Chemistry of Heterocyclic Compounds, Vol. 46, No. 2, 2010

POLYFUNCTIONAL PYRAZOLES

6.* CONVENIENT METHOD FOR THE SYNTHESIS OF 1-ARYL-1H-PYRAZOLE-3,4-DICARBOXYLIC ACIDS

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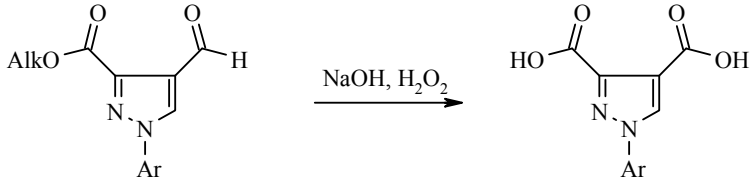
A preparatively convenient method was developed for the synthesis of 1-aryl-1H-pyrazole-3,4-dicarboxylic acids based on the alkaline hydrolysis and oxidation of 1-aryl-4-formyl-1H-pyrazole-3-carboxylic esters with hydrogen peroxide in an aqueous medium.

Keywords: pyrazole-3,4-dicarboxylic acids, 4-formylpyrazole-3-carboxylic esters, aqueous medium, hydrolysis, oxidation.

Pyrazole-3,4-dicarboxylic acids and their derivatives are used as the main subjects for the production of a series of pharmacologically important condensed pyrazole systems [2] and heterocyclic assemblies with clearly defined electroluminescent effects [3] and also exhibit a wide range of biological activity. In particular, certain amides of pyrazole-3,4-dicarboxylic acids are characterized by high sedative and anti-inflammatory activity [4]. The esters of the acids have been tested as bactericidal [5, 6] and antineoplastic [7] agents.



1 a–k **2 a–f**

1 a–f Alk = Me, **a** Ar = Ph, **b** Ar = 4-BrC_6H_4, **c** Ar = 2-MeC_6H_4, **d** Ar = 4-MeC_6H_4, **e** Ar = 4-MeO(O)CC_6H_4, **f** Ar = 2-naphthyl, **g–k** Alk = Et, **g** Ar = Ph, **h** Ar = 4-BrC_6H_4, **i** Ar = 2-MeC_6H_4, **j** Ar = 4-MeC_6H_4, **k** Ar = 2-naphthyl; **2 a** Ar = Ph, **b** Ar = 4-BrC_6H_4, **c** Ar = 2-MeC_6H_4, **d** Ar = 4-MeC_6H_4, **e** Ar = 4-HO(O)CC_6H_4, **f** Ar = 2-naphthyl

*For Communication 5 see [1].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 243-247, February, 2010. Original article submitted January 20, 2009.

Several methods used for the production of pyrazole-3,4-dicarboxylic acids have certain preparative disadvantages. Thus, the use of alkaline hydrolysis of the corresponding diesters is restricted by their relatively poor availability [8-10]. The synthetic significance of the method involving oxidation of 3,4-dimethyl-1-phenylpyrazole with potassium permanganate is reduced by the formation of 4-methyl-1-phenylpyrazole-3-carboxylic acid as side product [11]. The oxidation of ethyl 4-formyl-5-methyl-1-phenylpyrazole-3-carboxylate with silver oxide has only found use for analytical purposes [12]. Thus, the problem of an effective method for the production of pyrazole-3,4-dicarboxylic acids remains urgent.

We have developed a preparatively convenient approach to their synthesis based on the use of the accessible alkyl esters of 1-aryl-4-formylpyrazole-3-carboxylic acids **1a-k** [1, 13]. It was found that compounds **1a-k**, irrespective of the nature of the alkyl substituent, are easily converted into 1-arylpyrazole-3,4-dicarboxylic acids **2a-f** with almost quantitative yields when treated successively with an aqueous solution of NaOH at 40-50°C and with 30% hydrogen peroxide at room temperature. Here in the case of compound **1e** ` of the ester group of the aryl substituent and the formation of the tricarboxylic acid **2e** are also observed.

TABLE 1. The Characteristics of the Synthesized Compounds **2a-f**

Compound	Empirical formula	Found, % / Calculated, %			M^+	mp, °C	Yield, %*	
		C	H	N			*a*	*b*
2a	$C_{11}H_8N_2O_4$	57.07 / 56.90	3.58 / 3.47	12.19 / 12.06	232.8	235-237	97	95
2b	$C_{11}H_7BrN_2O_4$	42.66 / 42.47	2.35 / 2.27	9.18 / 9.00	311.6	250-252	95	98
2c	$C_{12}H_{10}N_2O_4$	58.79 / 58.54	4.22 / 4.09	11.30 / 11.38	246.9	225-227	93	96
2d	$C_{12}H_{10}N_2O_4$	58.41 / 58.54	4.17 / 4.04	11.25 / 11.38	257.2	235-237	98	96
2e	$C_{12}H_8N_2O_6$	52.34 / 52.18	3.04 / 2.92	10.29 / 10.14	277.0	>280	98	—
2f	$C_{15}H_{10}N_2O_4$	63.69 / 63.83	3.69 / 3.57	10.05 / 9.92	283.1	265-267	94	97

*Compounds **2a-f** were obtained from the esters **1a-f** (*a*) and **1g-k** (*b*) respectively.

TABLE 2. The Spectral Characteristics of Compounds **2a-f**

Compound	IR spectrum, ν, cm^{-1}		^1H NMR spectrum, δ, ppm (*J*, Hz)*
	C=O	O–H	
2a	1720	2550-2900	7.40 (1H, t, *J* = 7.0, H Ar); 7.52 (2H, d, *J* = 7.5, H Ar); 7.94 (2H, d, *J* = 7.5, H Ar); 9.09 (1H, s, H-5)
2b	1720	2570-2940	7.70 (2H, d, *J* = 9.5, H Ar); 7.94 (2H, d, *J* = 9.5, H Ar); 9.14 (1H, s, H-5)
2c	1725	2560-2920	2.19 (3H, s, CH_3); 7.37-7.43 (4H, m, H Ar); 8.66 (1H, s, H-5)
2d	1720	2580-2890	2.40 (3H, s, CH_3); 7.33 (2H, d, *J* = 8.5, H Ar); 7.83 (2H, d, *J* = 8.5, H Ar); 9.04 (1H, s, H-5)
2e	1715	2560-2900	8.09 (4H, s, H Ar); 9.22 (1H, s, H-5)
2f	1720	2565-2920	7.52-7.58 (2H, m, H Ar); 7.94–8.16 (4H, m, H Ar); 8.52 (1H, s, H Ar); 9.25 (1H, s, H-5)

*The signals of the protons of the carboxyl groups of the acids **2a-f** are in exchange with the protons of the water contained in the DMSO-d_6.

TABLE 3. The ^{13}C NMR Spectra of Compounds **2a-f**

Compound	Chemical shifts, δ, ppm					
	C(3)	C(4)	C(5)	C(O)OH	C Ar	CH_3
2a	145.15	116.77	133.26	163.28 163.44	120.64, 121.50 132.53, 137.08	—
2b	145.15	116.75	133.31	163.28 163.48	120.63, 121.45 132.37, 137.70	—
2c	144.23	115.51	136.94	163.43 163.82	126.15, 126.86, 129.48, 131.27, 133.14, 138.40	17.33
2d	144.52	116.55	133.08	163.43 163.78	119.42, 130.06, 136.26, 137.63	20.50
2e	145.66	117.30	133.42	163.32 163.55 166.50	119.19, 129.98, 130.84, 141.50	—
2f	144.96	116.84	133.58	163.52 163.85	117.29, 118.20, 126.76, 127.37, 127.81, 128.14, 129.74, 132.05, 132.91, 135.94	—

We note that hydrogen peroxide in the absence of other reagents has been used extremely rarely for the conversion of an aldehyde group into a carboxyl group. Only examples of the oxidation of aromatic aldehydes to carboxylic acids in an alkaline medium [14] and also of aromatic and certain heteroaromatic aldehydes in acidic media [15, 16] are known.

An advantage of our proposed method for the synthesis of the acids **2a-f** is also realization of the two-stage hydrolysis and subsequent oxidation of the esters **1a-k** in a one-pot regime without isolation of the intermediate 1-aryl-4-formylpyrazole-3-carboxylic acids [1].

The composition of the synthesized pyrazoledicarboxylic acids **2a-f** agrees with the data from elemental analysis and mass spectra (Table 1), and the structure was proved by the IR and ^1H (Table 2) and ^{13}C (Table 3) NMR spectra.

EXPERIMENTAL

The IR spectra were recorded in tablets with KBr on a UR-20 instrument. The ^1H and ^{13}C NMR spectra were obtained in DMSO-d_6 on a Bruker Avance DRX-500 spectrometer (500 and 125 MHz respectively) with TMS as internal standard. The chromato-mass spectra of compounds **2a-f** were obtained on an Aligent 1100/DAD/HSD/VLG 119562 instrument. Compounds **1a-k** were synthesized by the method in [1].

Compound 1d. Yield 78%; mp 100-101°C (mp 98°C [13]).

Compound 1h. Yield 82%; mp 155-156°C (EtOH). IR spectrum, ν, cm^{-1}: 1680, 1740 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (3H, t, *J* = 7.0, CH_3); 4.21 (2H, d, *J* = 7.0, CH_2); 7.69 (2H, d, *J* = 8.4, H Ar); 7.92 (2H, d, *J* = 8.4, H Ar); 9.08 (1H, s, H-5); 10.24 (1H, s, CH=O). Found, %: C 48.07; H 3.57; N 8.51. $C_{13}H_{11}BrN_2O_3$. Calculated, %: C 48.32; H 3.43; N 8.67.

Compound 1i. Yield 71%; mp 108-109°C (EtOH). IR spectrum, ν, cm^{-1}: 1685, 1740 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (3H, t, *J* = 7.0, CH_3); 2.25 (3H, s, CH_3); 4.41 (2H, q, *J* = 7.0, CH_2); 7.38-7.50 (4H, m, H Ar); 8.74 (1H, s, H-5); 10.34 (1H, s, CH=O). Found, %: C 62.33; H 5.55; N 10.69. $C_{14}H_{14}N_2O_3$. Calculated, %: C 65.11; H 5.46; N 10.85.

Compound 1j. Yield 75%; mp 116-117°C (EtOH). IR spectrum, ν, cm^{-1}: 1685, 1735 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, t, *J* = 7.0, CH_3); 2.40 (3H, s, CH_3); 4.24 (2H, d, *J* = 7.0, CH_2);

7.34 (2H, d, J = 8.5, H Ar); 7.85 (2H, d, J = 8.5, H Ar); 9.15 (1H, s, H-5); 10.31 (1H, s, CH=O). Found, %: C 64.89; H 5.56; N 10.71. $C_{14}H_{14}N_2O_3$. Calculated, %: C 65.11; H 5.46; N 10.85.

Compound 1k. Yield 67%; mp 171-172°C (EtOH). IR spectrum, ν, cm^{-1}: 1690, 1730 (C=O). ^1H NMR spectrum, δ, ppm (J, Hz): 1.44 (3H, t, J = 7.0, CH_3); 4.46 (2H, d, J = 7.0, CH_2); 7.57-7.63 (2H, m, H Ar); 7.97-8.15 (4H, m, H Ar); 8.55 (1H, s, H Ar); 9.34 (1H, s, H-5); 10.35 (1H, s, CH=O). Found, %: C 69.16; H 4.93; N 9.68. $C_{17}H_{14}N_2O_3$. Calculated, %: C 69.38; H 4.79; N 9.55.

1-Aryl-1H-pyrazole-3,4-dicarboxylic Acids 2a-f. A suspension of the alkyl ester **1a-k** (1 mmol) and NaOH (2 g, 5 mmol) in water (50 ml) was heated at 40-50°C with stirring until completely dissolved (~30 min). The reaction mixture was cooled to room temperature, 2 ml of 30% hydrogen peroxide was added, and the mixture was stirred for 2 h and acidified to pH 2 with dilute hydrochloric acid. The precipitate was filtered off, dried, and recrystallized from acetic acid.

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