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Assembly of substituted phenanthridines via a cascade palladium-catalyzed coupling reaction, deprotection and intramolecular cyclization

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The discovery and development of a general method for one-pot synthesis of substituted phenanthridines is presented. In the presence of $Pd(PPh_3)_4$, accessible precursors undergo Suzuki cross-coupling reaction with 2-(Boc-amino)benzeneboronic acid pinacol ester and then spontaneously undergo a deprotection and intramolecular condensation to form the corresponding phenanthridines in one step. This reaction has a wide range of substrates with various functional groups, and the corresponding products have been obtained in good yields.

Introduction

Substituted phenanthridines are an important class of heterocyclic compounds in material science and in medicinal chemistry due to their significant biological activities.[1-3] Molecules containing the phenanthridine core are the subject of considerable interest as potent antitumor agents,[4] anti-tuberculosis agents,[5, 6] and antibacterial agents.[7] Structures, shown in **Figure 1**, are representative examples of natural products and biologically relevant compounds containing phenanthridine core structures.[8-17] Because of these applications, synthesis of substituted phenanthridine motif has spurred vigorous research for the development of new methodologies.

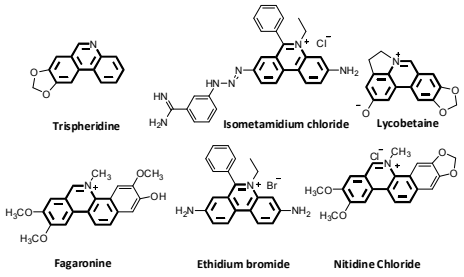
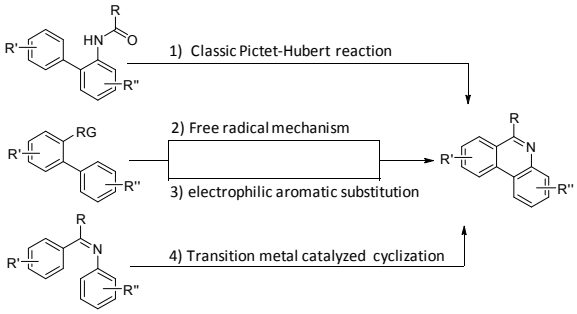


Figure 1. Examples of natural products and biologically relevant compounds

Traditionally, phenanthridines are synthesized by the Pictet-Hubert reaction, which usually performed in the presence of P_4O_{10}, $POCl_3$, or PCl_5 at elevated temperatures.[18-21] The limitation of functional group tolerance was observed in the Pictet-Hubert reaction due to the harsh conditions. Besides the traditional methods, phenanthridines have recently been successfully prepared by transition metal catalyzed approaches,[22-30] radical promoted cyclization,[31-41] cycloaddition,[42-45] and other methods.[46-48] The general synthetic approaches leading to phenanthridines are summarized in **Scheme 1**. Although a number of methods are available for the synthesis of these phenanthridines, many are limited because of the lack of generality, limited functional group tolerance, and lengthy synthetic time. Thus, a simple, efficient, and general method to synthesize phenanthridines would be still attractive.



Scheme 1. Synthetic approaches leading to phenanthridines

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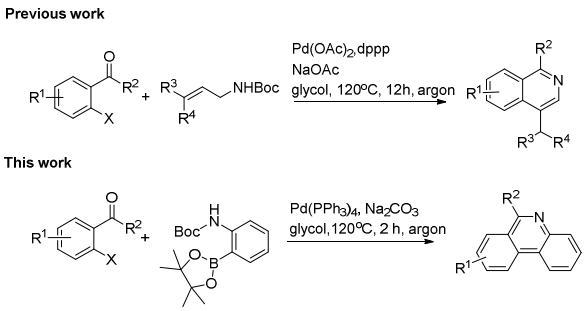


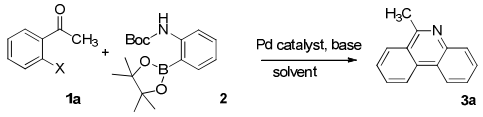
Scheme 2. Strategies for the construction substituted phenanthridines

Among synthesis methodology research towards phenanthridines, James and his coworker first attempted to use 2'-Bromoacetophenone and (2-Boc-aminophenyl)boronic acid to construct the phenanthridines scaffold using a stepwise strategy by a Suzuki cross-coupling reaction, followed by acid-catalyzed N-Boc removal, intramolecular cyclization and basification.[49] Subsequently, Marko published the synthesis method of a Lycobetaine–Tortuosine analogue, which also included the metal catalyzed coupling and acid hydrolysis steps.[50] Obviously, amide or ester substituted materials were not tolerated during the second acid work up step. Additionally, Graham also mentioned a Suzuki coupling/ring closure to prepare the norallonitidine and norntidine. However, the reactions were claimed to be sluggish and the products were achieved with low yields.[51] Recently, Dhara also reported a method to synthesize substituted phenanthridines using substituted aromatic *ortho*-bromoaldehydes and *ortho*-aminobenzeneboronic acid as starting substrates.[52] In our previous studies, we showed a new approach for constructing 1-substituted-4-methylisoquinolines via a cascade Pd-catalyzed Heck reaction, intramolecular cyclization and isomerization.[53] In order to extend our study about synthetic methodology of heterocyclic compound, [54-57] we applied this strategy to the construction of phenanthridines (**Scheme 2**).

Results and discussion

Initially, 2-iodoacetophenone (**1a**) and 2-(Boc-amino)benzeneboronic acid pinacol ester (**2**) were chose as the model substrates to explore the possible formation of 6-methyl phenanthridine(**3a**) and the results were summarized in **Table 1**. The reaction proceeded in glycol at 120 °C for 2 hours with $Pd(OAc)_2$ as the catalyst, 1,3-Bis(diphenylphosphine)propane (dppp) as the ligand, Cs_2CO_3 as the base. To our delight, **3a** was obtained in 44% yield (**Table 1**, **entry 1**), indicating that it was feasible to construct the phenanthridine scaffold based on our hypothesis. However, changing the base Cs_2CO_3 to NaOAc or organic base Et_3N failed to show any improvement (**Table 1**, **entries 2-3**). When ligand dppp was replaced with 1, 1'-bis(diphenylphosphino)ferrocene (dppf), the result was similar to dppp with a yield of 37% (**Table 1**, **entry 4**). We then screened catalysts such as $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ (**Table 1**, **entries 5-7**).

Table 1. Screening of the reaction conditions[a]



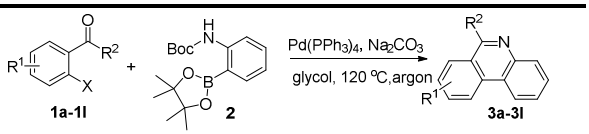
Entry	X	Catalyst	Ligand	Base	Solvent	Yield[b]
1	I	$Pd(OAc)_2$	dppp	Cs_2CO_3	glycol	44%
2	I	$Pd(OAc)_2$	dppp	NaOAc	glycol	0
3	I	$Pd(OAc)_2$	dppp	Et_3N	glycol	10%
4	I	$Pd(OAc)_2$	dppf	Cs_2CO_3	glycol	37%
5	I	$Pd(PPh_3)_2Cl_2$		Cs_2CO_3	glycol	14%
6	I	$Pd_2(dba)_3$		Cs_2CO_3	glycol	17%
7	I	$Pd(PPh_3)_4$		Cs_2CO_3	glycol	73%
8	I	$Pd(PPh_3)_4$		Na_2CO_3	glycol	80%
9	I	$Pd(PPh_3)_4$		K_2CO_3	glycol	76%
10	I	$Pd(PPh_3)_4$		K_3PO_4	glycol	67%
11	OTf	$Pd(PPh_3)_4$		Na_2CO_3	glycol	75%
12	Br	$Pd(PPh_3)_4$		Na_2CO_3	glycol	71%
13[c]	I	$Pd(PPh_3)_4$		Na_2CO_3	EtOH	6%
14	I	$Pd(PPh_3)_4$		Na_2CO_3	DMF	20%

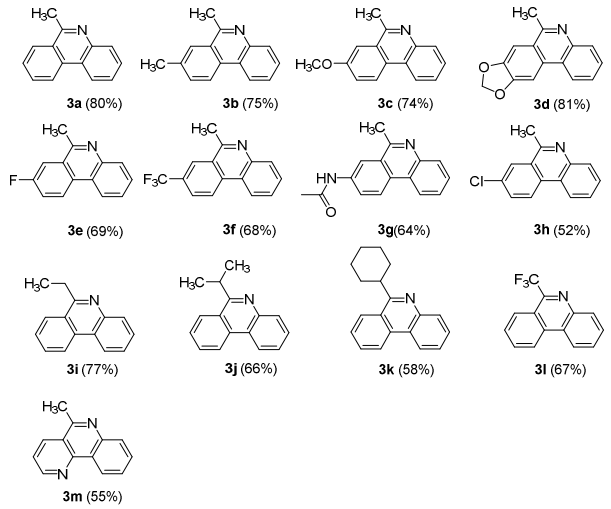
[a]all reactions were conducted using **1a** (1mmol, 1.0 equiv), **2** (1.2mmol, 1.2 equiv), base (2mmol, 2.0 equiv), Pd catalyst (3mmol%), solvent (3.0 mL), stirred at 120 °C for 2 h under argon. [b]Isolated yields. [c]the reaction was conducted at 85 °C for 4 h under argon.

The results showed that $Pd(PPh_3)_4$ displayed the highest catalytic activity toward the formation of **3a** in 80% yield. Keeping the $Pd(PPh_3)_4$ as the catalyst, other bases such as Na_2CO_3, K_2CO_3 and K_3PO_4 were examined subsequently (**Table 1**, **entries 8-10**). The results showed that carbonates were better than K_3PO_4, but there was little difference among Na_2CO_3, K_2CO_3 and Cs_2CO_3. We also investigated the effect of reactive group X in substrates. It was found that Br and OTf gave a similar performance as I (**Table 1**, **entries 11-12**). Varying the solvents proved glycol to be optimal (**Table 1**, **entries 8**, **13-14**). Consequently, we decided to use entry 8 as the optimal condition to investigate the application of this transformation.

After the optimized reaction condition was established, we then attempted to apply it to synthesize a series of 6-alkylphenanthridines. As shown in **Table 2**, when R^1 were electron-donating groups such as alkyl and alkoxyl as well as

Table 2. Synthesis of 6-alkylphenanthridines [a,b]





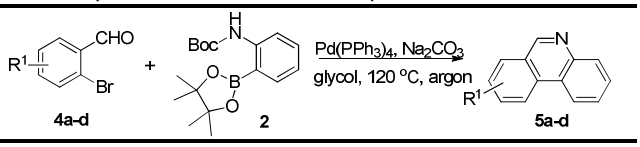
[a]all reactions were conducted using **1a-l** (1mmol, 1.0 equiv), **2** (1.2mmol, 1.2 equiv), base (2mmol, 2.0 equiv), $Pd(PPh_3)_4$ (3mmol%), solvent (3.0 mL), stirred at 120°C for 2 h under argon. [b] Isolated yields.

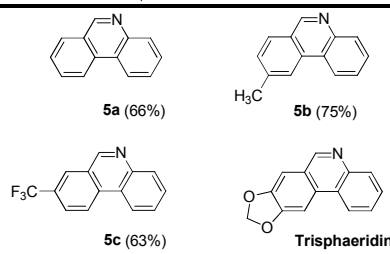
electron-withdrawing groups like fluoro, trifluoromethyl, substituted 6-methylphenanthridines were successfully obtained in good yields (**Table2**, **3b-3f**). We were pleased to find that amide group, sensitive to acid condition, was observed to tolerate this condition (**Table 2**, **3g**). A chloro group substituent of acetophenone had a negative effect on this reaction (**Table 2**, **3h**). This observation, combined with the fact that some aryl chlorides failed to be compatible well with palladium-catalyzed coupling reaction.[58, 59]

On the other hand, the R^2 substitution effect of phenones was then investigated in reactions with **2**. The ethyl, isopropyl and cyclohexyl substituted phenones reacted efficiently, affording corresponding phenanthridine derivatives in yields ranging from 58 to 77% (**Table 2**, **3i-3k**). Interestingly, when R^2 was trifluoromethyl group, the corresponding product was obtained in 67% yield (**Table 2**, **3l**). Additionally, pyridine fused phenanthridine was also constructed in the current reaction system and obtained with 55% yield (**Table 2**, **3m**).

Next, we turned our attention to explore whether substituted bromobenzaldehyde could work well in this reaction system. It was found that substrates bearing an electron-donating group smoothly afford the corresponding phenanthridines in good yields (**Table 2**, **5b**). Moreover, trifluoromethyl group substituted phenanthridine was

Table 3. Synthesis of 6-unsubstituted phenanthridines [a,b]



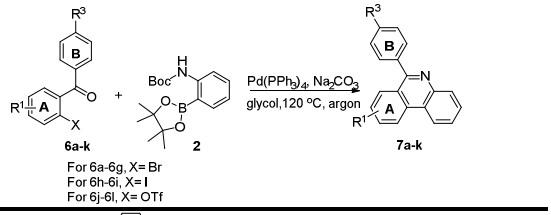


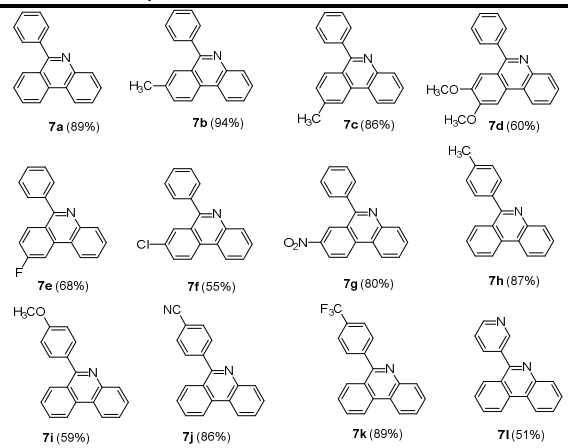
[a]all reactions were conducted using **4a-d** (1mmol, 1.0 equiv), **2**(1.2mmol, 1.2 equiv), base (2mmol, 2.0 equiv), $Pd(PPh_3)_4$ (3mmol%), solvent (3.0 mL), stirred at 120 °C for 2 h under argon. [b]Isolated yields.

obtained in 63% yield (**Table 2**, **5c**). Trisphaeridine, a natural product isolated from plants of *Amaryllidaceae*, was then synthesized through this method with 85% yield (**Table 2**, **5d**).[8]

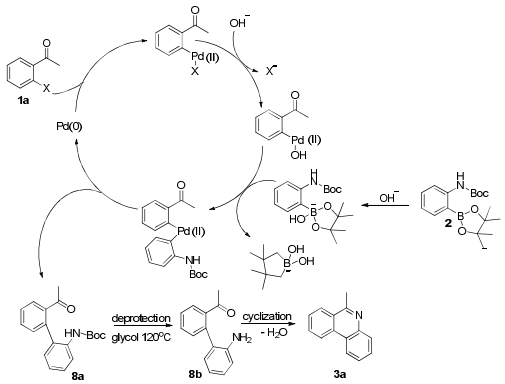
In light of the above results, 2-OTf/halide substituted benzophenones were then subjected to the same conditions to test the scope of the reaction. *o*-Bromobenzophenones reacted smoothly with **2** delivering corresponding phenylphenanthridines in good to excellent yields. In general, electron-donating and electron-withdrawing groups were found to be compatible on both the A and B phenyl rings. For A

Table 4. Synthesis of 6-arylphenanthridines [a,b]





[a]all reactions were conducted under argon using **6a-k** (1mmol, 1.0 equiv), **2** (1.2mmol, 1.2 equiv), $Pd(PPh_3)_4$ (3mmol%), Na_2CO_3 (2mmol, 2.0 equiv), solvent (3.0 mL), stirred at 120°C for 2 h under argon. [b]Isolated yields.



Scheme 3. A plausible reaction mechanism

phenyl ring, after two monosubstituted-6-phenyl-phenanthridines were obtained (**Table 4**, **7b-7c**), the 8, 9-dimethoxy -6-phenyl-phenanthridine was also obtained in 60% yield (**Table 4**, **7d**). With respect to halide-substituted substrate, the chloro-substituted substrate afforded the product in a lower yield than the corresponding fluoro-substituted substrate (**Table 4**, **7e-7f**), which was consistent with our previous finding. Moreover, 3-nitro-6-phenylphenanthridine was also successfully obtained in 80% yield (**Table 4**, **7g**). When the substituted groups at the *para*-position of B phenyl ring were methyl, nitrile and trifluoromethyl groups, the corresponding substituted phenanthridines were obtained in good yields (**Table 4**, **7h, 7j-k**). However, When the R^3 group of B phenyl ring was methoxy group, the yield was 59% (**Table 4**, **7i**). Noticeably, changing the B phenyl ring to pyridine ring, the corresponding product was obtained in 51% yield (**Table 4**, **7l**)

On the basis of above observations, a plausible mechanism for the reaction is proposed in **Scheme 3**. First, the substrate **1a** and **2** undergo a typical Suzuki coupling reaction to afford intermediate **8a**. Then the deprotection of N-Boc group occurs by the promotion of glycol to afford intermediate **8b**. Finally, product **3a** is obtained by the intramolecular condensation reaction between amino and carbonyl group.

Conclusions

In summary, we have reported a practical method for one-pot synthesis of substituted phenanthridines, using 2-acylphenyl triflates/halide and 2-(Boc-amino)benzeneboronic acid pinacol ester as the starting materials. A series of substituted phenanthridines with various functional groups are obtained by this method. Our method has several advantages as follows: (a) easily accessible precursors; (b) short reaction time; (c) good functional groups compatibility. The present method therefore would serve as a powerful tool to construct heterocyclic scaffolds that are beneficial for medicinal chemistry and material science.

Acknowledgements

This work was financially supported by National Natural Science Foundation of China (No. 81473096).

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