Turkish Journal of Chemistry

Volume 28 | Number 5 Article 13

1-1-2004

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ŞENER, AHMET; GENÇ, HASAN; TOZLU, İSRAFİL; and ŞENER, M. KASIM (2004) "Studies on the Reactions of 4-Ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3- furandione with Some NH Nucleophiles," *Turkish Journal of Chemistry*: Vol. 28: No. 5, Article 13. Available at: https://journals.tubitak.gov.tr/chem/vol28/iss5/13

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Turk J Chem
28 (2004) , 659 – 665.
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# Studies on the Reactions of 4-Ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione with Some NH Nucleophiles

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Received 07.05.2004

4-Ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione **1** was reacted with o-phenylenediamine, substituted ureas and methylcarbamate or acetamide to give quinoxaline **2**, pyrimidine **3** and benzoylmalonic acid **4** derivatives, respectively. Benzoylmalonic acid derivative **4a** was converted into a new oxozinedione derivative, **5**, by refluxing its solution in xylene containing a catalytic amount of p-toluene sulfonic acid. In addition, triphenylpyrazole carboxylic acid derivative **6** was obtained from the reaction of **4a** with diphenylhydrazine.

**Key Words:** Cyclic oxalyl compounds, quinoxaline, pyrimidine, benzoylmalonic acid, oxazine, pyrazole carboxylic acid.

## Introduction

4,5-Disubstituted-2,3-furandiones are important starting materials for the synthesis of many different heterocyclic compounds since they are capable of undergoing thermolysis and nucleophilic addition reactions depending on the reaction conditions and structures of the nucleophiles [1,5]. Thermolysis of the furandiones leads to the in situ generation of acylketenes as intermediates, which are trapped with nucleophiles or by [2+4] cycloaddition reactions with heterodienophiles having double or triple polar bonds [6]. A simple synthesis of dioxine and 4-pyrone derivatives based on the [2+4] cycloaddition reactions of acylketene intermediate generated in situ from furandione **1** with some carbonyl compounds has been reported previously [7]. Here, in order to shed light partially upon the versatility of furandione **1**, we investigated the chemical behavior of **1** towards various nucleophilic reagents.

# Experimental

Solvents were dried by refluxing with appropriate drying agents and distilled before use. Melting points were determined on an Electrothermal Gallenkamp apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer Model 1108. The IR spectra were obtained as potassium bromide pellets using a Mattson 1000 FTIR spectrometer. The $^{1}$H and $^{13}$C-NMR spectra were recorded on a Varian XL-200 (200 MHz) and a Varian XL-200 (50 MHz) spectrometer, respectively, using TMS as an internal standard. All experiments were followed using DC Alufolien Kieselgel 60 F 254 Merck and a Camag TLC lamp (254/366 nm).

**3-Oxo-2-(3,4-dihydroquinoxalin-2-yl)-3-phenylpropionic acid ethyl ester (2)**

To a cold solution of compound **1** (0.246 g, 1 mmol) in dry benzene (15 mL) was added a cold solution of 1,2–phenylenediamine (0.140 g, 1 mmol) in dry benzene (15 mL) under stirring and the stirring was continued at room temperature for 30 min. The yellow product that precipitated from the reaction medium was isolated by filtration and washed with benzene, yield 0.262 g (78% ), mp 183$^{o}$C; IR: 3400-3350 cm$^{-1}$ (O-H and N-H); 3060 cm$^{-1}$(Ar-H); 2905-2861 cm$^{-1}$(R-H); 1687, 1635, 1620 cm$^{-1}$(C=O); $^{1}$H-NMR (DMSO-d$_6$): $\delta$=11.8 (b, N-H), 10.6 (b, O-H); 8.1-7 (m, Ar-H), 6.3 (s, methine group), 5-3.2 (b, N-H), 4.19 (q, $OCH_2$), 4.05 (q, $OCH_2$), 1.15 (t, $CH_3$), 1.06 ppm (t, $CH_3$); $^{13}$C-NMR (DMSO-d$_6$): $\delta$ 194.1 (C=O, benzoyl); 169.4 (C=O, ester), 168.6 (C=O, ester), 156.9 (C=O), 155.5 (C=O), 145.2 (C-3), 137.8, 135.4, 133.9, 133.4, 133.3, 133.0, 132.5, 131.0, 130.6, 130.3, 130.0, 129.9, 129.6, 128.1, 127.9, 127.8, 126.8, 125.5, 125.3, 124.7, 117.5, 116.1, 110.2 (methine group), 63.5 ($OCH_2$), 61.7 ($OCH_2$), 15.7 ppm ($CH_3$).

Anal.Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N. 8.33; found: C, 67.74; H, 4.80; N, 8.32

**5-Ethoxycarbonyl-1-ethyl-4-phenyl-1*H* –pyrimidine-2-one (3a)**

Compound **1** (0.246 g, 1 mmol) and ethylurea (0.088 g, 1 mmol) were refluxed in xylene for 6 h. After the solvent was removed by evaporation, the oily residue was treated with ether and the formed crude product was crystallized from ethyl alcohol to give 0.117 g (48% ) of **3b**; mp 156$^{o}$C. $^{1}$H-NMR ($CDCl_3$): $\delta$ 8.4 (s, 1H, H-6), 7.43-7.25 (m, 5H, Ar-H), 3.99 (q, 2H, $CH_2$), 3.93 (q, 2H, $CH_2$), 1.32 (t, 3H, $CH_3$), 0.93 ppm (t, 3H, $CH_3$); $^{13}$C-NMR ($CDCl_3$): $\delta$ 175.6 (C=O), 165.9 (C=O), 156.4 (C-4), 154.4 (C-6), 139.7, 132.2, 130.3, 129.6, 110.6 (C-5), 63.2 (O-$CH_2$), 48.9 (N-$CH_2$), 16.2 ($CH_3$), 15.7 ppm ($CH_3$).

Anal.Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N. 11.47; found: C, 64.04; H, 4.93; N, 11.45

**5-Ethoxycarbonyl-1-(3,4-dimethoxyphenylmethylenamino)-4-phenyl-1*H*–pyrimidine-2-one (3b)**

An equimolar mixture of furandione **1** (0.246 g, 1 mmol) and semicarbazone of 3,4-dimethoxybenzaldehyde (0.239 g, 1.1 mmol) was heated to 115$^{o}$C over approximately 40 min without any solvent. After cooling to room temperature, the residue was treated with ether for about 12 h with stirring and the formed crude product was crystallized from isopropanol to give 0.148 g (35% ) of a yellow solid, mp 150$^{o}$C; IR: 3060 cm$^{-1}$ (Ar-H), 2950-2844 cm$^{-1}$ (R-H), 1749 cm$^{-1}$ (C=O, ester), 1732 cm$^{-1}$ (C=O), 1672 cm$^{-1}$ (CH=N); $^{1}$H-NMR ($CDCl_3$): $\delta$ 9.5 (s, 1H, CH=N), 8.7 (s, 1H, H-6), 7.6-6.9 (m, 8H, Ar-H), 4.16 (q, 2H, $OCH_2$), 3.98 (s, 3H, $OCH_3$), 3.97 (s, 3H, $OCH_3$), 1.5 ppm (t, 3H, $CH_3$).

Anal.Calcd. for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92; found: C, 65.37; H, 5.93; N, 9.94

**2-Methoxycarbonylaminocarbonyl-3-oxo-3-phenylpropionic acid ethyl ester (4a) General procedure**

An equimolar mixture of **1** and methylcarbamate was refluxed in dry benzene for 4 h. After the solvent was removed by evaporation, the oily residue was treated with ether and the crude product formed was crystallized from ethyl alcohol. The yield was 0.191g (65% ) ; mp 167$^o$C; IR: 3274 cm$^{-1}$ (NH), 3029 cm$^{-1}$ (Ar-H), 2985-2905 cm$^{-1}$ (R-H), 1743, 1721, 1692, 1660 cm$^{-1}$ (C=O); $^1$H-NMR ($CDCl_3$): $\delta$ 10.9 (b, 1H, NH), 7.9-7.4 (m, 5H, Ar-H), 6.0 (s, 1H, methine group), 4.2 (q, 2H, $OCH_2$), 3.7 (s, 3H, $OCH_3$), 0.9 ppm (t, 3H, $CH_3$); $^{13}$C-NMR ($CDCl_3$): $\delta$ 191.4 (C=O, benzoyl), 172.6 (C=O), 166.9 (C=O), 153.8 (C=O), 138.7 (quarternary C, Ph), 134.5, 130.7, 129.8, 98.5 (methine carbon), 64.5 ($OCH_2$), 55.3 ($OCH_3$), 15.3 ppm ($CH_3$).

Anal.Calcd. for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N. 4.78; found: C, 57.23; H, 5.17; N, 4.76

**3- Acetylamino-2-benzoyl-3-oxo-propionic acid ethyl ester (4b)**

Compound **4b** was prepared according to the general procedure with a reflux time of 5 h (acetamide), resulting in a 55% yield (0.152 g) (ethanol); mp 209$^o$C; IR: 3387 cm$^{-1}$ (NH), 3064 cm$^{-1}$ (Ar-H), 2989-2940 cm$^{-1}$ (R-H), 1790, 1747, 1679, 1650 cm$^{-1}$ (C=O); $^1$H-NMR ($CDCl_3$): $\delta$ 9.47 (b, 1H, NH), 7.4-7.2 (m, 5H, Ar-H), 6.9 (s, 1H, methine), 4.13 (q, 2H, $OCH_2$), 2.0 (s, 3H, $CH_3$), 1.2 ppm (t, 3H, $CH_3$).

Anal.Calcd. for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N. 5.05; found: C, 60.82; H, 5.43; N, 5.04

**5–(Hydroxy-phenyl-methylene)-2-methoxy-[1,3]-oxazine-4,6-dione (5)**

A solution of **4a** in xylene containing a catalytic amount of p-toluenesulfonic acid was refluxed for 7 h. After cooling to room temperature, the product that precipitated from xylene was recrystallized from ethanol to give 0.183 g (74% ) of **5,** mp 201$^o$C; IR: 3150-2800 cm$^{-1}$ (b. OH), 3039 cm$^{-1}$ (Ar-H), 2905 cm$^{-1}$ (R-H), 1799, 1749, 1679, 1612 cm$^{-1}$ (C=O, lacton group, C=N); $^1$H-NMR (DMSO-$d_6$): $\delta$ 12.3 (b, 1H,OH), 7.65-7.45 (m, 5H, Ar-H); 3.7 ppm (s, 3H, $OCH_3$); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 165.1, 164.4, 162.0 (C-2, C-4, C-6), 148.3, (Ph-C-OH), 134.0, 131.3,130.8, 129.3, 110.6 (C-5), 54.5 ppm (O-$CH_3$).

Anal.Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.67; N. 5.67; found: C, 58.39; H, 3.66; N, 5.69

**(3-Oxo-1,2,5-triphenyl-2,3-dihydro-1*H*–pyrazole-4-carbonyl) carbamic acid methyl ester (6)**

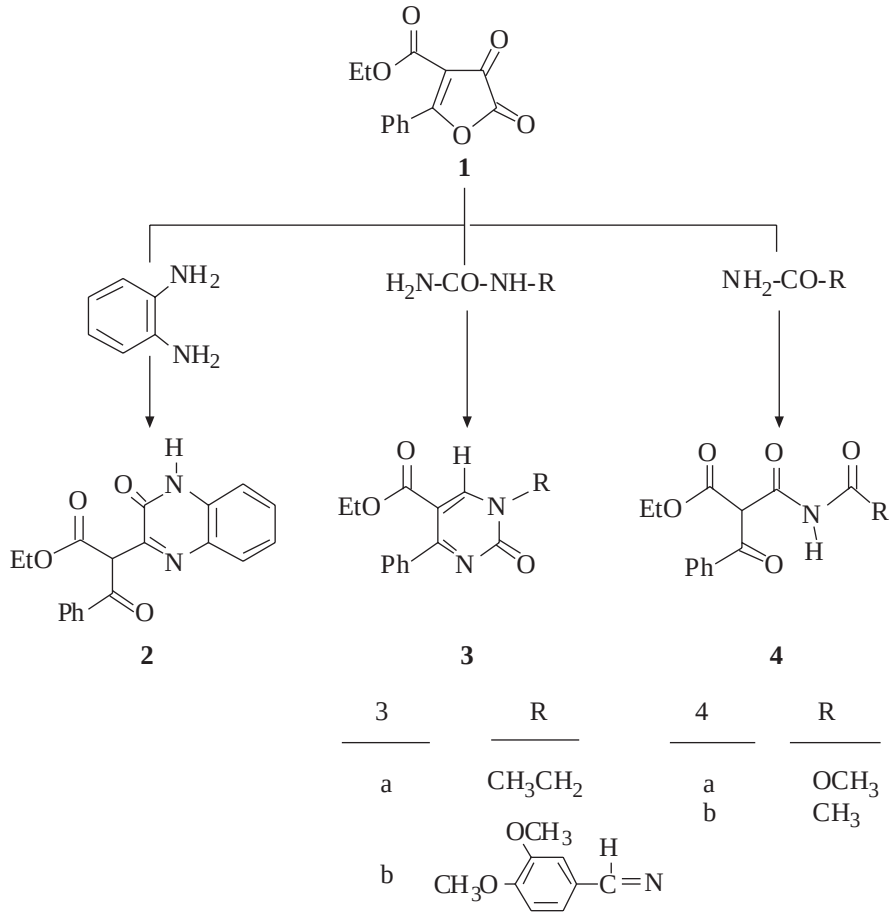
Compound **4a** (0.293 g) and diphenylhydrazine (0.203 g) (molar ratio 1:1.1) were refluxed in dry benzene for 4 h. After evaporation of the solvent, the crude product that was obtained by trituration of the residue with ether, was recrystallized from ethyl alcohol to give 0.182 g (44% ) of **6**; mp 185$^o$C; IR: 3234 cm$^{-1}$ (NH), 3069 cm$^{-1}$ (Ar-H), 2950 cm$^{-1}$ (R-H), 1738, 1703, 1646 cm$^{-1}$ (C=O); $^1$H-NMR ($CDCl_3$): $\delta$ 11.2 (b, 1H, NH), 7.35-6.97 (m, 15H, Ar-H), 3.66 ppm (s, 3H, $OCH_3$); $^{13}$C-NMR ($CDCl_3$): $\delta$ 165.5, 161.1, 160.1 (C=O), 153.8 (N-Ph), 137.4 (N-Ph), 135.5, 132.2, 132.1, 131.4, 131.2, 131.1, 130.6, 130.1, 129.8, 129.1, 128.7 (C-5), 102.9 (C-4), 54.2 ppm ($OCH_3$).

Anal.Calcd. for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N. 10.16; found: C, 69.81; H, 4.62; N, 10.13

## Results and Discussion

In this work, we studied nucleophilic addition reactions of 4-ethoxycarbonyl-5-phenyl-2,3-furandione **1**, obtained by cyclocondensation between ethyl benzoylacetate and oxalyl chloride [8], with some mono- and bi-

functional NH-nucleophiles. Thus, furandione **1** was easily converted into various 6-membered heterocycles or open chain derivatives depending on the nature of the NH-nucleophiles applied (Scheme 1).

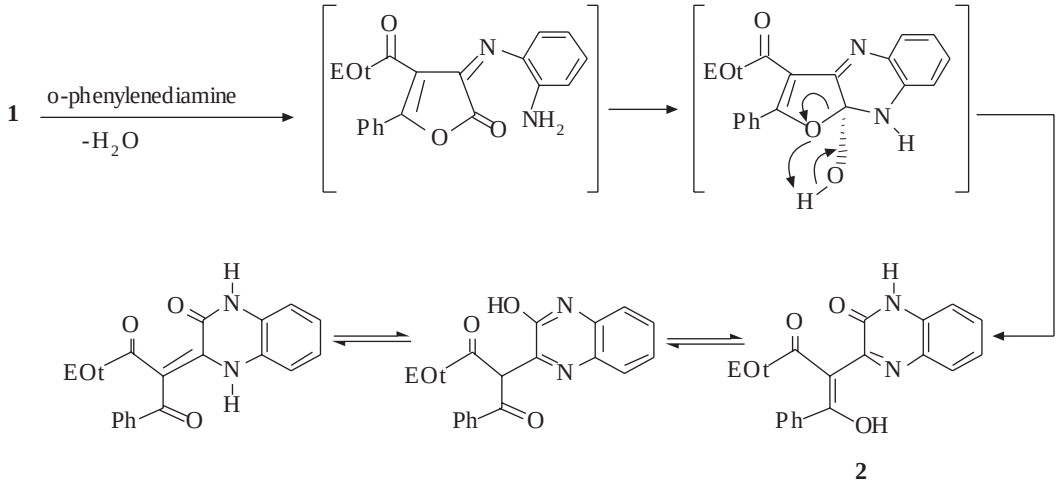



**Scheme 1**

The furandione **1** reacted easily with o-phenylenediamine via the binucleophilic attacks of amino groups of o-phenylenediamine that occurred on the C-3 position followed by an attack on the C-2 position of **1** that opened the lacton ring system to give quinoxaline nucleus **2** in a similar manner to the reactions of 4-benzoyl–5-phenyl-2,3-furandione with diamines [9]. A mechanistic rational for a likely reaction pathway from furandione **1** to quinoxalinone **2** is outlined briefly in Scheme 2.

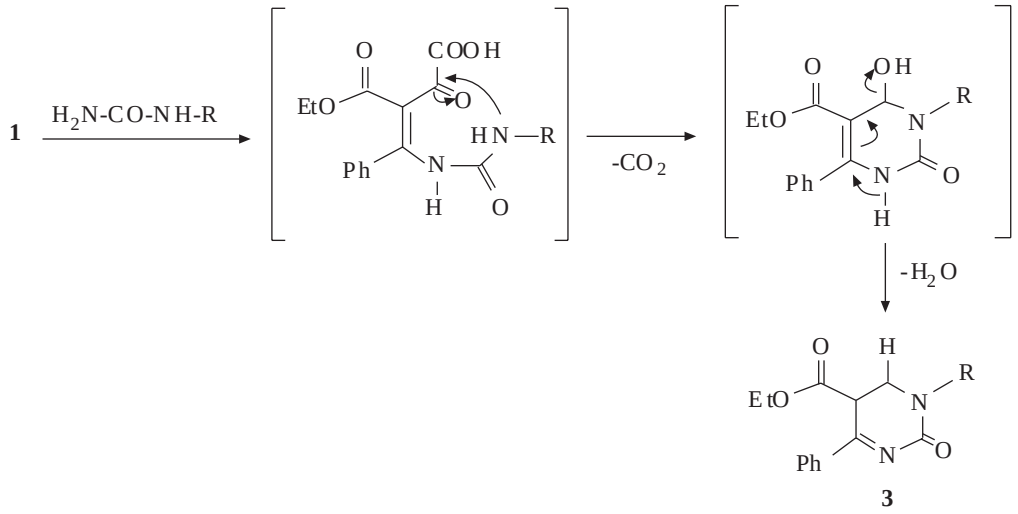
The structure of **2** was confirmed by analytical and spectral data (see Experimental). Both the $^{1}$H-NMR and $^{13}$C-NMR spectra showed evidence of the presence of tautomeric equilibria between its tautomeric forms. Similar observations have also been made with closely related compounds in DMSO-$d_6$ solution [10,11].

Pyrimidines in general have attracted much interest for biological and medicinal reasons [12,13]. From the reactions of the furandione **1** with some substituted urea compounds, 1,4,5-substituted 1*H*-pyrimidine-2-ones **3** was obtained in moderate yields (Scheme 1). A reasonable reaction pathway leading to the pyrimidines **3** is outlined briefly in Scheme 3.




**2**

**Scheme 2**



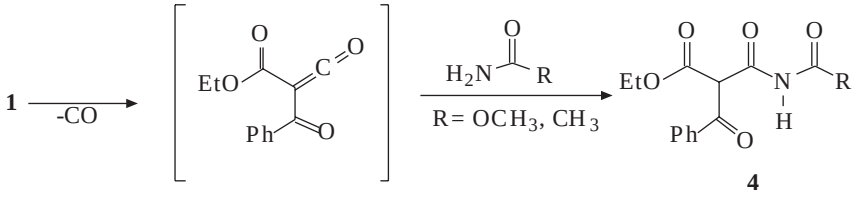

**3**

**Scheme 3**

Carbon atoms C-2, C-3 and C-5 in compound **1** are electrophilic sites that can exhibit different reactivity depending on the structures of the nucleophiles [3,9]. Indeed, while the formation of **2** is initiated by nucleophilic attacks on the C-2 or C-3 positions in **1**, the formation of **3** should start with a nucleophilic attack of the $NH_2$ group of the substituted urea at the C-5 position of the furandione **1** [14,19] similar to a Michael-type addition. Syntheses of pyrimidines via Michael-type additions of ureas, thioureas, amidines and similar compounds to $\alpha,\beta$-unsaturated carbonyls are well established [15]. Ring opening, decarboxylation of $\alpha$-oxocarboxylic acid intermediate, to yield the aldehyde, and subsequent ring closure via addition of the NH group to the aldehyde C=O and final loss of water should be the additional steps [14]. The structures of the functionalized 1*H*-pyrimidine derivatives **3** obtained in this way were confirmed by analytical and spectral data. In the $^1$H-NMR spectra, the appearance of singlet signals originating from H-6 protons in compounds **3** at approximately 8.0-8.9 ppm is characteristic for this type of pyrimidine [14].

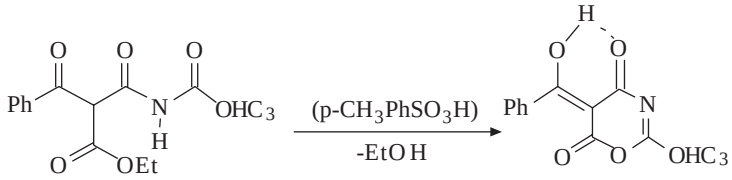
While the furandione **1** reacts with an N-alkylurea to give functionalized 1*H*-pyrimidine derivatives **3**, the reaction between **1** and methylcarbamate (or acetamide) did not lead to the formation of the corresponding oxazine derivative. However, the furandione **1** was reacted with methylcarbamate (or acetamide),

yielding an open chain benzoylmalonic acid derivative **4**. Compounds **4** are obviously derived from the nucleophilic additions of the $NH_2$ groups of methyl carbamate and acetamide to the ethoxycarbonylbenzoylketene intermediate [6], formed by decarbonylation of **1**. Addition of nucleophiles to $\alpha$-oxoketenes [16] as well as ketenes [17] is a familiar process and usually leads to carboxylic acid derivatives depending on the nature of the nucleophile in the reaction medium. Addition reactions to the ethoxycarbonylbenzoylketene can lead to the formation of the corresponding N-acylamides **4** (Scheme 4).




**Scheme 4**

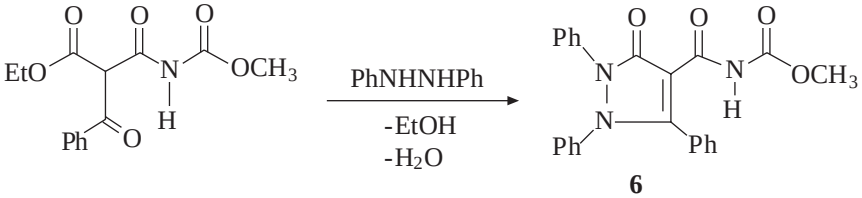
Structure elucidation of compounds **4a** and **4b** is deduced mainly from their elemental analysis, IR, $^1$H-NMR and $^{13}$C-NMR spectroscopic data (see Experimental). Remarkably, **4a** and **4b** do not show any tendency to enolize in $CDCl_3$ solution although their enol forms may be stabilized by intramolecular hydrogen bridges. Similar observations have been made with closely related compounds [18]. Therefore, through the $^1$H-NMR spectra (**4a**: $\delta$ 6.0, **4b**: $\delta$ 6.9) as well as $^{13}$C-NMR spectra of **4a** and **4b** (**4a**: $\delta$ 98.5), the presence of a CH-moiety is unambiguously established. In the $^1$H-NMR spectra, the appearance of singlet signals originating from the methine group in compounds **4** at approximately 6-7 ppm is characteristic for this type of compound [18]. However, **4a** could be cyclized to a new oxazinone derivative **5** (Scheme 5); the structure of which was also elucidated by elemental analysis and spectroscopic data (see Experimental).




**4a** **5**

**Scheme 5**

In addition, the benzoylmalonamide **4a** could be easily converted into the corresponding pyrazole acid derivative **6** via its reaction with 1,2-diphenylhydrazine in boiling benzene (Scheme 6).




**Scheme 6**

The spectral and analytical data of **6** are in full agreement with the proposed structure (see Experimental).

## Acknowledgment

The authors thank the research fund of Y.Yıl University for its financial support.

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