DOI: 10.1002/adsc.201700227

Advanced Synthesis & Catalysis

Efficient Generation of C–S Bonds *via* a By-Product-Promoted Selective Coupling of Alcohols, Organic Halides, and Thiourea

Xiantao Ma,[a,b] Lei Yu,[c] Chenliang Su,[b,*] Yaqi Yang,[a] Huan Li,[a] and Qing Xu[a,c,*]

[a] College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang 325035, People's Republic of China
Fax: (+86)-577-8668-9302; phone: (+86)-138-5774-5327; e-mail: qing-xu@wzu.edu.cn
[b] SZU-NUS Collaborative Innovation Center for Optoelectronic Science & Technology, Key Laboratory of Optoelectronic Devices and Systems of Ministry of Education and Guangdong Province, College of Optoelectronic Engineering, Shenzhen University, Shenzhen 518060, People's Republic of China
Fax: (+86)-755-2653-6206; phone: (+86)-130-6687-0440; e-mail: chmsuc@szu.edu.cn
[c] School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou, Jiangsu 225002, People's Republic of China

Received: February 22, 2017; Published online: ■■ ■■, 0000

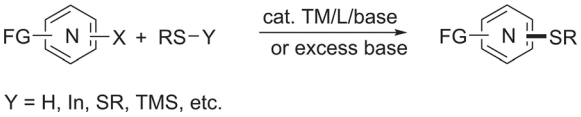
Dedicated to the memory of Professor Xian Huang for his contributions in organochalcogen chemistry.

Supporting information for this article can be found under http://dx.doi.org/10.1002/adsc.201700227.

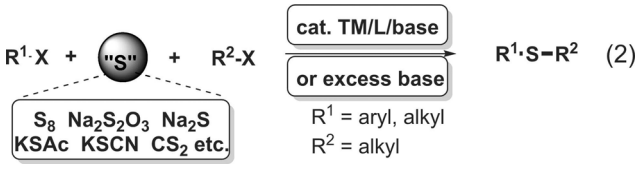
Abstract: A metal- and base-free three-component coupling of alcohols, heteroaryl halides, and thiourea has been developed for direct and selective synthesis of heteroaryl thioethers. This method can be easily scaled up to the gram scale and extended to dialkyl thioethers, heteroaryl selenides, benzothiazoles, and some antimycobacterially-active thioethers. Mechanistic studies revealed that a by-product-promoted *in situ* C–O activation of alcohols to more reactive alkyl halides and slow release of the thiol and alkyl halide intermediates are the key to the high selectivity and success of the reaction.

Keywords: alcohols; by-product-promoted reaction; C–S coupling; organo halides; sulfur surrogates; sulfur transfer reaction; thioethers; thioureas

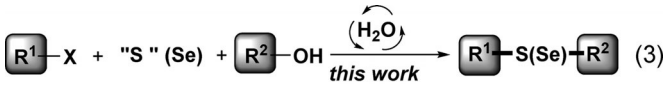
Heteroaryl thioethers are important motifs in natural products, biological, and agrichemical compounds having antibacterial, antimycobacterial, anticancer, anti-HIV, and anti-inflammatory activities.[1] The most well-developed C–S bonding methods for their preparation are based on catalytic or non-catalytic substitution of the halides in ArX with RS groups [Eq. (1)]. For example, they used to be obtained by tedious multi-step reactions of heteroaryl halides and disulfides under harsh conditions.[2] Recently, more straightforward transition metal (TM)-catalyzed cross-coupling reactions with thiols[3] or $In(SR)_3$,[4] and TM-free nucleophilic aromatic substitution (S_NAr) reactions with thiols,[5] disulfides,[6] or $PhSSiMe_3$[7] were also reported as more preferable methods.



Meanwhile, the recent sulfur transfer C–S coupling of two organo halides with the cheaper, more available, odorless sulfur powder (S_8),[8] $Na_2S_2O_3$,[9] thioureas,[10] thioacetates or thiocarbonates,[11] and etc.[12] as a sulfur surrogate has emerged as an alternative new protocol for thioether synthesis, because the use of conventional toxic and smelly organosulfur reagents such as thiols can be avoided [Eq. (2)]. Even so, the requirements of transition metal catalysts/ligands, large amounts of bases/additives, and reactive and toxic alkyl halides as the coupling partner severely narrowed its applications. Therefore, it is still highly desirable to develop efficient and practical methods for C–S bonding especially in heteroaryl thioether synthesis by employing greener and safer sulfur and alkyl surrogates instead of thiols and alkyl halides.



With our ongoing interests in organochalcogen[6,7,13] and alcohol[14] chemistry, herein we report a totally new C–S bonding approach for the synthesis of useful thioethers *via* construction of two C–S bonds by one-step using thiourea as an odorless sulfur surrogate and alcohols as a greener alkyl source [Eq. (3)]. This new sulfur transfer method requires no external TM catalysts/ligands, additives, bases, and solvents, but can tolerate a wide range of alcohols including the less reactive, sterically more bulky, and even functionalized ones, and can be scaled up to the gram scale and extended to dialkyl thioethers, unsymmetrical selenides, benzothiazoles, and some antimycobacterially-active thioethers. To the best of our knowledge, such a direct and efficient transformation of a wide range of alcohols under TM-free conditions is rare in the literature.[14,15] More surprisingly, alcohols are indispensible coupling reagents in the reaction because the use of alcohols as the alkyl source was found to be much more advantageous than the use of alkyl halides.



(3)

(a) R^1: heteroaryl, alkyl, aryl

(b) "S " (Se) = thio(seleno)urea: green S(Se) surrogate

(c) R^2: 1°, 2° and 3° benzyl, heterobenzyl, alkyl, fuctionalized alkyl, allyl, etc.

(d) metal-free, base-free, solvent-free, operable under air, broad FG tolerance, chemoselective, scalable

The reaction of 2-pyridyl bromide (**1a-Br**) and benzyl alcohol (**2a**) was firstly screened with various sulfur surrogates (**3**) under metal-, base- and solvent-free conditions under air. The target product 2-pyridyl benzyl thioether (**4aa**) and by-products 2-pyridylthiol (**5a**) and di(2-pyridyl) thioether (**6a**) were observed in varying ratios.[16] Among the sulfur surrogates tested, thiourea (**3a**) gave the highest 84% isolated yield of **4aa** in the highest selectivity of >99%.[16] Then, screening of solvents, atmosphere, and temperature showed that this sulfur transfer reaction was best performed in air under metal-, base- and solvent-free conditions at 140 °C.[17] The conditions for the more readily available and more economic 2-pyridyl chloride (**1a-Cl**) were also optimized by reversing the reactant loadings (**4aa**, 81% yield), being a good complement to the bromide method (**1a-Br**).[16]

Various alcohols and heteroaryl halides were then tested to extend the scope of the method. As shown in Table 1, except the basic 2-pyridylmethanol that may interact with by-product HBr (*vide infra*), various alcohols from the more reactive primary (hetero)-benzylic alcohols, secondary arylmethanols, and allylic alcohols to the less reactive primary aliphatic alcohols, even the functionalized and sterically more bulky tertiary alcohols could all react effectively with **1a** and thiourea to afford moderate to high yields of the desired products (runs 2–24). Notably, primary aliphatic alcohols, usually much less reactive especially in the absence of TM catalysts,[14,15] were also found to be good alkylating reagents in the present reaction (runs 12–18).

For heteroaryl halides, except the basic NH_2-substituted 2-pyridyl chloride and 3-pyridyl bromide (runs 27 and 36), both electron-rich and electron-deficient 2-pyridyl halides, 4-pyridyl halides and other activated heteroaryl halides such as 2-quinolyl, 4-quinolyl, 2-pyrimidyl, 2-pyrazyl, 3-pyridazyl, and 2-benzothiazolyl halides all reacted smoothly to give moderate to good yields of the target products under similar conditions (runs 24–26, 28–35, and 37–47), revealing a rather broad scope of this new method.

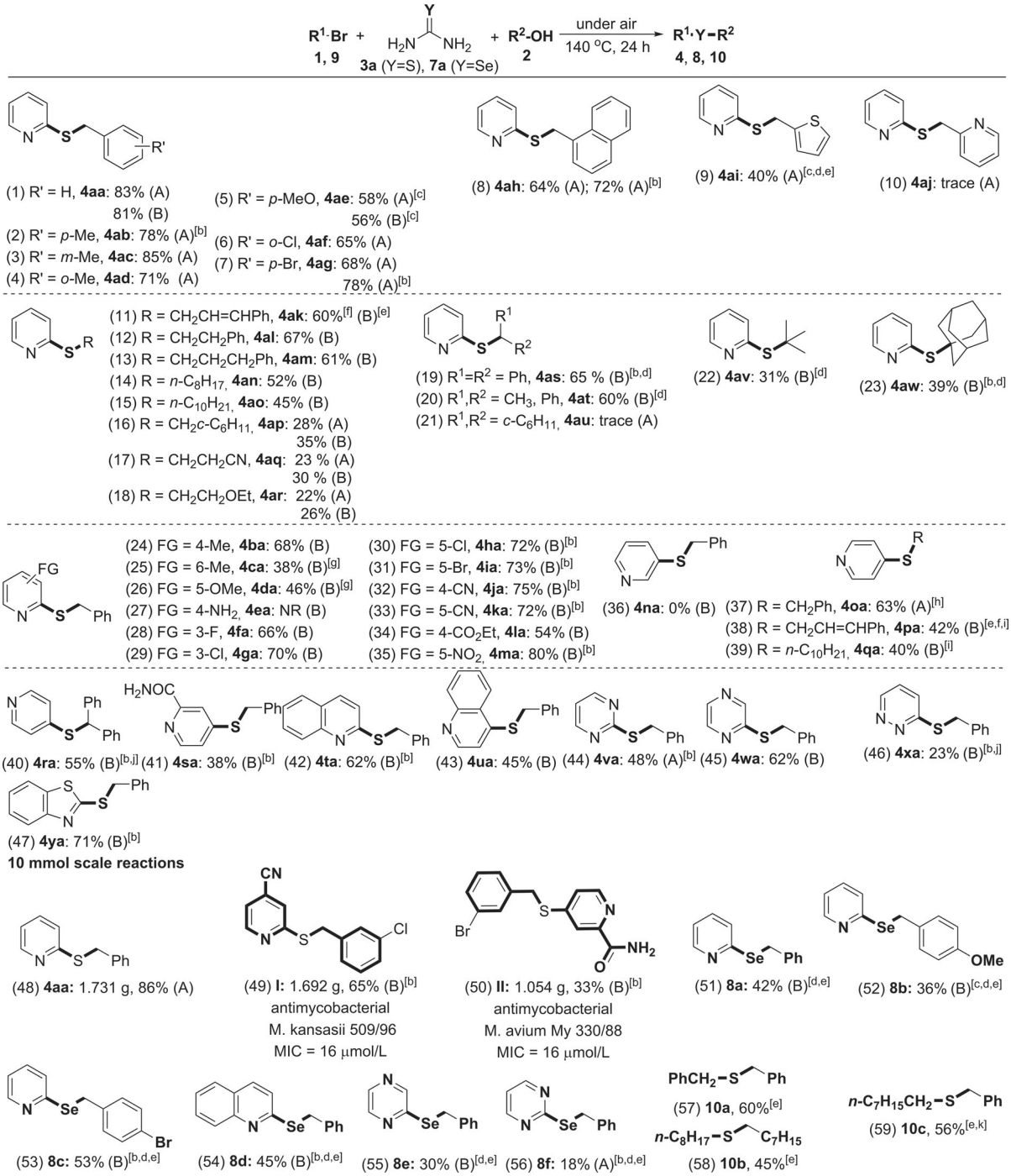
The potential of this sulfur transfer method in large-scale synthesis was also investigated. As shown in Table 1, the model reaction could be easily performed on a gram scale to afford **4aa** in a higher yield of 86% (run 48). Similarly, one-step and gram-scale syntheses of the antimycobacterially-active thioethers **I** and **II**[1c–d] could also be achieved in 65% and 33% isolated yields, respectively (runs 49 and 50), which are in comparison much superior than the wasteful multi-step methods described in the literature.[1c,d]

By replacing thiourea (**3a**) with selenourea (**7a**), this method could be easily extended to the one-step synthesis of organoselenides. Thus, heteroaryl selenides **8** were obtained in low to moderate yields under similar conditions (runs 51–56), which may be due to the lower reactivity of **7a** than **3a**. Similarly, symmetrical and unsymmetrical dialkyl thioethers **10** could also be also obtained by using alkyl halides **9** instead of heteroaryl halides **1** (runs 57–59).

Moreover, this method can also been extended to *o*-nitrohalobenzenes **11** as the organic halide substrate, which led to a one-step synthesis of the benzothiazole heterocycles **12**, but not the *o*-nitrophenyl alkyl sulfide **13** (Table 2). This result may be due to the ready cyclocondensation potential of intermediates **13**. These results revealed again the relatively broad substrate scope of the new sulfur transfer method.

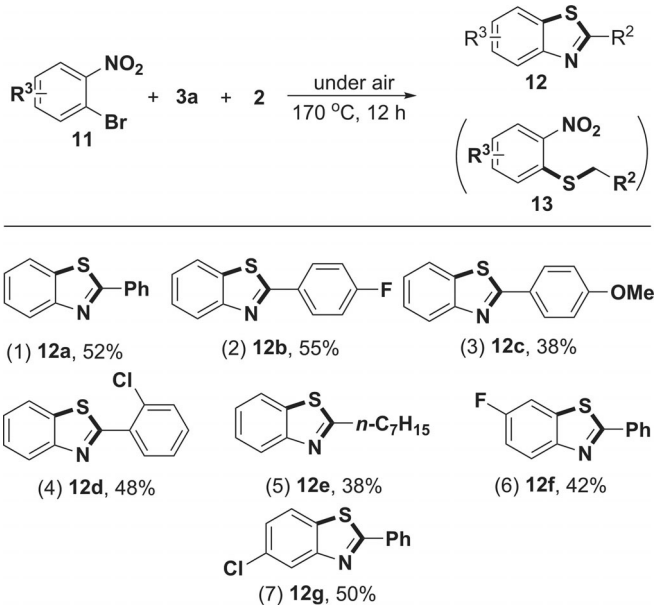
Control reactions were then investigated to understand the reaction mechanism. As shown in Eq. (4), the reaction of **1a-Br** and **3a** afforded a mixture of **5a**, **6a**, and dipyridyl disulfide **14a**. Products **6a** and **14a** were obviously produced by reaction of **5a** with **1a** and oxidation of **5a** by air, respectively. In contrast, no reaction occurred with the mixture of **1a-Br** and **3a** and that of **2a** and **3a** under the same conditions.[16] These results implied that generation of heteroarylthiols (**5**) from the reaction of **1a** and **3a** should be the first step of the whole reaction.

Table 1. Substrate extension of the sulfur transfer method in thio(seleno)ether synthesis.[a]

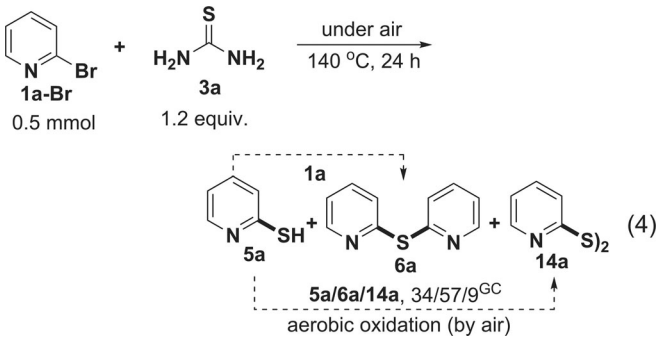


[a] *Method A* (X = Br): **1** (0.50 mmol), **2** (0.60 mmol), **3a** (0.60 mmol), isolated yield based **1**. *Method B* (X = Cl): **1** (0.60 mmol), **2** (0.50 mmol), **3a** (0.60 mmol), isolated yield based on **2**.
[b] 1.0 equiv H_2O added.
[c] 1.0 mmol **3a** (**7a**) used.
[d] At 120 °C.
[e] Under N_2.
[f] Ratio $\alpha/\gamma = 95/5$ (GC).
[g] At 170 °C.
[h] **1o-Br**·HCl was used.
[i] **1o-Cl**·HCl was used.
[j] At 100 °C.
[k] **9c** and **3a** were heated first for 1 h at 140 °C. **2a** was then added and heated for 23 h.

Table 2. Extension to the synthesis of benzothiazoles.[a]

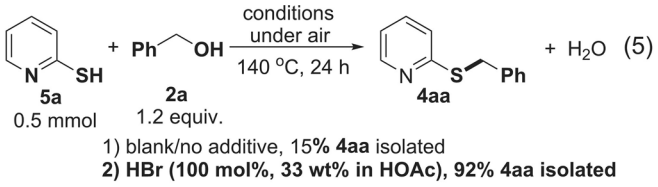


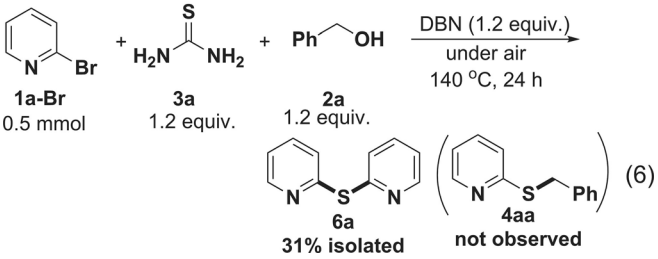
[a] *Modified method A:* **11** (0.50 mmol), **2** (1.0 mmol), **3a** (1.0 mmol). Isolated yields based on **11**.



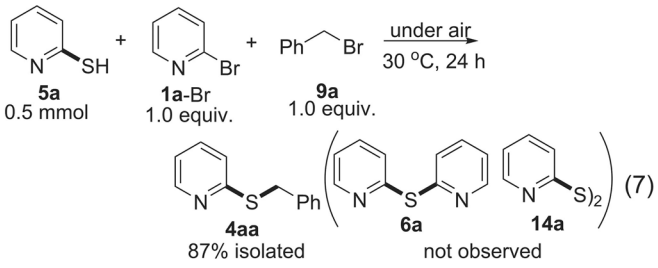
Then, the further reaction of thiol intermediates (**5**) and alcohols was investigated. As shown in Eq. (5), the blank reaction of **5a** and **2a** only afforded a low yield of **4aa** (run 1). In contrast, the reaction with addition of 100 mol% HBr gave a high 92% yield of **4aa** [Eq. (5), run 2]. *Vice versa*, when DBN (1,5-diazobicyclo[4.3.0]non-5-ene) was added to neutralize the potential by-product HBr, the target reaction was terminated instantly to give **6a** as the only product [Eq. (6)]. These results revealed that the key role of by-product HX in the system is to promote the target reaction to occur more efficiently.

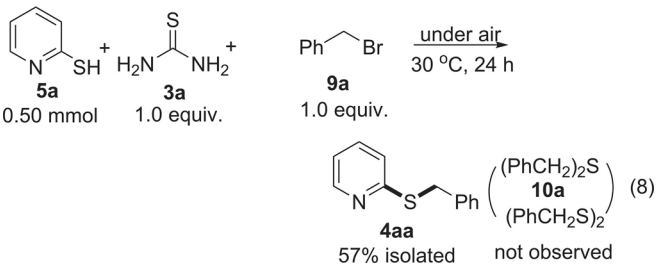
Competing reactions were then investigated to understand the high selectivity of the reaction. As shown in Eq. (7), the reaction of **5a** with both **1a-Br** and $PhCH_2Br$ (**9a**) could give **4aa** as the only product at 30 °C. This clearly showed that the target reaction of heteroarylthiols **5** and alkyl halides **9** giving products **4** is a favored process, far more efficient than the





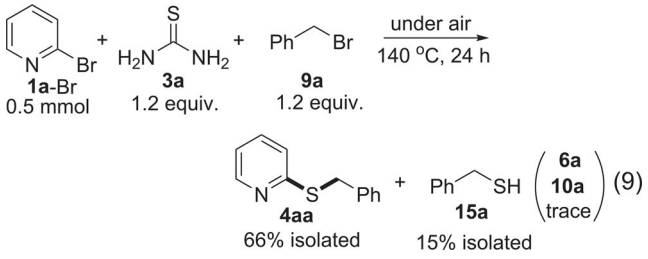
side-reactions of **5** to give **6** or **14**.[18] Likewise, the reaction of **9a** with both **3a** and **5a** also gave **4aa** as the only product [Eq. (8)]. This suggested that the target reaction of **5** and **9** is also a favored process, far more efficient than the side-reactions of alkyl halides **9** and thiourea **3a**. These results demonstrated that alkyl halides **9** are indeed the reactive intermediates and can also account for the observed high selectivity of the target thioethers in the reaction.





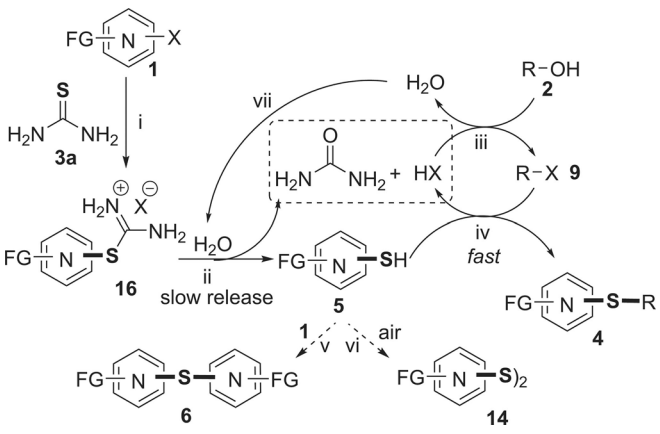
However, even though alkyl halides **9** are the reactive intermediates in the reaction, it was then found that the direct reaction of **1a**, **3a** with benzyl bromide **9a** instead of benzyl alcohol **2a** only afforded a lower yield of **4aa** in a lower selectivity [Eq. (9)]. This result implied that an initial high concentration of alkyl halide is not beneficial for the reaction. Thus, a low concentration of the alkyl halide intermediates generated by a slow release process from the reaction of alcohols and by-product HX[19] is the key for the high

selectivity of the product. This also clearly demonstrated that alcohols are indispensible coupling reagents in the reaction since they can be much superior over the more reactive and toxic alkyl halides [Eq. (9)].



Based on above results, a possible mechanism for the typical sulfur transfer coupling reaction of alcohols, heteroaryl halides, and thiourea was postulated. As shown in Scheme 1, heteroaryl halide **1** may firstly react with thiourea *via* an S_NAr reaction to give ionic intermediate **16** (step i) according to some literature reports.[10c–e] Then by hydrolysis with the contaminant water in the substrates,[20] **16** generates heteroarylthiol **5** and by-products urea and HX (step ii). Since only *ca.* 24 mol% contaminant water is present in the substrates,[16,20] this low amount of water is responsible for the slow-releasing of **5** and HX from **16**. HX then reacts with alcohol **2** to slowly release alkyl halide **9** and water (step iii). Once **9** is generated, it selectively reacts with **5** to efficiently give heteroaryl thioethers **4** and regenerate HX (step iv). Herein the observed ineffective side-reactions of **5** (steps v and vi) also result in the highly selective formation of the product thioethers.

In addition, although HX was generated as the by-product in the reactions (Scheme 1), the reaction media is not so acidic owing to the buffer-like feature of the urea/thiourea/HX system that can absorb and release HX.[21] Therefore, this method can tolerate some acid-sensitive functional groups such as the basic heteroaryl moieties of the heteroaryl halides, as well as ether, nitrile, and ester linkages in some reactants (Table 1), which also accounts for the relatively broad substrate scope of the method.



Scheme 1. Possible reaction path for the typical coupling of alcohols, heteroaryl halides, and thiourea.

In conclusion, we have developed a totally new metal-, base-, and solvent-free three-component coupling of heteroaryl halides and thiourea with the indispensible alcohols for the direct and highly selective synthesis of unsymmetrical heteroaryl thioethers by constructing two C–S bonds in only one step. This new method can be easily scaled up to larger scales and extended to the synthesis of heteroaryl selenides, dialkyl thioethers, benzothiazoles, and even some antimycobacterially-active thioethers. Due to the buffer-like feature of the urea/thiourea/HX system,[21] a wide range of substituted and functionalized alcohols and organo halides can be tolerated in the method. Mechanistic studies revealed that the slow release of alkyl halide and thiol intermediates and a by-product-promoted C–O activation of the alcohols to generate the reactive alkyl halides are the keys to the success of the reaction, which also accounts for the high selectivity of the target products. Further extensions of this sulfur transfer C–S coupling method are our next concern.

Experimental Section

Typical Procedures for Synthesis of Unsymmetrical Heteroaryl Thioethers by Three-Component Coupling of Alcohols, Heteroaryl Halides, and Thiourea

Method A: The mixture of 2-bromopyridine **1a-Br** (78.5 mg, 0.50 mmol), benzyl alcohol **2a** (64.8 mg, 0.60 mmol, 1.2 equiv.), and thiourea **3a** (45.6 mg, 0.60 mmol, 1.2 equiv.) was directly sealed in a Schlenk tube (20 mL) under air, and stirred at 140 °C for 24 h. The reaction was then monitored by TLC and/or GC-MS. After completion of the reaction, the reaction mixture was purified by flash column chromatography on silica gel using ethyl acetate and petroleum ether (0≈1/50) as the eluent, giving **4aa** in 83% isolated yield.

Method B: The mixture of 2-chloropyridine **1a-Cl** (67.8 mg, 0.60 mmol, 1.2 equiv.), benzyl alcohol **2a** (54.0 mg, 0.50 mmol), and thiourea **3a** (45.6 mg, 0.60 mmol, 1.2 equiv.) was directly sealed in a Schlenk tube (20 mL) under air, and stirred at 140 °C for 24 h. The reaction was then monitored by TLC and/or GC-MS. After completion of the reaction, the reaction mixture was purified by flash column chromatography on silica gel using ethyl acetate and petroleum ether (0≈1/50) as the eluent, giving **4aa** in 81% isolated yield.

Acknowledgements

This work is supported by NNSF (21672163, 51502174, 21502143), ZJNSF (LR14B020002), Postdoctoral Science Foundation of China (2016M592520), and Science and Technology Project of Shenzhen (JCYJ20150324141711616).

References

[1] For antimycobacterial properties of 2- and 4-substituted pyridyl alkyl thiothethers, see: a) V. Klimešová, M. Svoboda, K. Waisser, M. Macháček, V. Buchta, Ž. Odlerová, *Arch. Pharm. Pharm. Med. Chem.* **1996**, *329*, 438; b) V. Klimešová, M. Svoboda, K. Waisser, M. Pour, J. Kaustová, *Collect. Czech. Chem. Commun.* **1999**, *64*, 417; c) V. Klimešová, M. Svoboda, K. Waisser, J. Kaustová, V. Buchta, K. Králová, *Eur. J. Med. Chem.* **1999**, *34*, 433; d) V. Klimešová, P. Herzigová, K. Palát, M. Macháček, J. Stolaříková, H.-M. Dahse, U. Möllmann, *ARKIVOC* **2012**, 90. For examples of 2-substituted pyridyl alkyl thiothethers as inhibitors of the *Staphylococcus aureus* NorA efflux pump, see: e) F. Fotaine, A. Hequet, A.-S. Voisin-Chiret, A. Bouillon, A. Lesnard, T. Cresteil, C. Jolivalt, S. Rault, *Eur. J. Med. Chem.* **2015**, *95*, 185. For reports on other heteroaryl thioethers, see: f) A. K. Pathak, V. Pathak, L. E. Seitz, W. J. Suling, R. C. Reynolds, *J. Med. Chem.* **2004**, *47*, 273; g) G. Liu, J. R. Huth, E. T. Olejniczak, R. Mendoza, P. DeVries, S. Leitza, E. B. Reilly, G. F. Okasinski, S. W. Fesik, T. W. von Geldern, *J. Med. Chem.* **2001**, *44*, 1202; h) L. Liu, J. E. Stelmach, S. R. Natarajan, M.-H. Chen, S. B. Singh, C. D. Schwartz, C. E. Fitzgerald, S. J. O'Keefe, D. M. Zaller, D. M. Schmatz, J. B. Doherty, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3979; i) S. W. Kaldor, V. J. Kalish, J. F. Davies II, B. V. Shetty, J. E. Fritz, K. Appelt, J. A. Burgess, K. M. Campanale, N. Y. Chirgadze, D. K. Clawson, B. A. Dressman, S. D. Hatch, D. A. Khalil, M. B. Kosa, P. P. Lubbehusen, M. A. Muesing, A. K. Patick, S. H. Reich, K. S. Su, J. H. Tatlock, *J. Med. Chem.* **1997**, *40*, 3979.

[2] For some reports, see: a) A. Leprêtre, A. Turck, N. Plé, G. Quéguiner, *Tetrahedron* **2000**, *56*, 3709; b) S. Kumar, H. Johansson, T. Kanda, L. Engman, T. Muller, M. Jonsson, L. Valgimigli, *Org. Lett.* **2008**, *10*, 4895; c) N. T. T. Chau, M. Meyer, S. Komagawa, F. Chevallier, Y. Fort, M. Uchiyama, P. C. Gros, *Chem. Eur. J.* **2010**, *16*, 12425.

[3] For a review, see: a) C.-F. Lee, Y.-C. Liu, S. S. Badsara, *Chem. Asian J.* **2014**, *9*, 706, and references cited therein. For some reports, see: b) C. C. Eichman, J. P. Stambuli, *J. Org. Chem.* **2009**, *74*, 4005; c) M. C. Bagley, V. Fusillo, E. G. B. Hills, A. T. Mulholl, J. Newcombe, L. J. Pentecost, E. L. Radley, B. R. Stephens, C. C. Turrell, *ARKIVOC* **2012**, *7*, 294; d) M. C. Bagley, T. Davis, M. C. Dix, V. Fusillo, M. Pigeaux, M. J. Rokicki, D. Kipling, *J. Org. Chem.* **2009**, *74*, 8336.

[4] a) P. H. Lee, Y. Park, S. Park, E. Lee, S. Kim, *J. Org. Chem.* **2011**, *76*, 760; b) J. Mo, D. Eom, S. H. Kim, P. H. Lee, *Chem. Lett.* **2011**, *40*, 980982.

[5] a) Y. J. Cherng, *Tetrahedron* **2002**, *58*, 4931; b) Z. Duan, S. Ranjit, X. Liu, *Org. Lett.* **2010**, *12*, 2430; c) S. S. Badsara, C.-C. Chan, C.-F. Lee, *Asian J. Org. Chem.* **2014**, *3*, 1197.

[6] X. Ma, Q. Liu, X. Jia, C. Su, Q. Xu, *RSC Adv.* **2016**, *6*, 56930.

[7] X. Jia, L. Yu, J. Liu, Q. Xu, M. Sickert, L. Chen, M. Lautens, *Green Chem.* **2014**, *16*, 3444.

[8] a) Y. Jiang, Y. Qin, S. Xie, X. Zhang, J. Dong, D. Ma, *Org. Lett.* **2009**, *11*, 5250; b) A. Rostami, A. Rostami, N. Iranpoor, M. A. Zolfigol, *Tetrahedron Lett.* **2016**, *57*, 192.

[9] a) Z. Qiao, H. Liu, X. Xiao, Y. Fu, J. Wei, Y. Li, X. Jiang, *Org. Lett.* **2013**, *15*, 2594; b) Y. Li, J. Pu, X. Jiang, *Org. Lett.* **2014**, *16*, 2692; c) A. Rostami, A. Rostami, A. Ghaderi, *J. Org. Chem.* **2015**, *80*, 8694.

[10] For some reports, see: a) H. Firouzabadi, N. Iranpoor, M. Gholinejad, *Adv. Synth. Catal.* **2010**, *352*, 119; b) J. Mondal, A. Modak, A. Dutta, S. Basu, S. N. Jha, D. Bhattacharyya, A. Bhaumik, *Chem. Commun.* **2012**, *48*, 8000; c) P. Manivel, K. Prabakaran, V. Krishnakumar, F.-R. N. Khan, T. Maiyalagan, *Ind. Eng. Chem. Res.* **2014**, *53*, 7866; d) H.-Y. Niu, C. Xia, G.-R. Qu, S. Wu, Y. Jiang, X. Jin, H.-M. Guo, *Chem. Asian J.* **2012**, *7*, 45; e) H. Firouzabadi, N. Iranpoor, M. Abbasi, *Tetrahedron* **2009**, *65*, 5293.

[11] a) K. M. Wager, M. H. Daniels, *Org. Lett.* **2011**, *13*, 4052; b) L. C. Schmidt, V. Rey, A. B. Peñéñory, *Eur. J. Org. Chem.* **2006**, 2210; c) D. J. C. Prasad, G. Sekar, *Org. Lett.* **2011**, *13*, 1008; d) V. K. Akkilagunta, R. R. Kakulapati, *J. Org. Chem.* **2011**, *76*, 6819.

[12] For a review, see: a) H. Liu, X. Jiang, *Chem. Asian J.* **2013**, *8*, 2546. For some reports: b) H. Firouzabadi, N. Iranpoor, A. Samadi, *Tetrahedron Lett.* **2014**, *55*, 1212; c) M. Gholinejad, *Eur. J. Org. Chem.* **2015**, 4162; d) Y. Liu, J. Kim, H. Seo, S. Park, J. Chaea, *Adv. Synth. Catal.* **2015**, *357*, 2205.

[13] We have been engaged in organochalcogen chemistry including the (hetero)aryl thioethers (refs.[6,7,13d,e]) and recently reported a direct [3+2] cycloaddition reaction of methylenecyclopropanes for methylene-1,2-dithiolane synthesis using elemental S_8 as the sulfur source (ref.[13c]). See: a) X. Zhang, J. Ye, L. Yu, X. Shi, M. Zhang, Q. Xu, *Adv. Synth. Catal.* **2015**, *357*, 955; b) L. Yu, H. Li, X. Zhang, J. Ye, J. Liu, Q. Xu, M. Lautens, *Org. Lett.* **2014**, *16*, 1346; c) L. Yu, Y. Wu, T. Chen, Y. Pan, Q. Xu, *Org. Lett.* **2013**, *15*, 144; d) X. Yu, B. Li, B. Yu, Q. Xu, *Chin. Chem. Lett.* **2013**, *24*, 605; e) C. Liu, X. Zang, B. Yu, X. Yu, Q. Xu, *Synlett* **2011**, 1143; f) Q. Xu, X. Huang, J. Yuan, *J. Org. Chem.* **2005**, *70*, 6948; g) X. Huang, C.-G. Liang, Q. Xu, Q.-W. He, *J. Org. Chem.* **2001**, *66*, 74.

[14] For a review, see: a) X. Ma, C. Su, Q. Xu, *N-Alkylation by hydrogen autotransfer reactions*, in: *Hydrogen transfer reactions: reductions and beyond,* (Eds.: G. Guillena, D. J. Ramón), *Topics in Current Chemistry*, Vol. 374, Springer, Berlin, Heidelberg, **2016**, pp 1–74. For reports: b) Q. Xu, J. Chen, H. Tian, X. Yuan, S. Li, C. Zhou, J. Liu, *Angew. Chem.* **2014**, *126*, 229; *Angew. Chem. Int. Ed.* **2014**, *53*, 225; c) Q. Xu, H. Xie, P. Chen, L. Yu, J. Chen, X. Hu, *Green Chem.* **2015**, *17*, 2774; d) Q. Xu, H. Xie, E.-L. Zhang, X. Ma, J. Chen, X.-C. Yu, H. Li, *Green Chem.* **2016**, *18*, 3940; e) C. Liu, S. Liao, Q. Li, S. Feng, Q. Sun, X. Yu, Q. Xu, *J. Org.*

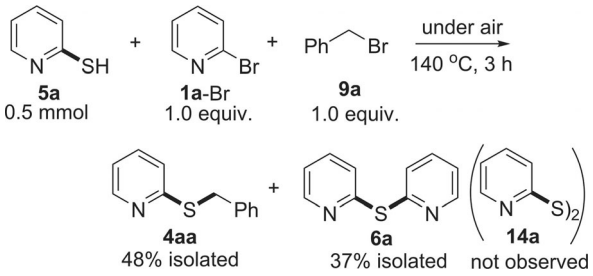
Chem. **2011**, *76*, 5759; f) X. Yu, C. Liu, L. Jiang, Q. Xu, *Org. Lett.* **2011**, *13*, 6184; g) Q. Li, S. Fan, Q. Sun, H. Tian, X. Yu, Q. Xu, *Org. Biomol. Chem.* **2012**, *10*, 2966; h) S. Liao, K. Yu, Q. Li, H. Tian, Z. Zhang, X. Yu, Q. Xu, *Org. Biomol. Chem.* **2012**, *10*, 2973; i) Q. Xu, Q. Li, *Chin. J. Org. Chem.* **2013**, *33*, 18; j) Q. Xu, Q. Li, X. Zhu, J. Chen, *Adv. Synth. Catal.* **2013**, *355*, 73; k) Q. Xu, J. Chen, Q. Liu, *Adv. Synth. Catal.* **2013**, *355*, 697; l) S. Li, X. Li, Q. Li, Q. Yuan, X. Shi, Q. Xu, *Green Chem.* **2015**, *17*, 3260.

[15] For reviews, see: a) J. Muzart, *Tetrahedron* **2005**, *61*, 4179; b) Q. Yang, Q. Wang, Z. Yu, *Chem. Soc. Rev.* **2015**, *44*, 2305; c) M. Bandini, G. Cera, M. Chiarucci, *Synthesis* **2012**, *44*, 504; d) D.-H. Lee, K.-H. Kwon, C. S. Yi, *Science* **2011**, *333*, 1613; e) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937; f) E. Skucas, M.-Y. Ngai, V. Komanduri, M. J. Krische, *Acc. Chem. Res.* **2007**, *40*, 1394.

[16] See the Supporting Information for details.

[17] A scarcely observed beneficial effect of a higher reaction temperature in improving the product's selectivity was observed. See the Supporting Information for details.

[18] The same reaction of **5a**, **1a-Br**, and **9a** at 140 °C afforded by-product **6a** in 37% yield in addition to 48% **4aa** (see the equation below). This implied that an initial high concentration of thiols **5** is not beneficial for high selectivity of the target reaction; whereas a slow generation of **5** from **1** and **3a** should be preferred, making the target reaction of **5** and **9** to occur in high selectivity. This can also account for the scarcely observed higher selectivity of a reaction at higher temperatures by slow release of the intermediates.



[19] Alkyl halides can be generated from alcohols and HX. See: a) J. McMurry, *Organic Chemistry*, 7th edn., Thomson, Brooks/Cole, **2008**; b) J. March, *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, 4th edn., Wiley, New York, **1992**.

[20] During the condition screening, we found that the reaction could be facilitated by a catalytic amount of contaminant water in the substrates. According to a water content analysis of commercial **1a-Br**, **2a**, and **3a** by atomic absorption measurement, *ca.* 24.2 mol% water is present in a standard reaction. See Section 3 of the Supporting Information for details.

[21] For the buffer-like features of the urea/thiourea/HX system, see: a) J. Walker, J. K. Wood, *J. Chem. Soc. Trans.* **1903**, *83*, 484; b) E. A. Werner, *J. Chem. Soc. Trans.* **1918**, *113*, 84.