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Synthesis of 2-substituted benzothiazoles by a solvent-free reaction using *Grindstone* technique

Aatika Nizam*[1] and M. A. Pasha[2]

[1]Department of Chemistry, Christ (Deemed to be University, Hosur Road, Bengaluru-560029, INDIA
[2]Department of Studies in Chemistry, Jnanabharathi Campus, Bangalore University, Bengaluru–560056, INDIA

*E-mail: aatika.nizam@christuniversity.in

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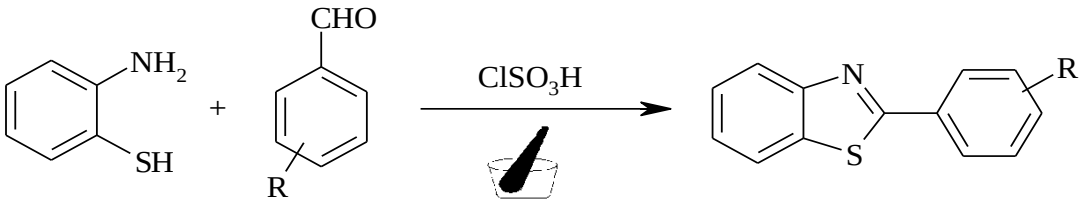
ABSTRACT

A rapid, efficient and green route for the synthesis of 2-substituted benzothiazoles using chlorosulphonic acid as a catalyst under solvent-free condition employing *grindstone* methodology has been described. This method is much better and is an improved protocol for the synthesis of 2-substituted benzothiazoles in terms of yield of the products and the reaction duration. It involves simple work-up procedure and it has an ability to tolerate a variety of functional groups.



1 **2** **3**

Key words: Benzothiazoles, 2-aminothiophenol, aryl aldehydes, chlorosulphonic acid, solvent-free reaction.

1. Introduction

Benzothiazoles are an important class of heterocyclic molecules which are of interest as this heterocyclic scaffold is found in many biologically active and medicinally significant compounds. Some of the benzothiazoles such as: 2-(4'-aminophenyl) benzothiazole is used as

*Address for correspondence: Department of Chemistry, Christ (Deemed to be University), Hosur Road, Bengaluru-560029, INDIA.
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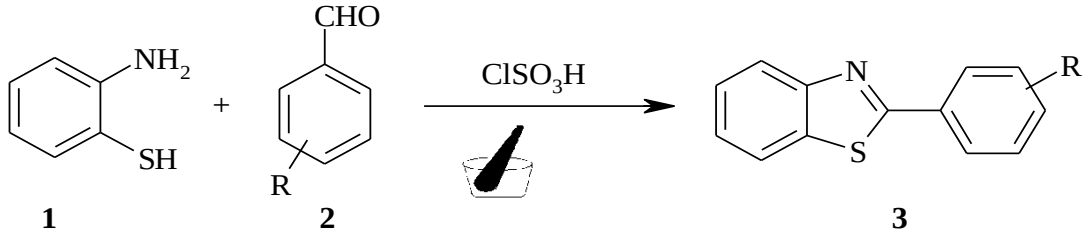
potent and selective antitumor agent.[1] Krapcho has reported that, some derivatives have therapeutic activity and act as central nervous system depressants, ataractic agents and as anti-pasedics.[2] Benzothiazoles have also found application in a variety of industries and find application as antioxidants, vulcanization accelerators and as dopants in light-emitting organic electroluminescent devices.[3,4] Recently, the synthesis as well as biological evaluation and biological importance of 2-substituted benzothiazoles has been reviewed.[5–10] 2-Substituted benzothiazoles are usually synthesized by one of the two major routes; the most commonly used direct method involves the condensation of *ortho*-aminothiophenol with substituted aldehydes, carboxylic acids, acyl chlorides or nitriles.[11] Another method involves the cyclization of thiobenzanilides using potassium ferricyanide (Jacobson's method).[12] Roe and Tucker have reported the synthesis of 2-substituted benzothiazoles from substrates having a bromo substituent *ortho* to the anilido nitrogen giving a benzyne intermediate followed by intramolecular cyclization.[13] There are a few more methods which involve the reaction of *ortho*-aminothiophenols with an aldehyde in the presence of Ag_2CO_3/Celite,[14] sodium bisulfite,[15] Ligand-Free Pd/C,[16] as catalysts and under catalyst-free condition[17] and solvent and catalyst-free conditions.[18] Alternatively, benzothiazoles are derived from 1-iodo-2-nitrobenzene by a copper-catalysed one-pot three-component reaction,[19] and under microwave irradiation.[20] Most of the reported protocols, however, suffer from drawbacks, such as: longer reaction periods, use of toxic metallic catalysts which results in the generation of hazardous waste, unsatisfactory yields and tedious isolation procedures and involve synthesis of thiobenzanilide precursors through multistep transformations[21]. Chlorosulphonic acid was discovered in 1854 and is undoubtedly an important industrial chemical having widespread use. It has found application in many diverse types of reactions such as: halogenation, rearrangements, alkylation, polymerization and cyclization reactions; in addition is useful as an efficient dehydrating agent.[22]

Recently, we have reported a metal-free, one-pot route to sulphur heterocycles such as: benzo[*b*]thiophenes and their hetero-fused analogs *via* iodine mediated intramolecular arylthiolation of *in situ* generated β-(het)aryl-β-cyanoenethiolates,[23] and a one-pot synthesis of 2-(aryl/alkyl) amino-3-cyanobenzo [*b*] thiophenes and their hetero-fused analogues by Pd-catalyzed intramolecular oxidative CH functionalization/arylthiolation;[24] and herein, we report a simple and efficient one-pot synthesis of 2-substtituted benzothiazole derivatives by the reaction of various aromatic aldehydes with 2-aminothiophenol under solvent-free condition in the presence of $ClSO_3H$ as a catalyst by using *grindstone* technique as shown in the **Scheme 1**.



Scheme 1: Synthesis of 2-substituted benzothiazoles.

2. Present Work

To verify the versatility of the protocol, a few preliminary experiments were carried out taking 4-methoxybenzaldehyde and treating it with 2-aminothiophenol in the absence of any catalyst at 25 °C; no formation of the product was noticed, further the reactants were

heated at 80 °C under the solvent-free condition and at reflux in solvents like DCM and acetonitrile, in both the cases the yield improved but was not satisfactory. Hence, we decided to use a catalyst, making use of very little $ClSO_3H$ and grinding the reactants using a pestle and mortar at 25 °C afforded the product in very high yield within 5 min. There was no need to purify the product using column chromatography, the purity of the product was checked directly by GC, and was characterized by the spectral analysis. The utility of the reaction was tested by using various substituted aryl aldehydes and was noted that, the electronic nature of the substituents in the aromatic ring of the aldehydes did not show strong effects in terms of yield of the products and the rate of the reactions. Thus, aromatic aldehydes bearing both electron withdrawing or electron-donating groups on the aromatic ring underwent clean conversion under the said reaction condition to produce the corresponding benzothiazoles in very high yields. The results of this study are presented in the **Table 1**. The reaction is equally good with heteroaromatic aldehyde (**Table 1**, 3k). The present reaction conditions are very simple, $ClSO_3H$ acts as an effective catalyst, and analytically pure products were obtained by recrystallization from aqueous alcohol.

Table 1: Synthesis of 2-substituted-benzothiazoles[a]

Entry	Aldehyde (**2**)	Product	Time (min)	Yield[b] (%)
1.	C_6H_5CHO	**3a**	4	92
2.	4-$MeOC_6H_4CHO$	**3b**	3	95
3.	3-$MeOC_6H_4CHO$	**3c**	3	95
4.	3-$NO_2C_6H_4CHO$	**3d**	4	90
5.	4-ClC_6H_4CHO	**3e**	4	95
6.	3-ClC_6H_4CHO	**3f**	4	95
7.	2-HOC_6H_4CHO	**3g**	4	95
8.	2,4-$Cl_2C_6H_3CHO$	**3h**	4	85
9.	4-HO,3-$MeOC_6H_3CHO$	**3i**	4	90
10.	4-$(CH_3)_2NC_6H_4CHO$	**3j**	4	90
11.	Furyl-CHO	**3k**	4	90

[a]Reaction condition: Aldehyde (1 mmol), 2-aminothiophenol (1 mmol) and $ClSO_3H$ (0.1 mL) were ground well using a pestle and a mortar at 25 °C until the overall mixture turned into a solid. Purity of all the products was established by GC, and all the products are characterized by the mass spectral analysis.
[b]Yields refer to yield of the pure isolated products.

3. Experimental

3.1 *Materials and Methods:*

2-Aminothiophenol and all aldehydes are commercial products and were used without further purification, except liquid aldehydes which were distilled before use. Yields refer to yield of the isolated products. Melting points were measured on a Raaga, Indian make melting point apparatus; GC-Mass spectra were recorded on a Shimadzu GC-MS QP 5050A instrument. Infrared spectra were recorded using Shimadzu FT-IR-8400s Spectrophotometer as KBr pellets.

3.2 *General procedure for the preparation of 2-substituted benzothiazoles*:

A mixture of 2-aminothiophenol (1 mmol), aldehyde (1 mmol) and $ClSO_3H$ (0.1 mL) were ground together in a mortar with a pestle at 25 °C for an appropriate time (**Table 1**). The progress of the reaction was monitored by TLC [eluent, 10:1::light petrol:ethyl acetate]. After the completion of the reaction, the reaction mixture was quenched with cold water, and the solid thus separated was filtered to get the desired product.

3.3 *Spectral Data*

2-Phenylbenzothiazole[25]: Mp: 113−115 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.48 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.54−7.60 (m, 4H, Ar- H), 8.07−8.12 (m, 3H, Ar-H), 8.16 (d, *J* = 7.8 Hz, 1H, Ar-H) ppm; MS: m/e = 211 (M^+).
2-(4'-Methoxyphenyl)benzothiazole[26]: Mp: 122−124 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 3.85 (s, 3H), 7.10 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.40 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.50 (t, *J* = 8.0 Hz, 1H, Ar-H), 8.00 (d, 1H, *J* = 8.2 Hz, Ar-H), 8.05 (d, *J* = 8.2 Hz, 2H, Ar-H), 8.10 (d, *J* = 7.6 Hz, 1H, Ar-H) ppm; MS: m/e = 241 (M^+).

2-(3'-Methoxyphenyl)benzothiazole[27]: Mp: 80−82 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H, OCH_3), 6.73−6.79 (m, 1H, Ar-H), 6.99−7.04 (m, 2H, Ar-H), 7.21−7.26 (m, 3H, Ar-H), 7.55−7.60 (m, 1H, Ar-H), 8.12 (d, *J* = 8.0 Hz, 1H, Ar-H) 8.23 (d, *J* = 8.0 Hz, 1H, Ar-H) ppm; MS: m/e = 241 (M^+).

2-(3'-Nitrophenyl)benzothiazole[28]***:*** Mp:185−186 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.54 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.60 (t, *J* = 8.0 Hz, 1H, ArH), 7.88 (t, J = 8.0 Hz, 1H, Ar-H), 8.16 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.24 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.41 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.44 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.84 (s, 1H, Ar-H) ppm; MS: m/e = 256 (M^+).

2-(4'-Chlorophenyl)benzothiazole[25]***:*** Mp: 116−117 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.40 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.47 (m, 1H), 7.50 (t, *J* = 7.1 Hz, 1H), 7.90−7.92 (m, 1H), 8.00−8.10 (m, 3H) ppm; MS: m/e = 245 (M^+).

2-(3'-Chlorophenyl)benzothiazole[29]***:*** Mp: 97−98 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.23−7.36 (m, 3H, Ar-H), 7.49−7.55 (m, 3H, Ar-H), 8.12 (t, *J* = 8.0 Hz, 1H, Ar-H), 8.23 (t, *J* = 8.0 Hz, 1H, Ar-H) ppm; MS: m/e = 245 (M^+).

2-(2'-Hydroxyphenyl)benzothiazole[25]***:*** Mp: 130−131 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.00 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.10 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.40 (m, 2H, Ar-H), 7.50 (t, *J* = 7.1 Hz, 1H, Ar-H), 8.05 (d, 1H, Ar-H), 8.10 (m, 2H, Ar-H), 11.10 (s, 1H, OH) ppm; MS: m/e = 227 (M^+).

2-(2',4'-Dichlorophenyl)benzothiazole[30]***:*** Mp: 146−147 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 7.21−7.26 (m, 1H, Ar-H), 7.34−7.37 (m, 2H, Ar-H), 7.55 (t, *J* = 8.8 Hz, 2H, Ar-H), 8.12 (t, *J* = 8.0 Hz, 1H, Ar-H), 8.23 (t, *J* = 8.0 Hz, 1H, Ar-H) ppm; MS: m/e = 279 (M^+).

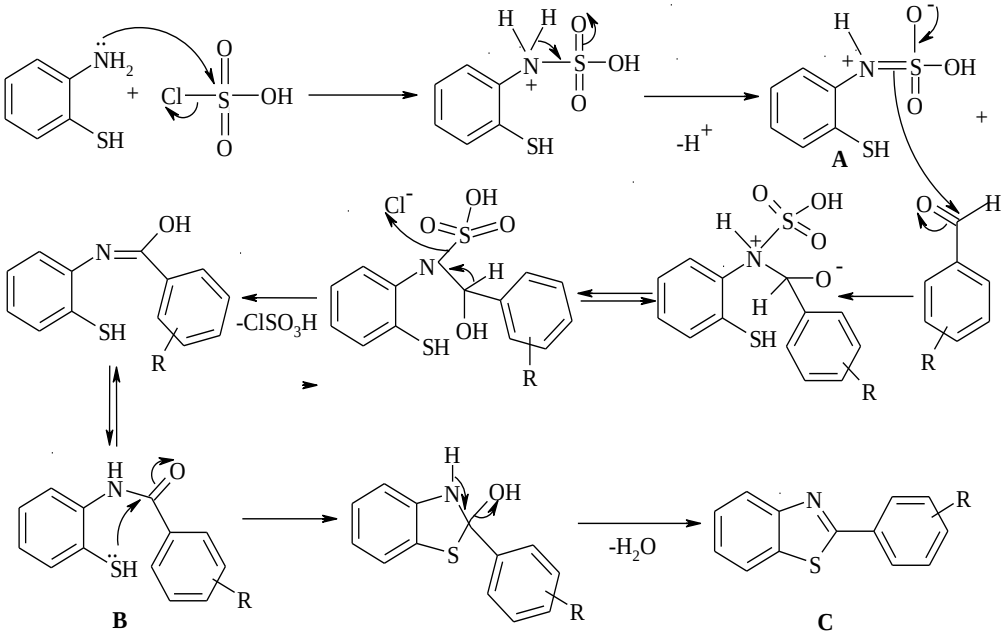
2-(4'-Hydroxy-3'-Methoxyphenyl)benzothiazole[31]***:*** Mp: 162−164 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 3.73 (s, 3H, OCH_3), 5.0 (s, 1H, OH), 6.68 (d, *J* = 8.8 Hz, 1H, Ar-H), 6.82−6.87 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.55−7.60 (m, 2H, Ar-H), 8.12−8.16 (t, *J* = 8.0 Hz, 1H, Ar-H) 8.23 (t, *J* = 8.0 Hz, 1H, Ar-H) ppm; MS: m/e = 257 (M^+).

2-(4'-N,N-Dimethylphenyl)benzothiazole[32]***:*** Mp: 170−172 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 2.85 (s, 6H, 2 × CH_3), 6.65 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.30 (d, *J* = 8 Hz, 2H, Ar-H), 7.55 (t, *J* = 8.8 Hz, 2H, Ar-H), 8.12 (t, *J* = 8 Hz, 1H, Ar-H), 8.23 (t, *J* = 8 Hz, 1H, Ar-H) ppm; MS: m/e = 254 (M^+).

2-Furyl-benzothiazole[28]***:*** Mp:102−104 °C; ^{1}HNMR (DMSO-d_6, 400 MHz): δ 6.30 (t, *J* = 8.8 Hz, 1H, Ar-H), 7.40 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.55 (t, *J* = 8.8 Hz, 2H, Ar-H), 7.83 (t, *J* = 8.8 Hz, 1H, Ar-H), 8.12 (t, *J* = 8.0 Hz, 1H, Ar-H), 8.23 (t, *J* = 8.0 Hz, 1H, Ar-H) ppm; MS: m/e = 201 (M^+).

4. Mechanism

The reaction may be mechanistically considered to proceed through the sulfamation of amino group of 2-aminothiophenol, followed by removal of a proton to give the intermediate **A**. **A** in the next step may attack the carbonyl group of the aldehyde and subsequent loss of $ClSO_3H$ (which is ready for another catalytic cycle) to afford substituted *N*-(2-mercapto-phenyl)-benzamide (**B**), cyclization of **B** followed by the loss of a molecule of water may give the product **C** as shown in the **Scheme 2**.



Scheme 2: A plausible mechanism for the formation of 2-substituted benzothiazoles

5. Conclusions

In conclusion, $ClSO_3H$ has been found to be an efficient catalyst for the synthesis of a series of 2-substituted benzothiazoles from 2-aminothiophenol and aromatic aldehydes at 25 °C under solvent-free condition. The present method can provide several advantages such as: mild reaction condition, easy workup, excellent yields of the products and all the reactions go to completion within 4 min. As the reaction is carried out using *Grindstone* technique, there is scope for use of 'Ball mills' in future for the large scale production of these biologically important molecules.

6. Acknowledgement

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7. Conflict of Interest

The authors declare that, there is no conflict of interest in publishing this work.

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