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Direct Synthesis of 2-Methylbenzofurans from Calcium Carbide and Salicylaldehyde *p*-Tosylhydrazones

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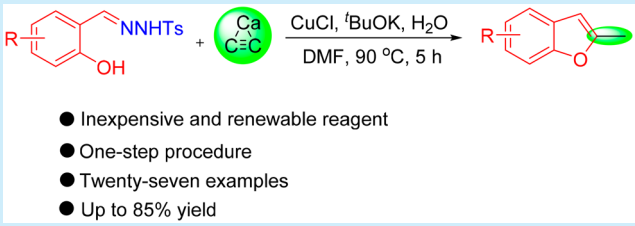
Supporting Information

ABSTRACT: A new methodology for the construction of methyl-substituted benzofuran rings from the reactions of calcium carbide with salicylaldehyde *p*-tosylhydrazones/2-hydroxyacetophenone *p*-tosylhydrazones is described. Various 2-methylbenzofurans and 2,3-dimethylbenzofurans could be obtained in satisfactory yield by using a cuprous chloride catalyst. The advantages of this protocol include the use of a readily available and easy-to-handle acetylene source and simple workup procedure.



Heteroarenes, such as furans, indoles, pyrroles, and their benzo-fused derivatives, are privileged scaffolds. Among them, the applications of benzofurans are efficient and important in pharmacology.[1] The core structures of benzofuran are present in many biologically active compounds, showing a wide range of drug activities, including anti-HIV, anticancer, and antimicrobial activities.[2] In particular, compounds containing a 2-methylbenzofuran core have found many applications, such as glucokinase activator,[3] thrombin inhibitor,[4] and insecticide,[5] because of their wide range of biological activities (Figure 1). Therefore, the development of novel synthetic methods for their direct preparation from readily accessible materials is very important.

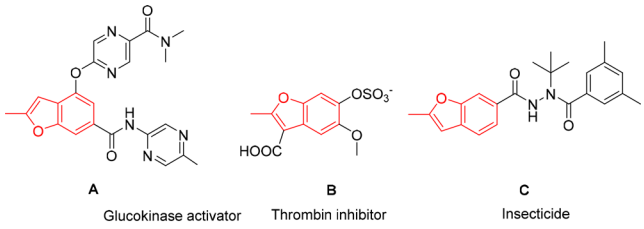
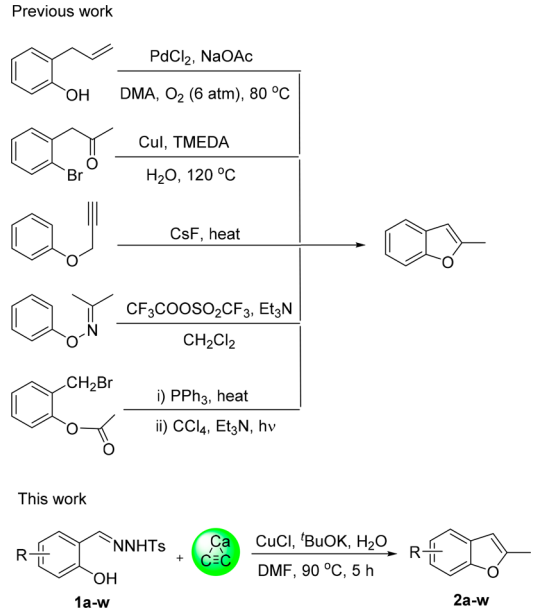


Figure 1. Representative examples bearing 2-methylbenzofuran structure.

Various synthetically viable procedures have been used for the construction of 2-methylbenzofurans in the literature (Scheme 1), which include: (i) Pd-catalyzed oxidative cyclization of 2-allylphenol;[6] (ii) copper-TMEDA complex-catalyzed transformation of 1-(2-bromophenyl)propan-2-one;[7] (iii) Claisen rearrangement and further cyclization of phenyl propargyl ether in the presence of cesium fluoride;[8] (iv) [3,3]-sigmatropic rearrangement and further cyclization of acetone *O*-phenyloxime in the presence of trifluoroacetyl triflate and trimethylamine;[9] and (v) the reaction of 2-(bromomethyl)-phenyl acetate with triphenylphosphine through the formation of the corresponding phosphonium bromides intermediate and a further intramolecular photochemical Wittig reaction onto the aryloxycarbonyl group.[10]

Scheme 1. Preparation of 2-Methylbenzofurans



However, some drawbacks still remain for the existing synthetic methods, such as using valuable transition metals or difficult-to-obtain substrates.

For the past few years, calcium carbide as a green material and inexpensive and easily attainable molecule has become an important reagent for many organic transformations. The advantages derived from the use of calcium carbide, instead of

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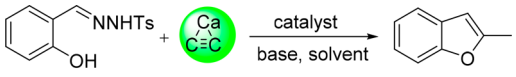
organic acetylene gas, are mainly embodied in the safety of no risk of explosion and no requirement for complex equipment. Until now, there have been a few reports of utilizing calcium carbide directly in organic synthesis.[11] In particular, Jiang[12] reported the reactions of *N*-tosylhydrazones with calcium carbide to synthesize various substituted pyrazoles. Our group recently also made great efforts to research the direct use of calcium carbide in organic synthesis and reported the synthesis of 1,3,5-triaroylcyclohexanes[13] and symmetric diarylethynes,[14] and *N*-propargylation of secondary amines[15] using calcium carbide as an acetylene source.

As an extension of our investigation on the use of calcium carbide as an acetylene source, in this work, we report a novel synthetic approach to 2-methylbenzofurans by using calcium carbide as an acetylene source and salicylaldehyde *p*-tosylhydrazones as starting materials through a one-pot procedure.

At the beginning of this transformation, the reaction of salicylaldehyde *p*-tosylhydrazone (**1a**) with calcium carbide was selected as the model reaction to screen the optimal conditions, including the use of catalysts, bases, and solvents at a certain temperature for the appropriate time. The results are summarized in Table 1. It was found that copper(I) halides,

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

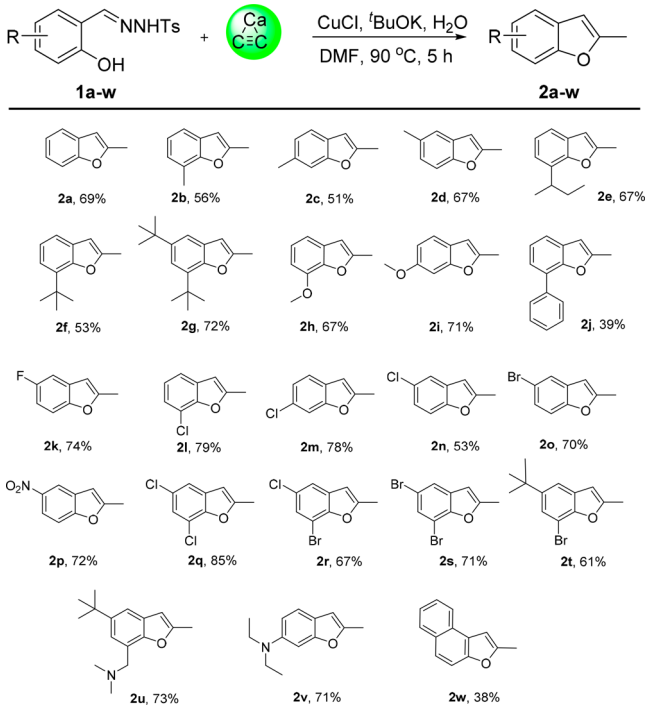
entry	catalyst	base	solvent	yield[b] (%)
1		^{t}BuOK	DMF	
2	CuI	^{t}BuOK	DMF	59
3	CuBr	^{t}BuOK	DMF	61
4	CuCl	^{t}BuOK	DMF	69
5	CuCl	^{t}BuOLi	DMF	17
6	CuCl	K_2CO_3	DMF	
7	CuCl	Cs_2CO_3	DMF	54
8	CuCl	KOH	DMF	12
9	CuCl	KOAc	DMF	trace
10	CuCl	Et_3N	DMF	
11	CuCl	^{t}BuOK	EtOH	trace
12	CuCl	^{t}BuOK	THF	trace
13	CuCl	^{t}BuOK	PhMe	
14	CuCl	^{t}BuOK	DMSO	15
15	CuCl	^{t}BuOK	MeCN	7
16	CuCl	^{t}BuOK	DMF	57[c]
17	CuCl	^{t}BuOK	DMF	32[d]

[a]Reaction conditions: **1a** (1 mmol), CaC_2 (3 mmol), H_2O (4 mmol), CuCl (0.1 mmol), and base (2 mmol) in solvent (4 mL) was heated at 90 °C for 5 h. [b]Isolated yield. [c]H_2O (2 mmol). [d]H_2O (6 mmol).

such as CuI, CuBr, and CuCl, could catalyze the reaction to give 2-methylbenzofuran (**2a**) in good yield (entries 2−4), and CuCl exhibited the best catalytic effect (entry 4). ^{t}BuOLi, ^{t}BuOK, K_2CO_3, Cs_2CO_3, KOH, KOAc, and Et_3N as bases were tested (entries 4−10). It was found that ^{t}BuOK was a more efficient base than the others (entry 4). In addition, the selection of the solvents was also important. The reaction did not take place in EtOH, THF, and PhMe because of the poor solubility for calcium carbide (entries 11−13). In contrast, DMF, DMSO, and MeCN were practicable solvents, and the reaction in these solvents could proceed to a certain extent (entries 4, 14, and 15). The most effective solvent was DMF, which could give **2a** in 69% yield (entry 4). In addition, 4 equiv of water based on **1a** is an appropriate amount for the reaction (entry 4). The increase or decrease of the water amount both can cause the drop of the yield (entries 16 and 17).

Using the optimized conditions, synthesis of 2-methylbenzofurans was conducted by reactions of varous salicylaldehyde *p*-tosylhydrazones with calcium carbide catalyzed by CuCl in the presence of ^{t}BuOK at 90 °C in DMF. The results are shown in Scheme 2. The reactions worked well for a wide range of

Scheme 2. Synthesis of 2-Methylbenzofurans[a]



[a]Reaction conditions: **1a−w** (1 mmol), CaC_2 (3.0 mmol), H_2O (4 mmol), CuCl (0.1 mmol), and ^{t}BuOK (2 mmol) in DMF (4 mL) was heated at 90 °C for 5 h.

substrates bearing both electron-donating and electron-withdrawing groups on their aromatic rings, such as Me, ^{i}Bu, ^{t}Bu, MeO, F, Cl, Br, NO_2, Me_2NCH_2, and Et_2N, and afforded the desired products in satisfactory yield (Scheme 2, **2b−i,k−v**). However, the substrates, including biphenyl and naphthyl groups, gave the corresponding products in lower yield, possibly because of steric hindrance (Scheme 2, **2j,w**).

In addition, 2,3-dimethylbenzofurans could also be synthesized by reactions of 2-hydroxylacetophenone *p*-tosylhydrazones **3a−d** with calcium carbide under similar conditions at 100 °C (Scheme 3). The representative 2,3-dimethylbenzofurans **4a−d** could be obtained through this approach in moderate yield.

A plausible mechanism is proposed for the synthesis of **2a** by a reaction of **1a** with calcium carbide (Scheme 4). Initially, 2-(diazomethyl)phenol is formed in situ by a reaction **1a** with ^{t}BuOK (Bamford−Stevens reaction).[16] Simultaneously, calcium carbide reacts with water in the presence of CuCl to give ethynylcopper as an intermediate,[17] which further reacts with 2-(diazomethyl)phenol to give copper−carbene species **A**.[18] The reductive elimination of **A** gives intermediate **B**.[17] Intermediate **B** may undergo one of two methods to afford the final product

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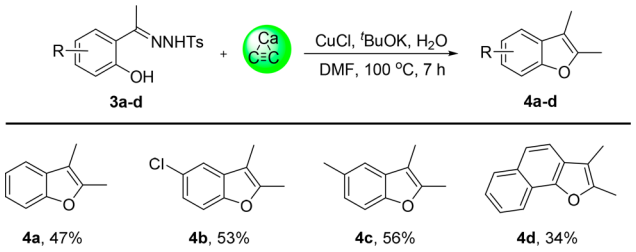
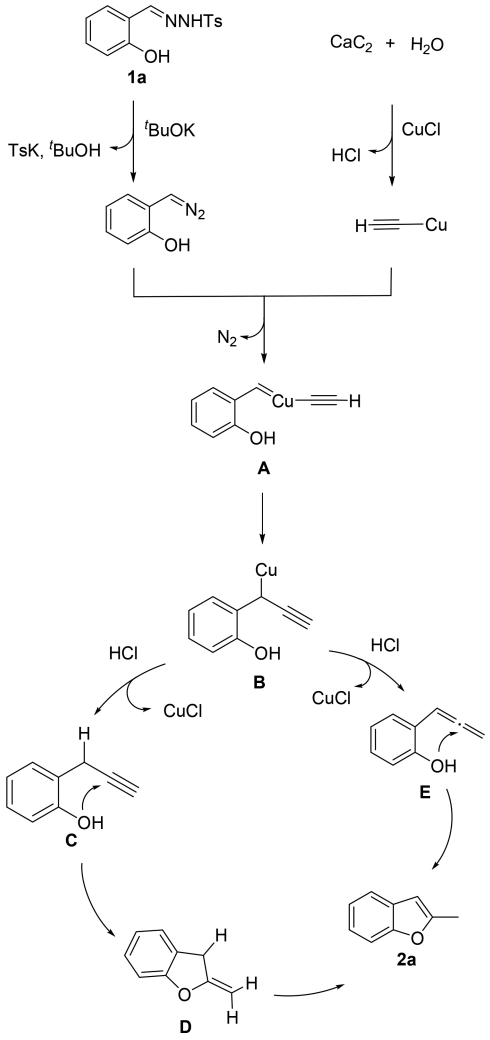
Scheme 3. Synthesis of 2,3-Dimethylbenzofurans[a]



[a]Reaction conditions: **3a–d** (1 mmol), CaC_2 (3.0 mmol), H_2O (4 mmol), CuCl (0.1 mmol), and ^{t}BuOK (2.5 mmol) in DMF (4 mL) was heated at 100 °C for 7 h.

Scheme 4. Proposed Mechanism for the Synthesis of 2a



2a. In the first method, **B** is acidolyzed by HCl, which formed from the system, to first produce 2-propargylphenol (**C**).[19] Then **C** undergoes the intramolecular addition to afford intermediate **D**,[20] which can be readily isomerized to the final product **2a**. In the second method, **B** is acidolyzed by HCl to form 2-allenylphenol (**E**).[18] 2-Allenylphenol **E** directly undergoes the intramolecular addition to give the final product **2a**.

In summary, an efficient method for the synthesis of 2-methylbenzofurans and 2,3-dimethylbenzofurans from CuCl-catalyzed reactions of salicylaldehyde *p*-tosylhydrazones/2-hydroxylacetophenone *p*-tosylhydrazones with calcium carbide has been developed. Various substituted 2-methylbenzofurans could be obtained in satisfactory yield. These reactions represent an efficient and alternative strategy for the synthesis of 2-methylbenzofurans. The cost-efficient procedure can be easily employed for the preparation of important 2-methylbenzofuran building blocks using standard laboratory equipment. Moreover, these reactions confirm the potential of using calcium carbide as an acetylene gas replacement in organic synthesis and provide an opportunity to establish calcium carbide as a sustainable and cost-effective carbon source in modern chemical industries.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00676.

Additional data on condition optimization, general experimental information, synthetic procedure, characterization data, and ^{1}H/^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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