Organic LETTERS

Letter

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$ZnBr_2$-Mediated Cascade Reaction of *o*-Alkoxy Alkynols: Synthesis of Indeno[1,2-*c*]chromenes

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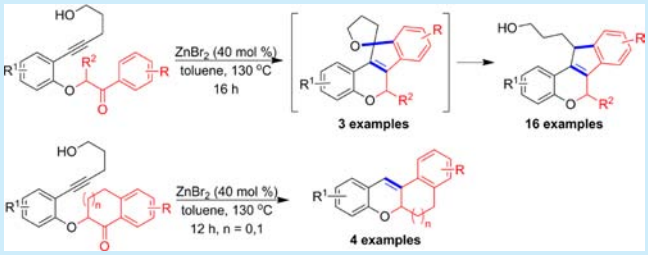
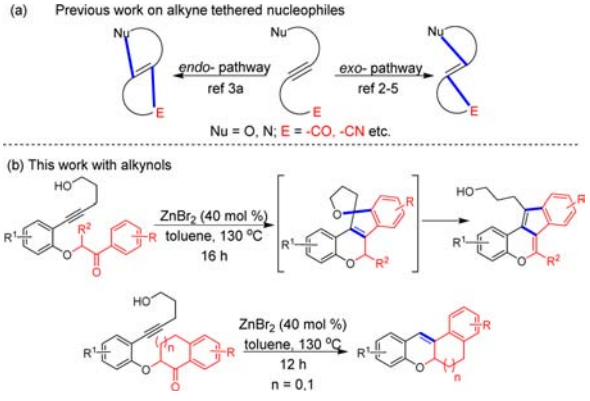
Supporting Information

ABSTRACT: A Lewis acid-mediated cascade annulation of *o*-alkoxy alkynols in the presence of $ZnBr_2$ has been developed. The cascade cyclization proceeds through a 5-*exo*-dig cyclization followed by a Friedel–Crafts reaction and ring-opening sequence to synthesize indeno[1,2-*c*]chromenes. This protocol provides a broad substrate scope in moderate to good yields with high regioselectivity. The reaction with benzo-fused cycloalkyl ketones gave an unexpected alkyne C–C bond cleavage resulting in fused polycycles.



Alkynols are becoming one of the important building blocks for the construction of various heterocycles. The key point about alkynols is that they can undergo cycloisomerization via *endo* or *exo* pathways to synthesize different heterocycles with 100% atom economy.[1] Furthermore, the cascade reactions of alkynols proceed via cyclization with diverse transformations such as Prins-type cyclization,[2] Diels–Alder reaction,[3] Povarov reaction,[4] etc. Several groups have utilized this idea to construct various heterocycles[5] (Scheme 1a). In this context and as a part of our research interest in Lewis acid-promoted cascade reactions,[6] we herein report a Lewis acid-mediated cascade cyclization of *o*-alkoxy alkynols to construct indeno[1,2-*c*]chromenes through a 5-*exo*-dig cyclization followed by a Friedel–Crafts reaction and ring-opening sequence (Scheme 1b).

Scheme 1. Generalized Cyclization via Alkyne-Tethered Nucleophiles



Indenochromenes are one of the privileged classes of *O*-heterocycles because of their presence in natural products with versatile biological properties.[7,8,11] Indeno[1,2-*c*]chromene is a precursor of gnetuhainin S (Figure 1A), which was isolated from *Gnetum macrostachyum* lianas and displays potent antioxidant activity as a radical scavenger against DPPH.[7a,b] Parvifolols A–C exhibit strong inhibitory activity against the Maillard reaction (Figure 1B–D).[8] In addition, they have been used in the synthesis of new organic JH dyes (donor–π-linker–acceptor dyes) as a new donor moiety as well as a π-linker for use in high-performance dye-sensitized solar cells.[11]

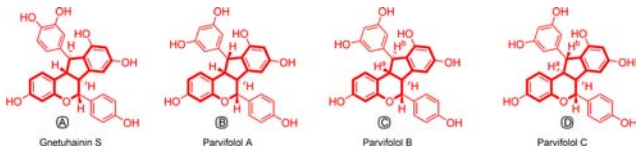


Figure 1. Representative examples of bioactive indeno[1,2-*c*]-chromenes.

Despite their potential usefulness, only a few synthetic methods have been documented in the literature.[9−11] For instances, in 2011 Wu and co-workers reported a Pd-catalyzed intermolecular reaction of 2-alkynylphenols with 2-alkynylhalobenzenes to synthesis indeno[1,2-*c*]chromenes.[9a] Later, in 2014, the same group developed an alternative approach from 1-bromo-2-(cyclopropylidenemethyl)benzene with 2-alkynylphenols.[9b] In 2011, Li and co-workers displayed the $FeCl_3$-promoted intramolecular [3 + 2] cyclization of 1-phenyl-2-(2-

Received: December 7, 2016
Published: January 25, 2017

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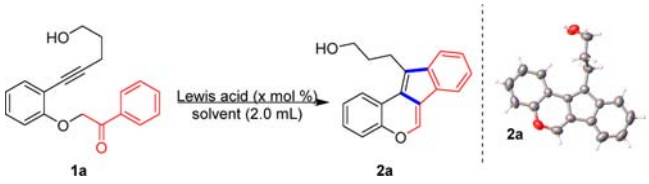
DOI: 10.1021/acs.orglett.6b03642
Org. Lett. 2017, 19, 488–491

(phenylethynyl)phenoxy)ethan-1-one to construct indeno[1,2-*c*]chromene derivatives.[10] Recently, in 2015, Jin and co-workers reported a triflic acid-mediated cascade cyclization of *o*-anisole-substituted aryldiynes to give indeno[1,2-*c*]chromenes.[11] Therefore, the development of new synthetic approaches for indeno[1,2-*c*]chromenes is still considered an interesting area of research.

Our studies began with the reactions of 2-(2-(5-hydroxypent-1-yn-1-yl)phenoxy)-1-phenylethan-1-one (**1a**) in the presence of iron(III) and iron(II) salts in 1,2-dichloroethane at 85 °C. Unfortunately, there was no progress in the reaction (Table 1, entries 1−3). Interestingly, 3-(indeno[1,2-*c*]chromen-11-yl)-propan-1-ol (**2a**) was produced in 25% yield in the presence of $ZnBr_2$ (entry 11), while other Zn and Cu salts exhibited no product formation (entries 4−10). The structure of the compound was confirmed unambiguously with the help of X-ray analysis.[12] Changing from metal halides to metal triflates resulted in slightly lower yields of **2a** (entries 12 and 13). Next, the effect of different solvents was surveyed at refluxing temperature to improve the yield of **2a** (entries 14−18). The desired compound **2a** was obtained in slightly higher yield in the presence of toluene as the solvent (entry 18). Subsequently, the effect of the $ZnBr_2$ loading was investigated (entries 19−21), and it was found that 40 mol % $ZnBr_2$ gave the maximum yield of **2a** (72%) at 130 °C for 16 h (entry 20).

Table 1. Optimization of the Reaction Conditions[a]

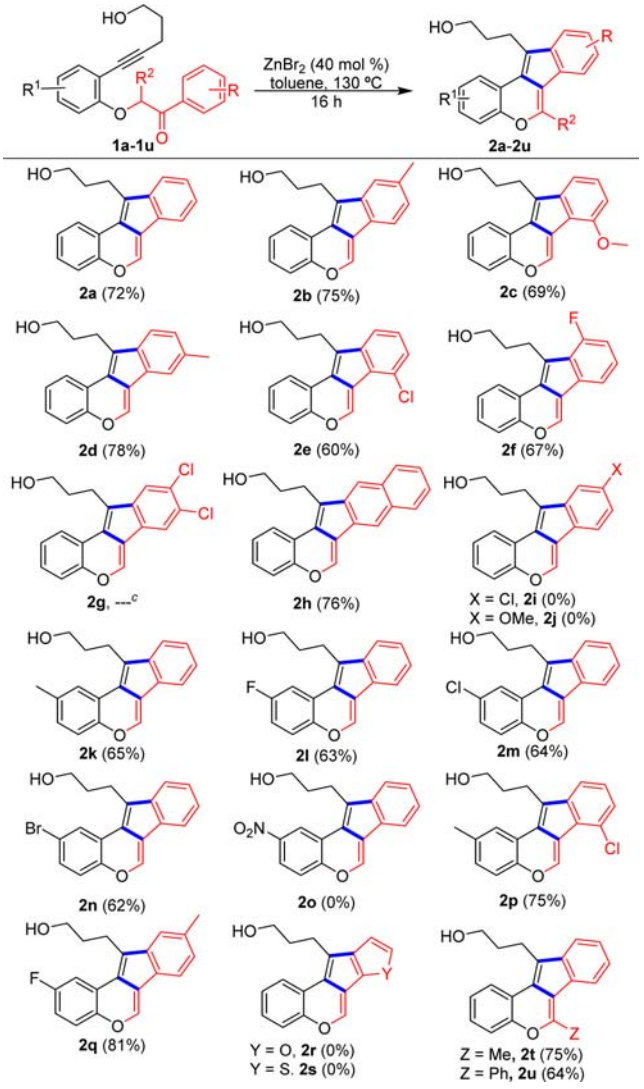


entry	Lewis acid (*x* mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	$FeCl_3$ (10)	1,2-DCE[c]	85	24	0
2	$FeBr_3$ (10)	1,2-DCE	85	24	0
3	$FeCl_2$ (10)	1,2-DCE	85	24	0
4	CuI (10)	1,2-DCE	85	24	0
5	CuCl (10)	1,2-DCE	85	24	0
6	CuBr (10)	1,2-DCE	85	24	0
7	$CuBr_2$ (10)	1,2-DCE	85	24	0
8	$Cu(OAc)_2$ (10)	1,2-DCE	85	24	0
9	ZnI_2 (10)	1,2-DCE	85	24	0
10	$ZnCl_2$ (10)	1,2-DCE	85	24	0
11	$ZnBr_2$ (10)	1,2-DCE	85	24	25
12	$Sc(OTf)_3$ (10)	1,2-DCE	85	24	17
13	$In(OTf)_3$ (10)	1,2-DCE	85	24	15
14	$ZnBr_2$ (10)	DMSO[d]	130	24	0
15	$ZnBr_2$ (10)	DMF[e]	130	24	0
16	$ZnBr_2$ (10)	xylene	140	24	24
17	$ZnBr_2$ (10)	PhCl[f]	130	24	25
18	$ZnBr_2$ (10)	toluene	130	20	33
19	$ZnBr_2$ (20)	toluene	130	20	46
20	**$ZnBr_2$ (40)**	**toluene**	**130**	**16**	**72**
21	$ZnBr_2$ (60)	toluene	130	16	70

[a]All of the reactions were carried out using **1a** (0.5 mmol) and the Lewis acid (*x* mol %) in the solvent (2.0 mL) at the indicated time and temperature in a sealed tube. The entry in bold (entry 20) highlights the optimized reaction conditions. [b]Isolated yields. [c]1,2-DCE = 1,2-dichloroethane. [d]DMSO = dimethyl sulfoxide. [e]DMF =*N*,*N*-dimethylformamide. [f]PhCl = chlorobenzene.

With the optimized conditions in hand, the scope of this $ZnBr_2$-mediated cascade reaction was investigated with respect to the R , R^1, and R^2 functionalities present on the *o*-alkoxy alkynol. As shown in Scheme 2, the reactions with electron-donating R substituents, such as *p*-Me (**2b**), *o*-OMe (**2c**), and *m*-Me (**2d**), proceeded faster than those with electron-withdrawing groups, such as *o*-Cl (**2e**) and *m*-F (**2f**). However, the 3,4-dichloro-substituted substrate (**2g**) reacted sluggishly, and trace product was formed. Also, the reaction did not work with R substituents such as *p*-Cl (**2i**) and *p*-OMe (**2j**). This might be due to the *para* effect of the electron-donating and electron-withdrawing substituents. The reaction also tolerated well fused ring systems such as 2-naphthyl (**2h**). Next, R^1 substituents such as *p*-Me (**2k**), *p*-F (**2l**), *p*-Cl (**2m**), and *p*-Br (**2n**) were investigated, and all of them gave the corresponding products in 62−65% yield irrespective of electronic factors.

Scheme 2. Substrate Scope of *o*-Alkoxy Alkynols[a,b]

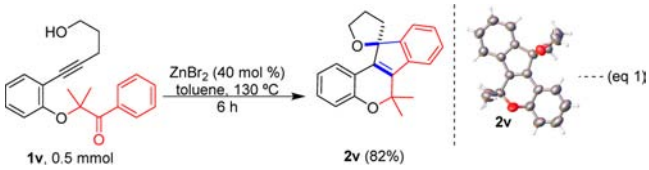


[a]Reactions were carried out with **1a−u** (0.5 mmol) and $ZnBr_2$ (40 mol %) in the presence of toluene at 130 °C for 16 h. [b]Isolated yields of products are shown. [c]Trace product formation was observed after 36 h, but the product was not isolated.

DOI: 10.1021/acs.orglett.6b03642
Org. Lett. 2017, 19, 488−491

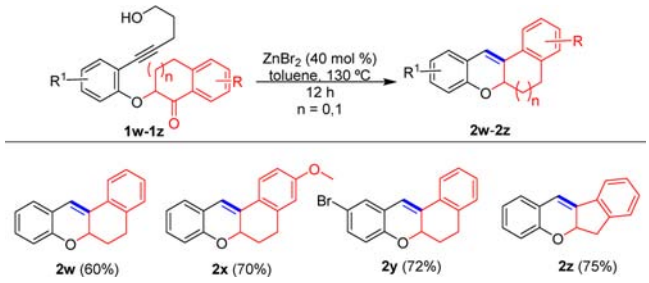
However, the *p*-NO_2 group at the same position (**2o**) did not work out efficiently. The reason might be the strong coordination of the Lewis acid with the nitro group, preventing it from getting the desired compound. The reaction also tolerated well substrates disubstituted at both R and R^1 (**2p** and **2q**). Heteroaromatic derivatives such as furan and thiophene at the R position did not give the desired compounds (**2r** and **2s**); instead, the starting materials were consumed to multiple spots. Next, we focused on the R^2 substituent with functional groups like Me and Ph. The reaction worked well, giving corresponding α-substituted products (**2t** and **2u**) in 64−75% yield.

When both hydrogen atoms at the α-position were replaced by methyl groups, the reaction stopped at the spiro intermediate compound (**2v**), preventing the subsequent ring-opening step. This example proves that the reaction proceeds through a spirocyclic intermediate (eq 1). The structure of the compound was confirmed by X-ray analysis.[12]



We later carried out examples with tetralones and indanone (Scheme 3) and observed an unusual alkyne C−C bond

Scheme 3. Substrate Scope of Tetralones and Indanone[a,b]

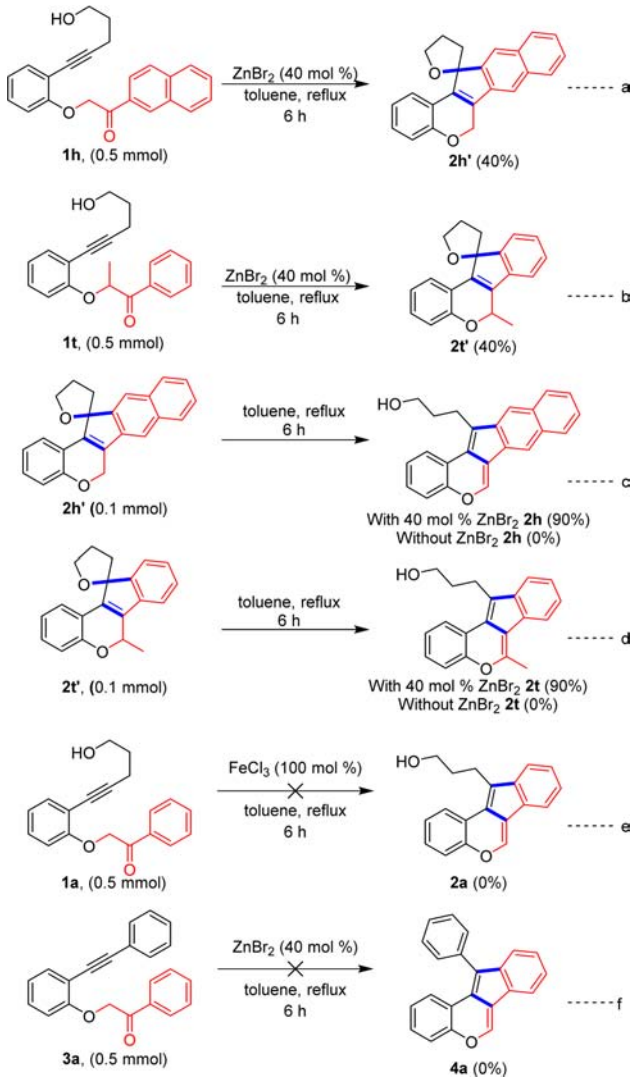


[a]Reactions were carried out with **1w−z** (0.5 mmol) and $ZnBr_2$ (40 mol %) in the presence of toluene at 130 °C for 12 h. [b]Isolated yields of products are shown.

cleavage that resulted in the formation of polycyclic compounds known as benzoxanthenes (**2w−z**) in 60−75% yield. The structure of compound **2w** was confirmed with the help of X-ray analysis.[12] These compounds possess several biological activities[13] such as analgesic,[14a] anti-inflammatory,[14b] anti-bacterial,[14c] and antiviral[14d] activities. These heterocycles have been utilized as antagonists for paralyzing action of zoxazolamine[14e] and in photodynamic therapy.[14f]

To elucidate the mechanism, we carried out a few control experiments, as shown in Scheme 4. While examining the substrate scope, we observed that when both α-positions were blocked the product was stopped at the spiro intermediate **2v**. On the basis of this observation, we again carried out reactions with typical *o*-alkoxy alkynols (**1h** and **1t**) and reduced the time to 6 h, and the corresponding spiro intermediate compounds (**2h′** and **2t′**) were isolated with trace amounts of the final products (Scheme 4a,b). Furthermore, we carried out the reaction of spiro intermediates in the presence and absence of $ZnBr_2$ and obtained the desired compounds **2h** and **2t** in high

Scheme 4. Control Experiments

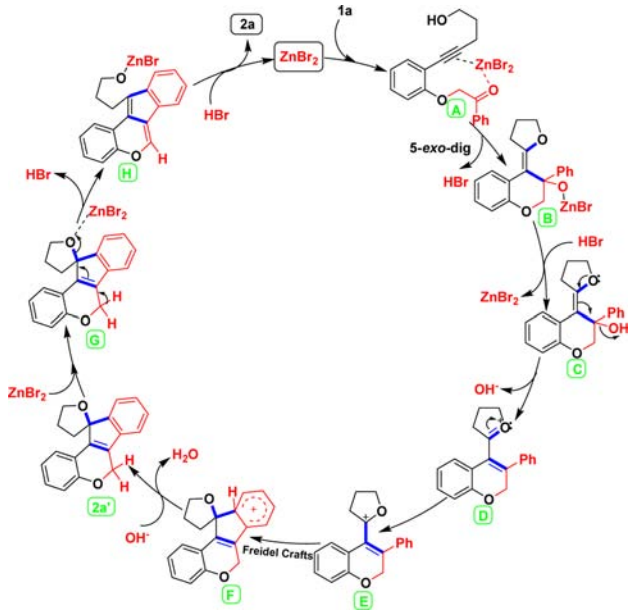


yields only with $ZnBr_2$ (Scheme 4c,d). In 2011, Li and co-workers[10] synthesized indeno[1,2-*c*]chromene from 1-phenyl-2-(2-(phenylethynyl)phenoxy)ethan-1-one (**3a**) using stoichiometric $FeCl_3$ as a Lewis acid promoter via a seven-membered cationic intermediate. To confirm the mechanism and to understand the role of $ZnBr_2$ in our protocol, we carried out the reaction of **1a** under their standard conditions (Scheme 4e), but we could not obtain the desired compound **2a**. Furthermore, we carried out the reaction of **3a** under our standard conditions, and the expected product **4a** was not obtained (Scheme 4f).

A plausible mechanism was proposed on the basis of the previous reports[15,16] and control experiments, as shown in Scheme 5. The $ZnBr_2$-mediated[15] reaction was initiated through coordination of the Lewis acid with the alkyne as well as the ketone group. With this driving force, the alkynol underwent 5-*exo*-dig cyclization to form **B**, followed by regeneration of $ZnBr_2$ to give tetrasubstituted alkene intermediate **C**. The hydroxide anion was then eliminated via generation of oxonium ion intermediate **D**. Further, the tertiary carbocation **E**, rearranged from intermediate **D**, smoothly underwent a Friedel−Crafts-type reaction[16] to give spiro skeleton compound **2a′**, which was finally converted to

DOI: 10.1021/acs.orglett.6b03642
Org. Lett. 2017, 19, 488−491

Scheme 5. Plausible Reaction Mechanism



indeno[1,2-*c*]chromene **2a** via a 1,5-H shift in the presence of $ZnBr_2$.

In conclusion, we have developed a Lewis acid-mediated cascade approach toward the synthesis of indeno[1,2-*c*]-chromenes. A reasonable mechanism for the formation of indeno[1,2-*c*]chromenes has been proposed with the help of spiro intermediate isolation and spectral characterization. On the other hand, we also observed an unexpected alkyne C−C bond cleavage product, and their respective mechanistic studies are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03642.

Experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds (PDF)
X-ray crystallographic data for **2a** (CIF)
X-ray crystallographic data for **2v** (CIF)
X-ray crystallographic data for **2w** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge funding from the Ministry of Science and Technology (MOST), Taiwan. We also thank the Centre for Research Resources and Development of Kaohsiung Medical University for providing 400 MHz NMR, GC−MS, and LC−MS analyses.

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DOI: 10.1021/acs.orglett.6b03642
Org. Lett. 2017, 19, 488−491