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Synthesis of some benzo[*d*]thiazole derivatives via suzuki cross-coupling reaction

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Abstract

In this study, 5 benzo[d]thiazole (**3a-3e**) derivatives were successfully synthesized in 2 steps through Suzuki cross-coupling reaction from 2-(4-bromophenyl)benzo[d]thiazole (**2**) and arylboronic acid derivatives in 80-95%.These compounds' structure was determined through NMR and mass spectral analysis. Besides, The key compound **2** was synthesized with a domestic microwave oven which helps to save cost and time in the synthesis process.

Keywords: benzo[d]thiazole, Suzuki reaction, microwave oven

1. Introduction

Due to its important contribution to improving the efficiency of organic synthesis, the Suzuki cross-coupling reaction was recognized by scientists with the 2010 Nobel Prize in Chemistry for chemist Suzuki A. The most efficient way to prepare the π-conjugated heterocyclic system through the formation of a carbon-carbon bond is the most important part of the Suzuki reaction. Thus "Suzuki coupling" is a versatile synthesis method, which has many advantages such as adaptability to many halogen derivatives as well as to arylboronic acid derivatives.

Benzo[*d*]thiazole derivatives show remarkable bioactivities such as: anti-tumor [1], anti-cancer activities [2], antibacterial [3], and plant growth-regulating activities [4, 5, 6]. Recently, the application of benzo[*d*]thiazole derivatives has been investigated. For example, new fluorescent heterocyclic Mmaterials [7, 8], organic light-emitting diodes (OLEDs) [9].

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Therefore, in this study, benzo[d]thiazole derivatives were further synthesized and investigated through Suzuki cross-coupling reaction, incorporating the use of a domestic microwave oven to make the key compound 2 [10].

2. Materials and methods or Experiments

2.1. Experimental

2.1.1. Solvents, chemicals and equipment

Palladium(II) chloride (PdCl2) was purchased from Sigma-Aldrich; 2-Aminothiophenol, 4-bromobenzaldehyde, dimethylformamide (DMF) were bought from Merck and used as received. Arylboronic acids were ordered on Aladdin.com. The organic solvents acetone, ethanol, methanol, *n*-hexane, ethyl acetate, acetic acid originated from China. The 1D and 2D NMR spectra were recorded on the Bruker Avance 500 NMR spectrometer in $CDCl_3$ at Institute of Chemistry, VAST. Mattson 4020 GALAXY Series FT-IR, LC-MSD-Trap-SL spectrometers were used to take IR and MS spectra. Progress of the reaction was monitored by thin-layer chromatography (TLC, silicagel on aluminum plate with particle size 0.04 - 0.063 mm from Merck, Germany. Goldsun MWO-G2051, 1200W Microwave Power, made in China 2017, was used. The determination of melting points was carried out on a Gallenkamp melting-point apparatus in the opening in a capillary tube.

2.1.2. Synthetic procedure

2.1.2.1. Using a household microwave synthesize 2-(4-bromophenyl)benzo[d] thiazole (2) [4]

To a mixture of *o*-aminothiophenol (0.34 mL, 2.1 mmol) and 4-bromo benzaldehyde (0.372g, 2.0 mmol) in a 100 mL beaker was irradiated 3-4 min at 400W power level. The progress of reaction was monitored with TLC in every 30 seconds (eluent: ethyl acetate/*n*-hexane 1/1, v/v). After crystallization, white needle-shaped crystals were obtained. The product is 2-(4-bromophenyl)benzo[*d*]thiazole (0.540g, 95%). Melting point 133.0-134.0 ^oC.

2.1.2.2. Suzuki coss-coupling reaction of 4-bromo(benzo[d]thiazol-2-yl)phenol (2) with arylboronic acids

General Procedure

K_2CO_3 (380 mg, 2.75 mmol) was added to a Schlenk tube equipped with a stirring bar and the tube was dried under vacuum and filled with argon, $PdCl_2$ (1.24 mg, 0.007 mmol), 2-phenylimidazole (2 mg, 0.014 mmol), 2-(4-bromophenyl) benzo[*d*]thiazole (**2**, 397 mg, 1.37 mmol), and arylboronic acid (2.06 mmol) in anhydrous DMF (12 mL). Then the mixture was stirred at 120 ^oC for the indicated time from 17h - 48h under argon atmosphere. The mixture was cooled and then poured over ice-water (250 mL) containing 1M HCl (2 mL) aqueous solution and extracted with $CHCl_3$ (5 × 40 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried (Na_2SO_4). Removal of solvent followed by column chromatographic purification (silica gel, hexane-$CHCl_3$) afforded the coupling product **3a, 3b, 3c, 3d, 3e**.

2-(3'-methyl-[1,1'-biphenyl]-4-yl)benzothiazole ***(3a)***

mp: 213.0-214.0 ^oC. ^1H NMR (500 MHz, $CDCl_3$) δ *(ppm)*: 2.43 (s, 3H), 7.20 (d, J = 7.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.37 (td, J = 8.0 Hz, J = 1.0 Hz, 1H), 7.44 (d, J = 9.5 Hz, 1H), 7.45 (d, J = 0.5 Hz, 1H), 7.48 (td, J = 8.0 Hz, J = 1.0 Hz, 1H), 7.70 (dt, J = 8.5 Hz, J = 2.0 Hz, *meta*, 2H), 7.89 (dd, J = 8.0 Hz, J = 0.5 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.14 (dt, J = 8.5 Hz, J = 2.0 Hz, *ortho*, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ *(ppm)*: 21.5 (CH_3), 121.6, 123.2, 124.2, 125.2, 126.3, 127.6, 127.8, 127.9, 128.7, 128.8, 132.4, 135.0, 138.5, 140.0, 143.9, 154.2 (aromatic and olefinic), 167.8 (S-C=N), ESI-MS *m/z*:

301.9 $[M+1]^+$.

2-([1,1'-biphenyl]-4-yl)benzothiazole ***(3b)***

mp: 208.0-209.0 ^oC; ^1H NMR (500 MHz, $CDCl_3$) δ *(ppm)*: 7.37 (td, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, *meta*, 2H), 7.49 (td, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.65 (dt, *J* = 8.0 Hz, J_1 = 1.5 Hz, J_2 = 2.0 Hz, *ortho*, 2H), 7.71 (dt, *J* = 8.5 Hz, *J* = 2.0 Hz, *meta*, 2H), 7.90 (dd, *J* = 8.0 Hz, *J* = 0.5 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.16 (dt, *J* = 8.5 Hz, *J* = 2.0 Hz, *ortho*, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ *(ppm)*: 121.6, 123.2, 125.2, 126.3, 127.1, 127.6, 127.9, 128.0, 128.9, 132.5, 135.0, 140.0, 143.7, 154.2 (aromatic and olefinic), 167.7 (S-C=N), ESI-MS *m/z*: 287.9 $[M+1]^+$.

2-(4'-methyl-[1,1'-biphenyl]-4-yl)benzothiazole ***(3c)***

mp: 215.0-216.0 ^oC, ^1H NMR (500 MHz, $CDCl_3$) δ *(ppm)*: 2.41 (s, 3H), 7.28 (d, *J* = 8.0 Hz, *meta*, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, *ortho*, 2H), 7.70 (d, *J* = 8.0 Hz, *meta*, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, *ortho*, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ *(ppm)*: 21.1 (CH_3), 121.6, 123.1, 125.2, 126.4, 126.9, 127.4, 128.0, 129.6, 132.0, 134.9, 137.1, 137.9, 143.8, 154.0 (aromatic and olefinic), 167.9 (S-C=N), ESI-MS *m/z*: 301.9 $[M+1]^+$.

2-(4'-methoxy-[1,1'-biphenyl]-4-yl)benzothiazole ***(3d)***

mp: 233.0-234.0 ^oC, ^1H NMR (500 MHz, $CDCl_3$) δ *(ppm)*: 3.86 (s, 3H), 7.00 (dt, *J* = 4.5 Hz, J_1 = 3.0 Hz, J_2 = 2.0 Hz, *meta*, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.50 (td, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.60 (dt, *J* = 4.5 Hz, J_1 = 3.0 Hz, J_2 = 2.0 Hz, *ortho*, 2H), 7.68 (d, *J* = 8.0 Hz, *meta*, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, *ortho*, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ *(ppm)*: 55.4 (CH_3-O), 114.4, 121.6, 123.1, 125.2, 126.4, 127.1, 128.0, 128.2, 132.5 (aromatic and olefinic), 159.7 (C-O aromatic), ESI-MS *m/z:* 317.9 $[M+1]^+$.

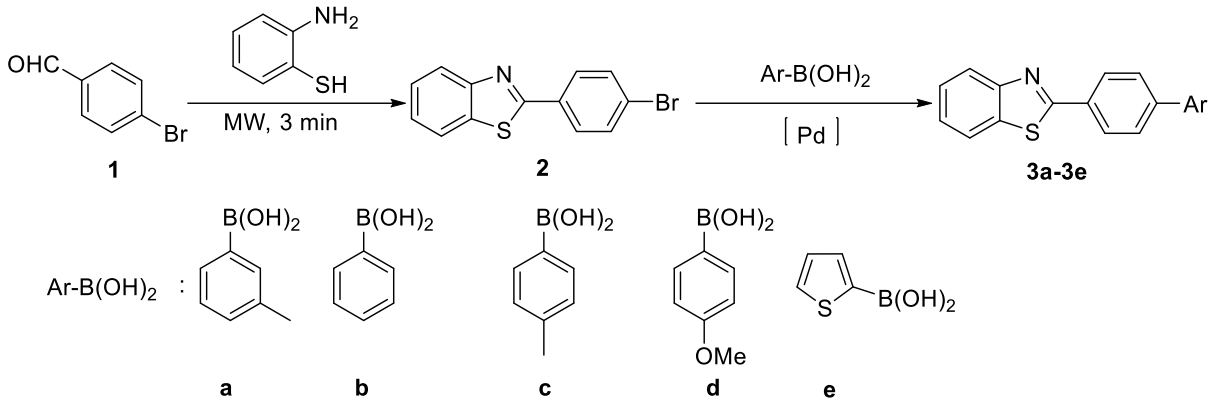
2-(4-(thiophen-2-yl)phenyl)benzothiazole ***(3e)***

mp: 210.0-211.0 ^oC, ^1H NMR (500 MHz, $CDCl_3$) δ *(ppm)*: 7.12 (t, *J* = 5.0 Hz, 1H), 7.35 (dd, *J* = 5.0 Hz, *J* = 1.0 Hz, 1H), 7.39 (td, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.42 (dd, *J* = 3.5 Hz, *J* = 1.0 Hz, 1H), 7.50 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.73 (dt, *J* = 8.5 Hz, J_1 = 1.5 Hz, J_2 = 2.0 Hz, *meta*, 2H), 7.91 (dd, *J* = 7.5 Hz, *J* = 0.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.11 (dt, *J* = 9.0 Hz, *J* = 2.0 Hz, *ortho*, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ *(ppm)*: 121.6, 123.1, 124.0, 125.2, 125.8, 126.2, 126.4, 128.1, 128.2, 132.4, 134.9, 136.3, 143.3, 154.1 (aromatic and olefinic), 167.4 (S-C=N), ESI-MS *m/z:* 293.8 $[M+1]^+$.

2.2. Results and discussion

2.2.1. Synthesis

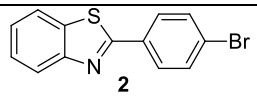
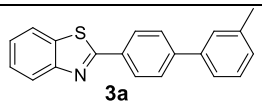
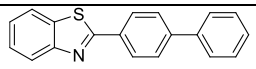
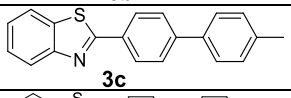
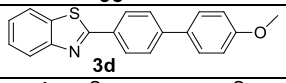
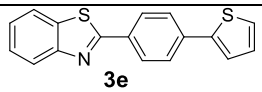
Some benzo[*d*]thiazole derivatives are synthesized as shown in scheme 1.



Scheme 1. Synthesis of 2-arylbenzothiazole derivatives 3a-3e

First, the benzo[*d*]thiazole ring-closing reaction was performed by condensing 4-bromo benzaldehyde (**1**) with 2-aminothiophenol under the domestic microwave irradiation, for about 3 minutes, the yield was 95.0 %, yielding the key compound 2-(4-bromophenyl)benzo[*d*]thiazole (**2**), [10]. Next, suzuki cross-coupling reaction from 2-(4-bromophenyl)benzo[*d*]thiazole (**2**) with arylboronic acids obtained 5 2-arylbenzo[*d*]thiazole derivatives (**3a-3e**), the reaction yield is 80-95%. The **3b-3e** compounds have physical and spectral properties which are consistent with those reported by Vasudevan Dhayalan *et al.* [11].

Table 1. Some properties of benzo[*d*]thiazole derivatives

Entry	Compounds	Shapes, colors	Efficiency (%)	Melting temperature (ºC)	Reaction time
1	 **2**	colorless needles	95	133.0-134.0	3 min
2	 **3a**	colorless powder	83	213.0-214.0	24h
3	 **3b**	colorless powder	80	208.0-209.0	20h
4	 **3c**	pale yellow needle	85	215.0-216.0	24h
5	 **3d**	colorless powder	95	233.0-234.0	21h
6	 **3e**	pale yellow needle	92	210.0-211.0	24h

2.2.2. Structural determination

Key compound 4-bromo(benzo[*d*]thiazol-2-yl)phenol (**2**) was checked for melting point, and it matched with our previous report [10]. From key compound **2**, 5 compounds **3a-3e** were obtained through Suzuki cross-coupling reaction for structural study by NMR, MS spectroscopic methods.

As a result of spectral analysis, the structures of compound **3a-3e** is consistent with the expected structure, in which **3a** is a new compound, so the structure should be studied with further HSQC and HMBC spectra. First, since compound **3a** contains heteroatoms, **3a** was tested by ESI-MS method. The

expected structure was compatible with a pseudo molecular weight [M+1] of 301.9 au that matches with the expected formula $C_{20}H_{15}NS$.

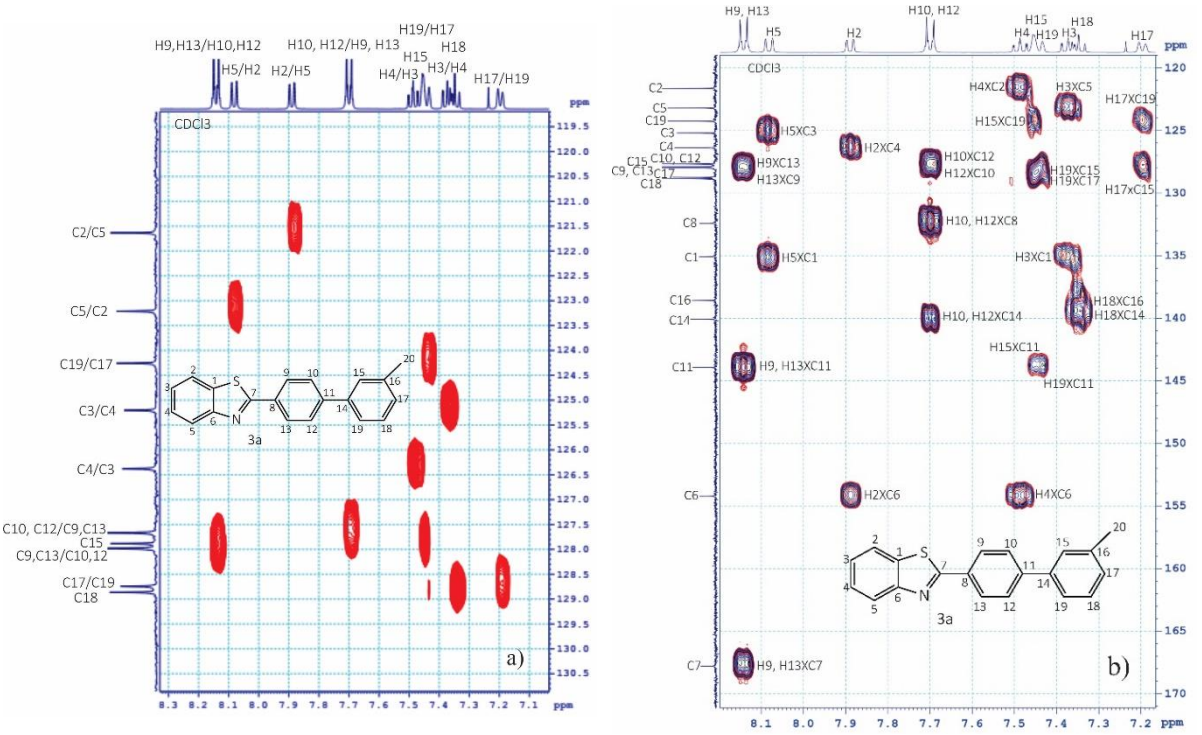


Figure 1. Part of HSQC (a), HMBC (b) spectra of compound **3a**

The ^{1}H NMR spectrum of compound **3a** shows a signal at δ 2.43 ppm (s, 1H) which is attributed to the proton of the methyl group; δ 7.45 ppm (d, J = 0.5 Hz, 1H) attributed to H15; δ 7.34 (t, J = 7.5 Hz, 1H) attributed to H18. The ^{13}C NMR spectrum of compound **3a** showed 17 peaks for 17 carbon atoms. Based on the chemical shift, the signal δ 21.56 ppm belongs to the methyl group. Then to accurately determine each carbon and hydrogen of compound **3a**, the HSQC and HMBC spectra were studied and analyzed specifically as follows: in the HSQC direct interaction spectrum (Figure 1a), each cross peak shows the protons which are attaching to the corresponding carbon atoms; however, there were still some pairs of carbons or protons that were difficult to identify such as C2/C5; C3/C4; C1/C6; C9, C13/C10, C12; C17/C19; H2/H5; H3/H4; H9, H13/H10, H12; H17/H19. To solve this issue, HMBC (figure 1b) spectrum was analyzed. For example, to distinguish H17 and H19, it is easy to see that H15 and H17 have a cross peak with C20 while H19 does not; In addition, H17 intersects with C15, C19 and H19 intersects with C11, C15, C17. Other protons and carbons are shown in the figure 1b. The known compounds **3b-3e** were also checked with NMR, MS spectra, and melting points. As a result, the studied structures were matched with the results published by Vasudevan Dhayalan *et al.* [11].

3. Conclusions

Five benzo[*d*]thiazole heterocyclic derivatives were successfully synthesized in only two steps. In which, the key compound **2** was synthesized with green method; the Suzuki reaction was carried out under the following conditions: anhydrous DMF, K_2CO_3, $PdCl_2$ and 2-phenylimidazole at 120^{o}C. Applications of compounds containing benzo[*d*]thiazole are being investigated.

Acknowledgements

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