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Synthesis of 2,4,5-Trisubstituted Furans via a Triple C(sp^3)−H Functionalization Reaction Using Rongalite as the C1 Unit

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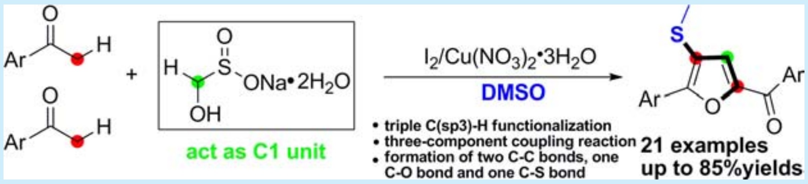
Supporting Information

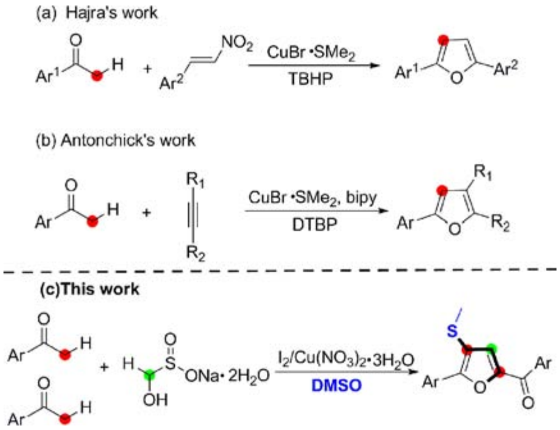


ABSTRACT: A highly efficient $I_2/Cu(NO_3)_2\cdot 3H_2O$-mediated triple C($sp^3$)−H functionalization reaction for the synthesis of 2,4,5-trisubstituted furans from aryl methyl ketones and rongalite by employing rongalite as a C1 unit has been developed. This method allows rapid access to (2-acyl-4-methylthio-5-aryl) furans. Preliminary mechanistic studies indicate that *in situ* generated dimethyl(phenacyl)-sulfonium iodine and HCHO were probably the key intermediates in this transformation.

Rongalite ($Na^+HOCH_2SO_2^-\cdot 2H_2O$) is a useful and cheap industrial product which has been widely used in the dye, rubber, and veterinary industries.[1] It is also used as a versatile reagent in synthetic chemistry.[2] The most common uses of rongalite are (i) as a source of SO^{2-} anions for the preparation of sulfones and sultines;[3] (ii) as a promoter of SET reactions;[4] and (iii) as a reduction system in combination with tellurium.[5] In our research process, we found that rongalite could be employed as a HCHO source, which could act as a C1 unit to participate in subsequent transformations. To the best of our knowledge, the application of rongalite as a C1 unit in synthesis methodology has not yet been reported. We aim to use this highly efficient process in the construction of a valuable heterocyclic scaffold.

Furans constitute one of the most common and important classes of heterocycles. They exhibit a range of pharmaceutical activities[6] and present as key structural units in many natural products.[7] They have also been used as basic building blocks in synthetic chemistry and materials science;[8] as a consequence, considerable research has been devoted to constructing polysubstituted furans.[9−12] The most common synthetic routes to furans are (i) the cyclocondensation of 1,4-dicarbonyl compounds (Paal−Knorr furan synthesis);[9] (ii) the intermolecular annulation of 1,3-dicarbonyl compounds with α-halogen ketones (Feist−Benary furan synthesis);[10] (iii) the cycloisomerization of unsaturated carbonyl compounds, alcohols, and esters;[11] and (iv) the cycloaddition reactions of unsaturated compounds.[12] In the past few years, advances have shed light on the methods involving direct C−H bond functionalization to construct the furan's scaffold.[13] Among these, the methods involving a direct C(sp^3)−H bond are still challenging due to their inertia and weak coordination. Significantly, Hajra and coworkers reported a novel synthesis of furans through the Cu-mediated C(sp^3)−H bond functionalization of aryl methyl ketones (Scheme 1a).[14] Recently, Antonchick's group developed a furan synthesis via a Cu-catalyzed C(sp^3)−H bond functionalization of aryl methyl ketones with alkynes (Scheme 1b).[15] Despite these recent advances, the direct C(sp^3)−H bond functionalization of aryl methyl ketones with more readily available substrates is still a fascinating topic. Herein, we report the first known example of an $I_2/Cu(NO_3)_2\cdot 3H_2O$ mediated triple C(sp^3)−H bond functionalization reaction of aryl methyl ketones and rongalite for the convenient construction of the furan skeleton by employing rongalite as a C1 unit (Scheme 1c).

Scheme 1. Selective Examples of Furans Synthesis via the C(sp^3)−H Bond Functionalization



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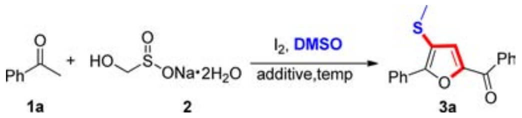
Initially, the reaction of acetophenone **1a** and rongalite **2** was screened in DMSO at 100 °C in the presence of I_2. To our delight, the desired compound (4-(methylthio)-5-phenylfuran-2-yl)(phenyl)methanone **3a** was obtained in 15% yield (Table 1, entry 1). Thus, we screened a series of Brønsted acids for this reaction, such as PTSA, HOAc, TFA, and CF_3SO_3H (entries 2–5), and PTSA and CF_3SO_3H gave a slightly higher yield. Alternatively, Lewis acids including $AlCl_3$, $FeCl_3$, $H_3PO_4\cdot 12MoO_3$, $CuSO_4\cdot 5H_2O$, $Cu(OAc)_2$, and $Cu(NO_3)_2\cdot 3H_2O$ (entries 6–11) were also investigated for this reaction. Gratifyingly, $Cu(NO_3)_2\cdot 3H_2O$ afforded the desired product in 62% yield. A range of different temperatures were subsequently screened in order to further improve the yield (entries 12–15), and 100 °C was shown to be optimal. Finally, the dose of I_2 was altered (entries 16–19), with 1.5 equiv giving the best yield of **3a**.

Table 1. Optimization of the Reaction Conditions[a]

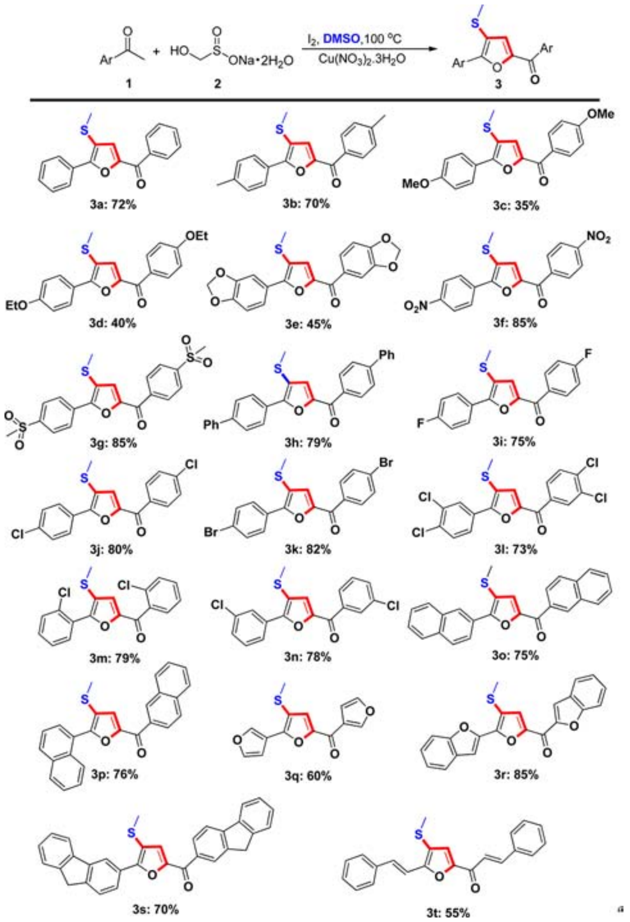


entry	I_2 (equiv)	additive	temp (°C)	yield[b] (%)
1	1.0	–	100	15
2	1.0	PTSA	100	30
3	1.0	HOAc	100	trace
4	1.0	TFA	100	trace
5	1.0	CF_3SO_3H	100	32
6	1.0	$AlCl_3$	100	40
7	1.0	$FeCl_3$	100	46
8	1.0	$H_3PO_4\cdot 12MoO_3$	100	48
9	1.0	$CuSO_4\cdot 5H_2O$	100	52
10	1.0	$Cu(OAc)_2$	100	30
11	1.0	$Cu(NO_3)_2\cdot 3H_2O$	100	62
12	1.0	$Cu(NO_3)_2\cdot 3H_2O$	rt	trace
13	1.0	$Cu(NO_3)_2\cdot 3H_2O$	50	trace
14	1.0	$Cu(NO_3)_2\cdot 3H_2O$	80	50
15	1.0	$Cu(NO_3)_2\cdot 3H_2O$	120	55
16	–	$Cu(NO_3)_2\cdot 3H_2O$	100	0
17	0.5	$Cu(NO_3)_2\cdot 3H_2O$	100	45
18	**1.5**	**$Cu(NO_3)_2\cdot 3H_2O$**	**100**	**72**
19	2.0	$Cu(NO_3)_2\cdot 3H_2O$	100	65

[a] Reaction conditions: **1a** (1.0 mmol), **2** (2.0 mmol), additive (0.25 mmol), solvent (1.0 mL) for 8 h. [b] Isolated yields based on **1a**. Reactions were carried out in a pressure vessel.

The substrate scope of this transformation was subsequently evaluated, and the optimized reaction conditions were found to be applicable to a broad range of substrates. As shown in Scheme 2, aryl methyl ketones bearing electronically neutral (4-H, 4-Me), electron-donating (4-OMe, 4-OEt, and 3,4-OCH_2O), and electron-withdrawing (4-NO_2, 4-SO_2Me, 4-Ph) substituents all reacted smoothly to afford the corresponding polysubstituted furans in moderate to excellent yields (35–85%; **3a–h**). Much to our satisfaction, the conditions were found to be mild enough to be compatible with halogenated (4-F, 4-Cl, 4-Br, 3,4-Cl_2, 2-Cl, 3-Cl) substrates (73–82%, **3i–n**), which provides the potential for further functionalization. Meanwhile, sterically hindered 2-naphthyl methyl ketone and 1-naphthyl methyl ketone furnished the desired products **3o** and **3p** in 75% and 76% yields, respectively. Furthermore, the optimal conditions were successfully applied to the heteroaryl methyl ketones, such as furyl, benzofuryl, and fluorenyl, giving the corresponding products in good yields (60–85%, **3q–s**). Gratifyingly, the optimized conditions were also successfully applied to an unsaturated methyl ketone, giving the corresponding products **3t** in 55% yield. The structure of **3k** was identified by single-crystal X-ray diffraction (please see Supporting Information (SI)).

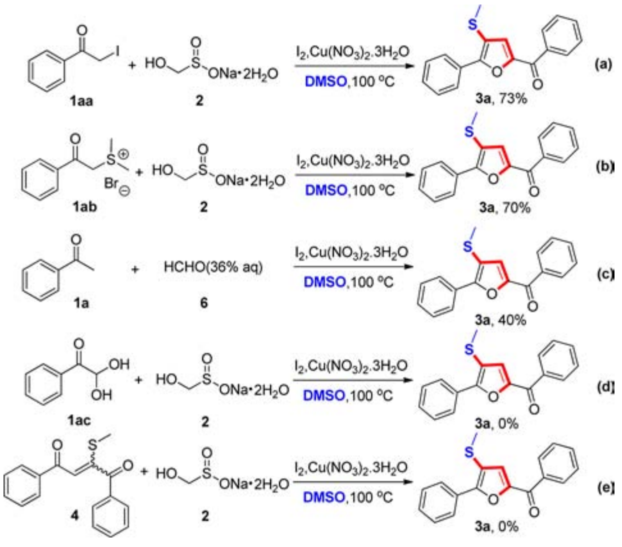
Scheme 2. Substrates Scope of Three-Component Reaction with Aryl Methyl Ketones[a,b]



[a] Reaction conditions: **1** (2.0 mmol), **2** (4.0 mmol), I_2 (3.0 mmol), $Cu(NO_3)_2\cdot 3H_2O$ (0.5 mmol), solvent (2.0 mL) for 8 h. [b] Isolated yields based on **1**. Reactions were carried out in a pressure vessel.

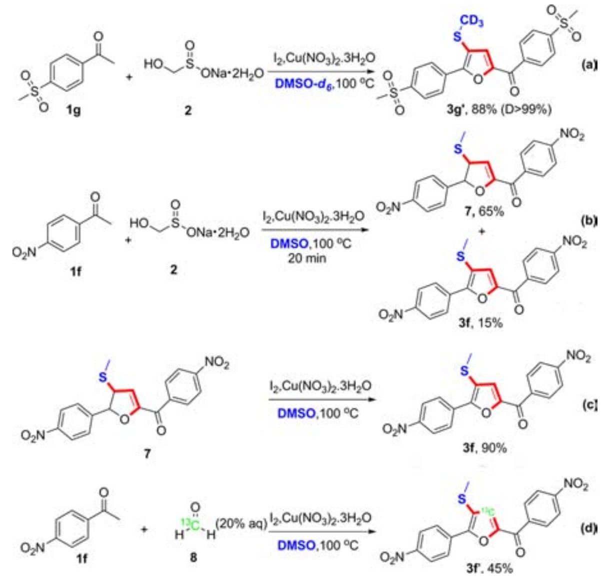
To gain some insights into the reaction mechanism, a series of control experiments were performed (Scheme 3). The reaction of α-iodo acetophenone **1aa** with rongalite **2** was found to be successful, and the expected product **3a** was obtained in 73% yield under the standard conditions (Scheme 3a). This indicates that **1aa** may be an important intermediate in this transformation. Furthermore, the reaction of dimethyl(phenacyl)-sulfonium bromide **1ab** with rongalite **2** under the standard conditions afforded **3a** in 70% yield (Scheme 3b). When **2** was replaced with formalin **6**, **3a** was obtained in 40% yield (Scheme 3c). Inspired by our previous work involving aryl methyl ketones in an I_2/DMSO system,[16] the hydrated hemiacetal **1ac** and 2-(methylthio)-1,4-diphenylbut-2-ene-1,4-dione **4** were subjected to the optimized conditions; however, the desired product **3a** was not obtained (Scheme 3d, 3e). These results clearly confirm that **1aa**, **1ab**, and HCHO were probably intermediates in the transformation, but **1ac** and **4** were not.

Scheme 3. Control Experiments (part a)

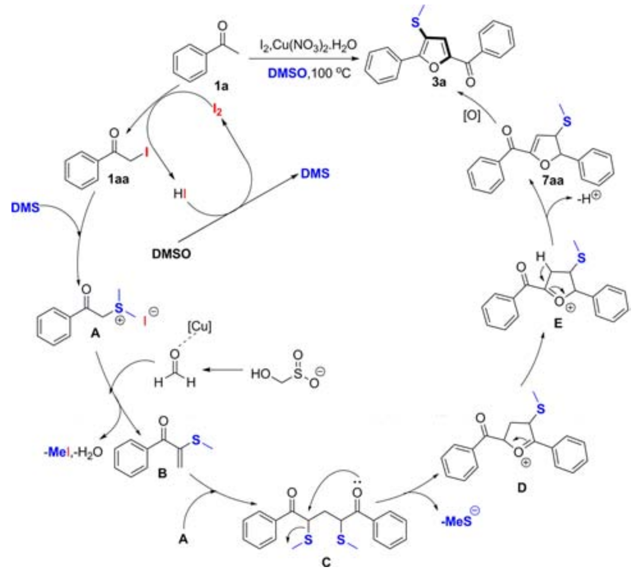


The reaction of **1g** and **2** was also performed in DMSO-d_6 to investigate the mechanism further. Deuterated product **3g′** was generated (Scheme 4a), clearly confirming that DMSO is the source of the methylthio group. When the reaction of 4-NO$_2$-phenylmethyl ketone **1f** and **2** under the standard conditions was stopped at 20 min, the dihydrofuran product **7** was obtained (Scheme 4b), which could be transformed to the aromatized product **3f** in 90% yield under the standard conditions (Scheme 4c). This demonstrates that dihydrofuran product **7** is likely to be an intermediate in the transformation. Furthermore, the ^{13}C labeled experiment of HCHO-^{13}C and **1f** was performed under the standard conditions to afford the 3-position ^{13}C labeled product **3f′** (Scheme 4d).

Scheme 4. Control Experiments (part b)



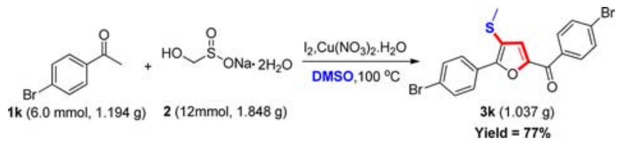
Scheme 5. A Possible Mechanism



On the basis of the results in the current study and previous reports, a possible mechanism has been proposed using **1a** and **2** as examples (Scheme 5). Initially, the reaction of **1a** with molecular iodine results in the formation of α-iodo acetophenone **1aa**, which is subsequently converted into dimethyl (phenacyl)-sulfonium iodine **A** in the presence of dimethyl sulfide (DMS) generated from the reduction of dimethyl sulfoxide (DMSO). At the same time, HCHO is generated *in situ* from the decomposition of rongalite,[2,17] which could be captured by **A** to form intermediate **B** (determined by GC-MS; please see SI) with the help of Cu(NO$_3$)$_2$·3H$_2$O. Compound **B** is then attacked by another molecule **A** to produce intermediate **C**. An intramolecular nucleophilic addition of the carbonyl oxygen atom then occurs to produce the oxonium intermediate **D**, with subsequent isomerization to form **E**. Finally, intermediate **E** would undergo a sequential deprotonation and oxidative aromatization to afford the desired product **3a**.

To demonstrate the synthetic potential of this method, the reaction of 4-Br-phenylmethyl ketone **1k** and rongalite **2** was carried out on a gram scale (Scheme 6). To our delight, the reaction proceeded well, and the desired product **3k** was isolated in 77% yield.

Scheme 6. Gram Scale Experiment



In summary, we have developed a novel I$_2$/Cu(NO$_3$)$_2$·3H$_2$O-mediated triple C(sp^3)−H functionalization reaction for the synthesis of 2,4,5-trisubstituted furans from aryl methyl ketones and rongalite by employing rongalite as a C1 unit. This method is facile and highly efficient and has a broad scope. A mechanistic study revealed that the *in situ* generated dimethyl-(phenacyl)-sulfonium iodine and HCHO were probably the key intermediates in this transformation. Remarkably, this reaction allows rapid access to (2-acyl-4-methylthio-5-aryl) furans, which were challenging to prepare using existing methods. Further studies to elucidate a detailed mechanism and identify further applications of this strategy 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.5b03552.

Crystallographic data for **3k** (CIF)

Crystallographic data for **3u** (CIF)

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra are involved (PDF)

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Notes

The authors declare no competing financial interest.

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