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Approach to Isoindolinones, Isoquinolinones, and THIQs via Lewis Acid-Catalyzed Domino Strecker-Lactamization/Alkylations

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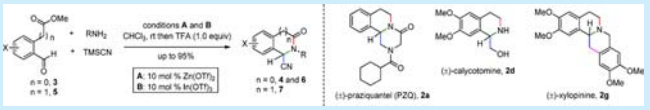
Supporting Information

ABSTRACT: A one-pot, three-component synthesis of widely substituted isoindolinones and isoquinolinones, featuring a Lewis acid-catalyzed efficient Strecker reaction and lactamization sequence, affording products in good to high yields is reported. The method has also been extended to the synthesis of tetrahydroisoquinolines (THIQs) in high yields.



Isoindolinones are an important class of heterocycles found in many biologically active natural products[1] and are also useful intermediates in the synthesis of a variety of drug molecules[2] (**1a**−**b**; Figure 1) having important biological

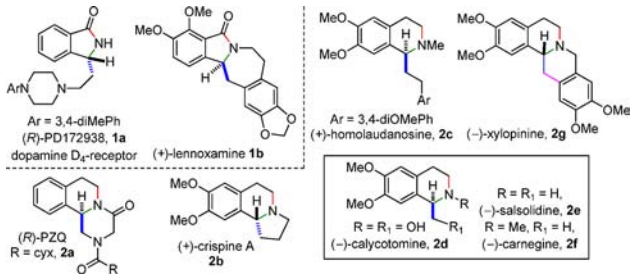
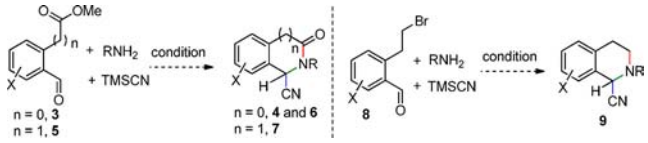


Figure 1. Selected active isoindolinones and THIQs.

activities such as antihypertensive,[3] antipsychotic,[4] anti-inflammatory,[5] anesthetic,[6] antiulcer,[7] vasodilatory,[8] antiviral,[9] and antileukemic[10] agents. In addition, a few members of this class are known to have platelet aggregation inhibitory activity[11] and are shown to induce dose-dependent p53-dependent gene transcription in MDM2-amplified SJSA human sarcoma cell lines.[12] On the other hand, tetrahydroisoquinolines[13] (THIQs) (**2a**−**g**; Figure 1) are widespread in nature and have interesting biological activities. They are also found to be the building blocks for synthesis of many complex alkaloids.[14]

Approaches in literature for isoindolinone synthesis include Heck cyclization,[15] Diels−Alder approach,[16] ring-closure of hydrazones,[17] reactions of acyliminium ion,[18] exploiting carbanion methodology,[19] and various enantioselective approaches[20] including our recent domino[21] Cu(I)-catalyzed enantioselective propargylation/lactamization and organocatalytic Mannich/lactamization sequence.[22] On the other hand, synthesis of isoquinolines involves various diastereoselective processes[13c,23] and catalytic enantioselective processes.[21,24] Although some elegant approaches to these targets have been reported, still there exist a fewer number of reports to synthesize them applying a general catalytic route. To this end, recently, we reported the Lewis acid-catalyzed allylation-lactamization domino process[25] for synthesis of diversely substituted isoindolinones and THIQs. Herein, we report a practical approach to isoindolinones, isoquinolinones, and THIQs via a Lewis acid-catalyzed domino Strecker-lactamization/alkylations of readily available *o*-formyl methylbenzoates, *o*-formyl methylarylacetates, and *o*-formyl arylethyl bromides (Scheme 1).

Scheme 1. Proposed Strecker-Lactamization/Alkylations



At the outset, optimization of domino Strecker-lactamization was performed by taking 1.0 equiv of each ester-aldehyde **3a** and $PMPNH_2$ (*p*-anisidine) with 1.5 equiv of TMSCN without any catalyst. We found that only Strecker product **10a** was formed in 28−42% yields, and no trace of isoindolinone **4a** were observed (Scheme 2). Following extensive optimization, it was found that 10 mol % of $Zn(OTf)_2$ and $In(OTf)_3$ each afforded **4a** in 93% yield (condition **A**) and 91% yield (condition **B**), respectively, when 1.0 equiv of TFA was used (see the SI for details).

Scheme 2. Domino Strecker-Lactamization Process

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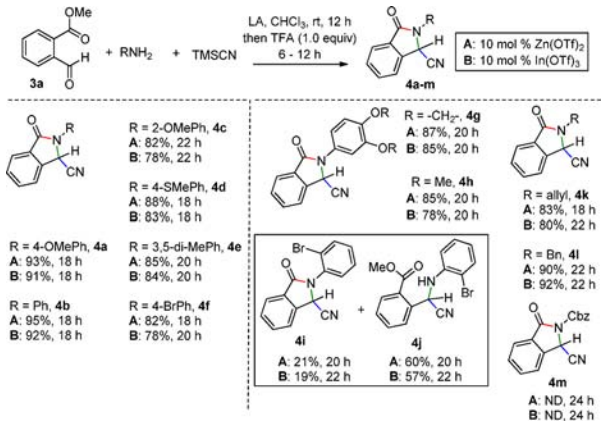
With optimized conditions, a variety of amines such as aromatic, aliphatic, and amine having an electron-withdrawing group (Cbz-NH_2) were studied. To our delight, various aromatic amines, such as aniline, *o*-methoxyphenyl (OMP), *p*-thiomethoxyphenyl (PTMP), 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethylphenyl, and *p*-bromophenyl, all afforded expected Strecker-lactamization products **4b−h** in up to 95% yield (Scheme 3) under conditions **A** and **B**. It is

Scheme 3. Scope of Reaction with Various Amines[a−c]



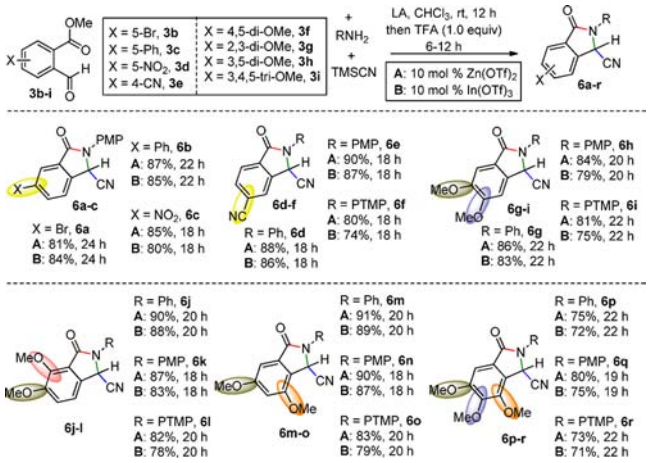
[a]Condition **A**: 10 mol % $Zn(OTf)_2$. [b]Condition **B**: 10 mol % $In(OTf)_3$. [c]1.0 equiv of TFA was used after 12 h as an additive. LA = Lewis acid, TFA = trifluoroacetic acid.

important to note that isoindolinones with *N*-aryl groups having electron-donating groups (such as **4a**, **4c−d**, and **4g−h**) in the ring can be cleaved under oxidative conditions so as to obtain free amines.[26] To our surprise, in the case of *o*-bromophenylamine, we could only isolate the expected isoindolinone in 21% yield, where uncyclized benzylamine **4j** was obtained in 57−60% yields. We speculate that this could be because of the −I effect of the −Br group at the *ortho*-position of the aryl ring, which hampers the formation of isoindolinone (Scheme 3).[27]

Then, we turned our attention to domino Strecker-lactamization using an aliphatic amine having easily removable groups such as allyl and benzyl. Gratifyingly, under optimized conditions we were able to synthesize isoindolinones **4k−l** having *N*-allyl and *N*-benzyl protecting groups in 80−92% yields. We also used $CbzNH_2$ as a protected amine source having an electron-withdrawing group;[28] however, to our displeasure, we were not able to assess expected isoindolinone **4m**, and this led to a multitude of spots on the TLC, indicating the nucleophilicity of amines plays a crucial role in the domino Strecker-lactamization process.

Further, we investigated the substrate scope of domino Strecker-lactamization using different amines *viz.* aniline (R = Ph), *p*-methoxyphenylamine (R = PMP), and *p*-thiomethoxyphenylamine (R = PTMP) with various *o*-formyl benzoates under optimized conditions **A** and **B** (Scheme 4). Gratifyingly, it was found that various *o*-formyl benzoates such as **3b−i** are suitable substrates under optimized conditions. In the presence of 10 mol % $Zn(OTf)_2$ (condition **A**) and $In(OTf)_3$ (condition **B**) followed by treatment with 1.0 equiv of TFA as an additive, these *o*-formyl benzoates afforded a variety of products having *N*-aryl groups in synthetically viable yields. Methyl *o*-formyl benzoates, having bromo, phenyl, and nitro substitution at the

Scheme 4. Substrate Scope of Isoindolinone Synthesis[a−c]



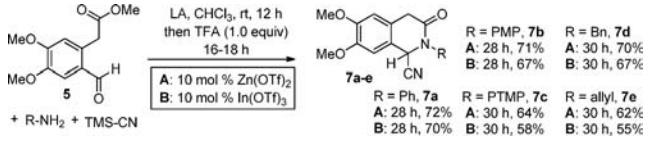
[a]Condition **A**: 10 mol % $Zn(OTf)_2$. [b]Condition **B**: 10 mol % $In(OTf)_3$. [c]1.0 equiv of TFA was used after 12 h as additive. LA = Lewis acid, TFA = trifluoroacetic acid.

p-position of aldehyde such as **3b−d**, all afforded products **6a−c** in high yields (Scheme 4).

Methyl *o*-formyl benzoates having cyano substitution at the *p*-position of an ester such as **3e** also afforded products **6d−f** in good to excellent yields (Scheme 4). Importantly, less reactive methyl *o*-formyl benzoates having the −OMe group as an electron-rich substituent at the *p*-positions of aldehyde, such as **3f−i**, also underwent a domino Strecker-lactamization sequence efficiently to afford **6g−r** in synthetically viable yields (Scheme 4).

Having secured the synthesis of isoindolinones, we attempted a one-pot, three-component synthesis of isoquinolinones using various amine partners as per our hypothesis (Scheme 1). As most of the naturally occurring THIQ alkaloids contain the dimethoxy substituent, we explored the possibility of the formation of domino Strecker-lactamization using *o*-formyl methylarylacetate **5** (Scheme 5). To our delight, we were able to synthesize a variety of isoquinolinones **7a−e** in synthetically useful yields, following our optimized conditions **A** and **B** (Scheme 5).

Scheme 5. Substrate Scope of Isoquinolinone Synthesis[a−c]



[a]Condition **A**: 10 mol % $Zn(OTf)_2$. [b]Condition **B**: 10 mol % $In(OTf)_3$. [c]1.0 equiv of TFA was used after 12 h as additive. LA = Lewis acid, TFA = trifluoroacetic acid.

Further, we thought to apply the domino Strecker-*N*-alkylation sequence for the synthesis of tetrahydroisoquinolines (THIQs). Toward this, a few *o*-formyl phenethyl bromides **8a−c** were employed in the domino Strecker-*N*-alkylation which afforded a variety of *N*-protected THIQs **9a−l** in 70−92% yields (Scheme 6). Interestingly, in these cases an additive (TFA) is not required, thus indicating S_N^2 type *N*-alkylation is a faster process than a lactamization (Schemes 3−5).

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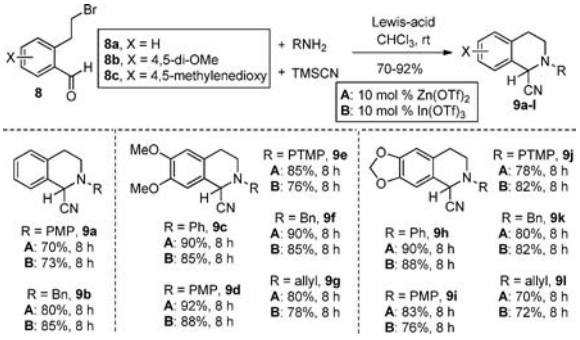
Scheme 6. Substrate Scope Using Various Bromo Aldehydes[a,b]

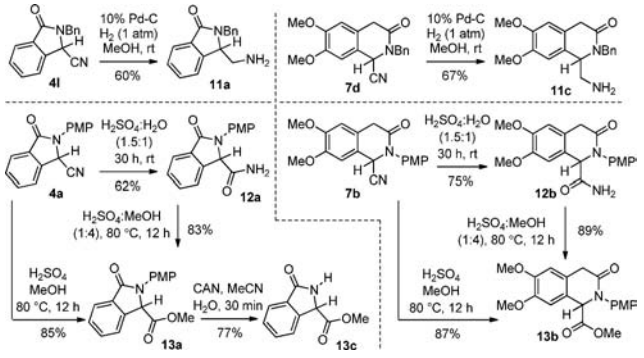


[a]Condition **A**: 10 mol % $Zn(OTf)_2$. [b]Condition **B**: 10 mol % $In(OTf)_3$.

The domino Strecker-lactamization was also carried out on a 1.0 g scale of *o*-formyl methylbenzoates **3a** and *o*-formyl arylacetate **5** under condition **A**, which afforded products **4a, 7b**, and **7d** in 90%, 78%, and 93% yields, respectively (see the SI for details). Similarly, a gram scale reaction of bromoaldehyde **8b** with *p*-methoxyphenylamine and **8a** with benzylamine under condition **A** afforded THIQs **9d** and **9b** in 76% and 78% yields, respectively (see the SI for details).

To show versatility, compounds **4l** and **7d** were treated under hydrogenolysis separately to obtain amine compounds **11a** and **11c** in 60% and 67% yields, respectively (Scheme 7),

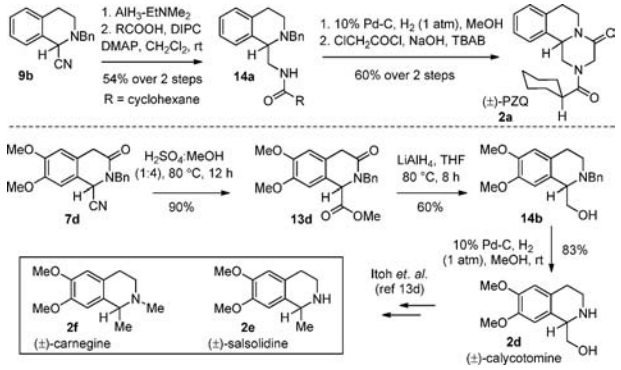
Scheme 7. Synthetic Elaborations



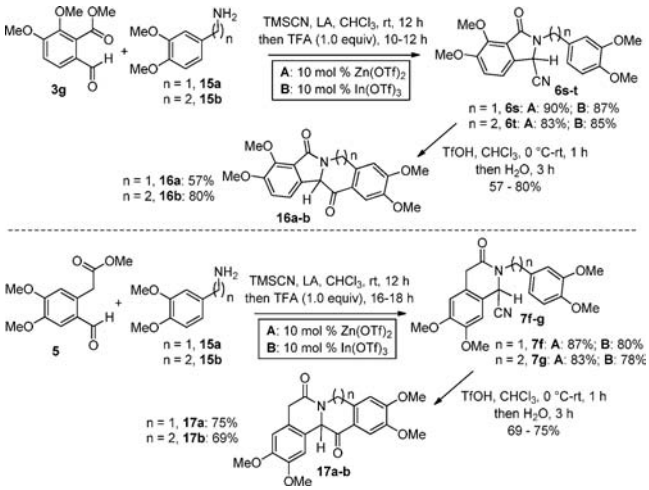
where *N*-benzyl groups were found to be untouched. We also reacted compounds **4a** and **7b** in the presence of aqueous H_2SO_4 to afford carboxamides **12a** and **12b** in 62% and 75% yields, respectively (Scheme 7). Esters **13a** and **13b** can be obtained from **4a** and **7b**, respectively, when reactions were carried out in MeOH. Oxidative cleavage of the PMP group can simply be accomplished with CAN to afford isoindolinone **13c** (Scheme 7). Later, synthesis of the anthelmintic drug (±)-praziquantel **2a**[29] and alkaloid (±)-calycotomine **2d**[13d] has been accomplished from **9b** and **7d** via intermediacy of **14a** and **13d**, respectively (Scheme 8).

Nevertheless, Lewis acid-catalyzed domino Strecker-lactamization was applied for the synthesis of isoindolinones **6s–t**, which on subsequent treatment with triflic acid (TfOH) afforded tetracyclic structures **16a–b** (Scheme 9), resembling the core structure of lennoxamine **1b** (Figure 1). Along similar lines isoquinolinones **7f–g** can also be utilized for the synthesis of tetracyclic structures **17a–b** (Scheme 9), which are common structural features of the protoberberine alkaloid, xylopinine

Scheme 8. Synthesis of (±)-PZQ 2a and (±)-Calycotomine 2d



Scheme 9. Synthesis of Tetracyclic Structures 16a–b and 17a–b



(**2g**) (Figure 1). In these transformations, we have shown that Friedel–Crafts type C–C bond-forming reactions can be performed on nitrile functionality.

In conclusion, we report a Lewis acid-catalyzed highly efficient domino Strecker-lactamization for the synthesis of isoindolinones and isoquinolinones. The reaction itself is operationally simple and proceeds under mild conditions to afford isoindolinones with high yields. A variety of valuable intermediates have been synthesized utilizing the aforementioned method. Further exploration of the enantioselective version of this process is currently under active investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03331.

Experimental procedures and analytical data (^1H, ^{13}C NMR spectra and HRMS) for all new compounds (PDF)

CIF file of **4a** (CIF)

CIF file of **9d** (CIF)

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[§]S.D. and A.S. contributed equally.

Notes

The authors declare no competing financial interest.

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(27) Isoindolinone **4i** can be obtained in 47% yield along with 25% of **4j** under refluxing $CHCl_3$ for 24 h.

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