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On water direct arylation of imidazo[1,2-*a*]pyridines with aryl halides

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Introduction

C—C bond formation constitutes an important strategy for the synthesis of chemically diverse compounds.[1] Some of the prominent strategies include, for instance, Suzuki, Kumada, Stille, Negishi and Hiyama cross-coupling reactions.[1c,2] Despite the large applicability of these reactions, most of them proceed via stoichiometric organometallic reagents.[3] In such cases, the preparation of such organometallic reagents becomes troublesome and their instability may jeopardise these reactions. Large amount of metallic salts, as by-products, are generally produced in these reactions.[3b,4] In such a scenario, metal catalysed direct arylation method is advantageous, since it leads to a reduced/limited amount of byproducts as well as no prior preparation of organometallic reagents is required.[5] Hence, strategies for direct functionalization of sp2 C—H bond are becoming more attractive in recent times.[6] The direct arylation holds a significant place in medicinal chemistry and drug discovery as many pharmaceutical companies uses this strategy to synthesize the drug molecules.[7] Solvents including, DMSO, NMP, dioxane, DMAc, xylene and toluene have been reported to effect the palladium catalysed direct arylation reactions, more so at higher temperature (>100 °C) and requiring sterically demanding phosphine ligands.[8] These two factors limit the applicability of metal catalysed direct arylation reactions in industry. In view of these factors, water as a solvent in organic transformations has attracted much interest due to its low cost, easy availability; nontoxic and non-flammable nature.[9] In addition, simple work-up procedures and mild reaction condition may signify its role as solvent in such reactions. Continuing our efforts to generate heterocycle based inhibitors as antibacterial agents, we became interested in 3-aryl imidazo[1,2-*a*]pyridines. The imidazo[1,2-*a*]pyridines are biologically important class of molecule and have shown wide variety of pharmacological effects including anticancer, antiapoptotic, anxiolytic, analgesic, anti-inflammatory, antiviral, antituberculosis.[10] Recently we have shown antibacterial activity of 3-aryl imidazo[1,2-*a*]pyridines against *Staphylococcus aureus*.[11] The imidazo[1,2-*a*]pyridine scaffold (**1a**) is present in commonly used drugs such as, olprinone, zolmidine, zolpidem, alpidem, necopidem and saripidem.[10] As a result, direct arylations on **1a** and its analogues have been reported.[12] Kwong et al. studied the direct arylation of **1a** with aryl tosylates and mesylate using K_3PO_4 base at 120 °C in presence of SPhos ligand in *t*-BuOH[12c] whereas, Doucet et al. reported the direct arylation using aryl bromide in DMA at 150 °C with KOAc as base.[12b] Lee et al. reported the direct arylation of **1a** and aryl bromide in DMA at 140 °C with Pd(II) complexes having monodentate abnormal and normal carbene ligands.[12d] Sames et al. reported the direct arylation of **1a** and aryl iodide in DMA at 125 °C with palladium complexes ($L^1L^2PdX_2$ wherein L^1 = *N*-heterocyclic carbene (NHCs) and L^2 = phosphine).[12a] All the above methods are reported in organic solvents and at high temperature. Additionally, three of the methods need ligand, either added during reaction or in the form of palladium precatalyst; while ligandless method reported by Doucet et al. is carried out at 150 °C in DMA. This suggests that there is a need for a general arylation protocol under mild reaction condition.

Herein, we report the first example of palladium-catalysed direct arylation of imidazo[1,2-*a*]pyridines on water. This ligand-free method is a simple, mild and ecofriendly protocol for the direct arylation.

Results and discussion

The **1a** undergoes arylation at 3 position. This regioselectivity may be due to π-excessive nature of the fused five membered ring.[8,13] The bromination occurs exclusively at 3-position of **1a** suggesting potential of high regioselectivity in arylation reaction.[14] We began initial optimization of direct arylation between **1a** with 4-iodoanisole (**2a**) in the presence of catalytic amount of $Pd(OAc)_2$ at 100 °C as a model reaction. The results are summarized in Table 1. Keeping in mind, the cost factor and water based protocol; KOH was selected as the base for conducting this reaction. A reaction between **1a**, (1 equivalent) **2a**, (1.5 equivalent) and KOH (3 equivalent) using palladium(II)acetate (5 mol%) in dioxane, acetonitrile, DMSO, DMF, DMA, and toluene at 100 °C for 24 h was investigated (entry 1 to 6, Table 1). Reaction in DCE was carried out at 80 °C. In DMA, 70% yield of **3a** was observed while other organic solvents gave lower yields. In case of acetonitrile, only trace amount of product was formed, while no product was observed in case of DCE. When the reaction was carried out in water (entry 8, Table 1), we were pleased to observe that LCMS based yield of product was 94% and isolated yield was 85%. Further reduction in the amount of catalyst to 2 and 1 mol% afforded lower yields of product **3a** (entry 10 and 11, Table 1). Change in base from

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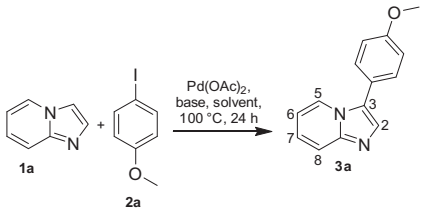
Table 1
Optimization of $Pd(OAc)_2$ catalysed direct arylation reaction.[a]



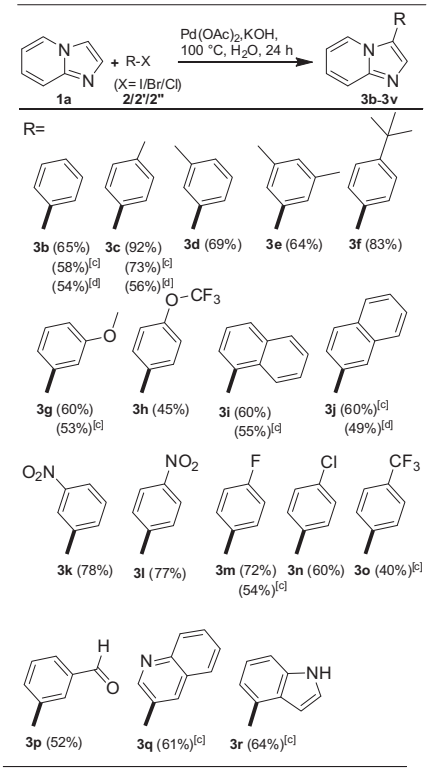
Entry	Solvent[e]	Base	Catalyst, mol%	**3a** (% yield)
1	1,4-Dioxane	KOH	$Pd(OAc)_2$, 5	38
2	Acetonitrile	KOH	$Pd(OAc)_2$, 5	Trace
3	DMSO	KOH	$Pd(OAc)_2$, 5	40
4	DMF	KOH	$Pd(OAc)_2$, 5	49
5	Toluene	KOH	$Pd(OAc)_2$, 5	24
6	DMA	KOH	$Pd(OAc)_2$, 5	70
7[f]	DCE	KOH	$Pd(OAc)_2$, 5	00
8	H_2O	KOH	$Pd(OAc)_2$, 5	94 (85)[b]
9	H_2O	NaOH	$Pd(OAc)_2$, 5	90 (80)[b]
10	H_2O	KOH	$Pd(OAc)_2$, 2	60
11	H_2O	KOH	$Pd(OAc)_2$, 1	10
12	H_2O	KOH	$PdCl_2$, 5	80
13	H_2O	KOH	$Pd(dppf)Cl_2{\cdot}DCM$, 5	74
14	H_2O	KOH	$Pd(TFA)_2$,5	82
15	H_2O	KOH	$PdCl_2{\cdot}(CH_3CN)_2$, 5	80
16	H_2O	K_2CO_3	$Pd(OAc)_2$, 5	51
17	H_2O	Cs_2CO_3	$Pd(OAc)_2$, 5	81
18	H_2O	K_3PO_4	$Pd(OAc)_2$, 5	82
19	H_2O	KOAc	$Pd(OAc)_2$, 5	00
20[c]	H_2O	KOH	$Pd(OAc)_2$, 5	80 (63)[b]
21[d]	H_2O	KOH	$Pd(OAc)_2$, 5	00

[a] Reaction conditions: **1a** (30 mg, 1 equivalent), **2a** (1.5 equivalent), base (3 equivalent), $Pd(OAc)_2$ (shown mol%) in 1 mL solvent at 100 °C for 24 h, yield of **3a** is calculated based on LCMS analysis of crude reaction mixture.
[b] Isolated yields.
[c] 4-Bromoanisole was used instead of 4-iodoanisole.
[d] 4-Chloroanisole was used instead of 4-iododanisole.
[e] Nitrogen purged deionised water was used.
[f] Reaction in DCE was carried out at 80 °C.

KOH to NaOH in presence of 5 mol% $Pd(OAc)_2$ resulted in slightly lower yield. The use of 5 mol% of other palladium (II) salts resulted in lower yield of **3a** as compared to $Pd(OAc)_2$ condition (entry 12–15 versus entry 8, Table 1). A moderate yield of product was observed when bases like K_2CO_3, Cs_2CO_3 and K_3PO_4 were used whereas KOAc failed to give any conversion. Finally, when 4-bromoanisole was used instead of 4-iodoanisole, 80% product was observed while 4-chloroanisole failed to give **3a**. This led to the identification of optimized reaction condition as illustrated in Table 1, entry 8. We observed that **1a**, aryl iodide, base and palladium(II)acetate at 100 °C resulted in heterogeneous mixture indicating that it is an example of "on-water" reaction. Sharpless termed such reaction as "on-water" reaction wherein organic components react in heterogeneous aqueous suspension.[15] "On-water" direct arylation of biologically important thiazole was studied by Greaney and co-workers.[16] More examples are reported on cross-coupling reactions using "on-water" reaction concept.[17–20]

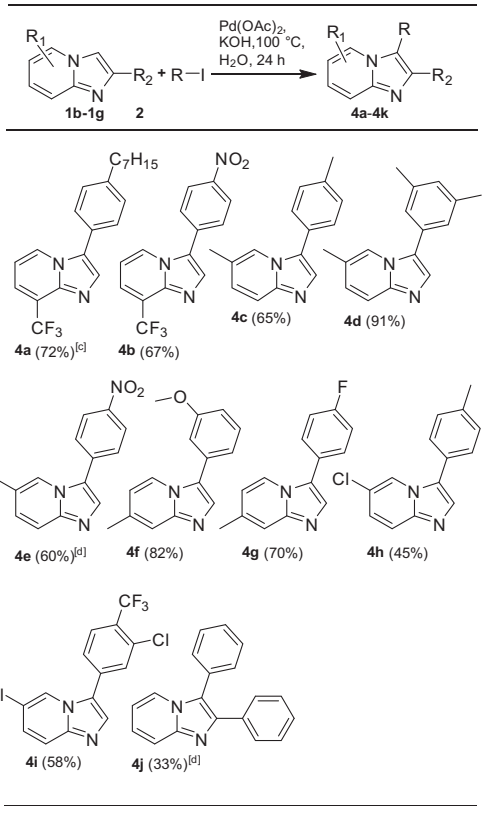
The substrate scope and generality of direct arylation was investigated under optimized reaction condition and the results are summarized in Table 2. Electron rich aryl iodides reacted with **1a** to produce coupled products **3a**, **3c**–**3h** in moderate to excellent yields. **3b**, **3i** and **3j** also produced in moderate yields. It is important to note that 4-iodotoluene successfully furnished **3c** in 92% yield. The disubstituted 3,5-dimethyl iodobenzene furnished **3e** in modest yield. Moreover, the sterically hindered 1-iodonaphthalene underwent successful transformation to produce **3i** in 60% yield. The electron deficient aryl iodides produced **3k**–**3p** in low to moderate yield. Specifically, nitro containing aryl iodide produced **3k** and **3l** in 78% and 77% yield respectively, while 4-fluoroiodobenzene and 4-chloroiodobenzene produced halogenated **3m** and **3n** respectively in moderate yield. Such halogen substituents, fluoro and chloro, modulate the physicochemical properties of inhibitors and inhibitor-protein interactions; and hence are important in early phase of drug discovery.[21] The other electron deficient aryl iodides produced **3o**, **3p** in low yields. We further studied the cross-coupling of aryl chlorides and bromides with **1a**. In case of aryl bromides, products **3a**–**3c**, **3g**, **3i**, **3j**, **3m** and **3o** were successfully produced, albeit in lower yields compared to their aryl iodide counterparts. A similar pattern was observed when aryl chlorides were treated with **1a** to produce **3b**, **3c** and **3j** in lower yields as compared to their aryl iodide and or aryl bromide counterparts. The successful coupling of 3-bromoquinoline with **1a** produced **3q** in 61% yield. Its noteworthy to mention that the reaction tolerated free NH group in case of indole derivative **3r**. We observed that 4-chloroanisole, 4-chlorobenzaldehyde and 2,4-difluorochlorobenzene failed to give the products indicating limitation of this reaction for few aryl chlorides. The lower yields in case of aryl chlorides and bromides may be attributed to their reac-

Table 2
Scope of aryl halides in direct arylation of imidazo[1,2-*a*]pyridine on water. [a,b]



[a] Reaction conditions: **1a** (0.1 g, 1 equivalent), **2**/**2′**/**2″** (1.5 equivalent), KOH (3 equivalent), 5 mol% $Pd(OAc)_2$ in 4 mL nitrogen purged deionised water at 100 °C for 24 h. [b] Isolated yields. [c] Aryl bromides were used. [d] Aryl chlorides were used. See supplementary information for aryl iodide (**2**), bromide (**2′**) and chloride (**2″**) structures.

Table 3
Scope of imidazo[1,2-*a*]pyridines in direct arylation reaction on water [a,b]



[a] Reaction conditions: **1b**–**1f** (0.1 g, 1 equivalent), **2** (1.5 equivalent), KOH (3 equivalent), 5 mol% $Pd(OAc)_2$ in 4 mL nitrogen purged deionised water at 100 °C for 24 h. [b] Isolated yields. See supplementary information for aryl iodide (**2**) structures. [c] Reaction completed in 10 h. [d] Reaction carried out using 20 mol% Pd $(OAc)_2$ for 48 h.

tivities in the cross coupling reactions.[22] In general, the reaction tolerated variety of electron withdrawing and donating substituents as shown in Table 2.

The scope of reaction was evaluated with respect to various imidazo[1,2-*a*]pyridines (Table 3). The electron withdrawing groups like CF_3 and Cl, on imidazo[1,2-*a*]pyridine core and on aryl halide, are tolerated in the reaction (4**a**, **4b**, **4h**, **4i**). It is noteworthy to mention that many inhibitors contain CF_3 as a bioisostere to methyl group; owing to its significance in metabolic stability, improving potency and enhancing selectivity potential.[23] Along this line; **4a** and **4b** may be useful chemotypes to be probed for various biological activities. The presence of 6-chloro group in **4h** and **4i** can provide scope for further modifications of these chemotypes. No additional products were detected in the reaction producing **4h** and **4i**, indicates arylation at 3-position is the prime reaction. Furthermore, electron donating methyl groups at 6 and 7-position of imidazo[1,2-*a*]pyridine were well tolerated and produced **4c**-**4g** in moderate to good yield. The reaction was much faster in the case of 1-*n*-heptyl-4-iodobenzene as compared to all other substrates, and completed in 10 h (**4a**). Inquisitively, 2-phenylimidazo[1,2-*a*]pyridine produced **4j** in low yield (33%) with extended reaction time (48 h) required to complete the reaction and needed 20 mol% palladium catalyst. The lower reactivity in this case may be attributed to the bulky substituent at the 2 position of imidazo[1,2-*a*]pyridine.

Conclusion

In conclusion, we have developed a simple, mild, ecofriendly and relatively inexpensive method for palladium-catalysed direct arylation of imidazo[1,2-*a*]pyridines with aryl halides on water. The method does not require any ligand and tolerate variety of functional groups. The protocol uses simple base KOH and hence may have significance in industry.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.06.010.

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