Oxazolidin-2-one as Efficient Ligand for the Copper-Catalyzed *N*-Arylation of Pyrrole, Imidazole and Indole

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Abstract: Oxazolidin-2-one was found to be a facile ligand for the N-arylation of pyrrole, indole, and imidazole with aryl and heteroaryl iodides, bromides, and chlorides by applying CuI as catalyst. The easy preparation, commercial availability, lower molecular weight, and broad substrate applicability, as well as substituent compatibility of this catalysis system render oxazolidin-2-one great advantages over the Cu-catalyzed methods that have already been utilized in a number of applications.

Keywords: Copper, coupling, catalysis, ligands, arylations.

1. INTRODUCTION

Nitrogen-containing heterocycles, such as *N*-arylpyrroles, *N*-arylindoles, and *N*-arylimidazoles, are an important class of privileged core structure that are ubiquitous in numerous natural products and biologically active pharmaceuticals [1]. Traditionally, the copper-catalyzed Ullmann-Goldberg coupling is the general method for introduction of amine functionality using aromatic halides [2]. However, this protocol necessitates the use of high temperature and often requires stoichiometric amount of copper regents, which, on scale, leads to problems of waste disposal, handlely inconvenience, and also narrow substrates scope. Thus, numerous efforts have been devoted to the development of the methods for the preparation of *N*-arylazole unit. Despite the great progress of Pd-catalyzed C-N formation by using some sterically hindered phosphine ligands [3], the high cost and air sensitivity of catalysis systems commonly limit their application to large- and industrial-scale formation of these bonds. In recent years, the use of ligands to facilitate the copper-catalyzed *N*-arylation of nucleophiles with aryl halides is one of the hottest branches of research due to their economic attractiveness and excellent efficiency. Indeed, some efficient ligands have been disclosed in these coupling reactions, including diamines [4], amino acids [5], diimines [6], aminoarenethiolate [7], phosphine ligands [8], 2-aminopyrimidine-4, 6-diol [9a], 1,10-Phenanthroline [9b], hydroxyquinoline [10], (*S*)-pyrrolidinylmethylimidazoles [11], 4, 7-dimethoxy-1, 10-phenanthroline [12], 2-oxocyclohexanecarboxylate [13], and benzotriazole [14]. While many significant results have been achieved for the copper-catalyzed *N*-arylation of a variety of nitrogen-containing heterocycles through the use of those ligands mentioned above, the applications of these Ullmann methods might be limited in certain degree by the high expense, unavailability, or specificity of the ligands. It should be noted that the successful arylation methods for each of major classes of nitrogren heterocycles such as imidazoles, pyrroles, indoles, etc. have been scarcely reported [4, 12-14]. Therefore, more efficient, versatile, and facile ligands for these coupling reactions under relatively milder conditions are still in demand.

Recently, our research group disclosed the copper-catalyzed *N*-arylation of nucleophiles with aryl halides facilitated by ligands of *N*-hydroxyimides [15]. In the ongoing research program, we found that oxazolidin-2-one could be applied as more efficient ligand in the amidation of aryl halides and cyclization of ortho-halobenzanilides [16]. Herein, we describe our preliminary investigations on the use of oxazolidin-2-one as ligand for the copper-catalyzed *N*-arylation of nitrogen-containing heterocycles.

2. RESULTS AND DISCUSSION

In our initial screening experiments, a set of oxazolidin-2-one-based derivatives was screened for the comparison models of pyrrole **1a** with iodobenzene **2a** and imidazole **1b** with 4-bromoanisole **2b**. As shown in Fig. (**1**), the skeletal divergence of ligands in this transformation presented significant different results. Ligands L3 and L4 were not able to be applied as promoters in our catalysis system. The sterically more hindered ligands L6, L7, and L8 afforded **3a** and **3n** in lower yields. Ligand L5 was evidently less favorable than ligands L1 and L2. The best results were obtained only when the ligands contained O or S atom located in the lactam ring. Presumably, L1 and L2 acted as tridentate O, N, S-donor ligands that might be sterically more effective in stabilizing or solublizing the copper complex [17]. In our cases, ligand L1 was recommended due to the easily preparation, lower molecular weight, and more efficient catalysis behavior. It was observed clearly that base

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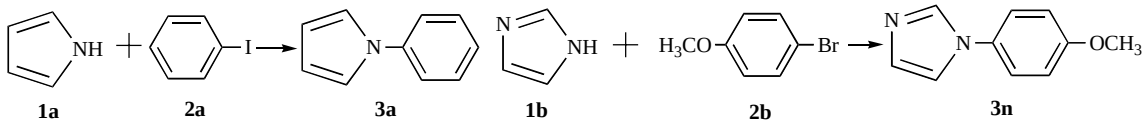
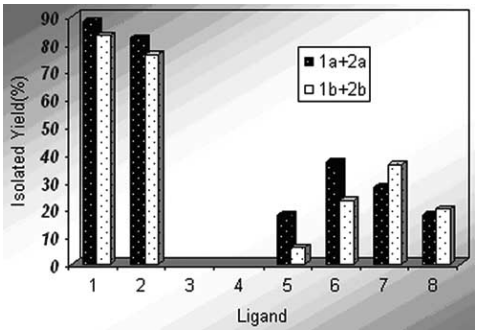
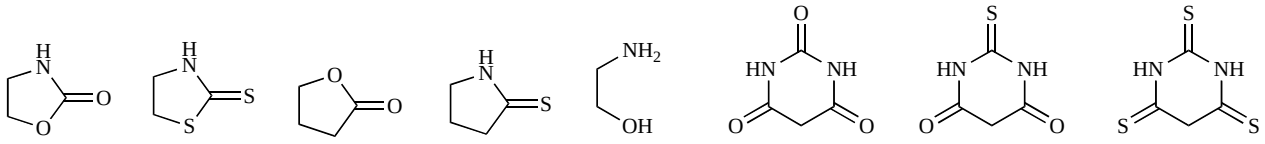


1a **2a** **3a** **1b** **2b** **3n**

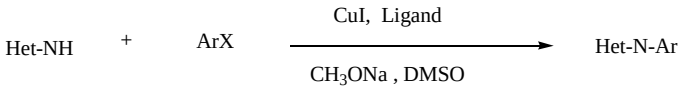




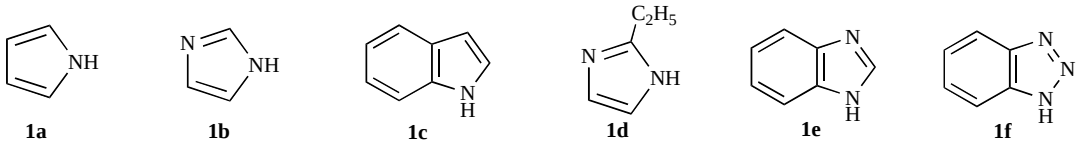
L1 **L2** **L3** **L4** **L5** **L6** **L7** **L8**

Fig. (1). Effect of various ligands on the aryl amidation reaction.The reaction of **1a** + **2a** was performed with 5 mol % of CuI, 10 mol % of ligand, 1.0 equiv of **1a** and **2a**, and 1.5 equiv of CH_3ONa in DMSO at 80 °C for 10 h. The reaction of **1b** + **2b** was performed with 10 mol % of CuI, 20 mol % of ligand, 1.0 equiv of **1b** and **2b**, and 1.5 equiv of CH_3ONa in DMSO at 120 °C for 12 h.

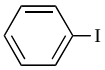
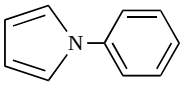
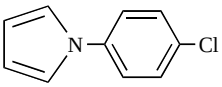
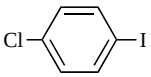
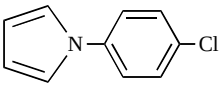
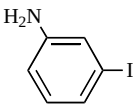
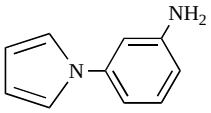
Table 1. Copper Oxazolidin-2-One-Catalyzed N-Arylation of N-H Heterocycles[a]



1a~1f **2a~2p** **3a~3z**



1a **1b** **1c** **1d** **1e** **1f**

Entry	ArX	Product	(°C/h)	Yield[b]
1	 **2a**	 **3a**	80/10	93
2	 **2c**	 **3b**	110/12	81
3	 **2d**	 **3b**	80/8	86
4	 **2e**	 **3c**	80/10	78

(Table 1). Contd…..

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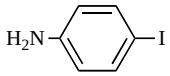
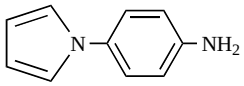
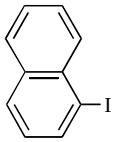
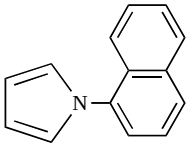
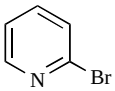
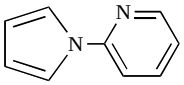
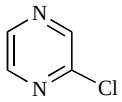
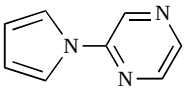
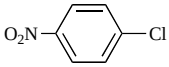
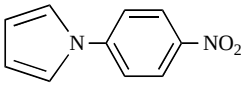
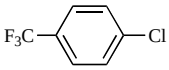
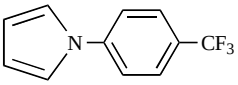
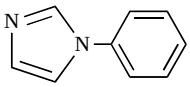
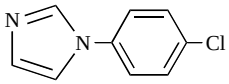
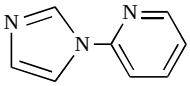
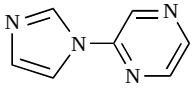
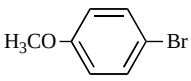
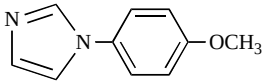
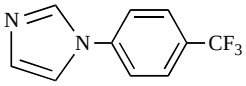
5	 **2f**	 **3d**	80/10	95
6	 **2g**	 **3e**	80/14	92
7	 **2h**	 **3f**	80/12	88
8	 **2i**	 **3g**	120/20	78
9	 **2j**	 **3h**	120/24	32
10	 **2k**	 **3i**	120/24	35
11	**2a**	 **3j**	80/10	91
12	**2c**	 **3k**	120/24	78
13	**2h**	 **3l**	80/15	85
14	**2i**	 **3m**	120/16	67
15	 **2b**	 **3n**	120/12	83
16	**2k**	 **3o**	120/24	45

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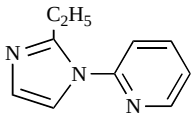
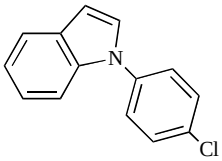
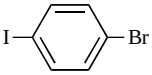
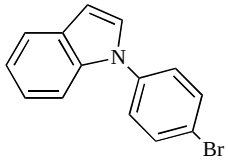
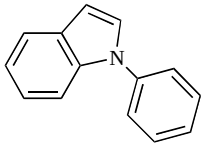
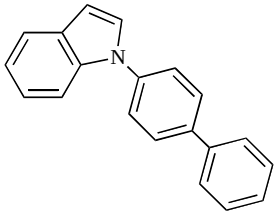
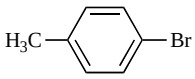
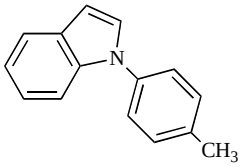
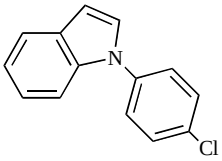
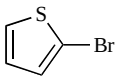
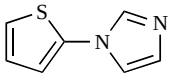
17	**2h**	 **3p**	80/12	81
18	**2c**	 **3q**	80/18	85
19	 **2I**	 **3r**	80/16	94
20	**2a**	 **3s**	80/13	90
21	**2m**	 **3t**	120/24	62
22	 **2n**	 **3u**	120/24	52
23	**2c**	 **3q**	120/24	78
24	 **2o**	 **3v**	120/12	79

(Table 1). Contd…..

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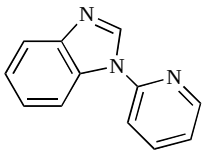
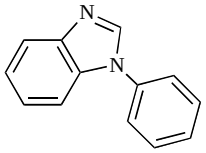
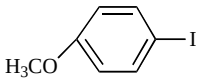
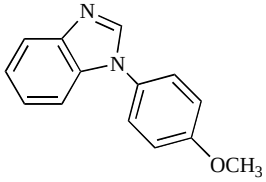
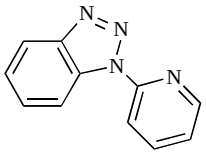
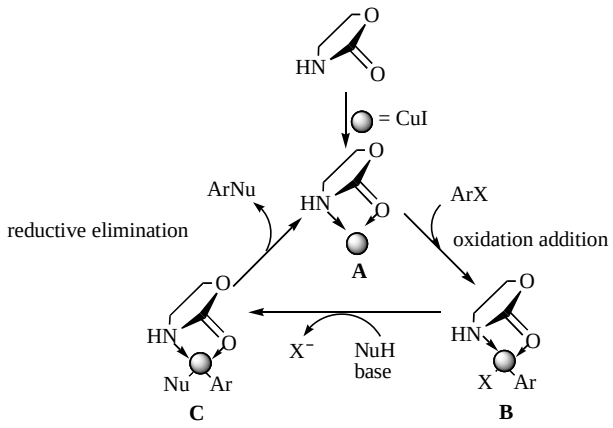
25	**2h**	 **3w**	80/12	94
26	**2a**	 **3x**	80/18	87
27	 **2p**	 **3y**	80/12	92
28	**2h**	 **3z**	80/12	84

[a]Reaction conditions: ArX (1.5 mmol), Het-NH (1.5 mmol), CH_3ONa (1.5 equiv), DMSO (4 mL); X = I, with CuI (5 mol %)/L1 (10 mol %); X = Br or Cl, with CuI (10 mol %)/L1 (20 mol %).
[b]Isolated yield.

plays a very important role in the transformation. The common used bases K_2CO_3, K_3PO_4 were found to be ineffective, amine bases such as DBU or $N(CH_2CH_3)_3$ gave inferior results. However, in the presence of stronger organic base of CH_3ONa, model reactions could sharply ascend coupling efficiency. As documented that more polar solvents can accelerate the Ullmann-type reactions [4], thus, DMF, DMSO, toluene were investigated, and DMSO demonstrated more effectively. Copper salts applied as an alternative catalyst precursor were tested; the readily available copper salts such as CuI, CuBr, CuCl afforded a satisfactory result in the arylation of **1a** with **2a**, however, for the less reactive aryl halides, bromo- and chloro-substituted aromatic compounds, CuI was turned out to give the best results.

From Table **1**, we can discern that the coupling reactions not only tolerate a wide scope of functional groups, but also have broad substrate availability, especially, imidazole, 2-ethylimidazole and benzoimidazole which are known less reactive parterners in C-N cross-coupling reaction, displayed great efficiency. Interestingly, substrates **2e** and **2f** reacted with N-H heterocycles to give corresponding products in excellent yields (78 %, 95 %, entries 4, 5, Table **1**). Since free NH_2 group substituted iodides are of possibility to self-polymerizing in Pd-catalyzed C-N formation methods. Therefore, this result implicated that the formation of different C-N bonds could be accomplished simply by choosing Pd- or Cu-based catalysis system. As reported previously in the copper-catalyzed N-arylation reactions, certain groups in the ortho position of aryl halides prefer to coordinate metal ions and hasten the Ullmann-type reaction [9]. In our cases, we also found that the accelerating nitrogen atom in 2-bromopyridine possessed the ability to promote the coupling reactions (entries 7, 13, 17, 25, and 28, Table **1**). Encouraged by these results, the less active 2-chloropyrazine (**2i**) was then treated with pyrrole **1a** and imidazole **1b**, and gave the coupling products in 78 % and 67 % yields (entries 8, and 14, Table **1**). Our catalysis system provided complete bias to favor more active halogens amidated compounds when halide bearing both of chloric and bromo, as well as iodic groups (entries 2, 3, 12, 18 and 19, Table **1**). Generally, aryl bromides and chlorides react more slowly than aryl iodides and typically require 10 mol % of CuI and 20 mol % of ligand and heating at higher temperature 110 °C for longer time (up to one day). With respect to the reactivity for N-H heterocycles, pyrrole and imidazole are more active partners than others.

Based on the previous documents [5, 15], we have formulated a possible mechanism as described in Scheme **1**. Oxazolidin-2-one acted as tridentate O, O, N -donor ligand chelated with CuI to generate species **A**. The subsequent oxidative addition of aryl halides led to heterocycles reacted with **B** readily to afford complex **C**, which undergoes reductive elimination to provide the desired product and finished a catalysis cycle.



Scheme 1. The possible mechanism.

3. EXPERIMENTAL

3.1. General Information

All NMR spectra are recorded on Bruker Avance Digital (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) spectrometers; chemical shifts are expressed in δ units relative to TMS signal as internal reference in $CDCl_3$. Mass spectra are recorded on a HP5989B mass spectrometers.

3.2. General Procudure for the Arylation of Nitrogen-Containing Heterocycles with Halides

To a solution of CH_3ONa (2.25 mmol) in DMSO (2 mL) was added CuI (5 mol% & 10 mol%), and ligand (10 mol% & 20 mol%). After stirring at room temperature for 30 minutes, a mixture of halide (1.5 mmol) and nitrogen-containing heterocycle (1.5 mmol) in 2 mL DMSO were added to the flask. The flask was immersed in an oil bath, and the reaction mixture was stirred at the indicated temperature for the corresponding reaction time. The mixture was cooled to room temperature, 10 mL water was added, and the resulting suspension was extracted with ethyl acetate (10 mL×4). The extraction was concentrated, and purified by column chromatography on silica gel to provide the desired product.

3.3. The Data for Representative Products

3.3.1. 1-Phenyl-1H-pyrrole (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.44 (m, 4H), 7.32-7.28 (m, 1H), 7.15 (s, 2H), 6.41 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.74, 129.49, 125.56, 120.48, 119.27, 110.34.

LRMS (EI, 20eV) m/z (%) 143 (M+,100).

3.3.2. 2-(1H-imidazol-1-yl)pyridine (3l)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27-8.26 (m, 1H), 8.20 (s, 1H), 7.63-7.61 (m, 1H), 7.48 (s, 1H), 7.17-7.15 (d, *J* = 8.0 Hz, 1H), 7.05-7.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.88, 138.88, 134.79, 130.35, 121.86, 116.03, 112.14.

LRMS (EI, 20 eV) m/z (%) 145 (M+, 100).

4. CONCLUSIONS

In summary, we have disclosed that oxazolidin-2-one acted as a facile ligand for the CuI-catalyzed arylation of N-H heterocycles. The practical benefits of this arylation methodology were not only contributed to its easy preparation and commercial availability as well as lower molecular weight, but also broad substrate applicability, substituent compatibility. In short, we believe that the present catalyst system could provide a good complement to the Pd- or Cu-catalyzed methods that have already been utilized in a number of applications, and is of great importance to the research and development in the pharmaceutical industry.

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