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Journal Name

ARTICLE

Synthesis of multisubstituted furans via Cu(I)-catalyzed annulation of ketones with alkynoate under ligand- and additive-free conditions†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Zaigang Luo,*[a] Yuyu Fang,[a] Yu Zhao,[a] Peng Liu,[b] Xuemei Xu,[a] Chengtao Feng,[a] Zhong Li,[a] Jie He*[a]

A facile and efficient annulation strategy for the synthesis of multisubstituted furan derivatives has been achieved under mild conditions. The developed transformation via C(sp3)–H bond functionalization catalyzed by copper(I) salts using benzoyl peroxide as an external oxidant possess some obviously advantages. This ligand- and additive-free cyclization protocol offers an environmentally and efficient access to biologically important scaffolds from readily available substrates.

Introduction

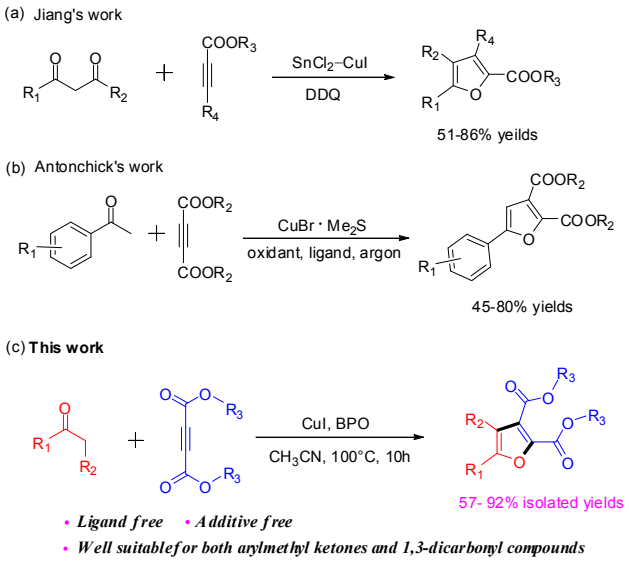
Multisubstituted furans represent an important class of five membered heterocycles ubiquitous in natural products, pharmaceuticals, and agrochemicals as well as act as useful intermediates in organic synthesis.[1] Hence, the development of efficient methods for their preparation has been an important research orientation in organic chemistry. The classical approaches such as Paal–Knorr synthesis[2] and Feist–Benary synthesis[3] have already been established for the assembly of multisubstituted furans. The Paal–Knorr method relies on acid catalyzed intramolecular cyclization of 1,4-dicarbonyl compounds and Feist–Benary method represents one of first approaches for the intermolecular annulation of 1,3-dicarbonyl compounds and α-halogen ketones.

In the past few decades, transition-metal-catalyzed approaches to the synthesis of furan derivatives have been developed, such as Pd-catalyzed cyclization of 2,3-allenoic acids in the presence of allenes,[4] Pd-catalyzed cyclization of alkynylbenziodoxolones and imine derivatives of acetophenone,[5] Au-catalyzed cycloisomerizations of bromoallenyl ketones,[6] Co-catalyzed cyclization of alkynes and α-diazocarbonyls,[7] Ag-catalyzed cycloisomerizations of phenyl and tertbutyl alkynyl ketones utilizing [3,3] acyloxy migration,[8] successive Ru-catalyzed dimerization of terminal alkynes and Cu(II)-catalyzed cyclization of 1.3-dienyl ethers[9] and so forth. However, the synthetic potential of these strategies is still suffer from limitations like the requirement of functionalized precursors, harsh conditions and low conversions. As a consequence, the development of a new synthetic route to synthesize furan derivatives from simple and commercially available starting materials is still desirable.

Despite the recent advances with these transition metal catalysts, copper catalyzed synthesis of furans is highly attractive. Because copper salts are inexpensive and possess low toxicity. Recently, copper catalyzed C–H functionalization reactions to the construction of heterocycles have been successfully developed.[10] In 2010, Jiang' group demonstrated the synthesis of furans from alkynoates and 1,3-dicarbonyl compounds through Sn(II)- and Cu(I)-involved addition/oxidative cyclization (Scheme 1a).[11] Subsequently, they reported a novel and convenient one-pot Cu(I)-catalyzed approach for the preparation of 2-carbonyl furans via (2-furyl)carbene complexes.[12] Very recently, Antonchick and Manna described the first copper-catalyzed annulation of acetophenone derivatives and an alkyl acetylenedicarboxylate with a broad reaction scope (Scheme 1b).[13] This reaction provides a useful method for the synthesis of multisubstituted furans from readily available acetophenones and electron-deficient alkynes via Cu(I)-catalyzed direct C(sp3)–H bond functionalization under radical reaction conditions, which are generally difficult to access from other conventional methods. However, this reaction was proceeded in the presence of a ligand such as 2,2'-bipyridine, and the ligand was essential for the catalytic activity of the copper(I) salt. Moreover, the substrate scope is limited to the electron-poor arylmethyl ketones. Hence, copper catalyzed C(sp3)–H functionalization reactions between arylmethyl ketones and alkyonate to the construction of furans is still filled with challenges.

[a] College of Chemical Engineering, AnHui University of Science & Technology, Huainan 232001, P. R. China.
Email: luozi139@163.com; aust_jhe@163.com
[b] Guang Zhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou 510530, China.

† Electronic Supplementary Information (ESI) available: [NMR Spectra for products **3**]. See DOI: 10.1039/x0xx00000x



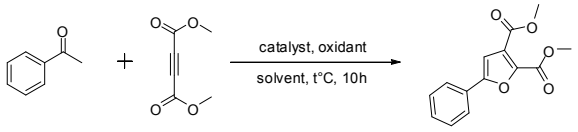
Scheme 1. Synthesis of furan from ketone and alkynoate.

Herein we present a facile and efficient Cu(I)-catalyzed annulation of simple and readily available ketones with alkynoate under mild conditions (Scheme 1c). Comparing to the research work of Antonchick and Manna's,[14] the advantages of our current study are clear, such as ligand- and additive-free, high yield, large-scale processes and broad substrate scope (well suitable for both nonactivated arylmethyl ketones with electron-donating or electron-withdrawing groups and 1,3-dicarbonyl compounds with an activated methylene group).

Results and discussion

Initially, acetophenone **1a** and dimethyl acetylenedicarboxylate (DMAD) **2a** were chosen as the model substrates to optimize the reaction conditions, including the catalyst, oxidant, solvent, and temperature under ambient air. As described in Table 1, six oxidants, air, O_2, H_2O_2, *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP) and benzoyl peroxide (BPO) were investigated at 100°C in 2 mL of CH_3CN using CuI as the catalyst, and BPO was found to be the most effective oxidant (90%) (entries 1–6). When the reaction was carried out without CuI, a significant decrease of the yield was observed (entry 7). Changing the counterion of copper salt, such as CuCl and CuBr (entries 8–9), or replacing Cu(I) with Cu(II), such as CuI_2, $CuCl_2{\cdot}2H_2O$, $CuBr_2$, $CuCO_3$, led to inferior results (entries 10–13). Variations in the loading of CuI and BPO did not provide an improvement in yield of product **3aa** (entries 14–17). Afterward, the solvents, including CH_3CN, DMF, CH_3CN/H_2O (1:1), DMSO, CH_3OH, 1,2-dichloroethane (DCE) and N,N-dimethylacetamide (DMA) were tested using CuI as the catalyst and BPO as the oxidant at 100 °C, and CH_3CN provided the highest yield (entries 6, 18–23). Finally, when the temperature was dropped to 90 °C, the target product was not be found (entry 24), and the yield dramatically decreased when the temperature was elevated to 110 °C (entry 25). After the optimization process for catalyst, oxidant, solvent, and temperature, the multisubstituted furans **3** were synthesized under our standard conditions: 0.2 equiv of CuI as the catalyst, 2 equiv of BPO as the oxidant, and CH_3CN as the solvent under air atmosphere at 100 °C.

Table 1 Optimization of the reaction conditions [a]



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

Entry	catalyst(.eq)	Oxidant (.eq)	Solvent	yield(%)[b]
1	CuI(0.2)	Air	CH_3CN	n.r
2	CuI(0.2)	O_2	CH_3CN	5
3	CuI(0.2)	H_2O_2(2)	CH_3CN	13
4	CuI(0.2)	TBHP(2)	CH_3CN	15
5	CuI(0.2)	DTBP(2)	CH_3CN	26
6	**CuI(0.2)**	**BPO(2)**	**CH_3CN**	**90**
7	——	BPO(2)	CH_3CN	22
8	CuCl(0.2)	BPO(2)	CH_3CN	16
9	CuBr(0.2)	BPO(2)	CH_3CN	37
10	CuI_2(0.2)	BPO(2)	CH_3CN	70
11	$CuCl_2{\cdot}2H_2O$ (0.2)	BPO(2)	CH_3CN	54
12	$CuBr_2$(0.2)	BPO(2)	CH_3CN	56
13	$CuCO_3$(0.2)	BPO(2)	CH_3CN	50
14	CuI(0.3)	BPO(2)	CH_3CN	85
15	CuI(0.1)	BPO(2)	CH_3CN	55
16	CuI(0.1)	BPO(1)	CH_3CN	52
17	CuI(0.2)	BPO(1)	CH_3CN	83
18	CuI(0.2)	BPO(2)	DMF	54
19	CuI(0.2)	BPO(2)	CH_3CN:H_2O(1:1)	68
20	CuI(0.2)	BPO(2)	DMSO	52
21	CuI(0.2)	BPO(2)	CH_3OH	32
22	CuI(0.2)	BPO(2)	DCE	34
23	CuI(0.2)	BPO(2)	DMA	48
24[c]	CuI(0.2)	BPO(2)	CH_3CN	n.r.
25[d]	CuI(0.2)	BPO(2)	CH_3CN	28

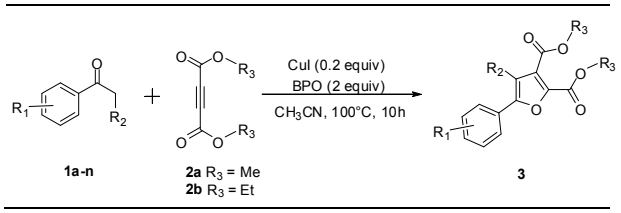
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), solvent (2 ml), 100°C, 10h. [b] Isolated yield. [c] 90°C. [d]110°C. n.r. No reaction.

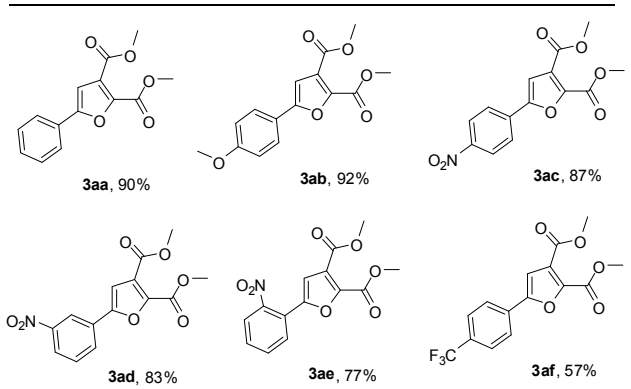
Having established the reaction conditions, various arylmethyl ketones were examined in the cyclization with DMAD (Table 2). To our delight, aryl methyl ketones with electron-donating substituents (*p*-OMe) or electron-withdrawing substituents (*p*-NO_2, *m*-NO_2, *o*-NO_2, *p*-CF_3), as well as the para-, ortho- and meta-substituted groups both gave the desired products in good yields (**3ab**–**3af**), showing no obvious electronic effect in this reaction. While electron-rich aryl methyl ketones were not well tolerated

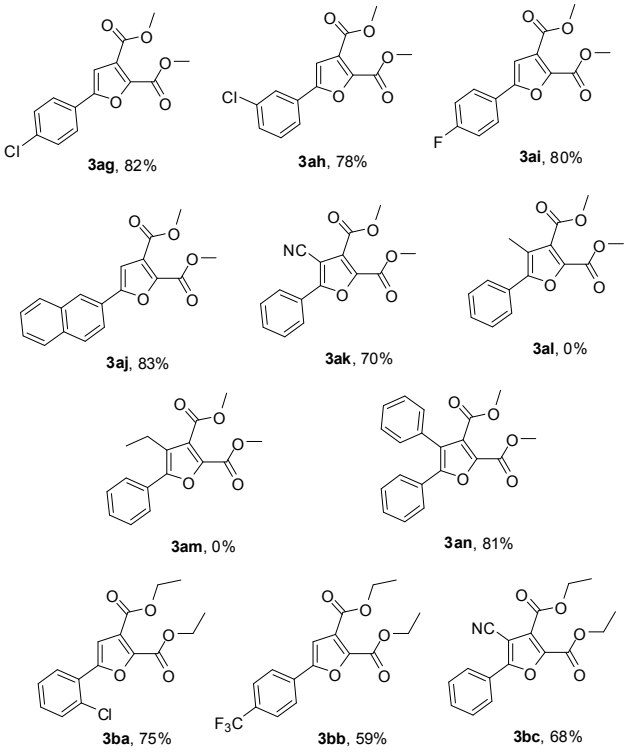
under reported conditions.[13] The para- and meta-substituted halogen atoms such as chlorine and fluorine were well tolerated, affording the corresponding products in 82%, 78% and 80% isolated yields, respectively (**3ag**–**3ai**). Notably, 2-acetonaphthone **1j** is also a suitable substrate for this reaction, which reacted smoothly to give the expected annulation products in good yields (**3aj**, 83%). Interestingly, benzoylacetonitrile **1k** undergoes the annulation and the desired product **3ak** was isolated with 70% yield under the reaction conditions. However, when R_2 was an electron-donating group, such as methyl or ethyl, the corresponding product **3al** and **3am** could not be obtained. Obviously, *α*-position of acetophenones bearing an electron-withdrawing group can afford the desired products smoothly. It is also worth noting that the reaction was insensitive to the sterically hindered substrate 2-phenyl acetophenone **1n** and the corresponding product **3an** was obtained in 81% isolated yield. In addition, the presence of ethyl groups in acetylenedicarboxylate, diethyl acetylenedicarboxylate **2b**, also allowed the synthesis of the corresponding furan derivatives (**3ba**–**3bc**). Generally speaking, aryl methyl ketones without sterically hindered groups were cyclized in higher yields than those with sterically hindered groups or sterically hindered substrate.

Afterward, the application of our present protocol for cyclization of 1,3-dicarbonyl compound and *β*-ketoester with DMAD, including acetylacetone **1o** and ethyl acetoacetate **1p**, were explored (scheme 2). Gratifyingly, the target furan derivatives **3ao** and **3ap** were isolated in 89% and 85% yields, respectively. In terms of the NMR spectra and related literature,[11,15] the structure of **3ap** was confirmed, and there was no evidence indicating that the regioisomer of **3ap** existed. Obviously, this developed transformation via C(sp3)–H functionalization catalyzed by copper(I) salts using benzoyl peroxide as an external oxidant is well suitable for both nonactivated arylmethyl ketones with electron-donating or electron-withdrawing groups and 1,3-dicarbonyl compounds with an activated methylene group.

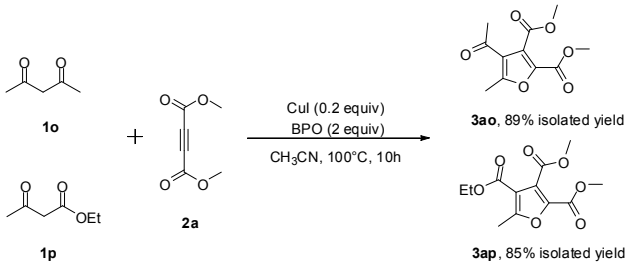
Table 2 Copper catalyzed synthesis of furans [a]



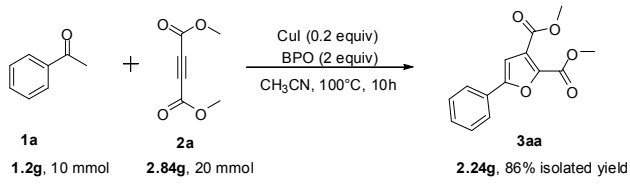




[a] Reaction conditions: arylmethyl ketones **1** (0.5 mmol), **2** (1 mmol), CH_3CN (2 ml). Isolated yield.



Scheme 2. Synthesis of furan from 1,3-dicarbonyl compounds and alkynoate.

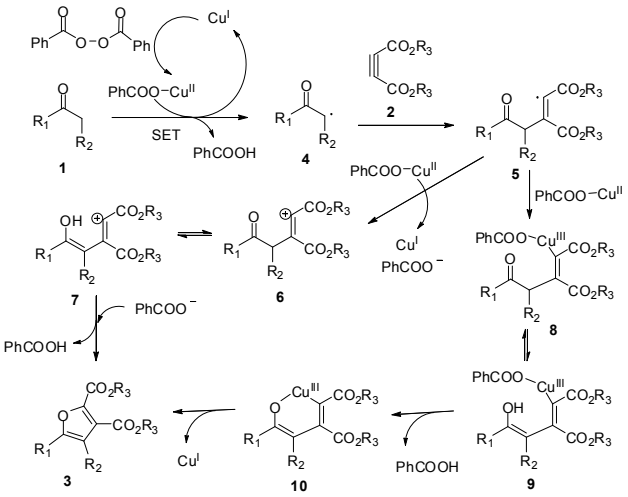


Scheme 3. Synthesis of **3aa** in a Gram scale.

Gram-scale applications for the present method were also explored. As shown in Scheme 3, the proposed reaction of **1a** and **2a** was investigated under the standard conditions, which could

give 2.44 g of **3aa** in 86% yield without any significant loss of reactive efficiency. Thus, this simple, ligand- and additive-free protocol could be extended as an efficient and practical method to construct various potentially bioactive multisubstituted furan derivatives.

To gain further insight into the reaction mechanism, we added the radical scavenger 2,2,6,6-tetramethyl-1-piperridinyloxy (TEMPO) to the model reaction system. While the product (**3aa**) was not obtained, which indicated that a free radical pathway might be involved. The mechanism of the copper catalyzed furan synthesis has been proposed by previous related literature.[10,13] One common process is the Cu^{II}/Cu^{I} catalytic cycle initiated via one-electron oxidation by Cu^{II} (single electron transfer, SET)(scheme 4). The combination of one- and two-electron processes was also proposed to occur via a $Cu^{I}/Cu^{II}/Cu^{III}$ catalytic cycle, in which the key step is the formation of an organocopper^{III} intermediate (scheme 4). In addition, the plausible mechanism of cyclization of 1,3-dicarbonyl compound and β-ketoester with alkynoate is similar to the related literature.[15]



Scheme 4. Plausible Reaction Mechanism.

Conclusions

In conclusion, we have disclosed the annulation method of ketones with alkynoate catalyzed by CuI. The developed reaction is highly practical, because diverse, easily available starting materials can be used without preliminary functionalization. Also, This undecorated cyclization protocol is characterized by mild conditions, inexpensive catalyst, wide substrate scope and large-scale processes, as well as no any ligand and additive, allowing an environmentally and efficient access to biologically important scaffolds.

Experimental

Unless otherwise noted, all materials were obtained from commercial suppliers and dried and purified by standard procedures. The melting point was measured on a SGW X-4 monocular microscope melting point apparatus with thermometer unadjusted. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker Avance III 400 MHz spectrometer with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. The chemical shifts were reported in δ (ppm). Mass spectra (MS) data were obtained using Esquire 6000 Mass Spectrometer. HRMS were obtained by ESI on a TOF mass analyzer. Column chromatography was performed with silica gel (200～300 mesh, Qingdao Haiyang Chemical Co., Ltd, China). Petroleum ether used for column-chromatography has a boiling range of 60-90 ºC.

Caution! Organic peroxides can be severe fire and explosion hazards.

General methods for preparing compounds 3. A 25 mL Schlenk tube was charged with various ketone (**1**) (0.5 mmol), alkynoate (**2**) (1 mmol), CuI (0.1 mmol), BPO (1 mmol) and CH_3CN (2 mL). The tube was sealed, and then the mixture was stirred under air at 100 ºC for 10 h. After cooling, the solvent was diluted with water (5 mL) and extracted with dichloromethane (3×4 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated by a rotary evaporator, and the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 4:1) to provide the desired products (**3**).

*Dimethyl 5-phenylfuran-2,3-dicarboxylate (**3aa**)*. Yellow solid, m.p. 99-101ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.68 (d, 1H, *J* = 8.0 Hz, Ar*H*), 7.54 (m, 2H, Ar*H*), 6.83 (s, 1H, *CH*=C), 3.90 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.2, 161.7, 147.0, 134.1, 130.5, 128.7, 128.2, 117.2, 53.3, 52.1; MS (ESI) *m/z*: 286.8 $[M+Na]^+$, 550.9 $[2M+Na]^+$; HRMS *m/z*: calcd for $C_{14}H_{12}NaO_5$ $[M + Na]^+$, 283.0577; found, 283.0579.

*Dimethyl 5-(4-methoxyphenyl)furan-2,3-dicarboxylate (**3ab**)*. White solid, m.p. 64-66ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, 2H, *J* = 4.0 Hz, Ar*H*), 6.99 (d, 2H, *J* = 8.0 Hz, ArH), 6.83 (s, 1H, *CH*=C), 3.92 (s, 3H, OCH_3), 3.91 (s, 3H, ArOCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 134.0, 130.6, 130.5, 128.7, 117.2, 113.7, 55.5, 53.3, 52.1, 26.3; MS (ESI) *m/z*: 312.9 $[M+Na]^+$, 603.0 $[2M+Na]^+$; HRMS *m/z*: calcd for $C_{15}H_{14}NaO_6$ $[M + Na]^+$, 313.0683; found, 313.0687.

*Dimethyl 5-(4-nitrophenyl)furan-2,3-dicarboxylate (**3ac**)*. Yellow solid, m.p. 82-84ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (t, 2H, *J* = 4.0 Hz, Ar*H*), 7.55 (t, 2H, *J* = 6.0 Hz, Ar*H*), 6.83 (s, 1H, *CH*=C), 3.91 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.2, 161.8, 147.0, 134.0, 130.5, 128.7, 128.2, 117.2, 53.3, 52.1; MS (ESI) *m/z*: 304.1 $[M-H]^-$; HRMS *m/z*: calcd for $C_{14}H_{11}NNaO_7$ $[M + Na]^+$, 328.0428; found, 328.0430.

*Dimethyl 5-(3-nitrophenyl)furan-2,3-dicarboxylate (**3ad**)*. Yellow solid, m.p. 68-72ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (s, 1H, Ar*H*), 7.69 (t, 1H, *J* = 6.0 Hz, Ar*H*), 7.55 (t, 2H, *J* = 6.0 Hz, Ar*H*), 6.83 (s, 1H, *CH*=C), 3.91 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 163.2, 162.0, 147.0, 134.0, 130.5, 128.7, 128.2,

117.2, 53.3, 52.1; MS (ESI) *m/z*: 304.1 [M−H]$^-$; HRMS *m/z*: calcd for $C_{14}H_{11}NNaO_7$ [M + Na]$^+$, 328.0428; found, 328.0431.

*Dimethyl 5-(2-nitrophenyl)furan-2,3-dicarboxylate (**3ae**)*. Yellow solid, m.p. 78-80ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.67 (d, 1H, *J* = 4.0 Hz, Ar*H*), 7.54 (t, 2H, *J* = 6.0 Hz, Ar*H*), 6.83 (s, 1H, *CH*=C), 3.90 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ:164.0, 163.2, 161.7, 147.0, 134.0, 130.5, 128.7, 128.3, 117.2, 53.3, 52.1; MS (ESI) m/z: 304.1 [M−H]$^-$; HRMS *m/z*: calcd for $C_{14}H_{11}NNaO_7$ [M + Na]$^+$, 328.0428; found, 328.0429.

*Dimethyl 5-(4-(trifluoromethyl)phenyl)furan-2,3-dicarboxylate(**3af**)*. White solid, m.p. 55-58ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, 2H, *J* = 4.4 Hz, Ar*H*), 7.39 (m, 2H, Ar*H*), 6.71 (s, 1H, *CH*=C), 3.77 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.3, 161.8, 147.0, 134.1, 133.9, 130.5, 130.2, 129.4, 128.7, 128.5, 124.8, 117.5, 53.3, 52.2; HRMS *m/z*: calcd for $C_{15}H_{11}F_3NaO_5$ [M + Na]$^+$, 351.0456; found, 351.0450.

*Dimethyl 5-(4-chlorophenyl)furan-2,3-dicarboxylate (**3ag**)*. White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (m, 2H, Ar*H*), 7.54 (t, 2H, *J* = 6.0 Hz, Ar*H*), 6.83 (s, 1H, *CH*=C), 3.90 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.2, 161.8, 147.0, 134.1, 130.5, 128.7, 128.2, 117.2, 53.3, 52.1; MS (ESI) *m/z*: 316.9 [M+Na]$^+$, 611.0[2M+Na]$^+$; HRMS *m/z*: calcd for $C_{14}H_{11}ClNaO_5$ [M + Na]$^+$, 317.0187; found, 317.0190.

*Dimethyl 5-(3-chlorophenyl)furan-2,3-dicarboxylate(**3ah**)*. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, 2H, *J* = 4.4 Hz, Ar*H*), 7.64 (t, 1H, *J* = 4.8 Hz, Ar*H*), 7.50 (d, 1H, *J* = 4.4 Hz, Ar*H*), 6.79 (s, 1H, *CH*=C), 3.86 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9, 161.5, 161.2, 146.9, 134.0, 130.5, 128.6, 128.3, 117.5, 62.6, 61.2; HRMS *m/z*: calcd for $C_{14}H_{11}ClNaO_5$ [M + Na]$^+$, 317.0193; found, 317.0190.

*Dimethyl 5-(4-fluorophenyl)furan-2,3-dicarboxylate (**3ai**)*. White oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, 2H, *J* = 4.0 Hz, Ar*H*), 6.99 (d, 2H, *J* = 8.0 Hz, Ar*H*), 6.83 (s, 1H, *CH*=C), 3.92 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 163.2, 161.8, 147.0, 134.1, 130.5, 128.7, 128.2, 117.2, 52.3, 52.1; MS (ESI) *m/z*: 300.9 [M+Na]$^+$, 579.1 [2M+Na]$^+$; HRMS *m/z*: calcd for $C_{14}H_{11}FNaO_5$ [M + Na]$^+$, 301.0483; found, 301.0485.

*Dimethyl 5-(naphthalen-2-yl)furan-2,3-dicarboxylate (**3aj**)*. Brown solid. m.p. 123-126ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (m, 2H, Ar*H*), 7.66 (m, 2H, Ar*H*), 7.53 (m, 3H, Ar*H*), 6.84 (s, 1H, *CH*=C), 3.91 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.3, 161.8, 147.0, 134.1, 133.8, 130.5, 130.2, 128.7, 128.5, 117.2, 53.3, 52.2; MS (ESI) m/z: 332.8 [M+Na]$^+$, 642.9 [2M+Na]$^+$; HRMS *m/z*: calcd for $C_{18}H_{14}NaO_5$ [M + Na]$^+$, 333.0733; found, 333.0735.

*Dimethyl 4-cyano-5-phenylfuran-2,3-dicarboxylate(**3ak**)*. Yellow solid, m.p. 57-60ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, 2H, *J* = 4.8 Hz, Ar*H*), 7.64 (m, 1H, Ar*H*), 7.50 (m, 2H, Ar*H*), 3.86 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.0, 161.3, 146.9, 134.0, 133.8, 130.5, 130.2, 129.3, 128.6, 128.5, 117.5, 106.0, 62.6, 61.2; HRMS *m/z*: calcd for $C_{15}H_{12}NO_5$ [M + H]$^+$, 286.0715; found, 286.0711.

*Dimethyl 4,5-diphenylfuran-2,3-dicarboxylate (**3an**)*.[16] Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, 4H, *J* = 4.0 Hz, Ar*H*), 7.65 (m, 2H, Ar*H*), 7.51 (m, 4H, Ar*H*), 6.84 (s, 1H, *CH*=C), 3.95 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 163.8, 163.3, 161.8, 147.0, 134.1, 133.8, 130.5, 130.2, 128.7, 128.5, 117.2, 53.3, 52.2; MS (ESI) *m/z*: 360.9 [M+Na]$^+$, 699.0 [2M+Na]$^+$.

*Diethyl 5-(2-chlorophenyl)furan-2,3-dicarboxylate(**3ba**)*. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (d, 2H, *J* = 4.8 Hz, Ar*H*), 7.62 (d, 1H, *J* = 4.0 Hz, Ar*H*), 7.50 (t, 1H, *J* = 4.8 Hz, Ar*H*), 6.77 (s, 1H, *CH*=C), 4.32 (q, 2H, *J* = 6.8 Hz, OCH_2CH$_3$), 4.18 (q, 2H, *J* = 6.8 Hz, OCH_2CH$_3$), 1.32 (t, 3H, *J* = 6.8 Hz, OCH$_2$$CH_3$), 1.18 (t, 3H, *J* = 6.8 Hz, OCH$_2$$CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.0, 161.2, 146.9, 134.0, 130.5, 128.6, 128.3, 117.5, 62.6, 61.2, 14.0; HRMS *m/z*: calcd for $C_{16}H_{15}ClNaO_5$ [M + Na]$^+$, 345.0506; found, 345.0501.

*Diethyl 5-(4-(trifluoromethyl)phenyl)furan-2,3-dicarboxylate(**3bb**)*. Yellow solid, m.p. 51-53ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, 2H, *J* = 4.0 Hz, Ar*H*), 7.50 (m, 2H, Ar*H*), 6.77 (s, 1H, *CH*=C), 4.32 (q, 2H, *J* = 6.8 Hz, OCH_2CH$_3$), 4.18 (q, 2H, *J* = 7.2 Hz, OCH_2CH$_3$), 1.32 (t, 3H, *J* = 6.8 Hz, OCH$_2$$CH_3$), 1.18 (t, 3H, *J* = 7.2 Hz, OCH$_2$$CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 163.3, 161.8, 147.0, 134.1, 133.8, 130.5, 130.2, 128.7, 128.5, 124.4, 117.2, 53.3, 52.2, 14.6, 14.4; HRMS *m/z*: calcd for $C_{17}H_{15}F_3NaO_5$ [M + Na]$^+$, 379.0769; found, 379.0765.

*Diethyl 4-cyano-5-phenylfuran-2,3-dicarboxylate(**3bc**)*. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (m, 2H, Ar*H*), 7.55 (m, 1H, Ar*H*), 7.40 (m, 2H, Ar*H*), 4.25 (q, 2H, *J* = 6.4 Hz, OCH_2CH$_3$), 4.10 (q, 2H, *J* = 6.8 Hz, OCH_2CH$_3$), 1.24 (t, 3H, *J* = 6.4 Hz, OCH$_2$$CH_3$), 1.10 (t, 3H, *J* = 6.8 Hz, OCH$_2$$CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 162.9, 161.2, 146.9, 134.0, 133.8, 130.5, 130.2, 129.3, 128.6, 128.5, 117.5, 106.0, 62.6, 61.2,14.0, 13.9; HRMS *m/z*: calcd for $C_{17}H_{16}NO_5$ [M + H]$^+$, 314.1028; found, 314.1021.

*Dimethyl 4-acetyl-5-methylfuran-2,3-dicarboxylate (**3ao**)*.[15] White solid, m.p. 114-116ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.02 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 2.72 (s, 3H, ArCH_3), 2.45 (s, 3H, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.7, 164.2, 160.9, 157.7, 139.2, 125.5, 122.5, 53.2, 52.5, 29.4, 14.9; MS (ESI) *m/z*: 262.8 [M+Na]$^+$, 503.0 [2M+Na]$^+$.

*Trimethyl 5-methylfuran-2,3,4-tricarboxylate (**3ap**)*.[15] White solid, m.p. 131-133ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.34 (q, 2H, *J* = 4.0 Hz, OCH_2CH$_3$), 3.99 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 2.71 (s, 3H, Ar-CH_3), 1.38 (t, 3H, *J* = 4.0 Hz, OCH$_2$$CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 162.3, 157.7, 138.9, 133.7, 130.2, 128.5, 61.1, 52.9, 52.5, 14.1; MS (ESI) *m/z*: 280.9 [M+Na]$^+$, 539.0 [2M+Na]$^+$.

Acknowledgements

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (21102003) and Scientific Research Foundation for the Introduction of Talent of Anhui University of Science & Technology.

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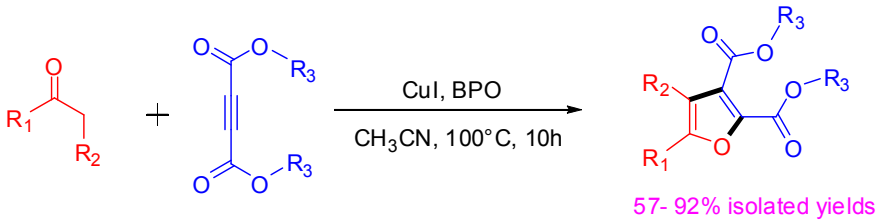
Synthesis of multisubstituted furans via Cu(I)-catalyzed annulation of ketones with alkynoate under ligand- and additive-free conditions†

Zaigang Luo,*[a] Yuyu Fang,[a] Yu Zhao,[a] Peng Liu[b], Xuemei Xu,[a] Chengtao Feng,[a] Zhong Li,[a] Jie He*[a]



R_1 = -Me, Aryl; R_2 = -H, -CN, -Ph, -COOEt; R_3 = -Me, -Et

- ***Ligand free*** • ***Additive free***
- ***Well suitable for both arylmethyl ketones and 1,3-dicarbonyl compounds***

A simple and efficient Cu(I)-catalyzed strategy for synthesis of mutisubstituted furans has been developed and this ligand- and additive-free annulation method is well suitable for both nonactivated arylmethyl ketones with electron-withdrawing or electron-donating groups and 1,3-dicarbonyl compounds with an activated methylene group.