RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 31003

Received 3rd May 2014
Accepted 14th July 2014

DOI: 10.1039/c4ra04047c

www.rsc.org/advances

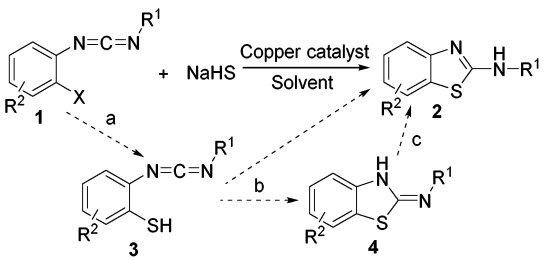
Copper-catalyzed synthesis of 2-aminobenzothiazoles from carbodiimide and sodium hydrosulfide†

Weilan Zeng,[a] Pan Dang,[a] Xiaoyun Zhang,[a] Yun Liang*[a] and Caiyun Peng*[b]

An efficient copper-catalyzed method for the synthesis of a variety of 2-aminobenzothiazoles has been developed. The reaction proceeded from carbodiimide and sodium hydrosulfide *via* a tandem reaction in the presence of copper(II) trifluoromethanesulfonate to afford the corresponding 2-aminobenzothiazole derivatives in good to perfect yields.

2-Aminobenzothiazoles,[1–5] categorized as significant derivatives of benzothiazoles, are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of various diseases, such as AIDS,[2] diabetes,[3] epilepsy,[4] and tuberculosis.[5] Consequently, many efficient methods were developed for the synthesis of 2-aminobenzothiazoles. Among them, the common method was based on metal-catalyzed intermolecular cross-coupling reaction between 2-halobenzothiazoles and amines,[6] 2-aminobenzothiazoles and aryl halides,[7] or simple benzothiazoles and amines.[8] The other two methods of direct construction of 2-aminobenzothiazole have attracted more attention from the viewpoints of operational simplicity: (1) intramolecular cyclization of *o*-haloarylthioureas or arylthioureas;[9] and (2) intermolecular cyclization of 2-halophenylamines or 2-aminobenzenethiols with isothiocyanates.[10] However, these methods usually require several steps and harsh reaction conditions for the preparation of sulfur-containing substrates such as benzothiazoles, arylthioureas, isothiocyanates, which limit their application in synthesis. Recently, Ma and co-worker developed a simple method for the synthesis of 2-aminobenzothiazoles used the carbon disulfide as sulfur source.[11] Nevertheless, the toxicity and unpleasant odor of carbon disulfide impedes its application. Therefore, used simple, nontoxic, readily available sulfur sources for the synthesis of 2-aminobenzothiazoles are of great value.

Recently, the nontoxic, odorless, and readily available sulfur sources such as metal sulfides have received considerable attention to synthesize the sulfur-containing heterocyclic compounds *via* a double thiolation reaction.[12] We are also interested in this synthetic strategy, and have successfully synthesized benzo[*b*]thiophene,[13] benzo[*d*]thiazole[14] and benzo[*d*]thiazol-2(3*H*)-one[15] used potassium sulfide as sulfur source. In the present research, we found that *o*-haloarylcarboniimide[16] and metal sulfides could undergo a cascade process to afford 2-aminobenzothiazoles. As shown in Scheme 1, the proposed reaction might proceed through a cross-coupling of *o*-haloarylcarboniimide **1** and NaHS under copper-catalyzed conditions (step a, the plausible intermediate **3** would be formed, and copper catalyst was regenerated),[12–15,17] followed by the formation of 2-aminobenzothiazoles **2** or the intermediate of benzo[*d*]thiazol-2(3*H*)-imine **4** *via* an intramolecular nucleophile addition (step b, the process might be analogous to those reported nucleophile addition to a certain extent).[16,18] Rearrangement and isomerization of the intermediate **4** also give rise to the product **2** (step c). Here in, we wish to detail our results.



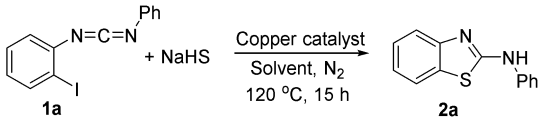
Scheme 1 Proposed one-pot synthesis of 2-aminobenzothiazoles *via* a copper-catalyzed coupling/addition process.

[a]*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. E-mail: yliang@hunnu.edu.cn; paudy@126.com; Fax: +86 0731 88872533*

[b]*School of Pharmaceutical Science, Hunan University of Chinese Medicine, Changsha, Hunan, 410208, China*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ra04047c

Table 1 Optimization of reaction conditions[a]



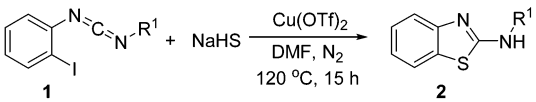
Entry	Sulfur source	Catalyst	Ligand	Solvent	Yield[b]/2a
1	K_2S	$CuBr_2$	—	DMF	48
2	NaHS	$CuBr_2$	—	DMF	66
3	Na_2S	$CuBr_2$	—	DMF	53
4	$Na_2S_2O_3$	$CuBr_2$	—	DMF	58
5[c]	S	$CuBr_2$	—	DMF	36
6	NaHS	CuI	—	DMF	46
7	NaHS	CuBr	—	DMF	53
8	NaHS	CuCl	—	DMF	41
9	NaHS	CuCN	—	DMF	45
10	NaHS	CuOTf	—	DMF	48
11	NaHS	$Cu(OAc)_2$	—	DMF	60
12	NaHS	$Cu(OTf)_2$	—	DMF	74
13	NaHS	—	—	DMF	11
14	NaHS	$Cu(OTf)_2$	1,10-Phen	DMF	71
15	NaHS	$Cu(OTf)_2$	2,2-Py	DMF	62
16	NaHS	$Cu(OTf)_2$	TMEDA	DMF	68
17	NaHS	$Cu(OTf)_2$	L(−)-Proline	DMF	73
18	NaHS	$Cu(OTf)_2$	—	DMSO	60
19	NaHS	$Cu(OTf)_2$	—	NMP	67
20[d]	NaHS	$Cu(OTf)_2$	—	DMF	70
21[e]	NaHS	$Cu(OTf)_2$	—	DMF	64

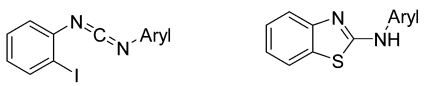
[a] Conditions: **1a** (0.30 mmol), sufur source (0.90 mmol), Cu catalyst (20 mol%), ligand (20 mol%), solvent (2 mL), N_2, 120 °C, 15 h. [b] Isolated yield. [c] Cs_2CO_3 (0.90 mmol). [d] 100 °C. [e] $Cu(OTf)_2$ (10 mol%).

In this work, *N*-phenylbenzo[*d*]thiazol-2-amine was obtained in good yields from *N*-(2-iodophenyl)-*N*-phenylmethanediimine **1a** and NaHS in one pot, *via* a copper-catalyzed double thiolation. The results of the screening for optimal reaction conditions are shown in Table 1. Our investigation started by an attempted thiolation of substrate **1a** with K_2S in DMF at 120 °C in the presence of $CuBr_2$ as the catalyst, and the desired product **2a** was isolated in 48% yield (entry 1). This result encouraged us to develop an efficient system to synthesize 2-aminobenzothiazole using *N*-(2-iodophenyl)-carbodiimine as a starting substrate. A variety of sulfur sources, such as K_2S, Na_2S, NaHS, S, NaS_2O_3, were screened (entries 1–5). The results indicated that NaHS was the best one for this reaction. Subsequently, the effects of copper catalysts (including CuBr, CuI, CuCl, CuCN, CuOTf, $Cu(OAc)_2$, $Cu(OTf)_2$) are examined (entries 6–12). $Cu(OTf)_2$ achieved the best result, and the product **2a** was obtained in 74% yield. It is noteworthy that copper II has much better catalysis activity than copper I. The possible reason attributes copper II could promote the nucleophile addition of carboniimide.[18] Without the copper catalyst, the desired product decreased to 11% yield (entry 13). Then, the effects of ligands (include 2,2′-bipyridine, 1,10-phen, L(−)-proline, TMEDA) were checked also (entries 14–17). However, the ligands did not show better results. Solvents such as DMSO and NMP were evaluated, and 60% and 67% yield of the product **2a** were isolated respectively (entries 18–19). Finally, the amount of catalyst and the reaction temperature were evaluated, and relatively low yields were found with any reduction in the reaction temperature or the amount catalyst (entries 20–21). Thus, the optimized reaction condition were as follow: **1a** (0.3 mmol), NaHS (0.9 mmol), $Cu(OTf)_2$ (20 mol%), in DMF (2 mL) under a N_2 atmosphere at 120 °C.

Under the optimized conditions, the substituent of the nitrogen moiety of *o*-iodobenzylcarboniimide was screened, and the results were summarized in Table 2. Various N-substituted 2-aminobenzothiazoles were obtained from good to perfect yields. Initially, the substituents of aryl were screened. The results showed that increasing the electron density on the nonhalogenated ring might favor the intramolecular addition process. For instance, the presence of a weak electron-donating group (*m*-Me) and a weak electron-withdrawing group (*p*-Cl) on the aromatic ring of **1** provided 93% and 81% yield of corresponding products. Similarly, *N*-benzyl substituted 2-aminobenzothiazoles could be obtained in good to high isolated yields. For example, *N*-benzylbenzo[*d*]thiazol-2-amine was obtained in 95% yield under the optimized condition. For the *N*-alkyl substituted benzo[*d*]thiazol-2-amine, they with linear-chain, branched-chain, and cycloalkyl groups could all be afforded in perfect yields. This result showed that the alkyl

Table 2 Synthesis of N-substituted 2-aminobenzothiazoles

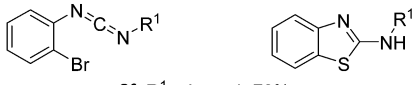




2b: Aryl = 3-Me-Ph, 93%
2c: Aryl = 3,4-$(Me)_2$-Ph, 95%
2d: Aryl = 4-Cl-Ph, 81%
2e: Aryl = 4-OCF_3, 82%

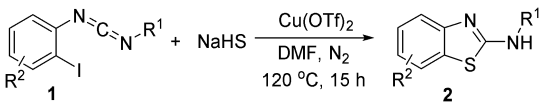
2f: Aryl = Ph, 95%
2g: Aryl = 3-Me-Ph, 91%
2h: Aryl = 4-F-Ph, 84%

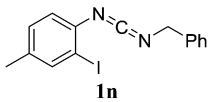
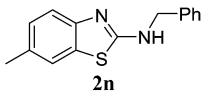
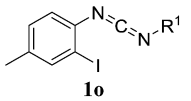
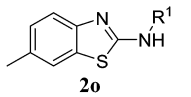
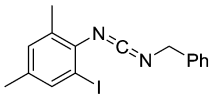
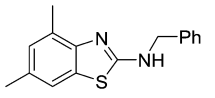
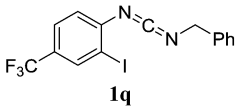
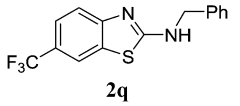
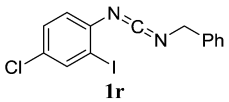
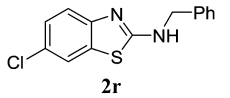
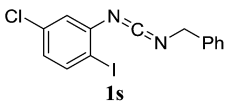
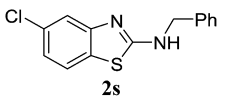
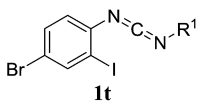
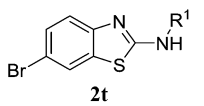
2i: Alkyl = Et, 90%
2j: Alkyl = *i*-Pr, 87%
2k: Alkyl = *t*-Bu, 93%
2l: Alkyl = cyclohexyl, 92%
2m: Alkyl = $(CH_2)_2$-Ph, 77%



2f: R^1 = benzyl, 79%
2g: R^1 = 3-Me-Ph, 70%
2i: R^1 = Et, 80%

Table 3 Synthesis of 2-aminobenzothiazolones from substituted *o*-iodobenzylcarboniimide[a]

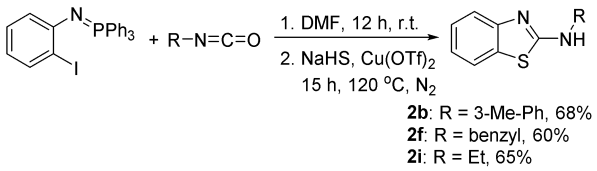


Entry	Substrate	Product	Yield[b] (%)
1	 **1n**	 **2n**	85
2[c]	 **1o**	 **2o**	96
3	 **1p**	 **2p**	87
4	 **1q**	 **2q**	89
5	 **1r**	 **2r**	90
6	 **1s**	 **2s**	92
7[c]	 **1t**	 **2t**	66

[a] Conditions: **1** (0.30 mmol), NaHS (0.90 mmol), $Cu(OTf)_2$ (20 mol%), DMF (2 mL), N_2, 120 °C, 15 h. [b] Isolated yield. [c] R^2 = 4-Cl-Ph.

substituent did not remarkably affect the reaction. Finally, we investigated the reactivity of *o*-bromobenzylcarboniimides. Importantly, the *o*-bromobenzylcarboniimides could efficiently reacted with NaHS and good yields of the products were given.

To expand the scope of this methodology, we also examined a series of substituted *N*-benzyl-*N*-(2-iodophenyl)methanediimine and *N*-(4-chlorophenyl)-*N*-(2-iodophenyl)methanediimine. As summarized in Table 3, for *N*-benzyl-*N*-(2-iodophenyl)methanediimine with either electron-withdrawing groups such as chloro (4-Cl, 5-Cl) and trifluoromethyl or electron-donating group such as methyl (4-methyl, 4,6-dimethyl) on iodobenzene ring, all well-tolerated under the reaction conditions and proceed with almost equal efficiency. These results indicated that electronic effect on benzene ring did not play a significant role in regulating the reaction, and revealed the inherent high reactivity of *o*-iodobenzylcarboniimide. Unfortunately, bromo-substituted 2-aminobenzothiazole only afforded in 66% yield. However, bromo-substituted



Scheme 2 One-pot synthesis of 2-aminobenzothiazoles.

2-aminobenzothiazole could offer an opportunity for further cross-coupling, and facilitating the expedient synthesis of complex compounds.

To our delight, this synthetic method to synthesize 2-aminobenzithiazoles could be further extend from the initial starting material in one step. For example, *N*-(2-iodophenyl)-triphenyliminophosphrane reacted with isocyanate in DMF for 12 h, then NaHS and $Cu(OTf)_2$ were added, and the reaction was further stirred for 15 h at 120 °C, and the corresponding 2-aminobenzithiazoles were obtained in good yields (Scheme 2).

In summary, we have developed an efficient coupling/addition tandem reaction from *o*-haloarylcarboniimide and NaHS for the synthesis of 2-aminobenzothiazoles. In this copper-catalyzed system, the tolerance of diverse functional groups in *o*-haloarylcarboniimide makes this present system attractive in the synthesis of various 2-aminobenzothiazoles. To our best knowledge, this is the first example of the use of NaHS as the sulfur source in the synthesis of 2-aminobenzothiazole derivatives.

Acknowledgements

This work was supported by the Natural Science Foundation of China (21072054), the Research Project of Chinese Ministry of Education (213027A, 20094306120003), 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.

Notes and references

1 For selected examples, see: (*a*) S. Bondock, W. Fadaly and M. A. Metwally, *Eur. J. Med. Chem.*, 2010, **45**, 3692; (*b*) R. D. Carpenter, M. Andrei, O. H. Aina, E. Y. Lau, F. C. Lightstone, R. Liu, K. S. Lam and M. J. Kurth, *J. Med. Chem.*, 2009, **52**, 14; (*c*) A. D. Jordan, C. Luo and A. B. Reitz, *J. Org. Chem.*, 2003, **68**, 8693; (*d*) A. R. Katritzky, D. O. Tymoshenko, D. Monteux, V. Vvedensky, G. Nikonov, C. B. Cooper and M. Deshpande, *J. Org. Chem.*, 2000, **65**, 8059.

2 S. Massari, D. Daelemans, M. L. Barreca, A. Knezevich, S. Sabatini, V. Cecchetti, A. Marcello, C. Pannecouque and O. Tabarrini, *J. Med. Chem.*, 2010, **53**, 641.

3 H. Suter and H. Zutter, *Helv. Chim. Acta*, 1967, **50**, 1084.

4 S. J. Hays, M. J. Rice, D. F. Ortwine, G. Johnson, R. D. Schwartz, D. K. Boyd, L. F. Copeland, M. G. Vartanian and P. A. Boxer, *J. Pharm. Sci.*, 1994, **83**, 1425.

5 V. G. Shirke, A. S. Bobade, R. P. Bhamaria, B. G. Khadse and S. R. Sengupta, *Indian Drugs*, 1990, **27**, 350.

6 (*a*) S. Toulot, T. Heinrich and F. R. Leroux, *Adv. Synth. Catal.*, 2013, **355**, 3263; (*b*) M. D. Charles, P. Schultz and S. L. Buchwald, *Org. Lett.*, 2005, **7**, 3965; (*c*) M. W. Hooper, M. Utsunomiya and J. F. Hartwig, *J. Org. Chem.*, 2003, **68**, 2861.

7 (*a*) S. N. Murthy, B. Madhav, V. P. Reddy and Y. V. D. Nageswara, *Adv. Synth. Catal.*, 2010, **352**, 3241; (*b*) Q. Shen, T. Ogata and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 6586; (*c*) A. Miloudi, D. EI-Abed, G. Boyer, J. P. Finet, J. P. Galy and D. Siri, *Eur. J. Org. Chem.*, 2004, 1509; (*d*) J. Yin, M. M. Zhao, M. A. Huffman and J. M. McNamara, *Org. Lett.*, 2002, **4**, 3481.

8 (*a*) A. Armstrong and J. C. Collins, *Angew. Chem., Int. Ed.*, 2010, **49**, 2282; (*b*) D. Monguchi, T. Fujiwara, H. Furukawa and A. Mori, *Org. Lett.*, 2009, **11**, 1607; (*c*) Q. Wang and S. L. Schreiber, *Org. Lett.*, 2009, **11**, 5178; (*d*) S. H. Cho, J. Y. Kim, S. Y. Lee and S. Chang, *Angew. Chem., Int. Ed.*, 2009, **48**, 9127.

9 (*a*) S.-G. Kim, S.-L. Jung, G.-H. Lee and Y.-D. Gong, *ACS Comb. Sci.*, 2013, **15**, 29; (*b*) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, *J. Org. Chem.*, 2009, **74**, 8719; (*c*) K. Inamoto, C. Hasegawa, K. Hiroya and T. Doi, *Org. Lett.*, 2008, **10**, 5147; (*d*) J. Wang, F. Peng, J.-L. Jiang, Z.-J. Lu, L.-Y. Wang, J. Bai and Y. Pan, *Tetrahedron Lett.*, 2008, **49**, 467; (*e*) L. L. Joyce, G. Evindar and R. A. Batey, *Chem. Commun.*, 2004, 446; (*f*) C. Benedí, F. Bravo, P. Uriz, E. Fernández, C. Claver and S. Castillón, *Tetrahedron Lett.*, 2003, **44**, 6073.

10 (*a*) R. Yao, H. Liu, Y. Wu and M. Cai, *Appl. Organomet. Chem.*, 2013, **27**, 109; (*b*) W. Zhang, Y. Yue, D. Yu, L. Song, Y. Y. Xu, Y. J. Tian and Y. J. Guo, *Adv. Synth. Catal.*, 2012, **354**, 2283; (*c*) Y. J. Guo, R. Y. Tang, P. Zhong and J. H. Li, *Tetrahedron Lett.*, 2010, **51**, 649; (*d*) J. W. Qiu, X. G. Zhang, R. Y. Tang, P. Zhong and J. H. Li, *Adv. Synth. Catal.*, 2009, **351**, 2319; (*e*) G. Shen, X. Lv and W. Bao, *Eur. J. Org. Chem.*, 2009, 5897; (*f*) Q. Ding, X. He and J. Wu, *J. Comb. Chem.*, 2009, **11**, 587.

11 D. Ma, X. Lu, L. Shi, H. Zhang, Y. Jiang and X. Liu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1118.

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

13 X. Zhang, W. Zeng, Y. Yang, H. Huang and Y. Liang, *Synlett*, 2013, **24**, 1693.

14 X. Zhang, W. Zeng, Y. Yang, H. Huang and Y. Liang, *Org. Lett.*, 2014, **16**, 876.

15 Y. Yang, X. Zhang, W. Zeng, H. Huang and Y. Liang, *RSC Adv.*, 2014, **4**, 6090.

16 (*a*) G. Qiu, Y. Lu and J. Wu, *Org. Biomol. Chem.*, 2013, **11**, 798; (*b*) G. Qiua and J. Wu, *Chem. Commun.*, 2012, **48**, 6046; (*c*) B. Roberts, D. Liptrot, T. Luker, M. J. Stocks, C. Barber, N. Webb, R. Dods and B. Martin, *Tetrahedron Lett.*, 2011, **52**, 3793; (*d*) F. Zeng and H. Alper, *Org. Lett.*, 2010, **12**, 1188.

17 (*a*) R. Cano, D. J. Ramon and M. Yus, *J. Org. Chem.*, 2011, **76**, 654; (*b*) Y. Jiang, Y. Qin, S. Xie, X. Zhang, J. Dong and D. Ma, *Org. Lett.*, 2009, **11**, 5250.

18 (*a*) F. Zhao, Y. Wang, W.-X. Zhang and Z. Xi, *Org. Biomol. Chem.*, 2012, **10**, 6266; (*b*) F. Wang, S. Cai, Q. Liao and C. Xi, *J. Org. Chem.*, 2011, **76**, 3174; (*c*) D. Li, J. Guang, W.-X. Zhang, Y. Wang and Z. Xi, *Org. Biomol. Chem.*, 2010, **8**, 1816; (*d*) X. Lv and W. Bao, *J. Org. Chem.*, 2009, **74**, 5618; (*e*) Z. Wang, Y. Wang, W.-X. Zhang, Z. Hou and Z. Xi, *J. Am. Chem. Soc.*, 2009, **131**, 15108.

