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Optimization of the Conditions for Copper-Mediated *N*-Arylation of Heteroarylamines

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Simple and inexpensive copper-mediated *N*-arylation of heteroarylamines was achieved by using *N*,*N*′-dimethylethylenediamine as a ligand and K_2CO_3 as a base in dioxane heated at 100 °C. In this coupling reaction, the influence of the copper species, ligand, base and solvent was investigated in detail. *N*-Arylated derivatives of several heteroarylamines were synthesized under optimized reaction conditions, and all the products were isolated in good yields. By controlling the amount of CuI/DMEDA added, heteroarylamines with weak nucleophilic activity were coupled with aryl iodides or aryl bromides. The activity of the copper catalyst for this C–N bond-forming reaction follows the order $Cu^{I} > Cu^{0} > Cu^{II}$.

Introduction

As well as being important synthetic intermediates, *N*-arylheteroarylamines serve as the pharmacophore in many natural and synthetic biologically active compounds, such as STI571 (Imatinib or Gleevec),[1] BMS354825 (Dasatinib),[2] RO438596,[3] GW3733,[4] CGP60474,[5] CL387626 and its analogue RFI641[6] and some interferons (IFN).[7] However, such structures are difficult to prepare directly from heteroarylamines and aryl halides by using traditional Ullmann–Goldberg couplings, possibly due to the weak nucleophilicity of the amine nitrogen atom as a result of the neighbouring heteroatom.

Traditionally, *N*-aryl-2-aminopyrimidines have been prepared by reaction of the enamine derivatives of β-aldehydes or ketones with guanidine derivatives[8] or by reaction of 2-arylsulfonylpyrimidine or 2-alkylsulfonylpyrimidine derivatives with amines.[8c,9] Both of these approaches often require either well-defined starting materials or multistep syntheses, which restrict their use in the synthesis of *N*-arylpyrimidine analogues. In the last decade, palladium-catalyzed C–N bond formation (Buchwald–Hartwig reaction) has been extensively developed.[10] Because of the simplicity of such a palladium-catalyzed coupling reaction, this approach was immediately used in the synthesis of *N*-arylheteroarylamines,[11] and a number of heteroarylamines, including 2-aminopyridines, 2-aminothiazoles and their analogues, have been arylated by using this method with the use of organophosphorus reagents as the ligands.[12] However, problems, such as the high cost of palladium and the use of toxic organophosphorus reagents, still remain for this method.

In contrast to palladium, copper is an inexpensive and moderately effective catalyst in Ullmann-type coupling reactions, and consequently, it has attracted much attention in the synthesis of *N*-arylheteroarylamines. Copper-catalyzed *N*-arylation of aliphatic amines,[13] arylamines,[14] amides,[15] hydrazides[16] and nitrogen-containing heterocycles[17] has been reported. Joshi[18] and coworkers also reported *N*-arylation of 2-aminopyrimidine derivatives with arylboronic acids in moderate yields by employing a catalytic amount of $Cu(OAc)_2$ at room temperature. Although arylboronic acids are very active substrates, their cost is very high. In addition, Arterburn[19] and Zhang[20] have, respectively, reported their cross-coupling reaction between 2-aminopyrimidine and 1,3-dibenzyl-5-iodouracil in different copper/ligand catalytic systems. Studies on the copper-catalyzed *N*-arylation of arylamine derivatives thus far suggest that only heteroarylamines possessing strongly electron-donating groups or aryl halides possessing strongly electron-withdrawing group can be coupled smoothly. For heteroarylamines with neighbouring nitrogen or sulfur atoms within the aryl ring, it was difficult to perform the *N*-arylation reaction. Therefore, we attempted the coupling reaction in the presence of a copper salt and *N*,*N*′-dimethylethylenediamine (DMEDA) as a ligand. Thus, the reaction conditions for the copper-mediated *N*-arylation of heteroarylamines were optimized. Here we report our investigation and the results of these studies.

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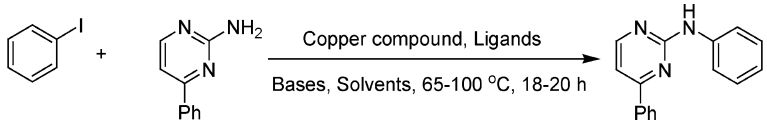
Results and Discussion

Optimization of Reaction Conditions

In a preliminary study, we used iodobenzene and 2-amino-4-phenylpyrimidine as substrates and varied the copper source, ligand, base and solvent in order to find the most effective conditions (Table 1). As anticipated, no desired coupling product was obtained in the absence of copper or ligand (Table 1, Entries 1 and 8). The absence of product was a result of the poor solubility of CuI combined with the low nucleophilicity of the substrates. Upon addition of a strongly electron-donating agent such as DMEDA, however, the reaction mixture quickly turned deep green in colour and the product was obtained in good yield after 22 h. We also found that the catalytic activity of copper source decreased in the order $Cu^{I} > Cu^{0} > Cu^{II}$ (Table 1, Entries 4, 14–18). This observation is consistent with previous reports.[21] Cuprous salts such as CuI and CuCl were the most efficient. Unexpectedly, Cu_2O (Table 1, Entry 19) was almost ineffective under our conditions, whereas Cu powder displayed better efficacy. It is also notable that the stoichiometry of the copper is a key factor in the success of the reaction. For example, the reaction of iodobenzene with 2-amino-4-phenylpyrimidine proceeded smoothly in the presence of CuI (≥0.25 equiv.; Table 1, Entries 4–7). In contrast, less than 10% of the desired product was formed with lower quantities (<10 mol-%) even with increased reaction time and higher temperatures. With regard to the ligand, *N*,*N*′-dimethylethylenediamine was initially selected and employed in the reaction, because it was previously reported to be an excellent ligand in various copper-catalyzed coupling reactions.[15b,21a] Indeed, in our case, it was more effective than other agents, such as L-proline or 1,10-phenanthroline (Table 1, Entries 12–14). Another variable is the base; although K_2CO_3, NaOH and Cs_2CO_3 all proved effective (Table 1, Entries 4, 20 and 21), the yields were higher when K_2CO_3 or Cs_2CO_3were used. Therefore K_2CO_3 was selected as the base of choice due to its cost effectiveness. Other bases tested, including $K_3PO_4{\cdot}3H_2O$, Na_2CO_3, Et_3N and pyridine, were ineffective (Table 1, Entries 22–25). Of the solvents investigated, dioxane was found to be effective, whereas toluene, DMF and DMSO were less effective (Table 1, Entries 28–30). Moreover, the reaction in THF required long reaction times, presumably

Table 1. Optimization of reaction conditions.



Entry	Catalyst [equiv.]		Ligand	Base	Solvent	Time[h]	Yield [%][a]
1	–	–	DMEDA	K_2CO_3	dioxane	18	0[b]
2	CuI	0.05	DMEDA	K_2CO_3	dioxane	22	<5[b]
3	CuI	0.1	DMEDA	K_2CO_3	dioxane	22	<10[b]
4	CuI	0.25	DMEDA	K_2CO_3	dioxane	18	86
5	CuI	0.5	DMEDA	K_2CO_3	dioxane	14	89
6	CuI	1.0	DMEDA	K_2CO_3	dioxane	14	87
7	CuI	2.0	DMEDA	K_2CO_3	dioxane	14	89
8	CuI	0.25	–	K_2CO_3	dioxane	18	0[b]
9	CuI	0.25	DMEDA	K_2CO_3	dioxane	18	68[c]
10	CuI	0.25	DMEDA	K_2CO_3	dioxane	18	65[d]
11	CuI	0.25	DMEDA	K_2CO_3	dioxane	18	71[e]
12	CuI	0.25	L-proline	K_2CO_3	dioxane	18	<15[b]
13	CuI	0.25	1,10-phenanthroline	K_2CO_3	dioxane	18	<10[b]
14	CuCl	0.25	DMEDA	K_2CO_3	dioxane	18	85
15	Cu powder	0.25	DMEDA	K_2CO_3	dioxane	18	46
16	$CuSO_4$	0.25	DMEDA	K_2CO_3	dioxane	18	26
17	$Cu(OAc)_2$	0.25	DMEDA	K_2CO_3	dioxane	18	31
18	$CuBr_2$	0.25	DMEDA	K_2CO_3	dioxane	18	27
19	Cu_2O	0.25	DMEDA	K_2CO_3	dioxane	18	<5[b]
20	CuI	0.25	DMEDA	NaOH	dioxane	18	81
21	CuI	0.25	DMEDA	Cs_2CO_3	dioxane	18	88
22	CuI	0.25	DMEDA	$K_3PO_4{\cdot}3H_2O$	dioxane	18	<2[b]
23	CuI	0.25	DMEDA	Na_2CO_3	dioxane	18	<3[b]
24	CuI	0.25	DMEDA	Et_3N	dioxane	18	<2[b]
25	CuI	0.25	DMEDA	pyridine	dioxane	18	<4[b]
26	CuI	0.25	DMEDA	K_2CO_3	*n*-butanol	18	<4[b]
27	CuI	0.25	DMEDA	K_2CO_3	THF	48	56[f]
28	CuI	0.25	DMEDA	K_2CO_3	toluene	18	61
29	CuI	0.25	DMEDA	K_2CO_3	DMF	18	53
30	CuI	0.25	DMEDA	K_2CO_3	DMSO	18	34

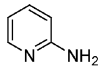
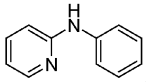
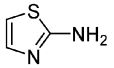
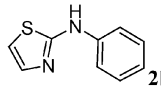
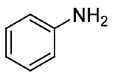
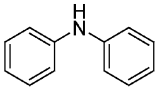
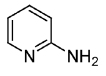
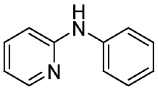
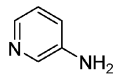
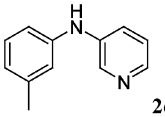
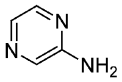
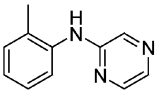
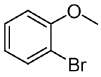
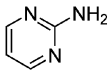
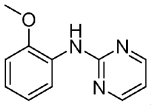
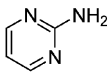
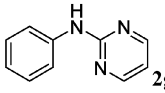
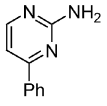
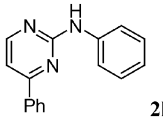
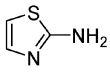
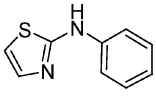
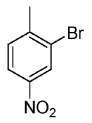
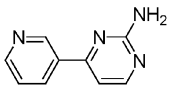
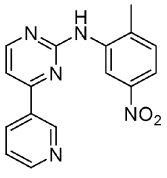
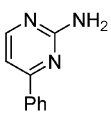
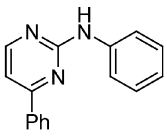
[a] Isolated yields (average of two runs). [b] GC yields (average of two runs). [c] Performed in air. [d] Performed in the presence of H_2O (2.0 equiv.). [e] Performed with a catalyst/ligand ratio of 1:2. [f] Performed at 65 °C.

because the temperature of this system is too low (Table 1, Entry 27), and *n*-butanol was ineffective (Table 1, Entry 26). The impact of water and oxygen were also studied (Table 1, Entries 9 and 10). Pleasingly, only a slightly lower yield of product was obtained in the presence of air or H_2O (2 equiv.).This implies that this procedure has potential use in large-scale industrial applications.

Results of the Copper-Mediated *N*-Arylation of Heteroarylamines

Further investigation of the reaction of iodobenzene with other heteroarylamines, as well as aniline, under the optimized conditions was also undertaken (Table 2). It was found that both aniline and 2-aminopyridine can be trans-

Table 2. Copper-mediated *N*-arylation of heteroarylamines.

Entry	ArX	$ArNH_2$	Product	Equiv. of CuI/DMEDA	Time [h]	Yield [%][a]
1			 **2a**	0.25	20	83
2			 **2b**	1.0	22	78
3			 **2c**	0.10	21	84
4			 **2a**	0.50	24	83[b]
5			 **2d**	0.25	22	81[b,c]
6			 **2e**	0.35	24	74[b,c]
7			 **2f**	0.50	24	70[[b,c,d]
8			 **2g**	0.50	22	78[b,c,d]
9			 **2h**	0.25 0.50 1.0	24 24 24	< 10 77[b,c,d] 69[c,d]
10			 **2b**	0.50	24	62[b,c,d]
11			 **2i**	0.50	24	82[b,c,d]
12			 **2h**	0.25 1.0	30 48	< 5[b,c,d,e]

[a] Isolated yields (average of two runs). [b] Aryl halide (1.5 mmol). [c] KI (2.0 equiv.). [d] Heteroarylamine (1.0 mmol). [e] GC yields (average of two runs).

formed smoothly into the desired adducts (Table 2, Entries 1 and 3). However, 2-aminothiazole as a substrate gives low yields (<5%) under the same conditions. When CuI/DMEDA (1:1, 1.0 equiv.) was employed, product **2b** was generated in 78% yield (Table 2, Entry 2). It is known that the nucleophilicity of the amine decreases in the order aniline > 2-aminopyridine > 2-aminothiazole. We discovered that these amines required 0.1, 0.25, and 1.0 equiv., respectively, of the CuI/EMEDA catalyst to accomplish the reaction. These results imply that more nucleophilic amines react more readily with the aryl halide. In contrast, the use of bromobenzene instead of iodobenzene resulted in a decreased yield under the same reaction conditions (Table 2, Entry 10). Nevertheless, the addition of KI (2.0 equiv.) [17c]or CuI/DMEDA (1.0 equiv.) under the same conditions resulted in the efficient transformation of a range of bromides into the desired products in moderate-to-good yields (Table 2, Entry 4–11). Amination of chlorobenzene was unsuccessful under the same conditions, even with prolonged reaction times and greater quantities of CuI/DMEDA (Table 2, Entry 12). It is noteworthy that *N*-(2-methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (Table 2, Entry 11), an important intermediate in the synthesis of the anticancer drug Imatinib, was first synthesized by this Cu-catalyzed C–N bond-forming reaction. Additionally, we also found that steric hindrance persists in this system. For example, when the amination of 2-bromo-4-nitrotoluene was carried out, an increased amount of 2-bromo-4-nitrotoluene (1.5–2.0 equiv.) and a longer reaction time were required (Table 2, Entry 11). Diarylation products were detected in almost all reactions, but in this case, no bis(arylated) product was detected because of the sterically hindered nature of 2-bromo-4-nitrotoluene.

Conclusions

We developed a mild, convenient and inexpensive copper-catalyzed system for the *N*-arylation of heteroarylamines. By using this protocol, heteroarylamines were coupled with aryl iodides and aryl bromides in good yields. The right combination of copper source, ligand, base and solvent, and the amount of CuI/DMEDA was the key in the amination reaction of aryl iodides and aryl bromides. The activity of the copper catalyst decreases in the order $Cu^{I} > Cu^{0} > Cu^{II}$. Aryl iodides react more readily with heteroarylamines than aryl bromides. Phenyl chloride showed very low reactivity towards heteroarylamines. For most heteroarylamines, the high nucleophilicity of the amino group resulted in facile coupling with aryl halides. The important compound, *N*-(2-methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine, an intermediate in the synthesis of Imatinib, was first prepared by copper-mediated *N*-arylation of heteroarylamines in 82% yield, under these optimized conditions. In comparison to the conventional, Pd-catalyzed protocol, we anticipate that such a copper-catalyzed approach could be see wider application in the fields of medicinal chemistry and pesticide synthesis.

Experimental Section

General: All reactions were carried out under a nitrogen atmosphere in oven-dried, Schlenk-type glassware. Elemental analyses were performed with an Elementar Vario EL III. IR spectra were recorded with a Bruker Equinox-55. ^{1}H NMR spectra were recorded with a Varian Inova 400 MHz instrument with chemical shifts reported relative to tetramethylsilane (TMS). GC–MS spectra were recorded with a Varian 3800 spectrometer. Gas chromatography analyses were performed with a Hewlett Packard 5890 instrument. All materials were weighed in the open atmosphere. Flash column chromatography was performed with silica gel (100–200 mesh). All reagents were purchased from commercial suppliers and used without further purification.

General Procedure for the copper-Mediated *N*-Arylation of Heteroarylamines: The heteroarylamine (1.1 mmol), CuI (0.019–0.19 g, 0.1–1.0 mmol) and anhydrous K_2CO_3 (0.276 g, 2.0 mmol) were added to a Schlenk-type, three-neck flask fitted with a thermometer, magnetic stirbar and septum. The flask was evacuated and back filled with nitrogen gas three times. Dioxane (5 mL), aryl halide (1.0 mmol) and DMEDA (0.1–1.0 mmol) were added by syringe at room temperature. The reaction mixture was stirred at 100 °C for 20 h and then cooled to room temperature. Concentrated ammonia (4 mL) and a saturated solution of NaCl (20 mL) were added, and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was concentrated in vacuo, and the residue was purified by column chromatography on silica gel.

***N*-Phenylpyridin-2-amine (2a):** M.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 4.0 Hz, 1 H), 7.48–7.53 (m, 1 H), 7.26–7.34 (br. m, 4 H), 7.06–7.08 (br. m, 1 H), 6.89 (d, J = 8.4 Hz, 1 H), 6.73–6.76 (m, 1 H), 6.69 (s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3223, 3174, 3096, 3006, 1592, 1529, 1492, 1464, 1325, 1152, 988, 769, 747, 694, 510 cm^{-1}. MS: m/z = 170 $[M]^+$, 169 $[M - 1]^+$. $C_{11}H_{10}N_2$ (170.21): calcd. 77.62, H 5.92, N 16.46; found C 77.49, H 5.90, N 16.53.

***N*-Phenylthiazol-2-amine (2b):** M.p. 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.16 (s, 1 H), 7.64 (d, J = 7.8 Hz, 2 H), 7.28 (t, J = 7.6 Hz, 2 H), 7.24 (d, J = 3.6 Hz, 1 H), 6.92 (t, J = 7.2 Hz, 1 H), 6.89 (d, J = 3.6 Hz, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3410, 3290, 3140, 3120, 3082, 1598, 1520, 1496, 1460, 1330, 990 cm^{-1}. MS: m/z = 176 $[M]^+$. $C_9H_8N_2S$ (176.24): calcd. C 61.34, H 4.58, N 15.90; found C 61.15, H 4.24, N 16.03.

***N*,4-Diphenylpyrimidin-2-amine (2h):** M.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (t, J = 7.2 Hz, 1 H), 7.19 (d, J = 4.8 Hz, 1 H), 7.38 (t, J = 7.8 Hz, 2 H), 7.52 (t, J = 3.0 Hz, 4 H), 7.72 (d, J = 10.8 Hz, 2 H), 8.09–8.08 (m, 2 H), 8.49 (s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3432, 3254, 3113, 1609, 1580, 1557, 1494, 1438, 1403, 1333, 752, 690 cm^{-1}. MS: m/z = 247 $[M]^+$, 246 $[M - 1]^+$. $C_{16}H_{13}N_3$ (247.30): calcd. C 77.71, H 5.30, N 16.99; found C 77.68, H 5.36, N 16.86.

***N*-(2-Methyl-5-nitrophenyl)-4-(pyridin-3-yl)pyrimidin-2-amine (2i):** M.p. 194–195 °C. ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 9.34 (s, 1 H), 9.28 (s, 1 H), 8.81 (dd, J = 7.2, 2.4 Hz, 1 H), 8.72 (d, J = 4.4 Hz, 1 H), 8.64 (d, J = 4.8 Hz, 1 H), 8.50 (d, J = 8.0 Hz, 1 H), 7.91 (dd, J = 8.4, 2.0 Hz, 1 H), 7.52–7.61 (m, 3 H), 2.44 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 3441, 3253, 3097, 1584, 1557, 1534, 1407, 1346, 792, 735, 698, 651 cm^{-1}. MS: m/z = 307 $[M]^+$, 292, 260, 246. $C_{16}H_{13}N_5O_2$ (307.31): calcd. C 62.53, H 4.26, N 22.79; found C 62.72, H 4.31, N 22.66.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for arylation products **2c**–**g**.

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