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An unusual reactivity of BBr_3: Accessing tetrahydroisoquinoline units from *N*-phenethylimides†

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Isoindoloisoquinalinone, pyrroloisoquinolinone and benzo[a]quinolizinone units are constructed *via* intramolecular cyclization of the methoxy substituted *N*-phenethylimides using BBr_3.

The heterocycles containing a tetrahydroisoquinoline unit constitute a major class in the pharmacologically active isoquinoline alkaloid family[1] and hence attracted the great attention of synthetic chemists.[2] Molecules containing tetrahydroisoquinoline skeleton have generally been constructed through the synthetic protocols such as Pictet–Spengler,[3] Bischler–Napieralski,[4] Pomeranz-Fritsch-Bobbitt,[5] *N*-acyliminium ion cyclization,[6] Parham type cyclization,[7] base induced aryl mediated cyclization,[8] and other sophisticated methods.[9] These methods either involve the harsh condition or multiple steps to effect the cyclization.

During the course of our investigation on the preparation of resorcinol **1** from dimethoxyderivative **2a** (Fig. 1) on treatment with boron tribromide, a reagent commonly used for the demethylation of aryl methyl ether,[10] we have observed an unusual reactivity. The methyl group remained unaffected even with excess of BBr_3; instead, the reaction proceeded smoothly to afford the cyclized product, isoindoloisoquinolinone derivative, **3a**.

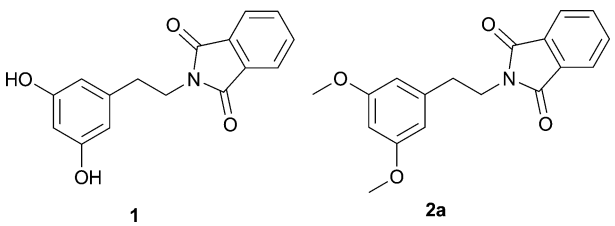
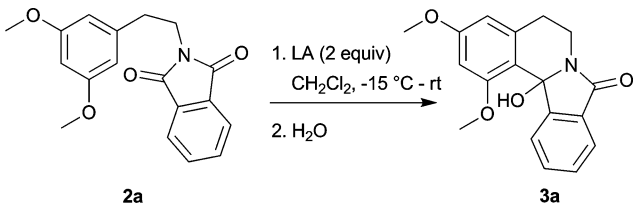


Fig. 1

This observation prompted us to investigate the feasibility of this unexpected reaction of BBr_3 with methoxy substituted phenethylimides and herein we report the first single step synthesis of tetrahydroisoquinoline derivatives such as isoindoloisoquinolinone, pyrroloisoquinolinone and benzo[a]-quinolizinone units using BBr_3. Preliminary experiments revealed that the cyclization reaction required two equivalents of BBr_3 with **2a**, while the lesser



Scheme 1 Screening of Lewis acids for cyclization.

Table 1 Cyclization of **2a** using common Lewis acids

Entry	Lewis Acid	Equiv.	Reaction time/h	**3a (%)**[a]
1	$BF_3{\cdot}OEt_2$	2	96	58
2	$FeCl_3$	2	6.5	53
3	$TiCl_4$	2	12	72
4	$AlCl_3$	2	8	75
5	$AlBr_3$	2	4.5	83
6	BBr_3	4	0.5	88
7	**BBr_3**	**2**	**0.5**	**91**
8	BBr_3	1	0.5	46

[a] Isolated yield.

equivalent led to incomplete reaction. To examine the efficacy of other Lewis acids to effect this cyclization process, the reactions were carried out with substrate **2a** in presence of other Lewis acids (LA) such as $BF_3{\cdot}OEt_2$, $FeCl_3$, $TiCl_4$, $AlCl_3$, $ClTi(O^iPr)_3$, $Ti(O^iPr)_4$, $ZnCl_2$, $SnCl_4$ and $AlBr_3$ (Scheme 1). The results are summarized in Table 1.

When **2a** was treated with 2 equivalents of Lewis acids such as $ClTi(O^iPr)_3$, $Ti(O^iPr)_4$, $ZnCl_2$ and $SnCl_4$ the reactions failed to afford the cyclized product and revealed that the Lewis acidities of these reagents are not sufficient enough to facilitate the cyclization process. Whereas, the Lewis acids $AlCl_3$, $AlBr_3$, $FeCl_3$, $TiCl_4$ and BBr_3 were successfully afforded the cyclized product. Depending on the Lewis acids the time required for the completion of the reaction and yield varied. For example, the Lewis acids $TiCl_4$, $AlCl_3$, $FeCl_3$ and $AlBr_3$ required 12 h, 8 h, 6.5 h and 4.5 h for complete conversion of the starting material **2a** to the cyclized product **3a** in 72%, 75%, 53% and 83% yield respectively. The reaction was sluggish when $BF_3{\cdot}OEt_2$ was used as a Lewis acid; the reaction was incomplete even after 3 days of stirring at room temperature (entry no. 1; Table no. 1). The cyclization of **2a** using BBr_3 (in CH_2Cl_2 at −15 °C to room temperature) was fast, clean and gave the cyclized product within 30 min.

Further utility of BBr_3 for this cyclization reaction was examined by treating mono/di/tri methoxy substituted phenethylphthalimides and the results are summarized in Table 2 (Scheme 2). For example, the substrates **2b** and **2e** underwent regioselective cyclization at C-6 position which is *para* to the C-3 methoxy

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† Electronic supplementary information (ESI) available: Detailed synthetic procedure and characterization of all compounds; ^1H, ^{13}C NMR spectra and crystallographic data for selected compounds. CCDC reference numbers 768894–768899. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00269k

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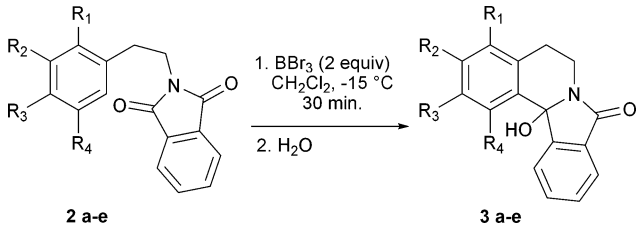


Scheme 2 Cyclization of **2a–e** using BBr_3.

Table 2 Cyclization of **2a–e** using 2 equiv. of BBr_3

S. No.	Entry	Substitutions R^1	R^2	R^3	R^4	**3** (%)[a]
1	**2a**	H	OMe	H	OMe	**3a** (91)
2	**2b**	H	OMe	OMe	H	**3b** (72)
3	**2c**	OMe	OMe	H	H	**3c** (37)
4	**2d**	H	OMe	OMe	OMe	**3d** (42)
5	**2e**	H	OMe	H	H	**3e** (81)
6	**2f**	H	$-OCH_2O-$		H	—[b]
7	**2g**	H	H	H	H	N.R.[c]

[a] Isolated yield. [b] Only demethylenated product was obtained. [c] No reaction.

group to afford **3b** and **3e** respectively. The reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]phthalimide **2b** gave 72% of the cyclized product **3b** along with a mixture of both mono and di demethylated products. Reaction temperature (−78 °C and 27 °C) as well as the quantity of BBr_3 did not alter the yields of both cyclized and demethylated product from **2b**. Similarly, 2,3-dimethoxy and 3,4,5-trimethoxy derivatives furnished the corresponding cyclized products **3c** and **3d** in 37% and 42% yield respectively; along with demethylated products. Methylenedioxy phenethylphthalimide **2f** underwent complete ether cleavage to the catechol derivative. The success of the cyclization depend on the relative position of the methoxy groups with respect to the phenyl ring carbon that participates in the cyclization; a methoxy group must be present at C-3/C-5 positions so that the phenyl carbons C-6/C-2 respectively participate in the C–C bond forming reaction (Scheme 2). When methoxy group was present at C-4 carbon, demethylation was a competing reaction (**2b–d**).

Unsubstituted phenethylphthalimide failed to give the cyclized product even after stirring **2g** with BBr_3 for the extended period of time. These examples revealed that the sufficient mesomeric activation of the reacting nucleophilic carbon is important for a successful cyclization.

Preferential coordination of BBr_3 with imide carbonyl group over methoxy group was evidenced from the ^1H NMR studies[11] of the reaction mixture and the mixture of hydroxy lactam **3a** and BBr_3 in $CDCl_3$ (Fig. 2). This complexation facilitated the electrophilic substitution at C-6 *via* nucleophilic addition on the imide carbonyl group to furnish the boron derivative of hydroxylactam **A** prior to the *N*-acyliminium ion formation. With the expulsion of boron species (Br_2BO^-) from **A** produced the stable intermediate **I** the *N*-acyliminium ion (Scheme 3). Further, this speculation was supported by the fact that the phenethylphthalimide **2g** failed to give the cyclized product; the reactivity generally observed for the *N*-acyliminium ion cyclization.

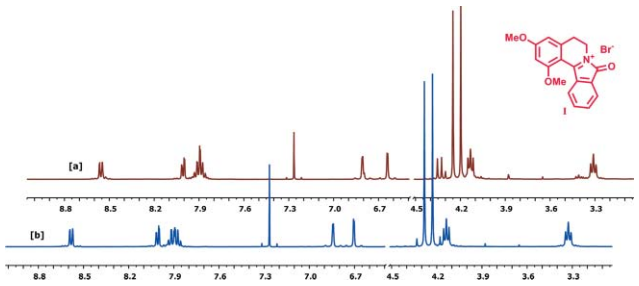
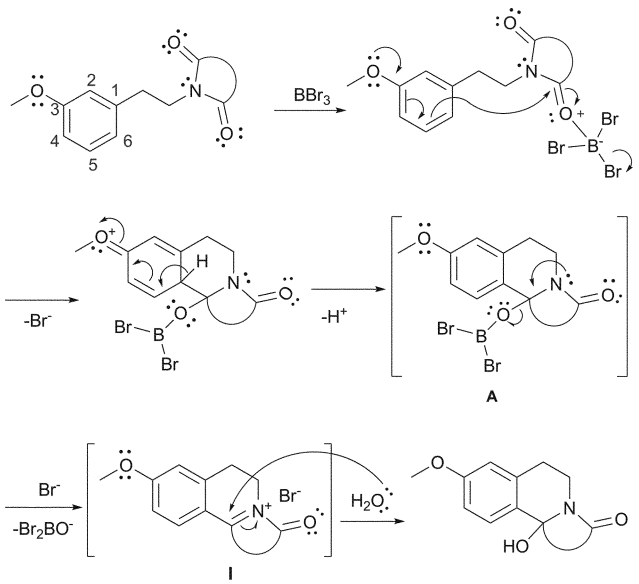


Fig. 2 ^1H NMR spectra of a) **2a** + BBr_3; b) **3a** + BBr_3.



Scheme 3 Proposed reaction mechanism.

Next we turned our attention to examine the applicability of this methodology to the methoxy substituted phenethyl aliphatic imides such as *N*-[2-(3,5-dimethoxyphenyl)- ethyl]succinimide **5a** (Scheme 4). On treatment with BBr_3, **5a** furnished the cyclized product **6a**, which underwent dehydration readily to a very unstable compound **7a** in 60% yield.[7a] Hence the *in situ* generated intermediate **II**, *N*-acyliminium ion, was reduced with $NaBH_4/CH_3OH$ instead of quenching with water in a one pot fashion to deliver the tricyclic lactam, pyrroloisoquinolinone **8a** in 88% yield.[12] Similarly, the imide **5c** gave **8c** in 69% yield along with demethylated products. Glutarimides **5b** and **5d** gave the cyclized tricyclic lactams, tetrahydroisoquinoline core **8b** and **8d**, present in the α-glucosidase inhibitors schulzeine-A/B/C,[13] in 89% and 71% yields respectively.

The formation of hydroxy lactam from phthalimides and lactam from aliphatic imides were unambiguously confirmed through spectral techniques as well as single crystal X-ray structural analysis of selected molecules (Fig. 3).[14]

In conclusion we have documented a simple methodology to construct the tetrahydroisoquinoline containing skeleton, employing the boron tribromide as Lewis acid. Applicability of this reaction towards the synthesis of tetrahydroisoquinoline unit present in the alkaloid schulzeine-A/B/C was successfully carried out. Further investigations on extending the scope of this cyclization

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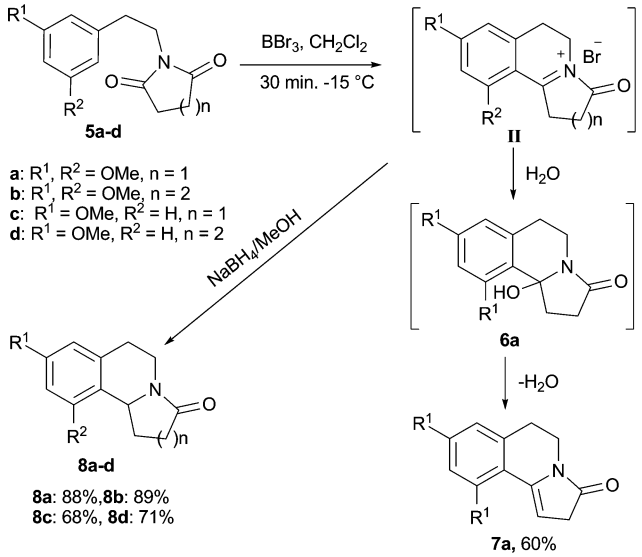

Scheme 4 One pot conversion of aliphatic imides to lactam.

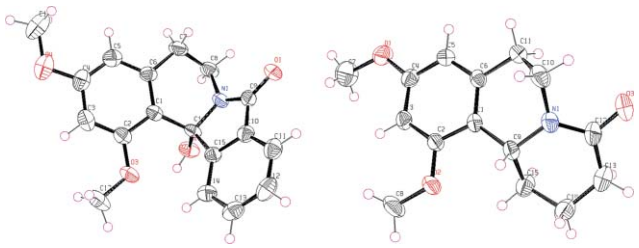

Fig. 3 ORTEP diagram of **3a** and **8b** (50% probability ellipsoids).

process as well as the modification of Lewis acids to facilitate cyclization reaction is in progress.

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