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Reactions of Some Pyrazole-3-Carboxylic Acid Chlorides with Various Anilides

ILHAN ÖZER ILHAN* and MEHMET ÇADIR

Department of Chemistry, Erciyes University, 38039 Kayseri, Turkey

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

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1*H*-pyrazole-3-carboxylic acid chlorides (**3**) can easily be converted into the corresponding 1*H*-pyrazole-3-carboxamide (**5**) by reaction with various anilides. 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, FT-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, Carboxamide.

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 phenyl-hydrazones 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]. The possible biological properties of the pyrazol, pyridazinone, pyrazolopyridazinone[30] and oxazin derivatives make it attractive to study these compounds. In view of these important properties, we decided both to provide reproducibility of the reactions of 1*H*-pyrazole-3-carboxylic acid chlorides (**3a-b**) with some anilide derivatives 4 and to extend our investigations related to preparing new hetrocycles, which include the pyrazole ring in their structure.

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).

***N*-Acetyl,4-benzoyl-1-(2,4-dinitrophenyl)-*N*,5-diphenyl-1*H*-pyrazole-3-carboxamide (5a):** 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.35 g, 0.76 mmol) and acetanilide (0.10 g, 0.76 mmol) were refluxed in xylene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product which was recrystallized from ethanol and dried on P_2O_5. m.p.: 230 ºC, yield 0.31g (71 %). FT-IR: 3062, 2890 (arom. and aliph. CH), 1697, 1668, 1614 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.43-7.19 (m, 18H, Ar-H), 2.20 (3H, CH_3); ^{13}C NMR (DMSO-d_6): δ = 192.68 (t, PhCO), 151.90 (C-3), 145.68 (C-5), 143.00 and 140.77 (C-NO_2), 133.33-122.51 (m, aromatic C), 26.11 (CH_3). Anal. calcd. for $C_{31}H_{21}N_5O_7$: C, 64.69; H, 3.68; N, 12.17. Found: C, 64.82; H, 3.48; N, 12.25.

***N*-Acetyl-4-benzoyl-1-(2,4-dinitrophenyl)-*N*-(4-methylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5b):** 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1H-pyrazole-3-carboxylic acid chloride (**3a**) (0.35 g, 0.76 mmol) and *p*-methylacetanilide (0.11g, 0.76 mmol) were refluxed in xylene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product which was recrystallized from methanol and dried on P_2O_5. m.p.: 239 ºC, yield 0.29 g (65 %). FT-IR: 2985, 2872 (arom. and aliph. CH), 1690, 1629, 1623 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.33-7.18 (m, 17H, Ar-H), 2.34 and 2.20 (6H, CH_3); ^{13}C NMR (DMSO-d_6): δ = 189.66 (t, PhCO), 150.05 (C-3), 144.10 (C-5), 142.25 and 141.77 (C-NO_2), 138.70-120.62 (m, aromatic C), 26.10 and 21.30 ($2CH_3$). Anal. calcd. for $C_{32}H_{23}N_5O_7$: C, 65.19; H, 3.93; N, 11.88. Found: C, 65.39; H, 3.88; N, 11.80.

***N*-Acetyl-4-benzoyl-1-(2,4-dinitrophenyl)-*N*-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5c):** 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.35 g, 0.76 mmol) and *p*-nitroacetanilide (0.13 g, 0.76 mmol) were refluxed in xylene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product, which was recrystallized from ethanol and dried on P_2O_5. m.p.: 251 ºC, yield 0.29 g (62 %). FT-IR: 2948, 2828 (arom. and aliph. CH), 1690, 1635, 1611 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.97-7.23 (m, 17H, Ar-H), 2.18 (3H, CH_3). Anal. Calcd for $C_{31}H_{20}N_6O_9$: C, 60.00; H, 3.25; N, 13.54. Found: C, 60.23; H, 3.18; N, 13.41.

***N*-Acetyl-4-benzoyl-1-(2,4-dinitrophenyl)-*N*-(4-bromphenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5d):** 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1H-pyrazole-3-carboxylic acid chloride (**3a**) (0.35 g, 0.76 mmol) and *p*-bromoacetanilide (0.16 g, 0.76 mmol) were refluxed in xylene (40 mL) for 9 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product, which was recrystallized from *n*-propanol and dried on P_2O_5. m.p.: 233 ºC, yield 0.33 g (65 %). FT-IR: 2965, 2883 (arom. and aliph. CH), 1677, 1638, 1618 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.87-7.22 (m, 17H, Ar-H), 2,38 (3H, CH_3); Anal. calcd for $C_{31}H_{20}N_5O_7Br$: C, 56.89; H, 3.08; N, 12.21. Found: C, 57.02; H, 2.88; N, 11.98.

***N*-Acetyl-4-benzoyl-1-(2,4-dinitrophenyl)-*N*-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5e):** 4-Benzoyl-1-[2,4-dinitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3a**) (0.35 g, 0.76 mmol) and *p*-chloroacetanilide (0.13 g, 0.76 mmol) were refluxed in xylene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product, which was recrystallized from methanol and dried on P_2O_5. m.p.: 243 ºC, yield 0.32 g (67 %). FT-IR: 2953, 2849 (arom. and aliph. CH), 1674, 1640, 1612 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.63-7.31 (m, 17H, Ar-H), 2.20 (3H, CH_3); Anal. calcd for $C_{31}H_{20}N_5O_7Cl$: C, 61.04; H, 3.30; N, 11.48. Found: C, 61.28; H, 3.52; N, 11.19.

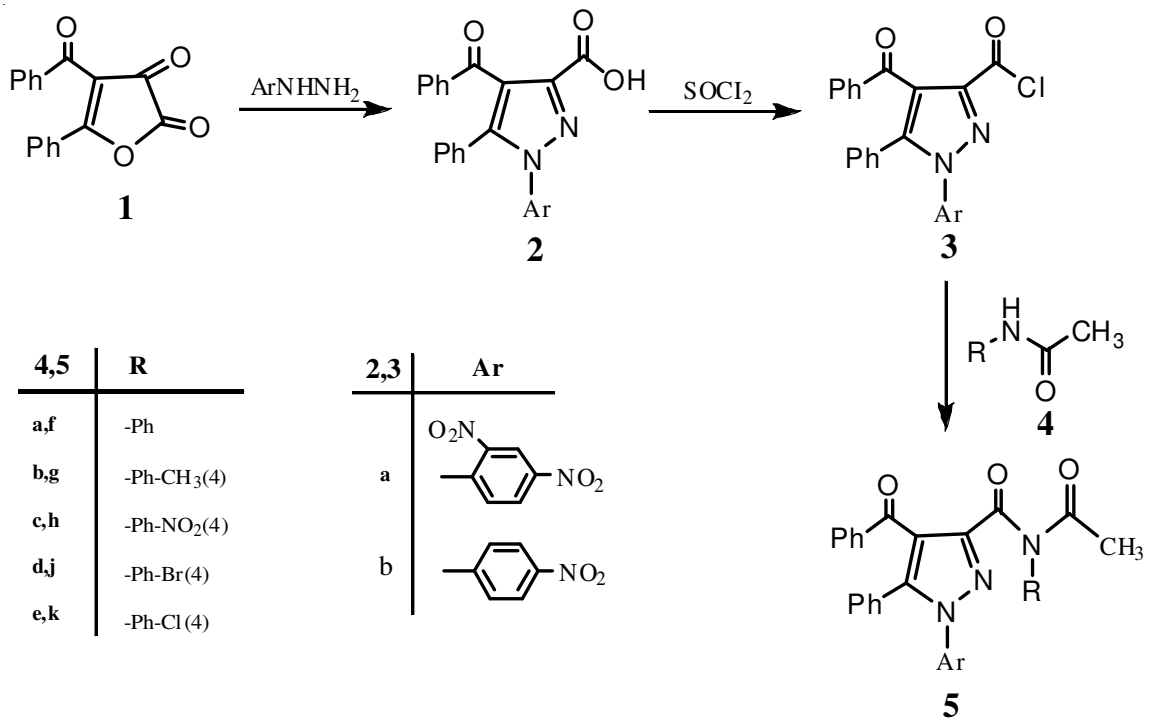
***N*-Acetyl-4-benzoyl-1-(4-nitrophenyl)-*N*,5-diphenyl-1*H*-pyrazole-3-carboxamide (5f):** 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3b**) (0.35 g, 0.82 mmol) and acetanilide (0.11 g, 0.82 mmol) were refluxed in xylene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product which was recrystallized from ethanol and dried on P_2O_5. m.p.: 252 ºC, yield 0.33 g (77 %). FT-IR: 2972, 2853 (arom. and aliph. CH), 1677, 1654, 1622 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.61-7.32 (m, 19H, Ar-H), 2,25 (3H, CH_3); ^{13}C NMR (DMSO-d_6): δ = 191.61 (t, PhCO), 150.53 (C-3), 145.28 (C-5), 143.00 (C-NO_2), 136.95-120.94 (m, aromatic C), 26.19 (CH_3). Anal. calcd. for $C_{31}H_{22}N_4O_5$: C, 70.18; H, 4.18; N, 10.56. Found: C, 70.45; H, 3.95; N, 10.48.

***N*-Acetyl-4-benzoyl-1-(4-nitrophenyl)-*N*-(4-methylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5g):** 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (**3b**) (0.35 g, 0.82 mmol) and *p*-methylacetanilide (0.12 g, 0.82 mmol) were refluxed in toluene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product, which was recrystallized from ethanol and dried on P_2O_5. m.p.: 235 ºC, yield 0.31 g (70 %). FT-IR: 2979, 2839 (arom. and aliph. CH), 1662, 1651, 1634 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.50-7.36 (m, 18H, Ar-H), 2.45 and 2,18 (6H, CH_3); ^{13}C NMR (DMSO-d_6): δ = 190.01 (t, PhCO), 152.15 (C-3), 143.10 (C-5), 142.25 (C-NO_2), 137.75-121.14 (m, aromatic C), 25.1 and 20.31 ($2CH_3$). Anal. calcd for $C_{32}H_{24}N_4O_5$: C, 70.58; H, 4.44; N, 10.29. Found: C, 70.78; H, 4.35; N, 10.49.

***N*-Acetyl-4-benzoyl-1-(4-nitrophenyl)-*N*-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5h):** 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1H-pyrazole-3-carboxylic acid chloride (**3b**) (0.35 g, 0.82 mmol) and *p*-nitroacetanilide (0.15 g, 0.82 mmol) were refluxed in xylene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product, which was recrystallized from ethanol and dried on P_2O_5. m.p.: 242 ºC, yield 0.32 g (69 %). FT-IR: 2968, 2821 (arom. and aliph. CH), 1687, 1658, 1625 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.63-7.20 (m, 18H, Ar-H), 2,11 (3H, CH_3). Anal. calcd. for $C_{31}H_{21}N_5O_7$: C, 64.69; H, 3.68; N, 12.17. Found: C, 64.48; H, 3.47; N, 12.33.

***N*-Acetyl-4-benzoyl-1-(4-nitrophenyl)-*N*-(4-bromphenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5j):** 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1H-pyrazole-3-carboxylic acid chloride (**3b**) (0.35 g, 0.82 mmol) and *p*-bromoacetanilide (0.17 g, 0.82 mmol) were refluxed in toluene (40 mL) for 10 h. The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product, which was recrystallized from *n*-propanol and dried on P_2O_5. m.p.: 231 ºC, yield 0.34 g (68 %). FT-IR: 2962, 2863 (arom. and aliph. CH), 1687, 1646, 1621 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.24-7.31 (m, 18H, Ar-H), 2.42 (3H, CH_3). Anal. calcd. for $C_{31}H_{21}N_4O_5Br$: C, 61.10; H, 3.47; N, 9.19. Found: C, 61.132; H, 3.65; N, 9.45.

***N*-Acetyl-4-benzoyl-1-(4-nitrophenyl)-*N*-(4-chlorophenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide (5k):** 4-Benzoyl-1-[4-nitrophenyl]-5-phenyl-1H-pyrazole-3-carboxylic acid chloride (**3b**) (0.35 g, 0.82 mmol) and *p*-chloroacetanilide (0.14 g, 0.82 mmol) were refluxed in xylene (40 mL) for 10 h.



Scheme-I: Synthesis of the pyrazole-3-carboxamide derivatives **5a-k**

The solvent was evaporated and the remaining oily residue was treated with dry ether to give a crude product, which was recrystallized from methanol and dried on P_2O_5. m.p.: 229 ºC, yield 0.33 g (73 %). FT-IR: 2952, 2842 (arom. and aliph. CH), 1677, 1658, 1611 (C=O). ^{1}H NMR (DMSO-d_6): δ = 8.64-7.05 (m, 18H, Ar-H), 2,18 (3H, CH_3). Anal. calcd. for $C_{31}H_{21}N_4O_5Cl$: C, 65.90; H, 3.75; N, 9.92. Found: C, 66.13; H, 3.52; N, 9.78.

RESULTS AND DISCUSSION

In the present study, our 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[1,14,31-33].

We carried out the reaction of the compounds **3a-b** treament with various anilide derivatives in boiling xylene and toluene gave the corresponding new structures pyrazole-3-carboxamide derivatives **5a-k** as main product. The progress of the reactions was monitored by thin-layer chromatography until complete consumption of the starting materials. The compounds **5a-k** were obtained in good yields (62-77 %), after evaporation of the organic solvents and recrystallization from proper solvents (like methanol, ethanol, *n*-propanol). The reactions of the compound **3a** with acetanilide led to the formation of **5a**, under reflux in xylene for 10 h, in 71 % yield without opening the pyrazole ring. In order to make the reaction selective, we had to determine the parameters, in other words, the reaction pathway, leading to such results. The good yield of the reaction can be explained by the chemical behaviour of compounds **3a-b** towards H-active nucleophiles, such as anilides. It should start with a nucleophilic attack of the nitrogen atoms' lone pair electrons of the hydrazine to the antibonding (π^*) orbital at the carbonyl carbon at C3 position of the pyrazol ring. The by-products formed in this way are removed when the raw products are treated with diethyl ether. The new products **5a-k** obtained arise followed by the elimination of hydrogen chloride. In the IR spectrum of compound **5a**, the C=O absorption were seen at 1697, 1668 and 1614 cm^{-1}. The ^{1}H NMR signals were found to be at 8.43-7.19 (m, 18H, Ar-H). The ^{13}C NMR signals were observed at 192.68 (t, PhCO), 151.90 (C-3), 145.68 (s, C-5). Finally, the elemental analysis data along with spectroscopic data confirm the structure of **5a**.

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