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# A new entry to the phenanthridine ring system

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ABSTRACT

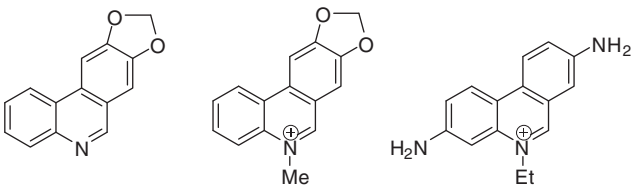
A new synthesis of phenanthridine derivatives having three-point diversity has been developed based on the sequential application of three-atom economic processes viz. aza-Claisen rearrangement, ring-closing enyne metathesis and Diels–Alder reaction as key steps. An unexpected isomerisation was observed during aza-Claisen rearrangement of *N*-allylanilines which may open up new opportunities in heterocyclic synthesis.



Phenanthridines represent important core structures of a variety of both naturally occurring (**1–3**, Fig. 1) and synthetic molecules having biological activities ranging from antibacterial, antiprotozoal activities to antitumor property through DNA intercalation.[1] They are also currently receiving attention in material science applications.[2] Therefore, reports in the development of a new synthetic route to such ring systems continue to appear.[3] Although diverse and elegant approaches have been reported, the need for a simple but efficient protocol from easily available starting materials with selective control in the substitution pattern does exist. Herein, we report a new synthesis of the phenanthridine ring system using sequential applications of three-atom economic processes viz. aza-Claisen rearrangement, ring-closing enyne metathesis reaction (RCEYM) and Diels–Alder reaction.[4]

Our retro-synthetic analysis of the phenanthridine ring system **4** relied on the construction of the ring C through a Diels–Alder reaction-aromatisation sequence of an appropriate 3-vinylquinoline derivative **5**, which was thought to be obtainable from ring-closing enyne metathesis (RCEYM) reaction of the N-tethered enyne **6**. Further functional group manipulation sequence brought to us the 2-vinyl aniline derivative **7** as an appropriate precursor which we sought to prepare from isomerisation of the easily obtainable 2-allylaniline derivative **8** (Scheme 1).

Thus, we prepared the *N*-allylanilines **11a–f** from straightforward N-allylation of the corresponding Boc-protected anilines **9a–f** followed by acid mediated removal of the Boc-group in the resulting **10a–f** under conventional conditions (Scheme 2). The 4-nitro-*N*-allylaniline **11g** was however prepared by direct allylation of 4-nitroaniline. The thermal aza-Claisen rearrangement of *N*-allylanilines usually require drastic conditions.[5,6] On the other hand, Lewis or protic acid mediated aza-Claisen rearrangement of *N*-allylanilines is known to proceed with significant rate enhancements under either thermal[7] or microwave conditions.[8] However, the reaction is more general and more predictable with *N*-alkyl-*N*-allylanilines. During the rearrangement of simple *N*-allylanilines without additional substituent on the nitrogen atom or in the *N*-allyl moiety, cyclisation leading to undesired indoline derivatives has also been reported.[9] After some experimentation, we have found that the aza-Claisen rearrangement of the unsubstituted *N*-allylaniline **11a** proceeded better in refluxing chlorobenzene in the presence of $BF_3{\cdot}OEt_2$ (1.5 equiv) within a reasonable short period of time (6 h) to provide the rearranged aniline **13a** in good yield (71%). Attempted optimisation of the reaction using high boiling




**1**: Trispheridine **2**: Bicolorine **3**: Ethidium

**Figure 1.** Some phenanthridine derivatives of importance.

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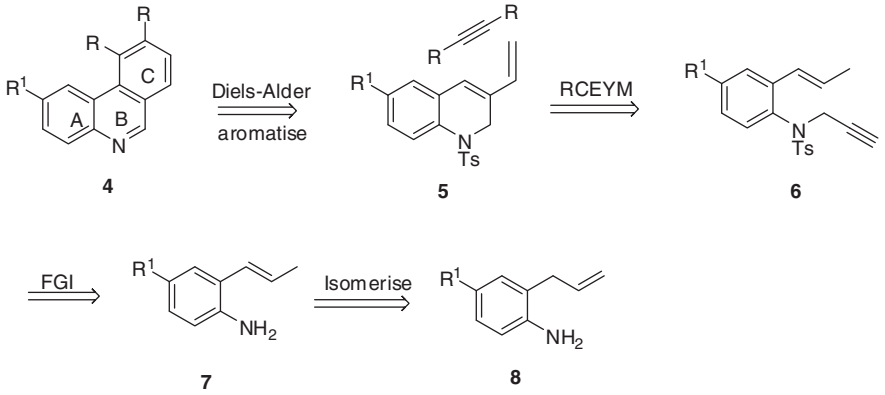
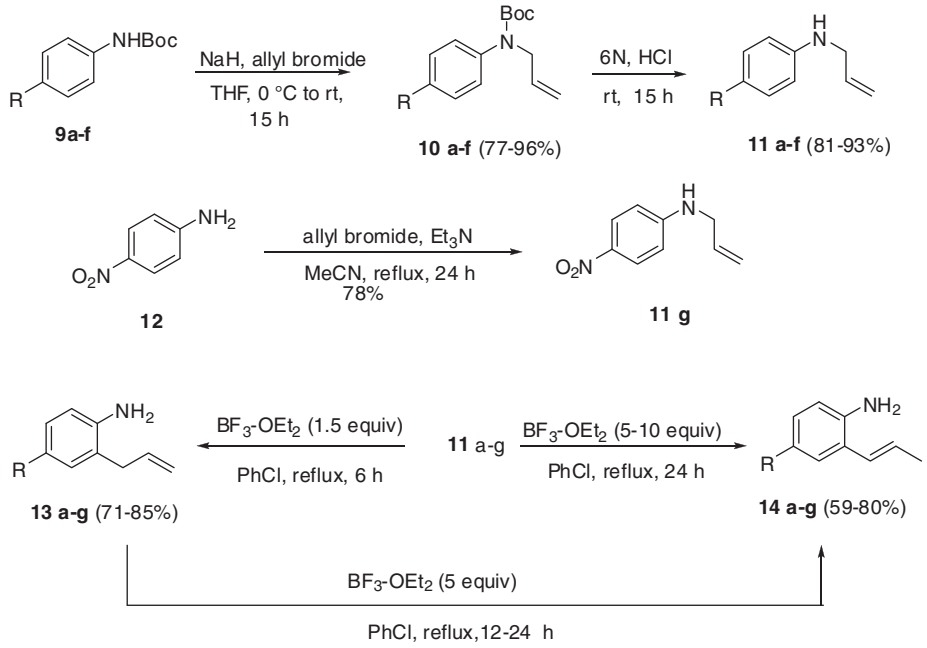


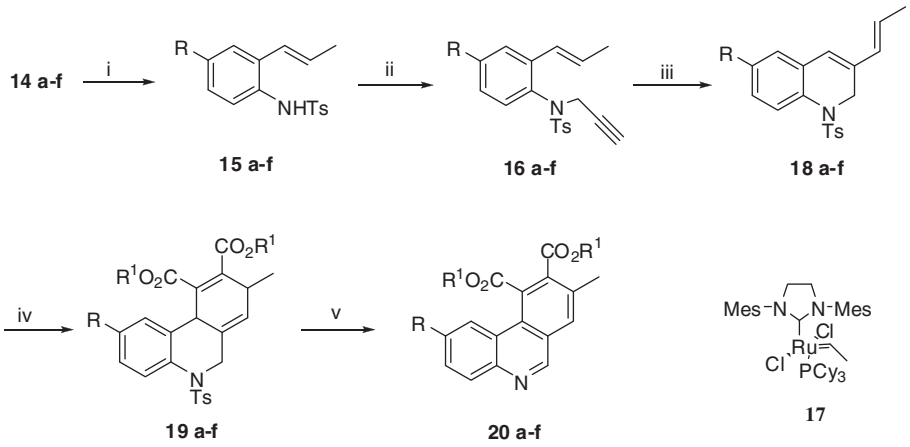

**Scheme 1.** Retrosynthetic analysis of the phenanthridine ring system.




**Scheme 2.** Preparation of the starting materials **14a–g**.

solvent and prolonged reaction time, either singly or in combination, met with limited success. However, during one such optimisation study we noticed that the use of five equivalents of $BF_3{\cdot}OEt_2$ and longer reaction time (24 h) led to the formation of the rearranged and isomerised product **14a** as *E*-isomer. The concurrent isomerisation, although unexpected and unplanned at this stage, was a fortunate outcome since this was projected in the retro-synthetic analysis as a subsequent step. To test the generality of the process, we subjected *N*-allylanilines **11b–g** to a similar course of reaction and found that all of these undergo facile rearrangement and isomerisation to provide either the rearranged anilines **13b–g** (71–85%) or the rearranged and isomerised anilines **14b–g** (69–80%) depending on the amount of Lewis acid and reaction time. Moreover, the rearranged 2-allylanilines **13a–g** could also be converted to the isomerised products **14a–g** separately, if desired, indicating that perhaps these are intermediates in the direct conversion of **11a–g** to **14a–g**.

Having access to the required 2-vinylaniline derivatives **14a–g**, we focused on their conversion to the phenanthridine derivatives along the projected pathway. Thus, the corresponding *N*-tosyl derivatives **15a–f** (Scheme 3) were prepared and N-alkylated with propargyl bromide under conventional conditions to obtain the enyne derivatives **16a–f** in good overall yield. Ring-closing enyne metathesis reaction (RCEYM)[10] of olefins other than terminal olefins has been studied less compared to that of the terminal olefins.[10] In a few instances studied, interesting mechanistic and stereochemical observations have been made.[11] However, heteroatom tethered enynes have been reported to show poor stereoselectivity.[12] Pleasingly, we observed that RCEYM of the compounds 16a–**f** proceeded well in the presence of Grubbs' 2nd generation catalyst **17** to provide each of the dienes **18a–f** as a single diastereomer in good yield. Mechanistically, the reaction may follow (Fig. 2) either of the 'ene-then-yne' or 'yne-then-ene' pathways[12] (Fig. 2). The ruthenium carbene complex may coordinate with the alkyne of the substrate **i** (path **A**), to produce the intermediate carbene complex **ii** which subsequently would cyclise to the product **v** where the product would be expected to exhibit stereoselectivity similar to that of the cross enyne metathesis reaction. On the other hand, the ruthenium carbene complex **III** produced during the reaction at the 'ene'-site would cyclise to **IV** and then may react with the olefin part of another substrate molecule leading to the 1,3-diene product **V** (path **B**).




**Scheme 3.** Preparation of the phenanthridine derivatives **20a–f**. Reagents and conditions: (i) *p*-TsCl, pyridine, rt, 1–2 h, 70–90%; (ii) propargyl bromide, $K_2CO_3$, acetone, reflux, 6 h, 74–94%; (iii) catalyst **17** (5 mol %), toluene, 90 °C, 24–48 h, 66–87%; (iv) dimethyl acetylenedicarboxylate (or diethyl acetylenedicarboxylate), toluene, reflux, 48 h, 66–81%; (v) DBU (2 equiv), toluene, reflux, 24 h, 66–90%.

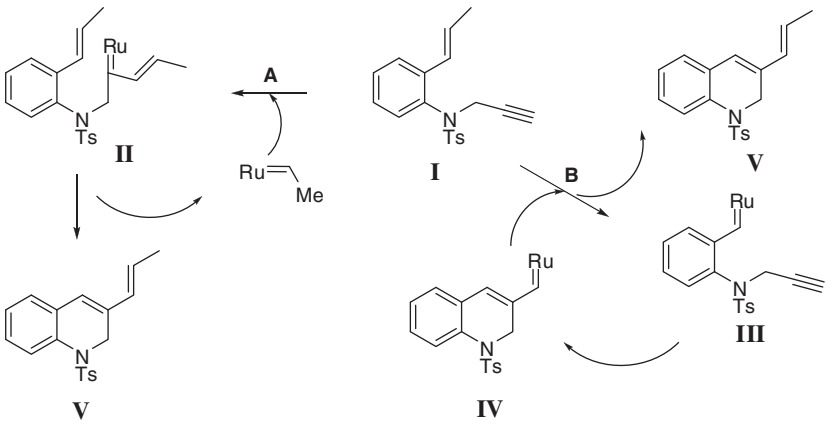



**Figure 2.** Representation of possible catalytic pathways: 'yne-then-ene' pathway (A) and 'ene-then-yne' pathway (B).

We next studied the Diels–Alder reaction of the dienes **18a–f**. Separate treatment of each of these dienes with diethyl acetylenedicarboxylate or dimethyl acetylene dicarboxylate proceeded sluggishly in refluxing toluene to provide the cycloadducts in moderate to good yields. These were mostly obtained as single diastereomers but the compounds proved to be slightly contaminated with partially oxidised product/s formed during chromatographic purification. Compounds **19c** and **19d** proved to be exceptions and these could be obtained as pure and single diastereomers. Base-mediated elimination[13] of the tosyl group from the adducts **19a–f** proceeded with concomitant aromatisation to deliver the desired phenanthridine derivatives **20a–f** in an overall yield of 16–25% over six steps from the starting *N*-allylanilines **11a–g**.[14]

In brief, we have developed aza-Clasien rearrangement of *N*-allylanilines in two different modes depending on the use of amount of Lewis acid and reaction time. The observed isomerisation[15] has been utilised to develop a simple protocol for the synthesis of phenanthridine derivatives having diversity in rings A and C, a pattern which is usually found in most of the known biologically active phenathridine derivatives. The procedure involves use of readily available precursors and operationally easy reactions which are highly atom economic. These attributes may aid to generate other phenanthridine derivatives of biological interest. The methodology may therefore complement the existing methodologies for the preparation of such compounds. The diversity observed in the aza-Claisen rearrangement may also prove to be useful in the synthesis of other heterocyclic systems of interest.

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## Supplementary data

Supplementary data (list of compounds along with their yield, melting points, and copies of $^1$H NMR and $^{13}$C NMR spectra are included) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.095.

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