Heteroatom Chemistry
Volume 14, Number 4, 2003

3-Methylthio-pyrano[4,3-*c*]pyrazol-4(2*H*)-ones from 3-(Bis-methylthio)methylene-2*H*-pyran-2,4-diones and Hydrazines

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Received 13 December 2002; revised 10 February 2003

ABSTRACT: *A useful synthesis of 3-methylthio-6-methyl-pyrano[4,3-c]pyrazol-4(2H)-ones via 3-(bis-methylthio)methylene-5,6-dihydro-6-alkyl(aryl)-2H-pyran-2,4-dione with hydrazine as well as methyl and phenyl hydrazines is described and the mechanism of the formation is discussed.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:342–344, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10158

INTRODUCTION

Being a structural subunit in numerous natural bioactivited products, pyrone exhibits a broad range of biological activity [1]. In addition, it is a useful intermediate in the synthesis of a variety of important heterocyclic molecules, which exhibit antimicrobial, antifungal, antiviral, or phytotoxic activity [2–4]. It is reported that β-keto-δ-valerolactone derivatives inhibit the activity of HIV proteases [5–7]. Recently we have reported that 3-anilinomethylene-5,6-dihydro-6-alkyl(aryl)-2*H*-pyran-2,4-diones have interesting fungicidal, tobacco virucidal activities [8–9].

As part of our program aimed at developing a new class of pesticides, we have been interested in synthesizing nitrogen heterocyclic compounds such as isothiazoles and pyrazoles because nitrogen heterocycles play an important role among useful herbicides [10]. Combining β-keto-δ-valerolactone and pyrazole, we expect to find better lead compounds of herbicides. With these considerations in mind, we synthesized substituted pyrano[4,3-*c*]pyrazol-4(2*H*)-ones.

RESULTS AND DISCUSSION

6-Methyl-5,6-dihydro-2*H*-pyran-2,4-dione (**1a**) was prepared from dehydroacetic acid in two steps [8]. 6-Methyl-6-benzyl and 6-methyl-6-piperonyl-5,6-dihydro-2*H*-pyran-2,4-dione (**1b,c**) were prepared as described [8]. It is generally believed that 6-alkyl(aryl)-5,6-dihydro-2*H*-pyran-2,4-diones react with carbon disulfide and methyl iodide to give low yields of 3-(bis-methylthio)methylene-5,6-dihydro-6-alkyl(aryl)-2*H*-pyran-2,4-diones (38%) [11]. We found that **1a–c** react with carbon disulfide in the presence of weak base such as anhydrous potassium carbonate and methyl iodide to give compounds

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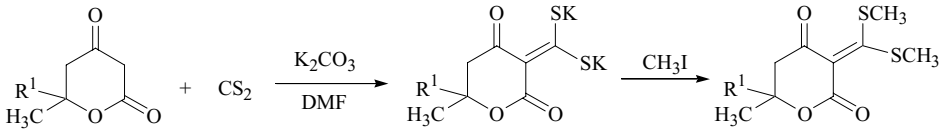
Contract grant number: NNSFC 29832050.



1a R^1=H;

1b R^1=$PhCH_2$;

1c R^1 =

2a-c

SCHEME 1

2a–c in reasonable yield (70%) (Scheme 1). Butyl bromide and phenyl iodide did not give analogous compounds.

3-Methylthio-6-methyl-pyrano[4,3-*c*]pyrazol-4(2*H*)-ones **4a–h** were synthesized by the process described in Scheme 2. Generally, the reactions proceeded quickly with excellent yields as shown in Table 1. However, for the coupling reaction with phenylhydrazine at room temperature, 3 h were needed (monitored by TLC).

Interestingly, although the reaction of **1c** with 2,4-dinitrophenylhydrazine failed to gain a compound **4**, we successfully separated an oily substance. ^{1}H NMR ($CDCl_3$): 1.49 (s, 3H, CH_3), 2.54 (s, 2H, CH_2), 2.84 (s, 6H, $2CH_3$), 2.94 (dd, 2H, J = 6.8 Hz, CH_2), 5.92 (s, 2H, CH_2), 6.70 (m, 3H), 7.92 (m, 3H), 11.68 (s, 1H, NH), and (EI) m/z = 546) of the compound show it is an uncyclized product **3** (R^1 = piperonyl, R^2 = 2,4-dinitrophenyl). The results indicated that the formation of the transition state **3** is reasonable.

EXPERIMENTAL

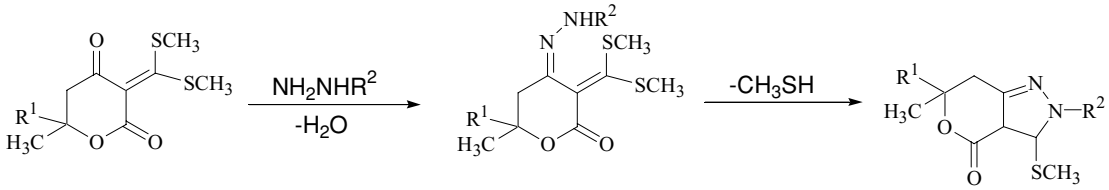
Melting points were conducted on a Yanaco MP-500 micromelting point apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ as solvent on AC-200 instrument, using TMS as internal standard. Elemental analyses were performed on MF-3 automatic elemental analyzer.

6-Methyl-5,6-dihydro-3-(bis-methylthio)-methylene-2H-pyran-2,4-diones **2a–c**

2a: Compound **1a** (1.28 g, 0.01 mol) was dissolved in 20 ml DMF. With constant agitation, 3.18 g (0.03 mol) of potassium carbonate anhydrous was added in portions to the mixture, which was agitated for 0.5 h at room temperature. The mixture was cooled to 0°C and 0.76 g (0.01 mol) carbon disulfide was added dropwise. After the addition, the reaction mixture was agitated for 0.5 h at 0°C, and then 2.84 g (0.02 mol) methyl iodide was added dropwise at 0°C. The brown suspension was agitated for 4 h. The suspension was poured into 200 ml ice-cooled water and extracted with 100 ml dichloromethane twice. The organic phase was separated and dried over magnesium sulfate. After the filtration, the solvent was evaporated in a vacuum. The crude product was purified with silicon gel column using ethyl acetate/petroleum ether (v/v, 1:3) as eluent and **2a** was obtained. Yield: 70.0%. mp 148–149°C. ^{1}H NMR ($CDCl_3$): 1.40 (d, 3H, J = 6.8, CH_3), 2.56 (m, 2H, CH_2), 3.70 (s, 6H, SCH_3), 4.45 (m, 1H, CH).

2b: Following the above method and using 2.18 g **1b**, 2.07 g **2b** was obtained. Yield: 64.3%. mp 112–113°C. ^{1}H NMR ($CDCl_3$): 1.40 (s, 3H, CH_3), 2.53 (s, 6H, SCH_3), 2.64 (s, 2H, CH_2), 2.97 (dd, 2H, J = 6.8, CH_2), 7.23 (m, 5H).

2c: Following the above method and using 2.62 g **1c**, 2.49 g **2c** was obtained. Yield: 68.2%. mp



2a-c **3** **4a-h**

SCHEME 2

TABLE 1 Data and Elemental Analyses of Compounds **4**

					Elemental Analysis (Calcd)		
	R^1	R^2	Yield (%)	mp (°C)	C	H	N
4a	H	CH_3	98.1	102–103	50.90 (50.94)	5.72 (5.66)	13.20 (13.20)
4b	H	Ph	94.3	167–169	61.20 (61.30)	5.12 (5.11)	10.18 (10.22)
4c	$PhCH_2$	H	68.7	145–146	62.55 (62.50)	5.54 (5.56)	10.00 (9.72)
4d	$PhCH_2$	CH_3	63.2	oil	63.60 (63.58)	6.02 (5.96)	9.20 (9.27)
4e	$PhCH_2$	Ph	73.5	140–141	69.08 (69.23)	5.54 (5.49)	7.69 (7.69)
4f	$CH_2O_2C_6H_3CH_2$	H	88.3	165–166	57.90 (57.83)	5.06 (4.82)	8.32 (8.43)
4g	$CH_2O_2C_6H_3CH_2$	CH_3	80.2	140–141	58.79 (58.96)	5.19 (5.20)	7.90 (8.09)
4h	$CH_2O_2C_6H_3CH_2$	Ph	85.6	169–170	64.75 (64.70)	4.93 (4.90)	6.82 (6.86)

129–131°C. ^{1}H NMR ($CDCl_3$): 1.39 (s, 3H, CH_3), 2.53 (s, 6H, SCH_3), 2.64 (s, 2H, CH_2), 2.93 (dd, 2H, $J = 6.8$, CH_2), 5.91 (s, 2H, CH_2), 6.70 (m, 3H).

3-Methylthio-6-methyl-5,6-dihydro-2H-pyrano[4,3-c]pyrazole-4(2H)-ones **4a–h**

4a: Methylhydrazine (0.28 g, 0.006 mol) was added dropwise to a mixture of 1.16 g (0.005 mol) **2a** in 30 ml ethanol. After agitation for 1 h at room temperature, the solvent was evaporated in vacuum and gave 1.03 g **4a**, which was purified with silicon gel column using ethyl acetate/petroleum ether (1:2) as eluent. ^{1}H NMR ($CDCl_3$): 1.49 (d, 3H, $J = 6.4$, CH_3), 2.57 (s, 3H, SCH_3), 2.85 (m, 2H, CH_2), 3.87 (s, 3H, NCH_3), 4.70 (m, 1H, CH).

4b: Following the above method and using 1.16 g **2a** and 0.65 g phenylhydrazine, 1.3 g **4b** was obtained. ^{1}H NMR ($CDCl_3$): 1.53 (d, 3H, $J = 6.2$, CH_3), 2.61 (s, 3H, SCH_3), 2.97 (m, 2H, CH_2), 4.65 (m, 1H), 7.44 (m, 5H).

4c: Following the above method and using 1.61 g **2b** and 0.3 g 85% hydrazine hydrate solution, 0.97 g **4c** was obtained. ^{1}H NMR ($CDCl_3$): 1.48 (s, 3H, CH_3), 2.68 (s, 3H, SCH_3), 2.94 (s, 2H, CH_2), 3.08 (dd, 2H, $J = 7.0$, CH_2), 7.20 (m, 5H), 8.18 (bs, 1H, NH).

4d: Following the above method and using 1.61 g **2b** and 0.28 g methylhydrazine, 0.95 g **4d** was obtained. ^{1}H NMR ($CDCl_3$): 1.43 (s, 3H, CH_3), 2.62 (s, 3H, SCH_3), 2.86 (s, 2H, CH_2), 3.02 (dd, 2H, $J = 5.6$, CH_2), 3.92 (s, 3H, NCH_3), 7.24 (m, 5H).

4e: Following the above method and using 1.61 g **2b** and 0.65 g phenylhydrazine, 1.32 g **4e** was obtained. ^{1}H NMR ($CDCl_3$): 1.46 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 2.95 (s, 2H, CH_2), 3.03 (dd, 2H, $J = 8.0$, CH_2), 7.16 (m, 5H), 7.45 (m, 5H).

4f: Following the above method and using 1.83 g **2c** and 0.3 g 85% hydrazine hydrate solution, 1.46 g **4f** was obtained. ^{1}H NMR ($CDCl_3$): 1.51 (s, 3H, CH_3), 2.56 (s, 3H, SCH_3), 2.90 (s, 2H, CH_2), 3.09 (dd, 2H, $J = 8.2$, CH_2), 5.90 (s, 2H, CH_2), 6.65 (m, 3H), 8.38 (bs, 1H, NH).

4g: Following the above method and using 1.83 g **2c** and 0.28 g methylhydrazine, 1.38 g **4g** was obtained. ^{1}H NMR ($CDCl_3$): 1.43 (s, 3H, CH_3), 2.52 (s, 3H, SCH_3), 2.85 (s, 2H, CH_2), 2.89 (dd, 2H, $J = 8.0$, CH_2), 3.72 (s, 3H, NCH_3), 5.89 (s, 2H, CH_2), 6.63 (m, 3H).

4h: Following the above method and using 1.83 g **2c** and 0.65 g phenylhydrazine, 1.73 g **4h** was obtained. ^{1}H NMR ($CDCl_3$): 1.46 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 2.88 (s, 2H, CH_2), 2.97 (dd, 2H, $J = 8.2$, CH_2), 5.88 (s, 2H, CH_2), 6.61 (m, 3H), 7.45 (m, 5H).

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