Synthesis of Bisalkylthiolydine Derivatives of Meldrum's Acid and Barbituric Acid

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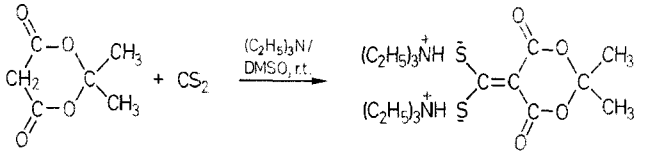
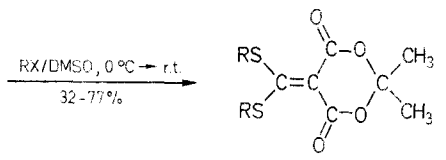
Meldrum's acid and barbituric acid were condensed with carbon disulfide in the presence of triethylamine and subsequently alkylated with alkyl halides to give the corresponding bisalkylthioylidene derivatives.

Bisalkylthioylidene derivatives of active methylene compounds have found useful applications in organic synthesis[1]. Isopropylidene malonate (**1**, Meldrum's acid) has high acidity (pka = 4.97) and a rigid cyclic structure. It has served as starting material for several synthetic manipulations[2–6]. However, there is no report on the preparation of bisalkylthioylidene derivatives **3** of Meldrum's acid. We report here the synthesis of this new type of compounds by condensation of isopropylidene malonate (**1**) with carbon disulfide under base catalysis followed by alkylation with alkyl halides. Aqueous solution of bases such as sodium hydroxide and potassium carbonate cause easy hydrolysis of Meldrum's acid and no required reaction took place. Due to the high acidity of **1**, we decided to use triethylamine as the base and allowed the reaction to take place under anhydrous condition. A dipolar aprotic solvent such as dimethyl sulfoxide or dimethyl formamide was used to increase the nucleophilic ability of the salt of bishydrothioylidene derivative **2**.



1 **2**

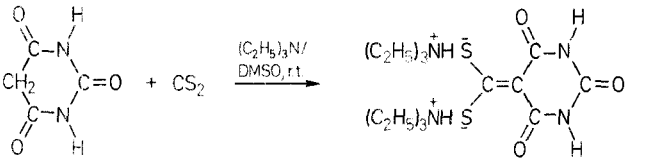


3a-e

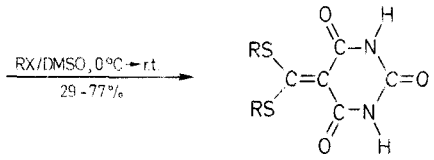
3	R or R_2
a	CH_3
b	C_2H_5
c	$C_6H_5CH_2$
d	$-(CH_2)_2-$
e	$-(CH_2)_3-$

The results obtained (Table 1) show that this procedure is a general one for the synthesis of isopropylidene bisalkylthioylidene malonates **3**. The advantages of this method are the manipulative convenience, mild condition and good yield. Similarly, barbituric acid (**4**), whose structure resembles closely to Meldrum's acid, also gave good results (Table 2).

This method is superior to the previous report[7] in which 5-(1',3'-dithiolan-2'-ylidene)barbituric acid (**6c**) was obtained in 46% yield by the reaction of dibromoethane with the difficultily obtainable sodium salt of bishydrothioylidenebarbituric acid for 17 h.



4 **5**



6a-d

6	R or R_2
a	CH_3
b	C_2H_5
c	$-(CH_2)_2-$
d	$-(CH_2)_3-$

Table 1. Isopropylidene Bisalkylthioylidene Malonates **3** Prepared

Product No.	Reaction Conditions Time [h]/Solvent	Yield [%]	m.p. [°C]	Molecular Formula[a]
3a	14/DMSO	53	119–121	$C_9H_{12}O_4S_2$ (248.3)
	14/DMF	32		
3b	4/DMF	51	66–68	$C_{11}H_{16}O_4S_2$ (276.4)
3c	8/DMSO	45	117–118	$C_{21}H_{20}O_4S_2$ (400.5)
3d	4/DMSO	77	236–237	$C_9H_{10}O_4S_2$ (246.3)
3e	4/DMSO	67	191–192	$C_{10}H_{12}O_4S_2$ (260.3)

[a] Satisfactory microanalysis obtained: C ±0.40, H ±0.37.

Table 2. Bisalkylthioylidene Barbituric Acids **6** Prepared

Product No.	Reaction Conditions Time [h]/Solvent	Yield [%]	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]
6a	4/DMSO	29	300	$C_7H_8N_2O_3S_2$ (232.3)
6b	4/DMSO	42	222–223	$C_9H_{12}N_2O_3S_2$ (260.3)
6c	4/DMSO	77	>340	>340[7]
6d	4/DMSO	72	>340	>340[7]

[a] Satisfactory microanalysis obtained: C ±0.35, H ±0.37, N ±0.39.

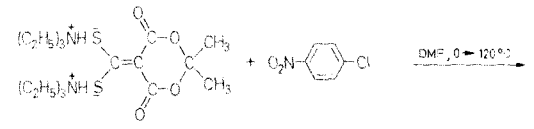
The structures of all the products were confirmed by their microanalysis and IR, ^{1}H-NMR spectra (Table 3).

When *p*-nitrochlorobenzene was used as the alkylating reagent, no expected product with the structure **3** was obtained, instead di-*p*-nitrophenylsulfide (**7**) was isolated in 60% yield. A probable mechanism is given below.

Table 3. Spectral Data of Compounds **3** and **6**

Compound	I.R. (KBr) ν[cm^{-1}]	^{1}H-NMR[a] δ[ppm]
3a	1728, 1690, 1410, 1040, 955, 720	1.72 (s, 6H); 2.60 (s, 6H)
3b	1745, 1710, 1415, 1035, 955, 710	1.28 (t, 6H, J = 7.2 Hz); 1.66 (s, 6H); 3.04 (q, 4H, J = 7.2 Hz)
3c	1715, 1700, 1415, 1030, 955, 710	1.64 (s, 6H); 4.26 (s, 4H); 7.22 (s, 10H)
3d	1720, 1690, 1425, 1040, 960, 725	1.68 (s, 6H); 3.48 (s, 4H)
3e	1720, 1700, 1405, 1040, 960, 725	1.68 (s, 6H); 2.35 (m, 2H); 3.01 (t, 4H, J = 7.2 Hz)
6a	3300–3040, 1750, 1675, 1650, 1415, 1060, 920, 785, 765	2.52 (s, 6H); 10.91 (s, 2H)
6b	3200–3030, 1765, 1675, 1650, 1440, 1060, 920, 780, 755	1.14 (t, 6H, J = 7.0 Hz); 3.00 (q, 4H, J = 7.0 Hz); 10.91 (s, 2H)
6c	3200–3030, 1740, 1680, 1640, 1430, 1055, 920, 790, 755	3.36 (s, 4H); 11.06 (s, 2H)
6d	3200–3040, 1750, 1685, 1640, 1430, 1060, 920, 795, 755	2.16 (m, 2H); 2.91 (t, 4H, J = 7.1 Hz); 10.91 (s, 2H)

[a] **3a–e** in $CDCl_3$/TMS, **6a–d** in DMSO-d_6/TMS.



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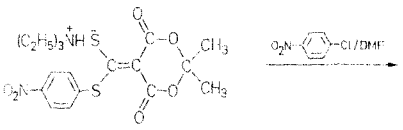

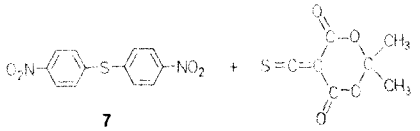

7

Isopropylidene Bismethylthioylidene Malonates 3; Typical Procedure:
To a well stirred solution of Meldrum's acid (**1**; 1.4 g, 10 mmol), are added triethylamine (2.8 ml, 20 mmol) and carbon disulfide (0.6 ml, 10 mmol) in succession. The mixture is stirred for 1 h at room temperature, cooled in an ice-bath and methyl iodide (1.3 ml, 20 mmol) is added. The mixture is stirred for 4 h at room temperature. Ice water (30 ml) is added to precipitate out the solid product, which is recrystallized from tetrahydrofuran petroleum ether (60–90 °C) to give pure isopropylidene bismethylthioylidene malonate (**3a**); yield: 1.3 g (51%); m.p. 119–121 °C.

Cyclohexydidene Barbituric Acid (6d); Typical Procedure:
To a well stirred solution of barbituric acid (**4**; 1.3 g, 10 mmol) in dimethyl sulfoxide (5 ml) are added, triethylamine (2.8 ml, 20 mmol) and carbon disulfide (0.6 ml, 10 mmol) in succession. The mixture is stirred for 1 h at room temperature and then 1,3-dibromopropane (1.0 ml, 10 mmol) in dimethyl sulfoxide (5 ml) is added. The stirring is continued for 4 h at room temperature. Ice water (60 ml) is added to give a solid which is recrystallied from dimethylformamide to afford the pure product **6d**; yield: 1.8 g (72%); m.p. > 340 °C (Lit.[7], m.p. > 340 °C).

Di-*p*-nitrophenylsulfide:
To a well stirred solution of Meldrum's acid (**1**; 1.4 g, 10 mmol) in dimethylformamide (5 ml), triethylamine (2.8 ml, 20 mmol) and carbon disulfide (0.6 ml, 10 mmol) are added in succession. The mixture is stirred for 1 h at room temperature and *p*-nitrochlorobenzene (2.9 g, 20 mmol) in dimethylformamide (5 ml) is added. The mixture is heated to 120 °C in a period of 45 min. Water (60 ml) is added to precipitate the crude product, which is recrystallized from benzene/petroleum ether (60–90 °C) to give pure di-*p*-nitrophenylsulfide (**7**); yield: 2.5 g (60%); m.p. 158–160 °C (Lit.[8], m.p. 160–161 °C).

$C_{12}H_8N_2O_4S$ (276.3)	calc.	C 52.17	H 2.92	N 10.14
	found	51.96	2.87	10.06

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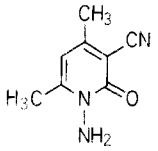
[1] Yokoyama, M., Imamoto, T. *Synthesis* **1984**, 797.
[2] McNab, H. *Chem. Soc. Rev.* **1978**, 345.
[3] Chen, C.C., Huang, X. *Synthesis* **1982**, 452.
[4] Huang, X., Chen, C.C., Wu, Q.L. *Tetrahedron Lett.* **1982**, *23*, 75.
[5] Wu, Q.L., Chen, C.C., Huang, X. *Org. Chem. (Yaogi Huaxue)* **1983**, 189.
[6] Chen, C.C., Huang, X. *Synthesis* **1984**, 244.
[7] Jensen, K.A., Henriksen, L. *Acta Chem. Scand.* **1968**, *22*, 1107.
[8] Price, C.C., Stacy, G.W. *J. Am. Chem. Soc.* **1946**, *68*, 489.

H. Herzog, H.D. Scharf *Synthesis* **1986**, 788. The heading for the experimental procedure on p. 789 (top, right) should be:
Step E: **(1*R*,2*S*,4*S*)-2-benzyloxybornan-3-one (8):**

A.N. Pudovick, I.V. Konovalova, L.A. Burnaeva *Synthesis* **1986**, 793. The text starting in line 2 on page 798 (top, right) should read: leads to 3,3a-dihydro-4*H*-1,2-azaphospholo[5,4-*b*]pyridines **41**[1,63].

R.C. Phadke, D.W. Rangnekar *Synthesis* **1986**, 860. The structure of compound **1** (p. 861) should be:



B. Byrne, K.J. Wengenroth *Synthesis* **1986**, 870. The heading for the first experimental procedure should be:
2-(1-Bromoethyl)-2-ethyl-1,3-dioxolane (1):

S. Torii *Synthesis* **1986**, 873. The heading for the experimental procedure on p. 882 should be:
Electrosynthesis of 1-Benzyl-6,9-dimethyl-2,5-dioxo-8-tosylamino-1,2,3,4,5,6-hexahydro-1-benzazocine (81):

N.G. Bushmakina, A.Y. Misharan *Synthesis* **1986**, 966. The heading for the first experimental procedure should be:
2,2,6,6-Tetramethyl-4-methylsulfonyloxy-1-piperidinyloxy Radical (3):

X. Huang, B.C. Chen *Synthesis* **1986**, 967. The title should be:
Synthesis of Bis(alkylthio)methylene Derivatives of Meldrum's Acid and Barbituric Acid
Throughout the paper the expression "bisalkylthioylide" should be replaced by "bis(alkylthio)methylene".
The heading for the second experimental procedure should be:
5-(1,3-Dithian-2-ylidene)barbituric Acid (6d); Typical Procedure: