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Unified Approach to Isoindolinones and THIQs via Lewis Acid Catalyzed Domino Mukaiyama−Mannich Lactamization/Alkylations: Application in the Synthesis of (±)-Homolaudanosine

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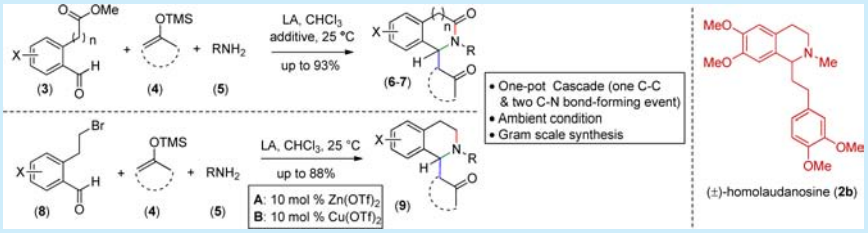
Supporting Information



ABSTRACT: A novel and efficient synthesis of a variety of isoindolinones and tetrahydroisoquinolines via a Lewis acid catalyzed domino Mukaiyama−Mannich lactamization/alkylation is achieved. This transformation comprises a sequential formation of three new bonds through a one-pot, three-component procedure to afford product in moderate to high yields. A concise synthesis of (±)-homolaudanosine (**2b**) has been achieved using this method.

Heterocyclic compounds like isoindolinones (**1a−d**; Figure 1) and tetrahydroisoquinolines (THIQs **2a−d**; Figure 1)

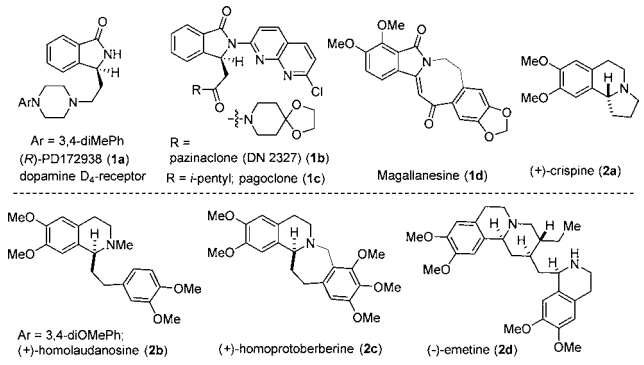


Figure 1. Selected active isoindolinones and THIQs.

are important structural scaffolds from a synthetic perspective. Substituted isoindolinones are useful advanced intermediates in the synthesis of a variety of drugs[1] and complex natural products.[2] Their biological properties such as antihypertensive,[3] antipsychotic,[4] anti-inflammatory,[5] anesthetic,[6] antiulcer,[7] vasodilatory,[8] antiviral,[9] and antileukemic[10] activities makes them attractive synthetic targets. Similarly, tetrahydroisoquinolines (THIQs **2a−d**)[11] exist widely in alkaloids and, because of their fascinating biological activities, they also attract special synthetic interest.

Existing approaches toward isoindolinone synthesis include Heck cyclization,[12] Diels−Alder approach,[13] ring-closure of hydrazones,[14] reactions of acyliminium ion,[15] exploitation of carbanion methodology,[16] and various enantioselective approaches.[17,18] On the other hand, synthesis of THIQs involves various multistep processes[11,19] and few enantioselective processes.[20] Although few elegant approaches to these targets have been reported, there is still a need to develop a straightforward synthesis of isoindolinones and THIQs employing a common strategy from cheaply available simple starting materials. Toward this end, we recently reported an efficient allylation−lactamization/alkylation[21] cascade in the synthesis of THIQ alkaloid (±)-crispine **2a**. Herein, we envisioned an expeditious approach to these targets following a direct Lewis acid catalyzed domino Mukaiyama−Mannich lactamization/alkylation of *o*-formyl methylbenzoates **3** and *o*-formyl-2-arylethyl bromide **8** to afford isoindolinones **6** and **7** and THIQs **9**, respectively (Scheme 1).[22]

Initially, we began our optimization studies by using *o*-formyl methylbenzoate **3a** and silyl enol ether **4a** in the presence of several potential catalysts to ultimately identify the most efficient catalytic system. We used *p*-methoxyphenylamine ($PMPNH_2$) as an amine component so as to obtain PMP-protected compound **6a**, which can be oxidatively cleaved,[18,21,23] leading to an *N*-protecting group free isoindolinone. It was observed that 10 mol % of $In(OTf)_3$, $Zn(OTf)_2$, and $Cu(OTf)_2$ afforded the expected isoindolinone **6a** in 73−77% isolated yields along with uncyclized **10a** in 10−11% (entries 1−3, Table 1). We envisioned that conversion of **10a** to **6a** may depend on

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Scheme 1. Proposed Mukaiyama–Michael Lactamization/Alkylation

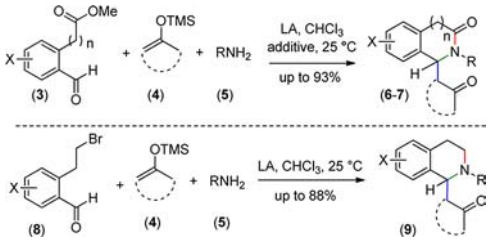
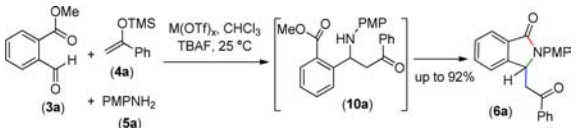


Table 1. Selected Optimization Studies[a]

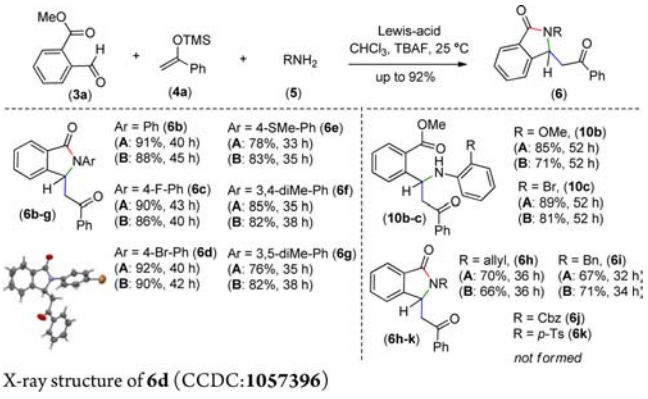


entry	Lewis acid (mol %)	solvent	time (h)	**10a** (% yield)[b]	**6a** (% yield)[b]
1[c]	$In(OTf)_3$ (10)	$CHCl_3$	24	10	73
2[c]	$Zn(OTf)_2$ (10)	$CHCl_3$	24	11	77
3[c]	$Cu(OTf)_2$ (10)	$CHCl_3$	24	10	76
4	$In(OTf)_3$ (10)	$CHCl_3$	35	0	76
5	$Zn(OTf)_2$ (10)	$CHCl_3$	30	0	92
6	$Cu(OTf)_2$ (10)	$CHCl_3$	28	0	90
7	$Sc(OTf)_3$ (10)	$CHCl_3$	33	0	83
8	$Bi(OTf)_3$ (10)	$CHCl_3$	28	0	85
9.	$Zn(OTf)_2$ (5)	$CHCl_3$	35	0	80
10	$Cu(OTf)_2$ (5)	$CHCl_3$	35	0	79

[a]All of the reactions were performed with 1 equiv of aldehyde, 1 equiv of amine, and 1.3 equiv of silyl enol ether under argon atmosphere. [b]Isolated yields. [c]Reactions were carried out in the absence of TBAF. Conditions A: 10 mol % of $Zn(OTf)_2$. Conditions B: 10 mol % of $Cu(OTf)_2$.

inefficient deprotection of the *N*-silyl group, and thus, we decided to use TBAF as an additive in the reaction. Following exhaustive optimization (see the Supporting Information for details), we found that 10 mol % of $Zn(OTf)_2$ and $Cu(OTf)_2$ furnished **6a** in 90–92% yields (entries 5 and 6). Other metal triflates such as $In(OTf)_3$, $Sc(OTf)_3$, and $Bi(OTf)_3$ also afforded **6a** in 76–85% yields (entries 4, 7, and 8). A brief solvent studies showed that chloroform was the most efficient (see the Supporting Information for details). Gratifyingly, it was observed that 5 mol % of $Zn(OTf)_2$ and $Cu(OTf)_2$ also afforded **6a** in 79–80% yields (entries 9 and 10). On the basis of optimization studies, it was decided to carry out further studies using 10 mol % of $Zn(OTf)_2$ (conditions A) and $Cu(OTf)_2$ (conditions B) in combination with a stoichiometric amount of TBAF as an additive in chloroform at rt. Interestingly, a gram-scale synthesis of **6a** under conditions A also afforded product in 75% (30 h) isolated yield (see the Supporting Information), thus making the strategy synthetically viable.

We then studied various amines in the domino Mukaiyama–Mannich lactamization. Gratifyingly, all aromatic amines, including electron-donating and electron-deficient ones, afforded isoindolinones **6b–g** in 76–92% isolated yields (Figure 2). The X-ray structure analysis of **6d** (CCDC no. 1057396) unambiguously proved the formation of an isoindolinone motif. Surprisingly, *ortho*-substituted anilines afforded only Mukaiyama–Mannich products **10b,c** in 71–89% yields, probably indicating that the sterics at the *o*-position of the



X-ray structure of **6d** (CCDC:**1057396**)

Figure 2. Scope of reaction with various amines.

anilines might be inhibiting the formation of isoindolinones. Aliphatic amines such as allyl- and benzylamines were also found to be good substrates to furnish **6h,i** in 66–71% yields. However, electron-deficient amines such as *p*-$TsNH_2$ and $CbzNH_2$[24] were not suitable for the one-pot process, and only starting aldehyde **3a** was recovered in 85–89% yields.

Notably, 3,4-(methylenedioxy)aniline as amine partner afforded isoindolinone **6l** only in 40–46% yields. In this case, however, we isolated quinoline **11a** in 25–28% yields under optimized conditions. Interestingly, 3,4-dimethoxyaniline, when used as aromatic amine, afforded quinolines **11b,c** as the sole products in 78–86% yields (Figure 3). A proposed mechanism for the synthesis of **11a–c** involving Mukaiyama–Mannich Friedel–Crafts alkylation–condensation followed by aerial oxidation is shown in Scheme 2.[25]

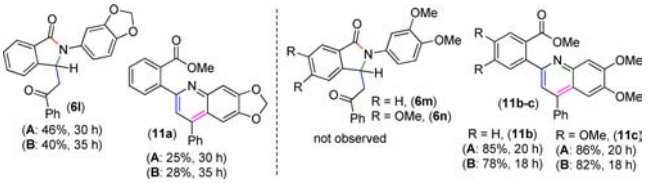
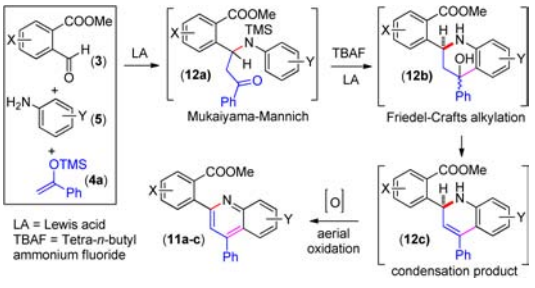


Figure 3. Scope of reaction with various amines.

Scheme 2. Plausible Mechanism of Quinoline Synthesis



Later, the Mukaiyama–Mannich lactamization was carried out with differently substituted *o*-formyl methylbenzoate **3**, silyl enol ether **4a**, and $PMPNH_2$ under both conditions A and B (Figure 4). To our delight, a variety of *o*-formyl methylbenzoates containing various electronic natures at the 4- and 5-positions of **3** (Figure 4) afforded isoindolinones **7a–h** in good to excellent yields. In addition, electron-donating groups at the 3- and 6-positions of **3** also afforded products **7i–l** in synthetically useful yields (65–89%, Figure 4).

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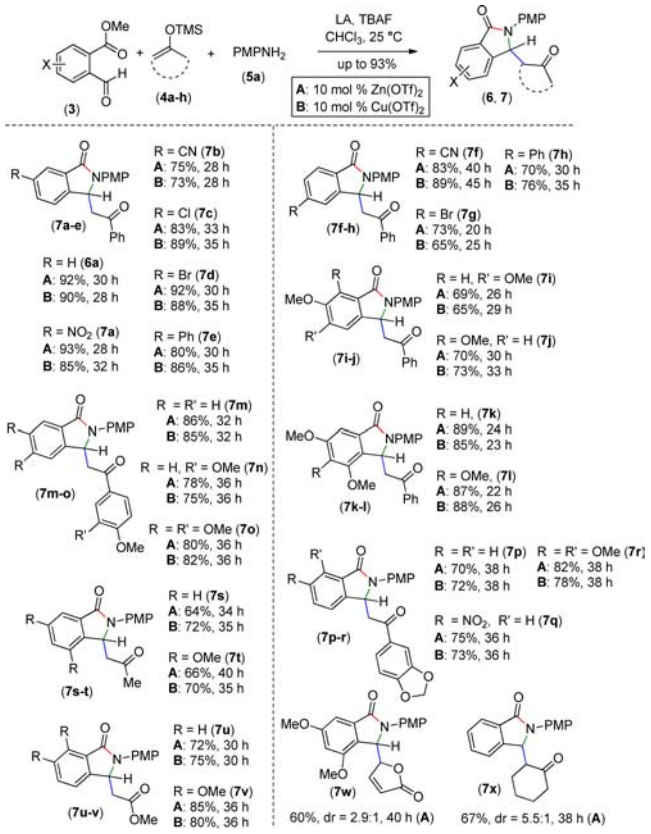
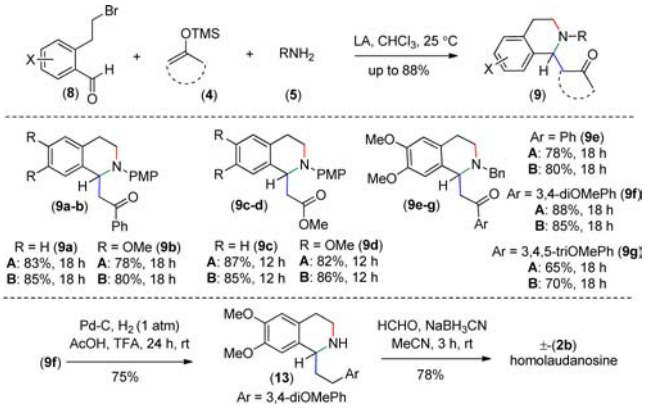


Figure 4. Substrate scope of isoindolinone synthesis.

Next, a variety of silyl enol ethers were selected for the domino Mukaiyama–Mannich lactamization using different *o*-formyl methylbenzoates **3** and $PMPNH_2$ (Figure 4). Rewardingly, silyl enol ethers (see the Supporting Information for synthetic details) of acetophenone derivatives furnished isoindolinones **7m–r** in synthetically useful yields. Silyl enol ethers of acetone afforded products **7s,t** in 64–72% yields. The silyl enol ether of methyl acetate was also found to be a good substrate and afforded **7u–v** in 72–85% yields, which could be an advanced intermediate for the synthesis of derivatives of medicinally important **1a–c** in a few steps (Figure 1). Gratifyingly, our optimized strategy works fine with silyl enol ethers of 2-hydroxyfuran and cyclohexanone, which afforded products **7w** and **7x** in 60% (dr = 2.9:1) and 67% (dr = 5.5:1), respectively (Figure 4).

Next, we became interested in applying our strategy in the synthesis of C_1-substituted THIQs (Figure 1). Toward this end, we have utilized a variety of *o*-formyl-2-arylethyl bromides **8** in the presence of a few silyl enol ethers and $PMPNH_2$ (Scheme 3). To our delight, a variety of THIQs were synthesized under optimized conditions A and B, where TBAF was not essential. This is probably indicative of the high reactivity of the intermediate Mukaiyama–Mannich product toward S_N2 reactions, and thus, reaction times were also reduced as compared to isoindolinone synthesis. Our strategy can be applied further in the efficient synthesis of THIQs **9a–e** in 78–87% isolated yields (Scheme 3). In particular, THIQ **9d** could be an advanced intermediate for the syntheses of (±)-**2a–c** (Figure 1) following further synthetic elaboration. However, for a direct synthesis of (±)-**2b,c**, we synthesized silyl enol ethers of 3,4-dimethoxyacetophenone and 3,4,5-trimethoxyacetophenone (see the Supporting Information for procedure) and utilized them in

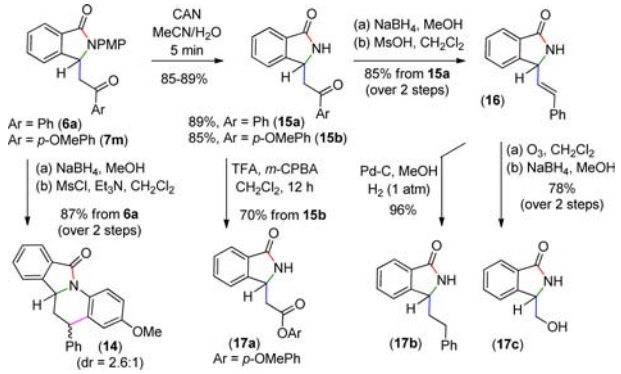
Scheme 3. Substrate Scope of THIQ Synthesis



the synthesis of THIQs **9f,g** (65–88% yields in 18 h). Gratifyingly, **9f** was synthesized in gram scale under conditions A, which afforded THIQ in 65% (24 h) yield (see the Supporting Information). One of these THIQs, **9f**, was then converted to **13** under reductive hydrogenolysis in the presence of a Pd–C, AcOH/TFA mixture to afford **13** in 75% yield (Scheme 3). This was later converted to (±)-**2b** in 78% yield following *N*-methylation using HCHO and $NaBH_3CN$, thus completing a concise total synthesis of (±)-homolaudanosine (**2b**).

Further, isoindolinones **6a** and **7m** were reacted with CAN to form protecting group free **15a,b** in 85–89% yield (Scheme 4).[18,21] Unprotected isoindolinone **15b** was converted to **17a** in

Scheme 4. Synthetic Elaborations to Important Intermediates



70% yield under the Baeyer–Villiger oxidation conditions. Compound **15a** was further reduced with $NaBH_4$, followed by treatment with methanesulfonic acid (MsOH), which afforded **16** in 85% yield over two steps (Scheme 4). The latter was then hydrogenated to furnish medicinally important 1-alkylisoindolinone **17b** in 96% yield.

In another sequence, isoindolinone **16** on reductive ozonolysis afforded **17c**, which has hydroxymethyl functionality in 78% yield (Scheme 4). The latter could be used for the syntheses of (±)-**1a–c** shown in Figure 1. Finally, the reactivity of the electron-donating PMP group of isoindolinone **6a** was explored in the synthesis of tetracyclic tetrahydroquinoline derivative **14** following a two-step sequence (87% overall yield) via $NaBH_4$ reduction followed by treatment with methanesulfonyl chloride.

In summary, we have shown an efficient Mukaiyama–Mannich lactamization/alkylation sequence for an expeditious synthesis of a variety of isoindolinones and THIQs under mild conditions. A variety of silyl enol ethers were utilized, and the

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strategy is amenable to gram-scale syntheses of isoindolinone as well as THIQs. Electron-rich anilines like 3,4-(alkyloxy)anilines can afford substituted quinolines as well.[25] Applying this strategy, a concise total synthesis of (±)-homolaudanosine **2b** has been accomplished.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data (^{1}H, ^{13}C NMR spectra and HRMS) for all new compounds, and X-ray data for **6d** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01197.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to Professor Tavarekere K. Chandrashekar on the occasion of his 60th birthday.

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(25) Elaboration of this domino reaction using various aromatic amines with electron-rich aromatics is under active investigation.

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