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Dedicated to Professor Raymond N. Castle on the occasion of his 80th birthday

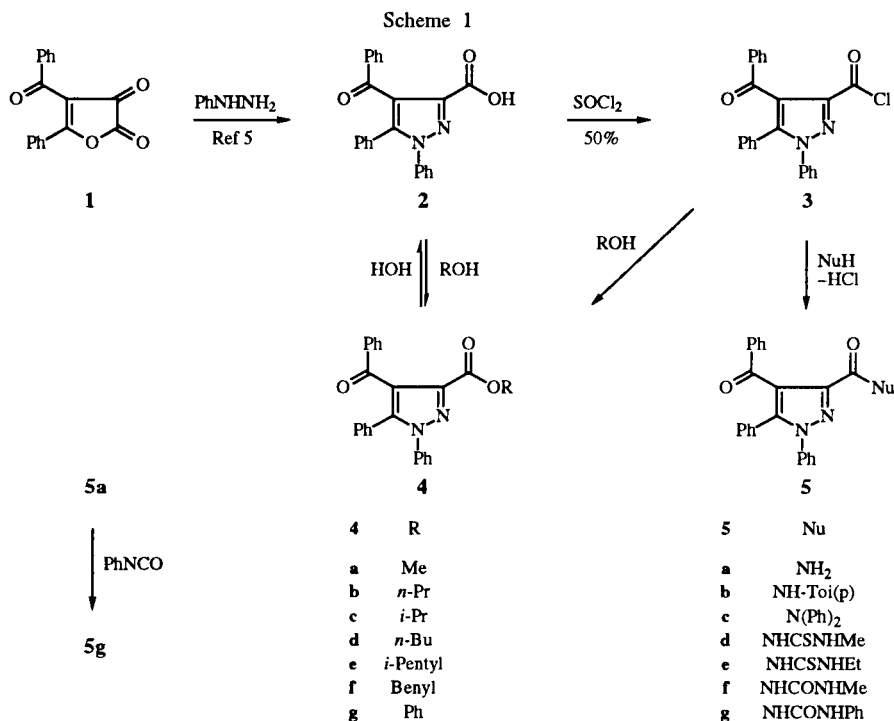
The 1*H*-pyrazole-3-carboxylic acid **2** or its remarkably stable acid chloride **3** can easily be converted into the corresponding ester or amide derivatives **4** or **5**, respectively, from reaction with alcohols or *N*-nucleophiles. Pyrazolo[3,4-*d*]pyridazines **6a,b** are obtained from cyclocondensation reactions of the pyrazoles **2** and **3**, respectively, with phenylhydrazine or hydrazine hydrate, while **6c** is formed in an one-pot procedure from the furan-2,3-dione **1** and hydrazine hydrate.

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The pyrazole nucleus in general and its chemistry [1] has found considerable attention during the decades due to outstanding biological activities as antipyretic, analgetic and anti-inflammatory drugs [2] as well as interesting properties in commercially important dyestuffs [3]. Our approach to that particular heterocyclic system was achieved by synthesis of the title compound **2** from 4-benzoyl-5-phenylfuran-2,3-dione (**1**) [4] and phenylhydrazine or phenylhydrazones, respectively [5]. The acid **2** can easily be transformed into the corresponding acid chloride **3**, esters **4** or amide derivatives **5** by the usual chemical procedures (Scheme 1).

The C=O absorption at 1760 cm⁻¹, the ¹³C nmr signals at 190.0 (t, PhCO), 162 (s, COCl), 145 (s, C-3), 144 (t, C-5), 124 (s, C-4) and the elemental analysis data (see Experimental) confirm its structure. Furthermore, the acid **2** as well as the acid chloride **3** are converted into esters **4a-g** (yields 44-85%) by simple treatment with the corresponding alcohols (for details see the Experimental). Their characteristic ir absorptions are found at 1740-1720 cm⁻¹ (ester-CO) and 1650-1660 cm⁻¹, respectively.

The amide derivatives **5a-f** are prepared in a similar way. In the case of the unsymmetrically substituted urea and

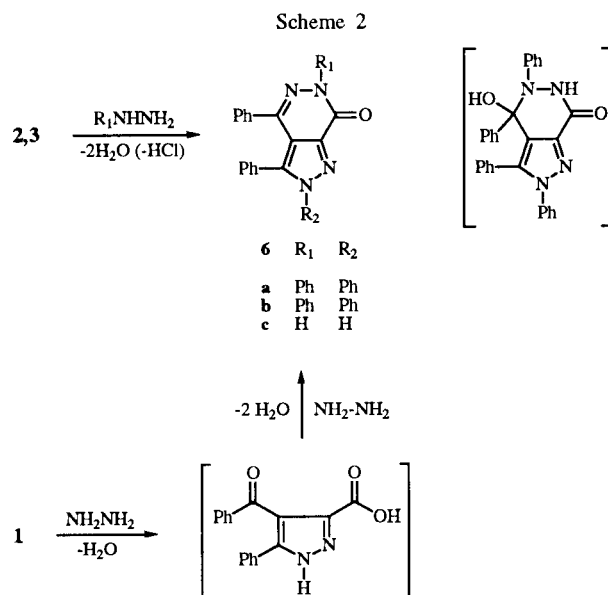


The pyrazole-3-carboxylic acid chloride **3**, obtained in approximately 50% yield, is remarkably stable (mp 161°).

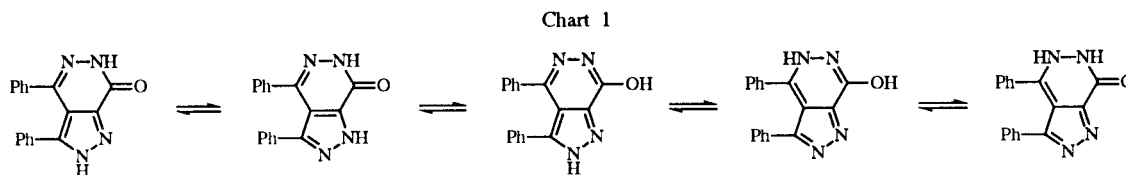
thiourea derivatives **5d-f** the correct structure was established by an ¹⁵N-INEPT spectrum of **5e** as an example, in

order to determine which nitrogen had attacked the acid chloride moiety in **3**. Two antiphase doublets at -233 and -246 ppm, respectively, referenced to nitromethane, indicate unequivocally an attack of the NH_2 -group. The ^{15}N -chemical shift values are found exactly within the expected region when compared with *e.g.* *N*-acetylthiourea [6]. The ^{13}C nmr spectrum of **5e** also agrees well with the proposed structure (for details see the Experimental). In the ^1H nmr spectrum of **5f**, the signal for the *N*-Me group is split into two peaks, which can be explained by hindrance of free rotation of the urea side-chain thus leading to rotamers. In addition, phenylurea derivative **5g**, originally prepared from the acid chloride **3** in the usual way, also resulted when the primary amide **5a** was reacted with phenylisocyanate.

Reaction of suitable vicinal dicarbonyl pyrazole derivatives with hydrazines in general is a convenient method to build the pyrazolo[3,4-*d*]pyridazine systems [7]. In a similar way, the pyrazole acid derivatives **2** or **3** and phenylhydrazine cyclize to the pyrazolo[3,4-*d*]pyridazine **6a**, while with hydrazine hydrate the corresponding derivative **6b** is obtained, both in 70-75% yield (Scheme 2). Structure elucidation of **6a,b** is mainly based upon H-coupled ^{13}C nmr spectroscopy. Signals at 155.9 (s, C-7), 144.1, 140.1 (t, C-3, C-4, exchangeable), 143.4 (s, C-7a), 116.8 (s, C-3a) are assigned to the ring-carbon atoms of **6a**, the corresponding values for **6b** are: 155.7 (s, C-7a), 143.1, 139.8 (t, C-3, C-4), 141.5 (s, C-7a) and 116.1 (s, C-3a). For further details of spectroscopic investigations see the Experimental.



to **2**. The ^{13}C nmr spectrum of **6c** exhibits significant line broadenings for the carbons C-3a (114.7 ppm), C-7 (153.5 ppm) and C-7a (131.1 ppm), respectively, thus indicating a rapid and intense exchange process among several tautomeric species. The $\text{C}=\text{O}$ absorption in the ir spectra of **6a-c** is found at 1670-1690 cm^{-1} . The primary nucleophilic attack of the hydrazine to open the furandione ring in **1** obviously occurs again at C-5 as observed with several other nucleophiles [5,8a].



While formation of **6b** is unequivocally taking place via reaction of the amino groups of hydrazine with the benzoyl carbonyl at C-4 and the carboxylic acid side chain at C-3 affording the pyridazine nucleus, attack of the phenylhydrazine could *a priori* lead to two isomeric intermediates (phenyl at N-5 or N-6, respectively, see Scheme 2). Considering the final step (elimination of water) it becomes apparent that formation of **6a** only can be the outcome of that reaction. Participation of the benzoyl moiety at C-4 in similar cyclization processes with different amino nucleophiles has also been observed [8].

It is remarkable that the *N*-unsubstituted pyrazolo-pyridazine derivative **6c** is formed from furandione **1** and hydrazine hydrate during an one-pot reaction probably occurring via a pyrazolecarboxylic acid intermediate similar

EXPERIMENTAL

Melting points were determined on a Tottoli-apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer Model 1106. The ir spectra were recorded on a Perkin Elmer Model 298 and a Shimadzu Model 435 V-O4 as potassium bromide pellets. The nmr spectra were recorded on Varian EM 360 L and Varian XL 200 Gemini spectrometers with TMS as the internal standard. The mass spectrum of **6a** was measured on a Varian MAT 111 at 80 eV.

4-Benzoyl-1,5-diphenyl-1*H*-pyrazole-3-carboxylic Acid Chloride (**3**).

4-Benzoyl-1,2-diphenyl-1*H*-pyrazolecarboxylic acid **2** [5] (1 g, 2.6 mmol) and thionyl chloride (1 ml, 13.8 mmol) were refluxed on a steam bath for 3 hours. After cooling the crude precipitate was filtered off and recrystallized from carbon tetra-

chloride to give 0.5 g (48%) of a colourless solid, mp 160-161°; ir: 1760, 1660 cm⁻¹ (C=O); ¹³C nmr: δ 190.1 (benzoyl), 161.9 (COCl), 144.7, 144.1 (C-3, C-5), 138.5, 137.2 (quaternary aryl carbons), 124.0 (C4).

Anal. Calcd. for C₂₃H₁₅N₂O₂Cl: C, 71.50; H, 3.89; N, 7.25; Cl, 9.07. Found: C, 71.20; H, 4.12; N, 7.14; Cl, 9.40.

Synthesis of the 1H-Pyrazole-3-carboxylic Esters 4a-g. General Procedures.

Method A. From 1H-Pyrazole-3-carboxylic Acid (2).

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic acid (2) (1 g, 2.6 mmoles), a large excess of the alcohol and catalytic amounts of sulfuric acid were refluxed for 1-3 hours. After cooling to 5° (refrigerator), the precipitate thus formed was filtered off and recrystallized from the corresponding alcohol.

Method B. From 1H-Pyrazole-3-carboxylic Acid Chloride (3).

The acid chloride 3 (0.25 g, 0.65 mmole) and a moderate excess of the corresponding alcohol (molar ratio 1:3) were refluxed together with catalytic amounts of pyridine for 1-3 hours. After cooling the solution was acidified by adding diluted hydrochloric acid to give a crude solid, recrystallized from a suitable alcohol.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic Acid Methyl Ester (4a).

By method A the yield was 0.78 g (75%), mp 177-178° (methanol); ir: 1725, 1660 cm⁻¹ (C=O).

Anal. Calcd. for C₂₄H₁₈N₂O₃: C, 75.39; H, 4.71; N, 7.33. Found: C, 75.23; H, 4.77; N, 7.27.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic Acid *n*-Propyl Ester (4b).

By method B the yield was 0.9 g (85%), mp 150° (1-propanol); ir: 1725, 1670 cm⁻¹ (C=O).

Anal. Calcd. for C₂₆H₂₂N₂O₃: C, 76.10; H, 5.36; N, 6.83. Found: C, 76.02; H, 5.38; N, 6.74.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic Acid *i*-Propyl Ester (4c).

By method A the yield was 0.37 g (74%), mp 160° (2-propanol); ir: 1730, 1660 cm⁻¹ (C=O).

Anal. Calcd. for C₂₆H₂₂N₂O₃: C, 76.10; H, 5.36; N, 6.83. Found: C, 75.89; H, 5.33; N, 6.72.

4-Benzoyl-1,5-diphenyl-*H*-pyrazole-3-carboxylic Acid *n*-Butyl Ester (4d).

By method A the yield was 0.5 g (44%), mp 125-126° (1-butanol); ir: 1730, 1660 (C=O).

Anal. Calcd. for C₂₇H₂₄N₂O₃: C, 76.42; H, 5.66; N, 6.60. Found: C, 76.13; H, 5.60; N, 6.65.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic Acid *i*-Pentyl Ester (4e).

By method B the yield was 0.85 g (75%), mp 106° (ethanol); ir: 1730, 1660 cm⁻¹ (C=O).

Anal. Calcd. for C₂₈H₂₆N₂O₃: C, 76.71; H, 5.94; N, 6.39. Found: C, 76.75; H, 5.82; N, 6.30.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic Acid Benzyl Ester (4f).

By method B the yield was 0.83 g (70%), mp 162° (ethanol); ir: 1725, 1660 cm⁻¹ (C=O).

Anal. Calcd. for C₃₀H₂₂N₂O₃: C, 78.60; H, 4.80; N, 6.11. Found: C, 78.54; H, 4.88; N, 6.05.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic Acid Phenyl Ester (4g).

By method B the yield was 0.70 g (61%), mp 192° (ethanol); ir: 1740, 1650 cm⁻¹ (C=O);

Anal. Calcd. for C₂₉H₂₀N₂O₃: C, 78.38; H, 4.50; N, 6.30. Found: C, 78.62; H, 4.63; N, 6.24.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-carboxylic Acid Amide (5a).

A moderate stream of gaseous ammonia was allowed to bubble through a solution of pyrazole-3-carboxylic acid chloride 3 (0.6 g, 1.55 mmoles) in 10 ml of carbon tetrachloride during 30 minutes with ice-cooling. Then the crude precipitate was filtered off and recrystallized from ethanol to give 0.55 g (85%) of 5a, mp 203-204°; ir: 3440 (NH₂), 1665 cm⁻¹ (C=O).

Anal. Calcd. for C₂₃H₁₇N₃O₂: C, 75.20; H, 4.63; N, 11.44. Found: C, 75.12; H, 4.75; N, 11.48.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-*p*-tolylamide (5b).

Acid chloride 3 (0.25 g, 0.65 mmole) and *p*-toluidine (0.14 g, 1.3 mmoles) were refluxed in benzene for 4 hours. After cooling to room temperature the precipitate which formed was filtered off and recrystallized from ethanol, yield 0.1 g (40%), mp 184-185°; ir: 3400 (NH), 1660 cm⁻¹ (C=O).

Anal. Calcd. for C₃₀H₂₃N₃O₂: C, 78.77; H, 5.03; N, 9.19. Found: C, 78.57; H, 4.95; N, 9.18.

4-Benzoyl-1,5-diphenyl-1H-pyrazole-3-diphenylamide (5c).

Acid chloride 3 (0.25 g, 0.65 mmole) and diphenylamine (0.11 g, 0.65 mmole) were refluxed in xylene for 3.5 hours. After cooling the precipitate was filtered off and recrystallized from acetic acid to afford 0.2 g (80%) pure 5c, mp 225-226°; ir: 1650 cm⁻¹ (C=O).

Anal. Calcd. for C₃₅H₂₅N₃O₂: C, 80.92; H, 4.82; N, 8.09. Found: C, 80.63; H, 4.97; N, 7.89.

1-(4-Benzoyl-1,5-diphenyl-1H-pyrazol-3-yl-carbonyl)-3-methylthiourea (5d).

Acid chloride 3 (0.52 g, 1.35 mmoles) and *N*-methylthiourea (0.12 g (1.35 mmoles) were refluxed in xylene for 5 hours. The solvent was evaporated and the remaining oily residue was treated with ether to give a crude product which was recrystallized from ethanol, yield 0.2 g (33%), mp 222°; ir: 3500-3100 (NH), 1675, 1660 cm⁻¹ (C=O).

Anal. Calcd. for C₂₅H₂₀N₄O₂S: C, 68.18; H, 4.55; N, 12.73. Found: C, 68.52; H, 4.64; N, 12.66.

1-(4-Benzoyl-1,5-diphenyl-1H-pyrazol-3-yl-carbonyl)-3-ethylthiourea (5e).

Under the same procedure as described for 5d from acid chloride 3 (0.52 g, 1.35 mmoles) and *N*-ethylthiourea (0.14 g, 1.35 mmoles) 0.33 g (55%) of 5e was obtained. It was crystallized from acetic acid, mp 200°; ir: 3450-3100 (NH), 1680, 1660 cm⁻¹ (C=O); ¹³C nmr (deuteriochloroform): δ 190.7 (benzoyl), 179.2 (C=S), 158.7 (C=O), 144.5, 142.0 (C-3, C-5 exchangeable), 138.4, 137.6 (quaternary Aryl-C), 124.0 (C-4), 40.5 (CH₂), 13.3 (CH₃); ¹⁵N nmr (deuteriochloroform): δ -233 (NHCO), -246 (NHET).

Anal. Calcd. for $C_{26}H_{22}N_4O_2S$: C, 68.72; H, 4.84; N, 12.33. Found: C, 68.49; H, 4.84; N, 12.23.

1-(4-Benzoyl-1,5-diphenyl-1*H*-pyrazole-3-yl-carbonyl)-3-methylurea (**5f**).

From acid chloride **3** (0.52 g, 1.35 mmol) and *N*-methylurea (0.1 g, 1.35 mmol) after refluxing in xylene for 5 hours and cooling to room temperature the precipitate was filtered off and recrystallized from ethanol yielding 0.3 g (50%) **5e**, mp 231°; ir: 3400, 3350 (NH), 1705, 1680, 1670 cm^{-1} (C=O); 1H nmr (deuteriochloroform): δ 9.0 (1H, NH), 8.1-7.0 (16 H, aromatic, NH), 2.8, 2.75 (3H, N-Me, rotamers).

Anal. Calcd. for $C_{25}H_{20}N_4O_3$: C, 70.75; H, 4.72, N, 13.21. Found: C, 70.73, H, 4.78; N, 13.20.

1-(4-Benzoyl-1,5-diphenyl-1*H*-pyrazole-3-yl-carbonyl)-3-phenylurea (**5g**).

a) Acid chloride **3** (0.15 g, 0.39 mmol) and phenylurea (0.060 g, 0.44 mmol) were refluxed in 2 ml of xylene for 1 hour. After cooling the solution was filtered to remove a small amount of solids, the solvent then was evaporated and the solid residue recrystallized from ethanol to give 0.09 g (48%) of **5g**, mp 212°; ir: 3400, 3250 (NH), 1710, 1690, 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{30}H_{22}N_4O_3$: C, 74.07; H, 4.53; N, 11.52. Found: C, 73.85; H, 4.77; N, 11.45.

b) The acid amide **5a** (0.25 g, 0.68 mmol) and phenylisocyanate (0.1 g, 0.84 mmol) were refluxed in 5 ml of xylene for 3 hours. Then the solvent was evaporated and the residue recrystallized from ethanol to give 0.26 g (80%) of **5g**, identical in mp and ir spectrum with that product obtained as described above.

2,3,4,6-Tetraphenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (**6a**).

The acid **2** (0.4 g, 1.08 mmol) or, alternatively, the acid chloride **3** (0.42 g, 1.08 mmol), and phenylhydrazine (0.12 g, 1.11 mmol) react in boiling xylene for 3 hours. Then the solvent was removed by evaporation and the oily residue was triturated with ether to give a crude solid, which then was recrystallized from ethanol yielding 0.33 g (70%) pure **6a**, mp 216-218°; ir: 1690 cm^{-1} (C=O); ^{13}C nmr (deuteriochloroform): 155.9 (s, C=O), 144.1, 140.1 (t, C-4, C-3, exchangeable), 143.4 (s, C-7a), 141.9, 140.1 (m, quarternary N-Ph), 134.1 (t, quarternary C-Ph), 116.8 (s, C-3a); ms: (80 eV): m/z 440 (M^+ , 100).

Anal. Calcd. for $C_{29}H_{20}N_4O$: C, 79.09; H, 4.55; N, 12.73. Found: C, 79.17; H, 4.75; N, 12.66.

2,3,4-Triphenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (**6b**).

The acid **2** (0.4 g, 1.08 mmol) and an excess (molar ratio 1:20) of hydrazine hydrate were heated in 10 ml of ethanol under reflux for 3 hours. Upon cooling the colourless solid precipitate was filtered and recrystallized from ethanol to give 0.3 g (75%) of pure **6b**, mp 291-293°; ir: 3100 (b, NH), 1670 cm^{-1} (b, C=O); ^{13}C nmr (d_6 -DMSO): 155.7 (s, C=O), 143.1, 139.8 (t, C-3, C-4), 141.5 (s, C-7a), 138.3 (t, quarternary N-Ph), 133.8 (t, quarternary C-Ph).

Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.82; H, 4.40; N, 15.38. Found: C, 76.02; H, 4.51; N, 15.36.

2,6-Diphenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (**6c**).

The furandione **1** (0.1 g, 1.8 mmol) and an excess (molar ratio 1:20) of hydrazine hydrate were refluxed in xylene for 1 hour. After cooling, the precipitate was treated with ether and then recrystallized from 1-butanol to give 0.23 g (45%) of **6c**, mp 304-306°; ir: 3400-2900 (b, NH), 1670 cm^{-1} (C=O); ^{13}C nmr (d_6 -DMSO): 153.5 (b, C=O), 143.0 (m, C-3, C-4), 134.6 (t, quarternary C-Ph), 131.1 (b, C-7a), 114.7 (b, C-3a).

Anal. Calcd. for $C_{17}H_{12}N_4O$: C, 70.83; H, 4.16, N, 19.44. Found: C, 70.94; H, 4.32; N, 19.42.

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