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POLYFUNCTIONAL PYRAZOLES 5*. PREPARATIVE SYNTHESIS OF 1-ARYL-4-FORMYLPYRAZOLE-3-CARBOXYLIC ACIDS

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Treatment of methyl pyruvate N-arylhydrazones with the Vilsmeier-Haack reagent gave methyl 1-aryl-4-formylpyrazole-3-carboxylates, basic hydrolysis of which yielded the corresponding acids.

Keywords: methyl pyruvate N-arylhydrazones, 1-aryl-4-formylpyrazole-3-carboxylic acids, Vilsmeier-Haack reaction.

Polyfunctional pyrazole-3-carboxylic acids are of interest for chemical and biological investigation. In particular, esters and amides of 4-halo(nitro)-1-glucosylpyrazole-3-carboxylic acid show clear antiviral and antitumor activity [2]. Fungicidal activity has been observed in 1-(2,4-dinitrophenyl)-4-formylpyrazole-3-carboxylate [3] which have also been used in the synthesis of the potential calcium channel blockers 4-(3-carboxypyrazol-4-yl)-1,4-dihydropyridines [4]. 1-Aryl-5-chloro-4-formylpyrazole-3-carboxylic acids are important intermediates in the preparation of 2,6-dihydropyrazolo[3,4-*d*]pyridazin-7-ones as novel antagonists of the cannabinoid receptor 1 (CB_1-R) [5]. As a whole, the synthetic potential of 4-formylpyrazole-3-carboxylic acid and its derivatives remains unexplored to this time and this is due, to a large degree, to the absence of convenient preparative methods.

The synthesis of a series of 5-substituted 4-formylpyrazole-3-carboxylic acids *via* formylation of the corresponding 3-ethoxycarbonylpyrazol-5-ones [6] and also by reduction of 4-[oxo(phenyl)acetyl]-1,5-diphenylpyrazole-3-carboxylic acid [7, 8] has been reported. The method discussed in [3, 4] of a Vilsmeier-Haack preparation of 4-formylpyrazole-3-carboxylic acid is limited to examples using only the 4-nitro- and 2,4-dinitrophenylhydrazones of alkyl pyruvate and, because of the marked acceptor properties of the aryl substituents, its universality cannot be judged. It should also be noted that the N-arylhydrazones of pyruvates are generally obtained from acids least stable on storage with subsequent esterification of the carboxyl group [9-11].

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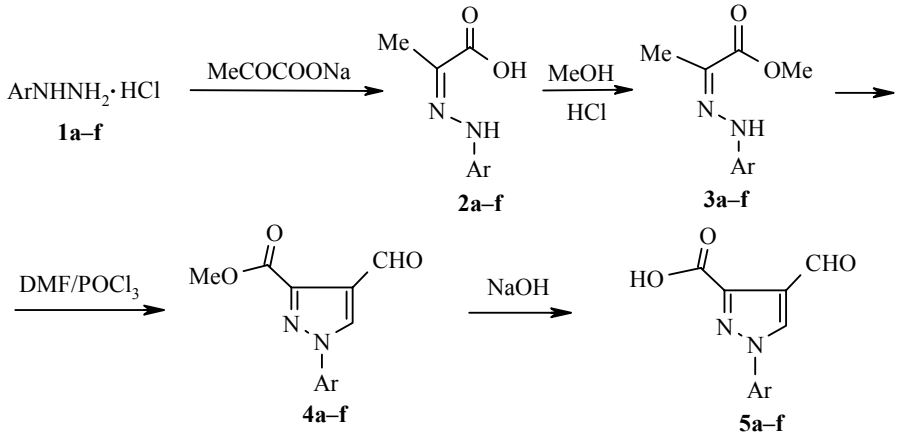
In this study we have carried out an improved method for synthesizing pyruvic acid N-arylhydrazones. It was found that the stable and cheap sodium salt could be used in place of the acid and this readily reacts with the arylhydrazine hydrochlorides **1a-f** in aqueous solution to give the hydrazones **2a-f**. Without further purification the latter were treated with a solution of HCl in methanol to form the methyl pyruvate hydrazones **3a-f**.

Under Vilsmeier-Haack conditions compounds **3a-f** are cyclized to the methyl 1-aryl-4-formylpyrazole-3-carboxylates **4a-f**. By analogy with methyl ketone hydrazones [12] it is likely that initial attack by the Vilsmeier-Haack reagent occurs at the most nucleophilic nitrogen atom of the hydrazones **3a-f** with a subsequent C-formylation of the methyl group to form the pyrazole ring functionalized by an N,N-dimethyliminium group.



1–5 a Ar = Ph, **b** Ar = C_6H_4Br-*p*, **c** Ar = C_6H_4Me-*o*, **d** Ar = C_6H_4Me-*p*, **f** Ar = 2-$C_{10}H_7$; **1–4 e** Ar = C_6H_4COOMe-*p*, **5 e** Ar = C_6H_4COOH-*p*

TABLE 1. Characteristics of Compounds **4a-f**, **5a-f**

Compound	Empirical formula	Found, % / Calculated, %			mp,°C	Yield, %
		C	H	N		
4a	$C_{12}H_{10}N_2O_3$	62.38 / 62.61	4.28 / 4.38	12.02 / 12.17	136-137	78
4b	$C_{12}H_9BrN_2O_3$	46.35 / 46.63	3.03 / 2.93	8.89 / 9.06	181-182	81
4c	$C_{13}H_{12}N_2O_3$	64.17 / 63.93	4.79 / 4.95	11.66 / 11.47	121-122	74
4d	$C_{13}H_{12}N_2O_3$	64.01 / 63.93	5.12 / 4.95	11.22 / 11.47	137-138	76
4e	$C_{14}H_{12}N_2O_5$	58.55 / 58.33	4.34 / 4.20	9.87 / 9.72	220-222	80
4f	$C_{16}H_{12}N_2O_3$	68.29 / 68.57	4.46 / 4.32	10.11 / 9.99	151-152	75
5a	$C_{11}H_8N_2O_3$	61.40 / 61.11	3.88 / 3.73	12.77 / 12.96	182-184	91
5b	$C_{11}H_7BrN_2O_3$	44.56 / 44.77	2.51 / 2.39	9.64 / 9.49	245-247	96
5c	$C_{12}H_{10}N_2O_3$	62.88 / 62.61	4.25 / 4.38	11.99 / 12.17	171-172	84
5d	$C_{12}H_{10}N_2O_3$	62.49 / 62.61	4.45 / 4.38	12.41 / 12.17	230-232	88
5e	$C_{12}H_8N_2O_5$	55.62 / 55.39	3.08 / 3.10	10.95 / 10.77	268-270	92
5f	$C_{15}H_{10}N_2O_3$	67.42 / 67.67	3.89 / 3.79	10.70 / 10.52	215-216	85

TABLE 2. Spectroscopic Characteristics of Compounds **4a-f**, **5a-f**

Compound	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm (*J*, Hz)*
	HC=O	C=O	O–H	
4a	1680	1745		3.94 (3H, s, CH_3O); 7.41-7.43 (1H, m, H Ar); 7.52-7.54 (2H, m, H Ar); 7.96 (2H, d, *J* = 8.0, H Ar); 9.20 (1H, s, H-5); 10.29 (1H, s, CH=O)
4b	1865	1740		3.95 (3H, s, CH_3O); 7.71 (2H, d, *J* = 8.4, H Ar); 7.96 (2H, d, *J* = 8.4, H Ar); 9.27 (1H, s, H-5); 10.29 (1H, s, CH=O)
4c	1690	1735		2.22 (3H, s, CH_3); 3.92 (3H, s, CH_3O); 7.37-7.45 (4H, m, H Ar), 8.72 (1H, s, H-5), 10.30 (1H, s, CH=O)
4d	1685	1745		2.37 (3H, s, CH_3); 3.94 (3H, s, CH_3O); 7.31 (2H, d, *J* = 6.0, H Ar); 7.83 (2H, d, *J* = 6.0, H Ar); 9.13 (1H, s, H-5); 10.28 (1H, s, CH=O)
4e	1680	1745		3.88 (3H, s, CH_3O); 3.95 (3H, s, CH_3O); 8.12 (2H, d, *J* = 5.9, H Ar); 8.16 (2H, d, *J* = 5.9, H Ar); 9.35 (1H, s, H-5); 10.28 (1H, s, CH=O)
4f	1685	1740		3.97 (3H, s, CH_3O); 7.52-7.54 (2H, m, H Ar); 7.96-8.13 (4H, m, H Ar); 8.54 (1H, s, H Ar); 9.34 (1H, s, H-5); 10.32 (1H, s, CH=O)
5a	1675	1695	2540-285	7.40-7.43 (1H, m, H Ar); 7.51-7.55 (2H, m, H Ar); 7.96 (2H, d, *J* = 7.5, H Ar); 9.15 (1H, s, H-5); 10.33 (1H, s, CH=O)
5b	1680	1700	2560-2880	7.73 (2H, d, *J* = 8.5, H Ar); 7.91 (2H, d, *J* = 8.5, H Ar); 9.14 (1H, s, H-5); 10.29 (1H, s, CH=O)
5c	1680	1705	2550-2850	2.20 (3H, s, CH_3); 7.32-7.44 (4H, m, H Ar); 8.86 (1H s, H-5); 10.24 (1H, s, CH=O)
5d	1680	1700	2540-2870	2.37 (3H, s, CH_3); 7.32 (2H, d, *J* = 8.0, H Ar); 7.83 (2H, d, *J* = 8.0, H Ar); 9.08 (1H, s, H-5); 10.32 (1H, s, CH=O)
5e	1685	1705	2570-2860	8.10 (2H, d, *J* = 6.0, H Ar), 8.16 (2H, d, *J* = 6.0, H Ar); 9.31 (1H, s, H-5); 10.25 (1H, s, CH=O)
5f	1675	1705	2540-2890	7.52-7.56 (2H, m, H Ar); 7.95-8.13 (4H, m, H Ar), 8.53 (1H, s, H Ar); 9.28 (1H, s, H-5); 10.36 (1H, s, CH=O)

* Signals for the carboxylic group protons of acids **5a-f** were not observed due to exchange with water present in the DMSO-d_6.

Hydrolysis of the latter gives the target aldehydes **4a-f** in 74-81% yields. It should also be noticed that, in contrast to the 4-nitro- and 2,4-dinitrophenylhydrazones of the alkyl pyruvates [4], compounds **3a-f** can be used with a 2.5 fold rather than 8 fold excess of $POCl_3$ and reaction time is shortened from 4 to 2 h.

Since a carboxyl function is more acceptable than an ester for subsequent modification the esters **4a-f** were converted using basic hydrolysis to the acids **5a-f** in close to quantitative yields. Moreover, in the case of compound **4e** the aryl substituent ester group is also hydrolyzed to form the diacid **5e**.

The composition of esters **4a-f** and acids **5a-f** was in agreement with the results of elemental analysis (Table 1) and the structure with IR and ^{1}H NMR spectroscopic data (Table 2). The IR spectra of compounds **4, 5** show aldehyde absorption bands in the range 1675-1680 cm^{-1}. The ester C=O bond of esters **4** absorbs at 1735-1745 cm^{-1} and the carboxyl group of acids **5** at 1695-1705 cm^{-1}. The broad absorption band for the OH group in the range 2540-2890 cm^{-1} suggests a dimer structure for acids **5a-f** in the solid state. The ^{1}H NMR spectra of compounds **4** and **5** show an aldehyde proton at 10.24-10.36 ppm and an H-5 pyrazole proton at 9.08-9.35 ppm. An exclusion is found in compounds **4c** and **5c** in which these protons are seen at 8.72 and 8.86 ppm respectively due to the shielding effect of the methyl group in the *o*-position of the phenyl substituent.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for KBr tablets. ^{1}H NMR spectra were obtained on a Bruker Avance DRX-500 instrument (500 MHz) using DMSO-d_6 and with TMS as internal standard.

Methyl 2-(Arylhydrazono)propionates 3a-f (General Method). A solution of the hydrazine hydrochloride **1a-f** (0.1 mol) in water (30 ml) was added with vigorous stirring to a solution of sodium pyruvate (11.0 g, 0.1 mol) in water (50 ml) followed by a solution of 2N HCl (25 ml) and then stirred for a further 0.5 h. The precipitated hydrazones **2a-f** were filtered off, dried, and added to methanol (50 ml) saturated with hydrogen chloride. The reaction mixture was refluxed for 2 h, cooled, poured into iced water (100 ml), and the precipitate formed was filtered off, washed with water (2×40 ml), dried, and crystallized from methanol.

Methyl 2-(Phenylhydrazono)propionate (3a). Yield 69%; mp 97-98ºC (mp 98ºC [13]).

Methyl 2-(4-Bromophenylhydrazono)propionate (3b). Yield 78%; mp 126-127ºC. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3320-3500 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.05 (3H, s, CH_3); 3.73 (3H, s, CH_3O); 7.20 (2H, d, *J* = 8.5, H Ar); 7.36 (2H, d, *J* = 8.5, H Ar); 9.86 (1H, s, NH). Found, %: C 44.03; H 4.29; N 10.24. $C_{10}H_{11}BrN_2O_2$. Calculated, %: C 44.30; H 4.09; N 10.33.

Methyl 2-(2-Methylphenylhydrazono)propionate (3c). Yield 70%; mp 71-72ºC. IR spectrum, ν, cm^{-1}: 1690 (C=O), 3340-3520 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.13 (3H, s, CH_3); 2.21 (3H, s, CH_3); 3.79 (3H, s, CH_3O); 6.81 (1H, t, = 7.0, H Ar); 7.09-7.15 (2H, m, H Ar); 7.42 (1H, d, *J* = 7.5, H Ar); 12.04 (1H, s, NH). Found, %: C 64.19; H 6.91; N 13.75. $C_{11}H_{14}N_2O_2$. Calculated, %: C 64.06; H 6.84; N 13.58.

Methyl 2-(4-Methyphenylhydrazono)propionate (3d). Yield 75%; mp 136-137ºC. IR spectrum, ν, cm^{-1}: 1695 (C=O), 3330-3520 (N–H). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (3H, s, CH_3); 2.24 (3H, s, CH_3); 3.72 (3H, s, CH_3O); 7.03 (2H, d, *J* = 7.0, H Ar); 7.15 (2H, d, *J* = 7.0, H Ar); 9.65 (1H, s, NH). Found, %: C 64.29; H 6.91; N 13.75. $C_{11}H_{14}N_2O_2$. Calculated, %: C 64.06; H 6.84; N 13.58.

Methyl 2-(4-Methoxycarbonylhydrazono)propionate (3e). Yield 82%; mp 164-165ºC (mp 166ºC [14]).

Methyl 2-(2-Naphthylhydrazono)propionate (3f). Yield 72%; mp 121-122ºC (mp 90-91ºC (*syn* form), 136-137ºC (*anti* form [15]). IR spectrum, ν, cm^{-1}: 1695 (C=O), 3310-3490 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.12 (3H, s, CH_3); 3.77 (3H, s, CH_3O); 7.27 (1H, t, *J* = 7.0, H Ar); 7.39 (1H, t, *J* = 7.0, H Ar); 7.57-7.76 (5H, m, H Ar); 9.99 (1H, s, NH). Found, %: C 69.44; H 6.01; N 11.69. $C_{14}H_{14}N_2O_2$. Calculated, %: C 69.41; H 5.82; N 11.56.

Methyl 1-Aryl-4-formylpyrazole-3-carboxylates 4a-f. $POCl_3$ (38.0 g, 0.25 mol) was added with stirring to DMF (50 ml) cooled to 0ºC at such a rate that the temperature of the reaction mixture did not exceed 10ºC. The hydrazone **3a-f** (0.1 mol) was added portionwise after 0.5 h and following its solution the cooling was ceased and the reaction mixture temperature spontaneously rose to 50-60ºC. The product was stirred for 2 h at 65-70ºC, cooled, poured into iced water (300 ml), and the precipitate was filtered off, washed with water, dried, and crystallized from methanol.

1-Aryl-4-formylpyrazole-3-carboxylic Acids 5a-f. A solution of NaOH (4 g, 0.01 mol) in water (20 ml) was added with stirring to a suspension of the methyl ester **4a-f** (0.005 mol) in ethanol (20 ml) and water (60 ml). After homogenization of the reaction mixture (~ 30 min) it was filtered, acidified with dilute hydrochloric acid to pH 2, and the precipitate formed was filtered off, washed with water, dried, and crystallized from a mixture of acetic acid and water (1:2).

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