Organic LETTERS

Letter

pubs.acs.org/OrgLett

Copper-Catalyzed Three-Component Synthesis of Benzothiazolethiones from *o*-Iodoanilines, Isocyanide, and Potassium Sulfide

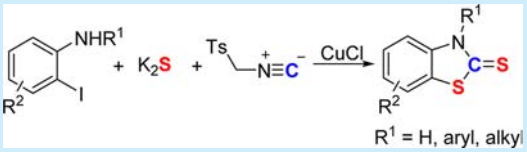
Pan Dang,[†] Weilan Zeng,[†] and Yun Liang*[,†,‡]

[†]National & Local Joint Engineering Laboratory for New Petro-chemical Materials and Fine Utilization of Resources, Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research, Ministry of Education, Hunan Normal University, Changsha, Hunan 410081, China

[‡]Beijing National Laboratory for Molecular Sciences, Beijing, 100871, China

Supporting Information

ABSTRACT: An efficient copper catalyzed strategy for the synthesis of a variety of benzothiazolethione derivatives has been developed. In the presence of CuCl, the three-component reaction of *o*-iodoanilines and K_2S with *p*-toluenesulfonylmethyl isocyanide proceeded smoothly to obtain the corresponding benzothiazolethiones in good to excellent isolated yields. Notably, isocyanide functioned as a carbon source and K_2S functioned as a sulfur source in this reaction.



Copper-catalyzed tandem C−S bond formations are powerful methods for the synthesis of sulfur-containing heterocyclic compounds from relatively simple starting materials in a convergent manner.[1] In particular, the usage of metal sulfides as a sulfur source for the efficient construction of sulfur-containing heterocycles is an important strategy in synthetic chemistry from the viewpoints of operational simplicity, economic raw material, and assembly efficiency.[2] Recently, we successfully synthesized benzo[*b*]thiophene,[3] benzo[*d*]thiazole,[4] benzo[*d*]thiazol-2(3*H*)-one,[5] and 2-amino-benzothiazole[6] using metal sulfides as a sulfur source for tandem C−S bond formations. However, three or greater tandem C−S bond formations for the synthesis of sulfur-containing compounds have been seldom reported. Therefore, tandem multiple C−S bond formations in a step reaction represent a significantly bigger challenge.

Benzothiazolethiones (2-mercapto benzothiazoles) are an important class of heterocycles that not only are encountered in a number of natural and non-natural biologically active compounds but also are versatile synthons toward antimicrobial, anti-inflammatory, anthelmintic, antitubercular, antihypertensive, and antihyperlipidemic drugs.[7] Consequently, the research and development of synthetic methods for benzothiazolethiones continues to be one of the most active areas in synthetic chemistry.[8−14] Classical methods involve the reaction of carbon disulfide with *o*-aminothiopheols,[9] *o*-halonitrobenzenes,[10] or *o*-haloaniline.[11] Due to required harsh conditions and poor tolerance of functional groups, the synthetic application of these approaches is limited. Recently, Xi and co-workers reported a DBU-promoted tandem reaction of the *o*-haloanilines with carbon disulfide toward 2-mercaptobenzothiazoles under relatively mild conditions.[12] Ma and co-workers developed a domino condensation/S-arylation reaction of the *o*-iodoanilines and carbon disulfide with thiols for the synthesis of 2-thio-substituted benzothiazoles.[13] Nevertheless, the toxicity and unpleasant odor of carbon disulfide still impedes its application. To overcome this drawback, Zhang and Yang reported a new method for the synthesis of benzothiazolethiones via the nucleophilic aromatic substitution reaction of *o*-haloanilines with potassium/sodium *o*-ethyl dithiocarbonate in good yields.[14] These reported synthetic methods are useful and interesting for the synthesis of benzothiazolethiones. However, for the synthesis of *N*-substituted benzothiazolethiones, they are limited. For these reasons, general and efficient methods for the synthesis of benzothiazolethiones and *N*-substituted benzothiazolethiones from simple and readily available precursors are of great value.

Isocyanides, which readily undergo similar transformations as carbon monoxide, are a class of powerful and versatile C1 building blocks. Moreover, isocyanides are more easily handled than carbon monoxide and contain a diversity point.[15] In our previous work, we found a copper-catalyzed three-component reaction to synthesize benzothiazolones from *o*-iodoanilines, DMF, and potassium sulfide (Scheme 1, eq 1).[5] In this reaction, DMF functioned both as the carbon monoxide source and as the reaction medium. We envisioned the DMF could be replaced by isocyanides as a C1 building block to synthesize 2-amino benzothiazoles (Scheme 1, eq 2). Unexpectedly, benzothiazolethiones were obtained in good yields, and no 2-amino benzothiazoles were observed (Scheme 1, eq 3). Herein, we wish to detail our results.

As shown in Table 1, *o*-iodoaniline **1a**, *p*-toluenesulfonylmethyl isocyanide (TosMIC), and potassium sulfide were selected as substrates to optimize the reaction conditions.

Received: November 3, 2014
Published: December 12, 2014

dx.doi.org/10.1021/ol503186w | *Org. Lett.* 2015, 17, 34−37

Scheme 1. Synthesis of Benzothiazolethiones

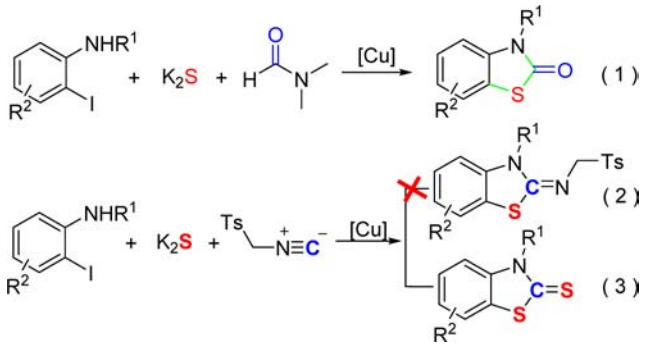
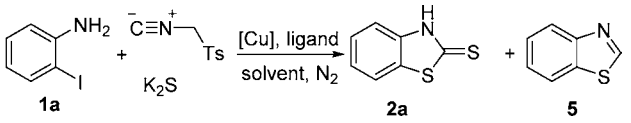


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	solvent	yield **2a** (%)[b]	yield **5** (%)[b]
1	CuI	–	DMF	44	9
2	CuBr	–	DMF	44	11
3	CuCl	–	DMF	47	9
4	CuCl	TEMED	DMF	57	13
5	CuCl	DEMED	DMF	28	36
6	CuCl	1,10-Phen	DMF	51	27
7	CuCl	L-Proline	DMF	52	20
8	CuCl	TEMED	NMP	53	6
9	CuCl	TEMED	DMSO	38	21
10	CuCl	TEMED	CH_3CN	47	12
11[c]	CuCl	TEMED	NMP	64	0
12[d]	CuCl	TEMED	NMP	78	0
13[e]	CuCl	TEMED	NMP	78	0
14[f,d]	CuCl	TEMED	NMP	76	0
15[g,d]	CuCl	TEMED	NMP	61	0
16[h,d]	CuCl	TEMED	NMP	67	0
17[d]	CuCl	TEMED	DMF	77	0

[a]Reaction conditions: **1a** (0.3 mmol), K_2S (0.9 mmol), TosMIC (0.3 mmol), Cu salt (20 mol %), ligand (40 mol %), solvent (2 mL), under a N_2 atmosphere in a sealed Schlenk tube, at 120 °C for 4 h. [b]Isolated yields. [c]K_2S (1.2 mmol). [d]K_2S (1.5 mmol). [e]K_2S (1.8 mmol). [f]140 °C. [g]100 °C. [h]CuCl (10 mol %), TEMED (20 mol %).

Initially, the CuI-catalyzed tandem thiolation reaction of substrate **1a** and TosMIC with K_2S was investigated in DMF at 120 °C, and the desired product **2a** could be isolated in 44% yield (entry 1). Simultaneously, 9% of benzothiazole was gained as a byproduct. Other copper salts, such as CuBr and CuCl, were examined (entries 2 and 3). The results showed that CuCl displayed high catalytic activity for this reaction. Then, a screening of ligands such as 1,10-phenanthroline, TEMED, L-proline, and DMEDA was also carried out, and the results indicated that TEMED gave the best yield of the product (entries 4−7). While investigating the effect of solvents, DMF and NMP gave high yields compared to DMSO and CH_3CN (entries 8−10). In the following studies, the metal sulfides such as Na_2S and Li_2S were not efficient sulfur sources for this reaction, and no corresponding benzothiazolethione was obtained in DMF. To our satisfaction, when the amount of K_2S increased to 5 equiv, the yield of benzothiazolethione increased to 78% and no benzothiazole was observed (entries 11−13). Our further studies indicated that relatively low yields were found when the reaction was carried out at 100 or 140 °C (entries 14 and 15) and when CuCl (10 mol %) and TEMED (20 mol %) were used as the catalyst (entry 16). Finally, under these optimized reaction conditions, a similar result was achieved when the NMP solvent was replaced by DMF (entry 17).

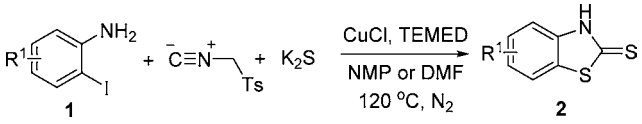
With the optimized conditions in hand, a series of substituted *o*-iodoanilines were examined in NMP or DMF respectively, and the results are summarized in Table 2. First, *o*-iodoanilines bearing an electron-withdrawing group such as fluoro, chloro, bromo, and trifluoromethyl were screened under the standard conditions, and these tandem thiolation reactions were observed to be more efficient in DMF than in NMP. The corresponding products all were afforded in moderate to good yields. Unfortunately, 4-amino-3-iodobenzonitrile could not produce the given product. The cyano group could not be tolerated under the optimized reaction conditions, and low yields of 2-thioxo-2,3-dihydrobenzo[*d*]thiazole-6-carbothioamide (**2g**) were obtained.[14] Both in NMP and in DMF, 2-iodoanilines bearing an electron-donating group such as methyl, methoxyl, and *N*,*N*-dimethyl performed with similar reactive activity and obtained higher yields than those bearing electron-withdrawing groups. These results indicated the electron-donating group favored the copper-catalyzed insertion of isocyanide to 2-iodoaniline due to increasing the electrophilicity of the amino group. Finally, we investigated the reactivity of *o*-bromoaniline. Unfortunately, the *o*-bromoaniline could not efficiently react with TosMIC and potassium sulfide, and a low yield of benzothiazolethione was afforded in DMF or in NMP.

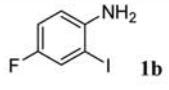
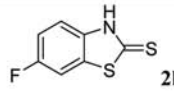
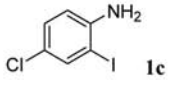
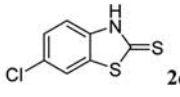
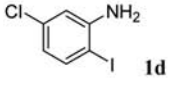
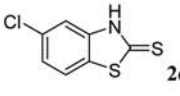
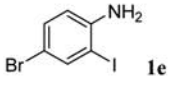
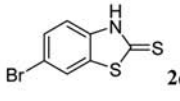
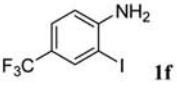
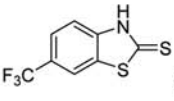
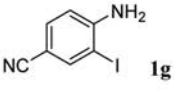
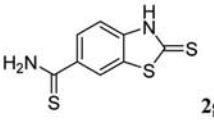
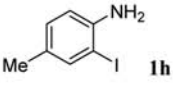
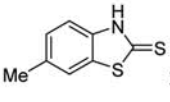
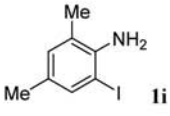
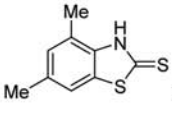
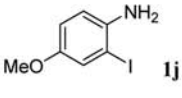
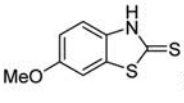
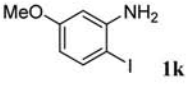
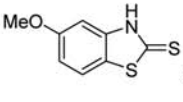
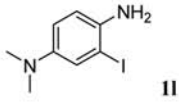
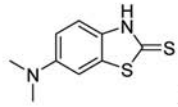
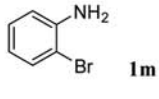
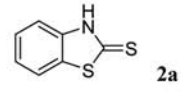
We next explored the possibility of employing *N*-substituted-2-iodoanilines as the substrate to react with K_2S and TosMIC, and the results are summarized in Scheme 2. The corresponding N-substituted benzothiazolethiones were obtained in good to perfect yields. First, the substituent of the nitrogen moiety was screened. As shown in type I (R = alkyl), the *N*-alkyl benzothiazolethiones with Me, Oct, and cyclohexyl groups were obtained in 93%, 74%, and 53% yield respectively when NMP was used as the reaction medium. The results showed the steric hindrance seemed to have a negative effect on the yields of final products. As shown in type II, the R could be substituted phenyl or naphthyl. Interestingly, the yield of 3-(4-methylbenzyl)benzo[*d*]thiazole-2(3*H*)-thione (**4f**) afforded in NMP was higher than that in DMF, and the yield of 3-(3,4-dichlorobenzyl)benzo[*d*]thiazole-2(3*H*)-thione (**4g**) obtained in DMF was higher than that in NMP. When the reaction was performed in NMP or in DMF, the yields of the products bearing benzyl and naphthal were not remarkably affected. Nevertheless, it was found that when type III (*N*-phenyl 2-iodoaniline) was used as the starting substrate, 3-phenylbenzo-[*d*]thiazole-2(3*H*)-thione (**4j**) was obtained in a low yield (37%) under optimized conditions. The most likely reason is that the decreased nucleophilicity of *N*-aryl 2-iodoaniline and the bigger steric hindrance effect of the benzene group result in low reactivity. Finally, the substituted *N*-methyl 2-iodoanilines (type IV) were examined, and the results showed that the presence of an electron-donating group (methyl) or electron-withdrawing group (fluoro, chloro) on the aromatic ring afforded good yields of the corresponding products under the optimized reaction conditions.

In order to probe the C1 source, the reaction of *o*-iodoaniline, K_2S, and *tert*-butyl isocyanide was performed, and 25% of benzothiazolethione and 37% of 2-amino benzothiazole were afforded (Scheme 3, eq 1). This result indicated that the

dx.doi.org/10.1021/ol503186w | *Org. Lett.* 2015, 17, 34−37

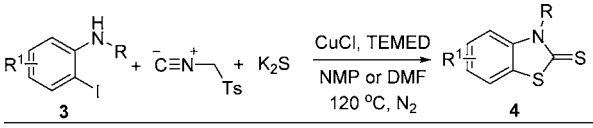
Table 2. Synthesis of Benzothiazolethiones[a,b]

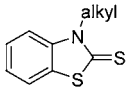


entry	substrate **1**	product **2**	yield (%)[b]
1	 **1b**	 **2b**	56 68
2	 **1c**	 **2c**	50 67
3	 **1d**	 **2d**	67 85
4	 **1e**	 **2e**	51 67
5	 **1f**	 **2f**	52 61
6	 **1g**	 **2g**	28 37
7	 **1h**	 **2h**	73 78
8	 **1i**	 **2i**	75 75
9	 **1j**	 **2j**	72 73
10	 **1k**	 **2k**	70 75
11	 **1l**	 **2l**	68 71
12	 **1m**	 **2a**	30 11

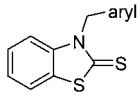
[a]Reaction conditions: **1** (0.3 mmol), K_2S (1.5 mmol), TosMIC (0.3 mmol), CuCl (20 mol %), TEMED (40 mol %), DMF or NMP (2 mL), under a N_2 atmosphere in a sealed Schlenk tube, at 120 °C for 4 h. [b]Isolated yields, the former in NMP, the latter in DMF.

Scheme 2. Synthesis of N-Substituted Benzothiazolethiones[a,b]

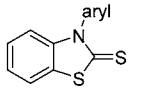


Type I 

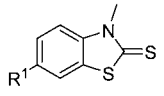
4a: alkyl = methyl, 93% (73%)
4b: alkyl = octyl, 74% (80%)
4c: alkyl = cyclohexyl, 53% (60%)
4d: alkyl = 2-(thiophen-2-yl)ethyl, 76% (79%)

Type II 

4e: aryl = Ph, 80% (82%)
4f: aryl = 4-Me-C_6H_4, 52% (75%)
4g: aryl = 3,4-2Cl-C_6H_3, 90% (76%)
4h: aryl = 4-CF_3-C_6H_4, 71% (69%)
4i: aryl = 2-naphthyl, 83% (84%)

Type III 

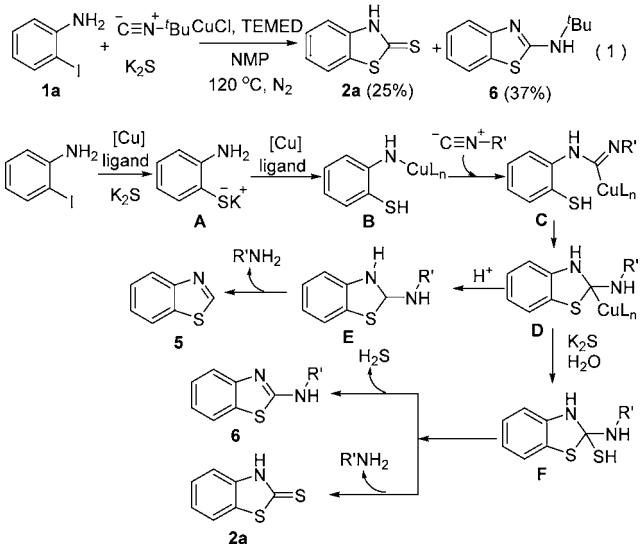
4j: aryl = Ph, 37% (39%)

Type IV 

4k: R^1 = methyl, 74% (79%)
4l: R^1 = F, 73% (81%)
4m: R^1 = Cl, 60% (39%)

[a]Reaction conditions: **1** (0.3 mmol), K_2S (1.5 mmol), TosMIC (0.3 mmol), CuCl (20 mol %), TEMED (40 mol %), DMF or NMP (2 mL), under a N_2 atmosphere in a sealed Schlenk tube, at 120 °C for 4 h. [b] Isolated yields, the former in NMP, the latter in DMF.

Scheme 3. Possible Mechanism



carbon of isocyanide as the C1 source was provided to the product. Meanwhile, this result also indicated that the 2-amino-2-thiol-benzothiazoline **F** should be a key intermediate, which would deliver benzothiazolethione or 2-amino benzothiazole upon elimination of an amine or hydrogen sulfide, respectively. According to the results of this transformation and previous reports,[2−6,13] a proposed catalytic cycle for the formation of benzothiazolethione from 2-iodoaniline, TosMIC, and potassium sulfide is given in Scheme 3. First, a cross-coupling reaction of *o*-iodoaniline and K_2S under copper-catalyzed conditions provides the intermediate **A**. Second, intermediate **A** undergoes a copper assisted insertion with isocyanide to produce the intermediate **C**. Subsequently, intermediate **C** via an intramolecular nucleophilic addition produced intermediate **D**. Intermediate **D** undergoes protonation and subsequently

dx.doi.org/10.1021/ol503186w | *Org. Lett.* 2015, 17, 34−37

elimination of an amine to produce the byproduct **5**. Intermediate **D** also undergoes a coupling reaction with K_2S to achieve the intermediate **F**. Finally, two pathways may take place from intermediate **F**: elimination of an amine or hydrogen sulfide from intermediate **F** affords benzothiazolethione **2a** or 2-amino benzothiazole **6**.

In conclusion, we have disclosed an efficient copper-catalyzed three-component reaction of *o*-iodoaniline, isocyanide, and potassium sulfide for the synthesis of benzothiazolethiones. Notably, this method could provide a general approach to *N*-substituted benzothiazolethiones from simple and readily available starting material. In this reaction, isocyanide acts as a C1 source for constructing complex benzothiazolethiones. Furthermore, two C−S bonds and one C═S bond are formed in this process.

■ ASSOCIATED CONTENT

Supporting Information

Supporting Information for this letter is available (Experimental details, and scanned NMR spectra of all new products). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yliang@hunnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of China (21072054), Ministry of Education of China (20094306120003, 213027A), Training Program Foundation for the Young Talents by Hunan Normal University (ET21003), Hunan Provincial Natural Science Foundation (12JJ2009), Scientific Research Fund of Hunan Provincial Education Department (12A095), and Aid Program for Science and Technology Innovative Research Team in Higher Educational Institutions of Hunan Province for financial support.

■ REFERENCES

(1) For recent reviews on transition-metal-catalyzed C−S coupling reactions, see: (a) Liu, H.; Jiang, X. *Chem.—Asian J.* **2013**, *8*, 2546. (b) Partyka, D. V. *Chem. Rev.* **2011**, *111*, 1529. (c) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.

(2) (a) Qiao, Z.; Liu, H.; Xiao, X.; Fu, Y.; Wei, J.; Li, Y.; Jiang, X. *Org. Lett.* **2013**, *15*, 2594. (b) Li, J.; Zhang, Y.; Jiang, Y.; Ma, D. *Tetrahedron Lett.* **2012**, *53*, 2511. (c) Sun, L.-L.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G. *J. Org. Chem.* **2011**, *76*, 7546. (d) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930. (e) Li, C.-L.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 7037. (f) Ma, D.; Xie, S.; Xue, P.; Zhang, X.; Dong, J.; Jiang, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222.

(3) Zhang, X.; Zeng, W.; Yang, Y.; Huang, H.; Liang, Y. *Synlett.* **2013**, *24*, 1693.

(4) Zhang, X.; Zeng, W.; Yang, Y.; Huang, H.; Liang, Y. *Org. Lett.* **2014**, *16*, 876.

(5) Yang, Y.; Zhang, X.; Zeng, W.; Huang, H.; Liang, Y. *RSC Adv.* **2014**, *4*, 6090.

(6) Zeng, W.; Dang, P.; Zhang, X.; Liang, Y.; Peng, C. *RSC Adv.* **2014**, *4*, 31003.

(7) For a summary of some representative reports on biological activities of 2-mercaptobenzothiazole derivatives, see the references cited in: Azam, M. A.; Suresh, B. *Sci. Pharm.* **2012**, *80*, 789.

(8) Wu, F.-L.; Hussein, W. M.; Ross, B. P.; McGeary, R. P. *Curr. Org. Chem.* **2012**, *16*, 1555.

(9) (a) Singh, M. S.; Singh, P.; Singh, S. *Indian J. Chem., Sect. B* **2007**, *46B*, 1666. (b) Harizi, A.; Romdhane, A.; Mighri, Z. *Tetrahedron Lett.* **2000**, *41*, 5833. (c) Ballabeni, M.; Ballini, R.; Bigi, F.; Maggi, R.; Parrini, M.; Predieri, G.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 1029. (d) Sugimoto, H.; Makino, I.; Hirai, K. *J. Org. Chem.* **1988**, *53*, 2263.

(10) (a) Chaudhuri, N. C. *Synth. Commun.* **1996**, *26*, 3783. (b) Dunbrook, R. F.; Zimmermann, M. H. *J. Am. Chem. Soc.* **1934**, *56*, 2734. (c) Teppema, J.; Sebrell, L. B. *J. Am. Chem. Soc.* **1927**, *49*, 1748.

(11) (a) Silva, G. L.; Ediz, V.; Yaron, D.; Armitage, B. *J. Am. Chem. Soc.* **2007**, *129*, 5710. (b) Leymarie-Beljean, M.; Pays, M.; Richer, J. C. *J. Heterocycl. Chem.* **1980**, *17*, 1175.

(12) (a) Wang, F.; Cai, S.; Wang, Z.; Xi, C. *Org. Lett.* **2011**, *13*, 3202. (b) Zhao, P.; Wang, F.; Xi, C. *Synthesis.* **2012**, *44*, 1477.

(13) Shi, L.; Liu, X.; Zhang, H.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2011**, *76*, 4200.

(14) (a) Hung, W.; Tan, Y.; Ding, M. W.; Yang, G. F. *Synth. Commun.* **2007**, *37*, 369. (b) Zhu, L.; Zhang, M.; Dai, M. *J. Heterocycl. Chem.* **2005**, *42*, 727. (c) Zhu, L.; Zhang, M. *J. Org. Chem.* **2004**, *69*, 7371.

(15) (a) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084. (b) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.