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Phosphine-Mediated MBH-Type/Acyl Transfer/Wittig Sequence for Construction of Functionalized Furo[3,2-*c*]coumarins

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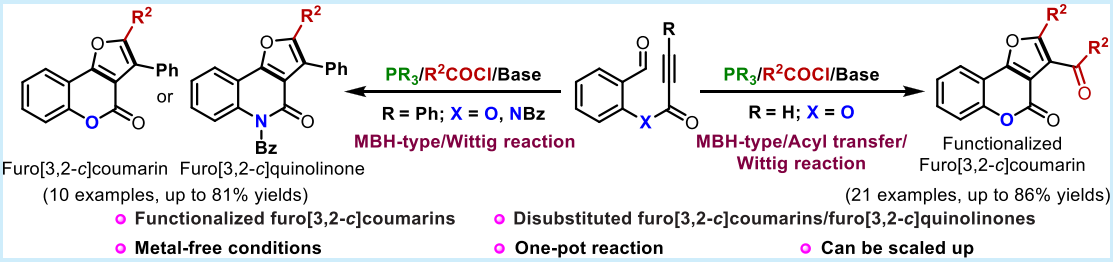

ABSTRACT: A new method for the construction of functionalized furo[3,2-*c*]coumarins via MBH-type/acyl-transfer/Wittig reaction is reported. The current approach would open a new route for the simultaneous formation of two rings in a one-pot reaction which is accompanied by incorporation of a keto functionality on the furan ring by activating the terminal alkynoates with phosphine. Furthermore, this protocol could also be applicable to the internal alkynoates/propiolamides to generate the 2,3-disubstituted furo[3,2-*c*]coumarins/furo[3,2-*c*]quinolinones by excluding the acyl-transfer reaction.

Phosphine-mediated reactions are ubiquitous in organic synthesis and have emerged as a powerful tool to construct several biologically active and medicinally important compounds.[1] Due to their unique synthetic potentials and high reactivity, activated alkynes have been manifested to be versatile substrates in phosphine-mediated reactions.[2] Consequently, the Wittig and Morita–Baylis–Hillman (MBH) reactions are potential C–C bond-forming phosphine-mediated reactions, and recently they have attracted the attention of synthetic chemists due to their multifaceted applications toward the synthesis of privileged heteroarenes and heterocycles.[3] Considering the prominence of phosphine-mediated reactions, the development of a single modular method that could efficiently facilitate both the MBH and Wittig reactions is a great challenge in modern organic chemistry.

Furocoumarin is an important class of privileged scaffold found in many natural products and exhibits a wide range of biological activities and pharmacological properties.[4] For example, neotranshinlactone is a natural product isolated from *Salvia miltiorrhiza*, a furo[3,2-*c*]coumarin derivative, which showed more potent and more selective anti-breast cancer activity than the prescribed drug tamoxifen citrate.[5] Tremendous work has explored the transition-metal catalysts in this field,[6] and recently, various metal-free alternatives have also attracted great interest.[7] Remarkably, the simultaneous formation of two heterocycle rings in a one-pot synthesis is an important task in organic synthesis, and installing a carbonyl functional group on the aryl ring of furo[3,2-*c*]coumarin is considered to be much more challenging.

Our research group has been working toward the development of new methods for the construction of diverse heteroarenes by Michael addition of PR_3 to α,β-unsaturated carbonyl compounds and subsequent acylation/Wittig reaction via in situ generation of phosphorus zwitterions.[8] To continue developing phosphine-mediated methods, we have conceived that the zwitterions can be generated from the alkynoates and PR_3 in an MBH-type reaction that could further be employed in Wittig reaction for the synthesis of functionally diverse heteroarenes. In such an instance, we are inquisitive to explore it following our approach, which could turn out to be a powerful method to access multifarious heteroaromatics. Herein, we report a new method for the synthesis of functionalized furo[3,2-*c*]coumarins and 2,3-disubstituted furo[3,2-*c*]coumarins/furo[3,2-*c*]quinolinones by using terminal alkynoates or internal alkynoates/propiolamides, PR_3, and acyl chlorides in the presence of a base (Scheme 1). It is worth noting that the installation of keto functionality on the furan ring via an unprecedented acyl-transfer reaction proceeds accompanied by the MBH and Wittig reactions of terminal alkynoates under phosphine-mediated reaction conditions.

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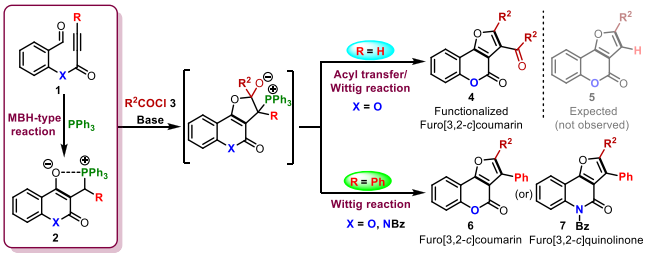
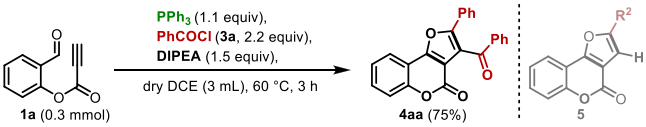
Scheme 1. Our Approach for the Synthesis of Furo[3,2-*c*]coumarins via MBH-Type/Acyl Transfer/Wittig Reaction



Our initial plan was to develop a new synthetic method for the preparation of furo[3,2-*c*]coumarins **5** from the alkynoates through an MBH-type/*O*-acylation/intramolecular Wittig reaction strategy (Scheme 1). Accordingly, we examined the reaction of terminal alkynoate **1a**, PPh_3, and PhCOCl (**3a**) in the presence of Et_3N in CH_3CN at 60 °C. To our surprise, an unexpected functionalized furo[3,2-*c*]coumarin derivative **4aa** was found in 29% yield instead of furo[3,2-*c*]coumarin derivative **5aa**. We realized that a double amount of acyl chloride participated in the reaction and it was further employed to improve the yield of the furo[3,2-*c*]coumarin **4aa** to 60% (see the SI). The structure of compound **4aa** was further unambiguously confirmed by the X-ray diffraction analysis.[9] Encouraged by the results of the MBH-type/unprecedented acyl-transfer/Wittig reaction sequence, we further investigated the optimal reaction conditions. Upon screening of various factors such as phosphines, bases, and solvents (see the SI for the detailed optimization), the most suitable conditions were established as shown in Scheme 2.

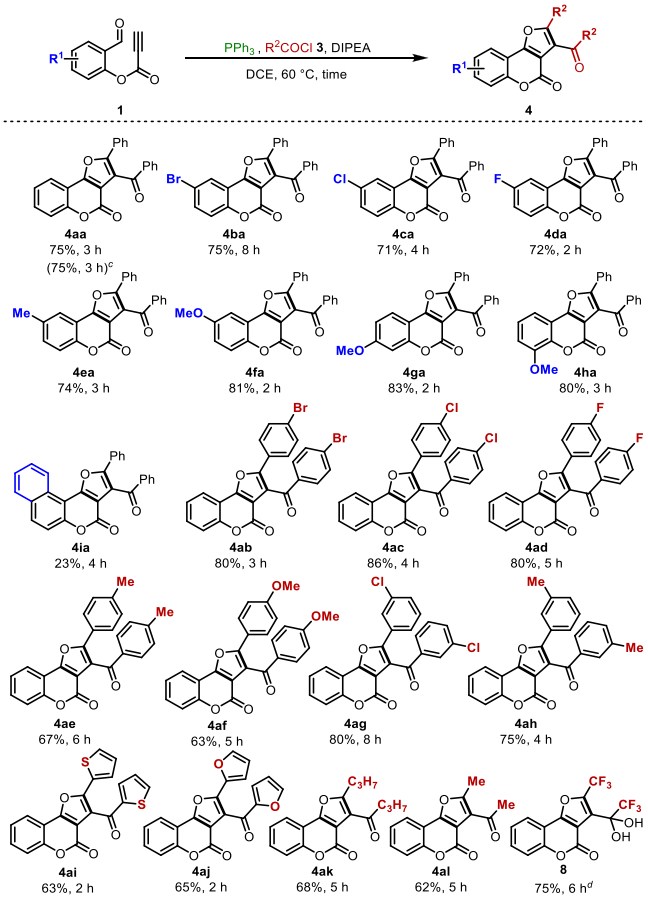
Scheme 2. Optimal Reaction Conditions for 4aa



Having established the optimal reaction conditions, the scope of the substrates was further investigated (Scheme 3). The alkynoates bearing different R^1 substituents reacted with PhCOCl (**3a**) to afford the desired furo[3,2-*c*]coumarins **4aa**−**4fa** in high yields, irrespective of the electronic effect of the substituent. Delightfully, the OMe group at different positions on the aryl ring of **1** furnished the corresponding furo[3,2-*c*]coumarins **4fa**−**4ha** in 80−83% yields within 3 h. Notably, the naphthyl substituent on alkynoate (**1i**) reacted with **3a**, and the desired product **4ia** was obtained in only 23% yield in 4 h, presumably due to the steric hindrance from the naphthyl group. In addition, the reaction could also be performed as a gram-scale synthesis of **4aa** in substantial quantities with similar efficacy.

Next, we tested various acyl chlorides **3** with **1a** to prepare a series of R^2-substituted furo[3,2-*c*]coumarins **4**. In general, the acyl chlorides bearing electron-withdrawing groups (**1b**−**1d**) were more efficient than electron-donating groups (**1e**, and **1f**) under the reaction conditions. The aroyl chlorides with Br, Cl, and F substituents smoothly furnished the desired products **4ab**−**4ad** in high yields, whereas aroyl chlorides containing Me and OMe groups afforded the corresponding products **4ae** and **4af** in relatively lower yields. Moreover, the aroyl chlorides

Scheme 3. Substrate Scope for the Functionalized Furo[3,2-*c*]coumarins 4[a,b]



[a]The reactions were carried out with alkynoate **1** (0.3 mmol), PPh_3 (1.1 equiv), R^2COCl **3** (2.2 equiv), and DIPEA (1.5 equiv) in dry DCE (3 mL) under argon at 60 °C. [b]Isolated yield. [c]Performed a gram-scale reaction (**1a:** 3 mmol, 1.04 g). [d]Trifluoroacetic anhydride (TFAA) (2.5 equiv) was used. DCE = 1,2-dichloroethane.

with *meta*-substituted Cl and Me groups also successfully underwent the reaction to provide the desired products **4ag** and **4ah** in 80% and 75% yields, respectively. Furthermore, the strong steric influence was noticed when the *ortho*-substituted aroyl chlorides reacted with **1a**; unfortunately, we could only found zwitterion intermediates **2** in all these cases. Excitedly, the heteroaryl and aliphatic acyl chlorides were also well-tolerated, albeit affording the desired furo[3,2-*c*]coumarins **4ai**-**4al** in only 62−68% yields. It should be noted that in case of TFAA (**3m**), the hydrated furo[3,2-*c*]coumarin **8** was resulted in high efficiency through **4am** due to the electron-deficient trifluoroacetyl group.

After successful examination of terminal alkynoates, we wish to explore the utility of the internal alkynoates in our protocol (Scheme 4). Accordingly, the reaction of internal alkynoate **9a** with PhCOCl (**3a**) was examined under the conditions of **4**. In contrast, we have found the formation of furo[3,2-*c*]coumarin **6aa** via the MBH-type/Wittig sequence by excluding the acyl-transfer reaction. Encouragingly, reducing the amount of **3a** also successfully furnished the desired product **6aa** in 79% yield within 6 h. Furthermore, the substrates bearing Br and OMe groups reacted with **3a** to provide the products **6ba** and **6ca** in 52% and 72% yields. Interestingly, the aroyl chlorides with 4-Cl, 4-Me, and heteroaryl (2-furyl) groups were

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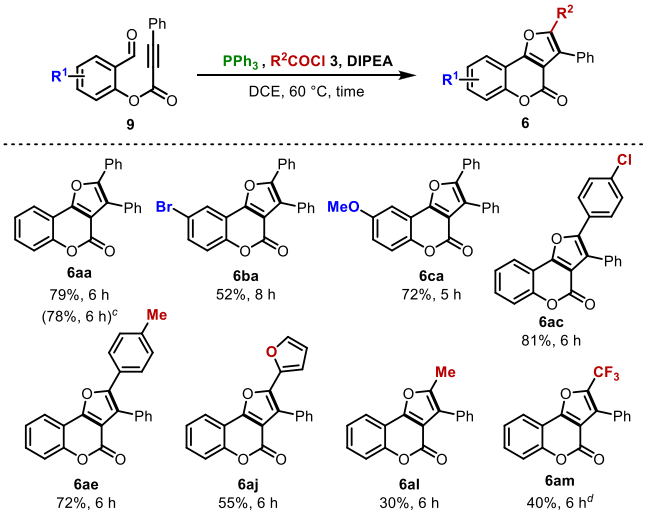
Scheme 4. Substrate Scope for the Furo[3,2-*c*]coumarins 6[a,b]



[a]The reactions were carried out with alkynoate **9** (0.3 mmol), PPh_3 (1.1 equiv), R^2COCl **3** (1.1 equiv), and DIPEA (1.5 equiv) in dry DCE (3 mL) under argon at 60 °C. [b]Isolated yield. [c]Performed a gram-scale reaction (**6a**: 4 mmol, 1.0 g). [d]TFAA (1.5 equiv) was used.

subjected to **3a**, affording the desired products **6ac**, **6ae**, and **6aj** in 55%−81% yields. In addition, the aliphatic acyl chlorides such as acetyl (**3l**), and TFAA (**3m**) were also tolerated, albeit providing the lower yields of the corresponding products **6al** and **6am**.

In order to investigate the mechanism, several experiments have been examined to find out the intermediates by monitoring the ^{31}P NMR analysis (Figure 1). The zwitterion

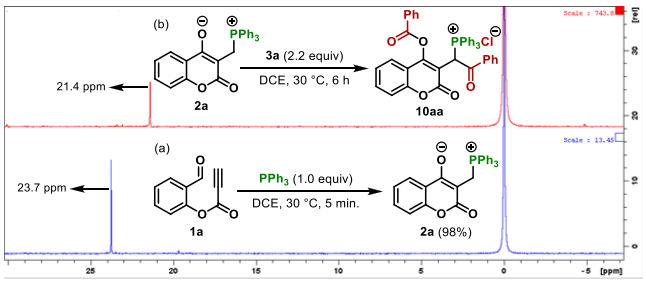
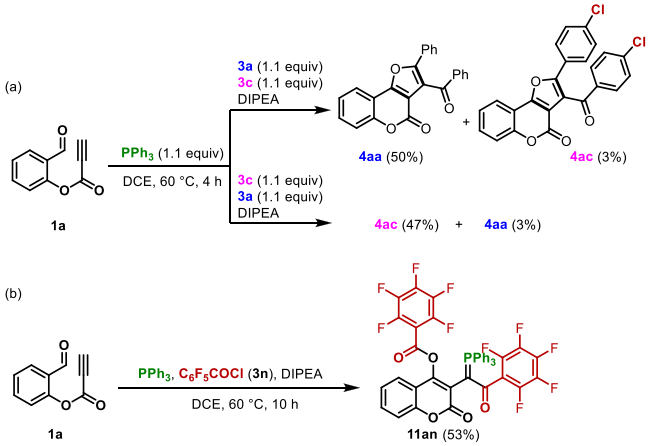


Figure 1. ^{31}P NMR analysis of phosphonium species **2a** and **10aa**.

2a (23.7 ppm) could be easily prepared in quantitative yields by the reaction of **1a** with PPh_3 in DCE at 30 °C within 5 min. We further attempted a reaction of the zwitterion **2a** with acyl chloride **3a** in the absence of a base. After 6 h, the bis-acylated phosphonium salt **10aa** peak at 21.4 ppm was found by diminishing the peak at 23.7 ppm in the reaction mixture by monitoring the ^{31}P NMR, and **10aa** was further confirmed by the ESI-HRMS analysis.[10] Notably, the monoacylated phosphonium species were not found even with use of 1.1 equiv of PhCOCl (**3a**) in the reaction mixture. It could be understood that the acyl transfer is highly feasible and the ylide **C** could be easily formed even in the absence of a base under our reaction conditions.

Next, to further illustrate the intramolecular acyl-transfer reaction, two reactions were carried out using two different acyl chlorides (PhCOCl **3a** and 4-ClC_6H_4COCl **3c**) with different addition sequence under the standard conditions (Scheme 5a). Interestingly, we could not found any crossover

Scheme 5. Control Experiments for (a) Elucidating the Intramolecular Acyl Transfer Reaction and (b) Confirming the Generation of Bis-Acylated Ylide 11an



products, and only two products **4aa** and **4ac** were obtained as major and minor products in both the reactions, depending on the first addition of acyl chloride. It clearly indicates that the intermolecular *C*-acylation has been ruled out under our conditions, and the rearrangement of betaine intermediate **D** would facilitate the intramolecular acyl-transfer reaction (Scheme 6).[3a] Furthermore, the phosphorus ylide **11an** was obtained in 53% yield while **1a** reacted with pentafluorobenzoyl chloride (**3n**) under optimal conditions in 10 h (Scheme 5b). Remarkably, it was found that further cyclization and Wittig reaction for **11an** did not occur. The *ortho*-substituted fluoro groups may hamper the attack of ylide **11an** to the ester functionality, and the ylide nucleophilicity was significantly weakened by the adjacent highly strong electron-withdrawing acyl functionality (COC_6F_5). The phosphorus ylide **11an** could be further characterized by X-ray diffraction analysis and ESI-HRMS.[9]

Based on the results and control experiments, a plausible reaction mechanism is described in Scheme 6. The phosphorus zwitterion **A**, which was formed by the initial phospha-Michael addition of PPh_3 to **1**, could easily be converted into the zwitterion **2** via isomerization. The *O*-acylation of zwitterion **2** with acyl chloride **3** would generate phosphonium salt **B** which is further transformed into phosphorus ylide **C** by the spontaneous elimination of HCl (Figure 1b).[11] In the case of terminal alkynoates (R = H), the intramolecular cyclization upon ylide **C** would provide the betaine **D** that further undergoes the C−O bond cleavage to generate the functionalized zwitterion **E** via acyl-transfer reaction. In the presence of a base, the zwitterion **E** would further react with the second equivalent of **3** to produce the ylide **11**, and subsequent intramolecular Wittig reaction of **11** would provide the functionalized furo[3,2-*c*]coumarin **4** via betaine **F**. In case of internal alkynoates (R = Ph), however, the phosphorus ylide **C** would undergo the intramolecular cyclization to generate the betaine **G**, and subsequent Wittig reaction of **G** leads to the furo[3,2-*c*]coumarin **6**. It is worthy to note that the fully substituted hindered betaine intermediates **F** and **G** preferred Wittig reaction whereas less steric hindered betaine **D** proceeds rearrangement reaction to incorporate the keto

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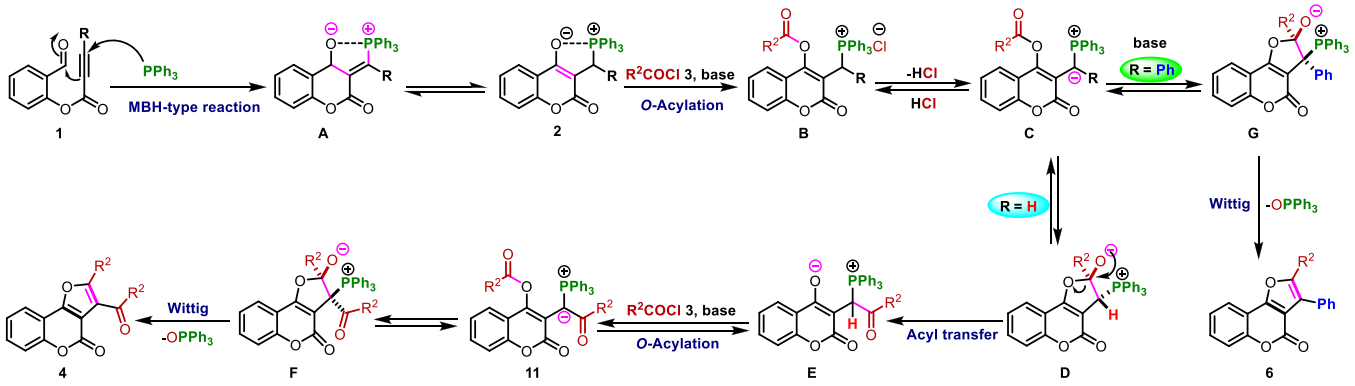
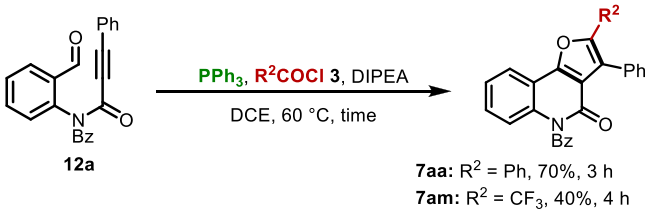
Scheme 6. Plausible Mechanism for 4 and 6



functionality in the products via an unprecedented acyl-transfer reaction.

Furthermore, to demonstrate the effectiveness of our protocol, 3-phenylpropiolamide derivative **12a** was tested with acyl chlorides **3a** and **3m** under the standard conditions of **6**. To our delight, the furo[3,2-*c*]quinolinones **7aa** and **7am** were obtained in 70% and 40% yields within 4 h, respectively (Scheme 7). Unfortunately, our efforts to prepare terminal propiolamide derivatives were unsuccessful, and therefore, they could not be further tested in our reaction conditions.

Scheme 7. Synthesis of Furo[3,2-*c*]quinolinones 7



In summary, we have developed a novel method for the synthesis of functionalized furo[3,2-*c*]coumarins from terminal alkynoates and acyl chlorides in moderate to high yields via a MBH-type/acyl-transfer/intramolecular Wittig strategy in a one-pot reaction. The most important feature of this strategy is installing a keto functionality at the aryl ring of furo[3,2-*c*]coumarins under metal-free conditions, which also demonstrates a new type of *C*-acylation of phosphorus ylide. Furthermore, 2,3-disubstituted furo[3,2-*c*]coumarins and furo[3,2-*c*]quinolinones were also prepared from the internal alkynoates and propiolamides via an MBH-type/intramolecular Wittig strategy. Further investigations to access multifarious heteroarenes utilizing this protocol are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04082.

Optimization data, control experiments, experimental procedures, characterization data and spectra of all compounds (PDF)

Accession Codes

CCDC 2039605, 2039742, 2039745, 2039752, 2039754, 2039756, and 2039765−2039766 contain 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.

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(9) See the Supporting Information for the detailed characterization of the products including X-ray diffraction analysis.

(10) The reaction of zwitterion **2a** and acyl chloride **3a** has been examined in DCE at 30 °C. After 6 h, the reaction mixture was monitored by ^{31}P NMR and ESI-HRMS analysis (see the Supporting Information for the experimental details).

(11) When the reaction was carried out with **2a** and **3a** in the absence of base in DCE, the bis-acylated phosphonium salt **10aa** (21.4 ppm) was detected by monitoring the ^{31}P NMR and ESI-HRMS analysis (see Figure 1b and the Supporting Information for the experimental details).

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