

Short Note

4-(7-Bromobenzo[*d*][1,2,3]thiadiazol-4-yl)morpholine

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Abstract: Dibromoderivatives of benzofused chalcogen-nitrogen heterocycles are important precursors in the synthesis of various photovoltaic materials. 4,7-Dibromobenzo[*d*][1,2,3]thiadiazole is a practically unexplored compound in this series. In this communication, it was shown that the nucleophilic substitution of 4,7-dibromobenzo[*d*][1,2,3]thiadiazole with morpholine gave selectively 4-substituted product—4-(7-bromobenzo[*d*][1,2,3]thiadiazol-4-yl)morpholine. The structure of the newly synthesized compound was established by means of elemental analysis, high resolution mass-spectrometry, ¹H, ¹³C NMR, and IR spectroscopy, mass-spectrometry, and X-ray analysis.

Keywords: 4-(7-bromobenzo[*d*][1,2,3]thiadiazol-4-yl)morpholine; 4,7-dibromobenzo[*d*][1,2,3]thiadiazole; morpholine; nucleophilic substitution

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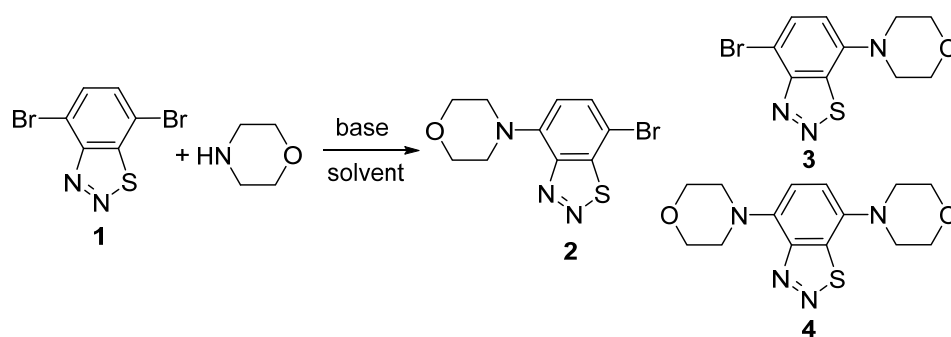
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1. Introduction

Electron-acceptor heterocycles find application in several photovoltaic materials such as dye sensitized solar cells, organic near-infrared materials, organic light emitting diodes (OLEDs), charge transfer materials and others [1–3]. Among them benzo[*c*][1,2,5]thiadiazole (BT) has been the most investigated unit [4–7]. Surprisingly, its isomer benzo[*d*][1,2,3]thiadiazole (iso-BT) is virtually unknown as a building block. Moreover, its easy availability from commercial 2-aminobenzenethiol [8] and facile bromination at the 4,7-position [9] make 4,7-dibromobenzo[*d*][1,2,3]thiadiazole **1** a very promising starting material. However, its chemistry is limited to Stille cross-coupling co-polymerization [9]. Further investigation of the chemistry of 4,7-dibromobenzo[*d*][1,2,3]thiadiazole **1**, including nucleophilic substitution, may have an impact on the preparation of new materials. Herein, we report on the study of the reaction between 4,7-dibromobenzo[*d*][1,2,3]thiadiazole **1** and morpholine and synthesis of 4-(7-bromobenzo[*d*][1,2,3]thiadiazol-4-yl)morpholine **2**.

2. Results and Discussion

A promising precursor of various photovoltaic materials—4,7-dibromobenzo[*d*][1,2,3]thiadiazole **1**—was easily prepared by a two-step synthesis from commercially available 2-aminobenzenethiol [8,9]. In this communication, its nucleophilic substitution with morpholine was investigated. In this reaction, three products could be formed: two monosubstituted derivatives **2** and **3**, and disubstituted compound **4**. The literature describes two examples of nucleophilic substitution for its isomer 4,7-dibromobenzo[*c*][1,2,5]thiadiazole; it was shown that refluxing in morpholine and piperidine leads to 4-monosubstituted derivatives [10,11]. Therefore, the study of the reaction of compound **1** with morpholine began with boiling it in an excess of nucleophile.



Scheme 1. Synthesis of 4-(7-bromobenzo[d][1,2,3]thiadiazol-4-yl)morpholine 2.

Refluxing 4,7-dibromobenzo[d][1,2,3]thiadiazole **1** in pure morpholine for 18 h (Entry 1, Table 1) led to a single product with a low yield of 35% (Scheme 1). In this case, complete conversion of the starting dibromide was observed, and other products were not isolated. To increase the yield of the product, as well as to reduce the excess of the used nucleophile, we carried out reactions in various solvents (Entries 2–4). We showed that among the investigated solvents, the highest yield was obtained when the reaction was carried out in dimethylsulfoxide (DMSO) (Entry 4). To reduce the excess of morpholine, we added an additional base into the reaction, to intercept the released hydrogen bromide (Entries 5–7). However, it turned out that DABCO (1,4-diazabicyclo[2.2.2]octane) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) reduce the overall product yield, while the reaction with Et₃N yielded 4-(7-bromobenzo[d][1,2,3]thiadiazol-4-yl)morpholine **2** in a high yield of 83% (Entry 5). The high selectivity of this process should be especially noted—even when the reaction is carried out in pure morpholine, the replacement of the bromine atom located next to the sulfur atom does not occur. Obviously, the reason for the absence of products **3** and **4**, in the reaction mixture is the significantly lower reactivity of bromine atoms in position 7 of the heterocycle, compared to the bromine atom in position 4. This is probably due to the greater stabilization of the σ -complex formed upon attack by the nucleophilic agent of the bromine atom in position 4, as compared to the σ -complex, which would lead to the formation of product **3**. This is owing to the immediate proximity of the nitrogen atom, which has a higher electronegativity than the sulfur atom and, as a consequence, an enhanced ability to stabilize the negatively charged σ -complex.

Table 1. Reaction of 4,7-dibromobenzo[d][1,2,3]thiadiazole **1** with morpholine.

Entry	Excess of Morpholine	Solvent	Base (equiv.)	Yield 2 , %
1		- ^a	-	35
2	2	DMF ^b	-	53
3	2	MeCN ^a	-	28
4	2	DMSO ^b	-	70
5	1.5	DMSO ^b	Et ₃ N (1.1)	83
6	1.5	DMSO ^b	DABCO (1.1)	63
7	1.5	DMSO ^b	DBU (1.1)	55

^a Conditions: 18 h at boiling point. ^b Conditions: 18 h at 110 °C.

The structure of 4-(7-bromobenzo[d][1,2,3]thiadiazol-4-yl)morpholine **2** was confirmed by means of high resolution mass-spectrometry, ¹H, ¹³C NMR, IR, and UV spectroscopy, mass-spectrometry, and X-ray analysis (Figure 1) (see Supplementary Materials).

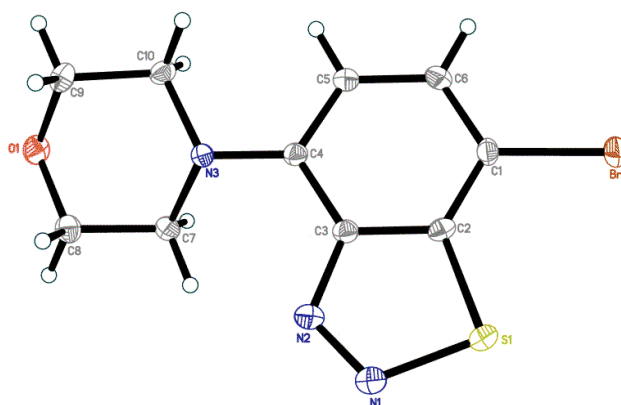


Figure 1. X-Ray structure (ORTEP at 50% level) of 4-(7-bromobenzo[d][1,2,3]thiadiazol-4-yl)morpholine **2**.

In conclusion, it was shown that the nucleophilic substitution of 4,7-dibromobenzo[d][1,2,3]thiadiazole **1** is regioselective and led to 4-monosubstituted derivative. This reaction opens up possibilities to synthesize functional derivatives of benzo[d][1,2,3]thiadiazoles, which may be of interest as compounds with useful physical properties.

3. Materials and Methods

4,7-Dibromobenzo[d][1,2,3]thiadiazole **1** was prepared according to the published method [9]. The solvents and reagents were purchased from commercial sources and used as received. Elemental analysis was performed on a 2400 Elemental Analyzer (Perkin Elmer Inc., Waltham, MA, USA). Melting point was determined on a Kofler hot-stage apparatus and is uncorrected. ^1H and ^{13}C NMR spectra were taken with a Bruker AM-300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) (at frequencies of 300 and 75 MHz) in CDCl_3 solution, with TMS as the standard. J values are given in Hz. MS spectrum (EI, 70 eV) was obtained with a Finnigan MAT INCOS 50 instrument (Hazlet, NJ, USA). IR spectra were measured with a Bruker “Alpha-T” instrument in KBr pellet. High-resolution MS spectra were measured on a Bruker micrOTOF II instrument (Bruker Daltonik GmbH, Bremen, Germany) using electrospray ionization (ESI). The measurement was performed in a positive ion mode (interface capillary voltage -4500 V) or in a negative ion mode (3200 V); mass range was from m/z 50 to m/z 3000 Da; external or internal calibration was performed with Electrospray Calibrant Solution (Fluka). Syringe injection was used for solutions in acetonitrile, methanol, or water (flow rate 3 L/min $^{-1}$). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C. Solution UV-visible absorption spectra were recorded using a OKB Spektr SF-2000 UV/Vis/NIR spectrophotometer controlled with SF-2000 software. All samples were measured in a 1 cm quartz cell at room temperature with 1×10^{-4} mol mL $^{-1}$ concentration in CH_2Cl_2 .

Crystal structure determination was performed in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry, Moscow. X-ray diffraction data were collected at 100 K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator, shutterless φ - and ω -scan technique), using Mo K-radiation (0.71073 Å). The intensity data were integrated by the SAINT program and were corrected for absorption and decay using SADABS. The structure was solved by direct methods using SHELXS-2013 and refined on F^2 using SHELXL-2018. All non-hydrogen atoms were refined with individual anisotropic displacement parameters. The positions of all hydrogen atoms were found from the electron density-difference map, these atoms were refined with individual isotropic displacement parameters. The Cambridge Crystallographic Data Centre contains the supplementary crystallographic data for this paper No. CCDC 2073153. These data can be obtained free of charge via

<http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

Synthesis of 4-(7-bromobenzo[d][1,2,3]thiadiazol-4-yl)morpholine 2

Morpholine (90 mg, 1.04 mmol) and triethylamine (77 mg, 0.76 mmol) were added to a solution of 4,7-dibromobenzo[d][1,2,3]thiadiazole **1** (200 mg, 0.69 mmol) in 10 mL of DMSO. The mixture was degassed for 20 min with a stream of argon and then left for 18 h at 110 °C. The reaction mixture was poured into 1% solution of HCl (20 mL) and was left for 15 min. Then CH₂Cl₂ (30 mL) was added and the organic layer separated, washed with water several times, dried over MgSO₄, filtered, and concentrated under reduced pressure. The brown residue was purified by recrystallization from petroleum ether to obtain a yellow solid (210 mg, 83%) with mp 129–130 °C. *R*_f = 0.40 (petroleum ether/ethylacetate—10/1). ¹H NMR (ppm): 7.59 (1H, d, *J* = 8.4), 6.75 (1H, d, *J* = 8.4), 4.00 (2H, dd, *J* = 5.9, 3.6), 3.71 (2H, dd, *J* = 5.8, 3.7 Hz). ¹³C NMR (ppm): 144.3, 141.3, 141.1, 127.5, 107.7, 95.3, 61.6, 45.6. HRMS-ESI (*m/z*): calcd for (C₁₀H₁₁BrN₃OS) [M+H]⁺ 299.9800, found *m/z* 299.9801. MS (EI, 70eV), *m/z* (*I*, %): 301 (38), 299 (38), 270 (29), 257 (25), 242 (15), 215 (31), 201 (11), 148 (15), 134 (100), 120 (27), 107 (23), 93 (25), 69 (29). IR, ν, cm⁻¹: 3433, 2956, 2863, 1632, 1563, 1471, 1284, 1242, 1121, 977, 813. UV-Vis spectra (in CH₂Cl₂), λ_{max}: 248 nm (ε = 11796 M⁻¹ cm⁻¹), 386 nm (ε = 3753 M⁻¹ cm⁻¹).

Crystallographic data are displayed in Table 2.

Table 2. Crystal data and structure refinement for compound **2**.

Empirical Formula	C ₁₀ H ₁₁ BrN ₃ OS
Formula weight	300.18
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pna2 ₁
Unit cell dimensions	a = 16.1571(3) Å b = 4.03990(10) Å c = 16.8719(3) Å
Volume	1101.28(4) Å ³
Z	4
Density (calculated)	1.810 g/cm ³
Absorption coefficient	3.903 mm ⁻¹
F(000)	600
Crystal size	0.400 × 0.100 × 0.100 mm ³
Theta range for data collection	2.41 to 33.81°.
Index ranges	−25 ≤ h ≤ 25, −6 ≤ k ≤ 6, −26 ≤ l ≤ 26
Reflections collected	29,723
Independent reflections	4615 [R(int) = 0.0466]
Completeness to theta = 33.81 °	99.7%
Absorption correction	Multi-scan
Max. and min. transmission	(not specified)
Refinement method	Full-matrix least-squares on F ²
Data/restraints/parameters	4615/1/146
Goodness-of-fit on F ²	1.020
Final R indices [I > 2σ(I)]	R1 = 0.0288, wR2 = 0.0510
R indices (all data)	R1 = 0.0462, wR2 = 0.0569
Absolute structure parameter	0.009(10)
Largest diff. peak and hole	0.540 and −0.673 e.Å ⁻³

Supplementary Materials: The following are available online, CIF file, copies of ^1H , ^{13}C NMR, IR, UV-Vis, and mass-spectra for compound **2**.

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Conflicts of Interest: The authors declare no conflict of interest.

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