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Synthesis of Functionalized Benzofurans from *para*-Quinone Methides via Phospha-1,6-Addition/*O*-Acylation/Wittig Pathway

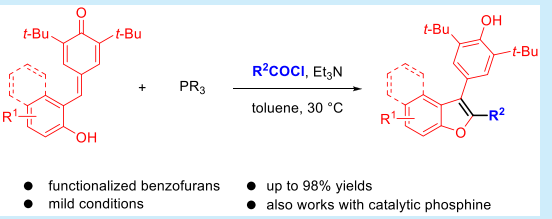
Yan-Cheng Liou,[†] Praneeth Karanam,[†] Yeong-Jiunn Jang,[‡] and Wenwei Lin*,[†]

[†]Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei 11677, Taiwan, R.O.C.

[‡]Chinese Medicine Research and Development Center, China Medical University Hospital, 2, Yuh-Der Road, Taichung 40447, Taiwan, R.O.C.

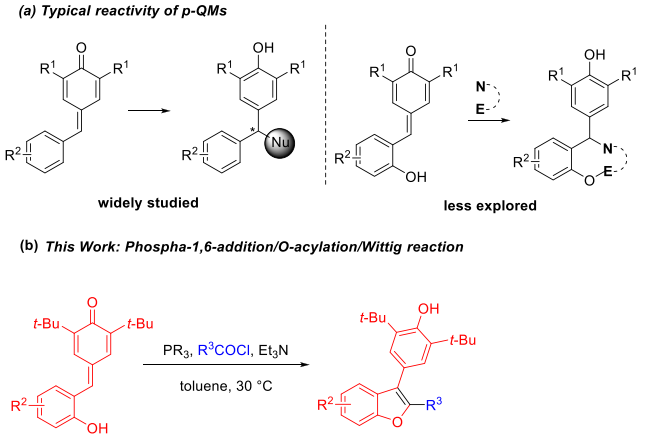
Supporting Information

ABSTRACT: An efficient synthesis of functionalized benzofurans is achieved under mild and metal-free conditions from stable *para*-quinone methides by treatment with phosphine, acyl chloride, and a base. This one-pot phospha-1,6-addition/*O*-acylation/Wittig reaction is also demonstrated under catalytic conditions with similar efficacy.



In recent times, *p*-quinone methides (*p*-QMs) have been subjected to extensive investigation for their interesting chemical and biological properties.[1,2] A typical reaction of *p*-QMs involves rearomatization via nucleophilic addition by a variety of carbon nucleophiles[3] such as malonates, oxindoles, dicyanoolefins, imines, etc. (Scheme 1). Furthermore, *ortho*-hydroxyphenyl substituted *p*-QMs could also participate in cycloaddition reactions as a four-atom partner in diverse [4 + *n*] cycloadditions with various coupling partners to generate five-, six-, or seven-membered rings.[4] However, to the best of our knowledge there are a few reports regarding the 1,6-addition of *p*-QMs by noncarbon nucleophiles.[5]

Scheme 1. Typical Reactivity Profile of *p*-QMs (a) and Our Phospha-Michael/*O*-Acylation/Wittig Reaction (b)



On the other hand, tertiary phosphines, being very good nucleophiles, could generally add onto a wide variety of Michael acceptors and the resultant phosphonium zwitterion could be effectively trapped by a carbonyl electrophile that could further participate in a Wittig reaction. This strategy has been well-explored by our group in the recent past for the generation of diverse heterocycles/heteroaromatics.[6] Despite the reactivity of *p*-QMs, we were surprised to see that the application of the *p*-QMs in the phosphine-mediated reactions has scarcely been explored.[5h] Therefore, in continuation of our interest in developing novel strategies for the generation of phosphorus ylides/phosphonium salts and their application toward the synthesis of various heterocycles/heteroaromatics via intramolecular Wittig reactions, we hoped to exploit the electrophilicity of these *p*-QMs by subjecting them to tandem phospha-Michael and intramolecular Wittig reactions. We plan to start with a stable and well-explored *p*-QM bearing a hydroxyl group. The proposed phospha-Michael reaction would involve 1,6-addition of R_3P to *p*-QM leading to aromatization of the quinone. The suitably placed hydroxyl group in the resultant phosphonium zwitterion would then be acylated with various carbonyl electrophiles to result in acylated species that would eventually be subjected to intramolecular Wittig reaction to afford 3-arylbenzofurans, which are considered as privileged heterocyclic scaffolds.[7] In this context, we report an efficient synthesis of functionalized benzofurans from the *p*-QMs bearing an ortho-hydroxy group through a 1,6-phospha-Michael addition/*O*-acylation/Wittig pathway under mild and metal-free conditions.

We initiated our studies by treating the stable *p*-QM **1a** with PPh_3 and PhCOCl, in the presence of Et_3N, in THF at room temperature. The reaction was not fruitful, as no consumption of starting material was noticed even after 4 h (Table 1, entry 1). We then examined several other phosphines and discovered that Et_2PPh and PBu_3 were efficient in promoting our expected tandem phospha-Michael/*O*-acylation/Wittig reaction to deliver the desired benzofuran **3aa** in 85% and 95% yields,

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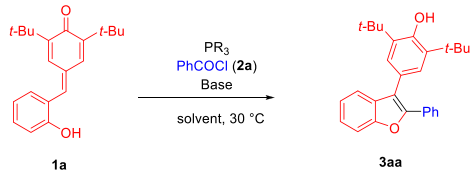
Table 1. Optimization of the Reaction Conditions for 3aa[a]



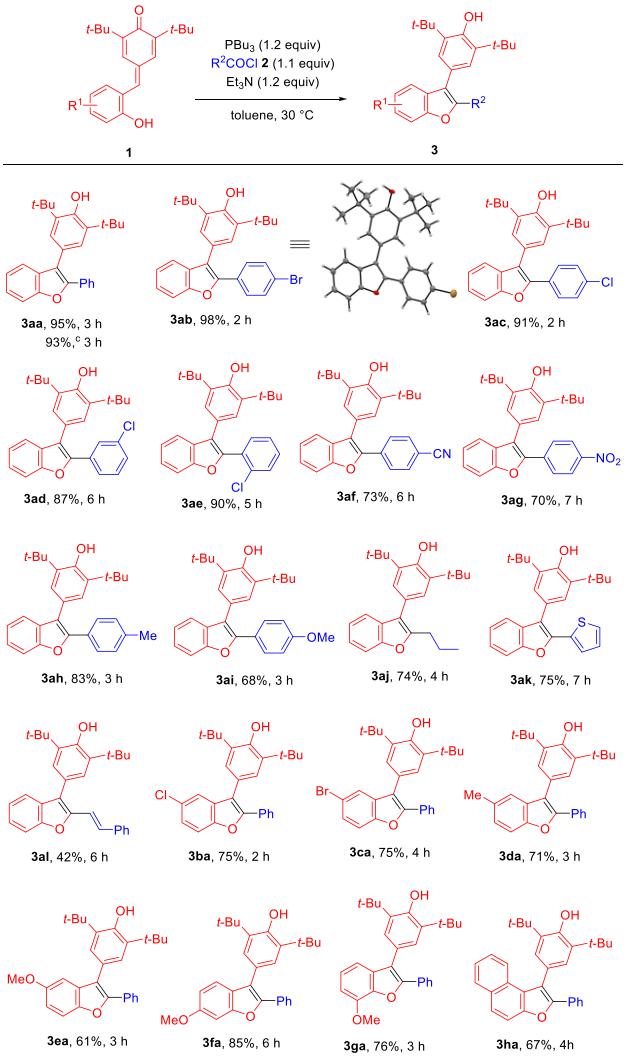
entry	PR_3	base	solvent	t (h)	3aa, yield (%)[b]
1	PPh_3	Et_3N	THF	4	NR[c]
2	PCy_3	Et_3N	THF	6	NR[c]
3	$PEtPh_2$	Et_3N	THF	6	NR[c]
4	PEt_2Ph	Et_3N	THF	6	85
5	PBu_3	Et_3N	THF	4	95
6	PBu_3	Et_3N	CH_2Cl_2	7	–
7	PBu_3	Et_3N	Et_2O	3	98
8	PBu_3	Et_3N	ClPh	3	85
9	PBu_3	Et_3N	toluene	3	98
10	PBu_3	DBU	toluene	6	60
11	PBu_3	TMG	toluene	3	51
12[d]	PBu_3	Et_3N	toluene	4	95
13[e]	PBu_3	Et_3N	toluene	3	44
14[d,f]	PBu_3	Et_3N	toluene	1	93
15[d,g]	PBu_3	Et_3N	toluene	3	98

[a]Unless otherwise specified, all the reactions were carried out using **1a** (0.1 mmol), PR_3 (1.2 equiv), PhCOCl (1.1 equiv), and base (2.4 equiv) in anhydrous solvent (0.5 mL) at 30 °C. [b]Determined by ^1H NMR analysis of crude reaction mixture using 1,3-dinitrobenzene as an internal standard. [c]NR = no reaction and starting metrials could be recovered. [d]1.2 equiv of Et_3N was used. [e]0.5 equiv of Et_3N was used. [f]Reaction was performed at 50 °C. [g]Reaction was carried out on 0.3 mmol scale in toluene (0.75 mL).

respectively (entries 4 and 5). Encouraged by these results, different solvents (entries 6–9) were screened. It was delightful to find that Et_2O and toluene were most suitable to furnish the benzofuran **3aa** in 98% yield. Bases such as DBU and TMG were also tested (entries 10 and 11), and they could not enhance the yield of **3aa**. After the effect of other parameters such as molar equivalents of Et_3N, reaction concentration, and temperature was examined, the optimal conditions were selected to be 0.3 mmol of **1a**, 1.2 equiv of PBu_3, 1.1 equiv of PhCOCl (**2a**), and 1.2 equiv of Et_3N in 0.75 mL of toluene at 30 °C.

With the optimal conditions for the formation of benzofuran **3aa** established, the substrate scope was then evaluated (Scheme 2). First, various acyl chlorides **2a**–**2l** were subjected to a reaction with the *p*-QM **1a**. It was interesting to note that all the aromatic acyl chlorides, irrespective of their electronic nature, afforded the desired benzofurans **3aa**–**3al** in good to excellent yields. Also, the positional effect of the substituents in the aromatic acyl chlorides did not influence the yield of the products. However, the aromatic acyl chlorides **2f** and **2g** bearing *p*-CN and *p*-NO_2 substitutions respectively resulted in comparatively lower yields of the products **3af** and **3ag** even after longer reaction times due to their poor solubility. Delightfully, aliphatic acyl chloride such as *n*-butyl chloride (**2j**) and heteroaromatic acyl chloride such as 2-thienyl chloride (**2k**) were also applicable in the reaction to provide the products **3aj** and **3ak** in good yields. Furthermore, cinnamoyl chloride (**2l**) also participated in the reaction, albeit providing a moderate yield of the benzofuran **3al**. Next, the scope of the differently substituted *p*-QMs was evaluated

Scheme 2. Substrate Scope of Benzofurans 3[a,b]



[a]Unless otherwise specified, all the reactions were carried out using **1** (0.3 mmol), PBu_3 (1.2 equiv), R^2COCl (1.1 equiv), and Et_3N (1.2 equiv) in dry toluene (0.75 mL) at 30 °C under argon atmosphere. [b]Isolated yield. [c]Rection was performed on the 1 mmol scale under optimized reaction conditions.

and the data revealed that all the *p*-QMs generated diverse benzofurans in good to excellent yields irrespective of the nature and position of the substitution. Moreover, a naphthol derived *p*-QM **1h** was also subjected to our standard conditions to generate naphtho(2,3-*b*)furan **3ha** in 67% yield. To demonstrate the synthetic utility of the protocol, a 1.0 mmol scale reaction was also carried out with the substrate **1a** and **2a** to result in **3aa** in 93% yield.

After evaluation of the substrate scope, we also wished to examine the effectiveness of our protocol by employing catalytic phosphine. We have earlier reported a mild synthesis of functionalized furans utilizing catalytic amounts of phosphine oxide and Et_3N. We demonstrated that TESCl can promote the activation of the phosphine oxide **4**, while phenylsilane reduces the activated phosphine oxide to generate free phosphine.[8] Following our reported procedure, we carried out the reaction of **1a** with **2a** in the presence of a catalytic amount of **4** (10 mol %), TESCl (20 mol %), $PhSiH_3$ (1.6 equiv), and Et_3N in THF at 50 °C (Scheme 3). After 29 h, the

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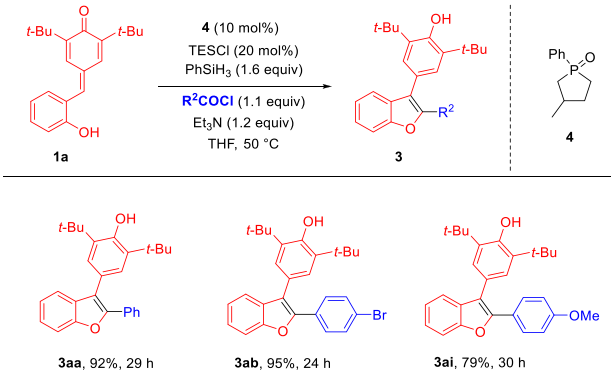
Scheme 3. Synthesis of Benzofurans 3 under Catalytic Conditions[a,b]

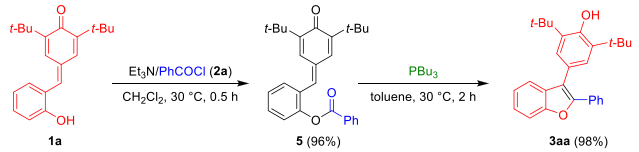


[a]Unless otherwise specified, all the reactions were carried out using **1a** (0.3 mmol), **4** (10 mol %), TESCl (20 mol %), $PhSiH_3$ (1.6 equiv), R^2COCl (1.1 equiv), and Et_3N (1.2 equiv) in anhydrous THF (0.75 mL) at 50 °C under an argon atmosphere. [b]Isolated yield.

desired benzofuran **3aa** could be isolated in 92% yield. Encouraged by the result, two other acyl chlorides **2b** and **2i**, having an EWG and an EDG respectively, were tested under the same conditions. Delightfully, the catalytic protocol worked well in each case affording the corresponding products in excellent yields (**3ab**, CCDC 1943703).

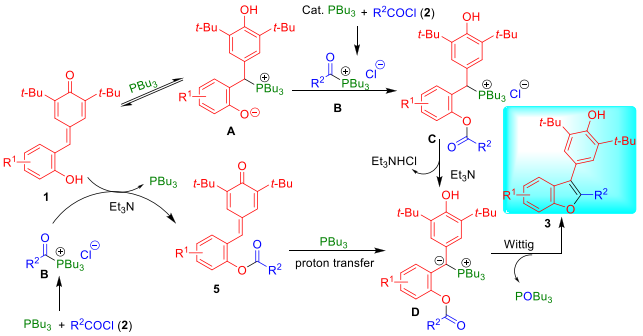
Several control experiments have been carried out to understand the reaction pathway. Unfortunately, our efforts to isolate the intermediates failed, but the formation of intermediate **A** was confirmed by HRMS analysis of the reaction of *p*-QM **1** and PBu_3. Also, we have been able to observe the formation of phosphonium salt **6** (CCDC 1952659) which is devoid of an acyl group. We believe that this might be formed from the intermediate **C**.[9] However, reversing the addition sequence like PBu_3 and PhCOCl to *p*-QM **1** in the presence of Et_3N also provided the benzofuran **3** in similar yields. It indicates *p*-QM **1** exhibits more affinity toward PBu_3 irrespective of the addition sequence which makes our reaction conditions more convenient. We have also carried out the reaction with *p*-QM **1a** and PhCOCl in the presence of Et_3N in CH_2Cl_2. The acylation of *p*-QM **5** was observed with a 96% yield within 0.5 h. Compound **5** further afforded the desired product **3aa** in 98% yield by using the 1.2 equiv of PBu_3 without a base (Scheme 4).

Scheme 4. Synthesis of Benzofuran via Compound 5



A tentative mechanism as depicted in Scheme 5 could be considered for the formation of benzofurans **3**. The addition of phosphine and PhCOCl to the *p*-QM **1** results in the formation of *O*-acylated phosphonium salt species **C**, via the zwitterionic species **A** which is equilibrium with *p*-QM **1**. The catalytic amount of PBu_3 would form phosphonium salt **B** with an acyl chloride to accelerate the *O*-acylation reaction.[10] Deprotonation of **C** by Et_3N generates reactive phosphorus ylide **D** which upon intramolecular Wittig reaction furnishes

Scheme 5. Plausible Mechanism for the Formation of 3



the desired benzofurans **3**. The formation of intermediate **C** from **1** via zwitterion **A** justifies the utility of only 1.2 equiv of Et_3N in promoting an *O*-acylation as well as a Wittig reaction. Alternatively, phosphonium salt **B** from PBu_3 and PhCOCl reacts with *p*-QM **1** to form **5** in the presence of Et_3N. Further 1,6-addition of PBu_3 to **5** followed by proton trasfer and intramolecular Wittig reaction leads to benzofuran **3** via ylide **D**.

In conclusion, we have efficiently exploited the reactivity of *p*-QMs to generate a series of benzofurans by employing a one-pot sequential phospha-1,6-addition/*O*-acylation/Wittig reaction. All the products have been obtained in good to excellent yields under mild and metal-free conditions in short reaction times. Further, we have also demonstrated the efficacy of our protocol by employing catalytic phosphine. Further studies to synthesize other heterocycles from *p*-QMs are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03001.

Experimental procedures, characterization data, and spectra of all compounds (PDF)

Accession Codes

CCDC 1943703 and 1952659 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wenweilin@ntnu.edu.tw.

ORCID

Praneeth Karanam: 0000-0003-3982-3525

Wenwei Lin: 0000-0002-1121-072X

Notes

The authors declare no competing financial interest.

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