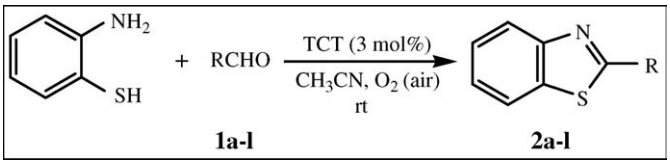
Efficient 2,4,6-Trichloro-1,3,5-triazine-Catalyzed Synthesis of 2-Arylbenzothiazoles and Bisbenzothiazoles by Condensation of 2-Aminithiophenol with Aldehydes under Mild Conditions

Behrooz Maleki,[a]* Davood Azarifar,[b] Seyede Fateme Hojati,[a] Hojat Veisi,[c] Mostafa Gholizadeh,[d] Hafezeh Salehabadi,[a] and Mona Khodaverdian Moghadam[a]

[a]Department of Chemistry, Sabzevar Tarbiat Moallem University, Sabzevar, Iran
[b]Department of Chemistry, Bu-Ali Sina University, Hamadan, Iran
[c]Department of Chemistry, Payame Noor University, Songhor, Kermanshah, Iran
[d]Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran
*E-mail: maleki@sttu.ac.ir

Received October 21, 2009
DOI 10.1002/jhet.462
Published online 21 October 2010 in Wiley Online Library (wileyonlinelibrary.com).



2,4,6-Trichloro-1,3,5-triazine efficiently catalyzed the condensation reactions between 2-aminothiophenol and aromatic aldehydes to afford 2-arylbenzothiazolles in good-to-excellent yields. Simple and mild reaction conditions, the use of a cheap catalyst and easy work up, and isolation are notable features of this method.

J. Heterocyclic Chem., **48**, 449 (2011).

INTRODUCTION

2-Arylbenzothiazoles have been investigated extensively by organic chemists due to their medicinal properties such as antitumor [1], antiviral, and antimicrobial drugs [2]. Also, some benzothiazoles have been found in some organisms [3]. Therefore, there is interest in developing methods for their synthesis.

Numerous methods are available for the synthesis of 2-arylbenzothiazoles and the important ones include the reaction of *o*-aminothiophenols with carboxylic acids [4], the potassium ferricyanide cyclization of thioacylbezanilides (Jacobson's method) [5], the palladium-catalyzed reaction of aryl halides with *o*-aminothiophenol in the presence of carbon monoxide [6], the ceric ammonium nitrate mediated reaction of thiophenols with aromatic nitriles [7], and flash vacuum pyrolysis and photolysis of 2-methylthio-*N*-(arenylidene)aniline [8].

On the other hand, the most general synthetic approaches for synthesis of 2-arylbenzothiazoles involve condensation of 2-aminothiophenols with aldehydes using various oxidants such as MnO_2/SiO_2 [9], *p*-TsOH or graphite on the surface of solid mineral supports under microwave irradiation [10], I_2/DMF [11], 1-phenyl-3-methylimidazolium bromide by microwave irradiation [12], activated carbon (Shirasagi KL or Darco® KB) under oxygen atmosphere [13], O_2 or H_2O_2 in the presence of $Sc(OTf)_3$ [14], tungstophosphoric acid impregnates zirconium phosphate [15], electrooxidation [16], Dowex 50W [17], and direct condensation of 2-aminothiophenol with aromatic aldehydes under microwave irradiation [18].

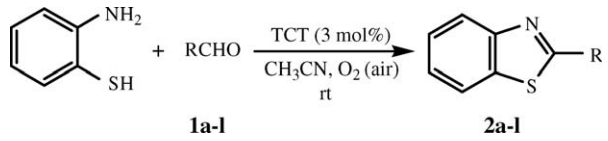
RESULTS AND DISCUSSION

In development of benzothiazoles synthetic methodologies [19] and as a part of our research interest toward the development of efficient and environmentally benign synthetic methodologies using eco-friendly conditions [20], we report here a facile synthesis of 2-arylbenzothiazoles in the presence of oxygen and a catalytic amount of 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) at room temperature (Scheme 1).

In recent years, 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) has been used in organic synthesis because it is stable, nonvolatile, inexpensive, commercially available, and easy-to-handle reagent [21].

In the initial exploratory experiments, we optimized the reaction condition by testing several parameters, such as different amounts of TCT and different solvents. As a test case, the reaction of 2-aminothiophenol (1.2 mmol) with benzaldehyde (1 mmol) was carried out in the presence of TCT in CH_3CN to afford the 2-phenylbenzothiazoles (**2a**). In the experiments carried out to establish the optimal amount of TCT, the reaction with a 3 mol % catalyst loading gave 87% yield after 3 h. Increasing the amount of the catalyst (5, 7, and 10 mol %) did not

Scheme 1



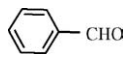
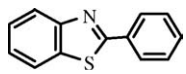
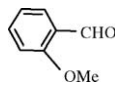
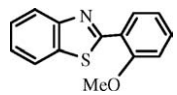
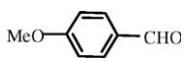
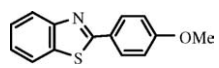
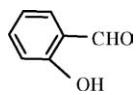
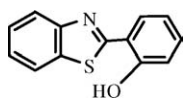
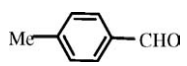
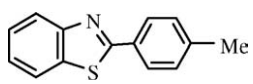
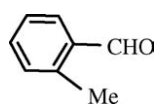
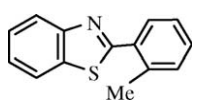
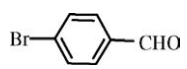
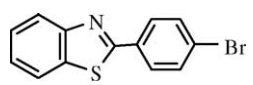
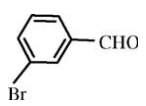
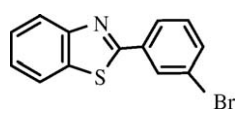
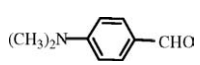
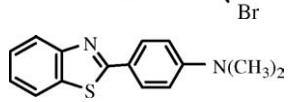
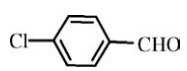
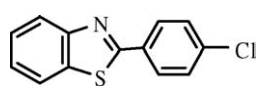
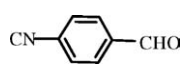
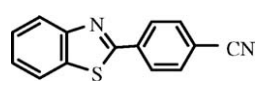
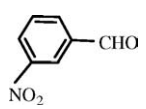
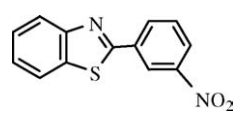
1a-l **2a-l**

change the isolated yield and the time reaction (3 h). The solvent effect in this reaction was also studied, and it was found that CH_3CN gave the best results among H_2O, MeOH, $CHCl_3$, CH_2Cl_2, and EtOH solvents. Similarly, by adopting optimized reaction conditions, the various 2-arylbenzothiazoles were prepared by condensation of 2-aminothiophenol with aromatic aldehydes (**1a–l**) in presence of 3 mol % TCT in CH_3CN (Table 1).

The present conversion did not precede under perfectly anhydrous reaction conditions. The proposed mechanism for the TCT-catalyzed synthesis of 2-arylbenzothiazoles may tentatively be visualized to occur via a tandem sequence of reactions as depicted in

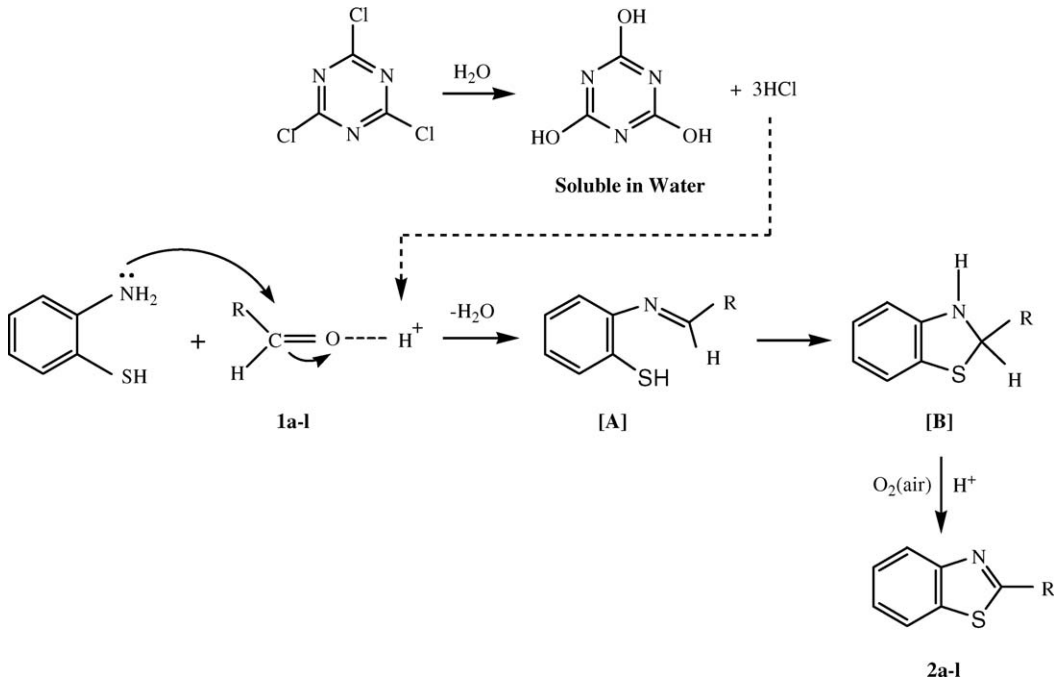
Table 1

The results of the reaction of 2-aminothiophenol with various aldehydes by TCT (3 mol %) in CH_3CN at room temperature.

Entry	Aldehyde (**1a–l**)	2-Arylbenzothiazole (**2a–l**)	Time (h)	Yield (%)[a]	Observed mp (°C)	References
1			3	87	111–112	112–114 [17]
2			3	84	103–105	101–103 [17]
3			2.5	80	119–120	120–121 [17]
4			3.5	84	127–128	127–128 [22a]
5			4	78	82–84	85 [22a]
6			4.5	80	52–54	53–54 [22a]
7			2.5	86	132–133	132 [17]
8			3	84	82–83	83–84 [17]
9			30[b]	80	157–159	160–161 [17]
10			2.5	80	116–118	115–117 [17]
11			2	90	161–162	162–164 [10]
12			3	86	179–180	181–182 [17]

[a] The yields refer to those of isolated products characterized by spectroscopic (IR, ^1H, ^{13}C-NMR) data.
[b] Reaction time is min.

Scheme 2



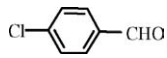
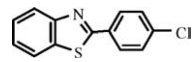
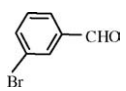
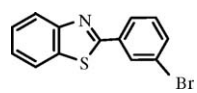
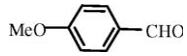
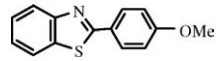
(Scheme 2) involving TCT [20e], which reacts with ''incipient'' moisture and releases 3 mol of HCl and cyanuric acid (removable by washing with water) as a by-product. The *in situ* generated HCl acts as a protic acid and activates the carbonyl oxygen to promote the condensation of 2-aminothiophenol with aldehydes to form adduct **[A]**, which then undergoes cyclization to give adduct **[B]**, followed by oxidation with oxygen (air) to form 2-arylbenzothiazoles (**2a–l**).

On the basis of previously reported mechanism for the synthesis of 2-arylbenzothiazoles in the presence of various catalytic amounts [9,13,17,18,20a,21a], and because of our observation in during the synthesis of 2-arylbenzothiazoles using TCT, we assume that HCl is generated from TCT as the active catalyst in the reaction medium. To confirm our assumption, we replaced the TCT by 10 mol % of HCl. A test reaction was performed between 4-chlorobenzaldehyde (1 mmol) and 2-aminothiophenol (1.2 mmol) in the presence of HCl (10 mol %) at 70°C without solvent. It was found that the generation of 2-(4-chlorophenyl) benzothiazole occurred in 54% after 5 h. To show the accessibility of the present work in comparison with the reported results with TCT, we summarized some of the results for the preparation of 2-arylbenzothiazoles using HCl in Table 2.

It is important to mention that, when the reaction of 2-chlorobenzaldehyde (1 mmol) and 2-aminothiophenol (1.2 mmol) was carried out in the presence of TCT (3

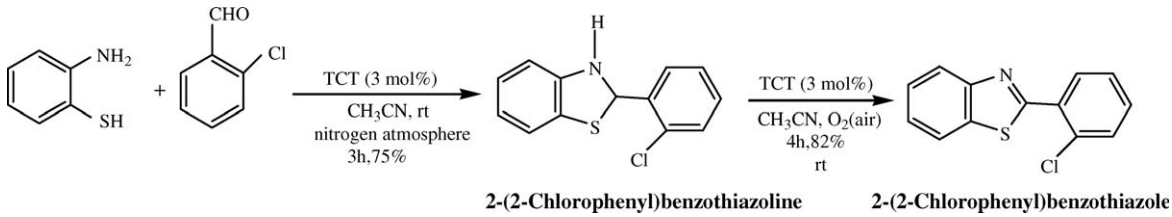
Table 2

Synthesis of 2-arylbenzothiazoles by HCl (10 mol %).

Entry	Aldehyde	2-Arylbenzothiazole	Time (h)	Yield (%)[a]	Observed mp (°C)	References
1			5[b]	54	115–116	115–117 [17]
2			20[c]	52	84–86	83–84 [17]
3			15[c]	48	120–121	120–121 [17]

[a] The yields refer to those of isolated products characterized by spectroscopic (IR, ^{1}H, ^{13}C-NMR) data.
[b] Reaction carried out under solvent-free condition at 70°C.
[c] Reaction carried out in EtOH at room temperature.

Scheme 3



2-(2-Chlorophenyl)benzothiazoline **2-(2-Chlorophenyl)benzothiazole**

mol %) under nitrogen atmosphere (in the absence of oxygen), the reactions stopped at the 2-(2-chlorophenyl)-benzothiazoline (mp 75–77°C, lit. 76°C [17]) stage, which never proceeded to benzothiazoles. The isolated 2-(2-chlorophenyl)benzothiazoline (1 mmol) reacted with TCT (3 mol %) in the presence of O_2 (air) to afford the corresponding 2-(2-chlorophenyl)benzothiazole (mp 82–83°C, lit. 81–83°C [10]). This surely proves that aerial oxygen is not essential for 2-arylbenzothiazoline **[B]** formation, though it is absolutely essential for the oxidation step leading to the formation of 2-arylbenzothiazoles (Scheme 3).

Having successfully performed the reactions of 2-aminothiophenol with a wide range of aldehydes, we focused our attention on examining the reaction of 2-aminothiophenol with 1,4-benzenedicarbaldehydes to TCT in CH_3CN at room temperature (Scheme 4). Finally, we have developed this synthetic method for the preparation of additional extended bisbenzothiazole derivatives in a 2:1 molar ratio of 2-aminothiophenol to 1,4-benzenedicarbaldehyde with 10 mol % TCT in CH_3CN. The reaction proceeded smoothly for 3 h at room temperature using the present protocol, and the desired product **2m** was obtained in 94% isolated yield, mp 258–260°C (lit. 258°C) [23].

In conclusion, we developed a new application for 2,4,6-trichloro-1,3,5-triazine. By using this catalyst, a series of 2-arylbenzothiazoles and bisbenzothiazoles were obtained in high yields via condensation of 2-aminiothiophenol with aldehydes under mild condition. Simple workup and easy isolation under mild reaction conditions are the best features of the present methodology.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr). ^{1}H-NMR spectra were obtained using JEOL FT NMR 90 MHz spectrometer in $CDCl_3$ using TMS as an internal reference. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected.

Typical experimental procedure for the synthesis of 2-arylbenzothiazoles by condensation 2-aminothiophenol with aldehydes using 2,4,6-trichloro-1,3,5-triazine. To a stirred solution of 2-aminothiophenol (1.2 mmol) in CH_3CN (5 mL), an aldehyde (**1a–l**, 1 mmol) and 3 mol % TCT were added. The reaction mixture was stirred at room temperature until the reaction was complete, as judged by TLC (eluent:hexane-EtOAc = 5:1) analysis. After completion, the solvent was evaporated and the residue was washed with water to give the crude products (**2a–l**). The residue was then recrystalized from (EtOH, 5 mL) to afford the pure product.

Selected physical and spectroscopic data of isolated the products. ***2-Phenylbenzothiazole (2a).*** Mp 111–112°C (lit. 112–114°C [17]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.41–8.08 (m, H—Ar); ^{13}C-NMR (22.5 MHz, $CDCl_3$): δ 77.10 ($CDCl_3$), 121.53, 123.23, 125.09, 126.22, 127.52, 128.91, 130.83, 133.64, 135.08, 154.19, 167.93; IR (KBr): 3064, 1588, 1555, 1509, 1478, 1433, 1244, 962, 766 cm^{-1}.

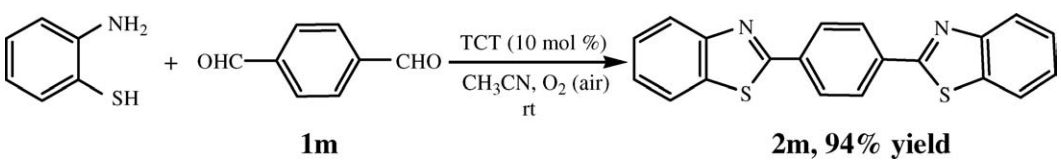
2-(4-Methoxyphenyl)benzothiazole (2c). Mp 119–120°C (lit. 120–121°C [17]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 3.82 (s, 3H, OMe), 7.00–7.95 (m, 8H, H—Ar); ^{13}C-NMR (22.5 MHz, $CDCl_3$): δ 77.10 ($CDCl_3$), 55.45 (OCH_3), 114.43, 121.53, 122.90, 124.81, 126.21, 129.16, 134.91, 154.38, 162,02, 167.85; IR (KBr): 3023, 2996, 2900, 2836, 1605, 1521, 1485, 1260, 832 cm^{-1}.

2-(4-Methylphenyl)benzothiazole (2e). Mp 84–86°C (lit. 85°C [22a]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 7.30–8.01 (m, 8H, H—Ar); IR (KBr): 3024, 2905, 1609, 1521, 1484, 1456, 1434, 1384, 1312, 760 cm^{-1}.

2-(4-Cyanophenyl)benzothiazole (2k). Mp 161–162°C (lit. 162–164°C [10]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.37–7.96 (m, H—Ar); ^{13}C-NMR (22.5 MHz, $CDCl_3$): δ 77.10 ($CDCl_3$), 113.93, 118.08, 121.66, 123.68, 125.96, 126.69, 127.68, 132.50, 137.20, 153.88, 165.09; IR (KBr): 3061, 2226, 1606, 1514, 1479, 1432, 1405, 764 cm^{-1}.

2-(3-Nitrophenyl)benzothiazoles (2l). Mp 179–180°C (lit. 181–182°C [17]); ^{1}H-NMR (90 MHz, $CDCl_3$): δ 7.44–8.30 (m, 7H, H—Ar), 8.85 (s, 1H); IR (KBr): 3058, 1611, 1576, 1529, 1459, 1433, 1347, 761 cm^{-1}.

Scheme 4



1m **2m, 94% yield**

Acknowledgments. Financial support of this work by the Tarbiat Moallem University of Sabzevar, Iran is gratefully acknowledged.

REFERENCES AND NOTES

[1] Wattenberg, L. W.; Page, M. A.; Leong, J. L. Cancer Res 1968, 28, 2539.

[2] (a) Paget, C. J.; Kisner, K.; Stone, R. L.; Denlog, D. C. J Med Chem 1969, 12, 1016; (b) Ramanatham, V. K.; Kotha, V. S. R. S. K.; Kotarkonda, R. G. J Heterocycl Chem 2005, 42, 153.

[3] Ulrich, H. Sci Synth 2002, 11, 835.

[4] Sharghi, H.; Omid, A. Synth Commun 2009, 39, 860.

[5] Hutchinson, I.; Stevens, M. G. F.; Westwell, A. D. Tetrahedron Lett 2000, 41, 4250.

[6] Perry, R. J.; Wilson, B. D. Organometallics 1994, 13, 3346.

[7] Tale, R. H. Org Lett 2002, 4, 1641.

[8] Chou, C. H.; Yu, P. C.; Wang, B. C. Tetrahedron Lett 2008, 49, 4145.

[9] Bougrin, K.; Loupy, A.; Soufiaoui, M. Tetrahedron 1998, 45, 8055.

[10] Rostamizadeh, S.; Housaini, K. S. A. Phosphorus Sulfur Silicon Relat Elem 2005, 180, 1321.

[11] Li, Y.; Wang, G. Y.; Wang, J. Y.; Jacquline, L. Chem Lett 2006, 35, 460.

[12] Ranu, B. C.; Jana, R.; Dey, S. Chem Lett 2004, 33, 274.

[13] Kawashita, Y.; Ueba, C.; Hayashi, M. Tetrahedron Lett 2006, 47, 4231.

[14] Itoh, T.; Nagata, K.; Ishikawa, H.; Ohsawa, A. Heterocycles 2004, 62, 197.

[15] Aliyan, A.; Fazlaeli, R.; Fazaeli, N.; Mssah, A. R.; Javaherian Naghash, H.; Alizadeh, M.; Emami, G. Heteroat Chem 2009, 4, 202.

[16] Okimoto, M.; Yoshida, T.; Hoshi, M.; Hottori, K.; Komata, M.; Tomozawa, K.; Chiba, T. Heterocycles 2008, 75, 35.

[17] Mukhopadhyay, C.; Datta, A. J Heterocycl Chem 2009, 46, 91.

[18] Mukhopadhyay, C.; Datta, A; Banik, B. K. Heterocycles 2007, 71, 181.

[19] (a) Addison, A. W.; Rao, T. N.; Whalgren, C. G. J Heterocycl Chem 1983, 20, 1481; (b) Choen, V. I. J Heterocycl Chem 1979, 16, 13.

[20] (a) Azarifar, D.; Maleki, B.; Setayeshnazar, M. Phosphorus Sulfur Silicon Relat Elem 2009, 184, 2097; (b) Azarifar, D.; Maleki, B. J Heterocycl Chem 2005, 42, 157; (c) Zolfigol, M. A.; Azarifar, D.; Maleki, B. Tetrahedron Lett 2004, 45, 2181.

[21] (a) Gao, S.; Yu, Z.; Kuo, C. W.; Liu, J. T.; Chu, C. M.; Yao, C. F. Org Biomol Chem 2006, 4, 2851; (b) Zhang, P.; Zhang, Z. H. Monatsh Chem 2009, 140, 199; (c) Blothny, G. Tetrahedron 2006, 62, 9507; (d) Das, B.; Laxminarayana, K.; Ravikanth, B.; Ramarao, B. Tetrahedron Lett 2006, 47, 9103; (e) Bigdeli, M. A.; Mahdavinia, G. H.; Jafari, S.; Hazarkhani, H. Catal Commun 2007, 8, 2229.

[22] (a) Kodomari, M.; Tamaru, Y.; Aoyama, T. Synth Commun 2004, 34, 3029; (b) Paul, S.; Gupta, M.; Gupta, R. Synth Commun 2002, 32, 3541.

[23] Ozaytekin, I.; Karatas, I. J Heterocycl Chem 2005, 42, 1283.