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Rapid Access of Alkynyl and Alkenyl Coumarins via a Dipyridinium Methylide and Propargylamine Cascade Reaction

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02674 Read Online

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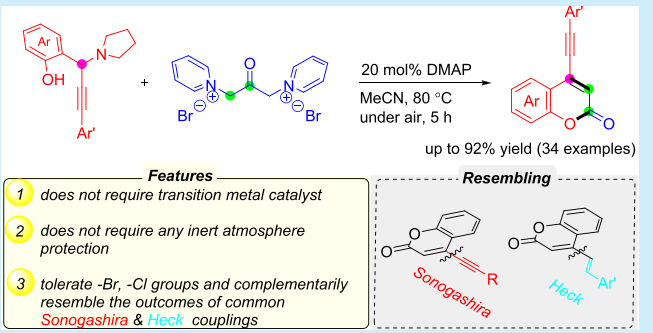
ABSTRACT: A DMAP-catalyzed cascade approach allowing facile assembly of alkynyl coumarins is reported. By virtue of reactive *o*-AQM (in situ generated from modular propargylamine) and a new synthetic equivalent of acyl carbene (from pyridinium ylide), the reaction proceeds smoothly to afford a variety of alkynyl coumarins in good-to-excellent yields. This transition-metal-free and oxidant-free process features moderate functional group tolerance, particularly the −Br group; thus, this protocol circumvents the inherent shortcomings of the existing Sonogashira coupling of coumarin triflates. This versatile method is also found to be applicable to the preparation of *β*-alkenyl coumarins, resembling the outcomes of the current Heck-type coupling reaction.



Coumarin scaffolds are abundantly found in many natural products and biologically active intermediates, and constitute one of the most important structural motifs for developing new pharmaceuticals.[1−3] Coumarins containing an unsaturated lactone skeleton are classically synthesized by aldol or Knoevenagel condensations.[4,5] A recent convergent synthetic tool, i.e., cross-coupling technology,[6] has emerged to allow rapid assembly of diversified coumarin structures. Particularly the alkynyl coumarins, which not only are found to be useful in pharmaceuticals[7] but also prevail in unique applications in functional organic materials, for instance laser dyes,[8,9] dye-sensitized solar cells (DSSCs),[10,11] organic light-emitting diodes (OLEDs),[12] semiconductors,[13] and photovoltaics,[14] are often synthesized by a Pd-catalyzed cross-coupling strategy.

With the electrophilic coumarin enol triflates made with expensive Tf_2O, the Sonogashira coupling of terminal alkynes proceeded well to give the alkynyl coumarins (Scheme 1a).[15−17] Wu also recently reported an improved procedure for the conversion of the coumarin −OH group to the −OTs moiety and subsequent coupling of terminal alkynes in a one-pot fashion.[18] Apart from pseudo halides, alkenyl bromides were found to be capable substrates for alkyne coupling as reported by Fairlamb (Scheme 1b).[19,20] These coumarin bromides were made by transforming the coumarin −OH moiety to the −Br group using $POBr_3$. In 2019, Knochel disclosed the application of alkynyl zinc pivalate nucleophiles for the construction of the $C_{(sp)}$−$C_{(sp2)}$ bond under the Ni catalyst system (Scheme 1c).[21] Despite the traditional cross-coupling between electrophilic and nucleophilic fragments, Hong recently showed a successful Pd-catalyzed oxidative coupling between two different nucleophiles (Scheme 1d).[22] Nonetheless, the aforementioned catalytic approaches usually require expensive transition metal catalyst systems and perform under inert atmospheric conditions, as well as often require prefunctionalization of coumarin to the corresponding electrophilic components using either Tf_2O or $POBr_3$. To circumvent the inherent difficulties, it is desirable to explore a new organocatalytic pathway, especially if it is complementary to the existing methods for assembling of the above pharmaceutically useful and materially valuable coumarin frameworks.

Propargylamine is highly versatile, as this structure can be simply attained by a three-component modular reaction of aromatic aldehyde, terminal alkyne, and amine.[23−25] Indeed, it exhibits rich entities of structural diversity. Inspired by this alkyne-containing precursor, we are intrigued by the possibility of it being favorably employed for rapid assembly of the alkynyl coumarin skeleton. Herein we report a DMAP-catalyzed cascade reaction between propargylamine and pyridinium ylide[26] (Scheme 1e). This process proceeds *via* the in situ generated *ortho*-alkynyl quinone methide (*o*-AQM)[27−30] intermediate from propargylamine under basic conditions and then continues the 1,4-conjugate addition and subsequent annulation process.

Received: August 11, 2020

Scheme 1. Modern Strategies for Accessing Alkynyl Coumarins

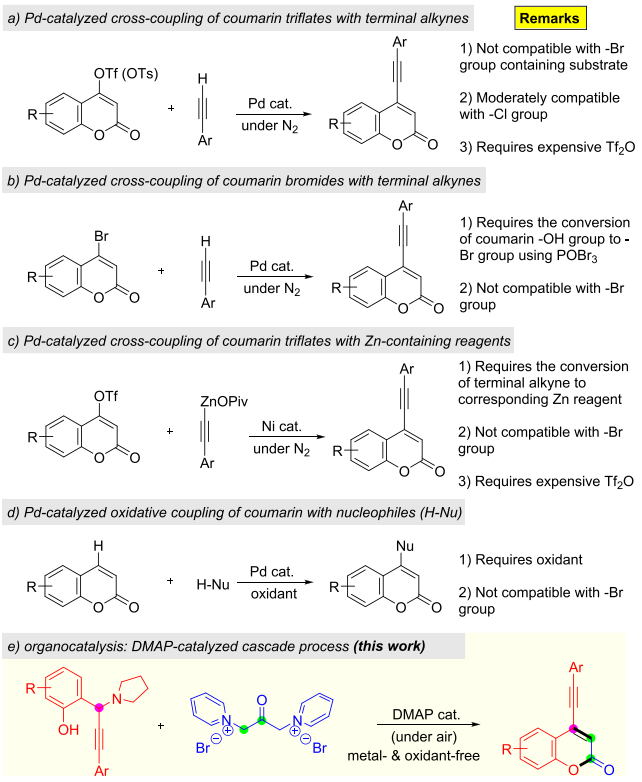
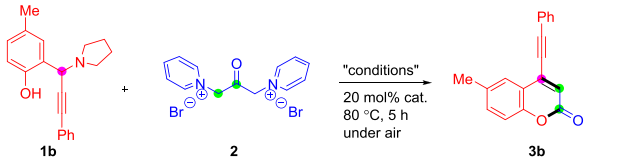


Table 1. Evaluation of Reaction Parameters[a]



entry	catalyst	solvent	yield (%)[b]
1	Et_3N	MeCN	83
2	DMAP	MeCN	92
3	DBU	MeCN	trace
4	DABCO	MeCN	37
5	Sparteine	MeCN	32
6	Na_2CO_3	MeCN	25
7	$NaHCO_3$	MeCN	16
8	NaOH	MeCN	trace
9[c]	DMAP	MeCN	33
10	DMAP	DCE	18
11	DMAP	DMF	34
12	DMAP	EtOH	78
13	DMAP	DMSO	28
14	DMAP	toluene	52
15[d]	DMAP	MeCN	8
16[e]	DMAP	MeCN	89
17[f]	DMAP	MeCN	61

[a]Reaction conditions: 4-methyl-2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)phenol (**1b**) (0.2 mmol), 1,1′-(2-oxopropane-1,3-diyl)bis-(pyridin-1-ium) bromide (**2**) (0.24 mmol), and catalyst (20 mol %) in solvent (3 mL) at 80 °C for 5 h. [b]Isolated yields were reported. [c]The catalyst loading was 10 mol %. [d]At 50 °C. [e]At 100 °C. [f]For 2 h.

We initially explored the new reagent, dipyridinium ylide **2**, as a two-carbon feedstock for assembling the coumarin scaffold. Thus, we employed propargylic amine **1b** and **2** as model substrates for this organocatalytic reaction (Table 1). In the presence of 20 mol % organocatalysts, for instance Et_3N and DMAP, the reaction proceeded smoothly to give an up to 92% product yield (entries 1−2). Nevertheless, DBU, DABCO, and sparteine were found to be less successful (entries 3−5). Apart from the organic bases, commonly used Na_2CO_3, $NaHCO_3$, and NaOH did not facilitate this transformation (entries 6−8). MeCN was the best solvent of choice among other common organic solvents screened, e.g., DCE, DMF, EtOH, DMSO, and toluene (entries 10−14 vs 2). There was no extra benefit of product yield at elevated reaction temperature, e.g., 100 °C (entry 16 vs 2).

Having the optimized reaction conditions in hand, we next explored the substrate scope (Scheme 2). In general, the coumarin products were obtained in good-to-excellent yield. Particularly noteworthy is that the −Br and −Cl groups remained intact during the course of the reaction. This outcome allows these products to be further modified by established cross-coupling strategies at a later stage. There was no significant electronic effect of the substituents displayed at the phenolic ring (products **3a**−**3d** and **3e**−**3h**). Likewise, the electronic property of the alkynyl arenes was also insignificant (products **3i**−**3l** vs **3m**−**3p**). It is important to show that the sterically hindered phenolic fragment did not affect the efficiency of the cyclization (products **3q**−**3s**). Even the highly sterically bulky *tert*-butyl group was well-tolerated (product **3r**). There were no steric influences at the alkynyl arenes as well (products **3t** and **3w**). Dihalo-substituents at either phenolic or alkynyl arene rings were also compatible (products **3s**−**3u**). The product **3t** was unambiguously characterized by single crystal X-ray crystallography. The highly electron-withdrawing nitro group did not affect the yield of coumarin scaffold assembly (products **3v** and **3x**). The possible gram-scale synthesis showed the potential practicability for large-scale preparation of substituted coumarins.

In addition to aromatic alkyne substituents, the applicability of other alkenyl-, thienyl-, and alkyl-containing substrates were examined (Scheme 3). It is worth noting that the conjugated enyne moiety was also well-suited in this catalyst system (product **3y**). There was no deleterious effect of a heterocyclic substrate under these reaction conditions (product **3z**).

Not only the alkynyl coumarin scaffold has rich application in material sciences, the corresponding alkenyl coumarin skeleton also displays unique photophysical properties.[31] Common modular assembly of these alkenyl coumarin units relies on the palladium-catalyzed Suzuki−Miyaura and Heck couplings of coumarin sulfonates/bromides with either alkenylboronic acids[32] or alkenes,[33] respectively. The inherent limitation of these existing protocols would be the incompatibility of −Br or −Cl groups. Indeed, it would be highly attractive if we can develop an organocatalytic method particularly fit for moderate functional group tolerance. Our further attempts of using dipyridinium ylide **2** as the acyl carbene surrogate led us to have a variety of halo-containing alkenyl coumarins (Scheme 4). There was no significant substrate electronic effect with regard to the desired product yields (products **5b**−**5f**). The steric effect, where the −Br group at the *ortho*-position to the phenolic group, was insignificant (product **5g**). It is noteworthy to show that this catalyst system displayed entire compatibility with −Br and −Cl groups. Thus it exhibits rich potential for subsequent functionalization using cross-coupling technology.

https://dx.doi.org/10.1021/acs.orglett.0c02674
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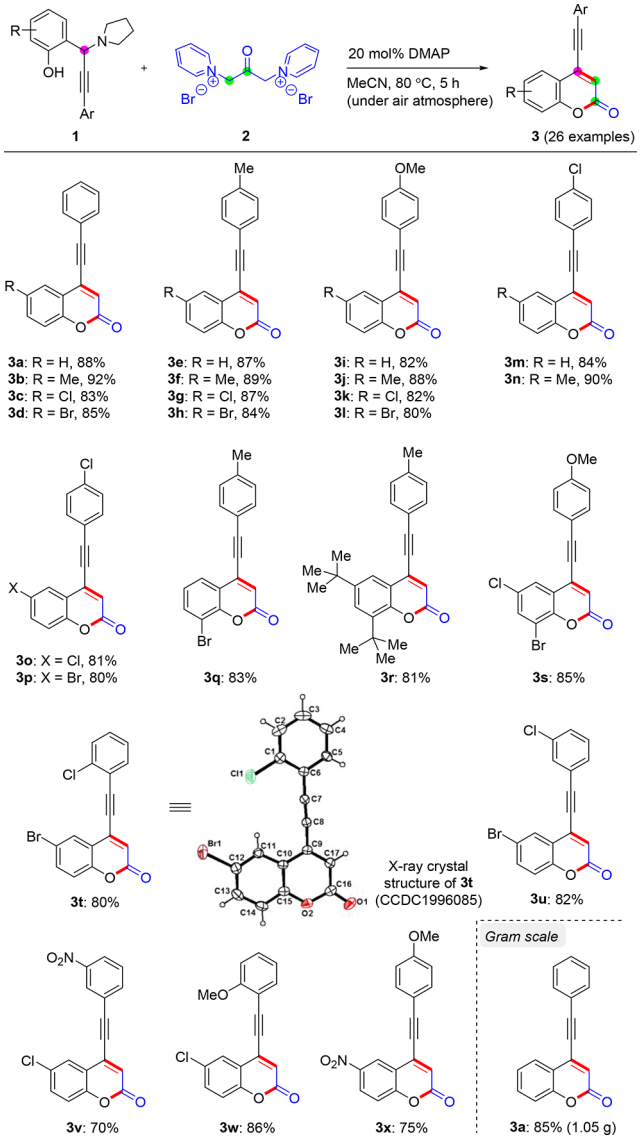
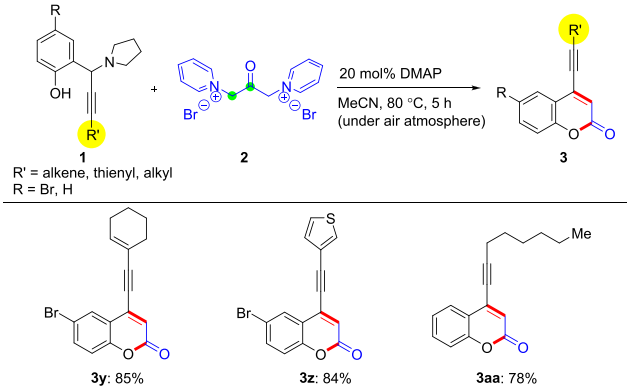
Scheme 2. Scope of Propargylamine Towards Coumarin Scaffold Assembly[a]



[a]Reaction conditions: propargylamines **1** (0.3 mmol), 1,1′-(2-oxopropane-1,3-diyl)bis(pyridin-1-ium) bromide (**2**) (0.36 mmol), and DMAP (20 mol %) in MeCN (3 mL) at 80 °C for 5 h. Isolated yields were reported.

In order to gain insight into the reaction mechanism, we performed the deuterium-labeling experiment (Scheme 5a). The H/D exchange of pyridinium methylide **2** was carried out in the presence of D_2O. ^1H NMR analysis revealed that all hydrogen atoms on the methylene group of **2** were completely exchanged with deuterium within 10 min. Further reacting of *d*-**2** with **1g** afforded the product *d*-**3g** in 85% yield. This experiment suggested that the reaction involves a 1,4 conjugate addition of pyridinium methylide to *o*-AQM, and subsequent intramolecular annulation proceeds. A proposed mechanism is shown in Scheme 5b. On the basis of precedent reports,[27,34] we postulate that this one-pot cascade reaction involves the initial deamination of the propargylamine **1a** and subsequently generates the *o*-AQM intermediate in the presence of the DMAP catalyst. The 1,4-conjugate addition of dipyridinium methylide to *o*-AQM proceeds to give intermediate **A**. The

Scheme 3. Scope of Alkenyl, Thienyl, and Alkyl Substituted Propargylic Amine for Accessing Coumarin Scaffolds[a]



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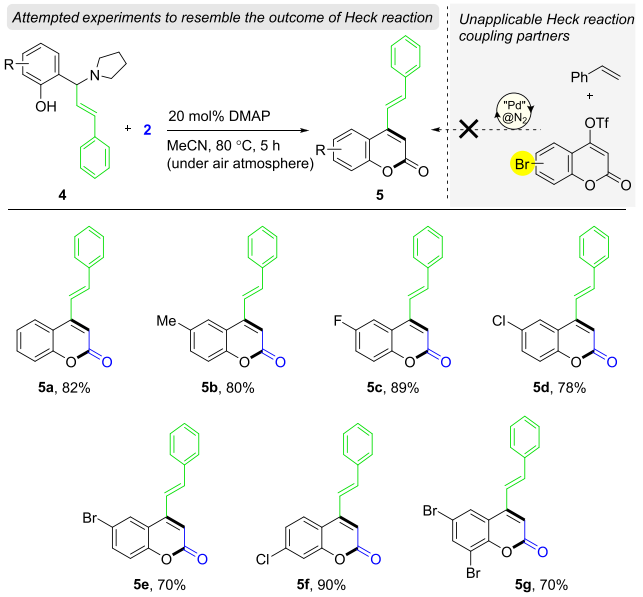
Scheme 4. Attempted Experiments for Resembling the Outcome of Heck Coupling Reaction[a]



[a]Reaction conditions: (*E*)-2-(3-phenyl-1-(pyrrolidin-1-yl)allyl)-phenols **4** (0.2 mmol), 1,1′-(2-oxopropane-1,3-diyl)bis(pyridin-1-ium) bromide (**2**) (0.24 mmol), and DMAP (20 mol %) in MeCN (3 mL) at 80 °C under air atmosphere for 5 h. Isolated yields were reported.

intramolecular nucleophilic addition of intermediate **B** affords the species **C**, which then converts to intermediate **D** upon release of alkylpyridinium salt by a mechanism similar to that involving the fission of *β*-carbonyl compound. Finally, intermediate **D** undergoes *β*-H elimination and C−N bond cleavage to deliver the product **3a**.

In summary, the manipulation of the physical properties of coumarin by installing alkynyl or alkenyl moieties has been found to be highly useful toward the advancement of material science. Precedent methods for accessing these structural motifs depend on the transition-metal-catalyzed cross-coupling of prefunctionalized coumarin triflate/tosylate/bromide with an alkyne or alkene under an inert atmosphere, or the oxidative

https://dx.doi.org/10.1021/acs.orglett.0c02674
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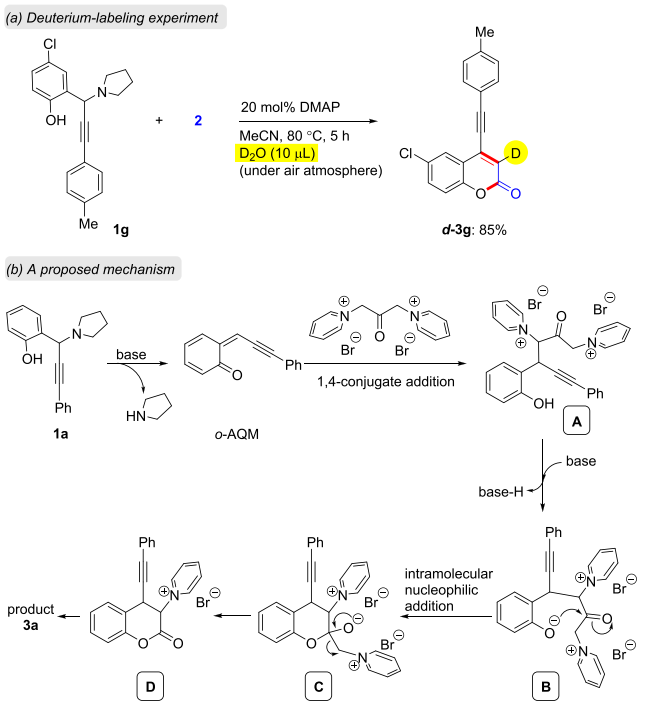
Scheme 5. Deuterium-Labeling Experiment and Proposed Mechanism



coupling between two nucleophilic fragments in the presence of an oxidant. In fact, it would be highly attractive to develop an organocatalytic method for tackling this issue, in which it features transition metal-free and oxidant-free conditions, as well as the reaction can be conveniently carried out under an operationally simple air atmosphere. We have succeeded in showing that the new acyl carbene surrogate, the dipyridinium ylide, was able to react modular *ortho*-alkynyl quinone methide (*o*-AQM) in generating a variety of alkynyl coumarins. This metal-free process does not require inert atmosphere protection and allows moderate functional group tolerance, particularly the −Br and −Cl groups; thus, this protocol is complementary to the inherent shortcomings of the existing Sonogashira coupling of coumarin triflates. This versatile method is also found to be applicable to the preparation of *β*-alkenyl coumarins, resembling the outcomes of current Heck-type coupling reactions. We believe this finding will be versatile and offer a breadth of interest to organic material scientists working in coumarin-related modifications and their corresponding material advancements.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02674.

Experimental procedures and spectroscopic data for all compounds (PDF)

Accession Codes

CCDC 1996085 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Research Grants Council of Hong Kong (GRF: 14307418-18P), the CUHK Direct Fund (4442353) and the Anhui Provincial Natural Science Foundation (No. 1808085MB41) for financial support. We are thankful for the financial support from the Innovation and Technology Commission (HKSAR, China) to the State Key Laboratory of Synthetic Chemistry.

■ DEDICATION

Dedicated to Prof. Albert S. C. Chan on the occasion of his 70th birthday.

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