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Synthesis and Some Reactions of 4-Benzoyl-5-Phenyl-1-Pyridin-2-yl-1*H*-Pyrazole-3-Carboxylic Acid

Ahmet ŞENER, Esvet AKBAŞ, M. Kasım ŞENER
Yüzüncü Yıl University, Art and Science Faculty, Chemistry Department, 65080 Van-TURKEY
e-mail: asener2001@yahoo.com

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The 1*H*-pyrazole-3-carboxylic acid **2**, obtained from the furandione **1** and 2-hydrazinopyridine, was decarboxylated to give 4-benzoyl-5-phenyl-1-pyridin-2-yl-pyrazole derivative **3**. Some ester **4** derivatives of **2** were prepared by the Fischer esterification reactions of **2** with various alcohols. Cyclocondensation reactions of **2** with phenyl hydrazine or hydrazine hydrate led to the formation of derivatives of pyrazolo[3,4-d]pyridazine **5** derivatives.

Key Words: Cyclic oxalyl compounds, Pyrazole, Pyrazolo [3,4-d] Pyridazinone.

Introduction

The synthesis of novel pyrazole derivatives and investigations of their chemical and biological behavior have gained more importance in recent decades for biological[1,2], medicinal[3,4], and agricultural[5,6] reasons. Concerning the attempt to synthesize some novel pyrazole and fused pyrazole derivatives from 4-benzoyl-5-phenyl-2,3-furandione **1** and various hydrazines or hydrazones, the synthesis of 4-benzoyl-1,5-substituted-1*H*-pyrazole-3-carboxylic acids and some of their derivatives has been reported recently[7,8]. It is well known from a previous study that reactions of furandione **1** with hydrazines led to the formation of pyrazole-carboxylic acid and pyridazinone derivatives simultaneously[9]. However, in that study, the reactions of 4-benzoyl-1,5-substituted-1*H*-pyrazole-3-carboxylic acids with 2-hydrazinopyridine, instead of phenyl hydrazine or hydrazine hydrate, to prepare new pyrazolo-pyridazine derivatives, did not produce the corresponding pyrazolo-pyridazine systems. The failure or the difficulty in forming the pyridazine nucleus from 2-hydrazinopyridine was explained by the low nucleophilicity of the nitrogen atom adjacent to the pyridine ring[7,10]. In the present work, keeping the above reports in mind, we investigated the chemical behavior of furandione **1** against 2-hydrazinopyridine nucleophile.

Experimental

Solvents were dried by refluxing with appropriate drying agents and were distilled before use. Melting points were determined on an Electrothermal Gallenkamp apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba elemental analyzer model 1108. The IR spectra were obtained in potassium bromide pellets using a Mattson 1000 FTIR spectrometer. The ^{1}H- and ^{13}C–NMR spectra were recorded on Varian XL-200 (200 MHz) and Varian XL-200 (50 MHz) spectrometers, respectively, using TMS as an internal standard. All experiments were followed by TLC using DC Alufolien Kieselgel 60 F 254 Merck and a Camag TLC lamp (254/366 nm).

4-Benzoyl-5-Phenyl-1-Pyridin-2-yl-1*H*-Pyrazole-3-Carboxylic Acid (2)

An equimolar mixture of furandione **1** (0.278 g, 1 mmol) and 2-hydrazinopyridine (0.109 g, 1 mmol) was refluxed in dry benzene for approximately 30 min. After evaporation, the oily residue obtained was treated with dry ether. The crude product formed was recrystallized from a mixture of benzyl alcohol and n-butanol to give 0.258 g (70%) of **2**, mp 208 ^{o}C; IR: 3130-3050 cm^{-1} (Ar-H), 1676 cm^{-1} (C=O, benzoyl), 1635, 1580 cm^{-1} (C=O, COO^{-}); ^{1}H-NMR (DMSO-d$_6$): δ=8.6-7.2 ppm (Ar-H). ^{13}C-NMR (DMSO-d$_6$): δ=192.89 (C=O, benzoyl), 162.08 (C=O, COO^{-}), 152.48, 151.87, 149.81, 141.45, 138.68, 138.05, 135.77, 132.46, 130.91, 130.73, 130.64,130.39, 129.18, 125.91, 123.73, 119.40 ppm (C–4).

Anal. Calcd. for $C_{22}H_{15}N_3O_3$: C, 71.54; H, 4.09; N, 11.38. Found: C, 71.49; H, 4.11; N, 11.34.

4-Benzoyl-5-Phenyl-1-Pyridin-2-yl-1*H*-Pyrazole (3)

Compound **2** (0.369 g, 1 mmol) was heated to 210-220 ^{o}C in an oil bath for about 30 min without any solvent. After cooling to room temperature, the residue was treated with ether to give the crude product, which was recrystallized from methanol, to yield 0.276 g (85%); mp 106 ^{o}C; IR: 3080 cm^{-1} (Ar-H), 1651 cm^{-1} (C=O); ^{13}C-NMR (DMSO-d$_6$): δ=192.05 (C=O), 156.71, 152.82, 150.53, 141.02, 140.85, 134.71, 134.53, 134.04, 131.44, 130.92, 130.76, 130.45, 130.17, 124.32, 123.11, 115.01 ppm.

Anal. Calcd. for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.59; H, 4.63; N, 12.86.

Methyl 4-Benzoyl-5-Phenyl-1-Pyridin-2-yl -1*H*-Pyrazole-3-Carboxylate (4a)

General Procedure. To the cold solution of the pyrazole acid **2** (0.369 g, 1 mmol) in sulfuric acid was added a large excess of methanol with stirring. Then the reaction mixture was refluxed on a steam bath for 3 h with stirring. After cooling to 5 ^{o}C (refrigerator), the precipitate formed was filtered off and recrystallized from the same alcohol to give 0.172 g (45%) of **4a**; mp 165 ^{o}C; IR: 3090-3010 cm^{-1} (Ar-H), 2950 cm^{-1} (R-H), 1749 cm^{-1} (C=O, ester), 1665 cm^{-1} (C=O).

Anal. Calcd. for $C_{23}H_{17}N_3O_3$: C, 72.05;H, 4.47; N, 10.96. Found: C, 72.11;H, 4.44; N, 10.99.

n-Propyl 4-Benzoyl-5-Phenyl-1-Pyridin-2-yl-1*H*-Pyrazole-3-Carboxylate (4b)

Compound **4b** was obtained by the general procedure above with a reflux time of 5 h. The was yield 0.226 g (55%); mp 135 ^{o}C; (n-Propanol) IR: 3106 cm^{-1} (Ar-H), 2978-2902 cm^{-1} (R-H), 1753 cm^{-1} (C=O, ester), 1651 cm^{-1} (C=O). ^{13}C-NMR ($CDCl_3$): δ=192.97 (C=O), 162.13 (C=O, ester), 153.60, 153.20, 149.97, 140.74, 139.61, 137.59, 135.40, 133.31, 131.67, 130.77, 130.42, 130.21, 125.32, 124.52, 118.91, 69.69, 23.43, 12.25 ppm.

Anal. Calcd. for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 73.03; H, 5.12; N, 10.25.

n-Butyl 4-Benzoyl-5-Phenyl-1-Pyridin-2-yl-1*H*-Pyrazole-3-Carboxylate (4c)

Compound **4c** was obtained by the general procedure above with a reflux time of 6 h. The was yield 0.170 g (40%); mp 110 ^{o}C; (n-Butanol) IR: 3106-3080 cm^{-1} (Ar-H), 2978-1805 cm^{-1} (R-H), 1755 cm^{-1} (ester), 1676 cm^{-1} (C=O).

Anal. Calcd. for $C_{26}H_{23}N_3O_3$: C, 73.39; H, 5.45; N, 9.88. Found: C, 73.46; H, 5.43; N, 9.83.

3,4-Diphenyl-2-Pyridin-2-yl-2,6-dihydropyrazolo[3,4-*d*]pyridazin-7-one (5a)

General Procedure. A milliequimolar mixture of **2** and hydrazine hydrate was refluxed in butanol for 5 h. After the solvent was removed by evaporation, the oily residue was treated with ether and the crude product formed was recrystallized from ethanol. The yield was 0.256 g (70%); mp 296 ^{o}C; IR: 3029 cm^{-1} (Ar-H), 3200-2850 cm^{-1} (b, NHΔOH), 1676 cm^{-1} (C=O). ^{13}C-NMR (DMSO-d$_6$): δ=155.11 (b, C=O), 155.01, 152.70, 151.48, 150.9, 146.88, 140.03, 136.02, 135.98, 132.51, 131.54, 130.58, 130.08, 129.57, 126.04, 122.14, 120,09 ppm.

Anal. Calcd. for $C_{22}H_{15}N_5O$: C, 72.32; H, 4.14; N, 19.17. Found: C, 72.27; H, 4.16; N, 19,20.

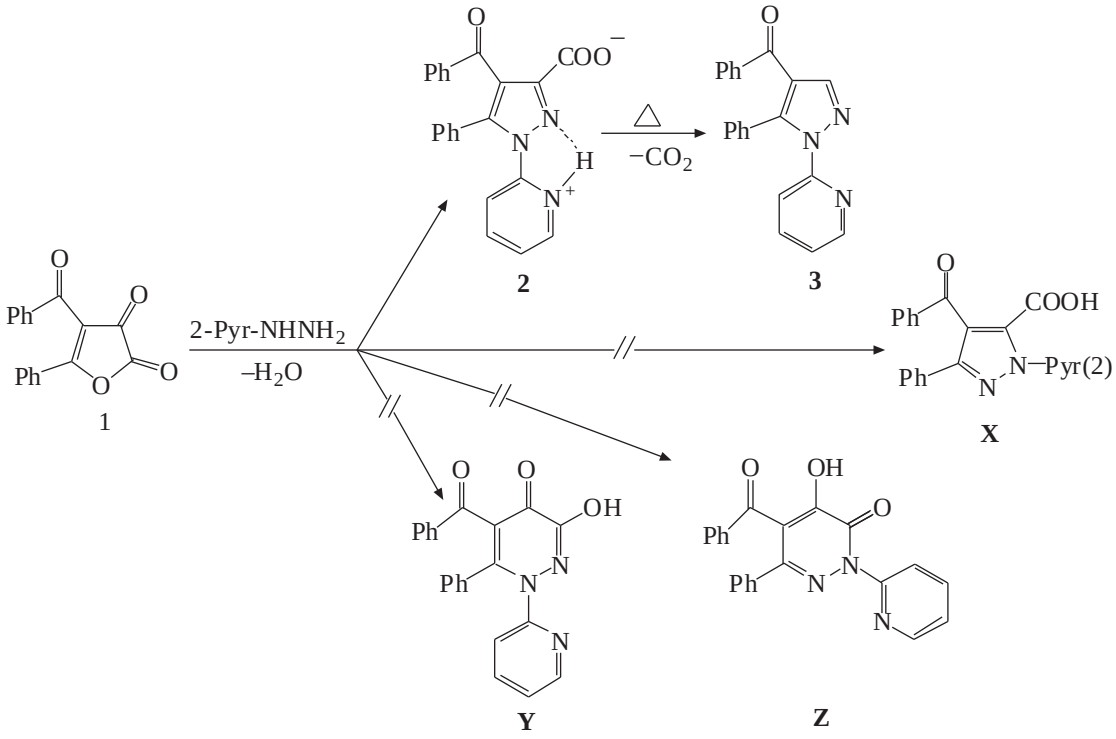
3,4,6-Triphenyl-2-Pyridin-2-yl-2,6-dihydropyrazolo[3,4-*d*]pyridazin-7-one (5b)

Compound **5b** was prepared according to the general procedure above with a reflux time of 8 h (phenyl hydrazine) in 65% yield (0.287 g); mp 199 ^{o}C (Ethanol); IR: 3055 cm^{-1} (Ar-H), 1702 cm^{-1} (C=O). ^{13}C-NMR (DMSO-d$_6$): δ=155.11 (C=O), 154.22, 152.96, 150.87, 146.00, 143.42, 140.01, 136.05, 133.01, 132.58, 131.01, 131.78, 131.44, 131.23, 130.89, 130.66, 130.31, 128.08, 126.50, 123.14, 120.37 ppm.

Anal. Calcd. for $C_{28}H_{19}N_5O$: C, 76.17; H, 4.34; N, 15.86. Found: C, 76.23; H, 4.32; N, 15.79.

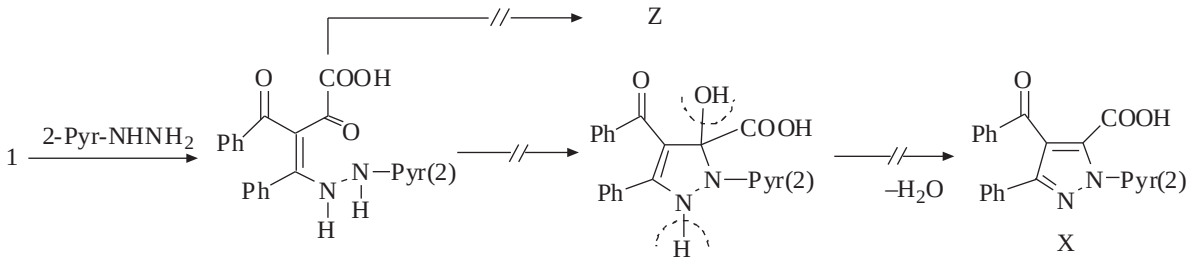
Results and Discussion

In this study, we studied the reaction of furandione **1** with 2-hydrazinopyridine. The preparation of 4-benzoyl-5-phenyl-1-pyridin-2-yl-1*H*-pyrazole-3-carboxylic acid (**2**) was achieved by refluxing equimolar amounts of 4-benzoyl-5-phenylfuran-2,3-dione (**1**) and 2-hydrazinopyridine in dry benzene for about 30 min (Scheme 1). While the reaction of furandione **1** with phenyl hydrazine led to the formation of the corresponding pyrazole carboxylic acid together with 5-benzoyl-2,6-diphenyl-4-hydroxypyridazine-3-one[9], the reaction of **1** with 2-hydrazinopyridine predictably provided the corresponding pyrazole acid **2** only but in a yield higher than that in the literature[9]. Additionally, the decarboxylation of **2** in an oil bath at elevated temperature led to cleavage of the C–C bond with a loss of CO_2, finally yielding the corresponding pyrazole derivative **3** (Scheme 1).



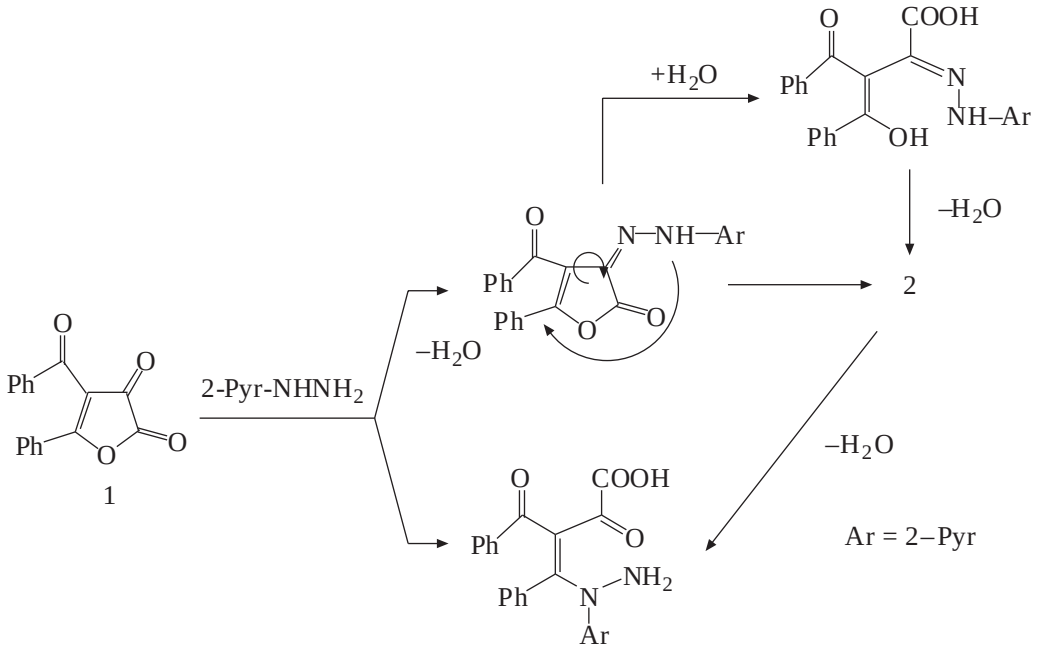
Scheme 1

The failure of the corresponding pyridazine compound to form can be explained by the disappearance of the nucleophilic attack of the NH group in 2-hydrazinopyridine at the C–2 position of the furan ring system due to the low nucleophilicity of the nitrogen atom adjacent to the pyridine ring. However, the formation of the pyrazole acid **2** in a high yield cannot be explained by this. However, the nucleophilic attack of the NH group of 2-hydrazinopyridine at the C–5 position of the furan ring, to form a stable intermediate, is still possible[11], and this intermediate may be predictably transformed into the corresponding pyrazole acid **2**, not into the corresponding pyridazine derivative[9] since the carbonyl group is a much more effective electrophile than the carboxyl group. On the other hand, the nucleophilic attack of NH group adjacent to the pyridine ring of the hydrazine compound at the C–3 position of the furandione **1** ring cannot form a stable intermediate, since the addition of the NH group to the C=O moiety is a reversible process[12]. Additionally, the synthesis of pyrazole acid of type **2** from furandione **1** with substituted hydrazine is well established and it has been proved that **X**, which is the isomer **2**, and **Y** cannot be formed during such a reaction, based on both the X-ray diffraction method and the analysis of their ^{1}**H-**^{15}**N NMR** coupling constants[9]. For this reason, the nucleophilic attack of the NH_2 group of 2-hydrazinopyridine at all positions of furandione **1** ring (except at the C–3 position) can start side reactions responsible for the non-quantitative formation of **2**[13]. This may be due to the presence of 3 large groups in ortho positions of the intermediate of **X** (a kind of ortho effect) or the necessity of an additional fragmentational process for elimination of water in forming **X** from the intermediate formed via the Michael addition of the NH_2 group followed by the addition of the NH group to C=O moiety, which is a reversible process (Scheme 2).



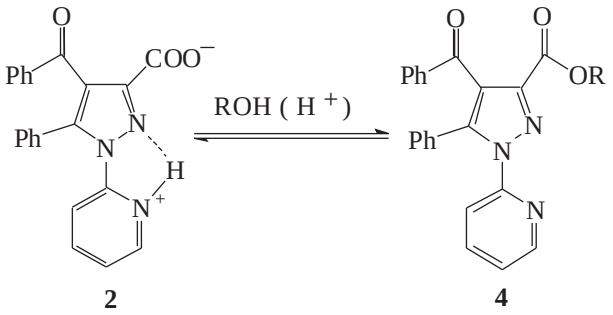
Scheme 2

Due to the reasons mentioned above, the reactions leading to pyrazole carboxylic acid **2** should be initiated by nucleophilic attacks of NH_2 and NH groups in 2-hydrazinopyridine at the C–3 and C–5 positions of the furandione **1** ring, respectively. A reasonable proposal for reaction pathway from furandione **1** to pyrazole acid **2** is outlined briefly in Scheme 3.



Scheme 3

The structure of compound **2** was confirmed by analytical and spectral data. Compounds **2** and **3** show characteristic IR absorption bands at 1676 cm^{-1}(C=O) and 1651 cm^{-1} (C=O), respectively. The IR spectra of compound **2** showed no absorption bands corresponding to the COOH group such as 3300-2500 cm^{-1}(b, OH, COOH) and 1700-1750 cm^{-1}(C=O, COOH) like that of 4-benzoyl-1,5-diphenyl pyrazole-3-carboxylic acid[9]. However, absorption bands at approximately 1635 cm^{-1} and 1580 cm^{-1} corresponding to the ionized carboxylate group[14] were observed. From its IR spectrum, it may be deduced that compound **2** is found in betaine form in the solid state. Their characteristic ^{13}C-NMR signals at δ=192.89 (C=O), 162.08 (COO^-), 152.48 (C–2′, Pyr) and 151.87 (C–6′, Pyr), and 192.05 (C=O), 156.71 (C–2′, Pyr) and 152.82 ppm (C–6′, Pyr), respectively, are in full agreement with their proposed structures. In addition, acid **2** could be easily converted into the corresponding ester **4** derivatives by the usual chemical procedure (Scheme 4).

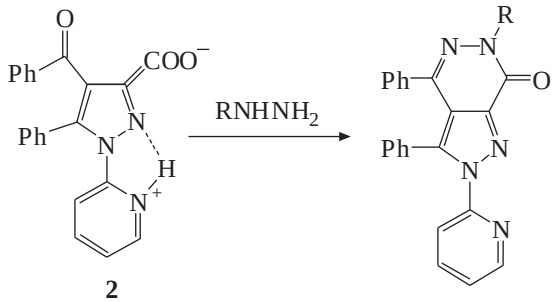


2 **4**

4 R
a n–Pr
b Me
c n-But

Scheme 4

Reactions of pyrazole derivatives having 2 carbonyl groups in the orthoposition with hydrazines are convenient methods to build pyrazolo[3,4-d]pyridazine systems[7,8]. Thus, the pyrazole acid **2** was cyclized with various hydrazine compounds to the pyrazolo[3,4-d]pyridazinones **5a-b**, in approximately 65-70% yields (Scheme 5).



2 **5**

5 **R**
a H
b Ph

Scheme 5

The structure elucidation of **5a-b** is mainly based on ^{13}C–NMR spectroscopy (see Experimental for details).

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References

1. R. Katoch-Rouse and A.G. Horti, **J. Label. Compd. Radiopharm.**, **46**, 93-98 (2003).
2. J.P. Meschler, D.M. Kraichely, G.H. Wilken and A.C. Howlett, **Biochemical Pharmacology**, **60**, 1315-1323 (2000).

3. A.B. Adnan, T.Y.F. Hesham, A.F.R. Sherif and A. Baraka, **Eur. J. Med. Chem.**, **38**, 27-36 (2003).
4. E. Badawey and I.M. El-Ashmawey, **Eur. J. Med. Chem.**, **33**, 349, (1998).
5. W.T. Thomson, Agricultural chemicals-Book II Herbicides, 13^{th} ed., pp 268-269-278, Thomson Publications, California, USA, 1997.
6. M. Londershausen, **Pestic. Sci.**, **48**, 269, (1996).
7. A. Şener, R. Kasımoğulları, M.K. Şener, İ. Bildirici and Y. Akçamur, **J. Heterocyclic Chem. 39**, 869, (2002).
8. Y. Akçamur, A. Şener, A.M. İpekoğlu and G. Kollenz, **J. Heterocyclic Chem.**, **34**, 221, (1997).
9. Y. Akçamur, G. Penn, E. Ziegler, H. Sterk, G. Kollenz, K. Peters, E.M. Peters and H.G. Von Schnering, **Monatsh Chem.**, **117**, 231, (1986)
10. R. Kasımoğulları, **"Synthesis and Reactions of 4-Benzoyl-1-(3 or 4-Nitrophenyl)-5-Phenyl-1*H*-Pyrazole-3-Carboxylic Acid"** PhD Thesis, Y.Yıl University, Van, Turkey, 2001.
11. Y. Akçamur, B. Altural, E. Sarıpınar, G. Kollenz, O. Kappe, K. Peters, E.M. Peters and H.G. Schnering, **J. Heterocyclic. Chem., 25**, 1419, (1988).
12. C. Tüzün, Organic Chemistry, 7^{th} ed., pp. 181-183, Palme Publishing, Ankara, 1996.
13. G. Kollenz, E. Ziegler, W. Ott and H. Igel, **Z. Naturforsh, 31b**, 1511, (1976).
14. G.C. Bassler and T.C. Morrill, Spectrometric Identification of Organic Compounds, R.M. Silverstein (ed), pp. 118, J. Wiley, New York, 1991.