Synthesis of 4-Aryl-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]-diazepin-6-ones from 4,5-Diamino-1*H*-pyrimidin-6-ones and 1-Aryl-3-(dimethylamino)-1-propanones

Braulio Insuasty* [a], Juan Carlos Argoti, Samuel Gómez [a] and Jairo Quiroga

Department of Chemistry, Universidad del Valle, A.A. 25360, Cali, Colombia
[a] Departamento de Química, Universidad de Nariño, Pasto, Colombia

Roberto Martínez, Enrique Angeles and Rubén Gabiño

Instituto de Química, FES Cuautitlán, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D.F.

Manuel Nogueras and Adolfo Sánchez

Department of Organic Chemistry, Universidad de Jaén, 23071 Jaén, Spain
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The reaction of 1-aryl-3-(dimethylamino)-1-propanones **1** with one equivalent of 4,5-diamino-1*H*-pyrimidin-6-ones **2**, in acidic medium, leads to the formation of 4-aryl-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*]-[1,4]diazepin-6-ones **3**. The structure elucidation of the products is based on detail nmr analysis of experiments such as ^{13}C, ^{1}H and DEPT including selective $^{13}C\{^{1}H\}$ decoupling experiments.

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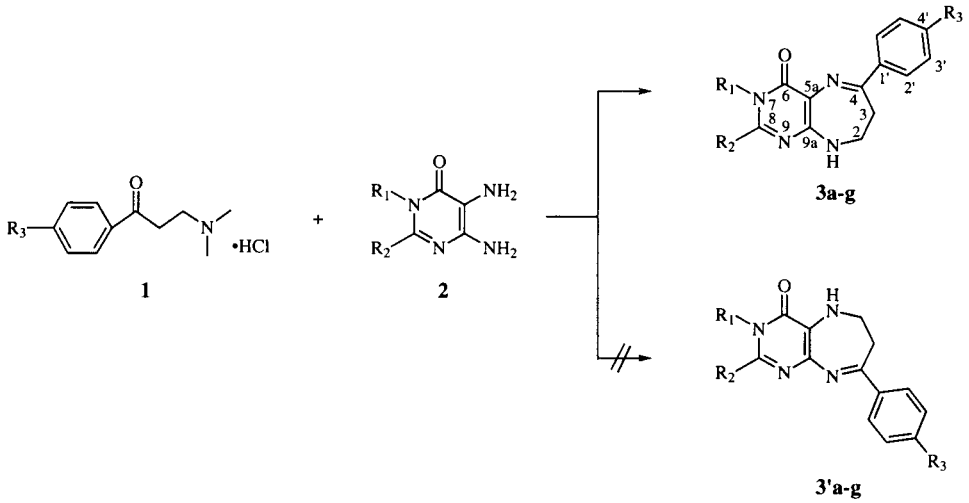
Derivatives of 1*H*-1,4-diazepines have properties of biological and pharmacological interest [1-3]. The reaction of α,β-unsaturated ketones with 1,2-diamines [4-13] is a very convenient and versatile method for the synthesis of these systems. Recently we have reported on reactions of some *ortho*-diaminopyrimidines with 1,3-diaryl-2-propenones to give pyrimido[1,4]diazepin-6-ones [7,8,10]. A predominant feature of these reactions is their high regioselectivity.

The aim of the present work was to further investigate the scope and limitations of this method, in particular the *in situ* generation of 1-aryl-2-propenones from 1-aryl-3-(dimethylamino)-1-propanones **1** and their reaction with 4,5-diamino-1*H*-pyrimidin-6-ones **2** (Scheme 1).

In a typical procedure 1-(4-bromophenyl)-3-(dimethylamino)-1-propanone, 4,5-diamino-2-methylthio-1*H*-pyrimidin-6-one and acetic acid were refluxed in ethanol to give **3a** (Table 1). Because diamine **2** has non-equivalent amino groups at the *ortho* position, the regioisomeric cyclization products **3a** and **3a'** were predicted. However, the formation of a single product **3a** was observed. We assume that, in the initial step, a condensation reaction between the carbonyl group of **1** and the more nucleophilic amino group (5-NH_2 in **2**) takes place [14-17]. In the second step, a Michael's addition of the less nucleophilic amino group (at the position 4, in **2**) to the C=C double bond of the

Scheme 1



aryl vinyl ketone, resulting from elimination of dimethylamine hydrochloride from **1**, may occur.

Table 1

Physicochemical Properties of Compounds **3a-g**

Compound	R_1	R_2	R_3	Yield (%)	mp °C
3a	H	SCH_3	Br	26	219
3b	H	SCH_3	Cl	35	228
3c	H	SCH_3	NO_2	60	250
3d	CH_3	SCH_3	Cl	28	269
3e	CH_3	SCH_3	NO_2	58	327
3f	CH_3	OCH_3	Cl	26	255
3g	CH_3	OCH_3	NO_2	51	260

Structural assignment of **3a-g** was made on spectroscopic grounds. The infrared spectrum of **3a-g** showed typical absorption between 3330 and 3470 cm^{-1} (N-H), 1640 and 1660 cm^{-1} (C=O) and 1540-1590 cm^{-1} (C=N). The uv/visible spectrum of **3a-g** in methanol contains three or four bands; most characteristic is an absorption maximum in the range of 250-280 nm and a second one shifted towards longer wavelengths ($360 \leq \lambda_{max} \leq 420$ nm).

The ^{1}H-nmr spectrum of **3a** showed the geminal protons joined to C-2 and C-3 at δ 3.40 (triplet) and δ 3.00 (triplet), respectively and the coupling constant between them is ^2J = 14.5 Hz. The proton in the amino group appears as a triplet at δ 7.74 ppm indicating the vicinal position of the proton on C-2. In addition, two doublets are observed in the spectra of **3a** related to aromatic protons (δ 7.54 and δ 8.26 ppm) with *ortho*-constant J = 7.8 Hz. ^{1}H-nmr spectrum data for all the products are summarized in Table 2.

The ^{13}C-nmr spectrum of **3a** showed 12 signals. DEPT experiments indicated that one signal corresponds to CH_3, two to CH_2, two to CH and seven to Cq. ^{1}H-^{13}C correlation (HETCOR) allowed us to identify six signals: δ 12.7 (SCH_3), 33.8 (C-2), 43.4 (C-3), 128.8 (C-3'), 131.1 (C-2') and 162.2 (C=O, amide); the ^{13}C-nmr data of **3a-g** are summarized in Table 3.

The isomeric structure **3'** was ruled out by results from selective low-power ^{13}C-^{1}H decoupling experiments. In fact, C-5a in **3a** shows as doublet with ^3J = 5.4 Hz in the coupled ^{13}C-nmr spectra. Radiation onto the proton signal of 1-NH turns the C-5a single signal [7,10]. Thus, the single frequency decoupling experiments are consistent with the structures **3a**.

No additional structural information was attained from the mass spectra of **3a**, was observed. All compounds show well-defined molecular ions and characteristic molecular ion fragmentation patterns [18].

Table 2

^{1}H-NMR Chemical shifts (δ) for Compounds **3a-g** (Dimethyl-d_6 Sulfoxide, 300 MHz)

Compound	1-NH	2-H	3-H	2'-H	3'-H	8-R_2	NMe
3a	7.74	3.40	3.00	7.85	7.54	2.43	–
3b	7.51	3.40	2.98	7.90	7.41	2.43	–
3c [a]	8.02	3.48	3.25	8.24	7.85	2.41	–
3d	7.79	3.42	3.37	8.00	7.27	2.65	3.48
3e [a]	8.40	3.44	3.11	8.57	8.14	2.73	3.73
3f	7.88	3.59	3.21	7.98	7.35	3.99	3.18
3g [a]	8.20	3.81	3.56	8.33	7.91	4.01	3.38

[a] In deuteriotrifluoroacetic acid.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on an ATI-Mattson spectrophotometer in potassium bromide pellets. The uv-vis spectra were recorded on a Shimadzu UV-160 A spectrophotometer on an ethanol solution. The ^{1}H-, ^{13}C and ^{1}H-^{13}C-nmr spectra were determined in a Varian Gemini 200 and a Varian-VXR-300S spectrometers FT-300 instrument. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and were determined in dimethyl-d_6 sulfoxide and deuterotrifluoroacetic acid solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from tetramethylsilane. Mass-spectra were obtained with Jeol SX-100 mass spectrometer. The elemental analyses were determinated on a LECO CHNS-900 analyzer.

4-(4-R_3-Phenyl)-7-R_1-8-R_2-2,3,6,7-tetrahydro-1*H*-pyrimido-[4,5-*b*][1,4]diazepin-6-ones, **3a-g**.

General Procedure (R_1 = H, R_2 = SCH_3, R_3 = Br).

Table 3

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

Compound	C-2	C-3	C-4	C-5a	C-6	C-8	C-9a	C-1'	C-2'	C-3'	C-4'	XMe	NMe
3a	43.4	33.8	162.1	106.9	162.2	153.4	158.4	139.5	131.1	128.8	122.6	12.7	–
3b	43.6	33.8	158.3	107.2	162.2	153.5	158.1	139.2	128.9	128.5	133.7	12.7	–
3c [a]	42.7	36.5	156.0	101.2	166.4	153.1	153.1	142.2	131.0	127.2	139.5	14.2	–
3d	43.6	33.6	157.9	105.6	161.0	157.7	152.5	138.7	128.3	127.7	133.5	14.2	29.9
3e [a]	42.7	32.5	154.5	101.6	168.3	153.0	152.7	139.6	131.1	126.9	131.3	15.6	32.5
3f	37.6	37.2	155.4	104.2	161.1	153.2	153.1	138.8	128.2	127.8	133.0	55.3	27.6
3g [a]	36.8	35.8	156.8	105.8	169.2	155.5	152.1	130.4	121.2	117.5	138.7	57.8	29.5

[a] In deuteriotrifluoroacetic acid

A solution of 1-(4-bromophenyl)-3-(dimethylamino)-1-propanone hydrochloride (0.68 g, 3.2 mmoles), 4,5-diamino-2-methylthio-1*H*-pyrimidin-6-one (0.51 g, 3.2 mmoles) and acetic acid (1 ml) was refluxed in 15 ml of absolute ethanol for 3 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 to give 0.30 g (26%) of **3a** mp 219°. The yields and melting points are summarized in Table 1.

4-(4-Bromophenyl)-8-methylthio-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one **3a**.

This compound had ms: EI m/z (relative abundance) = 364 (100, M^+), 349 (15), 318 (14), 183 (29).

Anal. Calcd. for $C_{14}H_{13}BrN_4OS$: C, 46.04; H, 3.59; N, 15.34. Found: C, 46.14; H, 3.44; N, 15.26.

4-(4-Chlorophenyl)-8-methylthio-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one **3b**.

This compound had ms: EI m/z (relative abundance) = 320 (100, M^+), 305 (12), 274 (12), 183 (15).

Anal. Calcd. for $C_{14}H_{13}ClN_4OS$: C, 52.42; H, 4.08; N, 17.46. Found: C, 52.56; H, 4.02; N, 17.32.

4-(4-Nitrophenyl)-8-methylthio-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one **3c**.

This compound had ms: EI m/z (relative abundance) = 333 (6, M^+), 332 (18), 331 (100), 330 (12), 329 (6), 316 (7), 285 (10), 209 (6), 183 (14).

Anal. Calcd. for $C_{14}H_{13}N_5O_3S$: C, 50.75; H, 3.95; N, 21.14. Found: C, 50.70; H, 3.87; N, 21.02.

4-(4-Chlorophenyl)-8-methylthio-7-methyl-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one **3d**.

This compound had ms: EI m/z (relative abundance) = 334 (25, M^+), 307 (100), 289 (50), 273 (12).

Anal. Calcd. for $C_{15}H_{15}ClN_4OS$: C, 53.81; H, 4.52; N, 16.73. Found: C, 53.92; H, 4.48; N, 16.79.

4-(4-Nitrophenyl)-8-methylthio-7-methyl-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one **3e**.

This compound had ms: EI m/z (relative abundance) = 347 (8, M^+), 346 (19), 345 (100), 344 (15), 223 (12), 197 (17), 88 (20).

Anal. Calcd. for $C_{15}H_{15}N_5O_3S$: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.23; H, 4.33; N, 20.20.

4-(4-Chlorophenyl)-8-methoxy-7-methyl-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one **3f**.

This compound had ms: EI m/z (relative abundance) = 318 (4, M^+), 289 (15), 185 (12), 154 (100).

Anal. Calcd. for $C_{15}H_{15}ClN_4O_2$: C, 56.52; H, 4.74; N, 17.58. Found: C, 56.67; H, 4.85; N, 17.47.

4-(4-Nitrophenyl)-8-methoxy-7-methyl-2,3,6,7-tetrahydro-1*H*-pyrimido[4,5-*b*][1,4]diazepin-6-one **3g**.

This compound had ms: EI m/z (relative abundance) = 330 (18, M^+), 329 (100), 328 (16), 207 (14), 181 (22), 180 (13), 150 (23).

Anal. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.71; H, 4.59; N, 21.27. Found: C, 54.80; H, 4.50; N, 21.12.

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