

Synthesis of New 1-Benzyl-4,6-diaryl-2,3-dihydropyrazolo[3,4-b][1,4]diazepines.

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Abstract: The reaction of 4-amino-3-aryl-5-benzylaminopyrazoles (**1a,b**) with 3-dimethylaminopropiophenones (**2**) in ethanol with acetic acid gave 1-benzyl-4,6-diaryl-2,3-dihydropyrazolo[3,4-b][1,4]diazepines (**3a-h**). The structure elucidation of the products is based on detailed nmr analysis (¹H, ¹³C and DEPT).

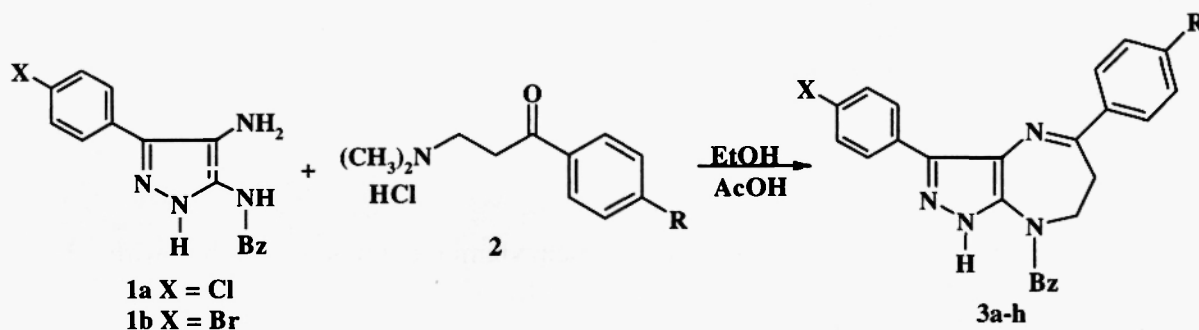
Introduction

The 1H-1,4-diazepine derivatives have interesting biological and pharmacological properties [1-3]. There have been several reports on the biological properties of pyrazolodiazepines. In particular, some of this kind of compounds are recognized to have psycotropics [1-4] and high CNS activities [5].

We have previously reported on reactions of 4,5-diaminopyrazoles with 1,3-diaryl-2-propenones [6-8], 1,5-diaryl-3-pentadienones [9] and 3-dimethylaminopropiophenones [10] to yield pyrazolo[1,4]diazepines. A predominant feature in the most cases of these reactions is their high regioselectivity.

Results and Discussion

Continuing with our studies of the synthesis of fused diazepines from heterocyclic diamines, in this work we report the reaction of 4-amino-3-aryl-5-benzylaminopyrazoles (**1a,b**) with 3-dimethylaminopropiophenones (**2**). Our aim was to study the influence of benzyl group over the selectivity owing to we previously found that the reaction of 4,5-diaminopyrazoles with compounds **2** yielded regioisomeric mixtures of pyrazolodiazepines [10]. The reaction of equimolar amounts of 4,5-diaminopyrazoles (**1a,b**) and 3-dimethylaminopropiophenones (**2**) in absolute ethanol with acetic glacial acid under reflux afforded 4,6-diaryl-1-benzyl-2,3-dihydropyrazolo[3,4-b][1,4]diazepines (**3a-h**) in good yields as unique products (Scheme 1).



	3a	3b	3c	3d	3e	3f	3g	3h
X	Cl	Cl	Cl	Cl	Br	Br	Br	Br
R	H	Cl	Br	NO ₂	OCH ₃	Cl	Br	NO ₂
m.p., °C	238	269	265	240	259	256	246	222
Yield, %	50	60	65	82	60	62	72	80

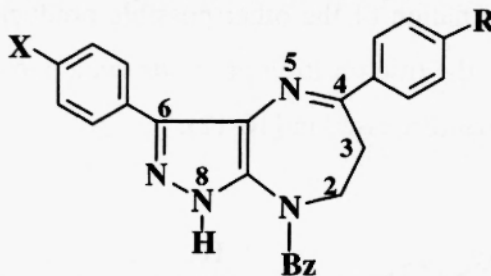
SCHEME 1

Formation of diazepines **3a-h** is supported by elemental analysis and spectroscopic data, as has been usual with analogous products obtained from the reaction of others *ortho*-diamines with 3-dimethylaminopropiophenones [10-12].

The structure of compounds **3a-h** was confirmed by nmr measurements. ¹H-nmr data are summarized in Table 1. The geminal protons on C-2 and C-3 appear at $\delta = 3.27$ -3.37 and 3.06-3.25 ppm as two triplets, respectively, with coupling constant between them ³J =

7.0±0.1 Hz. Benzyl protons appear as a singlet at $\delta = 4.52$ -4.63. In addition, four doublets observed in the spectra of **3a-h** at $\delta = 6.91$ -8.26 ppm, are related to aromatic protons of *p*-substituted aryl rings at position 4 and 6 with *ortho*-constant $J = 7.1$ -8.9 Hz.

TABLE 1.
¹H-NMR data of 1-benzyl-4-(4-R-phenyl)-6-(4-X-phenyl)-2,3-dihydropyrazolo-
 [3,4-b][1,4]diazepines
 (δ values, TMS as the Internal Standard, in DMSO-d₆, 300 MHz)

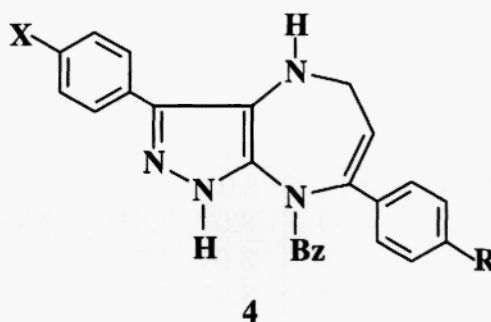


	H ₂ t	H ₃ t	H ₈ s	N-CH ₂ - s	X-Phenyl		R-Phenyl		Benzyl m
					H _o d	H _m d	H _o d	H _m d	
3a	3.34	3.18	12.49	4.61	8.07	7.55	7.89	7.34	7.25-7.45
3b	3.33	3.12	12.43	4.59	8.07	7.54	7.85	6.97	7.23-7.35
3c	3.33	3.16	12.49	4.60	8.03	7.55	7.82	7.60	7.25-7.35
3d	3.34	3.24	12.64	4.63	8.03	7.57	8.24	8.09	7.26-7.35
3e	3.27	3.06	12.29	4.52	7.93	7.61	7.79	6.91	7.18-7.27
3f	3.25	3.08	12.45	4.53	7.88	7.61	7.53	7.74	7.19-7.28
3g	3.33	3.16	12.49	4.60	7.68	7.97	7.45	7.89	7.28-7.35
3h	3.37	3.23	12.64	4.63	7.98	7.71	8.26	8.09	7.25-7.36

The final structure elucidation of compounds **3a-h** was carried out by analysis of the ¹³C-nmr spectra (experimental). Signal assignment was made based on DEPT and bidimensional experiments.

Relevant features are as follows. The signal of C-2 is in the range $\delta = 47.1$ -48.2 ppm whereas the signal of C-3 appears at $\delta = 33.3$ -34.4 ppm. A peak related to C-5a is at $\delta = 118.0$ -123.7 ppm. In contrast, C-8a shows signal at $\delta = 149.0$ -150.5 ppm. These findings can be explained in terms of the strong push-pull effect of the amino and C=N groups linked to the C=C double bond in structures **3**.

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_2 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. HMBC experiments indicate three-bond correlations of CH_2 protons of benzyl group with C-8a and C-2 and between 2- CH_2 -protons and C-8a and CH_2 -Ph. These experiments rule out the formation of the other possible product **4** in the studied reaction (scheme 2) and confirm that the title reaction proceeds *via* a two-step sequence with a high regioselectivity, similar to that discussed in [10-12].



Scheme 2

Experimental

Materials. All melting points are uncorrected. The ir spectra were recorded on a ATI-Mattson spectrophotometer in potassium bromide pellets. The ^1H - and ^{13}C nmr spectra were run on a Bruker AVANCE DRX 300 spectrometer in CDCl_3 . The mass spectra were recorded on a Fisons-Platform interface APCI in Methanol. The elemental analyses were determined on a LECO CHNS-900 analyzer.

1-Benzyl-4,6-diaryl-2,3-dihydropyrazolo[3,4-b][1,4]diazepines (**3a-h**).

General Procedure

A solution of 4-amino-3-aryl-5-benzylaminopyrazole (**1a,b**) (2 mmol) and 1-aryl-3-(dimethylamino)-1-propanone hydrochlorides (2 mmol) in 20 ml absolute ethanol and 3 ml of acetic glacial acid was refluxed for 0.75-1.5 hours (TLC control). The reaction mixture was concentrated under vacuum and the resulting precipitate was filtered, washing with ethanol and recrystallized from ethanol. The yields and melting points of compounds **3a-h** are summarized in Scheme 1.

1-Benzyl-6-(4-chlorophenyl)-4-phenyl -2,3-dihydropyrazolo[3,4-b][1,4]diazepine **3a**.

This compound was obtained according to general procedure as pale yellow crystals, ir (KBr): 3203, 1550 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 33.7 (C-3), 47.8 (C-2), 54.5 (N- CH_2 -Ph), 118.0 (C-5a), 159.5 (C-4). The mass spectrum shows m/z (%) = 412 (100, M^+).

Anal. Calcd. for $\text{C}_{25}\text{H}_{21}\text{ClN}_4$: C, 72.72; H, 5.13; N, 13.57. Found: C, 72.70; H, 5.40; N, 13.69.

1-Benzyl-4,6-bis-(4-chlorophenyl)-2,3-dihydropyrazolo[3,4-b][1,4]diazepine **3b**.

This compound was obtained according to general procedure as light yellow crystals, ir (KBr): 3200, 1580, 1550 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 33.3 (C-3), 48.1 (C-2), 55.4 (N- CH_2 -Ph), 123.0 (C-5a), 160.3 (C-4). The mass spectrum shows m/z (%) = 446 (100, M^+).

Anal. Calcd. for $\text{C}_{25}\text{H}_{20}\text{Cl}_2\text{N}_4$: C, 67.12; H, 4.51, N, 12.56. Found: C, 67.20; H, 4.40; N, 12.36.

1-Benzyl-4-(4-bromophenyl)-6-(4-chlorophenyl)-2,3-dihydropyrazolo[3,4-b]-[1,4]diazepine **3c**.

This compound was obtained according to general procedure as light yellow crystals, ir (KBr): 3205, 1579, 1550 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 33.5 (C-3), 47.5 (C-2), 55.5 (N- CH_2 -Ph), 123.0 (C-5a), 158.6 (C-4). The mass spectrum shows m/z (%) = 490 (100, M^+).

Anal. Calcd. for $C_{25}H_{20}ClBrN_4$: C, 61.05; H, 4.10; N, 11.39. Found: C, 61.00; H, 4.40; N, 11.36.

1-Benzyl-6-(4-chlorophenyl)-4-(4-nitrophenyl)-2,3-dihydropyrazolo[3,4-b][1,4]diazepine 3d.

This compound was obtained according to general procedure as red crystals, ir (KBr): 3205, 1574, 1534, 1512, 1340 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 34.2 (C-3), 47.1 (C-2), 54.0 (N-CH₂-Ph), 123.7 (C-5a), 161.0 (C-4). The mass spectrum shows m/z (%) = 456 (100, M^+).

Anal. Calcd. for $C_{25}H_{20}ClN_5O_2$: C, 65.57; H, 4.40; N, 15.30. Found: C, 65.47; H, 4.34; N, 15.39.

1-Benzyl-6-(4-bromophenyl)-4-(4-methoxyphenyl)-2,3-dihydropyrazolo[3,4-b]-[1,4]diazepine 3e.

This compound was obtained according to general procedure as light yellow crystals, ir (KBr): 3205, 1573, 1340 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 33.5 (C-3), 48.2 (C-2), 54.7 (N-CH₂-Ph), 121.1 (C-5a), 159.8 (C-4). The mass spectrum shows m/z (%) = 486 (100, M^+).

Anal. Calcd. for $C_{26}H_{23}BrN_4O$: C, 64.10; H, 4.80; N, 11.51. Found: C, 64.25; H, 4.86; N, 11.39.

1-Benzyl-6-(4-bromophenyl)-4-(4-chlorophenyl)-2,3-dihydropyrazolo[3,4-b][1,4]diazepine 3f.

This compound was obtained according to general procedure as light yellow crystals, ir (KBr): 3203, 1580, 1553 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 34.0 (C-3), 47.8 (C-2), 55.0 (N-CH₂-Ph), 122.8 (C-5a), 158.5 (C-4). The mass spectrum shows m/z (%) = 490 (100, M^+).

Anal. Calcd. for $C_{25}H_{20}BrClN_4$: C, 61.12; H, 4.11; N, 11.40. Found: C, 61.20; H, 4.25; N, 11.36.

1-Benzyl-4,6-bis-(4-bromophenyl)-2,3-dihydropyrazolo[3,4-b]-[1,4]diazepine 3g.

This compound was obtained according to general procedure as light yellow crystals, ir (KBr): 3204, 1592, 1550 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 33.9 (C-3), 47.7 (C-2), 54.7 (N- CH_2 -Ph), 121.3 (C-5a), 158.5 (C-4). The mass spectrum shows m/z (%) = 534 (100, M^+).

Anal. Calcd. for $\text{C}_{25}\text{H}_{20}\text{Br}_2\text{N}_4$: C, 56.00; H, 3.81; N, 10.39. Found: C, 56.12; H, 3.88; N, 10.31.

1-Benzyl-6-(4-bromophenyl)-4-(4-nitrophenyl)-2,3-dihydropyrazolo[3,4-b][1,4]diazepine 3h.

This compound was obtained according to general procedure as red crystals, ir (KBr): 3204, 1583, 1534, 1511, 1350 cm^{-1} . ^{13}C -nmr (DMSO- d_6 , ppm): 34.4 (C-3), 47.3 (C-2), 54.8 (N- CH_2 -Ph), 121.5 (C-5a), 157.5 (C-4). The mass spectrum shows m/z (%) = 501 (100, M^+).

Anal. Calcd. for $\text{C}_{25}\text{H}_{20}\text{BrN}_5\text{O}_2$: C, 59.75; H, 4.00; N, 13.90. Found: C, 59.67; H, 4.15; N, 13.85.

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