



# Synthesis of sulfonyl-substituted furans via copper-mediated annulation of acetylenic sulfones and activated methylenes



Shengke Wang, Changqing Liu, Jing Jia, Chao Zha, Meihua Xie\*, Nianrong Zhang

Key Laboratory of Functional Molecular Solids (Ministry of Education), Anhui Key Laboratory of Molecular Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu, 241000, PR China

## ARTICLE INFO

### Article history:

Received 26 June 2016

Received in revised form 27 August 2016

Accepted 30 August 2016

Available online 31 August 2016

### Keywords:

Acetylenic sulfones

Activated methylenes

Tetrasubstituted furans

## ABSTRACT

An efficient synthesis of diversely functionalized furans is developed via Cu-mediated intermolecular annulative couplings of acetylenic sulfones and activated methylenes, which provides a straightforward and atom-economic way to tetrasubstituted furan derivatives in good yields.

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## 1. Introduction

Furans constitute one of the most prominent classes of heterocyclic compounds. Substituted furans widely occur as key structural units in many biologically active natural products, pharmaceutical substances, and organic materials.<sup>1</sup> Functionalized furans have also frequently been used as useful building blocks in organic synthesis.<sup>2</sup> Therefore, considerable efforts have been devoted to the development of efficient synthetic methods for the construction of this heteroaromatic core.<sup>3</sup> Substituted furans are usually synthesized by the reaction of 1,3-dicarbonyl compounds and alkynes,<sup>4</sup> functionalization of an existing furan ring,<sup>5</sup> and transition metal-catalyzed intramolecular cyclization of alkyne-, allene-containing compounds.<sup>6</sup> Recently, the annulation of alkynes represents an efficient approach to furan derivatives.<sup>7</sup> However, these existing methods more or less have some limitations such as poor selectivity, and limited reaction scope with regard to product substitution patterns, especially for polyfunctionalized furans. The development of new approaches to multifunctionalized poly-substituted furans from readily available starting materials is still highly desirable in organic chemistry.

Sulfones are a versatile functional group and the chemistry of sulfones has been extensively studied in organic synthesis over the past several decades.<sup>8</sup> Sulfones have many remarkable properties and display a diverse range of behaviors. Some sulfonyl furans

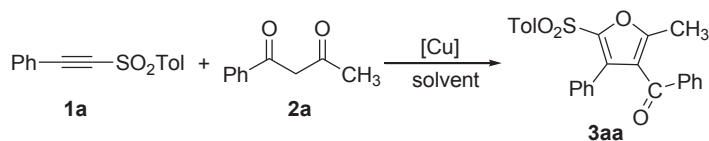
exhibit potent biological activities as an endothelial lipase inhibitor or EP1 receptor antagonist. Sulfonyl furans are also potential precursors to other useful differently substituted furans derivatives.<sup>9</sup> However, to the best of our knowledge, methods enabling the synthesis of sulfonyl-containing polysubstituted furan are limited. As part of our continued research interest in the reactivity of acetylenic sulfones,<sup>10</sup> we report herein the intermolecular reaction of acetylenic sulfones and activated methylenes, which provides a facile and atom-economical way to sulfonyl-containing tetrasubstituted furans.

## 2. Results and discussion

Firstly, we select 1-phenyl-2-(*p*-tolylsulfonyl)ethylene (**1a**) and benzoylacetone (**2a**) as the model substrates to optimize the reaction conditions. The results are compiled in Table 1. The experimental results show that in the absence of a copper promoter, no reaction occurred when a solution of **1a** and **2a** in DMF was stirred at 100 °C for 48 h (Table 1, entry 1). Different copper salts were examined to reveal Cu(acac)<sub>2</sub> and Cu(OAc)<sub>2</sub>·H<sub>2</sub>O as effective promoters for the reaction, and the desired product **3aa** was obtained in 51% yield when 1 equiv of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O was used (Table 1, entries 2–3). In contrast, Cu(OTf)<sub>2</sub> and CuBr<sub>2</sub> were not effective for this reaction and the substrate **1a** was recovered completely (Table 1, entries 4–5). Only trace of **3aa** was detected when AgOAc was used as promoter (Table 1, entry 6). Screening different loading amounts of the promoter showed the reaction was best performed with 1.6 equiv of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O to provide the product **3aa** in 82% yield, while either lower or higher loading amount led to decreased

\* Corresponding author. Fax: +86 0553 3883517; e-mail address: [xiemh@mail.ahnu.edu.cn](mailto:xiemh@mail.ahnu.edu.cn) (M. Xie).

**Table 1**  
Optimization of reaction conditions<sup>a</sup>



Entry	[Cu]	Solvent	Time (h)	Temp(°C)	Yield <sup>b</sup> (%)
1	—	DMF	48	100	NR
2	Cu(acac) <sub>2</sub> (1.0 equiv)	DMF	48	100	28
3	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.0 equiv)	DMF	24	100	51
4	Cu(OTf) <sub>2</sub> (1.0 equiv)	DMF	48	100	NR
5	CuBr <sub>2</sub> (1.0 equiv)	DMF	48	100	NR
6	AgOAc (1.0 equiv)	DMF	48	100	Trace
7	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.4 equiv)	DMF	13	100	64
8	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	DMF	13	100	82
9	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (10 mol %), NaOAc (1.6 equiv)	DMF	48	100	5
10	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.8 equiv)	DMF	13	100	75
11	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	DMSO	15	100	17
12	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	Toluene	15	100	28
13	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	THF	15	100	36
14	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	CH <sub>3</sub> CN	24	100	Trace
15	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	DMF	15	120	73
16	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	DMF	15	80	64
17 <sup>c</sup>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O (1.6 equiv)	DMF	15	100	56

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), 2 mL of solvent, air.

<sup>b</sup> Isolated yield based on **1a**.

<sup>c</sup> Run under argon atmosphere with DMF degassed with three freeze-pump-thaw cyclings.

yields (Table 1, entries 7–10). The use of other solvents, including DMSO, toluene, THF, and CH<sub>3</sub>CN, instead of DMF gave inferior results (Table 1, entries 11–14). Increasing the reaction temperature to 120 °C or decreasing the reaction temperature to 80 °C resulted in lower yields (Table 1, entries 15–16). A significantly decreased yield was obtained when the reaction was performed under argon atmosphere (Table 1, entry 17), which suggests that oxygen in air play an important role in the reaction. It is noteworthy that the reaction is highly regioselective and **3aa** was the only product detected in the reaction system. On the basis of the above results, we selected the following conditions for further experiments: **1a** (0.5 mmol), **2a** (0.6 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (1.6 equiv) in DMF (2 mL) at 100 °C.

Under the optimized reaction conditions, we examined the reaction scope with regard to various activated methylenes (**2**) with 1-phenyl-2-(*p*-tolylsulfonyl)ethylene (**1a**). The results are summarized in Table 2. The results show that acetylenic sulfone **1a** could react with different activated methylenes to afford corresponding furan derivatives in moderate to good yields. The activated methylenes could be 1,3-diketone (**2a–2f**), β-carbonyl ester (**2g** and **2h**) and benzoylacetone (**2i**). The corresponding tetrasubstituted furans containing sulfonyl and carbonyl (**3aa–3af**), ethyloxy carbonyl (**3ag** and **3ah**) or cyano (**3ai**) can be obtained in good yields. Notably, cyclohexane-1,3-dione was also compatible with this reaction to provide the corresponding bicyclic 6,7-dihydro-5*H*-benzofuran-4-ones **3ad–3af** in 75%–81% yields.

The structure of compound **3aa** was confirmed by X-ray diffraction analysis (Fig. 1).<sup>11</sup> The molecular structure of **3aa** shows that the methyl of **2a** is attached to the C2 position of the furan ring. The regioselectivity is different from that of previously reported relevant reactions of benzoylacetone with alkynoates, which provided 2-phenyl-3-acyl furan derivatives as product.<sup>12</sup>

To further explore the substrate scope, the reactions of benzoylacetone (**2a**) with a wide range of acetylenic sulfones were then examined and the results are summarized in Table 3. The reaction is

quite general with regard to differently substituted acetylenic sulfones and the desired sulfonyl and acyl-substituted furans were obtained in up to 86% yield. The substituent R<sup>1</sup> on acetylenic sulfones can be an aryl or an alkyl group such as phenyl, electron-rich aryl, electron-poor aryl, *n*-pentyl and cyclopropyl groups, with no appreciable difference in the yields being observed. The substituent R<sup>2</sup> on acetylenic sulfones can be a *p*-tolyl, phenyl, *p*-chlorophenyl or a methyl group, while a significant decrease in yield was observed in the case of R<sup>2</sup> being a methyl group (**3bc**, **3bf** and **3bj**).

To further extend the reaction scope, the reactions of benzoylacetone (**2a**) with differently substituted acetylenic sulfones were also investigated, which provided the corresponding sulfonyl and cyano-substituted furans **3ca–3cc** in good yields under the same reaction conditions (Scheme 1). However, when phenylacetylene was reacted with benzoylacetone under the optimized reaction conditions, no desired furan product was formed with only the homocoupling product of phenylacetylene being obtained.

To glean some insight into the reaction mechanism, some control experiments were conducted (Scheme 2). The addition of radical scavengers such as TEMPO and 2,6-di-*tert*-butyl-4-methylphenol (BHT) significantly inhibited the reaction (Scheme 2), which suggests the involvement of radical processes in the reaction.

Based on above experimental results and related previous studies,<sup>12b,13</sup> a mechanism for the annulation of acetylenic sulfones and activated methylenes was proposed as shown in Scheme 3. Firstly, a Michael-type addition of **2a** (probably via its enol form) to the electron-deficient acetylenic sulfone **1a** might occur under the catalysis of the Lewis acidic Cu(OAc)<sub>2</sub>·H<sub>2</sub>O to provide **Int-1**.<sup>14</sup> This intermediate would be converted into the thermodynamically more stable compound **4** via isomerization involving multiple proton transfers.<sup>15</sup> Compound **4** (or its enol form **4'**) might undergo a radical hydride process by oxygen or a SET (single electron-transfer) process by Cu(OAc)<sub>2</sub>·H<sub>2</sub>O to form the **Int-2** or **Int-2'**. Then, an intramolecular radical cyclization would generate the

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