# Synthesis of 2,3-Dihydropyrido- and 2,3-Dihydropyrimido-[1,4]diazepines from Triaminopyridine and Triaminopyrimidine



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The reaction of 2,3,6-triaminopyridine **1** and 4,5,6-triaminopyrimidine **2** with one equivalent of the chalcones **3**, in acetic acid, leads to the formation of the 8-amino-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]diazepine and 6-amino-2,3-dihydro-1*H*-pyrimido[4,5-*b*][1,4]diazepine derivatives **4** and **5**. The products were characterized by NMR techniques such as $^{13}C$, $^{1}H$, and DEPT including selective $^{13}C\{^{1}H\}$ decoupling experiments.

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Derivatives of 1*H*-1,4-diazepine have properties of biological and pharmacological interest [1-3]. The reaction of aromatic and heterocyclic 1,2-diamines with α,β-unsaturated ketones (chalcones) is a very convenient and versatile method for the preparation of condensed 1,4-diazepine systems [4-11]. A predominant feature of these reactions is their high regioselectivity.

The purpose of this work was to study the reaction of 2,3,6-triaminopyridine (1) and 4,5,6-triaminopyrimidine (**2**) with chalcones **3**, a synthetic route for 8-amino-2,4-diaryl-2,3-dihydro-1*H*-pyrimido[2,3-*b*][1,4]diazepines **4** and 6-amino-2,4-diaryl-2,3-dihydro-1*H*-pyrimido [4,5-*b*]-[1,4]diazepines **5**.

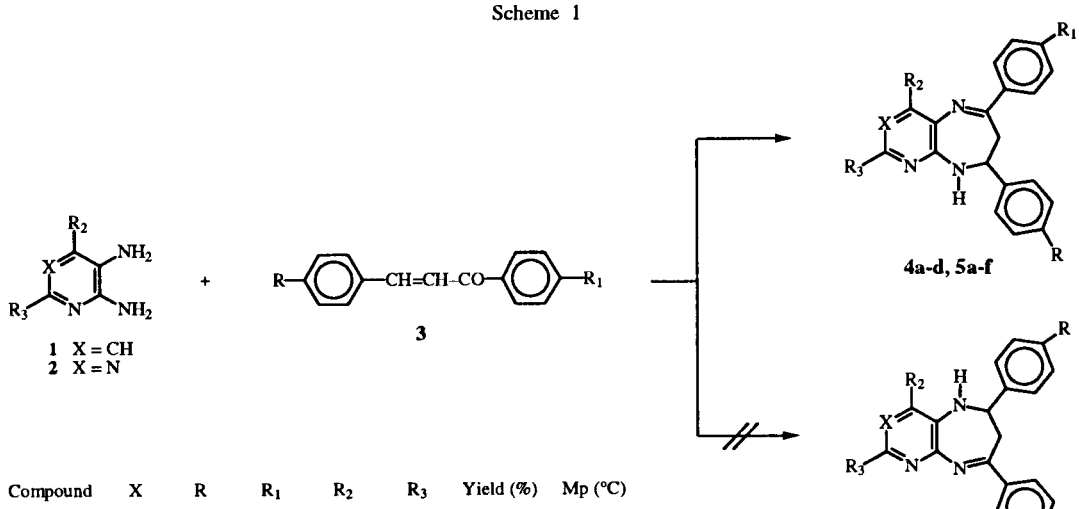
Upon heating, triamines **1** and **2** react with equimolar amounts of 1,3-diaril-2-propenones in ethanol solution, in the presence of catalytic amounts of acetic acid, to generate the desired structures **4a-d** and **5a-f** in good yields.

Because triamines **1** and **2** contain non-equivalent amino groups at the *ortho*-position, the regioisomeric cyclization products **4, 5** and **4', 5'** were expected. However, the formation of a single product was observed in both reactions. We assume that, in the initial step, a condensation reaction between the carbonyl group of **3** and the more nucleophilic amino group (3-$NH_2$ in **1** and 5-$NH_2$ in **2**, respectively) takes place [12-15]. In the second step, a Michael's addition of the less nucleophilic amino group (at the *ortho* position in 1 and 2) to the C=C double bond may occur.

The ir spectra show typical bands between 3330 and 3420 $cm^{-1}$ (N-H), 1600 and 1620 $cm^{-1}$ (C=N). In addition, compounds **4** and **5c** present absorption at 1340-1530 $cm^{-1}$ ($NO_2$ stretching vibrations).

The $^{1}H$-nmr data for all the products are summarized in Table 1. The proton on N-1 gives rise to a doublet (δ = 5.24-5.56, for **4** and 7.50-7.88, for **5**, $^{3}J$ = 4.9 ±0.3

Scheme 1




| Compound | X | R | $R_1$ | $R_2$ | $R_3$ | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|---|---|
| **4a** | CH | Cl | $NO_2$ | H | $NH_2$ | 35 | 156 |
| **4b** | CH | Br | $NO_2$ | H | $NH_2$ | 45 | 175 |
| **4c** | CH | H | $NO_2$ | H | $NH_2$ | 40 | 168 |
| **4d** | CH | $NO_2$ | $NO_2$ | H | $NH_2$ | 58 | 188 |
| **5a** | N | H | H | $NH_2$ | H | 77 | 212-213 |
| **5b** | N | H | Cl | $NH_2$ | H | 77 | 249-251 |
| **5c** | N | H | $NO_2$ | $NH_2$ | H | 68 | 292-294 |
| **5d** | N | H | $CH_3$ | $NH_2$ | H | 52 | 232 |
| **5e** | N | H | Br | $NH_2$ | H | 49 | 219-220 |
| **5f** | N | | $OCH_3$ | $NH_2$ | | 48 | 240-242 |

Hz), indicating coupling to the vicinal proton on C-2 (poorly resolved triplet at δ = 4.91-5.35 ppm). The geminal protons on C-3 are at δ = 2.82-4.08 ppm (two doublets of doublets) and the coupling constant between them is $^2J$ = -14.7 ±0.1 Hz. Vecinal coupling of geminal protons to 2-H are characterized by $_3J_{trans}$ = 6.0 ±0.2 Hz and $^3J_{cis}$ = 1.2 ±0.2 Hz. Protons in the amino groups appear as singlets at δ = 4.47-4.59 and 7.77-7.92 ppm, for **4** and **5**, respectively. In addition, two doublets are observed in the spectra of **4** related to protons 6H (δ = 7.52-7.57 ppm) and 7H (δ = 6.09-6.14 ppm) with *ortho*-constant J = 8.2 Hz.

The $^{13}$C-nmr data of **4** and **5** are summarized in Table 2. Signal assignment was made based on DEPT experiments and data from our previous work [9,10]. Relevant features are as follows. The signal of C-5a appear at δ 100.3-101.0 and 106.8-107.2 ppm for **4** and **5**, respectively. On the other hand, C-9a shows at δ 156.6-162.3 ppm. These findings can be explained in terms of the strong pushpull effect of the amino and C=N groups linked to the C=C double bond in structures **4** and **5**. The isomeric structures **4'** and **5'** were ruled out by results from selective low-power $^{13}$C, $^1$H decoupling experiments. In fact, C-5a in **4** and **5** show as doublets with $^3J$= 5.3-5.5 Hz in the coupled $^{13}$C nmr spectra. Radiation onto the proton signal of 1N-H turns the C-5a signal into a singlet. Thus, the single frequency decoupling experiments are consistent with the structures **4** and **5** only.

No additional structural information was attained from the mass spectra of **4** and **5**, was observed. All compounds show well-defined molecular ions and characteristic molecular-ion fragmentation patterns [16].

Table 1

$^1$-NMR Data of **4** and **5** (δ values, TMS as the Internal Standard, in DMSO-$d_6$, 400 MHz)

| Compound | 1-H | 2-H | 3-H | 6-H | 7-H | 6-$NH_2$ | 8-$NH_2$ | 8-CH | 2-Ar | 4-Ar | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | d | t | dd dd | | | s | | s | | | |
| 4a [a] | 5.56 | 4.95 | 3.20 3.58 | 7.52 | 6.10 | --- | 4.59 | --- | 7.14-7.30 | 7.73-8.15 | |
| 4b [a] | 5.24 | 4.91 | 3.24 3.63 | 7.55 | 6.09 | --- | 4.47 | --- | 7.11-7.47 | 7.72-8.18 | |
| 4c [a] | 5.40 | 4.93 | 3.22 3.28 | 7.56 | 6.09 | --- | 4.53 | --- | 7.20-7.32 | 7.73-8.13 | |
| 4d [a] | 5.32 | 5.18 | 3.22 3.43 | 7.57 | 6.14 | --- | 4.50 | --- | 7.41-8.12 | 7.71-8.16 | |
| 5a | 7.76 | 5.30 | 3.00 3.91 | --- | --- | 7.90 | --- | 6.04 | 7.19-7.41 | 7.29-7.76 | |
| 5b | 7.67 | 5.31 | 2.96 3.93 | --- | --- | 7.91 | --- | 6.08 | 7.20-7.32 | 7.37-7.80 | |
| 5c | 7.88 | 5.35 | 2.98 4.08 | --- | --- | 7.92 | --- | 5.94 | 7.17-7.36 | 7.96-8.18 | |
| 5d | 7.58 | 5.30 | 2.98 3.90 | --- | --- | 7.90 | --- | 5.73 | 7.12-7.40 | 7.12-7.72 | 2.38 ($CH_3$) |
| 5e | 7.88 | 5.18 | 2.82 3.80 | --- | --- | 7.77 | --- | 6.01 | 7.04-7.22 | 7.35-7.62 | |
| 5f | 7.50 | 5.27 | 2.96 3.88 | --- | --- | 7.88 | --- | 5.68 | 7.18-7.36 | 6.87-7.77 | 3.86 ($OCH_3$) |

[a] Measurements in deuteriochloroform.

Table 2

$^{13}$C-nmr Data of **4** and **5** (δ values, TMS as the Internal Standard, in DMSO-$d_6$, 400 MHz)

| Compound | | 4a [a] | 4b [a] | 4c [a] | 4d [a] | 5a | 5b | 5c | 5d | 5e | 5f |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | C-2 | 60.7 | 60.5 | 61.1 | 60.9 | 59.2 | 59.1 | 58.8 | 59.2 | 58.9 | 59.4 |
| | C-3 | 40.5 | 40.6 | 41.0 | 39.7 | 39.5 | 39.2 | 39.2 | 39.2 | 39.3 | 39.1 |
| | C-4 | 156.3 [b] | 156.5 [b] | 156.4 [b] | 162.0 [b] | 162.4 [b] | 162.4 | 162.8 | 162.4 [b] | 162.3 [b] | 162.2 [b] |
| | C-5a | 100.9 | 100.6 | 100.3 | 101.0 | 107.1 | 107.0 | 107.0 | 107.2 | 106.8 | 107.2 |
| | C-6 | 146.5 | 146.1 | 146.3 | 156.3 | 153.5 | 153.6 | 153.7 | 153.6 | 153.4 | 153.8 |
| | C-7 | 120.9 | 121.9 | 120.3 | 120.5 | --- | --- | --- | --- | --- | -- |
| | C-8 | 147.8 | 147.9 | 147.8 | 156.5 | 155.4 | 155.2 | 156.2 | 155.4 | 155.3 | 155.2 |
| | C-9a | 156.6 [b] | 156.6 [b] | 157.1 [b] | 162.3 [b] | 161.1 [b] | 159.8 | 158.3 | 161.2 [b] | 159.7 [b] | 161.5 [b] |
| Ar | $C_i$ | 141.9 | 142.3 | 143.3 | 144.0 | 140.3 | 139.0 | 143.8 | 137.6 | 139.2 | 133.2 |
| | | 143.3 | 143.9 | 144.0 | 145.8 | 144.1 | 144.0 | 146.9 [b] | 138.8 | 143.7 | 144.2 |
| | $C_{o,m}$ | 123.3 | 123.5 | 123.4 | 123.5 | 126.0 | 125.9 | 123.1 | 126.0 | 125.6 | 113.2 |
| | | 127.3 | 127.1 | 126.1 | 124.1 | 126.8 | 127.9 | 125.8 | 126.8 | 127.9 | 126.0 |
| | | 127.7 | 127.8 | 127.1 | 127.0 | 128.0 | 128.1 | 127.9 | 128.2 | 128.6 | 128.1 |
| | | 131.9 | 132.1 | 128.9 | 127.1 | 128.1 | 128.6 | 128.2 | 128.8 | 130.7 | 128.8 |
| | $C_p$ | 120.9 | 120.4 | 128.1 | 149.9 | 126.8 | 126.9 | 127.0 | 126.8 | 122.6 | 127.0 |
| | | 150.2 | 150.1 | 150.2 | 150.0 | 129.1 | 133.9 | 145.9 [b] | 144.2 | 126.7 | 160.6 |
| | | | | | | | | | 20.8 ($CH_3$) | | 55.4 ($OCH_3$) |

[a] Measurements in deuteriochloroform. [b] Interchangeable signals.

## EXPERIMENTAL

Melting points are uncorrected. The ir spectra were obtained in potassium bromide pellets with a Perkin-Elmer 599B spectrometer. The $^1H$ -and $^{13}C$ nmr spectra were run on a Bruker AM 400, in deuteriochloroform or DMSO-$d_6$. The mass-spectra were recorded on either Varian MAT 711 and Finnigan M 95, at 70 eV. Elemental analysis was done on a LECO CHNS-900.

8-Amino-2,3-dihydro-2,4-diphenyl-1*H*-pyrido[2,3-*b*]-[1,4]diazepines **4a-d**, and 8-Amino-2,3-dihydro-2,4-diphenyl-1*H*-pyrimido[4,5-*b*][1,4]diazepines **5a-f**.

General Procedure.

A solution of triamine **1** or **2** (3.2 mmoles) and 1,3-diaryl-2-propenone (chalcone **3**, 3.2 mmoles) in absolute ethanol (15 ml) and acetic acid (1 ml) was refluxed for 4 hours. After neutralizing with ammonia and cooling to 0°, the reaction mixture was allowed to stand overnight. The resulting precipitate was filtered. and recrystallized from methanol. All compounds **4** were obtained as red crystals. Compounds **5** were yellow except for **5c**, which was obtained as red crystals. Yields and melting points are summarized in Scheme 1.

8-Amino-2,4-diphenyl-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]-diazepine (**4a**).

This compound had ms: (70 eV) m/z (%) = 360/358 (36/70, $M^{+\bullet}$, Cl isotope pattern), 345/343 (9/23, $M^{+\bullet}$ -$CH_3$), 207/205 (31/100, $M^{+\bullet}$ -4-$ClC_6H_4CH{=}CH_2$).

*Anal.* Calcd. for $C_{20}H_{16}N_5O_2Cl$: C, 61.00; H, 4.09; N, 17.78. Found: C, 61.13; H, 4.02; N, 17.72.

8-Amino-2-(4-bromophenyl)-4-(nitrophenyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*][1,4]diazepine (**4b**).

This compound had ms: (70 eV) m/z (%) = 439/437 (60/71, $M^{+\bullet}$, Br isotope pattern), 424/422 (10/12, $M^{+\bullet}$ -$CH_3$), 282 (44, $M^{+\bullet}$ -$BrC_6H_4$), 256 (32), 255 (100, $M^{+\bullet}$ -4-$BrC_6H_4CH{=}CH_2$), 210 (29), 209 (61), 182 (13), 149 (17), 135 (48), 134 (14), 118 (20), 108 (44), 107 (29), 104 (16), 103 (19), 81 (45).

*Anal.* Calcd. for $C_{20}H_{16}N_5O_2Br$: C, 54.81; H, 3.68; N, 15.98. Found: C, 54.72; H, 3.56; N, 15.89.

8-Amino-2-phenyl-4-(nitrophenyl)-2,3-dihydro-1*H*-pyrido-[2,3-*b*][1,4]diazepine (**4c**).

This compound had ms: (70 eV) m/z (%) = 360 (24), 359 (100, $M^{+\bullet}$), 358 (13), 344 (16, $M^{+\bullet}$ -$CH_3$), 282 (27, $M^{+\bullet}$ -$C_6H_5$), 255 (32, $M^{+\bullet}$ -$C_6H_5CH{=}CH_2$), 253 (29), 252 (31), 223 (28), 211 (15), 210 (34), 209 (18), 150 (16), 149 (34), 105 (11), 104 (18), 103 (22).

*Anal.* Calcd. for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.94; H, 4.72; N, 19.54.

8-Amino-2,4-di(4-nitrophenyl)-2,3-dihydro-1*H*-pyrido[2,3-*b*]-[1,4]diazepine (**4d**).

This compound had ms: (70 eV) m/z (%) = 405 (21), 404 (100, $M^{+\bullet}$), 402 (11), 389 (10, $M^{+\bullet}$ -$CH_3$), 282 (41, $M^{+\bullet}$ -4-$NO_2$-$C_6H_4CH{=}CH_2$), 267 (11), 256 (21), 255 (39), 210 (17), 209 (26), 135 (11).

*Anal.* Calcd. for $C_{20}H_{16}N_6O_4$: C, 59.40; H, 3.99; N, 20.78. Found: C, 59.47; H, 3.92; N, 20.85.

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

This compound had ms: (70 eV) m/z (%) = 330 (100, $M^{+\bullet}$), 315 (29, $M^{+\bullet}$ -$CH_3$), 253 (17, $M^{+\bullet}$ -$C_6H_5$), 226 (63, $M^{+\bullet}$ -$C_6H_5CH{=}CH_2$), 104 (11), 103 (10).

*Anal.* Calcd. for $C_{19}H_{17}N_5$: C, 72.36; H, 5.43; N, 22.21. Found: C, 72.30; H, 5.36; N, 22.25.

6-Amino-4-(4-chorophenyl)-2-phenyl-2,3-dihydro-1*H*-pyrimido-[4,5-*b*][1,4]diazepine (**5b**).

This compound had ms: (70 eV) m/z (%) = 366/364 (9/17, $M^{+\bullet}$, Cl isotope pattern), 351/349 (9/23, $M^{+\bullet}$ -$CH_3$), 262/260 (29/100, $M^{+\bullet}$ -$C_6H_5CH{=}CH_2$), 77 (18), 68 (20).

*Anal.* Calcd. for $C_{19}H_{16}N_5Cl$: C, 65.24; H, 4.61; N, 20.02. Found: C, 65.18; H, 4.65; N, 20.08.

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

This compound had ms: (70 eV) m/z (%) = 375 (100, $M^{+\bullet}$), 360 (25, $M^{+\bullet}$ -$CH_3$), 298 (14, M+-$C_6H_5$), 271 (100, $M^{+\bullet}$ -$C_6H_5CH{=}CH_2$), 253 (19), 227 (20), 225 (27), 104 (39), 102 (22), 77 (24).

*Anal.* Calcd. for $C_{19}H_{16}N_6O_2$: C, 63.33; H, 4.48; N, 23.32. Found: C, 63.38; H, 4.52; N, 23.28.

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

This compound had ms: (70 eV) m/z (%) = 344 (42, $M^{+\bullet}$), 329 (42, $M^{+\bullet}$ -$CH_3$), 267 (16, $M^{+\bullet}$ -$C_6H_5$), 253 (29), 240 (100, $M^{+\bullet}$ -$C_6H_5CH{=}CH_2$), 227 (17), 91 (16), 77 (17), 68 (13).

*Anal.* Calcd. for $C_{20}H_{19}N_5$: C, 72.93; H, 5.81; N, 21.26. Found: C, 72.87; H, 5.76; N, 21.22.

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

This compound had ms: (70 eV) m/z (%) = 410/408 (67/75, $M^{+\bullet}$, Br isotope pattern), 395/393 (19/22, $M^{+\bullet}$ -$CH_3$), 333/331 (5/6, $M^{+\bullet}$ -$C_6H_5$) 306/304 (70/62, $M^{+\bullet}$ -$C_6H_5CH{=}CH_2$), 253 (21), 227 (31), 183 (21), 151 (16), 124 (31), 104 (62), 102 (67), 77 (36), 43 (100).

*Anal.* Calcd. for $C_{19}H_{16}N_5Br$: C, 57.88; H, 4.09; N, 17.76. Found: C, 57.84; H, 4.14; N, 17.82.

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

This compound had ms: (70 eV) m/z (%) = 360 (100, $M^{+\bullet}$), 345 (38, $M^{+\bullet}$ -$CH_3$), 283 (5, $M^{+\bullet}$ -$C_6H_5$), 256 (24, $M^{+\bullet}$ -$C_6H_5CH{=}CH_2$), 242 (5), 133 (7).

*Anal.* Calcd. for $C_{20}H_{19}N_5O$: C, 69.55; H, 5.54; N, 20.28. Found: C, 69.59; H, 5.60; N, 20.22.

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