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Brønsted Acid-Mediated Formal [3+3] Annulation Between Propargylic Alcohols and 1,3-Diketones

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Abstract. A Brønsted acid-mediated formal [3+3] cascade annulation of propargylic alcohols with 1,3-diketones proceeds through a sequential Meyer−Schuster rearrangement/1,2-addition. This protocol, which has a wide scope and is conducted under an ambient atmosphere, enables access to a broad array of valuable chromenone derivatives related to many natural products in satisfactory yields under mild conditions. This method could be scaled up to the gram scale, which highlights the latent applicability of this transformation.

Keywords: Brønsted acid-mediated; propargylic alcohols; 1,3-diketones; formal [3+3] cascade annulation; chromenone derivatives

Chromenone derivatives, which belong to an important class of oxygen-containing compounds, have been found to have numerous biological and pharmacological activities and serve as key intermediates in organic synthesis and functional materials science.[1] For example, the natural product ferprenin, which is a prenylated coumarin from *Ferulu communis*, was identified as the causative agent of a serious hemorrhagic disease (Figure 1).[2] Arisugacin H, isolated from the culture broth of *Penicillium*, exhibits inhibitory activities against human erythrocytes acetylcholinesterase and horse serum butyrylcholinesterase and has potential as a treatment for Alzheimer disease.[3] Tetrahydrocannabinol (THC) and cannabivarin (CBV), plant cannabinoids isolated from *Cannabis sativa*, are believed to hold therapeutic promise in various pathological conditions and diseases, ranging from anxiety disorders, inflammation, central nervous system disorders, myocardial infarction, to Huntington's disease.[4] Thus, the development of versatile, efficient, and environmentally benign tandem procedures and alternative methods for the construction of chromenone derivatives has attracted much attention. In 2014, Li et al. reported a novel hollow-structured ZIF-8-H nanosphere-catalyzed syntheses of valuable pyranyl heterocycles using 1,3-cyclohexanediones and α, β-unsaturated aldehydes as the substrates (Scheme 1a).[5] Three-component reactions of aromatic aldehydes with 1,3-cyclohexanediones and indoles for the facile assembly of the corresponding products using L-proline as the catalyst have been developed by the Gu group (Scheme 1b).[6] Recently, McGlacken and co-workers reported an elegant protocol for the synthesis of oxoisochromene derivatives through an intramolecular, one-step arylation of α,β-unsaturated ketones (Scheme 1c).[7] Therefore, the search for practical and convenient synthetic approaches for the generation of chromenone derivatives from easily prepared starting materials is still an attractive target for synthetic organic chemists.

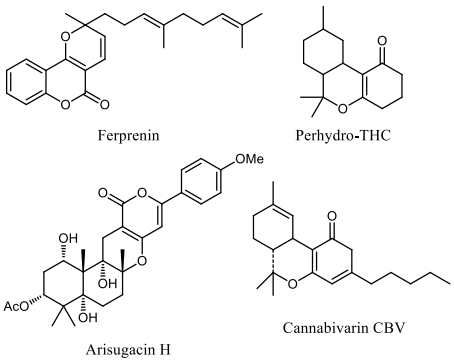


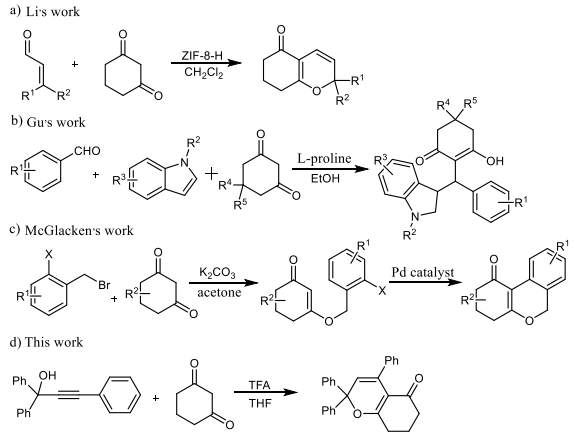
Figure 1. Representative chromenone-containing compounds

1,3-Dicarbonyl derivatives have been extensively used as important synthetic intermediates because they incorporate nucleophilic and electrophilic functionalities.[8] In particular, the use of 1,3-dicarbonyl derivatives as nucleophilic or electrophilic reagents for the construction of structurally diverse oxygen-containing compounds, such as pyrroles,[9] indoles,[10] dihydropyrans,[11] tetrahydroindolizines,[12] dihydrofurans,[13] β-hydroxyesters,[14] γ-alkylidenebutenolides,[15] and olefinic

10.1002/adsc.201701296

cyclopentanes,[16] has been widely investigated. Inspired by these intriguing reports and our continued interest in the transformations of propargylic alcohols, we herein report a novel Brønsted acid-mediated formal [3+3] annulation system involving reactions of propargylic alcohols with 1,3-diketones, which enables an efficient, single-step, atom-economical synthesis of chromenone derivatives under mild conditions.

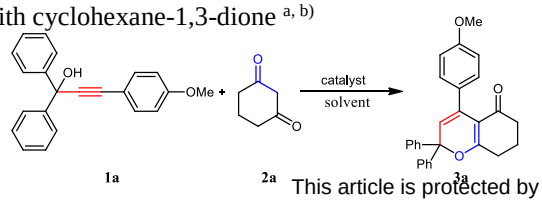
Scheme 1. Summary of current methods and our proposed pathway toward chromenone derivatives



At the outset, alkynol substrate 3-(4-methoxyphenyl)-1,1-diphenylprop-2-yn-1-ol (**1a)** and cyclohexane-1,3-dione (**2a**) were chosen as the model substrates for the optimization of the reaction conditions. Gratifyingly, desired product **3a** could be obtained in 17% yield when the reaction was conducted with one equivalent of BF_3Et_2O (1.0 equiv) in THF at 80°C for 8 h (Table 1, entry 1). Notably, various Brønsted acid catalysts were also screened in this cyclization reaction, and TFA was found to have the best catalytic activity; it furnished desired product **3a** in 65% yield (entries 2−6). Further screening of the temperature revealed that 100°C was most suitable for the formal [3+3] annulation reaction, and gave 71% yield of the desired product (entries 7−9). The product yield was increased to 77% by prolonging the reaction time to 24 h (entries 10−12). By decreasing the amount of the Brønsted acid (TFA) to 0.5 equiv, the yield increased from to 77% to 84% (entries 13−14). The reaction in various solvents such as DCE, 1,4-dioxane, toluene, acetonitrile and CH_3NO_2 did not result in any improvement in the yield (entries 15−19). Ultimately, the optimized conditions for the generation of **3a** were defined with the use of **1a** (0.1 mmol), cyclohexane-1,3-dione **2a** (3.0 equiv.) in the presence of TFA (0.5 equiv) in THF (2.0 mL) at 100°C for 24 h.

With the optimized reaction conditions established, the scope of the propargylic alcohol substrates of this formal [3+3] cascade annulation with respect to **2** was then evaluated, and the results are shown in Scheme 2. Both electron-rich aryl substituents, such as methoxy, methyl, ethyl, and 3,5-dimethyl groups (**3a**−**3e**), and electron-deficient aryl substituent, such as a phenyl

Table 1. Optimization of the conditions for the reaction of **1a** with cyclohexane-1,3-dione [a, b]



1a 2a 3a

entry	catalyst (equiv)	solvent	temp (°C)	*t* (h)	yield (%)[b]
1	BF_3Et_2O (1.0)	THF	80	8	17
2	TMSCl (1.0)	THF	80	8	21
3	TsOH (1.0)	THF	80	8	27
4	HCOOH(1.0)	THF	80	8	12
5	CH_3COOH(1.0)	THF	80	8	19
6	TFA (1.0)	THF	80	8	65
7	TFA (1.0)	THF	60	8	46
8	TFA (1.0)	THF	100	8	71
9	TFA (1.0)	THF	120	8	69
10	TFA (1.0)	THF	100	16	75
11	TFA (1.0)	THF	100	24	77
12	TFA (1.0)	THF	100	32	68
13	TFA (0.2)	THF	100	24	79
14	**TFA (0.5)**	**THF**	**100**	**24**	**84**
15	TFA (0.5)	DCE	100	24	54
16	TFA (0.5)	1,4-dioxane	100	24	52
17	TFA (0.5)	$PhCH_3$	100	24	60
18	TFA (0.5)	CH_3CN	100	24	38
19	TFA(0.5)	CH_3NO_2	100	24	11

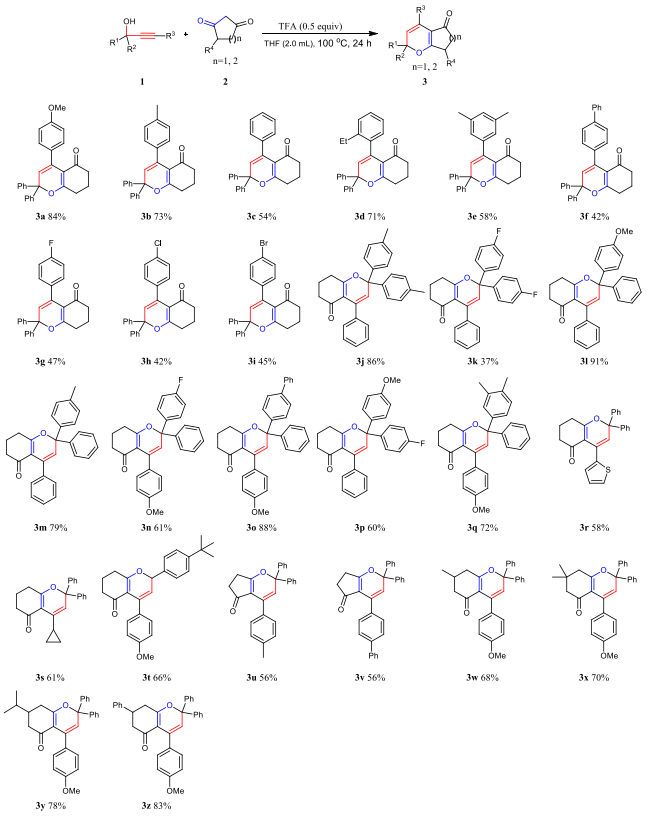
[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol) and cyclohexane-1,3-dione **2a** (3.0 equiv.) in solvent (2.0 mL). [b] Yields are given for isolated products.

group (**3f**), were well tolerated in the transformation and furnished the corresponding products in yields ranging from 42% to 84%. The structure of product **3c** was elucidated by NMR spectroscopy and X-ray crystal analysis (see the Supporting Information).[17] When halogen substituents, F, Cl, and Br are present on the phenyl ring of R^3, the reaction proceeded smoothly and delivered the corresponding products **3g**−**3i** in moderate yields; these substituents allow easier downstream chemical modifications of these products. Notably, symmetrical propargylic alcohols possessing two methyl groups or two fluoride groups were compatible with the reaction conditions and afforded desired products **3j** and **3k**, in 86% and 37% yields, respectively. Regarding unsymmetrical alkynols bearing either electron-donating (OMe or Me) or electron-withdrawing groups (F or Ph) on the aromatic rings (R^1 or R^2), the [3+3] cascade annulation efficiently produced the corresponding products in 60−91% yields (**3l**−**q**). The presence of heterocyclic substituents, for example, thienyl and cyclopropyl groups, on the propargylic alcohols afforded the anticipated products **3r** and **3s** with yields ranging from 58% to 61%. Notably, the reaction of secondary propargylic alcohol 1-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)prop-2-yn-1-ol (**1t)** gave

10.1002/adsc.201701296

corresponding product **3t** in moderate yield. Taking the protocol a step further, we sought to examine the scope of the reaction with respect to the 1,3-diketone. Cyclopentane-1,3-dione could be used as the 1,3-diketone substrate, and the corresponding [3+3] annulation products **3u** and **3v** were obtained in moderate yields. Remarkably, the reactions of propargylic alcohol **1a** with various substituted cyclohexane-1,3-diones **2** proceeded well, allowing the facile generation of chromenone derivatives in generally moderate to good yields. Cyclohexane-1,3-diones containing electron-rich (5-methyl, 5,5-dimethyl, or 5-isopropyl) or electron-deficient (5-phenyl) substituents were suitable substrates for this protocol and led to the respective products **3w**–**3z** in yields ranging from 68% to 83%.

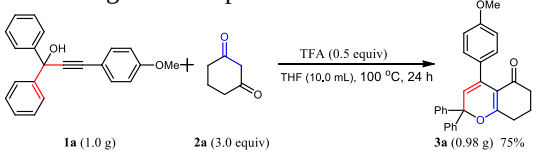
Scheme 2. Transformations of propargylic alcohols to chromenone derivatives [a, b]



[a] Unless otherwise noted, all reactions were performed with **1** (0.1 mmol) and **2** (3.0 equiv.) in the presence of TFA (50 mol %) in THF (2.0 mL) at 100°C for 24 h. [b] Yields are given for isolated products.

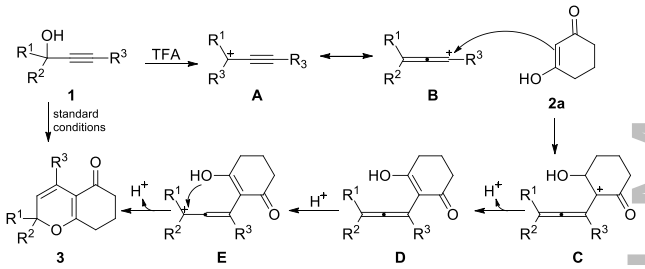
An advantage of our developed reaction system was that the [3+3] cascade annulation reactions could efficiently be scaled up to grams quantities using the optimal conditions, and desired product **3a** was obtained in good yield (75%), which highlights the potential applications of this transformation (Scheme 3).

Scheme 3. Large-scale experiment



Based on our previously work and the published literature,[18,19] a plausible mechanistic pathway for this [3+3] cascade annulation reaction was proposed as shown in Scheme 4. Initially, the dehydration of propargylic alcohol **1** affords propargyl cation intermediate **A**, which could furnish resonance-stabilized intermediate **B** via a Meyer-Schuster rearrangement in the presence of TFA. Subsequently, cyclohexane-1,3-dione **2a** undergoes tautomerization to yield intermediate **C** via an intermolecular nucleophilic attack. Intermediate **C** forms intermediate **D** by the release of a proton, which will be captured by a proton to give intermediate **E**. Finally, desired product **3** is generated through intramolecular nucleophilic attack of the carbon ion site with the release of a proton.

Scheme 4. Proposed mechanism for the formation of chromenone derivatives.



In summary, a simple method for the efficient assembly of functionalized chromenone derivatives by employing a TFA-mediated formal [3+3] cascade annulation of propargylic alcohols with 1,3-diketones has been developed. The developed reaction system is tolerant of a wide scope of propargylic alcohols and 1,3-diketones. The cost-effective catalytic system, good functional group compatibility, ambient reaction conditions, and operational simplicity inherent to this strategy are salient features of this transformation.

Experimental Section

General procedure for the synthesis of 4-(4-methoxyphenyl)-2,2-diphenyl-7,8-dihydro-2*H*-chromen-5(6*H*)-one (3a)

The reaction of propargylic alcohol **1a** (31.4 mg, 0.1 mmol), cyclohexane-1,3-dione **2a** (3.0 equiv), TFA (50 mol %) in THF (2.0 mL) was conducted at 100°C under an air atmosphere for 24.0 h. The reaction was completed by TLC monitoring. The resulting mixture was cooled down to room temperature. The mixture was evaporated under reduced pressure. The residue was further purified by chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to afford 34.2 mg of **3a**.

Acknowledgements

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[17] CCDC 1578243 {2,2,4-triphenyl-7,8-dihydro-2H-chromen-5(6H)-one **3c**} contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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