SYNTHESIS OF 5-CYANO-4,7-DIHYDROPYRAZOLO[3,4-b]PYRIDIN-4-ONES AND 5-CYANOPYRAZOLO[3,4-b]PYRIDIN-4-ONES IN ONE-STEP BY THE REACTION OF 5-AMINOPYRAZOLONE WITH BENZALDEHYDE AND BENZOYLACETONITRILE IN ETHANOL AND BY MICROWAVE RADIATION IN DRY MEDIA.

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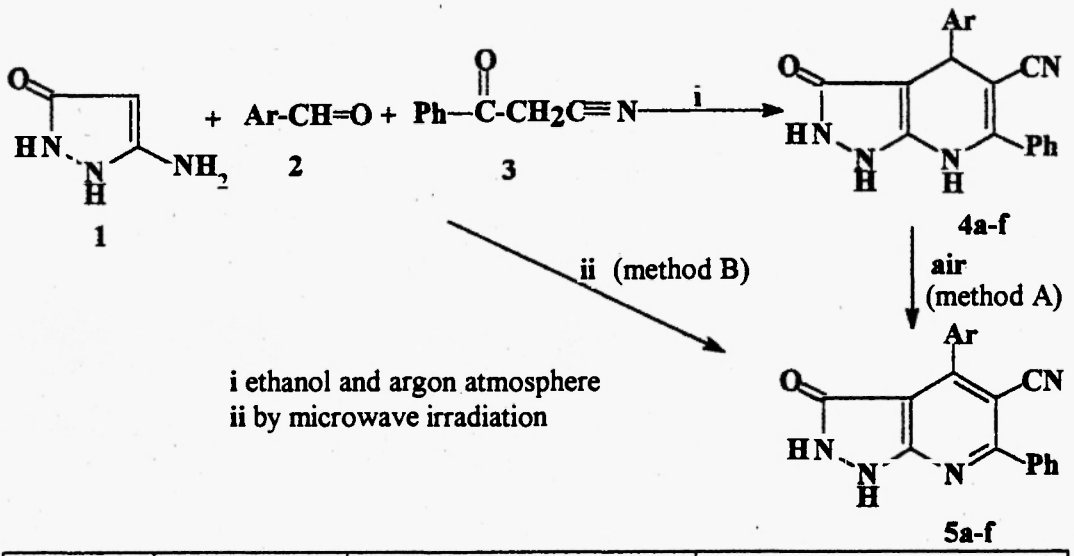
Abstract: The titled compounds **4** and **5** have been prepared in one-step reaction from 5-aminopyrazolone **1**, the corresponding 4-substituted benzaldehyde **2** and benzoylacetonitrile **3** in very good yields. Compounds **5** also were obtained by microwave irradiation of compounds **1**, **2** and **3** in solvent-free conditions, the results obtained over that conditions showed a considerable increase in the reaction rate with better yields. The structure of the final compounds was determined on the basis of nmr measurements.

Introduction

Continuing the study of the reactions of 5-aminopyrazoles with compounds α,β-unsaturated and its precursors as chalcones[1-4], α-cyanochalcones[5], β-dimethylamino-propiophenones[6,7], benzylidene derivatives of Meldrum's acid[8,9], malonodinitrile and ethyl cyanoacetate[10] and dimedone[11], we carried out experiments based on the interaction of 5-aminopyrazolone **(1)** with benzaldehydes **(2)** and benzoylacetonitrile **(3)**. The interest of studyng this aminopyrazole is due to the possibility of two cyclization routes: formation of pyrazolo[3,4-b]pyridines[1,3,5,9,11] or formation of pyrazolo[1,5-a]pyrimidines[2,4,7].

Results and Discussion

A solution of equimolar amounts of the amine (**1**), benzaldehydes (**2**) and benzoylacetonitrile (**3**) was heated to reflux in an argon atmosphere for 1-1.5 hours, the reaction mixture was cooled and the precipitate formed was filtered, to give 4-aryl-5-cyano-6-phenyl-4,7-dihydropyrazolo[3,4-b]pyridin-3-ones **4a-f**. The same reaction carried out under air gives the oxidated 4-aryl-5-cyano-6-phenylpyrazolo[3,4-b]pyridin-3-ones **5a-f** (Scheme 1). In other experiment, equimolar amounts of compunds **1**, **2** and **3** were placed into pyrex-glass open vessels and irradiated in a domestic microwave oven for 1–3 minutes (at 600 watts). When the irradiation was stopped, the solid was treated with ethanol and filtered to give the same oxidated products **5a-f** (Scheme 1).



1 2 3 4a-f 5a-f

Compound	Ar	Reaction time (min)		Yield, %	
		Method A[12]	Method B	Method A[12]	Method B
5a	C_6H_5	200	3	55	75
5b	*p*-$CH_3C_6H_4$	220	3	50	78
5c	*p*-$CH_3OC_6H_4$	240	3	45	70
5d	*p*-ClC_6H_4	200	2	60	82
5e	*p*-BrC_6H_4	180	2	60	85
5f	*p*-$O_2NC_6H_4$	160	2	70	85

Scheme 1

In the ^{1}H-nmr spectra (Table 1) of compounds **4a-f** measured in $(CD_3)_2SO$ besides the signals of the aromatic proton at 7.20-8.85 ppm, there were observed three singlets at δ = 4.82-5.48, 9.88-10.08 and 10.72-11.55 ppm with a 1:1:1 relation, corresponding to the protons 4H, 7-NH and 1-NH respectively of the pyrazolo[3,4-d]pyridinic system. For compounds **5a-f** in the ^{1}H-nmr

spectra were observed one singlet at δ = 11.20-11.42 ppm for 1-NH proton and a multiplet corresponding to aromatic protons at δ = 7.36-8.25 ppm. The ^{1}H-nmr spectra of compounds **4** and **5** showed the 1-NH group as a small broad singlet and 2-NH protons does not appears due to ceto-enolic tautomeric forms typically observed for this system[12,13]

Table 1. ^{1}H NMR chemical shifts (δ in ppm) of compounds **4**.

Comp.	H_1	H_4	H_7	Ar-H
4a	11.35	4.92	9.92	7.35-7.55
4b	11.50	4.98	9.88	7.20-7.75
4c	11.30	4.96	10.08	7.25-7.65
4d	10.72	4.82	9.91	7.30-7.88
4e	11.05	4.98	9.95	7.40-7.85
4f	11.55	5.48	9.90	7.50-8.85

The number of quaternary, tertiary and secondary carbon atoms for compounds **4** and **5** which are consistent with the proposed structures, were determined by ^{13}C-nmr and DEPT experiment.

Conclusion

In conclusion, we have developed a novel, one-step procedure to prepare dihydropyrazolo[3,4-b]pyridines from 5-aminopyrazolone, benzoylacetonitrile and benzaldehydes. The results demostrate the versatility and a high regioselectivity of the process. Additionally, a considerable reaction rate enhancement has been observed bringing down the reaction times from hours to minutes with improved yields when the process was carried out by microwave irradation.

Experimental

Melting points were taken on 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, in DMSO-d_6 as solvent and TMS as internal standart. Mass spectra (FAB) were performed with a Kratos MS-50 mass spectrometer using 2-hydroxyethyl disulfide as a matrix. The elemental analysis have been obtained using a LECO CHNS-900 equipment.

5-Cyano-4,6-diaryl -4,7-dihydropyrazolo[3,4-b]pyridin-3-ones (**4a-f**).

General Procedure

A solution of 1.40 mmoles of **1**, 1.40 mmoles of corresponding benzaldehyde **2** and 1.40 mmoles of benzoylacetonitrile **3** in 50 ml of absolute ethanol was refluxed in an argon atmosphere. The reaction was controlled by tlc on silica gel. After the starting compounds have almost completely disappeared (1.5-2 hours), the solution is cooled and the precipitate formed is filtered off and washed with ethanol.

5-Cyano-4,6-diphenyl-4,7-dihydropyrazolo[3,4-b]pyridin-3-one (**4a**).

This compound was obtained according to general procedure as white crystals, yield 60%, mp 286 °C; ir (potassium bromide): 2216 (CN), 1630 (C=O), 3366, 3476 cm^{-1} (NH). ^{13}C-nmr (DMSO-d_6, ppm): 39.3 (C-4), 81.2 (C-5), 85.3 (C-3a), 121.5 (CN), 160.8 (C=O). FAB m/z 315 (M^++1).

Anal. Calcd. for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.64; H, 4.57; N, 17.77.

5-Cyano-4-(p-methylphenyl)-6-phenyl-4,7-dihydropyrazolo[3,4-b]pyridin-3-one (**4b**).

This compound was obtained according to general procedure as white crystals, yield 60%, mp 292 °C; ir (potassium bromide): 2218 (CN), 1636 (C=O), 3361, 3450 cm^{-1} (NH). ^{13}C-nmr (DMSO-d_6, ppm): 20.5 (CH_3), 38.6 (C-4), 80.1 (C-5), 85.6 (C-3a), 121.9 (CN), 161.8 (C=O). FAB m/z 329 (M^++1).

Anal. Calcd. for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.04; H, 4.87; N, 17.17.

5-Cyano-4-(p-methoxyphenyl)-6-phenyl-4,7-dihydropyrazolo[3,4-b]pyridin-3-one (**4c**).

This compound was obtained according to general procedure as white crystals, yield 50%, mp 295 °C; ir (potassium bromide): 2219 (CN), 1624 (C=O), 3342, 3448 cm^{-1} (NH). ^{13}C-nmr (DMSO-d_6, ppm): 38.6 (C-4), 60.5 (OCH_3), 80.1 (C-5), 85.6 (C-3a), 121.9 (CN), 162.3 (C=O). FAB m/z 345 (M^++1).

Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.84; H, 4.62; N, 16.36.

4-(p-Chlorophenyl)-5-Cyano-6-phenyl-4,7-dihydropyrazolo[3,4-b]pyridin-3-one (**4d**).

This compound was obtained according to general procedure as white crystals, yield 65%, mp 300 °C; ir (potassium bromide): 2225 (CN), 1653 (C=O), 3362, 3419 cm^{-1} (NH). ^{13}C-nmr

(DMSO-d_6, ppm): 38.5 (C-4), 79.8 (C-5), 84.5 (C-3a), 121.7 (CN) 160.5. FAB m/z 350/352 (Cl-pattern) (M^++1).

Anal. Calcd. for $C_{19}H_{13}N_4OCl$: C, 65.43; H, 3.76; N, 16.06. Found: C, 65.33; H, 3.67; N, 16.18.

4-(p-Bromophenyl)-5-Cyano-6-phenyl-4,7-dihydropyrazolo[3,4-b]pyridin-3-one (**4e**).

This compound was obtained according to general procedure as white crystals, yield 70%, mp 314 °C; ir (potassium bromide): 2219 (CN), 1638 (C=O), 3380, 3486 cm^{-1} (NH). ^{13}C-nmr (DMSO-d_6, ppm): 38.8 (C-4), 80.5 (C-5), 85.1 (C-3a), 122.4 (CN), 161.3 (C=O). FAB m/z 394/396 (Br-pattern) (M^++1).

Anal. Calcd. for $C_{19}H_{13}N_4OBr$: C, 58.03; H, 3.33; N, 14.25. Found: C, 58.12; H, 3.27; N, 14.35.

5-Cyano-4-(p-nitrophenyl)-6-phenyl-4,7-dihydropyrazolo[3,4-b]pyridin-3-one (**4f**).

This compound was obtained according to general procedure as pale yellow crystals, yield 72%, mp 315 °C; ir (potassium bromide): 2220 (CN), 1619 (C=O), 3249, 3430 (NH), 1339, 1558 (NO_2) cm^{-1}. ^{13}C-nmr (DMSO-d_6, ppm): 41.0 (C-4), 80.8 (C-5), 85.6 (C-3a), 123.2 (CN), 162.1 (C=O). FAB m/z 361 (M^++1).

Anal. Calcd. for $C_{19}H_{13}N_5O_3$: C, 63.51; H, 3.65; N, 19.49. Found: C, 63.56; H, 3.69; N, 19.34.

5-Cyano-4,6-diarylpyrazolo[3,4-b]pyridin-3-ones (**5a-f**).

General Procedure

Method A.

A solution of 1.40 mmoles of **1**, 1.40 mmoles of corresponding benzaldehyde **2** and 1.40 mmoles of benzoylacetonitrile **3** in 50 ml of absolute ethanol was refluxed during 3-4 hours under air (tlc control). The reaction mixture was cooled. The cyclized products **5** were collected by filtration, washed with ethanol and recrystallized from ethanol.

Method B.

Equimolar amounts of amine **1**, benzaldehyde **2** and benzoylacetonitrile **3** were placed into pyrex-glass open vessels and irradiated in a domestic microwave oven for 2–4 min.(at 600 watts). The products were recrystallized from absolute ethanol and the authenticity was established by their spectral data. The reaction times and yields obtained have been compared with the reaction times and yields obtained by method A (Scheme 1).

5-Cyano-4,6-diphenylpyrazolo[3,4-b]pyridin-3-one (**5a**).

This compound was obtained according to general procedure (methods A and B) as white crystals, mp 292 °C (293-294, lit[12]); ir (potassium bromide): 2218 (CN), 1605 (C=O), 3341, 3403 cm^{-1} (NH). ^{1}H-nmr (DMSO-d_6, ppm): 7.56 (6H, m, ArH), 7.69 (2H, m, ArH), 7.86 (2H, d, ArH), 11.30 (1H, s, NH). FAB m/z 313 (M^++1).

Anal. Calcd. for $C_{19}H_{12}N_4O$: C, 73.07; H, 3.87; N, 17.94. Found: C, 73.11; H, 3.69; N, 17.89.

5-Cyano-4-(p-methylphenyl)-6-phenylpyrazolo[3,4-b]pyridin-3-one (**5b**).

This compound was obtained according to general procedure (methods A and B) as white crystals, mp 300 °C (300-302, lit[12]); ir (potassium bromide): 2225 (CN), 1610 (C=O), 3362, 3460 cm^{-1} (NH). ^{1}H-nmr (DMSO-d_6, ppm): 2.43 (3H, s, CH_3), 7.36 (2H, d, ArH), 7.55 (5H, m, ArH), 7.84 (2H, d, ArH), 11.21 (1H, s, NH). FAB m/z 327 (M^++1).

Anal. Calcd. for $C_{20}H_{14}N_4O$: C, 73.61; H, 4.32; N, 17.17. Found: C, 73.70; H, 4.27; N, 17.28.

5-Cyano-4-(p-methoxyphenyl)-6-phenylpyrazolo[3,4-b]pyridin-3-one (**5c**).

This compound was obtained according to general procedure (methods A and B) as white crystals, mp 320-321 °C (324-325, lit[12]); ir (potassium bromide): 2217 (CN), 1604 (C=O), 3330, 3392 cm^{-1} (NH). ^{1}H-nmr (DMSO-d_6, ppm): 3.87 (3H, s, OCH_3), 7.11 (2H, d, ArH), 7.59-7.85 (7H, m ArH), 11.2 (1H, s, NH). FAB m/z 343 (M^++1).

Anal. Calcd. for $C_{20}H_{14}N_4O_2$: C, 70.17; H, 4.12; N, 16.37. Found: C, 70.14; H, 4.05; N, 16.45.

4-(p-Chlorophenyl)-5-Cyano-6-phenylpyrazolo[3,4-b]pyridin-3-one (**5d**).

This compound was obtained according to general procedure (methods A and B) as white crystals, mp 310 °C (312-314, lit[12]); ir (potassium bromide): 2221 (CN), 1597 (C=O), 3390, 3460 cm^{-1} (NH). ^{1}H-nmr (DMSO-d_6, ppm): 7.60-7.80 (9H, m, ArH), 11.41 (1H, s, NH). FAB m/z 348/350 (Cl-pattern) (M^++1).

Anal. Calcd. for $C_{19}H_{11}N_4OCl$: C, 65.81; H, 3.20; N, 16.16. Found: C, 65.73; H, 3.27; N, 16.23.

4-(p-Bromophenyl)-5-Cyano-6-phenylpyrazolo[3,4-b]pyridin-3-one (**5e**).

This compound was obtained according to general procedure (methods A and B) as white crystals, mp 318 °C; ir (potassium bromide): 2220 (CN), 1602 (C=O), 3366, 3476 cm^{-1} (NH).

^{1}H-nmr (DMSO-d_6, ppm): 7.58-7.76 (9H, m, ArH), 11.32 (1H, s, NH). FAB m/z 392/394 (Br-pattern) (M^++1).

Anal. Calcd. for $C_{19}H_{11}N_4OBr$: C, 58.33; H, 2.83; N, 14.32. Found: C, 58.41; H, 2.97; N, 14.39.

5-Cyano-4-(p-nitrophenyl)-6-phenylpyrazolo[3,4-b]pyridin-3-one (**5f**).

This compound was obtained according to general procedure (methods A and B) as pale yellow crystals, mp 322 °C; ir (potassium bromide): 2221 (CN), 1640 (C=O), 3435, 3476 (NH), 1348, 1521 cm^{-1} (NO_2). ^{1}H-nmr (DMSO-d_6, ppm): 7.62-7.85 (5H, m, ArH), 7.92 (2H, d, ArH), 8.25 (2H, d, ArH) , 11.30 (1H, s, NH). FAB m/z 359 (M^++1).

Anal. Calcd. for $C_{19}H_{11}N_5O_3$: C, 63.87; H, 3.10; N, 19.60. Found: C, 63.75; H, 3.21; N, 19.54.

Acknowledgements

Authors thank The Colombian Institute for Science and Research (COLCIENCIAS, Project 1106-05-411-95) and UNIVERSIDAD DEL VALLE for financial support.

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Received on April 28, 2000