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OPPI BRIEF

Preparation and Properties of Some New Pyrazole Derivatives

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Pyrazoles and their derivatives constitute a structurally varied set of five-membered heterocyclic compounds and provide a rich source of materials suitable for drug design and discovery. Pyrazoles exhibit many different biological activities such as enzyme inhibitory,[1–3] anticancer,[4,5] antibacterial,[6,7] antioxidant,[8] anti-inflammatory,[9] neuroprotective,[9] and antimetastatic[5] properties. In particular, highly substituted pyrroles are desirable entities in the discovery process.[10,11] We would now like to report the convenient and concise syntheses of some novel pyrazoles, in which the five-membered nucleus is highly substituted, using classical reactions.

Thus, the useful precursor 4-benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl chloride (**1**)[12] (Scheme 1) was treated with aromatic amines in toluene to provide the novel pyrazoles **2**-**5**, in moderate yields averaging 66% (see Experimental section). The structures of the newly synthesized compounds were determined and confirmed by elemental analysis and by ^{1}H-NMR, ^{13}C-NMR, and IR spectra.

In cognate preparations, we used the reactions of chalcones **6** and **7** with the appropriate acid hydrazides to form the dihydropyrazoles **8** and **9** (Scheme 2). These reactions took place in 85% and 70% yields, respectively. Again the compounds were fully characterized.

Our synthetic procedures outlined below used simple, convenient and classical methods. It is our hope that these procedures will stimulate further research into these highly substituted and potentially useful heterocycles.

Experimental section

All the chemicals, which were obtained in analytical purity, were purchased from Merck, Carlo Erba, Sigma-Aldrich and Fluka. FT-IR spectra were recorded in cm^{-1} using a Shimadzu 8400 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz Ultra Shield NMR Spectrophotometer. Elemental analysis were taken using a Carlo-Erba 1180 HP 105 Model elemental analyzer apparatus. The melting points were taken with an Electrothermal Brand 9200 Model device and are corrected. The open structures of compounds 2-5 are given in Scheme 1.

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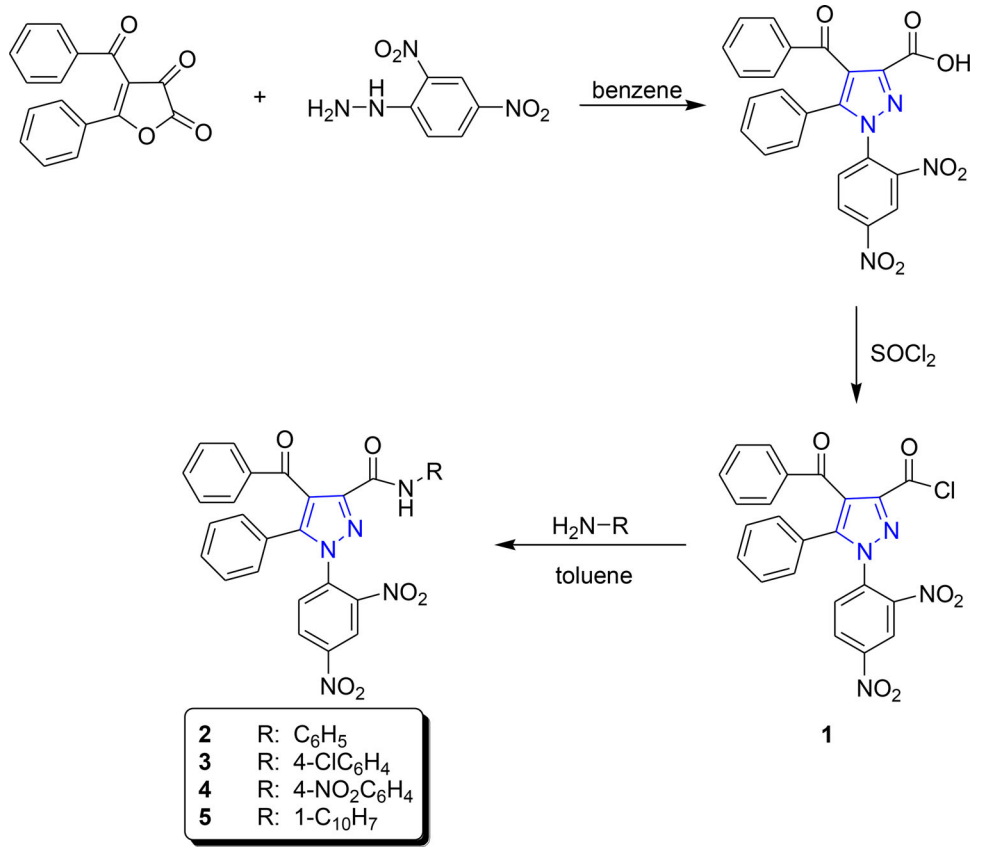
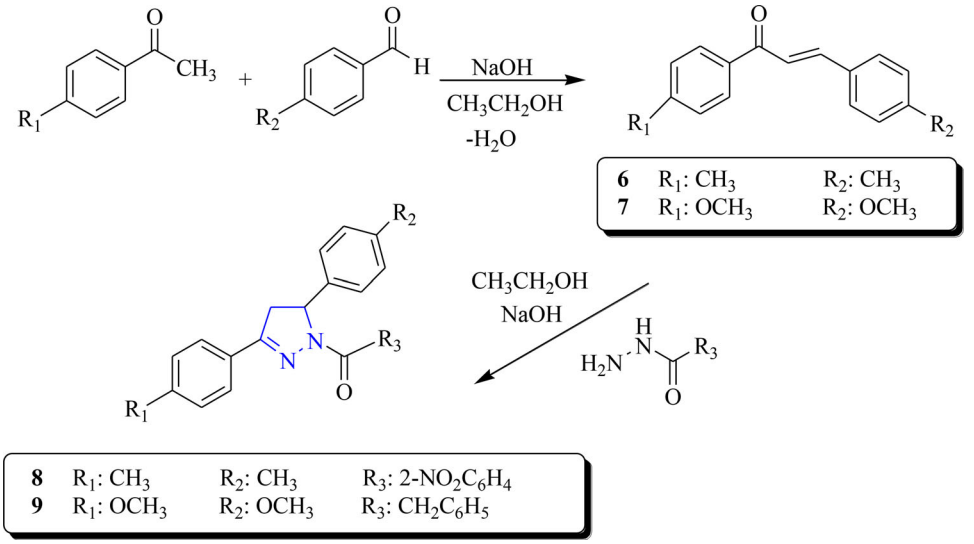


Scheme 1. Preparation of pyrazoles **2**-**5**.

4-Benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1H-pyrazole-3-carbonyl chloride (1)

4-Benzoyl-5-phenylfuran-2,3-dione (1.00 mmol) and 1-(2,4-dinitrophenyl)hydrazine (1.00 mmol) were dissolved in benzene and refluxed for 2h. The reaction was followed with thin layer chromatography (TLC), using silica gel 60 GF_{254} eluted with chloroform/ethyl acetate (20/1). After the reaction was completed, solvent was removed using a rotary evaporator. A yellow product, namely 4-benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid, was formed upon the addition of 10 ml of cyclohexane. This starting material was recrystallized from toluene. Compound **1** was subsequently obtained from 1.00 g of 4-benzoyl-1-(2,4-dinitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid and 0.15 mL of thionyl chloride upon heating at 85 °C for 4h. The acid chloride was isolated by filtration. Compound **1** was recrystallized from xylene. Yield: 50%, m.p.: 238 °C. IR (cm^{-1}): 1775 and 1680 (C = O). ^{1}H NMR (400 MHz, ppm, $CDCl_3$): 7.77-7.10 (m, 13H, Ar**H**). ^{13}C NMR (100 MHz, ppm, $CDC1_3$): 191.00 and 161.50 (**C**=O), 150.05 (**C**NO_2), 140.10, 135.13, 132.75, 130.21, 129.73, 129.30, 128.97, 128.19, 127.55, 122.05, 121.05.[12]

Anal. Calc. for $C_{23}H_{13}ClN_4O_6$: C, 57.93; H, 2.75; N, 11.75. Found: C, 57.73; H, 2.81; N, 11.71.



Scheme 2. Synthesis of chalcones and dihydropyrazoles.

4-Benzoyl-1-(2,4-dinitrophenyl)-N,5-diphenyl-1H-pyrazole-3-carboxamide (2)

Aniline (0.019 g, 1.00 mmol) was added to a solution of **1** (0.09 g, 1.00 mmol) in toluene (1 mL). The reaction mixture was refluxed for 2h. The relative reaction time was determined by TLC (silica gel 60 GF_{254} using chloroform/ethyl acetate (20/1)). The product was isolated by filtration. The new compound was crystallized from ethyl alcohol. Yield: 62%, color: orange, m.p: 278 °C. FT-IR (cm^{-1}): 3303 (-NH-), 3089 and 3024 (C-H), 1667 and 1643 (C = O), 1531-1442 (C ⋯ C and C ⋯ N), 1343 and 1285 (asymmetric N = O). ^{1}H-NMR (400 MHz, ppm, DMSO-d_6), δ: 10.85 (-N**H**), 7.15-9.10 (m, 18 H, Ar-**H**). ^{13}C-NMR (100 MHz, ppm, DMSO-d_6), δ: 192.39 and 159.39 (**C**=O), 147.86, 145.15, 136.20, 132.32, 131.14, 129.71, 129.47, 129.17, 126.56, 123.88, 121.15 and 115.22 (Ar-**C**).

Anal. Calc. for $C_{29}H_{19}N_5O_6$: C, 65.29; H, 3.56; N, 13.13. Found: C, 65.58; H, 3.77; N, 12.99.

4-Benzoyl-N-(4-chlorophenyl)-1-(2,4-dinitrophenyl)-5-phenyl-1H-pyrazole-3-carboxamide (3)

This new compound was synthesized from 0.100 g of **1** and 0.027 g of *p*-chloroaniline in toluene (1 mL). The reaction mixture was refluxed for 4h. The reaction was followed with TLC (silica gel 60 GF_{254} using chloroform/ethyl acetate (20/1). The precipitated product was filtered off from the reaction mixture and recrystallized from ethyl alcohol. Yield: 70%, color: yellow, m.p: 183 °C. FT-IR (cm^{-1}): 3087 (-N-H), 2852 (C-H), 1646 (C = O), 1594 and 1427 (C ⋯ C and C ⋯ N), 1512 (N-O), 1342 (N = O). ^{1}H-NMR (400 MHz, ppm, $CDCl_3$), δ: 9.12 (-N**H**), 7.10-8.68 (m, 17 H, Ar-**H**). ^{13}C-NMR (100 MHz, ppm, $CDCl_3$), δ: 194.28 and 158.09 (**C**=O), 154.45, 147.96, 145.02, 138.50, 136.29, 135.99, 134.39, 131.53, 130.20, 130.11, 129.69, 129.30, 128.55, 128.23, 125.93, 122.03 and 121.05 (Ar-**C**).

Anal. Calc. for $C_{29}H_{18}N_50_6Cl$: C, 61.32; H, 3.17; N, 12.33. Found: C, 60.99; H, 3.28; N, 12.58.

4-Benzoyl-1-(2,4-dinitrophenyl)-N-(4-nitrophenyl)-5-phenyl-1H-pyrazole-3-carboxamide (4)

This new compound was synthesized from 0.100 g of **1** and 0.029 g of *p*-nitroaniline in toluene (1 mL) for 2h. The reaction was followed with TLC (silica gel 60 GF_{254} in chloroform/ethyl acetate (20/1). The precipitated product was filtered off from the reaction mixture and recrystallized from ethyl alcohol. Yield: 65%, color: orange, m.p: 158 °C. FT-IR (cm^{-1}): 3063 and 2871 (CH), 1710 and 1680 (C = O), 1597-1496 (C ⋯ C and C ⋯ N), 1339 (N = O). ^{1}H-NMR (400 MHz, ppm, DMSO-d_6), δ: 8.97 (-N**H**), 6.58-8.81 (m, 17 H, Ar-**H**). ^{13}C-NMR (100 MHz, ppm, DMSO-d_6), δ: 191.64 and 159.12 (**C**=O), 156.17, 150.52, 147.97, 145.28, 137.74, 137.51, 136.07, 135.40, 134.71, 132.53, 130.87, 129.70, 129.57, 129.44, 129.04, 127.26, 126.87, 123.74, 121.16 and 112.83 (Ar-**C**).

Anal. Calc. for $C_{29}H_{18}N_6O_8$: C, 60.21; H, 3.11; N, 14.53. Found: C, 60.00; H, 3.12; N, 14.69.

4-Benzoyl-1-(2,4-dinitrophenyl)-N-(naphthalen-1-yl)-5-phenyl-1H-pyrazole-3-carboxamide (5)

This new compound was synthesized from 0.100 g of **1**, 0.030 g of 1-naphthylamine in toluene (1 mL). The reaction mixture was refluxed for 2h. The reaction was followed with TLC (silica gel 60 GF_{254} using chloroform/ethyl acetate (20/1). The precipitated product was filtered off from the reaction mixture and recrystallized from ethyl alcohol. Yield: 68%, color: orange, m.p: 303 °C. FT-IR (cm^{-1}): 3325 (-NH-), 3105 (C-H), 1608 (C = O), 1596-1495 (C ⋯ C and C ⋯ N), 1339 and 1282 (asymmetric N = O). ^{1}H-NMR (400 MHz, ppm, $CDCl_3$), δ: 11.07 (-N**H**), 7.18-9.64 (m, 20 H, Ar-**H**). ^{13}C-NMR (100 MHz, ppm, $CDCl_3$), δ: 192.69 and 172.71 (**C**=O), 161.98, 160.06, 152.53, 150.49, 147.63, 145.14, 138.74, 137.55, 136.99, 135.31, 135.06, 134.12, 131.74, 130.39, 129.81, 129.25, 128.79, 128.71, 128.05, 127.74, 127.17, 126.45, 124.35, 124.09, 120.79, 118.82, 118.71 and 113.15 (Ar-**C**).

Anal. Calc. for $C_{33}H_{21}N_5O_6$: C, 67.92; H, 3.60; N, 12.01. Found: C, 68.28; H, 3.99; N, 12.15.

Chalcones

Water and ethyl alcohol (200/140 mL) were added to 22.0 g of NaOH in a round bottom flask. After the NaOH was dissolved and the vessel placed on ice, the appropriate acetophenone derivative (*p*-methylacetophenone (0.38 moles) or *p*-methoxyacetophenone (0.38 moles)) was slowly added to this mixture. Then, the benzaldehyde derivative (*p*-methylbenzaldehyde or *p*-methoxybenzaldehyde) (0.38 moles) was added to the reaction mixture. The reaction was stirred in the salt-ice bath for 6 h, and the reaction temperature was kept near -10 °C. The precipitated solid product was filtered and washed several times with the mixture of water and ethyl alcohol. It was dried over P_2O_5 in a vacuum desiccator. The two respective chalcones, namely, 1,3-di-*p*-tolylprop-2-en-1-one (6), or 1,3-bis(4-methoxyphenyl)prop-2-en-1-one (7), were each obtained as yellow solids.

1,3-Di-p-tolylprop-2-en-1-one (6)[13]

This known compound was synthesized from 1.00 mmol of *p*-methylacetophenone, and 1.00 mmol of *p*-methylbenzaldehyde. Compound **6** was purified by recrystallization

from ethyl alcohol. Yield: 73%, color: yellow, m.p: 129-132 °C. IR (cm^{-1}): 3029, 2971, 2939, 2915, 2854, 1654, 1953, 1566, 1517, 1378, 994, 813, and 736. ^{1}H-NMR (600 MHz, ppm, $CDCl_3$) δ: 7.92 (d, 2H, *J*: 8.1), 7.78 (d, 1H, *J*: 15.6), 7.53 (d, 2H, *J*: 8.0), 7.48 (d, 1H, *J*: 15.6), 7.29 (d, 2H, *J*: 8.1), 7.21 (d, 2H, *J*: 8.0), 2.38 (s, 3H), 2.42 (s, 3H). ^{13}C-NMR (150.92 MHz, ppm, $CDCl_3$) δ: 190.06, 144.42, 143.42, 140.87, 135.79, 132.28, 129.65, 129.26, 128.59, 128.40, 121.14, 21.61 and 21.47.

Anal. Calc. for $C_{17}H_{16O}$: C, 86.40; H, 6.82. Found: C, 86.51; H, 6.74.

1,3-bis(4-Methoxyphenyl)prop-2-en-1-one (7)[14]

This known compound was synthesized from 51 mL of *p*-methoxyacetophenone, and 46 mL of *p*-methoxybenzaldehyde. Yield: 81%, color: yellow, m.p: 95-97 °C. IR (cm^{-1}): 1650, 1590, 1560, 822, 810, 750, and 670. ^{1}H-NMR (ppm) δ: 8.00 (d, 2H, *J*: 8.55), 7.75 (d, 1H, *J*: 15.56), 7.40 (d, 1H, *J*: 15.55), 7.56 (d, 2H, *J*: 8.26), 6.94 (d, 2H, *J*: 8.44), 6.89 (d, 2H, *J*: 8.22), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C-NMR (ppm) δ: 188.59, 163.19, 161.44, 143.67, 131.27, 130.60, 130.02, 127.72, 119.46, 114.30, 113.71, 55.36 and 55.29.

Anal. Calc. for $C_{17}H_{16O3}$: C, 76.10; H, 6.01. Found: C, 76.25; H, 6.12.

Dihydropyrazoles

(3,5-Di-p-tolyl-4,5-dihydropyrazol-1-yl)(2-nitrophenyl)methanone (8)

This new compound was synthesized from 0.39 g of **6**, 0.29 g of *o*-nitrobenzoic hydrazide, and 0.09 g of NaOH in 6 mL of ethyl alcohol. The reaction mixture was refluxed for 5h. After this time, ice was added to the reaction medium and the product was precipitated. The precipitated product was recrystallized from cyclohexane. Yield: 85%, color: white, m.p: 152.4 °C. FT-IR (cm^{-1}): 3068, 3002, 2936 and 2836 (C-H), 1631 (C = O), 1512 (N-O). ^{1}H-NMR (400 MHz, ppm, $CDCl_3$), δ: 7.09-8.21 (m, 12 H, Ar-**H**), 5.73 (t, 1 H, *J*: 4 Hz, C**H**), 3.83 and 3.23 (dd, 2 H, *J*: 12 Hz, *J*: 4 Hz, C$\mathbf{H}_2$), 2.48 (s, 6 H, C$\mathbf{H}_3$). ^{13}C-NMR (100 MHz, ppm, $CDCl_3$), δ: 164.13 (**C**=O), 155.96 (**C**=N), 147.13, 141.01, 138.30, 137.63, 133.78, 133.65, 132.19, 130.03, 129.89, 129.66, 129.38, 128.62, 128.45, 128.00, 127.26, 126.78, 125.88 and 123.59 (Ar-**C**), 60.56 (-**C**H), 42.78 (-**C**H_2-), 21.51 and 21.17 (-**C**H_3).

Anal. Calc. for $C_{24}H_{21}N_{3O3}$: C, 72.18; H, 5.26; N, 10.53. Found: C, 71.98; H, 5.28; N, 10.75.

1-(3,5-bis(4-Methoxyphenyl)-4,5-dihydropyrazol-1-yl)-2-phenylethanone (9)

This new compound, according to the same conditions and procedure as for **8**, was synthesized from 0.92 g of **7**, 0.52 g of phenylacetic hydrazide, 0.20 g of NaOH and 6 mL of ethyl alcohol. The product was crystallized from methyl alcohol. Yield: 70%, color: white, m.p: 114.5 °C. FT-IR (cm^{-1}): 3022, 2956 and 2927 (C-H), 1652 (Ph-C = O), 1245 (C-O). ^{1}H-NMR (400 MHz, ppm, $CDCl_3$), δ: 7.73-6.79 (m, 13 H, Ar-**H**), 5.53 and 5.50 (dd, 1H, *J*: 4 Hz, *J*: 4 Hz, NC**H**CH_2), 4.16 (s, 2H, -C$\mathbf{H}_2$-C = O), 3.91 and 3.88 (s, 6 H, -OC$\mathbf{H}_3$), 3.20 (d, 2H, *J*: 4 Hz, CHC$\mathbf{H}_2$). ^{13}C-NMR (100 MHz, ppm, $CDCl_3$), δ: 168.90 (**C**=O), 161.38, 158.95, 153.93, 135.51, 133.99, 130.61, 129.59, 128.95, 128.33, 128.25, 126.96, 126.56, 124.08, 114.20, 114.16 and 113.68 (Ar-**C**), 59.58 (N**C**HCH_2), 55.43, 55.27, 42.31 and 41.18 (NCH**C**H_2, -**C**H_2-C = O and -O**C**H_3).

Anal. Calc. for $C_{25}H_{24}N_{2O}$: C, 74.91; H, 6.01; N, 6.99. Found: C, 75.05; H, 6.25; N, 7.00.

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