Journal of Medicinal and Chemical Sciences 2019 (2) 38-40

J. Med. Chem. Sci.

Copper-catalyzed Ligand-Free Suzuki–Miyaura Coupling Reaction of Aryl Halides with Arylboronic Acid

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ARTICLE INFO

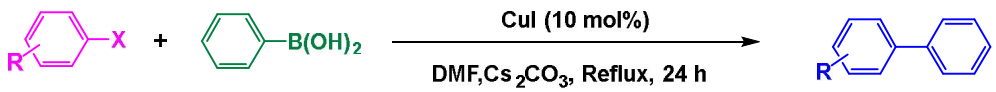
Article history:
Received 8 August 2018
Revised 3 September 2018
Accepted 6 September 2018
Available online 21 October 2018

Keywords:
CuI
Ligand-free
Suzuki–Miyaura Coupling
Aryl halides
Arylboronic acid

ABSTRACT

A highly efficient and ligand-free approach for the Suzuki–Miyaura cross-coupling reaction of aryl halides with arylboronic acid catalyzed by CuI/Cs_2CO_3 in DMF has been developed. Under the described conditions, a category of aryl halides including iodides and bromides, whether electron-rich or electron-deficient, were coupled with arylboronic acid to give the target products (moderate to excellent yields). This catalytic system was less efficient in the reactions of aryl bromides as a higher reaction temperature was required to improve the yield.

GRAPHICAL ABSTRACT



1. Introduction

Carbon-carbon bond formation is very important in organic synthesis due to its presence in natural products and bioactive molecules that have numerous applications in the pharm-aceutical, agrochemical and fine chemical industries.[1-2] Suzuki–Miyaura cross-coupling reaction is one of the powerful tools for the formation of C–C bonds.[3] The Suzuki–Miyaura cross-coupling, generally defined as the transition-metal-catalyzed cross-coupling between an organo-boron compound and an organic (pseudo)halide.[4] It is noteworthy that boron compounds show only low toxicities and the boron-containing by-products can be easily separated from the reaction mixtures.[5-6]

Over the last two decades, palladium-based catalysts have been the most frequently investigated Suzuki–Miyaura cross-coupling. In view of the economy, however, the recovery as well as the recycling of the Pd catalyst is mandatory because of the prices of these catalysts.[7-8] Nowadays, many reactions can be carried out under very mild conditions even at room temperature and in a short time (within only several min-utes).[9]

Recently, Cu is emerging as a viable catalyst for the Suzuki -Miyaura coupling reactions.[10] A number of protocols for Suzuki-Miyaura coupling reactions have been recently reported in literature.[11-14] In this article, we present copper-catalyzed Suzuki-Miyaura coupling of aryl iodides and bromides with arylboronic acids.

2. Result and discussion

In the preliminary stage of investigation, the reaction of 1-iodo-4-methoxy-benzene (**1a**) with phenylboronic acid (2a) was chosen as a model reaction to test the influence of various parameters (**Scheme 1**). As shown in **Table 1**, several catalysts and ligands were tested and the best results were observed when the reaction was performed using CuI as catalyst in the absence of ligand. Also, the results show that DMF and Cs_2CO_3 are the best solvents and base respectively. The results demonstrated that the highest yield of **3a** was obtained when CuI and Cs_2CO_3 was used in DMF (under ligand-free conditions).

Next, the optimized catalytic system was extended to various aryl iodides and bromides (**Scheme 2**), and the results are summarized in **Table 2**. As shown in **Table 2**, a variety of aryl halides including iodides and bromides, whether electron-rich or electron-deficient, were coupled with arylboronic acid to give moderate to excellent yields. It is noteworthy that the best results were obtained when aryl iodides were used as halides.

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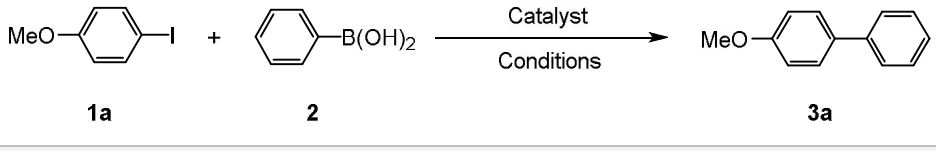
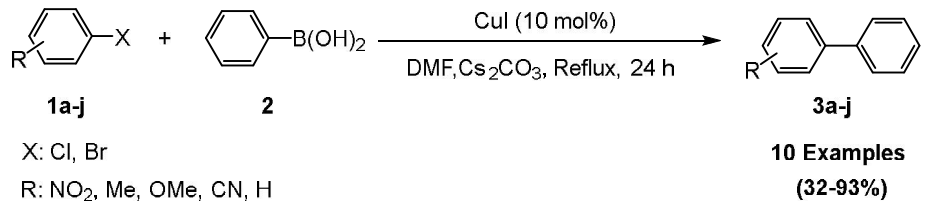


Scheme 1. Optimization of conditions for synthesis of **3a**.

Table 1. Optimization of conditions cross-coupling reaction of 1-iodo-4-methoxybenzene (**1a**) and phenylboronic acid (**2**).[a]

Entry	Catalyst	Ligand	Solvent	Base	Yield (%) [b]
1	CuI	---	DMF	Cs_2CO_3	89
2	CuI	Et_3N	DMF	Cs_2CO_3	76
3	CuI	PPh_3	DMF	Cs_2CO_3	28
4	CuI	TMEDA	DMF	Cs_2CO_3	5
5	--	---	DMF	Cs_2CO_3	NR
6	CuBr	---	DMF	Cs_2CO_3	51
7	$Cu(OAc)_2$	---	DMF	Cs_2CO_3	70
8	CuI	---	THF	Cs_2CO_3	13
9	CuI	---	CH_3CN	Cs_2CO_3	36
10	CuI	---	PhMe	Cs_2CO_3	21
11	CuI	---	DMF	K_2CO_3	32
12	CuI	---	DMF	K_3PO_4	55
13	CuI	---	DMF	t-BuOK	trace

[a] Reaction conditions: 1a (1 mmol), 2a (1.5 mmol), catalyst (10 mol-%), ligand (20 mol-%), and base (1 mmol) in solvent (5 mL) at reflux temperature for 24 h. [b] Isolated yield.



Scheme 2. CuI-catalyzed Suzuki-Miyaura coupling cross-coupling of aryl halides with arylboronic acid.

Table 2. CuI-catalyzed cross-coupling reactions of aryl halides with arylboronic acid.[a]

Entry	ArX	Product	Yield (%) [b]
1	4-$OMeC_6H_5I$	**3a**	89
2	4-$NO_2C_6H_5I$	**3b**	64
3	4-MeC_6H_5I	**3c**	93
4	4-CNC_6H_5I	**3d**	58
5	2-MeC_6H_5I	**3e**	83
6	C_6H_5I	**3f**	85
7	4-$OMeC_6H_5Br$	**3g**	49
8	4-$NO_2C_6H_5Br$	**3h**	32
9	4-MeC_6H_5Br	**3i**	58
10	C_6H_5Br	**3j**	88

[a]All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H-and ^{13}C-NMR spectral analysis and by direct comparison with authentic materials. [b] Isolated yield.

3. Conclusion

In summary, we have developed an inexpensive and efficient method for the CuI-catalyzed Suzuki-Miyaura coupling of aryl halides with arylboronic acid. A variety of aryl halides including iodides and bromides, whether electron-rich or electron-deficient, were all coupled with arylboronic acid to give moderate to excellent yields.However, the described catalytic system was less efficient in the reactions of aryl bromides, and a higher reaction temperature was required to improve the yield.

4. Experimental

4.1. General Procedure for the CuI-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions

A mixture of aryl halides (1mmol), arylboronic acid (1.5mmol), CuI (10 mol%), Cs_2CO_3 (1 mmol) and DMF (5 mL) was stirred under nitrogen at reflux temperature until the starting material was consumed completely, as determined by TLC. The mixture was then filtered, washed with water, extracted with diethyl ether, and the solvent wasevaporated. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired coupled products.

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