CuI-Catalyzed Coupling Reactions of Aryl Iodides and Bromides with Thiols Promoted by Amino Acid Ligands

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Abstract: Novel mild conditions for the CuI-catalyzed coupling reactions of aryl iodides and bromides with aliphatic and aromatic thiols using amino acids as the ligand are reported.

Key words: copper iodide, aryl sulfide, cross-coupling, amino acid ligand

Transition-metal mediated C(aryl)-sulfur bond formation is an important reaction in synthetic organic chemistry because aryl sulfides and their sulfone derivatives are of great significance to the pharmaceutical industry.¹ However, only a few studies have been reported so far for the formation of aryl-sulfur bonds using either Pd or Ni catalysts.^{2,3} Alternatively, one can use Cu catalysts to mediate the C–S bond formation. This approach is attractive from an industrial perspective because Cu is much less expensive and toxic than Pd and Ni.⁴

The traditional Cu-mediated couplings between thiols and aryl halides require the use of copper salts in greater than stoichiometric amounts, polar solvents such as HMPA, and high temperatures around 200 °C.⁵ Recently, Venkataraman et al. reported an improved protocol for the coupling between aryl iodides and thiols using 10 mol% CuI and 10 mol% neocuproine, with NaOt-Bu as the base, in toluene at 110 °C.⁶ Buchwald et al. also reported an efficient Cu-catalyzed C–S coupling reaction between aryl iodides and thiols using 5 mol% CuI and 2 equivalents of HOCH₂CH₂OH as ligand.⁷ Wu and He then reported that microwave heating could enhance the CuI-catalyzed C-S couplings.⁸ Naus et al. successfully utilized the CuI catalyst for the arylation of 1-thiosugars.⁹

We were interested in finding more and better catalystligand systems for the Cu-catalyzed C-S coupling reactions. We were also interested in using aryl bromides, which are less expensive but also less reactive than aryl iodides, as the reactant for the coupling reactions. Thus we paid attention to a special group of ligand, i.e. amino acids. Any coupling reactions that can use amino acids as ligand would be very interesting because of the following reasons: (1) the amino acid ligand is inexpensive, conveniently available, and environmentally benign; and (2) there are a large number of different amino acids that can be tried. As to Cu(I)-catalyzed coupling reactions, Ma et al. reported that amino acids could accelerate the Cu-catalyzed coupling reactions between aryl halides and themselves.¹⁰ They found very recently that amino acids could also serve as ligands for the coupling reactions of other nucleophiles including amines and phenols.¹¹ At the same time we reported that amino acids could promote the CuI-catalyzed amidation reactions.¹² Herein, we report novel, mild conditions for the CuI-catalyzed coupling reactions of aryl iodides and bromides with thiols using amino acids as the ligand.

In the first stage of the study we focused on the coupling between thiophenol and iodobenzene. A variety of experimental conditions were examined (see Table 1). The

 Table 1
 CuI-Catalyzed Coupling Reaction of Thiophenol and Iodobenzene under Various Conditions^a

HS + I	Condition	\bigcup

Entry	Base	Ligand	Solvent ^b	Yield (%) ^c
1	K ₃ PO ₄	N-methyl glycine	Dioxane	79
2	K ₂ CO ₃	N-methyl glycine	Dioxane	76
3	NaH	N-methyl glycine	Dioxane	<5
4	КОН	N-methyl glycine	Dioxane	96
5	CaO	N-methyl glycine	Dioxane	19
6	NaOH	N-methyl glycine	Dioxane	87
7	КОН	N-methyl glycine	DMF	95
8	КОН	N-methyl glycine	THF	67
9	КОН	N-methyl glycine	Toluene	90
10	КОН	Glycine	Dioxane	66
11	КОН	N,N-dimethyl glycine	Dioxane	90
12	КОН	α-alanine	Dioxane	75
13	КОН	β-alanine	Dioxane	77

^a General conditions: 5 mol% CuI, 20 mol% ligand, 10 mL solvent, 5 mmol Ph-I, 6 mmol PhSH, 12.5 mmol KOH, reaction time = 24 h. ^b Reaction temperature: 100 °C for dioxane, 120 °C for DMF, and 70 °C for THF.

^c Isolated yield.

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highest yield (96%) was obtained when we used 5 mol% CuI as the catalyst, 20 mol% *N*-methyl glycine as the ligand, KOH as the base, and dioxane as the solvent. Other bases, including K_3PO_4 , K_2CO_3 , NaH, CaO, and NaOH, provided lower yields. Dioxane was found to be the best solvent, as DMF, THF, and toluene caused lower yields. Furthermore, using glycine as the ligand gave a yield of 66%. Using α - and β -alanine gave yields around 75%. Using *N*,*N*-dimethyl glycine gave a yield of 90%. Thus, *N*-methyl glycine was concluded to be the optimum amino acid type ligand for aryl thiolation.

Using the CuI/*N*-methyl glycine/KOH/dioxane procedure we studied the C-S coupling reactions between a number of thiols and aryl iodides (see Table 2). It is found that both aliphatic and aromatic thiols can be used in the coupling. The reaction also proceeds well with aryl iodides carrying either electron-donating (e.g. OCH_3) or electronwithdrawing groups (e.g. $COCH_3$). The yields are mostly 90–98%, except for 2-nitrophenol iodide. For this particular case, reduction of the NO₂ group was observed.

The above procedure is clearly successful for the coupling reaction between aryl iodides and thiols. However, using the same procedure for aryl bromide we obtained less than 5% yield (see Table 3). Thus different reaction conditions should be optimized for aryl bromide. For this purpose we increased the amount of CuI to 20 mol% but the yield was only 9%. We also increased the reaction time to 48 hours but the yield was only 12%.

Table 2 CuI-Catalyzed Coupling Reactions of Thiols and Aryl Iodides^a

Entry	Thiols	Aryl Iodide	Product	Yield (%) ^b
1	SH		() ^s ()	96
2	C SH	H ₃ C	C S C CH3	91
3	C SH	H ₃ CO	C S C OCH3	95
4	C SH	H ₃ COC	COCH3	90
5	SH		NO ₂	70
6	SH	Br	S C Br	92
7	H ₃ C SH		H ₃ C S C	97
8	H ₃ C SH	Hac	H ₃ C S C CH ₃	90
9	H ₂ C SH	HaCO	H ₃ C S OCH ₃	93
10	H ₃ C SH	HaCOC	H ₃ C S C COCH ₃	86
11	H ₃ C			68
12	H ₃ C SH	Br	H ₃ C S Br	90

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Entry	Thiols	Aryl Iodide	Product	Yield (%) ^b
13	CI SH			98
14	SH	Hac	CI CH ₃	88
15	SH	H ₂ CO	CI S C OCH3	96
16	SH	H ₂ COC	CI S C COCH	83
17	CI SH			33
18	SH	Pr I		98
19	C ₈ H ₁₇ SH		C ₈ H ₁₇ S	89
20	C ₈ H ₁₇ SH	H	C ₈ H ₁₇ S CH ₃	93
21	C ₈ H ₁₇ SH	H ₂ CO	C ₈ H ₁₇ S OCH ₃	90
22	C ₈ H ₁₇ SH	H-COC	C ₈ H ₁₇ S COCH ₂	90
23	C ₈ H ₁₇ SH		C ₈ H ₁₇ S O ₂ N	<5
24	C ₈ H ₁₇ SH	Br	C ₈ H ₁₇ S Br	92

^a General conditions: 5 mol% CuI, 20 mol% *N*-methyl glycine, 10 mL dioxane, 5 mmol aryl iodide, 6 mmol thiol, 12.5 mmol KOH, reaction time = 24 h, reaction temperature = 100 °C.

^b Isolated yield.

A dramatic increase of the yield to 51% was observed when DMF was used as the solvent instead of dioxane. It was also discovered that change of *N*-methyl glycine to *N*,*N*-dimethyl glycine could increase the yield from 59% to 75%. As it was observed that some DMF decomposed in the presence KOH at 120 °C, we changed the base to K_3PO_4 . The yield under this condition is 85%, which is sufficiently good for synthetic applications.

Using the CuI/N,N-dimethyl glycine/K₃PO₄/DMF procedure we studied the C-S coupling reactions between a number of thiols and aryl bromides (see Table 4). The yields are around 72–85%, which are good enough for many synthetic applications. It is interesting to note that both the bromo and iodo groups in 1-bromo-4-iodo-benzene can participate in the C-S coupling reaction in a onepot fashion. Moreover, the chloro group in 4-chloro-benzenethiol does not show any significant coupling. Therefore, the present condition is not sufficient for the C-S coupling reactions using aryl chlorides as reactants.

At present the mechanism of the Cu-catalyzed coupling reaction is not completely clear.¹³ Nonetheless, the results from the present study are consistent with the mechanism in which a four-coordinated Cu(III) intermediate is involved (See Scheme 1).¹³ According to the mechanism, the role of the amino acid ligand in the reaction is either to promote the oxidative addition of ArX to the Cu(I) species or to stabilize the Cu(III) intermediate.

Table 3 CuI-Catalyzed Coupling Reaction of Thiophenol and Bromobenzene under Various Conditions^a

HS $+$ Br $ -$							
Entry	CuI (%)	Base	Ligand	Solvent ^b	Time (h)	Yield (%) ^c	
1	5	КОН	N-methyl glycine	Dioxane	24	<5	
2	5	КОН	N-methyl glycine	Dioxane	48	12	
3	20	КОН	N-methyl glycine	Dioxane	24	9	
4	5	КОН	N-methyl glycine	DMF	24	51	
5	20	КОН	N-methyl glycine	DMF	48	59	
6	5	КОН	N,N-dimethyl glycine	DMF	48	69	
7	20	КОН	N,N-dimethyl glycine	DMF	48	75	
8	20	K ₃ PO ₄	N,N-dimethyl glycine	DMF	48	85	

^a General conditions: 20 mol% ligand, 10 mL solvent, 5 mmol Ph-Br, 6 mmol PhSH, 12.5 mmol base.

 $^{\rm b}$ Reaction temperature is 100 °C for dioxane and 120 °C for DMF.

^c Isolated yield.



Scheme 1

To summarize, novel mild conditions have been found for the CuI-catalyzed coupling reactions of aryl iodides and bromides with aliphatic and aromatic thiols with amino acids as the ligand. The coupling yields are 90–98% for aryl iodides and 72–85% for aryl bromides. We are working now on the Cu-catalyzed coupling reactions using aryl chlorides as reactants. Another challenge is how to use less expensive copper salts such as Cu₂O in the reaction.

Representative Procedure

An oven-dried three-neck flask was charged with CuI (0.25 mmol, 5.0 mol%), benzenethiol (6.0 mmol), *N*-methyl glycine (1.0 mmol, 20 mol%) and KOH (12.5 mmol), evacuated and backfilled with nitrogen. Aryl iodide (5.0 mmol) and dioxane (10.0 mL) were added under nitrogen. The reaction mixture was refluxed for 24 h. The resulting suspension was cooled to r.t. and filtered through a 2–3 cm pad of silica gel eluting with 100 mL of EtOAc. The filtrate was concentrated and the residue was purified by chromatography to afford pure product.^{14,15}

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Entry	Thiols	Aryl Bromide	Product	Yield (%) ^b
1	SH	Br	C ^s C	85
2	SH	Br	↓ S C	80
3	SH	Br	$O^{s}O_{s}O$	85
4	H ₂ C SH	Br	Hac	76
5	H ₃ C SH	Br	S C CH ₃	78
6	H ₃ C SH	Br	H ₃ C S C S C CH ₃	72
7	CI SH	Br		80
8	CI	Br	S C CI	75
9	CI SH	Br		80
10	C ₈ H ₁₇ SF	Br	C ₈ H ₁₇ S	82
11	C ₈ H ₁₇ S⊦	Br	SC ₈ H ₁₇	76
12	C ₈ H ₁₇ S⊦	Br	C ₈ H ₁₇ S SC ₈ H ₁₇	84

Table 4 CuI-Catalyzed Coupling Reactions of Thiols and Aryl Bromides^a

^a General conditions: 20 mol% CuI, 20 mol% *N*,*N*-dimethyl glycine, 10 mL DMF, 5 mmol aryl bromide, 6 mmol thiol (or 12 mmol for 1-bromo-4-iodobenzene), 12.5 mmol K_3PO_4 (or 25 mmol for 1-bromo-4-iodobenzene), reaction time = 48 h, 120 °C. ^b Isolated yield.

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- (14) All the products are known compounds except for 1,4bis(octylthio)benzene.
- (15) 1,4-Bis(octylthio)benzene: White solid. IR: 2954, 2921, 1465, 1113, 803 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ = 7.23 (s, 4 H), 2.88 (t, *J* = 7.3 Hz, 4 H), 1.63 (m, *J* = 6.8 Hz, 4 H), 1.40–1.26 (br m, 20 H), 0.88 (t, *J* = 6.4 Hz, 6 H). ¹³C NMR (300 MHz, CDCl₃): δ = 134.6, 129.8, 34.2, 32.0, 29.32, 29.29, 29.0, 22.8, 14.2. MS (EI): *m/z* (relative intensity): 366 (100), 254 (25), 142 (35). Anal. Calcd for C₂₂H₃₈S₂: C, 72.06; H, 10.46. Found: C, 72.20; H, 10.58.