Domino Suzuki-Miyaura cross-coupling and oxidative condensation reaction: an approach towards synthesis of phenanthridine and its analogues

Yasin Nuree and Jayanta K. Ray*

Department of Chemistry, Indian Institute of Technology, Kharagpur -721302, India

Introduction

The phenanthridines are very important class nitrogen containing heterocylic compounds and constitute core structure of many natural alkaloids[1, 2] such as trisphaeridine (**Fig. 1, 1**) and nitidine (**Fig. 1, 2**)[3-22]. Quarternarybenzo[*c*]phenanthridine alkaloids (QBA) represented by sanguinarine(SA), chelerythrine (CHE), and fagaronine (FA) (**Fig. 1, 3**) exhibit antifungal and nematocidal properties.[4, 5, 15, 18-20, 22, 23] These azaheterocyclic compounds also serve as the core structure of broad range of medicinally active molecules showing anti-tumor activity, anti-viral property, anti-neoplastic or mutagenic activity through DNA-intercalation.[5] Phenanthridines are also utilized for the synthesis of compounds of therapeutic interests such as anticancer platinum complex typified by phenanthriplatin (**Fig. 1, 4**),[24] antibacterial, anti-infectives, antprotozoal, antituberculosis, antitrypanosomiasis compounds[5, 18, 19, 25-32]. The phenanthridine ring systems are also used in lockable colorimetric fluorescence molecular switch, PET tracers, and in material science applications[4, 15, 22, 33-48].

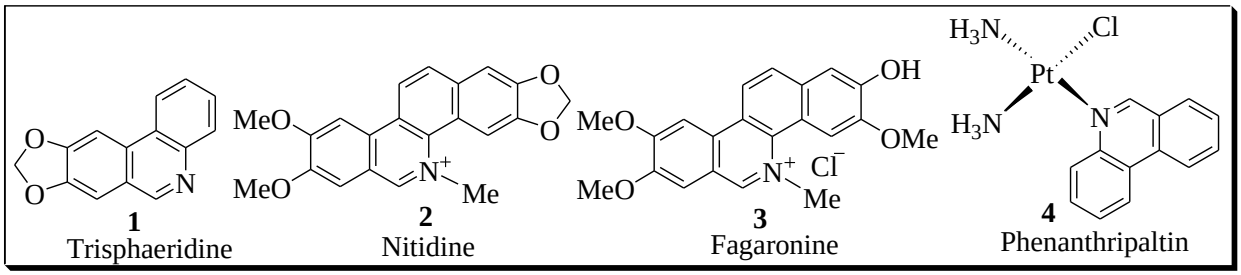
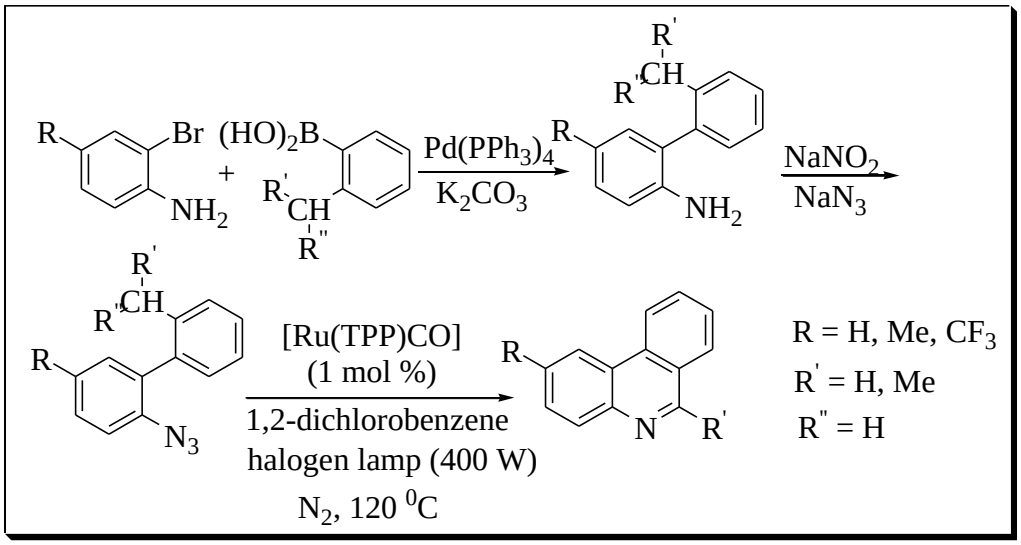


Figure 1. Structure of some bioactive molecules containing phenanthridine unit.

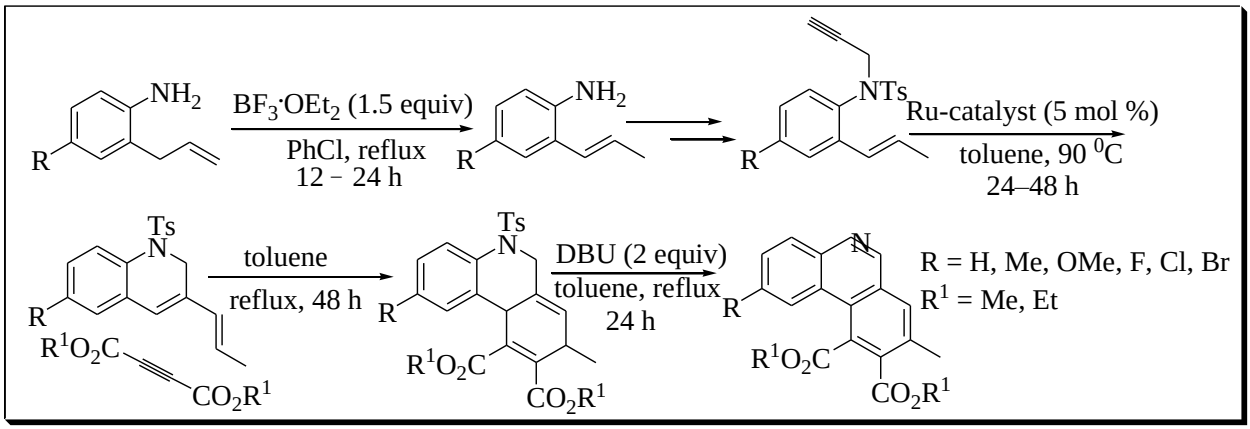
Potential biological activities and functional properties of phenathridines and its derivatives have

attracted the scientists over the decades towards the synthesis of these molecules. Various methods towards synthesis of these molecules are available in the literature. Recently, a three-step methodology to derive phenathridines via ruthenium catalyzed reactions was reported.

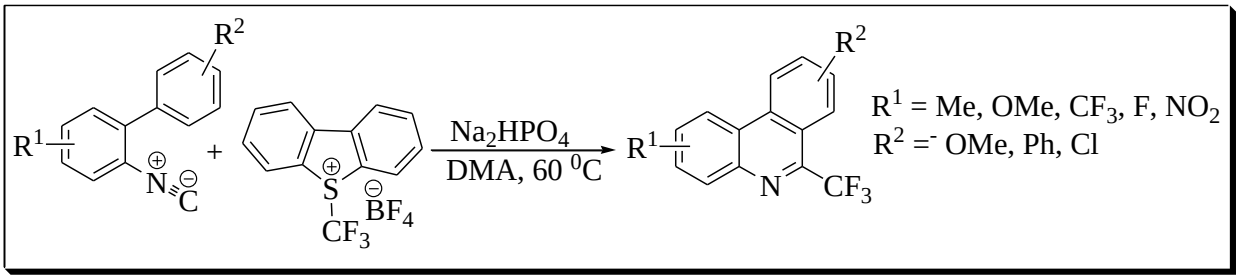


Scheme 1.1. Ruthenium catalyzed synthesis of phenanthridines

Mandal et al. designed a syntheticroute for the development of phenathridines based on aza-Claisen rearrangement, ring-closing enyne metathesis and Diels–Alder reaction.

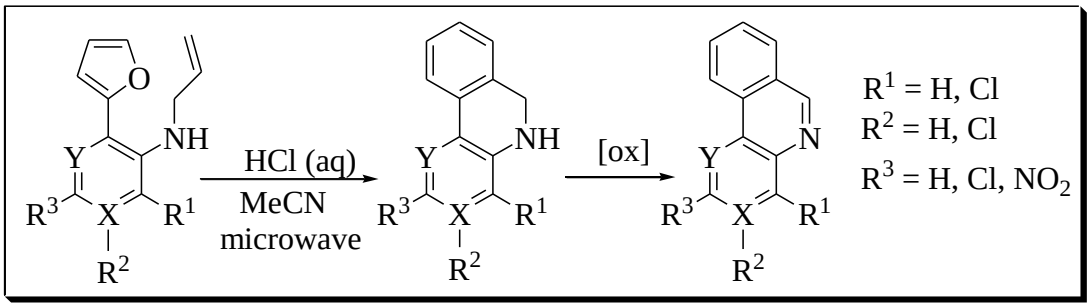


Scheme 1.2. Synthesis of phenanthridines via RCEYM followed and Diels-Alder aromatization



Scheme 1.3. De Novo Synthesisof Trifluoromethylated Phenanthridine Derivatives

Read et al. reported synthesis of phenanthridine derivatives through microwave-mediated cyclization of *o*-furyl(allylamino)arenes[49].



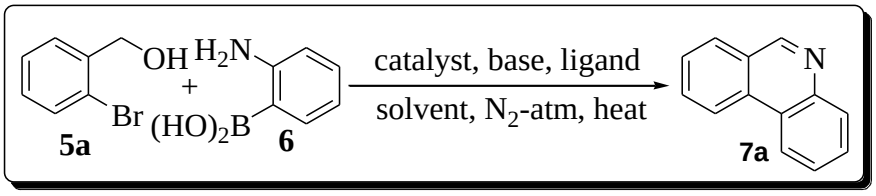
Scheme 1.4. Microwave assisted synthesis of phenanthridine derivatives.

Although these methods showed their own advantages, they generally involved either multistep processes with low yield, or starting materials which are not readily available or requirement of prefunctionalization. So, development of an efficient and convenient synthetic methodology is highly desirable.

Results and discussion

In the previous chapter we have used *o*-bromobenzyl alcohols and its analogues with 2-hydroxyphenylboronic acid for the synthesis of benzo[*c*]chromenones*via*palladium-catalyzed domino Suzuki-Miyaura cross coupling and oxidative lactonization. Here we have substituted 2-hydroxyphenylboronic acid with 2-aminophenylboronic acid. Our investigation started with our endeavor to get the optimal reaction condition.

Table 1 Screening of the reaction condition[a]



Entry	Catalyst	Base	Ligand	Solvent	Temp (^{0}C)	Time (h)	Yield (%)[b]
1	$PdCl_2$	Na_2CO_3	PPh_3	DMF	90	12	61
2	$PdCl_2$	Na_2CO_3	PPh_3	DMF	110	10	59
3	$PdCl_2$	Na_2CO_3	PPh_3	DMF	70	12	53
4	$Pd(PPh_3)_4$	Na_2CO_3	PPh_3	DMF	90	10	45
5	$Pd_2(OAc)_2$	Na_2CO_3	PPh_3	DMF	90	10	75
6	**$Pd_2(OAc)_2$**	**K_2CO_3**	**PPh_3**	**DMF**	**90**	**8**	**87**
7	$Pd_2(OAc)_2$	Cs_2CO_3	PPh_3	DMF	90	9	82
8	$Pd_2(OAc)_2$	Et_3N	PPh_3	DMF	90	10	70
9	$Pd_2(OAc)_2$	K_3PO_4	PPh_3	DMF	90	8	81
10	$Pd_2(OAc)_2$	K_2CO_3	PCy_3	DMF	90	9	85
11	$Pd_2(OAc)_2$	K_2CO_3	–	DMF	90	18	–
12	$Pd_2(OAc)_2$	K_2CO_3	PPh_3	CH_3CN	90	10	49
13	$Pd_2(OAc)_2$	K_2CO_3	PPh_3	Dioxane	90	10	63
14	$Pd_2(OAc)_2$	K_2CO_3	PPh_3	H_2O	90	24	–

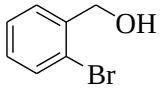
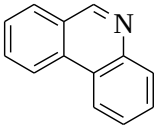
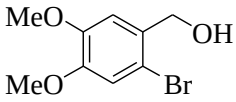
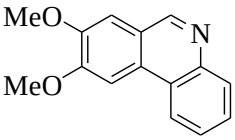
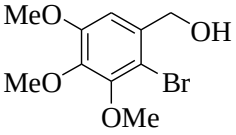
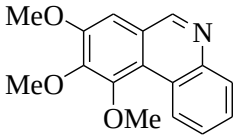
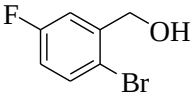
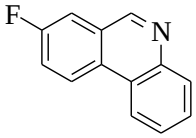
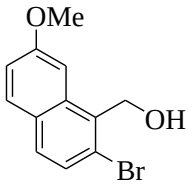
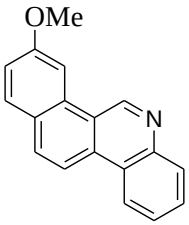
[a]Reagents and conditions: **5a** (0.5 mmol), 2-aminophenylboronic acid (0.55 mmol), palladium catalyst (10 mol %), base (1.5 equiv), ligand (0.25 equiv) and solvent (3 mL), N_2.

[b]Isolated yield after purification through column chromatography.

Initially **5a** was allowed to react with **6** in presence of $PdCl_2$catalyst, sodium carbonate base, PPh_3ligand and DMF as solvent at 90 ^{0}C. Then temperature, catalyst, base, ligand and solvent were varied successively in order to get the optimized reaction condition. The optimal condition was found to be $Pd(OAc)_2$-catalyst, K_2CO_3 base, PPh_3 ligand, and DMF solvent at 90 ^{0}C.

With this optimized condition, the methodology was generalized towards the synthesis of various substitutedphenanthridines (**Table 2**)

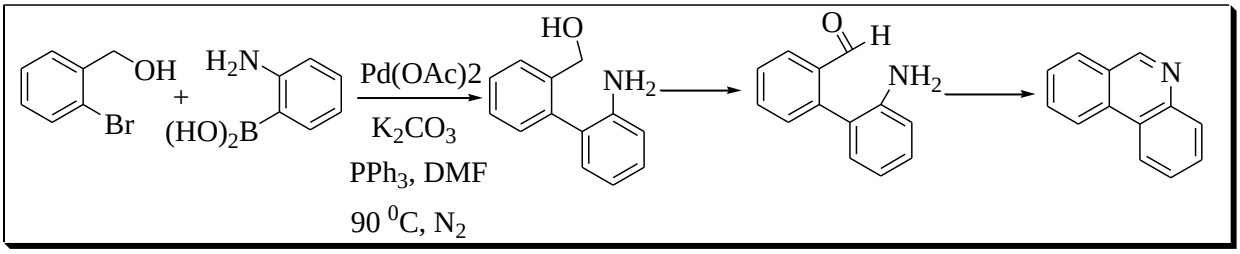
Table 2 Synthesis of phenanthridines [a]

Entry	Substrate	Product	Yield (%) [b]
1			87
2			76
3			70
4			63
5			72

[a]Reagents and conditions: **5a-e** (0.5 mmol), 2-aminophenylboronic acid (0.55 mmol), $Pd(OAc)_2$(10 mol %), K_2CO_3 (1.5 equiv), PPh_3 (0.25 equiv) and DMF (3 mL), N_2.

[b]Isolated yield after purification through column chromatography.

As a course of mechanistic explanation, it can be postulated that Suzuki-Miyaura cross-coupling occurs first, followed by oxidation of the benzylic alcohol group to aldehyde. Then condensation is followed. Isolation of the intermediate and more studies are underway to know the exact pathway



Scheme 2 Plausible rationale for the formation phenathridines

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Conclusion:

In summary we have developed a short and convenient methodology for the synthesis of phenanthridines from readily available starting material. Our methodology will be helpful towards the synthesis of substituted phenanthridine derivatives which can be further used for important pharmaceutical and material applications.

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