SYNTHESIS AND REACTIONS OF SOME 1*H*-PYRAZOLE-3 CARBOXYLIC ACID CHLORIDE

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Abstract : The pyrazole-carboxylic acid chloride **2** was obtained from the reaction of 4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid **1** and thionyl chloride. 1*H*-Pyrazole-3 carboxylic acid chlorides **2** can easily be converted into corresponding 1*H*-pyrazole-3-carboxylic acid amide derivatives **4** and 1*H*-pyrazole-3-carboxamide derivatives **6** from the reaction with various aliphatic and aromatic amines. The structures of these new synthesized compounds were determined from the IR, ^{1}H and ^{13}C NMR spectroscopic data and elemental anaylsis.

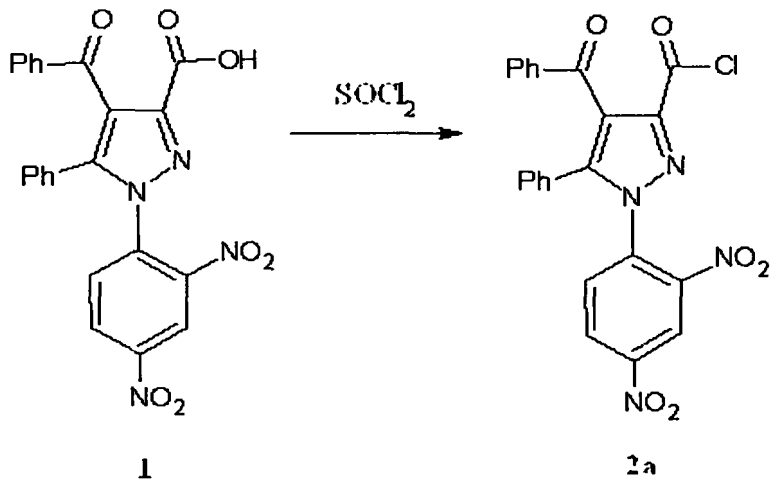
Introduction

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 [22-31]. In view of these important properties, we attempted both to prove reproducibility of the reaction of 4-benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic acid chlorides **2** with some amine derivatives **3** and to extend our investigations as to prepare new heterocycles, which include the pyrazole ring or two pyrazole rings in their structure. We are now reporting the reaction mechanism, synthesis and characterization of 1*H*-pyrazole-3-carboxylic acid amide derivatives **4a-d** and 1*H*-pyrazole-3-carboxamides **5** by the reaction of the pyrazole-3-carboxylic acid chlorides **2** with the corresponding amine derivatives such as *o*-toluidine **3a**, *p*-toluidine **3b** and *o*-phenylenediamine **5** (see Scheme-2).

Result and Discussion

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **2a**, obtained from the reaction of 4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid [32] **1** with $SOCl_2$ in 50% yield is remarkably stable (m.p. 238^{O}C). The C=O absorption at 1775 and 1680 cm^{-1}, and the ^{13}C NMR signals at 191.00 (t, J= 4.6 Hz, ArCO) and 161.50 (s, COCl) were found (Scheme-1).



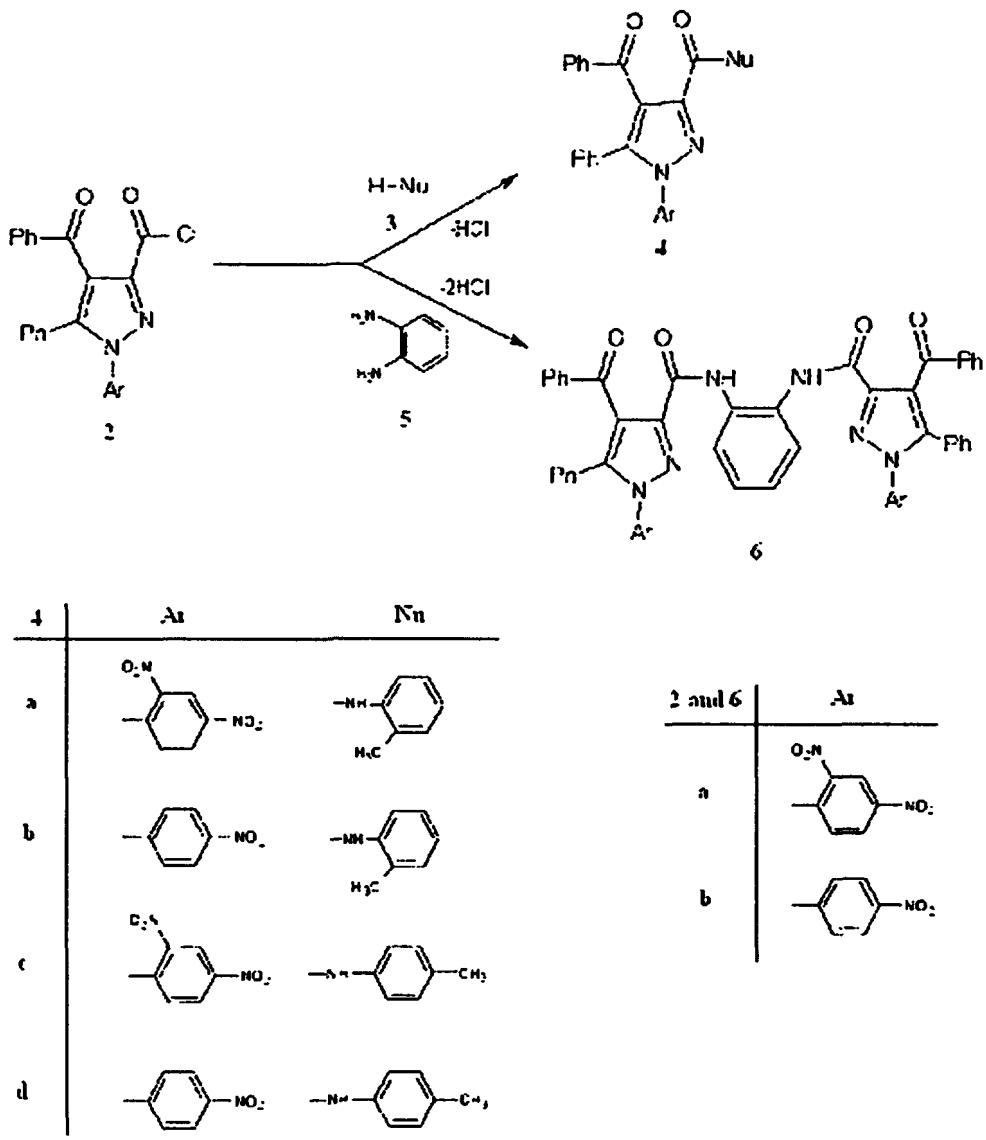
1 2a

Scheme-1

1*H*-pyrazole-3-carboxylic acid chloride **2**, which are used as important materials in the synthesis of the target heterocycles, were prepared using the literature procedures [1,14,15] as shown Scheme-1. The reaction of **2** with some toluidine led to formation of the corresponding amides **4** 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 treatment of the compound **2** treatment with various toluidine derivatives **3** in boiling benzene or toluene gave the corresponding 1*H*-pyrazole-3-carboxylic acid amides **4** as main product. The progress of the reactions was monitored by thin-layer chromatography until complete consumption of the starting materials. The compounds **4a-d** were obtained in moderate yields (50-55%) after evaporation of the organic solvents and recrystallization from proper solvents (like ethanol, see Scheme-2). The structures of synthesized compounds were assigned on the basis of analytical as well as spectroscopic data. Product **4a** obtained in 50% yield by treating **2a** with *o*-toluidine **3a** and refluxing in boiling benzene for 4 h. In the FT IR spectra of compound **4a**, the C=O absorption was seen at 1616 cm $^{-1}$. The ^{1}H NMR signals were at □ = 9.43 (b, 1H, -NH) and □ = 8.57-7.02 (m, 17H, Ar-H). The ^{13}C NMR signals were found to be at 191.01 (t, PhCO) and 168.94 (s, C=O) and elemental analysis data confirm the structure of **4a**.

In another work in this paper, the reaction of two-fold molar excess of the compounds **2** with *o*-phenylenediamine **5** led to the formation of the corresponding dicarboxamide derivatives **6** in good yields (70-75 %), without opening the pyrazole ring. All the reactions were performed in boiling benzene under reflux for 12 hours, by the usual chemical methods (for details the Experimental). Addition of binucleophiles to the acid chloride **2** usually starts nucleophilic attack at the acid chloride moieties in compounds **2** . Therefore, from sequential attacks of the *o*-phenylenediamine at the acid chloride moieties of two respective molecules of **2**, followed by elimination of hydrogen chloride, new products **6a-b** arise (Scheme-2). The structures of the compounds **6** were confirmed by IR, NMR spectroscopic techniques, besides the elemental analysis. These results are in full agreement with those obtained for substituted 1*H*-pyrazole-3-carboxamides [14-16,33]. In the experiment, product **6a** was obtained in 75% yield by treating **2a** with *o*-phenylenediamine **5** refluxing in boiling benzene for 12 hours. The formation of **6a** was affirmed by the results of both analytical and spectroscopic measurements (by the presence of four carbonyl characteristic absorption bands FT IR: 1701, 1688, 1670, 1659 cm^{-1}). The broad absorption bands of NH groups were at 3375 and 3230 cm^{-1}, and skeleton bands related to benzene or pyrazole rings with NH bending vibrations were observed at 1605, 1595, 1546, 1520, 1505, 1489, 1460 cm^{-1} (C---C, C---N). Important structural information about **6a** can be obtained from its ^{13}C NMR spectrum. The ^{13}C NMR peaks were found to be at 193.50 (t, PhCO), 164.34 (s, HNCO), 147.20 (s, C_3, $C_{3'}$), 145.80 (t, C_5, $C_{5'}$),

and 141.01, 140.16 (N-Ph). Final comfirmation of structure **6a** was derived from its ^{1}H NMR spectrum: δ=10.46 ppm (s, 2H, NH) and 8.43-6.98 ppm are a set of signals for aromatic protons [33,34].



Scheme-2

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 □ (ppm). All experiments were followed by TLC using DC Alufolien Kieselgel 60 F_{254} Merck and Camag TLC lamp (254/366 nm).

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride (2a).

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid **1** (1.0 g) and thionyl chloride (0.15 ml) were refluxed on a steam bath for 4 h. After cooling, the crude precipitate was filtered off and recrystallized from carbon tetrachloride and allowed to dry on P_2O_5; resulting in yield 0.52 g (50%); m.p.: 238°C; IR: ν = 1775, 1680 cm^{-1} (C=O); ^1H NMR (*CDCl₃*): □□ 7.77-7.10 (m, 13H, ArH); ^{13}C NMR (*CDCl₃*): □□191.00 (t, ArCO), 161.50 (s, COCl), 150.05 (s, C3), 140.10 (s, C5), 135.13-128.19 (m, aromatic C), 121.05 ppm (s, C4). Anal. Calcd. for $C_{23}H_{13}N_4O_6Cl$; C, 57.92; H, 2.83; N, 11.75. Found: C, 57.65; H, 3.09; N, 12.01.

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid-N-*o*-tolylamide (4a).

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **2a** (0.25 g) and *o*-toluidine **3a** (0.056 g) were refluxed in benzene (30 mL) for 4 hours. After cooling to room temperature the precipitate formed was filtered off and recrystallized from ethanol and allowed to dry on P_2O_5; resulting in yield 0.15 g (50%); m.p.: 228°C; IR: ν = 3500-3270 (s, N-H), 1616 cm^{-1} (Ph-C=O); ^1H NMR (*CDCl₃*): □□9.43 (1H-NH), 8.57-7.02 (m, 17H, ArH), 2.71 ppm (3H, C13); ^{13}C NMR (*CDCl₃*): □□191.01 (t, PhCO), 168.94 (s, C=O), 145.68 (s, C-5), 151.90 (s, C-3), 143.00 and 140.77 (C-NO_2) 136.79-127.53 (m, aromatic C), 23.03 ppm (q, CH_3). Anal. Calcd. for $C_{30}H_{21}N_5O_6$; C, 65.81; H, 3.84; N, 12.80. Found: C, 65.55; H, 3.98; N, 12.41.

4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid-N-*o*-tolylamide (4b).

4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **2b** (0.25 g) and *o*-toluidine **3a** (0.062 g) were refluxed in benzene (30 mL) for 4 hours After cooling to room temperature the precipitate formed was filtered off and recrystallized from ethanol and allowed to dry on P_2O_5; resulting in yield 0.17 g (55%); m.p.: 247°C; IR: ν = 3600-3500 (s, N-H), 1733 cm^{-1} (Ph-C=O); ^1H NMR (*CDCl₃*): □□9.88 (1H-NH), 8.94-7.00 (m, 18H, ArH), 1.73 ppm (3H, C13). Anal. Calcd. for $C_{30}H_{22}N_4O_4$; C, 71.71; H, 4.38; N, 11.16. Found: C, 71.50; H, 4.08; N, 10.87.

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid-N-*p*-tolylamide (4c).

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **2a** (0.25 g) and *p*-toluidine **3b** (0.056 g) were refluxed in benzene (30 mL) for 4 hours After cooling to room temperature the precipitate formed was filtered off and recrystallized from ethanol and allowed to dry on P_2O_5; resulting in yield 0.16 g (55%); m.p.: 196°C; IR: ν = 3550-3350 (s, N-H), 1652 cm^{-1} (Ph-C=O); ^1H NMR (*CDCl₃*): □□8.41 (1H-NH), 7.79-6.98 (m, 17H, ArH), 2.18 ppm (3H, C13). Anal. Calcd. for $C_{30}H_{21}N_5O_6$; C, 65.81; H, 3.84; N, 12.80. Found: C, 65.97; H, 4.10; N, 12.54.

4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid-N-*p*-tolylamide (4d).

4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid chloride **2b** (0.25 g) and *p*-toluidine **3b** (0.062 g) were refluxed in benzene (30 mL) for 4 hours After cooling to room temperature the precipitate formed was filtered off and recrystallized from ethanol and allowed to dry on P_2O_5; resulting in yield 0.15 g (50%); m.p.: 194°C; IR: ν = 3500-3140 (s, N-H), 1645 cm^{-1} (Ph-C=O); ^1H NMR (*CDCl₃*): □□9.12 (1H-NH), 8.67-6.98 (m, 18H, ArH), 1.26 ppm (3H, C13). Anal. Calcd. for $C_{30}H_{22}N_4O_4$; C, 71.71; H, 4.38; N, 11.16. Found: C, 72.00; H, 4.74; N, 10.74.

Synthesis of the 1*H*-Pyrazole-3-carboxamides 6a-b

General Procedures.

Appropriate amounts of the acid chloride **2a-b** (1 g) and the corresponding *o*-phenylenediamine **5** (molar ratio 2:1) were dissolved in benzene and refluxed together with catalytic amounts of pyridine for 12 hours. After cooling, the solution was acidified by adding diluted hydrochloric acid to give crude products **6**, and either recrystallized from the suitable alcohol and allowed to dry on P_2O_5.

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-*N*-(2-{[(4-benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-yl)carbonyl]amino}phenyl)-1*H*-pyrazole-3-carboxamide (6a).

This compound was obtained by the general procedure with a reflux time of 12 hours **2a** resulting in a yield of 1.55 g (75%); m.p.: 190°C; IR: ν = 3375, 3230 (b, N-H), 1701, 1688, 1670, 1659 cm^{-1} (s, C=O), 1605, 1595, 1546, 1520, 1505, 1489, 1460 cm^{-1} (C---C, C---N); ^1H NMR (*$CDCl_3$*): δ= 10.46 ppm (s, 2H, NH) and 8.43-6.98 ppm (m, 30H, Ar-H); ^{13}C NMR (*$CDCl_3$*): □□193.50 (t, PhCO), 164.34 (s, HNCO), 147.20 (s, C_3, $C_{3'}$), 145.80 (t, C_5, $C_{5'}$), 141.01, 140.16 (N-Ph) and 122.25 (s, C_4, $C_{4'}$). Anal. Calcd. for $C_{52}H_{32}N_{10}O_{12}$; C, 63.15; H, 3.24; N, 14.17. Found: C, 63.41; H, 3.58; N, 14.51.

4-Benzoyl-1-(4-nitrophenyl)-5-phenyl-*N*-(2-{[(4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazole-3-yl)carbonyl]amino}phenyl)-1*H*-pyrazole-3-carboxamide (6b).

This compound was obtained by the general procedure with a reflux time of 12 hours **2b** resulting in a yield of 1.46 g (70%); m.p.: 192°C; IR: ν = 3425, 3233 (b, N-H), 1694, 1684, 1658, 1640 cm^{-1} (s, C=O), 1600, 1590, 1536, 1527, 1461 cm^{-1} (C---C, C---N); ^1H NMR (*$CDCl_3$*): δ= 9.88 ppm (s, 2H, NH) and 7.87-6.90 ppm (m, 32H, Ar-H); ^{13}C NMR (*$CDCl_3$*): □□192.48 (t, PhCO), 160.85 (s, CON), 147.52 (s, C_3, $C_{3'}$), 145.15 (t, C_5, $C_{5'}$), 140.79, 139.16 (N-Ph) and 124.55 (s, C_4, $C_{4'}$). Anal. Calcd. for $C_{52}H_{34}N_8O_8$; C, 69.49; H, 3.79; N, 12.47. Found: C, 69.17; H, 3.48; N, 12.75.

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