Reaction of 5-Amino-1-aryl-3-methylpyrazoles with Benzylidene Derivatives of Meldrum's Acid: Synthesis and Characterization of Pyrazolo[3,4-*b*]pyridinones

Jairo Quiroga*, Angelina Hormaza and Braulio Insuasty

Department of Chemistry, Universidad del Valle, A. A. 25360 Cali, Colombia

Manuel Márquez

Department of Chemistry, Yale University, New Haven, CT 06511, USA

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A series of dihydropyrazolo[3,4-*b*]pyridin-6-ones **3** was prepared by cyclization of 5-amino-1-aryl-3-methylpyrazoles **1** and Meldrum's acid benzylidene derivatives **2** in nitrobenzene. The structure of 4,5-dihydropyrazolo[3,4-*b*]pyridin-6-ones and reaction orientation were determined by nmr measurements.

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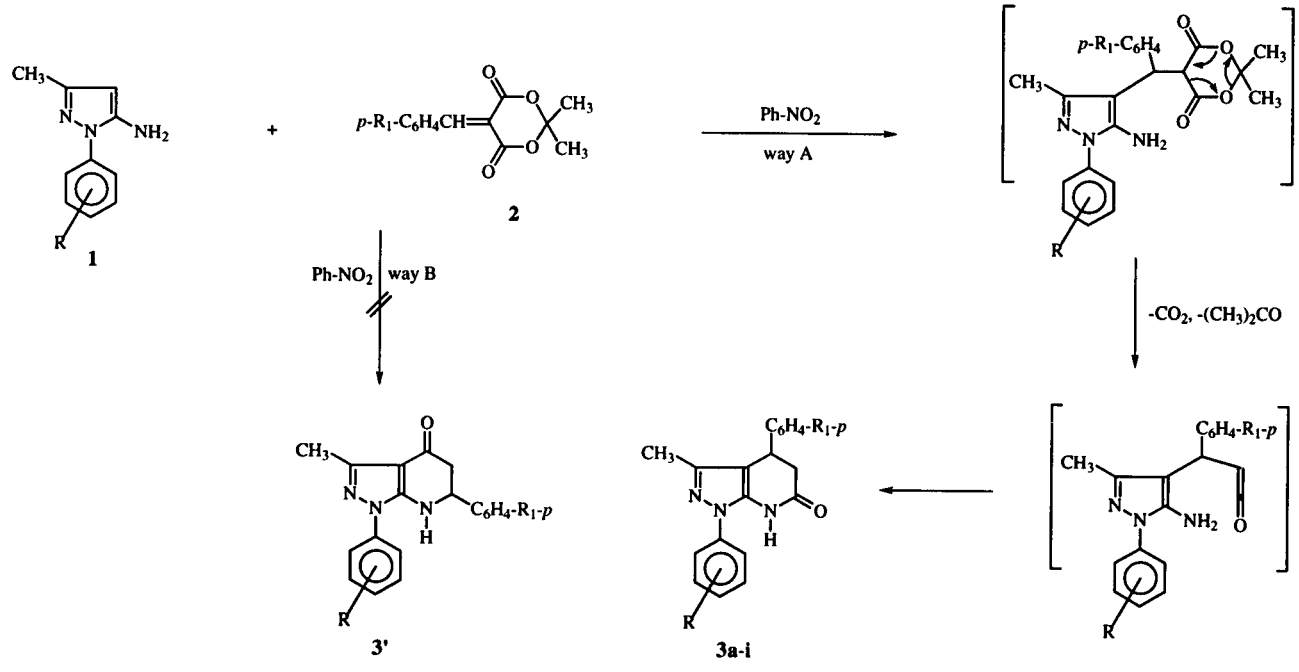
The pyrazolo[3,4-*b*]pyridine ring system has aroused great interest in recent years because of the wide variety of its biological and pharmacological properties [1,2]. Research on dihydropyridine systems is of current interest due to their exceptional properties as calcium antagonists [3-5] and arteriolar vasodilators [6,7].

Our recent publications have provided an efficient method for the synthesis of various fused heterocyclic compounds containing the dihydropyridine moiety [8-11]. In this work, we apply our approach to the synthesis of novel 1,4-diaryl-3-methyl-4,5-dihydropyrazolo[3,4-*b*]-pyridin-6-ones which results in a new route to pyrazolo[3,4-*b*]pyridin-6-one. Dihydropyrazolo[3,4-*b*]-pyridin-6-ones **3** were synthesized by refluxing equimolar amounts of aminopyrazole **1** and the appropriate Meldrum's acid benzylidene derivatives **2** in absolute nitrobenzene for 20-30 minutes. The general method has been described [11]. The novel compounds were obtained as stable crystalline solids, in good yields, and readily purified by recrystallization from ethanol.

Scheme 1



	3a	3b	3c	3d	3e	3f	3g	3h	3i
R	H	H	4-NO_2	4-NO_2	4-Cl	4-Cl	4-Cl	2-Cl	2-Cl
R_1	Cl	NO_2	H	Cl	H	Cl	NO_2	Cl	NO_2

In principle, the amines **1** may attack on the carbonyl carbon or on β-C of the α,β-unsaturated cyclic ester **2**. Thus, amines **1** might enter a cyclization reaction with **2** to form the products **3** or **3'**. In practice, however, only one reaction route is observed. We assume that the initial step is an addition reaction of the C-5 of amine **1** to the β-C of the cyclic ester and that the second step is the loss of one molecule of acetone and CO_2 through the formation and further cyclization of an intermediate ketene. This behavior is well known for the thermolysis of derivatives of Meldrum's acid [12,13].

Elemental analysis and spectroscopic data for the pyrazolo[3,4-*b*]pyridines **3** show distinctive, expected features. The ir spectra of compounds **3** measured in potassium bromide pellets show bands at 1670-1690 cm^{-1} and at 3145-3370 cm^{-1} related to the elongation of the C=O and NH groups, respectively. The ^{1}H-nmr spectra of compounds **3** measured in dimethyl-d_6 sulfoxide exhibit signals for aromatic protons (7.20-8.36 ppm), two protons on C-5 (2.59-2.70 and 3.01-3.12 ppm), a proton on C-4 (4.23-4.47 ppm), and the NH proton (10.62-10.87 ppm). The protons on C-4 and C-5 form an ABX system with coupling constants $J_{a,b}$ = 15.5-15.9, $J_{a,x}$ = 3.6-4.8 and $J_{b,x}$ = 7.0-7.6 Hz. This last coupling suggests a *trans*-diaxial configuration between the proton on C-4 and one of the protons on C-5.

The number of quaternary, tertiary and secondary carbon atoms for compounds **3**, which are consistent with the spectroscopic analysis above, were determined by ^{13}C-nmr (DEPT experiment) spectroscopy (Table 2).

Table 1

^{1}H-NMR Data of **3**. δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide, 400 MHz

Compound	4-H_x t	5-H_b dd	5-H_a dd	NH s	CH_3 s	1-Ar m	4-Ar m
3a	4.26	3.04	2.65	10.62	1.90	7.33-7.56	7.22-7.41
3b	4.45	3.12	2.70	10.70	1.92	7.35-7.57	7.52-8.24
3c	4.27	3.01	2.69	10.84	1.92	7.83-8.37	7.21-7.36
3d	4.31	3.07	2.68	10.87	1.93	7.84-8.38	7.23-7.42
3e	4.23	3.03	2.66	10.64	1.89	7.53-7.58	7.20-7.35
3f	4.27	3.03	2.64	10.69	1.89	7.55-7.60	7.22-7.41
3g	4.46	3.12	2.70	10.77	1.91	7.56-7.61	7.50-8.24
3h	4.28	3.02	2.59	10.73	1.89	7.45-7.66	7.23-7.42
3i	4.47	3.11	2.65	10.81	1.90	7.49-7.67	7.52-8.25

Table 2

^{13}C-NMR Data of **3**. δ Values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide, 400 MHz

Compound			**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**
	C-3	[a]	138.9	139.1	139.6	139.7	139.0	139.1	139.3	140.8	140.9
	C-3a		103.0	102.2	105.0	104.5	103.6	103.1	102.4	100.4	99.7
	C-4		33.4	33.8	33.9	33.2	34.0	33.3	33.8	33.3	33.8
	C-5		40.2	39.8	40.1	40.0	40.2	40.1	40.0	40.3	39.7
	C-6		169.8	169.5	170.1	169.9	170.0	169.7	169.4	169.3	169.0
	C-7a		145.3	146.5	147.5	147.4	145.8	145.7	146.5	145.3	146.4
	CH_3		12.1	12.1	12.1	12.1	12.0	12.0	12.0	12.0	12.0
Ar	C_i	[a]	138.0	137.9	142.6	141.6	136.8	136.8	136.7	135.2	135.1
			142.0	145.3	143.0	142.9	143.0	141.9	145.7	142.4	145.3
	$C_{o,m}$		122.7	122.8	122.2	122.3	124.4	124.4	123.9	128.7	124.0
			128.7	124.0	124.9	124.9	126.9	128.7	124.5	128.8	128.3
			128.9	128.4	126.9	128.7	128.7	128.8	128.4	130.1	130.1
			129.2	129.2	128.8	128.9	129.1	129.1	129.1	130.7	130.8
										131.4	131 4
	C_p		126.8	126.9	126.9	131.5	126.8	131.0	131.2	127.9	127.9
			131.4	151.0	144.8	144.9	130.9	131.4	150.8	131.3	151.3

[a] Interchangeable signals.

In the ^{13}C-nmr spectra, the high-field signal at δ = 39.7-40.2 ppm corresponds to an aliphatic carbon (C-4 in **3** or C-6 in **3'**). We rule out structure **3'** for two reasons. First, the signal of C-6 in **3'**, because of its proximity to the nitrogen atom of the pyridine ring, should have appeared at a lower field and, second, the signal of the NH proton is not a doublet but a singlet.

EXPERIMENTAL

Melting points were taken on a Buchi melting point apparatus and are uncorrected The ir spectra were obtained in potassium bromide pellets with a Perkin-Elmer 599B spectrometer. The ^{1}H- and ^{13}C-nmr spectra were run on a Varian 360-2 in dimethyl-d_6 sulfoxide. The mass spectra were measured with a Kratos MS-50RFA (FAB mode using 6 KeV Xenon atoms in the Magic Bullet Matrix) spectrometer. The elemental analysis was done using a LECO CHNS-900. Arylidene derivatives of Meldrum's acid were obtained by a modified method described in reference [14].

Synthesis of 1,4-Diaryl-3-methyl-4,5-dihydropyrazolo[3,4-*b*]-pyridin-6-ones **3**.

General Procedure.

A solution of 1 mmole of 5-aminopyrazole **1** and 1 mmole of arylidene Meldrum's acid derivative **2** in 5 ml of absolute nitrobenzene was heated to reflux for 20-30 minutes. The cyclized products **3** were isolated by cooling, filtrating, washing with ethanol, drying and recrystallizing from ethanol.

1-Phenyl-4-(4-chlorophenyl)-3-methyl-4,5-dihydropyrazolo[3,4-*b*]-pyridin-6-one **3a**.

This compound was obtained according to the general procedure as white crystals, mp 209-210°, yield 66%; ir (potassium bromide): 1688 (C=O), 3348 (NH); ms: FAB m/z 338/40 (M^++1).

Anal. Calcd. for $C_{19}H_{16}N_3OCl$: C, 67.56; H, 4.77; N, 12.44. Found: C, 67.45; H, 4.73; N, 12.40.

1-Phenyl-4-(4-nitrophenyl)-3-methyl-4,5-dihydropyrazolo[3,4-*b*]-pyridin-6-one **3b**.

This compound was obtained according to general procedure as yellow crystals, mp 223-224°, yield 57%; ir (potassium bromide): 1680 (C=O), 1348, 1515 (NO_2), 3350 (NH); ms: FAB m/z 349 (M^++1).

Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.55; H, 4.59; N, 16.02.

1-(4-Nitrophenyl)-4-phenyl-3-methyl-4,5-dihydropyrazolo[3,4-*b*]-pyridin-6-one **3c**.

This compound was obtained according to general procedure as yellow crystals, mp 215-216°, yield 42%; ir (potassium bromide): 1680 (C=O), 1341, 1518 (NO_2), 3373 (NH); ms: FAB m/z 349 (M^++1).

Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51, H, 4.63; N, 16.08. Found: C, 65.47; H, 4.65; N, 16.14.

1-(4-Nitrophenyl)-4-(4-chlorophenyl)-3-methyl-4,5-dihydropyrazolo[3,4-*b*]pyridin-6-one **3d**.

This compound was obtained according to general procedure as yellow crystals, mp 203-204°, yield 50%; ir (potassium bromide): 1680 (C=O), 1341, 1516 (NO_2), 3168 (NH); ms: FAB m/z 383/85 (M^++1).

Anal. Calcd. for $C_{19}H_{15}N_4O_3Cl$: C, 59.61; H, 3.95; N, 14.64. Found: C, 59.58; H, 3.91; N, 14.69.

1-(4-Chlorophenyl)-4-phenyl-3-methyl-4,5-dihydropyrazolo[3,4-*b*]-pyridin-6-one **3e**.

This compound was obtained according to general procedure as pale yellow crystals, mp 194°, yield 55%; ir (potassium bromide): 1677 (C=O), 3230 (NH); ms: FAB m/z 338/40 (M^++1).

Anal. Calcd. for $C_{19}H_{16}N_3OCl$: C, 67.56; H, 4.77; N, 12.44. Found: C, 67.59; H, 4.73; N, 12.49.

1,4-Di-(4-chlorophenyl)-3-methyl-4,5-dihydropyrazolo[3,4-*b*]-pyridin-6-one **3f**.

This compound was obtained according to general procedure as pale yellow crystals, mp 154°, yield 48%; ir (potassium bromide): 1689 (C=O), 3163 (NH); ms: FAB m/z 372/74/76 (M^++1).

Anal. Calcd. for $C_{19}H_{15}N_3OCl_2$: C, 61.30; H, 4.06; N, 11.29. Found: C, 61.24; H, 4.11; N, 11.25.

1-(4-Chlorophenyl)-4-(4-nitrophenyl)-3-methyl-4,5-dihydropyrazolo[3,4-*b*]pyridin-6-one **3g**.

This compound was obtained according to general procedure as yellow crystals, mp 198-199°, yield 70%; ir (potassium bromide): 1672 (C=O), 1346, 1498 (NO_2), 3187 (NH); ms: FAB m/z 383/85 (M^++1).

Anal. Calcd. for $C_{19}H_{15}N_4O_3Cl$: C, 59.61; H, 3.95; N, 14.64. Found: C, 59.64; H, 3.91; N, 14.68.

1-(2-Chlorophenyl)-4-(4-chlorophenyl)-3-methyl-4,5-dihydropyrazolo[3,4-*b*]pyridin-6-one **3h**.

This compound was obtained according to general procedure as yellow crystals, mp 198°, yield 72%; ir (potassium bromide): 1679 (C=O), 1340, 1514 (NO_2), 3146 (NH); ms: FAB m/z 372/74/76 (M^++1).

Anal. Calcd. for $C_{19}H_{15}N_3OCl_2$: C, 61.30; H, 4.06; N, 11.29. Found: C, 61.25; H, 4.10; N, 11.26.

1-(2-Chlorophenyl)-4-(4-nitrophenyl)-3-methyl-4,5-dihydropyrazolo[3,4-*b*]pyridin-6-one **3i**.

This compound was obtained according to general procedure as yellow crystals, mp 197°, yield 65%; ir (potassium bromide): 1687 (C=O), 1348, 1514 (NO_2), 3148 (NH); ms: FAB m/z 383/85 (M^++1).

Anal. Calcd. for $C_{19}H_{15}N_4O_3Cl$: C, 59.61; H, 3.95; N, 14.64. Found: C, 59.64; H, 3.89; N, 14.60.

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