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

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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 benzamides 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 fluoride ion mediated desulfonylation of 3-methyleneisoindolin-1-ones with benzynes, were developed. The method presented allows the opportunity for the construction of all the rings of aristolactams from easily available starting materials.

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Introduction

Aristolactams are naturally occurring phenanthrene lactam alkaloids. These alkaloids are isolated from Aristolochiaceae, Annonaceae, Piper Piperaceae, and Saururaceae plant species. 1-3 Aristolactams are frequently used as folk medicines in several countries.2d-f Meanwhile, these molecules show an interesting array of biological properties such as anti-inflammatory, antiplatelet, anti-mycobacterial, neuroprotective and anti-cancer activities.^{2,3} 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.4 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

Phos¹
$$R^2$$
 R^3 R^3 R^3 R^3 R^3 R^3 R^3 R^4 R^4 R^3 R^4 R^3 R^4 $R^$

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.⁵⁻⁷ 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 benzynes.^{8,9} However, this type of cycloaddition reaction is not very effective, because it provides competing side products along with the expected product (eqn (1)).⁴ⁱ To

 $[\]emph{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 benzynes, 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.

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Easily affordable: benzoic acids and alkyl amines

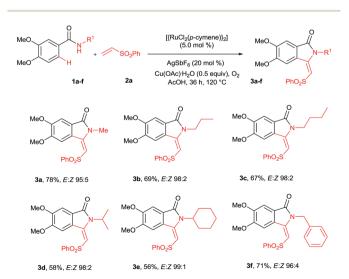
Scheme 1 Retrosynthetic analysis.

overcome this problem, we engineered a molecule that has a cleavable SO₂Ph group at the β-carbon of alkene of 3methyleneisoindolin-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 rutheniumcatalyzed oxidative cyclization of benzamides with vinyl phenyl sulfone. 6c,d,7l The oxidative cyclization of N-methyl benzamide 1a with phenyl vinyl sulfone (2a) in the presence of [{RuCl₂(pcymene) $_{2}$ (5 mol%), AgSbF₆ (20 mol%) and Cu(OAc) $_{2}$ ·H₂O (0.5 equiv.) under oxygen at 120 °C for 36 h provided 3methyleneisoindolin-1-one 3a in 78% yield in an 95 : 5 E/Z ratio (Scheme 2).

Initially, the cyclization reaction was examined with various solvents such as 1,2-dichloroethane, THF, 1,4-dioxane, DMF, toluene, CF₃COOH and CH₃COOH (Table 1). Among them, acetic acid was effective yielding product 3a in 78% yield (entry 7). Other solvents such as toluene and THF were less effective,



Scheme 2 Cyclization of N-substituted benzamides.

Table 1 Optimization studies

Entry	Solvent	Additive	Yield of $3a^b$ (%)
1	ClCH ₂ CH ₂ Cl	AgSbF ₆	_
2	THF	AgSbF ₆	15
3	1,4-Dioxane	AgSbF ₆	_
4	DMF	AgSbF ₆	_
5	Toluene	AgSbF ₆	20
6	CF_3COOH	AgSbF ₆	_
7	CH_3COOH	AgSbF ₆	78
8	CH_3COOH	$AgBF_4$	42
9	CH_3COOH	AgOTf	46
10	CH_3COOH	KPF_6	15
11	CH_3COOH	_	NR

^a All reactions were carried out under the following conditions: 1a (75 mg), 2a (1.5 equiv.), $[\{RuCl_2(p\text{-cymene})\}_2]$ (5 mol%), additive (20 mol%) and Cu(OAc)₂·H₂O (50 mol%) in solvent at 120 °C for 36 h under an oxygen atmosphere. b Isolated yield.

affording product 3a in 20% and 15% yields, respectively (entries 2 and 5). The remaining solvents were not effective. The cyclization reaction was further examined with additives AgSbF₆, AgBF₄, AgOTf and KPF₆. Among them, AgSbF₆ was effective, providing product 3a in 78% yield (entry 7). The remaining additives were less effective for the cyclization reaction (entries 8-10). The cyclization reaction did not proceed without AgSbF₆ (entry 11). AgSbF₆ is used to generate a cationic ruthenium species for activating weak amide group assisted C-H bonds.5c,d Cu(OAc)2·H2O has been widely used as an oxidant for weak chelating group assisted C-H bond activation.5c Usually, a 2.0 equiv. amount of copper source is needed for this type of reaction. However, in the present reaction, a 0.5 equiv. amount of copper source was used and the remaining amount of the copper source was regenerated under oxygen. The cyclization reaction was examined with various substrates such as methyl, propyl, butyl, isopropyl, cyclohexyl and benzyl substituted benzamides 1b-f (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 benzamides 1g-s were compatible for the cyclization reaction (Scheme 3). Electron-releasing (OMe and Me) and halogen (I, Br, Cl and F) substituted benzamides 1g-n efficiently reacted with 2a affording isoindolin-1-ones 3gn in good yields. The less reactive electron withdrawing (CF₃ and NO₂) substituted benzamides 10-p also efficiently reacted with 2a providing products 3o and 3p in good yields. Similarly, ortho and meta substituted benzamides 1q-s also efficiently participated in the reaction, giving products 3q-s in 47%, 64% and 61% yields, respectively. Particularly, in the meta substituted benzamides 1r-s, C-H bond activation takes place at a less hindered C₆-H.

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Scope of substituted benzamides. Scheme 3

The cyclization reaction proceeds *via* a cationic ruthenium(II) catalyzed ortho alkenylation of benzamide 1a with alkene 2a via intermediate 4a, providing ortho alkenylated benzamide 5a.71 Intramolecular addition of the amide N-H bond of 5a into an alkene moiety affords product 3 (eqn (1), for the detailed mechanism see the ESI†). It is important to note that a minor amount of Z stereoisomer was observed in the cyclization of electron-rich OMe and Me substituted benzamides. Intermediate 6b accounts for the formation of the Z stereoisomer. Presently, the exact reason for the observation of a minor amount of the Z stereoisomer is unclear. However, in halogen and electron-withdrawing substituted benzamides, the E stereoisomer was observed exclusively. The observation of high E stereoselectivity for product 3 is mainly due to the formation of intermediate 6a in which the sulfonyl moiety of the alkene and the cyclic tertiary C-N-Me bond are anti to each other (eqn (3)). Syn coplanarity is avoided due to the steric hindrance of the methyl and SO₂Ph groups of intermediate 6b.71

The cyclization reaction was further examined with various alkenes (Scheme 4). Methyl, n-butyl and cyclohexyl acrylates 2bd 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 benzyne was examined (Scheme 5). The cycloaddition of 3g with benzyne 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†).8 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 Nsubstituted 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 vields.

The scope of the cycloaddition reaction was further examined with substituted benzynes 7b-g (Scheme 7). Symmetrical benzynes such as 3,4-dimethoxy benzyne, 3,4-dimethyl benzyne, indene derivative and 1,3-benzodioxale reacted with 3j, providing cyclization products 9r-u in good yields. When

Scheme 4 Scope of alkenes

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Scheme 5 Dehydro-Diels-Alder reaction with benzynes

Scheme 6 Scope of substituted isoindolin-1-ones.

unsymmetrical benzyne 7f was used, regioisomeric products 9v and 9v' 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

Scheme 7 Scope of substituted benzynes.

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 benzamides.

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.3a Compound 10b is equally potent towards multidrugresistant cell lines compared with the commercially available drug etoposide.24 In a similar fashion, other alkaloids such as 2,3-dimethoxy-N-methyl-aristolactam 10c and 2,3,4trimethoxy-N-methyl-aristolactam 10d were prepared in good yields. It is important to note that the alkaloids 10cd 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) benzamides 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 benzyl 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

Scheme 8 Synthesis of N-methyl aristolactam alkaloids.

shown cytotoxic activity against several cancer cell lines 1c,2a and neuroprotective activity. 3b

By employing the present protocol, N-H aristolactams were also prepared by using N-PMB substituted benzamides (Scheme 9). The reaction of 1x with 2a at 120 °C for 16 h under similar reaction conditions provided product 3xa in 63% yield. Later, 3xa was treated with benzyne precursors 7a or 7b in the presence of CsF in CH₃CN 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 1y with 2a in the presence of a ruthenium catalyst followed by cycloaddition with 7a and subsequent PMB cleavage. Meanwhile, by using cepharanone B (10g), aristolactam FI (10j) can be prepared easily using a known procedure.45 Cepharanone B (10g) showed antimalarial activity with IC₅₀ values of 7.51-11.01 μ g mL⁻¹ (ref. 3c) and also exhibited significant cytotoxic activity against human CNS carcinoma cells.3d Piperolactam C showed cytotoxicity against P-388 cells with an IC₅₀ value of 78 μ M.^{3e} It is important to note that the E/Z ratio of indolin-1-one does not affect the yield of the benzyne cycloaddition reaction.

Scheme 9 Synthesis of N-H aristolactam alkaloids.

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.

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