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Copper (I) iodide - catalyzed Amidation of Phenylboronic acids /Aryl Bromides Using 4-Dimethylaminopyridine as Ligand

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Abstract

An efficient one-pot synthesis of *N*-arylbenzamide is described via reaction between Phenylboronic acid/arylbromide with benzamide in the presence of CuI (5 mol%) as catalyst, 4-dimethylaminopyridine (20 mol%) as the ligand, and Cs_2CO_3 (2 mmol) as the base. This protocol was applied to synthesize a small library of *N*-arylbenzamide in high yields.

KEYWORDS: Copper (I) iodide, 4-dimethylaminopyridine, Phenylboronic acid, benzamide, *N*-arylbenzamide

INTRODUCTION

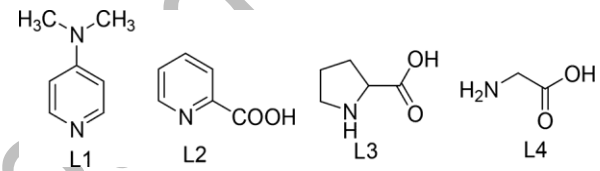
***N*-Aryl amides** are important structural motifs widely employed in the fields of pharmaceutical chemistry and materials science.[1] As a more efficient and facile method, the transition metal-catalyzed coupling reaction of arylboronic acid / aryl halides and

amides has been attractive for many years.[2] The Cu-promoted amide arylation synthesis was pioneered by Ullmann type reactions (Goldberg reaction) and Chan-Lam-type reactions more than one hundred years ago.[3] Till date many reports are available for the construction of *N*-aryl amides. Recently Stephen L. Buchwald et. al reported C–N bond forming reaction between aryl halides and amides catalyzed by copper(I) iodide.[4] Palladium-catalyzed cross coupling reactions are widely used alternation for similar C–N bond formation.[5] However, traditional C–N bond formation reactions are usually carried out under harsh conditions, which limit its broad application in organic synthesis. In recent decades, the ligand-assisted copper-catalyzed amidation of aryl halides has aroused great interest among organic chemists as a practical and efficient method for the construction of C-N bonds.[6] The use of this strategy in the Goldberg reaction greatly simplifies the synthesis of *N*-aryl amides [Scheme 1].[7] However, these protocols suffered from the limitation of harsh conditions, tedious synthetic procedures, and unsatisfactory yields. Therefore, there is a need to develop more economical, eco-friendly, and potential alternative methods for the synthesis of *N*-aryl amides. Catalytic activity of 4-dimethylaminopyridine DMAP has been well explored in organic synthesis.[8] However, there are a very few reports on the use of DMAP as a ligand for metal catalyzed cross-coupling reaction.[9]

It has been observed that Cu-based catalytic systems are found to be very attractive because of their low cost and low toxicity. Herein, we report novel and direct synthesis of *N*-arylamides from phenyl boronic acid / arylbromide using DMAP as a Ligand and employing CuI as the catalyst.

RESULT AND DISCUSSION

In an initial trial, we examined the reaction of benzamide (1a) with phenylboronic acid (2a) in the presence of various catalysts. By surveying different reaction conditions, the results are summarized in Table-1. The reaction was first tested with various terminal catalysts such as CuI, CuBr and $CuCl_2$. Among them, CuI was efficient for the reaction, giving **3a** in 81% yield (Table-1, entry 4). The other copper halides CuBr and $CuCl_2$ were totally ineffective for the reaction (Table-1, entries 10 & 11). Next, the reaction was tested with various bases such as K_2CO_3, K_3PO_4, Na_2CO_3 and Cs_2CO_3. Among the bases tested, Cs_2CO_3 was most effective. The other bases K_2CO_3, K_3PO_4 & Na_2CO_3 were less effective giving **3a** in 45%, 56% and 40% yields, respectively (Table-1, entries 1, 2 & 3). After screening, the reaction was examined by using different ligands and L1 was found to be most effective affording the desired product in 81% yield (Table 1, entry 4).



Other ligands did not make the reaction more effective, such as L2, L3 and L4 (Table-1, entries 5, 6 &7). Next, the reaction was tested with various phenylboronic acids, aryl bromides and aryl chlorides. Among them phenylboronic acids and aryl bromides results in good yields (Table 1, entries 4 and 9). In order to maximize the yield and to reduce the reaction time, we have optimized the reaction conditions. Thus, we investigated the effect of various solvents such as DMF, DMA, DMSO, Toluene and THF. Among them, DMF was more effective for the reaction, giving **3a** in 81% yield (Table 2, entry 5). Other

solvents such as DMA and DMSO were less effective, providing **3a** in 51% and 70% yields, respectively (Table-2, entries 2 and 3). The other solvents such as toluene, THF and DCM were less effective (Table-2, entries 1, 4 and 6).

By considering the optimized reaction conditions, the substrate scope was studied. As examined in Table 3, it was found that various substrates were converted into the corresponding products with excellent yields under the optimum conditions. Benzamides having electron-donating groups gave slightly lower yields (Table-3, entry 10) when compared to Benzamides having electron-withdrawing groups. Next, different phenylboronic acids and aryl halogens were investigated as the reaction substrates (Table 3). In general , the reactions of benzamide with various phenylboronic acid derivatives with an electron- withdrawing (such as NO_2) substituent gave higher yields of C-N arylated products than those with an electron-donating groups (such as CH_3, OCH_3) on the aromatic ring gave moderate to good yields. The Cu Catalyzed reaction of aryl bromide gave slightly lower yields. For example, arylation of benzamide with phenylboronic acid and bromobenzene furnished *N*-phenylbenzamide in 81% and 78% yield respectively (Table-3, entry 1 & 15).

EXPERIMENTAL

Melting points were recorded on a Mel-Temp melting point apparatus, in open capillaries and are uncorrected ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AMX 300 MHz NMR spectrometer using TMS as internal standard and the values for chemical shifts (δ) being given in ppm and coupling constants (*J*) in Hertz

(Hz). Mass spectra were recorded on an Agilent 1100 ESI. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively. Other chemicals were purchased from Sigma Aldrich and used without further purification.

General Experimental Procedure For The Synthesis Of 3a

A mixture of benzamide (1.8 mmol), phenylboronic acid (1.7 mmol) or arylbromide (1.7 mmol), DMF (5 ml), CuI (5 mol %) DMAP (20 mol %) and Cs_2CO_3 (1 mmol) was heated to 80^{o}C for 30 minutes under O_2 atmosphere . After completion of the reaction as monitored by TLC, reaction mixture was cooled to room temperature, aqueous Na_2CO_3 solution (10 ml) was added and extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude. The crude was purified by silica gel column chromatography using EtOAc : hexane (3:7) as eluents to afford pure (**3a**).

CONCLUSION

In conclusion, we have developed a simple, efficient and eco-friendly convenient general method for the synthesis of *N*-arylbenzamide from phenylboronic acid / arylbromide and benzamide, using DMF as a solvent and employing CuI as the catalyst and under mild conditions. This method provided structurally diverse *N*-arylbenzamides in very good to excellent yields. *N*-arylbenzamides derivatives are biologically and pharmaceutically active molecules, and therefore, the present protocol could be of wide application in medicinal chemistry and organic chemistry.

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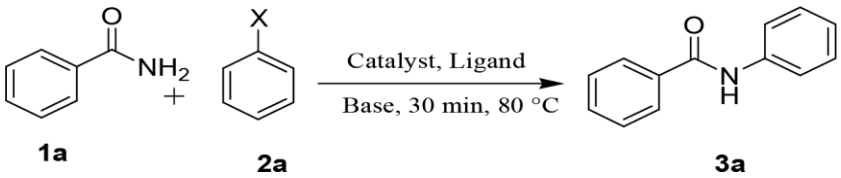
Table 1: Effect of various catalysts in the synthesis of **3a**[a]



1a **2a** **3a**

Entry	Catalyst (mol%)	Ligand	X	Base	Yield (%)[b]
1	CuI	L_1	$B(OH)_2$	K_2CO_3	45
2	CuI	L_1	$B(OH)_2$	K_3PO_4	56
3	CuI	L_1	$B(OH)_2$	Na_2CO_3	40
4	CuI	L_1	$B(OH)_2$	Cs_2CO_3	81(80,68)[c]
5	CuI	L_2	$B(OH)_2$	Cs_2CO_3	15
6	CuI	L_3	$B(OH)_2$	Cs_2CO_3	12
7	CuI	L_4	$B(OH)_2$	Cs_2CO_3	26
8	CuI	L_1	Cl	Cs_2CO_3	NR[d]
9	CuI	L_1	Br	Cs_2CO_3	78
10	CuBr	L_1	$B(OH)_2$	Cs_2CO_3	NR[d]
11	$CuCl_2$	L_1	$B(OH)_2$	Cs_2CO_3	NR[d]

[a]Reaction conditions: **1a** (1.8 mmol), **2a** (1.7 mmol), Catalyst (5 mol%), Ligand (20 mol%), Base (1.0 mmol), DMF (5 ml) and temperature 80 °C, under O_2 atmosphere.

[b]Isolated yield after column chromatography.

[c]Isolated yields at 90 ^oC and 70 ^oC, respectively.

[d]No reaction.

Table 2: Effect of various solvents in the synthesis of **3a**[a]

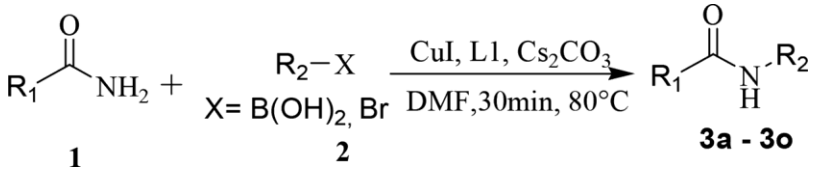
Entry	Solvent	Time (min)	Yield (%)[b]
1	Toluene	45	32
2	DMA	48	51
3	DMSO	43	70
4	THF	50	30
5	DMF	30	81[c]
6	DCM	30	43

[a]Reaction conditions: **1a** (1.8 mmol), **2a** (1.7 mmol), CuI (5 mol%), DMAP (20 mol%), Cs_2CO_3 (1.0 mmol), Solvent (5 ml) and temperature 80 °C, under O_2 atmosphere.

[b]Isolated yield after column chromatography.

[c]Entry 4, Table 1

Table 3: Synthesis of various substituted *N*-arylbenzamide from the corresponding phenylboronic acids/arylbromides and benzamides.[a]



1 **2** **3a - 3o**

Entry	R_1	R_2	X	Product	Yield (%)[b]
1	Ph	Ph	$B(OH)_2$	**3a**	81[c]
2	Ph	4-MePh	$B(OH)_2$	**3b**	84
3	Ph	4-OMePh	$B(OH)_2$	**3c**	86
4	Ph	4-NO_2Ph	$B(OH)_2$	**3d**	89
5	Ph	2-ClPh	$B(OH)_2$	**3e**	80
6	Ph	3-ClPh	$B(OH)_2$	**3f**	86
7	Ph	4-ClPh	$B(OH)_2$	**3g**	86
8	4-NO_2Ph	Ph	$B(OH)_2$	**3h**	91
9	4-MePh	Ph	$B(OH)_2$	**3i**	80
10	4-MePh	4-MePh	$B(OH)_2$	**3j**	81
11	4-MePh	4-OMePh	$B(OH)_2$	**3k**	81
12	4-MePh	4-NO_2Ph	$B(OH)_2$	**3l**	86
13	4-MePh	3-ClPh	$B(OH)_2$	**3m**	85
14	4-MePh	4-ClPh	$B(OH)_2$	**3n**	84
15	Ph	Ph	Br	**3a**	78
16	Ph	4-ClPh	Br	**3g**	81
17	Ph	4-FPh	Br	**3o**	85

18	Ph	4-NO_2Ph	Br	**3d**	83
19	4-CH_3Ph	Ph	Br	**3i**	72
20	4-CH_3Ph	4-BrPh	Br	**3n**	76
21	4-CH_3Ph	3-ClPh	Br	**3m**	74

[a]Reaction conditions: **1** (1.8 mmol), **2** (1.7 mmol), CuI (5 mol%), DMAP (20 mol%), Cs_2CO_3 (1.0 mmol), DMF (5 ml) and temperature 80°C, under O_2 atmosphere.

[b]Isolated yield

[c]Entry 4, Table 1

Scheme 1. Preparation of substituted *N*-Arylbenzamide.