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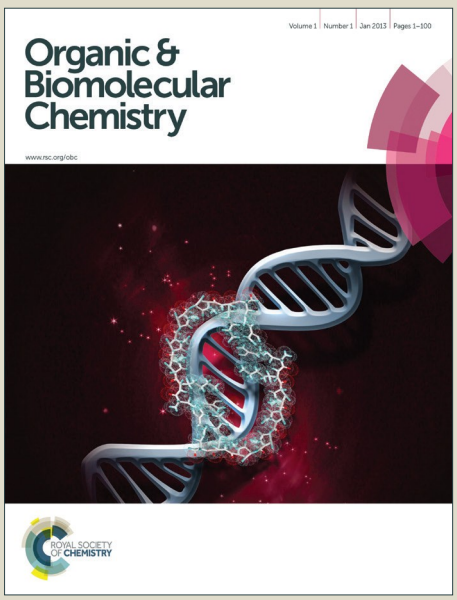

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Highly Regio- and Diastereoselective Synthesis of Novel Tri- and Tetracyclic Perhydroquinoline Architectures Through an Intramolecular [3 + 2] Cycloaddition Reaction

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A facile and efficient synthetic protocol was established for the construction of novel tri- and tetracyclic pyrrolo / pyrrolizinoquinoline architectures through *in situ* formation of azomethine ylide followed by an intramolecular [3 + 2] cycloaddition reaction strategy. This protocol leads to the creation of two / three new rings and three / four contiguous stereocentres in which one of them being a tetra substituted carbon center in a highly diastereoselective fashion with excellent yields.

Introduction

In the domain of heterocyclic compounds, tetrahydroquinoline derivatives are very important and recognized as small molecule transformers of hepatic micro RNA function, reducing the replication of Hepatitis C virus and also responsible for apoptosis inducers.[1] They are well known for their potential utility in medicinal chemistry such as antioxidant, antimalarial, anticoagulant, anti-HIV and antitubercular activities. Among various aza-heterocyclic compounds containing pyrrolo[3,2-c]quinoline[2] frameworks, martinelline alkaloids isolated from the roots of Martinella iquitosensis were known to exhibit antibiotic activities and also reported as the first non-peptide antagonists for B2 receptors and bradykinin B1.[3] Due to the interesting medicinal applications of these entities in drug discovery, the development of new and novel synthetic strategies towards the efficient construction of tetrahydroquinoline derivatives remains an important endeavour in the arena of chemical research.[4] A representative example of tetrahydroquinoline, pyrroloquinoline based molecules[5] viz., Torcetrapib, (+)-Melonine, (±)-Heliotridane, (±)-Isoretronecanol, Martinelline and Antitrypanosomal[1e] are shown in Figure 1.

The 1,3-dipolar cycloaddition reaction is one of the prominent and efficient protocol towards the synthesis of five membered heterocyclic compounds particularly pyrrolidines.[6] Even though an array of methods[7] are available in the literature, the 1,3-dipolar cycloaddition encompassing azomethine ylides trapped with alkenes is the most expedient synthetic strategy for the construction of diversified pyrrolidine and pyrrolizidine architectures.

The Baylis-Hillman reaction is one of the versatile classes of reactions in the field of modern organic synthesis. To be precise, the derivatives of Baylis-Hillman adducts are widely employed as crucial synthons for various intermediates leading towards the synthesis of several natural products and bio-active compounds.[8] To the best of our knowledge, the Baylis-Hillman derivatives[9] have not been utilized for the synthesis of fused tri and tetracyclic pyrrolo /pyrrolizinoquinoline derivatives via 1,3-dipolar cycloaddition reaction to date.

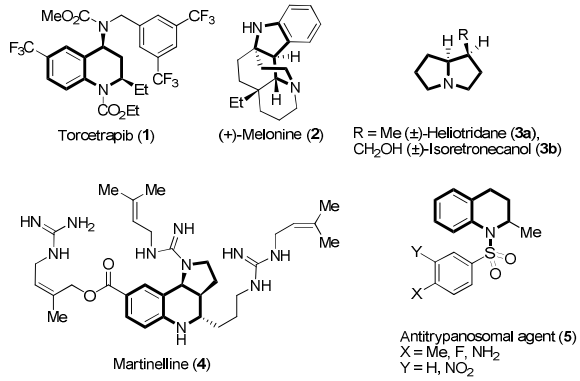
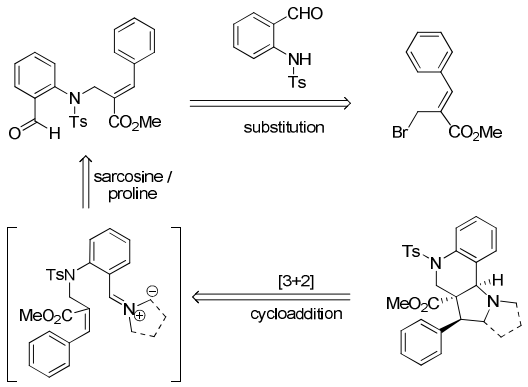


Figure 1. Some of the bioactive molecules and natural products embodying tetrahydroquinoline and other privileged motifs

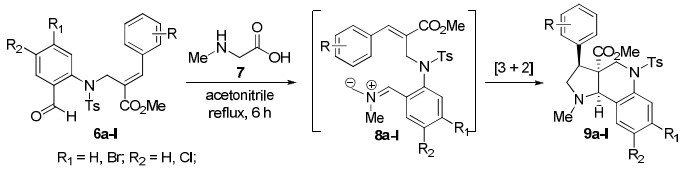
Therefore, we envisaged that the Baylis-Hillman derivatives (**6a-k** & **10a-g**) can be effectively employed as a key starting material for the synthesis of tri- and tetracyclic perhy droquinolines as other Baylis-Hillman derivatives were successfully utilized from our laboratory for the synthesis of wide variety of polyheterocyclic frameworks *via* cycloaddition reaction.[6f-h] The requisite precursors can be prepared by the treatment of various Baylis-Hillman bromides with *N*-tosylated aminoaldehyde.[9c,10] Further treatment of various *N*-tosyl-*N*-allyl 2-aminobenzaldehydes bearing conjugated ester or nitrile moieties with *N*-methyl glycine / *L*-proline will afford the tricyclic pyrroloquinolines and tetracyclic pyrrolizinoquinolines with ester / nitrile functionality in the ring junction as shown in the retrosynthetic analysis (Scheme 1).

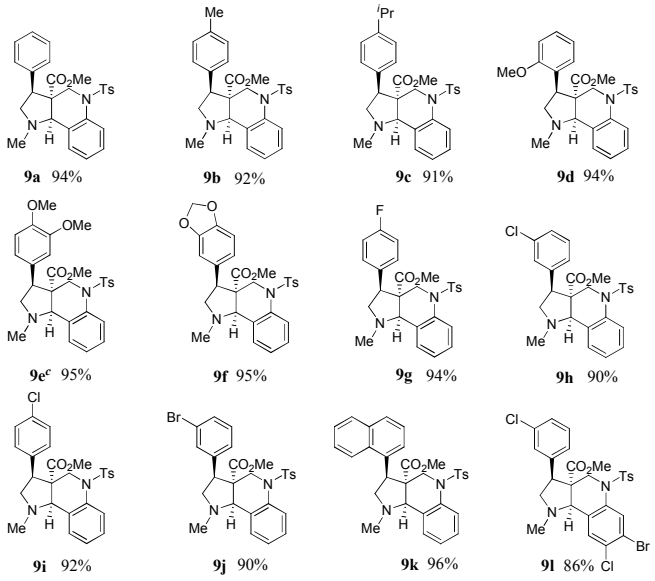
To execute our idea, we treated *N*-allylated aldehyde (**6a**) and *N*-methyl glycine (**7**) in acetonitrile as solvent under reflux condition which successfully led to the formation of desired tricyclic pyrrolo[3,2-c]quinoline (**9a**) containing ester functionality at the angular position in excellent yield (94%) *via* 1,3-dipolar cycloaddition reaction comprising of an imine formation, decarboxylation followed by [3 + 2] cycloaddition reaction sequence as shown in Table 1.



Scheme 1. Retrosynthetic strategy for the synthesis of tri- and tetracyclic pyrroloquinoline architectures

Table 1. Synthesis of tricyclic pyrroloquinoline frameworks (**9a-l**)[a,b] with ester functionality at angular position





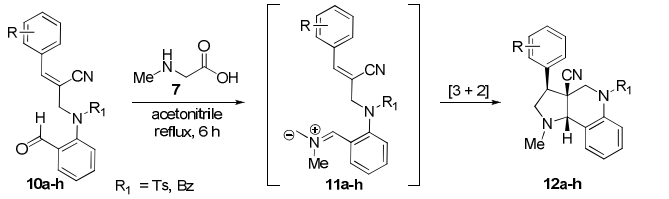
[a]All reactions were carried out on 1 mmol scale of *N*-allylated derivatives (**6a-l**) with 1.1 mmol of *N*-methyl glycine (**7**) in acetonitrile as a solvent at reflux temperature for 6 h. [b] Isolated yields of the pure product. [c]Structure of the molecule was further confirmed by single-crystal X-ray data (See Supporting Information).

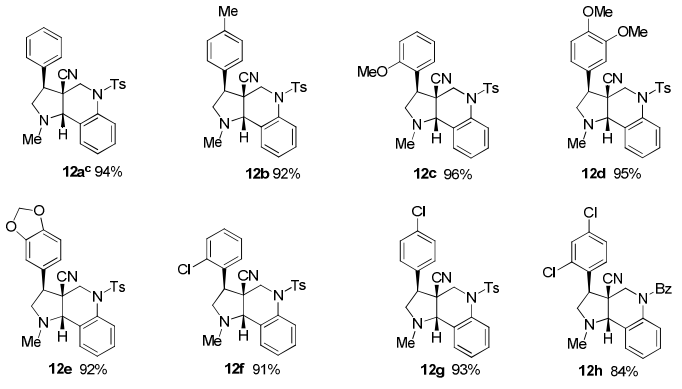
Encouraged by this result, we subjected variety of *N*-allylated aldehydes (**6b-l**) with *N*-methyl glycine under aforementioned reaction condition which smoothly afforded the anticipated tricyclic pyrrolo[3,2-c]quinolines (**9b-l**) containing ester functionality at the angular position in the racemic form with excellent yields (86-96%) and the results are shown in Table 1. It is important to note that this is the first report for the efficient construction of tricyclic pyrrolo[3,2-c] quinolines from Baylis-Hillman derivatives.

After obtaining this fruitful result, we have decided to extend the methodology further to *N*-allylated aldehydes (**10a-h**) containing nitrile functionality. Therefore, the similar reaction of *N*-allylated aldehydes (**10a-h**) with *N*-methyl glycine (**7**) in acetonitrile solvent at reflux temperature for 6 h successfully provided the desired tricyclic pyrroloquinolines (**12a-h**) as racemates in excellent yields (84-96%) as shown in Table 2.

It is very important to mention here that the tricyclic martinelline core structure has been achieved using B.H derivatives through [3 + 2] cycloaddition for the first time. Delighted by these results, we have also decided to utilize this methodology towards the synthesis of tetracyclic pyrrolizoquinolines.

Table 2. Synthesis of tricyclic pyrroloquinoline frameworks (**12a-h**)[a,b] with nitrile functionality at angular position



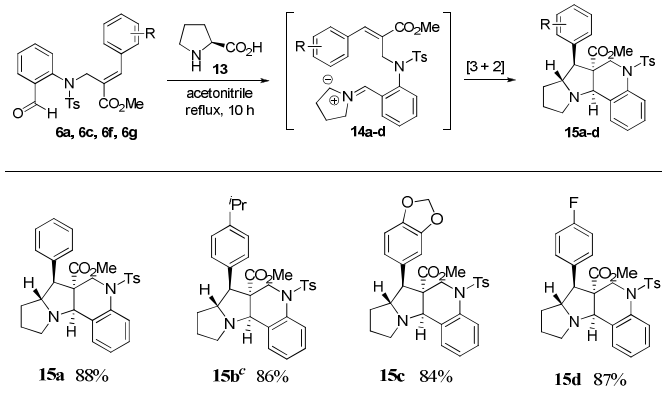


[a]All reactions were carried out on 1 mmol scale of *N*-allylated aldehydes (**10a-h**) with 1.1 mmol of *N*-methyl glycine (**7**) which are allowed to stir in acetonitrile as solvent at reflux for 6 h. [b]Isolated yields of the pure product. [c]The structure of the molecule was further confirmed by single-crystal X-ray data (See Supporting Information).

In order to construct pyrrolizinoquinolines, we have treated various *N*-allylated aldehydes (**6a, 6c, 6f & 6g**) with *L*-proline (**13**) in acetonitrile solvent at reflux temperature for 10 h which successfully provided the anticipated tetracyclic pyrrolizinoquinolines (**15a-d**) possessing angular ester functionality in very good yields (84-88%) as shown in Table 3. To probe the reaction further, we have also treated various *N*-allylated aldehydes (**10a-b, 10e, 10g**) with *L*-proline (**13**) in acetonitrile solvent at reflux temperature for 10 h

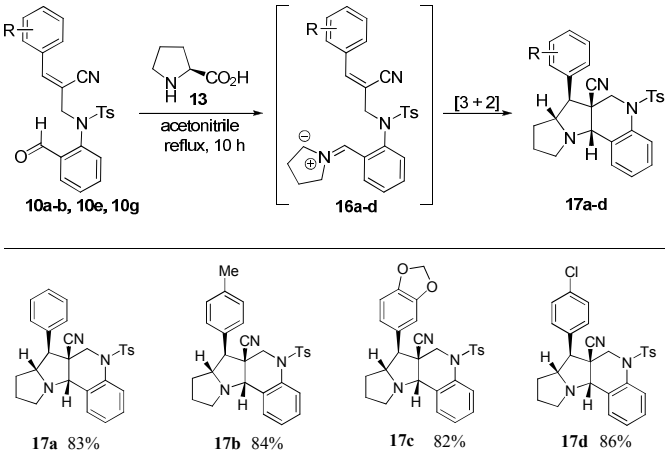
successfully afforded the desired tetracyclic pyrrolizinoquinolines (**17a-d**) containing nitrile functionality at angular position in excellent yields (82-86%) as shown in Table 4.

Table 3. Synthesis of tetracyclic pyrrolizinoquinoline frameworks (**15a-d**)[a,b] with ester functionality at angular substitution



[a]All reactions were carried out on 1 mmol scale of *N*-allylated aldehydes (**6a, 6c, 6f, 6g**) with 1.1 mmol of *L*-proline (**13**) in acetonitrile at reflux temperature for 10 h. [b]Isolated yields of the pure product. [c]The structure of the molecule was further confirmed by single-crystal X-ray data. (See Supporting Information)

Table 4. Synthesis of tetracyclic pyrrolizinoquinoline frameworks (**17a-d**)[a,b] with nitrile functionality at angular substitution



[a]All reactions were carried out on 1 mmol scale of *N*-allylated aldehydes (**10a-b, 10e, 10g**) with 1.1 mmol of *L*-proline (**13**) in acetonitrile under reflux condition for 10 h. [b]Isolated yields of the pure product. (See Supporting Information).

Based on the ORTEP diagram of the pyrroloquinoline **9e**, shown in Figure 2, the relative stereochemistry of the phenyl group and the adjacent ester moiety are in *trans* orientation, also the ester moiety and the ring junction proton exist in a *cis* orientation. In addition to that the X-ray crystal structure of tricyclic pyrroloquinoline **12a**, reveals that the phenyl group, adjacent nitrile moiety, and ring junction proton are in *cis* orientation (Figure 2). It is quite obvious to note that the *trans* product was formed, when olefin **6a**, having a *trans* geometry (aryl and ester groups present in the *vicinal* positions of compound **6**). Similarly, olefin **10a**, having a *cis* geometry (aryl and nitrile moieties present in the *vicinal* positions of compound **10**), led to formation of the *cis* product, which clearly shows the stereospecificity of the [3 + 2] cycloaddition reaction.

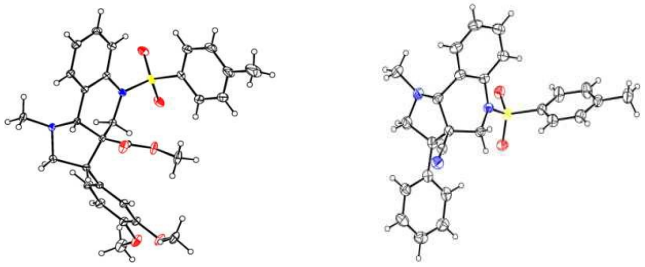


Figure 2. ORTEP diagram of compound **9e** and **12a**

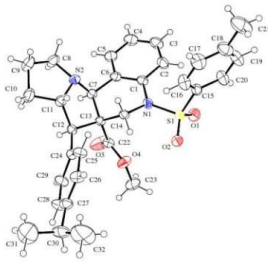
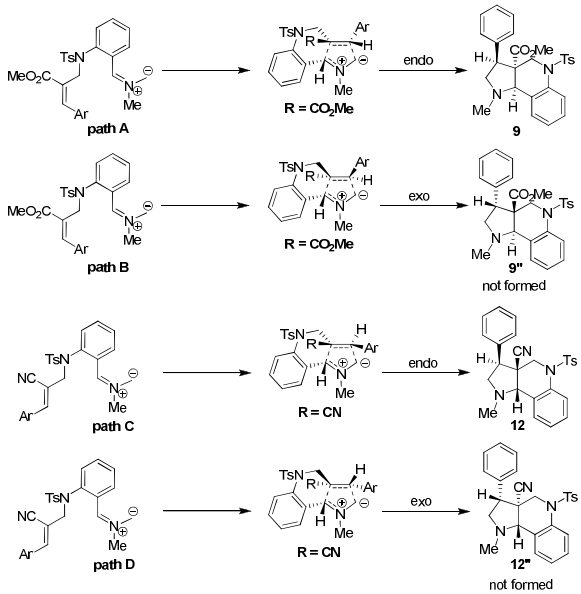


Figure 3. ORTEP diagram of compound **15b**

Furthermore, the relative stereochemistry of tetracyclic pyrrolizinoquinoline compound **15b**, the aryl moiety and the adjacent ester moiety are in *trans*-orientation, whereas the ester unit and the ring junction proton are in *cis* orientation based on the ORTEP diagram shown in Figure 3.



Scheme 2. Plausible pathway for the formation of pyrrolo quinolines

The plausible pathways for the formation of tricyclic pyrroloquinoline ring system can be explained based on the transistion state depicted in Scheme 2. It is important to mention here that, both *endo* (path A & C) and *exo* (path B & D) transition states are possible for the formation of pyrroloquinoline frameworks. However, *endo* transition state

(path A & C) is the more favorable and predominant due to attractive *π-interactions* and repulsive *steric intractions* in the 1,3-dipolar cycloaddition reactions.

Conclusions

We have successfully developed a simple and efficient protocol for the facile synthesis of complex angularly substituted tri- and tetracyclic frameworks containing a pyrrolo / pyrrolizino quinoline ring system *via* an intramolecular 1, 3- dipolar cycloaddition reaction using Baylis-Hillman derivatives. Angularly substituted tri- and tetracyclic compounds were obtained in a highly diastereoselective fashion with high yields. This approach also opens a new opportunities for the preparation of library of pyrroloquinoline compounds for further biological screening.

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Notes and references

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Electronic Supplementary Information (ESI) available: Representative experimental procedures, with all spectral data of **9a-k**, **12a-g**, **15a-d**, **17a-d**, crystal data, ORTEP diagram and the CCDC number for **9e** is **764210**, CCDC number for **12a** is **833470** and CCDC number for **15b** is **976506** respectively. For ESI and crystallographic data]. See DOI: 10.1039/c000000x/

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10. Starting materials **6** and **10** were prepared from the *O*-aminobenzyl alcohol according to the reported procedure[9c] .

