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A new synthetic approach to 6-unsubstituted phenanthridine and phenanthridine-like compounds under mild and metal-free conditions†

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A new and mild synthetic approach for the synthesis of 6-unsubstituted phenanthridine and phenanthridine-like compounds under metal-free conditions at room temperature has been developed. The strategy involved a tandem azide rearrangement/intramolecular annulation and oxidation reactions of biarylmethyl azide precursors to obtain the desired products in up to 99% yields with high regioselectivity.

Phenanthridines and related heterocyclic systems are important frameworks of natural products, pharmacologically active compounds and fluorescence staining agents.[1] Several synthetic strategies have been reported including C–C bond and C–N bond formation of the *o*-functionalized biaryl compounds. Numerous approaches have been described utilizing metal-catalyzed processes which always proceeded at high reaction temperatures,[2] except for a recently published procedure using an iridium complex.[3] Nevertheless, transition metal-free reaction is one of the most important processes, especially in the pharmaceutical industry where the requirement for final products to be completely free of trace metals is crucial. Such metal-free phenanthridine syntheses involving radical processes have been disseminated employing photochemical reactions,[4] microwave irradiation[5] and the combination of the Togni reagent and Bu_4NI.[6] Other metal-free conditions include KO^t-Bu-mediated C–H bond arylation[7] and hydrothermal reaction of *o*-phenylaniline derivatives[8] (Fig. 1 and Scheme 1).

Although an array of synthetic methods for phenanthridine has been described, the approaches for the preparation of 6-unsubstituted phenanthridines are relatively rare, especially under the metal-free conditions. The construction of such systems can be accomplished *via* two known methods, which include the photo-irradiation of the iminylbiaryl compounds and the modified Pictet–Spengler reaction involving the methyleneiminium ion formation from biarylaniline and formaldehyde and cyclization under refluxing toluene.[9] In this regard, the formation of such iminium ions can be difficult and provided the desired product in moderate yields, possibly

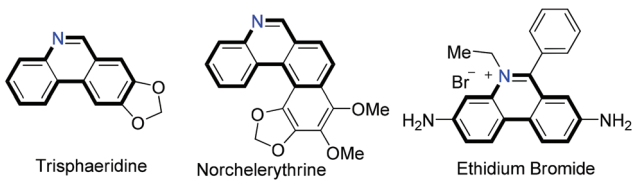
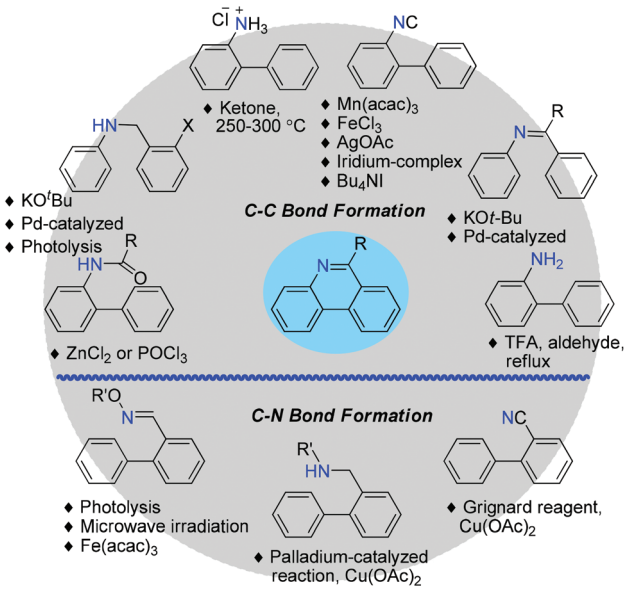


Fig. 1 Some phenanthridine natural products and a staining agent.



Scheme 1 Literature methods for phenanthridine synthesis.

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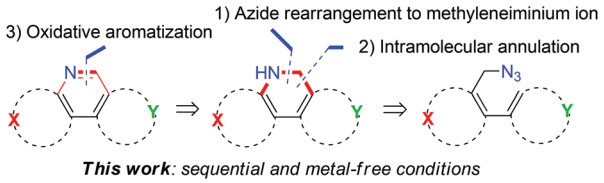


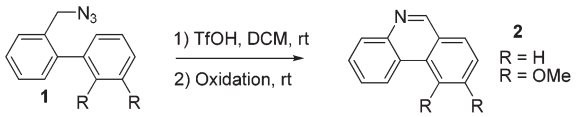
Scheme 2 Strategy of our proposed methodology.

due to the use of formaldehyde. We envision that the generation of the methyleneiminium ion could be more efficient starting from arylmethyl azide.[10] In this work, we reported for the first time the utilization of *o*-biarylmethyl azide rearrangement and intramolecular annulation as two key sequential steps, followed by oxidative aromatization for preparing phenanthridine and phenanthridine-like derivatives under mild and metal-free conditions at ambient temperature as shown in Scheme 2.

To examine our proposed strategy, non-substituted biphenylmethyl azide was employed as the model substrate in search of the optimal conditions. Our previous work has demonstrated that the ability of TfOH to initiate the azide rearrangement was crucial for generating the iminium ion intermediate *in situ*.[10] Therefore in this work, 1.5 equivalents of TfOH were used in the first step to promote the rearrangement for generating the iminium ion intermediate followed by an intramolecular annulation furnishing the crude dihydrophenanthridine product. In the crude product, we could observe slight autoxidation of dihydrophenanthridine to phenanthridine after work-up. In order to fully oxidize the crude product, it was dissolved in CH_3CN and stirred open to air at room temperature. However, only a marginal increase in conversion was observed (entry 1) after stirring overnight. When searching the literature for methods for the conversion of dihydrophenanthridine to a fully aromatic system, several oxidizing agents were reported, including $Cu(OAc)_2$,[2i] Pd/C,[11] Ru(TPP)CO,[12] CrO_3,[13] MnO_2,[14] and PCC,[15] but only a few examples of metal-free conditions were presented, such as those employing air/irridation,[4c] DDQ,[16] and O_2.[17] However, the decomposition of the desired product was observed under some of these conditions[17] (Table 1).

In view of our interest, the metal-free conditions are very important; we then tried several oxidizing agents such as $NaBO_3$, oxone and DDQ (entries 2–5), and the results showed that DDQ oxidation could provide the desired phenanthridine product in the highest yield (56%). However, we also have a difficulty in purifying the product from colored impurities of DDQ as reported in the earlier work.[17] To confirm the capability of DDQ in the oxidation process, 2,3-dimethoxybiphenyl methyl azide was investigated under these conditions (entry 6). Unfortunately, we observed only decomposition in the reaction mixture and only a trace amount of the desired product was obtained after purification. Oxidation using oxygen gas was also employed to afford the phenanthridine product in 82% yield (entry 7). Unfortunately, we were unable to reproduce this outcome, observing incomplete oxidation in several attempts.

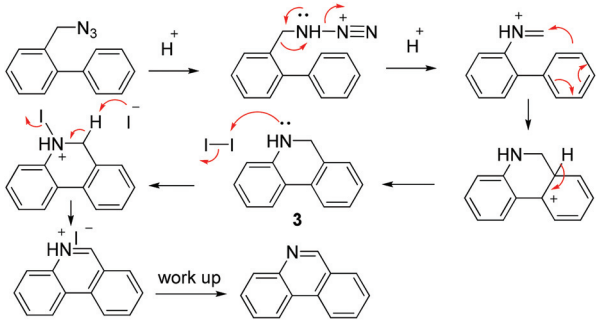
Table 1 Screening for the optimal conditions



Entry	R	TfOH[e]	Oxidant[e]	Yield[a] (%)
1	H	1.5 eq., o/n	Air, DCM–MeCN, o/n	—[b]
2	H	1.5 eq., o/n	1.1 eq. $NaBO_3$ MeCN–H_2O, 1 h	—
3[c]	H	1.5 eq., o/n	1.0 eq. oxone, MeCN–H_2O, 0.5 h	16
4	H	1.5 eq., o/n	1.0 eq. oxone, MeCN–H_2O, 1 h	33
5	H	1.5 eq., o/n	1.0 eq. DDQ, DCM, 0.5 h	56
6	OMe	1.5 eq., o/n	1.0 eq. DDQ, DCM, 0.5 h	Trace
7	OMe	1.5 eq., o/n	O_2, CH_3CN–DCM (1 : 1), o/n	82
8	OMe	1.5 eq., o/n	DAIB, DCM	—
9	OMe	1.2 eq., 3 h	3.0 eq. I_2, THF, o/n	85
10	OMe	1.2 eq., 3 h	3.0 eq. I_2, DCM, o/n	81
11	OMe	1.2 eq., 3 h	2.0 eq. I_2, THF, 3 h	99
12	OMe	1.2 eq., 3 h	1.2 eq. I_2, THF, 3 h	93
13	OMe	1.2 eq., 3 h	1.2 eq. I_2 in one pot, 3 h	25[d]
14	OMe	1.2 eq., 3 h	1.0 eq. PCC, 1 h	—
15	H	1.2 eq., 3 h	1.2 eq. I_2, THF, 3 h	60

[a] Isolated yield. [b] Incomplete conversion was observed and the yield was not determined. [c] The reaction was carried out at 0 °C. [d] NMR yield. [e] o/n = overnight.

Diacetoxyiodobenzene was also examined and provided a complex mixture (entry 8). We found that dihydrophenanthridine could be effectively oxidized using I_2 in THF for overnight providing the phenanthridine product in 85% yield (entry 9). In fact, I_2 has been reported previously to affect oxidation in a similar system, namely *N*-alkyldihydrophenanthridine to phenanthridinium salt.[18] However to the best of our knowledge, only one example has been reported to oxidize *N*-unprotected-dihydrophenanthridine (**3**) using I_2 in the presence of NaOAc under refluxing conditions.[19] Using I_2 oxidation could provide the advantage in avoiding the decomposition of multiply-oxygenated compounds. After switching the solvent to DCM, the desired product was obtained in slightly lower yield (81%) (entry 10). To improve the yield, we tried to reduce the equivalent of I_2 (2.0 equiv., entry 11) and time (3 h) which could provide the product in excellent yield (99%). The yield became slightly lower when the equivalent of I_2 was decreased (1.2 equivalents, entry 12). We also tried to perform reaction in one pot by adding I_2 to the reaction mixture after the first step (entry 13). However, the dihydroquinoline could not be oxidized to a fully aromatic system under acidic conditions. We also compared our method with the reported oxidation conditions using PCC as the oxidant which gave only a complex mixture (entry 14). To further confirm our method, we repeated the oxidation of the unsubstituted dihydrophenanthridine using I_2 in THF as the oxidizing agent instead of DDQ and we could obtain the corresponding phenanthridine product in 60% yield. Therefore, the optimal conditions of our method was concluded using 1.2 equivalents of TfOH in DCM in the first step and 2.0 equivalents of I_2 in THF in the second step.

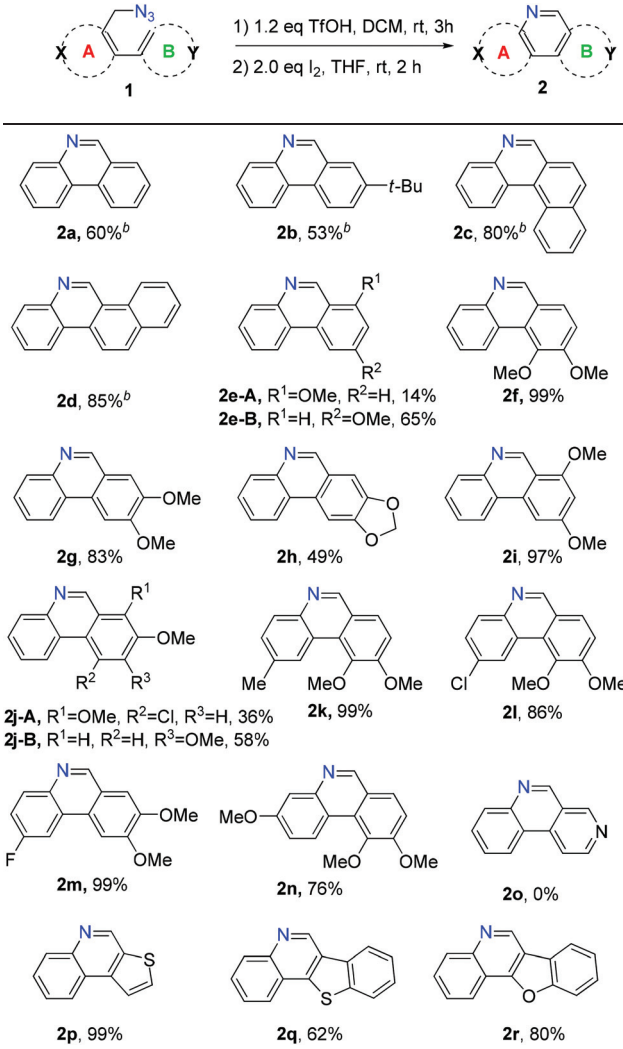


Scheme 3 Proposed reaction mechanism.

The proposed mechanism is illustrated in Scheme 3. The biarylmethyl azide under the TfOH-promoted aryl migration generated iminium ions *in situ* followed by intramolecular nucleophilic addition to form the carbocation intermediate which could be stabilized by the adjacent aromatic system. After rearomatization, dihydrophenanthridine was obtained and was further oxidized using I_2. Under these conditions, the nitrogen nucleophile attacked I_2 to furnish the ammonium ion intermediate, followed by the elimination of HI to give the protonated phenanthridine salt, which upon workup afforded phenanthridine as the final product.

With the optimal reaction conditions in hand, the generality of this synthetic methodology was studied as shown in Table 2. The unactivated aromatic nucleophile could successfully provide the phenanthridine products in moderate yields (**2a**, **2b**) which is in contrast to our previous report where toluene could not react intermolecularly with the iminium ion generated from the rearrangement of arylmethyl azide.[10a] This is an indication that the intramolecular nucleophile could facilitate the cyclization better whereby the carbocation intermediate generated in the reaction could be well-stabilized by the adjacent aromatic system as shown in Scheme 3. The 1- and 2-naphthyl aromatic nucleophiles furnished the desired products in good yields (**2c**, **2d**). The results revealed that the steric hindrance at the *ortho*-position of the arylmethyl azide was not a problem in the aryl migration step. It was important to note that a single regioisomeric product was obtained in both cases. The electron-donating substituents on the aromatic nucleophiles were also investigated. 3-Methoxy biphenylmethyl azide provided a mixture of isolable regioisomeric products in good combined yields (**2e–A**, **2e–B**). The majority of the phenanthridine product was obtained from the cyclization by the less sterically hindered carbon nucleophile at the *para*-position of the methoxy group. In the case of the 2,3-dimethoxyphenyl aromatic nucleophile, we fruitfully obtained the phenanthridine (**2f**) in excellent yield. Interestingly, a single regioisomeric product (**2g**) was obtained in good yield when 3,4-dimethoxybiphenylmethyl azide (**1g**) was used as a precursor. This result indicated that the most reactive nucleophilic center was the carbon atom at the *para*-position to the 3-methoxy group of the diarylmethyl azide. When we attempted the aromatic nucleophile which bears the

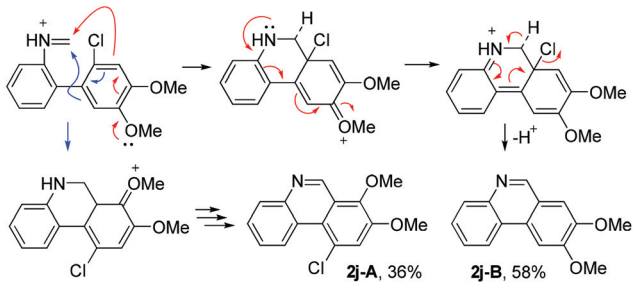
Table 2 Substrate scope for the synthesis of phenanthridines[a]



[a] Isolated yield. [b] Overnight reaction in the first step.

3,4-methylenedioxy substituent on the phenyl ring, a single regioisomeric product was obtained in lower yield (**2h**) due to the decomposition of the methylenedioxy moiety. The reaction of 3,5-dimethoxybiarylmethyl azide (**1i**) effortlessly provided the phenanthridine product in excellent yield. Remarkably, the azide precursor **1j** provided the electrophilic aromatic substitution product **2j–A** as the minor product (36%) whereas the dechlorinative cyclization product **2j–B** was obtained as the major product (58%). We found that compound **2j–B** was formed directly in the cyclization step without the need for I_2 oxidation while compound **2j–A** was formed after the addition of I_2. Therefore the reaction mechanism of these transformations was proposed as shown in Scheme 4.

We next explored the variation of both electron-donating and -withdrawing substituents on the aryl ring of arylmethyl azide (ring A) which were found to afford products in good to excellent yields (**2k–2n**). We would like to point out that the multimethoxy-substituted system was also tolerated under



Scheme 4 Proposed reaction mechanism for **2j–A** and **2j–B**.

these conditions (**2n**). To show the generality of our synthetic procedure, we applied this method to synthesize the polycyclic hetero-aromatic compounds using ring B as a hetero-aromatic moiety. We could obtain products in good to excellent yields (**2p–2r**) except for the pyridine ring moiety where no corresponding phenanthridine product (**2o**) was observed.

Conclusions

In conclusion, we have demonstrated a simple and metal-free 2-step protocol for 6-unsubstituted phenanthridine and phenanthridine-like synthesis involving a cascade TfOH-promoted aryl migration and intramolecular annulation in the first step to form dihydrophenanthridine, followed by I_2 oxidation. This highlights our strategy as a novel approach to construct the 6-unsubstituted phenanthridine ring system *via* tandem C–C and C–N bond formation. The reactions proceeded at room temperature and the conditions are applicable to a wide range of substrates. This strategy obviates the use of transition metal reagents rendering metal contamination-free products, and solves decomposition problems, especially in multiply-oxygenated compounds.

Acknowledgements

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