

## Synthesis of 1-Benzyl-6-(4-chlorophenyl)-2-(4-R-phenyl)-4-(4-R-styryl)-2,3-dihydropyrazolo[3,4-b][1,4]diazepines<sup>‡</sup>.

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**Abstract.** The reaction of 4-amino-5-benzylamino-3-(4-chlorophenyl)-1*H*-pyrazole (**1**) with substituted diarylidenketones (**2**) constitutes a convenient synthetic route to the hitherto unknown 1-benzyl-6-(4-chlorophenyl)-2-(4-R-phenyl)-4-(4-R-styryl)-2,3-dihydropyrazolo[3,4-b][1,4]diazepines (**3**). Structures of all products were consistent with their IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and MS spectral data. X-ray crystallography data confirm the assigned structures.

**Keywords:** Diazepine derivatives, diarylidenketones.

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### Introduction

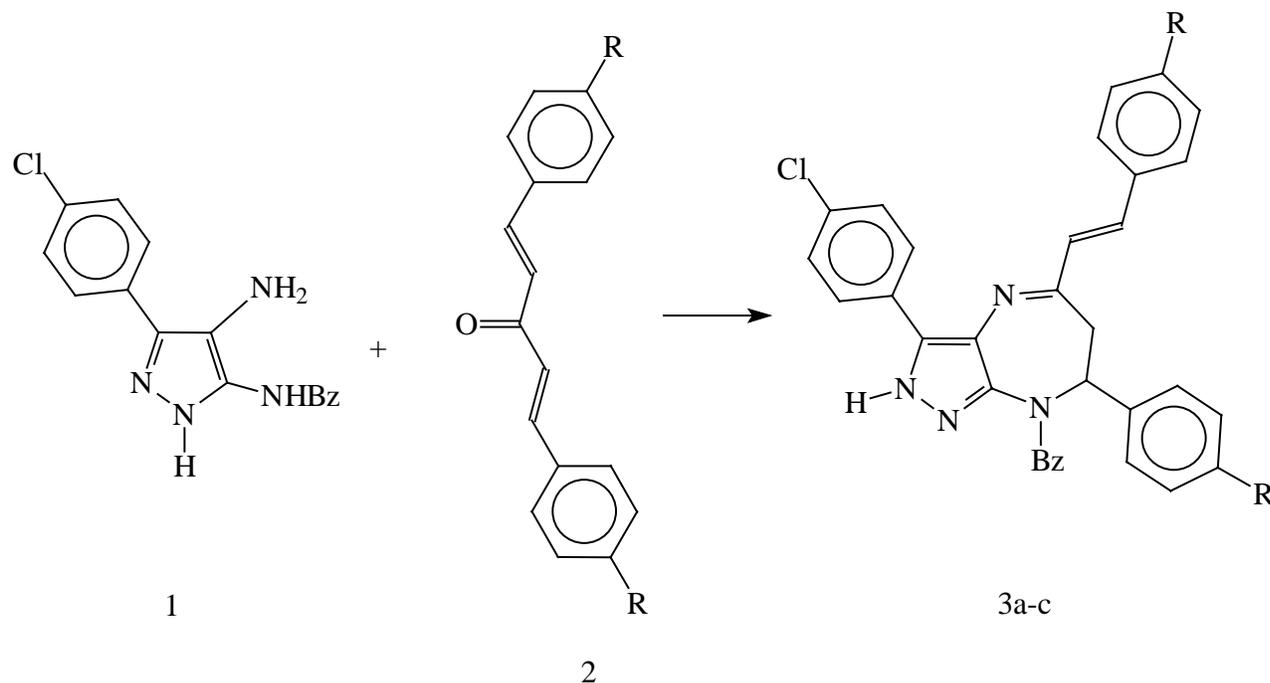
The history of benzodiazepines as pharmacologically important agents starts in 1960 when one of them was introduced as a tranquilizer under the trade name Librium [1]. Extensive structural

modifications of the prototype compound have resulted in numerous clinically effective tranquilizers that display pharmacological properties superior to those of the lead compound [2]. Some of the most interesting novel developments in the area are the diazepines containing an additional heterocyclic ring fused to the different faces of the diazepine ring nucleus [3]. During the course of our investigations in this area we have reported the synthesis of several such diazepine systems [4-6]. Recently we reported the preparation of some pyrazolo[1,4]diazepines by condensation of 4-amino-5-benzylamino-3-(4-chlorophenyl)-1*H*-pyrazole (**1**) with chalcones [7]. As a logical extension of this chemistry we now report in this paper the reaction of compound **1** with symmetrically substituted diarylidene ketones (**2**) (Scheme 1).

## Results and Discussion

When the aminopyrazole **1** was refluxed in ethanol with diarylidene ketones **2** in the presence of acetic acid, the pyrazole[3,4-b[[1,4]diazepines **3a-3c** were formed (Scheme 1).

Scheme 1

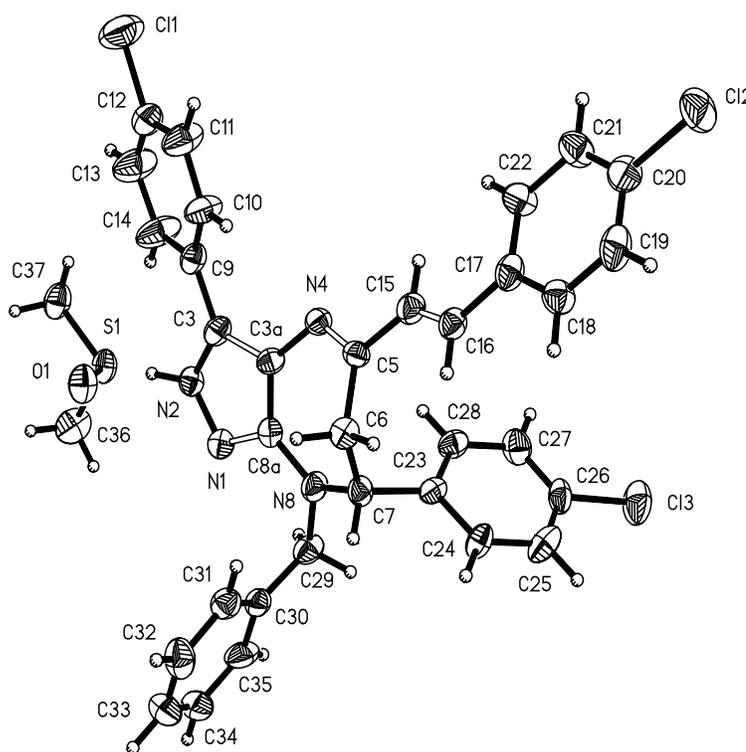


Compound	3a	3b	3c
R	CH <sub>3</sub>	Cl	NO <sub>2</sub>

The analytical and spectral data of compounds **3a-c** were consistent with the proposed structures. In the  $^1\text{H-NMR}$  spectra the proton signals for the  $\text{CH}_2\text{-CH}$  fragment are observed as an AMX system at  $\delta$  2.73-2.79, 3.63-3.88 and  $\delta$  5.98-5.26; the signals for the  $\text{CH}_2\text{-Ph}$  group between  $\delta$  4.58-4.69; the signals for the *trans*-vinyl protons, which appear without splitting, at  $\delta$  6.71-6.91 and finally a multiplet that appears at  $\delta$  6.90-8.20 is assigned to the aromatic protons. The main feature of their mass spectra is that the base peak is also the molecular ion. It is important to observe that the orientation in this cycloaddition is the same as that discussed in our previous work [8-11], where it was shown that the azomethine bond on the seven-member ring is formed with participation of the amino group at the 4-position on the pyrazole ring.

The structure of **3b** was further confirmed by a single crystal X-ray diffraction study. The compound was crystallized as the corresponding DMSO solvate and, although the rather high R-index precludes a detailed discussion of the structure, the atom connectivity and the overall conformation of the molecule is firmly established (Figure 1). The pyrazole ring and its 4-chlorophenyl substituent form a dihedral angle of  $157^\circ$ . The 1,4-diazepine ring adopts a boat conformation (N4, C5, C7 and N8 in the plane) with the 4-chlorophenyl group at C7 and the benzyl group at N8 directed towards opposite sides forming dihedral angles that approach normal values ( $119.8$  and  $74.5^\circ$  respectively), while the essentially planar styryl group tends to be coplanar ( $30^\circ$ ). The DMSO solvent molecule is hydrogen bonded (N2-H2 O1:  $1.91(13)\text{\AA}$ ) to the pyrazole hydrogen atom.

Figure 1.



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## Experimental

### General

All melting points are uncorrected. The IR spectra were recorded on an ATI-Mattheson spectrophotometer in KBr pellets. The  $^1\text{H}$ -MR and  $^{13}\text{C}$ -NMR spectra were run on Varian Gemini 200 and Varian VRX-300S instruments using DMSO- $d_6$  as solvent. Mass spectra (FAB) were recorded on a JEOL SX-102 spectrometer. The elemental analyses were determined on a LECO CHNS-900 analyzer.

### General Method for the Preparation of 1-Benzyl-6-(4-chlorophenyl)-2-(4-R-phenyl)-4-(4-R-styryl)-2,3-dihydropyrazolo[3,4-b][1,4]diazepines (**3a-c**).

A mixture of diarylidene ketones **2a**, **2b** or **2c** (0.002 mol), 4-amino-5-benzylamino-3-(4-chlorophenyl)-1H-pyrazole (**1**), (0.74 g, 0.002 mol) and glacial acetic acid (3 mL) in absolute ethanol (20 mL) was stirred under reflux for 3.5-6 hours. The reaction mixture was then concentrated under vacuum and the resulting precipitate was filtered, washed with ethanol and recrystallized from a suitable solvent.

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

Yield 0.56 g (52%); m.p. 208° C (from hexane/ethyl acetate); IR ( $\nu_{\text{max}}/\text{cm}^{-1}$ ) = 3243, 1607, 1363;  $^1\text{H}$ -NMR ( $\delta/\text{ppm}$ ) = 12.40 (1H, s, H-8), 8.08 (1H, d,  $\text{H}_\beta$ ), 7.46 (1H, d,  $\text{H}_\alpha$ ), 6.70-7.32 (17H, m, Ph-H), 4.98 (1H, dd, H-2), 4.58 (2H, dd, N- $\text{CH}_2$ -Ph), 3.63 (1H, dd, H-3), 2.73 (1H, dd, H-3), 2.28 (3H, s,  $\text{CH}_3$ ), 2.17 (3H, s,  $\text{CH}_3$ );  $^{13}\text{C}$ -NMR ( $\delta/\text{ppm}$ ) = 20.2 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_3$ ), 36.6 (C-3), 52.7 (N- $\text{CH}_2$ -Ph), 63.1 (C-2), 128.0 (2C,  $\text{C}_\alpha$  and  $\text{C}_\beta$ ), 160.0 (C-4).- MS: m/z (%), 543 (100,  $\text{M}^+ + 1$ ), 91 (38), 77 (8); Anal. calcd. for  $\text{C}_{35}\text{H}_{31}\text{ClN}_4$ : C 77.40, H 5.75, N 10.32; found: C 77.15, H 5.72, N 10.22.

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

Yield 0.81 g (70%); m.p. 178-180 °C (from ethanol); IR ( $\nu_{\max}/\text{cm}^{-1}$ ) = 3185, 1629;  $^1\text{H-NMR}$  ( $\delta/\text{ppm}$ ) = 12.50 (1H, s, H-8), 8.07 (1H, d, H $_{\beta}$ ), 7.50 (1H, d, H $_{\alpha}$ ), 6.78-7.47 (17H, m, Ar-H), 5.06 (1H, dd, H-2), 4.62 (2H, dd, N-CH $_2$ -Ph), 3.74 (1H, dd, H-3), 2.73 (1H, dd, H-3);  $^{13}\text{C-NMR}$  ( $\delta/\text{ppm}$ ) = 36.3 (C-3), 52.9 (N-CH $_2$ -Ph), 62.6 (C-2), 128.1 (2C, C $_{\alpha}$  and C $_{\beta}$ ), 159.4 (C-4); MS m/z (%) = 584 (100, M $^{+}$ +1), 91 (55), 77 (13); Anal. calcd. for C $_{33}$ H $_{25}$ Cl $_3$ N $_4$ : C, 67.88 H, 4.32, N, 9.60; found: C 67.82, H 4.40, N 9.49.

*X-ray structure of 3b-DMSO.* Compound **3b** was crystallized from dimethylsulfoxide. Crystal data: C $_{35}$ H $_{31}$ Cl $_3$ N $_4$ OS, Mw = 662.05, triclinic, space group P-1, Z = 2, unit cell dimensions [ $\text{\AA}$ ]  $a$  = 5.585(1),  $b$  = 11.618(1),  $c$  = 25.483(2),  $\alpha$  = 100.68(1) °,  $\beta$  = 92.54(1) °,  $\gamma$  = 92.45(1) °, Volume [ $\text{\AA}^3$ ] = 1621.1(3),  $\rho$  [ $\text{g cm}^{-3}$ ] = 1.356, F(000) = 4840 measured intensities, 4304 unique refl.,  $\lambda(\text{Cu-K}\alpha)$  [ $\text{mm}^{-1}$ ] 3.436, 1.54178 $\text{\AA}$ . Intensity data was measured on a Siemens P4/PC diffractometer using  $\omega:2\theta$  scan technique up to  $2\theta = 113.5^\circ$  and corrected by absorption using the 'face-indexed method' (max. min. transmission: 0.8659, 0.4381). The structure was solved by direct methods using SIR97[12] and refined by full matrix least squares using SHELXL97 [13], minimizing the function  $(F_o^2 - F_c^2)^2$  Final discrepancy factor:  $R = 13.03\%$  (on 'observed'  $F$ ),  $wR = 34.35\%$  (on  $F^2$ ).

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

Yield 1.14 g (95%); m.p. 254-256 °C (from ethanol); IR ( $\nu_{\max}/\text{cm}^{-1}$ ) = 3408, 1594, 1513, 1342;  $^1\text{H-NMR}$  ( $\delta/\text{ppm}$ ) = 12.67 (1H, s, H-8), 8.30 (1H, d, H $_{\beta}$ ), 8.02 (1H, d, H $_{\alpha}$ ), 6.90-8.20 (17H, m, Ar-H), 5.26 (1H, dd, H-2), 4.69 (2H, dd, N-CH $_2$ -Ph), 3.88 (1H, dd, H-3), 2.79 (1H, dd, H-3);  $^{13}\text{C-NMR}$  ( $\delta/\text{ppm}$ ) = 36.2 (C-3), 53.1 (N-CH $_2$ -Ph), 62.8 (C-2), 128.5 (2C, C $_{\alpha}$  and C $_{\beta}$ ), 158.1 (C-4); MS m/z (%) = 605 (M $^{+}$ +1, 100), 91 (17), 77 (12); Anal. calcd. for C $_{33}$ H $_{25}$ ClN $_6$ O $_4$ : C 65.51, H 4.16, N 13.89; found C 65.32, H 4.30, N 13.69.

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