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# **Graphical Abstract**





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# N-Arylation of heterocycles promoted by tetraethylenepentamine in water

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# ARTICLE INFO

ABSTRACT

Article history: Received Received in revised form Accepted Available online Tetraethylenepentamine and triethylenetetramine are found to be efficient organic bases for the N-arylation of pyrazole and imidazole with aryl and heteroaryl -iodides and -bromides catalyzed by CuI in water at moderate temperature. The cross-couplings proceed smoothly with good to excellent yields and a variety of functional groups are tolerated under this condition.

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### 1. Introduction

N-Arylheterocycles are common and important motifs in pharmaceutical and material fields,<sup>1</sup> thus many efforts have been devoted to the improvement in the formation of C-N bond catalyzed by transition metals by now. Among these various progressive strategies of direct N-arylation of heterocycles with aromatic halogen compounds, Pd-catalyst systems possess inevitable drawbacks of high cost and toxicity, which limited their massive applications for industrial scales,<sup>2</sup> so the modified copper-catalyzed Ullmann reactions have become an attractive alternative. However, in the most of these successful examples, ligands must be applied.<sup>3</sup> In recent years, with the development of the nanotechnology, some ligand-free copper-catalyzed Narylation reactions have been reported, but they showed high substrate limitation.<sup>4</sup> Meanwhile, it's worth mentioning that the arylation methods of N-heterocycles with aryl boronic acids have been discovered. Unfortunately, they are often trapped by the high cost and less availability of the functionalized boronic acids.5

As far as Ullmann-type cross coupling, inorganic bases (KOH,  $K_2CO_3$ ,  $Cs_2CO_3$ ,  $K_3PO_4$  *etc.*) are commonly used in most reported methods,<sup>2,3,4</sup> which make the transformation suffer heterogeneous reaction in organic solvents. Only a few organic bases such as

1,8-diazabicyclo(5,4,0)undec-7-ene,<sup>6</sup> tetraalkylammonium salts,<sup>7</sup> and alkoxide<sup>8</sup> have been reported. In addition, these catalytic systems possess disadvantages, for example, requirement of additional ligands,<sup>7a-d,8a,8b,8d</sup> stoichiometric [Cu] as catalyst,<sup>6</sup> and protection of inert gas.<sup>7,8b-d</sup> Therefore, it is necessary to explore more efficient organic bases to simplify the process.

In view of the importance of industrial exploitation, it is becoming urgent to develop the sustainable methods. The media of water has many merits, such as low cost, safety and environmentally benign nature, so reactions in aqueous media have attracted more interests of researchers for large scale industrial processes,9 and we prefer to perform the cross-coupling reactions in water. To the best of our knowledge, only a few methods about the N-arylation of heterocycles have been reported in aqueous media so far, and most of them need the organic ligands.<sup>10</sup> Herein, as a part of our ongoing research about environmentally friendly catalyst system for the C-N coupling reactions,<sup>4n</sup> we introduce a novel protocol to form C-N bond catalyzed by CuI and using TEPA (tetraethylenepentamine) as base and ligand in water. The transformation of pyrazole and imidazole with aryl iodides or bromides proceeds smoothly at moderate temperature with good to excellent yields. We believe

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that this catalyst system will enrich the methods of the Ullmann-type reaction.

#### 2. Results and discussion

In our initial experiment, pyrazole (1.5 equiv) is treated with iodobenzene (1 equiv), CuI (0.1 equiv), TBAB (0.3 equiv) and TEPA in water at 125°C for 12 h. To our delight, 1-phenyl-1H-pyrazole is formed in excellent yield. Encouraged by this result, different amines are tested under the same conditions. In addition, we investigate the effects of the amount of base and the precursor catalyst on the yields. The results are shown in Table 1.

## Table 1

 $\square$ 

Screening reaction conditions for N-arylation of pyrazole with iodobenzene<sup>a</sup>

</th <th></th> <th>+ HN <math></math> TBAB;</th> <th></th> <th></th>		+ HN $$ TBAB;		
Entry	[Cu]	Base <sup>b</sup>	Time (h)	Yield <sup>c</sup> (%)
1	CuI	TEPA (2mmol)	12	92, <mark>37</mark> <sup>g</sup>
2	CuI	TETA (2mmol)	12	89
3	CuI	$N(C_2H_5)_3$ (2mmol)	12	0, <mark>0</mark> <sup>h</sup>
4	CuI	$NH(C_2H_5)_2(2mmol)$	12	51, <mark>54<sup>h</sup></mark>
5	CuI	TMEDA (2mmol)	12	45
6	CuI	Thiourea (2mmol)	12	0
7	CuI	NH <sub>3</sub> (2mmol)	20	$0,71^{d}$
8	CuI	TEPA (5mmol)	12	94
9	CuI	TEPA (3mmol)	12	91
10	CuI	TEPA (1mmol)	12	84
11	CuI	TEPA (0.5mmol)	12	67
12	CuCl <sub>2</sub>	TEPA (2mmol)	18	87
13	CuBr	TEPA (2mmol)	16	88
14	CuO	TEPA (2mmol)	16	72
15	Cu	TEPA (2mmol)	20	74
16	Cu(OAc) <sub>2</sub>	TEPA(2mmol)	12	85
17	_	TEPA(2mmol)	12	$0^e$
18	CuI	TEPA(2mmol)	12	54 <sup>f</sup>
19 <sup> i</sup>	CuI	TEPA (2mmol)		60, 93

<sup>a</sup> reaction conditions : iodobenzene (1 mmol), pyrazole (1.5 mmol), [Cu] (0.1 mmol) and TBAB (tetrabutyl ammonium bromide (0.3mmol) in 2 mL water at 125°C for 12 h; <sup>b</sup> TEPA (tetraethylenepentamine), TETA (triethylene-tetramine), TMEDA (tetramethyl-ethylenediamine), <sup>c</sup> GC yield determined by using methoxybenzene as internal standard; <sup>d</sup> in the present of KOH (2 mmol) and ammonia(2 mmol); <sup>e</sup> in the absence of CuI ; <sup>f</sup> at 100°C for 12 h; <sup>g</sup> in the absence of TBAB; <sup>h</sup> 0.2 mmol TEPA was added; <sup>i</sup> at 125°C for 6h and 24 h respectively.

According to the results in table 1, it is observed clearly that the base plays a very important role in the transformation. There is no coupling product when only using ammonia. However, the reaction proceeds smoothly with the addition of KOH. The speculated reason is that only the basicity of the ammonia is not enough for the reaction (table 1, entry 7). Therefore, with the increasing basicity, thiourea, triethylamine, TMEDA, diethylamine, triethylenetetramine and tetraethylenepentamine lead coupling efficiency to ascend sharply (table 1, entries 1~6). In addition, the amount of the base is screened and obviously, the 2 equiv. base is appropriate (table 1, entries 1, 8, 9). The copper source has been studied in the reactions, and the readily available copper salts such as CuI, CuBr, CuCl<sub>2</sub>, CuO, Cu and Cu(OAc)<sub>2</sub> all can afford satisfactory results in the arylation of pyrazole. These results are in agreement with the previously reported conclusions that copper catalyst precursors in different oxidation states presumably could be transformed into the same active catalyst firstly under the reaction conditions.<sup>10k</sup> Here, CuI turns out to give the best results (table 1, entries 1, 12~16), so CuI is chosen as the catalyst precursor for subsequent experiments. As expected, no product is observed in the absence of copper source (table 1, entry 17). The temperature proved to be crucial, the yields are 54% and 92% at lower temperature  $(100^{\circ}C)$  and at higher temperature  $(125^{\circ}C)$  respectively (table 1, entries 1 and 18). In the absence of TBAB, the yield only is 37% (table 1, entry 1). When 0.2 mmol TEPA was added in the reaction in which N(C<sub>2</sub>H<sub>5</sub>)<sub>3</sub> or NH(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub> is used as base, the yields change small (table 1, entries 3 and 4); moreover, we observed that the CuI can dissolve in water in the presence of TEPA. Therefore, we could speculate that the main contribution of TEPA in this reaction is as base, and followed by as ligand which can promote the dissolution of CuI in water. In addition the yields would not dramatically increase with the prolonging of the reaction time and 12 h is the proper time (table 1, entries 1 and 19).

Therefore, the optimal results have been obtained when amine (1.5 equiv) and aryl halide (1.0 equiv) are allowed to react with tetraethylenepentamine (2.0 equiv), CuI (0.1 equiv) and TBAB (0.3 equiv) in water at 125°C.

# Table 2

N-arylation of heterocycles with aryl halides in water<sup>a</sup>

Ar-X + Nu-H	Cul; TEPA or TETA _ Ar-Nu
	H <sub>2</sub> O; 125°C
X=I;Br. Nu-	H=N-containing heterocycles

Entry	Aryl halide	products	Time(h)	Yield(%) <sup>b</sup>
1	< <u> →</u> I		12	92(88)
2		<b>√−</b> N <sup>∧</sup> N 2b	12	86(87)
3			12	73
4			12	64
5	N	N	12	93
6	⟨ı		12	89
7			12	57(62)
8		✓—N2h	12	64
9			12	76
10	_0-{	0-(-)-N <sup>N</sup> 2j	12	81(84)
11	_oI	$O \rightarrow N \rightarrow N _{2k}$	12	77
12	FI	$F \rightarrow N \rightarrow 21$	12	80(76)
13			12	65
14	<i>─</i> Br		22	63(67)
15	⟨Br		24	58
16	⟨Br		36	45



<sup>a</sup> reaction conditions : iodide (1 mmol), nucleophile (1.5 mmol), TEPA(2 mmol), CuI (0.1 mmol) and TBAB (0.3mmol) in 2 mL water at 125°C; <sup>b</sup> isolated yields; the yields in brackets is catalyzed by TETA.

With the optimized conditions in hand, then, we examined the scope of the substrates for this catalyst system. As shown in table 2, firstly, both aryl iodides and bromides give the coupling products under the optimized conditions, but the aryl iodides react more quickly than aryl bromides with the same nucleophiles and afford higher yields. However, it is regretful that the N-arylations of N-heterocycles with aryl chlorides are not observed under this condition. Secondly, aryl halides with electron-donating substituents proceed with nucleophile more smoothly than those with electron-withdrawing ones (table 2, entries 17~25). Thirdly, it is remarkable that any heterocycle halides such as 4-bromopyridine, 4-iodopyridine and 2bromothiophene can couple with pyrazole or imidazole in higher yields in this catalytical system (table 2, entries 5, 6, 19, 20, 26). Fourthly, the obviously reduced yields of 2-methylimidazole and 2-iodotoluene suggest that the adverse impact of steric hindrance exists in the current system (table 2, entries 4, 13). Finally, it is notable that there are no obvious byproducts in this transformation, and the operation procedure is simplified.

Catalyst recycle experiments have been carried out and the results were presented in Table 3. The catalyst system in aqueous phase was reused after the extraction with ethyl acetate. Immol TEPA and 0.1 mmol TBAB should have been complemented to the reaction system before the next test. According to the yields, the catalytic activity of CuI was gradually declining in the coupling reaction.

#### Table 3.

Recycle studies of catalyst for N-aryllation of pyrazole with iodobenzene<sup>a</sup>



<sup>a</sup> Reaction conditions: pyrazole (1.5 mmol), iodobenzene (1 mmol), TEPA (2 mmol), CuI (10 mol%) and TATB (0.3 mmol) at 125°C for 12 h in water (2 mL). <sup>b</sup> GC yield determined by using methoxybenzene as internal standard.

#### 3. Conclusion

In summary, to our knowledge, it is the first time that the tetraethylenepentamine and triethylenetetramine have been found to be efficient organic bases for the CuI-catalyzed N-arylation of N-containing heterocycles with aryl iodides or aryl bromides. A variety of arylation products have been obtained with good yields by this method. The simple reaction conditions, the easy separation of the products and the broad scope of substrate render this method particularly attractive. Even so, to develop an effective catalytic system for the arylation of amines in water is still far from being satisfied, our further work is to enlarge the applications of this catalytic system.

# 4. Experimental

General procedure: iodobenzene (1.0mmol), imidazole (1.5 mmol), TEPA (2.0 mmol), TBAB (0.3 mmol), CuI (0.1 mmol) and 3 mL H<sub>2</sub>O were added to a 10 mL flask which was subsequently capped with a rubber balloon. The mixture was stirred in a preheated oil bath at 125 °C for 12 h. After cooling the mixture to the room temperature, 5 mL water was added and the product was extracted by ethyl acetate (10 mL×3). The combined organic layer was washed by brine (15 mL), dried over anhydrous MgSO<sub>4</sub> and evaporated under the reduced pressure. Further purification by silica gel column chromatography (6:1 petroleum ether/ethyl acetate) give the 1-phenyl-1H-imidazole.

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### Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:

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