Synthesis of 2-Substituted 5-(1,3-Dithiolan-2-ylidene)-1,3-dioxane-4,6-dione Derivatives

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Some 2-substituted 5-(1,3-dithiolan-2-ylidene)-1,3-dioxane-4,6-dione derivatives **3** were prepared from the condensation reaction of 1,3-dithiolan-2-ylidenemalonic acid (**2**) with carbonyl compounds in 40-93% yields.

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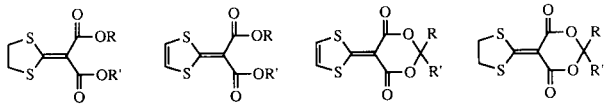
Bisalkylthioylidene derivatives of active methylene compounds have found useful applications in organic synthesis [1,2]. 1,3-Dithiolane derivatives such as **A** have attracted much interests because of their fungicidal activity [3-6]. For example, diisopropyl 1,3-dithiolan-2-ylidenemalonate [5] has been developed as fungicide for the control of rice blast and planthoppers [3,6]. Some 1,3-dithiol derivatives of active methylene compounds such as **B** and **C** have exhibited a hepatic protecting activity [7,8]. In spite

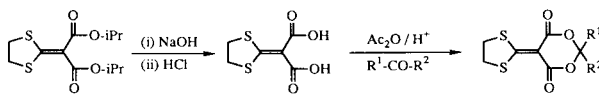


A B C D

of the biological importance of compounds **A-C**, there has been only one report dealing with the synthesis of 2,2-dimethyl 5-(1,3-dithiolan-2-ylidene)-1,3-dioxane-4,6-dione (**D**, R = R′ = Me) from the reaction of isopropylidene malonate (Meldrum's acid) with carbon disulfide followed by alkylation with dibromoethane [9].

Thus, our interest prompted us to develop a general synthetic method of 2-substituted 5-(1,3-dithiolan-2-ylidene)-1,3-dioxane-4,6-dione derivatives **3** by the condensation reaction of 1,3-dithiolan-2-ylidenemalonic acid (**2**) with appropriate carbonyl compounds, as shown in Scheme I.

Scheme I



1 2 3

Product 3	R^1	R^2	Product 3	R^1	R^2
a	Me	Me	**h**	Me	2-ClC_6H_3
b	Me	Et	**i**	Me	2-propargyloxy-C_6H_3
c	Me	-CH_2CH_2COOMe	**j**	Me	2-furyl
d	cyclopropyl	cyclopropyl	**k**	Et	Ph
e	-$CH_2(CH_2)_2CH_2$-		**l**	Et	4-allyloxy-C_6H_3
f	-$CH_2(CH_2)_3CH_2$-		**m**	Ph	Ph
g	Me	Ph			

1,3-Dithiolan-2-ylidenemalonic acid (**2**) was prepared by hydrolysis of the diisopropyl 1,3-dithiolan-2-ylidenemalonate (**1**) in 85% yield. The desired compounds **3** were prepared from the condensation reaction of **2** with carbonyl compounds in acetic anhydride with the aid of an acid catalyst. The structures of all the products were confirmed by their ir, ^{1}H nmr spectra and microanalysis as summarized in Table 1. The results show that this procedure is a general route for the synthesis of 2-substituted 5-(1,3-dithiolan-2-ylidene)-1,3-dioxane-4,6-dione derivatives.

All the compounds thus prepared have interesting biological activities. Most of all, the compounds have significant plant growth regulatory activities toward some root crops such as sugar beet, radish, and ginseng. Such biological activities will be published elsewhere in due course.

EXPERIMENTAL

Melting points were measured with a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded with a Varian FT-80A NMR spectrometer. Tetramethylsilane served as the internal standard. Infrared spectra were recorded on a Perkin-Elmer 283 infrared spectrophotometer. Elemental analysis (C and H) were performed with Perkin-Elmer 240C elemental analyzer.

1,3-Dithiolan-2-ylidenemalonic Acid (**2**).

To a stirred solution of diisopropyl 1,3-dithiolan-2-ylidenemalonate (11.6 g, 40 mmoles) in 50 ml of 2-propanol was added a solution of 20 g of sodium hydroxide in 50 ml of water. The mixture was warmed to 30-40° for three hours. The reaction mixture was separated into two layers on standing. The aqueous layer was separated, diluted with 70 ml of water, and then acidified by slow addition of 2 *N* hydrochloric acid to *p*H = 1. The resulted white solid was collected by filtration, washed with water (3 x 30 ml) and ethyl acetate/methanol (10:1, 40 ml), and dried to give pure **2** (7.0 g, 85%), mp 210-212°; ^{1}H nmr (DMSO-d_6 + deuterium oxide): δ 3.40 (s, 4H).

Anal. Calcd. for $C_6H_6O_4S_2$: C, 34.94; H, 2.93. Found: C, 34.74; H, 2.78.

General Procedure for the Synthesis of 2-Substituted 5-(1,3-Dithiolan-2-ylidene)-1,3-dioxane Derivatives **3a-m**.

Table 1

Physical and Analytical Data of Compounds 3a-m

Product	Mp (°C) Recrystallization Solvent [a]	Yield (%)	^{1}H NMR (δ, ppm) [b]	IR (KBr) cm^{-1}	Molecular Formula (MW)	Elemental Analysis (%) (Calcd. / Found) C	H
3a	235-237[c] [A]	88	1.70 (s, 6H), 3.50 (m, 4H) [A]	1700	$C_9H_{10}O_4S_2$ (246.3)	43.90 43.75	4.07 4.05
3b	181-183 [A]	91	1.05(t, 3H), 1.60 (s, 3H), 2.00 (q, 2H), 3.50 (m, 4H), [A]	1700	$C_{10}H_{12}O_4S_2$ (260.3)	46.13 45.94	4.65 4.54
3c	131-133 [A]	75	1.70 (s, 3H), 2.30 (t, 2H), 2.55 (t, 2H), 3.50 (m, 4H), 3.70 (s, 3H) [A]	1700 1760	$C_{12}H_{14}O_6S_2$ (318.4)	45.27 45.13	4.43 4.30
3d	186-188 [G]	60	0.50-0.70 (m, 8H), 1.20-1.60 (m, 2H), 3.50 (m, 4H) [B]	1700	$C_{13}H_{14}O_4S_2$ (298.4)	52.33 52.21	4.73 4.63
3e	206-208 [A]	93	1.60-2.20 (m, 8H), 3.60 (m, 4H) [B]	1700	$C_{11}H_{12}O_4S_2$ (272.3)	48.51 48.57	4.44 4.37
3f	245-247 [A]	88	1.20-2.00 (m, 10H), 3.50 (m, 4H) [B]	1700	$C_{12}H_{14}O_4S_2$ (286.4)	50.33 50.08	4.92 4.69
3g	243-245 [F]	40	1.80 (s, 3H), 3.40 (m, 4H), 7.20-7.60 (m, 5H) [A]	1700	$C_{14}H_{12}O_4S_2$ (308.4)	54.52 54.70	3.93 4.03
3h	239-241 [D]	76	2.00 (s, 3H), 3.50 (m, 4H), 7.20-7.40 (m, 4H) [B]	1700	$C_{14}H_{11}ClO_4S_2$ (342.8)	49.05 48.98	3.23 3.16
3i	199-201 [A]	66	1.90 (s, 3H), 3.40 (m, 1H), 3.50 (s, 4H), 4.70 (d, 2H), 6.70-7.40 (m, 4H) [B]	1690 2100	$C_{17}H_{14}O_5S_2$ (362.4)	56.34 56.05	3.90 3.86
3j	205-207 [B]	69	2.00 (s, 3H), 3.50 (m, 4H), 6.20-6.30 (m, 2H), 7.30 (d, 1H) [A]	1710	$C_{12}H_{10}O_5S_2$ (298.3)	48.31 47.94	3.38 3.40
3k	208-210 [D]	83	0.95 (t, 3H), 2.15 (q, 2H), 3.40 (m, 4H), 7.20-7.40 (m, 5H) [A]	1700	$C_{15}H_{14}O_4S_2$ (322.4)	55.88 55.83	4.38 4.36
3l	176-178 [C]	55	1.10 (t, 3H), 2.10 (q, 2H), 3.40 (m, 4H), 4.50-4.70 (m, 2H), 5.20-5.60 (m, 2H), 6.00-6.20 (m, 1H), 6.70-7.40 (m, 4H) [A]	1710	$C_{18}H_{18}O_5S_2$ (378.4)	57.12 56.76	4.79 4.72
3m	259-261 [E]	86	3.50 (m, 4H), 7.40 (s, 10H) [B]	1720	$C_{19}H_{14}O_4S_2$ (370.4)	61.60 61.34	3.81 3.74

[a] Recrystallization Solvent: [A] acetone / water, 3:1, [B] acetone / water, 4:1, [C] acetone / water, 5:1, [D] acetone / water, 2:1, [E] acetone / water, 3:2, [F] chloroform, [G] column separation (hexane / chloroform, 15:1). [b] Solvent: [A] deuteriochloroform, [B] DMSO-d_6. [c] lit [4] mp 236-237 °C.

The following procedure for the synthesis of 2-methyl-2-phenyl 5-(1,3-dithiolan-2-ylidene)-1,3-dioxane-4,6-dione (**3g**) is representative; the other compounds **3a-f** and **3h-m** were obtained similarly.

2-Methyl-2-phenyl-5-(1,3-dithiolan-2-ylidene)-1,3-dioxane-4,6-dione (**3g**).

To a vigorously stirred mixture of 1,3-dithiolan-2-ylidenemalonic acid (5.0 g, 24 mmoles) and acetic anhydride (4.8 g, 47 mmoles) was treated with 0.3 ml of concentrated sulfuric acid at ambient temperature. The reaction mixture was stirred vigorously for 10 minutes during which time the mixture became a reddish color. To the reaction mixture was added acetopheneone (6.0 g, 50 mmoles) and stirred for 8 hours at room temperature. The reaction mixture was diluted with 30 ml of 2 parts of acetone and one part of water with stirring. The precipitate was filtered, washed with acetone/chloroform (3:1, 30 ml), and dried to give the desired **3g** as a white solid. Purification by recrystallization from chloroform gave analytically pure **3g** (2.96 g, 40%).

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