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COMMUNICATION

Brønsted acid assisted activation of imide carbonyl group: regioselective synthesis of isoindoloisoquinolinone alkaloid (±)-nuevamine†

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Activation of imide carbonyl group with trifluoromethanesulfonic acid facilitates the intramolecular cyclization of phenethylphthalimides to give a fused isoindoloisoquinolinone skeleton. The first one pot regioselective synthesis of isoindoloisoquinolinone alkaloid (±)-nuevamine has been successfully executed using this methodology.

Among various alkaloids, nitrogenous natural products, tetrahydroisoquinoline (THIQ) skeleton containing molecules are a very important class owing to their widespread occurrence in nature[1] (Fig. 1).

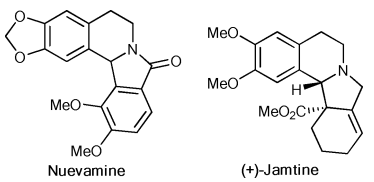


Fig. 1 Representative isoquinoline natural products.

Several synthetic protocols such as Pictet–Spengler,[2] Bischler–Napieralski,[3] Pomeranz–Fritsch–Bobbitt,[4] *N*-acyliminium ion cyclization[5] and Parham type cyclization[6] are generally employed to synthesise THIQ scaffolds. Close analysis of these methods divulges the fact that the intramolecular cyclization was effected either by increasing the nucleophilicity of the aromatic ring through metal halogen exchange reaction or by increasing the electrophilicity of the carbonyl/imide carbon, which is involved in the C–C bond formation. Base induced aryne mediated cyclization[7] and other sophisticated methods[8] have also been developed for the synthesis of THIQ scaffolds. The tetrahydroisoquinoline unit fused with isoindole has generally been constructed through Pomeranz–Fritsch–Bobbitt reaction, Pictet–Spengler reaction, *N*-acyliminium ion cyclization and other sophisticated methods involving either harsh conditions or sensitive reagents and multiple steps. Bischler–Napieralski conditions,[9] which have never been employed for the construction of isoindoloisoquinolinone skeleton, involving the intermediate I (Fig. 2, I), were examined first. Among the various reagents ($POCl_3$, PPA, H_3PO_4, P_2O_5, TFAA, Tf_2O or Tf_2O/2-ClPyr) screened, the reagents P_2O_5 and Tf_2O furnished the cyclized product from 3,4-dimethoxy phenethylphthalimide **1a** in poor yield (41% & 54% respectively) after 48 h with excess of reagents (Scheme 1). Akin to amide carbonyl activation,[10] the carbonyl group of phenethylimides has been activated using Lewis acid BBr_3 to furnish the fused THIQ derivatives through complexation with imide carbonyl oxygen (Fig. 2, II). Reaction of methoxy substituted phenethylimides with BBr_3 furnished demethylated product as well in certain cases.[11] Hence, we are in the search of a reagent system lacking the ether cleavage property for intramolecular cyclization through imide carbonyl activation.

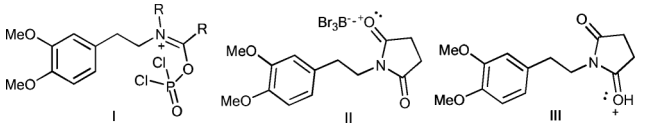
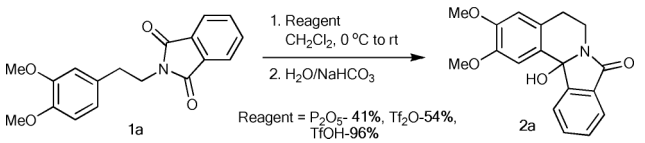


Fig. 2 Activation of amide/imide carbonyl groups.



Scheme 1 Cyclization of imide **1a**.

Brønsted acid is known to activate the carbonyl group without affecting the ether functionality in many C–C bond forming reactions.[12] Hence, imide **1a** was treated with Brønsted acids to effect the cyclization through imide carbonyl group activation (Fig. 2, III).

Acids such as AcOH, TFA, *p*-TSA and $MeSO_3H$, failed to effect the cyclization, whereas the imide **1a** furnished the cyclized product **2a** in 96% yield after 30 min on treatment with trifluoromethanesulfonic acid (TfOH). After careful examination of the reaction conditions, the optimum amount of TfOH required for complete conversion was found to be four equivalents.

Encouraged by this result, the generality of this methodology was justified through the formation of cyclized products from various methoxy/methyl/hydroxy/bromo substituted

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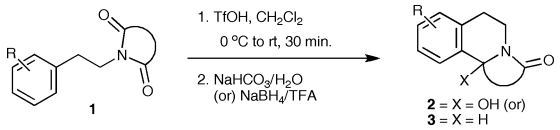
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra for new compounds. CCDC & X-ray crystallography details for the compounds **2h**, **2j**, **2k** and **2m**. CCDC reference numbers 828124–828126 and 828128. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06349a

Table 1 Scope of the cyclization of phenethylphthalimides[a]



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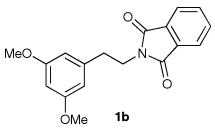
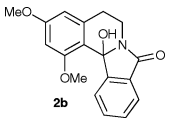
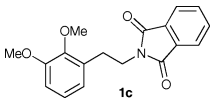
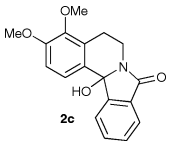
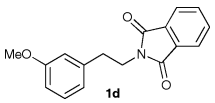
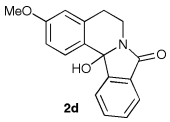
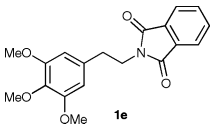
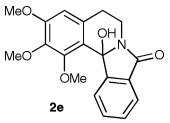
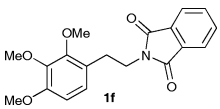
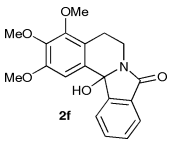
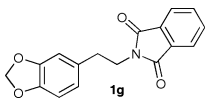
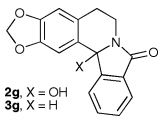
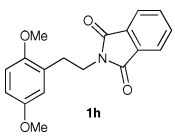
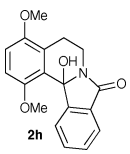
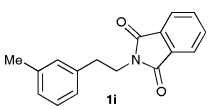
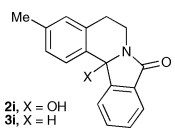
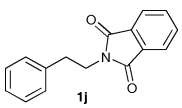
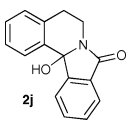
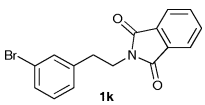
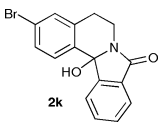
1			91
2			85
3			93
4			89
5			91
6			**2g**, 65 **3g**, 85
7[c]			87
8[d]			**2i**, 78 **3i**, 93
9[e]			78
10[f]			66

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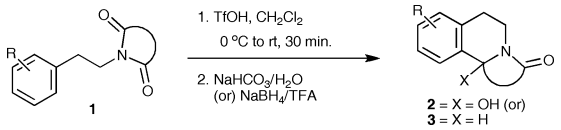
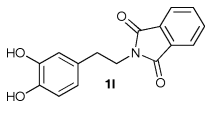
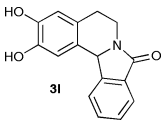


Entry	Imide **1**	Product	Yield (%)[b]
11			77

[a] Reaction conditions: 1) **1** (0.5 mmol), TfOH (2 mmol, 4 equiv), CH_2Cl_2 (15 ml), 0 °C to rt, 30 min; 2) H_2O (10 ml)/$NaHCO_3$ (1 g) or $NaBH_4$ (2 mmol)/TFA (1 ml), 15 min. [b] Isolated yield. [c] The reaction was carried out for 12 h. [d] The reaction was carried out for 1 h. [e] The reaction was carried out with TfOH (5 equiv), 60 °C, 24 h. [f] The reaction was carried out with TfOH (8 equiv), 70 °C, 48 h.

phenethylphthalimides (Table 1). For example, substrates such as 3,5-dimethoxy **1b**, 2,3-dimethoxy **1c**, 3-methoxy **1d**, 3,4,5-trimethoxy **1e**, 2,3,4-trimethoxy **1f** and 3,4-methylenedioxy **1g** phenethylphthalimides successfully furnished the cyclized products **2b–2g** in excellent yields (Table 1, entries **1–6**). Even weakly activated 2,5-dimethoxy phenethylphthalimide **1h** delivered the cyclized product **2h** in 87% yield after 12 h in the presence of 4 equivalents of TfOH. Phenethylphthalimide **1j**, which failed to undergo cyclization in the presence of BBr_3, has successfully furnished the fused THIQ **2j** in 78% yield after heating the phenethylphthalimide for 24 h (Table 1, entry **9**). Similarly the phenethylimide **1k** with an inductively deactivating bromide group at the 3rd position also gave the cyclized product **2k** in moderate yield (66%) after heating the reaction mixture for 48 h at 70 °C, though the reaction required 8 equivalents of TfOH. Formation of these cyclised molecules was characterized by IR, NMR and HRMS analysis; some of them were further confirmed by single crystal structural analysis[13] (Fig. 3).† Imides with functional groups such as methylenedioxy **1g**, phenolic -OH **1l** and methyl group **1i** on the phenyl ring of the phenethyl moiety smoothly delivered the corresponding fused THIQ. Better yields were observed when cyclized product was reduced *in situ* using $NaBH_4$/TFA mixture[14] (Table 1, entries **6**, **8** and **11**).

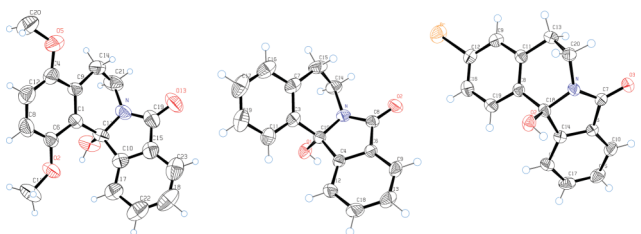


Fig. 3 The crystal structures of the cyclized products **2h**, **2j** and **2k**.

Based on these results, the synthesis of isoindoloisoquinolinone alkaloid nuevamine, isolated from *Berberis darwinii* Hook,[15a] was initiated. Due to the presence of regioisomer formation during the synthesis of nuevamine, multiple synthetic steps have been employed in the reported synthetic protocols.[7,15] Whereas the present methodology lends the opportunity for a simple

C_{12b}–C_{12c} disconnection of nuevamine **5a** to phenethylphthalimide **4**, which can be easily accessed from homopiperonyl amine and 3,4-dimethoxyphthalic anhydride (Fig. 4).

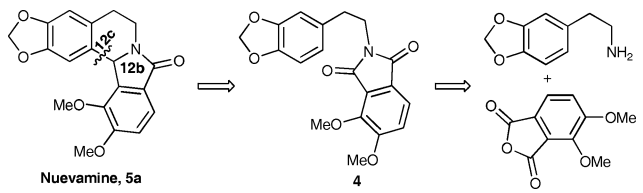
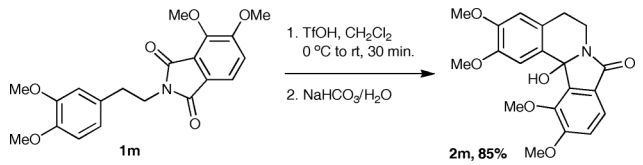


Fig. 4 Synthetic strategy for nuevamine.

Before executing the synthesis of nuevamine, the model substrate, 3,4-dimethoxyphenethyl[3′,4′-dimethoxy]isoindolodione **1m** was subjected to the cyclization reaction and elegantly furnished the regioisomer **2m** similar to the nuevamine skeleton (Scheme 2) as evidenced from the single crystal X-ray structural analysis[13] (Fig. 5).†



Scheme 2 Cyclization of nuevamine model substrate.

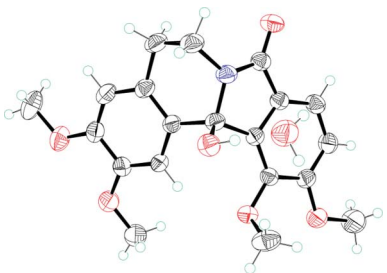
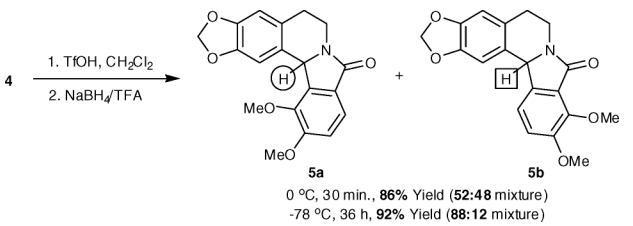


Fig. 5 The crystal structure of the cyclized product **2m**.

Accordingly the nuevamine precursor **4** was treated with TfOH followed by reduction using $NaBH_4$/TFA mixture and, unexpectedly, furnished the 52 : 48 mixture (based on ^{1}H-NMR analysis)[13] of nuevamine **5a** and isonuevamine **5b** in 86% yield (Scheme 3).



Scheme 3 Short synthesis of nuevamine.

This observation prompted us to examine the effect of temperature on the regioselectivity of this cyclization reaction and hence the experiment was carried out at –20 °C followed by reduction (at 0 °C to rt); the imide **4** furnished a product mixture in which the nuevamine concentration increased from 52% to 71% based on the ^{1}H-NMR spectral analysis (Fig. 6, [a]). Further lowering

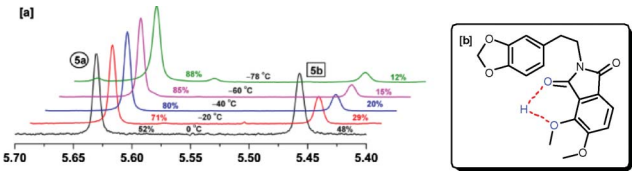
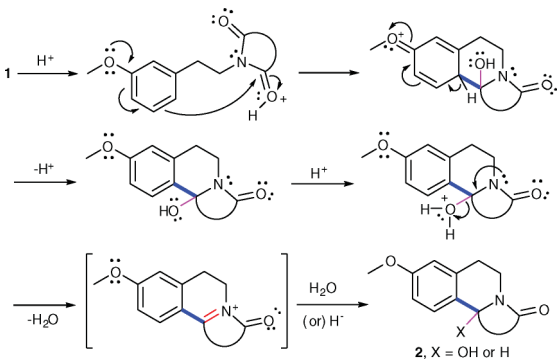


Fig. 6 [a] ^{1}H-NMR spectrum showing effect of temperature on yield of **5a**. [b] Possible interaction for regioselectivity.

of the temperature from –20 °C to –40 °C, –60 °C and –78 °C followed by reduction (at 0 °C to rt) gratifyingly delivered the cyclized product mixture with 80%, 85% and 88% respectively in favour of nuevamine. This regioselectivity may presumably be due to the preferential activation of the carbonyl group adjacent to the methoxy group present in the imide portion by proton (Fig. 6, [b]) at low temperature.

Based on these observations we propose a plausible mechanism for this transformation in analogy with Lewis acid assisted cyclization sequence[11] (Scheme 4).



Scheme 4 Plausible mechanism for the cyclization.

In conclusion, we have developed a simple and efficient method to construct a condensed tetrahydroisoquinoline such as the isoindoloisoquinolinone scaffold. Using this cyclization reaction as the key step, the synthesis of alkaloid nuevamine was successfully demonstrated. The regioselectivity of cyclization of unsymmetrical imides depends on the reaction temperature. Investigations into the further utility of this methodology towards alicyclicimides and the synthesis of other natural products are progressing in this laboratory.

Acknowledgements

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