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Lewis Acid-Catalyzed Intramolecular [3+2] Cycloaddition of Cyclopropane 1,1-Diesters with Alkynes for the Synthesis of Cyclopenta[*c*]chromene Skeletons

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Polycyclic structures are found in the core of most synthetic and natural bioactive products. Highly efficient construction of polycyclic skeletons is one of the most important research topics in organic synthesis. Chromans are valuable structures in biological chemistry as well as important structural units found in many natural and artificial products such as vitamin E and its derivatives and flavonoids.[1] More specifically, cyclopenta[*c*]chromene, one of the chroman derivatives, is found in a wide variety of alkaloids and bioactive agents, which exhibit a broad range of biological activities (Figure 1).[2] Although diverse synthetic approaches toward chromans have been developed,[3] versatile methodologies to construct cyclopenta[*c*]chromene were rarely reported until now.[4] Consequently, the development of new synthetic procedures to access cyclopenta[*c*]chromene derivatives needs to be actively pursued. This prompted us to develop an efficient method for the straightforward synthesis of cyclopenta[*c*]chromene structures from simple, easily available, and cheap starting materials.

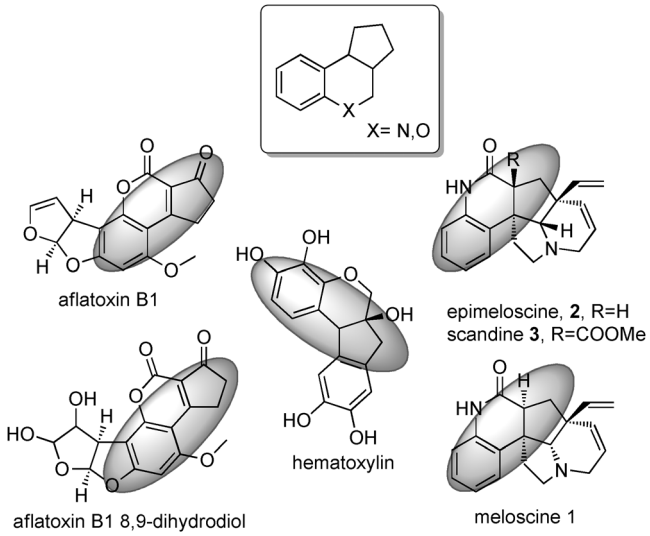

Figure 1. Some representative cyclopenta[*c*]chromene natural products.

Undoubtedly, cycloadditions are one of the most facile and direct transformations for the rapid formation of highly complex molecular scaffolds. Donor–acceptor (DA) cyclopropanes are particularly useful synthetic building blocks, which serve as excellent synthetic equivalents of 1,3-dipolar compounds under Lewis acid-mediated conditions to access cycloaddition products often not readily available through traditional routes.[5] Especially, the ease of running the reaction and the regio- and stereoselectivity make intramolecular [3+2] cycloaddition an efficient methodology to construct complex cyclic skeletons using DA cyclopropanes.[6] Although the annulation of DA cyclopropanes with alkynes has been highly successful in the last decades for the synthesis of cyclopentenes, the modest stereoselectivity and the need for stoichiometric amounts of a strong Lewis acid have hampered the applicability of this reaction.[7] Yadav's group have reported a formal intermolecular [3+2] addition of acceptor-substituted cyclopropylmethylsilanes with aryl acetylenes to afford cyclopentene-based skeletons.[7c] However, silicon substituents attached to cyclopropane are required and a stoichiometric amount of $TiCl_4$ was used in this reaction, thus limiting the scope and applicability of the cycloaddition. Therefore, a straightforward methodology having wider scope is strongly desired. Our research group was also interested in searching for an efficient method for construction of synthetically useful compounds using cyclopropane as the substrate.[8] We envisioned that the cyclopropane ring of cyclopropane 1,1-diesters can be expanded by using alkyne moieties in an intramolecular [3+2] reaction, thereby resulting in cyclopenta[*c*]chromene-type structures (Scheme 1). Herein, we wish to report a successful realization of this concept.

To realize the concept of our design, cyclopropane 1,1-diesters were synthesized from cheap starting material salicylaldehyde in four steps, as shown in Scheme 2 (for further details, see the Supporting Information). Then we started our study by using compound **1a** as a model substrate to optimize the reaction conditions for an intramolecular [3+2]

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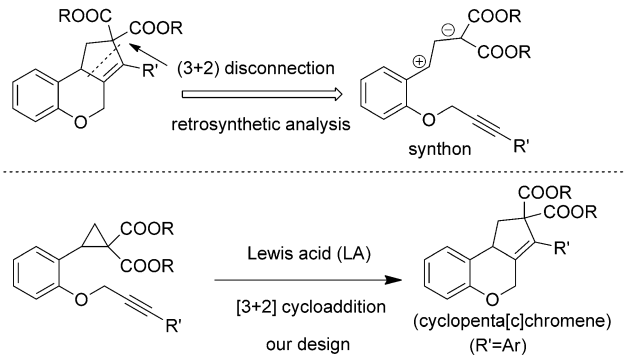
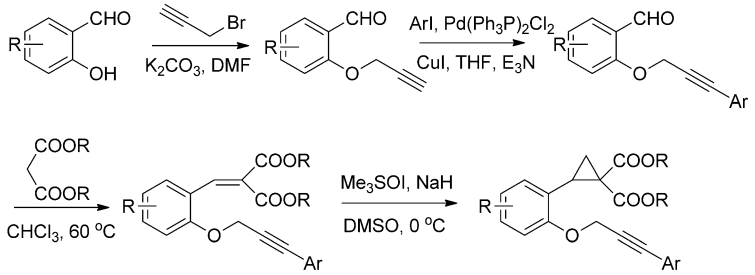


Scheme 1. Design of a Lewis acid-catalyzed ring expansion of cyclopropane 1,1-diesters.

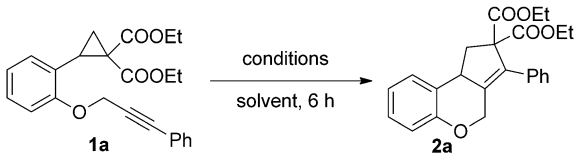


Scheme 2. Modular preparation of cyclization precursors from salicylaldehyde. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide.

cycloaddition. A variety of Lewis acids were first examined as catalysts. Using $SnCl_2$ and other Lewis acids such as $PtCl_2$ and $PtCl_4$, the desired cycloaddition product was not detected. However, when $FeCl_3$ was added to the reaction system, a trace amount of **2a** was formed (Table 1, entry 2). As trifluoromethanesulfonate salts are often reported as good catalysts to catalyze ring-opening reactions of DA cyclopropanes,[6j] we concentrated on using these catalysts (Table 1, entries 5–9). We found that $Sc(OTf)_3$ was the best potential catalyst and afforded the desired product in 56% yield (Table 1, entry 9). To optimize the yield of the product further, we studied the influence of different reaction media (Table 1, entries 10–14). From the results obtained, $(CH_2)_2Cl_2$ was chosen to be the best solvent (Table 1, entry 9). After this, we screened the amount of catalyst employed (Table 1, entries 15–17). When 10 mol% of $Sc(OTf)_3$ was used as the catalyst and 4 Å MS as an additive, **2a** was obtained in 68% yield (Table 1, entry 15). A decrease in the reaction temperature from 75°C to 60°C led to low conversion and yield of **2a** (Table 1, entry 18). A similar result was obtained when the concentration of the reaction system was reduced (Table 1, entry 19).

With the optimized reaction conditions (Table 1, entry 15), we then extended the scope of this transformation to a wide range of cyclopropane 1,1-diesters. The protocol was found to be tolerant to both electron-withdrawing and electron-donating substituents in both aromatic rings (R^1 and Ar). No difference in reactivity was observed between the ethyl diester **1a** and the methyl diester **1b** in the reaction. Better yields were obtained when R^1 was an electron-donating substituent (Table 2, entries 3–7), whereas an electron-withdrawing group slightly hindered the reaction (Table 2, entry 8). This might be due to the fact that the R^1 electron-donating substituent enhances the reactivity of cyclopropane. Sterically demanding *ortho*-substitued cyclopropanes always gave lower yields of the desired product despite the presence of an electron-donating or an electron-withdrawing substituent (Table 2, entries 9–12). The reaction tolerated a variety of functional groups at the *ortho*, *meta*, and *para* positions in the Ar group (Table 2, entries 13–16). When an alkyne with an electron-donating substituent at the *para* position of Ar was employed, **2m** was obtained in 94% yield. The relative configuration of product **2m** was unambiguously assigned by single-crystal X-ray crystallography (see the Supporting Information).[9] The sterically demanding *ortho*-substituted substrate was also tolerated and gave **2o** in 74% yield (Table 2, entry 15). Nevertheless, a relatively lower yield was observed when an alkyne moiety with an electron-withdrawing substituent in Ar was employed (Table 2, entry 16). The thienyl

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (%)	Solvent	*T* [°C]	Yield [%][b]
1	$SnCl_2$ (10)	$(CH_2)_2Cl_2$	75	–[d]
2	$FeCl_3$ (10)	$(CH_2)_2Cl_2$	75	<10
3	$PtCl_2$ (10)	$(CH_2)_2Cl_2$	75	–
4	$PtCl_4$ (10)	$(CH_2)_2Cl_2$	75	–
5	$Cu(OTf)_2$ (10)	$(CH_2)_2Cl_2$	75	<10
6	$Zn(OTf)_2$ (10)	$(CH_2)_2Cl_2$	75	–
7	$Yb(OTf)_3$(10)	$(CH_2)_2Cl_2$	75	40
8	$Bi(OTf)_3$ (10)	$(CH_2)_2Cl_2$	75	<10
9	$Sc(OTf)_3$ (10)	$(CH_2)_2Cl_2$	75	56
10	$Sc(OTf)_3$ (10)	toluene	75	40
11	$Sc(OTf)_3$ (10)	CH_2Cl_2	40	–
12	$Sc(OTf)_3$ (10)	1,4-dioxane	75	–
13	$Sc(OTf)_3$ (10)	CH_3CN	75	–
14	$Sc(OTf)_3$ (10)	THF	60	–
15	**$Sc(OTf)_3$(10)[c]**	**$(CH_2)_2Cl_2$**	**75**	**68**
16	$Sc(OTf)_3$ (5)[c]	$(CH_2)_2Cl_2$	75	60
17	$Sc(OTf)_3$(15)[c]	$(CH_2)_2Cl_2$	75	57
18	$Sc(OTf)_3$(10)[c]	$(CH_2)_2Cl_2$	60	50
19	$Sc(OTf)_3$(10)[c,e]	$(CH_2)_2Cl_2$	75	66

[a] Standard reaction conditions: **1a** (0.1 mmol) in 1 mL of solvent for 6 h. [b] Yields of isolated products. [c] Using 4 Å MS as the additive. [d] No reaction. [e] **1a** (0.1 mmol) in 2 mL of solvent for 6 h.

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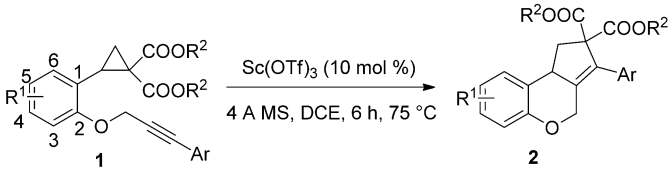
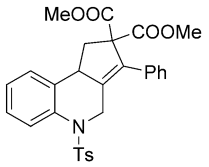
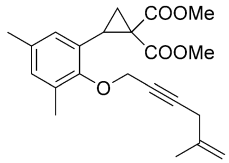
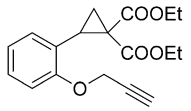
Table 2. $Sc(OTf)_3$-catalyzed [3+2] cycloaddition.[a]



Entry	R^1	R^2	Ar	Product	Yield [%][b]
1	H	Et	Ph	**2a**	68
2	H	Me	Ph	**2b**	73
3	5-Me	Me	Ph	**2c**	69
4	5-MeO	Et	Ph	**2d**	72
5	5-*t*Bu	Me	Ph	**2e**	70
6	3,5-di-Me	Me	Ph	**2f**	81
7	3,5-di-*t*Bu	Me	Ph	**2g**	62
8	5-Cl	Et	Ph	**2h**	65
9	3-*t*Bu	Et	Ph	**2i**	57
10	3-MeO	Me	Ph	**2j**	48
11	3-Br	Me	Ph	**2k**	60
12	6-Me	Me	Ph	**2l**	41
13	H	Me	4-MeO-C_6H_4	**2m**	94
14	H	Me	3-Me-C_6H_4	**2n**	63
15	H	Et	2-MeO-C_6H_4	**2o**	74
16	H	Me	4-Cl-C_6H_4	**2p**	57
17	H	Me	thienyl	**2q**	77
18				**2r**	83
19				–	–[c]
20				–	–[c]

[a] Standard reaction conditions: **1** (0.2 mmol), catalyst (10 mol%), and 50 mg of activated 4 Å MS in 2 mL of DCE at 75°C. [b] Yields of isolated products. [c] No product.

substituent was also tolerated and the corresponding product **2q** was isolated in 77% yield. Aliphatic and terminal alkynes failed to give any desired [3+2] product (Table 2, entries 19 and 20). Nitrogen-based functional groups are especially important in synthetic and medicinal chemistry. In this respect, tetrahydroquinoline derivatives constitute an important subclass of cyclic structures, which are the key structural elements in many natural products, particularly alkaloids. Under the optimized reaction conditions, tetrahydroquinoline derivative **2r** could be obtained in 83% yield using our designed method. Some derivatives of **2r** are inhibitors of human Cdc25B dual specificity phosphatase.[10]

To further establish the synthetic potential of this method, the transformation of the cyclopenta[*c*]chromene product **2h** was examined (Scheme 3). The reaction worked smoothly on a 1 mmol scale without loss of reactivity. The two ester groups in product **2h** reacted with urea, and then a barbituric acid derivative product **4** was easily obtained in two steps from easily prepared substrate **1h**.[6d] Barbituric acid derivatives can act as central nervous system depressants and are used as sedatives and hypnotics. In our opinion, this method may be used as a platform for new drug screening in the future.

In conclusion, we have reported a successful method for the construction of cyclopenta[*c*]chromene structures through an intramolecular [3+2] cycloaddition of cyclopropane 1,1-diesters with alkynes in good to excellent yields in a single step. The efficiency and functional-group tolerance of this procedure have been demonstrated by synthesizing a variety of substituted cyclopenta[*c*]chromenes, for which truly general synthetic methods are scarce. The products are expected to be useful intermediates for the preparation of biologically active compounds and drugs. Our developed protocol can be used to prepare useful barbituric acid derivatives in acceptable yields.

Experimental Section

*General Procedure for the Preparation of **2a–2r***

Cyclopropane 1,1-diester **1a** (0.2 mmol, 78.4 mg), $Sc(OTf)_3$ (0.02 mmol, 7.8 mg), 4 Å molecular sieves (50 mg), and $(CH_2)_2Cl_2$ (2 mL) were added to a test tube, then the mixture was allowed to stir at 75°C. When the reaction was considered complete as determined by TLC analysis, ethyl acetate (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with ethyl acetate (2×20 mL). The combined organic phases were washed with brine and dried over sodium sulfate. The residue was purified by flash chromatography on silica gel to afford corresponding product **2a** in 68% yield (53 mg).

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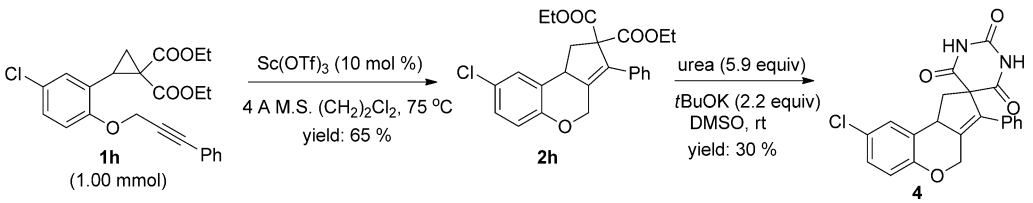

Scheme 3. Transformation of the cyclopenta[*c*]chromene.

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Keywords: alkynes · cycloaddition · cyclopenta[*c*]chromene · donor–acceptor cyclopropanes · lewis acids

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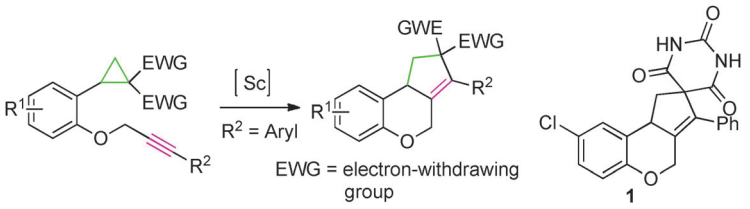

An efficient method to construct cyclopenta[*c*]chromene skeletons by Lewis acid-catalyzed intramolecular [3+2] cycloaddition of cyclopropane 1,1-diesters with alkynes is presented. Two new fused cycles can be formed in one step in moderate to excellent yields (up to 94%), and the products can be converted into bioactive barbituric acid derivatives (**1**) under simple reaction conditions.

Cycloaddition

*Xiao-Feng Xia, Xian-Rong Song, Xue-Yuan Liu, Yong-Min Liang**

Lewis Acid-Catalyzed Intramolecular [3+2] Cycloaddition of Cyclopropane 1,1-Diesters with Alkynes for the Synthesis of Cyclopenta[*c*]chromene Skeletons