Vietnam Journal of Chemistry, International Edition, **55**(4): 433-437, 2017
DOI: 10.15625/2525-2321.2017-00486

Preparation of some new benzo[*d*]thiazole derivatives

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Received 9 February 2017; Accepted for publication 28 August 2017

Abstract

In this work, four new benzo[*d*]thiazole derivatives were synthesized successfully from vanillin. Nitration of vanillin gave nitrovanillin followed by cyclization reaction with *o*-aminothiophenol under microwave irradiation in 4 minutes to give nitroaromatic compound **3**. The reduction to convert the nitro group to amino group was optimized. It was found that Fe/ con. HCl in ethanol was the best condition for this case about both yield (~95 %) and simple procedure to give compound **4** as a salt. Acetylation occurs at both phenolic hydroxyl group and amino group of the salt **4** to form *N,O*-acetyl compound **5**. Under mild hydrolysis **5** produces *N*-acetyl compound **6**. The structures of these compounds were established by IR, ^{1}H and ^{13}C NMR and mass spectral analyses.

Keywords. Benzo[*d*]thiazole, vanillin, reduction, microwave.

1. INTRODUCTION

Benzo[*d*]thiazole was first synthesized in 1880 by Hofmann A. W from formic acid and *o*-aminothiphenol [1]: however, the application of benzo[*d*]thiazole derivatives has been studied recently and in the past two decades they have been extensively studied for their anticancer activity [2,3,4]. For example, 2-(4-aminophenyl) benzothiazoles (**A**), an amino aromatic compound, and their corresponding N-acetylated derivatives (**B**) have shown surprisingly remarkable anticancer activity against certain cancer cell lines particularly against breast, colon and ovarian cell lines in vitro anticancer screening [5, 6]. Surprisingly, compound **C** exhibited remarkably potent anticancer activity [7]. In 2013, J. Pan *et al.* showed that complexes **D** of Re metal containing benzo[*d*]thiazole with various substituent Rs exhibited the lipophilicities in range $\log P_{C18}$ = 1-4, their binding affinities (K_i = 30-617 nM) to $A\beta_{1\text{-}40}$ fibrils. Nitroaromatic compounds play an essential role not only in organic synthesis but also in human life. For instance, they are pesticides, bacterial degradation, etc. [8]. Therefore, in this work, benzo[*d*]thiazole derivatives **E** were designed by retaining the structure of vanillin and connecting with a benzo[*d*]thiazole ring synthesized from vanillin, figure 1. To take advantages of amino, amide and nitroaromatic compounds, R1 is either NO_2 group, an amino group or an acetamido groups. R2 is an acetyl group or a hydrogen atom as vanillin moiety.

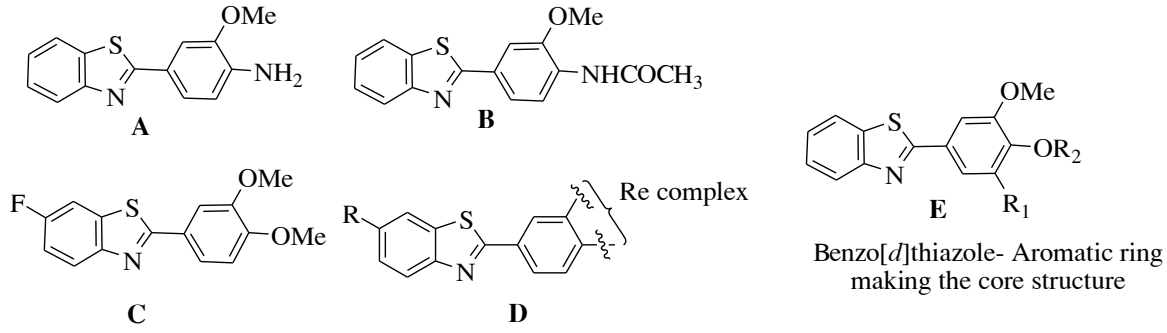


Figure 1: Examples of benzo[*d*]thiazole derivatives and Design target compounds **E**

2. EXPERIMENTAL

2.1. General

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck and used as received, unless otherwise indicated. The ^{1}H NMR and ^{13}C NMR spectra were recorded on the Bruker Avance 500 NMR spectrometer in deuterated solvents such as $CDCl_3$, DMSO, and or D_2O. Chemical-shift data for each signal was reported in ppm unit. IR spectra were recorded on the Mattson 4020 GALAXY Series FT-IR. Mass spectra were obtained from Mass Spectrometry Facility of The Vietnam Academy of Science and Technology on LC-MSD-Trap-SL spectrometer.

2.2. Synthetic procedure

*2.2.1. Synthesis of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (**2**) [9, 10]*

Concentrated HNO_3 (2 mL) was carefully added to a cooled (5 °C) solution of vanillin (5 g, 33 mmol) and acetic acid (50 mL) over a period of 30 min. The gold colored precipitate that formed was filtered, washed with water, and allowed to dry (5.21 g, 80 %): mp. 171 °C.

*2.2.2. Synthesis of 4-(benzo[d]thiazol-2-yl)-2-methoxy-6-nitrophenol (**3**)*

4-Hydroxy-3-methoxy-5-nitrobenzaldehyde (**2**, 0.55 g, 3.3 mmol) and 2-aminothiophenol (0.35 mL, 3.3 mmol) were mixed well in an 100 mL beaker. The resulting mixture was irradiated with a domestic microwave oven for 4 minutes at 400 W level. The mixture was stood for cooling down at room temperature and solidifying. The by re-crystallization from hot ethyl acetate/*n*-hexane (1:1) yielded the title compound **3** as a pale pink solid (0.98 g, 98 %, 302.3 g/mol), mp. 163 °C. IR (cm^{-1}): 3435 (br), 3100, 2914, 2852, 1613, 1545, 1430, 1263, 1143, 1021. ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm): 8.14 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 8.06 (d, J = 8.0, 1H), 7.83 (s, 1H), 7.55 (t, J = 7.5, 1H), 7.46 (t, J = 7.5, 1H), 4.02 (s, 3H); ^{13}C NMR (DMSO-d6, 125 MHz) δ (ppm): 165.44, 153.34, 150.12, 145.08, 137.30, 134.50, 126.78, 125.60, 123.26, 122.76, 122.35, 115.38, 113.01, 56.87; ESI-MS *m/z*: 273 $[C_{14}H_{11}NO_3S]^+$ and 271 $[C_{14}H_9NO_3S]^-$.

*2.2.3. Synthesis of 2-amino-4-(benzo[d]thiazol-2-yl)-6-methoxyphenol hydrochloride (**4**)*

Iron powder (8 g, 0.14 mol) was added portionwise with stirring to a hot mixture of 4-(benzo[*d*]thiazol-2-yl)-2-methoxy-6-nitrophenol (**3**) (6.4 g, 20 mmole) in ethanol (20 ml) and concentrated hydrochloric acid (30 ml) at reflux temperature. After completion of the addition, the refluxing was continued for 6 hours. Upon cooling a yellow precipitate formed, which was filtered off, washed with ethanol, dried to yield the title product as a yellow powder (5.6 g, 95%, 308.8 g/mol) mp: decomposed at 280 °C. IR (cm^{-1}): 3100, 2954, 2797, 3100-2500 (br), 1540, 1401, 1170. ^{1}H NMR (D_2O, 500 MHz) δ (ppm): 7.31 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.94 (d, J = 5.0 Hz, 1H), 6.80 (d, J = 6.5 Hz, 1H), 6.75 (s, 1H), 6.40 (s, 1H), 3.46 (s, 3H); ^{13}C NMR (D_2O, 125 MHz) δ (ppm): 167.31, 149.09, 147.60, 142.87, 137.30, 132.08, 126.78, 125.58, 121.45, 119.88, 117.45, 114.05, 108.90, 55.86. ESI-MS *m/z*: 273 $[C_{14}H_{13}N_2O_2S]^+$ and 271 $[C_{14}H_{11}N_2O_2S]^-$.

*2.2.4. Synthesis of 2-acetamido-4-(benzo[d]thiazol-2-yl)-6-methoxyphenyl acetate (**5**)*

To a solution of *2-amino-4-(benzo[d]thiazol-2-yl)-6-methoxyphenol hydrochloride (**4**)* (0.3 g, 1 mmol) and triethyl amine (0.42 mL, 3 mmol) was added acetic anhydride (0.3 mL, 2.5 mmol) in DMF (5 mL). The resulting solution was stirred at room temperature for 1 h. The solvent was evaporated in vacuum. Water was added to obtain solid. Re-crystallization in ethanol 96 % gave 2-acetamido-4-(benzo[*d*]thiazol-2-yl)-6-methoxyphenyl acetate (**5**) as a white crystal in 80 % (285 mg, 356.4 g/mol). IR (cm^{-1}): 3347, 3169, 2923, 2837, 1735, 1692, 1605, 1543, 1217, 1103. ^{1}H NMR (DMSO-d6, 500 MHz) δ (ppm): 9.58 (s, 1 H), 8.43 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.47 (t, J = 7.5 Hz, 1H), 3.90 (s, 3H), 2.33 (s, 3H), 2.14 (s, 2H). ^{13}C-NMR (DMSO-d6, 125 MHz) δ (ppm): 169.11, 167.89, 166.72, 153.45, 151.71, 134.56, 132.69, 131.5, 130.42, 126.70, 125.58, 122.88, 122.36, 113.89, 105.51, 56.29, 23.85, 20.79. ESI-MS *m/z*: 357 $[C_{18}H_{17}N_2O_4S]^+$ and 355 $[C_{18}H_{15}N_2O_4S]^-$.

*2.2.5. Synthesis of N-(5-(benzo[d]thiazol-2-yl)-2-hydroxy-3-methoxyphenyl)acetamide (**6**)*

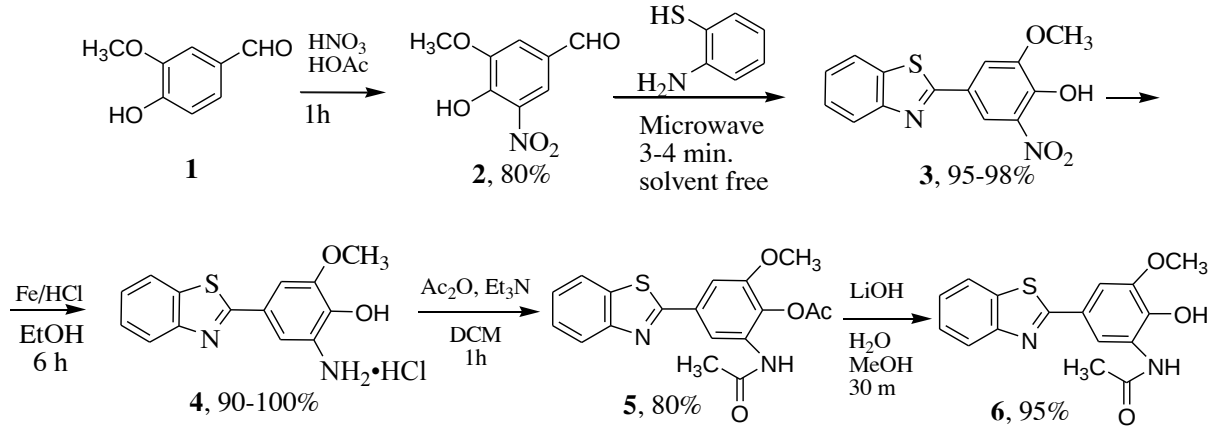
To a solution of 2-acetamido-4-(benzo[*d*]thiazol-2-yl)-6-methoxyphenyl acetate (**5**) (0.356 g, 1 mmol) in MeOH/H_2O (1:2), (5 mL) was added LiOH (60 mg, 2.5 mmol). The mixture was refluxed until all solid was dissolved completely, then acidified with (1:1) HCl up to pH = 5. The precipitate was

collected as a white crystal (0.3 g, 95 %), mp: 172 °C. IR (cm^{-1}): 3325 (br), 3080, 2928, 2817, 2797, 1690, 1542, 1401, 1179; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 8.33 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.79 (br, 1H), 7.53 (d, J = 1.5 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.18 (s, 1H), 3.96 (s, 3H), 2.26 (s, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ (ppm):169.18, 168.14, 154.02, 147.62, 138.06, 135.08, 132.50, 126.21, 125.72, 124.91, 122.78, 121.59, 113.80, 105.60, 56.44, 24.50; ESI-MS *m/z*: 315 $[C_{16}H_{15}N_2O_3S]^+$, 313 $[C_{16}H_{13}N_2O_3S]^-$.

3. RESULTS AND DISCUSSION

3.1. Synthesis

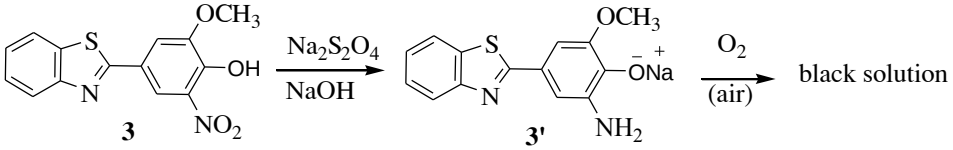
The series of benzo[*d*]thiazole derivatives was driven as shown in the Scheme 1. First, nitration of vanillin was carried out in 80 % yield to give nitrobenzaldehyde **2**. Then, the benzo[*d*]thiazole cyclization was furnished in 4 minutes when the nitrobenzaldehyde **2** was treated with *o*-aminothiophenol to yield nitroaromatic compound **3** in 98 % yield.



1 **2**, 80% **3**, 95-98% **4**, 90-100% **5**, 80% **6**, 95%

Scheme 1: Synthesis of the target compounds

Reduction of nitro group to amino group was optimized by using some classic methods, table 1. All entries were carried out up to 20 hours and monitored with thin layer chromatography (TLC). In the first entry, $Na_2S_2O_4$/NaOH reagents were used [11]. Unfortunately, as soon as the reagents added, the reaction solution turned black due to the reason that in the basic condition, free aniline **3'** was formed and oxidized by oxygen in the air, scheme 2. Nevertheless, there was a question: why was amine **3'** oxidized easily? Because the benzene ring contains 4 donating electron groups –OCH_3, -O^-, -NH_2 and benzo[*d*]thiazole ring [12] that raises the electron density on the benzene ring, consequently, it is oxidized quickly called the aniline black.



3 **3'**

Scheme 2: Aniline black observation

This result helps us think about the use of acidic conditions [13] and save the amine as a salt form. Hence, the entries 2-7 were treated with either concentrated HCl or NH_4Cl in water and in ethanol. It was found thaethanol was better solvent than water since ethanol could dissolve substrates well but could not dissolve salt form **4.** In comparison of Zn with Fe, both gave good yields, but it was difficult to separate the unreacted Zn out of the mixture, while iron could be attached to the stirring bar so the unreacted iron was removed just by washing the stirring bar simply. Finally, the salt **4** was easily filtered and dried for next step without further purification. Surprisingly, Fe/NH_4Cl [14] did not work in this case because the acidity of ammonium chloride is weaker than the salt form **4** and the free amine was formed then oxidized

immediately resulting in black solution as observed. All entries taken place in water were slowly or no reaction due to small solubility of substrates in water.

Table 1: Reduction optimization results

Entry	Reagent	Solvent	Time (h)	Observation	Yield (%)
1	$Na_2S_2O_4$/NaOH	H_2O	0.5, reflux	Black solution	0
2	Zn/con. HCl	H_2O	14, reflux	Yellow solution	75
3	Zn/con. HCl	C_2H_5OH	7, reflux	Yellow solid	95 (impure)
4	Fe/NH_4Cl	H_2O	18, 50 °C	Black solution	0
5	Fe/NH_4Cl	C_2H_5OH	20, 50 °C	Black solution	0
6	Fe/con. HCl	H_2O	12, reflux	Yellow solution	70
7	Fe/con. HCl	C_2H_5OH	7, reflux	Yellow solid	95 (pure)

As there was an amine salt **4** in hand, it was treated with acetic anhydride to form *N*,*O*-diacetyl compound **5** in 80 % yield. Then *N*,*O*-diacetyl compound **5** was hydrolyzed in methanol and LiOH giving *N*-acetyl amide **6** in 95 % yield.

3.2. Structure determination

Nitrovanillin **2** was checked for melting point, and it matched with the previous report [9, 10]. Because compounds **3, 4, 5** and **6** are new, so they were recorded for IR, MS and NMR spectra to determine their structures. Spectroscopic data were analyzed carefully [15]. First, IR spectrum of nitro compound **3** did not show the vibration of carbonyl group of vanillin that indicated cyclization of benzo[*d*]thiazole occurred. IR of compound **4** showed broad band of N-H bond in range 3100-2500 cm^{-1} that was for N-H vibration in the ammonium-like form. IR spectrum of compound **5** showed two signals of carbonyl groups at 1735 and 1692 cm^{-1}, that indicated two acetyl groups must be in the structure of *N*,*O*-diacetyl compound **5**. IR spectrum of *N*-acetyl amide **6** showed a band at 1690 cm^{-1} and vibration of N-H amide at 3325 cm^{-1} and overlapped with vibration of O-H bond. Next, ^{1}H NMR spectrum of nitroaromatic compound **3** and salt **4** showed 6 protons of aromatic rings and 3 protons of methoxy group; however, ^{1}H NMR spectra of both the nitroaromatic compound **3** and the salt **4** did not show a proton of OH group since it appeared in the block of solvent peaks. ^{13}C NMR spectrum of compound **4** showed 14 peaks for 14 carbon atoms. Meanwhile, ^{1}H NMR and ^{13}C NMR of *N*,*O*-diacetyl compound **5** showed two signals at δ 2.33 ppm (s, 3H) and 2.14 ppm (s, 3H) and 2 peaks in the weak field at 169.11 ppm and 167.98 ppm assigned for two carbonyl groups of acetyl amide and acetyl ester. Other two peaks at δ 23.85 ppm and δ 20.79 ppm belonged to two methyl groups of these acetyl groups. After hydrolysis of *N*,*O*-diacetyl compound **5** to obtain *N*-acetyl compound **6**, ^{1}H NMR and ^{13}C NMR of *N*-acetyl compound **6** showed only a peak at δ 2.25 ppm for methyl of the acetyl amide associated with the peak at δ 25.50 ppm on the ^{13}C NMR spectrum.

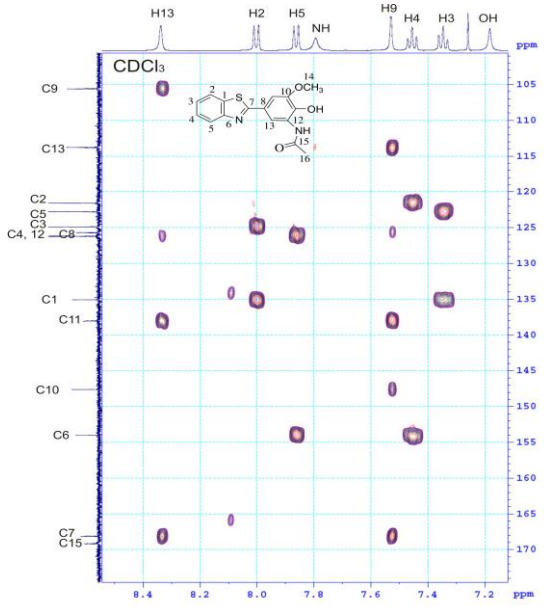


Figure 2: A part of HMBC spectrum

Then, in order to assign each carbon and hydrogen in the target product **6**, HSQC and HMBC spectra were studied carefully. First, HSQC spectrum indicated cross-peaks of carbons bearing protons. Although, there were still some pairs of carbons or protons that were difficult to indentify such as C7/C15; C3/C4; C1/C6; C9/C13; C10/C12; H4/H3; H9/H13; H2/H5 and NH/OH, HMBC spectrum distinguished all. For example, C7 had HMBC cross-peaks with H9 and H13 but C15 did not. In addition, C15 had an HMBC cross-peak with H15, on the other hand, C7 hadn't got further peaks.

The most difficult assignment was identification of C13/C19 and H13/H9. Fortunately, it was easily to find H14 that had an HMBC cross-peak with H9. Therefore, H13 and C13 were identified and so on. Other assignments were shown in the figure 2.

Finally, compounds **3**, **4**, **5** and **6** were recorded for mass spectroscopy. MS spectrum of compound **3** indicated the first fragment was NO [M-30+H] at *m/z* 273 au, [M-30-H] at *m/z* 271 au that matched with calculated. MS spectra of compounds **4**, **5** and **6** also confirmed the expected structure as shown in the experimental section.

4. CONCLUSION

Four new benzo[*d*]thiazole derivatives (**3**, **4**, **5** and **6**) were successfully synthesized in high yield. Fe powder and concentrated HCl in ethanol was the best condition for converting nitro group to amine group in our case. All reactions worked under simple conditions and gave excellent yields. Structures of compounds nitroaromatic **3**, salt **4**, *N,O*-diacetyl **5** and *N*-acetyl **6** were confirmed with IR, NMR and MS analyses.

Acknowledgements. *This research is supported by Hanoi National University of Education (HNUE) under the project code SPHN16-25TT.*

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