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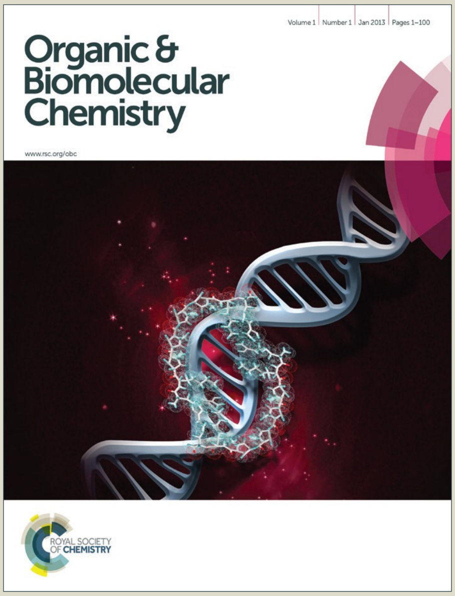

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COMMUNICATION

Copper(I) Chloride Promoted Csp^2-N Cross-Coupling of 1,2-Di(pyrimidin-2-yl) Disulfides with Amines: An Efficient Approach to C2-Amino Functionalized Pyrimidines

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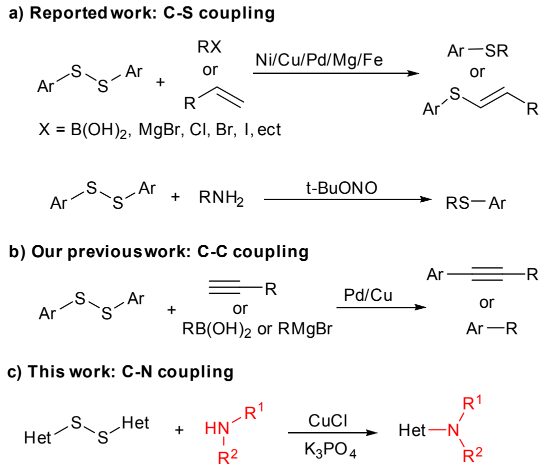
The copper(I)-promoted cross-coupling of 1,2-di(pyrimidin-2-yl) disulfides with aromatic amines and aliphatic amines to deliver C-N coupling products in moderate to good yields was reported. Central to this strategy is the conversion of disulfides into aryl- and alkyl amines by a copper-promoted chemoselectively C–S bond cleavage.

Transition-metal-catalysed cross-coupling reactions, which provide versatile methods for the formation of carbon-nitrogen bonds, play a more and more important role in materials chemistry and medicinal chemistry.[1] Especially, some nitrogen-containing compounds reveal considerable biological activity[2] and medicinal value.[3] Ullmann coupling reactions and Buchwald–Hartwig cross-coupling reactions are efficient method to construct C-N bond. Generally, such procedures involve the coupling of an activated electrophilic substrate[4,1a] with a nucleophile catalysed by transition metals. Palladium[5] and nickel[6] as catalysts were common, but these metals are costly or toxic and often require sophisticated and expensive ligands.[1a] Nevertheless, in most cases, the electrophiles were confined to aryl halides[7] and aryl sulfonates[8,6b] due to their high reactivity towards transition-metal catalysis. Despite the elegance of these methods, there are several disadvantages associated with the use of halides. For example, the synthesis of aryl halides often involves tedious steps, harsh reaction conditions, and waste production.[9] In addition, alkenyl halides are also difficult to synthesize. Therefore, the search for alternative electrophiles as novel substrates to organic halides for the cross-coupling reactions has been the focus of much attention.



Scheme 1. Cross coupling of disulfides with various nucleophiles.

In recent years, O-based and S-based electrophiles as alternatives for the halides are particularly attractive due to the ubiquitous presence of the O- and S-based starting materials in both the natural world and synthetic systems. Diaryl disulfides are important organosulfur reagents for the construction of C-S bonds through S-S bond cleavage.[10] Sicne 2000, various nucleophilic reagents such as aryl halides,[11] boronic acids,[12] alkenes,[13] and amines[14] have been employed to react with disulfides to construct C-S bonds (Scheme 1a). In 2014, we have developed a unique method to construct C-C bond through C-S bond cleavage of di(hetero)aryl disulfides with arylboronic acids or alkynes.[15] In 2015, we have completed the excellent chemoselectivity of C-S and C-C cross coupling of di(hetero)aryl disulfides with Grignard reagents providing C-S and C-C coupling products (Scheme 1b).[16] Consequently, it was logical to question whether disulfides could also serve as an electrophilic partner in reaction with amines by simple catalytic system to construct C-N bond (Scheme 1c). To the best of our knowledge, there is an absence of literature on the couplings of disulfides to construct C-N bonds.

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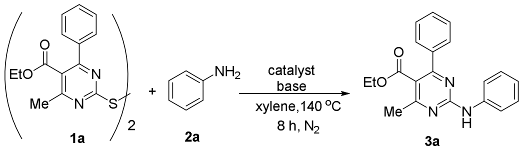
Herein, we explored the possibility of application of 1,2-di(pyrimidin-2-yl) disulfides in the C-N cross-coupling reaction with amines giving pyrimidine motif functionalized with amino group under Cu accelerated conditions.

Generally, 2-amino substituted pyrimidines were obtained via two types of method from Biginelli 3,4-dihydropyrimidin-2(1H)-ones (DHPMs): substitution of 2-methylsulfonyl-pyrimidines with amines developed by Kappe et al[17] and the substitution (or coupling) of pyrimidin-2-yl tosylates/phosphates with amines performed by our group.[18]

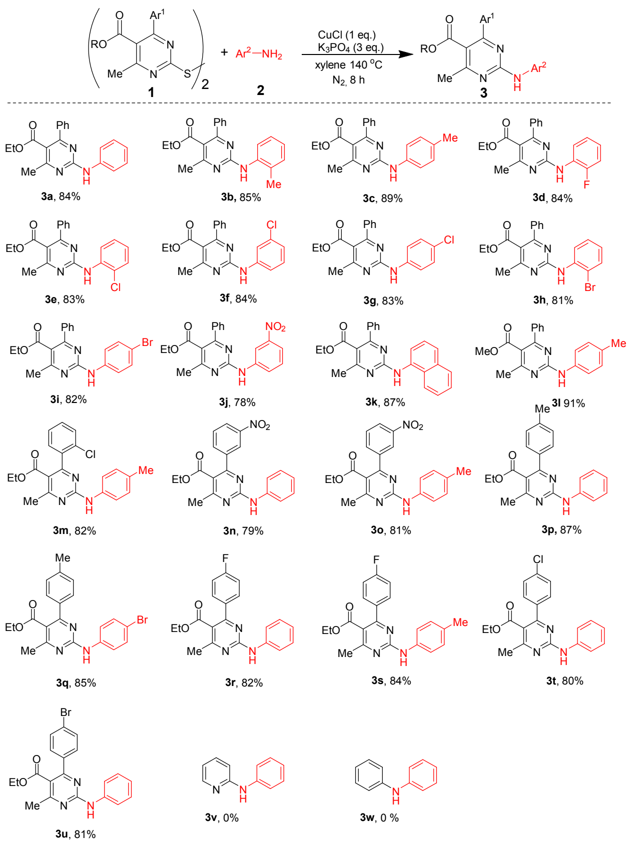
Table 1. Optimization of the cross-coupling reaction of disulfides **1a** and aniline **2a**.[a]



Entry	Catalyst (eq.)	Base	Yield[b](%)
1	--	K_3PO_4	N.R.
2	Cu_2O (1.0)	K_3PO_4	20
3	CuBr (1.0)	K_3PO_4	39
4	CuI (1.0)	K_3PO_4	68
5	CuTC (1.0)	K_3PO_4	81
6	CuCl (1.0)	K_3PO_4	84
7	CuCl (1.0)	Cs_2CO_3	78
8	CuCl (1.0)	K_2CO_3	69
9	CuCl (1.0)	*t*-BuONa	65
10	CuCl (2.0)	K_3PO_4	84
11	CuCl (0.5)	K_3PO_4	51
12	CuCl (0.15)	K_3PO_4	<20
13[c]	CuCl (1.0)	K_3PO_4	<5

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), bases (3.0 mmol), xylene (3 mL). [b]Isolated yield after column chromatography (based on both pyrimidine groups from one molecule). [c]The reaction was carried out at air atmosphere.

Initially, in order to optimize the C-N coupling reaction, the cross-coupling of disulfide **1a** with aniline **2a** was chosen as a model reaction under nitrogen atmosphere (Table 1). Obviously, no product **3a** was detected under catalyst-free condition, but the starting material **1a** was recovered (entry 1). Cu_2O, when used in the reaction in the presence of K_3PO_4, facilitated the formation of product **2a** albeit with only 20% yield (entry 2). Subsequent evaluation of various copper sources led to further improvements with CuCl providing the best results (entry 6). Notably, when CuTC was used as an accelerator the product **3a** was isolated in 81 % yield (entry 5). Next, the effects of bases in this reaction were also investigated. Replacement of K_3PO_4 for either Cs_2CO_3, K_2CO_3 or *t*-BuONa led to inferior results (entries 7-9). When the loading of CuCl was increased to 2 eq., the yield was the same as the 1 eq (entry 10 vs entry 6). Besides, when the loading of CuCl was decreased to 0.5 eq. or 0.15 eq., a considerably lower yield was obtained (entries 11-12). Finally, the reaction almost could not occur in the air (entry 13). Based on the above research, the reaction was best conducted with CuCl as the catalyst, the K_3PO_4 as the base, and xylene as the solvent at 140 °C for 8 h.



Scheme 2. The coupling reactions of disulfides with aromatic amines.

With the optimized conditions in hand, various 1,2-di(pyrimidin-2-yl) disulfides **1** and a diverse set of aromatic amines **2** were used to test the scope of the reaction (Scheme 2). The process proved to be relatively broad in scope, tolerating a variety of steric and electronic changes to both reaction partners. In general, moderate to good yields of 78-91% were obtained under the standard reaction conditions (**3a**-**3u**). The reaction conditions were suitable for a variety of aromatic amines containing electron-donating group (Me) on the phenyl ring as well as electron-withdrawing (F Cl, Br, and NO_2) on the phenyl ring (**3b**-**3l**). The reaction conditions were suitable for a variety of disulfides and anilines to give products (**3m**-**3u)**. The steric effects were negligible and the 4-(2-chlorophenyl) substituted disulfide gave the target product **3m** in 82% yield Unfortunately, the cross-coupling reaction of 2,2'-dithiodipyridine or diphenyl disulfide with aniline failed to obtain the desired product **3v** or **3w** by using CuCl as the accelerator, but we recovered the starting material 2,2'-dithiodipyridine and diphenyl disulfide concurrently.

Further experiments were performed to explore the C-N coupling reaction of disulfides with aliphatic amines under the optimal conditions (**Scheme 3**). Cyclic aliphatic amines including morpholine and piperidine reacted smoothly with disulfides to give the corresponding amination products **5a**-**5i** in good yields. Besides, we also attempted to apply other kinds of aliphatic amines in this reaction, such as benzylamine,

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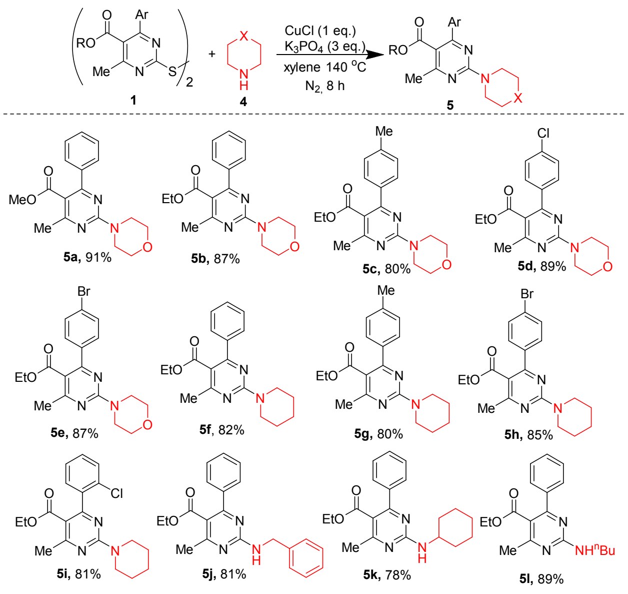
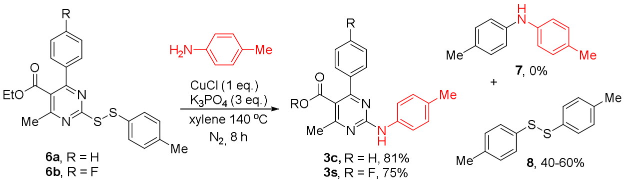
cyclohexylamine, *n*-butylamine, and obtained satisfactory results yielding the products **5j-5l** in high yield.



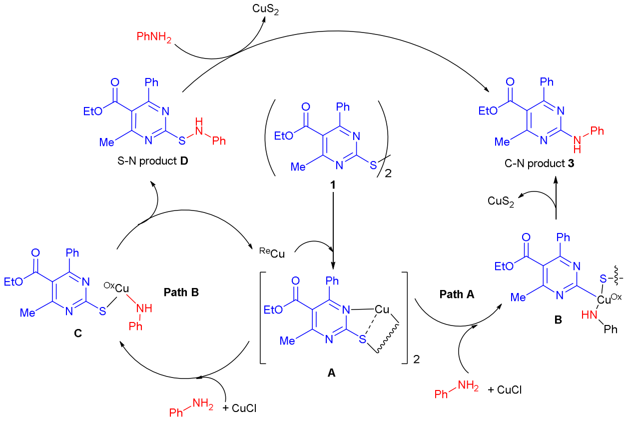
Scheme 3. The cross-coupling reactions of disulfides with aliphatic amines.

After the tests towards symmetrical diheteroaryl disulfides, an unsymmetrical disulfide **6a** and **6b** as a reaction substrate was examined.[19] When the reaction of **6a** with **2b** was performed under optimized conditions, the corresponding **3c** was obtained in a high yield of 81% with the formation of diaryl disulfide **8**, but the diaryl amine **7** was not detected. Similarly, using disulfide **6b** as substrate gave the corresponding **3s** (75%) and **8** (**Scheme 4**).



Scheme 4. Cross-coupling of unsymmetrical disulfides.

Based on these experimental results, it can be informed that pyrimidine-containing disulfides are more efficient than aryl disulfides in the reaction, which may be due to the coordination of a soft basic atom (such as N atom) to the copper salt promoting C-S activation to give the C-N cross-coupling products. Therefore, we proposed two possible mechanisms path A and path B (**Scheme 5**). The formal transition state for the reaction of C-N coupling is proposed as **A**[20], in which the sulfur atoms of both difulfide moiety and nitrogen atom of pyrimdine ring are coordinated to the Cu(I). Subsequently, in path A, the complex **A** react with amine by an oxidative addition generating the intermediate species **B**, which subsequently undergoes reductive cleavage of the C-S bond forming the corresponding C-N coupling products. Possibly, CuS_2 formed in this reaction due to that catalytic amount of copper could not furnished product in high yield. Furthermore, an excess loading of CuCl such as 2 eq. could not improve the product yield compared with those of 1 eq. CuCl (Table 1, entry 10 vs entry 6). In path B, the intermediate **A** subsequently occurs oxidative addition to form intermediate species **C**, which subsequently undergoes S-N coupling leading to the formation of the corresponding S-N coupling product **D**. Possibly, the C-S coupling products can convert to the C-N product with formation of CuS_2 instantly, which was proven by our previous work.[21]



Scheme 5. Possible mechanism for the C-N coupling reaction of disulfides with amines.

Conclusion

Compared with our previous method for the synthesis of C2-amino functionalized pyrimidines using 2-methylsulfonyl-pyrimidines[17] or pyrimidin-2-yl tosylates as the starting materials,[18a-c] the cross-coupling of disulfides with anilines performs some unique advantages. First, 1,2-di(pyrimidin-2-yl) disulfides is more available from DHPMs in a one-pot reaction with yield (up to 90%). Second, the cheaper CuCl was used instead of palladium and ligand. Finally, the process proved to be broad in scope, not only tolerating aromatic amines, but also aliphatic amines.

In summary, we developed an efficient method for C-N bond formation through the cross-coupling of disulfides with anilines under ligand-free conditions involving the cleavage of the C-S bond of 1,2-di(pyrimidin-2-yl) disulfides by amines. The use of a copper salt such as CuTC or CuCl was necessary for efficient formation of the C-N bond in this C-N coupling reaction. The reaction tolerated a wide substrate scopes. Further investigating on the effect of the copper(I) on the reaction and the C-N coupling reaction of other nitrogen-containing aromatic disulfides as substrates with amines is being carried out in our laboratory

Acknowledgements

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19 Procedures for the synthesis of unsymmetrical disulfides **6a** and **6b**: the mixture of ethyl 6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5 mmol), *p*-toluenethiol (5 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (5 mmol) and NaH (5 mmol) in dioxane (15.0 mL) in 100 mL round-bottom flask was stirred at rt for 5 min. Then, 2 mL diluted hydrochloric acid was added to the mixture to quench the reaction and extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/ petroleum ether 1:10) to give the product.

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