The Synthesis and Reactions of Novel Pyrazole Derivatives by 4-phenylcarbonyl-5-phenyl-2,3-dihydro-2,3-furandione Reacted with Some Hydrazones

AHMET ERDEM[1], HASAN GENC[2], NEJDET SEN[3], RAFET KILINCARSLAN[1]*, EMIN ERDEM[1]

[1]Pamukkale University, Department of Chemistry, 20017-Kinikli, Denizli Turkey

[2]Yuzuncu Yil University, Faculty of Education, Department of Sciences, 65080, Van Turkey

[3]Selcuk University, Faculty of Science, Department of Chemistry, 42031, Konya, Turkey

We report some novel pyrazole derivatives taking 4-phenylcarbonyl-5-phenyl-2,3-dihydro-2,3-furandione, ***1****. For this, 4-phenylcarbonyl-5-phenyl-2,3-dihydro-2,3-furandione,* ***1*** *was reacted with benzaldehyde(2- or 4-fluorophenyl)hydrazone to give 4-benzoyl-1-(2- or 4-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid* ***2a,b.*** *Pyrazol derivative containing 2-fluorophenyl group* ***2a*** *was converted into carboxylic chloride derivative* ***3a*** *by thionyl chloride and then the compound* ***4a*** *was obtained from reaction ammonia with compound* ***3a****. In the next step, 4-benzoyl-1-(2-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid* ***2a*** *was reacted with MeOH/H_2SO_4, EtOH/H_2SO_4, 2-nitrophenylhydrazine and 3-nitrophenylydrazine to give* ***5a,b*** *and* ***6a,b*** *pyrazol derivatives, respectively. The structures regarding all compounds synthesized were determined by the IR, NMR and elemental analysis method.*

Keywords: 2,3-furandione; pyrazole-3-carboxylic acid; nucleophiles; hydrazones.

The 4,5-disubstituted 2,3-furandiones in furandione derivatives which are extremely versatile synthons in heterocyclic chemistry are remarkable starting materials due to the fact that many heterocyclic compounds can be obtained from their high reactivity properties. They shows the ability to enter carbonyl, lacton and a,b-unsaturated carbonyl and thermolysis reactions depending on the reaction conditions and structures of the nucleophiles [1-15]. Practical synthetic methods, mechanism of the reactions as well as semi-empirical and *ab initio* calculations on the interaction of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) with some ureas, semicarbazones, thioureas and anilides have been reported recently [1-18] The reactions of 2,3-furandiones with various phenylhydrazones and phenylhydrazine leads to pyrazole-3-carboxylic acid and pyridazinones [4,9,19-21].

The pyrazole chemistry has been the area of much interest due to the importance of pyrazol derivatives for widespread potential. More especially, it has proven biological and pharmacological activities such as anti-inflammatory, antipyretic, analgesic, antimicrobial, antiviral, antitumor, antifungal, pesticidal, anti-convulsant, antihistaminic, antibiotics, anti-depresant, and CNS regulant activities [22-29]. More continued attention on the pyridazines has been received for improving medicinal drugs in relation with for blood pressure control like hydralazine, which has been used for many years in the remedy of essential hypertension [30,31]. In continuation to our previous efforts [13,14], the nucleophilic and cycloaddition reactions between various *N*-nucleophiles and carbonyls with 4-benzoyl-5-phenyl-2,3-furandione which is novel bicyclic oxalyl compound were investigated, and synthesized. The new compounds shows their characterization studies and routes of synthesis.

Experimental part

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded with a Varian 400 Mercury instrument in $CDCl_3$ or [D_6]-DMSO, using TMS as an internal standard. The chemical shifts are reported in parts per million (δ scale), and all coupling constant (*J*) values are in Hertz [Hz]. The following abbreviations have been used to denote the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet) and dd (double doublet). Melting points (m.p. [°C]) were determined on an Electrothermal Gallenkamp apparatus, and were taken with the samples in open capillary tubes. The mass spectrum of **2** was measured on a Varian mat III at 80 eV. IR absorption spectra were obtained in potassium bromide pellets with a Perkin Elmer spectrum BX spectrometer, and values are reported in cm^{-1}. Monitoring of reactions was performed with silica gel TLC plates (silica Merck 60 F254). Spots were visualized with UV light at 254 nm and 366 nm. Column chromatography was performed with silica gel 60 (0.063-0.200 mm, Merck). Microanalyses were performed on a Carlo Erba elemental analyzer model 1108. Reactions requiring anhydrous conditions were performed under argon. All solvents were freshly distilled under argon prior to being used. All other reagents were purchased from Merck, Fluka, Aldrich and Acros Chemical Co. and used without further purification. 4-benzoyl-5-phenyl-2,3-furandione (**1**) was also prepared according to the literature [41] and purified in our laboratory and kept in vacuo over P_2O_5.

4-(Benzoyl)-1-(2-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2a)

An equimolar mixture of **1** (0.278 g, 1 mmol) and *N*-benzylidene-*N'*-2-fluorophenyl hydrazine (0.214 g, 1mmol) was heated at 80°C in dry benzene (10 mL) for 5h. After the system had cooled to room temp., the solvent was evaporated under the reduced pressure. The formed crude product was crystallized from toluene. Yield: 0.116 g, 30%, m.p.: 232°C. IR: 3435-2600 cm^{-1} (b, OH, COOH), 3062 cm^{-1} (Ar-H), 1685 cm^{-1} (C=O), 1673 cm^{-1} (C=O); ^{1}H NMR (400 Mhz, $CDCl_3$): δ = 8.06 (s, H, COO*H*), 7.01-7.65 ppm (m, 14 H, Ar-*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.4 (C=O, benzoyl), 163.6 (C=O, COOH), 153.8 (C-F), 146.8 (C-3), 144.7 (C-5), 139.2 (N-PhF), 138.8 (C-Ph), 135.2,

* email: rkilincarslan@pau.edu.tr; Phone:+90 258 2963604

133.4, 132.3, 132.0, 131.7, 131.5, 130.6, 130.4, 128.8 (C-Ph), 125.5 (C-4), 125.3, 122.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -121 ppm (s, 1F). Mass (80 eV): m/e = 387.4; 358.6. *Anal.* Calcd. for $C_{23}H_{15}N_2O_2F$: C, 71.50; H, 3.91; N, 7.25. Found: C, 71.36; H, 3.93; N, 7.27.

4-(Benzoyl)-1-(4-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2b)

Compound **2b** was prepared by following the procedure for **2a** by using *N*-benzylidene-*N'*-4-fluorophenyl hydrazine (0.214 g, 1 mmol) and **1** (0.278 g, 1 mmol). Yield: 0.155 g, 40%, m.p.: 216°C. IR: 3410-2600 cm^{-1} (b, OH, COOH), 3056 cm^{-1} (Ar-H), 1721 cm^{-1} (C=O), 1686 cm^{-1} (C=O); ^{1}H NMR (400 Mhz, $CDCl_3$): δ = 7.98 (s, H, COO*H*), 7.01-7.72 ppm (m, 14 H, Ar-*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.4 (C=O, benzoyl), 161.8 (C=O, COOH), 152.7 (C-F), 145.4 (C-3), 144.6 (C-5), 138.1 (N-PhF), 138.4 (C-Ph), 134.9, 133.5, 132.1, 131.8, 131.2, 130.9, 130.1, 129.9, 128.9 (C-Ph), 125.2 (C-4), 125.1, 122.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -121 ppm (s, 1F). Mass (80 eV): m/e = 387.4; 358.5. *Anal.* Calcd. for $C_{23}H_{15}N_2O_3F$: C, 71.50; H, 3.91; N, 7.25. Found: C, 71.41; H, 3.97; N, 7.29.

4-(Benzoyl)-1-(2-fluorophenyl)-5-phenyl-1H-pyrazole-3-carbonyl Chloride (3a)

Compound **2a** (0.386 g, 1 mmol) and thionylchloride (1 mL, 13.8 mmol) were refluxed on a steam bath for 6 h. After cooling, the crude precipitate was isolated by filtration and recrystallized from a mixture of toluene / *n*-hexane (1:3). Yield: 0.332 g, 82%, m.p.: 218°C. IR: 1746 cm^{-1} (C=O, acyl), 1664 cm^{-1} (C=O, benzoyl); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.4 (C=O, benzoyl), 162.2 (C=O, acyl), 153.9 (C-F), 146.8 (C-3), 147.1 (C-5), 139.0 (N-PhF), 138.5 (C-Ph), 135.7, 133.3, 132.6, 132.2, 131.4, 131.5, 130.0, 129.7, 128.3 (C-Ph), 126.1 (C-4), 124.9, 122.3 ppm. *Anal.* Calcd. for $C_{23}H_{14}N_2O_2FCl$: C, 68.24; H, 3.49; N, 6.92. Found: C, 68.19; H, 3.42; N, 6.90.

4-(Benzoyl)-1-(2-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxamide (4a)

A moderate stream of gaseous ammonia was allowed to bubble through a solution of **3a** (0.405 g, 1 mmol) in CCl_4 (20 mL) during 30 min with ice-cooling. Then the crude precipitate was isolated by filtration and recrystallized from methanol. Yield: 0.239 g, 62%, m.p.: 184°C. IR: 3473 cm^{-1} (NH_2), 1740 cm^{-1} (C=O, benzoyl), 1676 cm^{-1} (C=O, amide). ^{1}H NMR (400 Mhz, DMSO-d_6): δ = 5.62 and 6.87 (b, NH_2), 7.08-7.96 ppm (m, 14H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.2 (C=O, benzoyl), 163.5 (C=O, acyl), 153.8 (C-F), 147.8 (C-3), 145.4 (C-5), 139.2 (N-PhF), 138.9 (C-Ph), 135.4, 132.9, 132.4, 132.1, 131.3, 131.5, 130.0, 129.7, 128.8 (C-Ph), 126.9 (C-4), 124.6, 122.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -121 ppm (s, 1F). *Anal.* Calcd. for $C_{23}H_{16}N_3O_2F$: C, 71.68; H, 4.18; N, 10.90. Found: C, 71.94; H, 4.17; N, 10.96.

4-Benzoyl-1-(2-fluorophenyl)-5-phenyl-1H-Pyrazole-3-carboxylic Acid Methyl Ester (5a)

4-Benzoyl-1,5-diphenyl-1*H*-Pyrazole-3-carboxylic acid (**2a**) (1 g, 2.58 mmol), a large excess of the alcohol and catalytic amounts of sulfuric acid were refluxed for 3 h. After cooling to 5°C (refrigerator), the precipitate thus formed was filtered off and recrystallized from the methanol. Yield: 0.220 g, 55%, m.p.: 167°C. IR: 1725 cm^{-1} (C=O, benzoyl), 1656 cm^{-1} (C=O, ester). ^{1}H NMR (400 Mhz, $CDCl_3$): δ = 3.76 ppm (s, 3H, OCH_3), 7.10-7.92 ppm (m, 14 H, Ar-*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 193.0 (C=O, benzoyl), 162.8 (C=O, ester), 158.2 (C-F), 145.1 (C-3), 139.8 (C-5), 137.2 (N-PhF), 138.6 (C-Ph), 135.6, 133.4, 132.1, 132.0, 131.9, 131.4, 131.0, 130.4, 128.7 (C-Ph), 125.1 (C-4), 125.2, 122.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -121 ppm (s, 1F). *Anal.* Calcd. for $C_{24}H_{17}N_2O_3F$: C, 71.99; H, 4.28; N, 7.00. Found: C, 71.91; H, 4.34; N, 6.94.

4-Benzoyl-1-(2-fluorophenyl)-5-phenyl-1H-Pyrazole-3-carboxylic Acid n-Propyl Ester (5b)

Compound **5b** was prepared by following the procedure for **5a** by using *n*-propanol and **2a**. Yield: 0.287 g, 67%, m.p.: 222°C. IR: 1741 cm^{-1} (C=O, benzoyl), 1667 cm^{-1} (C=O, ester). ^{1}H NMR (400 Mhz, $CDCl_3$): δ = 0.74 ppm (t, *J* = 7.4 Hz, 3H, $OCH_2CH_2CH_3$), 1.42 ppm (m, 2H, $OCH_2CH_2CH_3$), 4.05 ppm (t, *J* = 7.2 Hz, 2H, $OCH_2CH_2CH_3$), 7.05-7.95 ppm (m, 14 H, Ar-*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.0 (C=O, benzoyl), 162.2 (C=O, ester), 158.5 (C-F), 144.2 (C-3), 139.8 (C-5), 142.6 (N-PhF), 138.2 (C-Ph), 134.9, 133.5, 132.2, 132.1, 131.8, 131.4, 131.0, 130.3, 128.5 (C-Ph), 125.1 (C-4), 125.1, 122.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -121 ppm (s, 1F). *Anal.* Calcd. for $C_{26}H_{21}N_2O_3F$: C, 72.88; H, 4.94; N, 6.54. Found: C, 72.72; H, 4.97; N, 6.45.

2-(2-fluorophenyl)-6-(2-nitrophenyl)-3,4-diphenyl-2,6-dihydropyrazolo-[3,4-d]-pyridazin-7-one (6a)

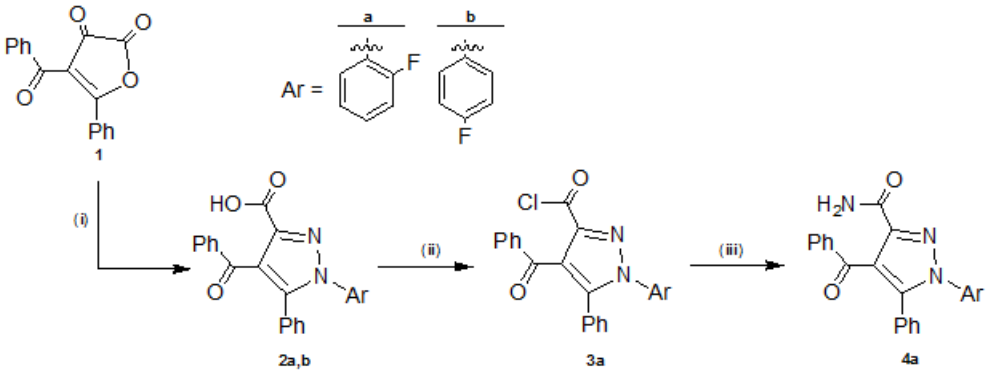
A millequimolar mixture of **2a** and 2-nitrophenylhydrazine was refluxed in xylene for 5h. After the solvent was removed by evaporation, the oily residue was treated with diethyl ether and the formed crude product was recrystallized from methanol. Yield: 0.282 g, 56%, m.p.: 191°C. IR: 1725 cm^{-1} (C=O). ^{1}H NMR (400 Mhz, DMSO-d_6): δ =6.65-8.17 ppm (m, 18H, Ar*H*). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.0 (C-F), 154.8 (C=O), 147.4 (C-NO_2), 145. 2 (C-4), 143.8 (C-3), 141.6 (N-PhNO_2), 139.4 (N-PhF), 133.6, 132.7, 132.2 (C-Ph), 132.1 (C-Ph), 131.9, 131.8, 130.6, 130.5, 129.6, 129.3, 127.8, 125.5, 123.1, 119.2 ppm (C-Ph). *Anal.* Calcd. for $C_{29}H_{18}N_5O_3F$: C, 69.18; H, 3.60; N, 13.91. Found: C, 69.45; H, 3.58; N, 13.88.

2-(2-fluorophenyl)-6-(3-nitrophenyl)-3,4-diphenyl-2,6-dihydropyrazolo-[3,4-d]-pyridazin-7-one (6b)

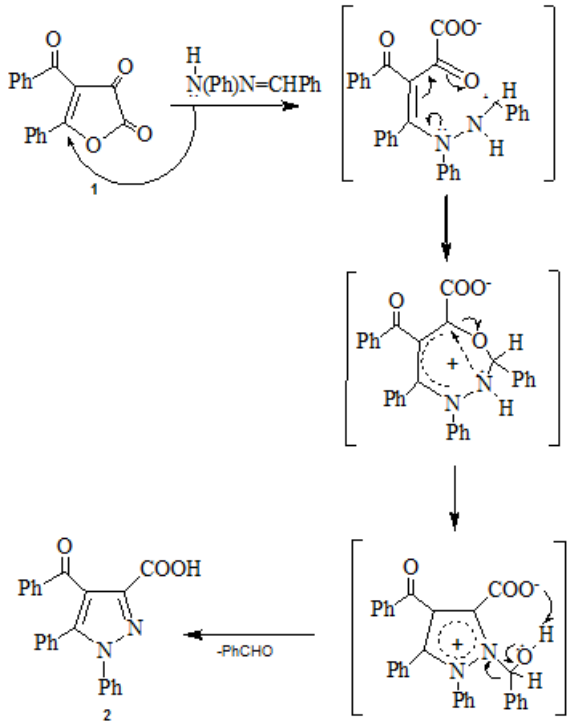
Compound **6b** was prepared by following the procedure for **6a** by using 3-nitrophenylhydrazine and **2a**. Yield: 0.292 g, 58%, m.p.: 188°C. IR: 1698 cm^{-1} (C=O). ^{1}H NMR (400 Mhz, DMSO-d_6): δ =6.67-8.05 ppm (m, 18H, Ar*H*). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.0 (C-F), 153.9 (C=O), 146.8 (C-NO_2), 145. 1 (C-4), 143.4 (C-3), 140.9 (N-PhNO_2), 139.3 (N-PhF), 133.6, 132.6, 132.2 (C-Ph), 132.0 (C-Ph), 131.8, 131.7, 130.6, 130.4, 129.7, 129.3, 127.8, 125.4, 123.0, 119.2 ppm (C-Ph). *Anal.* Calcd. for $C_{29}H_{18}N_5O_3F$: C, 69.18; H, 3.60; N, 13.91. Found: C, 69.42; H, 3.57; N, 13.84.

Results and discussion

Firstly, sequential treatment of 4-benzoyl-5-phenyl-2,3-furandione (**1**) with an equimolar of *N*-benzylidene-*N'*-2-fluorophenyl hydrazine or *N*-benzylidene-*N'*-4-fluorophenyl hydrazine in dry benzene for about 5h gave access to the formation of pyrazole-3-carboxylic acid derivative **2a** and **2b**, in approximately %30 yield, respectively, which are important starting materials in the synthesis of the target heterocycles [20,21,32] and were subjected to treatment of thionyl chloride [19] in order to give the expected 4-benzoyl-1-(2-fluorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxyl chloride **3a** in 80% yield while obtaining not isolated to **3b**. The carboxyl chloride was then treated with concentrated ammonia solution to provide the corresponding amine derivative **4a** (scheme 1) in satisfactory yield.



Scheme 1. The synthesis of pyrazol derivatives: (i) PhCH=NNH-C_6H_4-*o*-F or PhCH=NNH-C_6H_4-*p*-F, benzene, 80°C; (ii) SO_2Cl_2, 90°C; (iii) NH_3 solution

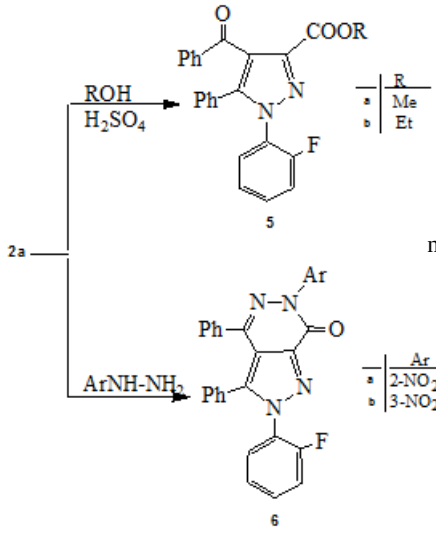


Scheme 2. The reaction pathway for the synthesis of 3-carboxylic acid derivative **2**

The moderate yield of the first step can be explained by the chemical behavior of furandione (**1**) towards *H*-active nucleophiles. The carbons C-2, C-3 and C-5 in furandiones are electrophilic sites having different reactivity and could be used for the formation reactions with nucleophiles [16,33]. Concurrent attacks of *H*-active nucleophiles to both C-2 and C-3 positions of the furan moiety could convert furandiones into starting materials; these compounds are dibenzoylmethane and oxalic acid derivatives [34]. The by-products formed during this stage are removed by treatment of the raw product with diethyl ether. The reaction pathway from 4-benzoyl-5-phenyl-2,3-furandione **1** to pyrazole acid **2** is outlined briefly in scheme 2 and the compounds **2a** and **2b** were obtained according to the reported method [9,14] and the structures are in agreement with the reported data.

Experimental part

In addition, while 4-benzoylpyrazole-3-carboxylic acid **2a** could be easily converted by $SOCl_2$ into the corresponding acid chloride **3a** and then amide derivative **4a** by the usual chemical procedures (scheme 1), conversion of **2b** with only $SOCl_2$ (also tested with PCl_5), and with difficulty and no isolation by impurities due to by-products, into the corresponding acid chloride **3b** may be referred to a *p*-effect originated from 4-fluorophenyl at C-1 position of **2b**. On the other hand, the esterification



Scheme 3. The synthesis of novel compounds by nucleophilic addition

reaction[21] between carboxylic acid group at C-3 position of **3a** and methanol or ethanol in the presence of concentrated sulphuric acid as catalyst (scheme 3) gave easily access to corresponding novel compound **5a** and **5b**, respectively, in approximately 70-75% yields.

Reaction of many pyrazole derivatives having functionalities such as carboxylic acids, carbonyls, esters and nitriles in the *o*-positions according to each other with hydrazines may be a convenient method to build the pyrazolo[3,4-*d*]pyridazine system [9,39,40]. On this basis, the 4-benzoylpyrazole-3-carboxylic acid **2a** was cyclized with various hydrazine compounds were synthesized novel pyrazole-pyridazine derivatives **6a** and **6b**, respectively, which are the pyrazolo[3,4-*d*]pyridazinones, in approximately 65-70% yields (scheme 3).

Conclusions

In this study, we report the synthesis of novel pyrazole and pyrazolo-[3,4-*d*]-pyridazine derivatives from 4-benzoyl-5-phenyl-2,3-furandione (**1**) precursor compound. All the compounds have been synthesized using methods known from literature and characterized using appropriate spectroscopic techniques. Each subfamily was prepared in moderate to good yields. Other assays are currently in progress in order to increase our library size and to use the method to develop biologically active compounds.

Acknowledgments: Financial support from Selçuk University (Project No: 10201091) are gratefully acknowledged.

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Manuscript received: 16.05.2016