Tetrahedron 67 (2011) 8895–8901

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Efficient synthesis of unsymmetrical disulfides

Jaya Kishore Vandavasi [a], Wan-Ping Hu [b], Chung-Yu Chen [c], Jeh-Jeng Wang [a,*]

[a] Department of Medicinal and Applied Chemistry, Life Sciences, Kaohsiung Medical University, Kaohsiung City 807, Taiwan
[b] Department of Biotechnology, Life Sciences, Kaohsiung Medical University, Kaohsiung City 807, Taiwan
[c] School of Pharmacy, Kaohsiung Medical University, Kaohsiung City 807, Taiwan

ARTICLE INFO

Article history:
Received 9 July 2011
Received in revised form 15 September 2011
Accepted 15 September 2011
Available online 22 September 2011

Keywords:
Disulfide
DDQ
Thiol
Oxidation
Symmetrical and unsymmetrical

ABSTRACT

A novel way of synthesizing unsymmetrical disulfides from thiols with DDQ is presented here. This procedure ran in a straightforward manner to give high product yields. Unsymmetrical disulfides were directly synthesized from the corresponding mixture of thiols in equimolar amounts under mild conditions.

1. Introduction

Organic compounds containing disulfides play vital roles in chemistry and biology.[1] Biological transformation of thiols to disulfides is extremely common and is a critical process for maintaining the redox state within and without cells for latentiating thiols in prodrugs.[2–8] Perusal of the literature reveals a variety of methods for synthesizing both symmetric and unsymmetric disulfides, many of which are based upon the reaction of a thiol with a sulfenylating reagent (sulfur transfer)[9] or from aromatic sulfonyl chlorides using samarium metal,[10] triphenyl phosphine[11] or neutral alumina.[12] Other areal oxidation reactions include sonication,[13] or iron metal catalyzed areal oxidation.[14] Oxidative coupling of thiols in the presence of Iodine,[15] H_2O_2,[16] organometallic manganese complex[17] and electrochemical oxidation of thiols[18] have also been reported. Thiols with Burgess reagent,[19] strong bases,[20] CAN,[21] Al_2O_3/KF,[22] CsF,[23] Benzyltriethylammoniumtetrathiomolybdate,[24] Silica sulfuric acid/$NaNO_2$,[25] ammonium,[26] Polyvinylpyrrolidone/N_2O_4,[27] have also been shown to produce symmetric dithio compounds. Unsymmetrical disulfides are generally synthesized using 2,2′-dithiobis(benzothiazole),[28] where the benzothiazole is the resultant fragment in the products. Other methodologies synthesize unsymmetrical dithio compounds from symmetrical disulfides by oxidative coupling using rhodium metal,[29] with sulfenic acid and thiosulfenate intermediates as precursors.[30] In some instances, unstable nitroso thiols were exploited as substrates to form unsymmetrical dithio compounds via sulfonamide intermediates[31] and benzotriazole precursors.[32] A variety of unsymmetrical disulfides have been synthesized via dialkoxylthiophosphorane sulfenyl halide precursors[33] and a series of unsymmetrical glycosyl disulfides have also been synthesized using different dialkyl azodicarboxylate through a standard protocol.[34] A combination of diazoniumsalts/CS_2,[35] *N*-trifluoroacetyl arenesulfenamides-thiol[36] were also demonstrated to be practical substrates for the synthesis of unsymmetrical disulfides. Very recently, thiols were protected with [[(*tert*-Butyl)dimethylsilyl]oxy]-methyl group during the synthesis of disulfides.[37] Chemical interaction studies of 1,3-benzothiazole-2-thiol with π-acceptors yielding the formation of corresponding symmetrical compounds were conducted with DDQ, but unfortunately yields were very low.[38] Early studies in this field describe the synthesis of unsymmetrical dithio compounds, however toxic reagents, the need for high temperature, highly unstable reactive intermediates, and costly reagents diminished the applicability of this technique. In our previous study, we explored a mild and efficient way to include S–S bond formation of thioamides in the presence of DDQ.[39] Herein, we describe our studies to a more general investigation of this phenomenon, with the formation of disulfide bonds. Based on our literature survey, until the present study DDQ has not been exploited as a reagent for the synthesis of various unsymmetrical dithio compounds directly from equimolar mixtures of different thiols.

* Corresponding author. Fax: +886 7 312 5339; e-mail address: jjwang@kmu.edu.tw (J.-J. Wang).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.071

2. Results and discussion

Over the course of optimization studies, we discovered that we could generate unsymmetrical disulfide bond formation. First, optimization of the reaction conditions for the formation of S–S bond in symmetrical disulfide **1** with the selected oxidizing reagents is presented in Table 1.

Table 1
Optimization of reaction conditions to synthesize disulfides

A 1

Entry	Reagent	Solvent	Equiv	Temp (°C)	Time	Yield (%)
1	DDQ	CH_2Cl_2	0.5	0	5 min	95
2	DDQ	THF	0.5	0	5 min	51
3	DDQ	CH_3CN	0.5	0	5 min	91
4	DDQ	CH_2Cl_2	0.2	0	5 min	40
5	DDQ	CH_2Cl_2	0.4	0	5 min	50
6	CAN	CH_2Cl_2	3.0	0	5 min	78
7	PCC	CH_2Cl_2	1.0	0	5 min	86
8	$K_3Fe(CN)_6$	CH_2Cl_2	2.0	0–28	12 h	20
9	$K_3Fe(CN)_6$	CH_3CN	1.5	80	5 h	70
10	$Mn(OAc)_2$	CH_3CN	1.5	0–28	5 h	84
11	DMP	CH_2Cl_2	0.5	0	5 min	67
12	$AgNO_3$	CH_2Cl_2	1.0	0–28	5 h	15
13	$AgNO_3$	CH_3CN	1.0	0–28	5 h	35
14	$Mg(NO_3)_2$	CH_2Cl_2	1.5	0–28	24 h	12
15	IBX	CH_2Cl_2	1.0	0–28	45 min	85

The study began with compound **A** and commercially available DDQ (0.5 equiv) in dichloromethane solvent at 0 °C for 5 min to create disulfide **1** with a 95% yield. In contrast, utilizing tetrahydrofuran gave significantly less yield (51%, entry 2) under similar reaction conditions. To compare, conducting the reaction in acetonitrile solvent yielded 91% (entry 3) of the desired product **1a**. Furthermore, reactions were also carried out while varying the amount of DDQ from 0.2 to 0.4 equiv in dichloromethane under similar reaction conditions. These reactions gave 40% and 50% yields, respectively (entries 4 and 5).

We were curious to continue our investigation with other possible oxidizing reagents, such as ceric(IV) ammonium nitrate (CAN), pyridiniumchlorochromate (PCC), potassium ferricyanide $K_3Fe(CN)_6$, manganese (II) acetate ($Mn(OAc)_2$), Dess–martin periodinane (DMP), silver nitrate ($AgNO_3$), magnesium nitrate $Mg(NO_3)_2$ and 2-iodoxybenzoic acid (IBX) under different reaction conditions. The CAN mediated reaction was performed with excess (3.0 equiv) of reagents and resulted in a 78% yield of **1a**. Reaction with 1.0 equiv of PCC was also found to be effective and produced 86% of the desired product. $K_3Fe(CN)_6$ in dichloromethane required a longer reaction time and excess reagent at 0°–28 °C but only yielded 20% of the desired disulfide **1a** (entry 8). In this particular case, a change of the solvent from dichloromethane to acetonitrile increased the yield of disulfide **1a** to 70% at higher temperature (80 °C for 5 h) (entry 9). With $Mn(OAc)_2$ in dichloromethane at 28 °C for 5 h we were able to obtain 84% yield (entry 10). The DMP catalyzed reaction in dichloromethane yielded 67% of **1a** (entry 11). Reactivity of $AgNO_3$ in dichloromethane (entry 12) was considerably worse than other reagents with a 35% yield even by switching over to other solvent, like acetonitrile (entry 13). An attempted reaction with $Mg(NO_3)_2$ in dichloromethane was found to produce very less yield, 12% (entry 14). 2-Iodoxybenzoic acid in dichloromethane was also found to be effective, but with moderate yield of 85% as compared to DDQ (entry 15). Comparative study of the optimization reaction conditions mentioned in Table 1 clearly indicated that DDQ in dichloromethane could be a versatile reagent for the synthesis of disulfides from the corresponding thiols. We synthesized various aromatic as well as aliphatic dithio derivatives by choosing selected commercially available aromatic and aliphatic thiols listed in Fig. 1.

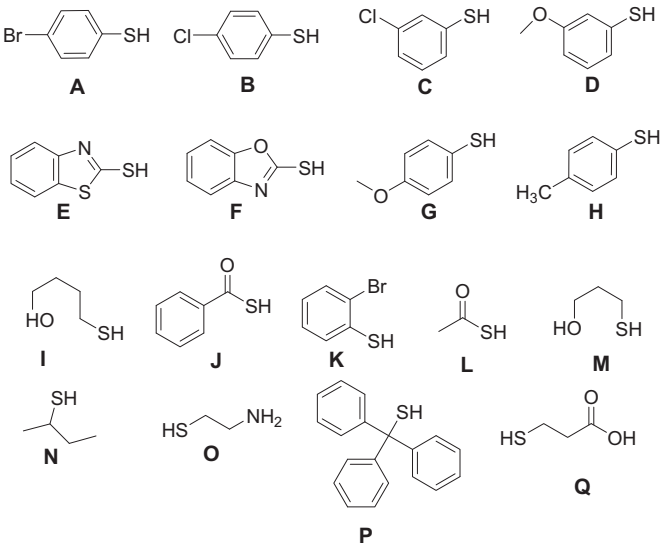


Fig. 1. Thiols used for S–S bond formation reactions.

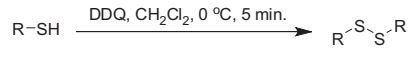
A broad range of thiols reacted smoothly under our optimized reaction conditions. The reaction was tolerant of various substituents, including hydroxy, carboxylic, halides, methoxy, and methyl. These results are summarized in Table 2. Aromatic thiols from A to H (in Fig. 1) underwent disulfide formation to furnish desired products with excellent yields (90–98%, entries 1–8, Table 1). An example of aliphatic dithio compound was synthesized in 92% yield (entry 9, Table 1). It is noteworthy to mention that the aliphatic thio compounds underwent reaction in the presence of unprotected hydroxyl groups. We also observed dithio compound formation with 82% yield from corresponding thiocarboxylic acid (entry 10, Table 1).

Further, to investigate the synthesis of unsymmetrical disulfides, various reaction conditions were screened with compounds E and G serving as initial substrates (Table 3). Dichloromethane with PCC at 0–28 °C for 1 h gave the corresponding unsymmetrical disulfide at a 65% yield (entry 1, Table 3). The reaction was not successful with many of the other reagents including $Mn(OAc)_2$, $K_3Fe(CN)_6$, $Mg(NO_3)_2$, and $AgNO_3$ (entries 2, 3, 8, and 9, Table 3).

Only a 23% yield was obtained with CAN. Moderate to high yields were observed with IBX, DMP and DDQ (85%, 77% and 89%, respectively) (entries 5, 6, and 7, Table 3). With these results in mind, we concluded that the reaction was not successful with inorganic reagents like $Mn(OAc)_2$, $K_3Fe(CN)_6$, $Mg(NO_3)_2$, and $AgNO_3$. Likewise the yield was also quite low when CAN was utilized. Interestingly, with symmetrical disulfide synthesis, congruent with our previous work,[39] we found that the DDQ to be an efficient reagent for this reaction. These results are presented with relevant details in Table 4.

Reactions with mixture of different aromatic mercaptans (entries 1, 2, and 8–10, Table 4) led to the formation of the dithio compounds in relatively high yields (81–92%) as compared to reactions between aromatic and aliphatic substrates (entries 3–7 and 11–22, Table 4). The reaction was successful using a secondary thiol, and afforded a moderate yield (75%) (entry 23, Table 4), whereas reactions utilizing a tertiary thiol were not successful (entry 29, Table 4) perhaps due to steric hindrance. Reaction mass was decomposed when amine substituted thiol was reacted with substituted thiols like *para*-OMe/*meta*-Cl/*ortho*-Br/*para*-Cl (entries 24–28, Table 4). Low yield was obtained with a carboxylic acid substituted thiol (37%) (entry 30, Table 4).

Table 2
Formation of disulfides from thiols and thiocarboxylic acids



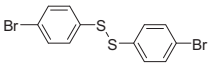
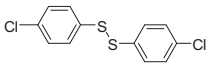
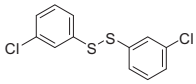
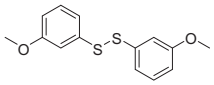
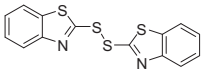
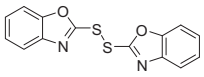
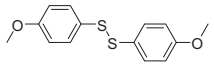
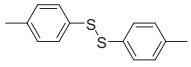
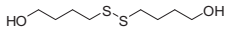
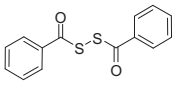
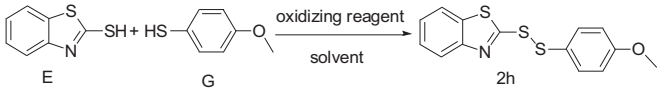
Entry	Substrate	Product	1	Yield (%)
1	A		**1a**	95
2	B		**1b**	94
3	C		**1c**	93
4	D		**1d**	91
5	E		**1e**	90
6	F		**1f**	92
7	G		**1g**	97
8	H		**1h**	98
9	I		**1i**	92
10	J		**1j**	82

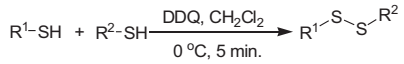
Table 3
Screening different oxidizing reagents to synthesize the unsymmetrical disulfides

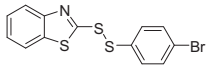
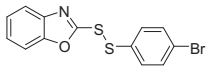
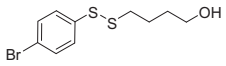
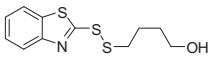
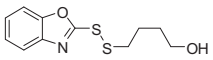
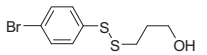
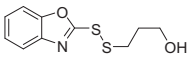
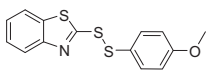
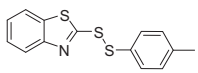
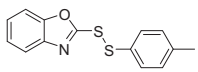
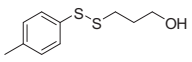
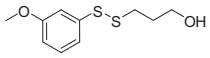
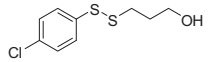
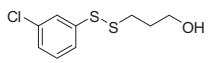
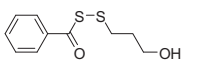
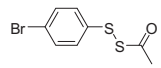
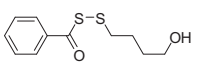
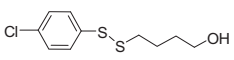
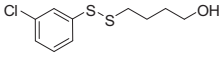
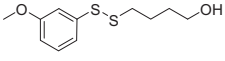
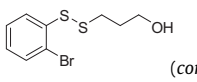


Entry	Reagent	Solvent	Equiv	Temp (°C)	Time	Yield (%)
1	PCC	CH_2Cl_2	2	0–28	1 h	65
2	$Mn(OAc)_2$	CH_2Cl_2	3	0–28	4 h	N.R.
3	$K_3Fe(CN)_6$	CH_2Cl_2	4	0–28	24 h	N.R.
4	CAN	CH_2Cl_2	6	0–28	1 h	23
5	IBX	CH_2Cl_2	2	0–28	1 h	85
6	DMP	CH_2Cl_2	1	0	5 min	77
7	DDQ	CH_2Cl_2	1	0	5 min	89
8	$Mg(NO_3)_2$	CH_2Cl_2	3	0–28	24 h	N.R.
9	$AgNO_3$	CH_2Cl_2	2	0–28	24 h	N.R.

Our data show that the position of the substituents on the aromatic ring does not play a vital role in the yield of the product. Chain length in aliphatic thiols play a significant role e.g., yield of dithio compounds **2q**–**t** and **2v** (Table 3) with a 4-carbon aliphatic chain produced less yield (65–72%) when compared with that of **2k**–**o** (80–85%) having a 3-carbon aliphatic thiol. By compiling the above results we came to the determination that hydroxy substituted thiols are favorable to the formation of S–S bonds.

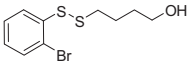
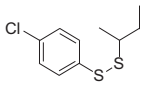
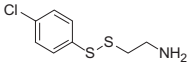
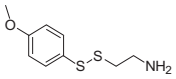
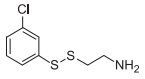
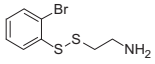
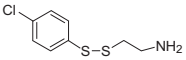
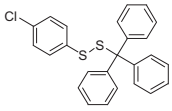
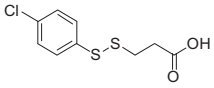
Table 4
Scope and limitations of unsymmetrical disulfides formation from thiols



Entry	Substrates[a]	Product	2 [Yield (%)][b]
1	A+E		**2a** (83)
2	A+F		**2b** (81)
3	A+I		**2c** (80)
4	E+I		**2d** (83)
5	F+I		**2e** (82)
6	A+M		**2f** (91)
7	F+M		**2g** (88)
8	E+G		**2h** (89)
9	E+H		**2i** (92)
10	F+H		**2j** (90)
11	H+M		**2k** (83)
12	D+M		**2l** (82)
13	B+M		**2m** (80)
14	C+M		**2n** (83)
15	J+M		**2o** (85)
16	A+L		**2p** (81)
17	I+J		**2q** (72)
18	B+I		**2r** (65)
19	C+I		**2s** (68)
20	D+I		**2t** (70)
21	K+M		**2u** (68)

(*continued on next page*)

Table 4 (*continued*)

Entry	Substrates[a]	Product	**2** [Yield (%)][b]
22	I+K		**2v** (65)
23	B+N		**2w** (75)
24	B+O		**2x** (N.R.)
25	G+O		**2y** (N.R.)
26	C+O		**2z** (N.R.)
27	K+O		**2aa** (N.R.)
28	B+O		**2ab** (N.R.)
29	B+P		**2ac** (N.R.)
30	B+Q		**2ad** (37)

[a] Equimolar ratio of thiols were used in all reactions (entries 1–22).
[b] Minor amounts of symmetrical dithio compounds were observed by analytical TLC.

The structure of the resultant S–S bonds was confirmed by X-ray crystallographic analysis of single crystals of unsymmetrical disulfide **2m** (Fig. 2A) and symmetrical disulfide **1j** (Fig. 2B). In addition, Raman spectral data of 15 examples were selected from both Tables 2 and 3 to demonstrate S–S bond stretching vibration in the range of 528–558 cm^{-1} (see Supplementary data).

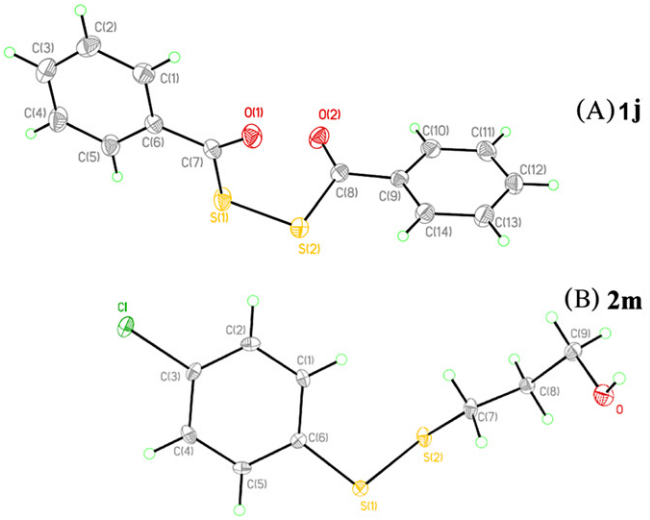


Fig. 2. ORTEP diagram of **1j** and **2m** (crystals were obtained from a mixture of chloroform and hexane at low temperature).

3. Conclusions

In conclusion, we have developed a mild and efficient 'one pot' method for the synthesis of unsymmetrical dithio compounds directly from corresponding thiols and thiocarboxylic acids in the presence of DDQ. This method may be useful for the preparation of both classes of dithio compounds in a single step. Further biological studies of these molecules are in progress.

4. Experimental section

4.1. General information

Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. ^1H NMR chemical shifts are referenced to TMS or residual chloroform in $CDCl_3$ (7.26 ppm). ^{13}C NMR was referenced to residual chloroform in $CDCl_3$ (77.0 ppm). Mass spectra and high-resolution mass spectra (HRMS) were obtained using the electron-impact (EI, 70 eV) technique. Raman Spectroscopy were recorded on an iHR-320- monochromometer, He–Ne laser excitation was set to 632.8 nm, power was 15 MW per to sample, temperature was −133 °C and exposure time was 1 s with 10 accumulations. Flash chromatography was carried out on silica gels (230–400 mesh).

4.2. General procedure for the synthesis of disulfides

Procedure for symmetrical molecules: DDQ (0.5 mmol) was added to an ice-cooled solution of thiol (1 mmol) in dichloromethane (3.0 mL). The reaction mixture stirred for 5 min at 0 °C and monitored by TLC analysis. The reaction mixture was concentrated under reduced pressure and directly purified by column chromatography by gradient elution of ethyl acetate in hexanes to give the title compounds.

Procedure for unsymmetrical molecules: Thiol A (1.0 mmol) and thiol B (1.0 mmol) were dissolved in 3.0 ml of dichloromethane and cooled to 0 °C. DDQ (1.0 mmol) was added slowly to the reaction mixture and stirred for 5 min at 0 °C. The reaction was monitored by TLC analysis. Solvents were removed under reduced pressure and the crude compound was directly purified by column chromatography by gradient elution of ethyl acetate in hexanes to give the title compounds along with the side products.

*4.2.1. Compound **1a**.* White solid; 95% yield; mp 94–95 °C (lit[40] mp=95 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.42 (m, 4H, Ph), 7.31–7.33 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 121.5, 129.3, 132.2, 135.6.

*4.2.2. Compound **1b**.* White solid, 94% yield, mp 71–73 °C (lit[41] mp=69–71 °C), ^1H NMR ($CDCl_3$, 400 MHz): δ 7.25–7.27 (m, 4H, Ph), 7.38–7.40 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 129.2, 133.5, 135.0; LRMS (EI, *m*/*z*)=286 [M^+]; HRMS (EI, *m*/*z*) calcd for $C_{12}H_8Cl_2S_2$ [M^+] 285.9444, found 285.9449.

*4.2.3. Compound **1c**.* Colorless oil, 93% yield, ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18–7.24 (m, 2H, Ph), 7.32–7.35 (m, 1H, Ph), 7.46–7.47 (m, 1H, Ph), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 125.2, 126.9, 127.5, 130.1, 135.0, 138.3; LRMS (EI, *m*/*z*)=286 [M^+]; HRMS (EI, *m*/*z*) for $C_{12}H_8Cl_2S_2$ calcd 285.9440, found 285.9450; Raman spectra: S–S 530 cm^{-1}.

*4.2.4. Compound **1d**.* White solid, 91% yield, mp 105–107 °C (Lit[42] mp=114 °C), ^1H NMR ($CDCl_3$, 400 MHz): δ 3.75 (s, 6H, CH_3), 6.73–6.76 (m, 2H, Ph), 7.05–7.08 (m, 4H, Ph), 7.18–7.24 (m, 2H, Ph);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.2, 112.4, 113.0, 119.5, 129.8, 138.2, 159.9, HRMS (EI, *m*/*z*) for $C_{14}H_{14}O_2S_2$ [M^+] calcd 278.0435, found 278.0432, Raman spectra: S–S 540 cm^{-1}.

4.2.5. Compound ***1e***. Off white solid, 90% yield, mp 181–183 °C (lit[43] mp=182–183.5 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76–7.78 (m, 2H, Ph), 7.44–7.48 (m, 2H, Ph), 7.76–7.78 (m, 2H, Ph), 7.93–7.95 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 121.2, 122.6, 125.2, 126.5, 136.1, 154.5, 167.8; LRMS (EI, *m*/*z*)=333 [M^+]; HRMS (EI, *m*/*z*) for $C_{14}H_8N_2S_4$ [M+H]$^+$ calcd 332.9649, found 332.9647.

4.2.6. Compound ***1f***. Yellow sticky mass, 92% yield, mp 111–113 °C (lit[44] mp: 114 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.34 (m, 4H, Ph), 7.48–7.54 (m, 2H, Ph), 7.67–7.70 (m, 2H, Ph);^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.5, 119.7, 124.9, 125.4, 141.7, 152.5, 159.8; LRMS (EI, *m*/*z*)=301 [M^+]; HRMS (EI, *m*/*z*) for $C_{14}H_8N_2O_2S_2$ [M+H]$^+$ calcd 301.0105, found 301.0103.

4.2.7. Compound ***1g***. Off white solid, 97% yield, mp 33–34 °C (lit[41] mp=31–34 °C), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.76 (s, 1H, CH_3), 6.82–6.80 (m, 2H, Ph), 7.39–7.37 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.2, 114.5, 128.2, 132.5159.8; LRMS (EI, *m*/*z*)=278.1 [M^+]; HRMS (EI, *m*/*z*) for $C_{14}H_{14}O_2S_2Na$ [M+Na]$^+$ calcd 301.0331, found 301.0331.

4.2.8. Compound ***1h***. Off white solid, 98% yield, mp 38–40 °C (lit[41] mp=40–42 °C), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.30 (s, 3H, CH_3), 7.08–7.10 (m, 4H, Ph), 7.35–7.39 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 128.5, 129.7, 133.8, 137.4; LRMS (EI, *m*/*z*)=[M^+]; HRMS (EI, *m*/*z*) for $C_{14}H_{14}S_2$ [M^+] calcd 246.0537, found 246.0535; Raman spectra: S–S 540 cm^{-1}.

4.2.9. Compound ***1i***. Light yellow oil, 92% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62–1.69 (m, 2H, CH_2), 1.74–1.81 (m, 2H, CH_2), 2.72 (t, *J*=7.2 Hz, 2H, CH_2), 3.02 (br s, 1H, OH),3.64 (t, *J*=6.4 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.4, 31.1, 38.6, 61.9; LRMS (EI, *m*/*z*)=233 [M^+]; HRMS (EI, *m*/*z*) for $C_8H_{18}O_2S_2Na$ [M+Na]$^+$ calcd 233.0646, found 233.0644; Raman spectra: S–S 540 cm^{-1}.

4.2.10. Compound ***1j***. White solid, 82% yield, mp 127–129 °C (lit[45] temp 127–128 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49–7.53 (m, 4H, Ph), 7.62–7.66 (m, 2H, Ph), 8.06–8.08 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 128.0, 128.9, 134.3, 135.1, HRMS (EI, *m*/*z*) for $C_{14}H_{10}O_2S_2Na$ [M+Na]$^+$ calcd 297.0020, found 297.0022.

4.2.11. Compound ***2a***. Off white solid, 83% yield, mp 65–67 °C (lit[28] temp 67–68 °C), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.35 (m, 1H, Ph), 7.41–7.50 (m, 5H, Ph), 7.76–7.78 (m, 1H, Ph), 7.87–7.89 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 121.1, 122.3, 122.7, 124.8, 126.3, 130.5, 132.4, 134.1, 135.8, 154.7, 170.5; LRMS (EI, *m*/*z*)=354 [$M]^+$; HRMS (EI, *m*/*z*) for $C_{13}H_8BrNS_3$ [M^+] calcd 353.9080, found 353.9079.

4.2.12. Compound ***2b***. Colorless oil, 81% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.35 (m, 1H, Ph), 7.45–7.57 (m, 5H, Ph), 7.62–7.71 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 110.3, 119.6, 123.2, 124.7, 125.0, 131.7, 132.4, 134.4, 141.8, 152.4, 162.2; LRMS (EI, *m*/*z*)=338 [$M]^+$; HRMS (EI, *m*/*z*) for $C_{13}H_8BrNOS_2$ [M+H]$^+$ calcd 337.9309, found 337.9311.

4.2.13. Compound ***2c***. Colorless oil, 80% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.59–1.67 (m, 2H, CH_2), 1.72–1.79 (m, 2H, CH_2), 2.75 (t, *J*=6.8 Hz, 2H, CH_2), 3.62 (t, *J*=6.4 Hz, 2H, CH_2), 7.38–7.45 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0 (–CH_2), 31.2 (–CH_2), 38.5 (–CH_2), 62.2 (–CH_2), 120.5, 128.9, 131.9136.7; LRMS (EI, *m*/*z*)=315 [M^+]; HRMS (EI, *m*/*z*) for $C_{10}H_{13}BrOS_2Na$ [M+Na]$^+$ calcd 314.9489, found 314.9487.

4.2.14. Compound ***2d***. Oil, 83% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62–1.69 (m, 2H, CH_2), 1.79–1.87 (m, 2H, CH_2), 2.19 (br s, 1H, OH), 2.95 (t, *J*=7.2 Hz, 2H, CH_2), 3.62 (t, *J*=6.4 Hz, 2H, CH_2), 7.27–7.31 (1 m, 1H, Ph), 7.37–7.41 (m, 1H, Ph), 7.74–7.83 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.3 (–CH_2), 31.2 (–CH_2), 39.1 (–CH_2), 61.8 (–CH_2), 121.0, 121.9, 124.5, 126.1, 135.6, 154.8172.9; LRMS (EI, *m*/*z*)= 294 [M^+]; HRMS (EI, *m*/*z*) for $C_{11}H_{13}NOS_3Na$ [M+Na]$^+$ calcd 294.0057, found 294.0055. Raman spectra: S–S 528 cm^{-1}.

4.2.15. Compound ***2e***. Colorless oil, 82% yield, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67–1.74 (m, 2H, CH_2), 1.84–1.91 (m, 2H, CH_2), 2.63 (br s, 1H, OH), 3.02 (t, *J*=7.2 Hz, 2H, CH_2), 3.67 (t, *J*=6.4 Hz, 2H, CH_2), 7.27–7.33 (m, 1H, Ph), 7.45–7.50 (m, 1H, Ph), 7.64–7.68 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.9 (–CH_2), 31.0 (CH_2), 39.0 (CH_2), 61.8 (CH_2), 110.1, 119.1, 124.5, 124.7, 141.6, 152.2, 163.5; LRMS (EI, *m*/*z*)=278 [M^+]; HRMS (EI, *m*/*z*) for $C_{11}H_{13}NO_2S_2Na$ [M+Na]$^+$ calcd 278.0285, found 278.0284.

4.2.16. Compound ***2f***. Colorless oil, 91% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.87–1.94 (m, 3H, CH_2), 2.82 (t, *J*=7.2 Hz, 2H, CH_2), 3.69 (t, *J*=6.0 Hz, 2H, CH_2), 7.37–7.45 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 31.3 (–CH_2), 35.0 (–CH_2), 60.7 (–CH_2), 120.6, 128.9, 131.9, 136.4; HRMS (EI, *m*/*z*) for $C_9H_{11}BrOS_2$ [M^+] calcd 277.9435, found 277.9428.

4.2.17. Compound ***2g***. Colorless oil, 88% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.97–2.04 (m, 2H, CH_2), 3.16 (t, *J*=7.2 Hz, 2H, CH_2), 3.23 (br s, 1H, OH), 3.82 (t, *J*=5.6 Hz, 2H, CH_2), 7.27–7.33 (m, 2H, Ph), 7.45–7.50 (m, 1H, Ph), 7.64–7.68 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.9 (–CH_2), 36.0 (–CH_2), 60.1 (–CH_2), 110.2, 119.0, 124.6, 124.7, 141.3, 152.3163.9; HRMS (ESI, *m*/*z*) for $C_{10}H_{11}NO_2S_2$ [M+H]$^+$ calcd 242.0304, found 242.0304; Raman spectra: S–S 544 cm^{-1}.

4.2.18. Compound ***2h***. Yellow solid, 89% yield, mp 59–61 °C (lit[33] temp 61–62 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.77 (s, 3H,), 6.82–6.86 (m, 2H), 7.29–7.33 (m, 1H), 7.39–7.43- (m, 1H), 7.60–7.63 (m, 2H), 7.78–7.80 (m, 1H), 7.84–7.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.3, 114.9, 121.0, 122.1, 124.5, 125.7, 126.1, 133.3, 135.7, 154.8, 160.7, 171.9; LRMS (EI, *m*/*z*)=305.1 [M^+]; HRMS (EI, *m*/*z*) for $C_{14}H_{11}NOS_3$ [M^+] calcd 305.0003, found 305.0000, Raman spectra: S–S 532 cm^{-1}.

4.2.19. Compound ***2i***. Off white solid, 89% yield, mp 37–38 °C (lit[28] temp 61–62 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H, CH_3), 7.09 (d, *J*=8.4 Hz, 2H, Ph), 7.24–7.28 (m, 1H, Ph), 7.35–7.39 (m, 1H, Ph), 7.40–7.51 (m, 2H, Ph), 7.70–7.72 (m, 1H, Ph), 7.83–7.85 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.0, 120.9, 122.0, 124.4, 126.0, 129.7, 129.9, 131.3, 135.7, 138.9, 154.8, 171.8; LRMS (EI, *m*/*z*)=289 [M^+]; HRMS (EI, *m*/*z*) for $C_{14}H_{11}NS_3$ [M^+] calcd 289.0054, found 289.0063; Raman spectra: S–S 532 cm^{-1}.

4.2.20. Compound ***2j***. Light yellow sticky solid, 90% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.32 (s, 3H, CH_3), 7.13 (d, *J*=8 Hz, 2H, CH_2), 7.24–7.33 (m, 2H, Ph), 7.46–7.50 (m, 1H, Ph), 7.56–7.60 (m, 2H, Ph), 7.66–7.70 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 21.1, 110.2, 119.5, 124.5, 124.7, 130.0, 131.2, 131.8, 139.4, 141.9, 152.4, 162.9; LRMS (EI, *m*/*z*)=273.1 [M^+]; HRMS (EI, *m*/*z*) for $C_{14}H_{11}NOS_2$ [M^+] calcd 273.0282, found 273.0276; Raman spectra: S–S 529 cm^{-1}.

4.2.21. Compound ***2k***. Yellow oil, 83% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89–1.96 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.82 (t, *J*=6.8 Hz, 2H, CH_2), 3.69 (t, *J*=6.4 Hz, 2H, CH_2), 7.12 (d, *J*=7.6 Hz, 2H,

Ph), 7.41–7.43 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.9 ($-CH_2$), 31.3 ($-CH_2$), 35.0 ($-CH_2$), 60.9 ($-CH_2$), 128.5, 129.7, 133.76, 137.1; LRMS (EI, *m*/*z*)=214.2 [M^+]; HRMS (EI, *m*/*z*) for $C_{10}H_{14}OS_2$ [M^+] calcd 214.0486, found 214.0482; Raman spectra: S–S 532 cm^{-1}.

4.2.22. Compound ***2l***. Colorless oil, 82% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.79 (br s, 1H, OH), 1.89–1.95 (m, 2H, CH_2), 2.83 (t, *J*=6.8 Hz, 2H, CH_2), 3.70 (t, *J*=6.0 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 6.73–6.76 (m, 1H, Ph), 7.08–7.11 (m, 2H, Ph), 7.20–7.25 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.4 ($-CH_2$), 35.0 ($-CH_2$), 55.2, 60.8 ($-CH_2$), 112.4, 112.5, 119.4, 129.7, 138.5, 159.9; LRMS (EI, *m*/*z*)=230.1 [M^+]; HRMS (EI, *m*/*z*) for $C_{10}H_{14}O_2S_2$ [M^+] calcd 230.044, found 230.043; Raman spectra: S–S 538 cm^{-1}.

4.2.23. Compound ***2m***. Off white solid, 80% yield, mp 36–38 °C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89–1.95 (m, 2H, CH_2), 2.83 (t, *J*=6.8 Hz, 2H, CH_2), 3.71 (t, *J*=6.0 Hz, 2H, CH_2), 7.28–7.30 (m, 2H, Ph), 7.45–7.47 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.4 ($-CH_2$), 35.0 ($-CH_2$), 60.8 ($-CH_2$), 128.9, 129.0, 132.8, 135.8; LRMS (EI, *m*/*z*)= 234 [M^+]; HRMS (EI, *m*/*z*) for $C_9H_{11}ClOS_2$ [M^+] calcd 233.994, found 233.994.

4.2.24. Compound ***2n***. Colorless oil, 83% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.63 (br s, 1H, OH), 1.89–1.96 (m, 2H, CH_2), 2.84 (t, *J*=6.8 Hz, 2H, CH_2), 3.72 (t, *J*=6.0 Hz, 2H, CH_2), 7.16–7.26 (m, 2H, Ph), 7.36–7.39 (m, 1H, Ph), 7.53 (t, *J*=2 Hz, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.4 ($-CH_2$), 35.1 ($-CH_2$), 60.8 ($-CH_2$), 125.0, 126.6, 126.8, 129.9, 134.9, 139.4; LRMS (EI, *m*/*z*)=234.1 [M]$^+$; HRMS (EI, *m*/*z*) for $C_9H_{11}ClOS_2$ [M^+] calcd 233.994, found 233.995; Raman spectra: S–S 550 cm^{-1}.

4.2.25. Compound ***2o***. Colorless oil, 82% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.89–1.95 (m, 2H, CH_2), 2.50 (br s, 1H, OH), 2.92 (t, *J*=7.2 Hz, 2H, CH_2), 3.81 (t, *J*=6.0 Hz, 2H, CH_2), 7.45–7.50 (m, 2H, Ph), 7.59–7.63 (m, 1H, Ph), 7.97–8.00 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3 ($-CH_2$), 35.4 ($-CH_2$), 60.6 ($-CH_2$), 127.6, 128.8, 134.0, 135.4, 190.7; HRMS (EI, *m*/*z*) for $C_{10}H_{12}O_2S_2Na$ [M^+] calcd 251.0176, found 251.0174; Raman spectra: S–S 540 cm^{-1}.

4.2.26. Compound ***2p***. Sticky solid, 81% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.47 (s, 3H, CH_3), 7.32–7.44 (m, 4H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.6, 122.6, 122.9, 129.3, 132.1, 132.1, 134.8, 193.3; LRMS (EI, *m*/*z*)=262 [M]$^+$; HRMS (EI, *m*/*z*) for $C_8H_7BrOS_2$ [M^+] calcd 261.9122, found 261.9117, Raman spectra: S–S 528 cm^{-1}.

4.2.27. Compound ***2q***. Colorless oil, **7**2 % yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.72–1.74 (m, 4H, CH_2), 2.32 (br s, 1H, OH), 2.81 (t, *J*=6.8 Hz, 2H, CH_2), 3.66 (t, *J*=6.0 Hz, 2H, CH_2), 7.45–7.49 (m, 2H, Ph), 7.59–7.63 (m, 1H, Ph), 7.97–7.99 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.1 ($-CH_2$), 31.1 ($-CH_2$), 38.5 ($-CH_2$), 61.9 ($-CH_2$), 127.5, 128.7, 133.9, 135.5, 190.6; HRMS (EI, *m*/*z*) for $C_{11}H_{14}O_2S_2Na$ [M+Na]$^+$ calcd 265.0333, found 265.0334, Raman spectra: S–S 550 cm^{-1}.

4.2.28. Compound ***2r***. Colorless oil, 65% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.46 (br s, 1H, OH), 1.60–1.67 (m, 2H, CH_2), 1.71–1.79 (m, 2H, CH_2), 2.75 (t, *J*=7.2 Hz, 2H, CH_2), 3.62 (t, *J*=6.4 Hz, 2H, CH_2), 7.26–7.30 (m, 2H, Ph), 7.44–7.48 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0 ($-CH_2$), 31.2 ($-CH_2$), 38.5 ($-CH_2$), 62.2 ($-CH_2$), 128.8, 129.0, 132.7, 136.0; LRMS (EI, *m*/*z*)=248.1 [M]$^+$; HRMS (EI, *m*/*z*) for $C_{10}H_{13}ClOS_2$ [M^+] calcd 248.0086, found 248.0099; Raman spectra: S–S 545 cm^{-1}.

4.2.29. Compound ***2s***. Oil, 68% yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (br s, 1H, OH), 1.61–1.69 (m, 2H, CH_2), 2.77 (t, *J*=7.2 Hz, 2H, CH_2), 3.62 (t, *J*=6.4 Hz, 2H, CH_2), 7.16–7.26 (m, 2H, Ph), 7.36–7.39 (m, 1H, Ph), 7.53 (t, *J*=2 Hz, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0 ($-CH_2$), 31.2 ($-CH_2$), 38.5 ($-CH_2$), 62.2 ($-CH_2$), 125.0, 126.5, 126.7, 129.9, 134.9, 139.6; LRMS (EI, *m*/*z*)=248.1 [M]$^+$; HRMS (EI, *m*/*z*) for $C_{10}H_{13}ClO_2S_2$ [M^+] calcd 248.0096, found 248.0101; Raman spectra: S–S 533 cm^{-1}.

4.2.30. Compound ***2t***. Colorless oil, 70% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (br s, 1H, OH), 1.60–1.67 (m, 2H, CH_2), 1.73–1.80 (m, 2H, CH_2), 2.77 (t, *J*=6.8 Hz, 2H, CH_2), 3.61 (t, *J*=6.4 Hz, 2H, CH_2), 3.81 (s, 3H, CH_3), 6.73–6.76 (m, 1H, Ph), 7.08–7.12 (m, 2H, Ph), 7.20–7.24 (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0 ($-CH_2$), 31.3 ($-CH_2$), 38.5 ($-CH_2$), 55.2 ($-CH_2$), 62.2 ($-CH_2$), 112.4, 112.4, 119.4, 129.7, 138.7, 160.0; LRMS (EI, *m*/*z*)=244.0 [M^+]; HRMS (EI, *m*/*z*) for $C_{11}H_{16}O_2S_2$ [M^+] calcd 244.0592, found 244.0586; Raman spectra: S–S 533 cm^{-1}.

4.2.31. Compound ***2u***. Colorless oil, 70% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.66 (br s, 1H, OH), 1.91–1.97 (m, 2H, CH_2), 2.83 (t, *J*=7.2 Hz, 2H, CH_2), 3.73 (t, *J*=6.4 Hz, 2H, CH_2), 7.05–7.09 (m, 1H, Ph), 7.33–7.37 (m, 1H, Ph), 7.49–7.51 (m, 1H, Ph), 7.79 (dd, *J*=1.6, 8 Hz, 1H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.5 ($-CH_2$), 34.7 ($-CH_2$), 60.8 ($-CH_2$), 121.3, 127.1, 127.4, 127.8, 132.8, 137.6; LRMS (EI, *m*/*z*)= 278.1 [M]$^+$; HRMS (EI, *m*/*z*) for $C_9H_{11}BrOS_2$ [M^+] calcd 277.9435, found 277.9429; Raman spectra: S–S 533 cm^{-1}

4.2.32. Compound ***2v***. Colorless oil, 65% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.46 (br s, 1H, OH), 1.62–1.69 (m, 2H, CH_2), 1.75–1.82 (m, 2H, CH_2), 2.77 (t, *J*=7.2 Hz, 2H, CH_2), 3.64 (t, *J*=6.4 Hz, 2H, CH_2), 7.05–7.09 (m, 1H, Ph), 7.33–7.37 (m, 1H, Ph), 7.50 (dd, *J*=1.6, 7.8 Hz, 1H, Ph), 7.79 (dd, *J*=1.6 Hz, 1H, 8); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.2 ($-CH_2$), 31.3 ($-CH_2$), 38.2 ($-CH_2$), 62.2 ($-CH_2$), 121.2, 127.1, 127.4, 127.8, 132.8, 137.8; LRMS (EI, *m*/*z*)=292.0 [M]$^+$; HRMS (EI, *m*/*z*) for $C_{10}H_{13}BrOS_2$ [M^+] calcd 291.9591, found 291.9596; Raman spectra: S–S 558 cm^{-1}.

4.2.33. Compound ***2w***. Colorless oil, 75% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.943 (t, *J*=7.2 Hz, 3H, CH_3), 1.26 (d, *J*=6.4 Hz, 3H, CH_3), 1.45–1.56 (m, 1H, CH_2), 1.63–1.74 (m, 1H, CH_2), 2.77–2.85 (m, 1H, CH), 7.24–7.28 (m, 2H, Ph), 7.44–7.48 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.4 ($-CH_3$), 19.8 ($-CH_3$), 28.7 ($-CH_2$), 48.5(–CH), 128.4, 128.8, 129.2, 129.3, 132.3, 136.9; HRMS (ESI, *m*/*z*) for $C_{10}H_{13}ClS_2$ [$M-H]^-$ calcd 231.0063, found 231.0069.

4.2.34. Compound ***2ad***. Pale pink **S**olid, 37% yield, mp 89–91 °C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.78 (t, *J*=6.8 Hz, 2H, CH_2), 2.95 (t, *J*=6.8 Hz, 2H, CH_2), 1.75–1.82 (m, 2H, CH_2), 2.77 (t, *J*=7.2 Hz, 2H, CH_2), 3.64 (t, *J*=6.4 Hz, 2H, CH_2), 7.28–7.31 (m, 2H, Ph), 7.45–7.47 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.7 ($-CH_2$), 33.4 ($-CH_2$), 129.1, 129.2, 133.1, 135.3, 177.0; HRMS (ESI, *m*/*z*) for $C_9H_9ClO_2S_2$ [$M-H]^-$ calcd 246.9654, found 246.9648.

Acknowledgements

We thank the National Science Council of the Republic of China, and the KMU Center of Excellence for Environmental Medicine for financial support. We gratefully acknowledge Mr. Yu-Lung Lin for recording the Raman spectral data. The authors would like to thank Dr. Jennifer S. Dickey for helpful discussions during the preparation of this manuscript.

Supplementary data

^{1}H, ^{13}C, DEPT, and Raman spectra of all compounds and crystallographic data tables of **1b**, **1j**, and **2m**. Supplementary data

associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.071.

References and notes

1. (a) Shinkai, H.; Maeda, K.; Yamasaki, T.; Okamoto, H.; Uchida, I. *J. Med. Chem.* **2000**, *43*, 3566–3572; (b) Hamachi, I.; Nagase, T.; Shinkai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12063–12064; (c) Gamblin, D. P.; Garnier, P.; van Kasteren, S.; Oldham, N. J.; Fairbanks, A. J.; Davis, B. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 828–833; (d) Winum, J.; Rami, M.; Scozzafava, A.; Montero, J.; Supuran, C. *Med. Res. Rev.* **2008**, *28*, 445–463; (e) Atkinson, A.; Winge, D. R. *Chem. Rev.* **2009**, *109*, 4708–4721.
2. Lees, W. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 740–745.
3. Sevier, C. S.; Kaiser, C. A. *Antioxid. Redox Signaling* **2006**, *8*, 797–811.
4. Ishikawa, H.; Kim, S.; Kwak, K.; Wakasugi, K.; Fayer, M. D. *Proc. Natl. Acad. Sci. U. S.A.* **2007**, *104*, 19309–19314.
5. (a) Vrudhula, V. M.; MacMaster, J. F.; Li, Z.; Kerr, D. E.; Senter, P. D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3591–3594; (b) Bittman, R.; Li, Z.; Samadder, P.; Arthur, G. *Cancer Lett.* **2007**, *251*, 53–58; (c) Peterson, Q. P.; Hsu, D. C.; Goode, D. R.; Novotny, C. J.; Totten, R. K.; Hergenrother, P. J. *J. Med. Chem.* **2009**, *52*, 5721–5731.
6. (a) Lee, K.-D.; Saito, G.; Swanson, J. A. *Adv. Drug Delivery Rev.* **2003**, *55*, 199–215; (b) For a brief description see, for example Kosower, E. M. In *Glutathione*; Dolphin, D., Poulson, R., Avramovic, O., Eds.; John Wiley: New York, NY, 1989; Part A, pp 115–120; (c) For a presentation of in vitro protection of thiol groups as disulfides and the corresponding in vitro deprotedion see, for example Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, NY, 1991; p. 302.
7. (a) Bodanszky, M. *Principles of Peptide Synthesis;* Springer- Verlag, Berlin, 1984 p. 307; (b) Jocelyn, P. C. *Biochemistry of the Thiol Group*; American: NewYork, NY, 1992; (c) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452; (d) Schmidt, B.; Lindman, S.; Tong, W.; Lindeberg, G.; Gogoll, A.; Lai, Z.; Thornwall, M.; Synnergren, B.; Nilson, A.; Welch, C. J.; Sohtell, M.; Westerlund, C.; Nyberg, F.; Karlen, A.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 903–919.
8. (a) Nicholas, G. M.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2001**, *64*, 341–344; (b) Eisenbarth, S.; Gehling, M.; Harderc, A.; Steffan, B. *Tetrahedron* **2002**, *58*, 8461–8464; (c) O'Donnell, G.; Poeschl, R.; Zimhony, O.; Gunaratnam, M.; Moreira, J. B. C.; Neidle, S.; Evangelopoulos, D.; Bhakta, S.; Malkinson, J. P.; Boshoff, H. I.; Lenaerts, A.; Gibbons, S. *J. Nat. Prod.* **2009**, *72*, 360–365.
9. For an overview see Okuyama, T. In *The Chemistry of Sulphenic Acids and Their Derivatives*; Patai, S., Ed.; John Wiley: New York, NY, 1990, Chapter 18; For a review see*Organic Sulfur Chemistry: Structure and Mechanism*; Oae, S., Ed.; C.R.C.: Boca Raton, 1991; pp 216–253; (a) See, also: Singh, P. I. C.; Field, L. *J. Org. Chem.* **1988**, *53*, 2608–2612 and references cited therein (b) Field, L.; Parson, T. F.; Pearson, D. E. *J. Org. Chem.* **1966**, *31*, 3550–3555; (c) Field, L.; Giles, P. M. *J. Org. Chem.* **1971**, *36*, 309–313; (d) Brocklehurst, K.; Brocklehurst, S. M.; Kowlessur, D.; ODriscoll, M.; Patel, G.; Salih, E.; Templeton, W.; Thomas, E.; Topham, C. M.; Willenbrock, F. *Biochem. J.* **1988**, *256*, 543–555; (e) Mannervic, B.; Larson, K. *Methods Enzymol.* **1981**, *77*, 420–424.
10. Liu, Y.; Zhang, Y. *Tetrahedron Lett.* **2003**, *44*, 4291–4294.
11. Kabalka, G. W.; Reddy, M. S.; Yao, M. L. *Tetrahedron Lett.* **2009**, *50*, 7340–7342.
12. Jerome, K. D.; Rucker, P. V.; Xing, L.; Shieh, H. S.; Baldus, J. E.; Selness, S. R.; Letavic, M. A.; Braganza, J. F.; McClure, K. F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 469–473.
13. Ruano, J. L. G.; Parra, A.; Alemán, J. *Green Chem.* **2008**, *10*, 706–711.
14. (a) Rao, T. V.; Sain, B.; Murthy, P. S.; Rao, T. S. R. P.; Jain, A. K.; Joshi, G. C. *J. Chem. Res.* **1997**, 300–301; (b) Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H. *Chem. Commun.* **2010**, *46*, 6476–6478.
15. Bourles, E.; Sousa, R. A.; Galardon, E.; Selkti, M.; Tomas, A.; Artaud, I. *Tetrahedron* **2007**, *63*, 2466–2471.
16. Harusawa, S.; Yoshida, K.; Kojima, C.; Araki, L.; Kurihara, T. *Tetrahedron* **2004**, *60*, 11911–11922.
17. Tan, K. Y. D.; Kee, J. W.; Fan, W. Y. *Organometallics* **2010**, *29*, 4459–4463.
18. Freeman, F.; Po, H. N.; Ho, T. S.; Wang, X. *J. Phys. Chem. A* **2008**, *112*, 1643–1655.
19. Banfield, S. C.; Omori, A. T.; Leisch, H.; Hudlicky, T. *J. Org. Chem.* **2007**, *72*, 4989–4992.
20. (a) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Green Chem.* **2007**, *9*, 315–317; (b) Singh, D.; Galetto, F. Z.; Soares, L. C.; Rodrigues, O. E. D.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, 2661–2665.
21. Nair, V.; Augustine, A. *Org. Lett.* **2003**, *5*, 543–544.
22. Lenardão, E. J.; Lara, R. G.; Silva, M. S.; Jacob, R. G.; Perin, G. *Tetrahedron Lett.* **2007**, *48*, 7668–7670.
23. Ruggles, E. L.; Deker, P. B.; Hondal, R. J. *Tetrahedron* **2009**, *65*, 1257–1267.
24. Sinha, S.; Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron* **1999**, *55*, 14769–14776.
25. Zolfigol, M. A. *Tetrahedron* **2001**, *57*, 9509–9511.
26. Sun, J.; Xia, E.; Wu, Q.; Yan, C. *Tetrahedron* **2010**, *66*, 7794–7798.
27. Iranpoor, N.; Firouzabadi, H.; Pourali, A. *Tetrahedron* **2002**, *58*, 5179–5184.
28. Brzezinska, E.; Ternay, A. L. *J. Org. Chem.* **1994**, *59*, 8239–8244.
29. Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, *45*, 5677–5679.
30. Han, M.; Lee, J. T.; Hahn, H. G. *Tetrahedron Lett.* **2011**, *52*, 236–239.
31. Pan, J.; Xian, M. *Chem. Commun.* **2011**, *47*, 352–354.
32. (a) Hunter, R.; Caira, M.; Stellenboom, N. *J. Org. Chem.* **2006**, *71*, 8268–8271; (b) Stellenboom, N.; Hunter, R.; Caira, M. R. *Tetrahedron* **2010**, *66*, 3228–3241; (c) Stellenboom, N.; Hunter, R.; Caira, M. R.; Szilagyi, L. *Tetrahedron Lett.* **2010**, *51*, 5309–5312.
33. Kowalczyk, J.; Barski, P.; Witt, D.; Grzybowski, B. A. *Langmuir* **2007**, *23*, 2318–2321.
34. Morais, G. R.; Falconer, R. A. *Tetrahedron Lett.* **2007**, *48*, 7637–7641.
35. Barba, F.; Ranz, F.; Batanero, B. *Tetrahedron Lett.* **2009**, *50*, 6798–6799.
36. Bao, M.; Shimizu, M. *Tetrahedron* **2003**, *59*, 9655–9659.
37. Wang, L.; Clive, D. L. J. *Org. Lett.* **2011**, *13*, 1734–1737.
38. Hassan, A. A.; Mohamed, N. K.; El-Tamany, E. H.; Ali, B. A.; Mourad, A. E. *Monatsh. Chem.* **1995**, *126*, 653–662.
39. Lo, W. S.; Hu, W. P.; Lo, H. P.; Chen, C. Y.; Kao, C. L.; Vandavasi, J. K.; Wang, J. J. *Org. Lett.* **2010**, *12*, 5570–5572.
40. Karabinos, Y. *J. Org. Chem.* **1963**, *28*, 3246–3248.
41. Raghvendra, S. S.; Victor, N. N.; Partha, B. *New J. Chem.* **2003**, *27*, 1115–1123.
42. Colichman, E. L.; Love, D. L. *J. Am. Chem. Soc.* **1953**, *75*, 5736–5737.
43. Habib, F.; Daryoush, M.; Mobsen, E.-M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2185–2189.
44. Rajendra, G.; Madhu shri, V. *Indian J. Chem., Sect. A: Inorg., Bio-inorg., phys., Theor. Anal. Chem.* **1996**, *35*, 281–287.
45. Albanese, D.; Penso, M. *Synthesis* **1991**, *11*, 1001–1002.