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COMMUNICATION

Chemospecific and ligand free CuI catalysed heterogeneous N-arylation of amines with diheteroaryl halides at room temperature†

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A ligand free, copper-catalyzed N-arylation reaction of amines with diheteroaryl halides in heterogeneous medium at room temperature has been developed. The protocol is very effective for low boiling amines and useful for amines available in aqueous solution. The reaction gives chemospecific arylation of amines with diheteroaryl halides in the mixture monoheteroaryl halides, diheteroaryl halides and carbocyclic aryl halides. The reaction is also chemospecific with respect to arylation of aliphatic amines. Monoarylated piperazines were also synthesized at room temperature following this protocol.

Introduction

N-Heteroaryl compounds are common motifs in pharmaceutical research.[1] Usually these compounds are synthesized *via* aromatic nucleophilic substitution reaction (SNAr) of amines with heteroaryl halides or *via* the copper mediated Ullmann type coupling at higher temperature.[2] The transition metal catalyzed formation of carbon–nitrogen bonds *via* cross-coupling reactions represents a powerful means for the preparation of N-heteroaryl compounds.[3] In addition to numerous versatile methods for the arylation of amines, most convenient methods such as palladium catalyzed[4,5] and copper catalysed systems[6–17] have also been reported. However most of the synthesis requires either stoichiometric amount of metal or the use of additional supporting ligands.[18–22] The supporting ligands decrease the reaction time and reaction temperature, however having own limitation of the catalyst deactivation through competitive reactions.[22] Furthermore dry conditions are generally required with the use of ligands. A plethora of effective chemical approaches have been devised for ligand free N-arylation of amines,[23–25] however the problem of long reaction time, moisture sensitivity, high temperature and the use of costly reagents still persist.[26–29] To the best of our knowledge, there is only one example where ligand free room temperature N-arylation is reported, however that also require longer reaction times.[30]

In continuation of our work for the synthesis of bioactive compounds,[31] there was a requirement for the synthesis of different diheteroaryl amines by SnAr reaction between diheteroaryl halides and amines of lower boiling point. Since no method is available in literature, we developed a novel method which overcomes all the limitation for the diheteroarylation of amines which are sensitive to heat and moisture. Herein, we report the first example of copper-catalyzed N-arylation of amines with diheteroaryl halides at lower temperature (35–40 °C) in a biphasic solvent system of chloroform and water in the absence of any additional ligand.

During the literature search, we observed that various factors like base, phase transfer catalyst (PTC), copper source ligand and solvent have significant effect on the course of the reaction and also on the yield.[21] In this study, diethyl amine and 2-chlorobenzothiazole were chosen as model reactants and subjected to reaction condition involving 10 mole% each of CuI and $Bu_4N^+Br^-$ (PTC) in organic as well as aqueous medium using K_2CO_3 as base. Unfortunately, the reaction didn't proceed even after 24 h of continuous stirring. The reaction was also attempted with the change of reaction conditions (*e.g.* solvent, temperature and N_2 atmosphere) however the results remain the same. The role of ligands in aryl substitution is well documented.[18–22] These ligands increase the electron density on metal centre hence increase the reaction yield. We attempted the reaction by prior ligation of CuI with diethyl amine as reported in literature[32] and then reacted with aryl halide, $Bu_4N^+Br^-$ and K_2CO_3 in organic as well as in aqueous medium, the reaction again didn't proceed. However when the same reaction was attempted in chloroform with a few drops of water surprisingly the reaction occurs with 35% yield (Entry b, Table 1). The result indicates that the ligation of metal with reactant amine in appropriate conditions can give the reaction in desired direction. The reaction conditions were further modified to give better result and it is found that the catalyst system containing 10 mol% CuI, 10 mol% benzyltributyl ammonium bromide (PTC), 2 equivalents of KOH and $CHCl_3$–H_2O (9 : 1) at 35 °C was optimum to get maximum yield. The standardized reaction conditions were attempted with different heteroaryl halides with various amines and are presented in Table 2. As shown in the table, the desired arylation of aliphatic amine with different diheteroaryl halides were obtained in good to excellent yields (Entries a–f, h–k, Table 2). Even the reaction was successful with low boiling amines such as dimethylamine (40% aqueous solution), diethylamine (55 °C) and pyrrolidine (87–88 °C) which were otherwise not possible with any reported method.[33–34] Syntheses of these compounds are also difficult through N-alkylation of aryl amines because of competitive secondary and quaternary amine formations. Entries (g, Table 2)

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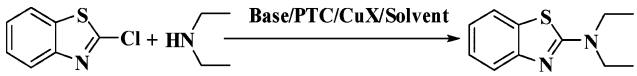
Table 1 Standardization of reaction conditions



Entry	Base	CuX (mol%)	PTC (mol%)	Solvent (A:B)	Yield[a]
a	K_2CO_3	CuI (10)	$Bu_4N^+Br^-$ (10)	Water	0
b	K_2CO_3	CuI (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	35
c	K_2CO_3	CuI (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (2 : 9)	30
d	K_2CO_3	CuI (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (3 : 9)	20
e	K_2CO_3	CuI (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (0.5 : 9)	23
f	K_2CO_3	CuI (10)	$Bu_4N^+Br^-$ (10)	$CHCl_3$	0
g	Cs_2CO_3	CuI (10)	$Bu_4N^+Br^-$ (10)	Water/C_2H_5OH (1 : 9)	30
h	$NaHCO_3$	CuI (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	40
i	KOH	CuI (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	70
j	KOH	CuCl (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	50
k	KOH	CuBr (10)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$(1 : 9)	60
l	KOH	CuI (15)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	68
m	KOH	CuI (5)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	40
n	KOH	CuI (0)	$Bu_4N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	0
o	KOH	CuI (10)	$Bz.Bu_3N^+Br^-$ (10)	Water/$CHCl_3$ (1 : 9)	80
p	KOH	CuI (10)	$Bz.Bu_3N^+Br^-$ (15)	Water/$CHCl_3$(1 : 9)	80
q	KOH	CuI (10)	$Bz.Bu_3N^+Br^-$ (0)	Water/$CHCl_3$(1 : 9)	20

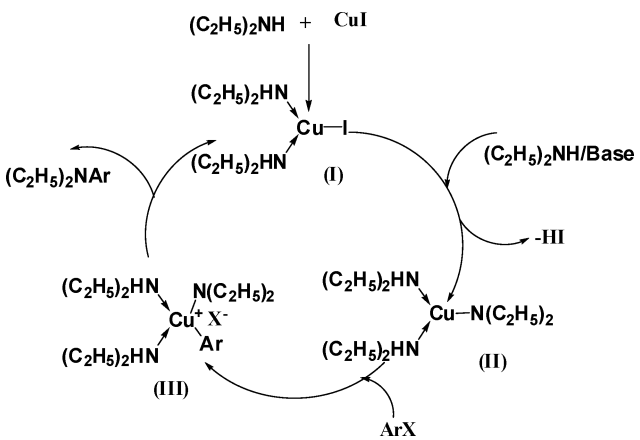
[a] HPLC Yield.

indicated that the reactions at room temperature is specific only to aliphatic amine. To study the chemospecificity of the reaction we have reacted 1a with 4-(aminomethyl)aniline(2q) having both aliphatic and aromatic amine. It was observed from the Entry q, Table 2 that chemospecific aryaltion at aliphatic amine only occurs. The same reaction when attempted with the reflux condition in DMF or DMSO, mixture of products were observed, which establishes the superiority of this method.

The monoarylated piperazine derivatives of thiazole[33] and benzothiazole[34] are of great interest for their broad application in medicinal chemistry. They are generally prepared by refluxing 2-chlorothiazole derivatives with piperazine in DMSO/DMF or other higher boiling polar solvents for a long time.[34] The general method is not applicable for thermal sensitive reactants and further leads several side product formations. So their synthesis at room temperature is very advantageous. Entry p (Table 2) shows that the coupling reactions of diheteroaryl halides and diamines such as piperazine gave only diarylated product. The result remains the same even with higher ratio of piperazine to halides (5 : 1). A possible explanation of the uncontrollable diarylation of piperazine under these conditions is that the monoarylated intermediate is more soluble in chloroform than piperazine and reacts preferentially with the aryl chloride to provide predominantly the observed diarylated product. So modifications of the reaction conditions were required for chemoselective monoarylation in piperazine. To achieve chemoselective monoarylation at room temperature with the given method heterogeneous system was then changed to homogeneous system in which the solubility of piperazine was higher. Chloroform was replaced with water miscible solvents such as methanol or ethanol or acetonitrile and it is found that the best result was obtained with the use of a mixture of ethanol and water. The higher reactivity in the reaction medium is attributed to higher solubility of the piperazine in the reaction system.

The chemoselective coupling reactions of different heteroaryl halides with piperazine were carried out under the standardized reaction conditions. The desired monoarylated products of piperazine were obtained in good to excellent yields (entries q–u, Table 3).

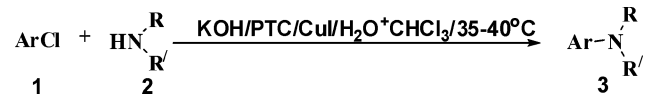
On the basis of the above observations and literature reports, a plausible mechanism for the observed diheteroarylation amines is proposed in Scheme 1. The reaction of CuI with amine produce a co-ordinated complex **I**[32] the complex **I** reacted with another molecule of amine in basic medium to product complex **II**[18] The treatment of **II** with diheteroaryl halides provides a complex **III** and then the reductive elimination of **III** gave the N-arylated product and complex **I**.

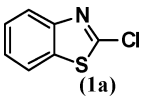
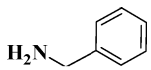
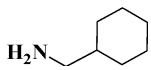
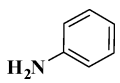
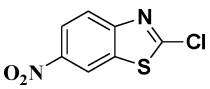
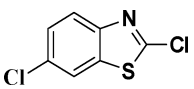
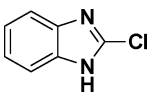
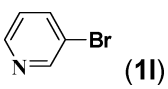
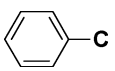
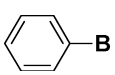
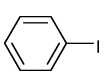
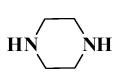
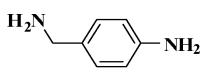


Scheme 1

The mechanism could explain the reactivity order of aryl halides. Only the diheteroaryl halides may gave the reaction because of higher reactivity and inability of Complex **II** to catalyse reaction with lesser reactive substituents. The use of minimum quantity of water might be required for the solvation of inorganic base (KOH) and also to convert benzyltributyl ammonium bromide to benzyltributyl ammonium hydroxide as reported by Xu *et al.*[35] The role of water might also be attributed to the formation of Cu

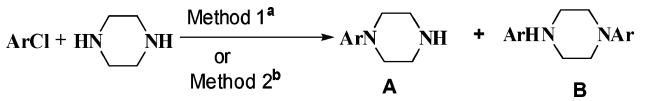
Table 2 Arylation of amines with heteroarylhalides

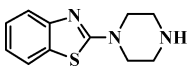
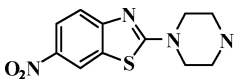
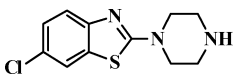
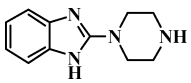
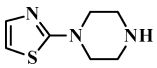


Entry	ArCl	Diamine	Yield[a]
a	 (1a)		**80**
b	**(1a)**		**78**
c	**(1a)**		**82**
d	**(1a)**	 (2d)	**82**
e	**(1a)**		**88**
f	**(1a)**	 (2f)	**85**
g	**(1a)**		**0**
h		**2f**	**70**
i		**2f**	**76**
j		**2f**	**78**
k		**2f**	**91**
l	 (1l)	**2f**	**0**
m		**2f**	**0**
n		**2f**	**0**
o		**2f**	**0**
p	**(1a)**		**80**[b]
q	**(1a)**	 2q	**78**[c,d]

[a] Isolated Yield. [b] Yield of diarylated piperazine. [c] Yield only for the arylation at aliphatic amine. [d] Ratio of arylation at aliphatic to aromatic amine (1 : 0).

Table 3 Monarylation of amines with heteroaryl halides



Entry	ArCl	Product	Ratio A:B[c](A:B)[d]	Yield. A[e](A)[f]
r	**1a**		9 : 1 (8 : 2)	80 (70)
s	**1h**		9 : 1 (8 : 2)	75(62)
t	**1i**		9 : 1 (8 : 2)	85(75)
u	**1j**		9 : 1 (8 : 2)	72(65)
v	**1k**		9 : 1 (8 : 2)	65(52)

[a] Method 1:KOH/PTC/CuI/H_2O+C_2H_5OH/35–40 °C/12 h. [b] Method 2: DMSO/Reflux/12h. [c] A:B by Method 1. [d] A:B by Method 2. [e] Yield of A by Method 1. [f] Yield of B by Method 2.

amine complex [**II**] in the basic aqueous solution.[36] More quantity of water resulted in lower yield, because of poor solubility of other substrate/reactant. The superiority of the benzyltributyl ammonium bromide over the other PTC might be due to its ease of conversion to an organic base in aqueous medium and its good solubility in both aqueous as well as organic medium.

Conclusions

In conclusion, we have developed a simple and mild CuI catalyzed N-arylation with diheteroaryl halides in the absence of additional ligand. The developed reaction protocol is not moisture sensitive hence cheap source of copper is used. The catalytic system reduced the reaction temperature below 40 °C with 6 h stirring. It is particularly noteworthy that this protocol is applicable to thermally sensitive reactants and low boiling amines. Higher level of chemoselectivity was achieved for amination between carbocyclic, monoheteroaryl and diheteroaryl halides. Similarly chemo selectivity was achieved between aliphatic and aromatic amines.

Experimental section

Synthesis of benzothiazol-2-yl-diethyl-amine (general procedure 1)

In a round bottom flask 0.95 gm (0.013 mol) of diethyl amine and 0.19 gm (0.001 mol) of CuI was stirred for half hour. A blue colour solution was formed. To this add 0.56 gm (0.01 mol) of KOH dissolved in 5 ml of water. Stirred it for another half hour. Orange coloured precipitate was formed. After stirring for another 30 min, 0.274 gm (0.001 mol) of tributylbenzyl ammonium chloride was added followed by the addition of 1.69 gm (0.01 mol) diheteroaryl halide in 45 ml chloroform. The reaction mixture was stirred for

6 h at room temperature. The progress of reaction was monitored by the consumption of aryl halide. The organic layer was collected and the aqueous layer was washed with chloroform (3 × 25 ml). The combined organic layer is dried over anhydrous Na_2SO_4 and solvent was evaporated at reduced pressure. Products were purified either by crystallizing or by flash chromatography.

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