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Copper(I)-Catalyzed Radical Addition of Acetophenones to Alkynes in Furan Synthesis

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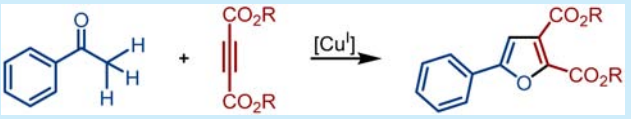
Supporting Information

ABSTRACT: A synthesis of multisubstituted furans from readily available acetophenones and electron-deficient alkynes via direct C(sp^3)−H bond functionalization under radical reaction conditions is described. The developed transformation is catalyzed by copper(I) salts using di-*tert*-butyl peroxide as an external oxidant. This method offers an efficient access to biologically important scaffolds from simple compounds.



Furans represent one of the most versatile and important classes of heterocycles, being present in many natural products and biologically active drug molecules (Figure 1).[1]

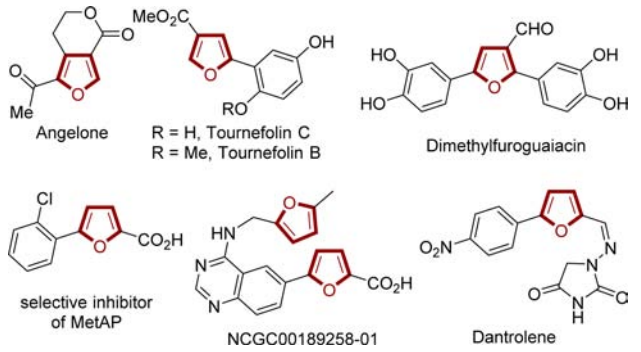


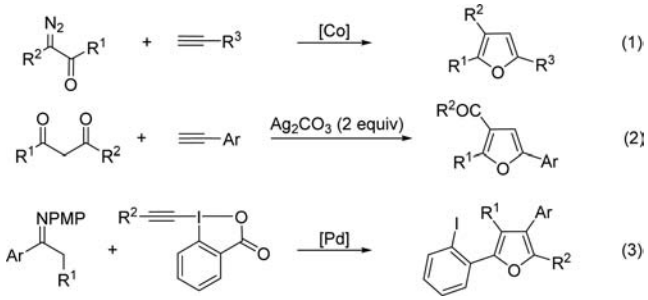
Figure 1. Furan derived natural products and drugs.

Multisubstituted derivatives have found widespread application in biological studies, agrochemicals, and pharmaceuticals. Furthermore, furans are important in organic synthesis as targets and building blocks.[2] The development of novel methods for the synthesis of multisubstituted furans is in high demand.

Historically, the Paal−Knorr method, which relies on acid catalyzed intramolecular cyclization of 1,4-dicarbonyl, found wide application in organic synthesis.[3] The Feist−Benary method represents one of first approaches for the intermolecular annulation of β-dicarbonyl compounds and α-halogen ketones in the synthesis of substituted furan derivatives.[4] In the past few decades, transition-metal-catalyzed and metal-free intramolecular approaches to the synthesis of multisubstituted furan derivatives have been reported.[2a−f] Intermolecular approaches offer an attractive method for the straightforward formation of the furan scaffold from simple building blocks. In this context an annulation of alkynes represents an efficient approach for the synthesis of the furan core.[5]

In the past few decades several attractive methods for furan synthesis have been developed using transition-metal-catalyzed or metal-free processes with alkynes. Zhang's group demonstrated the synthesis of furans from alkynes and α-diazocarbonyls through cobalt-catalyzed cyclization (Scheme 1, eq 1).[6] Lei and co-workers reported a novel silver-mediated

Scheme 1. Synthesis of Furan from Alkynes



efficient furan synthesis method by annulation of alkynes with 1,3-diketones (Scheme 1, eq 2).[7] However, this method requires a stoichiometric amount of silver carbonate. Recently, this method was realized in a catalytic reaction using molecular iodine as an effective redox catalyst for the oxidative cross-coupling of terminal alkynes with β-dicarbonyl compounds.[8] A palladium-catalyzed synthesis of furan has been developed by Yoshikai and co-workers employing imine derivatives of acetophenone and alkynylbenziodoxolones (Scheme 1, eq 3).[9] Nevertheless, the reported methods require activated or prefunctionalized precursors. The synthesis of furans from nonactivated carbonyl compounds without an active methylene group, such as acetophenones, requires the use of stoichiometric amounts of metal salts.[10] Despite the recent advances with Rh, Pd, Au, and Ag catalysts, Cu-catalyzed synthesis of

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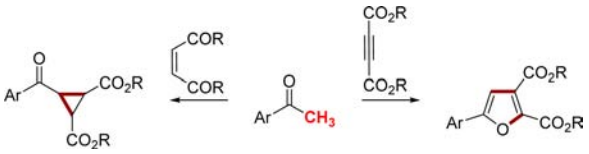
furans through a radical mechanism is highly attractive.[11] We envisaged a novel strategy of copper(I)-catalyzed annulation of acetophenone with alkyne to access multisubstituted furan derivatives. Here we report the first catalytic C(sp^3)−H bond functionalization of acetophenones in an annulation reaction for the synthesis of multisubstituted furans.

Our group focuses on the development of novel methods for the synthesis and transformation of heterocycles through direct C−H bond functionalization.[12] Recently, we developed the intermolecular annulation of electron-deficient alkenes with acetophenones for the synthesis of cyclopropane derivatives (Scheme 2).[12m] The developed reaction was catalyzed by a

Scheme 2. Radical Annulation of Acetophenones

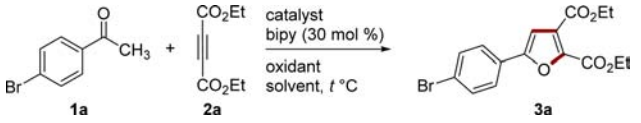


copper(I) salt in the presence of a ligand such as 2,2′-bipyridine (bipy). The ligand was essential for the catalytic activity of the copper(I) salt. During those studies, we were interested in the annulation of electron-deficient alkynes with arylmethyl ketones.

To test our hypothesis, 4-bromoacetophenone **1a** was treated with diethyl acetylenedicarboxylate **2a**, CuI (20 mol %), bipyridine (30 mol %), and 3 equiv of di-*tert*-butylperoxide (DTBP) as an oxidant in PhCl at 110 °C for 12 h under argon (Table 1, entry 1). To our delight, the substituted furan **3a** was obtained in 45% yield. Variations in the loading of CuI did not provide an improvement in yield of product **3a** (entries 2 and 3). Afterward, various solvents were tested and the reaction showed a strong solvent dependence (entries 4−9). Surprisingly, we observed that PhBr, PhF, and 1,2-dichloroethane (DCE) were suitable solvents to deliver the desired product. Product **3a** was formed in 47% yield at lower temperature (75 °C) using DCE as solvent. It is notable that application of nonpolar solvents such as benzene and polar solvents such as MeCN and *i*-PrOH were not productive (entries 5, 8, 9). Therefore, we selected DCE as the solvent of choice for the annulation of arylmethyl ketone and acetylenedicarboxylate. Afterward, we tested various ligands (see Supporting Information). Nevertheless, the best results were obtained using bipy as the ligand. Subsequently we screened different metal salts, such as CuBr, CuI, CuCl, Cu_2O, $Fe(acac)_3$, CuF_2, and CuBr·Me_2S (entries 10−17). Pleasingly, we found that the application of CuBr·Me_2S as a precatalyst produced **3a** in a higher yield (70%). Finally, several peroxides were tested (entries 18−20). However, those experiments did not lead to an improvement in yield of the desired compounds. Remarkably, the formation of product **3a** drastically decreased under atmospheric conditions and dioxygen cannot be used as the oxidant for the cascade radical annulation of acetophenones with diethyl acetylenedicarboxylate **2a**.

Having established the reaction conditions, various arylmethyl ketones were examined in the annulation with diethyl acetylenedicarboxylate (Scheme 3). We were pleased to find that the application of various acetophenone derivatives led to formation of the furan derivatives in moderate to good yields. Various functional groups such as fluoro, chloro, bromo, ester, ketone, and trifluoromethyl on the aryl group of the

Table 1. Screening of Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst (mol %)	solvent	*t*, °C	oxidant	yield (%)
1	CuI (20)	PhCl	110	DTBP	45
2	CuI (15)	PhCl	110	DTBP	42
3	CuI (30)	PhCl	110	DTBP	40
4	CuI (20)	DCE	75	DTBP	47
5	CuI (20)	C_6H_6	75	DTBP	traces
6	CuI (20)	PhBr	75	DTBP	46
7	CuI (20)	PhF	75	DTBP	39
8	CuI (20)	*i*-PrOH	75	DTBP	n.d.
9	CuI (20)	MeCN	75	DTBP	traces
10	CuBr (20)	DCE	75	DTBP	53
11	CuCl(20)	DCE	75	DTBP	32
12	CuCN (20)	DCE	75	DTBP	traces
13	CuF_2 (20)	DCE	75	DTBP	n.d.
14	Cu_2O (20)	DCE	75	DTBP	traces
15[b]	CuBr (20)	DCE	75	DTBP	68
16[b]	**CuBr·Me_2S (20)**	**DCE**	**75**	**DTBP**	**70**
17[b,c]	CuBr (20)	DCE	75	DTBP	44
18[b]	CuBr·Me_2S (20)	DCE	75	TBHP	traces
19[b]	CuBr·Me_2S (20)	DCE	75	BPO	traces
20[b]	CuBr·Me_2S (20)	DCE	75	DCP	66

[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.25 mmol), 2,2′-bipyridine (30 mol %), catalyst and oxidant (0.75 mmol) in solvent (2.0 mL) for 8−12 h under argon. [b]Reaction mixture was degassed. [c]Me_2S (1 equiv) was used. DCE = 1,2-dichloroethane; n.d.= not detected; DTBP = $(t\text{-BuO})_2$; TBHP = *t*-BuOOH; BPO = benzoyl peroxide; DCP = dicumyl peroxide.

acterophenones were well tolerated under optimized conditions (**3a**−**3j**). To our delight, several substituents at the *para*-, *meta*-, and *ortho*-positions of the acetophenones were compatible with the copper-catalyzed reaction conditions affording the desired products smoothly. Unfortunately, electron-rich aryl methyl ketones were not well tolerated under our conditions. However, an electron-rich heteroaromatic ketone such as 2-acetylthiophene could be efficiently converted into the corresponding product **3n** in 48% yield. Afterward, we explored the scope of the reaction with a series of alkyl acetylenedicarboxylates under the developed reaction conditions. Gratifyingly, the presence of various alkyl groups in acetylenedicarboxylates allowed the synthesis of the corresponding furan derivatives (**3o**−**3t**). Interestingly, diallyl but-2-ynedioate undergoes the annulation and the desired product **3r** was isolated with 51% yield under the reaction conditions. Gratifyingly, complex derivatives obtained by esterification of but-2-ynedioic acid with (+)-menthol and (+)-borneol also can be utilized in the radical annulation. The corresponding products **3s** and **3t** were isolated in moderate to good yield. Unfortunately, the application of ethyl propiolate, phenylacetylene, and 1,2-diphenylethyne did not yield the desired products under optimized reaction conditions. Therefore, for successful formation of furan derivatives, electron-deficient alkynes are required. To demonstrate the practicability of the developed method, we carried out the reaction of 4-cyanoacetophenone and diethyl acetylenedicarboxylate at 6 mmol scale. The target product **3d** was isolated in 65% yield.

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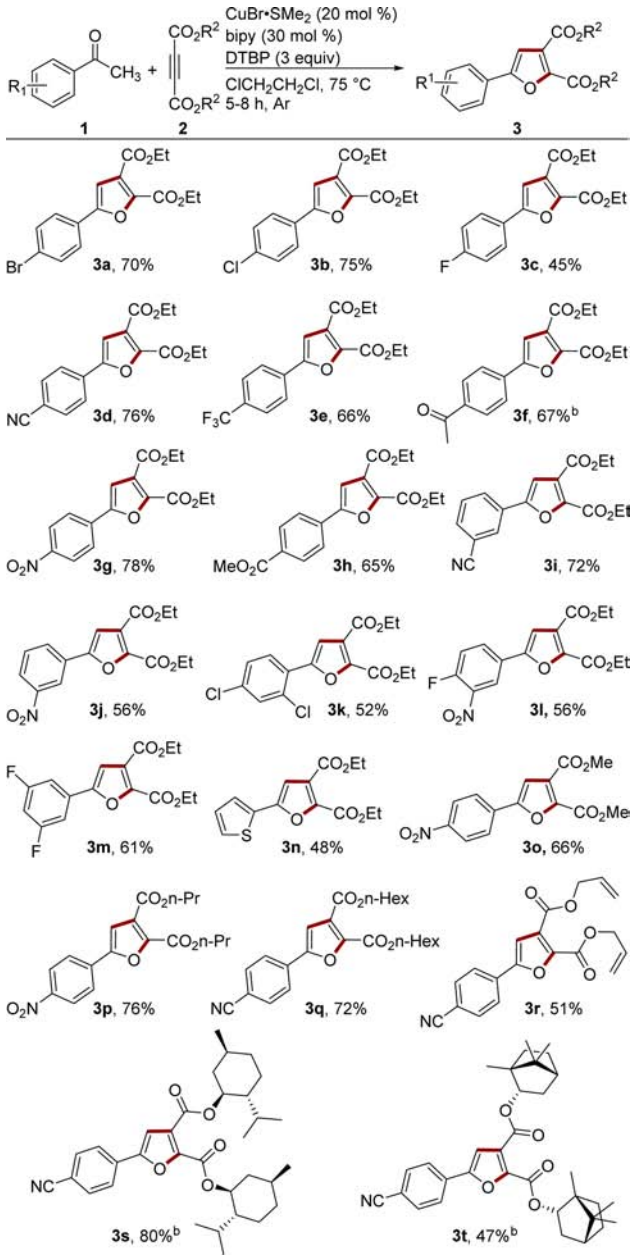
Scheme 3. Copper Catalyzed Synthesis of Furans[a]

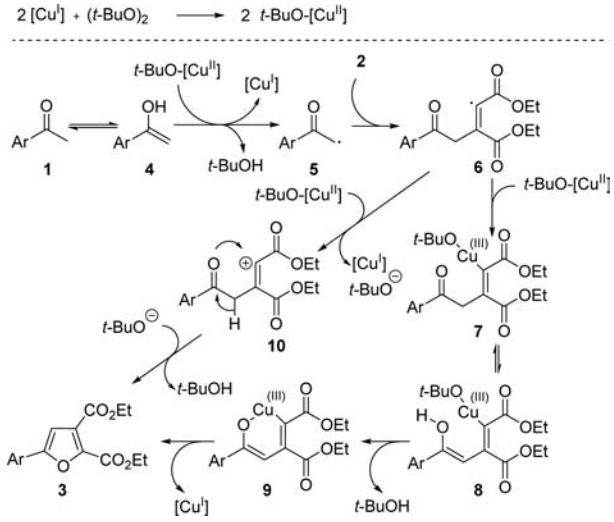


[a]Reaction conditions: **1** (0. 75 mmol), **2** (0.25 mmol), DTBP (3 equiv), CuBr·Me_2S (20 mol %), 2,2′-bipyridine (30 mol %) in DCE (2.0 mL) at 75 °C for 5−8 h under argon. [b]4 equiv arylmethyl ketone were used.

Having established the reaction scope, we turned out attention to understanding the mechanism of the copper-catalyzed furan synthesis. We conducted kinetics isotope effect (KIE) and radical inhibition studies under standard reaction conditions. The kinetic-isotope effect determination was carried out under the optimized reaction conditions with 4-fluoro-acetophenone and deuterated 4-fluoroacetophenone (see Supporting Information for the details). We observed a relatively large kinetic isotope effect ($k_H/k_D \approx 4.5$). It showed that abstraction of at least one hydrogen from acetophenone is the rate-determining step under the developed conditions. Furthermore, in the presence of radical scavengers such as TEMPO, (*Z*)-*N*-*tert*-butyl-1-phenylmethanimine oxide, and 2,6-di-*tert*-butylphenol, formation of the desired product was not observed under standard conditions. This supports the idea that the reaction proceeds via a radical mechanism.

Based on our previous report[12m] and preliminary experimental studies, a plausible mechanism was proposed in Scheme 4. First, the copper(II) species is generated from

Scheme 4. Plausible Reaction Mechanism



copper(I) species in the presence of DTBP. Then the reaction of the enol of acetophenone with the copper(II) species forms radical **5**. In an alternative mechanism the reaction of copper(I) with DTBP occurs by electron transfer, thereby generating the copper(II) species along with the *tert*-butoxyl radical. The *tert*-butoxyl radical may react with acetophenone **1** to generate radical **5** by hydrogen abstraction. A subsequent attack of radical **5** on the electron-deficient alkyne **2** generates intermediate **6**. Afterward, intermediate **7** could be generated from intermediate **6** after oxidative addition of the copper(II) species. Intermediate **8** is in equilibrium with intermediate **7** via enolization. A ligand exchange leads to the formation of metallocycle **9**. Finally, product **3** is generated by reductive elimination of copper(I) from **7**. The copper(II) catalyst is regenerated by oxidation of copper(I) with DTBP. In a complementary mechanism, radical **6** can be oxidized by copper(II) to cation **10** with elimination of a *tert*-butylate anion. In the following step, this anion could promote the intermolecular cyclization giving the desired product **3**. However, this pathway is unlikely because in control experiments the intermediate was not trapped using various nucleophiles.

In summary, we have reported the first copper-catalyzed annulation of acetophenone derivatives and an alkyl acetylene-dicarboxylate with a broad reaction scope. The operationally simple method offers direct access to multisubstituted furan derivatives. The presented method employs simple, readily available acetophenones to the synthesis of furans. Mechanistic studies strongly supported a radical reaction mechanism. The developed reaction is highly practical, because diverse, easily available starting materials can be used without preliminary functionalization.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02114.

Experiment details and spectral data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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