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Synthesis of Polysubstituted Furans via Copper-Mediated Annulation of Alkyl Ketones with α,β-Unsaturated Carboxylic Acids

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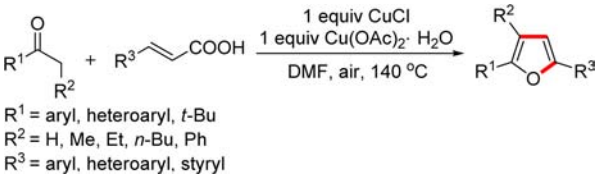
ABSTRACT



A novel copper-mediated annulation of alkyl ketones with α,β-unsaturated carboxylic acids has been accomplished. This reaction provides a facile and regio-defined method for the synthesis of 2,3,5-trisubstituted furans from simple chemical reagents.

Furans, one of the most important classes of five-membered heterocyclic compounds, can be found as key structural units in many natural products and diverse therapeutic agents.[1] They are also served as useful intermediates in synthetic chemistry.[2] Accordingly, tremendous efforts have been devoted to the development of versatile methods for constructing this heteroaromatic core.[3] Apart from the classical cyclocondensation of dicarbonyl compounds, strategies exploring transition-metal-catalyzed intramolecular cycloisomerization of alkyne- and allene-containing compounds have been extensively studied during the past decades.[3c] Although this intramolecular approach offers an important method in furan synthesis, the preparation of starting alkyne- and allene-containing compounds usually requires a multistep synthesis which may possesses troublesome operation. On the other hand, the intermolecular approach would provide a more direct and regio-defined route to furans with operational simplicity from simple and readily available chemical reagents.[4] Given the great importance of furans in natural and synthetic substances, the development of a more selective and straightforward intermolecular approach to construct polysubstituted furans from simple and cheap chemical reagents is still in great demand.

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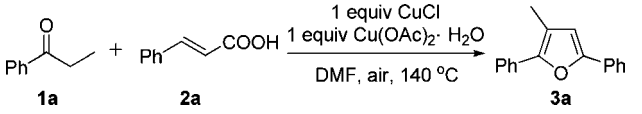
Carboxylic acids have been recognized as important starting materials in synthetic chemistry due to their low cost and ready availability.[5] Decarboxylative coupling represents a novel strategy to form carbon−carbon and carbon−heteroatom bonds by the extrusion of carbon dioxide from carboxylic acids.[6] During recent years, the area of decarboxylative dehydrogenative cross-coupling has received much attention, and significant progress including arylation,[7] alkenylation,[8] acylation,[9] and etherification[10] has been made. In particular, Liu et al have demonstrated copper-catalzyed decarboxylation reactions via a free-radical process involving $C(sp^3)-C(sp^2)$ coupling and trifluoromethylation.[11] In the course of our continuing efforts toward reactions of α,β-unsaturated carboxylic acids involving both C−H functionalization and decarboxylation process,[12] we previously investigated a copper-catalyzed annulation of 2-alkylazaarenes with α,β-unsaturated carboxylic acids leading to C-2 arylated indolizines.[12b] Herein, we wish to report a copper-mediated reaction of alkyl ketones with α,β-unsaturated carboxylic acids, illustrating a novel and convenient access to 2,3,5-trisubstituted furans.

We selected propiophenone and cinnamic acid as the model substrates for the optimization. It was found that the combination of 1 equiv of CuCl and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ afforded the furan product **3a** in the highest 72% yield after stirring at 140 °C for 24 h (Table 1, entry 1). It is important to note that the reaction is highly regioselective with respect to both ketone and acid: we did not observe any regioisomer of **3a**. The reaction appeared to be more effective in the presence of both CuCl and $Cu(OAc)_2 \cdot H_2O$ since the yields decreased when one copper source was employed in this reaction (Table 1, entries 2−9). The amount of the two copper salts was also examined. Increasing or decreasing the amount of both CuCl and $Cu(OAc)_2 \cdot H_2O$ resulted in lower yields (Table 1, entries 10−11). The yields were also lowered when the ketone/acid ratio was changed (Table 1, entries 12−14). Screening of other solvents such as DMA, DMSO, NMP, and mesitylene (Table 1, entries 15−18) indicated that only DMA delivered a comparable yield with that in DMF (Table 1, entry 16). No product was detected in the absence of copper salts (Table 1, entry 19). However, employing a catalytic amount of copper salts with external oxidants (such as $K_2S_2O_8$, BQ, DDQ, BPO, DTBP, and TBHP) and additives (such as LiOAc, NaOAc, KOAc, CsOAc, and Et_3N) did not yield better results (see Supporting Information).

Table 1. Reaction Optimization[a]



1a 2a 3a

entry	change of the standard conditions	yield (%)[b]
1	none	72
2	1 equiv of CuCl	46
3	1 equiv of $Cu(OAc)_2 \cdot H_2O$	50
4	1 equiv of CuBr	39
5	1 equiv of CuI	12
6	1 equiv of $CuCl_2$	trace
7	1 equiv of $CuBr_2$	0
8	2 equiv of CuCl	51
9	2 equiv of $Cu(OAc)_2 \cdot H_2O$	56
10	0.5 equiv of CuCl/$Cu(OAc)_2 \cdot H_2O$	55
11	1.5 equiv of CuCl/$Cu(OAc)_2 \cdot H_2O$	67
12	2.0 equiv of cinnamic acid	35
13	1.0 equiv of ketone	53
14	3.0 equiv of ketone	67
15	DMA	69
16	DMSO	45
17	NMP	57
18	mesitylene	31
19	no copper salts	0

[a] Reaction conditions: propiophenone (1.0 mmol), cinnamic acid (0.5 mmol), CuCl (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol), DMF (1 mL), 140 °C, air, 24 h. [b] Isolated yield.

With the optimized reaction conditions established, we turned our attention toward examining the acid scope of this furan synthesis process in Scheme 1. A variety of substituents on the aryl moiety of cinnamic acids were tolerated to provide the corresponding furans. Comparison of these results indicated that the product yield is slightly affected by the position of substituents on the aryl ring. The yields for the methyl and chloro substituted products **3b**−**d** and **3i**−**k** follow the order *ortho* < *meta* < *para*. The observed trend could be rationalized by the steric effect of the substrates. It was also found that substituted cinnamic acids with electron-donating groups such as methyl and methoxyl delivered relatively lower yields than those obtained with electron-withdrawing groups such

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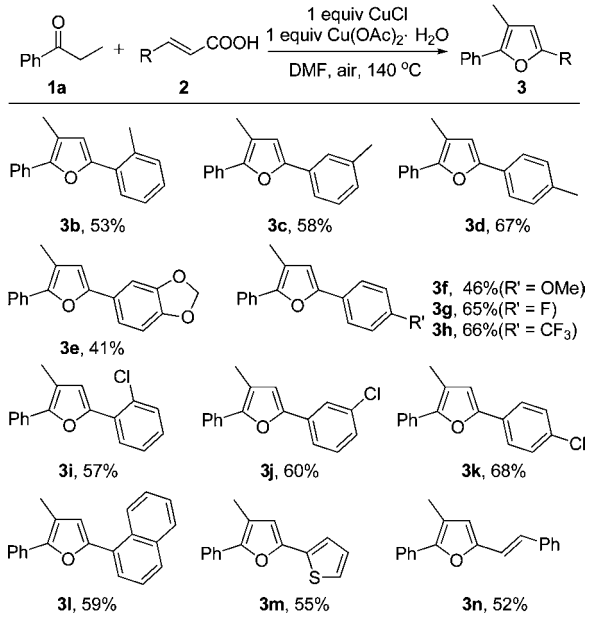
as trifluoromethyl, fluoro, and chloro. The stucture of **3e** was comfirmed by single crystal X-ray analysis (Figure 1). Naphthyl and thiophenyl substituted α,β-unsaturated carboxylic acids could also be employed in this reaction to afford the products **3l** and **3m** in moderate yields. In addition, C-5 alkenylated furan product **3n** was accessed by employing 5-phenylpenta-2,4-dienoic acid as the annulation partner. Unfortunately alkyl substituted α,β-unsaturated carboxylic acid such as crotonic acid was not suitable under the current reaction conditions.

Scheme 1. Annulation of Propiophenones with Different α,β-Unsaturated Carboxylic Acids[a]



[a] Reaction conditions: propiophenone (1.0 mmol), α,β-unsaturated carboxylic acid (0.5 mmol), CuCl (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol), DMF (1 mL), 140 °C, air, 24 h. Isolated yield.

To further explore the substrate scope, various alkyl ketones were then investigated as depicted in Scheme 2. Propiophenones bearing substituents such as phenyl and *n*-Bu delivered the corresponding furans **3o** and **3p** in moderate yields. Particularly, 2,2-dimethyl-3-hexanone could be readily employed, allowing the preparation of furan **3q** with alkyl substituents on both C-2 and C-3 positions. 2,5-Disubstituted furan products **3r** and **3s** were synthesized from methyl ketones such as acetophenone and napthphenone under modified reaction conditions, albeit in lowered yields. 1-(2-Thienyl)-1-propanone was compatible in this reaction to give the desired product **3t** with double heterocyclic structure. Propiophenones bearing a methoxy group on the para position of the aryl ring furnished the product **3u** in higher yield than the product **3v** with a fluoro group.

It is noteworthy that replacing cinnamic acid with styrene under the above reaction conditions in Table 1 could also deliver the same furan product **3a**. After optimization of this reaction, the furan product **3a** was isolated in 65% yield in the presence of 2 equiv of CuCl in DMF as shown in Scheme 3. The effect of the substitution on the ketone moiety was examined, and similar results were obtained with the previous method using cinnamic acids

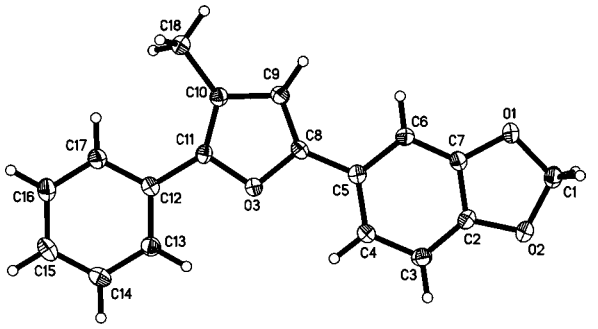
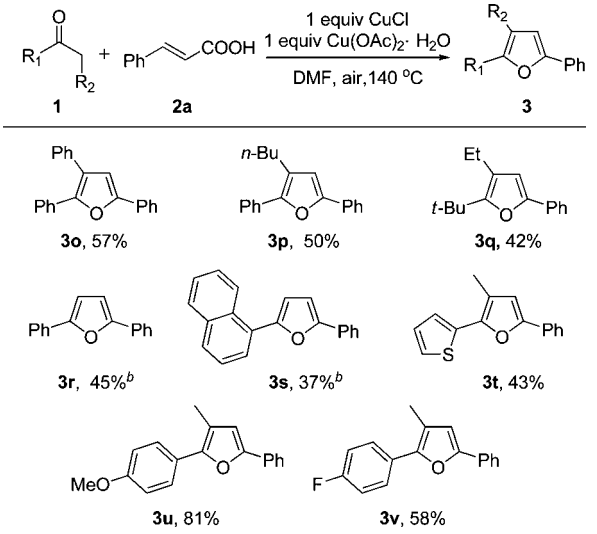


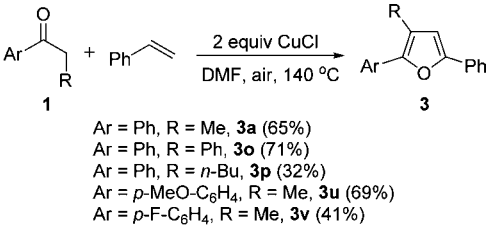
Figure 1. X-ray single crystal structure of **3e**.

Scheme 2. Annulation of Different Alkyl Ketones with Cinnamic Acids[a,b]



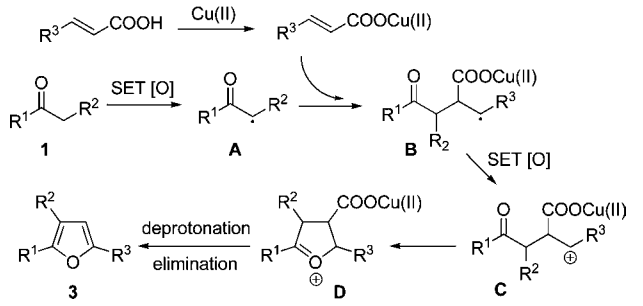
[a] Reaction conditions: alkyl ketone (1.0 mmol), cinnamic acid (0.5 mmol), CuCl (0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol), DMF (1 mL), 140 °C, air, 24 h. Isolated yield. [b] CuCl (1.0 mmol), KOAc (1.0 mmol), DMF (1 mL), 140 °C, air, 24 h.

Scheme 3. Annulation of Alkyl Ketones with Styrenes[a]

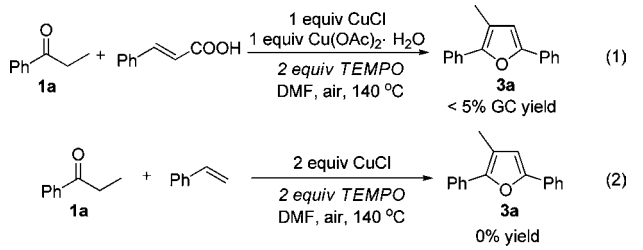


[a] Reaction conditions: ketone (1.0 mmol), styrene (0.5 mmol), CuCl (1.0 mmol), DMF (1 mL), 140 °C, air, 24 h. Isolated yield.

Scheme 4. Plausible Mechanism



as the annulation partner. Comparing the yields of the same furan products in Schemes 2 and 3 indicates that, except for the furan product **3o** in a higher yield, other products such as **3p**, **3u**, and **3v** were isolated in lower yields in Scheme 3 than the yields in Scheme 2. Although copper has been reported to catalyze the protodecarboxylation reaction of cinnamic acid to generate styrene,[6d] we did not detect the formation of styrene in the annulaton reaction of cinnamic acids.



In the above two reactions, the addition of 2 equiv of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) as the radical inhibitor blocked the formation of expected furan product **3a** (eqs 1 and 2), which may support a radical initiation pathway. Based on the above experimental results and previous reports,[11,13] a plausible reaction mechanism could be proposed in Scheme 4. Under the oxidative conditions, reaction of the acrylic acid with copper salts would generate cupric cinnamate, and alkyl ketone would produce the carbon-centered radical **A**. Addition of radical **A** to the α-position of the double bond in cupric cinnamate would give the adduct radical **B**. Through further single electron oxidation, this adduct radical **B** would be converted to intermediate **C**. The subsequent intramolecular cyclization of intermediate **C** resulted in the formation of intermediate **D**, which proceeds via deprotonation and elimanation to generate the furan product. In the case of employing styrene in the annulation reaction, the reaction mechanism is similar except that this process involves dehydrogenation and generates intermediates without the cupric carboxylate group.

In summary, we have demonstrated the copper-mediated annulation via an oxidative free-radical process from alkyl ketones and α,β-unsaturated carboxylic acids in a wide substrate scope. This reaction provides a novel synthetic route to 2,3,5-trisubstituted furans.

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Supporting Information Available. Experimental procedure, characterization of all compounds, and crystallographic information file for compound **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.