# Copper Mediated Coupling of 2-(Piperazine)-pyrimidine Iodides with Aryl Thiols using Cu(I)Thiophene-2-carboxylate

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## Abstract

A copper-mediated synthesis of diaryl sulfides utilizing Cu(I)-thiophene-2-carboxylate (CuTC) is described. We demonstrate the use of CuTC as a soluble, non-basic catalyst in the coupling of aryl iodides and aryl thiols in the synthesis of synthetically advanced diaryl sulfides. This method allows for the successful coupling of challenging substrates including *ortho*-substituted and heteroaryl iodides and thiols. Additionally, most of the aryl iodide substrates used here contain the privileged piperazine scaffold bound to a pyrimidine, pyridine, or phenyl ring and thus this method allows for the elaboration of complex piperazine scaffolds into molecules of biological interest. The method described here enables the incorporation of late-stage structural diversity into diaryl sulfides containing the piperazine ring, thus enhancing the number and nature of derivatives available for SAR investigation.

## Graphical Abstract
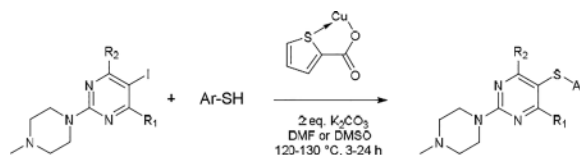


## Keywords

diarylsulfide; thioether; piperazine; CuTC

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The synthesis of aryl sulfides has been a major focus in organic chemistry in recent years because of their presence as intermediates in numerous biologically and pharmaceutically active molecules as well as in organic materials.[1] A number of drugs in such diverse therapeutic areas as cancer, Alzheimer's and Parkinson's disease, diabetes, inflammation, immune and infectious diseases contain the aryl sulfide moiety.[1d, e] Since Migita and co-

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workers reported the first Pd-catalyzed cross-coupling reaction of aryl iodides and bromides with thiols,[2] numerous reports have described transition-metal mediated synthesis of C(aryl)-S bonds through the coupling of thiols with aryl halides (iodides, bromides, chlorides) or pseudohalides (triflates). In addition to Pd,[3] other metals including Cu,[1c, 4] Ni,[5] Co,[6] and Fe[7] have been used to effect this transformation. A number of useful protocols exist for each of these metals, typically in combination with a chelating ligand and a base. Of these, Cu-based methods offer some distinct advantages including functional simplicity, high substrate tolerance and low cost.[8] Numerous copper-based procedures for the coupling of thiols with aryl halides are known including CuI/neocuproine,[4b] CuI/ethylene glycol,[4c] CuI/N-methylglycine or N,N-dimethylglycine,[4e] CuI/*cis*-1,2-cyclohexanediol.[9] Additionally, ligand-free procedures are known utilizing CuO nanoparticles[4a, 10] or CuI in NMP.[11]

Our interest in this chemistry originates from efforts directed towards the synthesis of purine-scaffold heat shock protein 90 (Hsp90) inhibitors, whereby the key step was a C(aryl)-S(aryl) transformation.[12] CuI/neocuproine catalyzed coupling of 8-mercaptoadenine to aryl iodides enabled the efficient creation of a library of 8-arylsulfanyl adenine derivatives as intermediates for Hsp90 structure activity relationship (SAR) studies.[12b, c] More recently, we have been engaged in the discovery of heat shock protein 70 (Hsp70) inhibitors and have reported a class of 2,5'-thiodipyrimidine and 5-(phenylthio)pyrimidine inhibitors.[13] As before, the key step in the synthesis of these molecules involved the formation of a C(aryl)-S(aryl) bond. The coupling of *p*-methoxybenzyl (PMB)-protected 2-amino-5-iodopyrimidine **1** with thiol **2** was successfully accomplished with 20 mol% CuI/20 mol% neocuproine and $K_2CO_3$ after heating at 120 °C in DMSO for 16 h to yield disulfide **3** in 65% yield (Scheme 1). **3** was a key intermediate in SAR efforts which resulted in compound **4**, a potent allosteric inhibitor of Hsp70 (Scheme 1). It also led to the identification of *N*-methylpiperazine as a favorable moiety in this series of compounds. However, attempts to couple 2-*N*-methylpiperazine-5-iodopyrimidines with a variety of thiols under the same conditions were not as successful. Generally, the reaction could be made to proceed but required excess CuI and neocuproine (≥ 30 mol%). Also, due to the basic nature of both desired product and neocuproine, as well as the increased amount of CuI, we found it difficult to purify the resulting product. Based on these results, we surmised that the reaction was hampered by chelation of copper by the *N*-methylpiperazine moiety. We also attempted this with little success using some established protocols including CuI/ethylene glycol,[4c] CuI/*cis*-1,2-cyclohexanediol,[9] and Pd₂(dba)₃/Xantphos.[3b] As a result, we sought an alternative method for coupling 2-*N*-methylpiperazine-5-iodopyrimidines to aryl thiols.

Since ligands function by chelating and solubilizing the metal, we hypothesized that more soluble copper sources such as copper(I) acetate (CuAc) or copper(I)-thiophene-2-carboxylate (CuTC) would yield better results. In an initial experiment evaluating these two as possible catalysts in the synthesis of **5** we found that CuTC was superior to CuAc in promoting the reaction. Whereas the reaction was incomplete with 1 eq. CuAc, the use of 0.3 eq. CuTC resulted in complete conversion to **5** in 74% yield (Table 1). CuTC represents an electron rich and soluble copper source that has previously been used in diverse organic transformations. For instance, it has been used in Stille cross-coupling of aryl-, heteroaryl- and alkenylstannanes with alkenyl and aryl iodides,[14] to prepare thioethers from the reaction

of boronic acids with N-thioimides,[4g] in Ullmann-like reductive coupling of substituted aromatic iodides and bromides, 2-iodoheteroaromatics, and alkenyl iodides,[15] synthesis of ketones by coupling of thiol esters and boronic acids,[16] and synthesis of 1-sulfonyl-1,2,3-triazoles from *in situ* generated copper(I) acetylides and sulfonyl azides.[17] CuTC is a stable, dry, free flowing powder that is commercially available from a number of vendors.

The standard protocol we developed to ensure complete reaction consisted of heating a mixture of aryl iodide (1 eq.), aryl thiol (1.2 eq.), CuTC (0.4 eq.) and $K_2CO_3$ (2 eq.) at 120–130 °C in DMF or DMSO for 3–24 h (Scheme 2).[18] DMSO was used as solvent only in cases of thiopyrimidines which displayed limited solubility in DMF (see entry **8**, **15–17**, **24**, **27**). It should be noted that conditions were not optimized for reaction time. Using this general method, we were able to synthesize a variety of diaryl sulfides in good to moderate yields (Table 1–5). The scope of aryl iodide explored here include 2-*N*-methylpiperazine-5-iodopyrimidines (Table 1–2), 2-piperazine-5-iodopyrimidines (Table 3), 5-iodouracils (Table 4), 2-*N*-methylpiperazine-5-iodopyridines and 2-*N*-methylpiperazine-5-iodophenyls (Table 5). These were coupled to a variety of aryl thiols including substituted benzene, pyrimidine and pyridine.

5-Iodopyrimidines containing methoxy (**5–8**) or benzyloxy (**9–17**) substituted at 4-position were efficiently coupled to a variety of mercaptobenzenes and mercaptopyrimidines in yields ranging from 64–92% (Table 1). A range of thiols were used and remarkably the reaction was not adversely affected by *ortho*-substitution. For example, comparison of entry **11** (82%), **12** (76%), and **14** (82%) shows no decrease in yield upon substitution of 4-mercaptobenzonitrile with one or two methyl groups in the *ortho*-position. This reaction was also tolerant of steric hindrance on the iodopyrimidine as the 4,6-dimethoxy (**18–19**) and 4,6-dimethyl (**20–21**) derivatives could also be prepared in yields ranging from 65–83% (Table 2). We were also able to successfully synthesize piperazine derivatives **22–24** (Table 3) in 47–73% yield.

As further example of the utility of this method we were able to couple 5-iodouracil and 5-iodo-4-trifluoromethyluracil to 4-mercaptobenzonitrile to give **25** and **26** in 66 and 86% yield, respectively (Table 4). We were also able to couple 2-amino-5-iodopyrimidin-4-ol to 4-mercaptobenzonitrile to give **27** in 46% yield. Finally, we wanted to investigate the effect of changing the pyrimidine group of the aryl iodide to pyridine or phenyl (Table 5). We found that the reaction was still successful with pyridine [either when $X_1$=N, $X_2$=C (entry **28–30**) or $X_1$=C, $X_2$=N (entry **31**)] or phenyl (entry **32–33**) iodides. In the case of pyridine, the yields ranged from 74 to 85% (entry **28–31**) while in the case for phenyl the yields were 47 to 82% (entry **32–33**). Direct comparison of coupling with 4-mercaptobenzonitrile shows similar yields with pyrimidine **11** (82%), pyridine **28** ($X_1$=N, $X_2$=C; 85%), pyridine **31** ($X_1$=C, $X_2$=N; 82%) and phenyl **32** (82%), highlighting the broad substrate scope that can be successfully coupled in good yield using this method.

In summary, we report the synthesis of synthetically advanced diaryl sulfides through CuTC-mediated coupling of aryl iodides and aryl thiols. The couplings shown here include *ortho*-substituted and heteroaryl substrates, which are generally known to pose significant challenges.[8] Additionally, most of the aryl iodides exemplified here contain a piperazine ring

which is significant because it is considered a privileged scaffold and as such is a common motif in medicinal chemistry.[19] The piperazine group can positively impact drug-like characteristics of molecules and enhance pharmacokinetic properties by improving water solubility and metabolic stability. The method described here allows for the ability to incorporate late-stage structural diversity into diaryl sulfides containing the piperazine ring and thus enhancing the diversity of derivatives available for SAR investigation. Therefore, we believe this method may be of great value and have broad appeal to medicinal chemists and other researchers engaged in SAR investigations.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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18. *General procedure:* A mixture of aryliodide (1 eq.), arylthiol (1.2 eq.) and $K_2CO_3$ (2 eq.) in DMF or DMSO was evacuated and backfilled with argon. CuTC (0.4 eq.) was added and evacuated and backfilled with argon. The reaction mixture was heated at 120–130 °C for 3–24 h under argon. Solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the desired product.

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**Highlights**

- A novel copper-mediated synthesis of synthetically advanced diaryl sulfides utilizing CuTC

- CuTC is a soluble, non-basic catalyst used to couple aryl iodides and aryl thiols to diaryl sulfides

- Coupling of challenging substrates including *ortho*-substituted and heteroaryl iodides and thiols

- Incorporation of late-stage structural diversity into diaryl sulfides containing the piperazine ring
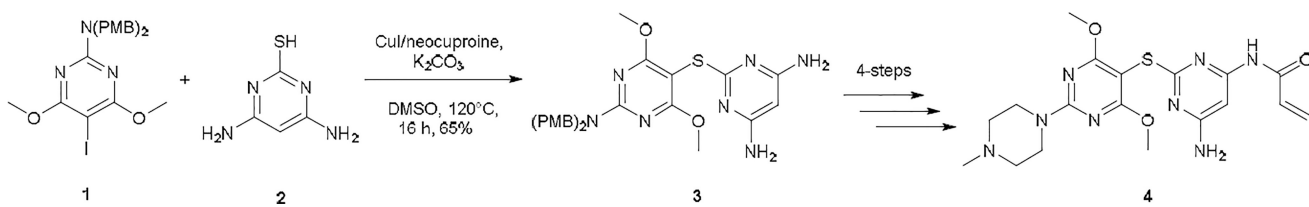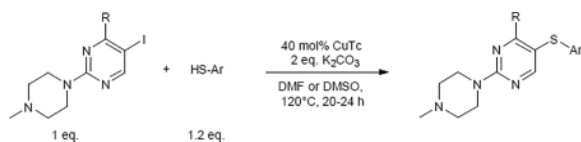
**Scheme 1.**
CuI/neocuproine catalyzed coupling of PMB-protected 2-amino-5-iodopyrimidine **1** with thiol **2** to give **3** and conversion to the Hsp70 allosteric inhibitor **4**.
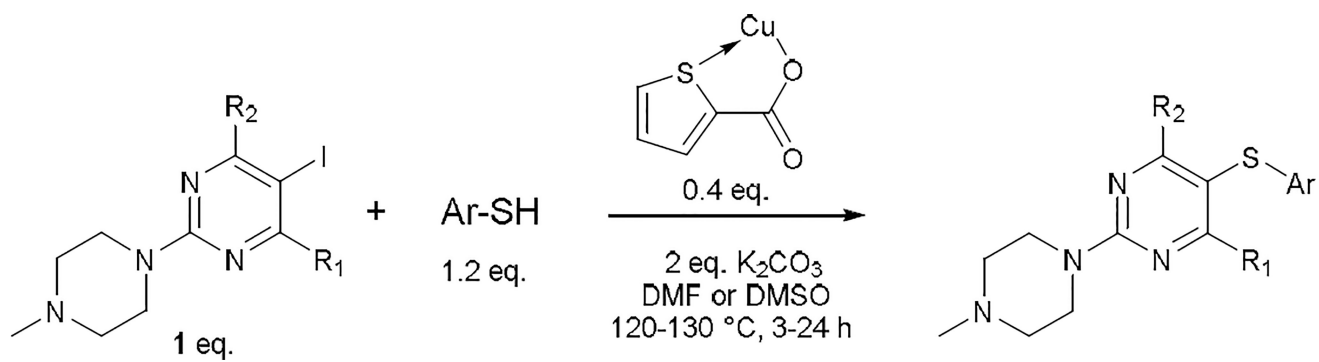
**Scheme 2.**
Standard protocol for the CuTC-promoted coupling of aryl iodide with arylthiol.

**Table 1**

CuTC promoted coupling of 4-substituted 2-*N*-methylpiperazine-5-iodopyrimidines with arylthiols.
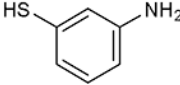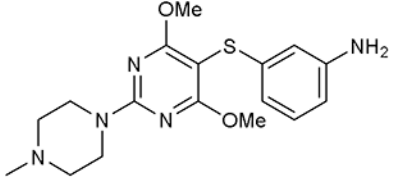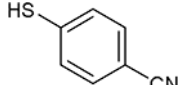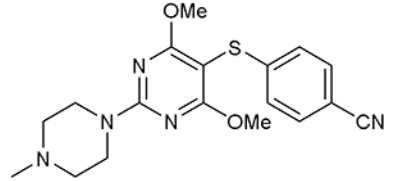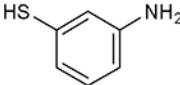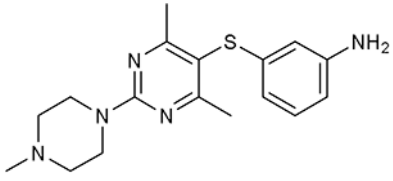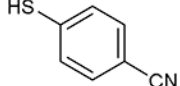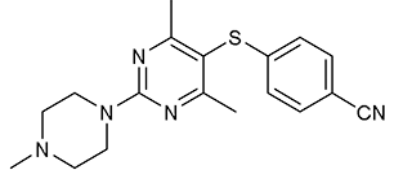


| entry | R | HS-Ar | product | % yield |
|-------|---|-------|---------|---------|
| 5 | OMe |  |  | 74[a] |
| 6 | OMe |  |  | 76 |
| 7 | OMe |  |  | 68 |
| 8 | OMe |  |  | 73 |
| 9 | OBn |  |  | 79 |
| 10 | OBn |  |  | 75 |
| 11 | OBn |  |  | 82 |
| 12 | OBn |  |  | 76 |
| 13 | OBn |  |  | 78 |

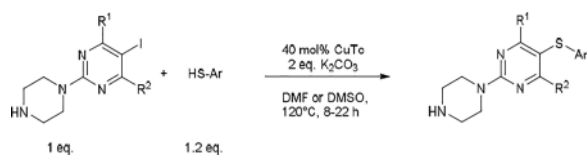| entry | R | HS-Ar | product | % yield |
|-------|---|-------|---------|---------|
| **14** | OBn | | | 82 |
| **15** | OBn | | | 92 |
| **16** | OBn | | | 64 |
| **17** | OBn | | | 76 |
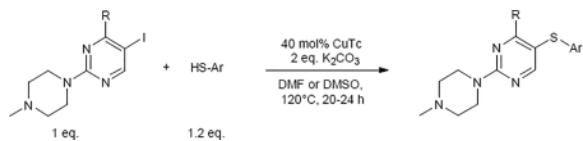
[a]0.3 eq. CuTC used.

**Table 2**

CuTC promoted coupling of 4,6-disubstitued 2-*N*-methylpiperazine-5-iodopyrimidines with arylthiols.
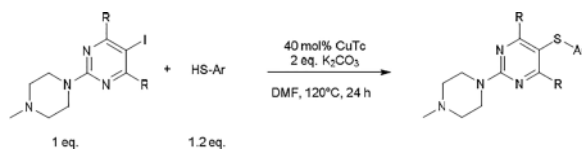


| entry | R | HS-Ar | product | % yield |
|-------|-----|-------|---------|---------|
| 18 | OMe |  |  | 71 |
| 19 | OMe |  |  | 72 |
| 20 | Me |  |  | 65 |
| 21 | Me |  |  | 83 |

**Table 3**

CuTC promoted coupling of 2-piperazine-5-iodopyrimidines with arylthiols.



| entry | R¹, R² | HS-Ar | product | % yield |
|-------|--------|-------|---------|---------|
| 22 | OBn, H |  |  | 73 |
| 23 | OMe, OMe |  |  | 47 |
| 24 | OMe, OMe |  |  | 54 |

**Table 4**

CuTC promoted coupling of 5-iodouracils with arylthiols.
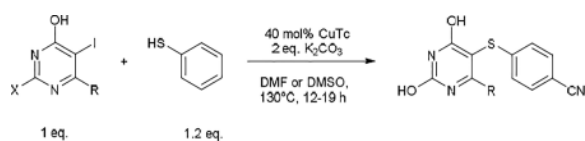


| entry | X | R | product | % yield |
|---|---|---|---|---|
| **25** | OH | H |  | 66 |
| **26** | OH | CF$_3$ |  | 86 |
| **27** | NH$_2$ | H |  | 46 |

**Table 5**

CuTC promoted coupling of 4-benzyl 2-*N*-methylpiperazine-5-iodopyridine or -phenyl with arylthiols.
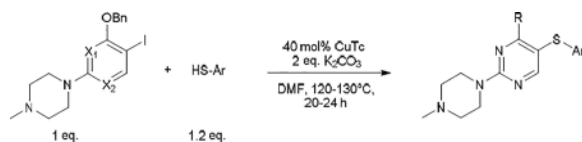


| entry | X₁, X₂ | HS-Ar | product | % yield |
|-------|--------|-------|---------|---------|
| 28 | N, C | | | 85 |
| 29 | N, C | | | 74 |
| 30 | N, C | | | 77 |
| 31 | C, N | | | 82 |
| 32 | C, C | | | 82 |
| 33 | C, C | | | 47 |