Synthesis of 2-Aryl-2,3-dihydro-4-styrylpyrimidodiazepines in the Reaction of 4,5,6-Triaminopyrimidine and 2,4,5,6-Tetraaminopyrimidine with Diarylidenacetones

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New 6-amino and 6,8-diamino-2-aryl-2,3-dihydro-4-styryl-1*H*-pyrimido[4,5-*b*][1,4]diazepines were obtained in the reaction of 2,4,5,6-tetraaminopyrimidine **1a** and 4,5,6-triaminopyrimidine **1b** with one equivalent of the diarylideneacetones **2** in absolute ethanol with acetic acid as the catalyst. Structure analysis of 6-amino and 6,8-diamino-2-aryl-2,3-dihydro-4-styryl-1*H*-pyrimido[4,5-*b*][1,4]diazepines **3a-i**, determined by detailed nmr measurements, reveals a high regioselectivity of this reaction.

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Introduction.

The reactions of aromatic and heterocyclic 1,2-diamines with α,β-unsaturated ketones opens the way to the synthesis of 5-, 6-, and 7-membered nitrogen heterocycles [1,2]. A feature of these reactions is their high regioselectivity but the actual direction of the reaction in the case of diarylideneacetones is usually quite complex.

The aim of this work was the study of the reaction of 2,4,5,6-tetraaminopyrimidine **1a** and 4,5,6-triaminopyrimidine **1b** with diarylideneacetones **2**. Instead of the usual systematic series of ketones traditional for such investigations, we have studied the reaction of the symmetric and asymmetric diarylideneacetones showing a difference in the electronic character of C=C double bonds.

Results and Discussion.

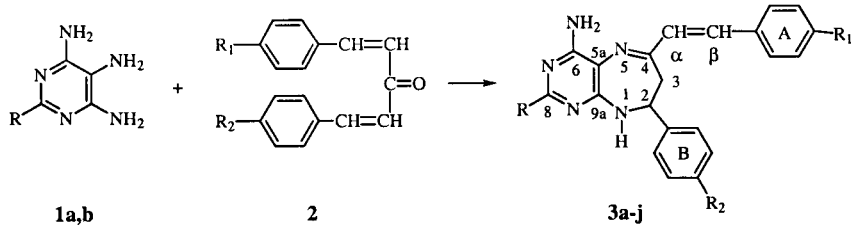
Diamines **1** react with ketones **2** in refluxing ethanol in the presence of acetic acid as the catalyst. The 2-aryl-2,3-dihydro-4-styryl-1*H*-pyrimido[4,5-*b*][1,4]diazepines **3a-i** are formed in good yields (Scheme 1).

Formation of diazepines **3a-i** is supported by elemental analytical and spectroscopic parameters, which are similar to analogous products obtained in the reaction of others *ortho*-diamines with diarylideneacetones [3,4].

The uv/visible spectrum of **3a-i** in ethanol contains three bands; most characteristic is an absorption maximum in the range of 263-284 nm and a second one shifted towards longer wavelengths ($385 \leq \lambda_{max} \leq 444$ nm).

The structure of compounds **3** was confirmed by nmr measurements. The ^{1}H-nmr spectra of **3a-i** showed the geminal protons joined to C-3 at 3.65-3.93 ppm and 2.57-2.68 ppm respectively and the methynic proton joined to C-2 at 4.89-5.17 ppm. This CH_2-CH fragment describes a AMX system with the following coupling constants: $J_{a,m}$ = -14.7 Hz, $J_{a,x}$ = 0-1.7 Hz and $J_{m,x}$ =

Scheme 1



1a,b **2** **3a-j**

Compound	R	R_1	R_2	mp, °C	Yield,%
3a	NH_2	H	H	122	78
3b	NH_2	NO_2	H	270	88
3c	NH_2	CH_3	CH_3	150 (d)	70
3d	NH_2	Cl	Cl	159 (d)	90
3e	NH_2	NO_2	NO_2	212	85
3f	H	H	H	282	73
3g	H	CH_3	CH_3	271	71
3h	H	Cl	Cl	294	62

5.0-6.0 Hz. The proton of the 1-NH group appear as a doublet at δ = 6.97-7.65 ppm with $J_{NH,x}$ = 5.0-6.0 Hz, vinylic *trans* configuration. The ^{1}H-nmr data for all the products **3a-h** are summarized in Table 1.

Table 1

^{1}H-NMR Chemical Shifts (δ) for Compounds **3a-h** (Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide, 300 MHz)

Compound	1-NH [1]	6-NH_2 [1]	8-NH_2 [1]	H_a	H_m	H_X [2]	H_α	H_β	Aryl A			Aryl B			8-H
	d	s	s	dd	dd	t	d	d	H_o	H_m	H_p	H_o	H_m	H_p	
3a	7.05	6.25	5.75	2.61	3.75	4.95	6.75	6.85		7.50-7.20			7.20-7.00		---
3b	7.15	6.40	5.85	2.61	3.77	4.95	7.07	6.93	7.78	8.16	---		7.27-7.15		---
3c	6.97	6.27	5.70	2.58	3.65	4.89	6.75	6.82	7.13	7.35	---	7.02	7.07	---	---
3d	7.15	6.32	5.77	2.57	3.73	4.98	6.86	6.79	7.37	7.47	---	7.19	7.26	---	---
3e	7.54	6.58	6.07	2.66	3.93	5.17	6.98	7.07	8.12	8.17	---	7.68	7.46	---	---
3f	7.59	6.59	---	2.68	3.76	5.10	6.83	6.95		7.50-7.20			7.20-7.00		7.75
3g	7.52	6.56	---	2.66	3.71	5.01	6.81	6.94	7.37	7.15	---	7.07	7.03	---	7.73
3h	7.65	6.61	---	2.67	3.78	5.09	6.85	6.98	7.50	7.41	---	7.20	7.30	---	7.76

CH_3 groups 2.17, 2.27 ppm for **3c** and 2.17, 2.29 ppm for **3g**. [1] Disappear with deuterium oxide. [2] Collapse to a doublet with deuterium oxide.

indicating the vicinal position of the protons on C-2. In addition, two singlets and a multiplet are observed in the spectra of **3a-i**, which are related to the NH_2 groups at C-6 and C-8 (δ = 6.25-6.61 ppm and 5.70-6.07 ppm) and aromatic protons (δ = 7.00-8.17 ppm), respectively. In fact, for compounds **3f-h** we observed complete disappearance of one NH_2 group and the appearance of a new signal ascribed to the proton at position 8 of the pyrimidodiazepine ring at 7.73-7.76 ppm. Protons α and β appear as doublets at 6.75-7.07 ppm and 6.79-7.07 ppm respectively. The $J_{\alpha,\beta}$ value 16.6 Hz is indicative of the

The final elucidation of structure of compounds **3a-h** was carried out by analysis of the ^{13}C-nmr spectra (Table 2). Signal assignments were made based on DEPT and bidimensional experiments.

Relevant features are as follows. The signal of C-2 is in the range 55.3-57.4 ppm whereas the signal of C-3 appears at 36.7-37.6 ppm. A peak related to C-5a is at 101.9-107.3 ppm. In contrast, C-9a shows at 153.2-155.0 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**.

Table 2

^{13}C NMR Data of **3a-h** (δ values, Tetramethylsilane as the Internal Standard, in Dimethyl-d_6 Sulfoxide. 90 MHz)

Compound	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
C-2	55.8	55.4	55.3	55.3	55.4	57.4	56.8	57.0
C-3	37.0	37.0	37.1	37.0	36.7	37.6	37.6	37.5
C-4	153.8	152.5	153.9	153.4	152.7	160.6	160.6	160.2
C-5a	101.9	102.3	101.9	102.1	102.1	107.2	107.2	107.3
C-6	160.5	160.9	160.4	160.7	160.0	162.1	162.1	161.2
C-8	163.5	163.8	163.5	163.7	163.2	155.3	155.2	155.4
C9a	154.7	155.0	154.7	154.8	154.5	153.3	153.3	153.2
C_α	133.6	138.1	132.8	134.4	137.7	132.9	132.9	133.3
C_β	129.8	126.5	129.8	128.4	127.6	128.2	129.3	131.6
Aryl A								
C_i	143.5	144.0	134.1	135.9	143.8	143.2	133.6	135.2
C_o	129.8	127.0	126.4	128.2	127.2	128.6	126.8	128.4
C_m	128.6	123.9	129.2	128.6	124.0	127.9	129.3	128.7
C_p	133.6	145.8	137.1	132.0	146.2	132.6	137.8	132.6
CH_3	---	---	20.4	---	---	---	20.5	---
Aryl B								
C_i	136.8	143.3	140.5	142.5	150.6	136.2	140.3	142.1
C_o	125.7	125.6	125.6	127.7	127.1	125.7	125.7	127.7
C_m'	126.4	127.9	128.5	127.9	123.2	126.4	128.5	127.9
C_p	127.6	127.9	135.4	131.1	146.0	126.8	135.5	131.1
CH_3	---	---	20.7	---	---	---	20.8	---

Assignment of the ^1H and ^{13}C resonances of compounds **3** was deduced from the concerted application of both direct and long-range heteronuclear chemical shift correlation experiments. One-bond proton-carbon chemical shift correlations were established using the HMQC sequence and $(CH)_n$ groups were unambiguously characterized from the analysis of long-range correlation responses over two and three bonds (^2J or ^3J couplings) using the HMBC technique. The HMBC experiments indicate three-bond correlations between 1-NH proton and C-5a and between 2-CH_2-protons and C-9a. These experiments rule out the formation of the regioisomeric product **4** (Scheme 2) and confirm that the title reaction proceeds *via* a two-step sequence, similar to that discussed in references [5-8]. This procedure was exemplified for compound **3d** for which the most important connectivities observed in the HMBC diagram are given in Table 3.

Scheme 2

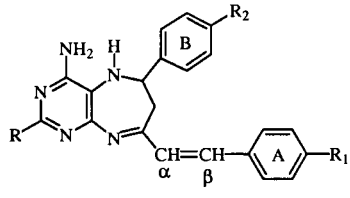


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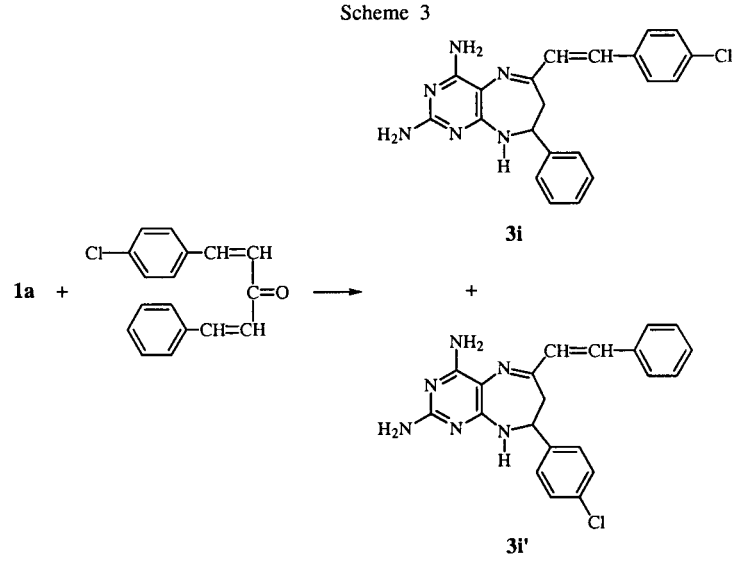
Table 3
Long-range Proton-carbon Couplings found in the HMBC Spectra of Compound **3d**
Protons showing HMBC correlation (^2J and ^3J couplings)

Carbon	^2J	^3J
C-2	1-NH, 3-H	H_o (B)
C-3	2-H	1-NH, C_α
C-4	3-H, H_α	2-H, H_β
C-5a	---	1-NH
C-9a	1-NH	2-H
C_α	C_β	3-H
C_β	C_α	H_o (A)

It is important to stand out that the reaction of compound **1a** with the benzylidene-(4-chlorobenzylidene)-acetone under the same conditions leads to the formation of the mixture of regioisomeric products **3i** and **3i'** (Scheme 3), which were impossible to separate by the usual chromatographic methods. In this case, we consider that the presence of a chlorine atom does not produce marked difference in the electronic density over the two vinyl groups in the unsaturated ketone, which, however, is possible when the electron-withdrawing nitro-group is present in the ketone. In such a situation, due to the diference of the vinyl groups, only compound **3b** is obtained.

Scheme 3



3i

3i'

EXPERIMENTAL

Melting points were taken on a Büchi Melting Point Apparatus and are uncorrected. The ^1H-and ^{13}C nmr spectra were obtained on a Bruker DPX 300 spectrometer operating at 300 MHz and 75 MHz respectively, in dimethyl-d_6 sulfoxide as the solvent and tetramethylsilane as the internal standard. 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 LECO CHNS-900 equipment.

General Procedure for the Preparation of 6,8-Diamino-2-aryl-2,3-dihydro-4-styryl-1*H*-pyrimido[4,5-*b*][1,4]diazepines and 6-Amino-2-aryl-2,3-dihydro-4-styryl-1*H*-pyrimido[4,5-*b*]-[1,4]diazepines **3a-i**.

A solution of 1.40 mmoles of **1a,b** and 1.40 mmoles of diarylideneacetone **2** and acetic acid (1 ml) was refluxed in 50 ml of absolute ethanol for 10-20 hours (tlc control). After neutralizing with ammonia and cooling to 0°, the reaction mixture was allowed to stand overnight. The resulting precipitate was filtered and purified by silica gel chromatography with ethyl acetate as the eluent. The yields and melting points are summarized in Table 1.

6,8-Diamino-2,3-dihydro-2-phenyl-4-styryl-1*H*-pyrimido-[4,5-*b*][1,4]diazepine **3a**.

This compound was obtained by the general procedure as a yellow powder; ir (potassium bromide): ν 3192, 3318, 3460 for NH and NH_2, 1549, 1578 for C=N and C=C; ms: (70 eV) m/z (%) 356 (100, M^+), 341 (19), 265 (11), 251 (8), 227 (4), 214 (8), 180 (4), 176 (4), 128 (6), 115 (6), 106 (5), 104 (9), 91 (8), 82 (5), 78 (6), 77 (13), 68 (10), 55 (7), 51 (8), 43 (32).

Anal. Calcd. for $C_{21}H_{20}N_6$: C, 70.77; H, 5.66; N, 23.58. Found: C, 70.62; H, 5.62; N, 23.41.

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

This compound was obtained by the general procedure as a red powder; ir (potassium bromide): ν 3248, 3408, 3448 for NH

and NH_2, 1548, 1584 for C=N and C=C; ms: (70 eV) m/z (%) 401 (100, M^+), 384 (10), 356 (8), 313 (5), 299 (9), 264 (80), 226 (30), 209 (7), 164 (12), 137 (18), 104 (20), 91 (22), 77 (21), 43 (25).

Anal. Calcd. for $C_{21}H_{19}N_7O_2$: C, 62.83; H, 4.77; N, 24.42. Found: C, 62.49; H, 4.71; N, 24.53.

6,8-Diamino-2,3-dihydro-2-(*p*-methylphenyl)-4-(*p*-methylstyryl)-1*H*-pyrimido[4,5-*b*][1,4]diazepine **3c**.

This compound was obtained by the general procedure as a yellow powder; ir (potassium bromide): ν 3181, 3320, 3385, 3470 for NH and NH_2, 1550, 1579 for C=N and C=C; ms: (70 eV) m/z (%) 384 (100, M^+), 369 (20), 279 (19), 265 (14), 228 (16), 208 (10), 176 (4), 157 (5), 128 (6), 91 (5), 68 (3), 43 (13).

Anal. Calcd. for $C_{23}H_{24}N_6$: C, 71.85; H, 6.29; N, 21.86. Found: C, 71.79; H, 6.34; N, 21.77.

6,8-Diamino-2-(*p*-chlorophenyl)-4-(*p*-chlorostyryl)-2,3-dihydro-1*H*-pyrimido[4,5-*b*][1,4]diazepine **3d.**

This compound was obtained by the general procedure as a yellow powder; ir (potassium bromide): ν 3329, 3385, 3470 for NH and NH_2, 1549, 1580 for C=N and C=C; ms: (70 eV) m/z (%) 428/426/424 (12/40/100, M^+), 409 (14), 382 (2), 299 (15), 286 (13), 248 (22), 176 (7), 164 (4), 128 (5), 68 (3), 43 (13).

Anal. Calcd. for $C_{21}H_{18}N_6Cl_2$: C, 59.30; H, 4.27; N, 19.76. Found: C, 59.25; H, 4.22; N, 19.72.

6,8-Diamino-2,3-dihydro-2-(*p*-nitrophenyl)-4-(*p*-nitrostyryl)-1*H*-pyrimido[4,5-*b*][1,4]diazepine **3e**.

This compound was obtained by the general procedure as a red powder; ir (potassium bromide): ν 3241, 3364, 3488 for NH and NH_2, 1549, 1593 for C=N and C=C; ms: (70 eV) m/z (%) 446 (10, M^+), 401 (11), 324 (48), 313 (23), 309 (29), 308 (10), 307 (32), 277 (26), 176 (26), 164 (27), 150 (28), 137 (89), 102 (32), 91 (77), 77 (41), 65 (57), 51 (24), 43 (52).

Anal. Calcd. for $C_{21}H_{18}N_8O_4$: C, 56.50; H, 4.06; N, 25.10. Found: C, 56.40; H, 4.17; N, 25.18.

6-Amino-2,3-dihydro-2-phenyl-4-styryl-1*H*-pyrimido[4,5-*b*]-[1,4]diazepine **3f**.

This compound was obtained by the general procedure as a yellow powder; ir (potassium bromide): ν 3081, 3202, 3446 for NH and NH_2, 1558, 1583, 1608 for C=N and C=C; ms: (70 eV) m/z (%) 341 (100, M^+), 326 (13), 264 (5), 250 (19), 236 (17), 180 (9), 161 (6), 144 (9), 128 (7), 115 (4), 77 (6), 43 (4).

Anal. Calcd. for $C_{21}H_{19}N_5$: C, 73.88; H, 5.61; N, 20.51. Found: C, 73.94; H, 5.55; N, 20.55.

6-Amino-2,3-dihydro-2-(*p*-methylphenyl)-4-(*p*-methylstyryl)-1*H*-pyrimido[4,5-*b*][1,4]diazepine **3g**.

This compound was obtained by the general procedure as a yellow powder; ir (potassium bromide): ν 3208, 3441, 3460 for NH and NH_2, 1557, 1613 for C=N and C=C; ms: (70 eV) m/z (%) 369 (100, M^+), 354 (23), 264 (30), 250 (21), 213 (7), 208 (11), 158 (10), 128 (7), 91 (4), 77 (2), 43 (3).

Anal. Calcd. for $C_{23}H_{23}N_5$: C, 74.77; H, 6.27; N, 18.96. Found: C, 74.69; H, 6.22; N, 19.04.

6-Amino-2-(*p*-chlorophenyl)-4-(*p*-chlorostyryl)-2,3-dihydro-1*H*-pyrimido[4,5-*b*][1,4] diazepine **3h**.

This compound was obtained by the general procedure as a yellow powder; ir (potassium bromide): ν 3218, 3255, 3440 for NH and NH_2, 1557, 1581, 1615 for C=N and C=C; ms: (70 eV) m/z (%) 413/411///409 (11, 78, 100, M^+), 396 (11), 394 (16), 284 (41), 270 (29), 248 (18), 233 (20), 231 (17), 178 (15), 161 (13), 140 (8), 128 (13), 124 (13), 95 (13), 77 (5), 32 (10).

Anal. Calcd. for $C_{21}H_{17}N_5Cl_2$: C, 61.47; H, 4.18; N, 17.07. Found: C, 61.52; H, 4.22; N, 17.17.

6,8-Diamino-4-(*p*-chlorostyryl)-2,3-dihydro-2-phenyl-1*H*-pyrimido[4,5-*b*][1,4]diazepine **3i** and 6,8-Diamino-4-(*p*-chlorophenyl)-2,3-dihydro-2-styryl-1*H*-pyrimido[4,5-*b*]-[1,4]diazepine **3i'**.

This mixture was obtained by the general procedure as yellow powder; ir (potassium bromide): ν 3347, 3384, 3469 for NH and NH_2, 1555, 1578 for C=N and C=C; ^{1}H-nmr (dimethyl-d_6 sulfoxide, ppm): 7.06/7.12 (1H, d, 1-NH), 6.28 (2H, s, 6-NH_2), 5.74 (2H, s, 8-NH_2), 2.57/2.60 (1H, dd, H_a), 3.65/3.73 (1H, dd, H_m), 4.96/4.98 (1H, t, H_x), 6.78/6.79 (1H, d, H_α), 6.84/6.85 (1H, d, H_β); ^{13}C-nmr (dimethyl-d_6 sulfoxide, ppm): 55.3/55.8 (C-2), 36.8/37.1 (C-3), 153.5/153.7 (C-4), 102.0 (C-5a), 154.6/154.8 (C-9a), 133.6/134.4 (C_α), 128.3/129.9 (C_β); ms: (70 eV) m/z (%) 392/390 (16/47, M^+), 128 (12), 82 (15), 55 (26), 43 (100).

Anal. Calcd. for $C_{21}H_{19}N_6Cl$: C, 64.53; H, 4.90; N, 21.50. Found: C, 64.44; H, 4.86; N, 21.42.

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