellent yields.[13-16] In most transformation, highly toxic reagents were used, including Br_2, $SOCl_2$, S_2Cl_2, and SO_2Cl_2; in addition, harsh conditions of pH may promote the thiol exchange reaction. Few examples of one-pot formation of disulfide bonds have been reported. Recently, Hunter et al. described the one-pot synthesis of asymmetric disulfides by using 1-chlorobenzotriazole,[17] which is an economical and environmentally friendly oxidizing reagent and is able to convert a thiol into an N-sulfenyl derivative. This derivative can efficiently react with a second thiol to form an asymmetric disulfide.

Despite the fact that researches have opened new routes to efficient synthesis of disulfides, many thiols are toxic and foul-smelling compounds. Thus, the development of simple and convenient disulfide synthetic methods by using non-thiolic, commercially available, and inoffensive precursors and regents will be very valuable. As far as we know, thiourea, a most attractive starting material owing to its low cost and readily accessibility, is an ideal alternative thiol reagent. Very recently, thiourea was used to synthesize asymmetric sulfides[18,19] and symmetric disulfides.[20,21] Although the reported protocols didn't use the above-mentioned highly toxic reagents, they often employ harmful organic solvents as the media. Organic solvents are generally toxic, expensive, and need additional recycling procedures. Nowadays, removing harmful organic solvents is a main problem for chemical industries. On the contrary, water is generally considered as an ideal "green" solvent for organic synthesis based on the low cost, safety, and environmental impacts. As a result, designing organic reactions in water has become one of the most attractive areas in green chemistry.[22]

Herein, we report a novel and efficient route for the synthesis of asymmetric disulfides via a microwave-assisted method,[23-26] which promotes the reaction. The use of microwave irradiation in organic synthesis has ensured simple workup coupled with higher yield, shorter reaction time, lower energy consumption, and better selectivity in certain reactions.[27] The direct sulfanylation of benzyl thiocyanate with thiourea and a series of alkyl halides with potassium phosphate in water afforded disulfides in moderate to excellent yields.

Experimental

Materials and Methods

All reactions were conducted in a Discover SP microwave synthesizer and Easy Max™ 102. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance III 400MHz spectroscope in CD_3OD using TMS as internal standard. Chemical shifts are

reported in ppm (δ), and coupling contants (J) in Hz. GC/MS analyses were performed on a Polaris Q GC/MS instrument. All the products are known compounds and were identified by comparing of their spectra data with those reported in literatures. All chemicals (AR grade) were commercially available and used without further purification.

Typical procedure for the reaction of benzyl thiocyanate, alkyl halides and thiourea

To a solution of 3 mL water were added benzyl thiocyanate (1 mmol), alkyl halides (1.5 mmol), thiourea (1.2 mmol), K_3PO_4 (1.2 mmol), KI (1.5 mmol), and TBAH (1.5 mmol). The mixture was put into the cavity of the microwave and irradiated at 50 W at 90°C for 10 min. Then the reaction mixture was extracted with dichloromethane (DCM). The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation to give a crude product. Purification by silica gel chromatography eluting with *n*-hexane afforded pure thioethers.

Characterization data of the compounds

1-Benzyl-2-octyldisulfane (**4a**). Colorless oil. 163 mg (0.61 mmol, 61% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 - 7.14 (m, 5H), 3.88 (s, 2H), 2.34 (t, *J* =7.3Hz, 2H), 1.56 - 1.48 (m, 2H), 1.33 - 1.24 (m, 10H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 139.37, 130.40, 129.43, 128.30, 44.38, 39.29, 32.75, 30.03, 29.92, 23.70, 14.44. GC-MS (EI) calcd for $[C_{15}H_{24}S_2 + H]^+$ requires m/z 269.1319, found m/z 269.0130.

1-Benzyl-2-heptyldisulfane (**4b**). Colorless oil. 224 mg (0.88 mmol, 88% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 7.37 - 7.26 (m, 5H), 3.91 (s, 2H), 2.39 -2.35 (t, *J* = 7.35 Hz, 2H), 1.30 (m, 8H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 139.29, 130.37, 129.41, 128.27, 44.39, 39.30, 32.85, 30.02, 29.91, 29.43, 23.63, 14.44. GC-MS (EI) calcd for $[C_{14}H_{22}S_2 + H]^+$ requires m/z 255.1163, found m/z 254.9696.

1-Benzyl-2-hexyldisulfane (**4c**). Colorless oil. 214 mg (0.89 mmol, 89% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 - 7.23 (m, 5H), 3.88 (s, 1H), 2.35 (t, *J* = 7.3 Hz, 2H), 1.52 (dt, *J* = 14.8, 7.5 Hz, 2H), 1.34 - 1.20 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 137.98, 129.02, 128.05, 126.91, 42.98, 37.90, 31.09, 28.60, 27.77, 22.18, 12.96. GC-MS (EI) calcd for $[C_{13}H_{20}S_2 + H]^+$ requires m/z 241.1006, found m/z 241.9353.

1-Benzyl-2-pentyldisulfane (**4d**). Colorless oil. 203 mg (0.90 mmol, 90% yield).^{1}H NMR (400 MHz, CD_3OD) δ 7.55 - 6.98 (m, 5H), 3.88 (s, 2H), 2.35(t, *J* = 7.3Hz, 2H), 1.58 - 1.48 (m, 2H), 1.31 - 1.22 (m, 4H), δ 0.89 (q, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ139.35, 130.41, 129.44, 128.30, 44.37, 39.26, 31.71, 29.73, 23.25, 14.28. GC-MS (EI) calcd for $[C_{12}H_{18}S_2 + H]^+$ requires m/z 227.0850, found m/z 226.9525.

1-Benzyl-2-isopentyldisulfane (**4e**). Colorless oil. 170 mg (0.75 mmol, 75% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 7.36 - 7.26 (m, 6H), 3.91 (s, 2H), 2.26 (d, *J* = 6.8 Hz, 2H), 1.84 - 1.76 (m, 1H), 1.31 (m, 2H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.7 Hz,3H); ^{13}C NMR (150 MHz, CD_3OD) δ 139.36, 130.42, 129.44, 128.28, 44.27, 32.75, 29.09, 23.70, 21.96, 14.44. GC-MS (EI) calcd for $[C_{12}H_{18}S_2 + H]^+$ requires m/z 227.0850, found m/z 227.8624.

1-Benzyl-2-(cyclohexylmethyl)disulfane (**4f**). Colorless oil. 136 mg (0.54 mmol, 54% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 7.35 - 7.24 (m, 5H), 3.88 (s, 2H), 2.24 (d, *J* = 6.8 Hz, 2H), 1.75 - 1.60 (m, 5H), 1.45 (s, 1H), 1.30-1.11 (m, 5H); ^{13}C NMR (150 MHz, CD_3OD) δ 139.40, 130.43, 129.44, 128.29, 47.17, 44.25, 38.44, 33.48, 27.46, 27.08. GC-MS (EI) calcd for $[C_{14}H_{20}S_2 + H]^+$ requires m/z 253.1006, found m/z 252.9727.

1-Benzyl-2-propyldisulfane (**4g**). Colorless oil. 82 mg (0.41 mmol, 41% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 7.34 - 7.23 (m, 5H), 3.89 (s, 2H), 2.34 (t, *J* = 7.3 Hz, 2H), 1.57 (h, *J* = 7.3 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 139.28, 130.40, 129.42, 128.29, 44.31, 41.27, 23.24, 13.30. GC-MS (EI) calcd for $[C_{10}H_{14}S_2 + H]^+$ requires m/z 199.0537, found m/z 199.8958.

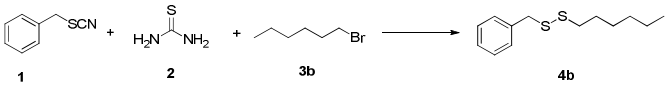
6-(Benzyldisulfanyl)hexanenitrile (**4h**). Colorless oil. 100 mg (0.40 mmol, 40% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 7.36 - 7.24 (m, 5H), 3.89 (s, 2H), 2.38 (t, *J* = 7.1 Hz, 2H), 2.36 - 2.32 (m, 2H), 1.59 - 1.52 (m, 4H), 1.40 (t, *J* = 7.9 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 139.30, 130.43, 129.47, 128.35, 121.04, 44.27, 38.61, 29.09, 28.41, 25.98, 17.20. GC-MS (EI) calcd for $[C_{13}H_{17}NS_2 + H]^+$ requires m/z 252.0802, found m/z 252.0108.

5-(Benzyldisulfanyl)pentan-1-ol (**4i**). Colorless oil. 69 mg (0.27 mmol, 27% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 7.32 - 7.21 (m, 5H), 4.87 (s, 1H), 3.87 (s, 2H), 3.59 (q, *J* = 7.0 Hz, 1H), 3.54 (t, *J* = 6.7 Hz, 1H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.37 - 2.33 (m, 2H), 1.54 (p, *J* = 7.4 Hz, 2H), 1.45 (dt, *J* = 14.8, 6.7 Hz, 2H), 1.33 (q, *J* = 8.1 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 139.29, 130.37, 129.41, 128.27, 44.39, 39.30, 32.85, 30.02, 29.43, 23.63, 14.44. GC-MS (EI) calcd for $[C_{13}H_{20}OS_2 + H]^+$ requires m/z 257.0956, found m/z.

Results and discussion

First of all, the coupling of benzyl thiocyanate, 1-bromohexane and thiourea were selected as a model system to optimize the reaction conditions. The results are summarized in Table 1.

Table 1 Synthesis of asymmetric disufides[a].



1 2 3b 4b

Entry	Base [equiv]	Addition [equiv]	Solvent	Temp/Time [°C/min]	Yield [%][b]
1	K_3PO_4	1.5TBAB	H_2O	90/15	47
2	K_3PO_4	1.5BTAC	H_2O	90/15	22
3	K_3PO_4	1.5TBAI	H_2O	90/15	44
4	K_3PO_4	1.5TBAH	H_2O	90/15	70
5	K_3PO_4	1.5KI/1.5TBAH	H_2O	90/15	90
6	K_3PO_4	1.5KI/1.5TBAH	H_2O	100/15	81
7	K_3PO_4	1.5KI/1.5TBAH	H_2O	80/15	87
8	K_3PO_4	–	PEG/H_2O[c]	90/15	51
9	K_3PO_4	–	DMF	90/15	68
10	KOtBu	1.5TBAH	H_2O	90/15	Trace
11	K_2CO_3	1.5TBAH	H_2O	90/15	57
12	KOH	1.5TBAH	H_2O	90/15	Trace
13	EtONa	1.5KI/1.5TBAH	H_2O	100/15	Trace
14	K_3PO_4	–	CH_3CN/H_2O[c]	90/15	Trace
15	K_3PO_4	–	MeOH	90/15	11
16	K_3PO_4	–	CH_3CN	90/15	Trace

[a]General reaction conditions: benzyl thiocyanate (1.0 mmol), thiourea (2 mmol), 1-bromohexane (1.5 mmol), and 1.2 equiv base in solvent (3 mL) with a microwave irradiation power of 50 W. [b]GC yield. [c]1:1.

We studied the solvent effect and found that H_2O is considerably better than DMF, MeOH, and Acetonitrile (Table 1, Entries 5, 9, 15 and 16). When the reactions were conducted in the mixed solvents, the yields are low (Table 1, Entries 8 and 14). We also found that the nature of bases has a pronounced impact on the reaction. K_3PO_4 results in higher yield of asymmetric disulfides than other bases such as KOH, K_2CO_3, CH_3CH_2ONa and KOtBu (Table 1, Entries 4, 10, 11, 12 and 13).

Table 2 Effects of different proportions of raw materials[a].

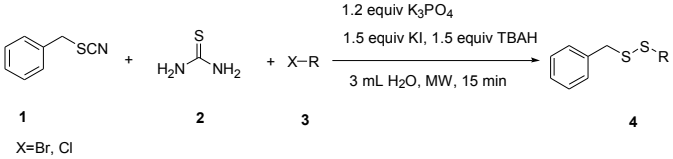
Entry	**1**:**2**:**3b**: K_3PO_4:KI:TBAH [Molar ratios]	Yield[b] [%]
1	1:2:1.5:1.2:1.5:0.25	64
2	1:2:1.5:1.2:1.5:1.2	80
3	1:2:1.5:1.5:1.5:1.5	55
4	1:3:1.5:1.2:1.5:1.5	66
5	1:2:1.5:1.2:1.5:1.5	85
6	1:2:1.5:1.2:2:1.5	82
7	1:1.2:1.1:1.2:1.1:1.5	60
8	1:2:1.5:1.2:0.7:1.5	77
9	1:2:1.5:1.2:0:1.8	23

[a]Each reaction was carried out in water at 90 °C for 7 h without microwave irradiation. [b]GC yield.

In addition, we changed the composition of the feeds; the results are summarized in Table 2. The reactions were carried out for longer reaction time (7 h) without microwave irradiation as we want to study the effectiveness of the conventional method and to explore the influences of composition of the feeds. The results show that the dosage of THAH plays a key role in the reaction. When the fraction of TBAH was too low or too high, the yield is low (Table 2, Entries 1 and 9). It should be noted that an appropriate amount of KI can effectively promote the reaction (Table 2, Entries 5, 6, 8 and 9). Thus, the optimal conditions were obtained as follows: benzyl thiocyanate (1.0 equiv), thiourea (2 equiv), and alkyl halide (1.2 equiv) were reacted under microwave irradiation using K_3PO_4 as the base in water at 90 °C for 15 min.

Under the optimized reaction conditions, a number of reactions using different organic halides were performed to demonstrate the generality and the scope of the proposed protocol. We found that steric hindrance plays a vital role in this reaction. As summarized in Table 3, benzyl thiocyanate and hexyl or heptyl halides were easily transformed into the corresponding thioethers with good to excellent yields at 90 °C; however, a much lower yield was found for 1-bromooctane (Table 3, Entries 1-4). The short-chain primary alkyl halides were more reactive substrates compared with those containing long chains. It is because that the reactions of primary alkyl halides with thiourea are bimolecular nucleophilic substitution (S_N2) in which less steric hindrance is beneficial to the reaction rate.[21] Tertiary alkyl halides and aryl halides failed to react with thiourea to produce S-alkylisothiouronium salts, owing to their steric hindrance effects and electronic effects, respectively (Table 3, Entries 12 and 13). Alkyl bromides bearing groups such as nitrile (-CN), hydroxyl (-OH) were also investigated. To our surprise, only 40% and 27% asymmetric disulfides were obtained (Table 3, Entries 10 and 11), respectively. The GC-MS analysis of the products from the reaction of 6-bromohexanenitrile or 6-bromohexan-1-ol revealed that symmetric disulfides make up a large proportion of the reaction products.

Table 3 Substrates of alkyl halides[a].

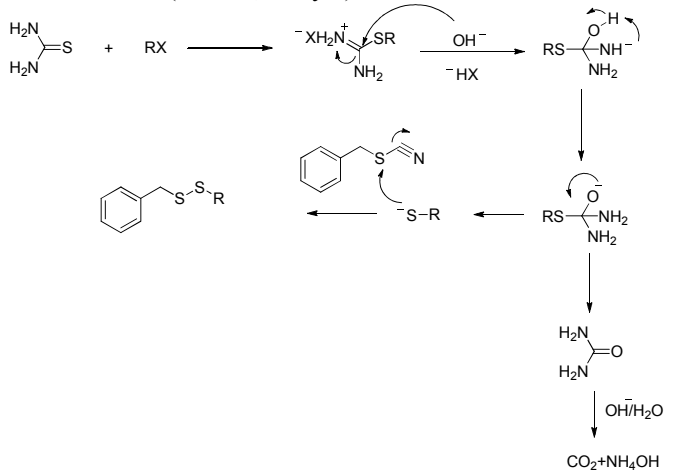


R= octyl, heptyl, hexyl, pentyl, isopentyl, cyclohexylmethyl, propyl, 1-cyano-6-hexyl, 1-ol-5-hexyl.

Entry	Halide	Product	Yield [%][b]
1	1-bromooctane	**4a**	61
2	1-bromoheptane	**4b**	88
3	1-iodohexane	**4c**	90
4	1-bromohexane	**4c**	89
5	1-bromopentane	**4d**	90
6	1-chloropentane	**4d**	84
7	1-bromo-3-methylbutane	**4e**	75
8	(bromomethyl)cyclohexane	**4f**	53
9	propyl 4-methylbenzenesulfonate	**4g**	41
10	6-bromohexanenitrile	**4h**	40
11	6-bromohexan-1-ol	**4i**	27
12	2-chloro-2-methylpropane	**4j**	-
13	iodobenzene	**4k**	-

[a]General reaction conditions: benzyl thiocyanate (1.0 mmol), thiourea (1.2 mmol), alkyl halides (1.5 mmol), and 1.2 equiv K_3PO_4 in water (3 mL) with microwave irradiation at 90 °C. [b]Yield of isolated product based on benzyl thiocyanate.

In addition, production of disulfides from alkyl tosylates is synthetically valuable because they can be readily prepared in one step from alcohols. In this regard, we tried to extend our studies. However, the yield of asymmetric disulfide (41.4%) is low in our case (Table 3, Entry 9).



Scheme 1. A proposed reaction mechanism.

A proposed reaction pathway is presented in Scheme 1. The alkyl halide undergoes nucleophilic substitution reaction with thiourea via an S_N2 mechanism to give the S-alkylisothiouronium salt intermediate. Next, the thiol moiety is gradually generated in situ due to alkaline hydrolysis of the salt, and subsequently reacts with benzyl thiocyanate to produce the corresponding disulfide.

Finally, it should be emphasized that, although this work features inexpensive starting materials, water solvent, one-pot reaction, and high yield, there will be one equivalent of cyanide produced with the synthesis of disulfide. Cyanide is very toxic. Therefore, Fe^{3+} should be used to remove the cyanide from the aqueous solution.

Conclusions

In conclusion, we have demonstrated a versatile and odorless protocol for direct synthesis of asymmetric disulfides from non-thiolic precursors under mild and eco-friendly conditions. Alkyl halides and benzyl thiocyanates were reacted with thiourea in water via a microwave-assisted process, which is time-saving compared with conventional procedures. In most cases, the yield is higher than 80%. However, use of alkyl tosylates leads to low yield of asymmetric disulfide. In this protocol, the substrates are readily available and their synthesis is much easier than the corresponding thiols.

Notes and references

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Graphical Abstract

Microwave-Assisted Synthesis of Asymmetric Disulfides

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This paper reports an efficient, odorless and one-pot procedure for the synthesis of benzyl alkyl disulfides using mixtures of thiourea, alkyl halides, and benzyl thiocyanates. The reactions carried out in water with the assistance of microwave enable a time-saving process.