The Formation of Pyrazolo[1,5-*a*]pyrimidines by the Reaction of 3-(4-Chlorophenyl)pyrazol-5-amine with Chalcones

Jairo Quiroga*

Universidad de los Andes, Department of Chemistry, A. A. 4976 Santa Fe de Bogota, Columbia

Braulio Insuasty

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

Ricardo Rincon and Marina Larrahondo

Universidad Distrital, Department of Chemistry,
Santa Fe de Bogota, Columbia

Norbert Hanold and Herbert Meier

University of Mainz, Institute of Organic Chemistry, 55099 Mainz, Germany

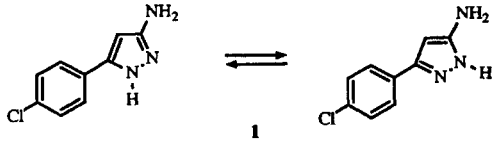
Received May 18, 1994

Cyclocondensation reactions of the pyrazol-5-amine **1** and the 1-aryl-3-phenyl-2-propen-1-ones **2a-d** yield the 6,7-dihydropyrazolo[1,5-*a*]pyrimidines **7a-d**. Whereas **7a-c** can be isolated in pure state, **7d** is subjected to a spontaneous oxidation.

J. Heterocyclic Chem., **31**, 1333 (1994).

Derivatives of pyrazolo[1,5-*a*]pyrimidine obtain a great deal of interest due to their physiological and biological activities [1,2]. Reactions of heterocyclic amines with α,β-unsaturated carbonyl compounds especially with chalcones are a general method for the fusion of a second heterocyclic ring [3-11]. Pyrazolamines contain three different nitrogen atoms for the initial formation of an N-C bond; consequently the generation of different reaction products, namely derivatives of pyrazolo[4,5-*b*]pyridine and of pyrazolo[1,5-*a*]pyrimidine were reported in the literature [8,9,12-16]. Continuing with the research on aminopyrazoles [8] we studied the reaction of 3-(4-chlorophenyl)pyrazol-5-amine (**1**) with the 1-aryl-3-phenyl-2-propen-1-ones **2a-d**. Compound **1** exists like other *N*-unsubstituted pyrazoles in two tautomeric forms [17-20].

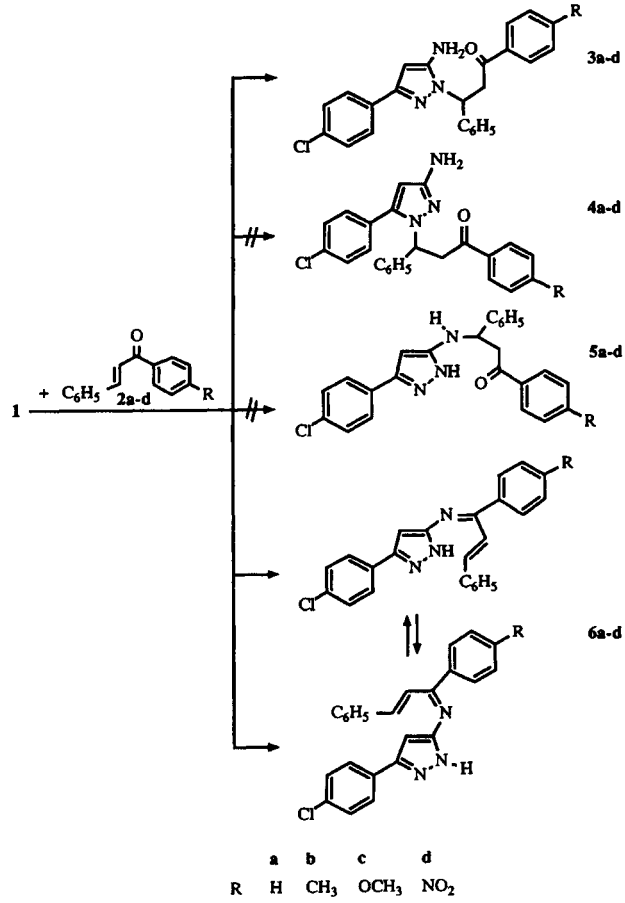
Scheme 1

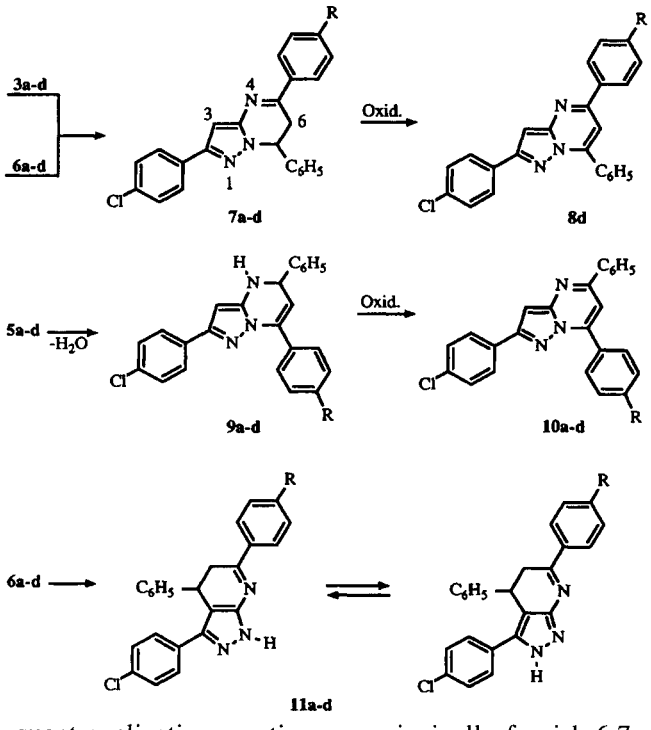


1

In principal, each of the three nitrogen atoms of **1** can attack on C-1 or C-3 of the chalcones **2a-d**. Scheme 2 shows the four most likely routes which lead to the Michael adducts **3a-d, 4a-d** and **5a-d** and to the Schiff bases **6a-d** (drawn in (*E,E*)-configuration). The subse-

Scheme 2





quent cyclization reaction can principally furnish 6,7-dihydropyrazolo[1,5-*a*]pyrimidines **7a-d** or 5,6-dihydropyrazolo[1,5-*a*]pyrimidines **9a-d** or 4,5-dihydropyrazolo[4,5-*b*]pyridines **11a-d.**

The ^1H and ^{13}C nmr spectra of the products obtained from **2a-c** prove a (-CH_2-CH-) building block and rule out an NH function which is consistent with structure **7a-c**. Furthermore NOE measurements reveal the neighborhood of the methin proton and the *ortho* protons of the phenyl group (CH-C_6H_5). The latter result excludes a rearrangement of **9a-c** to a 6,7-dihydropyrazolo[1,5-*a*]-pyrimidine which should lead to compounds like **7** but with interchanged aryl substituents on C-5 and C-7.

In the reaction with the nitro compound **2d** an additional autoxidation process **7d** → **8d** is involved.

The ^1H and ^{13}C nmr data of the products **7a-c** and **8d** are summarized in the Tables 1 and 2.

EXPERIMENTAL

Melting points are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Bruker AM 400 in deuteriochloroform. The mass spectra were obtained on a Finnigan M 95 spectrograph operating at 70 eV.

5-Aryl-2-(4-chlorophenyl)-6,7-dihydro-7-phenylpyrazolo[1,5-*a*]-pyrimidines **7a-c.**

General Procedure.

A solution of 0.37 g (1.9 mmoles) 3-(4-chlorophenyl)pyrazol-5-amine **1** and 1.9 mmoles of chalcone **2a-c** in 1 ml of DMF

Table 1

^1H NMR Data of **7a-c** and **8d** (δ Values, $CDCl_3$ as Solvent and Internal Standard, 400 MHz)

	Heterocyclic Skeleton			2-(4-Chlorophenyl)		5-Aryl			7-Phenyl		
Compound	3-H	6-H	7-H	*o*	*m*	*o*	*m*	*p*	*o*	*m*	*p*
7a	6.77	3.51/3.51	5.71	7.73	7.33	7.91	7.45	7.40	6.98	7.26	7.22
7b	7.02	3.61/3.62	5.80	7.83	7.44	7.91	7.00	2.32 CH_3	~7.25	~7.25	~7.25
7c	6.71	3.43/3.48	6.67	7.73	7.32	7.88	6.90	3.81 OCH_3	6.98	~7.24	~7.24
8d	7.10	7.38	---	7.94	7.41	8.37 /	8.31	---	8.18	7.63	7.62

Table 2

^{13}C NMR Data of **7a-c** and **8d** (δ Values, $CDCl_3$ as Solvent and Internal Standard, 100 MHz)

	Heterocyclic Skeleton						Substituents			
Compound	C-2	C-3	C-3a	C-5	C-6	C-7	*o,m*-CH	*p*-CH	C_q	CH_3
7a	139.9	99.9	162.5	150.9	34.7	57.0	129.0, 128.7, 128.7 127.0, 126.8, 125.6	131.4 128.1	146.3, 137.3 133.6, 131.9	
7b	140.4	99.2	163.0	149.1	33.5	55.9	129.2, 128.6, 128.5 127.0, 126.6, 125.6	127.7	146.0, 141.5, 134.1 132.1, 132.0	20.9
7c [a]	140.0	99.3	162.7*	150.8	34.4	56.9	129.0, 128.9, 128.7, 126.8, 125.7, 114.1	128.0	162.0*, 146.5, 133.6 131.9, 129.8	55.4
8d [a]	147.0	104.9	155.8	151.0*	94.5	148.9	129.5, 129.0, 128.7, 128.1, 127.9, 124.1	131.4	153.4*, 143.3, 135.1, 131.2, 131.0	

[a] Interchangeable signals are marked by an asterisk.

was refluxed for 1 hour. After cooling to 50° a precipitate was formed which could be recrystallized from DMF.

2-(4-Chlorophenyl)-6,7-dihydro-5,7-diphenylpyrazolo[1,5-*a*]-pyrimidine (**7a**).

The compound was obtained as 0.33 g (55%) pale yellow crystals of mp 221°. The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 385 / 383 (90, $M^{+\cdot}$, Cl pattern), 306 (25), 191 (20), 148 (42), 136 (26), 115 (41), 113 (62), 104 (42), 103 (100).

Anal. Calcd. for $C_{24}H_{18}ClN_3$: C, 75.09; H, 4.73; N, 10.95. Found: C, 74.89; H, 5.01; N, 11.26.

2-(4-Chlorophenyl)-6,7-dihydro-5-(4-methylphenyl)-7-phenyl-pyrazolo[1,5-*a*]pyrimidine (**7b**).

The compound was obtained as 0.37 g (61%) pale yellow crystals of mp 169°. The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 399 / 397 (9, $M^{+\cdot}$, Cl pattern), 222 (100), 221 (88), 207 (23), 179 (21), 131 (37), 119 (71), 103 (46), 91 (84).

Anal. Calcd. for $C_{25}H_{20}ClN_3$: C, 75.46; H, 5.07; N, 10.56. Found: C, 75.17; H, 5.05; N, 10.85.

2-(4-Chlorophenyl)-6,7-dihydro-5-(4-methoxyphenyl)-7-phenylpyrazolo[1,5-*a*]pyrimidine (**7c**).

The compound was obtained as 0.32 g (50%) yellow crystals of mp 192°. The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 415 / 413 (100, $M^{+\cdot}$, Cl pattern), 336 (16), 148 (36), 136 (18), 133 (86), 113 (42), 103 (22).

Anal. Calcd. for $C_{25}H_{20}ClN_3O$: C, 72.55; H, 4.87; N, 10.15. Found: C, 72.20; H, 5.16; N, 9.90.

2-(4-Chlorophenyl)-5-(4-nitrophenyl)-7-phenylpyrazolo[1,5-*a*]-pyrimidine (**8d**).

The compound was obtained as 0.48 g (72%) yellow crystals of mp 265-266°. The mass spectrum shows the following peaks; ms: (70 eV) m/z (%) 428 / 426 (100, $M^{+\cdot}$, Cl pattern), 380 (16), 269 (15), 242 (12), 213 (12), 204 (13), 203 (16), 189 (13), 177 (13), 176 (19), 113 (27), 111 (56), 102 (25).

Anal. Calcd. for $C_{24}H_{15}ClN_4O_2$: C, 67.53; H, 3.54; N, 13.13. Found: C, 67.38; H, 3.40; N, 12.83.

Acknowledgment.

We are grateful to COLCIENCIAS for financial support.

REFERENCES AND NOTES

[1] J. V. Greenhill in Comprehensive Heterocyclic Chemistry, Vol **5**, A. R. Katritzky and C. W. Rees, eds, 1984, p 305.

[2] M. H. Elnagdi, M. R. H. Elmoghayar and G. E. Elgemeie, *Adv. Heterocyclic Chem.*, **41**, 319 (1984).

[3] W. J. Irwin and D. G. Wibberley, *J. Chem. Soc. C*, 1745 (1967).

[4] Y. Tamura, T. Sakaguchi, T. Kawasaki and Y. Kita, *Heterocycles*, **3**, 183 (1975).

[5] S. Wawzonek, *J. Org. Chem.*, **41**, 3149 (1976).

[6] V. D. Orlov, J. Quiroga and N. N. Kolos, *Khim. Geterotsikl. Soedin.*, 1247 (1987).

[7] V. D. Orlov, S. M. Desenko, K. A. Potejin and Y. T. Struchkov, *Khim. Geterotsikl. Soedin.*, 229 (1988).

[8] V. D. Orlov, J. Quiroga, N. N. Kolos and S. M. Desenko, *Khim. Geterotsikl. Soedin.*, 962, (1988).

[9] J. Quiroga, B. Insuasty, M. Marin, A. Aguirre and H. Meier, *Rev. Col. Quim.*, **21**, 29 (1992).

[10] J. Quiroga, B. Insuasty, A. Sanchez, M. Nogueras and H. Meier, *J. Heterocyclic Chem.*, **29**, 1045 (1992).

[11] B. Insuasty, M. Ramos, J. Quiroga, A. Sanchez, M. Nogueras, N. Hanold and H. Meier, *J. Heterocyclic Chem.*, **31**, 61 (1994).

[12] E. C. Taylor and J. W. Barton, *J. Am. Chem. Soc.*, **81**, 2448 (1959).

[13] A. Dornow, M. Siebrecht, *Chem. Ber.*, **93**, 1106 (1960).

[14] W. Ried and E.-U. Köcher, *Liebigs Ann. Chem.*, **647**, 116 (1961).

[15] W. Ried and K.-P. Peuchert, *Liebigs Ann. Chem.*, **660**, 104 (1962).

[16] J.-L. Imbach, R. Jacquier and J.-L. Vidal, *Bull. Soc. Chim. France*, 1929 (1970).

[17] For the tautomeric equilibria see for example literature [18-20].

[18] S. Gelin and D. Hartmann, *J. Heterocyclic Chem.*, **15**, 813 (1978).

[19] E. Gonzalez, R. Faure, E.-J. Vincent, M. Espada and J. Elguero, *Org. Magn. Reson.*, **12**, 587 (1979).

[20] G. Ege and H. Franz, *J. Heterocyclic Chem.*, **21**, 689 (1984).