Efficient Synthesis of Phenanthridines Using Hendrickson Reagent Initiated Cascade Reaction under Mild Conditions

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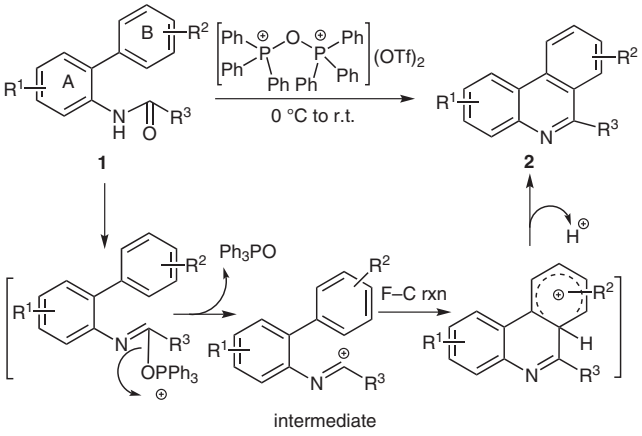
Received 16 April 2010

Abstract: A number of variously substituted phenanthridines have been synthesized using the newly developed methodology under mild conditions. The Hendrickson reagent initiated cascade annulation, which is composed of a mild conversion of stable amide precursor to highly reactive imido-carbonium intermediate and a subsequent intramolecular Friedel–Crafts reaction, successfully served as the key method.

Key words: phenanthridine, cascade reaction, Hendrickson reagent, carbocation, Friedel–Crafts reaction

Phenanthridine is a representative core structure of many alkaloids with interesting biological and pharmaceutical activities[1] and of some materials with optical properties.[2] Considerable attentions have been paid in organic synthesis to construction of variously substituted phenanthridines. In the past several decades, quite a number of methods have been developed, including Bischler–Napieralski cyclizations with P_4O_{10}, $POCl_3$, or PCl_5 under high-temperature conditions[3] and some recent achievements using multistep syntheses with metal catalysts under heating, microwave irradiation, or higher temperature conditions.[4] A three-component reaction has also been developed for the synthesis of phenanthridines by heating the mixture of aromatic aldehyde, aniline, and benzenediazonium-2-carboxylate in dichloroethane at 80 °C.[5] Because of broad applications of phenanthridine derivatives, further development of mild, efficient, and flexible syntheses of phenanthridines is of great significance.

In our recent total syntheses of camptothecin-family alkaloids,[6] Hendrickson reagent[7] was successfully employed as a powerful reagent to convert stable aniline amides to corresponding imidates at ambient temperature. Such reactive intermediates were further found to undergo a variety of subsequent reactions, such as intramolecular Diels–Alder reactions with the dienophiles[6] and intermolecular electrophilic reactions with acetylenes.[8] Following the mechanisms, it was speculated that the in situ generated imido carboniums might react with the electron-rich arenes via Friedel–Crafts reaction. If this cascade works in an intramolecular way, it will provide a new protocol for the synthesis of various phenanthridine derivatives (Scheme 1). Herein, we wish to report our results in the synthesis of phenanthridines using the above-mentioned cascade reaction.



Scheme 1 Design of the cascade synthesis of phenanthridines in this work

Following the above tentative idea (Scheme 1), a number of biphenyl-2-amine amides **1** were synthesized for the examination. At first, starting from commercially available 2-iodoaniline (**3**), substrates **1a–j** (Scheme 1, R^1 = H, R^3 = Me) bearing a variable substituent R^2 on ring B were prepared by corresponding Suzuki couplings and N-acetylation. Then, they were examined under the standard conditions of our previous work (Table 1).[6–8] Reactions of **1a–i** with Hendrickson reagent were all smoothly carried out at 0 °C to room temperature in short times, affording phenanthridines **2a–i** in satisfactory yields (Table 1, entries 1–9). Obviously, the initial design of cascade synthesis of phenanthridines works. As the exception (entry 10), the amide **1j** bearing a NO_2 group on phenyl ring B failed to undergo the cascade reaction. Such a result could be explained by the strong electron-withdrawing effects of nitro group, which makes the final intramolecular Friedel–Crafts reaction unfavorable (Scheme 1). However, amide **1i** bearing a bromine atom could work well under the same conditions, affording the corresponding product **2i** in 78% yield (entry 9). Introduction of a halogen in the product will help many further modifications to improve the chemical and physical properties of phenanthridines in various applications. Poor regioselectivity was observed when the substrate bearing a methoxyl group at the C-3 position of phenyl ring B (**1c**, entry 3), and two separable isomers **2ca** and **2cb** (ratio = 1:2.5) were given.

SYNLETT 2010, No. 11, pp 1674–1678
Advanced online publication: 10.06.2010
DOI: 10.1055/s-0030-1258081; Art ID: W04310ST
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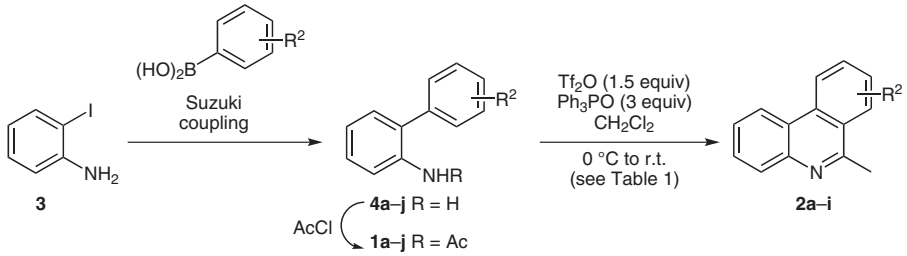
Table 1 Synthesis of Phenanthridines **2a–j** with a Variable Substituent (R^2)[a]



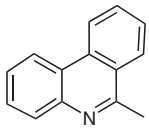
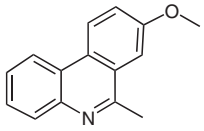
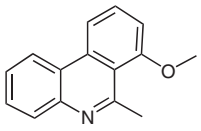
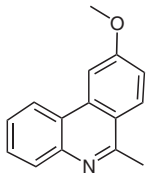
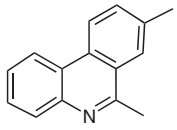
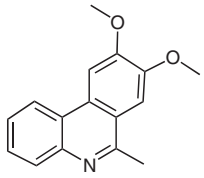
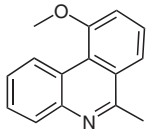
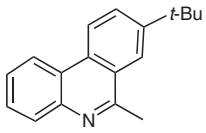
Entry	1	Yield of **2** (%)[b]
1	**1a** R^2 = H	 **2a** 95
2	**1b** R^2 = 4-MeO	 **2b** 95
		 **2ca** 26
3	**1c** R^2 = 3-MeO	 **2cb** 65
4	**1d** R^2 = 4-Me	 **2d** 90
5	**1e** R^2 = 3,4-di-MeO	 **2e** 87
6	**1f** R^2 = 2-MeO	 **2f** 91
7	**1g** R^2 = 4-*t*-Bu	 **2g** 89

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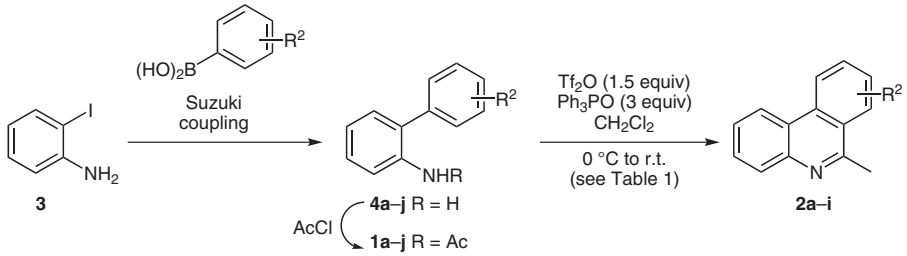
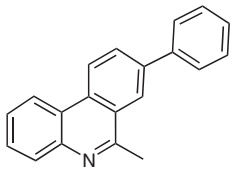
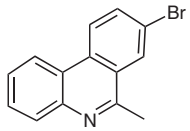
Table 1 Synthesis of Phenanthridines **2a–j** with a Variable Substituent (R^2)[a] (continued)

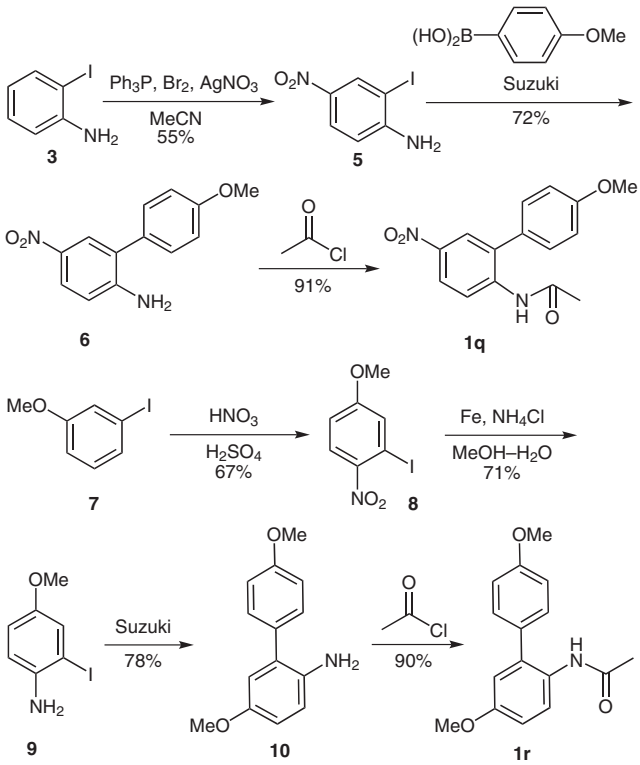


Entry	1	Yield of **2** (%)[b]
8	**1h** R^2 = 4-Ph	 **2h** 98
9	**1i** R^2 = 4-Br	 ***2i*** 78
10	**1j** R^2 = 3-O_2N	n.r.

[a] All reactions were completed in 5–30 min.
[b] Isolated yields.

To further examine the substrate scope and study the effects of substituent R^3 (Scheme 1, **1**, R^1 = H, R^2 = 4-MeO), several additional amides **1k–p** were prepared by acylation of a previously prepared amine **4b** with corresponding acid chlorides (Table 2). Again, smooth reactions were observed in all examined cases under the standard conditions, affording the corresponding phenanthridines **2k–p** in reasonable to satisfactory yields (Table 2). Compared to other substrates, reaction of formamide **1k** (entry 2) provided only 30% yield of product **2k**. It is believed that stability of the carbocationic intermediates involved in this type of reactions (Scheme 1) is crucial to achieve a better yield, and reaction of **1k** (entry 2, R^3 = H) proceeded via the relatively unstable carbocationic intermediates during its cascade process. In another experiment of amide **1l** having a bulky group (entry 3, R^3 = *t*-Bu), a relatively long reaction time (3 h) was observed. For those benzamides **1n–p** whose phenyl either with or without an electron-donating or an electron-withdrawing group, their reactions were carried out in short times, affording the corresponding products in satisfactory yields (entries 5–7).

In order to investigate electronic effects of phenyl ring A, two representative amides **1q–r** having a substituent R^1 (Scheme 1, **1**, R^2 = MeO and R^3 = Me) were prepared (Scheme 2). Amide **1q** with a nitro group was prepared by a three-step procedure, including aromatic nitration of 2-iodoaniline (**3**), Suzuki coupling with 4-methoxyphenyl boric acid, and N-acetylation. Similarly, the other amide **1r** having a methoxyl group was prepared from 3-iodoanisole **7**. Reduction of nitration product **8** with iron power in aqueous NH_4Cl afforded *o*-iodoaniline (**9**). Suzuki coupling of **9** with 4-methoxyphenyl boric acid followed by N-acetylation provided the required amide substrate **1r**.



Scheme 2 Synthesis of amide substrates **1q–r**

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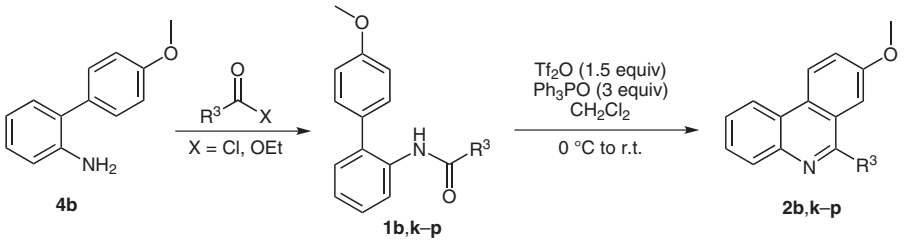
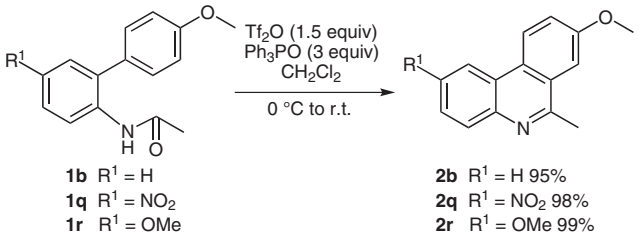
Table 2 Synthesis of Phenanthridines **2k–p** with a Variable Substituent (R^3)[a]



Entry	1	Yield of 2 (%)
1	**1b** R^3 = Me	**2b** 95
2[b]	**1k** R^3 = H	**2k** 30
3	**1l** R^3 = *t*-Bu	**2l** 93
4	**1m** R^3 = CH=CHOEt	**2m** 74
5	**1n** R^3 = Ph	**2n** 94
6	**1o** R^3 = 4-$MeOC_6H_4$	**2o** 97
7	**1p** R^3 = 4-$O_2NC_6H_4$	**2p** 75

[a] All reaction were completed in 5–30 min except entry 3 (3 h).
[b] Et_3N (3 equiv) was added.

Under the above mentioned conditions, two phenanthridines **2q** and **2r** were provided in excellent yields, respectively (Scheme 3). Results of these two examples and the previous reaction of **1b** (R^1 = H) indicate that electronic property of R^1 of amides **1** affects little in this type of cascade reactions.



Scheme 3 Synthesis of phenanthridines with a variable substituent R^1

In summary, a new efficient approach has been developed for the synthesis of various phenanthridines utilizing Hendrickson reagent initiated cascade reactions under mild metal-free conditions.[9] This newly developed methodology can tolerate a wide range of functional groups, and thus will facilitate future development of the substrates for material and medicinal applications.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Financial supports from MOST (2010CB833200), MOH (2009ZX09501) and NSFC (20621062) are greatly appreciated.

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(9) **Representative Procedure for the Synthesis of 6-Methylphenanthridine (2a)**

To a solution of Ph_3PO (260 mg, 0.9 mmol, 3 equiv) in anhyd CH_2Cl_2 (5 mL) was added Tf_2O (0.078 mL, 0.45 mmol, 1.5 equiv) dropwise under nitrogen atmosphere at 0 °C. After 15 min, amide **1a** (64 mg, 0.3 mmol, 1 equiv) in anhyd CH_2Cl_2 (2 mL) was added. The reaction was then warmed to r.t. and stirred until completion. The reaction was quenched by addition of sat. aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel using a mixture of PE and EtOAc (5:1 to 2:1, v/v) as the eluent to afford a light-yellow solid **2a** (51 mg, 95%).[4n] ^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (1 H, d, *J* = 8.4 Hz), 8.55 (1 H, d, *J* = 7.8 Hz), 8.24 (1 H, d, *J* = 7.8 Hz), 8.11 (1 H, d, *J* = 7.8 Hz), 7.88–7.61 (4 H, m), 2.98 (3 H, s). MS (EI): *m/z* = 193 [M^+].

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