Total synthesis of aristolactam alkaloids via synergistic C–H bond activation and dehydro-Diels–Alder reactions†

Mallu Chenna Reddy and Masilamani Jeganmohan

A concise total synthesis of aristolactam alkaloids by a synergistic combination of C–H bond activation and dehydro-Diels–Alder reactions is described. To achieve the synthesis two new synthetic methodologies, namely the oxidative cyclization of benzanilides with vinyl sulfone leading to 3-methyleneisoindolin-1-ones via a ruthenium-catalyzed C–H bond activation, and a dehydro-Diels–Alder reaction followed by the fluorine ion mediated desulfonylation of 3-methyleneisoindolin-1-ones with benzenes, were developed. The method presented allows the opportunity for the construction of all the rings of aristolactams from easily available starting materials.

Introduction

Aristolactams are naturally occurring phenanthrene lactam alkaloids. These alkaloids are isolated from Aristolochiaceae, Annonaceae, Piperaceae, and Saururaceae plant species. Aristolactams are frequently used as folk medicines in several countries. Meanwhile, these molecules show an interesting array of biological properties such as anti-inflammatory, anti-platelet, anti-mycobacterial, neuroprotective and anti-cancer activities. Due to their unique structural features and potential biological activities, a considerable amount of effort has been devoted to synthesizing these molecules by several research groups. After surveying all these elegant contributions, we understood that a general and easily approachable method for synthesizing these alkaloids with a minimum number of steps from easily affordable starting materials is needed. Meanwhile, the new method should be general for the preparation of numerous aristolactam derivatives in order to explore the utility of these molecules in various areas. Particularly, the utility of these alkaloids in various biological applications has been extensively increased in the past two decades.

Herein, we wish to report an efficient two step synthesis of aristolactam alkaloids from easily available and affordable starting materials such as aromatic acids, alkyl amines and alkenes. To execute the synthesis two new synthetic methodologies, namely the preparation of 3-methyleneisoindolin-1-ones via a ruthenium-catalyzed oxidative cyclization of aromatic amides with vinyl sulfone, and a dehydro-Diels–Alder reaction followed by SO2Ph cleavage of 3-methyleneisoindolin-1-ones with benzenes, were developed. The present method is compatible for the preparation of various aristolactam derivatives including sensitive I, Br, Cl, F and CF3 functional groups. The combination of C–H bond activation and dehydro-Diels–Alder reactions allows a short and efficient synthesis of several aristolactam alkaloids in good yields.

![Diagram](image_url)

The goal of this work is to construct aristolactam cyclic rings A–D in a simple manner from easily affordable starting materials (Scheme 1). Rings A and B having 3-methyleneisoindolone can be constructed via a metal-catalyzed C–H/N–H annulation of substituted benzamides with alkenes in one pot. Substituted benzamides can be easily prepared from benzoic acids and amines. Rings C and D can be constructed in one pot via the dehydro-Diels–Alder reaction of 3-methyleneisoindolin-1-ones with benzenes. However, this type of cycloaddition reaction is not very effective, because it provides competing side products along with the expected product (eqn (1)).

† Electronic supplementary information (ESI) available: Detailed experimental procedures and spectroscopic data. CCDC 1526825. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc00161d
Overcome this problem, we engineered a molecule that has a cleavable SO2Ph group at the β-carbon of alkene of 3-methyleneisoindolin-1-one. After the cycloaddition reaction, the sulfonyl group can be easily cleaved by a fluoride source in the same step (eqn (2)). Thus, the cycloaddition reaction can be done in a highly selective manner.

Results and discussion

Our continuous interest in ruthenium-catalyzed C–H bond activation reaction prompted us to explore the possibility of developing a new synthetic route for the synthesis of key intermediates 3-methyleneisoindolin-1-ones via the ruthenium-catalyzed oxidative cyclization of benzanides with vinyl phenyl intermediates 3-methyleneisoindolin-1-ones (Scheme 2). These reactions afford a useful and efficient method for the synthesis of key intermediates 3-methyleneisoindolin-1-one. A variety of substituted benzanides 1b-f were compatible for the cycloaddition reaction (Scheme 2). These reactions worked very well, providing the expected cyclization products 3b-f in 69%, 67%, 58%, 56% and 71% yields, respectively, in 96:4 to 99:1 E/Z ratios.

A variety of substituted benzanides 1g-s were compatible for the cycloaddition reaction (Scheme 3). Electron-releasing (OMe and Me) and halogen (I, Br, Cl and F) substituted benzanides 1g-n efficiently reacted with 2a affording isoindolin-1-ones 3g-n in good yields. The less reactive electron withdrawing (CF3 and NO2) substituted benzanides 1o-p also efficiently reacted with 2a providing products 3o and 3p in good yields. Similarly, ortho and meta substituted benzanides 1q-s also efficiently participated in the reaction, giving products 3q-s in 47%, 64% and 61% yields, respectively. Particularly, in the meta substituted benzanides 1r-s, C–H bond activation takes place at a less hindered Cα–H.

Table 1 Optimization studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield of 3a (%)</th>
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<tr>
<td>1</td>
<td>CICH2CH2Cl</td>
<td>AgSbF6</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>AgSbF6</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>1,4-Dioxane</td>
<td>AgSbF6</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>AgSbF6</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>AgSbF6</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>CF3COOH</td>
<td>AgSbF6</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>CH3COOH</td>
<td>AgSbF6</td>
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<tr>
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<td>CH3COOH</td>
<td>AgOTf</td>
<td>46</td>
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<tr>
<td>10</td>
<td>CH3COOH</td>
<td>KPF6</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>CH3COOH</td>
<td>— NR</td>
<td></td>
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</tbody>
</table>

All reactions were carried out under the following conditions: 1a (75 mg), 2a (1.5 equiv.), [RuCl2(p-cymene)]2 (5 mol%), additive (20 mol%) and Cu(OAc)2·H2O (50 mol%) in solvent at 120 °C for 36 h under an oxygen atmosphere. Isolated yield.
The cyclization reaction was further examined with various alkenes (Scheme 4). Methyl, n-butyl and cyclohexyl acrylates 2b–d efficiently reacted with 1a yielding cyclization products 3t–v in good yields. In these reactions, only E stereoselectivity was observed. Diethyl vinylphosphonate (2e) was also efficiently involved in the reaction, giving product 3w in 54% yield with a free exo double bond. In the product 3w, phosphonate (P=O(OEt)₂) was cleaved under the present reaction conditions. The cyclization reaction was not compatible with acrylonitrile, methyl vinyl ketone and styrene.

To explore the possibility of the preparation of aristolactam derivatives, the dehydro-Diels–Alder reaction of 3 with benzene was examined (Scheme 5). The cycloaddition of 3g with benzene precursor 7a in the presence of CsF in CH₃CN at 30 °C for 24 h gave aristolactam derivative 9a in 66% yield. It is believed that after cycloaddition reaction, intermediate 8a is formed in which SO₂Ph is cleaved by a fluoride ion. The formation of intermediate 8a was confirmed by MALDI-TOF experiment (for the detailed mechanism, see the ESI†). However, in the cycloaddition reaction of 3w with 7a, no product was observed. In the cycloaddition of 3t in which an ester substituent is present at the β-carbon of the alkene with 7a, a mixture of heterocyclic molecules 9b and 9b* was observed in a 42% combined yield in a 4:1 diastereoselective ratio. In the reaction, the CO₂Me group did not eliminate like SO₂Ph. This result clearly reveals that the SO₂Ph group is crucial in order to obtain aristolactams in greater yield with high selectivity.

The cycloaddition reaction was examined with various N-substituted indolin-1-one derivatives 3b–f (Scheme 6). N-propyl, butyl, iso-propyl, cyclohexyl and benzyl substituted isoindolin-1-ones 3b–f underwent cycloaddition with 7a providing aristolactam derivatives 9c–g in good yields. Meanwhile, OMe, Me, I, Br, Cl, F and CF₃ substituted isoindolin-1-ones 3h–s also efficiently participated in the reaction yielding products 9h–q in good yields.

The scope of the cycloaddition reaction was further examined with substituted benzenes 7b–g (Scheme 7). Symmetrical benzenes such as 3,4-dimethoxy benzene, 3,4-dimethyl benzene, indene derivative and 1,3-benzodioxole reacted with 3j, providing cyclization products 9r–u in good yields. When
unsymmetrical benzyne 7f was used, regioisomeric products 9v and 9w were observed in 66% yield in a 9 : 1 ratio. Interestingly, the unsymmetrical benzyne precursor 7g provided aristolactam 9w in 69% yield in a highly regioselective manner. The structure of compound 9w was supported by single crystal X-ray diffraction analysis. It is important to note that by using benzyne precursor 7g, several natural products can be prepared by changing the substituent on the benzaamides.

This result prompted us to explore the possibility of preparing N-methyl aristolactam alkaloids (Scheme 8). Treatment of compound 3a with benzyne precursors 7a or 7b in the presence of CsF in CH3CN at 30 °C for 24 h gave caldensine 10a and 10b in 63% and 55% yields, respectively. Caldensine exhibited an IC50 value of 25 mM against chloroquine-sensitive and also showed antiplasmodial activity. Compound 10b is equally potent towards multidrug-resistant cell lines compared with the commercially available drug etoposide. In a similar fashion, other alkaloids such as 2,3-dimethoxy-N-methyl-aristolactam 10c and 2,3,4-trimethoxy-N-methyl-aristolactam 10d were prepared in good yields. It is important to note that the alkaloids 10c–d were prepared for the first time in the literature. A highly useful sauristolactam (10e) and N-methyl piperolactam A (10f) were prepared in three steps. The reaction of 3-hydroxy-4-methoxy (1v) and 3-methoxy-4-hydroxy (1w) benzaamides with 2a provided products 3z and 3wa in good yields. Later, a free hydroxy group of 3z and 3wa was protected with benzyl bromide followed by a cycloaddition reaction with 7a affording products 12a–b. Later, the benzy1 group was deprotected by a palladium-catalyzed hydrogenation reaction, yielding alkaloids 10e–f in excellent yields. Sauristolactam (10e) and N-methyl piperolactam A (10f) have
shown cytotoxic activity against several cancer cell lines\textsuperscript{1c-2a} and neuroprotective activity.\textsuperscript{3b}

By employing the present protocol, \(N\)-H aristolactam alkaloids were also prepared by using \(N\)-PMB substituted benzamides (Scheme 9). The reaction of 1\textsubscript{x} with 2\textsubscript{a} at 120 °C for 16 h under similar reaction conditions provided product 3\textsubscript{xa} in 63\% yield. Later, 3\textsubscript{xa} was treated with benzoyl precursors 7\textsubscript{a} or 7\textsubscript{b} in the presence of CsF in CH\(_2\)CN at 30 °C for 24 h followed by PMB cleavage yielding cepharanone B (10g) and norcepharanone (10h) in good yields. In a similar fashion, piperolactam C alkaloid (10i) was prepared by the cyclization of 1\textsubscript{y} with 2\textsubscript{a} in the presence of a ruthenium catalyst followed by cycloaddition with 7\textsubscript{a} and subsequent PMB cleavage. Meanwhile, by using cepharanone B (10g), aristolactam FI (10j) can be prepared easily using a known procedure.\textsuperscript{4j} Cepharanone B (10g) showed antimalarial activity with IC\(_{50}\) values of 7.51–11.01 \(\mu\)g mL\(^{-1}\) (ref. 3c) and also exhibited significant cytotoxic activity against human CNS carcinoma cells.\textsuperscript{44} Piperolactam C showed cytotoxicity against P-388 cells with an IC\(_{50}\) value of 78 \(\mu\)M.\textsuperscript{4d} It is important to note that the E/Z ratio of indolin-1-one does not affect the yield of the benzoyl cycloaddition reaction.

**Conclusions**

In conclusion, we have demonstrated an efficient route to synthesize aristolactam alkaloids in good yields using a synergistic combination of C–H bond activation, dehydro-Diels–Alder and desulfonylation reactions. To prepare the target molecules two new synthetic methodologies namely, a ruthenium-catalyzed oxidative cyclization and dehydro-Diels–Alder reaction, were developed. A library of aristolactam derivatives that have substituents on all rings was prepared from easily available starting materials.

**Acknowledgements**

We thank the DST-SERB (EMR/2014/000978), India for the support of this research. M. C. R. thanks the CSIR for a fellowship.

**Notes and references**

1 (a) V. Kumar, Poonam, A. K. Prasad and V. S. Parmar, Nat. Prod. Rep., 2003, 20, 565; (b) K. W. Bentley, Nat. Prod. Rep.,

