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NUCLEOPHILIC SUBSTITUTION IN 1,5-BENZODIAZEPIN-2-ONES

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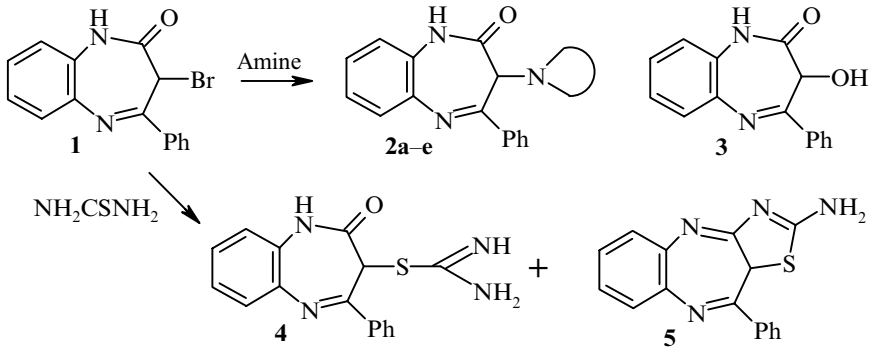
The reaction of 3-bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one with cyclic amines gives 3-aminoalkyl-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one. Thiazolo[4,5-b][1,5]benzodiazepine was isolated along with the substitution product when thiourea was used.

Keywords: 1,5-benzodiazepin-2-ones, thiazolo[4,5-*b*][1,5]benzodiazepine, bromination, phase-transfer catalysis, nucleophilic substitution.

Substituted 1,5-benzodiazepin-2-ones have pronounced diuretic and neuroleptic activity [1]. In the present work, we studied the nucleophilic substitution of halogen in 3-bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (**1**) with the amine fragments of pyrrolidine, piperidine, hexahydroazepine, tetrahydroisoquinoline, and 2-aminopyridine. Compound **1** was obtained by the bromination of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one under conditions close to those described by Barchet and Merz [2] with alteration of the benzodiazepine/bromine mole ratio to 1:1.25 and extension of the reaction time to 1.5 h. This procedure gave chromatographically pure bromobenzodiazepin **1** in yields up to 90%.



1 **2a–e** **3** **4** **5**

Amine in the case of: **2a** - pyrrolidine; **b** - piperidine; **c** - hexahydroazepine; **d** - 1,2,3,4-tetrahydroisoquinoline; **e** 2-aminopyridine

The nucleophilic substitution was carried out in ethanol. The mole ratio of bromide **1** to the amine was 1:1.5. Products **2a** and **2b** were obtained at room temperature. Heating the reaction mixture at reflux was necessary to obtain **2c-2e**. Heating leads to a more complicated reaction mixture as indicated by chromatographic monitoring of the reaction course. Carrying out the reaction with pyrrolidine in order to obtain **2a** under phase-transfer catalysis conditions with tetrabutylammonium bromide in 50% aq. NaOH and benzene gives the product of the replacement of bromine by the amine and a small yield of 3-hydroxy-4-phenyl-2,3-dihydro-1H-1,5-benzo-

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TABLE 1. Physical Characteristics of **2a-e** and **3**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent)	IR spectrum, cm^{-1}	Yield, %
		C	H	N			
2a	$C_{19}H_{19}N_3O$	74.42 / 74.75	6.10 / 6.23	13.21 / 13.77	280-281 (DMSO)	3160-3100, 1680, 1630, 1575-1465	68
2b	$C_{20}H_{21}N_3O$	74.93 / 75.24	6.63 / 6.58	12.89 / 13.17	187-188 (ethanol)	3300-3100, 1685, 1625, 1580-1430	81
2c	$C_{21}H_{23}N_3O$	75.21 / 75.68	6.45 / 6.91	12.12 / 12.61	172-173 (ethanol)	3175-3040, 1675, 1620, 1560-1465	80
2d	$C_{24}H_{21}N_3O$	78.21 / 78.47	5.35 / 5.71	11.20 / 11.44	95-96 (1:1 ethanol–water)	3185-3100, 1692, 1625, 1590-1475	96
2e	$C_{20}H_{16}N_4O$	72.87 / 73.17	4.60 / 4.88	16.86 / 17.07	269-270 (ethanol)	3325-3151, 1640, 1620, 1560-1450	71
3	$C_{15}H_{12}N_2O_2$	70.82 / 71.43	4.64 / 4.76	11.02 / 11.11	268-270 (methanol)	3565-3356, 3180-3100, 1653, 1620-1480	30

diazepin-2-one (**3**). The IR spectrum of **3** shows a broad band for the associated OH and NH groups at 3565-3356 and 3180-3100 cm^{-1} and carbonyl band at 1653 cm^{-1}. Increasing the heating time under the phase transfer conditions leads to decomposition of bromide **1** and formation of *o*-phenylenediamine.

The spectral data confirm the structure of amines **2** and are in accord with the data for 1,5-benzodiazepine systems [3]. The IR spectra contain strong carbonyl stretching bands at 1672-1692 cm^{-1} and bands for the $C_{(4)}=N_{(5)}$ and C=C bonds at 1620-1450 cm^{-1}. The ^1H NMR spectra show a singlet for the amide proton at 9.35-11.04 ppm, aromatic proton multiplet at 6.80-8.02 ppm, and signals for the substituent protons.

3-Thioureido-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (**4**) and 2-amino-10-phenylthiazolo-[4,5-*b*][1,5]benzodiazepine (**5**) were isolated in the reaction of **1** with thiourea. Closure of the tricyclic systems for 1,5-benzodiazepinones upon the action of nucleophiles has already been noted by Proshkina et al. [4]. The thiazole ring is formed by the standard pathway [5].

The IR spectrum of tricyclic derivative **5** lacks carbonyl bands, while the intensity of the azomethine absorption is enhanced.

Different mass spectral behavior was found for **4** and **5**. The mass spectrum of **5** show strong peaks for the molecular ion M^+ 292 (60%) and fragmentation ion 217* (70%), which corresponds to the loss of the thiazole fragment. The [M-H] peak (291) is the strongest in the spectrum. The molecular ion peak of **4** M^+ 310 (26%) is less strong. The peak at 235 formed upon elimination of the $SC(NH_2)=NH$ fragment from the molecular ion is the strongest in this spectrum.

EXPERIMENTAL

The reaction course and purity of the products were monitored by TLC on Silufol UV-254 plates using 7:4 benzene–ethyl acetate as the eluent. The IR spectra were taken on a UR-20 spectrometer for samples in KBr pellets. The ^1H NMR spectra were taken on a Varian VXR-300 spectrometer for solutions in DMSO-d_6 with TMS as the internal standard. The mass spectra were taken on a Varian MAT-443 spectrometer using direct sample inlet into the ion source. The ionizing electron energy was 70 eV.

* Here and henceforward, the *m/z* (I_{rel}, %) values are given for the ion peaks.

3-Bromo-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (1). Bromine (12.5 mmol) in acetic acid (5 ml) was added dropwise to a stirred solution of 4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (10 mmol) in glacial acetic acid (40 ml) warmed to 35°C. The reaction mixture was stirred for 1.5 h at about 20°C. A precipitate of **1** (2.7 g) was filtered off and washed with dilute aqueous ammonia and, then, water. The product was used without further purification.

4-Phenyl-3-pyrrolidino-2,3-dihydro-1H-1,5-benzodiazepin-2-one (2a). Pyrrolidine (7.5 mmol) and triethylamine (5 mmol) were added to **1** (5 mmol) in ethanol (25 ml). After 24 h, the precipitate of amine **2a** was filtered off and washed with water. The physical constants of **2a-e** are given in Table 1. ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 1.74 (4H, s, CH_2); 2.95, 3.18 (4H, s, CH_2N); 6.66 (1H, d, *J* = 7.5, 6-H); 6.88-7.16 (8H, m, Het + Ph), 7.33 (1H, s, CH); 10.87 (1H, s, NH).

4-Phenyl-3-piperidino-2,3-dihydro-1H-1,5-benzodiazepin-2-one (2b) was obtained as in the procedure for **2a** and isolated by adding water (100 ml) to the reaction mixture. ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 1.50 (4H, s, CH_2); 1.67 (4H, m, CH_2); 2.82-3.20 (4H, m, CH_2N); 4.76 (1H, s, CH); 6.60 (1H, d, *J* = 7.8, 6-H); 7.28-7.40 (8H, m, Ph + Ar); 10.67 (1H, s, NH).

3-Hexahydroazepino-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (2c) was obtained analogously. ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 0.98 (4H, s, CH_2); 1.18 (4H, s, CH_2); 2.20-2.50 (4H, m, CH_2N); 4.96 (1H, s, CH); 7.02-7.20 (3H, m, *m*-Ph, 8-H); 7.35 (1H, d, *J* = 8.1, 6-H); 7.48-7.58 (3H, m, *p*-Ph, 7-, 9-H); 8.02 (2H, d, *J* = 8.1, *o*-Ph); 10.77 (1H, s, NH).

4-Phenyl-3-tetrahydroisoquinolino-2,3-dihydro-1H-1,5-benzodiazepin-2-one (2d) was obtained analogously by heating the reaction mixture at reflux for 45 min. Amine **2d** was isolated by adding water (100 ml) to the reaction mixture. ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 3.60-3.85 (2H, m, 4-H isoquin.); 3.20-3.40 (2H, m, 2-H isoquin.); 4.26 (2H, dd, *J* = 10, *J* = 6.0, 1-H isoquin.); 6.68 (1H, d, *J* = 7.8, 6-H); 6.80-7.25 (13H, Het + Ph + Ar); 11.04 (1H, s, NH).

4-Phenyl-3-(2-pyridylamino)-2,3-dihydro-1H-1,5-benzodiazepin-2-one (2e) was obtained by heating the reaction mixture at reflux for 5 h. The mixture was then maintained at 4°C for 24 h to give **2e** as a precipitate. ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 4.87 (2H, s, CH, C=NH); 6.61 (1H, t, *J* = 7.5, 8-H); 6.75 (1H, d, *J* = 7.5, 6-H); 6.96 (1H, d, *J* = 7.5, 7-H); 7.10 (1H, t, *J* = 6.9, Py); 7.30 (1H, d, *J* = 7.5, 9-H); 7.35-7.55 (5H, m, Ph); 7.74 (1H, d, *J* = 6.9, Py); 7.91 (2H, d, *J* = 6.9, Py); 8.81 (1H, d, *J* = 6.9, C=NH); 9.35 (1H, s, NH).

3-Hydroxy-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-one (3). Pyrrolidine (10 mmol), 50% aq. NaOH (3 ml), and triethylammonium bromide (6 mmol) in benzene (10 ml) were added to **1** (10 mmol). The mixture was stirred for 1 h at 70°C and then cooled. The organic layer was separated, washed with water, and dried over $MgSO_4$. The solvent was removed and the residue was separated by fractional crystallization from aqueous methanol to give **2a** (1.35 g) and **3** (0.8 g).

Reaction of Bromide 1 with Thiourea. A solution of **1** (1.6 g, 5 mmol) and thiourea (0.37 g, 5 mmol) in ethanol (20 ml) was heated at reflux for 2 h. Cooling gave tricyclic derivative **5** (0.8 g); mp 138-140°C. IR spectrum (KBr), cm^{-1}: 1600 (C=N), 1520-1470 (C=C), 3390-3160 (NH). Mass spectrum: 292 (60), 291 (100), 235 (15), 217 (70). Found, %: N 18.98; S 10.74. $C_{16}H_{12}N_4S$. Calculated, %: N 19.18; S 10.96.

Removal of the solvent from the filtrate gave **4** (0.4 g), mp 236-237°C (ethanol). IR spectrum (KBr), cm^{-1}: 1630 (C=O), 1610 (C=N), 1532-1460 (C=C), 3300-3100 (NH). Mass spectrum: 310 (26), 235 (100), 194 (18.8), 133 (22.37). Found, %: N 18.01; S 10.32. $C_{16}H_{14}N_4OS$. Calculated, %: N 18.06; S 10.32.

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