Copper-Catalyzed Amidation of Aryl Iodides Using KF/Al₂O₃: An Improved Protocol

Rahman Hosseinzadeh,* Mahmood Tajbakhsh,* Maryam Mohadjerani, Hamidreza Mehdinejad

Faculty of Basic Science, Mazandaran University, Babolsar, Iran Fax +98(11252)42002; E-mail: r.hosseinzadeh@umz.ac.ir *Received 4 February 2004*

Abstract: A mild method for the copper-catalyzed amidation of aryl iodides is reported. This simple C-N bond forming procedure shows that the combination of air stable CuI and 1,10-phenanthroline in the presence of KF/Al_2O_3 comprises an extremely efficient and general catalyst system for the N-amidation of aryl iodides. Different functionalized aryl iodides were efficiently coupled with amides using this method.

Key words: amidation, aryl iodides, copper iodide, potassium fluoride on alumina, coupling reaction

During the past few years significant advances have occurred in the development of cross-coupling methodology. The formation of carbon-nitrogen bonds via crosscoupling reactions represents a powerful means for the preparation of numerous products important in pharmaceutical and material science.¹ Recently Buchwald,^{2a-c} Hartwig^{2d,e} and others^{2f} have developed a valuable and new palladium-catalyzed for C-N bond-forming process, which has supplanted the classical Ullmann coupling reaction (copper-catalyzed N-arylation of amines)³ and the related Goldberg coupling reaction (copper-catalyzed N-arylation of amides).⁴ However, despite significant improvements in these methods, some limitations still remain. For example, the amidation of electron-rich orthosubstituted electronically neutral aryl halides is difficult.⁵ Additionally, Pd-based methods can often be relatively sensitive to moisture.⁶ Moreover, the high cost of palladium and removal of palladium residues from polar reaction products, particularly in the late stage of the synthesis of a pharmaceutical substance, can be challenging.⁷ Recently, Buchwald, et al.⁸ reported a copper catalyst system for the amidation of aryl halides. Their method requires a diamine, such as N,N'-dimethylethylenediamine as a ligand, and Cs_2CO_3 as a base in a sealed tube.

The application of KF/Al_2O_3 to organic synthesis has provided new methods for a wide array of organic reactions, many of which are staples of synthetic organic chemistry.⁹ Its benefits have been achieved by taking advantage of the strongly basic nature of KF/Al_2O_3 which has allowed it to replace organic bases in a number of reactions.¹⁰ In many cases, the use of this base provides milder conditions and simpler procedures than previously reported methods.

SYNLETT 2004, No. 9, pp 1517–1520 Advanced online publication: 29.06.2004 DOI: 10.1055/s-2004-829099; Art ID: D02704ST © Georg Thieme Verlag Stuttgart · New York We have explored the CuI-catalyzed N-arylation of aryl iodides with amides using 1,10-phenanthroline (10 mol%) as a simple ligand and KF/Al₂O₃ as a suitable base in the presence of CuI (10 mol%) (Scheme 1). To find optimum conditions a series of experiments has been performed with iodobenzene and benzamide as model compounds, which are summarized in Table 1.





Of the ligands tested 1,10-phenanthroline, N,N'-dimethylethylenediamine, and ethylenediamine, 1,10-phenanthroline was the best choice (Table 1, entries 1, 6 and 7). Amidation of the aryl iodides proceeds best with KF/ Al₂O₃ as the base, the reaction being much slower if K₃PO₄ or K₂CO₃ is used instead. As a solvent toluene was better than other solvents.

The N-arylation of aryl iodides with amides was very sensitive to the substrates and the results are summarized in Table 2. Iodobenzene reacted with benzamide using CuI (10 mol%), 1,10-phenanthroline (10 mol%) as a ligand in toluene under reflux for 1.5 hours in the presence of KF/ Al₂O₃ to afford the N-arylation product in >99% yield (Table 2, entry 1). Similarly with other amides such as acetamide, acetanilide and $\delta\mbox{-valerolactam}$ under the same conditions the corresponding N-substituted amides were obtained in 95-100% yields (Table 2, entries 2-4). p-Iodoanisole with benzamide after 3.5 hours gave the coupling product in >99% yield (Table 2, entry 5). With acetamide and acetanilide as the amides the corresponding N-arylated amides afforded in 90-95% yield after longer reaction times (Table 2, entries 6 and 7). When oiodoanisole was employed as a substrate for N-arylation the corresponding benzamide and acetamide were obtained in 95% yield (Table 2, entries 8 and 9). However with acetanilide as amide, coupling occurred in only 67% yield, probably due to steric effects (Table 2, entry 10). Benzamide, acetamide and acetanilide were coupled with *p*-iodotoluene and afforded the N-arylation products in 90-95% yields (Table 2, entries 11-13). Similarly, o-iodotoluene coupled with benzamide and acetamide to give 92-100% yields (Table 2, entries 14 and 15). Under similar reaction conditions, again probably due to steric

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Entry	Ligand	Base	Solvent	Time (h)	Yield (%) ^a
1	1,10-Phenanthroline	KF/Al ₂ O ₃	Toluene	1.5	99
2	1,10-Phenanthroline	KF/Al ₂ O ₃	Dioxane	5	90
3	1,10-Phenanthroline	KF/Al ₂ O ₃	THF	7	75
4	1,10-Phenanthroline	K ₃ PO ₄	Toluene	4	90
5	1,10-Phenanthroline	K ₂ CO ₃	Toluene	5	85
6	N,N'-Dimethylethylenediamine	KF/Al ₂ O ₃	Toluene	3	98
7	Ethylenediamine	KF/Al ₂ O ₃	Toluene	5.5	85

 Table 1
 N-Arylation of Iodobenzene with Benzamide

^a Yields refer to isolated products.

effects after even 12 hours *o*-iodotoluene coupled with acetanilide only in 72% yield (Table 2, entry 16). Treatment of 1-bromo-4-iodobenzene with benzamide, acetamide and acetanilide gave the corresponding 4-bro-

mophenyl substituted amides in excellent yields (Table 2, entries 17 and 19).

 Table 2
 The Copper-Catalyzed Amidation of Aryl Iodides in the Presence of KF/Al₂O₃

Entry	Aryl iodide	Product ^a	Time (h)	Yield (%) ^b
1		Ph H	1.5	99
2		Me H	5	97
3		CH ₃ Ph	6	95
4			8	99
5	MeO-		3.5	99
6	MeO-		9.5	90
7	MeO-		8	95

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Entry	Aryl iodide	Product ^a	Time (h)	Yield (%) ^b
8	OMe		6.5	95
9	OMe		12	95
10	OMe		12	67
11	Me		3	95
12	Me	Me Ne	6	90
13	Me		6.5	95
14	Me I		5.5	92
15	Me		8	99
16	Me		12	72
17	Br —	Br N Ph	3	96
18	Br	H Br	11	90
19	Br —		8.5	95

Table 2 The Copper-Catalyzed Amidation of Aryl Iodides in the Presence of KF/Al2O3 (continued)

^a Performed using 10 mol% of 1,10-phenanthroline as ligand, 1.0 equiv of aryl iodide, 1.2 equiv of amide, and 5 equiv of KF/Al_2O_3 as base in 5 mL toluene at reflux.

^b Isolated yields. Products were characterized by spectroscopic data (IR, ¹H NMR, and GC).

In summary, we have developed an experimentally simple and inexpensive catalyst system for the amidation of aryl iodides. We believe that potassium fluoride supported on alumina (KF/Al₂O₃) provides an excellent complement to other bases such as Cs_2CO_3 in copper-catalyzed methodology. Efforts to expand the utility of this method to other coupling reactions are in progress in our laboratory.

Typical Procedure

To a stirred solution of amide (1.2 mmol) and aryl iodide (1 mmol) in toluene (5 mL) under argon atmosphere were added CuI (19 mg, 10 mol%) and 1,10-phenanthroline (20 mg, 10 mol%) followed by $KF/Al_2O_3^{11}$ (5 equiv, 780 mg) and the mixture stirred at 110 °C for the specified time (Table 2). The progress of the reaction was monitored by either GC or TLC. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was separated by column chromatography on silica gel using hexane–EtOAc (4:1) as eluent to afford the pure coupled product.

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