Turk J Chem
28 (2004) , 39 – 45.

One Step Synthesis and Some Reactions of 7-Hydrazino-3,4-Diphenyl-2*H*-Pyrazolo [3,4-d] Pyridazine

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Received 15.05.2003

The 7-hydrazino-3,4-diphenyl-2*H*-pyrazolo-[3,4-d]-pyridazine **3**, obtained in 2 different ways consisting of the reactions of anhydrous hydrazine with 4-benzoyl-5-phenyl-2,3- dihydro-2,3-furandione **1** or 3,4-diphenyl-2*H*-pyrazolo-[3,4-d]-pyridazin-7(6*H*)-one **2**, was converted into hydrazone derivatives **4** by the reactions of **3** with various salicylaldehydes.

Introduction

Hydrazino-pyridazines continue to be an object of interest for improving medicinal drugs for blood pressure control such as hydralazine, which has been used for many years in the treatment of essential hypertension [1-3]. Recently, therapeutic interest in this kind of drug has increased considerably due to their cytotoxic activities, notably decreasing blood flow to tumors [4]. Lately, the syntheses of potential biologically active compounds containing pyrazolo [3,4-d] pyridazine systems have also been of great importance for medicinal and biological reasons [5,6]. Generally, pirazolo [3,4-d] pyridazines have shown good antimicrobial, anti-inflammatory and analgesic activities [7]. From their structure–activity relationship, it may be expected that hydrazino-pyrazolo [3,4-d] pyridazines consisting of isosteric heterobicyclic systems, which are formed by the replacement of the benzene ring in hydralazine with a pyrazole nucleus, can exhibit interesting biological activities. On the other hand, furandiones of type **1** have been used successfully in the syntheses of various heterocycles for a long time [8]. As part of our research program on the reactions of cyclic oxalyl compounds with various hydrazines or hydrazones [9], we decided to investigate the reaction of **1** with anhydrous hydrazine.

Experimental

Solvents were dried by refluxing with appropriate drying agents and 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 a DC Alufolien Kieselgel 60 F 254 Merck and Camag TLC lamp (254/366 nm).

3,4-Diphenyl-1*H*-pyrazolo [3,4-d] pyridazin-7(6*H*)-one 2 [10,11]

This compound was prepared according to the literature procedure [11] given below. To a solution of furandione **1** (1 g, 3.6 mmol) in xylene (40 mL) at room temperature was added hydrazine hydrate (0.2 mL, 4.12 mmol) with stirring (the isolation of compound **2** from mixtures of furandione **1** and hydrazine hydrate except at the molar ratio given above is not possible). Then the reaction mixture was refluxed for 60 min. After cooling to room temperature, the precipitates (impurities) were removed by filtration. The filtrate was left overnight at room temperature for crystallization. The separated solid was recrystallized from methanol, mp 308 ^{o}C.

7-Hydrazino-3,4-diphenyl-1*H*-pyrazolo[3,4-d] pyridazine 3

Method A. From Furandione **1**

Furandione **1** (0.278 g, 1 mmol) and anhydrous hydrazine (0.2 mL, 4.12 mmol) were refluxed in xylene (30 mL) for about 1 h. The precipitate, which was formed in boiling xylene, was isolated by filtration and recrystallized from ethanol to give 0.197 g (65%) of **3**, mp 330 ^{o}C (White crystals). ir: 3420 cm^{-1} (NH_2), 3128, 2918 cm^{-1} (Ar-H), 3130-2915 cm^{-1} (b, N=C-NHΔNH-C=N-), 1678 cm^{-1} (C=N); ^{1}H-nmr (DMSO-d_6): δ=7.62-7.01 (m, Ar-H), 8.50-4.00 ppm (b, N-H); ^{13}C-nmr (DMSO-d_6) : δ=156.1 (b, C-7), 147.3 (C-7a), 145.3 (C-3), 139.4 (C-4), 136.9, 132.9, 131.1, 130.3, 130.2, 129.8, 129.4, 129.4, 116.8 ppm (C-3a).

Anal. Calcd. for $C_{17}H_{14}N_6$: C, 67.53; H, 4.67; N, 27.80; found: C, 67.42; H, 4.69; N, 27.89

Method B. From pyrazolo-pyridazine **2**

A milliequimolar mixture of **2** and anhydrous hydrazine was refluxed in xylene (30 mL) for approximately 1 h until the issuing of solid masses from the hydrazine phase at the bottom ceased. After cooling to room temperature, the precipitate thus formed was filtered off and recrystallized from ethanol to give 0.259 g (90%) of **3**, with an mp and ir spectrum identical to those of the product obtained as described above.

2-[(3,4-Diphenyl-1*H*-pyrazolo [3,4-d] pyridazin-7-yl) hydrazonomethyl] phenol 4a General Procedure

Compound **3** (0.302 g, 1 mmol) and a slight excess of salicylaldehyde were refluxed in ethanol (30 mL) for about 1 h. After cooling to room temperature, the separated yellow crystals were recrystallized from the same alcohol to give 0.285 g (70%) of **4a**, mp 281 ^{o}C; ir: 3400 cm^{-1} (OH), 3137, 3039 cm^{-1} (Ar-H), 3140-2850 cm^{-1} (b, N=C-NHΔNH-C=N-), 1676 cm^{-1} (C=N), 1623 cm^{-1} (CH=N).

Anal. Calcd. for $C_{24}H_{18}N_6O$: C, 70.92; H, 4.46; N, 20.68; found: C, 71.05; H, 4.47; N, 20.63

4-[(3,4-Diphenyl-1*H*-pyrazolo [3,4-d] pyridazin-7-yl) hydrazonomethyl] benzene-1,3-diol 4b

Compound **4b** was prepared according to the general procedure with a reflux time of 3 h using 1-propanol as solvent (2,4-dihydroxybenzaldehyde), resulting in a 65% yield (0.275 g) mp 294 ^{o}C; ir: 3464 cm^{-1} (OH), 3109, 3058 cm^{-1} (Ar-H), 3300-2910 cm^{-1} (b, N=C-NHΔNH-C=N-), 1676 cm^{-1} (C=N), 1616 cm^{-1} (CH=N); ^{13}C-nmr (DMSO-d_6): δ=163.9 (CH=N), 163.6 (C-1'), 162.5 (C-3'), 156.0 (b, C-7), 145.3 (C-7a), 136.8 (C-3 and C-4), 134.8, 131.1, 130.6, 130.3, 130.2, 130.1, 129.9, 129.7, 129.4, 116.1 (C-3a), 112.1, 110.0, 104.3 ppm.

Anal. Calcd. for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89; found: C, 68.33; H, 4.27; N, 19.94

2-[(3,4-Diphenyl-1*H*-pyrazolo [3,4-d] pyridazin-7-yl) hydrazonomethyl]-6-methoxy-phenol 4c

Compound **4c** was prepared according to the general procedure with a reflux time of 3 h using 2-propanol as solvent (2-hydroxy-3-methoxy benzaldehyde), resulting in a 62% yield (0.271 g) mp 285 ^{o}C; ir: 3419 cm^{-1} (OH), 3150, 3005 cm^{-1} (Ar-H), 3250-2800 cm^{-1} (b, N=C-NHΔNH-C=N-), 1674 cm^{-1} (C=N), 1624 cm^{-1} (CH=N); ^{13}C-nmr (DMSO-d$_6$) : δ=164.6 (CH=N), 156.0 (b, C-7), 150.3 (C-1' or C-6'), 149.8 (C-1' or C-6'), 145.3 (C-7a), 136.8 (C-3 and C-4), 131.1, 130.5, 130.4, 130.2, 129.9, 129.4, 129.4, 123.9, 121.1, 120.1, 117.1 (C-3a), 57.7 ppm (OCH_3).

Anal. Calcd. for $C_{25}H_{20}N_6O_2$: C, 68.79; H, 4.62; N, 19.25; found: C, 68.89; H, 4.61; N, 19.21

3-[(3,4-Diphenyl-1*H*-pyrazolo [3,4-d] pyridazin-7-yl) hydrazonomethyl] benzene-1,2-diol 4d

Compound **4d** was prepared according to the general procedure with a reflux time of 3 h using 2-propanol as solvent (2,3-dihydroxybenzaldehyde), resulting in a 55% yield (0.232 g) mp 312 ^{o}C; ir: 3394 cm^{-1} (OH), 3050, 3035 cm^{-1} (Ar-H), 3120-2950 cm^{-1} (b, N=C-NHΔNH-C=N-), 1672 cm^{-1} (C=N), 1626 cm^{-1} (CH=N).

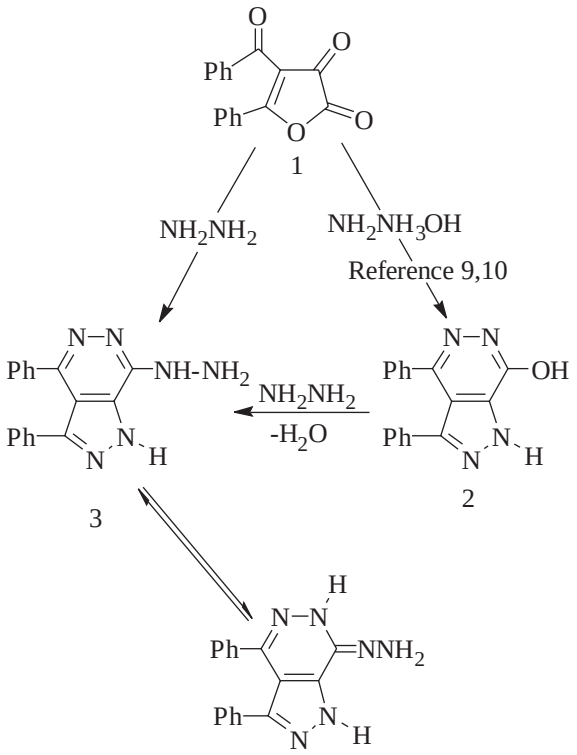
Anal. Calcd. for $C_{24}H_{18}N_6O_2$: C, 68.24; H, 4.29; N, 19.89; found: C, 68.29; H, 4.32; N, 19.95

Results and Discussion

The title compound **3** was prepared in good yield by refluxing **1** and a slight excess of anhydrous hydrazine in xylene. In addition, **3** was also synthesized by another chemical process consisting of refluxing equimolar amounts of 3,4-diphenyl-2*H*-pyrazolo [3,4-d] pyridazin-7-6*H*-one **2**, which was obtained previously [10,11], and anhydrous hydrazine in xylene in a high yield (Scheme 1).

Considering that *H*-active nucleophiles can attack the C-2, C-3 and C-5 positions of furandiones [12,13], a mechanistic rationale for likely reaction pathways from furandione **1** to hydrazino-pyrazolo-pyridazine **3** is outlined briefly in Scheme 2.

In the reaction pathway (a), a ring opening for the formation of the first formed intermediate may be initiated by a nucleophilic attack of one of the NH_2 groups in hydrazine at the C-5 position of the furan ring in **1**, similar to the reactions of furandione **1** with other hydrazines or hydrazones [9,10,12]. Ring closure of the first intermediate to the pyrazole acid intermediate may occur via the addition of an NH_2 group to the C=O moiety and finally the elimination of water in the second step affording a pyrazole nucleus [12]. Considering the reaction pathway (b) initiated by the nucleophilic attack of amino groups of hydrazine at the C-3 position of the furandione ring, ring opening for the formation of a second intermediate occurs via the addition again of water separated during the formation of hydrazone intermediate in the first step to the lacton group in the furandione **1** in the second step [14]. Then the elimination of water between NH_2 and OH groups in the third step leads to the formation of pyrazole acid intermediate. The formation of pyrazolo-pyridazine **2** intermediate (or derivative) unequivocally takes place via the reaction of NH_2groups of hydrazine with benzoyl carbonyl and carboxylic acid side chain, affording the pyridazine nucleus [10,15]. It is obvious that the nucleophilic attack of the NH_2 group in hydrazine at the C-2 position of the furan ring in **1** would lead to the formation of a pyridazine intermediate [12]. However, the formation of both pyrazolo-



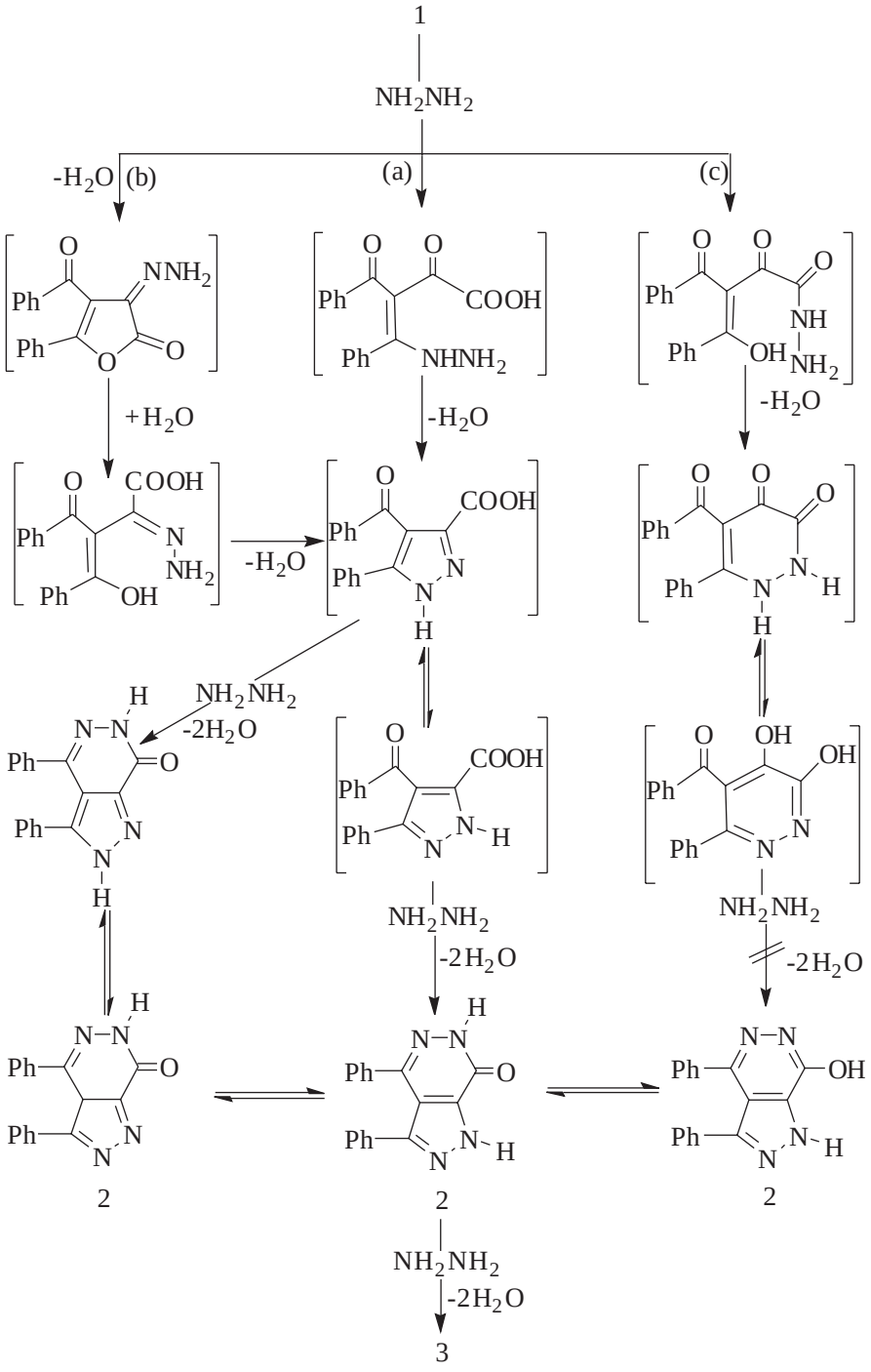
Scheme 1

pyridazine intermediate (or derivative) and compound **3** via such a reaction pathway (c) is impossible because the oxo group in the C-4 position of this kind of pyridazine is not essentially a keto group but probably a phenolic group. Additionally, experiments performed with analogous pyridazines demonstrated that they cannot react with hydrazines to give pyrazolo-pyridazines under ordinary reaction conditions. On the other hand, it is well known that compound **2** has several tautomeric species containing an acidic OH group at the C-7 position [10]. For this reason, it may be expected that **2** exhibits chemical behavior near the carbamic or carboxylic acids towards N- nucleophiles of hydrazine type.

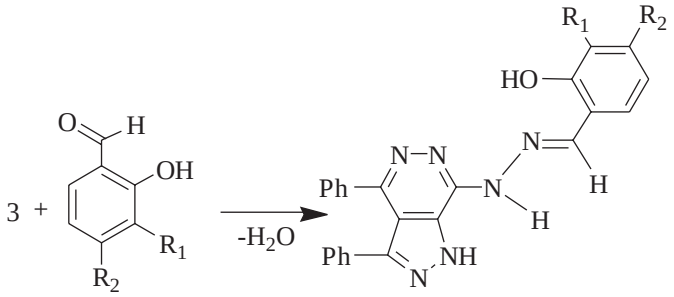
The structure of compounds **3** was confirmed by analytical and spectral data. The ^{13}C-nmr spectra of **3** exhibit significant line broadening for C-7, indicating a rapid and intense exchange process between 2 tautomeric species (see Experimental and Scheme 1). In addition, compound **3** was easily converted into the corresponding hydrazone **4** derivatives by the usual chemical procedures (Scheme 3).

The structures of compounds **4a-d** are supported by elemental analysis and spectroscopic data. In the ir spectra of **4a-d**, characteristic absorption bands at about 1673 and 1620 cm^{-1}for C=N and CH=N groups were observed, respectively. In the ^{13}C-nmr spectra of compounds **4** the signals at approximately δ=164 and 156 ppm are assigned to carbon atoms of C=N and CH=N groups, respectively. Other spectral and analytical data of **4a-d** are also in agreement with their proposed structures (see Experimental).

A comparison of the ^{13}C-nmr spectra of **4b** and **4c** demonstrates that **4b** may possess keto-enol tautomeric species having a rapid and intense exchange process between each other (see Experimental and Scheme 4).

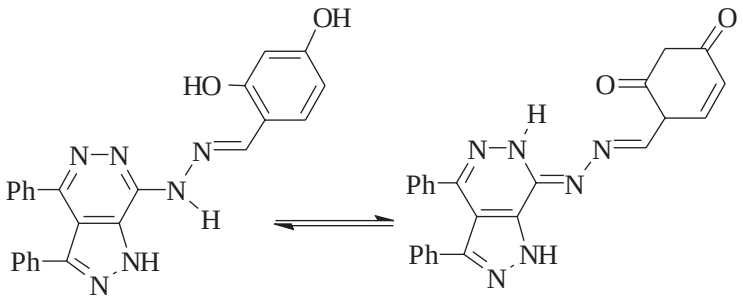

1
NH2NH2
-H2O
(b)
(a)
(c)
+H2O
-H2O
-H2O
-H2O
NH2NH2
-2H2O
NH2NH2
-2H2O
NH2NH2
-2H2O
2
2
2
NH2NH2
-2H2O
3

Scheme 2



4	R_1	R_2
a	H	H
b	H	OH
c	OCH_3	H
d	OH	H

Scheme 3



Scheme 4

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