Asian Journal of Chemistry Vol. 16, No. 2 (2004), 805–810

Synthesis of Novel 2,3-Dihydro-2,3-furandione and 1*H*-Pyrazole-3-Carboxylic Acid Derivatives

SEVKET HAKAN UNGOREN*, BAYRAM DENİZ† and BEHZAT ALTURAL†
Department of Chemistry, Erciyes University, 66200 Yozgat, Turkey
E-mail: hungoren@erciyes.edu.tr; Fax: 00 90 354 2421022

The reaction of oxalyl chloride with unsymmetricallly substituted diketones (**1a–e**) furnished the corresponding 2,3-dihydro-2,3-furandiones (**2a–e**). In addition, 1*H*-phrazole-3-carboxylic acids (**5c–e**) were synthesized by the reaction of (**2c–e**) with phenylhydrazine and 1,5-diphenylcarbazide.

Key Words: 2,3-Dihydro-2,3-furandione, 1*H*-Pyrazole-3-carboxylic acid, Michael-type addition, Cyclocondensation.

INTRODUCTION

Earlier 4-acyl-5-alkyl/aryl-2,3-dihydro-2,3-furandiones were obtained starting from 1,3-dicarbonyl compounds with oxalyl halides[1]. Recently, the reactions of thermolysis of cyclic oxalyl compounds have been reported to give substituted heterocyclic compounds[1d]. The reactions of substituted 2,3-dihydro-2,3-furandiones with various dienophiles or nucleophiles in different solvents and at various temperatures have also been studied[2]. These vicinal-dione compounds have been used as a starting material in the synthesis of the target heterocycles.

Pyrazole derivatives continue to attract interest due to a wide spectrum of biological activities. Some pyrazoles have been reported to possess significant anti-microbial, anti-viral, anti-tumor, anti-inflammatory, anti-histaminic, pesticidal, anti-fungal activites[3]. Recyclization reactions of 2,3-dihydro-2,3-furandiones with hydrazines are reported[4].

In the present work, the synthesis of 2,3-dihydro-2,3-furandiones (**2a–e**) and reactions of **2a–c** with different nucleophiles for the synthesis of pyrazole derivatives of potential pharmacological activity has been studied.

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agent and distilled before use. All melting points are uncorrected and were measured on a Buchi 510 apparatus. IR spectra: Shimadzu 435 V-04 IR-spectrophotometer ^{1}H and ^{13}C NMR spectra: Gemini-Varian, 200 MHz, TMS as internal standard (δ in ppm);

†Department of Chemistry, Erciyes University, 38039 Kayseri, Turkey.

elemental analyses: Carlo-Erba 1108 elemental analyzer. The results of the analyses were in good agreement with the calculated values.

1,5-Di-(4-methoxyphenyl)-4-penten-1,3-dione (1b)

To a solution of 1,5-di-(4-methoxyphenyl)-4,5-dibromo-l-penten-3-one (10 g, 22 mmol) in methanol (100 mL) was added $NaOCH_3$, which was formed by dissolving small pieces of sodium (1.01 g, 44 mmol) in dry methanole (12 mL), stirred for 1 h at 50°C. After the solution cooled to the room temperature, concentrated HCl was added until pH was maintained at about 1. The mixture was kept in a refrigerator for 2 h, filtered, washed with water, recrystallized from methanol and dried to give **1e**, as yellow crsytals yield 2.59 g (38%), m.p.: 157–159 °C; IR (cm^{-1}) (KBr): 3400 ν(broad, OHenol), 1630 ν(C=O); ^1H NMR (DMSO, δ): 8.20–6.46 (m, 11H, =CH), 3.92 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.22 (s, 2H, CH_2), ^{13}C NMR (DMSO, δ): 189.70, 180.34 (C=O), 163.5–96.0 (C=C), 56.7, 56.7 (OCH_3). Elemental analysis: found (calcd.): [C=73.56 (73.54), H= 5.77 (5.81)].

Reaction of dicabonyl compounds (1a-e) with oxalyl dichloride: General procedure

5 mmol of **1a–e** was dissolved in 30 mL of dry diethyl ether, 5 mmol of oxalyl chloride was added and the mixture was kept at 5°C for 24 h. The precipitate was filtered off and washed with dry diethyl ether/*n*-hexane (1 : 1) several times for **2a–e**. Exposure to light was avoided for **2c–e**.

4-Benzoyl-5-[(E)-2-phenyl-l-ethenyl]-2,3-dihydro-2,3-furandione (2a)

2a was prepared from **1a** and oxalyl chloride; yield: 1.22 g (80%); scarlet crystals; m.p.: 163–166°C; IR (cm^{-1}) (KBr): 1820, 1700, 1640 ν(C=O); ^1H NMR ($CDCl_3$, δ): 8.15–8.07 (d, 1H, =CH, *trans*), 7.82–7.78 (m, 10H, ArH), 7.78, 7.27 (d, 1H, =CH, trans); ^{13}C NMR ($CDCl_3$, δ): 188.82, 181.03, 155.10 (C=O), 175.1, 150.2, 138.2, 135.2, 135.1, 134.7, 131.5, 130.9, 130.8, 129.8, 116.7, 114.9 (=C, phenyl). Elemental analysis: found (calcd.): [C = 74.71 (75.00), H = 3.93 (3.94)].

4-(4-Methoxybenzoyl)-5-[(E)-2-(4-methoxyphenyl)-1-ethenyl]-2,3-dihydro-2,3-furandione (2b)

2b was prepared from **1b** and oxalyl chloride; yield: 1.51 g (83%); dark blue crystals; m.p.: 201–205°C; IR (cm^{-1}) (KBr): 1810, 1660, 1630 ν(C=O); ^1H NMR ($CDCl_3$, δ): 8.120, 8.043 (d, 1H, =CH, *trans*), 7.838–7.264 (m, 8H, ArH), 7.004, 6.942 (d, 1H, =CH, *trans*), 3.901, 3.858 (s, 6H, OCH_3); ^{13}C NMR ($CDCl_3$, δ): 188.028, 181.598, 157.814 (C=O), 175.357, 166.268, 150.728, 150.653, 134.718, 134.186, 131.875, 128.863, 117.178, 116.944, 115.743, 112.908 (=C, Arom.), 57.705, 57.540 (OCH_3). Elemental analysis: found (calcd.): [C = 69.09 (69.23), H = 4.32 (4.40)].

4-Acetyl-5-(4-methylphenyl)-2,3-dihydro-2,3-furandione (2c)

2c was prepared from **1c** and oxalyl chloride; yield: 0.48 g (42%); yellow

crystals: m.p.: 77–80°C; IR (cm^{-1}) (KBr): 1820, 1720, 1685 ν(C=O). Elemental analysis: found (calcd.): [C = 68.15 (67.97), H = 4.35 (4.34)].

4-Acetyl-5-(4-methoxyphenyl)-2,3-dihydro-2,3-furandione (2d)

2d was prepared from **1d** and oxalyl chloride; yield: 0.63 g (51%); yellow crystals; m.p.: 83–85°C; IR (cm^{-1}) (KBr): 1825, 1720, 1660 ν(C=O). Elemental analysis: found (calcd.): [C = 63.64 (63.39), H = 4.07 (4.06)].

4-Acetyl-5-(2-naphthyl)- 2,3-dihydro-2,3-furandione (2e)

2e was prepared from **1e** and oxalyl chloride; yield: 0.52 g (39%); yellow crystals; m.p.: 106–110°C; IR (cm^{-1}) (KBr): 1815, 1710, 1670 ν(C=O). Elemental analysis: found (calcd.): [C = 72.41 (72.29), H = 3.80 (3.76)].

1*H*-pyrazole-3-carboxylic acides (5c–e): General procedure

Method A. To a mixture of **2c–e** (4 mmol) and 25 mL dry ether, phenylhydrazine (0.44 mL, 0.48 g, 4 mmol) in 10 mL dry ether was added dropwise, and the reaction mixture were stirred at 25°C for 5 h. The precipitate was filtered off and recrystallized from ethyl acetate.

Method B. To 1,5-diphenylcarbazide (0.98 g, 4 mmol) in 30 mL of benzene at 25°C **2c–e** (4 mmol) was added and the reaction mixture was stirred at 25°C for 24 h. The precipitate was filtered and recrystallized from ethyl acetate.

4-Acetyl-5-(4-methylphenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (5c)

5c was prepared from **2c** and phenylhydrazine (Method A) or 1,5-diphenylcarbazide (Method B). Yield: 0.53 g (42%, Method A), 0.49 g (38%, Method B); colourless crystals; m.p.: 217–219°C; IR (cm^{-1}) (KBr): 3430 ν(OH), 1725–1720 ν(C=O); ^{1}H NMR ($CDCl_3$, δ): 7.356–7.175 (m, 9H, Ar-H), 2.396 (s, 3H, CH_3Ar), 2.093 (s, 3H, CH_3C=O); ^{13}C NMR ($CDCl_3$, δ): 201.059 (Me—C=O), 162.176 (COOH), 151.532 (C-5), 146.146 (C-3), 143.087, 132.080, 132.001, 131.097, 130.860, 130.294, 130.177, 127.925 (Ar-C), 122.627 (C-4), 31.827 (CH_3, Acyl), 23.440 (CH_3, Aryl.). Elemental analysis: found (calcd.): (C = 71.28 (71.25), H = 5.27 (5.00), N = 8.58 (8.75)].

4-Acetyl-5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (5d)

5d was prepared from **2d** and phenylhydrazine (Method A) or 1,5-diphenylcarbazide (Method B). Yield: 0.86 g (64%, Method A), 0.56 g (42%, Method B); colourless crystals; m.p.: 172–174°C: IR (cm^{-1}) (KBr), 3430 ν(OH), 1730–1720 ν(C=O); ^{1}H NMR ($CDCl_3$, δ): 7.361–6.935 (m, 9H, ArH), 3.844 (s, 3H, OCH_3), 2.115 (s, 3H, CH_3C=O), ^{13}C NMR ($CDCl_3$, δ): 201.174 (MeC=O), 163.213 (COOH), 151.405 (C_5), 145.978 (C_3). 162.287, 140.127, 140.086, 133.663, 131.042, 130.860, 130.278, 127.945 (Arom. C), 116.758 (C_4), 57.372 (OCH_3), 31.813 (CH_3, Acyl). [C = 67.85 (67.85), H = 4.88 (4.76), N = 8.04 (8.13)].

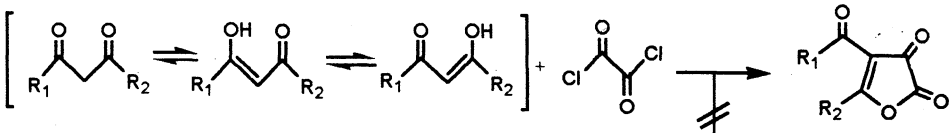
4-Acetyl-5-(2-naphthyl)-1-phenyl-1*H*-pyrazole-3-carboxylic acid (5e)

5e was prepared from **2e** and phenylhydrazine (Method A) or 1,5-diphenylcarbazide (Method B). Yield: 0.94 g (66%, Method A), 0.63 g (44%,

Method B); colourless crystals; m.p.: 163–165°C; IR (cm^{-1}) (KBr): 3440 ν(OH), 1730–1720 ν(C=O); ^1H NMR ($CDCl_3$, δ): 7.959–7.193 (m, 12H, ArH), 2.066 (s, 3H, CH_3C=O). [C = 74.05 (74.16), H = 4.49 (4.49), N = 7.59 (7.82)].

RESULTS AND DISCUSSIONS

The cyclocondensation reactions of the unsymmetrically substituted diketones (**1a–e**) with oxalyl chloride regiospecifically afforded 2,3-dihydro-2,3-furandiones (**2a–e**), which exhibits conjugation with double bonds more then (**3a–e**) (**Scheme-1**). The best yield of **2a–e** was achieved when dry ether was used as a solvent and at 0–5°C temperature. The structures of **2a–e** were confirmed by analytical, IR, NMR spectroscopic data which agree with those recorded for the similar substituted 2,3-dihydro-2,3-furandiones. In the IR spectra of compound **2a**, the absorption bands of ν(C=O) groups were found to be at 1820, 1700, 1640 cm^{-1}. The ^{13}C NMR signals were found to be at 188.820, 181.033, 155.088 ppm (C=O). Compound **2c–e** are very sensitive to light and decompose immediately. Therefore, the structures of **2c–e** were derived based on the NMR spectroscopic data of **5c–e**. The information provided by NMR spectrum of **5c–e** supports the **2c–e** configuration proposed for the 2,3-dihydro-2,3-furandiones. The elemental analysis data also support their structures.



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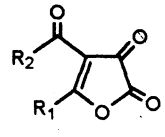
2

1, 2, 3	R_1	R_2
a	Ph	PhCH=CH
b	MeOPh (*p*)	MeOPhCH=CH (*p*)
c	Me	MePh (*p*)
d	Me	MeOPh (*p*)
e	Me	2-Napht



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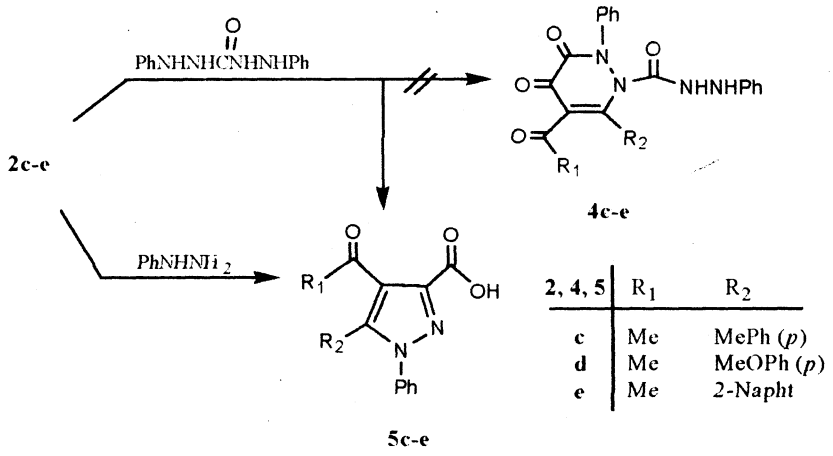
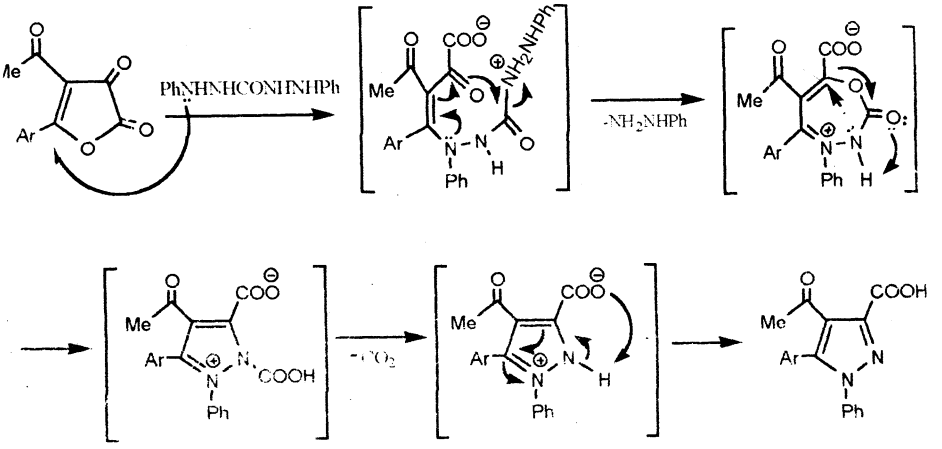
Scheme-1

The condensations of **2c–e** with phenylhydrazine and 1,5-diphenylcarbazide gave the corresponding 1*H*-pyrazole-3-carboxylic acids (**5c–e**). An attempt to cyclize **2c–e** to **4c–e** by reacting at various temperatures failed and the corresponding 1*H*-pyrazole-3-carboxylic acids (**5c–e**) were isolated instead (**Scheme-2**). 2,3-Dihydro-2,3-furandiones (**2c–e**) proved also to be versatile synthons for the preparation of new 1*H*-pyrazole-3-carboxylic acids. The reaction pathway from furandione **2** with 1,5-diphenylcarbazide to pyrazole carboxylic acid **5** is outlined briefly in **Scheme-3**.

Ring opening for the formation of first intermediate may be initiated by nucleophilic attack of the NH group adjacent to the phenyl ring of carbazide at C-5 position of the furandione ring similar to the reactions of furandione **2** with



Scheme-2



Scheme-3

various H-active nucleophiles[2c]. Ring closure of the first intermediate to the oxadiazepine intermediate *via* addition of C=O group to the N—C=O moiety takes place by the catalytic effect of carboxylic acid proton. Rearrangement of the second intermediate generates the pyrazole intermediates, and finally loss of CO_2 gives compound **5**.

The formation of the 1*H*-pyrazole-3-carboxylic acid derivatives, (**5c–e**) are supported by their IR and NMR data. In the IR spectra of **5c**, absorption bands of two C=O groups at 1730–1720 cm^{-1} and absorption of an —OH group in region of 3430 cm^{-1} have been located. In the ^{1}H-NMR spectra of **5e** the characteristic chemical shifts for CH_3C=O at 2.093 ppm were observed. But we could not detect the signal for OH. In the ^{13}C NMR spectra of **5c** the characteristic

chemical shifts of carbons at 201.059 (Me—C=O); 162.176 (COOH); 151.532 (C_5), 146.146 (C_3); 122.627 (C_4) are noted.

ACKNOWLEDGEMENT

The authors are grateful to Research Foundation of Erciyes University (Kaysen, Turkey) for the financial support.

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(*Received*: 03 July 2003; *Accepted*: 09 December 2003) AJC-3272