

## Reaction of 4-(4-Methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione with Various Amides

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The thermal decomposition of 4-acyl substituted furan-2,3-dione (**1**) leads to the  $\alpha$ -oxo ketene (**2**) as an intermediate which undergoes nucleophilic addition reactions with amides. The open-chain  $\alpha$ -N-acyl-oxo-amide derivatives (**4a-f**) which were obtained by these reactions show ketoenol tautomerism. The structures of all the products were confirmed by elemental analysis, IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR.

**Key Words:** Furan-2,3-dione,  $\alpha$ -Oxoketenes, Amide, Keto-enol, Oxo-amide.

### INTRODUCTION

The furan ring systems, though are not found in animal metabolism, occur widely in secondary plant metabolites, especially in terpenoids. Some furandione derivatives are important in medicine<sup>1</sup>. 2,3-Dihydro-2,3-furandione chemistry attracted a wide interest due to versatile biological activities of 2,3-furandione derivatives, which belong to an essential group of heterocycles<sup>2</sup>. Due to their high reactivity, numerous reports have highlighted their chemistry and use<sup>3</sup>. In furan-2,3-diones carbon atoms C-2, C-3, C-5 and C-6 represent electrophilic sites of different reactivity and could be used for the construction of condensed heterocyclic systems upon reaction with various nucleophiles and binucleophiles<sup>4</sup>. The reaction of substituted 2,3-furandiones with some dienophiles in different solvents at various temperatures have also been studied<sup>5</sup>. The derivatives of monocyclic heterocyclic 2,3-diones have been found to serve as versatile synthetic equivalents in thermolysis reaction<sup>6</sup>, cycloaddition reactions<sup>7</sup> and nucleophilic addition reactions<sup>8</sup>. Recently several attempts to change functional groups in furan- or pyrrol-2,3-diones and related systems have been reported<sup>9</sup>. A convenient method for the synthesis and the mechanism of reactions and calculations on the interaction of 2,3-dihydro-2,3-furandiones with several semicarbazones, ureas and their thio-analogues have been reported recently<sup>10</sup>. The reactions are generally initiated by the nucleophilic attack of the nitrogen atom of semicarbazone, urea or hydrazines, directed on the oxygen atom of the furan ring<sup>11</sup>. The reaction of furan-2,3-dione (**1**),

obtained easily from *p,p'*-dimethyldibenzoylmethane and oxalyl chloride<sup>12</sup>, with  $\alpha$ -naphthylamine, aniline, *p*-toluidine and *o*-toluidine derivatives in benzene at the room temperature led to the formation of the 2-oxo-3-butenoic acid derivative, the pyrole-2,3-dione, the pyrole-2-ones and the quinoxaline-2-ones derivatives, respectively<sup>13</sup>. Thermal decomposition of 2,3-furandiones lead to the formation of highly reactive  $\alpha$ -oxoketene intermediates<sup>14</sup>. The general reactivity of ketenes and the mechanism of the reactions with nucleophiles have been reviewed recently and a few *ab initio* and semi-empirical (AM1 and PM3) calculations on a series of differently substituted  $\alpha$ -oxoketenes, especially substituent effects on their stability as well as reactivity, have been published<sup>15</sup>. Therefore, these *vicinal* dione compounds (**1**) have been used as initial materials in the synthesis of the target heterocycles.

## EXPERIMENTAL

Solvents were dried by refluxing over the appropriate drying agent and distilled before use. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba elemental analyser, model 1108. The infrared spectra were recorded on a Jasco FT-IR spectrometer model 460, using potassium bromide pellets. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Varian Gemini 200 instrument. The chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in  $\delta$  (ppm). All experiments were followed by TLC using DC Alufolien Kieselgel 60 F<sub>254</sub> Merck and Camag TLC lamp (254/366 nm).

**N-[(2Z)-3-Hydroxy-2-(4-methylbenzoyl)-3-(4-methylphenyl)prop-2-enoyl]benzamide (4a):** 4-(4-Methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione (**1**) (0.2 g, 0.65 mmol) and benzamide (**3a**) (0.08 g, 0.65 mmol) were refluxed in toluene (50 mL) for 6 h. The solvent was evaporated and the remaining oily residue was treated with dry diethyl ether to give a yellow crude product which was recrystallized from methanol and allowed to dry on P<sub>2</sub>O<sub>5</sub>; yield 46% (0.12 g); m.p. 190°C; IR (KBr, cm<sup>-1</sup>) 3400-3150  $\nu$ (NH, OH), 1720, 1705, 1690, 1680  $\nu$ (C=O); <sup>1</sup>H NMR (DMSO,  $\delta$ ): 11.00 (br, -NH), 9.47 (s, enol-OH), 8.10-7.39 (m, 13H, Ar-H), 7.28 (s, keto-CH), 2.52-2.28 ppm (s, 6H, CH<sub>3</sub>); <sup>13</sup>C NMR (d<sub>6</sub>-DMSO,  $\delta$ ): 192.43 (t, ArCO), 172.68 (N-C=O), 167.81 (C=O), 137.54 (Ar-C3-OH), in enol form 134.22-126.91 (m, aromatic C), 106.40 (s, C2), 67.18 (diketo, CH) and 26.92 and 25.82 ppm (s, CH<sub>3</sub>). Elemental analysis: found (calcd.): [C = 75.18 (74.93), H = 5.26 (5.55), N = 3.51 (3.31)].

**N-[(2Z)-3-Hydroxy-2-(4-methylbenzoyl)-3-(4-methylphenyl)prop-2-enoyl]nicotinamide (4b):** 4-(4-Methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione (**1**) (0.3 g, 0.98 mmol) and nicotinamide (**3b**) (0.12 g, 0.98

mmol) were refluxed in benzene (50 mL) for 6 h. The solvent was evaporated and the remaining oily residue was treated with dry diethyl ether. The crude product was then filtered and recrystallized from methanol and allowed to dry on P<sub>2</sub>O<sub>5</sub>; yield 0.16 g (41%); m.p. 195°C; IR (KBr, cm<sup>-1</sup>) 3255-3155 ν(NH, OH), 1725, 1715, 1685, 1680 ν(C=O); <sup>1</sup>H NMR (DMSO, δ): 12.45 (br, -NH), 9.28 (s, enol-OH), 8.86-7.36 (m, 12H, Ar-H), 7.25 (s, keto-CH), 2.53-2.39 ppm (s, 6H, CH<sub>3</sub>); <sup>13</sup>C NMR (d<sub>6</sub>-DMSO, δ): 191.96 (t, ArCO), 170.52 (N-C=O), 165.46, 155.11 and 151.16 (C-N=C), (C=O), 138.04 (Ar-C3-OH, in enol form) 138.99-116.06 (m, aromatic C), 106.44 (s, C2), 68.33 (diketo, CH) and 26.82 and 25.82 ppm (s, CH<sub>3</sub>). Elemental analysis: found (calcd.): [C = 72.01 (71.72), H = 5.04 (5.08), N = 7.09 (7.25)].

**(2Z)-N-Acetyl-3-hydroxy-2-(4-methylbenzoyl)-3-(4-methylphenyl)acrylamide (4c):** 4-(4-Methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione (**1**) (0.2 g, 0.65 mmol) and acetamide (**3c**) (0.04 g, 0.65 mmol) were refluxed in toluene (50 mL) for 6 h. The solvent was evaporated and the remaining oily residue was treated with dry diethyl ether. The crude product was then filtered and recrystallized from methanol and allowed to dry on P<sub>2</sub>O<sub>5</sub>; yield 0.095 (45%); m.p. 180°C; IR (KBr, cm<sup>-1</sup>) 3270-3170 ν(NH, OH), 1735, 1715, 1690, 1680 ν(C=O); <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, δ): 11.27 (br, -NH), 9.23 (s, enol-OH), 7.84-7.33 (m, 8H, Ar-H), 7.05 (s, keto-CH), 2.52-2.28 ppm (s, 6H, arom, CH<sub>3</sub>) 2.10 ppm (s, CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO, δ): 190.37 (t, ArCO), 172.71 (N-C=O), 166.59 (C=O), 133.83 (enol-OH), 133.64-115.32 (m, aromatic C), 106.71 (s, C2), 66.96 (diketo, CH), 27.18 (methyl-C=O) and 26.92 and 25.82 ppm (s, CH<sub>3</sub>). Elemental analysis: found (calcd.): [C = 71.21 (71.43), H = 5.63 (5.35), N = 4.15 (4.12)].

**N-[(2Z)-3-Hydroxy-2-(4-methylbenzoyl)-3-(4-methylphenyl)prop-2-enoyl]butanamide (4d):** 4-(4-Methylbenzoyl)-5-(4-methylphenyl)furan-2,3-dione (**1**) (0.3 g, 0.98 mmol) and *n*-butyramide (**3d**) (0.085 g, 0.98 mmol) were refluxed in benzene (50 mL) for 6 h. The solvent was evaporated. The remaining oily residue was dissolved in dry diethyl ether. Petroleum ether was then added. The white product was then filtered and recrystallized from methanol and allowed to dry on P<sub>2</sub>O<sub>5</sub>; yield 0.16 g (45%); m.p. 205°C; IR (KBr, cm<sup>-1</sup>) 3280-3150 ν(NH, OH), 1735, 1705, 1695, 1675 ν(C=O); <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, δ): 11.21 (br, -NH), 8.92 (s, enol-OH), 8.11-7.30 (m, 8H, Ar-H), 7.09 (s, keto-CH), 2.53-2.50 (s, 6H, arom, CH<sub>3</sub>), 2.49-2.34 (-CO-CH<sub>2</sub>-), 1.56-1.44 (-CH<sub>2</sub>-), 0.89-0.82 ppm (-CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO, δ): 191.55 (t, ArCO), 172.50 (N-C=O), 167.01 (C=O), 136.54 (enol-OH), 133.72-123.91 (m, aromatic C), 106.50 (s, C2), 67.18 (diketo, CH) and 26.91 and 25.80 ppm (s, CH<sub>3</sub>). Elemental analysis: found (calcd.): [C = 72.32 (71.97), H = 6.30 (6.35), N = 3.83 (3.55)].

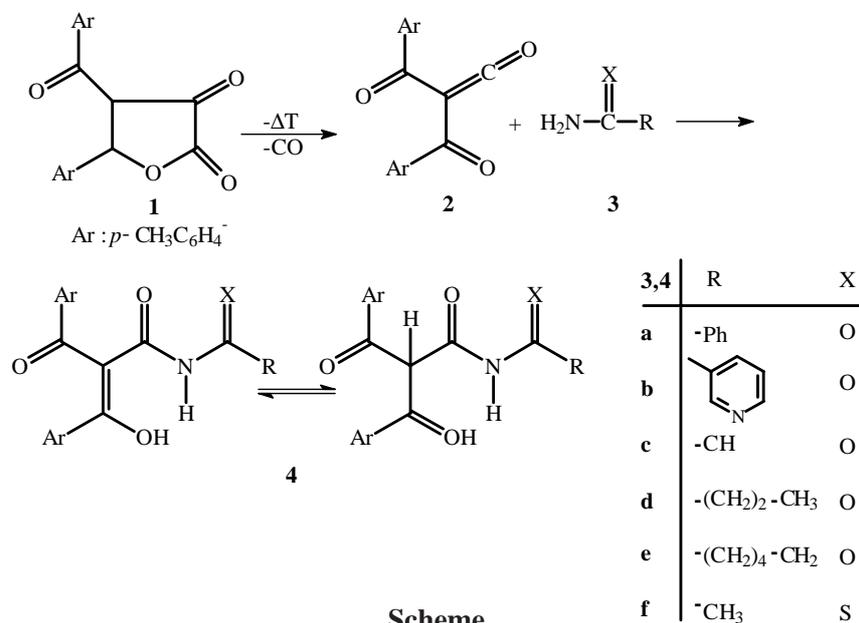
**N-[(2Z)-3-Hydroxy-2-(4-methylbenzoyl)-3-(4-methylphenyl)prop-2-enoyl]hexanamide (4e):** 4-(4-Methylbenzoyl)-5-(4-methylphenyl)-furan-2,3-dione (**1**) (0.2 g, 0.65 mmol) and *n*-hexanamide (**3e**) (0.075 g, 0.65 mmol) were refluxed in benzene (50 mL) for 6 h. The solvent was evaporated. The remaining oily residue was dissolved in dry diethyl ether. Petroleum ether was then added. The white product was filtered and recrystallized from methanol and allowed to dry on P<sub>2</sub>O<sub>5</sub>; yield 0.1 g (40%); m.p. 224°C; IR (KBr, cm<sup>-1</sup>) 3425-3170 ν(NH, OH), 1705, 1695, 1680, 1655 ν(C=O); <sup>1</sup>H NMR (d<sub>6</sub>-DMSO, δ): 11.28 (br, -NH), 9.42 (s, enol-OH), 8.11-7.24 (m, 8H, Ar-H), 6.69 (s, keto-CH), 2.49-2.40(s, 6H, arom, CH<sub>3</sub>), 0.89-0.81 ppm (s, CH<sub>3</sub>); <sup>13</sup>C NMR (DMSO, δ): 192.37 (t, ArCO), 171.68 (N-C=O), 165.81 (C=O), 137.54 (enol-OH) 130.22-126.91 (m, aromatic C), 67.22 (diketo, CH) and 26.92 and 25.82 ppm (s, CH<sub>3</sub>). Elemental analysis: found (calcd.): [C = 73.28 (73.55), H = 6.87 (6.55), N = 3.56 (3.33)].

**(2Z)-N-Ethanethioryl-3-hydroxy-2-(4-methylbenzoyl)-3-(4-methylphenyl)acrylamide (4f):** 4-(4-Methylbenzoyl)-5-(4-methylphenyl)-furan-2,3-dione (**1**) (0.2 g, 0.65 mmol) and thioacetamide (**3f**) (0.05 g, 0.65 mmol) were refluxed in benzene (50 mL) for 6 h. The solvent was evaporated and the remaining oily residue was treated with dry diethyl ether. The crude product was then filtered and recrystallized from methanol and allowed to dry on P<sub>2</sub>O<sub>5</sub>; yield 0.11 g (48%); m.p. 175°C; IR (KBr, cm<sup>-1</sup>) 3300-3150 ν(NH, OH), 1705, 1690, 1680 ν(C=O), 1300 ν(C=S); <sup>1</sup>H NMR (DMSO, δ): 11.11 (br, -NH), 9.30 (s, enol-OH), 8.11-7.36 (m, 8H, Ar-H), 7.29 (s, keto-CH), 2.53-2.41 ppm (s, 6H, CH<sub>3</sub>). Elemental analysis: found (calcd.): [C = 67.98 (67.82), H = 5.38 (5.57), N = 3.97 (3.65) S = 9.07 (9.38)].

## RESULTS AND DISCUSSION

In the present study, we carried out the reaction of the furan-2,3-dione (**1**) with amide derivatives (**3a-f**) yields  $\alpha$ -*N*-acyl-oxo-amide derivatives (**4a-f**) in boiling benzene and toluene (Experimental). The reaction equations are shown in **Scheme**. Compounds **4a-f** were obtained by the addition of amides to  $\alpha$ -oxoketene (**2**) which is formed by heating of **1**. The structures of **4a-f** were confirmed by elemental analysis, IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral data. The IR and NMR spectral data of compounds **4a-f** indicate the existence of keto-enol tautomerism in these compounds. Product **4a** was obtained by treating **1** with benzamide (**3a**) in 46% yield and refluxing the mixture in toluene for 6 h. In the IR spectra of compound **4a** the C=O absorption bands are found at about 1720, 1705, 1690, 1680 cm<sup>-1</sup>. The -NH and -OH absorption bands are found at about 3400-3150 cm<sup>-1</sup>. From the <sup>1</sup>H NMR spectrum of **4a**, important structural information can be obtained. The <sup>1</sup>H NMR peak of **4a** observed at 7.28 ppm belongs to the

-CH in the keto form for which the chemical shift values of very close analogs of  $\alpha$ -oxo-carboxylic and derivatives are found between 6.82 and 6.47 ppm<sup>6a,d,f</sup>. The peaks at 9.47 ppm is thought to represent the -OH in the enol form. The broad peak at 11.00 represents the -NH. This indicates the existence of a keto-enol tautomerism. In the <sup>13</sup>C NMR spectrum of **4a** the peak at 26.92 and 25.82 ppm belongs to the methyl groups the other peak at 67.18 ppm represents the -CH in the diketo form. The peaks corresponding to 172.68 and 192.43 ppm indicate imide-C=O and benzoyl-C=O, respectively. More information about the **4a-f** spectrums is given in the experimental section.



#### ACKNOWLEDGEMENT

The authors wish to express their gratitude to Prof. Dr. I. Yildirim for helpful and encouraging discussions. This study was financially supported by the Research Center of Erciyes University.

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