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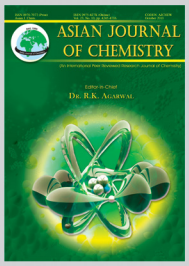

Reactions of Some Pyrazole-3-Carboxylic Acid and Carboxylic Acid Chlorides with Various Alcohols

ILHAN ÖZER ILHAN*, ÖZLEM BAHADIR, ZÜLBIYE ÖNAL and EMIN SARIPINAR

Department of Chemistry, Erciyes University, 38039 Kayseri, Turkey

*Corresponding author: E-mail: ilhano@erciyes.edu.tr

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The reactions of 4-benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid (**2b**), 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) and 4-benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3b**) can easily be converted into the corresponding ester **5**, from reaction with various alcohols. It has been demonstrated that with the variation in reaction conditions, the reaction changes leading to different products. All newly synthesized compounds were characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR spectral data. All compounds were compared with their previous analogues.

Key Words: Furan-2-3-dione, Pyrazole-3-carboxylic acid, Pyrazole-3-carboxylic acid chlorides, Carboxylate.

INTRODUCTION

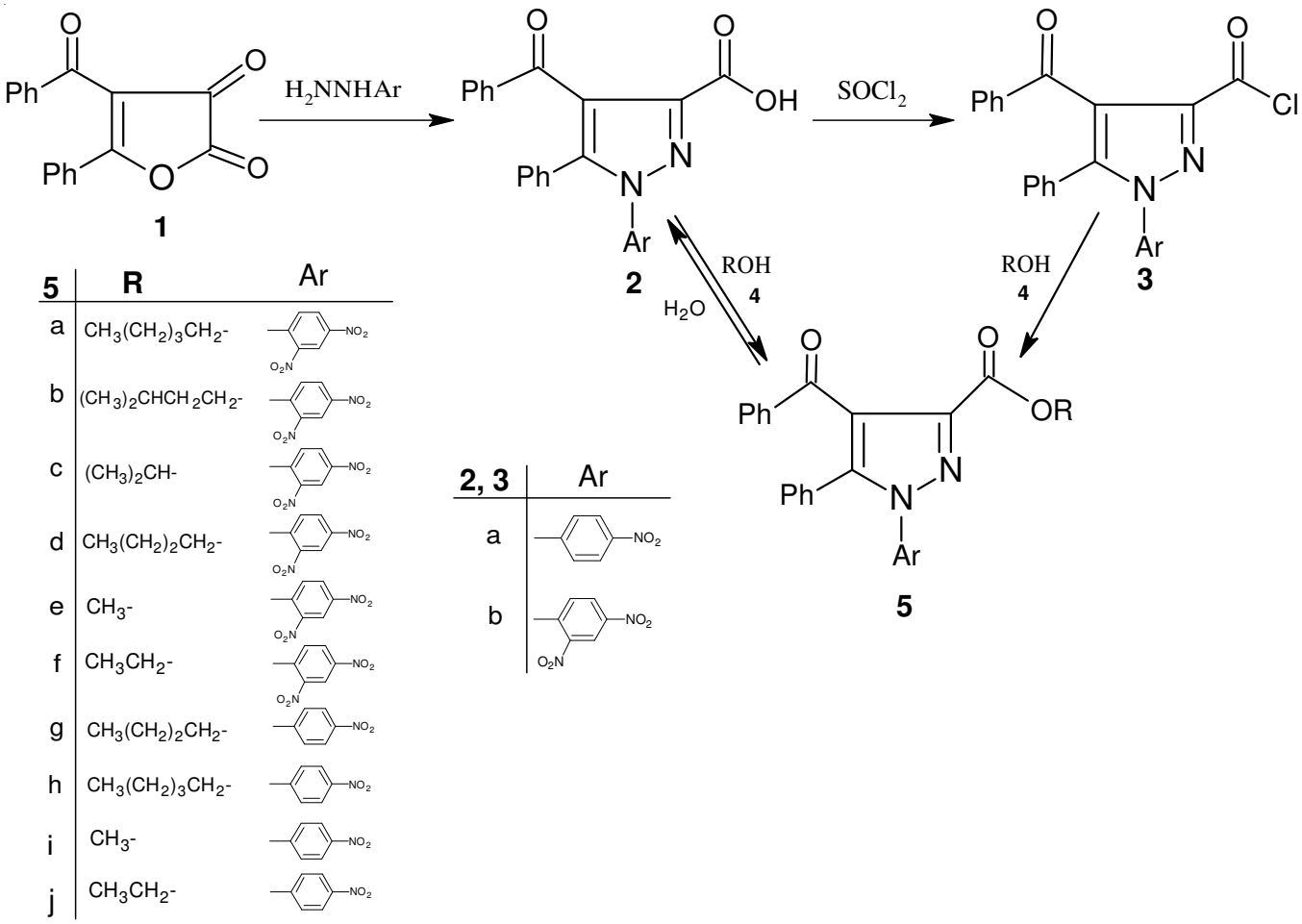
The cyclocondensation reaction of 1,3-dicarbonyl compounds with oxalyl chloride represents a convenient synthesis of furan-2,3-dione systems[1-3], which costitute an important group of oxygen-containing heterocyclic starting materials that have been widely explored during the last few decades[4-7]. A convenient method for their synthesis and the mechanism of the reactions, as well as semi-empirical (AM1 and PM3) and *ab initio* calculations on the interaction of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione **(1)** with several semicarbazones, ureas, thioureas and oximes, have been reported recently[8-13]. The reaction of the furan-2,3-dione with various phenylhydrazones and phenylhydrazine leads to pyrazole-carboxylic acid and pyridazinones[14-16].

Pyrazole derivatives in general are well-known nitrogen-containing heterocyclic compounds and various procedures have been developed for their syntheses[17-21]. The chemistry of pyrazole derivatives have been the subject of much research due to their importance in various applications and their widespread potential biological and pharmacological activities such as antiinflammatory, antipyretic, analgesic, antimicrobial, antiviral, antitumor, antifungal, pesticidal, anticonvulsant, CNS regulants, antihistaminic, antibiotics, antidepressant activities[22-29]. In view of these important properties, we attempted both to prove reproducibility of the reaction of 4-benzoyl-1-(2,4-dinitrophenyl-5-phenyl-1*H*-pyrazole-3-carboxylic acid **(2b)** and 1*H*-pyrazole-3-carboxylic acid chlorides (**3a-b**) with some alcohol derivatives and to extend our investigations related to preparing new heterocycles, which include the pyrazole ring in their structure. We are now reporting the reaction mechanism, synthesis and characterization of 1*H*-pyrazole-3-carboxylate derivatives (**5a-j**) by the reaction of the pyrazole-3-carboxylic acid (**2b**) and pyrazole-3-carboxylic acid chlorides (**3a-b**) with the corresponding alcohol derivatives **4** (**Scheme-I**).

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 IR spectra were recorded on a Shimadzu Model 8400 FT IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker-400 MHz Ultra Shield istrument. The chemical shifts are reported in ppm from tetramethylsilane as an internal standard and are given in δ (ppm). All experiments were followed by TLC using DC Alufolien Kieselgel 60 F_{254} Merck and Camag TLC lamp (254/366 nm).

Pentyl-4-benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5a): 4-Benzoyl-1-[2,4-dinitrophenyl] -5-phenyl-1*H*-pyrazole-3-carboxylic acid **(2b)** (1 g), a large excess of the *n*-pentyl (or *n*-amyl) alcohol and catalylic amounts of surfuric acid were refluxed for 4 h. After cooling, the precipitate thus formed was filtered off and recrystallized from the same alcohol and allowed to dry on P_2O_5; resulting in yield 40 % (0.40 g); m.p. 124 ºC; IR (KBr, ν_{max}, cm^{-1}) 1751 (C=O, ester), 1688 (C=O, benzoyl); ^{1}H NMR ($CDCl_3$, δ) 8.94-7.24 (m, 13H, ArH), 3.95 (t, 2H, OCH_2), 1.28-0.87 (m, 6H, $-CH_2-CH_2-CH_2-$), 0.79-0.68 ppm (t, 3H, $-CH_3$). ^{13}C NMR



Scheme-I: Synthesis of the pyrazole-3-carboxylate derivatives (**5a-j**)

($CDCl_3$, δ) 192.47 C=O, benzoyl), 162.91 (C=O, ester), 150.05 (C3), 144.10 (C5), 142.15 and 140.55 (C-NO_2), 130.31-127.49 (aromatic C), 125.05 (C4), 67.15 (O-CH_2), 64.58, 27.87, 22.08 (-CH_2-), 13.76 ppm (CH_3). Elemental analysis (%): found (calcd.): [C = 63.66 (63.63), H = 4.69 (4.54), N = 10.65 (10.60)].

Isopentyl 4-benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5b): 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid **(2b)** (1 g), a large excess of the *iso*-pentyl alcohol and catalytic amounts of surfuric acid were refluxed for 4 h. After cooling, the precipitate thus formed was filtered off and recrystallized from the same alcohol and allowed to dry on P_2O_5; resulting in yield 40 % (0.46 g); m.p. 142 ºC; IR (KBr, ν_{max}, cm^{-1}) 1753 (C=O, ester), 1670 (C=O, benzoyl); ^{1}H NMR ($CDCl_3$, δ) 7.78-7.24 (m, 13H, ArH), 3.92 (t, 2H, OCH_2), 1.28 (m, 2H, -CH_2-), 0.79 and 0.68 ppm (q, 6H, -CH_3); ^{13}C NMR ($CDCl_3$, δ) 193.13 C=O, benzoyl), 163.81 (C=O, ester), 145.85 (C3), 144.36 (C5), 143.00 and 140.77 (C-NO_2), 130.31-127.49 (aromatic C), 125.54 (C4), 67.15 (O-CH_2), 38.95 (CH), 26.55 (-CH_2-), 24.27 ppm (CH_3). Elemental analysis (%): found (calcd.): [C = 63.78 (63.63), H = 4.63 (4.54), N = 10.77 (10.60)].

Isopropyl 4-benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5c): 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid **(2b)** (1 g), a large excess of the *iso*propyl alcohol and catalytic amounts of surfuric acid were refluxed for 4 h. After cooling, the precipitate thus formed was filtered off and recrystallized from the same alcohol and allowed to dry on P_2O_5; resulting in yield 35 % (0.38 g); m.p. 114 ºC; IR (KBr, ν_{max}, cm^{-1}) 1730 (C=O, ester), 1660 (C=O, benzoyl); ^{1}H NMR ($CDCl_3$, δ) 7.85-7.20 (m, 13H, ArH), 4.06 (1H, OCH), 0.75 and 0.68 ppm (q, 6H, -CH_3). Elemental analysis (%): found (calcd.): [C = 62.10 (62.40), H = 3.83 (4.00), N = 11.09 (11.20)].

Butyl 4-benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5d): 4-Benzoyl-1-[2,4-dinitrophenyl] -5-phenyl-1*H*-pyrazole-3-carboxylic acid **(2b)** (1 g), a large excess of the *n*-butyl alcohol and catalytic amounts of surfuric acid were refluxed for 4 h. After cooling, the precipitate thus formed was filtered off and recrystallized from the same alcohol and allowed to dry on P_2O_5; resulting in yield 45 % (0.51 g); m.p. 137 ºC IR (KBr, ν_{max}, cm^{-1}) 1704 (C=O, ester), 1674 (C=O, benzoyl); ^{1}H NMR ($CDCl_3$, δ) 7.94-7.01 (m, 13H, ArH), 4.05 (t, 2H, OCH_2), 1.28 and 0.97 (m, 4H, -CH_2-CH_2-), 0.79 ppm (t, 3H, -CH_3); ^{13}C NMR ($CDCl_3$, δ) 192.13 (C=O, benzoyl), 163.51 (C=O, ester), 147.05 (C3), 144.10 (C5), 142.15 and 140.55 (C-NO_2), 134.31-127.65 (aromatic C), 124.05 (C4), 67.15 (O-CH_2), 31.87, 22.18 (-CH_2-), 14.76 ppm (CH_3). Elemental analysis (%): found (calcd.): [C = 63.15 (63.04), H = 4.01 (4.28), N = 10.60 (10.89)].

Methyl 4-benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5e): 4-Benzoyl-1-[2,4-dinitrophenyl] -5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **(3b)** (1.0 g)

and a moderate excess of the methyl alcohol were refluxed together with catalytic amounts of pyridine for 4 h. After cooling, the solution was acidified by adding diluted hydrochloric acid to give a crude solid that was recrystallized from a same alcohol and allowed to dry on P_2O_5; resulting in yield 65 % (0.64 g); m.p. 239 ºC; IR (KBr, ν_{max}, cm^{-1}) 1725 (C=O, ester), 1668 (C=O, benzoyl); ^1H NMR ($CDCl_3$, δ) 7.94-7.01 (m, 13H, ArH), 3.85 ppm (s, 3H, $-OCH_3$). Elemental analysis (%): found (calcd.): [C = 60.77 (61.01), H = 3.17 (3.38), N = 11.54 (11.86)].

Ethyl 4-benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5f): 4-Benzoyl-1-[2,4-dinitrophenyl] -5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **(3b)** (1.0 g) and a moderate excess of the ethyl alcohol were refluxed together with catalytic amounts of pyridine for 4 h. After cooling, the solution was acidified by adding diluted hydrochloric acid to give a crude solid that was recrystallized from a same alcohol and allowed to dry on P_2O_5; resulting in yield 60 % (0.61 g); m.p. 239 ºC; IR (KBr, ν_{max}, cm^{-1}) 1735 (C=O, ester), 1656 (C=O, benzoyl); ^1H NMR ($CDCl_3$, δ) 7.94-7.01 (m, 13H, ArH), 3.97 (s, 2H, $-OCH_2$). 0.79 ppm (t, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$, δ) 194.30 C=O, benzoyl), 157.97 (C=O, ester), 154.53 (C3), 148.00 (C5), 145.04 and 138.50 (C-NO_2), 135.50-128.65 (aromatic C), 121.04 (C4), 78.68 (O-CH_2), 12.65 ppm (CH_3). Elemental analysis (%): found (calcd.): [C = 61.99 (61.72), H = 3.46 (3.70), N = 11.70 (11.52)].

Butyl 4-benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5g): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **(3a)** (1.0 g) and a moderate excess of the *n*-butyl alcohol were refluxed together with catalytic amounts of pyridine for 3 h. After cooling, the solution was acidified by adding diluted hydrochloric acid to give a crude solid that was recrystallized from a same alcohol and allowed to dry on P_2O_5; resulting in yield 64 % (0.70 g); m.p. 245 ºC; IR (KBr, ν_{max}, cm^{-1}) 1732 (C=O, ester), 1622 (C=O, benzoyl); ^1H NMR ($CDCl_3$, δ) 8.43-7.29 (m, 14H, ArH), 3.23 (t, 2H, OCH_2), 1.63 and 1.27 (m, 4H, $-CH_2-CH_2-$), 0.84 ppm (t, 3H, $-CH_3$). Elemental analysis (%): found (calcd.): [C = 68.78 (69.08), H = 4.60 (4.90), N = 9.25 (8.95)].

Pentyl 4-benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5h): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **(3a)** (1.0 g) and a moderate excess of the *n*-pentyl alcohol were refluxed together with catalytic amounts of pyridine for 3 h. After cooling, the solution was acidified by adding diluted hydrochloric acid to give a crude solid that was recrystallized from a same alcohol and allowed to dry on P_2O_5; resulting in yield 64 % (0.72 g); m.p. 237 ºC; IR (KBr, ν_{max}, cm^{-1}) 1702 (C=O, ester), 1637 (C=O, benzoyl). Elemental analysis (%): found (calcd.): [C = 69.27 (69.56), H = 5.43 (5.17), N = 8.75 (8.69)].

Methyl 4-benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5i): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **(3a)** (1.0 g) and a moderate excess of the methyl alcohol were refluxed together with catalytic amounts of pyridine for 4 h. After cooling, the solution was acidified by adding diluted hydrochloric acid to give a crude solid that was recrystallized from a same alcohol and allowed to dry on P_2O_5; resulting in yield 66 % (0.65 g); m.p. 244 ºC; IR (KBr, ν_{max}, cm^{-1}) 1733 (C=O, ester), 1620 (C=O, benzoyl); ^1H NMR ($CDCl_3$, δ) 8.30-7.22 (m, 14H, ArH), 3.75 ppm (s, 3H, $-OCH_3$). Elemental analysis (%): found (calcd.): [C = 67.11 (67.45), H = 3.94 (3.98), N = 10.27 (9.84)].

Ethyl 4-benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylate (5j): 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **(3a)** (1.0 g) and a moderate excess of the ethyl alcohol were refluxed together with catalytic amounts of pyridine for 4 h. After cooling, the solution was acidified by adding diluted hydrochloric acid to give a crude solid that was recrystallized from a same alcohol and allowed to dry on P_2O_5; resulting in yield 65 % (0.66 g); m.p. 252 ºC; IR (KBr, ν_{max}, cm^{-1}): 1733 (C=O, ester), 1622 (C=O, benzoyl); ^1H NMR ($CDCl_3$, δ) 7.94-7.27 (m, 14H, ArH), 3.68 (s, 2H, $-OCH_2$). 1.15 ppm (t, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$, δ) 194.45 (C=O, benzoyl), 158.20 (C=O, ester), 154.98 (C3), 148.30 (C5), 145.32 (C-NO_2), 136.20-127.42 (aromatic C), 122.10 (C4), 78.50 (O-CH_2), 13.15 ppm (CH_3). Elemental analysis (%): found (calcd.): [C = 68.39 (68.03), H = 3.92 (4.31), N = 9.89 (9.52)].

RESULTS AND DISCUSSION

Present approach to obtaining the particular heterocyclic systems uses the synthesis of the 1*H*-pyrazole-3-carboxylic acid (**2a-b**) from 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione and 4-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine, respectively. The compounds **2a-b** can easily be transformed into the corresponding 1*H*-pyrazole-3-carboxylic acid chlorides **3a-b** by usual chemical procedures. Substituted 2,3-furandione, acid **2** and acid chlorides **3a-b**, which are used as important materials in the synthesis of the target heterocycles, were prepared using the literature procedures[1,14,30,31]. The reaction of the compound **2** or **3** with some alcohols led to the formation of the corresponding carboxylate derivatives **5** under reflux for 4 h, without opening the pyrazole ring. In order to make the reaction selective, we had to determine the parameters in other words the reaction pathways, leading to such results. The compounds **2b** and **3a-b** treatment with various alcohol derivatives **4** in boiling alcohols gave the corresponding 1*H*-pyrazole-3-carboxylate (**5**) as main product.

The progress of the reactions was monitored by thin-layer chromatography until complete consumption of the starting materials. The compounds **5a-j** were obtained in moderate yields (35-66 %) after evaporation of the organic solvents and recrystallization from proper solvents (like ethanol or methanol see **Scheme-I**). The structures of synthesized compounds were assigned on the basis of analytical as well as spectroscopic data. Product **5f** obtained in 65 % yield by treating **5** with ethanol and refluxing in boiling ethanol for 4 h. In the FT IR spectra of compound **5f**, the C=O absorption was seen at 1735 (C=O, ester), 1656 cm^{-1} (C=O, benzoyl). The ^1H NMR signals were at δ = 7.94-7.01 (m, 13H, ArH), 3.97 (s, 2H, $-OCH_2$). 0.79 ppm (t, 3H, $-CH_3$). The ^{13}C NMR signals were found to be at δ =194.30 (C=O, benzoyl), 157.97 (C=O, ester), 154.53 (C3), 148.00 (C5), 145.04 and 138.50 (C-NO_2), 135.50-128.65 (aromatic C), 121.04 (C4), 78.68 (O-CH_2), 12.65 ppm (CH_3) and elemental analysis data confirm the structure of **6f**.

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