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P_4O_{10}/TfOH mediated domino condensation–cyclization of amines with diacids: a route to indolizidine alkaloids under catalyst- and solvent-free conditions†

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A domino condensation–cyclization method is developed to synthesize indolizidine alkaloids using a P_4O_{10}/TfOH reagent system without the employment of either a catalyst or solvent. The use of a few aliphatic and aromatic dicarboxylic acids is shown along with various primary amines. This method is suitable for synthesizing pyrrolo[2,1-*a*]isoquinolines, pyrido[2,1-*a*]isoquinolines, and isoindolo[1,2-*a*]isoquinolinones in excellent yields. When phthalic acid is used, a workup with either $NaBH_4$ or a saturated $NaHCO_3$ solution provided 12*b*-H or 12*b*-OH isoindolo[1,2-*a*]isoquinolinones, respectively.

Indolizidine alkaloids are structurally important molecules that belong to the broader class of natural products.[1] These indolizidine alkaloids are isolated as lysine-derived metabolites from various animal and plant sources, like higher plants, invertebrates, vertebrates, fungi, and bacteria.[2] With their core structure of a fused six- and five-membered ring system with a bridgehead nitrogen atom, indolizidine compounds constitute 25–30% of all alkaloids.[3] Benzoindolizidine alkaloids that contain benzene rings fused to one of the indolizidine rings are also known in nature. A few selected examples are shown in Fig. 1. For instance, crispine contains a benzene ring attached to the indolizidine piperidine ring. Jamtine and erythraline, in addition to the benzene ring, have a six membered cyclohexene ring attached to indolizidine pyrrolidine. In elaeocarpaceae, a phenanthrene ring is attached to the indolizidine piperidene ring. In nuevamine, a benzene ring is attached to both the indolizidine piperidine and pyrrolidine rings. Alkaloids like lamellarin, which are well studied for their wide range of biological activity, contain an indolizidine ring fused to a benzene and a coumarin ring, making them unique in the indolizidine family.

Among current pharmaceuticals, ~40% are derived from or inspired by natural products.[4] Scientists have extensively worked on the construction of indolizidine core structures from various synthons.[5] The indolizidine compound class shows a wide range of promising biological activities such as cytotoxicity,[6] antibacterial activity, antiviral activity,[7] antioxidant activity,[8] antileishmanial activity,[9] antinociceptive activity,[10] *etc.* Manufactured compounds like CRR-271 act as poly(ADP-ribose) polymerase-1 inhibitors, while other derivatives have been prepared and tested for antioxidant activity for lipid peroxidation at a cellular level and for protection against genomic DNA damage at a nuclear level.[11]

We recently reported our work on constructing lamellarin scaffolds *via* a tandem Bischler–Napieralski reaction–Michael reaction–oxidation sequence wherein we fabricated fused isoquinoline and pyrrole ring structures around a coumarin ring.[12] However, the direct condensation of primary amines and dicarboxylic acids for the construction of the multi-ring structures has been less studied. Moreover, practicing chemists usually require two or more steps to construct the indolizidine ring core from different substrates under various conditions.[13] Ramanathan *et al.* elaborated a precise methodological syntheses of isoindoloisoquinolinones, pyrroloisoquinolinones, and benzo[*a*]quinolizinones using TfOH. They have also prepared numerous annulated tetrahydroisoquinolines. Imide phenylethylamine surrogates were cyclized using

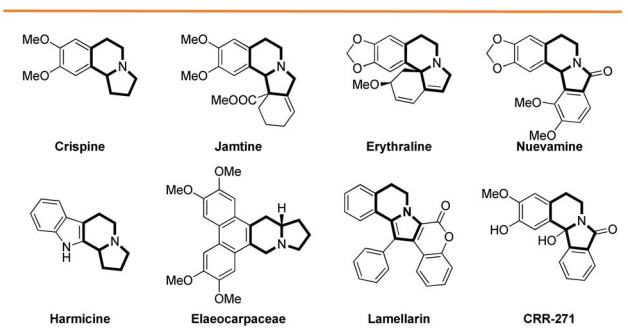

Fig. 1 Selected bioactive molecules containing indolizidine rings.

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excess TfOH with either succinic anhydrides, phthalic anhydrides, or glutaric anhydride before being reduced with sodium borohydride or water to get the corresponding pyrroloisoquinolinones, isoindoloisoquinolinones, benzo[*a*]quinolizinones, or hydroxyl derivatives. They synthesized a library of such compounds and even demonstrated the syntheses of many naturally occurring compounds in their racemic form. They have synthesized (±)-crispine A, (±)-trolline/oleracein E, (±)-erythrabine, and (±)-mescalotam from their respective imides in excellent yields. Later, they applied an iminium ion cyclization strategy to unsymmetrical succinimides to synthesize 1- or 2-alkylsubstituted pyrroloisoquinolinones and indolizinoindolones.[14]

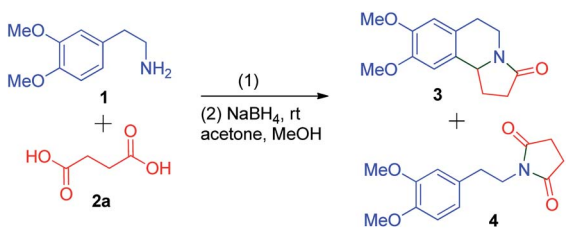
The present study describes a one-pot protocol for constructing an indolizidine ring system from 2-arylethanamines and dicarboxylic acids.

Results and discussion

We examined the reagents required for a reaction between primary amines and dicarboxylic acids and settled on the use of phosphorus pentaoxide (P_4O_{10}) to carry out the reaction. Many reports have focused on the cyclization of 1-phenethylpyrrolidine-2,5-dione *via* an acyliminium ion. Thus, our methodology also depends on a one-pot formation of an acyliminium ion followed by its cyclization and reduction.

Initially, a model reaction between **1** and succinic acid **2a** was carried out in the presence of 2.5 equivalents of P_4O_{10} in refluxing toluene (Table 1, entry 1). It did not cyclize to form tricyclic compound **3** but instead formed imide **4**. Further refluxing in dry xylene, to test whether the formation of **3** was temperature-dependent, also failed to give the desired product (Table 1, entry 2). The use of Eaton's reagent (7.5 wt% P_4O_{10} in MsOH) has been reported for dehydration and cyclization reactions in many cases.[15] So, in freshly prepared Eaton's reagent at room temperature another reaction was set between **1** and **2a** (Table 1, entry 3). Tricyclic product **3** was formed, after reduction, in a 28% yield and no imide **4** was isolated. The acidity of the reagents or the temperature are factors that could also affect the cyclization. Thus, with the same 7.5 wt% proportion of P_4O_{10}, we prepared a mixture of P_4O_{10} in TfOH and carried out the reaction at room temperature (Table 1, entry 4). This reaction produced compound **3** in a 45% yield after the reduction process. With the same mixture of P_4O_{10} and TfOH at 60 °C, a 20% increase in yield was found in comparison to the previous attempt (Table 1, entry 5). When the wt% of the P_4O_{10} in TfOH mixture was increased to 8.3 wt% and the temperature was increased to 100 °C, we could obtain the cyclized compound, after reduction using sodium borohydride, in a 79% yield in just 2 h (Table 1, entry 6).

Table 1 Optimization of the reagents

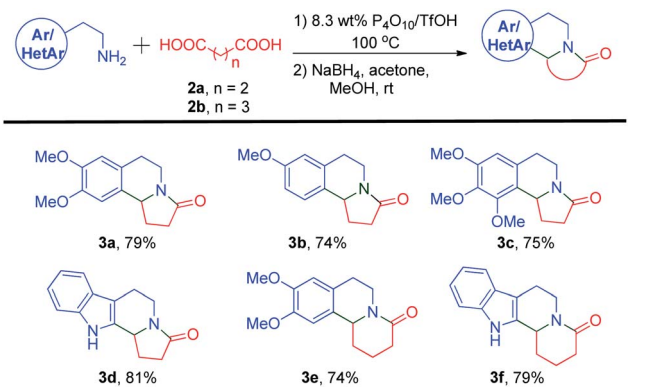


Entry	Reaction conditions (**1**)[a]	Time	Yield 3	Yield 4
1	P_4O_{10}, dry toluene, Δ	12 h	n.d.[b]	63%
2	P_4O_{10}, dry xylene, Δ	12 h	n.d.	65%
3	Eaton's reagent, rt	8 h	28%	n.d.
4	7.5 wt% P_4O_{10}/TfOH, rt	6 h	45%	n.d.
5	7.5 wt% P_4O_{10}/TfOH, 60 °C	6 h	65%	n.d.
6	8.3 wt% P_4O_{10}/TfOH, 100 °C	2 h	79%	n.d.

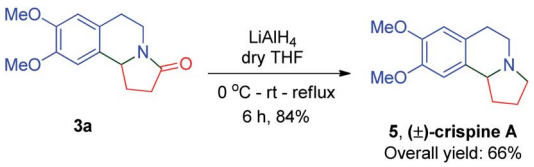
[a] The reaction was performed with homoveratrylamine **1** (1.5 mmol) and succinic acid **2a** (1 mmol) for the time periods indicated; this was followed by reduction with $NaBH_4$ (1 mmol) in MeOH at rt. [b] n.d. – not detected.

After successfully making **3a**, the reactions of other primary amines with succinic acid and glutaric acid were conducted to synthesize tricyclic structures (Scheme 1). The reaction of mono and trimethoxy phenethylamines with succinic acid proceeded smoothly to furnish compounds **3b** and **3c** in 74% and 75% yields, respectively. Compound **3c** is a naturally occurring compound, mescalotam, for which no biological activity study has been reported to date. The indole-containing heterocyclic amine tryptamine, a precursor for naturally occurring compound harmicine, was reacted with succinic acid to afford **3d** in an 81% yield. Instead of succinic acid **2a**, the five carbon dicarboxylic acid, glutaric acid **2b**, was incorporated into our methodology to assess its reactivity. The reaction of **2b** with homoveratrylamine and tryptamine gave quinolizidine alkaloids **3e** and **3f** in 74% and 79% yields, respectively.

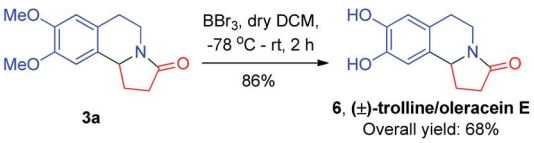
Furthermore, these compounds were, using reduction and demethylation reactions, utilized to synthesize naturally occurring compounds such as (±)-crispine A, (±)-trolline/oleracein E, and (±)-harmicine. The amide group in compound **3a** was reduced using lithium aluminium hydride to get (±)-crispine A **5** in an overall yield of 66% (Scheme 2). Likewise, **3a** was demethylated to its dihydroxy form using



Scheme 1 Syntheses of indolizidine and quinolizidine alkaloids.



Scheme 2 Total synthesis of (±)-crispine A.

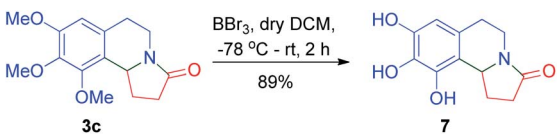


Scheme 3 Total synthesis of (±)-trolline/oleracein E.

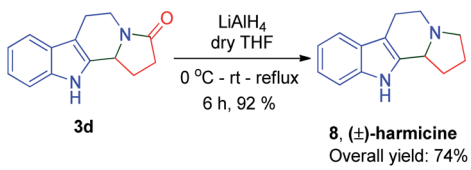
boron tribromide in dry dichloromethane to afford (±)-trolline/oleracein E **6** in an overall yield of 68% (Scheme 3).

As past reports do not suggest that mescalotam **3c** has any biological activity, we envisaged synthesizing and then studying the bioactivity of its trihydroxy derivative. We successfully synthesized **7** from compound **3c** in an 89% yield by complete demethylation using the same method employed to synthesize (±)-trolline/oleracein E (Scheme 4). Using the method employed to synthesize (±)-crispine A, we obtained (±)-harmicine **8** from its amide precursor **3d** in an overall yield of 74% starting from tryptamine (Scheme 5).

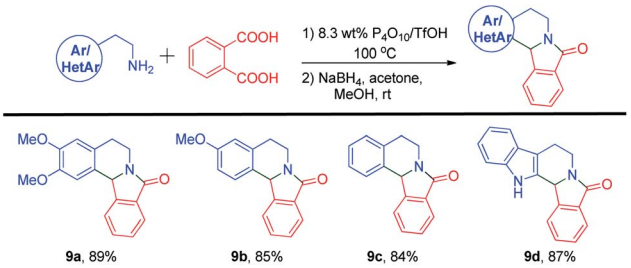
In addition, aromatic 1,2-dicarboxylic acids were also reacted with primary amines using the 8.3 wt% P_4O_{10}/TfOH reagent system. Four aryl/heteroaryl ethylamines were treated with phthalic acid **2c** and heated in an 8.3 wt% P_4O_{10}/TfOH mixture at 100 °C followed by reduction of the subsequent iminium ion to produce the final adducts (Scheme 6). Compound **9a** was prepared from homoveratrylamine **1** and phthalic acid **2c** in an 89% yield. Whereas the monomethoxy compound **9b** and the unsubstituted analog **9c** were prepared successfully from 3-methoxyphenethylamine and phenylethylamine in 85% and 84% yields, respectively. In addition to simple aryl compounds, a heteroaryl derivative with a pentacyclic ring structure **9d** was obtained from tryptamine and



Scheme 4 Synthesis of trihydroxy derivative of mescalotam.



Scheme 5 Total synthesis of (±)-harmicine.

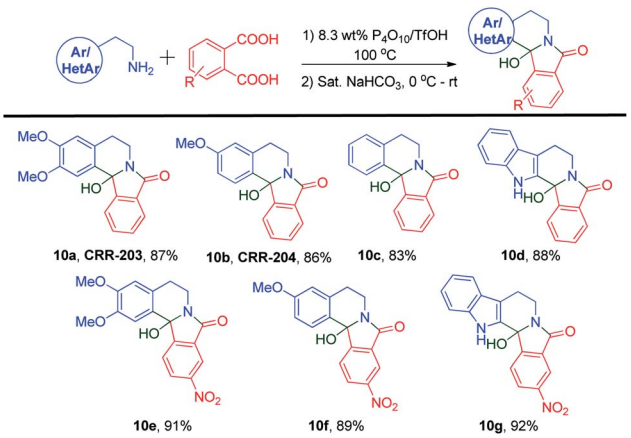


Scheme 6 Syntheses of isoindolo[2,1-*a*]isoquinolinone alkaloids.

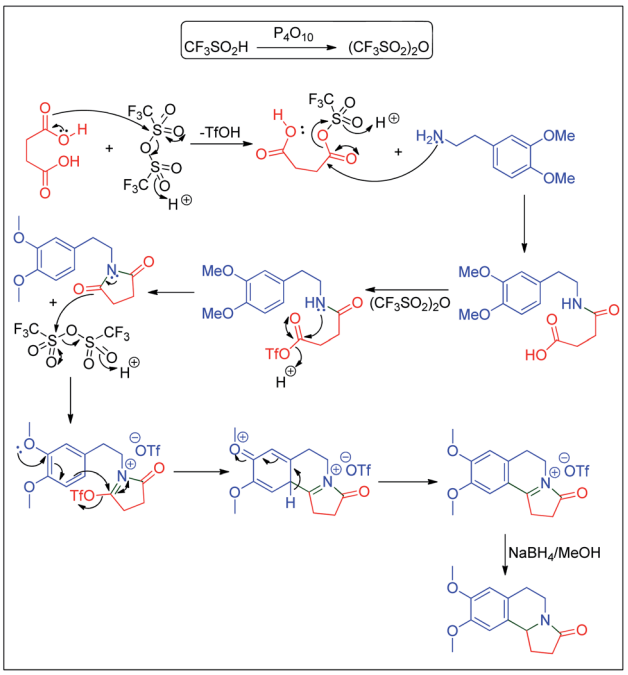
phthalic acid **2c** in an 87% yield. Successful incorporation of a hydride ion at the 12*b*-position furnished all the desired isoindoloisoquinolinone compounds successfully.

After accomplishing the target molecules, we synthesized their 12*b*-hydroxy analogs *via* a saturated sodium bicarbonate workup (Scheme 7). The respective aryl/heteroaryl ethylamines **11a**, **11b**, **11c**, and **11d** were condensed with two different phthalic acid derivatives. When condensed with simple phthalic acid **2c**, four 12*b*-hydroxy isoindoloisoquinolinone derivatives, **10a**, **10b**, **10c**, and **10d**, were prepared from their corresponding amines using just a simple basic workup. Novel analogs like **10e**, **10f**, and **10g** were prepared using 4-nitrophthalic acid **2d**. When **2d** was fused with homoveratrylamine, **10e** was obtained in a 91% yield. The reaction of 3-methoxyphenethyl amine went smoothly to form **10f** in an 89% yield. Also, tryptamine-derived 12*b*-hydroxy analog **10g** was synthesized in a slightly higher yield than the other amines.

A speculative mechanism is proposed in Scheme 8. The combination of P_4O_{10}/TfOH produces triflic anhydride which induces the activation of the diacid. The resulting mixed anhydride is attacked by the amine to form the amide acid. The amide acid is further activated by triflic anhydride to form the imide *via* a mixed anhydride. The imide undergoes a Bischler–Napieralski reaction mediated by triflic anhydride. Reduction of the resulting salt delivers the final product.



Scheme 7 Syntheses of 12*b*-hydroxyisoindolo[2,1-*a*]isoquinolinone alkaloids.



Scheme 8 Plausible mechanism for the formation of pyrrolo[2,1-*a*] isoquinolinone.

Conclusions

The present methodology allows the construction of indolizidine and quinolizidine rings adjacent to benzene rings. The reactions proceed *via* single pot domino reactions between phenethylamine derivatives and aliphatic and aromatic dicarboxylic acids in the presence of an 8.3 wt% mixture of P_4O_{10}/TfOH. In total, seventeen 12*b*-H and 12*b*-OH derivatives of pyrrolo[2,1-*a*]isoquinoline and isoindolo[1,2-*a*]isoquinoline alkaloids are synthesized in very good yields. The utility of this methodology was demonstrated by synthesizing naturally occurring compounds such as, (±)-crispine A, (±)-trolline/oleracein E, (±)-mescalotam and (±)-harmicine from commercially available synthons. A novel trihydroxy derivative of mescalotam was also synthesized successfully. Compounds such as CRR-203, CRR-204 were also synthesized in excellent yields.

Author contributions

SGT was involved in overall supervision, while KSM was involved in project planning, execution, experiments, and manuscript writing.

Conflicts of interest

There are no conflicts to declare.

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