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Synthesis of phenanthridine and its analogues via aerobic ligand-free domino Suzuki coupling–Michael addition reaction catalyzed by in situ generated palladium-nanoparticles in water

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ABSTRACT

A convenient methodology has been developed towards the synthesis of substituted phenanthridines and analogous benzo[*k*] and benzo[*i*] derivatives via aerobic ligand-free domino Suzuki coupling–Michael addition reaction in the presence of $Pd(OAc)_2$ and K_3PO_4 as a catalytic system in H_2O at 90 °C in good yields. Reaction was believed to be catalyzed by in situ generated palladium nanoparticles in water with the elimination of acetone.

Transition-metal catalyzed C–C bond formation reactions have been extensively exploited towards the synthesis of many important carbocycles and heterocycles over last few decades.[1] Palladium-based methodologies have been used as an important synthetic tool[2] because of their functional group tolerance[3], stereo- and regioselectivity,[4] and significant yields under mild reaction conditions.[5]

Phenanthridines serve as the core structure of a number of biologically active natural products demonstrating important pharmacological effects including antifungal, antibacterial, antitumor, anticancer activities,[6] and SPECT tracers.[7] Figure 1 represents some therapeutically promising compounds of this class.[7–9] They are also receiving growing attention in materials research because of their opto-electronic properties.[10]

Because of such potential therapeutic and material properties, synthesis of phenanthridine skeletons via novel and shorter synthetic methodology has become a research interest over the last few decades. Recently, Zhang et al. reported the copper-catalyzed synthesis of phenanthridine derivatives from biaryl-2-carbonitriles and Grignard reagents.[11] Buden et al. reported the electron-transfer-mediated synthesis of phenanthridines by the intramolecular arylation of anions from *N*-(*ortho*-halobenzyl)arylamines.[12] Chattopadhyay and co-workers synthesized phenanthridine skeleton from 2-allyl aniline derivatives via ring closing enyne metathesis (RCEYM) followed by Diels–Alder aromatization.[13] Li et al. synthesized phenanthridine and benzo[*i*]phenanthridine derivatives from nitroarylstannanes and 2-bromobenzaldehyde and/or 2-bromo-1-naphthaldehyde followed by reduction with zinc dust in acetic acid.[14] Our aim was to synthesize phenanthridine using environmentally benign and mild reaction conditions. Recently our group reported an aerobic ligand-free palladium nanoparticle catalyzed synthesis of benzo[*c*]chromene derivatives via domino Suzuki coupling–Michael addition reaction.[15]

Following this strategy, herein we report an aerobic ligand-free synthesis of phenanthridine and its analogues by the treatment of 2-aminophenylboronic acid with β-(2-bromoaryl)-α,β-unsaturated carbonyl compounds (**3a–3h**) which were synthesized by Wittig reaction from 2-bromocarboxaldehydes (**1a–1h**) using 1-(triphenylphosphoranylidene)-2-propanone **2** in dry dichloromethane (DCM) at 0 °C to rt for 3 h (Scheme 1).[16] Aromatic *ortho*-bromonaphthaldehydes were synthesized from the corresponding tetralones via the Vilsmeier–Haack type reaction followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation.[17] Here C–C and C–N bonds are formed simultaneously in a domino Suzuki coupling followed by Michael addition fashion in water with the elimination of acetone leading to the formation of phenanthridine (Scheme 2).

3a was initially reacted with 2-aminophenylboronic acid **4** in the presence of $Pd(OAc)_2$ catalyst, Et_3N base, PPh_3 ligand, and tetrabutylammonium bromide (TBAB) in water at 90 °C for 5 h to give

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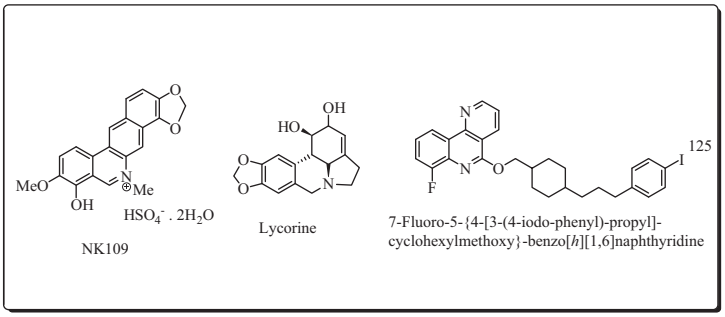
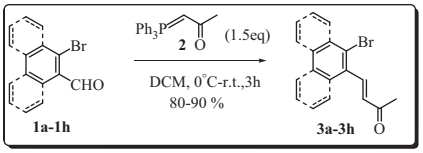


Figure 1. Bioactive molecules containing phenanthridine moieties.



Scheme 1. Wittig reaction with 2-bromocarboxaldehydes.

phenanthridine **5a** in 72% yield. After screening through a number of Pd catalysts and bases, the domino reaction was found to be most effective with Pd $(OAc)_2$ (10 mol %), K_3PO_4 (2 mmol), and TBAB (0.5 mmol) when 1 mmol of **3a** was reacted with 1.6 mmol of 2-aminophenylboronic acid in water at 90 °C for 5 h to give 85% isolated yield (Table 1, entry 4). The reaction was observed to be faster and high yielding in the absence of ligand and K_3PO_4 acted as a base as well as a stabilizer of Pd nanoparticles.[18]

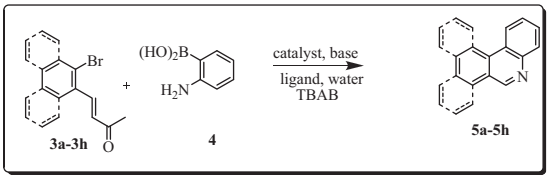
With this optimized conditions, the methodology was generalized towards the synthesis of various substituted phenanthridines (Table 2), its analogous benzo[*k*] (Table 3) and benzo[*i*] (Table 4) derivatives in good yield.

Next, the correct sequence for cyclization was determined by heating **3a** with 2-aminophenylboronic acid without Pd catalyst keeping all other conditions intact. No reaction was observed. This might be due to the bulkiness of the Michael donor and acceptor (Scheme 3).

Hence, the reaction course can be concluded to proceed through Suzuki coupling followed by intramolecular Michael addition and the elimination of acetone molecule (Scheme 4). Here, 2-aminophenylboronic acid itself acted as the reducing agent.[19] On heating a solution of 2-aminophenylboronic acid in water with Pd $(OAc)_2$ in the absence of β-(2-bromoaryl)-α,β-unsaturated carbonyl compound, TBAB or PPh_3, the solution turned black immediately indicating the formation of Pd(0).

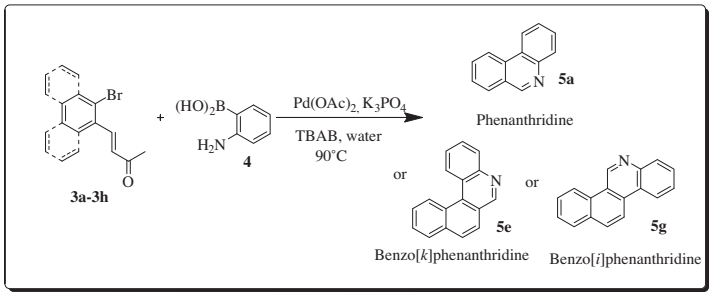
The intermediate after Suzuki coupling **6,** being a very reactive system because of the close proximity of NH^- ion and the β-carbon of the α,β-unsaturated ketone, underwent intramolecular Michael addition immediately. So, **6** could never be isolated. The cross coupling step was catalyzed by in situ generated Pd-nanoparticles. Finally, acetone was eliminated to furnish the product **5a**. Aromaticity might be the driving force for the elimination of acetone.

Table 1
Optimazition studies[a,b]



Entry	Catalyst	Ligand	Base	Temp (°C)	Yield[c] (%)
1	$Pd(OAc)_2$	PPh_3	Et_3N	90	72
2	$Pd(OAc)_2$	PPh_3	K_3PO_4	90	76
3	$Pd(OAc)_2$	—	Et_3N	90	75
4	**$Pd(OAc)_2$**	**—**	**K_3PO_4**	**90**	**85**
5	$Pd(OAc)_2$	—	K_2CO_3	90	65
6	$Pd(OAc)_2$	—	Cs_2CO_3	90	80
7	$Pd(OAc)_2$	—	NaOAc	100	64
8	$Pd(OAc)_2$	—	$KOBu^t$	90	73
9	$Pd(OAc)_2$	—	Na_2CO_3	100	59
10	$PdCl_2(CH_3CN)_2$	—	K_3PO_4	90	62
11	$PdCl_2$	—	K_3PO_4	100	52

Bold values signify optimal reaction condition.
[a] Reagents and conditions: **3a** (1 mmol), 2-aminophenylboronic acid (1.6 mmol), Pd catalyst (10 mol %), base (2 mmol), TBAB (0.5 mmol), and water (5 mL) for 5 h.
[b] Reaction was done in a two-necked round-bottomed flask fitted with condenser.
[c] Yields refer to the isolated yields after purification through column chromatography.



Scheme 2. Synthesis of phenanthridine and its analogues.