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Metal-Free, DBU-Mediated, Microwave-Assisted Synthesis of Benzo[*c*]xanthones by Tandem Reactions of Alkynyl-1,3-diketones

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Abstract: A base-mediated, green, microwave-assisted efficient preparation of a diverse benzoxanthone library from variety of readily accessible γ-alkynyl 1,3-diketones is reported. The synthesis is based on tandem reactions involving intramolecular cyclization, propargyl-allenyl isomerization, and electrocyclization in one pot. Some of the benzoxanthones are also synthesized by the one-pot reaction of 1,3-diketone and alkynyl bromide under basic heating conditions. This transformation also results in the construction of one new C-C bond and one new C-O bond.

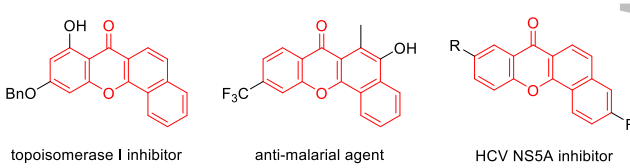
Keywords: Cyclization; Isomerization; Microwave chemistry; Synthetic methods; Tandem reactions

Introduction

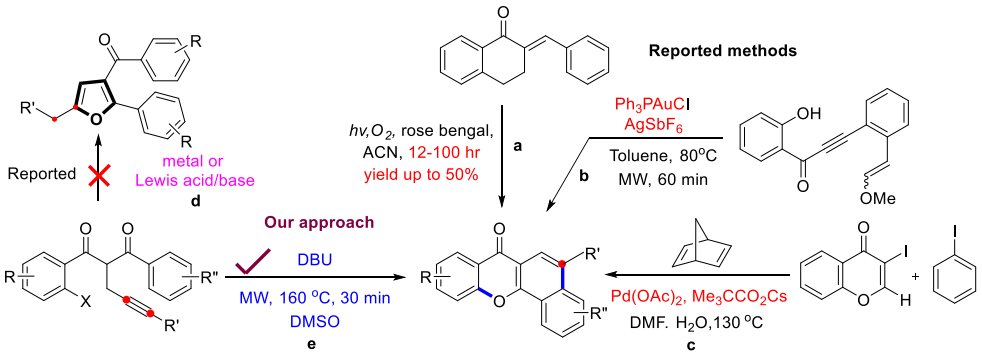
There is growing interest in the preparation of polycyclic heteroaromatic molecules because of their wide applicability in material and pharmaceutical sciences. Xanthone is the core structure of secondary metabolites in higher plants and microorganisms as well as in other pharmaceutically active compounds.[1] In recent decades, these secondary metabolites have been demonstrated to have diverse biological properties, including anti-hypertensive,[2] anti-oxidative,[3] anti-thrombotic,[4] and anti-cancer[5] activities. Additionally, the benzoxanthone template is a promising building motif for the development of several therapeutically important molecules (Fig. 1).[6-8] Moreover, xanthones possess distinct photophysical properties, implying their significance in the design of fluorescent compounds and dyes.[9]

Over the years, notable progress has been made in xanthone synthesis by utilizing different substrates and methods.[10] However, there is a scarcity of research on the preparation of benzo[*c*]xanthones.[11] Zheng et al. synthesized benzo[*c*]xanthones via the photocatalyzed

Figure 1. Selected biologically active benzo[*c*]xanthones.



reaction of 2-benzylidene-1-tetralones (Scheme 1, a).[11a] Liu and Cheng demonstrated a Au(I)-catalyzed Michael addition/6-endo-trig cyclization/aromatization approach (Scheme 1, b).[11b] Hu and co-workers reported palladium-catalyzed cascade reactions of 3-iodochromones with aryl iodides in the presence of norbornadiene (Scheme 1, c)[11c] and a base, microwave-assisted reaction of 2-methyl-3-(1-alkynyl)chromones with electron-deficient chromone-fused dienes.[11d] Wang and He described the Diels-Alder reactions of arynes with 2-styrylchromones for the generation of benzo[*c*]xanthones.[11e] The other reported protocols involved multiple procedures and various benzannulation approaches for the synthesis of



Scheme 1. Reported synthesis strategies for benzoxanthones and our approach.

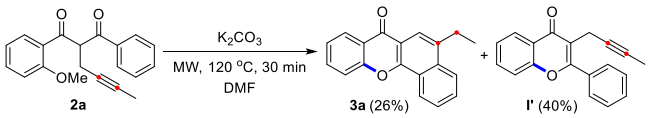
the desired benzo[*c*]xanthones.[12] Although the reported methods allow for efficient benzo[*c*]xanthone formation, they have certain drawbacks such as long reaction time with low yields;[11a,f,12d] need for expensive metal catalysts[11b-c,12g] and air/moisture-sensitive reactants;[11e,12d,12g] multiple/tedious substrate preparation steps;[11b-c] limited substrate scope (applicable only to 3-(furan-2-yl)-2-phenyl-4*H*-chromen-4-one, only one derivative is reported);[12f,12g] and multistep harsh synthetic routes.[12a-e] Therefore, a safe, expedient, atom-economic, and environmentally benign methodology for the synthesis of benzo[*c*]xanthones is highly desirable.

Microwave (MW) irradiation has proven effective in enhancing the reaction rate, particularly in reactions that require high-temperature and high-pressure conditions.[13] Additionally, tandem reactions have emerged as an important tool for the preparation of complex natural products and biologically valuable molecules, as well as for the construction of carbon−carbon or carbon−heteroatom bonds.[10f,14] Previous studies also suggest the use of the versatile γ-alkynyl groups of enynones for the preparation of substituted furans via the generation of allene and carbene intermediates under acidic, basic, or metal catalyst (Pd, Cu, Rh, or Zn) conditions (Scheme 1, d).[15] While investigating propargyl-based strategies for heterocyclic synthesis, we envisioned a novel synthetic route to benzoxanthones, wherein tandem reactions, intramolecular cyclization, and electrocyclization could be conducted. As mentioned earlier, the use of γ-alkynyl 1,3-diketones for furan synthesis through intramolecular cyclization is well known.[15] However, to the best of our knowledge, this is the first investigation on the use of γ-alkynyl 1,3-diketones to synthesize benzoxanthones.

Herein, we report novel, base-mediated, microwave-assisted tandem reactions to construct benzoxanthone frameworks from γ-alkynyl 1,3-diketones (Scheme 1, e). This metal-free, green synthetic route provides efficient access to a variety of benzoxanthones in excellent yields.

Results and Discussion

We began our investigation by treating 2-butynyl 1,3-diketone **2a** with K_2CO_3 in DMF under microwave irradiation at 120 °C (Table 1, entry 1). This reaction led to the formation of benzoxanthone **3a** and intramolecular cyclization product **I'** in 26% and 40% yields, respectively (Scheme 2). Initially, we assumed the formation of substituted furan,[15] but the generation of benzoxanthone and an interesting intermediate **I'**

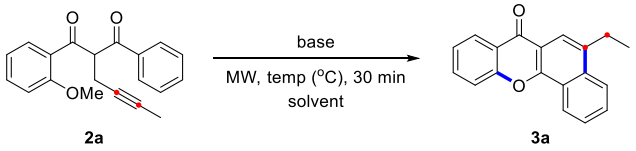


Scheme 2. Initial attempt for the generation of benzoxanthone.

prompted us to further investigate the present protocol. When the reaction was performed in DMSO in the presence of K_2CO_3 at elevated temperature (160 °C), the yield of **3a** improved significantly to 74% (Table 1, entry 2). The structure of **3a** was confirmed by X-ray crystal analysis.[16] With these preliminary exciting results in hand, we further optimized the reaction conditions using **2a** as the model reaction substrate in the presence of various bases and solvents. Weak inorganic bases (e.g., Cs_2CO_3, K_3PO_4, and KOAc) were found to initiate the tandem reaction (Table 1, entries 3–5). However, a stronger base (e.g., NaH) produced an unidentified mixture (Table 1, entry 6). The use of lithium bases (e.g., lithium *tert*-butoxide and lithium hydroxide) provided the desired products, albeit in moderate yields (Table 1, entries 7 and 8). We subsequently screened a range of organic bases such as secondary amines (Et_2NH and DIPA) and tertiary amines (Et_3N, DIPEA, DABCO, DBU, and DBN) in order to assess their ability to initiate the expected tandem reaction (SI, Table S1). Et_3N, DIPEA, and pyridine failed to trigger the reaction, as evidenced by the recovery of the starting material. Interestingly, sterically hindered strong amidine bases such as DBU and DBN triggered the expected tandem reaction and afforded the desired product **3a** in excellent yields (Table 1, entries 11, 12). Among all the bases evaluated, DBU (93%), DBN (91%), and KOAc (90%) gave excellent product yields under microwave irradiation. The reactivity of organic bases may play an important role in this transformation. DBU being stable, strong, and with the pK_a value of 13.5 was a superior base for

the current protocol. In the absence of microwave irradiation, benzoxanthone **3a** was formed but in lower yield, after a prolonged reaction (Table 1, entry 13). This result revealed that microwave irradiation is crucial for the current transformation. Subsequent optimization efforts revealed that the amount of DBU, reaction temperature, and type of solvent significantly affected the reaction yields (Table 1, entries 14 to 20). For example, adding two equivalents of DBU to the reaction afforded **3a** in excellent yield (93%). Among the various solvents screened in this study, DMSO proved the most effective under microwave irradiation. With the optimized reaction conditions in hand, we next treated **2a** with DBU (2.0 equiv.) and DMSO as a solvent in a sealed microwave reactor maintained at 160 °C (150 W) for 30 min (Table 1, entry 11). Then, we investigated the scope and generality of the current reaction. For this one-pot tandem reaction, a variety of γ-alkynyl 1,3-diketones were evaluated. Overall, a wide range of γ-alkynyl 1,3-diketones (**2a**–**2ab**) bearing an electron-donating or electron-withdrawing substituent on the phenyl ring of the diketone group were well tolerated under the reaction conditions. The corresponding benzoxanthones (Table 2, **3a**–**3ab**) were furnished in good yields. The yields of the benzoxanthones formed from **2f**, **2i**, **2p**, and **2q**, which contained a methoxy group on the phenyl ring, were

Table 1. Optimization of conditions for tandem reaction. [a]



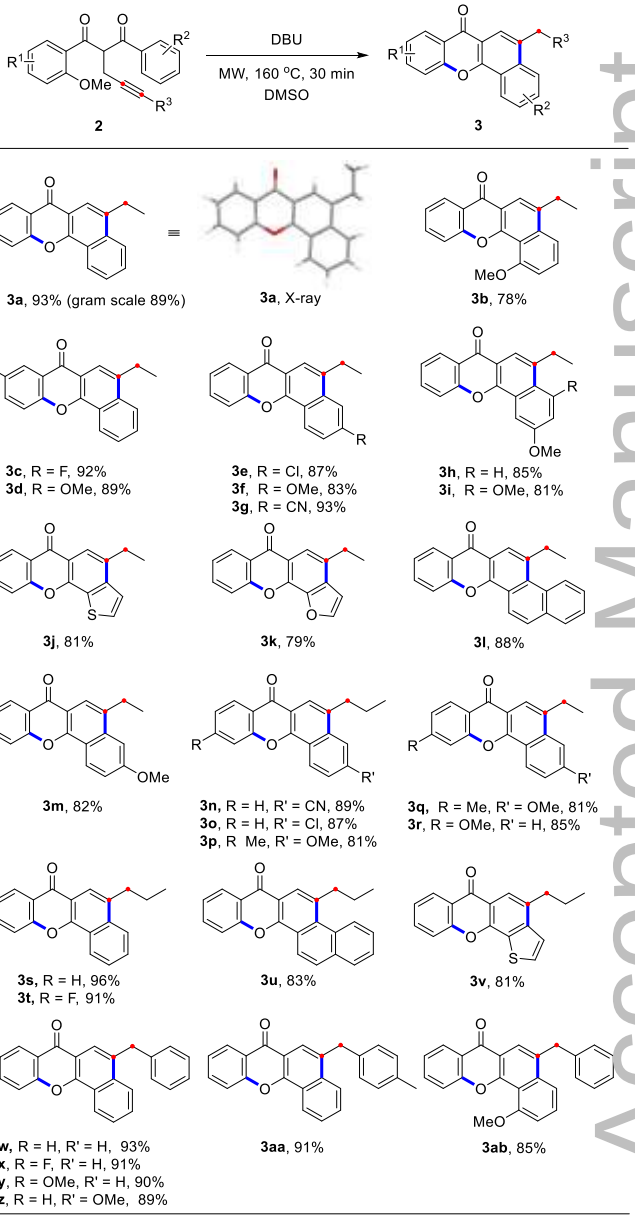
2a **3a**

Entry	Base	Solvent	Temp (°C)	Yield (**3a**, %)[a]
1	K_2CO_3	DMF	120	26[b]
2	K_2CO_3	DMSO	160	74[b]
3	Cs_2CO_3	DMSO	160	85[b]
4	K_3PO_4	DMSO	160	58
5	KOAc	DMSO	160	90[b]
6	NaH	DMSO	160	mixture
7	LiOH	DMSO	160	54
8	LiO^{t}Bu	DMSO	160	41
9	DIPEA	DMSO	160	NR[d]
10	DABCO	DMSO	160	34
11	**DBU**	**DMSO**	**160**	**93[b]**
12	DBN	DMSO	160	91[b]
13	DBU	DMSO	160	57[c]
14	DBU	1,4-Dioxane	160	NR[d]
15	DBU	DMF	160	65[b]
16	DBU	Xylene	160	54
17	DBU	DMSO	120	59
18	DBU	DMSO	140	77
19	DBU (1.0 equiv.)	DMSO	160	55
20	DBU (0.5 equiv.)	DMSO	160	40

[a]Reaction conditions: **2a** (0.5 mmol), base (1.0 mmol), and 2.0 mL of solvent. Yields were determined by the ^{1}H NMR integration method using dibromomethane as an internal standard. [b]Isolated yield. [c]Absence of microwave irradiation at 160 °C for 6 h. [d]No reaction.

comparatively lower than those of the benzoxanthones formed from **2a** and **2s** (without a methoxy group). Furthermore, γ-alkynyl 1,3-diketones **2j**, **2k**, and **2v** substituted with heteroaryls such as furanyl and thiophenyl rings successfully underwent the tandem reactions, affording the respective benzoxanthones **3j**, **3k**, and **3v** in good yields. Gratifyingly, other γ-alkynyl 1,3-diketones such as 2-pentynyl 1,3-diketones (**2n**–**2p**, **2s**–**2v**) and 3-phenyl-2-propynyl 1,3-diketones (**2w**–**2ab**) bearing ethyl or phenyl moieties on the terminal alkyne gave benzoxanthones **3n**–**3p** and **3s**–**3ab** in good yields (Table 2).

Table 2. Synthesis of benzoxanthones from γ-alkynyl 1,3-diketones.[a]



[a]Reaction conditions: **2** (0.5 mmol), DBU (1.0 mmol), and DMSO (2.0 mL) under microwave conditions at 160 °C for 30 min.

The current protocol could be successfully applied to γ-alkynyl 1,3-diketones incorporated with *ortho*-substituted halogens, and the target benzoxanthones were obtained in acceptable yields (Scheme 3, a). Interestingly, in the above conversions, there was no

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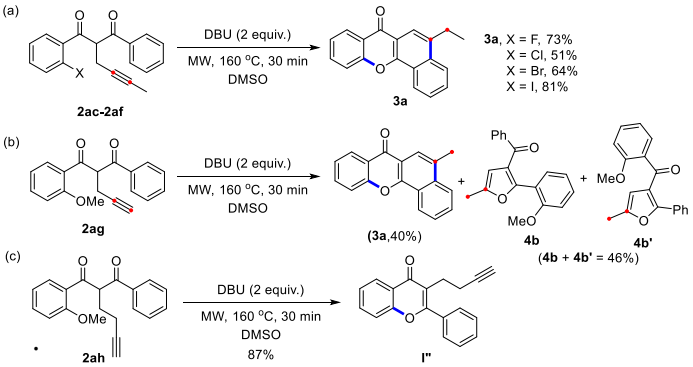
exclusive formation of substituted furans[15] and the corresponding benzoxanthones formed, except when treatment with 2-propynyl-1,3-diketone **2ag** generated a mixture of substituted furan and benzoxanthone in 46% and 40% yields, respectively (Scheme 3, b). The use of 3-butynyl 1,3-diketone **2ah** in the present reaction led to an intramolecular cyclization product 3-(3-butynyl) chromone **I**" (Scheme 3, c). We also investigated the feasibility of the current study by conducting the one-pot reaction of 1,3-diketone with alkynyl halides to produce benzoxanthone. The primary screening results (SI, Table S5) indicated that in the presence of DBU as a base under microwave irradiation, benzoxanthone **3a** was formed but in low yield (28%). Gratifyingly, when a combination of NaI and Cs_2CO_3 was used under heating conditions, benzoxanthone was formed in moderate yield (SI, Table S5, entry 5, 61%). We employed these conditions to prepare a few representative examples for a one-pot strategy, as shown in Scheme 4. The practicability of the present method was demonstrated by performing the reaction on a one-gram scale. The desired benzoxanthone was formed in excellent yield (Table 2, **3a**).

Scheme 3. Scope of various substrates for DBU-promoted tandem reactions.

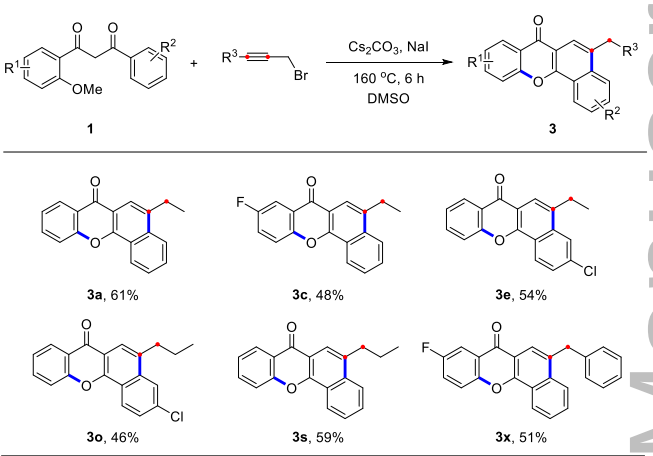


We also demonstrated the synthesis of substituted furans from γ-alkynyl 1,3-diketones under microwave irradiation. Specifically, when *p*-TSA or a metal catalyst $Pd(OAc)_2$ was added to the reaction, the furan derivatives were obtained in satisfactory yields (Scheme 5).[15]

Further, we attempted the treatment of *o*-methoxyphenyl diketone (in the absence of a substituted methylene alkyne) under the current reaction conditions. To our delight, the corresponding flavones were formed in excellent yields (Scheme 6). Thus, the present strategy is also a suitable alternative to traditional flavone synthesis methods.[17]

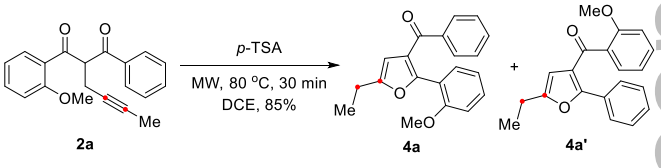
We then performed various control experiments to investigate the reaction mechanism (Scheme 7). The addition of a radical scavenger (2,6-ditert-butyl-4-methylphenol BHT) had no observable effect on the outcome of the reaction, suggesting that the reaction does not proceed via a radical intermediate. Additionally, we isolated 3-(2-butynyl) chromone intermediate **I'**, which when treated independently with DBU yielded the expected benzoxanthone. The formation of flavone derivatives involving *O*-arylation (cyclization), followed by demethoxylation, is reported. [18] We believe that a similar process is responsible for the generation of **I'**, which upon subsequent reactions, affords benzoxanthone. This was further confirmed by the observation of the methanol signal in the NMR and GC-MS spectra of the crude reaction mixture. Furthermore, when the reaction was conducted in the presence of two equivalents of D_2O, deuterium atoms were incorporated at two separate positions in benzoxanthone product **3a**', i.e., at the phenylic (9%, *d*-incorporation) and benzylic positions (27%, *d*-incorporation), revealing the *in situ* formation of an allene intermediate.

Scheme 4. One-pot reaction involving 1,3-diketones and propargyl bromide.[a]

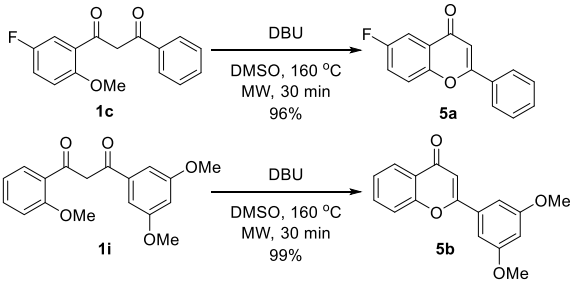


[a]Reaction conditions: **1** (0.4 mmol), alkyne (0.4 mmol), Cs_2CO_3 (1.2 mmol), NaI (1.2 mmol), and DMSO (2.0 mL) under heating at 160 °C for 6 h.

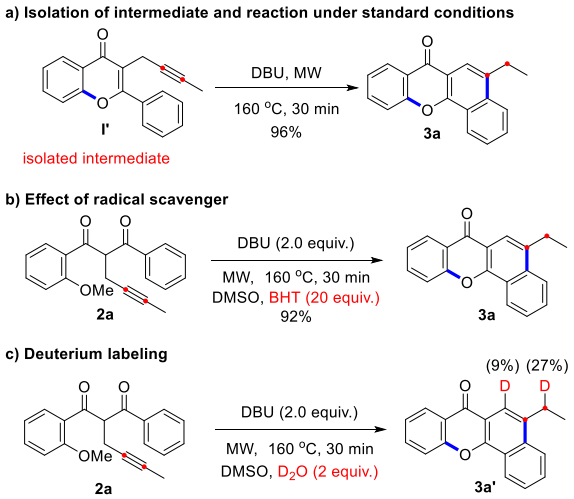
Scheme 5. Synthesis of substituted furans from 2-butynyl 1,3-diketones **2a**.



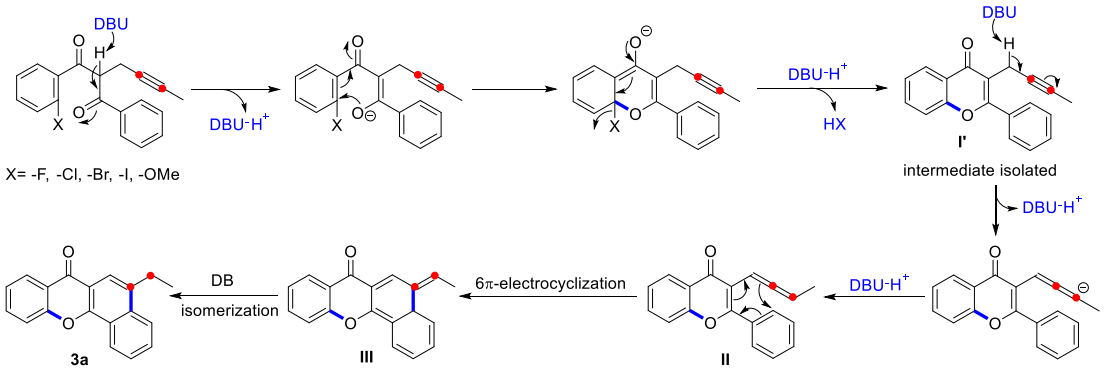
Scheme 6. Intramolecular cyclization.



Scheme 7. Control experiments for current method.



On the basis of our findings and the previous literature data on similar metal-free, tandem annulation reactions,[19] we propose a plausible mechanism for the current protocol (Scheme 8). Initially, base-mediated intramolecular cyclization of γ-alkynyl 1,3-diketone resulting in the formation of 3-alkynyl chromone intermediate **I**'.[18,20] Allene intermediate **II** is formed via the propargyl-allenyl isomerization of **I**'.[21] At this point, 6π–electrocyclization of **II** rapidly leads to the generation of the six-membered annulation product **III**.[22] Finally, double-bond isomerization provides the more stable benzoxanthone **3a**.



Scheme 8. Plausible reaction mechanism.

Conclusion

In summary, we have developed a novel, green, DBU-promoted, microwave-assisted tandem reaction for the synthesis of benzoxanthones, which involves metal-free intramolecular cyclization, propargyl-allenyl isomerization, and electrocyclization. We found that the γ-alkynyl 1,3-diketone leads to unexpected benzoxanthone formation under basic conditions, instead of following the conventional route to produce a substituted furan product. Intramolecular cyclization plays a key role in the yield of 3-(2-butynyl) chromone. We also successfully provided evidence for the reaction mechanism by isolating 3-alkynyl chromone intermediate **I**' and deuterium labeling for the formation of the allene. This metal-free, eco-friendly, one-pot tandem reaction can produce a diverse range of benzoxanthones in high yields, suggesting its potential application in the pharmaceutical industry and in bulk preparation. Attempts to extend this protocol to the development of novel benzoxanthones and the relevant natural product synthesis are underway in our laboratory.

Experimental Section

General information

All reactions were conducted under nitrogen atmosphere unless otherwise mentioned and in oven-dried glassware. All reagents were used as received from commercial suppliers unless otherwise stated. Starting materials were prepared according to the literature reported methods unless otherwise mentioned. The proton NMR spectra were obtained on Varian Unity Inova 500 (500 MHz) and Varian VNMRS600 (600 MHz) spectrometers. All NMR chemical shifts were reported as δ values in parts per million (ppm), and coupling constants (*J*) were given in hertz (Hz). Melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. Microwave reactions were performed using a CEM Discover SP microwave reactor (CEM, Matthews, NC, USA) and reaction vessel used CEM reaction vessels.

High-resolution mass spectra (HRMS) was carried out on Microsaic 4000MiD mass spectrometers. Purification was performed using preparative separations in flash column chromatography (Merck silica gel 60, particle size of 230-400 mesh). The compounds analyzed on the TLC plates were visualized using a UV light, I_2 vapor, or basic aqueous potassium permanganate ($KMnO_4$) with heating.

1. General procedure for synthesis of compound 2. Preparation of 2a as a representative example.

In two-neck round-bottom flask, to the solution of 1-(2-methoxyphenyl)-3-phenylpropane-1,3-dione **1a** (203 mg, 0.8 mmol), NaI (360 mg, 2.4 mmol), and Cs_2CO_3 (782 mg,

2.4 mmol) in THF (12 mL) under an N_2 atmosphere was added 1-bromo-2-butyne (106 mg 0.8 mmol). The mixture was heated in 70 °C oil bath for 4 h and the progress of the reaction was monitored by TLC. After completion of the reaction, the solution was quenched by addition of saturated aqueous NH_4Cl solution. The crude mixture was extracted with ethyl acetate (20 mL × 2) and combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (EtOAc/hexanes = 1:6) to give **2a** as yellow oil (211 mg, 86%).

2. General procedure for synthesis of benzoxanthone. Preparation of 3a as a representative example.

The microwave reaction was performed in a sealed microwave process vial. To an oven dried, 15 mL vial quipped with a teflon-coated magnetic stir bar, was added γ-alkyne-1,3-diketone **2a** (153 mg, 0.5 mmol) and 2.0 mL of DMSO followed by the addition of DBU (0.15 mL, 1.0 mmol). The reaction mixture was allowed to stir and heat at 160 °C for 30 min under microwave oven. The reaction was then quenched by addition of water and extracted with ethyl acetate (15 mL × 2). The combined organic layers were washed with brine solution (15 mL), dried over $MgSO_4$, and concentrated in vacuo. Finally, the residue was purified by flash column chromatography (EtOAc/hexanes =1:8) to obtain **3a** as a yellow solid (127 mg, 93 %).

Acknowledgements

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FULL PAPER

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