Synthesis of Substituted 1-Benzyl-2,4,6-triphenyl-2,3-dihydro-pyrazolo[3,4-*b*][1,4]diazepines

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Received December 18, 1996

The acid catalyzed condensation of 4,5-diaminopyrazoles and chalcones gave the hitherto unknown 1-benzyl-2,4,6-triphenyl-2,3-dihydropyrazolo[3,4-*b*][1,4]diazepines derivatives. The structure of all products was supported by ir, ^{1}H and ^{13}C-nmr and mass spectra.

J. Heterocyclic Chem., **34**, 1131 (1997).

There have been several reports on the biological properties of pyrazolodiazepines and their analogous. Some of these compounds are known to have activities as psycotropics [1-4]. It is also well known that reaction of α,β-unsaturated ketones and 1,2-diamines produces benzodiazepine derivatives [5-12]. Thus 4,5-diaminopyrazoles could be starting materials for the synthesis of pyrazolobenzodiazepines. Recently, we have reported that reaction of 4,5-diamino-1-phenyl-3-methylpyrazole with chalcone derivatives gave 2,3-dihydro-1*H*-pyrazolo[4,5-*b*][1,4]diazepines [7-9]. This reaction gave one of the two possible heterocyclic ring structures almost selectively. In this work, we report the extension of this synthetic strategy to a synthesis of substituted 1-benzyl-2,4,6-triphenyl-2,3-dihydropyrazolo[3,4-*b*][1,4]diazepines **3a-l.** Reaction of 3-(4-substituted-phenyl)-4,5-diaminopyrazoles **1** with chalcones **2** in alcohol, in the presence of acetic acid, afforded **3a-l** in good yield (Figure 1 and Table 1). Structural assignment of **3a-l** derivatives was made on spectroscopic grounds. In the infrared spectra of **3a-l** the appearance of absorption bands at 3440-3026 cm^{-1} was consistent with the presence of an amino group. The nmr spectroscopic data are consistent with the proposed pyrazolodiazepine structures. For example compound **3a** gave a ^{1}H nmr spectrum with five non exchangeable proton signals at δ 5.01, 4.97, 4.09, 3.56 and 2.98 with integrals in the ratio 1:1:1:1:1. The signal at δ 4.97 resonated as a doublet with an identical spin coupling constant (J 15.6 Hz) to the doublet at δ 4.09. These signals were readily assigned to the methylene protons of benzyl group joined to N1. The remaining signals comprised an ABX system with doublet of doublets at δ 3.56 and 2.98 with geminal coupling of 14.1 ±0.3 Hz and vicinal coupling of 6.0 and 2.1 Hz respectively, and a narrow signal at δ 5.01 with only a very small but undefined spin splitting. The former signals were assigned on the basis of their larger geminal coupling to the α and δ protons at C3. Meanwhile, the signal at δ 5.01 was readily assigned to the hydrogen at C2. Small vicinal couplings to

Table 1

Yields and Melting Points of Compounds **3a-l**

Compound	R	R_1	R_2	mp °C	Yield(%)	Time, h
3a	H	H	H	226-227	40	8
3b	H	CH_3	H	246-247	65	6
3c	H	Br	H	238-239	70	5
3d	H	Cl	H	244-245	72	5
3e	H	NO_2	H	233-234	81	4
3f	H	NO_2	NO_2	239-240	90	3.5
3g	Br	H	H	226-228	49	8
3h	Br	CH_3	H	233-234	57	5
3i	Br	Br	H	251-252	61	5
3j	Br	Cl	H	245-246	75	5
3k	Br	NO_2	H	257-258	69	4
3l	Br	NO_2	NO_2	253-254	81	3

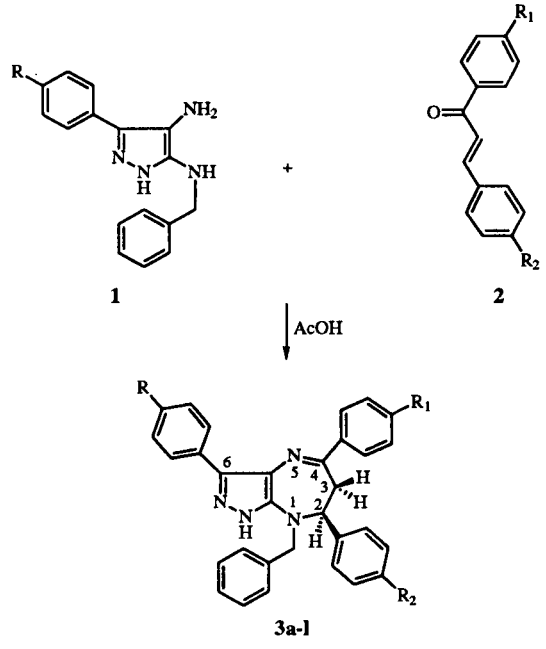

Figure 1

Table 2

^{1}H NMR Chemical Shift (δ) and Coupling Constants (J, Hz) for Compounds **3a-l** (Dimethyl sulfoxide-d_6, 300 MHz)

Compound	2Hα (J, Hz)	3Hβ (J, Hz)	3Hα (J, Hz)	H-Bz	H-Bz	NH	Ar-H
3a	5.01 (1.8)	3.56 (14.1, 6.0)	2.98 (14.4, 2.1)	4.97	4.09 (15.6)	12.2	7.10-7.95
3b	5.06	3.79 (14.7, 6.2)	2.90 (14.2)	4.96	4.15 (15.8)	12.7	6.99-8.01
3c	5.08	3.84 (14.6, 6.1)	2.90 (13.4)	4.99	4.19 (15.9)	12.5	7.10-7.98
3d	5.08	3.84 (14.6, 6.0)	2.91 (14.2)	5.0	4.18 (15.7)	12.5	7.10-7.98
3e	5.15	3.78 (14.7, 6.0)	3.03 (14.4, 1.5)	5.12	4.22 (15.6)	12.5	7.10-8.02
3f	5.27	3.94 (15.2, 6.0)	3.04 (14.7, 1.8)	5.14	4.28 (15.9)	12.6	7.20-8.31
3g	5.0	3.56 (14.4, 6.0)	3.01 (14.4, 2.1)	4.98	4.09 (15.9)	12.2	7.10-7.91
3h	5.06	3.81 (14.5, 6.0)	2.95 (14.4, 2.2)	4.99	4.20 (15.9)	12.5	7.0-7.98
3i	5.08	3.84 (14.8, 5.8)	2.88 (14.4)	4.99	4.21 (16.2)	12.6	7.10-7.96
3j	5.06	3.55 (14.4, 6.0)	3.06 (14.4, 2.2)	5.02	4.19 (15.9)	12.2	7.12-7.95
3k	5.19	4.03 (14.7, 5.9)	2.90 (15.0)	5.01	4.27 (15.3)	12.7	710-8.07
3l	5.27	3.95 (14.8, 6.0)	3.03 (13.6)	5.13	4.29 (15.7)	12.5	7.30-8.05

Table 3

Selected ^{13}C NMR Chemical Shifts (δ) for Compounds **3a-l** (dimethyl sulfoxide-d_6, 90 MHz)

Compound	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**
C2	64.8	64.1	63.7	63.8	64.1	63.1	64.9	64.0	63.7	64.8	63.3	63.0
NCH_2	52.2	52.5	52.6	52.6	52.4	52.8	52.2	52.4	52.7	52.2	52.8	52.8
C3	38.0	37.7	37.5	37.6	37.9	37.2	38.1	37.8	37.6	37.9	37.9	37.2

this proton indicated that it was held almost equidistant from the protons on the adjacent C3. Thus, the relative configuration of segment N1-C2-C3 of **3a** is depicted as in Figure 1. The remaining aromatic protons in compounds **3a** appeared as an unresolved multiplet at δ 7.95-7.1. The selected chemical shifts and coupling constant for compounds **3e-l** are summarized in Table 2.

The three signals in the ^{13}C nmr spectrum of **3a** at δ 64.8, 52.2 and 38.0 were assigned to C2, and the benzylic carbons joined to N1 and C3, respectively, on the basis of chemical shifts and the results of DEPT and ^{1}H-^{13}C correlation (HETCOR) experiments. The mass spectrum of compound **3a** showed the molecular ion as the base peak and characteristic fragments at m/z 377 (M-77), 363 (M-91) and 350 (M-104); this fragmentation is according to the assigned structure.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Nicolet FT-55X spectrophotometer. The ^{1}H, COSY and decoupling nmr spectra were determined on a Varian FT-200 instrument; the ^{13}C and ^{1}H-^{13}C nmr spectra were determined on a Varian FT-300 instrument. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and was determined in dimethyl sulfoxide-d_6 solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. Mass spectra were obtained with a Jeol SX-100 mass spectrometer.

1-Benzyl-2,4,6-triphenyl-2,3-dihydropyrazolo[3,4-*b*][1,4]-diazepines **3a-l.**

General Procedure (R = R_1 = R_2 = H).

A solution of 0.20 g (0.76 mmole) of **1a** [13] and 0.16 g (0.76 mmole) of chalcone **2a** was refluxed in 20 ml of absolute ethanol and 3 ml of acetic acid for 8 hours. The reaction mixture was cooled to 0° and the precipitates were collected by filtration. The solid obtained was recrystallized from ethanol to give 0.18 g (40%) of **3a** mp 226-227°. The yields and the melting points are summarized in Table 1.

1-Benzyl-2,4,6-triphenyl-2,3-dihydropyrazolo[3,4-*b*][1,4]-diazepine **3a.**

This compound had ir (potassium bromide): 3421-3030 cm^{-1} (NH); ms: EI m/z (relative abundance) 454 (M^+, 100), 377 (16.38), 363 (29.31), 350 (27.58).

Anal. Calcd. for $C_{31}H_{26}N_4$; C, 81.91; H, 5.76. Found: C, 81.87; H, 5.74.

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

This compound had ir (potassium bromide): 3421-3050 cm^{-1} (NH); ms: EI m/z (relative abundance) 468 (M^+ , 100), 391 (15.45), 377 (27.27), 364 (21.82).

Anal. Calcd. for $C_{32}H_{28}N_4$: C, 82.02; H, 6.02. Found: C, 81.98; H, 6.0.

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

This compound had ir (potassium bromide): 3434-3063 cm^{-1} (NH); ms: EI m/z (relative abundance) 532 (M^+, 100), 455 (12.61), 441 (30.63), 428 (23.42).

Anal. Calcd. for $C_{31}H_{25}N_4Br$: C, 69.79; H ,4.72. Found: C, 69.76; H, 4.70.

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

This compound had ir (potassium bromide): 3427-3061 cm^{-1} (NH); ms: EI m/z (relative abundance) 488 (M^+, 100), 411 (13.91), 397 (32.17), 384 (26.08).

Anal. Calcd. for $C_{31}H_{25}N_4Cl$: C, 76.14; H, 5.15. Found: C, 76.10; H, 5.13.

1-Benzyl-2,6-diphenyl-4-(4-nitrophenyl)-2,3-dihydropyrazolo[3,4-*b*][1,4]diazepine **3e.**

This compound had ir (potassium bromide): 3427-3061 cm^{-1} (NH); ms: EI m/z (relative abundance) 499 (M^+, 100), 422 (13.39), 408 (51.78), 395 (41.07).

Anal. Calcd. for $C_{31}H_{25}N_5O_2$: C, 74.53; H, 5.04. Found: C, 74.50; H, 5.0.

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

This compound had ir (potassium bromide): 3414-3078 cm^{-1} (NH); ms: EI m/z (relative abundance) 544 (M^+, 100), 467 (9.38), 453 (37.5), 440 (42.19).

Anal. Calcd. for $C_{31}H_{24}N_6O_4$: C, 68.37; H, 4.44. Found: C, 68.33; H, 4.42.

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

This compound had ir (potassium bromide): 3427-3058 cm^{-1} (NH); ms: EI m/z (relative abundance) 532 (M^+, 100), 455 (15.45), 441 (34.54), 428 (29.09).

Anal. Calcd. for $C_{31}H_{25}N_4Br$: C, 69.79; H, 4.72. Found: C, 69.76; H, 4.70.

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

This compouind had ir (potassium bromide): 3427-3026 cm^{-1} (NH); ms: EI m/z (relative abundance) 546 (M^+, 100), 469 (14.78), 455 (29.56), 442 (22.60).

Anal. Calcd. for $C_{32}H_{27}N_4$ Br: C, 70.20; H, 4.97. Found: C, 70.15; H, 4.94.

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

This compound had ir (potassium bromide): 3427-3091 cm^{-1} (NH); ms: EI m/z (relative abundance) 610 (M^+, 100), 533 (12.09), 519 (33.06), 506 (25.0).

Anal. Calcd. for $C_{31}H_{24}N_4Br_2$: C, 60.80; H, 3.95; Found: C, 60.77; H, 3.93.

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

This compound had ir (potassium bromide): 3421-3085 cm^{-1} (NH); ms: EI m/z (relative abundance) 566 (M^+, 100), 489 (10.71), 475 (27.67), 462 (22.32).

Anal. Calcd. for $C_{31}H_{24}N_4BrCl$: C, 65.56; H ,4.26. Found: C, 65.53; H, 4.23.

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

This compound had ir (potassium bromide): 3421-3085 cm^{-1} (NH); ms: EI m/z (relative abundance) 577 (M^+, 100), 500 (10.17), 486 (35.59), 473 (27.96).

Anal. Calcd. for $C_{31}H_{24}N_5BrO_2$: C, 64.36; H, 4.15. Found: C, 64.33; H, 4.15.

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

This compound had ir (potassium bromide): 3432-3086 cm^{-1} (NH); ms: EI m/z (relative abundance) 622 (M^+, 100), 545 (11.34), 531 (32.25), 518 (26.73).

Anal. Calcd. for $C_{31}H_{23}N_6BrO_4$: C, 59.72; H, 3.72. Found: C, 59.70; H, 3.70.

Acknowledgements.

We are grateful to R. Patiño, C. Contreras, H. Reyes, B. Quiroz, R. Gabiño, L. Velasco and F. J. Pérez for their assistance in obtaining the ir, ^1H nmr and mass spectral data. We are also grateful to COLCIENCIAS and Universidad del Valle for financial support.

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