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Reaction of 4-Ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione with Some Hydrazine Nucleophiles

HASAN GENÇ
Faculty of Education, Yüzüncü Yil University, 65080 Van, Turkey
E-mail: h_genc2000@yahoo.com

Some new pyridazinones **2a**, **2b**, **2c** and **3** were synthesized from reactions of the 4-ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione with some hydrazines. The structures of all the pyridazinones compounds were confirmed by analytical, IR, ^{1}H NMR and ^{13}C NMR spectroscopic data.

Key Words: 2,3-Furandione, Hydrazine, Pyridazinon.

INTRODUCTION

Furandiones are extremely versatile synthons for the synthesis of many different heterocyclic compounds since they are capable of undergoing thermolysis[1,2] and nucleophilic addition reactions[3-8]. These compounds can show typical carbonyl, lacton and α,β-unsaturated carbonyl reactions depending on the structures of the nucleophiles[9-15]. It has been well known that furandiones, depending on functionalities at particularly C-4 position, can exhibit different behaviours towards nucleophiles as well as cycloaddition processes[16-21]. A literature survey revealed that many work have been carried out on the reactions of furandiones with hydrazines to give corresponding pyrazole-3-carboxylic acids or pyridazine derivatives[9-15], no work has been reported on the reactions of 4-ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**), which is a different furandione, bearing ester group at C-4 position, with hydrazines. Thus, an attempt is made to investigate the reactions of compound **1** with various hydrazine derivatives. Present approach was achieved by synthesis of some new pyridazine derivatives, various analogues of which proved to be interesting in a chemical and biological context due to their pharmacological action with a wide spectrum[22-29].

EXPERIMENTAL

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 Varian XL-200 (200 MHz) and

(50 MHz) spectrometers, respectively, using TMS as an internal standard. All experiments were followed by TLC using a DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm).

1-(4-Carboxy-phenyl)-5,6-dioxo-3-phenyl-1,4,5,6-tetrahydro-pyridazine-4-carboxylic acid ethyl ester (2a): 4-Ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) (0.246 g, 1 mmol) and 4-carboxy-phenyl-hydrazine (0.152 g, 1 mmol) were refluxed in glacial acetic acid (20 mL) for about 3 h. After the solvent was removed by evaporation. The oily residue was treated with ether and the formed crude product was crystallized from glacial acetic acid. The yield was 0.250 g (63 %), m.p. 259-260 ºC; IR (KBr, ν_{max}, cm^{-1}): 3120 (OH), 3070 (Ar-H), 2980-2950 (R-H), 1637 (C=O, EtO), 1626 (C=O); 1610 (C=O); ^{1}H NMR (DMSO-d_6) δ: 12.6 (b, H, OH), 10.86 (b, OH, -COOH), 7.83-7.46 (m, Ar-H), 6.65 (H-3) 4.18 (2H, OCH_2), 1.23 ppm (3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 173.75, 169.20, 168.97, 168.18, 163.46, 163.23, 161.27, 160.90, 157.48 (C=O), 154.16 (C-4), 143.40, 142.86, 133.50, 132.90, 132.46, 130.92, 130.70, 129.80, 125.91, 122.36, 114.15, 112.87 (C-3), 62.43 (-OCH_2), 22.82, 15.66 ppm (-CH_3). Anal. calcd. (%) for $C_{20}H_{16}N_2O_6$: C, 63.16; H, 4.24; N, 7.37. Found: C, 63.34; H, 4.23; N,7.35.

1-Methyl-5,6-dioxo-3-phenyl-1,4,5,6-tetrahydro-pyridazine-4-carboxylic acid ethyl ester (2b): An equimolar mixture of 4-ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) (0.246 g, 1 mmol) and methyl hydrazine (0.046 g, 0.052 mL, 1 mmol) kept at room temperature in dry benzene (30 mL) for *ca.* 1 h. After the precipitate was filtered off and treated with dry ether to give a crude solid that was recrystallized from methyl alcohol. The yield 0.172 g (59 %), m.p. 156 °C; IR (KBr, ν_{max}, cm^{-1}): 3062 (OH), 2984 (Ar-H), 2965-2940 (R-H), 1733 (C=O, EtO), 1642 (C=O); 1610 (C=O); ^{1}H NMR ($CDCl_3$) δ: 11.97 (b, OH), 7.45-7.37 (m, Ar-H), 4.16 (q, 2H, OCH_2), 3.88 (N-CH_3), 0.99 ppm (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 168.98, 166.37, 162.45, 161.50, 158.85, 157.21, 154.86 (tauto, C=O), 148.25 (C-3), 137.91, 136.11, 134.45, 133.73, 132.88, 131.13, 130.36, 129.83, 63.99 (-CH_2), 42.42 (N-CH_3), 15.53 ppm (-CH_3); Anal. calcd. (%) for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.10; H, 5.15; N,10.22.

1-(3-Nitro-phenyl)-5,6-dioxo-3-phenyl-1,4,5,6-tetrahydro-pyridazine-4-carboxylic acid ethyl ester (2c): An equimolar mixture of 4-ethoxycarbonyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) (0.246 g, 1 mmol) and (3-nitrophenyl)-hydrazine hydrochloride (0.1896 g, 1 mmol were refluxed in glacial acetic acid (30 mL) for *ca.* 4 h, and after the solvent was removed by evaporation. The oily residue was treated with ether and the formed crude product was crystallized from ethyl-alcohol. The yield was 0.196 g (45 %), m.p. 223 ºC; IR (KBr, ν_{max}, cm^{-1}): 3354 (OH), 3061-3080

(Ar-H), 2989-2940 (R-H), 1697 (C=O, EtO), 1614 (C=O); ^{1}H NMR-(DMSO-d_6) δ: 13.72 (H, OH), 7.91-7.27 (m, Ar-H), 6.91 (tauto, H-4), 4.20 (q, 2H, OCH_2), 1.28 ppm (t, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 167.45, 166.15, 165.82,164.80, 158.56, 157.99, 155.46 (tauto, C=O),144.42, 138.30, 136.56, 134.37, 133.35, 132.42, 130.60, 129.65, 129.20, 128.14, 126.66, 125.74, 119.20, 114.35, 112.06 (C-4), 62.70 (-CH_2), 13.65 ppm (-CH_3); Anal. calcd. (%) for $C_{19}H_{15}N_3O_6$: C, 59.84; H, 3.96; N, 11.02. Found: C, 59.62; H, 3.97; N,11.03.

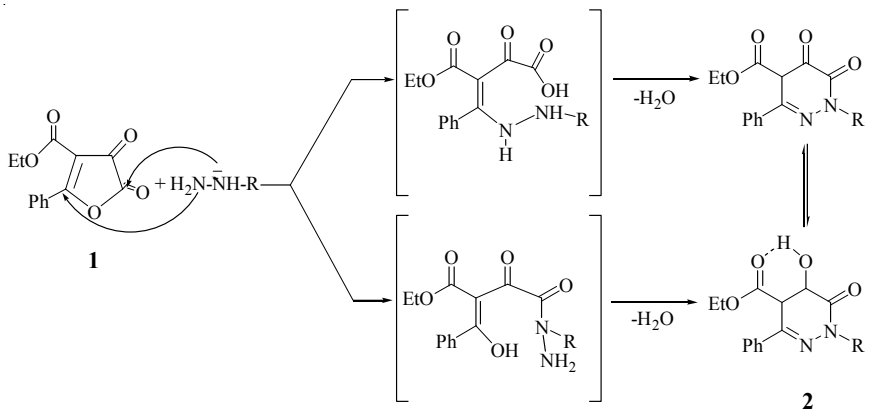
1,2-*bis*[-(1-Methyl-5,6-dioxo-3-phenyl-1,4,5,6-tetrahydro-pyridazine-4-carbonyl)-hydrazide] (3): An equimolar mixture of 1-methyl-5,6-dioxo-3-phenyl-1,4,5,6-tetrahydro-pyridazine-4-carboxylic acid ethyl ester (**2b**) (0.274 g, 1 mmol) and hydrazine hydrate (0.050 g, 0.0485 mL, 1 mmol) was mixture in room temperature in dry benzene (30 mL) for *ca.* 1 h. After the precipitate was filtered off and treated with dry ether to give a crude solid that was recrystallized from methyl alcohol. The yield 0.065 g (22 %), m.p. 191-192 °C; IR (KBr, ν_{max}, cm^{-1}): 3365 (NH), 3080-3061 (Ar-H), 2977-2949 (R-H), 1679 (C=O), 1634 (C=O), 1614 (C=O); ^{1}H NMR (DMSO-d_6) δ: 11.90 (b, 1H, NH), 6.33-7.37 (m, Ar-H), 3.58 (H-4), 2.52 ppm (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ: 169.98, 168.16, 165.56, 163.17, 162.71, 160.65, 155.43, 154.68, 150.73 (tauto, C=O), 142.44, 141.83, 133.36, 132.77, 129.86, 128.74, 128.49, 110.33, 91.22 (C-4), 39.83 ppm (N-CH_3); Anal. calcd. (%) for $C_{24}H_{20}N_6O_6$: C, 59.01; H, 4.13; N, 17.21. Found: C, 59.23; H, 4.12; N,17.19.

RESULTS AND DISCUSSION

In present study, a series of new pyridazine derivatives were obtained in *ca.* 45-65 % yield, by refluxing equimolar amounts of furandione **1** and hydrazine derivatives in appropriate dry solvents. The moderate yields of the reactions can be explained by the chemical behaviour of furandione **1** towards H-active nucleophiles. Addition of nuclephiles to furandiones of type 1 usually starts with nucleophilic attack at one of the C-2, C-3 and C-5 positions of the furan ring system. Simultaneous attacks of H-active nucleophiles to both C-2 and C-3 positions of furan ring could convert furandiones into starting materials are dicarbonyl compounds and oxalic acid derivatives[30]. The byproducts formed in this way, are removed when the raw product is treated with ether.

A reasonable proposal for reaction pathway from furandione **1** to pyridazine derivatives. **2a**, **2b**, **2c** is outlined briefly in **Scheme-I**.

Ring opening for the formation of intermediates may be initiated by nucleophilic attacks one of the NH_2 or NH groups of hydrazines at one of the C-5 or C-2 positions of the furandione ring[31,32], respectively, similar to the reactions of furandiones with various H-active nucleophiles[33]. Then,

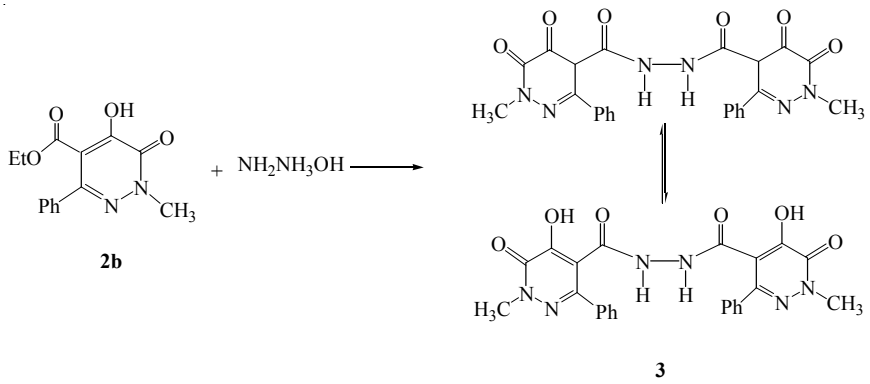


2	R
a	C_6H_4-COOH-4
b	CH_3
c	C_6H_4-NO_2-3

Scheme 1

separating of one molecule water from intermediates formed in this way in the first step gives compounds **2**.

Structure of compounds **2** were confirmed by analytical and spectral data. In addition, the one of these pyridazine derivatives **2b** could be easily converted into corresponding hydrazide compound **3** that in a *bis*-pyridazine derivative, the structure of which was also elucidated by elemental analysis and spectroscopic data (**Scheme-II**).



Scheme 2

Both ^{1}H NMR and ^{13}C NMR of all these pyridazine derivatives showed evidence of the presence of tautomeric equilibria between their tautomeric forms in DMSO-d_6 solution (**Scheme-I**).

In conlusion, while pyrazole-carboxylic acids as a major product together with pyridazindiones, which is a by-product, were obtained from the reactions

of 4-aroyl-2,3-furandiones with hydrazines[29,32], the reactions of 4-ethoxycarbonyl-5-phenyl-2,3-furandione (**1**) with hydrazines resulted in the formation of only pyridazine derivatives.

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