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Ligand free open air copper(II) mediated aryl formamidation and amination of aryl halides

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ABSTRACT

A simple synthetic procedure for direct formamidation and amination of aryl halides mediated by copper(II) salts was developed in open air, without an external ligand in formamide with potassium carbonate as a base. This approach is particularly efficient when electron active aryl halides are used as substrates. In these cases almost quantitative formamidation was observed.

Introduction

Metal catalyzed coupling reactions between aryl halides and amides have been recognized for years for their application in academia and pharmaceutical industries.[1] These reactions attract significant attention due to fact that many biologically active compounds possess aryl–nitrogen bond. In fact over 90% of commercially available drugs have at least one nitrogen in their structure.[2] In the past, several research groups reported the Pd catalyzed formation of C–N bond by coupling aromatic halides with amines,[3] amides,[4] and imides.[5] Recently the Zhang group reported Pd catalyzed amidation of aryl halides using 2-dialkylphosphino-2′-alkoxy-1,1′-binaphthyl as ligand.[6] Besides high cost of external ligands, it is also difficult to scale-up Pd catalyzed amination reactions. It is important to mention that removing Pd residues from the reaction media requires special methods, which increase its cost.

Copper catalyzed coupling has emerged as a very good alternate because it is easy to handle, cost less, and most importantly it is safer. In recent years several research groups reported their work on this area mostly by using external ligands such as α-amino acids,[7] bis-pyridylimines,[8] 1,2-diamines,[9] 1,10-phenanthroline,[10] and 1,3-diketones.[11] However, because of the use of Cu(I) and external ligands, these methods are also expensive. There are also some reports regarding the copper catalyzed formamidation of arylboronic acids.[12] Therefore, it is of paramount interest for both the academic and industrial community to develop simple, safe, and economical methods for preparation of aniline and aryl formamide derivatives from readily available and inexpensive aryl halides. The most economical approach to aryl coupling reactions is to use extremely inexpensive copper(II) sulfate as a source of the coupling catalyst.[13]

Results and discussion

Here we report a simple, efficient, ligand free, and inexpensive method for direct aryl formamidation and amination of readily available aryl halides. The reaction was performed by heating a formamide suspension of corresponding aryl halide, copper(II) sulfate pentahydrate, and potassium carbonate at 150–160 °C for few hours on open air (Fig. 1). The product was isolated by extraction of water diluted reaction mixture with dichloromethane followed by flash chromatography. Isolated yields are almost quantitative (Table 1).

The coupling reaction proceeds easily with aryl chlorides, bromides, and iodides. However the ideal substrates are aryl bromides because aryl chlorides are generally less reactive resulting in longer reaction time and lower conversion, while aryl iodides are more reactive resulting in formation of undesired byproducts. This makes the purification process difficult and isolated yields lower. Regardless of the nature of the aryl substituents, the first step of

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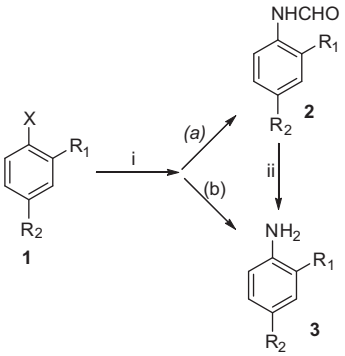
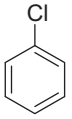
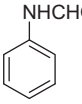
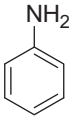
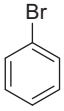
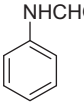
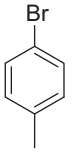
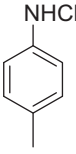
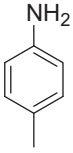
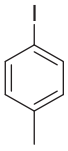
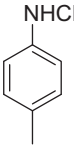
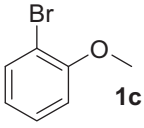
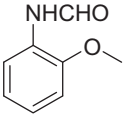
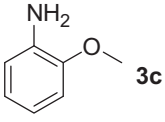
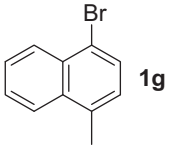
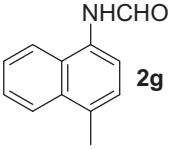
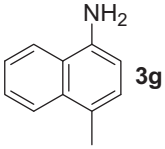
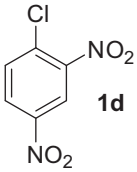
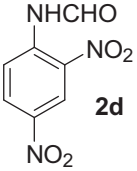
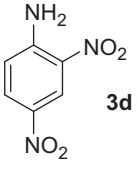
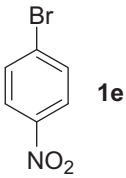
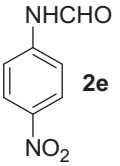
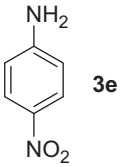


a: X = Cl and Br, $R_1 = R_2 = H$; **b**: X = Br and I, $R_1 = H$, $R_2 = CH_3$; **c**: X = Br, $R_1 = OCH_3$, $R_2 = H$; **d**: X = Cl, $R_1 = R_2 = NO_2$; **e**: X = Br, $R_1 = H$, $R_2 = NO_2$; **f**: X = Br, $R_1 = H$, $R_2 = CN$; *i* = H_2NCHO, $CuSO_4x5H_2O$, K_2CO_3, 2.5 h,150-160°C *ii* = $NaOH/H_2O$-C_2H_5OH, 1 h, 65-70°C. 93-98% *(a)* for aryl halides with electron donating groups(**1a**,**1b**, and **1c**) isolated yields are greater than 90% *(b)* for aryl halides with electron withdrawing groups (**1d**, **1e**, **1f**) isolated yields are around 50%

Figure 1. Reaction outcomes of copper(II) mediated aryl formamidation and amination.

Table 1
Isolated yields of formamidation and/or amination of aryl halides

Entry	Aryl halide	Formamide	Yield **2** (%)	Aniline	Yield **3** (%)
1	 **1aCl**	 **2a**	93	 **3a**	97[a]
2	 **1aBr**	 **2a**	95		
3	 **1bBr**	 **2b**	96	 **3b**	98[a]
4	 **1bI**	 **2b**	93		
5	 **1c**	 **2c**	90	 **3c**	96[a]
6	 **1g**	 **2g**	96	 **3g**	97[a]
7	 **1d**	 **2d**	Trace	 **3d**	56[b]
8	 **1e**	 **2e**	Trace	 **3e**	40[b]