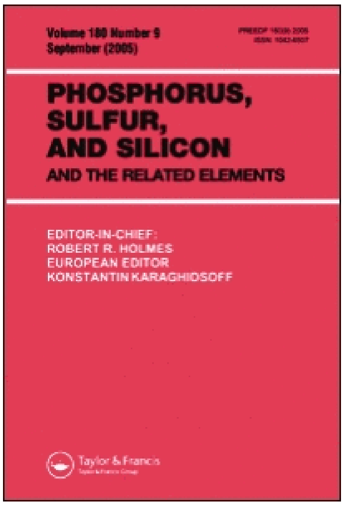


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of New β,β'-Diketodithioethers via Swern Oxidation and Study of Their Hydrazone Formation Rate

Seyed Mohammad Seyedi [a]; Hamid Sadeghian [a]; Zohreh Safari [a]
[a] Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

To cite this Article Seyedi, Seyed Mohammad, Sadeghian, Hamid and Safari, Zohreh(2009) 'Synthesis of New β,β'-Diketodithioethers via Swern Oxidation and Study of Their Hydrazone Formation Rate', Phosphorus, Sulfur, and Silicon and the Related Elements, 184: 9, 2297 — 2306

To link to this Article: DOI: 10.1080/10426500802453989

URL: http://dx.doi.org/10.1080/10426500802453989

Phosphorus, Sulfur, and Silicon, 184:2297–2306, 2009
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802453989

Synthesis of New β,β′-Diketodithioethers via Swern Oxidation and Study of Their Hydrazone Formation Rate

Seyed Mohammad Seyedi, Hamid Sadeghian, and Zohreh Safari
Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

The synthesis of β,β′-diketodithioethers ***4b–j*** *from corresponding β,β′-dihydroxydithioethers* ***3b–j*** *was carried out by a Swern oxidation using DMSO-oxalyl chloride as oxidizing agent. β,β′-Dihydroxydithioethers* ***3b–j*** *were prepared by the reaction of two molar equivalents of epoxides* ***1b–j*** *with dimercaptoethane* **2** *in the presence of a saturated aqueous solution of potassium carbonate. The reactivity behavior of imine formation of the β,β′-diketodithioethers* ***4b–j*** *by 2,4-dinitrophenylhydrazine was also investigated, and a mechanism was proposed by using molecular orbital (MO) calculations. To confirm the proposed mechanism, the role of the thia function to activate hydrazone formation by measuring HOMO-LUMO energy levels was also demonstrated.*

Keywords Ab initio; 2,4-dinitrophenylhydrazine; HUMO-LUMO; molecular orbital calculation; neighboring group participation

INTRODUCTION

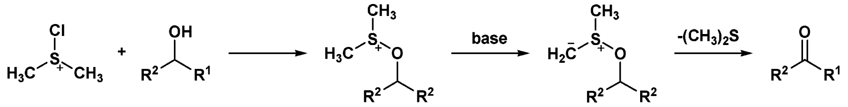
The Swern oxidation[1] is one of the useful procedures for conversion of a primary or secondary alcohol to an aldehyde or ketone. This oxidation proceeds via an alkylsulfonium ylide intermediate, which is usually derived from DMSO or dimethylsulfide (SCHEME 1). Formation of the activated intermediates [$(CH_3)_2SX^+$] from DMSO and oxalyl chloride,[2,3] trifluroacetic anhydride,[2,3] acetic anhydride,[4–6] pyridine–sulfur trioxide complex,[7] and phosphoruspentaoxide[8] have also been reported.

Herein, we report the selective oxidation of β,β′-dihydroxydithioethers, leaving the two susceptible thia functions intact, via Swern oxidation using DMSO-oxalyl chloride as an oxidizing agent. The

---

Received 5 April 2008; accepted 5 September 2008.

Address correspondence to Seyed Mohammad Seyedi, Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad, 91775, I. R. Iran. E-mail: smseyedi@yahoo.com



SCHEME 1

activity of the corresponding β,β'-diketodithioether products for imine formation by using 2,4-dinitrophenylhydrazine as a general reagent is also studied.

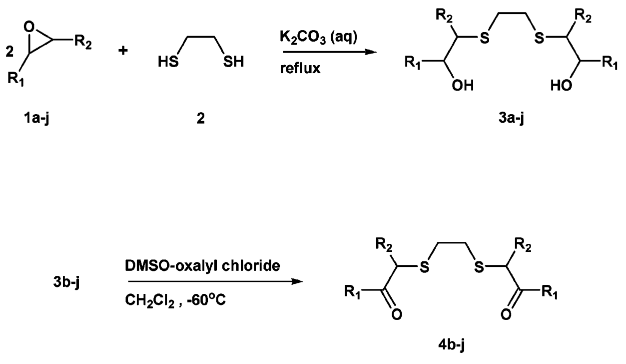
RESULTS

Synthesis

β, β'-Dihydroxydithioether **3a** and the mixture of two diastereomers of its derivatives **3b–j** were prepared from two molar equivalents of oxiranes **1a–j** with dimercaptoethane **2** in the presence of a saturated aqueous solution of potassium carbonate.[9] Treatment of dihydroxy compounds **3a–j** with a mixture of DMSO and oxalyl chloride in dry dichloromethane at −60°C and then reacting with triethylamine led to formation of corresponding diketo products **4b–j**, except compound **3a**, which was not converted to the corresponding dialdehyde (SCHEME 2).

Kinetic Study

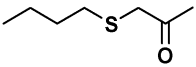
The relative rates of hydrazone formation of diketones **4b–j** were measured in alcoholic solution at 363 nm (383 nm for compound **4d**) for 60 seconds.[10] The final concentration of diketones **4b–j** and 2, 4-dinitrophenylhydrazine in ethanol was 50 and 500 μM, respectively. The experiment was repeated six times for each sample. The extent of



R_1	R_2	
H	H	a
$-CH_3$	H	b
$-C_2H_5$	H	c
-Ph	H	d
$-CH_2OCH_2CHCH_2$	H	e
$-CH_2OCH(CH_3)_2$	H	f
$-CH_2O\text{-}n\text{-}C_4H_9$	H	g
$-CH_2O\text{-}tert\text{-}C_4H_9$	H	h
$-CH_2OPh$	H	i
$-CH_2CH_2CH_2CH_2-$		j

SCHEME 2 General procedure for synthesis of compounds **4b–j**.

TABLE I Relative Rates of Hydrazone Formation of Compounds 4b-j and Butylthioacetone and the Data Obtained from Single Point Calculations

Compd.	Relative rate	$LUMO^1$	$LUMO^2$	ΔE_{2-1}
4b	9.10e-2	3.75	3.25	+68.8
4c	5.88e-2	3.74	3.26	+74.3
4d	0.55e-2	2.29	2.23	+86.4
4e	25.0e-2	3.54	3.06	+60.0
4f	6.25e-2	3.59	3.12	+75.2
4g	50.0e-2	3.68	3.09	+58.6
4h	37.0e-2	3.60	3.16	+79.2
4i	1	3.47	2.85	+52.3
4j	0.22e-2	3.64	3.09	+89.1
BTA	0.31e-2			
BTA = Butylthioacetone				

$LUMO^1$ and $LUMO^2$ refer to LUMO energy level (eV) of compounds **4b–j** before and after ring closing, respectively, and ΔE_{2-1} is the energy difference between the diketone derivative and the same molecule with carbonyl–sufur interaction.

increase in absorbance at the desired wavelength in comparison with **4i** (most reactive of the synthetic diketones) was the basis of reaction rate determination (Table I).

CALCULATION

Structures of desired molecules were simulated in Chem3D professional; Cambridge software.[11] The geometry of the structures was first modified under molecular mechanics calculations (MM^+ method). In the second optimization, output files were minimized under semi-empirical RHF/PM3 methods (convergence limit = 0.05; iteration limit = 50; RMS gradient = 0.05 kcal/mol; Polak–Ribiere optimizer algorithm).[12] Then the geometry optimization and single point properties of molecules were calculated using ab initio method with RHF/6-31G* basis set (convergence limit = 1e-6; iteration limit = 100; the initial guess of the MO coefficients is from eigenvectors of the core Hamiltonian) in HyperChem7.5.[12]

DISCUSSION

For carbonyl compounds **4b–j**, it was necessary to find out a method that would be capable of converting hydroxyl groups of **3b–j** to the corresponding carbonyl groups while leaving 1,4-dithia function intact. The lack of precedent would thus require a judicious choice of appropriate oxidant as well as reaction conditions. We focused on Swern oxidation and used an activated dimethylsulfoxide–based procedure, adopting the method reported by Fang et al.[13] To a mixture of dichloromethane and oxalyl chloride at −60°C, DMSO was added followed by gradual addition of the desired alcohols in dichloromethane. The reaction mixture stirred for 25 min and then completed by the addition of triethylamine. The mixture was allowed to reach 0°C or room temperature prior to quenching with water. This oxidation was also modified by addition of the dialcohols to DMSO instead of dichloromethane. The diketones so obtained were quite pure and could be used directly for further reactions. We could not prepare and isolate dialdehyde **4a** via Swern oxidation.

Table I shows the relative rate of hydrazone formation of diketones **4b–j** along with buthylthioacetone. This comparison is due to the existence of one α-thiacarbonyl groups in the chemical structure of buthylthioacetone. By considering the data in Table I, we supposed that high activity of these diketones towards hydrazone formation comes from neighboring group participation[14] of sulfur atoms cited at position six from each carbonyl group when compared with buthylthioacetone with no such thia group. Each carbonyl group attacks a remoter sulfur atom ($\pi \rightarrow$ d) and an unstable zwitterion structure appears. In this structure, the β and β ' carbons have higher activity and can be attacked easily by amines (Figure 1). To prove this idea, the LUMO energy levels of compounds **4b–j**, the corresponding zwitterions, and the energy differences between the diketones and their closed ring form (Δ E_{2-1}) were calculated (Table I). This calculation showed that the main density of the LUMO of the diketones belongs to carbonyl groups, and by the carbonyl oxygen attacking the sulfur atom, the LUMO energy of diketones decreases (Figure 2). The difference of LUMO energy levels of each diketone before ($LUMO^1$) and after ($LUMO^2$) ring closing with relative rate of hydrazone formation was also calculated. This calculation showed two good nonlinear relationships of $LUMO^1$-$LUMO^2$ energy differences (except **4j**) and (Δ E_{2-1}) versus relative rate of all compounds (Figure 3).

EXPERIMENTAL PROTOCOL

Instruments and Chemicals

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu

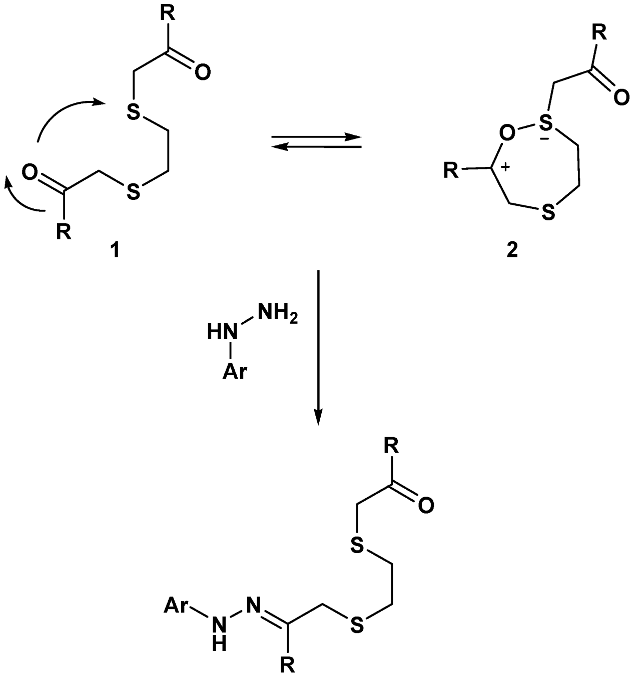


FIGURE 1 Proposed mechanism for the formation of *β* -thiahydrazone (Ar = 2,4-dinitrophenyl).

spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer in $CDCl_3$. Elemental analyses were obtained on a Thermo Finnigan Flash EA microanalyzer. All measurements of hydrazone formation rate were carried out using an Agilent 8453 spectrophotometer.

General Procedure for the Synthesis of *β,β′*-Diketodithioethers (4b–j)

To a stirring solution of oxalyl chloride (2.5 mL, 30 mmol) in dichloromethane (50 mL), dimethylsulfoxide (4 mL, 57 mmol) in dichloromethane (15 mL) was added over 3 min and cooled to −60°C using an external cooling bath. After 10 min, the hydroxyl compound **3a–j** (15 mmol) in dried dimethylsulfoxide (6 mL) was added, and the reaction mixture was stirred for a further 25 min. Triethylamine was distilled and added (20 mL) dropwise to the stirring solution. After 15 min, the cooling bath was removed, and the reaction mixture was

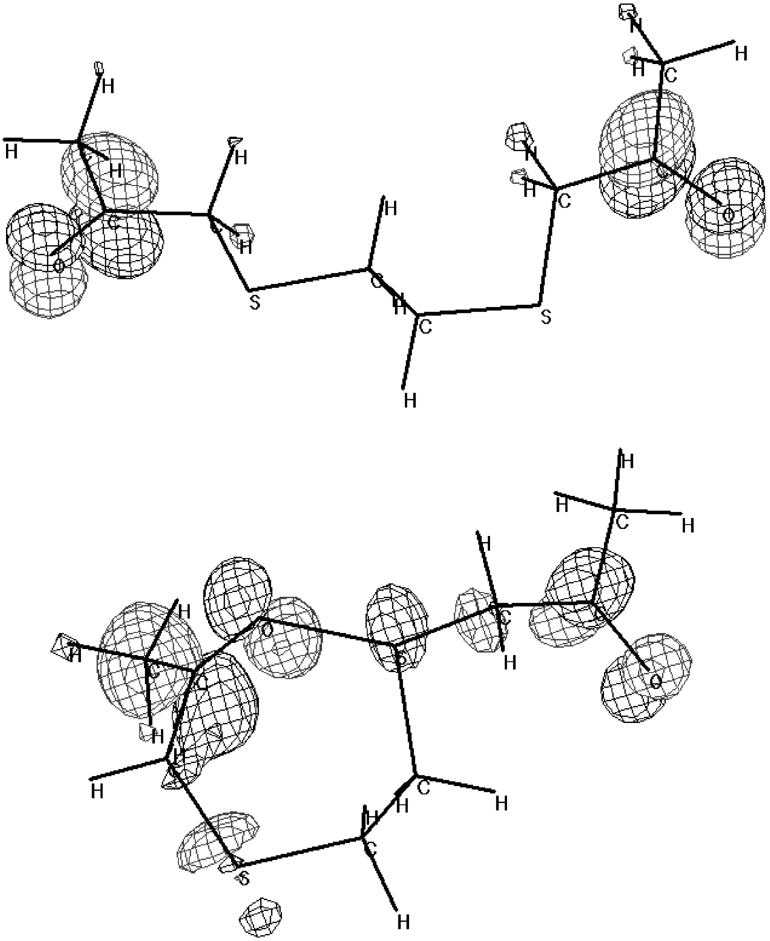


FIGURE 2 LUMO[1] (above) and LUMO[2] (below) graph of compound **4b** before and after ring closing, respectively.

allowed to warm to room temperature. Water (50 mL) was added, and the dichloromethane layer was separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined dichloromethane extracts were washed successively with HCl 1% (200 mL), sodium carbonate 5% (50 mL), and water (2 × 50 mL) and then dried over anhydrous sodium sulfate. The pale yellow filtrate was concentrated to give crude products. Thin layer chromatography (dichloromethane) indicated the presence of a small quantity of colored polar impurity, which was not easily removed. The crude products

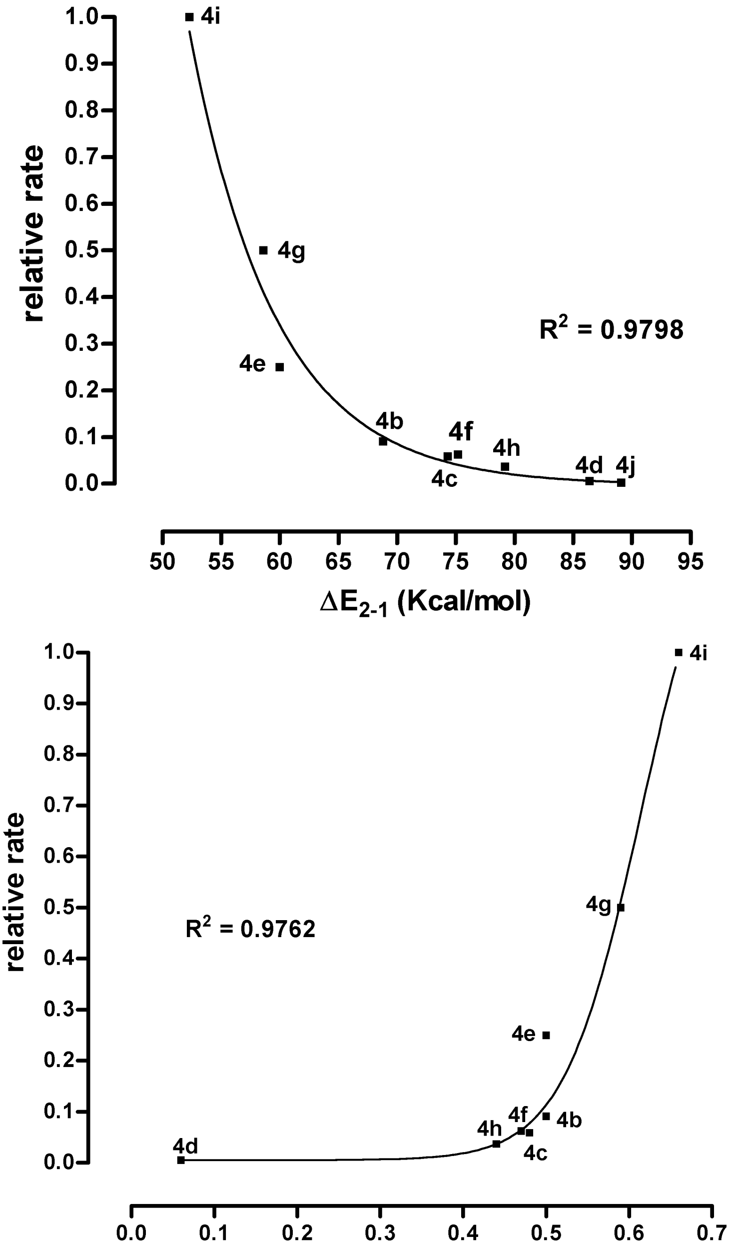


FIGURE 3 Diagrams of relative rates versus Δ E_{2-1} of compounds **4b–j** (above) and Δ ($LUMO^1$ and $LUMO^2$) of compounds **4b–i** (below).

were dissolved in 50 mL of hot dichloromethane containing 0.1 g of activated charcoal and filtered through a short plug of Celite filter aid. The plug was washed with further hot solvent, and the combined filtrate was concentrated to give the desired compounds **4b–j** (55–93%). Analytically pure materials were obtained by column chromatography (Silicagel 230–400; dichloromethane:hexane 50:50).

1-(2-[(2-Oxopropyl)sulfanyl]ethylsulfanyl)acetone (4b)

Colorless oil, (85%), IR: 1709 cm^{-1} (C=O). δ_H 2.30 (6H, s, 2 × CH_3), 2.71 (4H, s, 2 × CH_2S), 3.25 (4H, s, 2 × $COCH_2S$). Anal. Calcd. for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.08. Found: C, 46.81; H, 6.77; S, 30.89%.

1-(2-[(2-Oxobutyl)sulfanyl]ethylsulfanyl)-2-butanone (4c)

Yellow solid, (90%), mp: 45°C, IR: 1709 cm^{-1} (C=O). δ_H 1.05 (6H, t, $J = 6$Hz, 2 × CH_3), 2.30 (4H, q, $J = 6$Hz, 2 × CH_2), 2.66 (4H, s, 2 × CH_2S), 3.21 (4H, s, 2 × $COCH_2S$). Anal. Calcd. for $C_8H_{18}O_2S_2$: C, 51.24; H, 7.74; S, 27.36. Found: C, 51.51; H, 7.69; S, 27.22%.

2-(2-[(2-Oxo-2-phenylethyl)sulfanyl]ethylsulfanyl)-1-phenyl-1-ethanone (4d)

Yellow oil, (55%), IR: 1713 cm^{-1} (C=O). δ_H 2.79 (4H, s, 2 × CH_2S), 3.80 (4H, s, 2 × $COCH_2S$), 7.41–8.05 (10H, m, aromatic H). *Anal. Calcd.* for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49; S, 19.41. Found: C, 65.81; H, 5.57; S, 19.22%.

1-(allyloxy)-3-[(2-[3-(allyloxy)-2-oxopropyl]sulfanylethyl) sulfanyl]acetone (4e)

Yellow solid, (93%), mp: 46°C, IR: 1720 cm^{-1} (C=O). δ_H 2.75 (4H, s, 2 × CH_2S), 3.31 (4H, s, 2 × $COCH_2S$), 4.12 (4H, d, $J = 7$ Hz, 2 × CH_2O), 4.22 (4H, s, 2 × $COCH_2O$). Anal. Calcd. for $C_{14}H_{22}O_4S_2$: C, 52.80; H, 6.96; S, 20.14. Found: C, 52.91; H, 6.89; S, 20.21%.

1-Isopropoxy-3-(2-[(3-isopropoxy-2-oxopropyl)sulfanyl] ethylsulfanyl)acetone (4f)

Yellow oil, (74%), IR: 1722 cm^{-1} (C=O). δ_H 1.20 (12H, d, $J = 6$Hz, 4 × CH_3), 2.74 (4H, s, 2 × CH_2S), 3.35 (4H, s, 2 × $COCH_2S$), 3.65 (2H, m, CH), 4.19 (4H, s, 2 × $COCH_2O$). Anal. Calcd. for $C_{14}H_{26}O_4S_2$: C, 52.14; H, 8.13; S, 19.89. Found: C, 52.01; H, 8.26; S, 19.67%.

1-Butoxy-3-(2-[(3-butoxy-2-oxopropyl)sulfanyl] ethylsulfanyl)acetone (4g)

Yellow solid, (81%), mp: 37°C, IR: 1721 cm^{-1} (C=O). δ_H 0.92 (6H, t, $J = 6$Hz, 2 × CH_3) 1.20–1.60 (8H, m, 2 × CH_2CH_2), 2.74 (4H, s, 2 × CH_2S), 3.34 (4H, s, 2 × $COCH_2S$), 3.51 (4H, t, $J = 6$Hz, 2 × CH_2O), 4.20 (4H, s, 2 × $COCH_2O$). Anal. Calcd. for $C_{16}H_{30}O_4S_2$: C, 54.82; H, 8.63; S, 18.29. Found: C, 54.91; H, 8.57; S, 18.27%.

1-(tert-Butoxy)-3-[(2-[3-(tert-butoxy)-2-oxopropyl] sulfanylethyl)sulfanyl]acetone (4h)

Yellow oil, (78%), IR: 1719 cm^{-1} (C=O). δ_H 1.22 (18H, s, 6 × CH_3), 2.73 (4H, s, 2 × CH_2S), 3.35 (4H, s, 2 × $COCH_2S$), 4.12 (4H, s, 2 × $COCH_2O$). Anal. Calcd. for $C_{16}H_{30}O_4S_2$: C, 54.82; H, 8.63; S, 18.29. Found: C, 55.02; H, 8.72; S, 18.07%.

1-(2-[(2-Oxo-3-phenoxypropyl)sulfanyl]ethylsulfanyl)-3-phenoxyacetone (4i)

Yellow solid, (83%), mp: 96°C, IR: 1723 cm^{-1} (C=O). δ_H 2.78 (4H, s, 2 × CH_2S), 3.44 (4H, s, 2 × $COCH_2S$), 4.76 (4H, s, 2 × $COCH_2O$), 6.80–7.40 (10H, m, aromatic H). Anal. Calcd. for $C_{20}H_{22}O_4S_2$: C, 61.51; H, 5.68; S, 16.42. Found: C, 61.63; H, 5.63; S, 16.37%.

2-(2-[(2-Oxocyclohexyl)sulfanyl]ethylsulfanyl)-1-cyclohexanone (4j)

Yellow oil, (61%), IR: 1701 cm^{-1} (C=O). δ_H 1.20–2.60 (16H, m, $CH_2CH_2CH_2CH_2$), 2.68 (2H, s, 2 × CH_2S), 2.84 (2H, s, 2 × CH_2S), 3.36 (2H, m, 2 × COCHS). Anal. Calcd. for $C_{14}H_{22}O_2S_2$: C, 58.70; H, 7.74; S, 22.39 Found: C, 58.94; H, 7.91; S, 22.28%.

REFERENCES

[1] K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41,** 957 (1976).
[2] K. Omura and D. Swern, *Tetrahedron*, **34,** 1651 (1978).
[3] A. J. Mancuso and D. Swern, *Synthesis*, 165 (1981).
[4] J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87,** 4214 (1967).
[5] J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89,** 2416 (1967).
[6] J. D. Albright, *J. Org. Chem.*, **39,** 1977 (1974).
[7] J. R. Parikh and W. V. E. Doering, *J. Am. Chem. Soc.*, **89,** 5505 (1967).
[8] K. Onodera, S. Hirano, and N. Kashimura, *J. Am. Chem. Soc.*, **87,** 4651 (1965).
[9] S. M. Seyedi, H. Sadeghian, and M. Rezai, M. *Phosphorus, Sulfur, and Silicon*, **182,** 1709 (2007).
[10] H. H. Perkampus, *UV-VIS Spectroscopy and Its Applications* (H. C. Grinter and T. L. Threlfall, trans., Springer-Verlag, New York, 1992).

[11] ChemDraw® Ultra, *Chemical Structure Drawing Standard*, Cambridge Soft Corporation, Cambridge, MA, USA, http://www.cambrigesoft.com.

[12] HyperChem® Release 7, Hypercube Inc., http://www.hyper.com/.

[13] X. Fang, U. K. Bandarage, T. Wang, J. D. Schroeder, and D. S. Garvey, *J. Org. Chem.*, **66,** 4019 (2001).

[14] F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, 4th ed. (Kluwer Academic/Plenum Publication, New York, 2000), Part A, Chap. 5, p. 809.