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CHEMISTRY OF AZOBENZAZOLE SYSTEMS. 3.* REACTIONS OF 2-HYDRAZINOBENZOXAZOLE WITH CARBONYL COMPOUNDS

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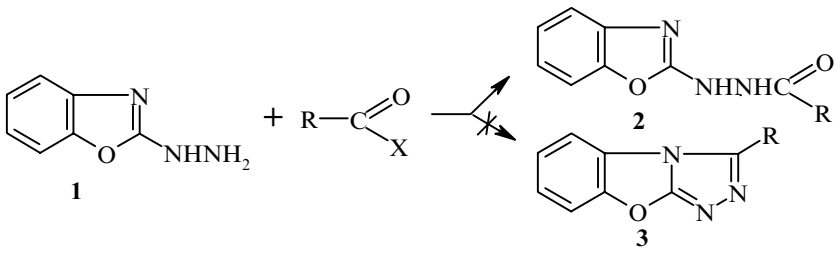
The reaction of 2-hydrazinobenzoxazole with various carbonyl compounds was studied. Only the corresponding azides were obtained with acylating agents such as acid anhydrides and acid chlorides and products with a fused triazole ring were not obtained. Only the corresponding hydrazones were obtained from furfural and 2-carboxy-3,4-dimethoxybenzaldehyde.

Keywords: 2-hydrazinobenzoxazole, reactions with anhydrides, acid chlorides and aldehydes.

In a continuation of a systematic investigation of 2-substituted benzazoles [2-4], we studied the reaction of 2-hydrazinobenzoxazole (**1**) with some carboxylic acids, acid anhydrides, acid chlorides, and aldehydes. The reactions with acylating reagents may lead to heterylhydrazides **2** or condensed tricyclic products **3** [5].

Scheme 1



Hydrazides **2** hold interest as potential biologically active compounds. Antituberculosis activity has been found for the hydrazide of isonicotinic acid and its derivatives [6].

Hydrazinobenzoxazole **1** does not react upon heating with acetic or propionic acids at reflux and only the starting reagents were isolated from the reaction mixture. The corresponding hydrazide **2a** (R = H) was obtained in 26% yield only in the case of formic acid. The formation of **2a** is indicated by an IR band for the formyl group at 1687 cm^{-1} and molecular ion peak M^+ 177 in the mass spectrum.

* Communication 2, see ref. [1].

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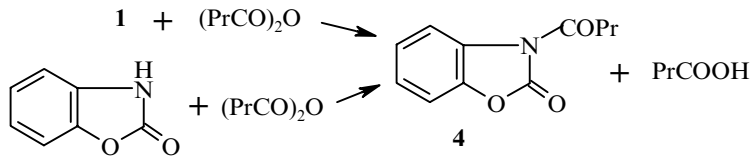
The reaction of hydrazinobenzoxazole **1** with a three-fold excess of acetic anhydride or propionic anhydride proceeds at room temperature immediately upon mixing the reagents to give hydrazides **2b** in 42% yield (R = Me) and **2c** in 53% yield (R = Et). The structure of these products was supported by their spectral data and elemental analysis results. Thus, the ^{1}H NMR spectrum of **2b** taken in deuteromethanol shows signals for four aromatic protons of the benzoxazole fragment as a well-defined system at 7.30-7.62 ppm and a singlet for the methyl group at 2.50 ppm (Table 1). The precise values of the chemical shifts and coupling constants were established using an iterative program for calculation of ^{1}H NMR spectra. The calculated chemical shifts and coupling constants are in good accord with the experimental data. The sequence of the *ortho, meta,* and *para* protons is readily established using the coupling constants. The assignment of the signals for 4-H and 7-H was carried out in a study of **7**. The ^{13}C NMR spectral data are also in good accord with the proposed structure (see Experimental). The signals were assigned on the basis of a two-dimensional spectrum using the direct and long-range coupling constants.

3-(Butyroyl)benzoxazolinone **4** was unexpectedly obtained in 63% yield in the reaction of **1** with butyric anhydride instead of hydrazide **2** (R = Pr) (Scheme 2).

Scheme 2



The structure of **4** was indicated by the lack of a primary amino group band at 3265 and 3170 cm^{-1} in the IR spectrum, the finding of bands at 1793 and 1728 cm^{-1} characteristic for the CO group, and the finding of a molecular ion peak with *m/z* 205 in the mass spectrum. The formation of N-(3-butyroyl)benzoxazolinone **4** in this reaction was also demonstrated by its convergent synthesis from benzoxazolinone and butyric anhydride. The melting point of a mixed probe of samples of **4** obtained starting from **1** and from benzoxazolinone was undepressed. Hydrazide **2c** is probably formed initially from hydrazinobenzoxazole and butyric anhydride. The reaction mixture grows warm and butyric acid is lost upon its distillation. Then, **2c** react with the released butyric acid, leading to benzoxazolinone as an intermediate and the final product **4** (Scheme 3).

Scheme 3

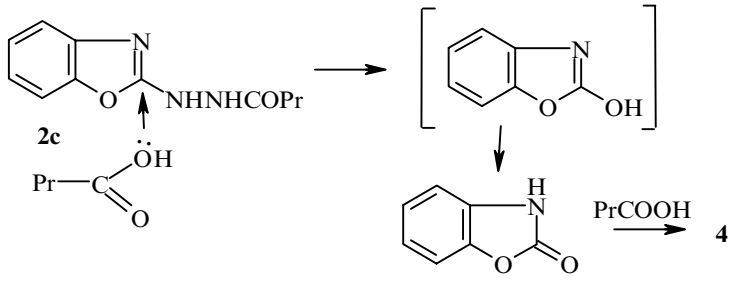


TABLE 1. ^{1}H NMR Spectra of Compound **2b** in CD_3OD

Proton	4-H, d	5-H, t	6-H, t	7-H, d	CH_3, s
Chemical shift, δ, ppm	7.541	7.328	7.352	7.592	2.50
Coupling constant (*J*), Hz	J_{45} = 7.82; J_{46} = 1.38; J_{47} = 0.85; J_{56} = 7.20; J_{57} = 1.35; J_{67} = 7.50				—

Indeed, product **4** was detected by thin-layer chromatography (R_f 0.30) after heating hydrazinobenzoxazole **1** with butyric acid for 2 h. We should, however, note that the formation of the corresponding benzoxazolinone was not observed upon heating **1** with acetic acid at reflux. This failure may be related to the length of the chain of the starting acid. The formation of products such as **4** was noted previously in the reaction of benzoxazole **1** with 1,3-diketones [7].

Only the corresponding hydrazides **2d** (R = Ph), **2e** (R = *o*-MeC_6H_4), and **2f** (R = $C_7H_4NO_2CH_2CH_2$) were obtained in moderate yields upon the acylation of hydrazinobenzoxazole **1** by benzoyl chloride, *o*-toluyl chloride, and β-(2-benzoxazolyl)propionyl chloride in the presence of triethylamine. Thus, **2d** was obtained in 17% yield upon carrying out the reaction in aqueous alkali and in 29% yield in acetonitrile. Products **2e** (35% yield) and **2f** (41% yield) were synthesized in acetone on heating at reflux.

These results indicate that products **3** are not formed in the reaction of hydrazinobenzoxazole **1** with carboxylic acids and their anhydride and chloride derivatives.

We also were unable to obtain the corresponding triazole derivative through the reported synthesis from the 2-(2-benzoxazolyl)hydrazide of acetic acid **2b**. Only benzoxazolinone was isolated from the reaction mixture in an attempt to cyclize **2b** using $POCl_3$. This failure may be linked to special features of the heterocyclic fragment in **2b**.

The reaction of 2-hydrazinobenzoxazole **1** with aldehydes was studied in the case of furfural and 2-carboxy-3,4-dimethoxybenzaldehyde (**5**). Sycheva et al. [8] have reported that **1** readily forms hydrazones with anisaldehyde and benzaldehyde.

The reaction of equimolar amounts of these reagents in ethanol gave the corresponding hydrazones **6** (obtained from furfural in 41% yield after heating at reflux) and **7a** (obtained in 82% yield from aldehyde-acid **7a** after maintenance at room temperature) (Scheme 4).

Scheme 4

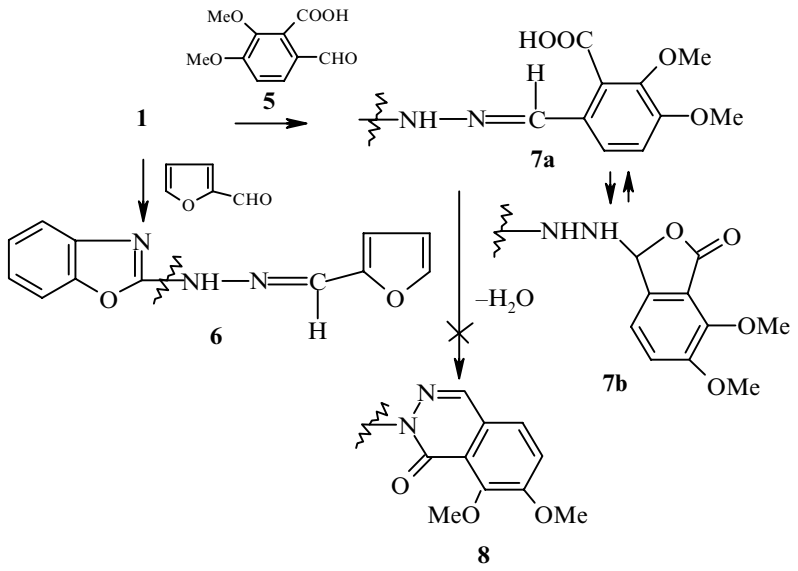


TABLE 2. ^{1}H NMR Spectra of Compound **7a**, Coupling Constants (*J*), Hz*

Proton	4-H, d	5-H, t	6-H, t	7-H, d	5'-H, d	6'-H d	N=CH, s	3'-OCH_3, s	4'-OCH_3, s
Chemical shift in CD_3OD	7.37	7.13	7.22	7.35	7.17	7.88	8.13	3.86	3.94
Chemical shift in DMSO-d_6	7.52	7.12	7.23	7.40	7.24	7.78	8.15	3.86	3.94

* $J_{45} = J_{56} = J_{57} = 7.1$; $J_{5'6'} = 8.8$.

The formation of **6** and **7a** was confirmed by the elemental analysis data, mass spectrometry (for **6**), IR spectroscopy, and ^{1}H and ^{13}C NMR spectroscopy (for **7a**). Hydrazone **7** may exist as **7a** and **7b** and cyclization may lead to **8**. However, structures **7b** and **8** were not indicated by the analytical data. The ^{1}H NMR spectrum of **7a** taken in deuteromethanol shows singlets for the –N=CH– group at 8.13 ppm (1H) and for the 3'-OMe and 4'-OMe groups at 3.86 (3H) and 3.94 ppm (3H), respectively. The signals for the benzoxazole protons, as in the case of **4**, give rise to a characteristic ABCD system with ortho coupling J = 7.1 Hz, while the two protons of the aryl substituent give rise to an AB system with J = 8.8 Hz (Table 2). The signals were assigned using double resonance techniques, in particular, by selective suppression of individual lines in the multiplets (INDOR method) for 4-H and 7-H and by the Overhauser effect (13.5%) from 4'-OMe on the doublet of 5'-H for the aryl protons. The conclusion concerning the position of the signals of 4-H and 7-H was made by comparing the ^{1}H NMR spectra of **7a** taken in deuteromethanol and DMSO-d_6. The coordination of DMSO at 3-N should have a greater effect on the chemical shift of 4-H than for 7-H. Table 2 shows that the signal at 7.37 ppm (in CD_3OD) undergoes the greatest change (by 0.15 ppm) upon replacing the solvent. The signals for 4-H, 5-H, and 7-H taken in DMSO-d_6 are broadened (the width of the individual lines reaches 9.0 Hz), which precludes measurement of ^{4}J and ^{3}J. This broadening indicates a solvent effect and significant hindrance to rotation of the aryl substituent. The signal for the proton in the –N=CH– group is a narrow singlet in both spectra.

The finding of a carbonyl group band at 1651 cm^{-1} in the IR spectrum of **7a** excludes the formation of **7b** and **8**.

Heating **1** and **5** in ethanol or toluene at reflux even in the presence of *p*-TsOH only leads to the formation of **7a**. The finding of IR bands at 2940, 2845, and 2482 cm^{-1} suggests that the molecule is highly associated and this may be one of the reasons accounting for hindered rotation.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer. The mass spectra were taken on a Kratos NS2SRF mass spectrometer with direct sample inlet into the ion source. The ionizing electron voltage was 70 eV. The ion source temperature was 250°C. The sample inlet system temperature was 150°C. The NMR spectra were taken on a Varian Unity-400 spectrometer at 400 MHz for the ^{1}H NMR spectra and 100 MHz for the ^{13}C NMR spectra with TMS as the internal standard. The course of the reactions and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using 1:2 benzene–ethanol as the eluent. The spots were developed with the solution of $KMnO_4$ (1 g) in a mixture of sulfuric acid (4 ml) and water (96 ml).

A sample of β-(benzoxazolyl)propionyl chloride was prepared according to Wigert et al. [11].

N-Formyl-N'-(2-benzoxazolyl)hydrazine (2a). A solution of compound **1** (0.5 g, 0.03 mol) in formic acid (5 ml) was heated at reflux for 3 h. Acid was then distilled off in vacuum. The residue was washed with water and dried in the air to give compound **2a** (0.06 g, 26%); mp 173-175°C (benzene), R_f 0.13. IR spectrum, cm^{-1}: 1687 (CHO). Mass spectrum, *m/z* (I_{rel}, %): M^+ 177 (90), 149 (100), 135 (80), 133 (45), 105 (55), 91 (35), 78 (70), 69 (50). Found, %: N 23.00. $C_8H_7N_3O_2$. Calculated, %: N 23.59.

N-Acetyl-N'-(2-benzoxazolyl)hydrazine (2b). A solution of compound **1** (0.75 g, 0.005 mol) and acetic anhydride (3 ml) was maintained for 1 h at room temperature. The residue was filtered off to give compound **2b** (0.7 g, 72%); mp 140-142°C (benzene), R_f 0.27. ^{13}C NMR spectrum, δ, ppm: 163.62 ($C_{(2)}$), 147.58 ($C_{(9)}$), 125.88 ($C_{(8)}$), 132.08 ($C_{(7)}$), 131.66 ($C_{(6)}$), 117.27 ($C_{(5)}$), 156.10 ($C_{(4)}$), 176.81 (C=O), 29.02 (CH_3). Found, %: N 21.59. $C_9H_9N_3O_2$. Calculated, %: N 21.90.

N-Propionyl-N'-(2-benzoxazolyl)hydrazine (2c) was obtained from compound **1** (0.75 g, 0.005 mol) and propionic anhydride (3 ml) as described for **2b**. Yield of **2c** 0.7 g (53%); mp 120-122°C (benzene). Mass spectrum, *m/z* (I_{rel}, %): 205 (63), 149 (100). Found, %: N 24.32. $C_{10}H_{11}N_3O_2$. Calculated, %: N 24.71.

N-2-Methylbenzoyl-N'-(2-benzoxazolyl)hydrazine (2e). A mixture of compound **1** (0.75 g, 0.005 mol), Et_3N (0.5 g, 0.005 mol), and 2-methylbenzoyl chloride (0.77 g, 0.005 mol) in acetone (15 ml) was heated at reflux for 1 h on a steam bath to give compound **2e** (0.45 g, 35%); mp 210-212°C (methanol). Mass spectrum, *m/z* (I_{rel}, %): 268 (10), 119 (100), 91 (39), 69 (17). Found, %: N 15.52. $C_{15}H_{10}N_3O_2$. Calculated, %: N 15.73.

N-Benzoyl-N'-(2-benzoxazolyl)hydrazine (2d). A. The reaction of compound **1** (0.745 g), NaOH (0.2 g) in water (5 ml), and benzoyl chloride (0.7 g, 0.005 mol) gave compound **2d** (0.7 g, 17%); mp 195-197°C (methanol), R_f 0.76.

B. Triethylamine (0.505 g), acetonitrile (15 ml), and benzoyl chloride (0.7 g, 0.005 mol) were added to compound **1** (0.75 g). The mixture was heated at reflux on a steam bath for 1 h to give compound **2d** (1.2 g, 29%); mp 196-197°C (ethanol), R_f 0.76. Mass spectrum, *m/z* (I_{rel}, %): 253 (M^+). Found, %: N 17.25. $C_{14}H_{11}N_3O_2$. Calculated, %: N 17.00.

C. Benzoyl chloride (0.7 g, 0.005 mol) was added to compound **1** (0.75 g, 0.005 mol) and NaOH (0.2 g) in water (5 ml). The mixture was maintained with stirring for 1 h at room temperature to give compound **2d** (0.7 g, 17%); mp 195-197°C (methanol), R_f 0.76. The melting point of a mixed sample of **2d** obtained by methods A, B, and C was undepressed.

N-[3-(2-Oxo-2-benzoxazolyl)propionyl]-N'-(2-benzoxazolyl)hydrazine (2f). The reaction of compound **1** (0.75 g, 0.005 mol) and β-(benzoxazolonoyl)propionyl chloride (1.13 g, 0.005 mol) in the presence of Et_3N (0.5 g, 0.005 mol) in acetone (15 ml) according to method B gave compound **2f** (0.7 g, 41%); mp 198-200°C (ethanol). Mass spectrum, *m/z* (I_{rel}, %): 338 (79), 204 (35), 190 (80), 148 (100), 134 (75), 119 (25), 91 (43), 77 (75). Found, %: N 17.25. $C_{17}H_{14}N_4O_3$. Calculated, %: N 17.00.

N-(Butyroyl)benzoxazolinone (4). A. Freshly distilled butyric anhydride (3 ml) was added to compound **1** (0.75 g, 0.005 mol). The reaction mixture was stirred for 1 h at room temperature and then heated for 2 h on a steam bath. The acid released was distilled off at 140-160°C to give compound **4** (0.1 g, 7.5%); mp 78-80°C (hexane). IR spectrum, cm^{-1}: 1793, 1728 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 205 (35), 135 (90), 91 (30), 79 (50), 71 (100). Found, %: N 6.95. $C_{11}H_{11}NO_3$. Calculated, %: N 6.95.

B. A mixture of benzoxazolinone (1.35 g, 0.01 mol) and butyric anhydride (5 ml) was heated at reflux for 2 h. The crystalline precipitate was filtered off to give compound **4** (1.3 g, 63%); mp 78-80°C, R_f 0.9. The melting point of a mixed probe of samples of **4** obtained according to methods A and B was undepressed.

N-Furfurolidene-N'-(2-benzoxazolyl)hydrazine (6). A mixture of compound **1** (0.4 g, 0.005 mol) and furfural (0.33 ml, 0.005 mol) was heated at reflux for 2 h. The precipitate was filtered off to give compound **6** (0.27 g, 49%); mp 158-160°C (ethanol), R_f 0.37. Mass spectrum, *m/z* (I_{rel}, %): 207 (100), 149 (60). Found, %: N 18.04. $C_{12}H_9N_3O_2$. Calculated%: N 18.52.

N-(2-Carboxy-3,4-dimethoxybenzylidene)-N'-(2-benzoxazolyl)hydrazine (7). Aldehyde-acid **5** (1.04 g, 0.005 mol) was added to compound **1** (0.75 g, 0.005 mol) in ethanol and the reaction mixture was stirred for 1 h at room temperature to give compound **7** (1.4 g, 82%); mp 202-204°C (butanol), R_f 0.37. IR spectrum: 1651 cm^{-1}. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 159.15 ($C_{(2)}$), 142.04 ($C_{(3a)}$), 109.26 ($C_{(4)}$), 121.31 ($C_{(5)}$), 124.09 ($C_{(6)}$), 116.38 ($C_{(7)}$), 147.89 ($C_{(7a)}$), 141.33 (N=CH), 123.13 ($C_{(1')}$), 130.22 ($C_{(2')}$), 144.54 ($C_{(3')}$), 153.21 ($C_{(4')}$), 113.78 ($C_{(5')}$), 121.67 ($C_{(6')}$), 167.45 (C=O), 60.90 (3'-OCH_3), 55.97 (4'-OCH_3). Found, %: N 12.73. $C_{17}H_{15}N_3O_5$. Calculated, %: N 12.31.

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