Synthesis of 6-(2-Hydroxybenzoyl)pyrazolo[1,5-*a*]pyrimidines by Reaction of 5-Amino-1*H*-pyrazoles and 3-Formylchromone

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Reaction of 3-formylchromone (**1**) with 5-amino-1*H*-pyrazoles (**2**) in ethanol, afforded 6-(2-hydroxybenzoyl)pyrazolo[1,5-*a*]pyrimidines (**3a-g**) in good yields. The structures and the regiospecificity of the reaction were established by nmr measurements and X-ray analysis, in which soft intermolecular hydrogen-bonded networks were found.

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Introduction.

Since becoming readily available, 3-formylchromone (**1**) has been used to prepare a variety of heterocyclic systems [1-6]. A molecule of 3-formylchromone represents a very reactive system owing to the presence of an unsaturated keto-function, a conjugated second carbonyl group at C-3 and above all, to the center at C-2, which is very reactive towards Michael addition of nucleophiles with opening of the γ-pyrone ring, and followed by a new cyclization. The reactivity of **1** towards several nucleophiles, such as hydrazine, phenylhydrazine and particulary two functional nucleophiles, *e.g.*, amidines, derivatives of guanidine and isothiourea, was investigated [7].

In our investigation on pyrazolo[1,5-*a*]pyrimidines we have established that the cyclocondensation reaction of 5-amino-1*H*-pyrazoles with α,β-unsaturated aromatic ketones is a versatile and efficient method for obtaining pyrazolo[1,5-*a*]pyrimidines [8-10].

Here we report a new approach for the preparation of the above pyrimidine fused rings using 3-formylchromone (**1**) with 5-amino-1*H*-pyrazoles (**2a-g**).

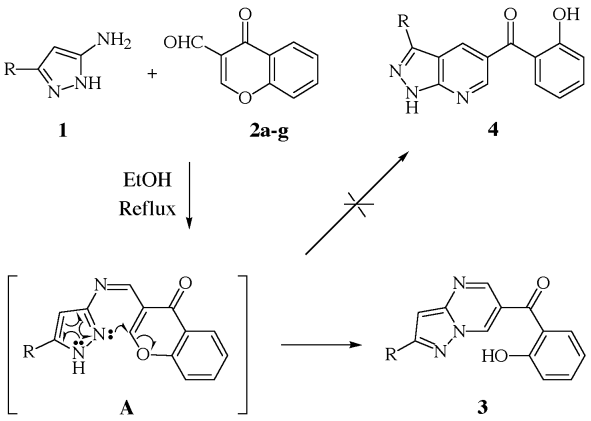
Results and Discussion.

3-Formylchromone (**1**) reacts with equimolecular amounts of aminopyrazole (**2**) in absolute ethanol to afford the desired 6-(2-hydroxybenzoyl)pyrazolo[1,5-*a*]-pyrimidines **3a-g** (Scheme 1). Those new compounds are isolated in good yields as stable crystalline solids and easily purified by recrystallization from ethanol.

This one-step cyclocondensation reaction can afford pyrazolo[1,5-*a*]pyrimidine and/or pyrazolo[3,4-*b*]pyridine products **3/4**, but regioselectively gave one, which was determined by tlc analysis, and afterward characterized as pyrazolo[1,5-*a*]pyrimidine **3** by the usual spectroscopic and analytical techniques.

The basic support for the structures for **3a-g** was provided by ^{1}H-nmr spectra in particular with respect to proton signal of C(3)-H at pyrazolic residue. We consider that compounds **3** result from a condensation between the amino group at the pyrazole and the aldehyde group at the chromone to give intermediate **A**. Such intermediate can evolve in two ways. One way is by intramolecular ring

Scheme 1



Compound	R	mp (C°)	Yield (%)
3a	CH_3	172	80
3b	C_6H_5	218	86
3c	4-$CH_3C_6H_4$	245	90
3d	4-$CH_3OC_6H_4$	215	84
3e	4-ClC_6H_4	223	66
3f	4-BrC_6H_4	229	75
3g	4-$O_2NC_6H_4$	283	90

opening of the chromone ring through nucleophilic displacement by attack of the nucleophilic nitrogen at the pyrazole ring to form the obtained compounds **3**. The other is by attack of the C-4 at the pyrazole instead of the nitrogen to give regioisomer **4**. The higher nucleophilicity of the nitrogen corroborates the findings (see Scheme 1)[11].

The ^{1}H-nmr spectra of compounds **3a-g** (dimethyl sulfoxide-d_6, see Table 1) contain four relatively sharp singlets at 7.34-7.50 (6.66 for **3a**), 8.70-8.79, 9.11-9.26 and 10.43-10.52 ppm for 3-H, 7-H, 5-H and -OH. The presence of the signal at 7.34-7.50 is proof for the proposed reaction route, discarding the formation of compounds **4**.

technique and ^{1}H,^{13}C shift correlation (HSQC, HMBC). Another characteristic feature of structures **3** is a NOE correlation between 3-H and the corresponding signal protons belonging to substituent at C-2 (C*H*$_3$ for **3a** and the *ortho* H for the rest) observed in the NOESY experiment.

The common feature on the mass-spectra is that the molecular peak is quite abundant and the main fragmentation is the loss of a fragment with 120 amu associated with the elimination of hydroxybenzoyl residue.

Compounds **3a** [12], **3b** [13] and **3g** [14] afforded crystalline solids, which were analyzed by X-ray diffraction. The molecular structures of such compounds are rather similar, in which the pyrazolopyrimidine

Table 1

^{1}H-NMR Data of Pyrrolo[1,5-*a*]pyrimidines **3**. δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl Sulfoxide-d_6, 300 MHz

Compound	3-H (d)	5-H (dd)	7-H[a] (d)	OH (s)	Phenolic ring (m)	2-Aryl[b]	
3a	6.66	9.11	8.70	10.43	6.98-7.53	---	
3b	7.42	9.25	8.79	10.48	7.00-7.50	7.52-8.10	
3c	7.38	9.22	8.78	10.48	6. 99-7.50	7.33	7.98
3d	7.34	9.20	8.76	10.49	6.99-7.55	7.34	8.02
3e	7.45	9.25	8.79	10.52	7.02-7.56	7.59	8.10
3f	7.45	9.26	8.79	10.51	7.02-7.56	8.31	8.03
3g	7.50	9.21	8.72	10.43	7.01-7.60	8.31	8.36

CH_3 groups and CH_3O group at 2.46, 2.37 and 3.83 ppm for **3a**, **3b** and **3c** respectively; [a] $J_{3,5}$ = 0,7-0,8 Hz; $J_{5,7}$ = 2,1 Hz; in **3c** and **3f** $J_{3,5}$ = 0 Hz; [b] Doublets for *ortho* and *meta* protons.

In the ^{13}C-nmr spectra, the number of signals belonging to quaternary, tertiary secondary and primary carbon atoms for compounds **3a-g** could be determined (DEPT experiment, see Table 2). The full assignment of the signals in the ^{1}H- and ^{13}C-nmr spectra of **3a-g** is supported by ^{1}H,^{1}H COSY

nucleus does not have aromatic character based on the alternating of double and single bond. In addition special features like the formation of a soft hydrogen-bonded network were found, in which the C(3)-H.....N(4) was involved in forming like a dimer in a $R_2^2(8)$ fashion in **3a**;

Table 2

^{13}C-NMR Data of Pyrrolo[1,5-*a*]pyrimidines **3**. δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl Sulfoxide-d_6, 75 MHz

Comp.	**3a**[a]	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**
C-2	158.0	158.1	158.2	158.1	156.8	156.9	156.8
C-3	96.9	94.5	94.2	93.8	94.6	94.6	94.5
C-3a	148.5	149.4	149.4	149.4	149.4	149.4	149.4
C-5	138.2	138.7	138.6	138.6	138.7	138.7	138.6
C-6	118.2	119.2	119.0	118.8	119.4	119.4	119.3
C-7	149.1	149.6	149.5	149.6	149.8	149.8	149.7
C=O	191.5	191.8	191.8	191.8	191.8	191.5	191.6
HOC_6H_4	116.9	116.9	116.9	116.8	116.9	116.9	117.2
	119.5	119.5	119.5	119.5	119.5	119.5	119.3
	124. 1	124.0	124.0	124.1	124.0	124.0	124.1
	130.5	130.7	130.7	130.6	130.7	130.7	130.6
	133.9	134.0	133.9	133.9	134.3	134.0	134.3
	156.3	156.5	156.4	156.3	156.5	156.5	156.7
2-Aryl		126.3	126.3	114.3	128.0	123.0	123.8
		128.9	128.9	124.0	129.0	128.3	127.3
		129.6	129.5	127.1	130.5	130.9	130.5
		131.7	139.3	160.4	134.0	131.9	147.9

CH_3- and CH_3O- groups at 20.9 and 55.2 ppm for **3c** and **3d** respectively; [a] CH_3 13.5 ppm.

C(63)-H....N(1) forming chains in a C(9) motif along b for **3b**; and finally C(5)-H....O(62), C(66)-H....O(67) and C(63)-H....N(1) forming chains that result in a complex three-dimensional network in **3g** (See Figure 1 for numbering). In all those structures a strong intramolecular hydrogen bond was found in the hydroxybenzoyl moiety as shown in scheme 1.

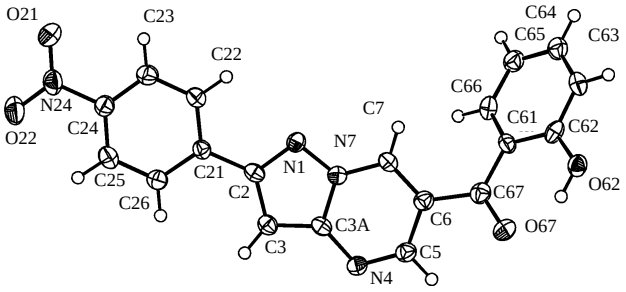


Figure 1. ORTEP view of **3g**. Displacement ellipsoids are scaled to 30% level.

EXPERIMENTAL

Melting points were determined in a Buchi Melting Point Apparatus and are uncorrected. The ^{1}H- and ^{13}C nmr spectra were run on a Bruker DPX 300 spectrometer operating at 300 MHz and 75 MHz respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) operating at 70 or 30 eV. The elemental analyses have been obtained using a LECO CHNS-900 analyser.

General Procedure for the Preparation of the Substituted Pyrazolo[1,5-*a*]pyrimidines **3**.

A solution of 2 mmol of 3-formylchromone and 2 mmol of aminopyrazole **2** in 15 ml of absolute ethanol was stirred at reflux for 10-15 minutes. The precipitated products **3** were isolated by cooling followed by filtration, washing with ethanol, drying and recrystallized from ethanol.

6-(2-Hydroxybenzoyl)-2-methylpyrazolo[1,5-*a*]pyrimidine (**3a**).

This compound was obtained according to the general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms:(30 eV) m/z (%) = 254 (19), 253 (M^+, 90), 252 (18), 236 (10), 229 (16), 173 (11), 16 (16), 134 (10), 133 (100), 132 (16), 121 (46), 120 (27), 93 (23), 92 (24), 84 (13), 83 (10), 77 (12), 65 (32), 64 (13), 63 (14), 39 (33).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.45; H, 4.23; N, 16.45.

6-(2-Hydroxybenzoyl)-2-phenylpyrazolo[1,5-*a*]pyrimidine (**3b**).

This compound was obtained according to the general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms:(30 eV) m/z (%) = 315 (M^+, 15), 336 (2), 274 (100), 242 (7), 218 (8), 190 (6), 147 (3), 83 (5), 43 (4).

Anal. Calcd. for $C_{19}H_{13}N_3O_2$: C, 72.37; H, 4.16; N, 13.33 Found: C, 72.51; H, 4.13; N, 13.24.

6-(2-Hydroxybenzoyl)-2-(4-methylphenyl)pyrazolo[1,5-*a*]-pyrimidine (**3c**).

This compound was obtained according to the general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms:(30 eV) m/z (%) = 329 (M^+, 15), 336 (2), 274 (100), 242 (7), 218 (8), 190 (6), 147 (3), 83 (5), 43 (4).

Anal. Calcd. for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76 Found: C, 72.85; H, 4.43; N, 12.90.

6-(2-Hydroxybenzoyl)-2-(4-methoxyphenyl)pyrazolo[1,5-*a*]-pyrimidine (**3d**).

This compound was obtained according to the general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms:(30 eV) m/z (%) = 346 (24), 345 (M^+, 100), 344 (12), 226 (11), 225 (68), 210 (13), 121 (14), 93 (10), 77 (10), 65 (25), 64 (10), 63 (11) 39 (13).

Anal. Calcd. for $C_{20}H_{15}N_3O_3$: C, 69.56; H, 4.38; N, 12.17. Found: C, 69.49; H, 4.23; N, 12.13.

6-(2-Hydroxybenzoyl)-2-(4-chlorophenyl)pyrazolo[1,5-*a*]pyrimidine (**3e**).

This compound was obtained according to the general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms:(30 eV) m/z (%) = 350 (23), 351/349 (M^+, 29/82), 348 (12), 231 (34), 230 (17), 229 (100), 228 (10), 121 (14), 93 (10), 65 (18), 39 (15).

Anal. Calcd. for $C_{19}H_{12}ClN_3O_2$: C, 65.24; H, 3.46; N, 12.01. Found: C, 65.35; H, 3.33; N, 12.12.

6-(2-Hydroxybenzoyl)-2-(4-bromophenyl)pyrazolo[1,5-*a*]-pyrimidine (**3f**).

This compound was obtained according to the general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms:(30 eV) m/z (%) = 396 (19), 395/393 (M^+, 86/89), 394 (29), 392 (11), 276 (14), 275/273 (98/100), 274 (21), 172 (12), 121 (22), 93 (12), 76 (10), 75 (12), 65 (28), 53 (10), 39 (22).

Anal. Calcd. for $C_{19}H_{12}BrN_3O_2$: C, 57.89; H, 3.07; N, 10.66. Found: C, 57.75; H, 3.13; N, 10.79.

6-(2-Hydroxybenzoyl)-2-(4-nitrophenyl)pyrazolo[1,5-*a*]-pyrimidine (**3g**).

This compound was obtained according to the general procedure as pale yellow crystals. The mass spectrum shows the following peaks: ms:(30 eV) m/z (%) = 361 (24), 360 (M^+, 100), 359 (10), 241 (13), 240 (77), 221 (10), 172 (12), 121 (49), 120 (82), 93 (25), 92 (17), 76 (12), 75 (11), 65 (40), 63 (11), 50 (10), 39 (17).

Anal. Calcd. for $C_{19}H_{12}N_4O_4$: C, 63.33; H, 3.36; N, 15.55. Found: C, 63.45; H, 3.26; N, 15.60.

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