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Green synthesis of 2-substituted benzothiazole derivatives under solvent-free conditions

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A series of benzothiazole derivatives were efficiently synthesized in good to excellent yields *via* the reaction of 2-aminothiophenol with aromatic benzoyl chlorides under solvent-free conditions at room temperature in excellent yields and short reaction time.

Keywords: 2-aminothiophenol, benzothiazole derivatives, benzoyl chlorides, catalyst free, green synthesis, solvent free reaction.

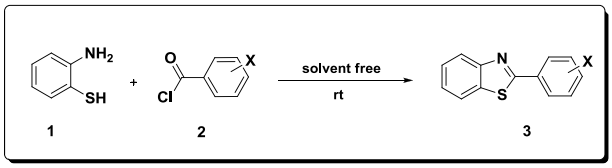
INTRODUCTION

Benzothiazole derivatives are known for different biological properties, including antitubercular, antimalarial, anticonvulsant, antihelmintic, analgesic, antidiabetic, antimicrobial, antibacterial, antifungal, herbicidal, antiproliferative and anti-inflammatory activities [1-3]. These compounds have antitumor activity against a range of human breast, ovarian, and colon cancers [4, 5]. They are also useful for the *in-vivo* diagnosis of Alzheimer's disease [6, 7].

Conventionally, 2-substituted benzothiazoles are synthesized by condensation of 2-aminothiophenol with aldehyde derivatives in different conditions. Various catalysts such as ZnO-beta zeolite [8], solid silica supported ferric chloride (SiO_2-$FeCl_3$) [9], glucose oxidase (GOX)/chloroperoxidase (CPO) [10], perchloric acid–doped polyaniline ($HClO_4$/PANI) [11], $Sc(OTf)_3$ [12], YCl_3 [13] and mixed metal oxide nano crystals of Al_2O_3-Fe_2O_3, Al_2O_3-V_2O_5 and Al_2O_3-CuO [14] were used in the synthesis of benzothiazoles. However, there is still room for improvement in the present methods so as to overcome the limitations and disadvantages of using organic solvents [9], long reaction times [10], low yields [11] and tedious work-up procedures [13]. In this paper we report our results on the development of an environmentally friendly protocol for the synthesis of 1,3-benzothiazole derivatives.

RESULTS AND DISCUSSION

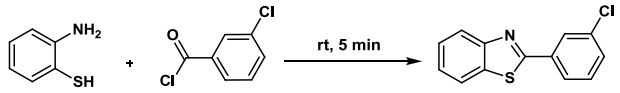
Condensation of 2-aminothiophenol (1) with benzoyl chlorides (2) under solvent free conditions at room temperature gives 2-substitued benzothiazoles (3) (Scheme 1).



Scheme 1. Reaction of 2-aminothiophenol (1) with benzoyl chlorides (2)

At first, the reaction of 2-aminothiophenol (1) and 3-chlorobenzoyl chloride (2) was examined as a model experiment in different solvents such as polar protic (H_2O, EtOH, MeOH) and polar aprotic (CH_3CN, CH_2Cl_2, acetone, EtOAc) solvents at room temperature to get an insight into the solvent effect on the reaction yield. As shown in Table 1, in acetone the reaction yield was low (Table 1, entry 3), but in other solvents and also in solvent free conditions, product yield was quantitative.

Table 1. Synthesis of benzothiazole derivatives in various solvents.



1 2 3

Entry	Solvent	Yield (%)
1	CH_3CN	quantitative
2	CH_2Cl_2	99
3	Acetone	79
4	EtOAc	quantitative
5	H_2O	quantitative
6	EtOH	quantitative
7	MeOH	99
8	-	quantitative

Therefore, solvent-free condition at ambient temperature was selected as the optimal condition and was used to the synthesis of other derivatives. The results are summarized in Table 2.

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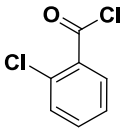
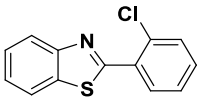
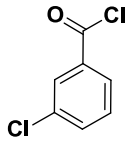
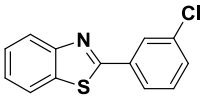
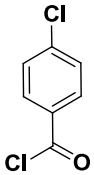
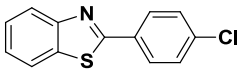
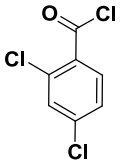
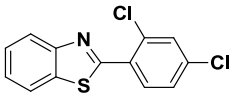
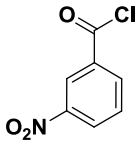
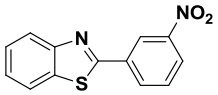
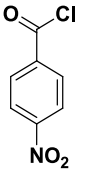
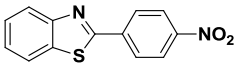
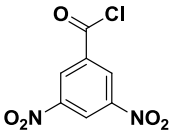
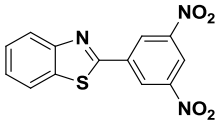
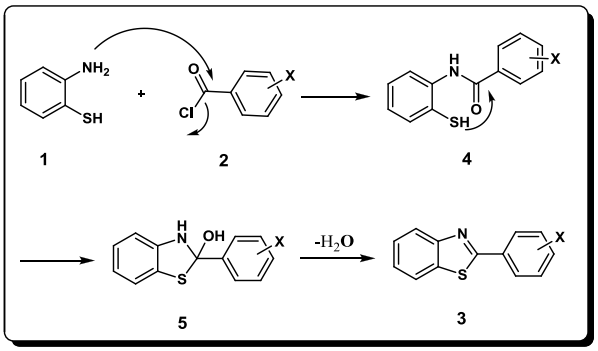
Table 2. Synthesis of benzothiazole derivatives under green conditions.

Entry	Benzoyl chloride	Product	Time (min)	Yield (%)	m.p. (°C)	m.p. (Ref.)
1		 3a	3	61	77-79	76-78 [15]
2		 3b	3	97	97-98	97-98 [16]
3		 3c	1-2	quantitative	118-119	117-118 [8]
4		 3d	1-2	quantitative	136-138	136 [17]
5		 3e	1	97	188 -189	186-188 [18]
6		 3f	2	quantitative	233-234	230-232 [18]
7		 3g	2	quantitative	237-238	-

These reactions were completed within 3 min. After completion of the reaction (monitored by TLC), the crude product was filtered and recrystallized in EtOH.

As shown in Table 2, in most cases, 2-aminothiophenol (1) reacted with a wide variety of substituted benzoyl chlorides (2) and afforded the corresponding benzothiazoles in good to excellent yields. Benzoyl chlorides with substituents at *ortho*, *meta*, and *para* positions were successfully employed to prepare the corresponding products, which shows the applicability of this protocol.

The suggested mechanism for the synthesis of 2-substitued benzothiazoles (3) is shown in Scheme 2. The NH_2 group of 2-aminothiophenol (1) attacks as nucleophilic reagent to the carbonyl group of the benzoyl chlorides (2) to give the intermediate (4). The nucleophilic attack of the SH group to the carbonyl group of intermediate (4) resulted in ring closure followed by dehydration to create 2-benzothiazole derivatives (3) (Scheme 2).



Scheme 2. Proposed mechanism

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Table 3. Comparison of different conditions in the synthesis of benzothiazole derivatives (3).

Entry	Solvent	Catalyst	Condition	Time (h)	Yield (%)	Year	Ref.
1	1-Methyl-pyrrolidin-2-one	-	100 °C	1	75-95	1990	[16]
2	Pyridine	-	reflux	1	74-82	1996	[19]
3	Ethanol	$SnCl_2.2H_2O$	reflux	4	85-95	1996	[19]
4	Pyridine		multi step	2	12-85	1996	[20]
5	Toluene	-	r.t.	0.25-1	80-100	2005	[21]
6	-	-	r.t.	1-3 (min)	61-100	**This work**	

The synthesis of benzothiazoles (**3**) with several catalysts in different solvents has been reported in the literature and the results are shown in table 3. In contrast with other existing methods, the present methodology which doesn't need any catalyst and solvent, offers several advantages, such as excellent yields, simple procedure, easy synthesis, simple work-up and greener conditions. The product structures were confirmed by IR, ^{1}H NMR and GC-mass data

EXPERIMENTAL SECTION

General information

GC-mass analysis was performed on a GC-mass model: 5973 network mass selective detector, GC 6890 Agilent. IR spectra were obtained with a Bruker 500 scientific spectrometer. ^{1}H NMR spectra of the products were recorded on a FT-NMR Bruker instrument at 250 MHz. Room temperature (r.t.) is 20–25 °C. Melting points were measured by the capillary tube method with an Electrothermal 9200 apparatus.

General procedure for the preparation of 2-(3-chlorophenyl) benzothiazole in various solvents (3b)

2-aminothiophenol (3.60 mmol, 0.38 mL) was dissolved in an appropriate solvent (5 mL) and 3-chlorobenzoyl chloride (3.60 mmol, 0.46 mL) was added to it. Then the mixture was stirred at room temperature for 5 min. After completion of the reaction (TLC: *n*-hexane/EtOAc, 2/1), the crude product was filtered and recrystallized from hot ethanol.

General procedure for the preparation of benzothiazole derivatives under solvent free conditions (3)

2-aminothiophenol (3.60 mmol, 0.38 mL) was placed in a flask and then benzoyl chloride (3.60 mmol) was added to it. The mixture was stirred at room temperature until completion of the reaction which was indicated by TLC (*n*-hexane/EtOAc, 1/1). The resulting crude product was recrystallized from EtOH. The spectroscopic and analytical data for selected compounds are presented in the following part.

Spectral Data of Products

2-(3-chlorophenyl)-1,3-benzothiazole ***(3b)****:* IR (KBr): υ_{max} = 3053, 1622, 1567, 1457, 759, 730, 674 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d$_6$): δ_H = 7.44-7.64 (m, 4H), 8.05 (t, 2H, *J* = 20 Hz), 8.02-8.13 (m, 2H) ppm.

2-(4-chlorophenyl)-1,3-benzothiazole ***(3c)****:* IR (KBr): υ_{max} = 3066, 1598, 1521, 1342, 851, 767, 728, 684 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d$_6$): δ_H = 7.43-7.64 (m, 4H), 8.04-8.16 (m, 4H) ppm. Mass (m/e): 245, 210, 122, 108.

2-(4-nitrophenyl)-1,3-benzothiazole ***(3f)****:* IR (KBr): υ_{max} = 3066, 1598, 1521, 1342, 851, 767, 728, 684 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d$_6$): δ_H =7.52-7.62 (m, 2H), 8.12-8.23 (dd, 2H, *J* = 8 Hz), 8.32-8.36 (m, 4H) ppm.

2-(3,5-dinitrophenyl)-1,3-benzothiazole ***(3g)****:* IR (KBr): υ_{max} = 3099, 1626, 1541, 1451, 1342, 769, 726 cm^{-1}. ^{1}H NMR (250 MHz, DMSO-d$_6$): δ_H = 7.55-7.65 (m, 3H), 8.17-8.26 (dd, 2H, *J* = 8 Hz), 8.92 (s, 1H), 9.06 (s, 1H) ppm.

CONCLUSION

In summary, a novel and highly efficient method for quick synthesis of benzothiazoles was developed by the reaction of aromatic benzoyl chlorides with 2-aminothiophenol. The reactions were carried out at r.t. and high yields obtained were comparable to those reported in the literature. A major advantage of our procedure is the very short reaction time (1-3 min) without use of any catalyst or solvents. Other attractive features of this protocol are: simple procedure, high yields, simple workup and non-chromatographic purification of the products.

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ЗЕЛЕНА СИНТЕЗА НА 2-СУБСТИТУИРАНИ ПРОИЗВОДНИ НА БЕНЗОТИАЗОЛА В ОТСЪСТВИЕ НА РАЗТВОРИТЕЛ

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(Резюме)

Успешно са синтезирани производни на бензотиазола чрез реакция на 2-аминофенол и ароматни бензоилхлориди в отсъствие на разтворител при стайна температура с отлични добиви и за кратко време.