The Reaction of 2,4,5,6-Tetraaminopyrimidine with Chalcones

Braulio Insuasty*, Alfredo Pérez, Diego González and Jairo Quiroga

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

Herbert Meier

Universität Mainz, Institut für Organische Chemie, 55099 Mainz, Germany

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The reaction of the tetraaminopyrimidine 1 with the chalcones **2a-f** yields, in the presence of catalytic amounts of acetic acid, the 1*H*-pyrimido[4,5-*b*][1,4]diazepine derivatives **3a-f**. The cyclization process consists of a condensation reaction and a Michael type addition.

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The reaction between aromatic or heteroaromatic 1,2-diamines and chalcones (1,3-diaryl-2-propenones) is a convenient and versatile method for the preparation of condensed 1,4-diazepines [1 - 7]. Alternatively two equivalents of functionalized acetophenones can enter with 1,2-diamine cyclization reactions [3,5,8].

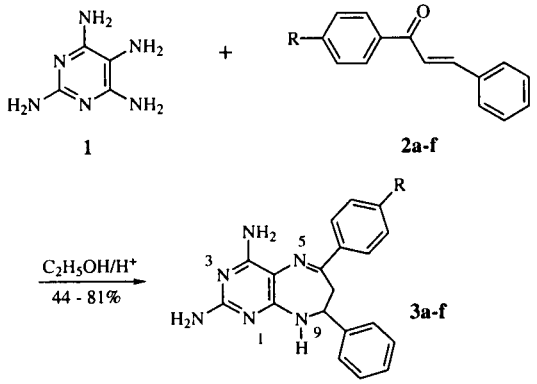
In the present paper, we report on the preparation of 2,4-diamino-6,8-diaryl-7,8-dihydro-9*H*-pyrimido[4,5-*b*]-[1,4]diazepines (**3**), compounds for which interesting biological and pharmacological properties can be expected [9,10]. Heating of 2,4,5,6-tetraaminopyrimidine (**1**) with molar quantities of chalcones **2a-f** in the presence of catalytic amounts of acetic acid generates the desired products **3a-f** in good yields.

The tetraamine **1** contains three types of non-equivalent amino groups. Due to the electronic effect of the pyrimidine ring, the amino group on C-5 has the highest nucleophilicity [11-14]. Its condensation reaction with the carbonyl group of **2a-f** can be followed by a Michael type addition of one of the two equivalent amino groups on C-4 and C-6. Electron withdrawing substituents R enhance the reactivity whereas electron releasing substituents R decrease it. The spectroscopic characterization of the products reveals a regioselective ring closure.

The ^{1}H nmr data of **3a-f** are summarized in Table 1. The four protons on the 1,4-diazepine ring give rise to an ABMX spin system. The coupling of the proton on N-9 with $^3J = (4.9 \pm 0.3)$ Hz indicates the vicinal position to the proton on C-8. The latter shows two couplings ($^3J = (6.0 \pm 0.2)$ Hz and $^3J = (1.2 \pm 0.2)$ Hz) to the methylene group H_2C-7. The geminal coupling constant ^2J amounts to $-(14.7 \pm 0.1)$ Hz.

The ^{13}C-nmr data of **3a-f** are summarized in Table 2; the correlation of the δ values with certain carbon atoms is based on DEPT measurements. The chemical shift of

Scheme 1



2,3	R	Yield [%]	mp [°C]
a	H	44	212 - 213
b	Cl	62	249 - 251
c	NO_2	81	292 - 294
d	CH_3	46	232
e	Br	76	219 - 220
f	OCH_3	48	240 - 242

C-4a ($\delta = 101.4 \pm 0.6$) is characteristic for the electron releasing effects of N-9 and 4-NH_2. Moreover, measurements of the single frequency decoupling by irradiation of the proton signal corresponding to HN-9 reveal the ^3J coupling with C-4a.

EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were run on Bruker AM 400 and AC 200 spectrometers in DMSO-d_6. The mass spectra were recorded on a Finnigan M 95 operating at 70 eV.

Table 1

^{1}H nmr Data of **3a-f** (δ values measured in DMSO-d_6 versus tetramethylsilane as internal standard, 400 MHz)

3	9-H	8-H	7-H	NH_2	2-C_6H_5	4-C_6H_4-R	others
a	7.34	5.17	2.97/3.87	6.52/6.04	7.16 - 7.38	7.16 - 7.77	
b	7.32	5.18	2.90/3.90	6.55/6.08	7.18 - 7.30	7.31 - 7.80	
c	7.39	5.21	2.87/4.03	6.45/5.94	7.19 - 7.29	7.96 - 8.15	
d	7.04	5.15	2.88/3.87	6.21/5.73	7.12 - 7.30	7.12 - 7.58	2.34 (CH_3)
e	7.30	5.18	2.89/3.88	6.50/6.01	7.18 - 7.32	7.48 - 7.68	
f	6.94	5.04	2.78/3.74	6.16/5.68	7.07 - 7.24	6.74 - 7.50	3.72 (OCH_3)

Table 2
^{13}C nmr Data of **3a-f** (δ values measured in DMSO-d_6 versus tetramethylsilane as internal standard, 100 MHz)

Compound	3a	b	c	d	e	f
HC-8	57.2	57.2	57.0	57.6	57.4	57.3
H_2C-7	39.0	38.8	38.7	38.7	38.8	38.5
C-6	159.4	159.4	161.2	160.5	160.0	160.0*
C-4a	100.8	101.2	102.0	101.5	101.3	101.2
C-4, C-9a	154.4	153.4	150.7	154.3	153.1	154.2
	154.8	154.5	155.3	154.9	154.7	154.4
C-2	163.2	163.0	164.3	163.8	163.5	163.5
Ar						
C_i	140.8	139.7	144.0	137.5	140.1	133.8
	144.0	144.0	146.9*	138.5	144.0	144.2
$HC_{o,m}$	125.8	126.8	123.2	126.0	125.9	112.6
	126.0	127.8	125.8	126.1	128.1	125.9
	127.6	128.0	127.0	128.1	128.2	127.8
	127.8	128.0	128.0	128.6	130.8	128.0
C_p	126.8	126.8	126.8	126.7	121.6	126.8
	128.0	132.8	146.4*	144.3	126.8	159.4*
others				23.6 (CH_3)		55.0 (OCH_3)

*signal correlation interchangeable

2,4-Diamino-7,8-dihydro-6,8-diaryl-9*H*-pyrimido[4,5-*b*][1,4]-diazepines (**3a-f**).

General Procedure

A solution of 0.45 g (3.2 mmoles) of 2,4,5,6-tetraaminopyrimidine (**1**) and 3.2 mmoles 1,3-diaryl-2-propenone (chalcone) **2** in 15 ml of dry ethanol and 1 ml acetic acid was refluxed for 4 hours. The reaction mixture was neutralized with ammonia and cooled to 0°C. The precipitate that formed overnight was filtered off and recrystallized from methanol.

2,4-Diamino-7,8-dihydro-6,8-diphenyl-9*H*-pyrimido[4,5-*b*][1,4]-diazepine (**3a**).

The compound was obtained in a yield of 44%. The ms spectrum showed peaks at m/z (%) 330 (100, $M^{+\bullet}$), 315 (29), 253 (17, $M^{+\bullet}$ - C_6H_5), 226 (63), 104 (11), 103 (10).

Anal. Calcd. for $C_{19}H_{18}N_6$: C, 69.07; H, 5.49; N, 25.44. Found: C, 69.26; H, 5.46; N, 25.13.

2,4-Diamino-6-(4-chlorophenyl)-7,8-dihydro-8-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepine (**3b**).

The compound was obtained in a yield of 62%. Its ms spectrum showed peaks at m/z (%) 366/364 (17, $M^{+\bullet}$, Cl isotope pattern), 351/349 (23) 262/260 (100), 77 (18), 68 (20).

Anal. Calcd. for $C_{19}H_{17}ClN_6$: C, 62.55; H, 4.70; N, 23.03. Found: C, 62.41; H, 4.92; N, 23.26.

2,4-Diamino-7,8-dihydro-6-(4-nitrophenyl)-8-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepine (**3c**).

The compound was obtained in a yield of 81%. Its ms spectrum showed peaks at m/z (%) 375 (100, $M^{+\bullet}$), 360 (25), 298 (14, $M^{+\bullet}$ - C_6H_5), 271 (100), 253 (19), 227 (20), 225 (27), 104 (39), 102 (22), 77 (24).

Anal. Calcd. for $C_{19}H_{17}N_7O_2$: C, 60.79; H, 4.56; N, 26.12. Found: C, 60.50; H, 4.78; N, 26.18.

2,4-Diamino-7,8-dihydro-6-(4-methylphenyl)-8-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepine (**3d**).

The compound was obtained in a yield of 46%. Its ms spectrum showed peaks at m/z (%) 344 (42, $M^{+\bullet}$), 329 (42), 267 (16, $M^{+\bullet}$ - C_6H_5) 253 (29), 240 (100), 227 (17), 91 (16), 77 (17), 68 (13).

Anal. Calcd. for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.56; H, 5.86; N, 24.20.

2,4-Diamino-6-(4-bromophenyl)-7,8-dihydro-8-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepine (**3e**).

The compound was obtained in a yield of 76%. Its ms spectrum contained peaks at m/z (%) 410/408 (75, $M^{+\bullet}$, Br isotope pattern), 395/393 (22), 333/331 (6, $M^{+\bullet}$ - C_6H_5), 306/304 (70), 253 (21), 227 (31), 183 (21), 151 (16), 124 (31), 104 (62), 102 (67), 77 (36), 43 (100).

Anal. Calcd. for $C_{19}H_{17}BrN_6$: C, 55.76; H, 4.19; N, 20.53. Found: C, 55.77; H, 3.99; N, 20.36.

2,4-Diamino-7,8-dihydro-6-(4-methoxyphenyl)-8-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepine (**3f**).

The compound was obtained in a yield of 48%. Its ms spectrum contained peaks at m/z (%) 360 (100, $M^{+\bullet}$), 345 (38), 283 (5, $M^{+\bullet}$ - C_6H_5), 256 (24), 242 (5), 133 (7).

Anal. Calcd. for $C_{20}H_{20}N_6O$: C, 66.65; H, 5.59; N, 23.32. Found: C, 66.56; H, 5.74; N, 23.18.

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