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N-heterocyclic carbene copper(I) complex-catalyzed direct C–H thiolation of benzothiazoles

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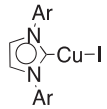
ABSTRACT

N-heterocyclic carbene (NHC) copper(I) complexes based on imidazol-2-ylidene and 1,2,3-triazol-5-ylidene catalyzed the direct C–H thiolation of benzothiazoles and benzoxazoles with aryl and alkyl thiols to give 2-aryl and 2-alkylthiobenzothiazoles in moderate-to-good yields. The NHC copper(I) complex [(IPr)CuI] was the most effective catalyst for the reaction among the NHC–Cu(I) complexes examined in this study.

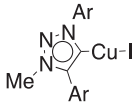
C–S bond formation represents a key step in the synthesis of aryl and heteroaromatic sulfides, which are biologically and pharmaceutically important compounds and functional materials.[1] A direct method for the formation of C–S bond is cross-coupling reaction of organic halide or organometallic compounds with organic thiol (or disulfide).[2] An alternative method is direct C–H thiolation of aromatic compounds, which does not require the presence of reactive functional groups such as halogens or metal moieties. Direct C–H thiolation was not known before Yu and co-workers succeeded in copper-catalyzed thiolation of 2-phenylpyridine under oxygen, where thiolation occurred at the ortho position of the phenyl ring.[3] Some other thiolation reactions based on the ortho-directing group-assisted C–H activation have been reported.[4] As an unassisted direct C–H thiolation method, we developed direct C–H thiolation of benzoxazoles using a CuI/2,2′-bipyridine complex under oxygen. In this reaction, thiolation occurred at the 2-position of benzoxazoles to give 2-thioethers.[5] Subsequently, other research groups expanded the copper-mediated direct C–H thiolation to arenes and heteroarenes.[6] Very recently, copper-catalyzed direct thiolation of pentafluorobenzene was reported, where thiolation proceeded through C–H and C–F bond activation.[7] Other metal complex catalysts in addition to copper complex have been developed for the C–S coupling reaction via direct C–H functionalization of arenes.[8]

Hou and Nolan research groups independently reported the direct C–H carboxylation of azoles using imidazolylidene carbene copper (NHC–Cu) complexes,[9] which was followed by our work demonstrating that 1,2,3-triazolylidene carbene copper complexes (*tz*NHC–Cu; this type of NHC is abbreviated as *tz*NHC to distinguish it from conventional NHCs) worked more effectively than the corresponding NHC–Cu complexes in carboxylation with benzothiazole.[10] Because a stoichiometric amount of CuI/2,2′-bipyridine complex is required for the thiolation with benzothiazole and imidazole, we are interested in NHC–Cu and *tz*NHC–Cu complexes as alternative copper catalysts for the C–H thiolation of azoles with aryl thiols.[11] We report here the direct C–H thiolation of benzothiazoles using a catalytic amount of NHC–Cu and *tz*NHC–Cu complexes.

We first examined the time-dependent yield of the C–H thiolation of benzothiazole using various NHC–CuI and *tz*NHC–CuI complexes as well as CuI to evaluate their catalytic activities (Fig. 1). In the procedure, copper complex (20 mol % relative to the amount of benzothiazole) and K_2CO_3 (two equivalents relative to the amount of benzothiazole) were added to a vial, followed by benzothiazole (**1a**), thiophenol (**2a**) (2 equiv relative to the amount of benzothiazole), and dimethylformamide (DMF) (Scheme 1). The vial was



(IPr)CuI: Ar = 2,6-Dipp
(IMes)CuI: Ar = Mes



(TPr)CuI: Ar = 2,6-Dipp
(TMes)CuI: Ar = Mes

Figure 1. NHC–CuI and *tz*NHC–CuI complexes.

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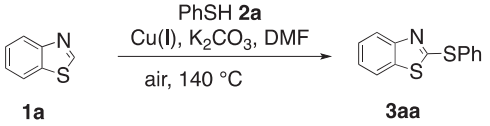


Scheme 1. Direct C–H thiolation of benzothiazole with thiophenol.

heated at 140 °C in the presence of air for a predetermined time. After the reaction was quenched with water, the product was extracted with ethyl acetate, and the yield was determined by GC using biphenyl as an internal standard. The yields obtained by different catalysts are shown in Figure 2 as a function of reaction time.

(IPr)CuI and (IMes)CuI, and (TPr)CuI, and (TMes)CuI were examined as typical NHC–Cu and *tz*NHC–Cu complexes, respectively. As seen in Figure 2, when (IPr)CuI (■)was used as a catalyst, the reaction was fastest and its yield reached 95% after 3 h of reaction time, while the reaction with (IMes)CuI (▲) reached a plateau after 6 h, giving a maximum yield of 85%. In the reaction with (TPr)CuI (□), the yield increased almost linearly and reached 95% after 7 h. The reaction rate with (TMes)CuI (△) was moderate and similar to (IMes)CuI, and the yield reached approximately 80% after 7 h. Interestingly, ligand-free CuI (○) also catalyzed the reaction, although it was earlier reported that CuI did not catalyze the direct thiolation of benzothiazole in the presence of K_3PO_4 in DMSO at 100 °C. The reaction was faster than those with (TMes)CuI, (IMes)-CuI, and (TPr)CuI, but slower than that with (IPr)CuI. Thus, (IPr)CuI was revealed to be the most active copper complex. NHC–CuI Mediated the reaction at a catalytic amount and completed it in 6–7 h, while the earlier reaction with CuI/2,2′-bipyridine was stoichiometric and required 24 h for the completion in heated DMF.[6d]

The reaction without the copper(I) catalyst or with the ligand only (IPr·HCl) gave 12% and 21% yields under the same reaction conditions, respectively. These control experiments showed that the base (K_2CO_3) and/or ligand may mediate the reaction, but they are not essential for it. When the reaction was carried out using 10 mol % of (IPr)CuI, the yield dropped to 55%; hence, 20 mol % catalyst loading was necessary to obtain a satisfactory yield. The reaction in the absence of air in a sealed tube resulted in 10% yield indicating that oxygen was necessary for the reaction.

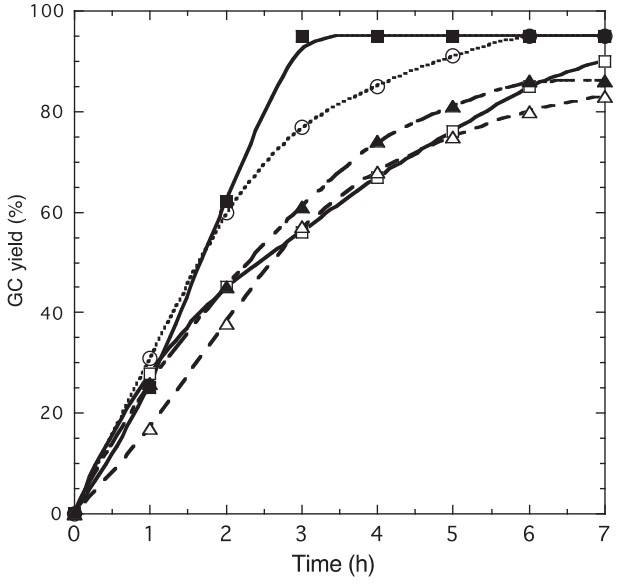
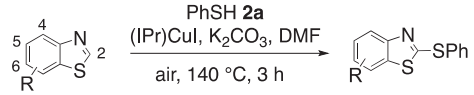


Figure 2. Reaction yield (%) as a function of time for copper-catalyzed direct arylation of benzothiazole with benzenethiol in the presence of different catalysts: ■(IPr)CuI, ▲(IMes)CuI, □(TPr)CuI, △(TMes)CuI, and ○CuI.

The scope of substituted benzothiazoles (**1b–i**) was examined by using the most effective catalyst (IPr)CuI (20 mol %) and thiophenol **2a** as a reactant in DMF at 140 °C with 3 h of reaction time.[12] The results are summarized in Table 1. The reactions of 4- and 6-substituted benzothiazoles were examined. Electron-donating substituents at 4- and 6-positions gave lower (moderate) yields than the electron-neutral substituents, regardless of their position; thus, the position of the substituent hardly affected the reaction (entries 2–5). 4- and 6-Chlorobenzothiazoles (**1f**,**g**) tolerated the thiolation and the reaction involved only the 2-oxazole carbon to give the corresponding thioethers (**3fa–3ga**) in good yields (entries 6 and 7). On the other hand, the reaction with 6-bromobenzothiazole produced a significant amount of **3aa** which resulted from reduction of the bromo group of thiolation product **3ha**. The reaction with 6-nitrobenzothiazole **1i** gave hardly any product (entry 9).

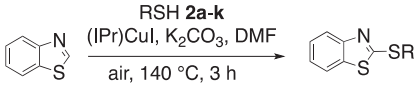
Table 1
Direct thiolation of substituted benzothiazoles with thiophenol[a]



Entry	R	Product, yield[b] (%)
1	**1a**, H	**3aa**, 81
2	**1b**, 6-Me	**3ba**, 59
3	**1c**, 4-Me	**3ca**, 46
4	**1d**, 6-MeO	**3da**, 61
5	**1e**, 4-MeO	**3ea**, 62
6	**1f**, 6-Cl	**3fa**, 82
7	**1g**, 4-Cl	**3ga**, 70
8	**1h**, 6-Br	**3ha**, 66[c]
9	**1i**, 6-NO_2	**3ia**, 0

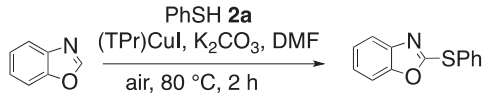
[a] Compounds **1b–h** (0.25 mmol), PhSH **2a** (0.50 mmol), K_2CO_3 (0.50 mmol), (IPr)CuCl (0.05 mmol), DMF (1.5 mL); 140 °C, 3 h.
[b] Isolated yield.
[c] Other product is **3aa** (ca. 10%).

Table 2
Direct thiolation of benzothiazole with various thiols[a]



Entry	R	Product, yield[b] (%)
1	**2a**, C_6H_5	**3aa**, 81
2[c]	**2b**, 4-MeC_6H_4	**3ab**, 80
3[c]	**2c**, 2-MeC_6H_4	**3ac**, 78
4	**2d**, 4-MeOC_6H_4	**3ad**, 66[d]
5	**2e**, 4-$NH_2C_6H_4$	**3ae**, 24
6	**2f**, 4-FC_6H_4	**3af**, 38
7	**2g**, 4-ClC_6H_4	**3ag**, 31
8	**2h**, 4-BrC_6H_4	**3ah**, 22
9[c]	**2i**, 2-$C_{10}H_7$	**3ai**, 68
10	**2j**, *n*-$C_{10}H_{13}$	**3aj**, 36
11	**2k**, Cy	**3ak**, 33

[a] Compounds **1a** (0.25 mmol), **2a–l** (0.50 mmol), K_2CO_3 (0.50 mmol), (IPr)CuCl (0.05 mmol), DMF (1.5 mL); 140 °C, 3 h.
[b] Isolated yield.
[c] 0.75 mmol of thiol was used.
[d] Other product is 4-methoxythioanisole.



4 5

Scheme 2. Direct C–H thiolation of benzoxazole **5** with thiophenol.

Table 2 summarizes the scope of alkyl and arylthiol substrates (**2a**–**i**) using **1a** as a reactant under the optimal reaction conditions. Both alkyl and aryl thiols could be coupled with **1a** to give the corresponding thioethers **3aa**–**3ak** in low-to-good yields. The reaction with thiophenols bearing electron-donating substituents such as 4-methyl (**2b**) and 2-methyl (**2c**) groups gave the corresponding thioethers in good yields (entries 2 and 3) using excess of thiols (three equivalent to **1a**). In the reaction with 4-methoxythiophenol (**2d**), the by-production of 4-methoxythioanisole was observed, decreasing the yield of the thiolation product (entry 4).[13] The reaction with amino-substituted benzenethiol (**2e**) gave the desired thiolation product as a sole product, but in low yield. No coupling product with the amino group was observed by GC/MS analysis (entry 5); the reaction proceeded chemoselectively with the thiol group.[14] 4-Fluorothiophenol (**2f**) reacted with **1a** to give the corresponding 4-fluorophenyl thioether **3af** in low yield (entry 6). Notably, the coupling reaction proceeded chemoselectively in the reaction with 4-chlorothiophenol (**2g**) or 4-bromothiophenol (**2h**) to give the corresponding 4-chlorophenyl or 4-bromophenyl thioethers **3ag**–**3ah** in low yields (entries 7 and 8). The reaction with halogenated arylthiols was carried out at extended reaction times (15 h) to improve the product yield, but without success (yields were 32–38%). The reaction of alkylthiols such as *n*-decyl and cyclohexylthiol with **1a** gave the corresponding 2-alkylthiobenzothiazoles **3ai**–**ak** in low yields (entries 9 and 11).

NHC–Cu complexes could be applied to the direct thiolation of benzoxazole **4** when the reaction was carried out in DMF at 80 °C for 2 h using (TPr)CuI as a catalyst and K_2CO_3 as a base, and the reaction with thiophenol quantitatively gave the corresponding thioether **5** (Scheme 2).

In conclusion, NHC–CuI is a useful catalyst in the direct C–H thiolation of benzothiazoles and benzoxazoles with aryl and alkylthiols, and various substituted 2-arylthio-benzothiazoles and benzoxazoles can be readily prepared in moderate-to-good yields in air.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.104.

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