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Synthesis of benzothiazole derivatives catalyzed by Zinc triflate

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ABSTARCT

A simple and efficient method has been developed for the synthesis of benzothiazoles from 2-aminothiophenol and substituted aldehydes in the presence of a catalytic amount of zinc triflate in ethanol solvent at reflux temperature.

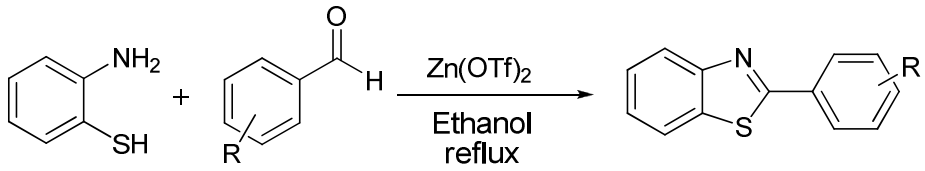
Key words*:* One-pot synthesis, benzothiazoles, 2-aminophenol, substituted aldehydes, zinc triflate..

INTRODUCTION

Benzothiazoles derivatives are very important group of heterocyclic systems and play an important role in biological and medicinal chemistry. These heterocycles showed a wide range of biological properties such as antimicrobial[1], anticancer[2], anthelmintic[3], anti-diabetic activities. Also, they can be used in industry as antioxidants and vulcanization accelerators that highlight their synthesis necessity[4].

In general, benzothiazoles are synthesized by one-pot reaction of 2-aminothiophenol with β-chlorocinam aldehydes using *p*-TsOH[5], condensation of 2-aminothio phenol with acid chlorides[6], carboxylic acid derivatives[7], esters[8]. On the other hand, the most general synthetic approach for synthesis of 2-arylbenzothiazoles involves condensation of 2-aminothiophenols with aldehydes using various oxidants such as I_2/DMF[9], CAN[10], H_2O_2/$Fe(NO_3)_3$[11], microwave irradiation[12], Bakers yeast[13], tungstophosphoric acid impregnated zirconium phosphate[14], trichloroisocyanuric acid[15] , $NaHSO_4$-SiO_2[16], O_2 or H_2O_2 in the presence of $Sc(OTf)_3$[17]. Although, these methods each have specific merits, they suffering from some drawbacks such as high temperature conditions, long reaction times and some low yields. Therefore, it was felt that there is a need to overcome the above limitations by developing an efficient, simple and green methodology for the synthesis of benzothiazoles.

Scheme-1



MATERIALS AND METHODS

All ^{1}H NMR spectra were recorded on 400 MHz Varian FT-NMR spectrometers. All chemical shifts are given as δ value with reference to Tetra methyl silane (TMS) as an internal standard. Products were purified by flash chromatography on 100-200 mesh silica gel. The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem and they were used without purification prior to use.

Zinc triflate catalyzed synthesis of 2-substituted benzothiazoles from 2-aminothiophenols and aldehydes.

A mixture of 2-Aminothiophenol (1 mmol), benzaldehyde (1.2 mmol) and $Zn(OTf)_2$ (10 mol %) in Ethanol (5 ml) was placed in a 50 ml round bottom flask and stirred at reflux for 5h. The progress of the reaction was monitored by TLC Hexane: EtOAc (8:2) after completion of the reaction, the reaction mixture was cooled and treated by dilution with 1N NaOH (5 mL). The solution was extracted with EtOAc (3x10 mL) Total organic layer was washed with water, brine solution and dried over Na_2SO_4 and evaporated under vacuum. Obtained crude residue was purified by column chromatography to give 2- substituted benzoxazoles.

2-Phenyl benzo[*d*]thiazole (Table-1, entry 1)[18]
Colourless solid; m.p: 110-112 ^{o}C; ^{1}H NMR ($CDCl_3$): δ8.11-8.07 (m, 3H), 7.91 (d, *J*= 8.4 Hz, 1H), 7.51-7.40 (m, 4H), 7.39-7.37 (m, 1H); ^{13}C NMR ($CDCl_3$): δ121.79, 123.38, 125.35, 126.48, 127.72, 129.19, 131.14, 133.75, 135.20, 154.28, 168.26; (LC-MS) m*/z:* 212.12 $[M+H]^+$; IR (KBr, cm^{-1}): 3063, 2924, 1686, 1477, 1311, 1223, 961, 766, 685. *Anal*. Calcd. For $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63; S, 15.18. Found: C, 73.87; H, 4.27; N, 6.59.

2-(4-Methoxyphenyl)benzo[*d*]thiazole (Table-1, entry 2)[18]

Off white solid; m.p.: 121□123 ^{o}C. ^{1}H NMR ($CDCl_3$): δ 7.00□7.95 (m, 8H), 3.82 (s, 3H); (LC-MS) m*/z:* 242.30 $[M+H]^+$

2-p-tolylbenzo[d]thiazole (Table-1, entry 3)[18]

White solid; m.p: 84-87 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.02 (d, *J*= 8.1 Hz, 1H), 7.96 (d, *J*= 8.1 Hz, 2H), 7.88 (d, *J*= 8.1 Hz, 1H), 7.45-7.43 (m, 1H), 7.37-7.34(m, 1H), 7.27 (d, *J*= 8.0 Hz, 2H),2.41 (s, 3H); (LC-MS) m*/z:* 226.21 $[M+H]^+$

2-(2-chlorophenyl) benzo[*d*]thiazole (Table-1, entry 4)[19]
Off white solid; m.p: 70-72 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.22-8.21 (m, 1H), 8.12 (d, *J*= 8.4 Hz, 1H), 7.93 (d, *J*= 7.6 Hz, 1H), 7.51-7.54 (m, 2H), 7.38-7.45(m, 3H); (LC-MS) m*/z:* 246.01 $[M+H]^+$

2-(4-chlorophenyl)benzo[d]thiazole (Table-1, entry 5) [18]
Off white solid; m.p: 110-112 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, *J*= 8.2 Hz, 1H), 7.96 (d, *J*= 8.2 Hz, 2H), 7.84(d, *J*= 8.0 Hz, 1H), 7.57-7.30 (m, 4H); (LC-MS) m*/z:* 246.01 $[M+H]^+$

2-(4-bromophenyl)benzo[d]thiazole (Table-1, entry 6) [18]

Off white solid; m.p: 129-130 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.04 (d, *J*= 8.2 Hz, 1H), 7.92 (d, *J*= 8.2 Hz, 2H), 7.86 (d, *J*= 8.0 Hz, 1H), 7.60 (d, *J*= 8.2 Hz, 2H), 7.47-7.39 (m, 2H); (LC-MS) m*/z:* 289.90 $[M+H]^+$

2-(furan-2-yl)benzo[d]thiazole (Table-1, entry 7) [18]

Off white solid; m.p: 99-101 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.03 (d, *J*= 8.1 Hz, 1H), 7.89 (d, *J*= 8.1 Hz, 1H), 7.59 (m,1H),7.51-7.40 (m, 2H), 7.16-6.79 (m, 2H); (LC-MS) m*/z:* 202.10 $[M+H]^+$

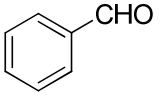
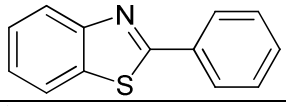
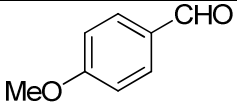
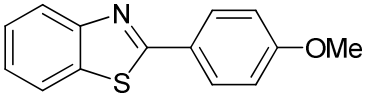
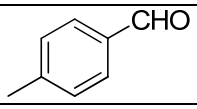
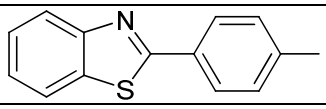
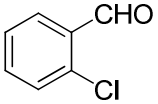
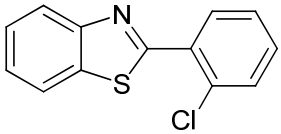
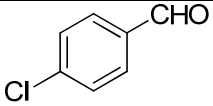
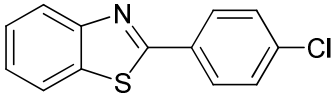
2-(thiophen-2-yl)benzo[d]thiazole (Table-1, entry 8) [18]

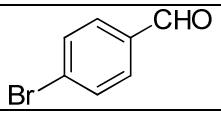
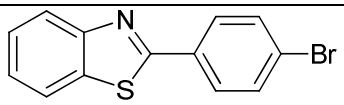
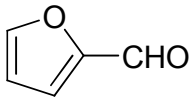
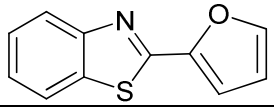
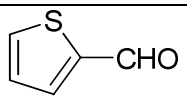
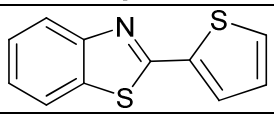
White solid; m.p: 97-98 ^{o}C; ^{1}H NMR ($CDCl_3$): δ 8.04 (m, 1H), 7.86 (m, 1H), 7.64 (m, 1H), 7.50-7.40 (m,2H), 7.36-7.28 (m, 2H); (LC-MS) m*/z:* 218.16 $[M+H]^+$

RESULTS AND DISCUSSIONS

In our preliminarily investigation on the model reaction of 2-aminothiophenol and 4-methoxy benzaldehyde, it was found that the reaction could be finished under very simple reaction conditions in the presence of catalytic amount of zinc triflate in reflux of ethanol solvent, which gives the desired corresponding benzothiazole product in good yield. The solvent play an important role in the model reaction. It was found that Ethanol was the best solvent among those tested (MeOH, THF, Toluene, CH_3CN, and Dioxane) for this condensation reaction, because the reaction was completed in 5h under reflux condition and gave 91% yield with only 10 mol% of catalyst. Having established the optimized reaction conditions, we turned over attention to explore the scope of this protocol. The results are listed in Table-1. As shown in Table-1, in the most of cases 2-amino thiophenol reacted with a wide variety of substituted benzaldehydes completely and afforded the corresponding benzothiazoles in good to excellent yields. Substituted benzaldehydes containing electron-donating (or) electron-withdrawing groups on the benzene rings reacted with 2-aminothiophenol smoothly under optimal reaction conditions to give the desired products. All synthesized compounds are matched with authentic data.

Table-1: synthesis of 2-substituted benzothiazoles from 2-aminothiophenol and aldehydes[a]

Entry	aldehyde	Benzothiazole	Yield[b]
1			92
2			91
3			90
4			89
5			88

6			82
7			89
8			87

[a]Reaction conditions: 2-Aminothiophenol (1 mmol) , aldehyde (1.2 mmol) , $Zn(OTf)_2$ (10 mol%) was stirred for 5h under reflux in ethanol solvent. [b]Isolated yield.

CONCLUSION

In conclusion we have developed a simple and efficient method for synthesis of 2-substitued benzothiazole derivatives by using this zinc triflate catalyst. The method offers several advantages like simple reaction conditions, short reaction time, high yields of products and simple experimental operation, which leads to a useful and attractive process for synthesis of benzothiazole derivatives.

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