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Syntheses of Some New 1*H*-Pyrazole, Pyridazin-3(2*H*)-one, and Oxazin-4-one Derivatives

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ABSTRACT: *The new 1H-pyrazole-3-carboxylic acid* **2**, *pyridazin-3(2H)-one* **3**, *and their various derivatives were prepared by the reactions of the 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione* **1** *and 2,5-dichlorophenylhydrazine. Pyrazolo[3,4-d]pyridazine* **7** *was obtained from cyclization of the pyrazole-3-carboxylic acid* **2** *with 2,5-dichlorophenylhydrazine. The reaction of* **1** *and pyrazole-3-carbonitriles* **6** *gave the new oxazin-4-one* **9** *derivatives. The structures of compounds were characterized on the basis of elemental analyses, mass, IR,* ^{1}H, *and* ^{13}C *NMR spectra.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:8–12, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20170

INTRODUCTION

Pyrazole derivatives are very important organic compounds because they are widely used as pharmaceuticals and agrochemicals. Their excellent control activities on various plant diseases are studied [1,2]. They can also be used as antifungal [3], antibacterial [4], antimicrobial [5,6], and anti-inflammatory [7] agents.

It was recently reported that the reactions of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**1**) and various hydrazines or hydrazones result new pyrazole carboxylic acids, pyrazolopyridazinones, and some of their derivatives. The pyrazole carboxylic acids can be easily transformed into the corresponding acid chloride, ester, or amide derivatives by the general chemical procedures. The reaction of suitable vicinal dicarbonyl pyrazole derivatives with hydrazines is a convenient method to build the pyrazolopyridazinone systems [4,8–10].

Furthermore, the thermal decomposition of the furandiones generates the α-oxoketen intermediates [11,12], which are often used as building blocks in chemical designs. The ketenes are usually added to multiple bond systems via a [2+2] process across their C=C as well as C=O double bonds, while α-oxoketenes show a pronounced behavior to form [4+2] hetero-Diels–Alder adducts when trapped with dienophiles. The reaction mixture includes an inert atmosphere; the —COC=C part in a primary ketene molecule acts as heterodiene, while in the other molecules the C=C bond of ketene acts as heterodienophile [13–15]. In the case of the reaction mixture containing a carbonyl compound or another heterodienophile such as a nitril, cyanamides, or isocyanate, various dioxin, pyranones, oxazinone, and oxazindione derivatives are obtained [12,16–20].

The possible biological properties of the pyrazol, pyridazinone [21,22], pyrazolopyridazinone [23], and oxazin [24,25] derivatives make it attractive to study these compounds.

Here, we report the chemical behavior of **1** toward 2,5-dichlorophenylhydrazine and pyrazole-3-carbonitriles. As a result of these reactions, new

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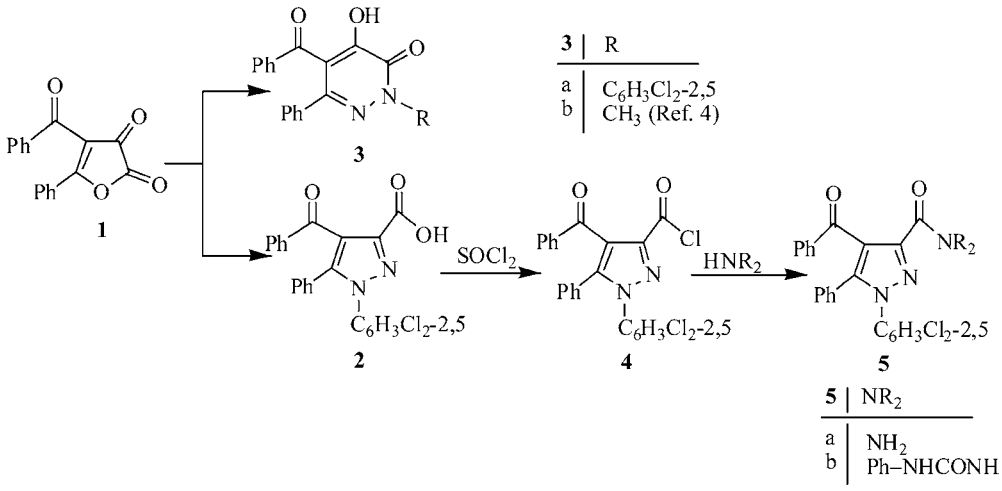


SCHEME 1

1*H*-pyrazole-3-carboxylic acid, pyridazin-3(2*H*)-one, oxazin-4-one, and their various derivatives were synthesized.

RESULTS AND DISCUSSION

The reaction of **1** with 2,5-dichlorophenylhydrazine gave pyrazole-3-carboxylic acid **2** and pyridazin-3(2*H*)-one **3**. Pyrazole-3-carboxylic acid **2** obtained in approximately 30% yield was remarkably stable. It was identified on the basis of its elemental analysis and spectra. Its IR spectrum showed absorption bands at 3100–2950 and 1707, 1673 cm^{-1} due to OH(COOH) and two carbonyl functions, respectively. The mass spectrum of the reaction product showed the molecular ion peak at *m/e* 437.0. The ^{13}C NMR spectrum of **2** revealed signals at δ 192.0 (C=O, benzoyl) and 159.0 (C=O, acid). The ^{1}H NMR spectrum of **2** exhibited a signal at δ 10.9–10.1 and multiple signals at 8.1–7.3 due to acid proton and aromatic protons, respectively.

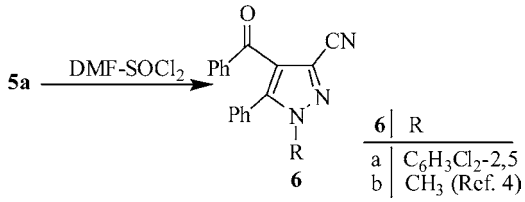
The IR spectrum of **3a** showed absorption band at 3321 cm^{-1} because of hydroxyl function besides two carbonyl absorption bands at 1684 and 1623 cm^{-1}. In the ^{1}H NMR spectra of **3a**, a singled signal at δ 10.7–10.4 was exhibited due to phenolic proton. The behavior of a phenolic protons is generally downfield (δ ~7.5–~4). If a carbonyl group in the orthoposition to the phenolic protons are available, the absorption is downfield to the range of about δ~12–~10 because of intramolecular hydrogen bonding [26]. The ^{13}C NMR spectrum of **3a** revealed signals at δ 191.0 (C=O, benzoyl) and 151.2 (C=O, acid). Its mass spectrum showed the molecular ion peak at *m/e* 437.0.

The compound **2** can be easily transformed into the corresponding acid chloride **4**, amide **5a**, and urea **5b** derivatives by the usual chemical procedures (Scheme 1). The structure of the compounds **4** and **5** was confirmed by analytical and spectral data (See Experimental for details).

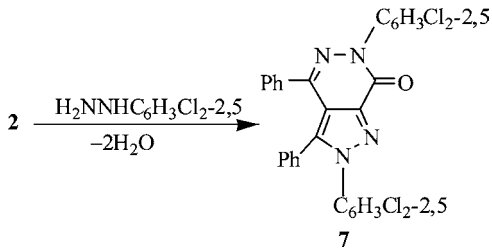
A cold solution of **5a** in a mixture of DMF and $SOCl_2$ gave carbonitrile **6a** (Scheme 2). Its IR spectrum showed absorption bands at 2239 and 1662 cm^{-1} that are characteristic for nitrile and carbonyl groups, respectively.

Reactions of pyrazole derivatives having the dicarbonyl group in the suitable position with hydrazines were convenient methods to build the pyrazolo[3,4-*d*]pyridazine systems [8,10]. Thus, **2** was cyclized with 2,5-dichlorophenylhydrazine to the pyrazolo[3,4-*d*]pyridazinone **7** (Scheme 3).

The structure of **7** was assigned on the basis of their satisfactory analytical and spectral data (See Experimental for details).



SCHEME 2



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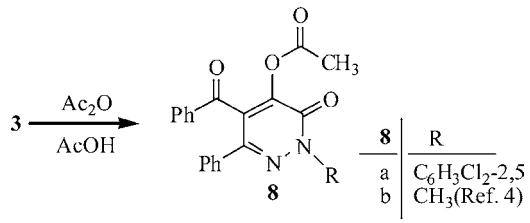


SCHEME 4

Treatment of the pyridazin-3(2*H*)-one **3a** with acetic anhydride afforded a single product that was identified as pyridazin-4-yl acetate **8a** on the basis of its elemental and spectral analyses in addition to their chemical transformations outlined in Scheme 4. The signals of hydroxyl function group disappeared in the IR and ^{1}H NMR spectra of compound **8a**. The ^{1}H NMR spectrum of compound **8a** revealed a singlet signal at δ 3.8 and 2.1 due to methyl protons. Its IR spectrum showed absorption bands at 1750, 1706, 1689 cm^{-1} due to three carbonyl functions, respectively.

Under the thermolysis conditions of **1**, an inert aprotic solvent as *p*-xylene at 138–140°C for 25–30 min, with the loss of carbon monoxide gave ketene intermediate as shown in Scheme 5 [12]. The reaction of the carbonitrile derivative **6a** with **1** afforded the corresponding oxazin derivative **9a** in poor yield (Scheme 5). The IR spectrum of oxazin derivative **9a** showed absorption bands at 1667, 1673, 1610 cm^{-1} due to carbonyl groups. The ^{13}C NMR spectrum of **9a** exhibited signals at δ 192.5 (C=O, benzoyl), 180.74 (C=O), and 162.2 (C^4=O).

EXPERIMENTAL

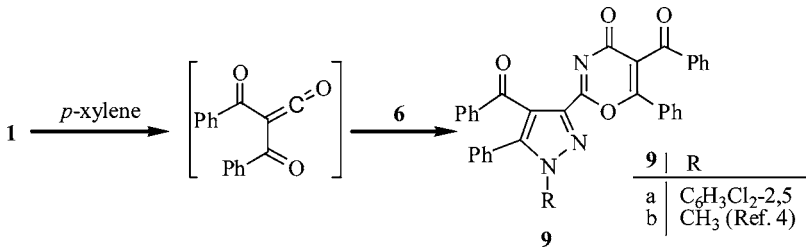
Solvents were dried by refluxing with the appropriate drying agents and distilled before use. Melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Microanalyses were performed on LECO CHNS 932 elemental analyzer. The IR spectra were obtained in as potassium bromide pellets using a Mattson 1000 FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DPX-400 spectrometers, using TMS as an internal standard. The mass spectra (100 eV) were run on an Agilent 1100 MSD mass spectrometer. All experiments were followed by TLC using DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm).

4-Benzoyl-1-(2,5-dichlorophenyl)-5-phenyl-1H-pyrazole-3-carboxylic Acid **2**

A mixture of **1** (0.278 g, 1 mmol) and 2,5-dichlorophenyl hydrazine (0.177 g, 1 mmol) was refluxed in 30 mL of dry benzene for approximately 60 min to obtain a homogeneous solution. The resulting mixture was kept at room temperature for 24 h. The precipitate was filtered off and washed with dry ether and recrystallized from ethanol to give 0.131 g (30%) of **2**. mp 207–208°C. IR (KBr): 3100–2950 cm^{-1} (OH, COOH), 1707 cm^{-1} (C=O, benzoyl), 1673 cm^{-1} (C=O, COOH). ^{1}H NMR (DMSO): δ = 10.9–10.1 ppm (bs, 1H, H_{acid}), 8.1–7.3 ppm (m, 15H, H_{arom}). ^{13}C NMR (DMSO): δ = 192.0, 159.0, 149.5, 139.2, 137.7, 135.6, 134.5, 132.4, 131.6, 131.4, 131.3, 130.3, 130.1, 129.6, 129.5, 129.3, 128.8, 127.3, 122.7 ppm. The mass spectrum (100 eV): *m/e*: 439.0, 438.0, 437.0, 419.0, 396.0, 394.0, 395.0, and 393.0. Anal. $C_{23}H_{14}Cl_2N_2O_3$ (437.27): calcd C 63.17, H 3.23, N 6.41; found C 63.18, H 3.20, N 6.39.

5-Benzoyl-2-(2,5-dichlorophenyl)-4-hydroxy-6-phenylpyridazin-3(2H)-one **3a**

The filtrate of **2** was evaporated, the oily residue was treated with ether, and the formed crude product was refluxed with ethanol. The precipitate was filtered off and washed with ethanol to give 0.174 g (40%) of **3a**. mp 211°C. IR: 3321 cm^{-1} (OH), 1684 cm^{-1} (C=O, benzoyl), 1623 cm^{-1} (C=O). ^{1}H NMR (DMSO): δ = 10.7–10.4 (bs, H, OH), 8.0–6.5 (m, 15H, H_{arom}). ^{13}C NMR (DMSO): δ = 191.0, 151.2, 145.3, 140.2, 137.7, 137.3, 134.2, 132.9, 132.5, 131.9, 131.4, 130.5, 129.2, 128.9, 120.1, 119.7, 116.0, 112.6 ppm. The mass spectrum (100 eV): *m/e*: 437.0, 434.0, 422.0, 421.0, 420.0, 400.1, 395.0, 394.0, 393.0, 105.0.



SCHEME 5

4-Benzoyl-1-(2,5-dichlorophenyl)-5-phenyl-1H-pyrazole-3-carboxamide **5a**

The 4-benzoyl-1-(2,5-dichlorophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl chloride **4** was obtained by the reaction of **2** with thionylchloride. The compound **2** (0.437 g, 1 mmol) and thionylchloride (1 mL, 13.8 mmol) were refluxed on a steam bath for 6 h. The solvent was evaporated, and then the residue was dissolved in 10 mL of carbon tetrachloride. Thereafter, a moderate stream of gaseous ammonia was allowed to bubble through a solution of pyrazole-3-carboxylic acid chloride **4** in 10 mL of carbon tetrachloride for 30 min with ice cooling. Then, the crude precipitate was filtered off and recrystallized from ethanol to give 0.165 g (38%) of **5a**. mp 252–253°C. IR: 3343 (NH_2), 1691 cm^{-1} (C=O, benzoyl) and 1647 cm^{-1} (C=O, amide).^{1}H NMR (DMSO): δ = 8.5–7.1 (m, 13H, H_{arom}), 5.6–5.5 (bs, 2H, NH_2). Anal. $C_{23}H_{15}Cl_2N_3O_2$ (436.29): calcd C 63.32, H 3.47, N 9.63; found C 63.30, H 3.48, N 9.63.

1-(4-Benzoyl-1-(2,5-dichlorophenyl)-5-phenyl-1H-pyrazole-3-carbonyl)-3-phenylurea **5b**

The compound **4** (0.456 g, 1 mmol) and phenylurea (0.136, 1 mmol) were refluxed in xylene for 7 h and cooled to room temperature; the precipitate was filtered off and recrystallized from xylene, yielding 0.166 g (30%). mp 207°C. IR: 3350–3140 cm^{-1} (NH), 1732 cm^{-1} (C=O, urea), 1680 cm^{-1} (C=O), 1634 cm^{-1} (C=O).^{1}H NMR (DMSO): δ = 10.3 (s, 1H, NH), 9.2 (s, 1H, NH), 8.8–6.8 (m, 20H, H_{arom}). Anal. $C_{30}H_{20}Cl_2N_4O_3$ (555.41): calcd C 64.87, H 3.63, N 10.09; found C 64.86, H 3.60, N 10.10.

4-Benzoyl-1-(2,5-dichlorophenyl)-5-phenyl-1H-pyrazole-3-carbonitrile **6a**

A cold solution of the carboxamide **5a** (0.436 g, 1 mmol) in a mixture of DMF (0.7 mL) and $SOCl_2$ (0.15 mL) was stirred at 0–5°C for 4 h. After heating to room temperature, stirring was continued for overnight, then the reaction mixture poured over crushed ice and the separated solid was filtered off, washed with water, and recrystallized from methanol to give 0.166 g (40%) of **6a**. mp 143–144°C. IR: 2239 cm^{-1} (CN), 1662 cm^{-1} (C=O, benzoyl).^{13}C NMR (DMSO): δ = 188.6, 156.1, 145.4, 139.3, 138.3, 137.6, 136.5, 135.0, 134.4, 134.0, 132.4, 131.9, 130.1, 129.6, 129.5, 128.9, 128.8, 128.7, 108.7 ppm. Anal. $C_{23}H_{13}Cl_2N_3O$ (418.27): calcd C 66.04, H 3.13, N 10.05; found C 66.06, H 3.10, N 10.09.

2,6-Bis(2,5-dichlorophenyl)-3,4-diphenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one **7**

A milliequimolar mixture of **2** (0.437 g, 1 mmol) and 2,5-dichlorophenylhydrazine (0.177 g, 1 mmol) were refluxed in xylene for 5 h. The solvent was evaporated, then the oily residue was treated with ether and the formed crude product was crystallized from ethanol. Compound **7a** was obtained in yield 0.202 g (35%). mp 239–240°C. IR: 1676 cm^{-1} (C=O). ^{13}C NMR (DMSO): δ = 159.7, 154.4, 144.8, 144.1, 143.2, 142.3, 141.9, 140.1, 139.5, 137.0, 133.2, 133.0, 132.6, 132.1, 131.0, 130.5, 129.4, 128.8, 128.6, 128.4, 128.2, 127.6, 125.9, 123.4, 117.4. Anal. $C_{29}H_{16}Cl_4N_4O$ (578.28): calcd C 60.23, H 2.79, N 9.69; found C 60.22, H 2.80, N 9.67.

5-Benzoyl-2-(2,5-dichlorophenyl)-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl Acetate **8a**

Compound **3a** (0.437 g, 1 mmol) was treated with 5 mL of acetic anhydride and H_2SO_4 (four drops), and then mixture was stirred at cautious heating (no gas evolution) for 30 more minutes. The reaction mixture was cooled, and then the solution was treated with 100 mL of water. The precipitate was filtered off and recrystallized from acetic acid. The compound **8a** was obtained in yield 0.286 g (60%). mp 197°C. IR: 1750, 1706, 1689 cm^{-1} (C=O). ^{1}H NMR (DMSO): δ = 8.2–5.9 (m, 13H, H_{arom}), 3.8 and 2.1 ppm (s, 3H, CH_3). Anal. $C_{25}H_{16}Cl_2N_2O_4$ (479.31): calcd C 62.65, H 3.36, N 5.84; found C 62.62, H 3.35, N 5.83.

5-Benzoyl-2-methyl-3-oxo-6-phenyl-2, 3-dihydropyridazin-4-yl Acetate **8b**

The compound **8b** was prepared according to the procedure for **8a** yielding 0.191 g (55%). mp 169–170°C. IR: 1788, 1668, 1602 cm^{-1} (C=O). Anal. $C_{20}H_{16}N_2O_4$ (348.11): calcd C 68.96, H 4.63, N 8.04; found C 68.97, H 4.60, N 8.03.

5-Benzoyl-2-(4-benzoyl-1-(2,5-dichlorophenyl)-5-phenyl-1H-pyrazol-3-yl)-6-phenyl-4H-1,3-oxazin-4-one **9a**

A solution of **1** (0.278 g, 1 mmol) and carbonitrile **6a** (0.418 g, 1 mmol) in 10 mL absolute *p*-xylene was refluxed for 5 h at 138–140°C. Thereafter solvent was removed by evaporation, the oily residue was treated with ether, and the formed crude product was refluxed from 2-propanol. The precipitate was filtered off and recrystallized from xylene to give 0.133 g (20%) of **9a**. mp 279°C. IR: 1667, 1632, 1610 cm^{-1} (C=O).^{13}C NMR (DMSO): δ = 192.5, 180.7, 162.2,

140.6, 136.5, 134.3, 132.5, 131.8, 130.9, 130.4, 129.3, 129.1, 128.4, 128.2, 126.8, 125.6, 124.8, 124.4, and 122.9 ppm. Anal. $C_{39}H_{23}Cl_2N_3O_4$ (667.11): calcd C 70.07, H 3.47, N 6.29; found C 70.06, H 3.49, N 6.30.

5-Benzoyl-2-(4-benzoyl-1-methyl-5-phenyl-1H-pyrazol-3-yl)-6-phenyl-4H-1,3-oxazin-4-one **9b**

A solution of **1** (0.278 g, 1 mmol) and carbonitrile **6b** (0.287 g, 1 mmol) in 10 mL absolute *p*-xylene was refluxed for 5 h at 138–140°C. Thereafter solvent was removed by evaporation, the oily residue treated was with ether, and the formed crude product was refluxed from ethanol. The precipitate was filtered off and washed from ethanol to give 0.096 g (18%) of **9b**. mp 275–276°C. IR: 1667, 1632, 1620 cm^{-1} (C=O). Anal. $C_{34}H_{23}N_3O_4$ (537.17): calcd C 75.97, H 4.31, N 7.82; found C 75.96, H 4.34, N 7.83.

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