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Synthesis of 1,4- and 1,3-Bis-(5-Alkylthio-1,3,4-Oxadiazol-2-yl) Benzenes

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1,4- and 1,3-Benzene dicarboxylic acid dihydrazides reacted with carbon disulfide in basic medium to afford bis-(5-mercapto-1,3,4-oxadiazol-2-yl) benzenes, **2a, b**. The latter compounds were alkylated by the reaction with alkyl halides in basic medium. The reaction of 1,2-benzene dicarboxylic acid dihydrazide under similar conditions was accompanied with unexpected rearrangement.

INTRODUCTION

5-Mercapto-1,3,4-oxadiazoles have been repoted to possess wide range of biological activities[1–8]. The reaction of acid hydrazides with carbon disulfide in basic medium was proved to be a convenient route for the synthesis of this class of compounds[9–12].

Despite the intensive research on the synthesis and caracterization of 5-mercapto-1,3,4-oxadiazoles, little is known about the synthesis and characterization of the substituted bis-5-mercapto-1,3,4-oxadiazoles. These observations prompted us to synthesize and characterize a series of these substituted heterocyclic compounds. The present paper summarizes our results in this area.

EXPERIMENTAL

Melting points were determined on an electrothermal-digital melting point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded on a Brucker WP 80-SY, WM-250 and AC-250 spectrometers in deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (d^6-DMSO) with tetramethylisilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on Brucker WM-250 and AC-250 spectrometers. Infrared spectra (IR) were recorded on Perkin-Elmer FT-IR SP-2000 spectrometer as potassium bromide (KBr) pellets. Mass spectra were determined on a sector field double focusing unit VG 7070E mass spectrometer. Elemental analyses were performed at M.H.W. Laboratories, Phoenix, Arizona, USA.

Phthalic, isophthalic and terephthalic acid dihydrazides were prepared following literature procedures[13]. Chemicals were purchased from Aldrich and Fluka and were used without further purification.

General procedure for the preparation of compounds 2a, b

To a solution of potassium hydroxide (103.0 mmol) in absolute ethanol (300 mL) was added acid dihydrazide **1a, b** (51.5 mmol). Carbon disulfide (113 mmol) was added to the reaction mixture dropwise; a pale yellow precipitate was readily formed. The reaction mixture was heated, under reflux, for 4 h, during which time the mixture became clear. The solvent was concentrated by distillation and the

residue was acidified with dilute hydrochloric acid to afford the products. The following compounds were prepared according to the above procedure:

2a: 1,4-Bis-(5-mercapto-1,3,4-oxadiazol-2-yl) benzene; Yield = 84%. m.p. > 300°C (dec.) (lit.[18] m.p. > 300°C (dec.)). ^{1}H-NMR (d^6-DMSO), δ: 12.05 (bs, 2H, SH); 8.07 (s, 4H, Ar).

2b: 1,3-Bis-(5-mercapto-1,3,4-oxadiazol-2-yl) benzene; Yield = 86%. m.p. = 270–2°C. ^{1}H-NMR (d^6-DMSO), δ: 14.76 (bs, 2H, SH); 8.23–7.77 (m, 4H, Ar).

General procedure for the preparation of compounds 4a–e and 5a–e

To a freshly prepared sodium ethoxide solution (20 mmol) in absolute ethanol (100 mL), a solution of bis-(5-mercapto-1,3,4-oxadiazol-2-yl) benzene, **2a, b** (10 mmol), was added with stirring. Then, a solution of the appropriate alkyl halide (21.6 mmol) in ethanol (20 mL) was added dropwise. The reaction mixture was heated, under reflux, for several hours. After cooling, water (100 mL) was added which led to a precipitate formation. The resulting solid was collected by filtration, dried and recrystallized from chloroform-ether (1 : 4). Tables 1 and 2 summarize physical and spectroscopic data for compounds **4a–e** and **5a–e.**

TABLE-1
MELTING POINTS, YIELDS, ^{1}H-NMR AND ^{13}C-NMR DATA OF COMPOUNDS **4a–e** AND **5a–e**

Compd.[a] No.	m.p. (°C)	Yield (%)	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm), J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ (ppm)
4a	204–5	55	8.12 (s, 4H, Ar); 2.80 (s, 6H, CH_3)	165.6; 164.6; 127.1; 126.1; 14.5
b	141–2	40	8.14 (s, 4H, Ar); 4.02–3.97 (m, 2H, CH); 1.55 (d, J = 6.8, 12H, CH_3)	164.9; 164.8; 127.3; 126.4; 39.3; 23.4
c	205–6	60	8.09 (s, 4H, Ar); 7.47–7.43 (m, 6H, Ar); 7.37–7.25 (m, 4H, Ar); 4.54 (s. 4H, CH_2)	165.1; 164.8; 135.6; 129.2; 128.9; 128.2; 127.3; 37.1
d	153–4	46	8.12 (s, 4H, Ar); 7.34–7.20 (m, 10H, Ar); 3.56 (t, J = 7.5, 2H, CH_2); 3.17 (t, J = 7.5, 2H, CH_2)	165.1; 164.9; 139.0; 128.7; 127.3; 126.9; 126.4; 35.7; 34.0
e[b]	234–6	66	8.17 (d, J = 8.7, 4H, Ar); 7.76 (d, J = 8.7, 4H, Ar); 8.11 (s, 4H, Ar); 4.71 (s, 4H, CH_2)	165.0; 163.7; 144.5; 130.3; 128.1; 127.5; 123.9; 123.6; 35.8
5a	139–40	79	8.58–7.54 (m, 4H, Ar); 2.80 (s, 6H, CH_3)	165.7; 164.7; 129.9; 129.2; 124.6; 124.3; 14.6
b	73–4	51	8.61–7.65 (m, 4H, Ar); 4.10–3.93 (m, 2H, CH); 1.55 (d, J = 6.6, 12H, CH_3)	164.7; 164.5; 129.9; 129.3; 124.7; 124.4; 39.1; 23.3
c	132–3	81	8.54–7.53 (m, 4H, Ar); 7.51–7.32 (m, 10H, Ar); 4.55 (s, 4H, CH_2)	164.9; 164.8; 135.6; 130.0; 129.5; 129.2; 129.0; 128.2; 124.4; 37.0

Compd.[a] No.	m.p. (°C)	Yield (%)	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm), J (Hz)	^{13}C-NMR ($CDCl_3$/TMS) δ (ppm)
d	131–2	52	8.59–7.61 (m, 4H, Ar); 7.41–7.20 (m, 10H, Ar); 3.57 (t, J = 7.3, 2H, CH_2); 3.17 (t, J = 7.3, 2H, CH_2)	165.0; 164.9; 139.0; 129.9; 129.2; 128.8; 127.0; 124.6; 124.5; 35.6; 33.9
e	176–7	69	8.53–8.11 (m, 4H, Ar); 8.21 (d, J = 8.6, 4H, Ar); 7.69 (d, J = 8.6, 4H, Ar); 4.60 (s, 4H, CH_2)	165.2; 164.0; 148.0; 143.2; 130.0; 129.5; 124.8; 124.0; 36.0

[a] All new compounds gave satisfactory C, H, N elemental analysis.

[b] ^{1}H-NMR and ^{13}H-NMR were recorded in deuterated dimethyl sulfoxide (d^6-DMSO)

TABLE-2
MASS SPECTRAL DATA FOR COMPONDS **4a–e** AND **5a–e**

Compd. No.	MS (m/z, rel. int. (%))
4a	308 (M^+ + 2, 8.3); 306 (M^+, 100); 259 (M-SCH_3, 27.4); 219 (71.3); 104 ($[PhC{\equiv}O]^{+\bullet}$, 21.0)
b	361 (M^+ −1, 110); 278 (M^+-C_6H_{12}, 100); 247 (47.8); 205 (44.0); 104 ($[PhC{\equiv}O]^{+\bullet}$, 7.6)
c	457 (M^+ −1, 3.2); 295 (M^+-$C_8H_7N_2S$, 14.7); 104 ($[PhC{\equiv}O]^{+\bullet}$; 14.0); 91 ($[PhCH_2]^+$, 100)
d	309 (M^+-$C_9H_9N_2S$, 7.8); 278 (M-$C_{16}H_{16}$, 48.4); 104 ($[PhC{\equiv}O]^{+\bullet}$, 100); 91 ($[PhCH_2]^{+\bullet}$, 72.0)
e	550 (M^+ +2, 4.46); 548 (M^+, 75.8); 340 (M^+-$C_8H_6N_3O_2S$, 13.4); 136 ($[NO_2C_6H_4CH_2]^+$, 64.3); 104 ($[PhC{\equiv}O]^{+\bullet}$, 14.0)
5a	308 (M +2, 11); 306 (M^+, 100); 259 (M-SCH_3, 42); 219 (M-$C_2H_3N_2S$, 57); 104 ($[PhC{\equiv}O]^{+\bullet}$, 7)
b	364 (M +2, 8.2); 362 (M^+, 75.8); 320 (M-C_3H_6, 41.2); 278 (M-C_6H_{12}, 100); 247 (M-$C_4H_7N_2S$, 46.1); 205 (278-CHN_2S, 50.5); 104 ($[PhC{\equiv}O]^{+\bullet}$, 17.4)
c	460 (M +2, 4.2); 458 (M^+, 33); 295 (M-$C_8H_7N_2S$, 25.4); 104 ($[PhC{\equiv}O]^{+\bullet}$, 6.3); 91 ($[PhCH_2]^{+\bullet}$, 100)
d	486 (M^+, 2.2); 309 (M-$C_9H_9N_2S$, 11.2); 278 (M-$C_{16}H_{16}$, 35); 104 ($[PhCH_2CH_2]^{+\bullet}$, 100); 91 ($[PhCH_2]^{+\bullet}$, 75.2)
e	548 (M^+, 12); 340 (M-$C_8H_6N_3O_2S$, 25.1); 136 ($[C_7H_6NO_2]^+$, 27.9)

Reaction of Phthalic acid dihydrazide 6 with carbon disuldide

Phthalic acid dihydrazide **6** (15 mmol) was added, with stirring, to ethanolic solution (100 mL) of potassium hydroxide (30 mmol). Carbon disulfide (34.1 mmol) was addded dropwise. The reaction mixture was heated, under reflux for 3 h. The solvent was concentrated by distillation. The residue was acidified with dilute hydrochloric acid. The solid was filtered, washed with cold ethanol and recrystallized from ethanol. The precipitate was identified to be 2,3-dihydro-1,4-phthalazine dione **7**.

Yield = 80%. m.p. > 300°C (dec.) (lit.[19] m.p. > 300°C (dec.)). ^{1}H-NMR (d^6-DMSO), δ: 11.52 (bs, 2H, NH); 8.17–7.84 (m, 4H, Ar). MS: 162 [M^+, 96.2]$^{+\bullet}$, 132 [M-N_2H_2, 15.9]$^+$, 104 [132–CO, 100]$^+$.

When the filtrate was concentrated, a yellow precipitate was formed which was identified to be 2,5-dimercapto-1,3,4-thiadiazole **8**.

Yield = 65%. m.p. = 166–8°C (lit.[20] m.p. = 168°C). ^{1}H-NMR (d^6-DMSO), δ: 7.8 (bs, 2H, SH). MS: 150 [M$^+$, 100]$^{+\bullet}$, 117 [M-SH, 1.4]$^+$, 91 [M-CHNS, 7.7]$^+$, 74 [M-CS_2, 89.4]$^+$, 59 [M-$CHNS_2$, 42.0]$^+$.

Reactions of diethyl fumarate and diethyl maleate with hydrazine hydrate

A solution of diethyl fumarate or maleate (10 mmol) and hydrazine hydrate (60 mmol) was stirred at room temperature for 3 h. The resulting solid was filtered, washed with ethanol and dried. The product was identified to be 5-hydrazido-3-pyrazolone **9**.

Yield = 90%. m.p. = 131–2°C. ^{1}H-NMR (d^6-DMSO), δ: 9.05 (bs, 1H, NH); 8.97 (s, 1H, NH); 4.01 (bs, 3H, NH, NH_2); 3.46–3.41 (dd, J_{12} = 8.6 Hz, J_{12}' = 5.4 Hz, 1H); 2.22 (d, J = 8.6 Hz, 1H) and 2.18 (d, J = 5.4 Hz, 1H). ^{13}C-NMR (d^6-DMSO); δ: 171.6, 169.4, 61.4, 34.8. MS: 144 [M$^+$, 2.5]$^{+\bullet}$, 114 [M-N_2H_2, 10.8]$^+$, 85 [114-HCO, 32.5]$^+$, 55 [85-N_2H_2, 100]$^{+\bullet}$.

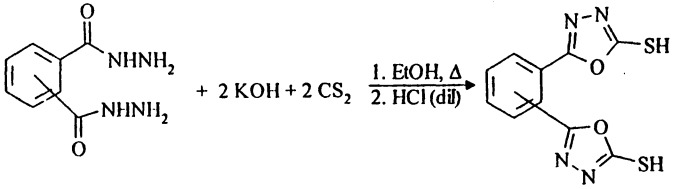
Reaction of maleic acid dihydrazide with carbon disulfide

The reaction of maleic acid dihydrazide with carbon disulfide was carried out under the same conditions that were described above for the reaction of phthalic acid dihydrazide. The products were identified to be compounds **8** and 1,2-dihydro-3,6-pyridazinedione.

Yield = 83%. m.p. > 300°C (dec.) (lit.[21] m.p. > 300°C (dec.)). ^{1}H-NMR (d^6-DMSO), δ: 11.28 (bs, 2H, NH); 6.92 (s, 2H, CH). MS: 112 [M$^+$, 100]$^{+\bullet}$, 82 [M-N_2H_2, 82.8]$^+$, 55 [M-CHN_2O, 93.9]$^+$.

RESULTS AND DISCUSSION

Bis-(5-mercapto-1,3,4-oxadiazol-2-yl) benzenes, **2a, b,** were prepared from the reaction of acid dihydrazides, **1a, b,** with carbon disulfide in ethanolic potassium hydroxide solution (Scheme 1). Compounds **2a, b** were isolated as colourless powders in good yelds. Precursors **1a, b** were prepared from the reactions of the corresponding esters with hydrazine hydrate[13].



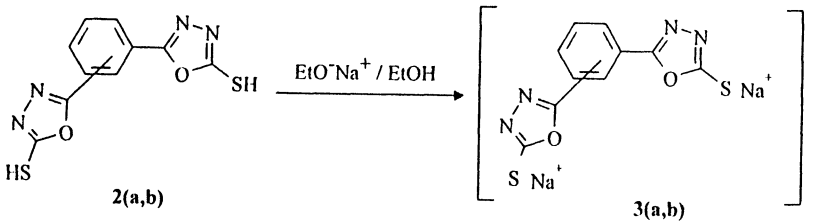
1(a,b) **2(a,b)**

Compound No. **1, 2**	Position
a	*p*–
b	*m*–

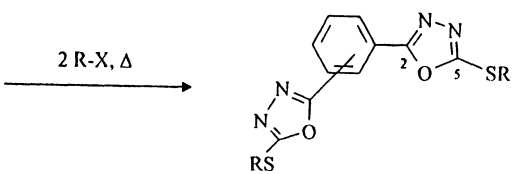
Scheme-1

Synthesis of bis-(5-alkylthio-1,3,4-oxadiazol-2-yl) benzenes

Compounds **2a, b** were converted into the corresponding disodium salts **3a, b** *via* their reactions with sodium ethoxide in absolute ethanol. The resulting di salts reacted with two equivalents of alkyl halides to give good yields of the corresponding bis-(5-substituted alkylthio-1,3,4-oxadiazol-2-yl) benzenes **4a–e** and **5a–e**, respectively, (Scheme 2). The latter compounds were crystallized from chloroform/ether and isolated as colourless powders except for compounds **4e** and **5e**, which were orange in color.



2(a,b) **3(a,b)**



4,5(a-c)

Compound No.	X	R
4, 5a	I	CH_3–
b	I	$(CH_3)_2CH$–
c	Br	$C_6H_5CH_2$–
d	Br	$C_6H_5CH_2CH_2$–
e	Br	*p*-$NO_2C_6H_4CH_2$–

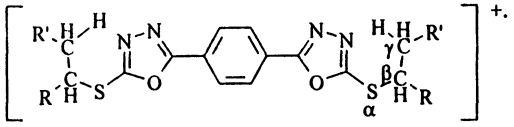
Scheme-2

The structures of compounds **4a–e** and **5a–e** were confirmed on the basis of their IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopic data, in addition to elemental analysis and ^{13}C-NMR. Table-1 summarizes melting points, yields, ^{1}H-NMR and ^{13}C-NMR spectroscopic data of these compounds.

The infrared spectra of compounds **4a–e** and **5a–e** show moderate absorption bands in the range 1605–1550 cm^{-1} assigned to the C=N functional group, whereas C—O bond of the 1,3,4-oxadiazole ring shows weak absorption bands in the range 1072–1035 cm^{-1}.

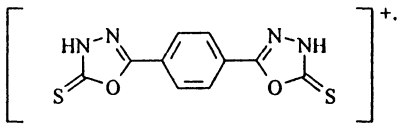
Reactions of phthalic acid dihydrazide with carbon disulfide

In analogy to the reactions of compounds **1a, b** with carbon disulfide, the reaction of phthalic acid dihydrazide **6** has been attempted. However, we were surprised that the reaction was accompained with unexpected rearrangement. Thus, compound **6** reacts with carbon disulfide in ethanolic solution of potassium hydroxide to afford, unexpectedly, 2,3-dihydro-1,4-phthalazinedione **7** and 2,5-dimercapto-1,3,4-thiadiazole **8** as the sole products, (Scheme 4). An analogous rearrangement has recently been encountered in the reactions of butanohydrazide and propanohydrazide with carbon disulfide and in the dehydration of aryolated butanohydrazides with phosphorus oxychloride[15, 16].



4(b,d)

-2 RCH=CHR'

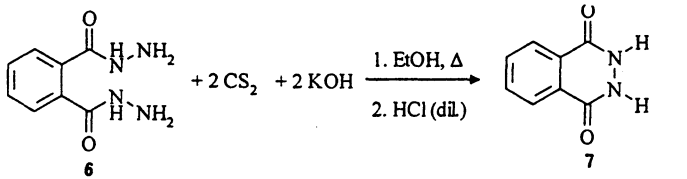


A

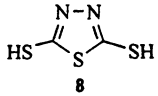
R = CH_3, R' = H

R = H, R' = Ph

Scheme-3



6 7



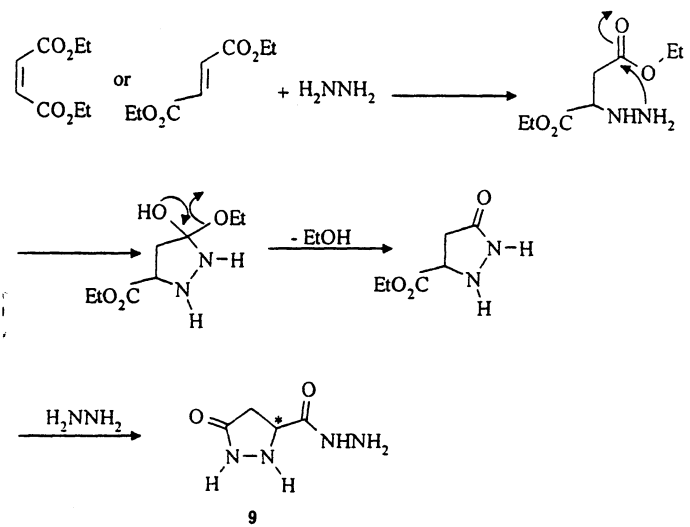
8

Scheme-4

Compound **6** was prepared from the reaction of diethylphthalate with excess hydrazine hydrate in absolute ethanol[13]. Compounds **7** and **8** are fully characterized by ^{1}H-NMR and MS spectroscopy. The data is given in the experimental section.

Reaction of Maleic Acid Dihydrazide and Fumaric Acid Dihydrazide with Carbon Disulfide

To examine the generality of the rearrangement encountered in the reaction of phthalic acid dihydrazide with carbon disulfide, the work has been extended to study the reactions of maleic acid dihydrazide and fumaric acid dihydrazide with carbon disulfide. However, the preparation of these compounds, following a literature procedure[17], was accompanied with unexpected problem. Thus, treatment of diethyl maleate or diethyl fumarate with excess hydrazine hydrate at room temperature afforded in a highly exothermic reaction, 5-hydrazido-3-pyrazolone, **9**, as the sole product (Scheme 5). The structure of compound **9** is fully identified by physical and spectroscopic methods, and the data is given in the experimental section.



9

Scheme-5

The formation of compound **9** is puzzling and in contrast to what was reported earlier[17]. It seems that the reaction proceeds through Michael-type addition reaction.

Despite this problem, maleic acid dihydrazide was prepared from the reaction of 1,2-pyridazinedione with excess hydrazine hydrate in ethanol. Treatment of this dihydrazide with carbon disulfide in alcoholic potassium hydroxide solution, under reflux, gave back 1, 2-pyridazinedione and 2,5-dimercapto-1,3,4-thiadiazole, **8**, as the only products. Thus, the rearrangement is encountered once more.

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