Synthesis of 2-Acylbenzothiazoles via the $Cu(OTf)_2$-Catalyzed Tandem Reaction of β,β-Dihalidestyrenes with 2,2′-Disulfanediyldianilines

Zeng-Le Zhou, Tao Fang, Ri-Yuan Tang, Xing-Guo Zhang, Chen-Liang Deng*

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, P. R. of China
Fax +86(577)86689300; E-mail: dengchenliang78@tom.com

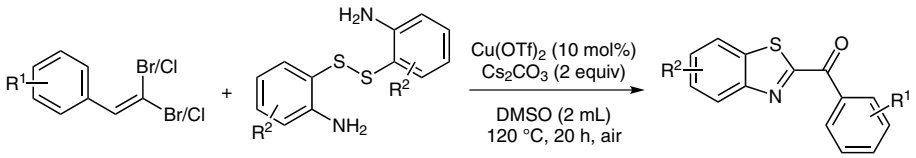
Received: 21.08.2013; Accepted after revision: 17.10.2013

Abstract: A new method has been developed for the one-pot construction of 2-acylbenzothiazoles via the $Cu(OTf)_2$-catalyzed tandem reaction of β,β-dihalidestyrenes with 2,2′-disulfanediyldianilines. A variety of different dihalidestyrenes and diphenyldisulfanes were efficiently converted into the corresponding 2-acylbenzothiszole derivatives in the presence of $Cu(OTf)_2$. Most importantly, this protocol allowed for the long chain 1,1-dibromohept-1-ene to be converted into the corresponding 2-hexylbenzo[*d*]thiazole in moderate yield.

Keywords: $Cu(OTf)_2$, dihalidestyrene, diphenyldisulfane, 2-acylbenzothiazole, tandem reaction

Benzothiazoles are an important class of heterocyclic compounds,[1] and examples belonging to this class can be found in a large number of natural products. Moreover, they are used as building blocks for the construction of pharmaceutical agents.[2] A large number of compounds containing the benzothiazole moiety have been reported in the literature to exhibit potent biological activities against a number of different targets of medicinal significance,[3] and 2-substituted benzothiazoles, in particular, have been shown to exhibit remarkable levels of biological and therapeutically relevant activity, which have attracted considerable interest from researchers working in the pharmaceutical sciences.[4] For example, RWJ-56423, which contains a benzothiazole 2-ketone structure, has been reported as a therapeutic agent for the treatment of allergic and inflammatory disorders.[5] Although a variety of different methods have been reported to date for the synthesis of 2-arylbenzothiazole derivatives, reports pertaining to the synthesis of 2-acylbenzothiazoles have been scarce because of the difficulties associated with introducing an acyl group at the 2-position of benzothiazoles.[6] Only a few methods have been reported in the literature for the formation of 2-acylbenzothiazoles, including the condensation of acyl chloride with organometallics,[7] palladium-catalyzed coupling of aryl halides with organometallic agents,[8] and the condensation reactions of 2-aminothiophenol with alkynyl bromides,[9] methyl ketones,[10] and dihalidestyrene.[11] Although these methods provide efficient access to the desired 2-acylbenzothiazoles, they generally require expensive catalysts, specially made starting materials, hazardous reagents or harsh reaction conditions. The development of a mild, environmentally benign and efficient method is therefore highly desirable. To the best of our knowledge, there have been no reports in the literature to date describing the synthesis of 2-acylbenzothiazoles via the $Cu(OTf)_2$-catalyzed tandem reaction of dihalidestyrenes with diphenyldisulfane.[12] Herein, we report our studies of $Cu(OTf)_2$-catalyzed tandem reaction of β,β-dihalidestyrenes with 2,2′-disulfanediyldianilines for the synthesis of 2-acylbenzothiazoles under mild conditions (Scheme 1).

The reaction between β,β-dibromo-4-methoxystyrene (**1a**) and 2,2′-disulfanediyldianiline (**2a**) was selected as a model reaction to optimize the reaction conditions for the transformation, and the results are shown in Table 1. The reaction of **1a** with **2a** was initially conducted in the presence of CuI (10 mol%) using Cs_2CO_3 (2 equiv) as a base and DMSO (2 mL) as a solvent. This reaction gave the desired product **3** in 45% yield (Table 1, entry 1). When the reaction was conducted in the absence of base, none of the target product was observed by GC–MS (Table 1, entry 2), demonstrating that the base plays a critical role in the reaction. Encouraged by this result, we proceeded to investigate the effects of a series of different bases on the outcome of the model reaction, including CsOAc, K_2CO_3, and *t*-BuONa (Table 1, entries 3–5). The results of these experiments revealed that strong bases gave better yields than weaker bases, with Cs_2CO_3 providing the best result. Having identified the best base for the reaction, we proceeded to investigate a number of different solvents, in-



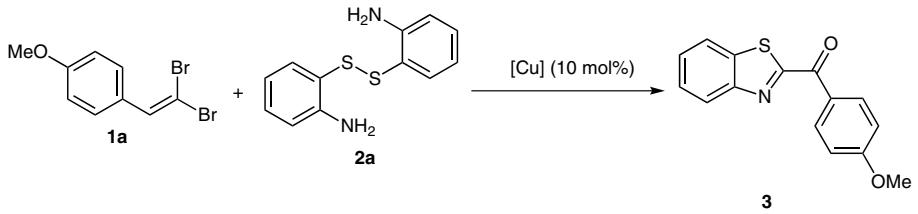
Scheme 1 $Cu(OTf)_2$-catalyzed tandem reaction and synthesis of 2-acylbenzothiazoles

SYNLETT 2014, 25, 0255–0260
Advanced online publication: 03.12.2013
DOI: 10.1055/s-0033-1340288; Art ID: ST-2013-W0804-L

cluding toluene, MeCN, DMF, THF and dioxane, although all of these solvents were inferior to DMSO in terms of the yield (Table 1, entries 6–10). We also investigated the effects of a series of cuprous and cupric salts, including CuI, CuBr, $Cu(OAc)_2$, $Cu(OTf)_2$, and $CuBr_2$. The results of these screening experiments revealed that all of the copper salts investigated enhanced the reactivity of the reaction, with $Cu(OTf)_2$ being the most efficient of all of the copper additives tested in this regard. For example, the use of CuBr, $Cu(OAc)_2$, $Cu(OTf)_2$ and $CuBr_2$ in the reaction afforded the target product in 17%, 34%, 53% and 31% yields, respectively (Table 1, entries 11–14). Finally, the reaction temperature was also investigated. Pleasingly, an increase in the reaction temperature to 100 °C led to a significant increase in the yield of the desired product **3** to 71% (Table 1, entry 15). Further increasing the reaction temperature to 120 °C led to the best yield for the reaction (Table 1, entry 16), whereas increasing the temperature to 130 °C led to a decrease in the yield (Table 1, entry 17).

With the optimized reaction conditions in hand, we proceeded to explore the scope of the reaction in terms of substrates **1** and **2**, and the results are summarized in Table 2. Generally, substrates **1a**–**g**, which contained electron-donating or electron-withdrawing groups, were well tolerated under the optimal conditions with the desired products obtained in moderate to good yields (Table 2, entries 1–6). For example, substrate **1b** reacted smoothly with **2a** to give the desired product in 68% yield (Table 2, entry 1). Substrates **1c** and **1d**, bearing electron-donating groups (i.e., Me and NMe_2, respectively) on their aromatic rings, also reacted successfully with **2a** under the optimized reaction conditions, although the corresponding products **5** and **6** were formed in lower yields (Table 2, entries 2 and 3). Substrates **1e**–**g**, bearing electron-withdrawing groups (i.e., NO_2, CN and F, respectively), were also compatible with the optimized conditions, and afforded the corresponding products in moderate yields (Table 2, entries 4–6). Substrates **1h**–**k**, which were substituted with bulky functional groups at the 2-position of their aromatic rings,

Table 1 Optimized Reaction Conditions[a]

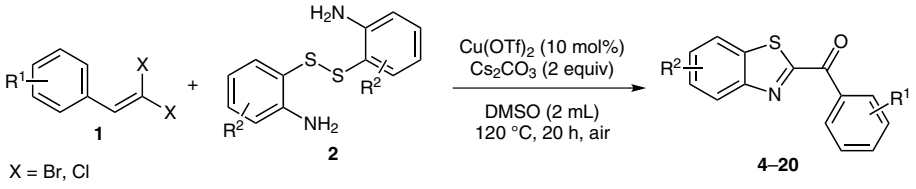


Entry	[Cu] (10 mol%)	Base (2 equiv)	Solvent (2 mL)	Temp (°C)	Yield (%)[b]
1	CuI	Cs_2CO_3	DMSO	80	45
2	CuI	–	DMSO	80	–
3	CuI	CsOAc	DMSO	80	<10
4	CuI	K_2CO_3	DMSO	80	20
5	CuI	*t*-BuONa	DMSO	80	39
6	CuI	Cs_2CO_3	toluene	80	trace
7	CuI	Cs_2CO_3	MeCN	80	20
8	CuI	Cs_2CO_3	DMF	80	32
9	CuI	Cs_2CO_3	THF	80	trace
10	CuI	Cs_2CO_3	dioxane	80	trace
11	CuBr	Cs_2CO_3	DMSO	80	17
12	$Cu(OAc)_2$	Cs_2CO_3	DMSO	80	34
13	$Cu(OTf)_2$	Cs_2CO_3	DMSO	80	53
14	$CuBr_2$	Cs_2CO_3	DMSO	80	31
15	$Cu(OTf)_2$	Cs_2CO_3	DMSO	100	71
16	$Cu(OTf)_2$	Cs_2CO_3	DMSO	120	86
17	$Cu(OTf)_2$	Cs_2CO_3	DMSO	130	73

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] (10 mol%), DMSO (2 mL), stirring at 120 °C for 20 h under air.
[b] Isolated yield.

were well tolerated under the optimized reaction conditions and gave the desired products in 38–56% yields (Table 2, entries 7–10). Substrate **1k**, for instance, contained a bulky CN group on its aromatic ring, and reacted smoothly with **2a** to give the corresponding 2-acylbenzothiazole product **13** in 48% yield (Table 2, entry 10). The *meta*-substituted substrates **1l** and **1m** also reacted successfully under the optimized conditions to afford the desired products **14** and **15** in 64% and 61% yields, respectively (Table 2, entries 11 and 12). The optimized reaction conditions were also tolerant of heterocyclic substrates such as **1n** and **1o**, which gave the corresponding cyclization products in 52% and 56% yields, respectively (Table 2, entries 13 and 14). It is noteworthy that the long-chain alkyl substrate **1p** converted into the product **18** in 50% yield under the optimal conditions (Table 2, entry 15). The scope of 2,2′-disulfanediyldianilines **2** was also examined. Substrates **2b** and **2c** bearing a Cl and a Me group on their aromatic ring, also reacted efficiently with **1a** to afford the corresponding substituted benzothiazoles in 65% and 62% yields, respectively (Table 2, entries 16 and 17). Surprisingly, substituted β,β-dichlorostyrenes, which are less active than the corresponding bromo-substituted compounds, were also found to be suitable substrates for the reaction, and afforded the target products in moderate to good yields, albeit following a longer reaction time (Table 2, entries 18–20). For example, the reaction of the dichlorostyrene substrate **1q** with **2a** proceeded smoothly under the optimized conditions to give the target product **3** in 81% yield (Table 2, entry 18). The β,β-dichlorostyrene **1r** reacted efficiently with **2a** to give the cyclized product in 64% yield (Table 2, entry 19). Substrate **1s**, bearing an electron-withdrawing NO_2 group at the *para*-position of its aromatic ring, reacted successfully with **2a** to give the 2-acylbenzothiazole **8** in 55% yield (Table 2, entry 20).

Table 2 $Cu(OTf)_2$-Catalyzed Tandem Reaction of β,β-Dihalidestyrenes with 2,2′-Disulfanediyldianilines[a]



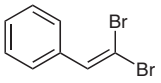
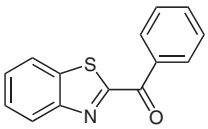
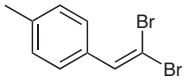
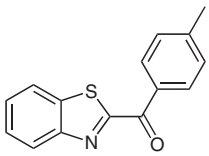
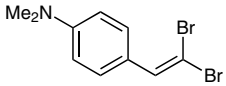
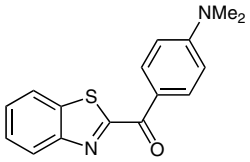
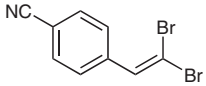
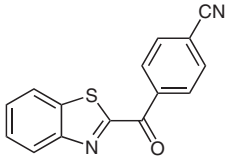
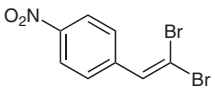
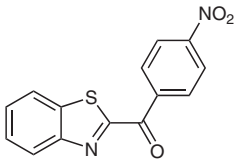
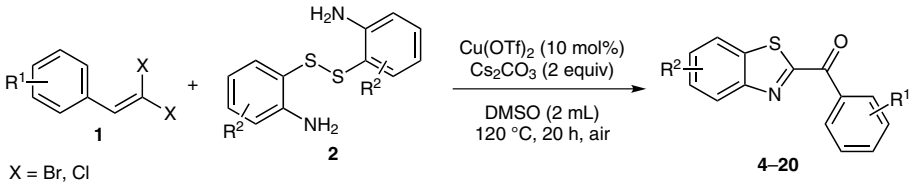
Entry	1	2	Products	Yield (%)[b]
1	**1b**		**2a**	**4** 	68
2	**1c**		**2a**	**5** 	31
3	**1d**		**2a**	**6** 	30
4	**1e**		**2a**	**7** 	53
5	**1f**		**2a**	**8** 	57

Table 2 $Cu(OTf)_2$-Catalyzed Tandem Reaction of β,β-Dihalidestyrenes with 2,2′-Disulfanediyldianilines[a] (continued)



X = Br, Cl

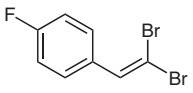
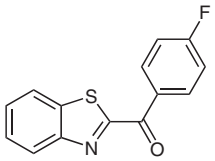
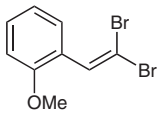
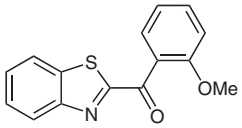
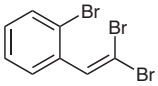
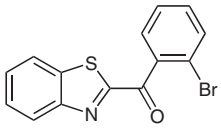
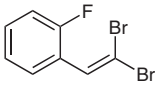
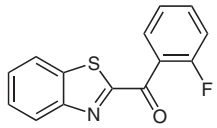
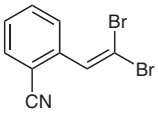
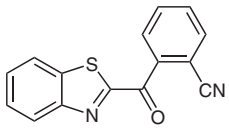
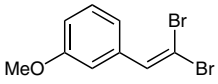
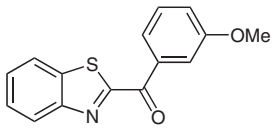
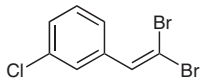
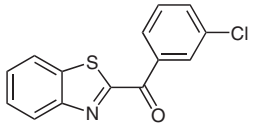
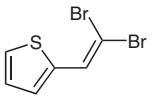
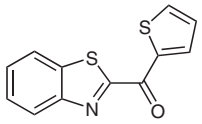
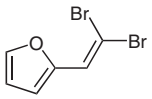
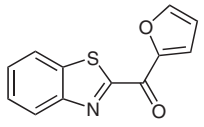
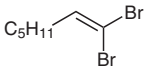
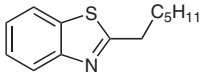
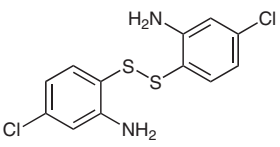
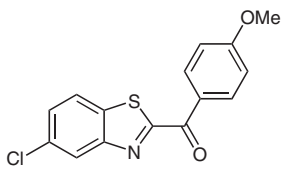
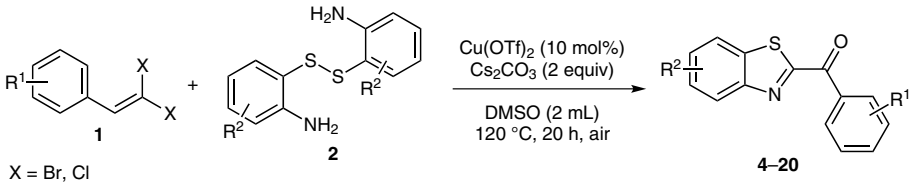
Entry	1	2	Products	Yield (%)[b]
6	**1g** 	**2a**	**9** 	52
7	**1h** 	**2a**	**10** 	39
8	**1i** 	**2a**	**11** 	56
9	**1j** 	**2a**	**12** 	38
10[c]	**1k** 	**2a**	**13** 	48
11	**1l** 	**2a**	**14** 	64
12	**1m** 	**2a**	**15** 	61
13	**1n** 	**2a**	**16** 	52
14	**1o** 	**2a**	**17** 	56
15	**1p** 	**2a**	**18** 	50
16	**1a**	**2b** 	**19** 	65

Table 2 $Cu(OTf)_2$-Catalyzed Tandem Reaction of β,β-Dihalidestyrenes with 2,2′-Disulfanediyldianilines[a] (continued)



Entry	1	2	Products	Yield (%)[b]
17	**1a**	**2c**	**20**	62
18[c]	**1q**	**2a**	**3**	81
19[c]	**1r**	**2a**	**4**	64
20[c]	**1s**	**2a**	**8**	55

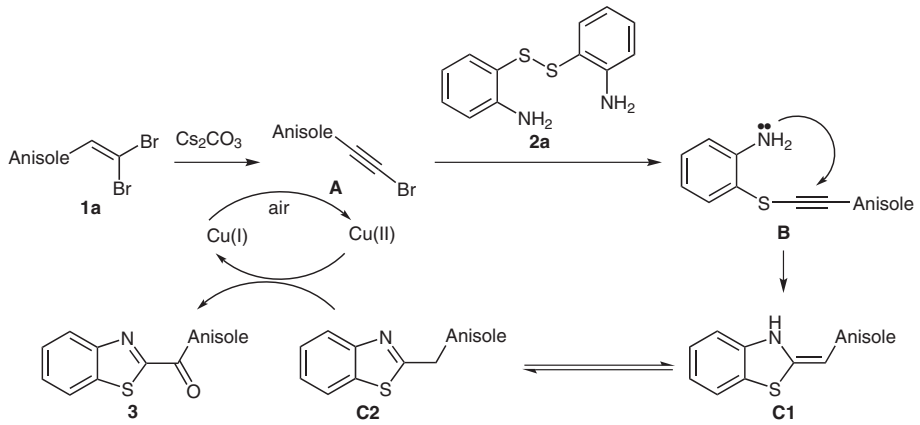
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $Cu(OTf)_2$ (10 mol%), Cs_2CO_3 (2 equiv), DMSO (2 mL) reacted at 120 °C under air until complete consumption of the starting material monitored by TLC and GC–MS.
[b] Isolated yield.
[c] Reaction time was 36–48 h.

Based on our own results, as well as information from the literatures,[6c,g,9,13] we have proposed a possible mechanism for the current transformation, which is shown in Scheme 2. The initial reaction of substrate **1a** with base would yield intermediate **A**, which would undergo a condensation reaction with **2a** to give intermediate **B**, followed by an intramolecular cyclization to afford **C**2. The Cu(II) catalyst would then oxidize intermediate **C2** to give the target product **3** together with the Cu(I) species. The Cu(I) species would then be oxidized by air to regenerate the Cu(II) catalyst to complete the catalytic cycle.

In summary, we have developed a $Cu(OTf)_2$-catalyzed tandem reaction for the synthesis of 2-acylbenzothiazoles derivatives via the reaction of β,β-dihalidestyrenes with 2,2′-disulfanediyldianilines. It is noteworthy that the protocol allowed for the long-chain 1,1-dibromohept-1-ene to be converted into 2-hexylbenzo[*d*]thiazole in moderate yield. Further studies aimed at expanding the scope of this reaction are currently underway in our lab.

Acknowledgment

We thank the National Natural Science Foundation of China (Nos. 21102104, 21002070), the Department of Education of the Zhejiang Province Fund (Nos. 201120337), and Wenzhou University for their financial support.



Scheme 2 Proposed mechanism

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Dondoni, A. *Comprehensive Heterocyclic Chemistry II*; Vol. 3; Shinkai, I. E., Ed.; Pergamon: Glasgow, **1996**, 373. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(2) (a) Yao, S.; Schafer-Hales, K. J.; Belfield, K. D. *Org. Lett.* **2007**, *9*, 5645. (b) Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y. H.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12696. (c) Zajac, M.; Hrobriák, P.; Magdolen, P.; Foltínová, P.; Zahradník, P. *Tetrahedron* **2008**, *64*, 10605. (d) Sahu, P. K.; Sahu, P. K.; Gupta, S. K.; Thavaselvam, D.; Agarwal, D. D. *Eur. J. Med. Chem.* **2012**, *54*, 366. (e) Christodoulou, M. S.; Colombo, F.; Passarella, D.; Leronimo, G.; Zuco, V.; Cesare, D. M.; Zunino, F. *Bioorg. Med. Chem.* **2011**, *19*, 1649. (f) Bradshaw, T. D.; Westwell, A. D. *Curr. Med. Chem.* **2004**, *11*, 1009.

(3) (a) Chekler, E. L. P.; Katoch-Rouse, R.; Kiselyov, A. S.; Sherman, D.; Ouyang, X. H.; Kim, K.; Wang, Y.; Hadari, Y. R.; Doody, J. F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4344. (b) Zhang, X.; Wang, B. L. *Green Chem.* **2012**, *14*, 2141. (c) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835. (d) Misra, R. S.; Barthwal, J. P.; Parmar, S. S.; Singh, S. P.; Stenberg, V. I. *J. Pharm. Sci.* **1976**, *65*, 405.

(4) (a) Marsilje, T. H.; Hedrick, M. P.; Desharnais, J.; Tavassoli, A.; Zhang, Y.; Wilson, I. A.; Benkovicd, S. J.; Boger, D. L. *Bioorg. Med. Chem.* **2003**, *11*, 4487. (b) Tsutsumi, S.; Okonogi, T.; Shibahara, S.; Ohuchi, S.; Hatsushiba, E.; Patchett, A. A.; Christensen, B. G. *J. Med. Chem.* **1994**, *37*, 3492. (c) Meltzer-Mats, E.; Babai-Shani, G.; Pasternak, L.; Urisky, N.; Getter, T.; Viskind, O.; Eckel, J.; Cerasi, E.; Senderowitz, H.; Sasson, S.; Gruzman, A. *J. Med. Chem.* **2013**, *56*, 5335.

(5) Costanzo, M. J.; Yabut, S. C.; Almond, H. R. Jr.; Andrade-Gordon, P.; Corcoran, T. W.; de Garavilla, L.; Kauffman, J. A.; Abraham, W. M.; Recacha, R.; Chattopadhyay, D.; Maryanoff, B. E. *J. Med. Chem.* **2003**, *46*, 3865.

(6) For recent paper of synthesis of 2-acylbenzothiazoles, see: (a) Park, N.; Heo, Y.; Kumar, M. R.; Kim, Y.; Song, K. H.; Lee, S. *Eur. J. Org. Chem.* **2012**, 1984. (b) Sun, Y. D.; Jiang, H. F.; Wu, W. Q.; Zeng, W.; Wu, X. *Org. Lett.* **2013**, *15*, 1598. (c) Fan, X. S.; He, Y.; Zhang, X. Y.; Guo, S. H.; Wang, Y. Y. *Tetrahedron* **2011**, *67*, 6369. (d) Mu, X. J.; Zou, J. P.; Zeng, R. S.; Wu, J. C. *Tetrahedron Lett.* **2005**, *46*, 4345. (e) Zhu, Y. P.; Jia, F. C.; Liu, M. C.; Wu, A. X. *Org. Lett.* **2012**, *14*, 4414. (f) Yang, Z. Y.; Chen, X.; Wang, S. Z.; Liu, J. D.; Xie, K.; Wang, A. W.; Tan, Z. *J. Org. Chem.* **2012**, *77*, 7086. (g) Fan, X. S.; He, Y.; Wang, Y. Y.; Xue, Z. K.; Zhang, X. Y.; Wang, J. J. *Tetrahedron Lett.* **2011**, *52*, 899.

(7) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.

(8) Boga, C.; Stengel, R.; Abdayem, R.; Vecchio, E. D.; Forlani, L.; Todesco, P. E. *J. Org. Chem.* **2004**, *69*, 8903.

(9) Fan, X. S.; He, Y.; Guo, S. H.; Zhang, X. Y. *Aust. J. Chem.* **2011**, *64*, 1578.

(10) (a) Zhu, Y. P.; Lian, Mi.; Jia, F. C.; Liu, M. C.; Yuan, J. J.; Gao, Q. H.; Wu, A. X. *Chem. Commun.* **2012**, *48*, 9086. (b) Gao, Q. H.; Wu, X.; Jia, F. C.; Liu, M. C.; Zhu, Y. P.; Cai, Q.; Wu, A. X. *J. Org. Chem.* **2013**, *78*, 2792.

(11) Fan, X. S.; He, Y.; Zhang, X. Y.; Guo, S. H.; Wang, Y. Y. *Tetrahedron* **2011**, *67*, 6369.

(12) Recently, Srogl reported a similar Cu(I) complex-catalyzed methodology of synthesis of 2-acylbenzothiazoles under acidic conditions, see: Hyvl, J.; Srogl, J. *Eur. J. Org. Chem.* **2010**, 2849.

(13) To a Schlenk tube were added a mixture of β,β-dibromostyrene **1a** (0.2 mmol) and 2,2′-disulfanediyldianiline **2a** (0.4 mmol), $Cu(OTf)_2$ (10 mol%), Cs_2CO_3 (2 equiv), and DMSO (2 mL). Then the mixture was stirred at 120 °C for the indicated time until complete consumption of starting material as monitored by TLC and GC–MS analysis. After the reaction was finished, the mixture was washed with brine. The aqueous phase was re-extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography (hexane–EtOAc) to afford the target product **3**.
Benzo[*d*]thiazol-2-yl(4-methoxyphenyl)methanone (3): white solid; mp 120–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 9.0 Hz, 2 H), 8.17 (d, *J* = 8.0 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.47–7.51 (m, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 3.85 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.4, 167.9, 164.4, 153.9, 136.9, 133.8, 127.8, 127.4, 126.8, 125.5, 122.1, 113.9, 55.6. LRMS (EI, 70 eV): *m*/*z* (%) = 269 (21) [M^+], 241 (13), 135 (100), 107 (13), 92 (16), 77 (23).

