Trichloroisocyanuric Acid (TCCA) as a Mild and Efficient Catalyst for the Synthesis of 2-Arylbenzothiazoles

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The condensation reaction of 2-aminothiophenol with aldehydes catalyzed by 1 mol % trichloroisocyanuric acid (TCCA) was investigated. As a result, a set of diverse 2-arylbenzothiazoles were obtained in good to excellent yields at room temperature.

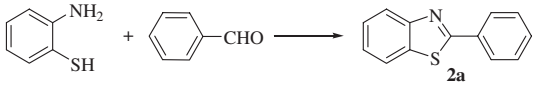
2-Substituted benzothiazoles is becoming one of the most important heterocyclic compounds in medicinal chemistry and organic synthesis.[1] Recently, Choo and co-workers reported that 2-arylbenzothiazoles exhibited topoisomerase II inhibitory activities.[2] One of the most practically and widely used routes for the synthesis of these compounds is the direct condensation of the 2-aminothiophenol with aldehydes, carboxylic acids, or its derivatives in the presence of various promoting agents, such as poly(phosphoric acid) (PPA),[3] poly(phosphate ester),[4] a mixture of methanesulfonic acid and phosphorous pentoxide,[5] acetic acid,[6] $FeCl_3$,[7] $Sc(OTf)_3$,[8] molecular iodine,[9] or ionic liquid under microwave irradiation.[10] Other general methods include palladium-catalyzed intramolecular cyclization of *o*-bromophenylthioureas,[11] the Suzuki biaryl coupling of 2-bromobenzothiazole with arylboronic acids,[12] coupling of benzothiazoles with aryl bromides,[13] microwave-mediated reaction of 2-aminothiophenol with β-chlorocinnamaldehydes,[14] the reaction between thiophenols and aromatic nitriles,[15] and the intramolecular cyclization of thiobenzamides via aryl radical cations as reactive intermediates.[16] Recently, Bahrami and co-workers reported that synthesis of 2-arylbenzothiazoles promoted by H_2O_2/CAN.[17] However, many of these methodologies suffer from one or more disadvantages such as requirement of excess reagents or catalysts,[9,14] prolonged reaction time,[8] toxic or expensive metallic compounds[17] that result in waste streams.[3–5] Therefore, the development of mild, efficient, inexpensive, and facile methods for the synthesis of benzothiazoles is necessary part of organic synthesis.

Trichloroisocyanuric acid (TCCA), an inexpensive, easily available reagent, low toxicity and less corrosive, has been widely used in organic reactions,[18] but it has not been carefully studied as a catalyst in the synthesis of 2-arylbenzothiazoles until now.

In continuation of our efforts to develop novel synthetic routes for the formation of carbon–carbon and carbon–heteroatom bond.[19] Herein, we report that a new and simple TCCA-promoted synthesis of 2-arylbenzothiazole by condensation of aldehydes with 2-aminothiophenol under mild conditions.

The model reaction of 2-aminothiophenol with benzaldehyde was conducted to screen the optimal reaction conditions and the results were listed in Table 1. Initially, the effect of solvents was tested. Among all the solvents screened (CH_3OH, DMF, H_2O, PEG-400, toluene $(C_2H_5)_2O$, CH_2Cl_2, $CHCl_3$, C_2H_5OH, EtOAc, and THF), THF afforded good yield (86%, Table 1, Entry 14).

Table 1. The reaction of 2-aminothiophenol with benzaldehyde under different reaction conditions[a]



2a

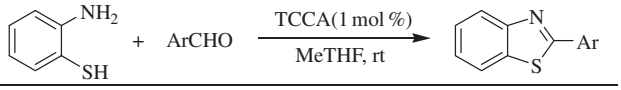
Entry	TCCA/mol %	Reaction medium	Time/h	Yield[b]/%
1	None	None	5	17
2	5	None	5	45
3	5	CH_3OH	5	71
4	5	CH_3CN	5	75
5	5	DMF	5	43
6	5	H_2O	5	15
7	5	PEG-400	5	28
8	5	Toluene	5	82
9	5	$(C_2H_5)_2O$	5	85
10	5	CH_2Cl_2	5	76
11	5	$CHCl_3$	5	79
12	5	C_2H_5OH	5	80
13	5	EtOAc	5	79
14	5	THF	5	86
15	5	2-CH_3-THF	5	95
16	1	2-CH_3-THF	5	94
17	2	2-CH_3-THF	5	95
18	1	2-CH_3-THF	1	85
19	1	2-CH_3-THF	2	95
20	None	2-CH_3-THF	5	27

[a]Reaction conditions: 2-aminothiophenol (1.1 mmol), benzaldehyde (1 mmol), reaction medium (1 mL), rt. [b]Isolated yield.

2-Methyltetrahydrofuran (MeTHF) can be easily dried with lower losses and lower recycle costs compared to THF and gives cleaner phase separations compared to processes that use solvent exchange of THF with toluene. Unlike THF, MeTHF has limited solubility in water and this property makes it easier to isolate the quenched reaction product and recycle dry MeTHF.

MeTHF's distinct advantages over THF prompted us to focus on the synthesis of **2a** using MeTHF as solvent. As expected, the excellent yield was obtained in MeTHF in the presence of TCCA (95%, Table 1, Entry 19). Moreover, we also studied influence of the amount of TCCA on the reaction yields. One mol % of TCCA was sufficient, excessive amount of catalyst did not increase the yield remarkably (Table 1, Entries 15–20). In light of these results, subsequent studies were carried out under the following optimized conditions, that is, with 1 mol % TCCA in 2-methytetrahydrofuran at room temperature.

Table 2. Synthesis of 2-substitued benzothiazoles catalyzed by TCCA[a]



Entry	Ar	Time/h	Product	Yield[b]/%
1	C_6H_5	2	**2a**	95 (93)[c]
2	1-Naphthyl	2	**2b**	91
3	*p*-$CH_3C_6H_4$	2	**2c**	97
4	*p*-$C_2H_5C_6H_4$	2	**2d**	96
5	*p*-$CH_3OC_6H_4$	2	**2e**	98[d]
6	*o*-$CH_3OC_6H_4$	2	**2f**	98[d]
7	*p*-FC_6H_4	2	**2g**	92
8	*p*-ClC_6H_4	2	**2h**	95
9	*p*-BrC_6H_4	2	**2i**	93
10	*p*-$NO_2C_6H_4$	5	**2j**	87
11	*p*-$COOMeC_6H_4$	5	**2k**	89
12		5	**2l**	95
13		2	**2m**	82
14		5	**2n**	96
15	$C_6H_5CH{=}CH{-}$	5	**2o**	50

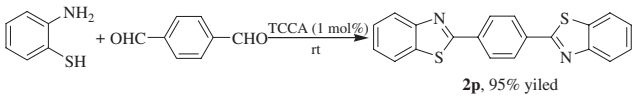
[a]Reaction conditions: 2-aminothiophenol (1.1 mmol), aldehydes (1 mmol), MeTHF (1 mL), rt. [b]Isolated yield. [c]2-Aminothiophenol (11 mmol), aldehydes (10 mmol), and MeTHF (5 mL). [d]2-Aminothiophenol (1 mmol) and aldehydes (1.1 mmol).

Next stage, we studied the scope of reaction for the synthesis of benzothiazoles from various aldehydes under optimized conditions (Table 2). A series of substituted aromatic aldehydes with electron-donating or electron-withdrawing groups attaching to aromatic ring were investigated. Electron-withdrawing substituents on the aromatic ring of aldehyde decrease the yield (Entries 7–11). The substituents on the ortho or opposite position have no obvious difference (Entries 5 and 6). Moreover, the reaction of aromatic heterocyclic aldehydes with 2-aminothiophenol proceeded smoothly and the desired products were obtained with excellent yields (Entries 12 and 14). However, α,β-unsaturated aldehyde such as cinnamaldehyde gave lower yield than aromatic aldehydes (Entry 15).

Furthermore, the present catalytic route to 2-arylbenzothiazoles was successfully applied to a large scale reaction. For instance, the reaction of benzaldehyde (1.06 g) with 2-aminothiophenol (1.38 g) catalyzed by 1 mol % of TCCA provided the desired product **2a** in 93% (Table 2, Entry 1).

Finally, we have developed this synthetic method for the preparation of additional extended bisbenzimidazole derivatives in a 2.2:1:0.01 molar ratio of 2-aminothiophenol to 1,4-benzenedicarbaldehyde to TCCA in 1 mL of MeTHF (Scheme 1). As expected, the reaction proceeded smoothly for 2 h at room temperature using the present protocol and the desired product **2p** was obtained in 95% isolated yield.

In summary, a new catalytic protocol to synthesize 2-substituted benzothiazoles has been developed. Compared to previous reported methodologies, the present protocol features simple work-up, easy and quick isolation of the products, cheap and a catalytic amount of catalyst. This protocol avoids the use of hazardous solvent, toxic metallic catalysts, low cost.



Scheme 1.

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