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METAL-FREE SYNTHESIS OF BENZOTHAZOLES FROM DISULFIDES OF 2-AMINOBENZENETHIOL AND CARBOXYLIC ACID VIA PCl_3 -PROMOTED TANDEM REACTION

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Abstract – A metal-free process for the synthesis of benzothiazoles via PCl_3 -promoted cleavage/acylation/ cyclization of disulfides and carboxylic acids has been developed. In addition to acting as the acylating reagent which converted carboxylic acids into acyl chlorides, PCl_3 also converted disulfides to thiols, which promoted disulfides of 2-aminobenzenethiol reacted with carboxylic acid to produce benzothiazoles. The developed method is applicable to a wide range of carboxylic acids containing different functional groups.

INTRODUCTION

Substituted benzothiazoles are an important class of heterocycles that exhibit valuable biological and therapeutic effects like antitumor, antimicrobial, antidiabetic, anticonvulsant, anti-inflammatory activities.¹ Moreover, they can be used as amyloid imaging agent.^{1b} For example, zopolrestat^{1c} (**1**) has been used for the treatment of diabetes, Phortress (**2**) and PMX610 (**3**) display excellent antitumor activity,^{1a} and ¹⁸F-labelled 2-(4'-fluorophenyl)-1,3-benzothiazole (**4**) can be used as amyloid imaging agent (Figure 1).^{1b} In addition, some benzothiazole-based compounds are useful as ratiometric fluorescent pH indicators.² Therefore, efficient methods to synthesize benzothiazoles and their structural analogues have been explored extensively in recent years.³

Among the many existing methods for the construction of benzothiazoles, the condensations of 2-aminobenzenethiols with aldehydes, carboxylic acids, orthoesters, alkylamines, aryl ketones, β -diketones or nitriles are the most common procedure (Scheme 1a).^{3a-e,4} However, the starting materials 2-aminobenzenethiols, especially those bearing additional substituents, are readily oxidized to stable disulfides and not always easily available. An alternative approach is the cyclization of thioformanilides, which is carried out by the radical cyclization or transition-metal catalyzed carbon-sulfur bond formation (Scheme 1b).^{3f,5}

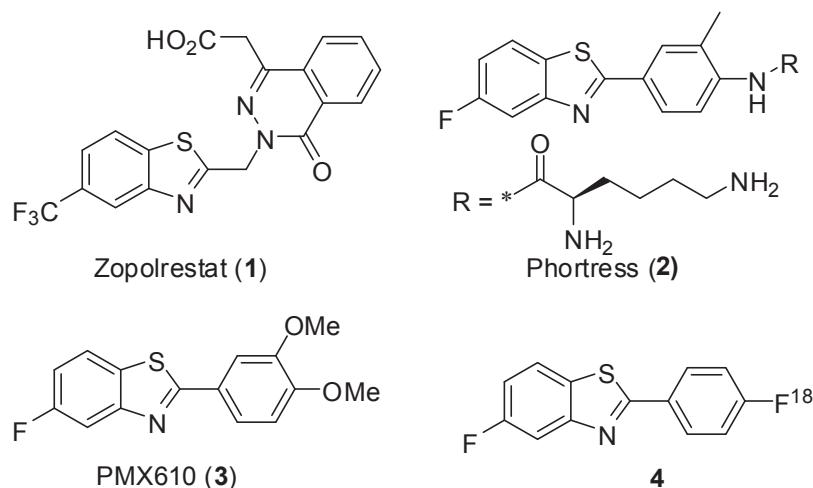
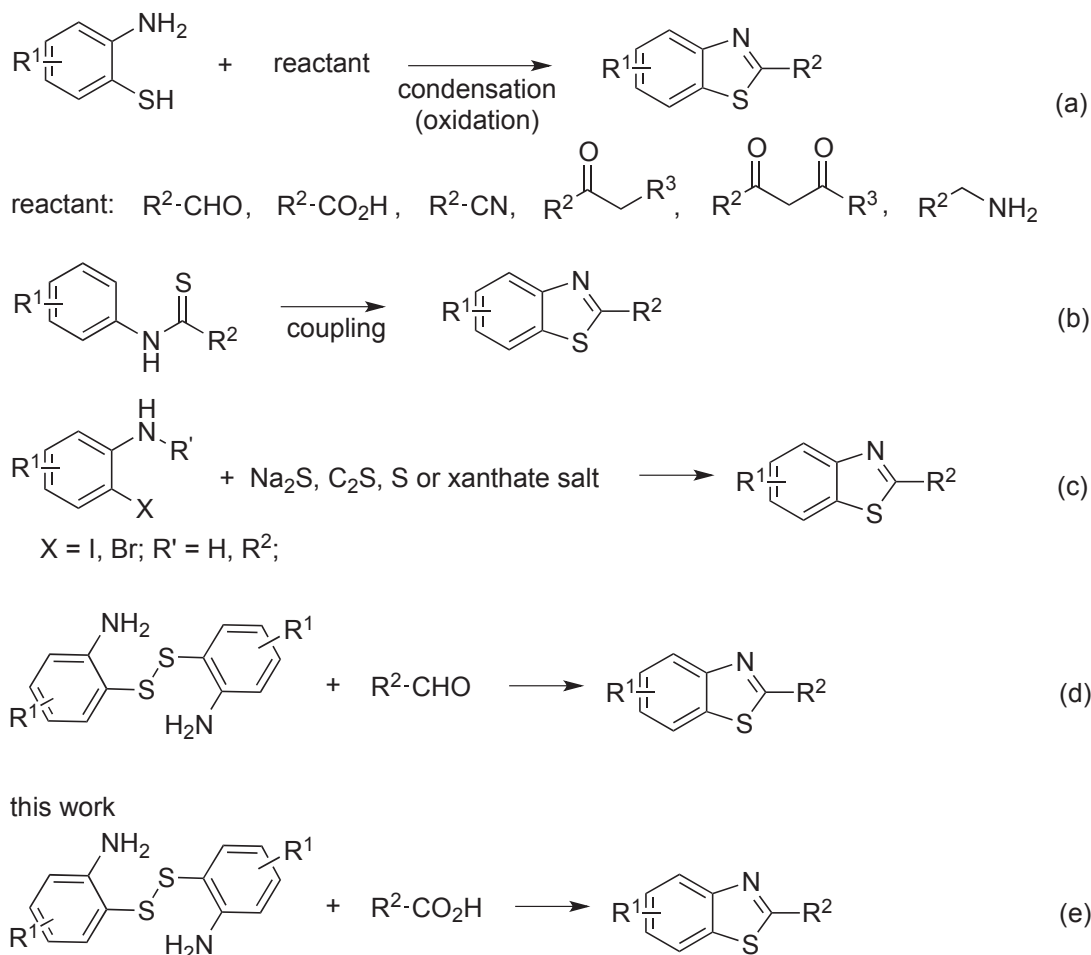


Figure 1. Examples of bioactive benzothiazoles



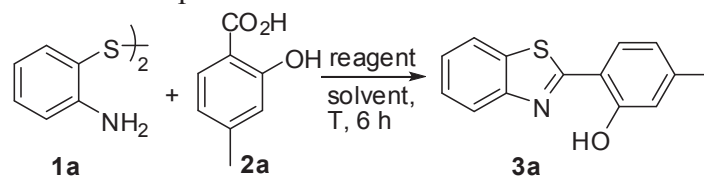
Scheme 1. Strategies for the synthesis of benzothiazoles

However, this method usually exhibits low tolerance for functional groups such as ketone, ester, and amide, because most of the reactions involve the transformation of the amide into the corresponding

thioamide by Lawesson's reagent.⁵ To overcome this drawback, methods using 2-haloanilides reacting with metal sulfides,^{3g,3h,6} carbon disulfide,^{3i,7} sulfur^{3j,3k} or xanthate salt⁸ are developed to synthesize 2-substituted benzothiazoles through copper-catalyzed cross-coupling reaction (Scheme 1c). Recently, 2-substituted benzothiazoles were prepared by the reaction of stable disulfide and aldehyde through the cleavage of the S-S bond via radical, copper-catalyzed, reductive or oxidative method (Scheme 1d).⁹ In the course of our studies on new methods for the synthesis of benzothiazoles using disulfides as starting materials,¹⁰ we found that disulfides reacted with carboxylic acids smoothly to afford benzothiazoles in moderate yields in a one-pot process (Scheme 1e). To the best of our knowledge, this is the first successful example of the synthesis of substituted benzothiazoles from stable and readily available disulfides and carboxylic acids in one-pot tandem reactions.

RESULTS AND DISCUSSION

Table 1. Optimization of the Reaction Conditions^a



Entry	Reagent	Ratio ^c	Solvent	T (°C)	Yield ^b (%)
1	—	1: 0	toluene	100	NP
2	SOCl ₂	1: 2.4	toluene	100	NP
3	POCl ₃	1: 2.4	toluene	100	6
4	Ph ₃ P	1: 2.4	toluene	100	NP
5	PCl ₃	1: 2.4	toluene	100	74
6	PCl ₃	1: 2.4	DMF	100	NP
7	PCl ₃	1: 2.4	DMSO	100	NP
8	PCl ₃	1: 2.4	1,4-dioxane	100	50
9	PCl ₃	1: 2.4	toluene	90	26
10	PCl ₃	1: 2.4	toluene	110	69
11	PCl ₃	1: 2.0	toluene	100	39
12	PCl ₃	1: 2.2	toluene	100	55
13	PCl ₃	1: 2.6	toluene	100	63
14	PCl ₃	1: 2.8	toluene	100	24
15 ^d	PCl ₃	1: 2.4	toluene	100	55

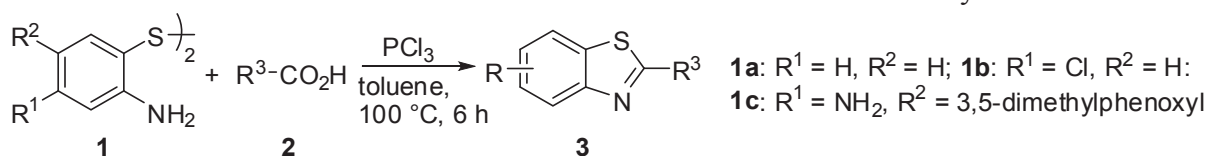
^a Conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), reagent (the ratio added according to Table 1), solvent (5.0 mL), 6 h under atmosphere of argon unless otherwise noted. ^b Isolated yield; ^c The ratio of disulfide to reagent; ^d The reaction was carried out under an atmosphere of air.

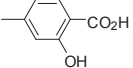
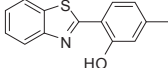
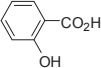
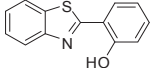
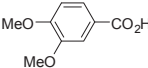
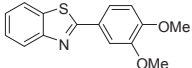
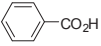
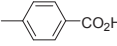
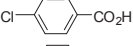
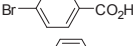
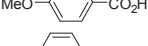


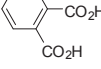
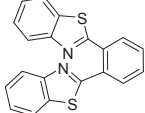
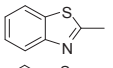
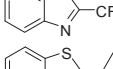

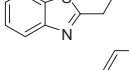
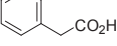
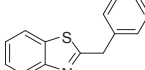
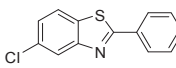
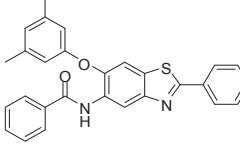
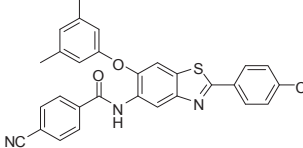
We began our study by examining the reaction of 2,2'-disulfanediylaniline (**1a**) with 2-hydroxy-4-methylbenzoic acid (**2a**) in organic solvent using different condensing agents under various

conditions. When **1a** reacted with 2.0 equiv. of **2a** in the absence of any condensing agents, no desired product **3a** was obtained in common organic solvents such as toluene, DMF and 1,4-dioxane as determined by LC-MS analysis (Table 1, entry 1). Furthermore, no or little desired product **3a** was obtained in the presence of condensing agents such as SOCl₂, POCl₃ or Ph₃P (entries 2-4). Much to our delight, when 2.4 equiv. of PCl₃ was used as the condensing agent in toluene, the anticipated product **3a** was obtained in 74% isolated yield (entry 5). When the solvent toluene was replaced with other solvents like DMF or DMSO, no the desired product **3a** was found (entries 6-7). The effect of solvent 1,4-dioxane was also investigated, and the products was obtained in a relatively low yield (entry 8). The reaction temperature was another important factor affecting the yield. The reaction yield decreased dramatically to 26% when carried out at 90 °C; when carried out at 110 °C, the yield decreased slightly to 69% (entries 9-10). Moreover, the reaction yield would decrease when the ratio of PCl₃ to disulfide was higher or lower than 2.4 (entries 11-14), which showed the ratio of PCl₃ to disulfide was also a key factor in determining the yield of desired product. Moderate yield was obtained when the reaction was carried out under an atmosphere of air (entry 15).

A variety of carboxylic acids were examined under the optimized reaction conditions to explore the scope of the substrates. As shown in Table 2, carboxylic acids containing electron-donating groups were employed to afford the corresponding benzothiazoles in moderate to good yields ranging from 54 to 74% (entries 1-8). The relative low yield of **3f** and **3g** showed that halides substituted group decreased the reactivity of the aromatic carboxylic acids in this one-pot reaction. Additionally, this PCl₃-mediated one-pot process exhibited compatibility with several functional groups such as hydroxyl (**3a** and **3b**), methoxyl (**3c** and **3h**), and halides (**3f** and **3g**). However, when carboxylic acids contained electron-withdrawing groups like nitro or nitrile, the corresponding benzothiazoles were obtained in low yields (entries 9-10). Phthalic acid and some aliphatic acids such as acetic acid, trifluoroacetic acid, butyric acid and 2-phenylacetic acid also reacted with disulfide to form the desired products, but the yields were relatively low (entries 11-15).

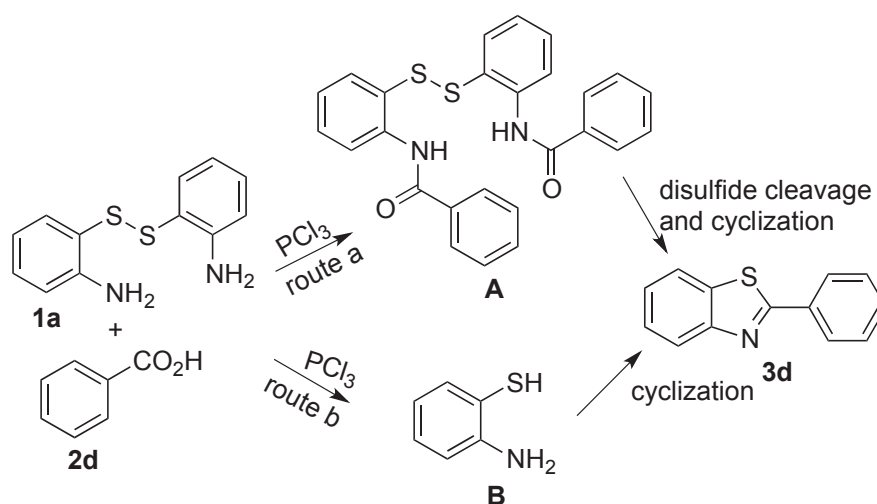
To expand the scope of this methodology, several different disulfides were employed to react with carboxylic acids under the optimized reaction conditions (entries 16-18). Various functional groups including chloro (**3p**) and phenoxy (**3q** and **3r**) were well tolerated under the standard reaction conditions, and the desired products were obtained in moderate to good yields. In addition, the free amino group reacted with carboxylic acid to form the amide product (**3q** and **3r**) under the standard reaction conditions.

Table 2. Reactions of Substituted Disulfides with Various Carboxylic Acids^a

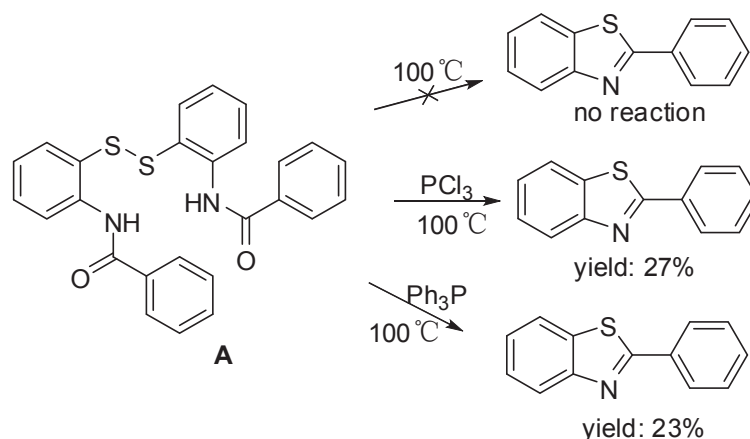
Entry	1	2	Product	Yield ^d (%)
1	1a	 2a		3a 74
2	1a	 2b		3b 66
3	1a	 2c		3c 54
4	1a	 2d	3d: R ⁴ = H	67
5	1a	 2e	3e: R ⁴ = Me	59
6	1a	 2f	3f: R ⁴ = Cl	55
7	1a	 2g	3g: R ⁴ = Br	56
8	1a	 2h	3h: R ⁴ = OMe	65
9	1a	 2i	3i: R ⁴ = CN	46
10	1a	 2j	3j: R ⁴ = NO ₂	21
11 ^b	1a	 2k		3k 34
12	1a	MeCO ₂ H 2l		3l 32
13	1a	CF ₃ CO ₂ H 2m		3m 23
14	1a	 2n		3n 34
15	1a	 2o		3o 50
16	1b	2d		3p 45
17 ^c	1c	2d		3q 75
18 ^c	1c	2i		3r 54

^a Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), PCl₃ (1.2 mmol), toluene (5 mL), 100 °C, 6 h. ^b 0.5 mmol **2k** was used. ^c **1c** (0.2 mmol), **2** (0.8 mmol), PCl₃ (0.96 mmol) was used. ^d Isolated yields.

The methods used to cleave the sulfur-sulfur bond are the key factor for the synthesis of benzothiazoles from disulfides.^{4a} To understand how benzothiazoles can be prepared from disulfides and carboxylic acids in the presence of PCl_3 , two possible reaction routes are considered which are illustrated in Scheme 2 using the reaction of **1a** with **2d** as an example. In route a, intermediate **A** is formed from disulfide **1a** and benzoic acid **2d** mediated by PCl_3 and then the sulfur-sulfur bond is cleaved and cyclized to form benzothiazole **3d**. In route b, the sulfur-sulfur bond of **1a** is cleaved by PCl_3 first to form 2-aminobenzenethiol **B**, which reacts with benzoyl chloride produced in situ to form benzothiazole **3d**. To test the hypothesis, intermediate **A** prepared by the reaction of **1a** with benzoyl chloride was used to synthesize the benzothiazole **3d** under different reaction conditions (Scheme 3). When the intermediate **A** was heated at 100 °C in toluene without PCl_3 , no desired product **3d** was detected by LC-MS. After adding PCl_3 or Ph_3P , benzothiazole **3d** was obtained in about 27% or 23% yields. These experimental results indicated the sulfur-sulfur bond of intermediate **A** could be cleaved by PCl_3 or Ph_3P , but the low yield of **3d** indicated that product **3d** was not mainly produced by the reaction route a.



Scheme 2. The possible routes for the formation of benzothiazole



Scheme 3. The benzothiazole formation from intermediate **A**

Overman, Bach and co-workers¹¹ provided some examples that S-S bond could be broken by Ph_3P to form thiol, which promoted us to think that PCl_3 could also break S-S bond under our experimental conditions. To prove PCl_3 could break S-S bond, the reaction of 2,2'-disulfanediyldianiline **1a** with PCl_3 in toluene was analyzed by LC-MS (Figure 2). Most of disulfide **1a** was converted into 2-aminobenzenethiol **B** after **1a** reacted with PCl_3 and minimal water in toluene for one hour (Figure 2a-b), which fully show PCl_3 could break the S-S bond of the disulfide to form thiol (Scheme 4, Eq. 1). After adding benzoyl chloride to the reaction, the desired product benzothiazole **3d** was isolated in 68% and another product **D** in 17% yield was also obtained (Eq. 2), which agreed with the literature report.¹² When **1a** and **2d** reacted in the presence of PCl_3 , the same product **D** was obtained in 11% yield in addition to the desired benzothiazole **3d** in 67% yield. Product **D** was determined to be S-2-benzamidophenyl benzothioate by NMR, MS and single crystal X-ray diffraction analysis (Eq. 3 and Figure 3). However, **D** was not converted to benzothiazole **3d** under the same reaction conditions (Eq. 4), which showed **D** was a byproduct, not a reaction intermediate. The similar diacylated products like **D** were also obtained in the reaction of **1a** and other carboxylic acids under the same reaction conditions.

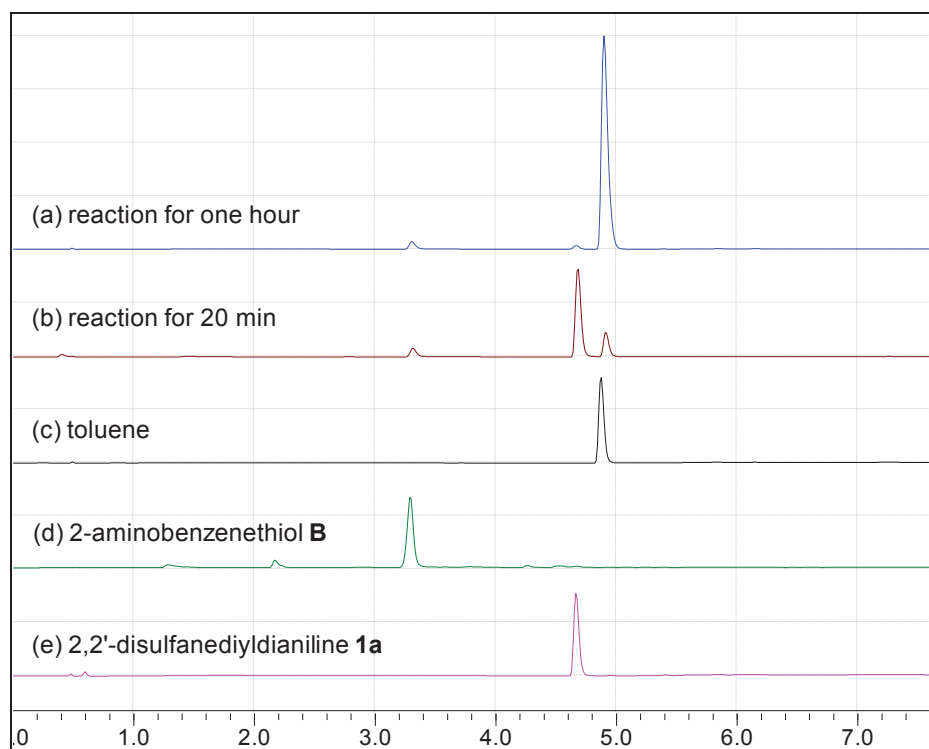


Figure 2. The reaction process of 2,2'-disulfanediyldianiline and PCl_3 detected by LC-MS

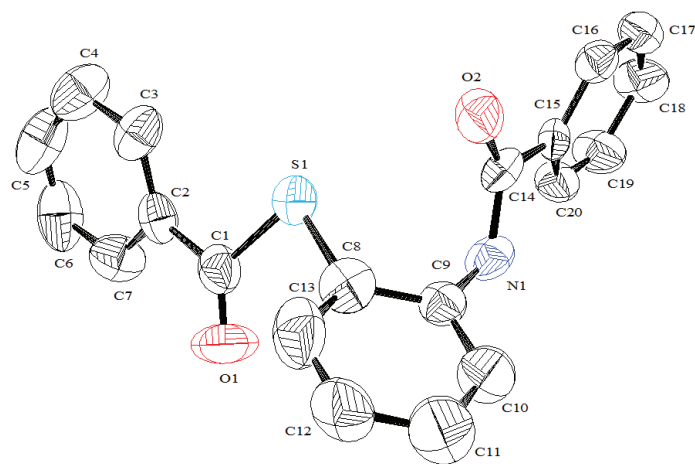
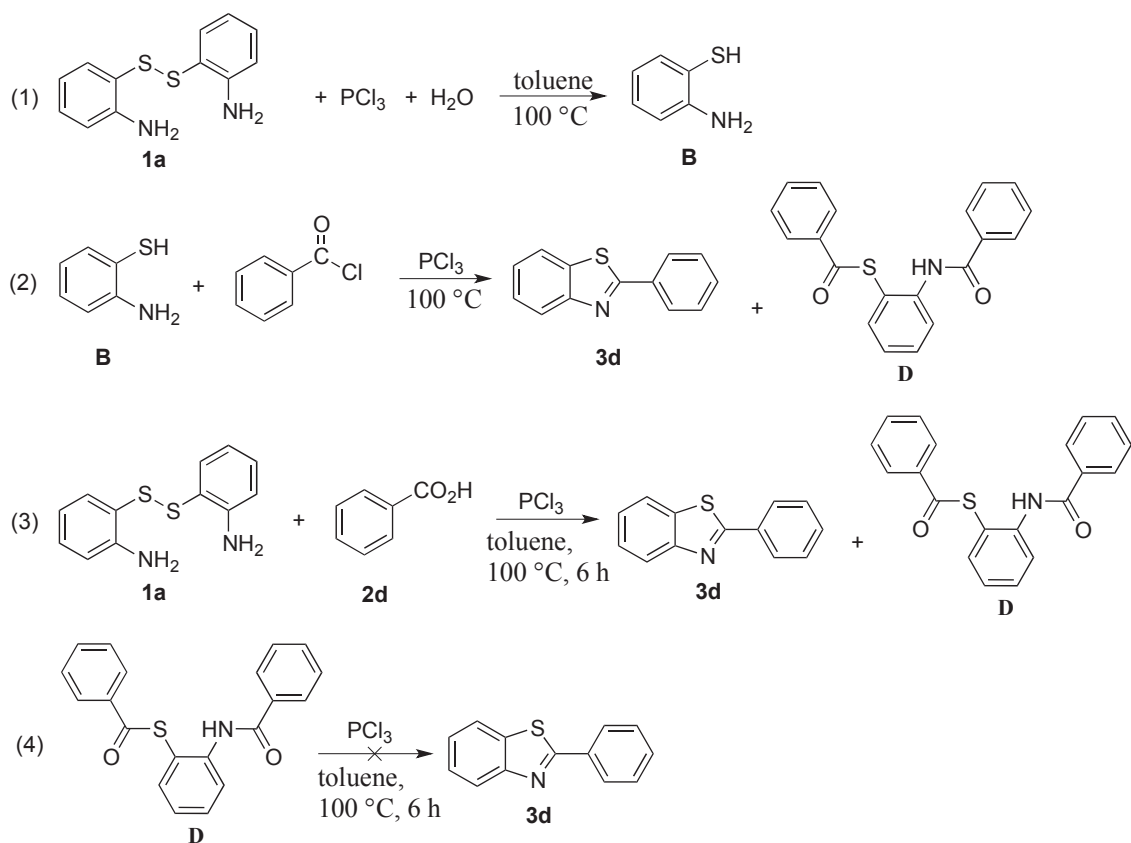
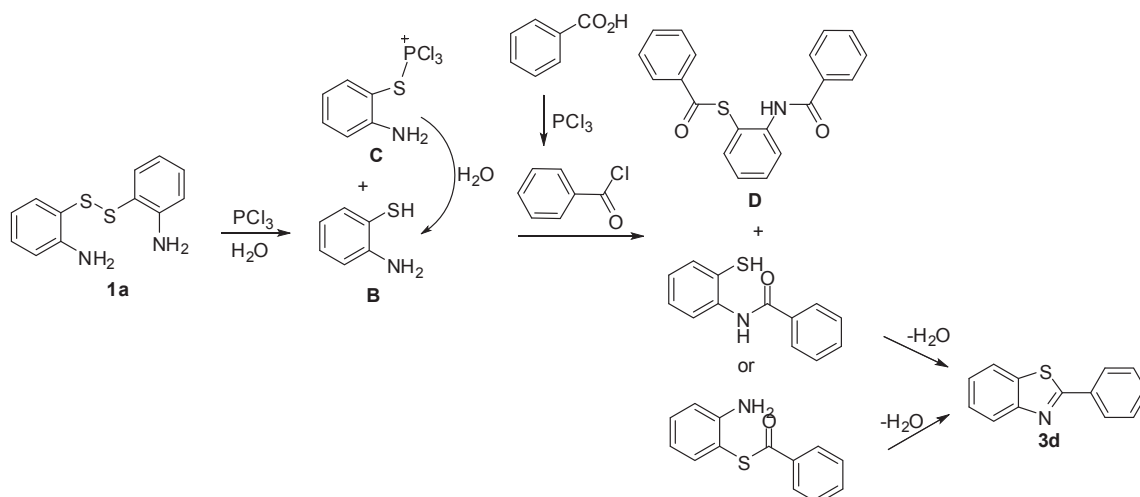


Figure 3. ORTEP molecular diagram of **D**



Scheme 4. Control Experiments



Scheme 5. Proposed mechanism of benzothiazole formation mediated by PCl_3

Therefore, we propose a tentative reaction mechanism for the formation of 2-substituted benzothiazoles from disulfides as shown in Scheme 5. Carboxylic acid reacts with PCl_3 to form acyl chloride first. Through the nucleophilic attack on disulfide **1a** by PCl_3 , 2-aminobenzenethiol **B** and an intermediate phosphonium cation-thiolate anion salt **C** are formed, and subsequently thiolate anion **C** reacts with water which produced from the formation of **3d** in the last step to form 2-aminobenzenethiol **B**.^{11a,11b} At last, the intermediate **B** reacts with the in-situ produced acyl chloride to give the desired product **3d** and byproduct **D**. In the reaction process, PCl_3 acts not only as an acylating reagent to convert carboxylic acid into acyl chloride, but also as a sulfur-sulfur bond reducing reagent to convert disulfide into thiol. Because SOCl_2 and POCl_3 only act as acylating agents and Ph_3P only as a sulfur-sulfur bond reducing reagent, SOCl_2 , POCl_3 and Ph_3P couldn't efficiently facilitate the reaction of disulfide and carboxylic acid (Table 1, entries 2-3).

In summary, we have developed a metal-free method for the synthesis of 2-substituted benzothiazoles from disulfides and carboxylic acids mediated by PCl_3 through a sulfur-sulfur bond cleavage/acylation/cyclization tandem reaction. Both the disulfides and carboxylic acids are stable and readily commercially available. In the reaction process, PCl_3 acted as an acylating reagent and a disulfide reducing reagent, which promoted disulfides of 2-aminobenzenethiol reacted with carboxylic acid to produce benzothiazoles. The new synthetic method offers a convenient alternative approach for the construction of biologically important compounds containing a benzothiazole structure.

EXPERIMENTAL

All reagents were purchased from different commercial sources and used without further purification. Solvents were dried over sodium and distilled prior to use. All reactions were performed under a dry argon atmosphere in oven-dried glassware. Reactions were monitored by analytical thin-layer

chromatography on silica gel GF254 precoated on glass plates. Column chromatography separations were carried out on silica gel (200-300 mesh). Melting points were measured with SGC X-4 microscopic melting point meter and are uncorrected. Molecular weights were determined by a low-resolution mass spectrometer (ESI) using automatic sampler to inject sample solution. The ^1H and ^{13}C NMR spectra were obtained in CDCl_3 on a 500 MHz spectrometer and referenced to the residual protonic solvent or TMS. The NMR results were processed by software MestReNova. Elemental analyses were recorded on an Elementar var III-type analyzer. The starting material **1a** was purchased from Aladdin Reagent Company. **1b** was prepared from 2-amino-4-chlorobenzenethiol¹³ and **1c** was prepared from 1,5-difluoro-2,4-dinitrobenzene (DFDNB) by literature method.^{10a}

General procedure for the synthesis of benzothiazole derivatives 3a-3p, D. 2,2'-Disulfanediyl dianiline **1a** or 6,6'-disulfanediylbis(3-chloroaniline) **1b** (0.5 mmol) and carboxylic acid (1.0 mmol, except 0.5 mmol for **2k**) were added to a three-neck flask under an atmosphere of Ar, and 5 mL dry toluene was added, then the mixture was stirred for 2.5 h at 70 °C to allow the solid to dissolve in toluene solvent completely. After the reaction solution was cooled down to 30 °C, PCl_3 (1.2 mmol, 0.165 g) was added dropwise. When the PCl_3 was added completely, the reaction mixture was further stirred for 4 - 6 h at 100 °C until no 2,2'-disulfanediyl dianiline or 6,6'-disulfanediylbis(3-chloroaniline) was detected by TLC analysis. The reaction solution was washed with saturated aqueous sodium bicarbonate solution and extracted with CH_2Cl_2 . The collected organic layers were dried over anhydrous MgSO_4 . After filtered to remove the MgSO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using PE / EtOAc.

General procedure for the synthesis of benzothiazole derivatives 3q and 3r. 6,6'-Disulfanediylbis[4-(3,5 -dimethylphenoxy)benzene-1,3-diamine] (**1c**) (0.2 mmol) and carboxylic acid (0.8 mmol) were added to a three-neck flask under an atmosphere of Ar, and 5 mL dry toluene was added, then the mixture was stirred for 2.5 h at 70 °C to allow the solid to dissolve in toluene solvent completely. After the reaction solution was cooled down to 30 °C, PCl_3 (0.96 mmol, 0.132 g) was added dropwise. When the PCl_3 was added completely, the reaction mixture was further stirred for 4-6 h at 100 °C until no starting material **1c** was detected by TLC analysis. The reaction solution was washed with saturated sodium bicarbonate solution and extracted with CH_2Cl_2 . The collected organic layers were dried over anhydrous MgSO_4 . After filtered to remove the MgSO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel.

ACKNOWLEDGEMENTS

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SUPPLEMENTARY MATERIALS

Experimental procedures, characterization data, and NMR spectra of all compounds could be obtained in Supplementary Materials.

REFERENCES

1. (a) K. Ahmed, S. Yellamelli Valli Venkata, N. A. K. Mohammed, F. Sultana, and K. R. Methuku, *Expert Opin. Investig. Drugs*, 2012, **21**, 619; (b) K. Serdons, T. Verduyck, D. Vanderghinste, J. Cleynhens, P. Borghgraef, P. Vermaelen, C. Terwinghe, F. Van Leuven, K. Van Laere, and H. Kung, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 602; (c) B. L. Mylari, E. R. Larson, T. A. Beyer, W. J. Zembrowski, C. E. Aldinger, M. F. Dee, T. W. Siegel, and D. H. Singleton, *J. Med. Chem.*, 1991, **34**, 108.
2. J. Han and K. Burgess, *Chem. Rev.*, 2009, **110**, 2709.
3. (a) G. Bastug, C. Eviolitte, and I. E. Markó, *Org. Lett.*, 2012, **14**, 3502; (b) G. Naresh, R. Kant, and T. Narender, *J. Org. Chem.*, 2014, **79**, 3821; (c) M. S. Mayo, X. Yu, X. Zhou, X. Feng, Y. Yamamoto, and M. Bao, *Org. Lett.*, 2014, **16**, 764; (d) Y. Sun, H. Jiang, W. Wu, W. Zeng, and X. Wu, *Org. Lett.*, 2013, **15**, 1598; (e) V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling, and S. Lang, *J. Org. Chem.*, 2013, **78**, 1471; (f) H. Wang, L. Wang, J. Shang, X. Li, H. Wang, J. Gui, and A. Lei, *Chem. Commun.*, 2012, **48**, 76; (g) X. Zhang, W. Zeng, Y. Yang, H. Huang, and Y. Liang, *Org. Lett.*, 2014, **16**, 876; (h) J. Liu, Q. Gui, Z. Yang, Z. Tan, R. Guo, and J.-C. Shi, *Synthesis*, 2013, **45**, 943; (i) G. Satish, K. H. V. Reddy, K. Ramesh, K. Karnakar, and Y. V. D. Nageswar, *Tetrahedron Lett.*, 2012, **53**, 2518; (j) H. Deng, Z. Li, F. Ke, and X. Zhou, *Chem. Eur. J.*, 2012, **18**, 4840; (k) R. Wang, Y.-l. Ding, H. Liu, S. Peng, J. Ren, and L. Li, *Tetrahedron Lett.*, 2014, **55**, 945; (l) W. Zhang, Y. Yue, D. Yu, L. Song, Y.-Y. Xu, Y.-J. Tian, and Y.-J. Guo, *Adv. Synth. Catal.*, 2012, **354**, 2283; (m) S. Liu, R. Chen, H. Chen, and G.-J. Deng, *Tetrahedron Lett.*, 2013, **54**, 3838; (n) M. Zhang, W.-T. Lu, W. Ruan, H.-J. Zhang, and T.-B. Wen, *Tetrahedron Lett.*, 2014, **55**, 1806; (o) A. B. Khemnar and B. M. Bhanage, *RSC Adv.*, 2014, **4**, 8939; (p) Y. Gao, Q. Song, G. Cheng, and X. Cui, *Org. Biomol. Chem.*, 2014, **12**, 1044.
4. (a) N. Zhu, Z. Zhang, M. Gao, L. Han, Q. Suo, and H. Hong, *Chin. J. Org. Chem.*, 2013, **33**, 1423; (b) K. Bahrami, M. M. Khodaei, and A. Nejati, *Green Chem.*, 2010, **12**, 1237; (c) A. K. Chakraborti, S. Rudrawar, and A. Kondaskar, *Synthesis*, 2005, 2521.
5. (a) D. S. Bose and M. Idrees, *J. Org. Chem.*, 2006, **71**, 8261; (b) K. Inamoto, C. Hasegawa, J. Kawasaki, K. Hiroya, and T. Doi, *Adv. Synth. Catal.*, 2010, **352**, 2643.
6. D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong, and Y. Jiang, *Angew. Chem. Int. Ed.*, 2009, **48**, 4222.
7. (a) S. Murru, H. Ghosh, S. K. Sahoo, and B. K. Patel, *Org. Lett.*, 2009, **11**, 4254; (b) F. Wang, S. Cai,

- Z. Wang, and C. Xi, *Org. Lett.*, 2011, **13**, 3202; (c) D. Ma, X. Lu, L. Shi, H. Zhang, Y. Jiang, and X. Liu, *Angew. Chem. Int. Ed.*, 2011, **50**, 1118.
8. L. Zhu and M. Zhang, *J. Org. Chem.*, 2004, **69**, 7371.
9. (a) Z. Wang, R. Tang, and Q. Xiao, *Chin. J. Chem.*, 2011, **29**, 314; (b) J. Srogl, J. Hývl, Á. Révész, and D. Schröder, *Chem. Commun.*, 2009, 3463; (c) A. A. Weekes, M. C. Bagley, and A. D. Westwell, *Tetrahedron*, 2011, **67**, 7743.
10. (a) N. Zhu, F. Zhang, and G. Liu, *J. Comb. Chem.*, 2010, **12**, 531; (b) G. Du, N. Zhu, H. Hong, L. Han, and Q. Suo, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2015, **190**, 1154.
11. (a) L. E. Overman, D. Matzinger, E. M. O'Connor, and J. D. Overman, *J. Am. Chem. Soc.*, 1974, **96**, 6081; (b) L. E. Overman and S. T. Petty, *J. Org. Chem.*, 1975, **40**, 2779; (c) O. Dmitrenko, C. Thorpe, and R. D. Bach, *J. Org. Chem.*, 2007, **72**, 8298.
12. V. N. Drozd, *Zh. Prikl. Khim.*, 1987, **23**, 355.
13. W. E. Fristad and J. R. Peterson, *Synth. Commun.*, 1985, **15**, 1.