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An Access to 2-Arylindoles *via* Decarboxylative C-C Coupling in Aqueous Medium and Heteroaryl Carboxylates under Base-Free Conditions using Diaryliodonium Salts

V. Arun,[a] Meenakshi Pilania,[a] and Dalip Kumar*[a]

Abstract: Easily accessible heteroaromatic carboxylic acids and diaryliodonium salts were successfully employed to construct valuable 2-arylindoles and heteroaryl carboxylates in a regioselective fashion. C2-arylated indoles were produced *via* Pd-catalyzed decarboxylative strategy in water without any base, oxidant and ligand. Heteroaryl carboxylates were prepared under metal and base-free conditions. This protocol was successfully utilized to synthesize Paullone, a CDK inhibitor.

Heteroaromatic carboxylic acids are ubiquitous in naturally occurring compounds that are frequently used as easily available potential building blocks for the construction of many drug-like molecules and pharmaceutical agents.[1],[2] In the recent years, carboxylic acids have been employed as traceless directing groups in transition metal-catalyzed arylation reactions.[2] This strategy provides effective ways for the selective functionalization of unreactive C-H bond by directing the metal to activate the proximal C-H bond. Concurrent C-H functionalization and removal of carboxylic acid group as non-toxic carbon dioxide, are the significant features of this strategy.[3] Many research groups have successfully utilized this approach to develop new organic transformations for the construction of therapeutic agents in fewer synthetic steps.[4]

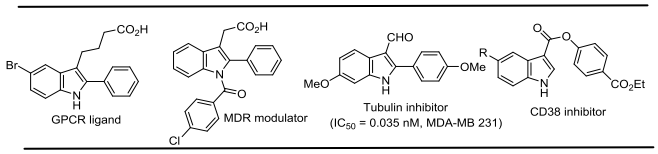

Figure. 1 Selected drug-like 2-arylindoles and indole carboxylate

2-Arylindoles are highly useful scaffolds in drug discovery beside their utility as precursors in the synthesis of complex synthetic molecules (Figure 1).[5],[6b] Consequently, preparation of 2-arylindoles has been pursued with increasing interest by organic and medicinal chemists. Recently, several elegant directing groups[6] and direct arylation[7] approaches have been developed to achieve 2-arylindoles and their analogues. In literature, there is one report employing carboxylic acid as a directing group[8] in the conversion of *N*-protected indole-3-carboxylic acids into the corresponding 2-arylindoles. Additionally, the reaction condition involves the use of Pd(0) carbene complex (2.5 mol%) and base (KOAc) under refluxing (160 °C) dimethylacetamide (DMA) for 24 h. Despite the availability of promising strategies, it is challenging to develop decarboxylative direct arylation in aqueous medium without any oxidant and base.

Diaryliodonium salts for being inherently stable solids and easy to access, are frequently used in organic synthesis as highly electrophilic arylating agents to prepare useful natural and bioactive heterocycles.[9] Hence, utilities of diaryliodonium salts got groundbreaking advancement for the arylation and assembly of heterocyclic frameworks.[10] With ongoing research focus to develop operationally simple protocols to assemble medicinally important heteroaryl molecules by employing diaryliodonium salts[11] herein we wish to disclose Pd-catalyzed decarboxylative C2-arylation of heteroaryl acids in water, and base-free synthesis of heteroaryl esters.

We initiated our investigation by using diphenyliodonium triflate (**1a)** and indole-3-carboxylic acid (**2a)** as model substrates. The decarboxylative arylation of **1a** with **2a** in the presence of 1.0 mol% $Pd(OAc)_2$ in acetic acid generated anticipated 2-phenylindole (**3a)** in 80% yield. To improve the yield of **3a**, different solvents were screened. No product was formed in DMF, whereas, other solvents including 1,4-dioxane, toluene and 1,2-dichloroethane resulted in inferior yield. Gratifyingly, the use of water as a solvent led to **3a** in excellent yield (91%). Water is a superior solvent with satisfactory properties such as non-combustible non-toxic, cheap and can be handled without any precaution.[12] Moreover, in present work, after the reaction, crude product **3a** was easily separated out from the reaction medium (water) as thick oil.

Having the optimized reaction conditions in hand, scope of diaryliodonium salts and heteroaromatic carboxylic acids was explored. All the diaryliodonium salts were synthesized from the corresponding arenes and iodoarenes.[9a] Unsymmetrical iodonium salts possessing electron-withdrawing groups such as ester and nitro, produced the corresponding 2-arylindoles **3b** and **3d** in 85 and 81% yields, respectively. Halogen (chloro) bearing iodonium salt **2c** successfully produced **3c** in 88% yield. Similarly, sterically hindered ortho substituted (OMe, CO_2Me and NO_2) iodonium salts **2e-f**, **2h** also delivered the anticipated products **3e-f, 3h** and **3j** in high yields (68-75%). Heterocyclic iodonium salts, indole(phenyl)iodonium tosylate (**2j**) and mesityl(thienyl)iodonium triflate (**2k**) also worked well to afford C2-heteroarene motifs **3l** (60%) and **3n** (70%) in good yields. Medicinally important candidate, 2-indolyluracil **3o** was easily obtained from **1a** and mesityl(uracil)iodonium triflate in 63% yield. Biologically important 4/5-methoxy indoles were also successfully arylated to prepare the corresponding 2-aryl-4/5-methoxyindoles **3i** and **3k** in better yields (82%). 4/5-Methoxyindoles are known to display interesting anticancer

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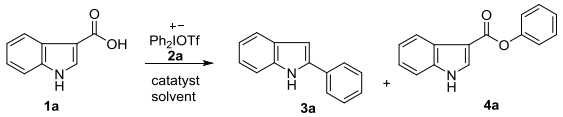
properties through the inhibition of tubulin.[5b] To further widen the scope of this decarboxylative C2-arylation strategy, indole-3,5-dicarboxylic acid **1g** was subjected to optimized reaction conditions.

Table 1. Solvents and catalyst screening[a]



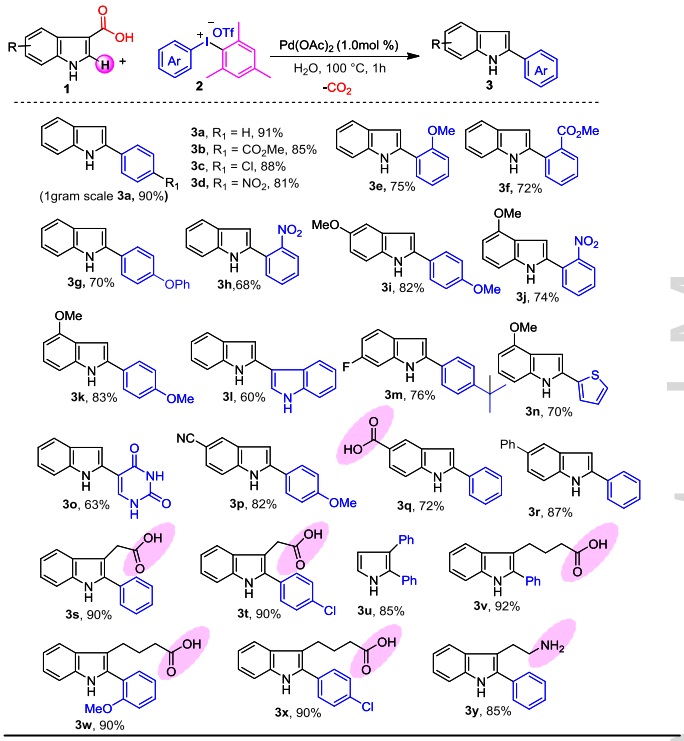
Entry	Catalyst	Solvent	Time (h)	Yield (%)[c]	
				3a	**4a**
1	$Pd(OAc)_2$	AcOH	2	80	-
2	$Pd(OAc)_2$	1,4-dioxane	2	64	-
3	$Pd(OAc)_2$	DMF	12	NR	-
4	$Pd(OAc)_2$	Toluene	2	45	-
5	$Pd(OAc)_2$	water	1	91	-
6[b]	$Pd(OAc)_2$	water	1	91	-
7	$Pd(OAc)_2$	DCE	2	66	-
8	-	water	24	-	NR
9	-	DMSO	24	-	30
10	-	1,4-dioxane	24	-	NR
11	-	DMF	12	-	80

[a]Reaction conditions: **1a** (100 mg, 0.62 mmol), **2a** (267 mg, 0.62 mmol), $Pd(OAc)_2$ (1.0 mol%), 100 °C, [b] used mesityl(phenyl)iodonium salt (**2b,** 0.62 mmol), [c]isolated yields, NR = no reaction

Interestingly, C-5 carboxylic acid remained unreactive and selectively afforded C2-arylated product **3q** in 72% yield. Formation of **3q** suggests activation of C2-position *via* co-ordination of C3-carboxylic acid with palladium. In case of pyrrole-3-carboxylic acid, we attained diarylated **3u** rather than monoarylated product. Diarylation of pyrrole-3-carboxylic acid (**1u**) is likely to proceed *via ortho*-arylation followed by *ipso*-arylation.[18e-f] Encouraged by the successful arylation of indole-3-carboxylic acids and diarylation of pyrrole, next analogue indole systems, indole-3-acetic acid, indole-3-butyric acid and tryptamine were examined. Interestingly, carboxylic acid and amine functionalities were successfully directed the incoming iodonium salts to furnish C2-arylated products **3s**-**t** and **3v**-**y** in excellent yields (85-90%). Compounds **3s**-**t** and **3v**-**y** with carboxylic acid and amine moieties could be used for further synthetic manipulation to generate complex bioactive molecules.

Subsequently, we also studied the O-arylation of indole-3-carboxylic acids using substrates **1a** and **2a** for the model reaction. Heating the reaction contents in DMF exclusively led to O-arylated indole-3-phenylcarboxylate **4a** (Table 1, entry 11) which was confirmed by the characteristic peak of ester >C=O at δ 163.6 ppm in ^{13}C NMR, and band at 1710 cm^{-1} in IR spectral data (See the Supporting Information).[14b] Heteroaryl carboxylates serve as prospective precursors in organic synthesis in addition to for being important subunits widely present in pharmaceutical molecules, agroproducts and polymers (Figure 1).[13] Generally, heteroaryl carboxylates are prepared *via* esterification of appropriate carboxylic acids with phenols in the presence of acid, base or coupling reagents.[10] Alternatively, various impressive synthetic developments accomplished heteroaryl carboxylates by employing carboxylic with either boronic acids or arenes under metal-catalyzed[14] and metal-free reaction conditions.[15] Recently, Olofsson *et al.* reported the arylation of carboxylic acids using diaryliodonium salts in the presence of KO*t*-Bu as a base in toluene.[16] The protocol proceeds under mild conditions and useful to make sterically hindered carboxylates in good yields. However, arylation of heteroaryl carboxylic acids using variety of diaryliodonium salts under base-free conditions is largely unexplored. It is noteworthy to mention that, under both the identified reaction conditions, C/O-arylated products were obtained without any trace of N-arylated heteroaryl acids despite the indole moiety having free -NH. Remarkably, our simple protocol showed excellent control over regioselectivity by C2 and O-arylations.

Table 2. Scope of 2-arylindoles[a]

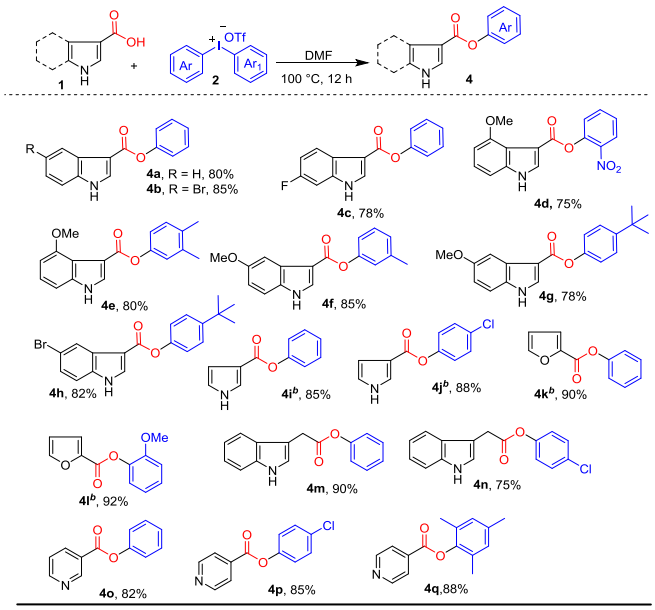


[a]Reaction Condition: **1**(1.0 equiv), **2** (1.0 equiv) and $Pd(OAc)_2$ (1.0 mol%) in water (1 mL) at 100 °C for 1 h; isolated yields

Differently substituted indole-3-carboxylic acids **1** were treated with substituted diaryliodonium triflates **2** under the optimized reaction conditions. Compared to unsubstituted indole, electron rich (4 and 5-methoxy) substituted indoles **1d-e** showed better reactivity towards diversely substituted diaryliodonium salts (NO_2, dimethyl, *t*-butyl & tolyl) to afford **4d**-**g** in 75-85% yields. To improve the significance of the developed strategy, we turned our attention to arylate pyrrole and furan carboxylic acids. We observed excellent reactivity of pyrrole-3-carboxyxlic acid and furan-2-carboxylic acid towards chloro **2c** and *o*-methoxy substituted iodonium salts **2e** to access the corresponding esters **4j** and **4l** in 85-92% yields within 3h. Gratifyingly, the developed esterification procedure was also amenable to six-

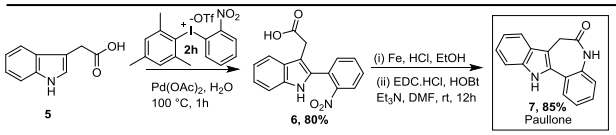
membered pyridyl carboxylic acids to produce nicotinic (**4o**) and isonicotinic acids (**4p-q**) in 82-88 % yields.

Table 3. Scope of hetero(aryl)carboxylates[a]



[a]Reaction Conditions: **1**(1.0 equiv), **2** (1.0 equiv), DMF (0.5 mL) 100 °C, 12 h; isolated product yields, [b]reaction time 3h

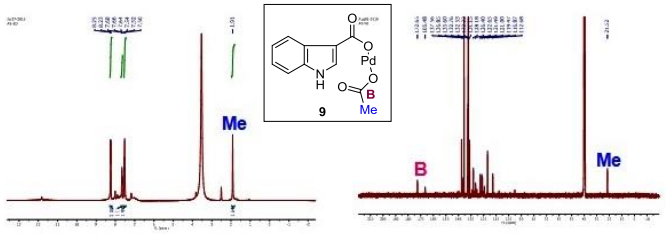
To prove the synthetic utility of identified protocol, we prepared Paullone (**7**), a well-known cyclin-dependent kinase (CDK) inhibitor,[17] in 85% yield from the reaction of indole-3-acetic acid (**5**) and iodonium salt **2h.** Aryl intermediate **6** was converted into Paullone **7** by reducing the nitro group and followed by amide coupling as depicted in scheme 1. To demonstrate the scalability of the reaction (Table 1), we successfully isolated **3a** (1.07g) in 90 % yield from the reaction



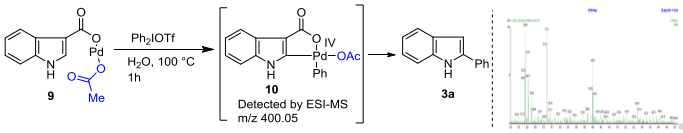
Scheme 1. Synthesis of CDK-Inhibitor, Paullone

of indole-3-carboxylic acid (**1a**, 1g) with mesityl(phenyl)iodonium salt (**2b**). Generated iodomesitylene during the reaction, was recovered and reused for the synthesis of mesityl(phenyl)iodonium salt (**2b**) indicating that the developed protocol is highly economical.

To gain the mechanistic understanding of decarboxylative C2-arylation, acid **1a** (0.31 mmol) was refluxed with equimolar quantity of $Pd(OAc)_2$ (0.31 mmol) in water for ten min. The resulting mixture was analyzed by NMR (^1H & ^{13}C), Mass and IR spectral data (See the Supporting Information). Appearance of characteristic peaks at δ 1.91 ppm ($-CH_3$) in ^1H NMR and at δ 172.6 ppm (>C=O) in ^{13}C NMR (Scheme 2) indicates the formation of Pd(II)carboxylate **9**.

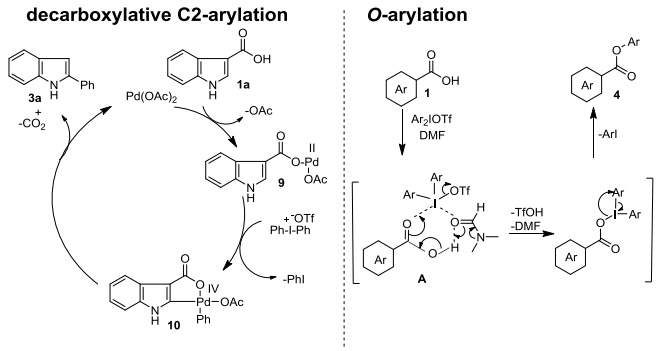


Scheme 2. Evidence for Pd(II) carboxylate 9



Scheme 3. Reaction of 2a with 9

Subsequently, isolated Pd(II)carboxylate **9** was treated with iodonium salt **2a** (0.31 mmol) under identical conditions (See the Supporting Information) and obtained **3a** in 90% yield**.** Also, during the reaction (after ten min), the crude mixture was subjected to mass spectrometry analysis which showed a peak at m/z 400.05, corresponds to the proposed Pd(IV) complex **10** (Scheme 3). These experimental observations are indicating that the C2-arylation is likely to proceed *via* palladium intermediates **9** and **10**. Literature reports[2c,18] and our findings (Schemes 2 and 3) in the formation of **3**, suggest that the initial reaction of indole-3-carboxylic acid (**1a**) with $Pd(OAc)_2$ provides Pd(II) carboxylate **10** with the concomitant release of acetic acid. Next, oxidative addition of complex **9** with diphenyliodonium triflate likely to furnish Pd(IV) **10** which upon reductive elimination and decarboxylation believed to produce the desired C2-arylated product **3a** along with regeneration of the catalyst (Scheme 4).



Scheme 4. Plausible mechanism for 3 and 4

In O-arylation of carboxylic acid **1**, it is believed that carboxylic acid **1** and iodonium salt **2** in DMF may form six-membered transition state **A** which undergoes migration and reductive elimination[18d] as depicted in scheme **4** to afford the anticipated product **4**.

In summary, we have developed a simple approach to prepare 2-arylindoles and heteroaryl carboxylates in a regioselective fashion using easily accessible heteroaryl carboxylic acids and diaryliodonium salts. The C2-arylation of indole derivatives proceed *via* decarboxylative coupling using

only catalytic amount of $Pd(OAc)_2$ (1.0 mol%) in water. Base-free O-arylation of heteroaryl carboxylic acids occurred in neat DMF. The developed protocol was successfully progressed without any ligand, oxidant, base and acid to prepare a range of heteroaryl carboxylic carboxylates in good to excellent yields. The synthetic utility of the developed procedure was proved by preparing CDK inhibitor, Paullone in good yield. Detailed mechanistic investigation and application of this strategy to other heterocyclic systems are ongoing and will be disclosed in due course.

Experimental Section

a) **Preparation of 2-phenylindole (3a)**

In an oven dried round bottomed flask (10 mL), indole-3-carboxylic acid (**1a**, 100 mg, 0.62 mmol) mesityl(phenyl)iodonium salt (**2b**, 293 mg, 0.62 mmol), $Pd(OAc)_2$ (1.4 mg, 0.0062 mmol) and water (1 mL) were added sequentially. The mixture was stirred at 100 °C for 1h. After the completion of reaction, contents were allowed to cool at room temperature. The reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. After removal of the organic solvent, the residue so obtained was purified by silica gel column chromatography (hexane/ethyl acetate 8:2) and obtained the desired 2-phenylindole **3a** in 91% (102 mg) yield.

b) **Preparation of phenyl-1*H*-indole-3-carboxylate (4a)**

In an oven dried 10 mL round bottomed flask, indole-3-carboxylic acid (**1a**) (100 mg, 0.62 mmol) and diphenyliodonium salt (**2a**, 267 mg, 0.62 mmol) were taken in DMF (0.5 mL). The mixture was stirred at 100 °C for 12h. Progress of the reaction was monitored by TLC. Once the reaction got completed, the contents were poured into ice and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained residue was purified through column chromatography (hexane/ethyl acetate 7:3) to afford white crystalline solid, phenyl-1*H*-indole-3-carboxylate (**4a**) in 80% (111 mg) yield.

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Keywords: Diaryliodonium salt • Decarboxylative C-C coupling • Pd-catalyst • Indole • Arylation

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[19] The reaction of indole with diphenyliodonium salt (**2a**) under the identified conditions afforded a mixture of 2-phenylindole (**3a**, 70% yield) and 3-phenyl-indole (10% yield).

Entry for the Table of Contents (Please choose one layout)

Layout 1:

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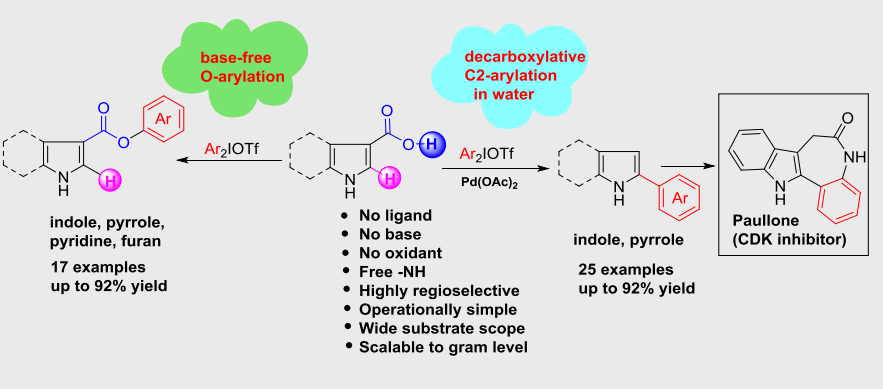

Diaryliodonium salts

*V. Arun, Meenakshi Pilania, Dalip Kumar**

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An Access to 2-Arylindoles *via* Decarboxylative C-C Coupling in Aqueous Medium and Heteroaryl Carboxylates under Base-Free Conditions using Diaryliodonium Salts

Diaryliodonium salts has been successfully employed to construct 2-arylindoles using decarboxylative C-C coupling strategy in water and heteroaryl carboxylates under base-free conditions