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DMAP-Catalyzed Annulation Approach for Modular Assembly of Furan-Fused Chromenes

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03374 Read Online

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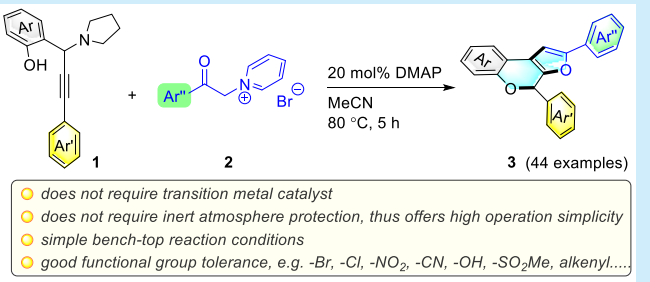
ABSTRACT: With a tandem DMAP-catalyzed reaction between *o*-AQM, in which it is generated in situ from propargylic amine, and acyl carbene surrogate (from pyridinium ylide), a variety of polyarylated chromenes are assembled in good yields. This process does not require transition-metal catalyst and exhibits easy manipulation of the arene group and good functional group compatibility, particularly the −Br group which can be further transformed to other functionalities by cross-coupling reactions. The modular feature of *o*-AQM substrates and the simple operation procedures add further advantages to this synthetic method.



Heterocycles embodying a chromene framework are often found in many natural products and pharmaceutically useful intermediates.[1] In particular, chromenes composed of a furan moiety display a range of activities in biological investigations and drug explorations,[2] for example, antibacterial,[3] -fungal,[4] -HIV,[5] -inflammatory,[6] and -osteoporotic actions.[7] There are two typical regioisomers of furochromene with respect to the reciprocal orientation of fused furan, namely furo[3,2-*c*]chromene and furo[2,3-*c*]chromene (Scheme 1a). It is worth noting that the furo[2,3-*c*]chromene isomer expresses exclusive activity in the treatment of liver diseases.[8] Recently, transition-metal-catalyzed strategies have emerged targeting arene-substituted furo[3,2-*c*]chromenes (Scheme 1b). By employing alkynylchromone as the key starting material, Larock[9] and Hu[10] have independently developed gold-catalyzed reaction systems for constructing furo[3,2-*c*]chromenes. Ma has disclosed a Rh-catalyzed two-step process by using diazochromanone and alkynes as starting material.[11]

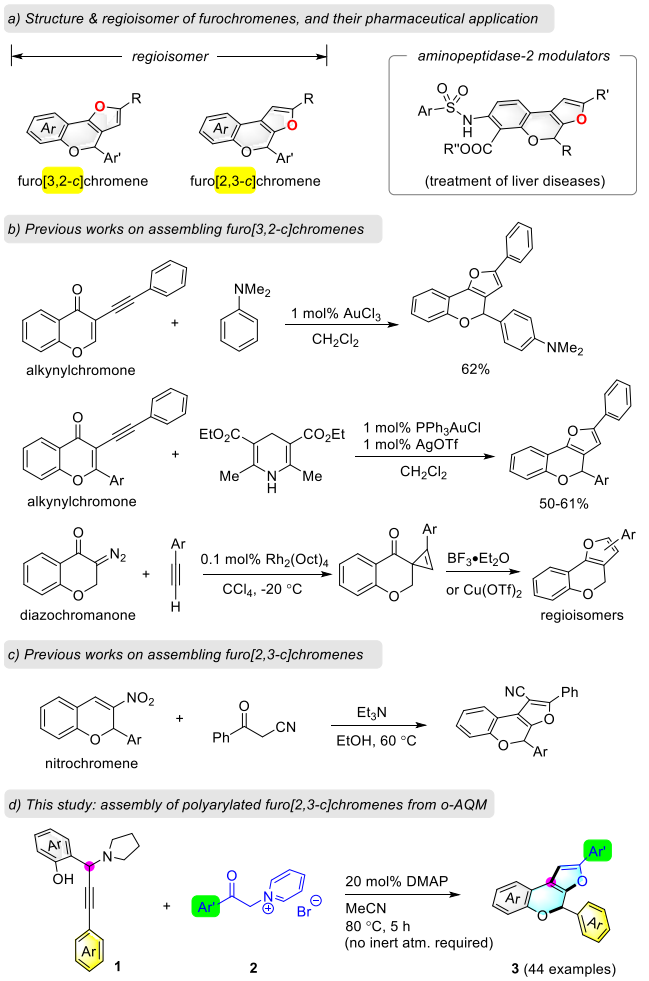
In conrast to furo[3,2-*c*]chromene, methods to access the furo[2,3-*c*]chromene skeleton remain sporadically investigated: The only examples were reported by Yan showing the reaction between nitrochromene and acylacetonitrile (Scheme 1c).[12] It would be of high interest to explore a synthetic method for assembling this unique furo[2,3-*c*]chromene bearing the following features: (i) transition-metal-free; (ii) capable of using modular substrates to allow broad product structure diversity; (iii) requiring only simple organic catalyst; (iv) operationally simple. *o*-Alkynyl quinone methide (*o*-AQM)[13−15] is a reactive intermediate generated in situ from modular propargylamines, which can be straightforwardly obtained via a three-component reaction between aromatic aldehyde, terminal alkyne, and amine.[16−18] Inspired by the rich reactivity of *o*-AQM for annulation and the chemistry of acylpyridinium methylides involving *O*-cyclization processes,[19] we are intrigued whether these two substrates could be combined to enable facile construction of structurally diversified furan-fused chromenes. In continuing our research interest in polycycle assembly[20,21] and *o*-AQM chemistry,[22−24] we here show our development of a tandem reaction between propargylamine and pyridinium ylide catalyzed by DMAP (Scheme 1d). This transition-metal-free procedure features simple operation (can be performed without inert atmosphere protection) and good functional group tolerance (e.g., −Br, −Cl, $-NO_2$, −CN, −OH, $-SO_2Me$, and alkene).

We initially test the feasibility of this reaction by employing propargylamine **1a** and *N*-phenacylpyridinium bromide (**2a**) as the exemplary substrates (Table 1). Upon surveying common organic bases, DMAP delivered the best product yield (entries 1−5). The use of an inorganic base such as K_2CO_3 and KOH or not led to decreased yields (entries 6−8). A screening of several solvents revealed that MeCN is the best (entry 2 vs entries 9−14). Lowering the reaction temperature to 60 °C gave decreased product yield (entry 15). Increasing the reaction temperature or catalyst loading failed to improve the yield (entries 16 and 18). When the amine moiety of **1a** was

Received: October 9, 2020

https://dx.doi.org/10.1021/acs.orglett.0c03374
Org. Lett. XXXX, XXX, XXX−XXX

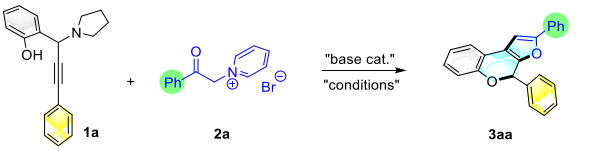
Scheme 1. Modern Approaches for Accessing Furochromenes



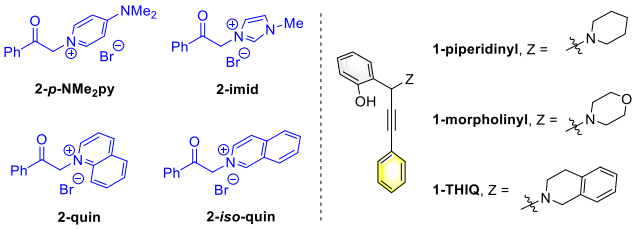
altered to piperidinyl, morpholinyl, or tetrahydroisoquinolinyl in 1-piperidinyl, 1-morpholinyl, or 1-THIQ, respectively, yields of the desired product were decreased (entries 20−22). Other relevant acyl carbene surrogates such as 2-*p*-NMe$_2$py, 2-imid, 2-quin, and 2-*iso*-quin were evaluated, and the pyridinium methylide **2a** was found to be the best choice (entry 2 vs entries 23−26).

With the optimized reaction conditions, we next investigated the substrate scope of propargylamines **1** (Scheme 2). Generally, the desired chromene products were obtained in high yields. It is notable to show that the −Br and −Cl groups, present at either the phenolic or the alkynyl arene moieties, remained intact in the reaction (products **3ca**, **3da**, **3ga**, **3ha**, **3ka**, **3la**, **3pa**, **3qa**). This beneficial outcome offers us an excellent opportunity to subsequently amend the product functionality by established cross-coupling protocols.[25] The product structure of **3ga** was characterized by single-crystal X-ray crystallography. The electronic nature of the substituents present at the phenolic and the alkynyl arene moieties showed no obvious effect in the reaction. Multiple halogens located at either the phenolic or the alkynyl arene rings were also tolerable (products **3sa** and **3va**), though the highly electron-deficient nitro group provided slightly lower yield (product **3ma**). The steric hindrance of the substituents also showed a negligible effect on the yield, and even the extremely steric bulky *tert*-butyl group was also well-suited (product **3ta**). The

Table 1. Evaluation of Reaction Parameters[a]



entry	catalyst	solvent	yield[b] (%)
1	Et_3N	MeCN	48
2	DMAP	MeCN	84
3	DBU	MeCN	24
4	DABCO	MeCN	62
5	pyridine	MeCN	61
6	K_2CO_3	MeCN	25
7	KOH	MeCN	16
8		MeCN	36
9	DMAP	toluene	60
10	DMAP	DCE	43
11	DMAP	DMF	66
12	DMAP	EtOH	58
13	DMAP	DMSO	74
14	DMAP	THF	68
15[c]	DMAP	MeCN	37
16[d]	DMAP	MeCN	83
17[e]	DMAP	MeCN	70
18[f]	DMAP	MeCN	83
19[g]	DMAP	MeCN	64
20[h]	DMAP	MeCN	68
21[i]	DMAP	MeCN	62
22[j]	DMAP	MeCN	15
23[k]	DMAP	MeCN	45
24[l]	DMAP	MeCN	53
25[m]	DMAP	MeCN	40
26[n]	DMAP	MeCN	42



[a]Reaction conditions: 2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)phenol (**1a**) (0.3 mmol), *N*-phenacylpyridinium bromide (**2a**) (0.36 mmol), and catalyst (20 mol %) in solvent (3 mL) at 80 °C for 5 h under air atmosphere. [b]Isolated yields were reported. [c]At 60 °C. [d]At 100 °C. [e]For 2 h. [f]The catalyst loading was 50 mol %. [g]The catalyst loading was 10 mol %. [h]1-Piperidinyl was used instead of **1a**. [i]1-Morpholinyl was used instead of **1a**. [j]1-THIQ was used instead of **1a**. [k]2-*p*-NMe$_2$py was used instead of **2a**. [l]2-Imid was used instead of **2a**. [m]2-Quin was used instead of **2a**. [n]2-*iso*-Quin was used instead of **2a**.

reaction with 3-bromo-2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)phenol (**1x**) provided a relatively poor product yield (product **3xa**), which might be due to the 3-subsituted phenolic moiety that is known to hinder the *o*-AQM formation. Other than aromatic alkyne substituents, alkenyl-, thienyl-, and alkyl-containing substrates were also examined. The conjugated enyne moiety was well-compatible in this reaction (product **3ya**) and so was the heterocyclic thienyl-bearing substrate (product **3za**). Nevertheless, only a single ring-closure step was observed when the alkyl-containing

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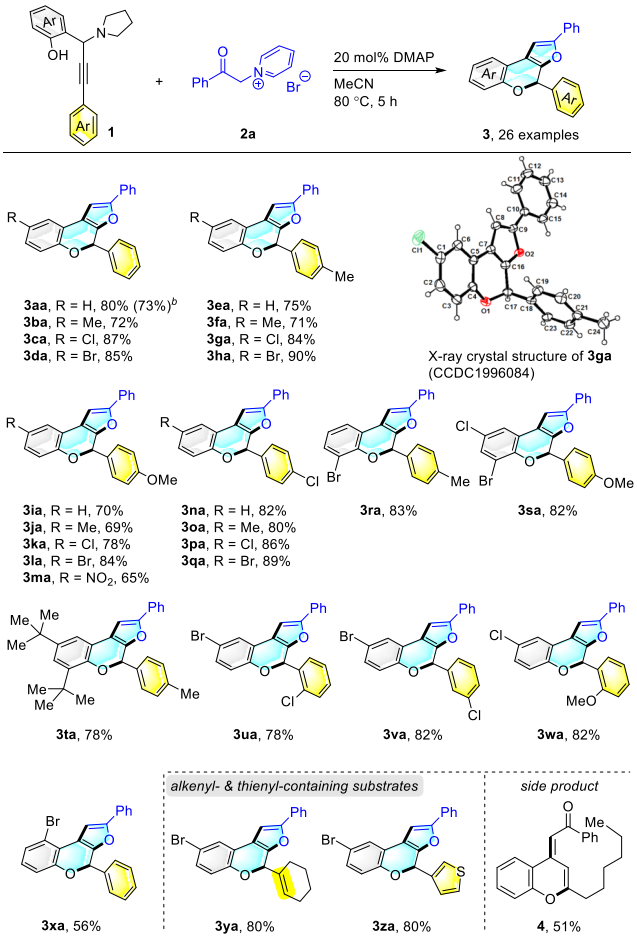
Scheme 2. Scope of Propargylamine 1[a]



[a]Reaction conditions: propargylamines **1** (0.3 mmol), pyridinium methylide **2a** (0.36 mmol), and DMAP (20 mol %) in MeCN (3 mL) at 80 °C for 5 h under benchtop air atmosphere. Isolated yields were reported. [b]A gram-scale synthesis; 1.18 g of product **3aa** was delivered.

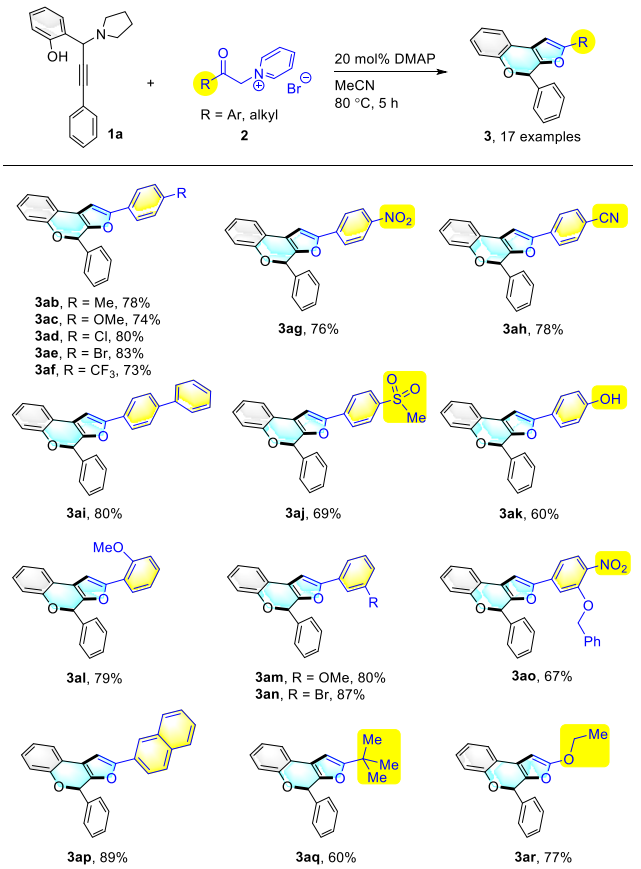
alkyne substrate was employed (product **4**).[26] A gram-scale experiment was performed to show the practicability of the new reaction system, and the product **3aa** was obtained in 73% yield.

Subsequently, we explored the scope of pyridinium methylides **2** in this reaction (Scheme 3). Substituents of both electron-withdrawing and electron-donating nature at the Ar group of **2** were well-tolerated in the reaction (products **3ab**−**3af**). Functional groups such as bromo, nitro, nitrile, methanesulfonyl, and hydroxyl moieties were all compatible (products **3ae**, **3ag**, **3ah**, **3aj**, and **3ak**, respectively). 2-Naphthyl substrate delivered the desired product in 89% yield (product **3ap**). Notably, alkyl- and alkoxyl-containing pyridinium methylides were tolerated, and the corresponding products were afforded in fair to good yields (products **3aq** and **3ar**).

In order to put forward of this synthetic strategy, we test the feasibility of a direct three-component assembly of the product (Scheme 4). To our delight, the reaction of α-bromoacetophenone, pyridine, and **1a** gave the intended product **3aa** in 60% yield.

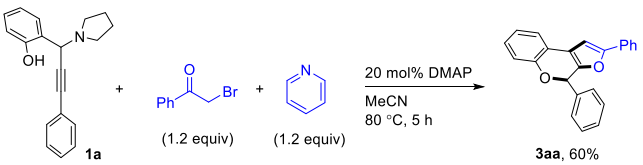
In order to have more insight toward the reaction mechanism, we carried out the deuterium-labeling experiment

Scheme 3. Scope of Aryl-Containing Pyridinium Methylide 2[a]



[a]Reaction conditions: propargylamines **1a** (0.3 mmol), pyridinium methylides **2** (0.36 mmol), and DMAP (20 mol %) in MeCN (3 mL) at 80 °C for 5 h under benchtop air atmosphere. Isolated yields were reported.

Scheme 4. Three-Component Strategy for Assembling the Furan-Fused Chromene 3aa[a]



[a]Reaction conditions: 2-(3-phenyl-1-(pyrrolidin-1-yl)prop-2-yn-1-yl)-phenol (**1a**) (0.2 mmol), 2-bromo-1-phenylethan-1-one (0.24 mmol), pyridine (0.24 mmol), and DMAP (20 mol %) in MeCN (2 mL) at 80 °C for 5 h under benchtop air atmosphere. Isolated yield was reported.

(Scheme 5a). The H/D exchange experiment of **2a** was performed in the presence of D_2O. Spectroscopic data showed that almost all H atoms on the methylene group of **2a** were exchanged with deuterium in 10 min. The deuterated product ***d*$_2$-3ga** was obtained in 80% yield. A proposed mechanism is presented in Scheme 5b. With reference to literature precedents,[13] we presume that this one-pot tandem reaction involves the initial deamination of the propargylic amine **1′** to generate the *o*-AQM intermediate under thermal conditions. The 1,4-conjugate addition of pyridinium methylide **2a′** to *o*-AQM occurs to give species **A**. Subsequent elimination

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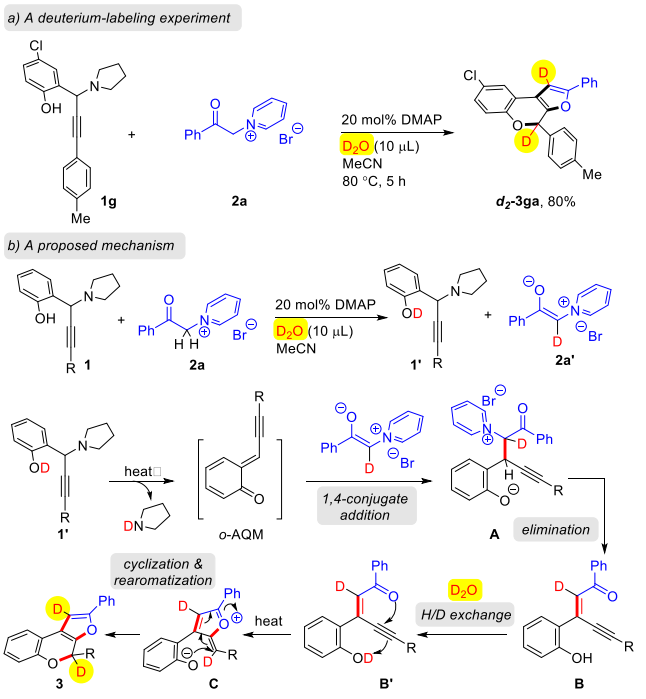
Scheme 5. Deuterium-Labeling Experiment and a Proposed Mechanism



proceeds to afford intermediate **B**. The intermediate **C** is then formed under thermal conditions. The next cyclization and rearomatization occur to form the desired product **3**.

In summary, we have demonstrated that the pyridinium ylide, an acyl carbene surrogate, was able to react with modular *o*-alkynyl quinone methide (*o*-AQM) via two ring-closure steps to give a diversity of arene-containing furochromenes in good yields. A three-component strategy was also demonstrated based on this reaction. This transition-metal-free process does not require inert atmosphere protection and shows good functional group tolerance (for instance, −Br, −Cl, $-NO_2$, −CN, −OH, $-SO_2Me$, alkenyl, and thienyl). We anticipate that this method would be a useful synthetic tool for chromene-related studies in related fields such as organic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03374.

Experimental procedures and spectroscopic data for all compounds (PDF)

Accession Codes

CCDC 1996084 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.

https://dx.doi.org/10.1021/acs.orglett.0c03374
Org. Lett. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

We thank the Science, Technology and Innovation Commission of Shenzhen Municipality (JCYJ20180307150641423) and Research Grants Council of Hong Kong (GRF: 14304519-19P), the CUHK Direct Fund (4053388), 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. Henry N. C. Wong on the occasion of his 70th birthday.

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