1,3-DIBROMO-5,5-DIMETHYLHYDANTOIN CATALYZED ONE-POT SYNTHESIS OF 2-ARYLBENZOTHIAZOLES

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A one-pot synthesis of 2-arylbenzothiazoles from the reaction of 2-aminothiophenol and aromatic aldehydes catalyzed by 1,3-dibromo-5,5-dimethylhydantoin is reported.

Keywords: Aldehydes; 2-Aminothiophenol; 2-Arylbenzothiazoles; 1,3-Dibromo-5,5-dimethylhydantoin; Heterocycles; Synthetic methods.

The synthesis of 2-arylbenzothiazoles has received an increasing amount of attention due to their important biological activities as antiparasitic[1], anti-inflammatory[2], anti-tumour[3], anticonvulsant[4], antibacterial[5], antiproliferative[6], antifungal[7], anthelmintic[8], antiproliferative[9], calcium-inhibiting[10] and topoisomerase II inhibitory activities[11]. In additions, 2-arylbenzothiazoles is also a privileged scaffold in drug discovery[12]. One of the most practically and widely used routes for the synthesis of these compounds is the direct condensation of the 2-aminothiophenol with aldehydes, carboxylic acids, or their derivatives in the presence of various promoting agents, such as oxalic acid[13], sulfuric acid immobilized on silica[14], ceric ammonium nitrate[15], $H_3PW_{12}O_{40}$ [16], acetic acid[17], $NaHSO_3$ [18], CAN [19], H_2O_2/$Fe(NO_3)_3$ [20] Dowex 50W [21], trichloroisocyanuric acid[22], $Cu_{3/2}PMo_{12}O_{40}$/SiO_2 [23], $[(bmim)BF_4]$ [24], methanesulfonic acid/SiO_2 [25], silica gel[26], I_2 [27], $Sc(OTf)_3$ [28]. However, most of these methods have following drawbacks: high thermal conditions, long reaction times, low yields of the products, harsh reaction conditions, and the use of toxic metallic compounds that result in waste streams. Therefore, it seems highly desirable to find a simple and efficient protocol for 2-arylbenzothiazoles synthesis.

The use of organic molecules as catalysts has become an attractive alternative to traditional metal-catalysts. Interest in the field of organocatalysis

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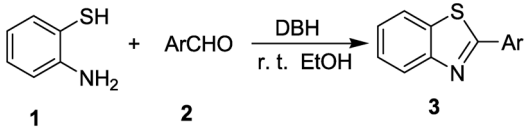
has increased spectacularly in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions[29]. 1,3-Dibromo-5,5-dimethylhydantoin (DBH) is one such catalyst, which has recently received considerable attention as a catalyst in various organic transformations[30], and is widely used as a brominating reagent[31]. In this paper, we wish to report a novel and efficient protocol for the synthesis 2-arylbenzothiazoles from the reaction of 2-aminothiophenol with aromatic aldehydes in the presence of a catalytic amount of DBH at room temperature, as depicted in Scheme 1.



SCHEME 1

RESULTS AND DISCUSSION

Initially, to optimize the reaction conditions, we conducted the reaction of 2-aminothiophenol with benzaldehyde in various solvents such as methanol, ethanol, water, acetonitrile, dichloromethane and chloroform (Table I). The results showed that the highest product yield was obtained in methanol and ethanol. However, because of the toxicity of methanol, all reactions were carried out in ethanol. Then, the effect of amount of catalyst on

TABLE I
Solvent effect on the formation of of 2-phenyl-1,3-benzothiazole **3a**[a]

Entry	Solvent	Time, h	Yield, %[b]
1	CH_3OH	3	85
2	CH_3CH_2OH	3	94
3	H_2O	5	24
4	CH_3CN	3	62
5	CH_2Cl_2	3	72
6	$CHCl_3$	4	70
7	–	5	56

[a] Reaction conditions: 2-aminothiophenol (1 mmol); benzaldehyde (1 mmol); DBH (0.02 mmol); r.t. [b] Isolated yield.

the conversion rate of the reaction was studied by varying the amount of DBH at room temperature (Table II). It was found that 2 mole % of DBH was sufficient to carry out this reaction smoothly. An increase in the amount of DBH to more than 3 mole % showed no substantial improvement in the yield.

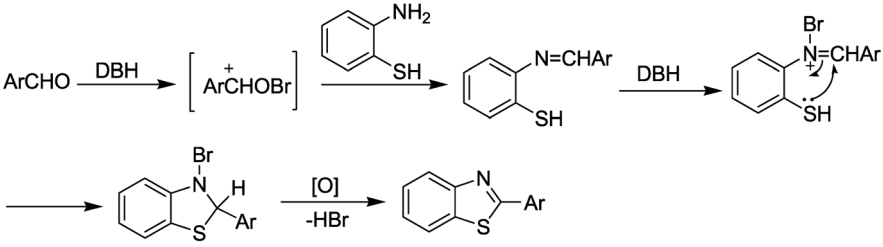
TABLE II
The amounts of catalyst optimization for the synthesis of 2-phenyl-1,3-benzothiazole **3a**[a]

Entry	DBH, mole %	Time, h	Yield, %[b]
1	0	5	trace
2	1	4	82
3	2	3	94
4	3	3	92
5	4	3	93
6	5	3	90

[a] Reaction conditions: 2-aminothiophenol (1 mmol); benzaldehyde (1 mmol); EtOH (2 ml); r.t. [b] Isolated yield.

Encouraged by this result, in order to build the generality of the reaction, our attention moved to the reactions of other aldehydes, and the results are summarized in Experimental. As expected, this reaction proceeded smoothly and the desired products were obtained in good to excellent yields. A series of aldehydes with either electron-donating or electron-withdrawing groups attaching to aromatic ring were investigated. The substitution groups on the aromatic ring had no obvious effect on the yield. When aromatic aldehydes were replaced by heteroaromatic aldehydes, the corresponding products were obtained with high yields as well. All of the structures were characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis.

A mechanism to account for the formation of **3** is proposed in Scheme 2. Since DBH contains bromine atoms which are attached to nitrogen atoms,



SCHEME 2

it is probable that Br^+, which can act as an electrophilic species in the reaction medium, is released *in situ*. In addition, the oxidation by air oxygen takes place in the final step.

A comparison of the efficiency of this method in preparation of compound **3a** with selected previous methods is collected in Table III. The results show that this method is superior to some previously reported methods in terms of yields, reaction times and conditions.

TABLE III
DBH-catalyzed synthesis of 2-phenyl-1,3-benzothiazole **3a** in comparison with literature

Entry	Catalyst and conditions	Time, h	Yield, %	Ref.
1	$Cu_{3/2}PMo_{12}O_{40}/SiO_2$ (9 mole %); 1,4-dioxane; reflux	1	85	19
2	Dowex 50W (10 mole %); H_2O; 70 °C	12	85	6
3	CAN (10 mole %); MeOH; 25 °C	12	75	15
4	$NaHSO_3$ (100 mole %); DMA; 100 °C	2	92.3	14
5	DBH (2 mole %); EtOH; 25 °C	3	94	this paper

CONCLUSION

In summary, this paper describes a simple, convenient and efficient method for the synthesis of 2-arylbenzothiazoles using DBH as a catalyst at room temperature. The notable features of this procedure are mild reaction conditions, cleaner reaction profiles, improved yields, enhanced rates and simplicity in operation which make it a useful and attractive process for the synthesis of 2-arylbenzothiazoles of biological importance.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were determined on Bruker AV-400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C) at room temperature using tetramethylsilane (TMS) as an internal standard ($CDCl_3$ or DMSO-d_6 solution). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Elemental analyses were performed by a Vario-III elemental analyzer. Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES). Melting points were determined on a XT-4 binocular microscope and were uncorrected. Commercially available reagents were used throughout without further purification unless otherwise stated.

Preparation of **3**. General Procedure

To a solution of aldehyde (1 mmol) and 2-aminothiophenol (1 mmol) in EtOH (2 ml), DBH (0.02 mmol) was added and the mixture was stirred at room temperature. Completion of the reaction was indicated by TLC, the mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 × 5 ml). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to afford crystalline 2-arylbenzothiazoles. The pure solid products were obtained by recrystallization from ethanol.

2-Phenyl-1,3-benzothiazole (**3a**). Yield 91%, white soild, m.p. 111–112 °C (110–112 °C)[17]. ^{1}H NMR ($CDCl_3$): 8.10–7.88 m, 4 H (Ar-H); 7.55–7.42 m, 5 H (Ar-H). ^{13}C NMR ($CDCl_3$): 165.2, 152.5, 134.8, 132.8, 131.7, 129.4, 127.0, 125.9, 125.6, 122.9, 122.0. For $C_{13}H_9NS$ (211.1) calculated: 73.90% C, 4.29% H, 6.63% N, 15.18% S; found: 73.72% C, 4.35% H, 6.56% N, 15.22% S.

2-(4-Chlorophenyl)-1,3-benzothiazole (**3b**). Yield 90%, yellow soild, m.p. 115–117 °C (116–117 °C)[17]. ^{1}H NMR ($CDCl_3$): 8.10–7.89 m, 4 H (Ar-H); 7.55–7.32 m, 4 H (Ar-H). ^{13}C NMR ($CDCl_3$): 167.2, 155.2, 138.1, 135.9, 133.4, 129.6, 129.0, 127.0, 125.2, 124.2, 120.9. For $C_{13}H_8ClNS$ (245.0) calculated: 63.54% C, 3.28% H, 5.70% N, 13.05% S; found: 63.60% C, 3.20% H, 5.66% N, 13.00% S.

2-(4-Methylphenyl)-1,3-benzothiazole (**3c**). Yield 87%, yellow soild, m.p. 87–88 °C (85–87 °C)[17]. ^{1}H NMR ($CDCl_3$): 8.09 d, 1 H, J = 8.0 (Ar-H); 8.01 d, 2 H, J = 8.0 (Ar-H); 7.90 d, 1 H, J = 8.0 (Ar-H); 7.47–7.43 m, 1 H (Ar-H); 7.38–7.30 m, 3 H (Ar-H); 2.44 s, 3 H (CH_3). ^{13}C NMR ($CDCl_3$): 167.9, 155.3, 142.3, 136.4, 132.2, 129.9, 128.1, 126.7, 125.6, 123.8, 122.0, 22.1. For $C_{14}H_{11}NS$ (225.1) calculated: 74.63% C, 4.92% H, 6.22% N, 14.23% S; found: 74.80% C, 4.99% H, 6.25% N, 14.19% S.

2-(4-Florophenyl)-1,3-benzothiazole (**3d**). Yield 92%, white soild, m.p. 96–98 °C (98–100 °C)[17]. ^{1}H NMR ($CDCl_3$): 8.10–8.02 m, 4 H (Ar-H); 7.90 d, 1 H, J = 8.0 (Ar-H); 7.50 d, 1 H, J = 7.6 (Ar-H); 7.39 d, 1 H, J = 7.6 (Ar-H); 7.18 t, 1 H, J = 8.0 (Ar-H). ^{13}C NMR ($CDCl_3$): 167.1, 162.9, 155.1, 136.0, 131.0, 129.5, 129.4, 126.2, 122.9, 121.9, 117.1. For $C_{13}H_8FNS$ (229.0) calculated: 68.10% C, 3.52% H, 6.11% N, 13.99% S; found: 68.06% C, 3.55% H, 6.15% N, 14.02% S.

2-(4-Nitrophenyl)-1,3-benzothiazole (**3e**). Yield 94%, yellow soild, m.p. 225–226 °C (228–229 °C)[21]. ^{1}H NMR ($CDCl_3$): 8.41–7.44 m, 8 H (Ar-H). ^{13}C NMR ($CDCl_3$): 165.4, 155.2, 149.4, 140.4, 136.0, 129.7, 127.1, 126.5, 124.4, 124.0, 120.9. For $C_{13}H_8N_2O_2S$ (256.0) calculated: 60.93% C, 3.15% H, 10.93% N, 12.51% S; found: 61.02% C, 3.19% H, 11.02% N, 12.55% S.

2-(4-Hydroxyphenyl)-1,3-benzothiazole (**3f**). Yield 85%, white soild, m.p. 224–226 °C (22–226 °C)[21]. ^{1}H NMR (DMSO-d_6): 10.23 brs, 1 H (OH); 8.10–7.89 m, 4 H (Ar-H); 7.51–7.42 m, 2 H (Ar-H); 6.99 d, 2 H, J = 8.4 (Ar-H). ^{13}C NMR ($CDCl_3$): 168.1, 160.9, 155.1, 136.7, 130.2, 127.0, 126.1, 124.8, 122.9, 122.5, 117.2. For $C_{13}H_9NOS$ (227.0) calculated: 68.70% C, 3.99% H, 16.16% N, 14.11% S; found: 68.77% C, 4.02% H, 6.12% N, 14.15% S.

2-(3-Nitrophenyl)-1,3-benzothiazole (**3g**). Yield 89%, yellow soild, m.p. 180–181 °C (182–184 °C)[17]. ^{1}H NMR ($CDCl_3$): 8.84–7.42 m, 8 H (Ar-H). ^{13}C NMR ($CDCl_3$): 165.3, 154.2, 149.1, 135.3, 135.2, 133.1, 130.2, 127.1, 126.2, 125.5, 124.1, 121.9, 121.5. For $C_{13}H_8N_2O_2S$ (256.0) calculated: 60.93% C, 3.15% H, 10.93% N, 12.51% S; found: 61.09% C, 3.16% H, 10.99% N, 12.58% S.

2-(3-Chlorophenyl-1,3-benzothiazole (**3h**). Yield 88%, yellow soild, m.p. 92–93 °C (95 °C)[24]. ^{1}H NMR ($CDCl_3$): 7.98–7.75 m, 4 H (Ar-H); 7.42–7.20 m, 4 H (Ar-H). ^{13}C NMR ($CDCl_3$):

167.0, 154.2, 136.5, 130.4, 129.9, 129.4, 128.8, 128.1, 126.5, 126.2, 125.6, 123.1, 122.0. For $C_{13}H_8ClNS$ (245.0) calculated: 63.54% C, 3.28% H, 5.70% N, 13.05% S; found: 63.58% C, 3.23% H, 5.60% N, 13.10% S.

2-(2-Chlorophenyl)-1,3-benzothiazole (**3i**). Yield 83%, yellow soild, m.p. 85–86 (81–83)[17]. ^{1}H NMR ($CDCl_3$): 8.26–8.19 m, 1 H (Ar-H); 8.15 d, 1 H, *J* = 8.0 (Ar-H); 7.98 d, 1 H, *J* = 7.6 (Ar-H); 7.56–7.51 m, 2 H (Ar-H); 7.46–7.35 m, 3 H (Ar-H). ^{13}C NMR ($CDCl_3$): 166.4, 154.2, 137.1, 133.4, 132.6, 132.0, 131.5, 130.3, 127.0, 126.6, 125.8, 122.9, 121.8. For $C_{13}H_8ClNS$ (245.0) calculated: 63.54% C, 3.28% H, 5.70% N, 13.05% S; found: 63.63% C, 3.20% H, 5.74% N, 13.12% S.

2-(2-Methoxyphenyl)-1,3-benzothiazole (**3j**). Yield 89%, white soild, m.p. 105–106 °C (106–108 °C)[22]. ^{1}H NMR ($CDCl_3$): 8.60–7.10 m, 8 H (Ar-H); 3.98 s, 3 H (OMe). ^{13}C NMR ($CDCl_3$): 164.2, 158.0, 153.4, 138.5, 132.2, 130.1, 126.2, 124.9, 122.6, 122.5, 121.1, 120.9, 112.4, 56.2. For $C_{14}H_{11}NOS$ (241.3) calculated: 69.68% C, 4.59% H, 5.80% N, 13.29% S; found: 69.75% C, 4.51% H, 5.72% N, 13.40% S.

2-(Benzo[1,3] dioxol-5-yl)-1,3-benzothiazole (**3k**). Yield 90%, white soild, m.p. 122–123 °C (124–126 °C)[22]. ^{1}H NMR ($CDCl_3$): 8.09 d, 1 H, *J* = 8.0 (Ar-H); 7.95 d, 1 H, *J* = 8.0 (Ar-H); 7.66–7.35 m, 4 H (Ar-H); 7.03 d, 1 H, *J* = 8.0 (Ar-H); 6.12 s, 2 H (OCH_2O). ^{13}C NMR ($CDCl_3$): 167.2, 155.2, 149.9, 147.9, 135.4, 128.8, 126.8, 125.2, 123.0, 122.6, 122.0, 108.7, 108.0, 102.1. For $C_{14}H_9NO_2S$ (255.0) calculated: 65.87% C, 3.55% H, 5.49% N, 12.56% S; found: 65.91% C, 3.50% H, 5.61% N, 12.70% S.

2-(Pyridin-2-yl)-1,3-benzothiazole (**3l**). Yield 90%, white soild, m.p. 131–132 °C (131–133 °C)[22]. ^{1}H NMR ($CDCl_3$): 8.66–8.02 m, 3 H (Ar-H); 7.92–7.77 m, 2 H (Ar-H); 7.51–7.35 m, 2 H (Ar-H). ^{13}C NMR ($CDCl_3$): 168.9, 155.6, 151.3, 150.0, 138.4, 136,5, 126.6, 126.0, 125.5, 124.1, 123.0, 121.1. For $C_{12}H_8N_2S$ (212.0) calculated: 67.90% C, 3.80% H, 13.20% N, 15.11% S; found: 68.00% C, 3.65% H, 13.16% N, 15.06% S.

2-(Furan-2-yl)benzo[d]thiazole (**3m**). Yield 89%, yellow soild, m.p. 103–105 °C (103–104 °C)[21]. ^{1}H NMR ($CDCl_3$): 8.10–6.63 m, 7 H (Ar-H). ^{13}C NMR ($CDCl_3$,): 158.0, 151.2, 148.7, 142.8, 132.9, 126.0, 125.7, 124.1, 120.8, 112.9, 112.1. For $C_{11}H_7NOS$ (201.0) calculated: 65.65% C, 3.51% H, 6.96% N, 15.93% S; found: 65.80% C, 3.27% H, 7.05% N, 15.99% S.

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