Synthesis of Pyrazolo[3,4-b]pyridines and Pyrido[2,3-d]pyrimidinones by Hetero-Diels-Alder Reaction of Pyrazolyl- and Pyrimidinilimines under Microwave Irradiation in Dry Media

Jairo Quiroga[1]*, Braulio Insuasty[1], Rodrigo Abonía[1], Pedro Hernandez[1], Manuel Nogueras[2] and Adolfo Sánchez[2].
[1]Grupo de Investigación de Compuestos Heterocíclicos, Departamento de Química, Universidad del Valle, A. A. 25360, Cali – Colombia
[2]Department of Inorganic and Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain.

Abstract: Microwave irradiation in dry media induces pyrazolyl- **1a** and pyrimidinil-2-azadiene **1b** to undergo hetero-Diels-Alder reaction with 3-dimethylaminopropiophenone hydrochlorides **2** within 2-3 minutes to give good yields of 5-aroylpyrazolo[3,4-b]pyridines **3a-c** and 6-aroylpyrido[2,3-d]pyrimidinones **4a-c**. The structure of compounds **3** and **4** and regiochemistry of reaction were determined on the basis of nmr measurements.

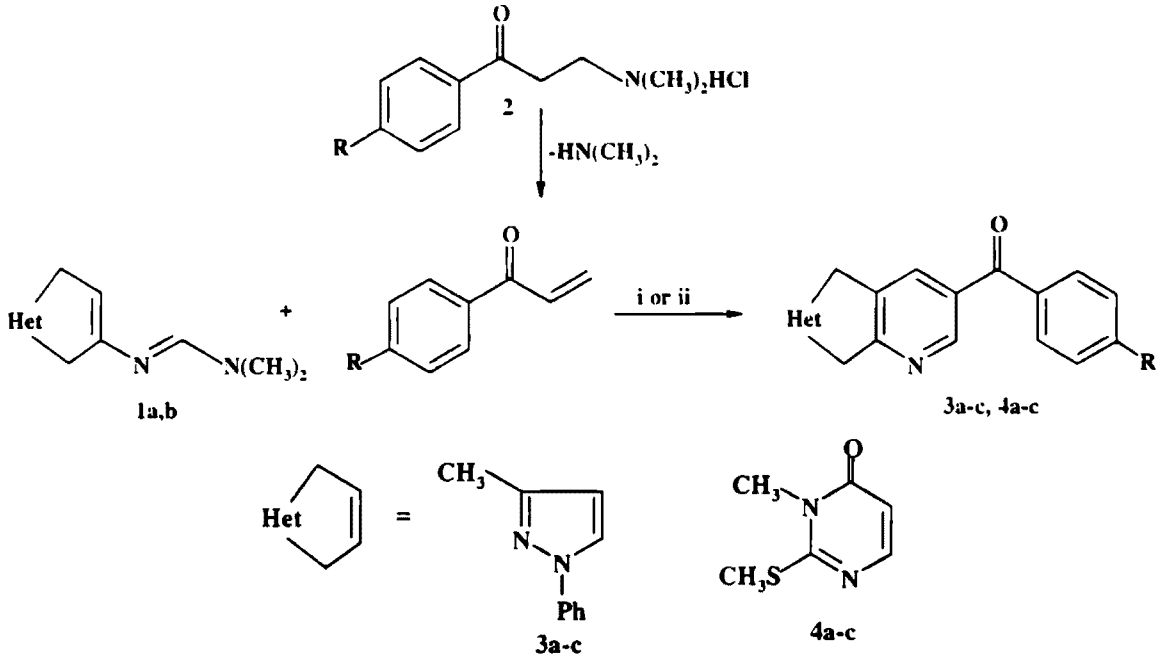
Introduction

The Diels-Alder cycloaddition is a convenient and versatile method for the synthesis of six-membered rings [1]. Continuing the study of reactions of aminopyrazoles and aminopyrimidines with compounds α,β-unsaturated and its precursors [2-9], we carried out experiments on the interaction of 5-dimethylaminometilenamino-3-methyl-1-phenylpyrazole (**1a**) and 6-dimethylaminometilenamino-2-methylthio-3-methyl-4-pyrimidinone (**1b**) with 3-dimethylaminopropiophenones (**2**) under microwave irradiation.

Results and Discussion

Equimolar amounts of 2-azadiene compounds (**1a,b**) and 3-dimethylaminopropiophenone hydrochlorides (**2**) were placed in a simple beaker and irradiated in a domestic microwave oven for 1.5–3 minutes (at 600 watts), then treated with ethanol, filtered and recrystallized from a dimethylformamide-water mixture (Scheme 1). In other experiment, by classical

heating of reactants **1a,b** and **2** in DMF for 25-145 minutes, this reaction afforded the same products (**3** and **4**) in minor yield (Scheme 1).



i) Microwave irradiation (Method A); ii) Reflux in DMF (Method B)

Compound	R	Time of reaction, min		Yield, %	
		MW	in DMF	MW	in DMF
3a	Cl	3	145	45	25
3b	Br	3	135	50	28
3c	NO_2	2.5	120	57	32
4a	Cl	2	30*	65	55*
4b	Br	2	25*	70	58*
4c	NO_2	1.5	25*	75	66*

* Data from reference [10].

Scheme 1

The reaction took place with loss of two $HNMe_2$ molecules, initially one in the process of aroyl vinyl ketone formation and second one in the cycloadditon pathway. This last elimination induces the aromatization of the final product and can be the driving force of the reaction avoiding the reversibility of the cycloaddition.

The formation of compounds **3** and **4** was confirmed by spectroscopic analysis. In the ^1H nmr spectra of compounds **3a-c** (DMSO-d_6) besides the signals of CH_3-group at 2.68-2.70 ppm with aromatic protons at 7.33-8.40 ppm, two doublets are observed with ^{meta}J = 1.93-2.00 Hz at δ = 8.50-8.54 and 9.01-9.04 ppm with a 1:1 relationship, corresponding to the H-4 and H-6 protons of pyridine ring respectively.

Compounds **4a-c** were previously prepared in 55-66% yield [10] in classical conditions by heating of **1b** and **2** in dimethylformamide for 20-30 minutes and their data agree with the synthetized by microwave radiation.

The observed high regioselectivity in the obtained products is in complete agreement with the calculated atomic coefficients in the frontier molecular orbital (see figure).

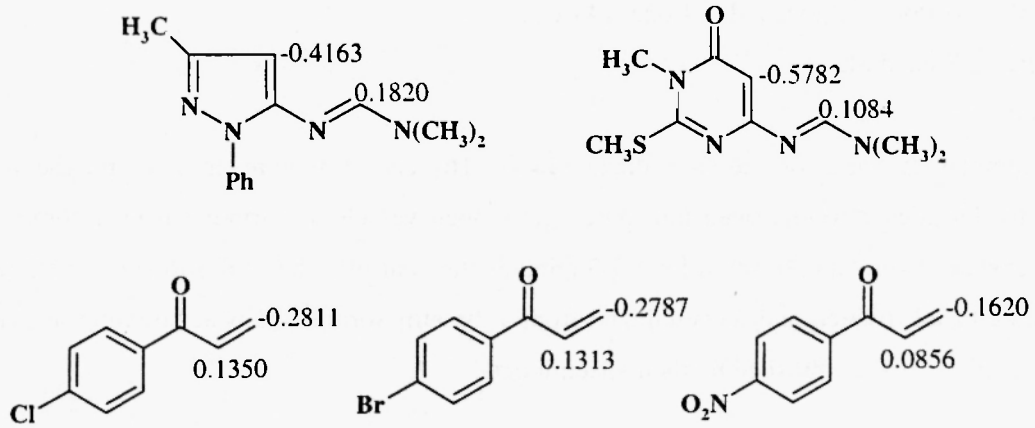


Figure: Structure of 2-azadienes (**1a,b**) and dienophiles with atomic coefficient values in HOMO (dienes) and LUMO (dienophiles).

Conclusion

We have carried out a new example of a [4+2] hetero-cycloaddition of a 2-azadiene involving a heterocyclic rings, which represents a convenient method for synthesis of pyrazolo[3,4-b]pyridines and pyrido[2,3-d]pyrimidines. 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. The mass

spectra were scanned on a Hewlett Packard HP Engine-5959 spectrometer (equipped with a direct inlet probe) operating at 70 eV. The elemental analysis have been obtained using a LECO CHNS-900 equipment. The 2-azadienes **1a** and **1b** were obtained by methods described in [11] and [10] respectively.

5-Aroyl-3-methyl-1-phenylpyrazolo[3,4-b]pyridines (**3a-c**) and 6-aroyl-2-methylthio-3-methylpyrido[2,3-d]pyrimidin-4-onas (**4a-c**).

General Procedure

Method A.

Equimolar amounts of the 2-azadiene (**1a** or **1b**) and 3-dimethylaminopropiophenone hydrochlorides **2** were placed into pyrex-glass open vessels and irradiated in a domestic microwave oven (at 600 watts) for 1.5-3 minutes (tlc control). The solid formed was treated with ethanol, filtered and recrystallized from a dimethylformamide-water mixture and the authenticity was established by their spectral data.

Method B.

A solution of 1.40 mmoles of **1a** and 1.40 mmoles of **2** in 5 ml of DMF was refluxed during 3-4 hours under air (tlc control). The reaction mixture was cooled. The cyclized products **3a-c** were collected by filtration, washed with ethanol and recrystallized from DMF-water mixture. The products **4a-c** were obtained by the classical method described in reference [10].

5-(4-Chlorobenzoyl)-3-methyl-1-phenylpyrazolo[3,4-b]pyridin-3-one (**3a**).

This compound was obtained according to general procedures (methods A and B) as pale yellow crystals, mp 262 °C. ^{1}H-nmr (DMSO-d_6, ppm): 2.68 (3H, s, CH_3), 7.34 (1H, t, H_p C_6H_5), 7.55 (2H, t, H_m C_6H_5), 8.25 (2H, d, H_o C_6H_5), 7.74 (4H, dd, *p*-ClC_6H_4), 8.51 (1H, d, H-4), 9.01 (1H, d, H-6). ^{13}C-nmr (DMSO-d_6, ppm): 12.5 (CH_3), 116.7 (C-3a), 135.7 (C-4), 151.1 (C-6), 192.8 (C=O). This compound had ms: EI m/z (relative abundance) = 348/346 (18/60, M^+), 312 (10), 236 (100, M^+-p-ClC_6H_4), 208 (12), 167 (12), 77 (38), 76 (17), 44 (18).

Anal. Calcd. for $C_{20}H_{14}ClN_3O$: C, 69.07; H, 4.06; N, 12.08. Found: C, 69.11; H, 4.19; N, 12.18.

5-(4-Bromobenzoyl)-3-methyl-1-phenylpyrazolo[3,4-b]pyridine (**3b**).

This compound was obtained according to general procedures (methods A and B) as pale yellow crystals, mp 287 °C. ^{1}H-nmr (DMSO-d_6, ppm): 2.69 (3H, s, CH_3), 7.33 (1H, t, H_p C_6H_5), 7.54 (2H, t, H_m C_6H_5), 8.25 (2H, d, H_o C_6H_5), 7.70 (4H, dd, *p*-BrC_6H_4), 8.50 (1H, d, H-4), 9.02 (1H, d, H-6). ^{13}C-nmr (DMSO-d_6, ppm): 12.5 (CH_3), 116.4 (C-3a), 136.2 (C-4), 151.4 (C-6), 193.4 (C=O). This compound had ms: EI m/z (relative abundance) = 393/391 (56/59,M^+), 312 (42), 237 (16), 236 (100, M^+-*p*-BrC_6H_4), 208 (18), 185 (21), 183 (21), 167 (15), 140 (31), 77 (50), 76 (20), 44 (14).

Anal. Calcd. for $C_{20}H_{14}BrN_3O$: C, 61.24; H, 3.60; N, 10.71. Found: C, 61.15; H, 3.69; N, 10.82.

5-(4-Nitrobenzoyl)-3-methyl-1-phenylpyrazolo[3,4-b]pyridine (**3c**).

This compound was obtained according to general procedures (methods A and B) as yellow crystals, mp 306 °C. ^{1}H-nmr (DMSO-d_6, ppm): 2.70 (3H, s, CH_3), 7.35 (1H, t, H_p C_6H_5), 7.54 (2H, t, H_m C_6H_5), 8.25 (2H, d, H_o C_6H_5), 7.98 (2H, d, H_m *p*-BrC_6H_4), 8.40 (2H, d, H_m *p*-BrC_6H_4), 8.54 (1H, d, H-4), 9.04 (1H, d, H-6). ^{13}C-nmr (DMSO-d_6, ppm): 12.4 (CH_3), 116.5 (C-3a), 132.4 (C-4), 150.9 (C-6), 192.6 (C=O). This compound had ms: EI m/z (relative abundance) = 358 (100, M^+), 237 (13), 236 (83, M^+-*p*-$O_2NC_6H_4$), 208 (15), 167 (15), 140 (33), 77 (57), 76 (26).

Anal. Calcd. for $C_{19}H_{12}N_4O$: C, 67.03; H, 3.94; N, 15.63. Found: C, 67.08; H, 3.84; N, 15.49.

6-(4-Chlorobenzoyl)-2-methylthio-3-methylpyrido[2,3-d]pyrimidin-4-ona **4a**.

This compound was obtained according to method A, mp 338 °C (339 °C, lit[10]).

Anal. Calcd. for $C_{16}H_{12}N_3O_2SCl$: C, 55.57; H, 3.50; N, 12.15. Found: C, 57.51; H, 3.57; N, 12.23.

6-(4-Bromobenzoyl)-2-methylthio-3-methylpyrido[2,3-d]pyrimidin-4-ona **4b**.

This compound was obtained according to method A, mp 341-342 °C (342 °C, lit[10]).

Anal. Calcd. for $C_{16}H_{12}N_3O_2SBr$: C, 49.24; H, 3.10; N, 10.77. Found: C, 49.29; H, 3.19; N, 10.88.

6-(4-Nitrobenzoyl)-2-methylthio-3-methylpyrido[2,3-d]pyrimidin-4-ona **4c**.

This compound was obtained according to method A, mp 338 °C (338 °C, lit[10]).

Anal. Calcd. for $C_{16}H_{12}N_4O_4S$: C, 53.93; H, 3.39; N, 15.72. Found: C, 53.81; H, 3.47; N, 15.63.

Acknowledgements

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