Ketene Dithioacetal Derivatives of 1-Phenyl-3,5-dioxopyrazolidine. Synthesis and NMR Characterization

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1-Phenyl-3,5-dioxopyrazolidine **1** reacts with carbon disufide and alkyl halides in presence of excess of sodium acetate in dimethylformamide to afford the ketene dithioacetals **3a-h**. The ^{13}C chemical shift assignments of these compounds were made on the basis of two-dimensional nmr studies performed on the *N*-methylketene dithioacetal derivative **4**.

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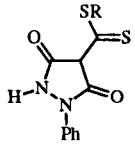
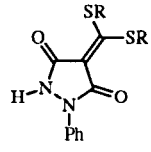
Because of our interest in the design and synthesis of heterocyclic sulfur-containing molecules with coordinative and extractive properties, we have focused our attention in alkyl dithiocarboxylate and ketene dithioacetal derivatives of pyrazolones [1-3].

The reaction of active methylene compounds with carbon disulfide and alkyl halides can afford alkyl dithiocarboxylate or ketene dithioacetal derivatives, depending on the stoichiometry of the reaction as well as the nature of the base. A good base to synthesize cyclic ketene dithioacetals by reaction of β-ketoesters with carbon disufide and 1,2 or 1,3-alkyldibromides is potassium carbonate in dimethylformamide [4]. We have studied the application of these conditions to obtain alkyl dithiocarboxylates **2** and ketene dithioacetals **3**, from 1-phenyl-3,5-dioxopyrazolidine **1** by careful control in the stoichiometry of the employed base. However, independent of the amount of potassium carbonate, **2** is not detected and a mixture of **3** and the undesired *N*-alkylketene dithioacetal **4** is formed.



2



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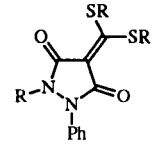
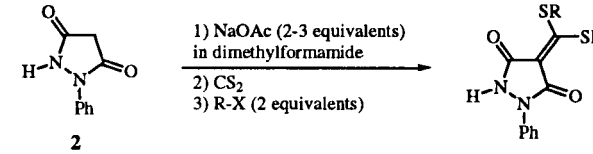


4

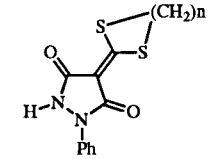
We found that sodium acetate is also a suitable base in the product control of the reaction, and recently we described the selective preparation of derivatives **2** using one equivalent of this base [5]. Now, we wish to report the results when 1-phenyl-3,5-dioxopyrazolidine **1** is treated with carbon disulfide and alkyl halides in the presence of 2 to 3 equivalents of sodium acetate in dimethylformamide. Under these conditions only the ketene dithioacetals **3a-h** are formed in 20-85% yields.

All compounds were characterized by spectroscopic techniques, principally ^1H nmr, ^{13}C nmr and FT-ir. The



2 → **3a-f**

3a, R = Me
3b, R = Et
3c, R = *n*-Butyl
3d, R = *n*-Dodecyl
3e, R = Allyl
3f, R = Benzyl



3g-h

3g, n = 2 **3h**, n = 3

carbon atoms in the heterocyclic ring and in the ketene dithioacetal moiety of the proposed structure **3a-h** are quaternary and the direct assignment of the chemical shifts from ^{13}C nmr spectra is not easy. Furthermore the information available in the literature related to these assignments is limited. In order to assign unequivocally quaternary carbon atoms, two-dimensional nmr experiments and heteronuclear NOE-difference experiments were performed on the *N*-alkylketene dithioacetal **4** (R = CH_3).

Direct and long range heteronuclear 2D-nmr correlations were carried out, observing the connectivities of protons with neighboring carbon atoms and reciprocally (Table 1).

Table 1

Connectivity Data from Direct and Long-range Heteronuclear $^1H/^{13}C$ NMR Correlations for Compound **4**

Carbon No.	δ	Attached H, δ	Long range connected H
3	162.4	–	8
9	136.6	–	10, 11, 12
6	185.4	–	7, 7'

The assignment of the remaining quaternary carbon atoms were made taking in account the {H}C NOE's observed on the irradiation of the aromatic and *N*-methyl protons (Table 2).

Table 2

NOE Differences Observed for **4**

{H}	Detected NOE's
10-12	5, 9, 10, 11
8	3, 9

According to all the information obtained from the nmr studies, the ^{13}C chemical shifts of compound **4** (Figure 1) are summarized in Table 3.

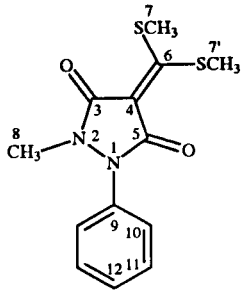


Figure 1

Table 3

^{13}C NMR Data for Compound **4**

Carbon No.	δ	Carbon No.	δ
3	164.2	8	33.4
4	108.0	9	136.6
5	160.9	10	123.0
6	185.4	11	129.0
7	21.1/21.3	12	126.4
7'	21.3/21.1		

In conclusion, by careful stoichiometric control of the reaction, sodium acetate in dimethylformamide is a suitable base to deprotonate 1-phenyl-3,5-dioxopirazolidine to afford alkyl dithiocarboxylate or ketene dithioacetal derivative. Also this base avoids the *N*-alkylation of the dione observed when potassium carbonate in dimethylformamide is used.

On the other hand, the complete assignments of signals in the ^{13}C nmr spectrum of compound **4**, has been achieved by means of two-dimensional heteronuclear H/C correlations and NOE experiments. These data have served as a model for assignment of signals in the ^{13}C nmr of the ketene dithioacetals synthesized.

EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were recorded at 200/50 MHz ($^1H/^{13}C$) in deuteriochloroform or dimethyl sulfoxide-d_6 solutions with internal tetramethylsilane and the chemical shifts are quoted in ppm. The ir spectra were recorded on a Perkin Elmer FT IR 1600 spectrophotometer in sodium chloride disc, and the absorption frequencies are quoted in reciprocal centimeters. Compound **1** was synthesized by a previously reported procedure [6].

General Procedure for Synthesis of 4-Bis(alkylthio)methylene-1-phenyl-3,5-dioxopyrazolidines, **3a-h**.

A solution of 500 mg (2.8 mmoles) of **1**, 580 mg (7.0 mmoles) of anhydrous sodium acetate and 20 ml of dry dimethylformamide is stirred 2-3 hours at 40-50°. Adding an excess of carbon disulfide (0.70 g, 9.2 mmoles), the reaction mixture is stirred 3 hours at the same temperature, followed by the addition of 5.6 mmoles of the corresponding alkyl halide. After stirring overnight at 40-50°, the mixture is poured over ice/water to precipitate the ketene dithioacetal formed. The crude product is purified by column chromatography with silicagel, using variable proportions of a hexane-ethyl acetate mixture as the eluent.

The trimethylated compound **4** is prepared by the same general procedure using 3 equivalents of potassium carbonate instead of sodium acetate.

4-Bis(methylthio)methylene-1-phenyl-3,5-dioxopyrazolidine (**3a**).

This compound was obtained in 70% yield as a granular, orange solid, mp 173.5-174.0°; ir: ν C=O 1650; ^1H nmr (deuteriochloroform): δ 2.71 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.30-7.80 (m, 5H, Ph), 7.06 (s broad, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 21.6 (CH_3), 22.1 (CH_3), 108.7 (C4), 118.7, 124.9, 129.0, 137.3 (Ph), 159.1 (C5=O), 163.7 (C3=O), 186.7 (CS_2).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S_2$: C, 51.40; H, 4.32; N, 9.99; S, 22.88. Found: C, 51.44; H, 4.30; N, 10.02; S, 22.93.

4-Bis(ethylthio)methylene-1-phenyl-3,5-dioxopyrazolidine (**3b**).

This compound was obtained in 52% yield as a pale, orange, granular solid, mp 143.0-144.0°; ir: ν C=O 1650; ^1H nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_3), 1.35 (t, 3H, CH_3), 3.20-3.40 (m, 4H, CH_2), 7.15-7.80 (m, 5H, Ph), 9.53 (s broad, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 13.8 (CH_3), 32.0 (CH_2), 33.0 (CH_2), 109.6 (C4), 118.6, 124.8, 129.0, 137.2 (Ph), 159.1 (C5=O), 163.7 (C3=O), 184.4 (CS_2).

Anal. Calcd. for $C_{14}H_{16}N_2O_2S_2$: C, 54.51; H, 5.23; N, 9.08; S, 20.80. Found: C, 54.47; H, 5.20; N, 9.10; S, 20.92.

4-Bis(butylthio)methylene-1-phenyl-3,5-dioxopyrazolidine (**3c**).

This compound was obtained in 43% yield as a orange, amorphous powder, mp 75.0-76.0°; ir: ν C=O 1656; ^1H nmr (deuteriochloroform): δ 0.89 (t, 3H, CH_3), 0.92 (t, 3H, CH_3), 1.41 (m, 4H, CH_2), 1.62 (m, 4H, CH_2), 3.24 (t, 2H, CH_2S), 3.28 (t, 2H, CH_2S), 7.13-7.80 (m, 5H, Ph), 9.88 (s broad, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 13.6 (CH_3), 21.9 (CH_2), 30.9 (CH_2), 37.4 (CH_2S), 38.6 (CH_2S), 109.6 (C4), 118.5, 124.7, 128.9, 137.3 (Ph), 159.0 (C5=O), 163.7 (C3=O), 184.4 (CS_2).

Anal. Calcd. for $C_{18}H_{24}N_2O_2S_2$: C, 59.30; H, 6.64; N, 7.69; S, 17.59. Found: C, 59.34; H, 6.58; N, 7.73; S, 17.61.

4-Bis(dodecylthio)methylene-1-phenyl-3,5-dioxopyrazolidine (**3d**).

This compound was obtained in 25% yield as a pale, yellow, amorphous powder, mp 45.0-45.5°; ir: ν C=O 1656; ^1H nmr

(deuteriochloroform): δ 0.88 (t, 6H, CH_3), 1.10-1.80 (m, 40 H, CH_2), 3.25 (t, 2H, CH_2S), 3.29 (t, 2H, CH_2S), 7.15-7.80 (m, 5H, Ph), 9.30 (s broad, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 14.1 (CH_3), 22.6, 28.8, 29.0, 29.1, 29.4, 29.6, 31.9 (CH_2), 37.7 (CH_2S), 38.9 (CH_2S), 109.5 (C4), 118.5, 124.7, 129.0, 137.3 (Ph), 159.2 (C5=O), 163.9 (C3=O), 184.6 (CS_2).

Anal. Calcd. for $C_{34}H_{56}N_2O_2S_2$: C, 69.33; H, 9.59; N, 4.76; S, 10.89. Found: C, 69.27; H, 9.55; N, 4.81; S, 10.90.

4-Bis(allylthio)methylene-1-phenyl-3,5-dioxopyrazolidine (3e).

This compound was obtained in 20% yield as a dark, orange, amorphous powder, mp 103.5-104.0°; ir: ν C=O 1656; ^1H nmr (deuteriochloroform): δ 3.80-4.00 (m, 4H, CH_2S), 5.10-5.40 (m, 4H, CH_2=CH), 5.60-5.90 (m, 2H, CH_2=CH), 7.17-7.70 (m, 5H, Ph), 8.00 (s broad, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 40.8 (CH_2S), 41.5 (CH_2S), 119.5 (CH_2=CH), 135.2 (CH_2=CH), 110.0 (C4), 118.7, 125.1, 129.1, 137.0 (Ph), 158.7 (C5=O), 163.6 (C3=O), 182.0 (CS_2).

Anal. Calcd. for $C_{16}H_{16}N_2O_2S_2$: C, 57.80; H, 4.85; N, 8.43; S, 19.29. Found: C, 57.86; H, 4.90; N, 8.45; S, 19.31.

4-Bis(benzylthio)methylene-1-phenyl-3,5-dioxopyrazolidine (3f).

This compound was obtained in 20% yield as a red-orange, amorphous powder, mp 198.5-199.0°; ir: ν C=O 1649; ^1H nmr (dimethyl sulfoxide-d_6): δ 4.58 (CH_2S), 4.60 (CH_2S), 7.27-7.80 (m, 5H, N-Ph), 7.38 (s, 10 H, Ph), 10.98 (s broad, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 40.9 (CH_2S), 41.3 (CH_2S), 111.6 (C4), 118.5, 124.4, 129.2, 137.2 (N-Ph), 127.7, 128.5, 128.7, 135.3 (Ph), 158.4 (C5=O), 164.0 (C3=O), 182.0 (CS_2).

Anal. Calcd. for $C_{24}H_{20}N_2O_2S_2$: C, 66.63; H, 4.66; N, 6.48; S, 14.83. Found. C, 66.57; H, 4.62; N, 6.50; S, 14.75.

4-(2,5-Dithiacyclopentylidene)-1-phenyl-3,5-dioxopyrazolidine (3g).

This compound was obtained in 62% yield as a yellow, granular solid, mp 252.0-253.0°; ir: ν C=O 1656; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.74 (s, 4H, S-CH_2-CH_2-S), 7.24-7.80 (m, 5H, Ph), 10.88 (s broad, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 37.6 (S-CH_2-CH_2-S), 105.3 (C4), 118.0, 124.1, 128.7, 137.2 (Ph), 159.5 (C5=O), 163.0 (C3=O), 179.8 (CS_2).

Anal. Calcd. for $C_{12}H_{10}N_2O_2S_2$: C, 51.77; H, 3.62; N, 10.07; S, 23.04. Found: C, 51.70; H, 3.69; N, 10.10; S, 23.08.

4-(2,6-Dithiacyclohexylidene)-1-phenyl-3,5-dioxopirazolidine (3h).

This compound was obtained in 85% yield as a yellow, granular solid, mp 253.0-254.0°; ir: ν C=O 1639; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.24 (t, 2H, S-CH_2-CH_2-CH_2-S), 3.15 (t, 4H, S-CH_2-CH_2-CH_2-S), 7.10-7.70 (m, 5H, Ph), 10.36 (s broad, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 21.4 (S-CH_2-CH_2-CH_2-S), 27.8 (S-CH_2-CH_2-CH_2-S), 108.5 (C4), 118.1, 123.8, 128.5, 137.5 (Ph), 159.5 (C5=O), 163.2 (C3=O), 178.0 (CS_2).

Anal. Calcd. for $C_{13}H_{12}N_2O_2S_2$: C, 53.40; H, 4.14; N, 9.58; S, 21.94. Found: C, 53.39; H, 4.10; N, 9.55; S, 21.90.

N-Methyl-4-bis(methylthio)methylene-1-phenyl-3,5-dioxopyrazolidine (4).

This compound was obtained in 82% yield as a yellow, granular solid, mp 141.0-142.0°; ir ν C=O 1672; ^1H nmr (deuteriochloroform): δ 2.72 (s, 3H, CH_3S), 2.73 (s, 3H, CH_3S), 3.13 (s, 3H, CH_3N), 7.26-7.50 (m, 5H, Ph); ^{13}C nmr (deuteriochloroform): δ 21.1 (CH_3S), 21.3 (CH_3S), 33.4 (CH_3N), 108.0 (C4), 123.0, 126.4, 129.0, 136.6 (Ph), 160.9 (C5=O), 164.2 (C3=O), 185.4 (CS_2).

Anal. Calcd. for: $C_{13}H_{14}N_2O_2S_2$: C, 53.03; H, 4.79; N, 9.52; S, 21.79. Found: C, 53.07; H, 4.83; N, 9.62; S, 21.82.

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