

Solvent- and catalyst-free synthesis of 2-aryl(heteroaryl)-substituted benzothiazoles†

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ABSTRACT

The condensation of several aromatic/heteroaromatic aldehydes with 2-aminothiophenol under melt reaction conditions afforded 2-arylbenzothiazoles under solvent-free conditions. The major advantages of the present method are high yields, short reaction times, and eco-friendly conditions.

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1. Introduction

Benzothiazoles and their derivatives are a very important group of heterocyclic compounds,¹ and are well known for their biological and pharmaceutical activities, such as antimicrobial,² and antihypertensive/antiparkinsonism agents³. Some of benzothiazoles exhibit nanomolar inhibitory activity against a range of human breast, ovarian, colon and renal cancer cell lines.⁴ Also, they can be used in industry as antioxidants and vulcanization accelerators that highlight their synthesis necessity.⁵ Benzothiazoles have been synthesized by different methods, such as condensation of 2-aminothiophenol with carboxylic acid derivatives,⁶ base induced cyclization of corresponding 2-haloanilides,⁷ or radical cyclization of thioacylbenzanilides.⁸ Some other methods include microwave-mediated reaction of 2-aminothiophenol with aldehydes in presences of SiO₂, Na₂S₂O₅ as a catalyst,⁹ palladium-catalyzed Suzuki biaryl coupling of 2-halobenzothiazoles with arylboronic acids,^{10,11} coupling of benzothiazoles with aryl bromides¹², the reaction between thiophenols and aromatic nitriles,¹³ Copper nanoparticles on activated carbon catalyzed.

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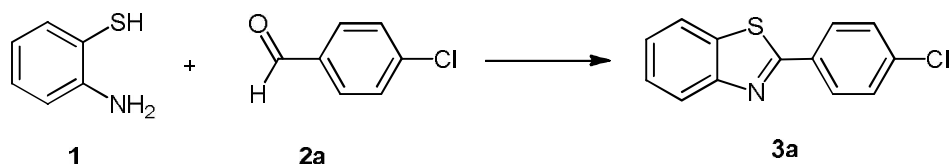
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However, most of these synthetic approaches suffer from some drawbacks such as harsh reaction conditions, lengthy procedures, and expensive catalysts, which may be harmful to the environment. Therefore, the introduction of some green methods to overcome these limitations is still an important challenge. The science of green chemistry is developed to meet the increasing demand of environmentally benign chemical processes. In this regard, we have recently developed the application of solvent-free solid-solid and melt reactions as efficient methods for organic preparations.¹⁴ We wish to report here a facile, environmentally friendly and clean synthesis of 2-substituted benzothiazoles via the reaction of aromatic or hetero aromatic aldehydes with *o*-aminothiophenol without using any catalyst, and under solvent-free melt reaction conditions.

2. Result and discussion

The reaction of 1.0 mmol of 2-aminothiophenol (**1**) with 1.0 mmol of *p*-chlorobenzaldehyde (**2a**) was chosen as a model reaction (Scheme 1).



Scheme 1. Synthesis of 2-(4-chlorophenyl)benzo[*d*]thiazole as model reaction

The reaction mixture was grounded by a pestle in a mortar that afforded a doughy mixture. After 5 minutes grinding, the thin layer chromatography (TLC) of the reaction mixture (with hexane/ethyl acetate as eluent) has shown that the starting materials are still present. The reaction mixture became solid on further grinding, but the reaction was not complete, even after 1 hour. After heating the grounded mixture at 125°C in an ordinary oven, the product **3a** was produced and the reaction was practically completed. By usual workup, the yield of the product **3a** was determined as 81%. Because of our previous successful works on using ball-milling in organic synthesis¹⁴, we also checked the model reaction by using a ball-mill apparatus. Although the reaction mixture became solid after 5 minutes grinding, but the starting materials did not disappeared even after 30 minutes grinding at room temperature. The model reaction was repeated as melt reaction. The starting materials were poured in a 10 mL round bottom flask and heated at 125°C in an ordinary oven. TLC showed that the reaction was completed after 1 hour. After crystallization in ethanol, 88% of pure **3a** was afforded.

By using the melt method, various aromatic and heteroaromatic aldehydes reacted with 2-aminothiophenol to produce the corresponding 2-arylbenzothiazoles with no need to any catalyst. Irrespective of the presence of electron withdrawing or releasing substituents in the ortho-, meta-, or para positions, the reactions proceeded fairly well and afforded the desired products in good to excellent yields (**3a-k**, Table 1). Heteroaromatic aldehydes needed higher temperatures, but they also afforded the corresponding 2-heteroaryl benzothiazoles with up to 97% yields (Table 1, entries **3h-k**).

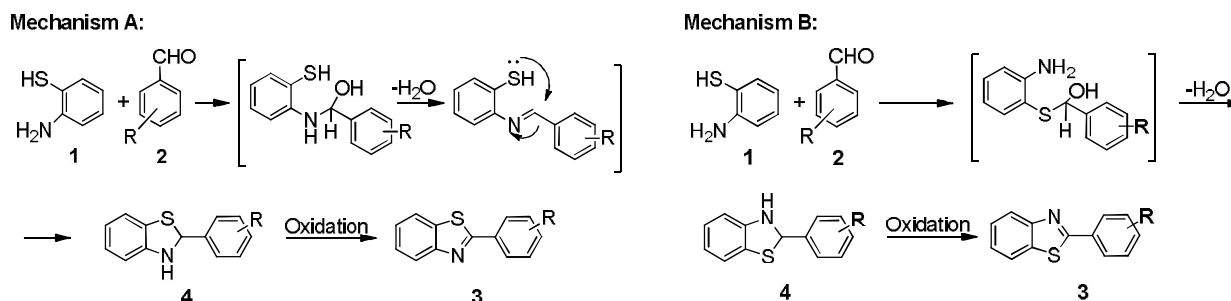
Two possible mechanisms of the reaction were shown in Scheme 2. Both of the mechanisms proceed via a 2,3-dihydrobenzo[*d*]thiazole intermediate (**4**) which will transform to **3** by an oxidation reaction. Although we could not prove whether the reaction starts with the nucleophilic attack of the nitrogen- or sulphur atom of **1** to the carbonyl group in **2**, the presence of the intermediate **4** was proved by the analysis of the reaction mixture of 2-aminothiophenol (**1**) with 1.0 mmol of *p*-bromobenzaldehyde (**2**, R=4-bromo). The reaction mixture was grounded by a pestle in a mortar. After 5 minutes grinding, the thin layer chromatography (TLC) of the reaction mixture (with hexane/ethyl acetate as eluent) has shown 3 points, which belonged to the starting materials along with a new material. After careful isolation of this product by plate chromatography and recording its FT-IR spectrum, the absorbance peak at 3432 cm⁻¹ of NH has proved the presence of the intermediate **4**. By heating the reaction mixture in air, the intermediate **4** was oxidized to **3**. Obviously no further oxidizing agent, except than air was needed. This is in contrast to the previously published methods,

which used the presence of an extra oxidant.^{16c-f} In order to prove the aerobic oxidation, we repeated the reaction of 4-bromobenzaldehyde and 2-aminothiophenol in a similar experiment in the absence of air. After heating the reaction mixture in vacuum, at 125 °C for 150 minutes, no benzothiazole product **3** was observed.

Table 1. Direct synthesis of 2-aryl benzothiazoles

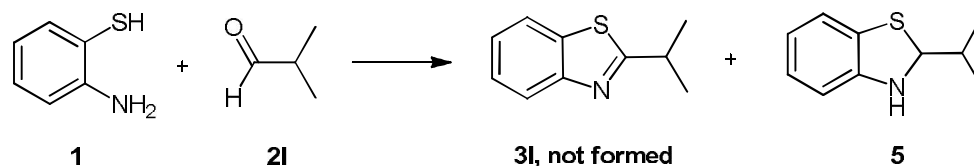
Entry	R	Temp. (°C)	Time (min)	Product	m.p. (lit) ^{15, 16}	Yield (%)
1	4-ClC ₆ H ₄	125	60	3a	116-117 (117-118)	88
2	4-BrC ₆ H ₄	125	60	3b	130-132 (133-134)	97
3	4-MeOC ₆ H ₄	125	60	3c	120-122 (121-122)	82
4	4-CNC ₆ H ₄	125	75	3d	159-161 (162)	83
5	4-NO ₂ C ₆ H ₄	125	60	3e	226-228 (229-230)	81
6	2-OHC ₆ H ₄	150	90	3f	130-132 (131-132)	85
7	3-NO ₂ C ₆ H ₄	125	60	3g	184-188 (185-186)	95
8	2-pyridyl	150	90	3h	135-136 (134-135)	97
9	4-pyridyl	150	90	3i	131-133 (134-135)	73
10	2-thiophyl	150	90	3j	95-97 (99)	76
11	2-furfuryl	150	90	3k	98-100 (103-104)	82
12	<i>i</i> -Bu	125	30	*	-	-

* 2,3-dihydro-2-isopropylbenzo[d]thiazole (**5**) was produced as the sole product



Scheme 2. Two possible mechanism of benzothiazole preparation

Unexpectedly, the reaction of alkyl aldehydes such as isobutyraldehyde did not afford the corresponding benzothiazoles **3** (Table 1, Entry 12). The melt reaction of 1.0 mmol isobutyraldehyde **2I** with 1.0 mmol of **1**, after 30 min heating at 125°C afforded 2,3-dihydro-2-isopropylbenzo[d]thiazole (**5**) as the sole product (Scheme 3). The structure of the compound **5** was confirmed by ¹H-NMR spectrum (Fig. 1). The doublet at 5.2 ppm (with ³J= 6.3 Hz) belongs to the 2-H in the thiazole ring and the broad signal at 4.2 ppm belongs to the NH. Other aliphatic aldehydes also showed similar results. This result is especially interesting, because similar methods have reported the formation of the corresponding benzothiazoles **3** in the reaction of aliphatic aldehydes, although with low yields.^{15a} To the best of our knowledge, none of similar methods reported on preparation of **5**.



Scheme 3. The reaction of 1.0 mmol of 2-aminothiophenol (**1**) with 1.0 mmol of isobutyraldehyde (**2I**)

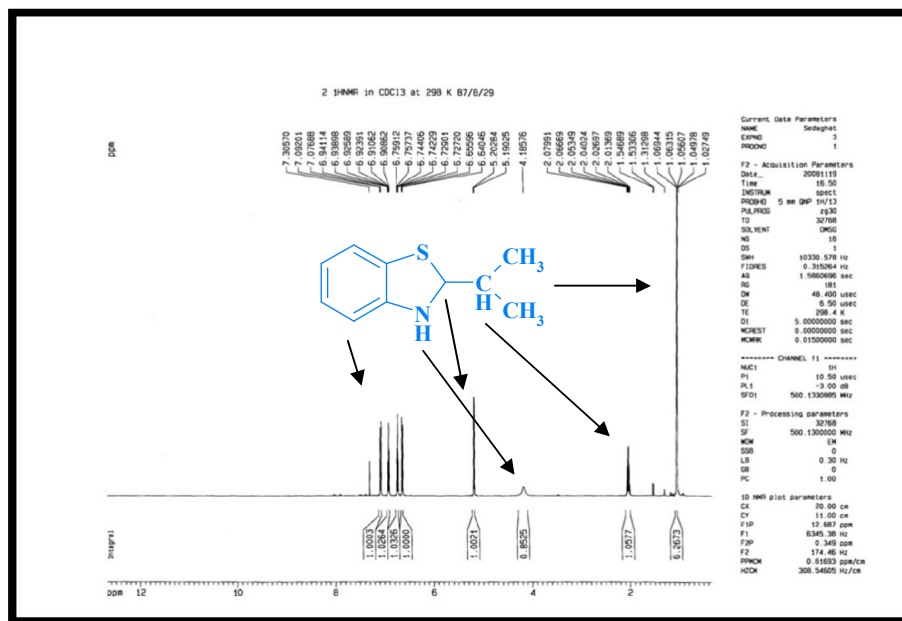


Fig. 1. ¹H-NMR spectrum of compound 5

3. Conclusion

In conclusion, the melt reaction in air was found to be an efficient method for the preparation of 2-aryl/heteroaryl benzothiazoles via the reaction of 2-aminothiophenol with substituted aryl/heteroaryl aldehydes, in good to excellent yields. The advantages of the present synthetic protocol are solvent-free conditions, eco-friendly and easy reaction work-up procedure with no need to a catalyst. Among these, the most important feature of this work is no need to an extra oxidizing agent, except than air. By using aliphatic aldehydes or performing the reaction in vacuum, 2,3-dihydrobenzo[d]thiazoles were prepared. The sustainability of this environmentally friendly technique may be compared to some previous techniques in Table 2. These methods are much more complicated, less atom-economic, and afford lower yields under severe conditions and longer reaction times (Table 2).

Table 2. Comparison of different synthesis method for 2-aryl benzothiazoles

Reactions Condition	Yield (%)
Melt condition (present work)	81-97
P ₂ O ₅ , CH ₃ SO ₃ H, Δ, 10 h ^{16a}	74-96
n-BuLi, THF, -80 °C ^{16b}	41-81
CAN, NaHCO ₃ , MeCN, 30 min ^{16c}	78-96
p-TsOH, MW ^{16d}	52-85
Pd ₂ (dba) ₃ , DME-Water, K ₂ CO ₃ , 100 °C, 6h ^{16e}	48-72
O ₂ , Xylene, 50 °C ^{16f}	72-86
DDQ, CH ₂ Cl ₂ , RT, 20 min ^{16g}	83-95

4. Experimental Section

4.1. Materials and methods

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on

a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with CDCl_3 as solvent. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland), or Merck and used without further purification.

4.2. General procedure for the preparation of benzothiazoles **3**, exemplified on **3b**:

A mixture of 1.0 mmol of 2-aminothiophenole (**1**) and 1.0 mmol of 4-bromobenzaldehyde (**2a**) was heated in a 10 mL round bottom flask in an ordinary oven at 125 °C for 60 minutes to afford the crude product (**3b**). The progress of the reaction was monitored by TLC. Further purification was recrystallization from 96% ethanol.

Representative spectral data:

2-(4-Bromophenyl)benzo[d]thiazole (3b): White powder, mp = 130-132 °C, yield 97 %. IR (KBr) (ν_{max} , cm^{-1}): 3000 (CH), 1400-1600 (Ar). ^1H NMR (500.13 MHz, CDCl_3): δ_{H} = 7.44 (1H, t, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar), 7.55 (1H, t, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar), 7.67 (2H, d, $^3J_{\text{HH}}$ = 8.5 Hz, 2CH of Ar), 7.94 (1H, d, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar), 8.0 (2H, d, $^3J_{\text{HH}}$ = 8.5 Hz, 2CH of Ar), 8.11 (1H, d, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar). ^{13}C NMR (125.75 MHz, CDCl_3): δ_{C} = 122.01 (CH of Ar), 123.76 (CH of Ar), 125.85 (C-N), 125.87 (CH of Ar), 126.93 (CH of Ar), 129.34 (2CH of Ar), 132.66 (2CH of Ar), 133.00 (C_{ipso}), 135.48 (C_{ipso}), 154.52 (C_{ipso}), 167.11 (C_{ipso}).

2-(Pyridin-2-yl)benzo[d]thiazole (3h): White powder, mp = 135-136 °C, yield 97 %. IR (KBr) (ν_{max} , cm^{-1}): 3053 (CH), 1405-1600 (Ar). ^1H NMR (500.13 MHz, CDCl_3): δ_{H} = 7.38-7.41 (1H, m, CH of pyridine), 7.45 (1H, t, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar), 7.53 (1H, t, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar), 7.86 (1H, t, $^3J_{\text{HH}}$ = 7.7 Hz, CH of pyridine), 7.98 (1H, d, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar), 8.13 (1H, d, $^3J_{\text{HH}}$ = 8.1 Hz, CH of pyridine), 8.40 (1H, d, $^3J_{\text{HH}}$ = 8.0 Hz, CH of Ar), 8.70 (1H, d, $^3J_{\text{HH}}$ = 4.7 Hz, CH of pyridine). ^{13}C NMR (125.75 MHz, CDCl_3): δ_{C} = 121.19 (CH of pyridine), 122.44 (CH of Ar), 124.02 (CH of Ar), 125.67 (CH of pyridine), 126.07 (CH of Ar), 126.70 (CH of Ar), 136.58 (C_{ipso}), 137.41 (CH of Ar), 150.08 (CH of pyridine), 151.85 (C_{ipso}), 154.73 (C_{ipso}), 169.80 (C_{ipso}).

2-Isopropyl-2,3-dihydrobenzo[d]thiazole (5): liquid, yield: 85 %. ^1H NMR (500.13 MHz, CDCl_3): δ_{H} = 1.05 (6H, d, $^3J_{\text{HH}}$ = 6.7 Hz, CH_3), 2.05 (1H, hep., $^3J_{\text{HH}}$ = 6.7 Hz, CH), 4.18 (1H, bs, NH), 5.19 (1H, d, $^3J_{\text{HH}}$ = 6.3 Hz, CH), 6.64 (1H, d, $^3J_{\text{HH}}$ = 7.7 Hz, CH of Ar), 6.74 (1H, t, $^3J_{\text{HH}}$ = 7.5 Hz, CH of Ar), 6.92 (1H, t, $^3J_{\text{HH}}$ = 7.7 Hz, CH of Ar), 7.08 (1H, d, $^3J_{\text{HH}}$ = 7.5 Hz, CH of Ar).

Supplementary data

Supplementary data are available under: http://www.growing-science.com/ccl/Vol3/ccl_2014_5_s.pdf

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