DOI: 10.1002/adsc.201900904

Advanced Synthesis & Catalysis

Copper-Catalyzed Reaction of Aryl Isocyanides with Active Methylene Isocyanides and Arylsulfonothioates: Synthesis of Sulfur-Containing Trisubstituted Imidazoles

Pei Xu,[a] Yi-Ming Zhu,[a] Xing-Jia Li,[a] Fei Wang,[a] Shun-Yi Wang,[a,]* and Shun-Jun Ji[a,]*

[a] Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science & Collaborative Innovation Center of Suzhou Nano Science and Technology, Soochow University, Suzhou 215123, People's Republic of China
E-mail: shunyi@suda.edu.cn; shunjun@suda.edu.cn

Manuscript received: July 22, 2019; Revised manuscript received: August 26, 2019;
Version of record online: ■■, ■■■

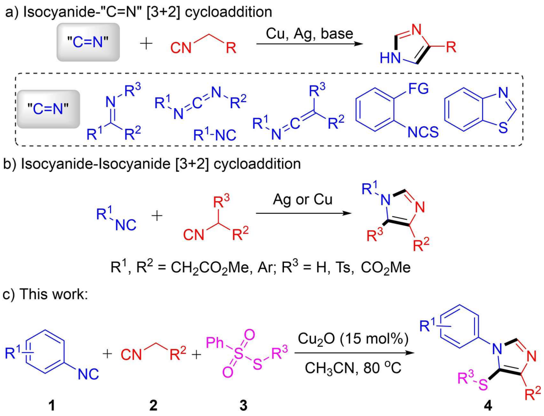
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201900904

Abstract: A Copper-catalyzed reaction of aryl isocyanides with active methylene isocyanides and arylsulfonothioates is developed for the synthesis of sulfur-containing trisubstituted imidazoles. This reaction not only forms new C–C, C–N, and C–S bonds in one step, but also provides a new strategy for the construction of trisubstituted imidazoles based on the isocyanide-isocyanide [3+2] cycloaddition.

Keywords: Copper-catalyzed; Aryl isocyanides; Active methylene isocyanides; Arylsulfonothioates; Sulfur-containing trisubstituted imidazoles

Imidazoles are one of the important classes of heterocyclic compounds which can be found in numerous pharmaceutical molecules.[1] For example, Losartan[2] and Econazole[3] frameworks are imidazoles, which have anticancer and antiallergic activities, respectively. Imidazoles have been also served as ligands in transition-metal-catalyzed reactions.[4] In addition, imidzaoles can catalyze organic reactions by themselves.[5] During the past decade, different methods have been developed to the synthesis of imidazoles.[6] In these methods, the [3+2] cycloaddition of active methylene isocyanides and "C=N" is a highly atomic economic method.[7,8] The "C=N" bond of imines,[7a] carbodiimides,[7b] isothiocynates,[7c,d] benzothiazoles,[7e] ketenimines,[7f] and isocyanides[8] have been succesfully appied to [3+2] cycloaddition to construct imidazoles (Scheme 1, a). While, there are only five methodologies based on the concept of two components of isocyanide-isocyanide [3+2] cycloaddition to construct imidazoles have been reported in the literature (Scheme 1, b). To the best our knowledge, there are no multi component reactions based on isocyanide-isocyanide [3+2] cycloaddition.

C–S bond formation reactions have attracted increasing attention for their importance in natural products and functional materials.[9] The most classical method for the building C–S bond usually utilizing mercaptans which have the unpleasant odor. In the past few years, arylsulfonothioates as thiolating agents have received increasing attention from the synthetic community of researchers.[10–14] Many groups such as Xu's group,[10] Song'group,[11] Orru's group,[12] Hosoya's group,[13a] and Reddy's group[13b] have been successfully constructed sulfur-containing compounds with arylsulfonothioates. Very recently, the reactions involving arylsulfonothioates have been well studied in our

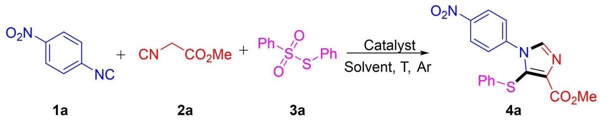


Scheme 1. Isocyanides-"C=N" [3+2] cycloaddition to imidazoles.

group.[14] In addition, our group has focused on the reactions of isocyanides for the decade.[15] As our ongoing interest in the reaction of isocyanides, we introduce arylsulfonothioates to the isocyanide-isocyanide [3+2] cycloaddition system. Herein, we describe a reaction of aryl isocyanides with active methylene isocyanides and arylsulfonothioates to construct sulfur-containing trisubstituted imidazoles (Scheme 1, c). This reaction provides a novel strategy for the construction of trisubstituted imidazoles through new C–C, C–N, and C–S bonds formation.

At the beginning, we tried the reaction of 1-isocyano-4-nitrobenzene **1a**, methyl 2-isocyanoacetate **2a** and *S*-phenyl benzenesulfonothioate **3a** in the presence of 10 mol% of Cu_2O in CH_3CN to optimize the reaction (Table 1, entry 1). To our delight, the desired product methyl 1-(4-nitrophenyl)-5-(phenylthio)-1*H*-imidazole-4-carboxylate (**4a**) was formed in 74% yield after 4 h. The structure of **4a** was confirmed by NMR, HRMS and X-ray analysis (see the Supporting Information). When CuTC applied to the reaction instead of Cu_2O, the reaction proceed smoothly to give **4a** in 64% yield (Table 1, entry 2). Other copper catalysts including Cu, CuI, CuO as well as nickel catalyst NiO and iron catalyst $Fe(acac)_3$ were also investigated under similar reaction conditions (Table 1, entries 3–7). However, all these catalysts were not effective. Screening different amounts of the Cu_2O revealed that 15 mol% of Cu_2O was the ideal amount (Table 1, entries 8–9). Other solvents such as THF, elicited a similar reactivity, while DCE, Toluene, DMSO or DMF could not improve the yield of the target product (Table 1, entries 10–14). Notably, increasing the concentration of the reaction revealed that 1 mL of CH_3CN was the ideal amount (Table 1, entry 15). Screening the temperature of this reaction revealed that 80 °C was the optimal reaction temperature (Table 1, entries 16–17). We try to employ *S*-phenyl methanesulfonothioate to improve atomic utilization, but **4a** was obtained in 73% yield (Table 1, entry 18). Therefore, the optimized reaction conditions included 1-isocyano-4-nitrobenzene **1a** (0.2 mmol), methyl 2-isocyanoacetate **2a** (0.3 mmol) and *S*-phenyl benzenesulfonothioate **3a** (0.3 mmol) in the presence of 15 mol% of Cu_2O in 1.0 mL CH_3CN at 80 °C.

Table 1. Optimization of the reaction conditions.[a]

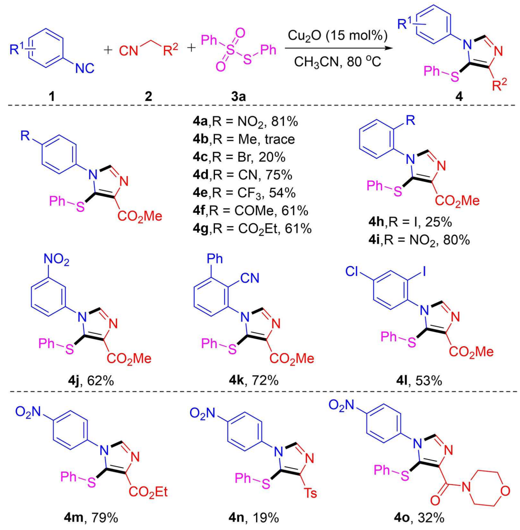


Entry	Catalyst (mol%)	Solvent (mL)	T (°C)	Yield[b] (%)
1	Cu_2O (10)	CH_3CN (2)	80	74
2	CuTC (10)	CH_3CN (2)	80	64
3	Cu (10)	CH_3CN (2)	80	trace
4	CuI (10)	CH_3CN (2)	80	ND
5	CuO (10)	CH_3CN (2)	80	ND
6	NiO (10)	CH_3CN (2)	80	ND
7	$Fe(acac)_3$ (10)	CH_3CN (2)	80	ND
8	Cu_2O (15)	CH_3CN (2)	80	78
9	Cu_2O (20)	CH_3CN (2)	80	73
10[c]	Cu_2O (15)	THF (2)	80	77
11[d]	Cu_2O (15)	DCE (2)	80	45
12	Cu_2O (15)	Toluene (2)	80	70
13[e]	Cu_2O (15)	DMSO (2)	80	59
14[f]	Cu_2O (15)	DMF (2)	80	75
15	Cu_2O (15)	CH_3CN (1)	80	81
16	Cu_2O (15)	CH_3CN (1)	60	71
17	Cu_2O (15)	CH_3CN (1)	100	78
18[g]	Cu_2O (15)	CH_3CN (1)	80	73

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv.), **3a** (0.3 mmol, 1.5 equiv.), catalyst, solvent, argon atmosphere, temperature, 4 h.
[b] Isolated yield.
[c] THF = Tetrahydrofuran.
[d] DCE = 1,2-Dichloroethane.
[e] DMSO = Dimethyl sulfoxide.
[f] DMF = N,N-Dimethylformamide.
[g] *S*-phenyl methanesulfonothioate instead of *S*-phenyl benzenesulfonothioate.

With the optimized conditions established, we first investigated the substrate scope of isocyanides **1** and **2** (Table 2). The reaction of 1-isocyano-4-methylbenzene **1b** with methyl 2-isocyanoacetate **2a** and *S*-phenyl benzenesulfonothioate **3a** failed to give the desired product **4b** under the optimized conditions. The reactions of the halogen group (Br, I) substituted ary isocyanides with **2a** and **3a** could furnish the corre-

Table 2. Substrate scope of isocyanides.[a,b]

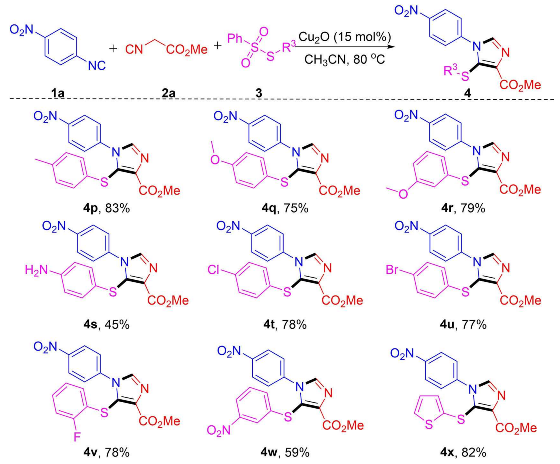


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **3a** (0.3 mmol), Cu_2O (15 mol%.), CH_3CN (1 mL), 80 °C, 4 h, argon atmosphere.
[b] Isolated yield.

sponding products **4c** and **4h** in 20% and 25% yield, respectively. The results indicated that the electron-withdrawing group on the aryl ring has significant effect on the cross-cycloaddition reaction. Then, a series of electron-withdrawing groups (CN, CF_3, COMe, CO_2Et) substituted aryl isocyanides have been subjected to the reactions with **2a** and **3a**. It should be noted that the desired products **4d**, **4e**, **4f**, **4g** were obtained in 54%-75% yield. When the nitro group shifted to the *ortho* or *meta* position of the aryl ring, the reaction proceeded smoothly to give the desired product **4i** and **4j** in 80% and 62% yields, respectively. The reaction of the multifunctionalized 3-isocyano-[1,1′-biphenyl]-2-carbonitrile **1k** with **2a** and **3a** led to the desired product **4k** in 72% yield. It is worth mentioning that there are two halogen groups (I and Cl) of the aryl isocyanide as the substrate the corresponding product **4l** was obtained in moderate yield. Unfortunately, the reaction of *tert*-butyl isocyanide with **2a** and **3a** failed to give the corresponding product. We also explored the scope of active methylene isocyanides. The imidazole product could be obtained in good yield when using ethyl 2-isocyanoacetate **2b** as the substrate. Additionally, other active methylene isocyanides such as 1-((isocyanomethyl)sulfonyl)-4-methylbenzene **2c** and 2-isocyano-1-morpholinoethan-1-one **2d** were employed in the reaction, the desired products **4n** and **4o** were performed in 19% and 32% yields, respectively.

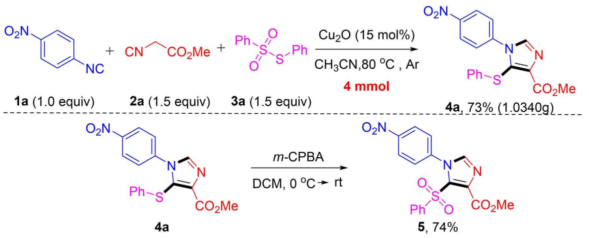
To further evaluate the scope of this method, differently substituted arylsulfonothioates were examined, and most of the tested substrates smoothly underwent to afford the corresponding products under the optimal conditions (Table 3). Explicitly, the reaction tolerated electron-donating (Me, OMe) or electron-withdrawing (Cl, Br, F, NO_2) substituents on the aryl ring, giving the desired products **4p**, **4q**, **4r**, **4t**, **4u**, **4v** and **4w** in 59% to 83% yields. To our delight, the amino group, which has active hydrogen atom, at the *para*-position of the aryl ring could reacted smoothly. It should be noted that *S*-(thiophen-2-yl) benzenesulfonothioate **3j** reacted with **1a** and **2a** under the standard reaction conditions to give **4x** in 82% yield. Next, we turned our attention to the *S*-alkyl benzenesulfonothioate. When *S*-propyl benzenesulfonothioate was employed in the reaction with **1a** and **2a** under the optimized conditions, we couldn't isolated the pure desired product. Unfortunately, the reaction of *Se*-phenyl benzenesulfonoselenoate with **1a** and **2a** failed to give the selenium functionalized imidazole due to the different reactivity of *Se*-phenyl benzenesulfonoselenoate.

Table 3. Substrate scope of *S*-aryl arylsulfonothioate.[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3** (0.3 mmol), Cu_2O (15 mol%.), CH_3CN (1 mL), 80 °C, 4 h, argon atmosphere.

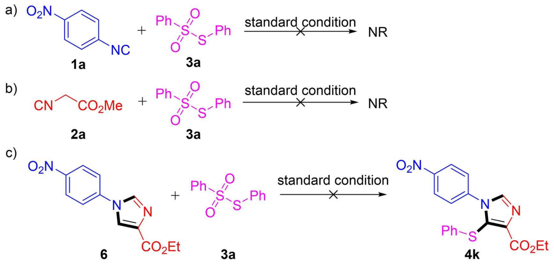
[b] Isolated yield.



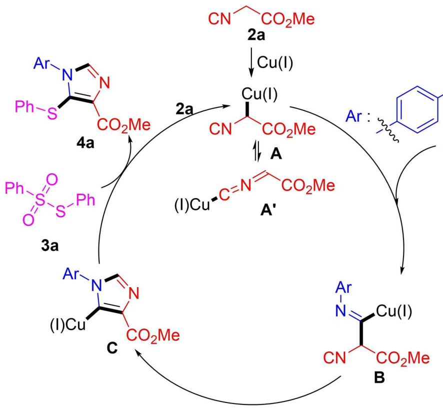
Scheme 2. Scale-up synthesis and transformations of **4a**.

To demonstrate the synthetic potential of our method, we tried to amplify the model reaction of **1a**, **2a** and **3a** under the standard reaction conditions in 4 mmol scale. Fortunately, **4a** could be observed in 73% yield (Scheme 2). In addition, the oxidation reaction of **4a** with 3-Chloroperoxybenzoic acid (*m*-CPBA) proceeded smoothly to afford methyl 1-(4-nitrophenyl)-5-(phenylsulfonyl)-1*H*-imidazole-4-carboxylate **5** in 74% yield (Scheme 2).

In order to understand the reaction mechanism, a series of controlled experiments have been conducted (Scheme 3). It was found that no reaction occurred between **1a** and **3a** under the standard reaction conditions (Scheme 3, a). A similar result was observed when **2a** was applied to the reaction with **3a**



Scheme 3. Control experiments.



Scheme 4. Proposed reaction mechanism.

(Scheme 3, b). After that, we prepared ethyl 1-(4-nitrophenyl)-1*H*-imidazole-4-carboxylate **6** according to the literature reported by Yamamoto's group.[8b] However, the reaction of **6** with **3a** failed to afford the target product **4k** under the standard conditions (Scheme 3, c). This result indicates that the 1,4-disubtituted imidazole is not the intermediate of this reaction.

Based on the above experiment results and related literatures,[8b,10a,12a] we proposed a plausible reaction mechanism for this Cu(I)-catalyzed reaction (Scheme 4). First, the intermediate **A** or its tautomer **A′** is generated by the reaction of methyl 2-isocyanoacetate **2a** and Cu_2O. Then, the nucleophilic addition of **A** or **A′** to 1-isocyano-4-nitrobenzene **1a** gives intermediate **B**. Subsequently, this intermediate **B** produces the copper intermediate **C** through intramolecular addition. Finally, *S*-phenyl benzenesulfonothioate **3a** reacts with intermediate **C** to furnish the product **4a** and releases the Cu species to complete the catalytic cycle.

In summary, we have developed a method to construct sulfur-containing trisubstituted imidazoles by the reaction of aryl isocyanides, active methylene isocyanides and arylsulfonothioates in the presence of Cu_2O. This reaction not only forms C–C, C–N, and C–S bonds in one step, but also provides a novel strategy for the construction of trisubstituted imidazoles based on the isocyanide-isocyanide [3+2] cycloaddition.

Experimental Section

General procedure for the synthesis of methyl 1-(4-nitrophenyl)-5-(phenylthio)-1*H*-imidazole-4-carboxylate (4a): In a 25 mL Schlenk tube, to a mixture of 1-isocyano-4-nitrobenzene (**1a**, 0.2 mmol, 1 equiv.), methyl 2-isocyanoacetate (**2a**, 0.3 mmol, 1.5 equiv.), *S*-phenyl benzenesulfonothioate (**3a**, 0.3 mmol, 1.5 equiv.), Cu_2O (0.03 mmol, 15 mol%), were added in 1 mL CH_3CN. The reaction mixture was stirred at 80 °C under argon atmosphere. After 4 h, the system cooled to room temperature. The system was evaporated under the reduced pressure directly. The residue was purified by flash column chromatography with ethyl acetate and petroleum ether as eluents to afford pure product **4a**.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21971174, 21672157, 21542015 and 21772137), PAPD, the Projiec of Scientific and Technologic Infrastructure of Suzhou (SZS201708), the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 16KJA150002), Soochow University, and State and Local Joint Engineering Laboratory for Novel Functional Polymeric Materials for financial support. We thank Nan Jiang in this group for reproducing the result of ***4d**, **4i**, **4k** and **4x**.*

References

[1] L. Zhang, X.-M. Peng, G. L. V. Damu, R.-X. Geng, C.-H. Zhou, *Med. Res. Rev.* **2014**, *34*, 340.
[2] J. P. Habashi, D. P. Judge, T. M. Holm, R. D. Cohn, B. L. Loeys, T. K. Cooper, L. Myers, E. C. Klein, G. Liu, C. Calvi, M. Podowski, E. R. Neptune, M. K. Halushka, D. Bedja, K. Gabrielson, D. B. Rifkin, L. Carta, F. Ramirez, D. L. Huso, H. C. Dietz, *Science* **2006**, *312*, 117.
[3] L. Leclercq, V. Nardello-Rataj, *Eur. J. Pharm. Sci.* **2016**, *82*, 126.
[4] D. Janssen-Müller, C. Schlepphorst, F. Glorius, *Chem. Soc. Rev.* **2017**, *46*, 4845.
[5] D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307.
[6] A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084.
[7] a) X. Zhang, X. Wang, Y. Gao, X. Xu, *Chem. Commun.* **2017**, *53*, 2427; b) G. Sapuppo, Q. Wang, D. Swinnen, J. Zhu, *Org. Chem. Front.* **2014**, *1*, 240; c) W. Hao, J. Zeng, M. Cai, *Chem. Commun.* **2014**, *50*, 11686; d) K. Yan, D. Yang, W. Wei, P. Sun, Y. Lu, H. Wang, *Org. Chem. Front.* **2016**, *3*, 556; e) J. Wang, J. Li, Q. Zhu, *Org. Lett.* **2015**, *17*, 5336; f) J. Cai, H. Bai, Y. Wang, X. Xu, H. Xie, J. Liu, *Chem. Commun.* **2019**, *55*, 3821.
[8] a) R. Grigg, M. I. Lansdell, M. Thornton-Pett, *Tetrahedron* **1999**, *55*, 2025; b) C. Kanazawa, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 10662; c) B. Pooi, J. Lee, K. Choi, H. Hirao, S. H. Hong, *J. Org. Chem.* **2014**, *79*, 9231; d) H. Wang, R. K. Kumar, Y. Yu, L. Zhang, Z. Liu, P. Liao, X. Bi, *Chem. Asian J.* **2016**, *11,* 2841; e) Z. Hu, J. Dong, Y. Men, Z. Lin, J. Cai, X. Xu, *Angew. Chem.* **2017**, *129*, 1831; *Angew. Chem. Int. Ed.* **2017**, *56*, 1085.
[9] I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596.
[10] a) W. Wang, X. Peng, F. Wei, C.-H. Tung, Z. Xu, *Angew. Chem.* **2016**, *128*, 659; *Angew. Chem. Int. Ed.* **2016**, *55*, 649; b) X. Peng, C. Ma, C.-H. Tung, Z. Xu, *Org. Lett.*

2016, *18*, 4154; c) H. Li, C. Shan, C.-H. Tung, Z. Xu, *Chem. Sci.* **2017**, *8*, 2610; d) S. Huang, H. Li, T. Xie, F. Wei, C.-H. Tung, Z. Xu, *Org. Chem. Front.* **2019**, *6*, 1663.

[11] a) W. Kong, H. An, Q. Song, *Chem. Commun.* **2017**, *53*, 8968; b) W. Kong, C. Yu, H. An, Q. Song, *Org. Lett.* **2018**, *20*, 4975; c) C. Rao, S. Mai, Q. Song, *Chem. Commun.* **2018**, *54*, 5964.

[12] a) P. Mampuys, Y. Zhu, T. Vlaar, E. Ruijter, R. V. A. Orru, B. U. W. Maes, *Angew. Chem.* **2014**, *126*, 13063; *Angew. Chem. Int. Ed.* **2014**, *53*, 12849; b) P. Mampuys, Y. Zhu, S. Sergeyev, E. Ruijter, R. V. A. Orru, S. V. Doorslaer, B. U. W. Maes, *Org. Lett.* **2016**, *18*, 2808.

[13] a) K. Kanemoto, S. Yoshida, T. Hosoya, *Org. Lett.* **2019**, *21*, 3172; b) R. J. Reddy, A. H. Kumari, J. J. Kumar, J. B. Nanubolu, *Adv. Synth. Catal.* **2019**, *361*, 1587.

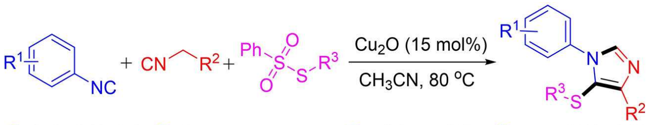
[14] Y. Fang, T. Rogge, L. Ackermann, S.-Y. Wang, S.-J. Ji, *Nat. Commun.* **2018**, *9*, 2240.

[15] a) T.-H. Zhu, S.-Y. Wang, T.-Q. Wei, S.-J. Ji, *Adv. Synth. Catal.* **2015**, *357*, 823; b) P. Xu, T.-H. Zhu, T.-Q. Wei, S.-Y. Wang, S.-J. Ji, *RSC Adv.* **2016**, *6*, 32467; c) P. Xu, F. Wang, T.-Q. Wei, L. Yin, S.-Y. Wang, S.-J. Ji, *Org. Lett.* **2017**, *19*, 4484; d) P. Xu, Y.-M. Zhu, F. Wang, S.-Y. Wang, S.-J. Ji, *Org. Lett.* **2019**, *21*, 683.

Copper-Catalyzed Reaction of Aryl Isocyanides with Active Methylene Isocyanides and Arylsulfonothioates: Synthesis of Sulfur-Containing Trisubstituted Imidazoles

Adv. Synth. Catal. **2019**, *361*, 1–6

P. Xu, Y.-M. Zhu, X.-J. Li, F. Wang, S.-Y. Wang*, S.-J. Ji*



● C-C, C-N, C-S ● three components ● mild condition ● up to 83% yield