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SYNTHESIS OF 2-(3-PHENOXYPHENYL)-SUBSTITUTED BENZOXAZOLES, BASED ON NITRILES CONTAINING THE DIPHENYL OXIDE FRAGMENT

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A method is proposed for the preparation of 2-(3-phenoxyphenyl)-substituted benzoxazoles, which are of interest as structural blocks for the synthesis of compounds possessing potential biological activity.

Key words: *o*-aminophenol, benzoxazole, diphenyloxide, nitrile, 3-phenoxyphenyl fragment.

Substituted benzoxazoles possess high biological activity. It is known that benzoxazole is produced by plants to protect themselves against diseases and pests. On the market there are insectoacaricides with contact and intestinal action – Zolon, based on a natural benzoxazole [1] and 2-aryl-substituted benzoxazoles may be used as herbicides [2]. Some derivatives of benzoxazoles are effective for treatment of diabetes, migraine, and display neuroleptic properties [3]. The preparations Rispolept, and Risperidone are derivatives of benzoxazole which have antipsychotic effects and are effective against schizophrenia [4, 5].

From the literature analysis it may be concluded that the practical value of benzoxazoles in the first place is determined by the substituent nature in a heterocyclic ring. In this connection there has been considerable interest in the introduction of the 3-phenoxyphenyl fragment in the benzoxazole ring since the combination of different pharmacophores in a molecule permits the broadening of the range of biological activity or its strengthening as a synergism result. For example, such derivatives of diphenyl oxide as Permethrin [(3-phenoxyphenyl)methyl ester of 3-(2,3-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid] and Phenothrin [(3-phenoxyphenyl)methyl ester of 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropanecarboxylic acid] are used as medicines possessing antiparasitic, anti-louse, insecticidal, ovicidal pharmacological effects. There are examples of the use of phenoxyphenylacetylenes, obtained on the basis of 1-(2-methyl-4-phenoxyphenyl)-ethanone and 1-(3-phenoxyphenyl)ethanone, as antithrombotic, anti-inflammatory, antipyretic agents, and analgesics [6].

In the present work we suggested the possibility of preparing 2-(3-phenoxyphenyl)-substituted benzoxazoles **3a–i** on the basis of the nitriles **1a–i**, which contain the diphenyl oxide fragment, and *o*-aminophenol hydrochloride **2** [7].

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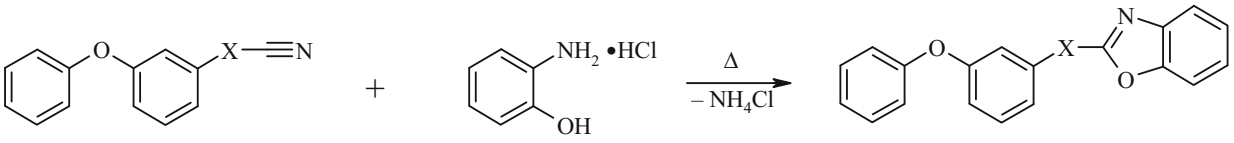
During the course of the study, it was established that the reaction occurred at 190–200°C without solvent, with yields of 32–80% after recrystallization from ethanol. The low yield of compound **3i** is a result of steric hindrance arising from the complex structure of the nitrile **1i** which contains two diphenyl oxide fragments. A period of 7–10 h was required for the synthesis of the 2-(3-phenoxyphenyl)-substituted benzoxazoles **3a–i**. Hydroquinone was added to the reaction mixture for the successful synthesis of benzoxazoles **3c,d,i** avoiding polymerization of the unsaturated nitriles **1c,d,i** at the high reaction temperature.



1a–i **2** **3a–i**

1, 3 a X is absent, **b** X= $–CH_2–$, **c** X= –CH=CH–, **d** X= –(Me)C=CH–, **e** X= $–(CH_2)_2$,
f X = $CH_2NH(CH_2)_2–$, **g** X= $–CH_2O(CH_2)_2–$, **h** X= –(C=O)OC(Me)$_2$–, **i** X= $–CH=C–C_6H_4OC_6H_5$

Compounds **3a–i** are dark-colored crystalline substances, soluble in DMF, DMSO, CCl_4, benzene, and ether, and on heating in ethanol and methanol. They are insoluble in water. The structures of compounds **3a–i** were confirmed by the absence of the nitrile stretching frequency from their IR spectra.

So previously unknown 2-(3-phenoxyphenyl)-substituted benzoxazoles have been synthesized, based on nitriles containing the 3-phenoxyphenyl unit and *o*-aminophenol hydrochloride.

EXPERIMENTAL

IR spectra of nujol mulls were recorded at a Specord M-83 spectrometer. ^{1}H NMR spectra of CCl_4 solutions (compounds **3a–c**) and DMSO-d_6 solutions (compounds **3d–i**) with HMDS internal standard (δ 0.05 ppm) were recorded at a Varian Mercury 300B spectrometer (300 MHz). Mass spectra were recorded at a Varian Saturn 2100T with an ionization energy of 70 eV.

Compounds 3a–i (General Method). A mixture of *o*-aminophenol hydrochloride **2** (0.012 mol) and nitrile **1** (0.01 mol) was heated for 7–10 h in a sealed glass ampoule at 190–200°C. Hydroquinone (1–2 mg) was added to the reaction mixture for the synthesis of benzoxazoles **3c,d,i** . The reaction mixture was triturated with ether, filtered, and washed with 4 N sodium hydroxide solution. The ether layer was filtered again, washed with water, the solvent was evaporated, and the residue recrystallized from ethanol.

2-(3-Phenoxyphenyl)benzoxazole (3a). Yield 74%; mp 130–132°C. ^{1}H NMR spectrum, δ, ppm: 7.15–7.75 (13H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 287 $[M]^+$ (100), 63 (16). Found, %: C 79.02; H 4.53; N 4.89. $C_{19}H_{13}NO_2$. Calculated, %: C 79.43; H 4.56; N 4.88.

2**-(3-Phenoxybenzyl)benzoxazole (3b).** Yield 80%; mp 137–140°C. ^{1}H NMR spectrum, δ, ppm: 7.10–7.80 (13H, m, H Ar); 3.81 (2H, s, CH_2). Mass spectrum, *m/z* (I_{rel}, %): 301 $[M]^+$ (64), 300 (100), 132 (25), 77 (17), 63 (11), 51 (13). Found, %: C 79.74; H 5.01; N 4.63. $C_{20}H_{15}NO_2$. Calculated, %: C 79.72; H 5.02; N 4.65.

2-[(*E*)-2-(3-Phenoxyphenyl)vinyl]benzoxazole (3c). Yield 76%; mp 120–122°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.10–7.65 (13H, m, H Ar); 7.44 (1H, d, *J* = 12.0, ArC<u>H</u>=CH); 5.25 (1H, d, *J* = 12.0, ArCH=C<u>H</u>). Mass spectrum, *m/z* ($I_{rel,}$%): 313 $[M]^+$ (36), 312 (100). Found, %: C 80.48; H 4.78; N 4.48. $C_{21}H_{15}NO_2$. Calculated, %: C 80.49; H 4.82; N 4.47.

2-[2-(3-Phenoxyphenyl)propen-1-en-1-yl]benzoxazole (3d). Yield 64%; mp 140–142°C. ^{1}H NMR spectrum, δ, ppm: 7.12–7.84 (13H, m, H Ar); 6.62 (1H, s, CH); 2.42 (3H, s, CH_3). Mass spectrum, *m/z* ($I_{rel,}$%): 327 $[M]^+$ (100), 207 (13). Found, %: C 80.72; H 5.18; N 4.29. $C_{22}H_{17}NO_2$. Calculated, %: C 80.71; H 5.23; N 4.28.

2-[2-(3-Phenoxyphenyl)ethyl]benzoxazole (3e). Yield 56%; mp 135–137°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.10–7.70 (13H, m, H Ar); 2.82 (2H, t, *J* = 6.0, $ArC\underline{H_2}CH_2$); 3.45 (2H, t, *J* = 6.0, $ArCH_2C\underline{H_2}$). Mass spectrum, *m/z* ($I_{rel,}$%): 315 $[M]^+$ (100), 207 (17). Found, %: C 80.00; H 5.41; N 4.44. $C_{21}H_{17}NO_2$. Calculated, %: C 79.98; H 5.43; N 4.44.

2-[2-(3-Phenoxybenzylamino)ethyl]benzoxazole (3f). Yield 80%; mp 127–130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.85–7.70 (13H, m, H Ar); 3.51 (1H, s, NH); 3.64 (2H, s, $ArCH_2N$); 2.26 (2H, t, *J* = 6.0, NCH_2); 2.69 (2H, t, *J* = 6.0, $NCH_2C\underline{H_2}$). Mass spectrum, *m/z* ($I_{rel,}$%): 344 $[M]^+$ (100), 312 (24), 285 (14), 63 (25). Found, %: C 76.69; H 5.85; N 8.09. $C_{22}H_{20}N_2O_2$. Calculated, %: C 76.72; H 5.85; N 8.13.

2-{2-[(3-Phenoxybenzyl)oxy]ethyl}benzoxazole (3g). Yield 51%; mp 143–145°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.00–7.75 (13H, m, H Ar); 4.20 (2H, s, $ArCH_2O$); 3.32 (2H, t, *J* = 6.0, $OC\underline{H_2}CH_2$); 2.23 (2H, t, *J* = 6.0, $OCH_2C\underline{H_2}$). Mass spectrum, *m/z* ($I_{rel,}$%): 345 $[M]^+$ (100), 63 (12). Found, %: C 76.52; H 5.50; N 4.00. $C_{22}H_{19}NO_3$. Calculated, %: C 76.50; H 5.54; N 4.06.

1-(Benzoxazol-2-yl)-1-methylethyl-3-phenoxybenzoate (3h). Yield 62%; mp 160–162°. ^{1}H NMR spectrum, δ, ppm: 6.80–7.20 (13H, m, Ar H); 1.80 (6H, s, $2CH_3$). Mass spectrum, *m/z* ($I_{rel,}$%): 373 $[M]^+$ (2), 289 (17), 287 (100). Found, %: C 74.02; H 5.18; N 3.73. $C_{23}H_{19}NO_4$. Calculated, %: C 73.98; H 5.13; N 3.75.

2-[1,2-Bis(3-phenoxyphenyl)vinyl]benzoxazole (3i). Yield 32%; mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 6.80–7.25 (23H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 481 $[M]^+$ (14), 480 (100), 352 (51), 281 (17), 207 (28), 77 (29), 51 (18). Found, %: C 82.32; H 4.88; N 2.89. $C_{33}H_{23}NO_3$. Calculated, %: C 82.31; H 4.81; N 2.91.

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