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

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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/H2SO4, EtOH/H2SO4, 2-nitrophenylhydrazine and 3-nitrophenylhydrazine 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 show the ability to enter carbonyl, lacton and a,b-unsaturated carbonyl and thermal isomerization 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 uras, 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 pyrazidones [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 interest due to the importance of pyrazol derivatives for biological and pharmacological activities such as antiviral, antitumor, antifungal, pesticidal, anti-convulsant, antihistaminic, antibiotics, anti-depressant, and CNS.

Experimental part

1H NMR, 13C NMR and 19F NMR spectra were recorded with a Varian 400 Mercury instrument in CDCl3 or [D2] 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 P2O5.

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); 1H NMR (400 MHz, CDCl3): δ = 8.06 (s, H, COOH), 7.01-7.65 ppm (m, 14 H, Ar-H); 13C NMR (101 MHZ, CDCl3): δ: 169.4 (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,
4-Benzoyl-1-(4-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid (2b)

Compound 2b was prepared by the following 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: 1340-2600 cm⁻¹ (b, OH, COOH), 3056 cm⁻¹ (Ar-H), 1721 cm⁻¹ (C=O), 1666 cm⁻¹ (C=O); ¹H NMR (400 MHz, CDCl₃): δ = 7.98 (s, H, COOH), 7.01-7.72 ppm (m, 14 H, Ar-H); ¹³C NMR (101 MHz, CDCl₃): 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, 130.1, 130.8, 129.8 ppm. ¹⁹F NMR (376 MHz, DMSO-d₆): δ = 197.2 (C=O, benzoyl), 162.2 (C=O, ester), 158.5 (C-Ph), 130.8, 130.7, 130.6, 130.5, 129.3, 129.8, 128.9 (C-Ph), 129.2 ppm. Anal. Calcd. for C₂₃H₁₅N₂O₃F: C, 71.50; H, 3.91; N, 13.91. Found: C, 71.41; H, 3.97; N, 13.67.

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

Compound 3a was prepared by the following procedure for 2a by using N-benzylidene-N'-4-fluorophenyl hydrazine or N-benzylidene-N'-2-fluorophenyl hydrazine in dry benzene for about 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). ¹H NMR (400 MHz, DMSO-d₆): δ = 6.65-8.17 ppm (m, 18H, ArH). ¹³C NMR (101 MHz, DMSO-d₆): δ = 160.0 (C=O), 154.8 (C-Ph), 147.8 (C-3), 145.4 (C-5), 139.9 (N-PhNO₂), 139.4 (C-Ph), 133.6, 132.7, 132.2 (C-Ph), 132.1 (C=Ph), 131.9, 131.8, 130.6, 130.5, 129.3, 129.8, 125.3, 123.1, 119.2 ppm (C-Ph). Anal. Calcd. for C₁₉H₁₅N₃O₂F: C, 69.18; H, 3.60; N, 13.91. Found: C, 69.45; H, 3.58; N, 13.88.

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 with thionyl chloride [19] in order to gain the expected 4-benzoyl-1-(2-fluorophenyl)-5-phenyl-1H-pyrazole-3-carboxyl chloride 3a in 80% yield while obtaining not isolated to 3b. The carbonyl chloride was then treated with concentrated ammonia solution to provide the corresponding amine derivative 4a (scheme 1) in satisfactory yield.

2-(2-fluorophenyl)-6-(2-nitrophenyl)-1H-pyrindazin-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). ¹H NMR (400 MHz, DMSO-d₆): δ = 6.65-8.17 ppm (m, 18H, ArH). ¹³C NMR (101 MHz, DMSO-d₆): δ = 160.0 (C=O), 154.8 (C-Ph), 147.8 (C-3), 145.4 (C-5), 139.9 (N-PhNO₂), 139.4 (C-Ph), 133.6, 132.7, 132.2 (C-Ph), 132.1 (C=Ph), 131.9, 131.8, 130.6, 130.5, 129.3, 129.8, 125.3, 123.1, 119.2 ppm (C-Ph). Anal. Calcd. for C₁₉H₁₅N₃O₂F: C, 69.18; H, 3.60; N, 13.91. Found: C, 69.45; H, 3.58; N, 13.88.
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 SOCl₂ into the corresponding acid chloride 3a and then amidé derivative 4a by the usual chemical procedures (scheme 1), conversion of 2b with only SOCl₂, (also tested with PCl₅), 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 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.

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**References**


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