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Synthetic Approach to Polysubstituted Furans: An Efficient Addition/Oxidative Cyclization of Alkynoates and 1,3-Dicarbonyl Compounds

Weibing Liu, Huanfeng Jiang,* Min Zhang, and Chaorong Qi

School of Chemistry and Chemical Engineering, South China University of Technology, 381 Wushan Road, Guangzhou 510640, China

jianghf@scut.edu.cn

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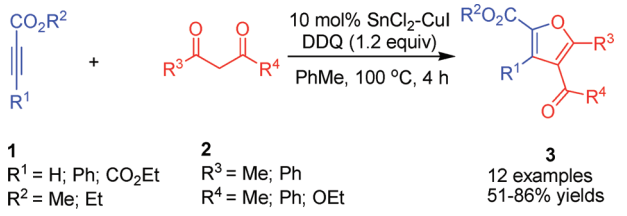

1
R^1 = H; Ph; CO_2Et
R^2 = Me; Et

2
R^3 = Me; Ph
R^4 = Me; Ph; OEt

3
12 examples
51-86% yields

A novel and reliable method for the direct construction of polysubstituted furans is reported. The key transformation involves Sn(II)- and Cu(I)-involved addition/oxidative cyclization of alkynoates and 1,3-dicarbonyl compounds in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone.

Furan derivatives widely occur as important structural units in a variety of synthetic and natural sources that can be applied as pharmaceuticals and organic materials.[1] Many of the naturally occurring furans have shown interesting biological activities, such as antiallergic and antiasthamatic,[2] as well as cytotoxic and antitumor properties,[3] antidiabetic activity,[4] and several other potentially useful activities.[5] In addition, furans are also present in important commercial products such as dyes, essential oils, cosmetics, flavor, and fragrance compounds.[6]

Our group recently focused on developing hydroalkylation and hydroamination of alkynes to construct heterocyclic molecules catalyzed by palladium, copper, or base, but these methodologies were never mentioned as oxidative processes.[7] Recently, Li and Zhang reported a new type of cross-dehydrogenative-coupling (CDC) reaction under mild conditions to construct diester ethers catalyzed by a combination of indium and copper catalysts in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[8] In view of the convergent and modular nature of the transformation, we were drawn to the prospect of utilizing of this methodology to heterocycles construction. Herein, we apply this methodology to construct furans in a way which has never been reported in the literature. To the best of our knowledge, reports about the synthesis of furan derivatives through an oxidative process are rather rare, although there are many strategies for their synthesis.[9]

Our preliminary investigations were focused on the systematic evaluation of different catalysts for the desired addition/oxidative cyclization of diethyl but-2-ynedioate (**1a**) and 1-phenylbutane-1,3-dione (**2a**) (Table 1). As shown in Table 1, the combination of $SnCl_2$ and CuI afforded the best result in 1,2-dichloroethane (DCE) (entries 1−4). Changing the counterion of copper salt or replacing Cu(I) with Cu(II) led to inferior results (entries 5−8). We also investigated the reactivity of some other oxidants, such as benzoyl peroxide, PIDA, benzoquinone, etc., but the results were not inspiring (entries 10−14). Among the various solvents examined, toluene, 1,2-dichloroethane (DCE), and dioxane (entries 4, 15, and 16) were practical for this transformation. When the reaction was carried out without oxidant (entry 9) as well as with a decreased the dosage of DDQ (entry 22),

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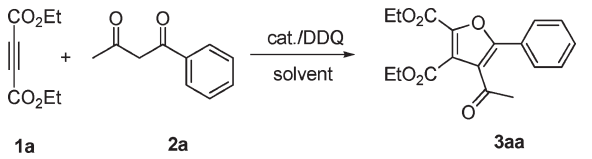
TABLE 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	catalyst (equiv)	oxidant (1.2 equiv)	solvent	yield[b] (%)
1	CuI (0.1)	DDQ	DCE	10
2	$CuCl_2$ (0.1)	DDQ	DCE	
3	$SnCl_2$ (0.1)	DDQ	DCE	
4	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	DCE	75
5	$SnCl_2$ (0.1)/$CuCl_2$ (0.1)	DDQ	DCE	71
6	$SnCl_2$ (0.1)/$Cu(OAc)_2$ (0.1)	DDQ	DCE	68
7	$SnCl_2$ (0.1)/CuBr (0.1)	DDQ	DCE	9
8	$SnCl_2$ (0.1)/Cu_2O (0.1)	DDQ	DCE	66
9	$SnCl_2$ (0.1)/CuI (0.1)	none	DCE	
10	$SnCl_2$ (0.1)/CuI (0.1)	benzoyl peroxide	DCE	21
11	$SnCl_2$ (0.1)/CuI (0.1)	H_2O_2	DCE	
12	$SnCl_2$ (0.1)/CuI (0.1)	PIDA	DCE	38
13	$SnCl_2$ (0.1)/CuI (0.1)	benzoquinone	DCE	trace
14	$SnCl_2$ (0.1)/CuI (0.1)	O_2 (1 atm)	DCE	
15	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	toluene	77
16	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	dioxane	50
17	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	CH_3CN	28
18	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	DMF	23
19[c,d]	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	toluene	80
20[c,e]	$SnCl_2$(0.1)/CuI(0.1)	DDQ	toluene	86
21[cc]	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	toluene	86
22[c,e,ff]	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	toluene	25
23[c,e,gg]	$SnCl_2$ (0.1)/CuI (0.1)	DDQ	toluene	83

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), in 2 mL of solvent at 80 °C for 5 h. [b]Isolated yields. [c]Reaction temperature: 100 °C. [d]Reaction time: 3 h. [e]Reaction time: 4 h. [f]DDQ (0.5 equiv). [g]DDQ (2.0 equiv).

a significant decrease of the yield was observed. However, there was no obvious influence on the reaction when the reaction time was decreased (entries 19−21) or the dosage of DDQ was increased (entry 23).

Under the optimized conditions, the reaction was applied to a range of different substrates. Different 1,3-dicarbonyl compounds could successfully react with alkynoates to afford the corresponding furan derivatives (Scheme 1). As revealed in Scheme 1, the electronic contribution of the substituents on the alkynes has a significant influence on the reaction. This transformation proceeded smoothly and afforded the desired product in good to excellent yields for those alkynes substituted with two electron-withdrawing groups. For example, the reaction of diethyl but-2-ynedioate with benzoylacetone led to **3aa** in 86% isolated yield, and the reaction on a larger scale (2.0 mmol) could also lead to 84% isolated yields, while methyl propiolate ethyl only gave **3ca** in 80% isolated yield. In addition, when ethyl 3-phenylpropiolate was used in the reaction with pentane-2,4-dione, only **3bd** was obtained in 51% yield.

A plausible mechanism of this transformation is shown in Scheme 2. The reaction starts with a double metal-activating process:[10] (1) 1,3-dicarbonyl compound is activated by Cu(I) to form **5**; (2) Sn(II) is used as the Lewis acid to activate the C−C triple bond of alkynoate and lead to **4**. Subsequently, the coupling of the two intermediates results in the Michael additional product **6** and regenerates the catalysts. 1,3-Hydrogen shift in **6** forms intermediate **7** due to the

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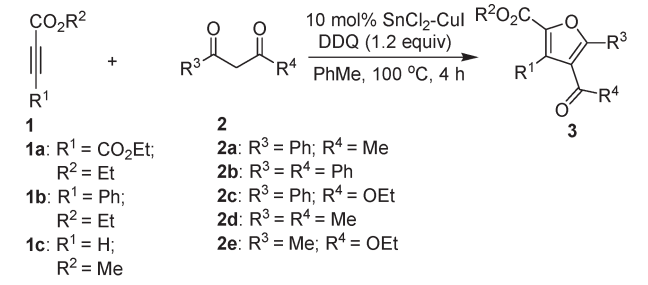
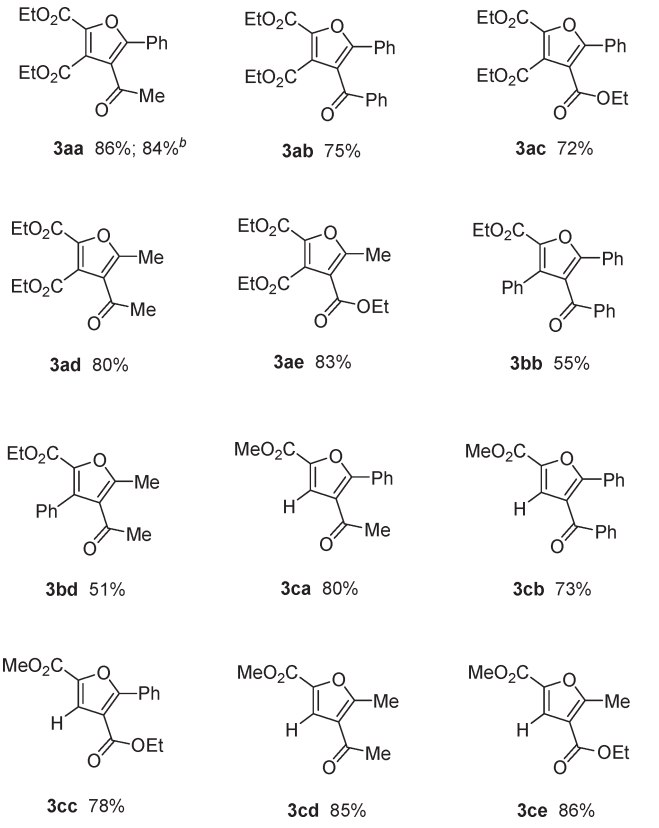
SCHEME 1. Synthesis of Polyfunctional Furans from Alkynoates and 1.3-Dicarbonyl Compounds[a]



1
1a: R^1 = CO_2Et; R^2 = Et
1b: R^1 = Ph; R^2 = Et
1c: R^1 = H; R^2 = Me

2
2a: R^3 = Ph; R^4 = Me
2b: R^3 = R^4 = Ph
2c: R^3 = Ph; R^4 = OEt
2d: R^3 = R^4 = Me
2e: R^3 = Me; R^4 = OEt

3



3aa 86%; 84%[b] **3ab** 75% **3ac** 72%

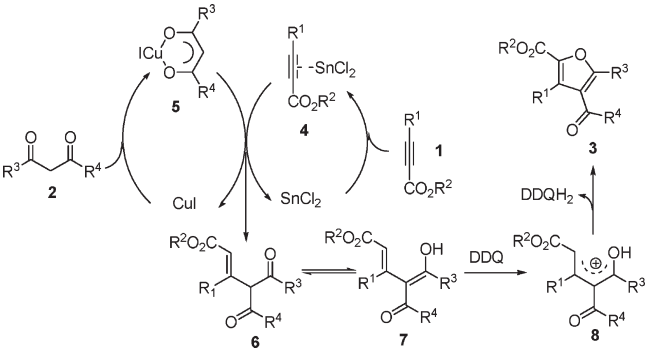
3ad 80% **3ae** 83% **3bb** 55%

3bd 51% **3ca** 80% **3cb** 73%

3cc 78% **3cd** 85% **3ce** 86%

[a]The yields of isolated products are listed. Conditions: (a) **1** (0.5 mmol), **2** (0.5 mmol); (b) **1a** (2.0 mmol), **2a** (2.0 mmol).

SCHEME 2. Plausible Reaction Mechanism



resonance phenomenon of keto−enol tautomerism in 1,3-dicarbonyl compounds.[7b] The following step involves a hydride abstraction from the tautomers **8** and **9** to generate a cationic species **8**.[8,11] Finally, the ultimate product **3** results from the dehydrocyclization process in the intermediate **8**.

In conclusion, we have established a facile and efficient method to synthesize polysubstituted furans via tin(II)- and copper(I)-involved addition/oxidative cyclization of alkynoates and 1,3-dicarbonyl compounds using DDQ as the oxidant. This methodology not only provides a simple way to construct polysubstituted furan derivatives but also opens a brand new way to build oxygen-containing vinyl ether compounds through oxidation. The readily accessible starting materials, relatively cheap oxidant DDQ and tin/copper catalyst, as well as the mild reaction conditions and good to excellent yields make the present reaction potentially useful in organic synthesis.

Experimental Section

Typical Procedure for the Synthesis of Diethyl 4-Acetyl-5-phenylfuran-2,3-dicarboxylate (3aa). To a stirring mixture of diethyl but-2-ynedioate (**1a**, 85 mg, 0.50 mmol) and 1-phenylbutane-1,3-dione (**2a**, 81 mg, 0.5 mmol) were added successively 2 mL of toluene, $SnCl_2$ (9.5 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), and DDQ (135.6 mg, 0.6 mmol). The mixture was stirred at 100 °C for 4 h in a round-bottom flask. After cooling, the solvent was diluted with water and extracted with diethyl ether. The ether layer was washed with saturated salt water and dried with anhydrous $MgSO_4$. The resulting mixture was then analyzed by GC and GC−MS. Volatiles were removed under reduced pressure, and the crude product was subjected to isolation by PTLC (GF_{254}) and eluted with a 10:2 petroleum ether−diethyl ether mixture to give 142.3 mg (86%) of diethyl 4-acetyl-5-phenylfuran-2,3-dicarboxylate (**3aa**)[12] as a pale yellow viscous oil. IR ν_{max} (KBr): 3065, 2996, 2938, 1724, 1659, 1597, 1410, 1252, 1171, 1060, 942, 910, 864, 772, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72−7.70 (m, 2H), 7.57−7.53 (m, 1H), 7.45−7.41 (m, 2H), 4.36 (q, 2H, J = 7.2 Hz), 3.94 (q, 2H, J = 7.2 Hz), 2.41 (s, 3H), 1.34 (t, 3H, J = 7.2 Hz), 1.05 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 262.2, 159.3, 157.4, 140.4, 137.8, 133.2, 128.8, 128.5, 125.5, 122.1, 67.8, 61.7, 14.0, 13.9, 13.5. GC−MS m/z (rel intens): 330.07 (M^+, 69.67), 240.92 (100).

Synthesis of Ethyl 4-Benzoyl-3,5-diphenylfuran-2-carboxylate (3bb). The product was synthesized in the same manner as **3aa** starting from ethyl 3-phenylpropiolate (87 mg, 0.5 mmol), 1,3-diphenylpropane-1,3-dione (112 mg, 0.5 mmol), 2 mL of toluene, $SnCl_2$ (9.5 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), and DDQ (135.6 mg, 0.6 mmol). Compound **3bb** was obtained as a yellow solid in 55% yield (110.1 mg). Mp: 109−110 °C. IR ν_{max} (KBr): 2961, 2896, 1815, 1710, 1659, 1401, 1270, 1236, 1173, 1029, 973, 900, 863, 765, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74−7.72 (m, 1H), 7.66−7.65 (m, 1H), 7.30−7.28 (m, 1H), 7.24−7.18 (m, 7H), 4.27 (q, 2H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 158.7, 154.1, 138.6, 136.9, 135.3, 133.6, 130.2, 129.7, 128.6, 128.5, 128.4, 128.3, 128.2, 127.6, 127.0, 123.4, 61.0, 14.0. GC−MS m/z (rel intens): 396.14 (M^+, 73.45), 104.98 (100). Anal. Calcd for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.60; H, 4.89.

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Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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