ORGANIC LETTERS

2013
Vol. 15, No. 7
1598–1601

Copper-Catalyzed Synthesis of Substituted Benzothiazoles via Condensation of 2-Aminobenzenethiols with Nitriles

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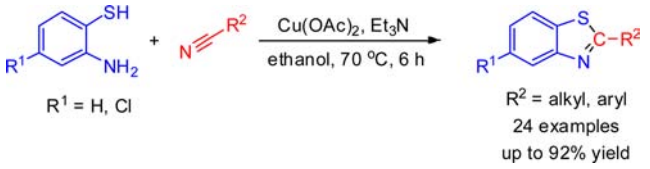
Received February 7, 2013

ABSTRACT



An efficient and convenient method was developed for the formation of 2-substituted benzothiazoles via a copper-catalyzed condensation of 2-aminobenzenethiols with nitriles. The developed method is applicable to a wide range of nitriles containing different functional groups furnishing excellent yields of the corresponding products.

Substituted benzothiazoles are present in many pharmaceuticals that exhibit remarkable biological and therapeutic activities. For example, zopolrestat (**1**) has been used for the treatment of diabetes,[1] while 5F203 (**2**) and PMX 610 (**3**) show excellent antitumor activity;[2] Schiff bases (**4**) are used as amyloid inhibitors for treatment of Alzheimer's disease[3] (Figure 1). Moreover, benzothiazole moieties are also found in many functional molecules such as ratiometric fluorescent pH indicators and ligands for catalytic reactions.[4] Therefore, the fascinating biological profiles of this group of compounds stimulated researchers to explore efficient methods for the synthesis of benzothiazoles and their structural analogues.[5]

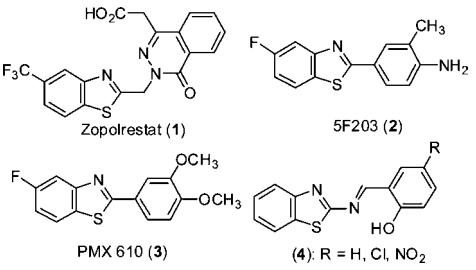


Figure 1. Examples of bioactive substituted benzothiazoles.

Different synthetic methods have been developed for the construction of benzothiazoles. Among these approaches,

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(1) Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Singleton, D. H. *J. Med. Chem.* **1991**, *34*, 108.

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(5) For selected recent benzothiazole syntheses, see: (a) Zhang, W.; Yue, Y.; Yu, D.; Song, L.; Xu, Y.; Tian, Y.; Guo, Y. *Adv. Synth. Catal.* **2012**, *354*, 2283. (b) Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948. (c) Liao, Y.; Qi, H.; Chen, S.; Jiang, P.; Zhou, W.; Deng, G. *Org. Lett.* **2012**, *14*, 6004. (d) Bastug, G.; Eviolitte, C.; Markó, I. E. *Org. Lett.* **2012**, *14*, 3502. (e) Deng, H.; Li, Z.; Ke, F.; Zhou, X. *Chem.—Eur. J.* **2012**, *18*, 4840. (f) Wang, H.; Wang, L.; Shang, J.; Li, X.; Wang, H.; Gui, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 76.

10.1021/ol400379z
Published on Web 03/15/2013

condensation of 2-aminobenzenethiols with carboxylic acids or aldehydes is the most common. However, most of these transformations involve the use of harsh reaction conditions, such as high reaction temperature or strong acidic or oxidative conditions (Figure 2a).[6] An alternative method is the cyclization of thioformanilides, which is performed with the aid of transition-metal catalysts, radical condition, or Jacobson's method.[7] However, these methods usually suffer from low functional group tolerance since in most cases the preparation of thioformanilides requires the use of P_4S_{10} or Lawesson's reagent. Meanwhile, Ma and co-workers developed a copper-catalyzed synthesis of benzothiazoles via coupling reactions of 2-haloanilides and $Na_2S\cdot 9H_2O$ to solve this problem.[8] More recently, Lewis-acid-catalyzed cyclization of orthoesters with 2-aminobenzenethiols has been reported,[5d] but this reaction also needs the preparation steps for the starting materials (Figure 2b). Therefore, a new strategy for the synthesis of substituted benzothiazoles from readily available materials under mild reaction conditions needs to be explored (Figure 2c).

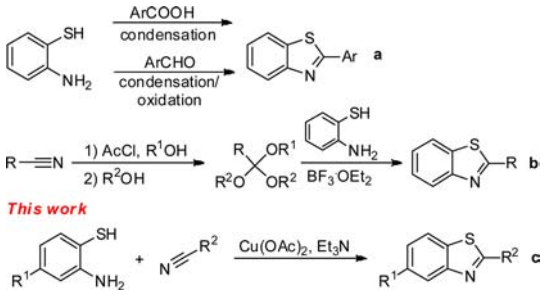
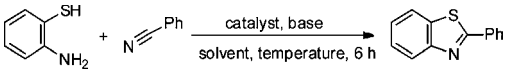


Figure 2. Strategies for the synthesis of benzothiazoles.

On the basis of the known ability of transition metals to activate nitriles[9] and recently developed copper-catalyzed method for the construction of heterocycles or γ-lactones,[10] we envisioned a direct synthesis of the substituted benzothiazole by the reaction of 2-aminobenzenethiol and nitriles involving transition-metal-catalyzed C−S and C=N bond formation. To explore this approach, we selected 2-aminobenzenethiol (**1a**) and benzonitrile (**2a**) for reaction development and screened several transition-metal catalysts in common solvents for their catalytic activity. When **1a** and **2a** were reacted in the presence of 10 mol % of CuI at 80 °C for 6 h, 2-phenylbenzo[*d*]thiazole (**3a**) was obtained in 38% yield (Table 1, entry 1). After metal catalyst evaluation, we found that $Cu(OAc)_2$ was the best and afforded **3a** with 81% GC yield (entry 6), while other metals just led to low yields (entries 2−5). In the absence of a metal source, no product formation was observed (entry 7). Further investigation revealed that the base played a critical role in this transformation (entries 8−12). Except for Et_3N, almost all kinds of bases, including NaOAc, $NaHCO_3$, Na_2CO_3, NaOH, and *t*-BuONa, were ineffective. The effects of different solvents were also studied (entries 13 and 14). Ethanol was found to be the best solvent, and the yield reached 86% (entry 14). Thus, the optimal catalytic conditions consist of $Cu(OAc)_2$ (10 mol %) and Et_3N (1.0 equiv) in ethanol at 70 °C for 6 h.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	temp (°C)	yield[b] (%)
1	CuI	Et_3N	1,4-dioxane	80	38
2	CuCl	Et_3N	1,4-dioxane	80	27
3	$ZnCl_2$	Et_3N	1,4-dioxane	80	29
4	$FeCl_3$	Et_3N	1,4-dioxane	80	3
5	$CuCl_2$	Et_3N	1,4-dioxane	80	41
6	$Cu(OAc)_2$	Et_3N	1,4-dioxane	80	81
7		Et_3N	1,4-dioxane	80	np
8	$Cu(OAc)_2$	NaOAc	1,4-dioxane	80	np
9	$Cu(OAc)_2$	$NaHCO_3$	1,4-dioxane	80	np
10	$Cu(OAc)_2$	Na_2CO_3	1,4-dioxane	80	np
11	$Cu(OAc)_2$	NaOH	1,4-dioxane	80	np
12	$Cu(OAc)_2$	*t*-BuONa	1,4-dioxane	80	np
13	$Cu(OAc)_2$	Et_3N	toluene	100	72
14	$Cu(OAc)_2$	Et_3N	ethanol	70	86
15	$Cu(OAc)_2$	Et_3N	ethanol	50	42
16	$Cu(OAc)_2$	Et_3N	ethanol	90	86

[a] Conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), catalyst (10 mol %), base (0.3 mmol), solvent (2.5 mL), 6 h. [b] GC yield based on **2a** using dodecane as internal standard.

With the optimum reaction conditions in hand, a wide range of aromatic nitriles and substituted 2-aminobenzenethiols were examined to explore the scope of the subsrrates, and the representative results are summarized in Table 2. Generally, benzonitriles containing

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(7) (a) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Wang, J.; Peng, F.; Jiang, J.; Lu, Z.; Wang, L.; Bai, J.; Pan, Y. *Tetrahedron Lett.* **2008**, *49*, 467. (d) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (e) Saha, P.; Ramana, T.; Purkati, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (f) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119. (g) Downer, N. K.; Jackson, Y. A. *Org. Biomol. Chem.* **2004**, *2*, 3039.

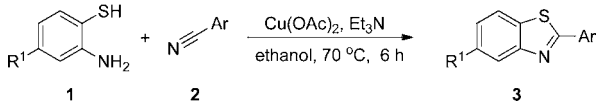
(8) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222.

(9) (a) Ueda, S.; Nagasawa, H. *J. Am. Chem. Soc.* **2009**, *131*, 15080. (b) Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7790. (c) Suri, M.; Jousseaume, T.; Neumann, J. J.; Glorius, F. *Green Chem.* **2012**, *14*, 2193.

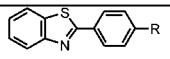
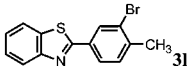
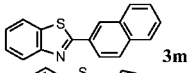
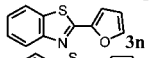
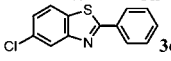
(10) (a) Huang, L.; Jiang, H.; Qi, C.; Liu, X. *J. Am. Chem. Soc.* **2010**, *132*, 17652. (b) Qi, C.; Jiang, H.; Huang, L.; Yuan, G.; Ren, Y. *Org. Lett.* **2011**, *13*, 5520. (c) Li, X.; Huang, L.; Chen, H.; Wu, W.; Huang, H.; Jiang, H. *Chem. Sci.* **2012**, *3*, 3463. (d) Jiang, H.; Zeng, W.; Li, Y.; Wu, W.; Huang, L.; Fu, W. *J. Org. Chem.* **2012**, *77*, 5179. (e) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194. (f) Kumar, R. K.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 2102. (g) Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* **2012**, *77*, 5063.

electron-donating and electron-withdrawing groups were well tolerated under the reaction conditions and gave the corresponding benzothiazoles in moderate to excellent yields. Additionally, this copper-catalyzed process exhibited compatibility with several functional groups, such as ether (**3c**), trifluoromethyl (**3f**), and nitrile (**3g**). It should be noted that halides (**3h**−**k**) were tolerated on the benzene ring, enabling further derivatizations through metal-catalyzed cross-coupling reactions. Furthermore, other aromatic or heterocyclic nitriles such as 2-naphthonitrile and furan-2-carbonitrile were also investigated and found to form the desired products in good yields ranging from 80 to 90% (Table 2, entries 13 and 14). The presence of halide on the 2-aminobenzenethiol did not interfere with the formation of the benzothiazole ring. For instance, when 2-amino-4-chlorobenzenethiol was used instead of 2-aminobenzenethiol, the yield remained quite stable at around 91% (Table 2, entry 15). A larger scale reaction (10 mmol rather than the typical 0.5 mmol) was also conducted for the synthesis of **3a**. A substantial change in yield was not observed for this larger scale reaction (that is, the yield for the 10 mmol reaction was only 2% less than that of the 0.5 mmol reaction). Unfortunately, substitutions on the ortho-position of benzonitriles had impact on the reaction; for example, 2-methylbenzonitrile and 2-bromobenzonitrile were ineffective in the reaction conditions.

Table 2. Reaction of Substituted 2-Aminobenzenethiol (**1a**) with Various Aromatic Nitriles[a]



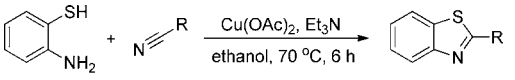
1 2 3

entry	product	yield[b] (%)
		
1	**3a**: R = H	86
2	**3b**: R = CH_3	87
3	**3c**: R = OCH_3	83
4	**3d**: R = $CH(CH_3)_2$	90
5	**3e**: R = $N(CH_3)_2$	92
6	**3f**: R = CF_3	75
7	**3g**: R = CN	77
8	**3h**: R = F	80
9	**3i**: R = Cl	82
10	**3j**: R = Br	93
11	**3k**: R = I	88
12	 **3l**	89
13	 **3m**	80
14	 **3n**	90
15	 **3o**	91

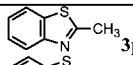
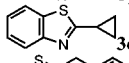
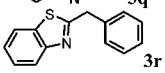
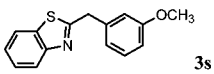
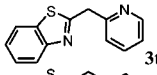
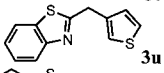
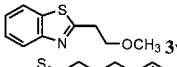
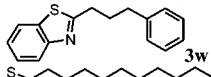
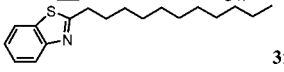
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), Et_3N (0.5 mmol), ethanol (2.5 mL), 70 °C, 6 h. [b] Isolated yields.

To expand the scope of this methodology, a series of aliphatic nitriles were employed to react with 2-aminobenzenethiol under the optimized conditions (Table 3). Various functional groups including cyclopropyl (**3q**) and methoxyl (**3v**) were well tolerated under the standard conditions, and the desired products were obtained in excellent yields. In addition, aromatics containing substituted phenyl (**3r**, **3s**, **3w**), pyridyl (**3t**), and thienyl (**3u**) were also good partners for this transformation. Interestingly, a long chain nitrile such as dodecanenitrile could also be employed to afford the desired product in 80% yield (**3x**). However, instead of the desired benzothiazole product, the attempt to use aliphatic nitrile with halide substituent such as 4-chlorobutanenitrile just led to the formation of thioether, which was formed by a nucleophilic substitution reaction of 2-aminobenzenethiol with 4-chlorobutanenitrile.

Table 3. Reaction of 2-Aminobenzenethiol (**1a**) with Various Aliphatic Nitriles[a]



1a 2 3

entry	product	yield[b] (%)
1	 **3p**	93
2	 **3q**	90
3	 **3r**	84
4	 **3s**	86
5	 **3t**	95
6	 **3u**	97
7	 **3v**	95
8	 **3w**	89
9	 **3x**	82

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), Et_3N (0.5 mmol), ethanol (2.5 mL), 70 °C, 6 h. [b] Isolated yields.

To further clarify the mechanism, several control experiments were carried out, as shown in Figure 3. In experiments 1 and 2, 2-aminobenzenethiol could transform to diaryl disulfide (**4**) in the absence of nitrile. Treatment of **4** with **2a** under optimized reaction conditions did not give the desired product. On the basis of this result, **4** did not play a significant role in the formation of benzothiazoles. In experiments 4 and 5, no addition products could be detected when aniline or 4-methylbenzenethiol was reacted with **2a** under the optimized reaction conditions.

According to the above observations and previous reports in literature,[9a] a tentative proposal is outlined in

Figure 4. The present reaction should consist of sulfilimine formation and intramolecular cyclization. Thus, copper catalyst first promotes the nucleophilic attack of **1a** to the nitrile, probably through the coordination with intermediate **A**, to provide sulfilimine **B**. Then, a copper-induced intramolecular nucleophilic addition of sulfilimine with amine affords intermediate **C**, which releases copper and NH_3 to furnish benzothiazoles **3**.

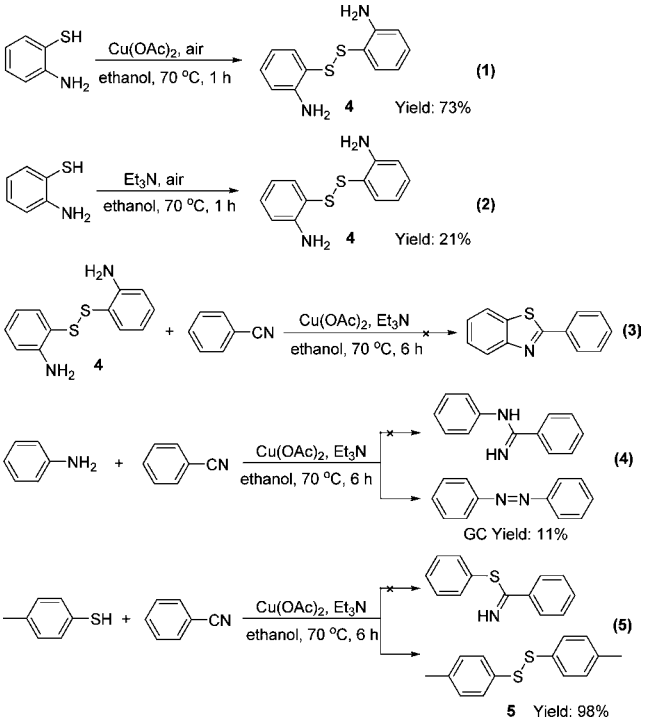


Figure 3. Control experiments.

In conclusion, we have developed an efficient method for the synthesis of 2-substituted benzothiazoles from

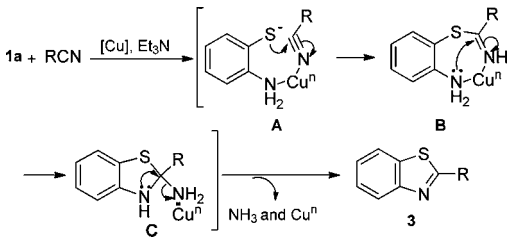


Figure 4. Proposed mechanism.

2-aminobenzenethiols and nitriles in the presence of Cu-$(OAc)_2$ catalyst. Both the 2-aminobenzenethiols and nitriles are cheap and commercially available. Considering the diverse substrates, ethanol as the environmentally friendly solvent, the inexpensive catalytic system, mild conditions combined with an operationally simple procedure render it a powerful component to traditional approaches for the synthesis of biologically important compounds containing a benzothiazole framework. Further investigation of the reaction mechanism and the synthetic applications is ongoing in our group.

Acknowledgment. We thank the National Natural Science Foundation of China (20932002), National Basic Research Program of China (973 Program) (2011CB808600), Guangdong Natural Science Foundation (1035106410-1000000), China Postdoctoral Science Foundation (2011M501318), and the Fundamental Research Funds for the Central Universities (2012ZB0011) for financial support.

Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.