Reaction of 4,5,6-Triaminopyrimidine and 2,4,5,6-Tetraaminopyrimidine with 3-Dimethylaminopropiophenones. Synthesis of New 4-Aryl-2,3-dihydropyrimido[4,5-*b*][1,4]diazepines

Braulio Insuasty O.,* Henry Insuasty I. and Jairo Quiroga P.

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

Claudio Saitz [a] and Carolina Jullian [b]

[a] Departamento de Química Orgánica y Fisico-Química, [b] CEPEDEQ, Facultad de Ciencias Químicas y Farmaceúticas, Universidad de Chile, Casilla 233 Santiago 1 - Chile

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Several new 6-amino- and 6,8-diamino-4-aryl-2,3-dihydropyrimido[4,5-*b*][1,4]diazepines were obtained from the reaction of 4,5,6-triaminopyrimidine **1a** and 2,4,5,6-tetraaminopyrimidine **1b** with one equivalent of 3-dimethylaminopropiophenones **2** in absolute ethanol. Structure analysis of 6-amino- and 6,8-diamino-4-aryl-2,3-dihydropyrimido[4,5-*b*][1,4]diazepines **3a-i**, determined by detailed nmr measurements, reveals a high regioselectivity of this reaction.

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Benzodiazepines are an important class of psychotherapeutic compounds. Although a benzene ring is usually needed for pharmacological activity, in recent years, however, some examples of heterocyclic rings fused to the seven-member diazepine ring system have appeared in literature [1,2]. In particular, good CNS activity was reported for various pyrazolodiazepines [3].

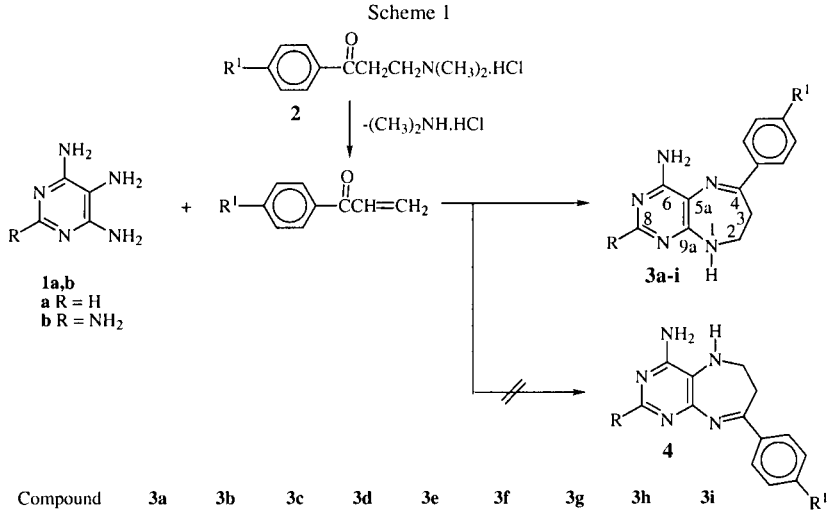
In previous papers [4-6], we reported the synthesis of pyrimidodiazepines from the reaction of 4,5-diaminopyrimidines with chalcones (α,β-unsaturated aromatic ketones). Because of the biological importance of these heterocycles, in this work we report on the reactivity of 4,5-diaminopyrimidines with 3-dimethylaminopropiophenones, as precursors of α,β-unsaturated ketones.

Reaction of 4,5,6-triaminopyrimidines (**1a, b**) with 3-dimethylaminopropiophenone hydrochlorides (**2**) in absolute ethanol under reflux afforded 6-amino-2,3-dihydro-4-arylpyrimido[4,5-*b*][1,4]diazepines (**3a-d**) and 6,8-diamino-2,3-dihydro-4-arylpyrimido[4,5-*b*][1,4]-diazepines (**3e-i**) in 35-65% yield (Scheme 1).

The uv/visible spectra of **3a-i** in ethanol contain three to four bands; most characteristic is an absorption maximum in the range of 268-296 nm and a second one shifted towards longer wavelengths ($359 \leq \lambda_{max} \leq 438$ nm). The ir spectra show typical bands between 3109 and 3535 cm^{-1} (NH and NH_2 groups) and 1529-1665 cm^{-1} (C=N and C=C groups).

The structure of compounds **3a-i** was confirmed by nmr measurements. ^{1}H-nmr data for all the products **3a-i** are summarized in Table 1. The 1-NH group of the diazepinic ring appears as a triplet at δ = 8.80-9.04 ppm for **3a-d** and 6.62-6.90 ppm for **3e-i** (one deuterium exchangeable

Scheme 1



Compound	3a	3b	3c	3d	3e	3f	3g	3h	3i
R	H	H	H	H	NH_2	NH_2	NH_2	NH_2	NH_2
R^1	H	Cl	Br	NO_2	H	CH_3O	Cl	Br	NO_2
mp, °C	275	254	253	242	215	212	250	250	285
Yield, %	40	50	45	65	40	35	55	50	65

proton), indicating the vicinal position of the geminal protons on C-2. The geminal protons on C-2 and C-3 appear as triplets at δ = 4.34-4.38 and 3.22-3.37 ppm for **3a-d** and 3.32-3.34 and 3.01-3.08 ppm for **3e-i** respectively. The coupling constant between them is ^3J = 7.0±0.1 Hz. In addition, two doublets are observed in the spectra of **3b-d**, **f-i** related to aromatic protons (δ = 6.93-8.57 ppm) with *ortho*-constant J = 7.1-8.9 Hz. The aromatic *meta/para*-protons for **3a** and **3e** appear as one multiplet. The assignment of the signals is supported by a ^1H, ^1H COSY and ^1H, ^{13}C shift correlation experiments.

Table 1

^1H-NMR data of **3a-i** (δ values, TMS as the Internal Standard, in DMSO-d_6, 300 MHz)

Compound	1-NH	2-CH_2	3-CH_2	6-NH_2	8-CH [a]	4-Ar		
	t	t	t	s	s	*ortho* (d)	*metha* (d)	*para*
3a	8.80	4.35	3.22	6.23	8.26	8.34	7.57-7.64	(m)
3b	8.90	4.35	3.30	6.64	8.25	8.33	7.61	----
3c	8.92	4.34	3.33	6.23	8.25	8.28	7.77	----
3d	9.04	4.38	3.37	6.46	8.27	8.57	8.34	----
3e	6.69	3.33	3.04	6.18	5.62	7.85	7.30-7.41	(m)
3f	6.62	3.33	3.01	6.15	5.58	7.82	6.93	----
3g	6.74	3.32	3.02	6.24	5.68	7.88	7.41	----
3h	6.72	3.32	3.01	6.19	5.64	7.81	7.54	----
3i	6.90	3.34	3.08	6.33	5.77	8.19	8.10	----

[a] For **3e-i** this signal corresponds to 8-NH_2. CH_3O for **3f** 3.79 ppm.

The final elucidation of structure of compounds **3a-i** was carried out by analysis of the ^{13}C-nmr spectra (Table 2). Signal assignment was made based on DEPT and two-dimensional experiments. Relevant features are as follows. The signal of C-2 is in the range δ 40.9-43.9 ppm whereas the signal of C-3 appears at δ 23.4-24.0 (for **3a-d**) and 34.5-34.8 ppm (for **3e-i**). A peak related to C-5a is at δ 100.7-107.2. In contrast, C-9a shows at δ 155.9-165.4 ppm. These findings can be explained in terms of the strong push-pull effect of the amino and C=N groups linked to the CC double bond in structures **3**. HMBC experiments show three-bond correlations between H1 and C-5a and between the geminal protons at position 2 and C-9a. These experiments rule out the formation of the regioisomeric product **4** (Scheme 1) and confirm that the title reaction proceeds *via* a two-step sequence, similar to that discussed in [4-6]. Thus, the initial step is the reaction of 4,5-diaminopyrimidines (**1**) with β-dimethylaminopropiophenones (**2**), through the condensation between the carbonyl group of **2** and the more nucleophilic amino group (5-NH_2 in **1**) [7-10]. In the second step, a Michael addition of the amino group at position 4 to the C=C double bond of the aryl vinyl ketone, formed by loss of one dimethylamine molecule, takes place.

EXPERIMENTAL

Melting points were taken on a Buchi melting point apparatus and are uncorrected. The UV-Vis and ir spectra were recorded on Philips PU-8600 and Nicolet FT-55X spectrophotometers, respectively. The ^1H- and ^{13}C nmr spectra were acquired on a Bruker AVANCE DRX 300 spectrometer in DMSO-d_6. The mass spectra were recorded on a Fisons-Platform interface APCI in MeOH. The elemental analyses have been obtained using a LECO CHNS-900 instrument.

6-Amino-2,3-dihydro-4-arylpyrimido[4,5-*b*][1,4]diazepines **3a-d** and 6,8-diamino-2,3-dihydro-4-arylpyrimido[4,5-*b*]-[1,4]diazepines **3e-i**.

General Procedure.

A solution of 3.2 mmoles of **1a, b** and 3.2 mmoles of a suitable 1-aryl-3-dimethylamino-1-propanone hydrochloride (3-dimethylaminopropiophenone) **2** was refluxed in 40 mL of absolute ethanol for 8-20 hours (tlc control). The reaction mixture was then cooled to 0°C overnight. The resulting solid was filtered and recrystallized from *p*-xylene. Yields and melting points are summarized in Scheme 1.

6-Amino-4-phenyl-2,3-dihydropyrimido[4,5-*b*][1,4]diazepine (**3a**).

Ir Data (KBr): 3148, 3343 for NH, NH_2 and 1662 for C=N, C=C. The mass spectrum shows $(M+H)^+$ = 240 (100).

Anal. Calcd. for $C_{13}H_{13}N_5$: C, 65.26; H, 5.48; N, 29.27. Found: C, 65.13; H, 5.52; N, 29.21.

Table 2

^{13}C-NMR data of **3a-i** (δ values, TMS as the Internal Standard, in DMSO-d_6, 300 MHz)

Compound		**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**
C-2		43.1	43.2	43.9	43.2	41.4	41.7	41.3	41.2	40.9
C-3		23.4	23.4	24.0	23.7	34.8	34.5	34.7	34.6	34.8
C-4		167.5	166.6	167.4	165.3	154.4	154.6	152.8	152.8	150.7
C-5a		106.2	106.0	107.2	106.0	100.9	101.0	100.9	100.7	101.0
C-6		149.6	148.9	147.6	148.4	160.5	160.3	160.6	160.6	161.0
C-8		156.2	156.3	151.8	149.2	164.1	163.9	164.2	164.2	164.5
C-9a		165.4	163.5	157.0	156.6	156.1	155.9	156.3	156.3	156.8
Ar	Ci	144.1	142.7	142.2	141.8	141.2	133.9	140.1	140.4	146.5
	$C_{o,m}$	128.2	128.7	130.9	123.5	126.3	113.7	128.1	128.4	123.5
		128.6	130.0	132.2	129.4	128.3	127.8	128.2	131.1	127.2
	C_p	128.7	130.3	123.5	141.2	128.2	159.8	132.9	121.7	147.1

CH_3O for **3f** 55.4 ppm.

6-Amino-4-(4-chlorophenyl)-2,3-dihydropyrimido[4,5-*b*]-[1,4]diazepine (**3b**).

Ir Data (KBr): 3182, 3251, 3328 for NH, NH_2 and 1576, 1619, 1659 for C=N, C=C. The mass spectrum shows $(M+H)^+$ = 273/275 (100/34).

Anal. Calcd. for $C_{13}H_{12}N_5Cl$: C, 57.04; H, 4.42; N, 25.59. Found: C, 57.12; H, 4.36; N, 25.49.

6-Amino-4-(4-bromophenyl)-2,3-dihydropyrimido[4,5-*b*]-[1,4]diazepine (**3c**).

Ir Data (KBr): 3184, 3253, 3324, 3379 for NH, NH_2 and 1576, 1619, 1658 for C=N, C=C. The mass spectrum shows $(M+H)^+$ = 317/319 (100/96).

Anal. Calcd. for $C_{13}H_{12}N_5Br$: C, 49.07; H, 3.80; N, 22.01. Found: C, 49.14; H, 3.72; N, 22.12.

6-Amino-4-(4-nitrophenyl)-2,3-dihydropyrimido[4,5-*b*]-[1,4]diazepine (**3d**).

Ir Data (KBr): 3152, 3256, 3350, 3439 for NH, NH_2, 1604, 1625, 1665 for C=N, C=C and 1345, 1512 for NO_2 group. The mass spectrum shows $(M+H)^+$ = 285 (100).

Anal. Calcd. for $C_{13}H_{12}N_6O_2$: C, 54.93; H, 4.25; N, 29.56. Found: C, 54.87; H, 4.22; N, 29.65.

6,8-Diamino-4-phenyl-2,3-dihydropyrimido[4,5-*b*][1,4]-diazepine (**3e**).

Ir Data (KBr): 3308, 3350, 3407, 3454 for NH, NH_2 and 1531, 1562, 1658 for C=N, C=C. The mass spectrum shows $(M+H)^+$ = 255 (100).

Anal. Calcd. for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.30; H, 5.46; N, 33.15.

6,8-Diamino-4-(4-methoxyphenyl)-2,3-dihydropyrimido[4,5-*b*]-[1,4]diazepine (**3f**).

Ir Data (KBr): 3180, 3347, 3448 for NH, NH_2 and 1529, 1595, 1655 for C=N, C=C. The mass spectrum shows $(M+H)^+$ = 285 (100).

Anal. Calcd. for $C_{14}H_{16}N_6O$: C, 59.14; H, 5.67; N, 29.56. Found: C, 59.18; H, 5.65; N, 29.48.

6,8-Diamino-4-(4-chlorophenyl)-2,3-dihydropyrimido[4,5-*b*]-[1,4]diazepine (**3g**).

Ir Data (KBr): 3134, 3246, 3473 for NH, NH_2 and 1535, 1586, 1628 for C=N, C=C. The mass spectrum shows $(M+H)^+$ = 289/291 (100/35).

Anal. Calcd. for $C_{13}H_{13}N_6Cl$: C, 54.08; H, 4.54; N, 29.11. Found: C, 54.14; H, 4.52; N, 29.18.

6,8-Diamino-4-(4-bromophenyl)-2,3-dihydropyrimido[4,5-*b*]-[1,4]diazepine (**3h**).

Ir Data (KBr): 3134, 3247, 3370, 3466 for NH, NH_2 and 1534, 1585, 1628 for C=N, C=C. The mass spectrum shows $(M+H)^+$ = 333/335 (100/97).

Anal. Calcd. for $C_{13}H_{13}N_6Br$: C, 46.86; H, 3.93; N, 25.22. Found: C, 46.81; H, 3.86; N, 25.29.

6,8-Diamino-4-(4-nitrophenyl)-2,3-dihydropyrimido[4,5-*b*]-[1,4]diazepine (**3i**).

Ir Data (KBr): 3109, 3247, 3435, 3535 for NH, NH_2, 1529, 1585 for C=N, C=C and 1334, 1506 for NO_2 group. The mass spectrum shows $(M+H)^+$ = 300 (100).

Anal. Calcd. for $C_{13}H_{13}N_7O_2$: C, 52.17; H, 4.38; N, 32.76. Found: C, 52.24; H, 4.34; N, 32.82.

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