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Cobalt-catalyzed direct arylation of imidazo[1,2-*a*]pyridine with aryl iodides

Dattatraya A. Babar,[a,b] Haridas B. Rode*[a,b]

Abstract: The $Co(II)Cl_2.6H_2O$ catalyzed C-H activation/direct arylation of imidazo[1,2-*a*]pyridine with aryl/heteroaryl iodide is reported. The cost effective, ligand and additive free protocol using KOAc successfully afforded 3-arylimidazo[1,2-*a*]pyridines in good yields. Imidazo[1,2-*a*]pyridines with electron withdrawing and electron donating substituents with various aryl iodides are well tolerated. The reaction is performed in a Screw-top V-Vial® to expedite the synthesis. The antibacterial 3-napthyl imidazo[1,2-*a*]pyridine is smoothly prepared using this protocol.

Introduction

Imidazo[1,2-*a*]pyridine is a "privileged scaffold" having broad spectrum of biological activities. It is found in many bioactive molecules, functional materials, agrochemicals and natural products.[1] Specifically, substituted imidazo[1,2-*a*]pyridines showed anti-inflammatory,[2] anticancer,[3] antiprotozoal,[4] antibacterial,[5] antiulcer,[6] antiviral,[7] antifungal,[8] analgesic and antipyretic,[9] and other biological activities.[10-12]

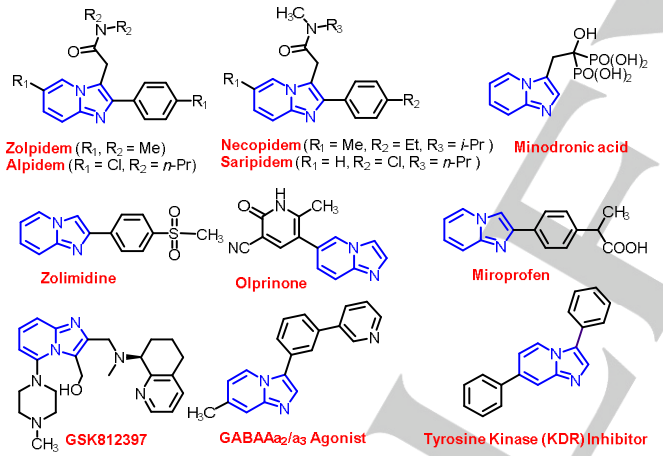

Figure 1. Drugs and bioactive compounds containing imidazo[1,2-*a*]pyridine

Recently, imidazo[1,2-*a*]pyridine derivative, Q203, has been reported with antitubercular activity against multi-drug resistant (MDR) and extensive drug resistant (XDR) tuberculosis bacteria.[13] As shown in the figure 1, imidazo[1,2-*a*]pyridine skeleton is present in various bioactive compounds and drugs i.e. alpidem,[14] zolpidem,[14] olprinone,[15] minodronic acid,[15] zolimidine,[16] necopidem,[16] saripidem,[16] rifaximin[17] and GSK812397.[18] Therefore, a variety of synthetic protocols have been designed for the functionalization of imidazo[1,2-*a*]pyridines. Specifically, because of the electron rich nature of C-3 position of imidazo[1,2-*a*]pyridine, many studies have been reported on the development of C-3 functionalization through formation of carbon-carbon bond, including regioselective arylation,[19] alkenylation,[20] formylation,[21] trifluoromethylation,[22] C-S bond formation[23] and C-X (C-halogen) bond formation reactions.[24]

The coupling of two different fragments through direct arylation is an important strategy for the preparation of heteroarenes. Such strategy, usually, avoids the prefunctinalization of starting material and also have shown the atom economy.[25] The Pd, Rh and Ru catalysts are often used for the direct arylation of arenes and heteroarenes.[25] Importantly, the comparativelly inexpensive metal catalyst such as Cu, Fe, Ni and Co-salts could be effective for such transformation.

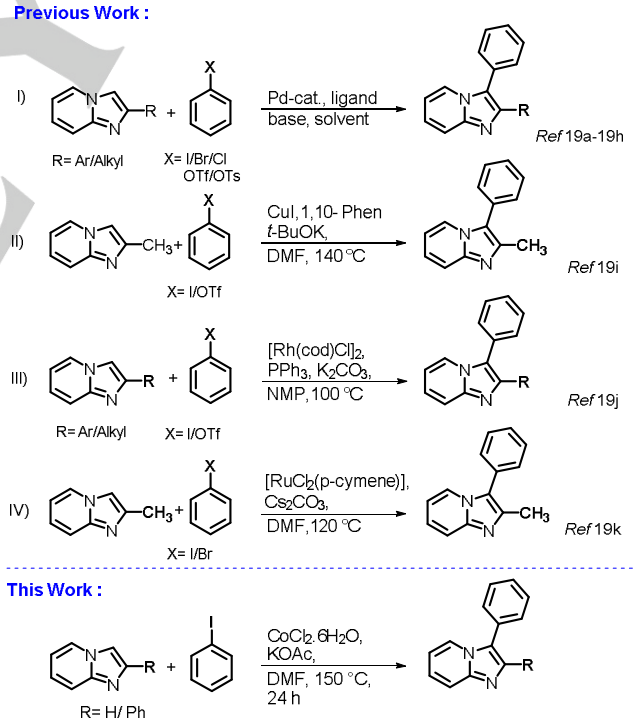

Figure 2. Synthetic routes to prepare 3-arylimidazo[1,2-*a*]pyridine by direct arylation of imidazo[1,2-*a*]pyridine

In the past few years, much progreses has been made in the synthesis of C-3 aryl/heteroaryl imidazo[1,2-*a*]pyridine derivatives by direct C-H arylation employing transition metals such as Pd, Rh, Ru and Cu-catalyst (Figure 2).[19] Of note, there is no report on cobalt catalyzed direct arylation of the imidazo[1,2-*a*]pyridine. Cobalt has been widely used in C-H bond functionalization reactions[26] whereas its application in

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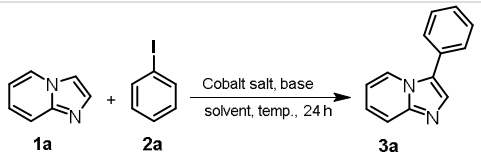
direct arylation of heteroarenes is scarce.[26h] As part of our ongoing interest in development of convergent synthetic methods for the versatile 3-arylimidazo[1,2-*a*]pyridines,[19g, 27] we anticipated the use of earth abundant metal catalyst for the synthesis of arylated imidazo[1,2-*a*]pyridines. This could be realized by replacing expensive and precious catalysts such as Ru, Rh, Pd with cobalt salt. Herein, we report the $CoCl_2.6H_2O$ catalyzed C-3 arylation of imidazo[1,2-*a*]pyrididnes with aryl/heteroaryl iodides.

Results and Discussion

We started initial experiment by employing imidazo[1,2-*a*]pyridine (**1a**) and iodobenzene (**2a**) with 20 mol% $CoCl_2.6H_2O$ and 2 equivalent of Cs_2CO_3 in DMF at 150 °C in a Screw-top V-Vial®. The desired 3-arylated product **3a** was observed in 10% yield after 24 h (Entry 1). Inspired from this result, we next screened different bases like K_2CO_3, LiOAc, $NaHCO_3$ and KOAc (Entry 2-5). The results obtained from above experiments showed that KOAc is a suitable base for this transformation (Entry 5).

Table 1. Optimization of reaction condition



1a **2a** **3a**

Entry	Catalyst (mol%)	Base (equiv.)	Solvent	Temp. (°C)	Yield[a] (%)
1	$CoCl_2.6H_2O$ (20 mol%)	Cs_2CO_3 (2 equiv.)	DMF	150	10%
2	$CoCl_2.6H_2O$ (20 mol%)	K_2CO_3 (2 equiv.)	DMF	150	40%
3	$CoCl_2.6H_2O$ (20 mol%)	LiOAc (2 equiv.)	DMF	150	65%
4	$CoCl_2.6H_2O$ (20 mol%)	$NaHCO_3$ (2 equiv.)	DMF	150	44%
5	**$CoCl_2.6H_2O$ (20 mol%)**	**KOAc (2 equiv.)**	**DMF**	**150**	**92%**
6	$CoBr_2$ (20 mol%)	KOAc (2 equiv.)	DMF	150	52%
7	$Co(OAc)_2.4H_2O$ (20 mol%)	KOAc (2 equiv.)	DMF	150	10%
8	$CoCl_2.6H_2O$ (20 mol%)	KOAc (2 Equiv.)	DMA	150	79%
9	$CoCl_2.6H_2O$ (20 mol%)	KOAc (2 equiv.)	Dioxane	110	NR
10	$CoCl_2.6H_2O$ (20 mol%)	KOAc (2 Equiv.)	DCE	150	NR
11	$CoCl_2.6H_2O$ (20 mol%)	KOAc (2 equiv.)	EtOH	90	Traces
12	$CoCl_2.6H_2O$ (20 mol%)	KOAc (2 equiv.)	H_2O	100	NR
13	$CoCl_2.6H_2O$ (10 mol%)	KOAc (2 equiv.)	DMF	150	38%
14	$CoCl_2.6H_2O$ (5 mol%)	KOAc (2 equiv.)	DMF	150	10%
15	$CoCl_2.6H_2O$ (30 mol%)	KOAc (2 equiv.)	DMF	150	90%
16	$CoCl_2.6H_2O$ (20 mol%)	KOAc (1 equiv.)	DMF	150	22%
17	$CoCl_2.6H_2O$ (20 mol%)	KOAc (3 equiv.)	DMF	150	86%
18	$CoCl_2.6H_2O$ (20 mol%)	KOAc (5 equiv.)	DMF	150	81%

Reaction conditions: 1a (0.05 g, 1 equiv.), **2a** (1.5 equiv.), KOAc, Cobalt salt in various solvents (2 mL) at 90-150 °C for 24 h in a 5 mL capacity Screw-top V-Vial®. NR indicate no reaction. [a]Isolated yields are shown.

Next, reactions were carried out with different cobalt salts including $CoBr_2$ and $Co(OAc)_2.4H_2O$ (Entry 6-7). Unfortunately, these reactions did not show any increment in the yield of **3a**. This indicates $CoCl_2.6H_2O$ was a suitable catalyst for this transformation. Further, the reaction was studied in different organic and non-organic solvents, such as *N,N*-dimethylacetamide (DMA), 1,4-dioxane, 1,2-dichloroethane (DCE), EtOH and H_2O. The reaction could be conducted in DMA but yield of **3a** was lower than that of DMF condition (Entry 8). The other solvents did not show any improvement in the yields of **3a** (Entry 9-12). Further, the variation in amount of catalyst required for the reaction was studied using different amounts of $CoCl_2.6H_2O$ i.e. 10 mol% and 5 mol% which gave **3a** in 38% and 10%, respectively (Entry 13, 14). By increasing the catalyst to 30 mol%, no improvement in the yield of **3a** was observed (Entry 15). The equivalence of base also varied to observe its effect on reaction product. The reduced amount of base to 1 equivalent decreased yield of **3a** to 22% (Entry 16). The increased amount of base to 3 and 5 equivalents afforded **3a** in 86% and 81%, respectively (Entry 17-18). This indicated that 2 equivalent of KOAc is optimal amount of base to carry out this reaction. Hence, 20 mol% $CoCl_2.6H_2O$, 2 equivalent of KOAc and DMF as a solvent at 150 °C in screw capped closed reaction vial was identified as optimal reaction condition for this transformation (Entry 5, table 1).

The optimized reaction condition was used to generate 3-arylimidazo[1,2-*a*]pyridines by employing different aryl iodides (**2a-2r**) with imidazo[1,2-*a*]pyridine (**1a**). The electron releasing substituents such as $-CH_3$, $-OCH_3$ containing iodobenzenes showed greater reactivity in this protocol affording moderate to excellent yields of **3a**-**3h** (Scheme 1). The electron withdrawing substituents (-F, -Cl, -CN, $-CF_3$, and $-NO_2$) on iodobenzenes also furnished desired products (**3i-3o**) in moderate to good yields. In brief, the 4-flouroiodobenzene and 4-chloroiodobenzene reacted with **1a** to afford **3i** and **3j** in 77% and 72%, respectively. The 1,2,5-trichloro-3-iodobenzene also produced corresponding derivative **3k** in 66% yield. The 3-iodobenzonitrile coupled with **1a** and produced **3l** in 74% yield. The electron withdrawing group such as $-CF_3$ and $-NO_2$ also afforded required products (**3m, 3n** and **3o**) with moderate to good yield. The $-NH_2$ and -OH substituted iodobenzenes didn't afford **3p** and **3q**. Importantly, the heterocyclic 2-iodothiophene successfully provided bi-heterocyclic compound **3r** with 56% yield. The scope of the reaction was extended using diphenyliodonium triflate as

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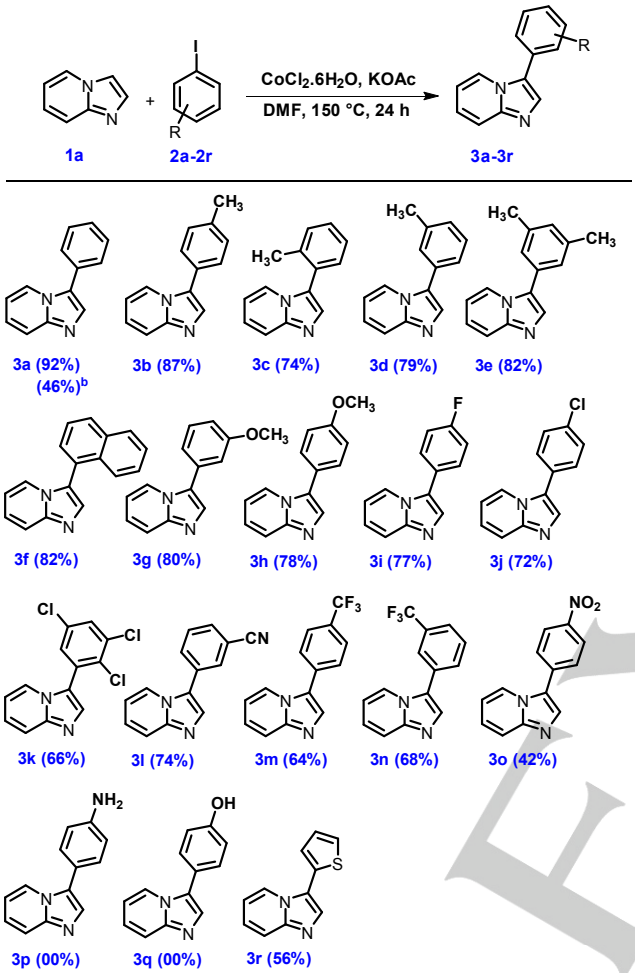
electrophile in the arylation reaction. In this case, the reaction of diphenyliodonium triflate and **1a** afforded product **3a** though in low yield (Scheme 1). In general, this study indicates that the reaction is well tolerated for both i.e. electron donating and electron withdrawing aryl iodides.

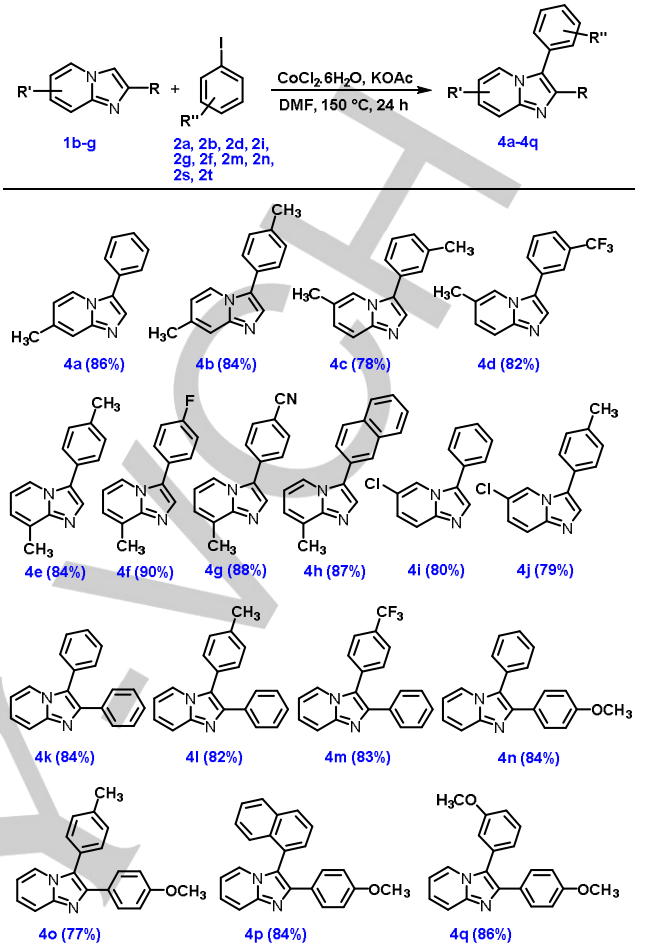
Scheme 1. Scope of aryl iodides



Scheme 1. Reagents and condition: **1a** (0.05 g, 1 equiv.), **2a-2r** (1.5 equiv.), KOAc (2 equiv.), 20 mol% $CoCl_2.6H_2O$, 2 mL DMF at 150 °C for 24 h in a 5 mL Screw-top V-Vial®. Isolated yields are shown. [b] Diphenyliodonium triflate used as aryl source.

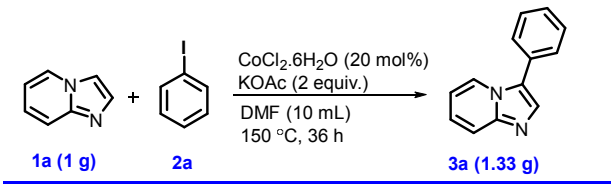
Further, the reaction scope was studied by using various substituted imidazo[1,2-*a*]pyridines (Scheme 2). The electron donating group i.e. -CH_3 at 6 or 7 or 8 position of imidazo[1,2-*a*]pyridines with various aryl iodides furnished the arylated products (**4a-4h**) in good yields. The 6-chloro imidazo[1,2-*a*]pyridine furnished **4i** and **4j** in moderate to good yields. Next, the reactions between 2-phenyl substituted imidazo[1,2-*a*]pyridines and different iodobenzenes were studied. It afforded corresponding 2,3-diphenylimidazo[1,2-*a*]pyridine derivatives **4k-4q** in good yields regardless of the substitution pattern. Of note, the 3-napthyl imidazo[1,2-*a*]pyridine (**4h**) was successfully prepared using this protocol. This compound was synthesized and tested against *Staphylococcus aureus* with minimum inhibitory concentration (MIC) of 25 μM in our earlier work.[27b] *Staphylococcus aureus* is one of the member of ESKAPE pathogens which are priority pathogens declared by WHO that pose high risk to humans.[28]

Scheme 2. Scope of imidazo[1,2-*a*]pyridines



Scheme 2. Reagents and condition: **1b-1f** (0.05 g, 1 equiv.), **2** (1.5 equiv.), KOAc (2 equiv.), 20 mol% $CoCl_2.6H_2O$, 2 mL DMF at 150 °C for 24 h in a 5 mL Screw-top V-Vial®. Yields are based on the recovered starting material.

The practical applicability of this protocol was studied using a gram scale synthesis of **3a** from **1a**. In this case, compound **3a** was obtained in 81% yield (Scheme 3).



Scheme 3. Gram scale experiment

The detail understanding of mechanistic aspects of cobalt catalysed direct arylation of arenes/heteroarenes is not clear. Sames *et al* reported the direct arylation of azole with iodobenzene and provided few thoughts on the arylation process.[26h] The cobalt (II) catalysed cross-coupling reaction of alkyl chloride with heteroaryl substituted arenes indicate the involvement of single electron transfer (SET) type processes.[29a] Similarly, in the alkylation of aromatic imines with alkyl halides suggested the SET to alkyl halide from a cobalt species.[29b] Based on this information, a plausible mechanism for the arylation of imidazo[1,2-*a*]pyridine with aryl iodide is proposed (Figure 3). Initially, the homolysis of aryl iodide in the presence of a cobalt species generates aryl radical which then forms an aryl-cobalt complex **II**. Next, the oxidative addition of

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imidazo[1,2-*a*]pyridine on aryl-cobalt complex produce species **III**. Finally, the reductive elimination will afford the 3-arylimidazo[1,2-*a*]pyridine along with generation of cobalt(II) species.

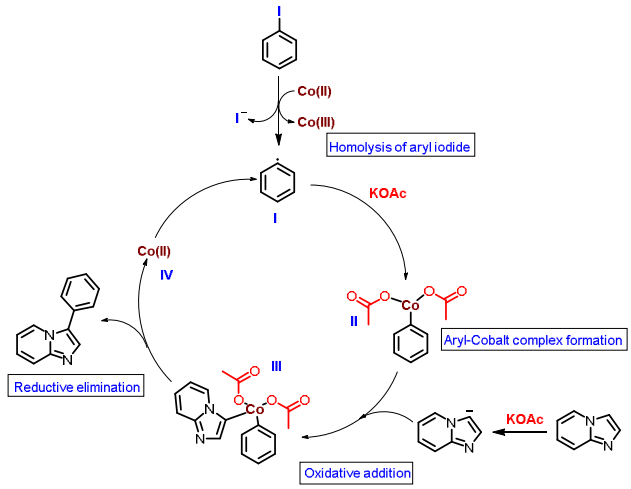

Figure 3. Plausible mechanism of the arylation of imidazo[1,2-*a*]pyridine with aryl iodides

Conclusions

In summary, by taking advantage of the inexpensive, earth abundant cobalt, we developed a ligand/additive free practical protocol for the direct C-3 arylation of imidazo[1,2-*a*]pyridines using aryl/heteroaryl iodides. This protocol features broad substrate scope with moderate to excellent yields, thus rendering it a highly versatile, atom economical and straightforward alternative to the available methods for the synthesis of 3-aryl imidazo[1,2-*a*]pyridines.

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Keywords:

Imidazo[1,2-*a*]pyridine, C-H activation, privileged scaffold, arylation, heterocyclic compounds, transition metals.

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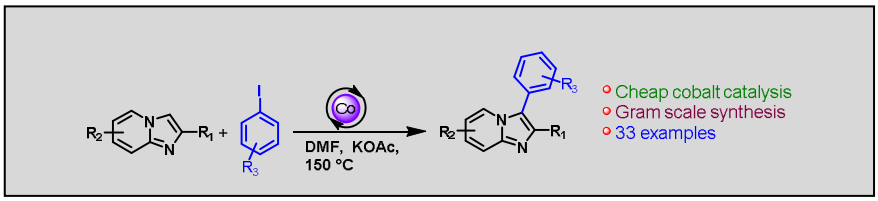

A practical protocol for the C-3 arylation of imidazo[1,2-*a*]pyridines with aryl/heteroaryl iodides using $Co(II)Cl_2.6H_2O$ is reported. The reaction can be performed in a Screw-top V-Vial® to expedite the synthesis.

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