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Lewis Acid Catalyzed Tandem Polycyclization of Internal Alkynols and Vinyl Azides

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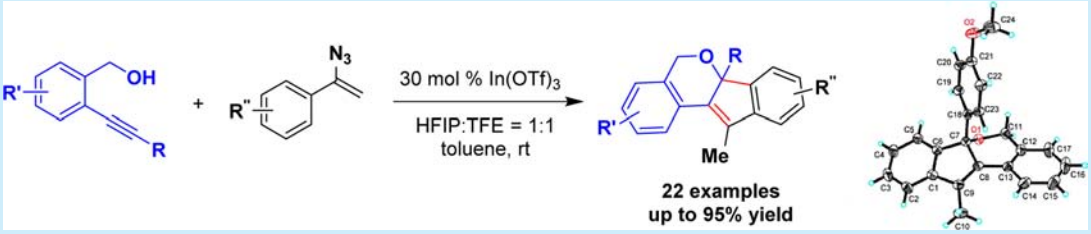
Supporting Information



ABSTRACT: A novel Lewis acid catalyzed tandem cyclization reaction of internal alkynols and vinyl azides has been achieved to afford a series of products containing a pyran-based indeno[1,2-*c*]isochromene scaffold in moderate to high yields. This tandem polycyclization protocol provides a straightforward entry to construct the complex polycyclic skeleton through cycloisomerization, formal [4 + 2] cycloaddition, and an elimination process.

Tetrahydropyran rings are prevalent in a wide array of biologically and pharmacologically relevant natural products. Of particular interest are the octahydrocyclopenta-[*b*]pyran structural units, which are present in a number of biologically active molecules.[1] For example, the triterpenoid alisol F (**I**)[1a,b] was isolated from the rhizomes of *Alisma orientalis*. Triterpene-based γ-secretase modulators (**II**),[1c] isolated from *Actaea racemose*, may be even more pharmacologically useful because of their superior metabolic stability.[1d] Elaeocarpucin C (**III**)[1e] was isolated from the fruits and stem bark of *Elaeocarpus chinensis* samples collected in Vietnam. Haplosamate A (**IV**) was isolated from the Indonesian sponge *Dasychalina* sp., and its desulfohaplosamate shows selective affinity for cannabinoid receptors[1f] (Figure 1). Furthermore, the compounds containing octahydrocyclopenta[*b*]pyran structural units have been used extensively as key intermediates.[2]

In recent years, alkynol-based tandem reactions have become increasingly important in chemical synthesis. These reactions involve the concatenation of several steps to form several new bonds to connect simple building blocks in a single operation.[3] As a result, these tandem reactions have been used to synthesize highly valuable nitrogen- and oxygen-containing heterocycles, as well as complex polycyclic structural units.[4]

Vinyl azides have worked well in tremendous synthetic procedures,[5] and in particular they have attracted much attention as versatile synthons for developing novel synthetic methods. These methods include the synthesis of indoles,[6] pyrazoles,[7] pyridines,[8] pyrroles,[9] and imidazoles.[10] Vinyl azides have also been used in metal-catalyzed systems involving rhodium,[11] rhodium−copper,[12] or manganese[13] to construct diverse heterocyclic compounds. Moreover, vinyl azides have been used to generate *N*-unsubstituted imines in situ,[12] and these imines are pivotal intermediates in organic synthesis.[14]

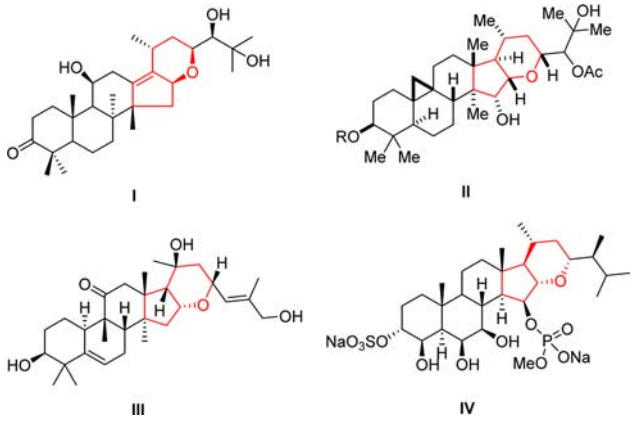


Figure 1. Natural products containing octahydrocyclopenta[*b*]pyran motif.

In the present study, we aimed to incorporate vinyl azides into alkynol-based tandem reactions as part of our ongoing interests in exploring synthetically useful alkynol-based systems for heterocyclic structure construction.[15] Here we report a novel Lewis acid catalyzed intermolecular tandem cyclization reaction that uses readily available internal alkynol and vinyl azide to generate a octahydrocyclopenta[*b*]pyran related polycyclic indeno[1,2-*c*]isochromene skeleton in a single operation.

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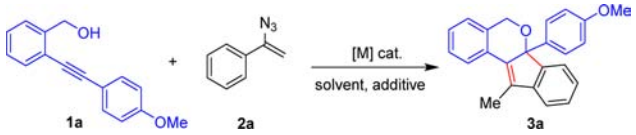
Our study of Lewis acid mediated polycyclization began by evaluating the model reaction of internal alkynol **1a** and vinyl azide **2a** (Table 1). Initially, treating **1a** and **2a** with 30 mol % $Cu(OTf)_2$ at 60 °C in toluene for 8 h gave the polycyclic product indeno[1,2-*c*]isochromene **3a** in 21% isolated yield (entry 1). The structure of **3a** was confirmed by single-crystal X-ray diffraction analysis (Figure 2). Next we optimized the reaction conditions for formation of **3a**. Other copper species such as CuBr, $Cu(acac)_2$, and $[Cu(CH_3CN)_4]PF_6$ failed to promote the desired transformation. Decreasing the catalyst loading to 20 mol % reduced the yield of **3a** to 18% (entry 2). The solvents CH_3CN, THF, DCE, DMF, and dioxane proved ineffective, giving **3a** in lower yield (entries 2−7). Gradually changing the ratio of **1a:2a** to 1:2 increased the yield of **3a** to 29% (entry 8).

Table 1. Optimization of Reaction Conditions for the Reaction between 1a and 2a[a]



entry	catalyst[b]	temp (°C)	t (h)	additive (equiv)[b]	solvent	3a (%)[c]
1	$Cu(OTf)_2$	60	8	–	toluene	21
2[d]	$Cu(OTf)_2$	60	8	–	toluene	18
3	$Cu(OTf)_2$	60	8	–	CH_3CN	<5%
4	$Cu(OTf)_2$	60	8	–	THF	<5%
5	$Cu(OTf)_2$	60	8	–	DCE	<5%
6	$Cu(OTf)_2$	60	8	–	DMF	0
7	$Cu(OTf)_2$	60	8	–	dioxane	9
8[e]	$Cu(OTf)_2$	60	12	–	toluene	29
9[e]	$Cu(OTf)_2$	60	12	AcOH/2	toluene	20
10[e]	$Cu(OTf)_2$	60	12	TFA/2	toluene	17
11[e]	$Cu(OTf)_2$	60	12	H_2O/2	toluene	8
12[e]	$Cu(OTf)_2$	60	12	HFIP/2	toluene	29
13[e]	$Cu(OTf)_2$	rt	20	HFIP/2	toluene	50
14[e]	$Cu(OTf)_2$	rt	20	HFIP/3	toluene	54
15[e]	$Cu(OTf)_2$	rt	20	TFE/3	toluene	48
16[e,f]	$Cu(OTf)_2$	rt	40	TFE-HFIP/3	toluene	65
17[e,f]	$Bi(OTf)_2$	rt	40	TFE-HFIP/3	toluene	29
18[e,f]	$Fe(OTf)_3$	rt	14	TFE-HFIP/3	toluene	43
19[e,f]	$In(OTf)_3$	rt	40	TFE-HFIP/3	toluene	50
20[f,g]	$Cu(OTf)_2$	rt	40	TFE-HFIP/3	toluene	66
21[f,g]	$In(OTf)_3$	rt	24	TFE-HFIP/3	toluene	72

[a]Reactions were performed in sealed tubes containing **1a** (0.3 mmol), **2a** (0.36 mmol), catalyst (0.09 mmol), and solvent (2 mL) under Ar, unless noted otherwise. [b]Equivalents based on **1a**. [c]Isolated yield. [d]$Cu(OTf)_2$ (0.06 mmol) was used. [e]**1a** (0.3 mmol) and **2a** (0.6 mmol) were used. [f]TFE (0.45 mmol) and HFIP (0.45 mmol) were used. [g]**1a** (0.3 mmol) and **2a** (0.9 mmol) were used.

Figure 2. Crystal structure of compound **3a**.

Next we examined the influence of several additives on the reaction. Screening various additives such as acetic acid (AcOH), trifluoroacetic acid (TFA), and water did not fulfill the expectations of increasing yield (entries 9−12), but carrying out the reaction in the presence of 2 equiv of hexafluoroisopropanol (HFIP) at a lower reaction temperature (rt) increased the yield of **3a** dramatically to 50% (entry 13). Using 3 equiv of HFIP slightly increased the yield to 54% (entry 14), whereas using 2,2,2-trifluoroethanol (TFE) gave **3a** in only 48% yield (entry 15). Surprisingly, using a mixed additive of TFE (3 equiv) and HFIP (3 equiv) enhanced the reaction, giving **3a** in higher yield (entry 16). As the catalyst was changed to $Bi(OTf)_3$ and $Fe(OTf)_3$ from $Cu(OTf)_3$, lower yields were observed (entries 17 and 18). Interestingly, when $In(OTf)_3$ was used as the catalyst and the mole ratio of **1a** and **2a** was increased to 1:3, the best 72% yield of **3a** was obtained with a shorter reaction time (entry 21).

After identifying a selective catalyst and suitable reaction conditions, we evaluated the substrate scope of this polycyclization protocol. As shown in Table 2, we examined the ability of various substituted alkynols **1** to react with vinyl azide **2a** using optimized reaction conditions [**1a:2a** = 1:3, 30 mol % $In(OTf)_3$, mixture of HFIP (3 equiv)/TFE (3 equiv) as additive, 2 mL of toluene, rt]. A substrate carrying a methoxyl group at position R^1 reacted smoothly, leading to the formation of **3b** in excellent 91% yield. The internal alkynols **1** with Me and F groups at the R^1 positions were both effective, affording the corresponding polycyclic indeno[1,2-*c*]isochromenes **3c** and **3d** in respective yields of 71% and 75%. However, placing the electron-withdrawing CF_3 group at position R^1 hampered the reaction a little, generating **3e** in 50% yield. The reaction also proceeded with **1** bearing an electron-donating methyl group at the R^2 position, although it produced **3f** in only 41% yield. Internal alkynol with fluorine at the same positions gave the corresponding product **3g** in 53% yield. Several other substrates that we tested, such as alkynols with alkyl substitution (R^3) and alkynols attached to cyclohexene instead of Ph, failed to give the desired products. Heteroaryl thiophene alkynol and chained alkoxy alkynols also worked well to produce **3h** and **3i** in respective isolated yields of 71% and 56%.

To explore the full scope of the reaction, we examined the ability of vinyl azides to react with internal alkynols **1**. Methyl-substituted vinyl azides were a good partner for an internal alkynol with a MeO substitution at the R^1 position, leading to **3j** in 70% yield. Steric hindrance in the substrates also worked well, delivering **3k** in 65% yield. Vinyl azide with an electron-donating group Me group at the *meta*-position also worked well, affording the corresponding **3l** in 56% yield. Similarly, vinyl azide with a methoxyl substitution at the *meta* position reacted with internal alkynol **1a** to produce **3m** in 55% yield. In contrast, naphthalene-based vinyl azide generated **3n** in 95% yield. The reaction also tolerated naphthalene-substituted vinyl azide, though **3o** was obtained in only 63% yield. Moreover, the reaction was applied to the natural product derivatization: an alkynol derived from cholesterol reacted with vinyl azide **2a** in the presence of $In(OTf)_3$, affording the desired product **3p** in 66% yield.

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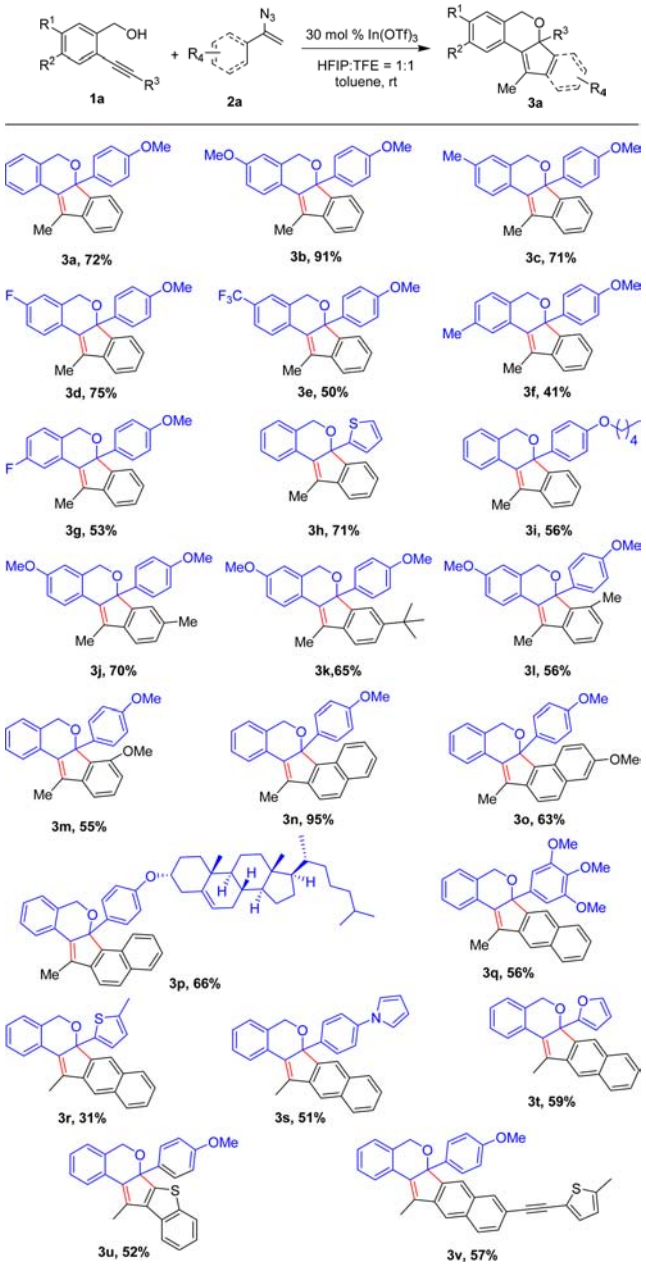
Table 2. Tandem Reactions of Various Internal Alkynols 1 and Vinyl Azide 2a in the Presence of $In(OTf)_3$[a,b]

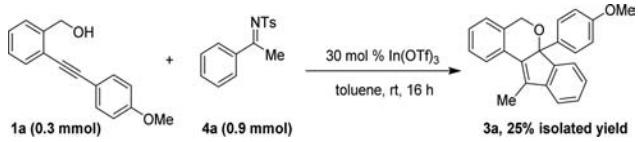


[a]Reactions were conducted under Ar at rt for 24 h using **1** (0.3 mmol), **2a** (0.9 mmol), $In(OTf)_3$ (0.09 mmol), TFE (0.45 mmol), and HFIP (0.45 mmol) in 2 mL of toluene, unless otherwise noted. [b]Isolated yields are shown.

The substrates with 3,4,5-trimethoxyphenyl, 5-methylthiophen-2-yl, 4-(1*H*-pyrrol-1-yl)phenyl, and furanyl at the R^3 position were tested in the reactions with 2-(1-azidovinyl)naphthalene to give the products **3q**−**3t** in moderate isolated yields. Moreover, the vinyl azides containing heteroatoms reacted smoothly with **1a** to give the products **3u**, **3v** in 52% and 57% yield, respectively.

In past work related to the reaction of vinyl azides, *N*-unsubstituted imines were proposed as an intermediate, although such species have not been isolated or detected in most cases.[13,15] Due to the fact that the *N*-substituted imines are much more stable than the *N*-unsubstituted analogues, we perform the reaction of **1a** with *N*-substituted imine **4a** instead of vinyl azide **2a** (Scheme 1). As expected, the product **3a**

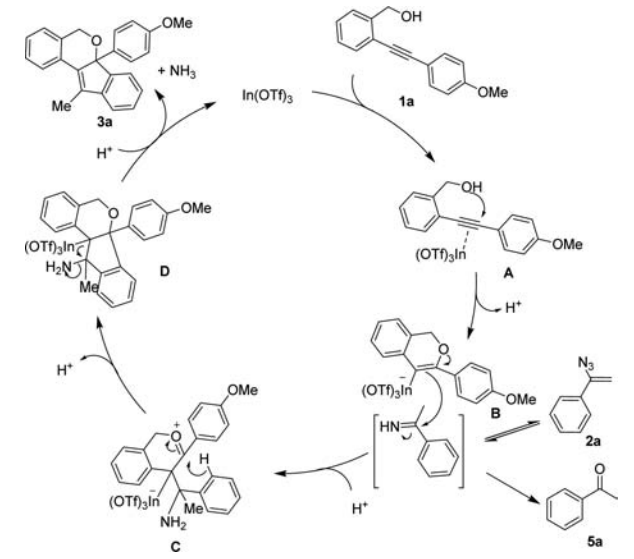
Scheme 1. Reaction of 1a and *N*-Substituted Analogues



formed in 25% isolated yield, verifying that the imine from vinyl azide may be the intermediate of this reaction. Moreover, the acetophenone **5a** was isolated from the above reactions but the reaction of **1a** with **5a** did not proceed, suggesting that the vinyl azide may convert to the imine and then transform to the acetophenone after hydration.

Based on our experimental findings and the literature,[16,17] we propose a tentative mechanism for the $In(OTf)_3$-catalyzed tandem polycyclization reaction of internal alkynol and vinyl azide to generate polycyclic indeno[1,2-*c*]isochromene (Scheme 2). The triple bond of **1a** coordinates with $In(OTf)_3$,

Scheme 2. Proposed Mechanism for $In(OTf)_3$-Catalyzed Tandem Polycyclization of Internal Alkynol and Vinyl Azide



increasing the electrophilicity of the alkyne. Then the hydroxyl group adds to the electron-deficient alkyne, producing vinylindium species **B**. Intermediate **B** is trapped by a *N*-unsubstituted imine produced in situ from **2a**,[14,18] which leads to intermediate **C**.[19] The following carbocyclization gives intermediate **D** to finish a formal [3 + 2] cycloaddition from **B**. Subsequent acid-promoted cleavage of the carbon−metal bond and elimination lead to the desired polycyclic **3a** and regenerate the catalytic species.

In summary, we have described a novel tandem polycyclization reaction that provides a straightforward route to polycyclic products containing a pyran-based indeno[1,2-*c*]isochromene scaffold, starting from readily available internal alkynols and vinyl azides. This tandem cyclization protocol, which requires only $In(OTf)_3$ as a promoter, provides a novel approach for constructing complex polycyclic units in a single operation, and it may expand the usefulness of transition-metal-catalyzed heterocycle synthesis. Further studies to expand the scope of

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alkynol-based polycyclization are under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02556.

Experimental procedures and compound characterization data (PDF)
Crystallographic data for **3a** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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