JOC The Journal of Organic Chemistry

Article

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Copper-Catalyzed [4 + 1] Annulation between α-Hydroxy Ketones and Nitriles: An Approach to Highly Substituted 3(2*H*)-Furanones

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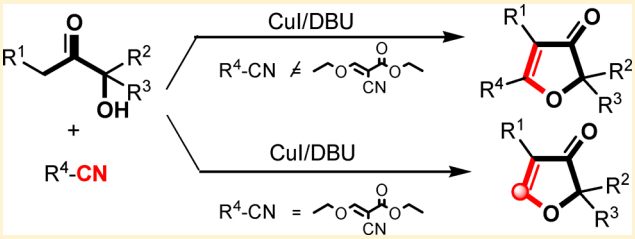
Supporting Information

ABSTRACT: A copper-catalyzed [4 + 1] annulation between α-hydroxy ketones and nitriles has been developed. The reaction provides a facile and efficient method for the construction of a wide range of highly substituted 3(2*H*)-furanones, a class of important compounds known to be associated with several biological activities.



INTRODUCTION

The synthesis of 3(2*H*)-furanones has attracted tremendous interest in the past decades because of the importance of these five-membered heterocycles in biologically active natural products[1] and pharmacologically interesting compounds.[2] Three representative examples, namely the antimicrobial active 14-norpseurotin A, the antitumor active nemoralisin A, and parvifloranine A, which were recently isolated from *Aspergillus sydowi*,[3] *Aphanamixis grandifolia*,[4] and *Geijera parviflora*,[5] respectively, are shown in Figure 1.

After the pioneering work by Smith and co-workers who established a general approach to substituted 3(2*H*)-furanones via acid-promoted cyclization/dehydration of 1-hydroxy-2,4-diketones,[6] many elegant strategies for the construction of this important class of compounds have been developed, mainly through (A) intramolecular cyclization via C5−O1 bond formation[6,7] and (B) intramolecular cyclization via C2−O1 bond formation[8] (Figure 2). In contrast, the transition-metal-catalyzed or metal free intermolecular annulations for the synthesis of 3(2*H*)-furanones have been scarcely explored.[9] Thus, from the viewpoints of starting material availability and step economy, the design of versatile intermolecular annulations between readily available substrates for constructing 3(2*H*)-furanones is highly desirable.

In 2011, we reported a carbon dioxide-triggered and copper-catalyzed domino process for the synthesis of fully substituted 3(2*H*)-furanones from propargylic alcohols and nitriles.[10] Despite the synthetic value of the transformation, 2,2,4-trisubstituted 3(2*H*)-furanones could not be synthesized by this method. Moreover, the reaction required a large excess of nitriles as solvent, which also constitutes a major limitation for the substrate scope and thus restricts its use. These drawbacks prompted us to reinvestigate the transformation. More recently, we successfully developed an efficient and green method for the synthesis of α-hydroxy ketones from propargylic alcohols.[11] On the basis of our previous work mentioned above, we envisioned that a more facile and versatile approach to highly substituted 3(2*H*)-furanones would be achieved via an intermolecular [4 + 1] annulation of readily available α-hydroxy ketones[12] with various nitriles. Herein we report in detail our research results.

RESULTS AND DISCUSSION

We started our study by examining the model reaction of 3-hydroxy-3-methyl-1-(pyridin-2-yl)butan-2-one (**1a**) and 4-acetylbenzonitrile (**2a**), and the results are summarized in Table 1. To our delight, when the reaction was carried out in the presence of 20 mol % of CuI and 0.50 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in wet methanol at 100 °C, the desired product, 5-(4-acetylphenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2*H*)-one (**3aa**), was obtained in an excellent yield after 24 h (entry 1). Two control experiments revealed that both copper salt and organic base are required for the transformation to proceed (entries 2 and 3). Among a variety of the copper catalysts, CuI was found to be the most effective for the reaction (entries 4−6). Moreover, the use of other organic bases such as triethylamine (NEt_3) or 1,4-diazabicyclo[2.2.2]octane (DABCO) resulted in a dramatic decrease in the yield (entries 7 and 8). The effect of solvent on the yield of **3aa** was then investigated, and it was shown that the solvent has an important influence on the reaction. Methanol was proven to be the most suitable media for the transformation while other solvents such as DMF, THF, 1,4-dioxane, or ethanol gave inferior results (entries 9−12). Further optimization showed that both decreasing and increasing the reaction temperature led to an obvious decrease in the yield of the product (entries 13 and 14). With the optimized reaction conditions in hand, we examined the scope of this transformation by using various nitriles and α-hydroxy ketones. Gratifyingly, a wide range of benzonitriles with different

Received: February 13, 2015
Published: April 16, 2015

DOI: 10.1021/acs.joc.5b00356
J. Org. Chem. 2015, 80, 4957−4965

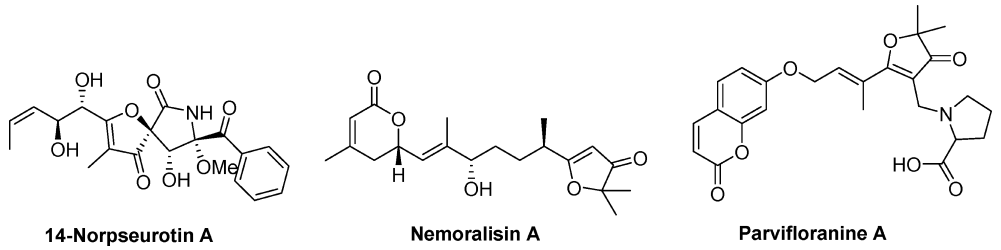


Figure 1. Naturally occurring products containing the 3(2*H*)-furanone skeleton.

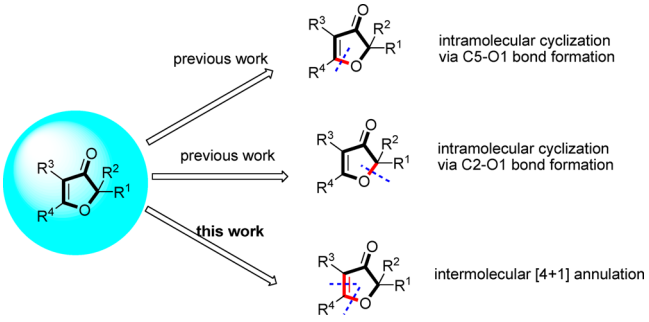
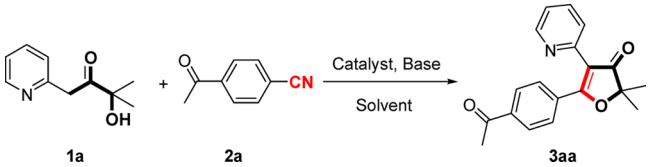


Figure 2. Synthetic strategies to 3(2*H*)-furanones.

Table 1. Optimization of the Reaction Conditions[a]



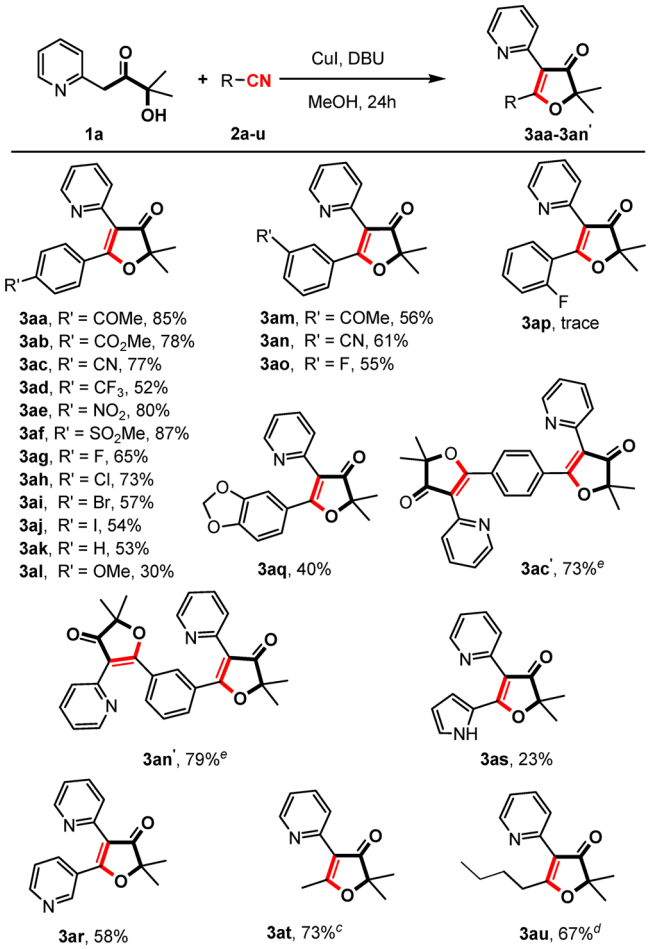
entry	catalyst	base	solvent	temperature (°C)	yield (%)[b]
1	CuI	DBU	MeOH	100	93 (85)
2	–	DBU	MeOH	100	n.r.[c]
3	CuI	–	MeOH	100	trace
4	CuBr	DBU	MeOH	100	66
5	$Cu(OAc)_2$	DBU	MeOH	100	68
6	$CuCF_3SO_3$	DBU	MeOH	100	58
7	CuI	Et_3N	MeOH	100	51
8	CuI	DABCO	MeOH	100	19
9	CuI	DBU	DMF	100	31
10	CuI	DBU	THF	100	47
11	CuI	DBU	1,4-dioxane	100	45
12	CuI	DBU	EtOH	100	69
13	CuI	DBU	MeOH	70	71
14	CuI	DBU	MeOH	120	66

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), catalyst (0.05 mmol), base (0.125 mmol), H_2O (0.5 mmol), solvent (1 mL), 24 h. [b]GC yield with dodecane as internal standard. Number in parentheses is the yield of isolated product. [c]n.r. = no reaction.

substitution patterns could be used in this reaction, affording the corresponding products in moderate to excellent yields (Table 2). Noteworthy, the present catalytic system tolerates different functional groups at positions 3 and 4 of the aryl ring of the benzonitriles, including acetyl, ester, cyano, trifluomethyl, nitro, methylsulfonyl, and halogen functionalities as well as methyl ether (**3aa**–**ao** and **3aq**). The data also shows that the electronic nature of the substituents on the aryl ring of the benzonitriles affects the yields of the desired products significantly. In general, benzonitriles with electron-withdrawing or electron-neutral substituents gave higher yields (**3aa**–**ak**) than those containing electron-donating groups (**3al** and **3aq**). Moreover, 4-substituted substrates gave better yields than 3-substituted ones, while ortho-substituted benzonitrile such as 2-fluorobenzonitrile (**3p**) only gave a trace amount of the desired product (**3ap**), and most of the starting material was recovered. We assume that steric hindrance reduces the reactivity greatly.

Interestingly, the dicyano aromatic compounds *p*-benzenedinitrile (**2c**) and *m*-benzenedinitrile (**2n**) could selectively undergo single or double annulations with **1a**, dependent on the amount of **1a** present. Thus, two structurally attractive products **3ac′** and **3an′**, both of which contain two 3(2*H*)-

Table 2. Substrate Scope of Nitriles[a,b]



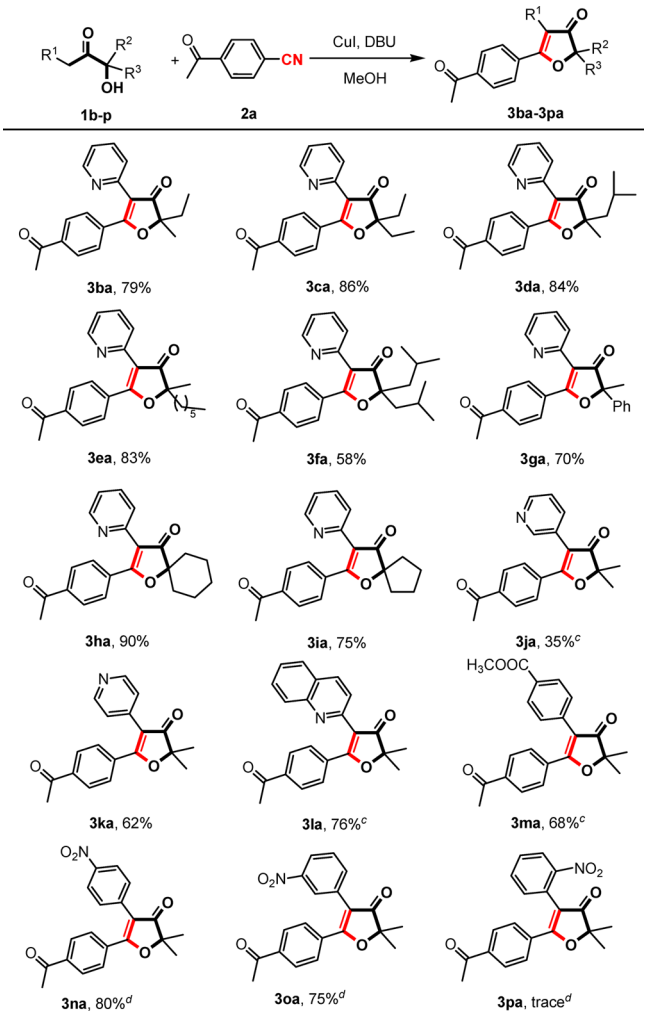
[a]Reaction conditions: *α*-hydroxy ketone **1a** (0.25 mmol), nitrile (0.30 mmol), CuI (0.05 mmol), DBU (0.125 mmol), H_2O (0.5 mmol), MeOH (1 mL), 100 °C, 24 h. [b]Isolated yields. [c]The reaction was carried out at 120 °C. [d]The reaction was carried out at 140 °C. [e]0.55 mmol nitrile was added.

DOI: 10.1021/acs.joc.5b00356
J. Org. Chem. 2015, 80, 4957–4965

furanone motifs, could be obtained in high yields when treating **2c** and **2n** with 2.2 equiv of **1a** under standard reaction conditions, respectively. Heteroaromatic nitriles such as nicotinonitrile (**2r**) and 2-cyanopyrrole (**2s**) could also participate in the reaction to generate the desired products, albeit in lower yields. We also examined the reactivity of aliphatic nitriles in this catalytic system. Satisfactorily, both acetonitrile (**2t**) and pentanenitrile (**2u**) entered the reaction smoothly, furnishing the desired products **3as** and **3at** in good yields, although higher temperatures are required in these cases.

Subsequently, the scope of α-hydroxy ketones was examined (Table 3). The transformation proceeds very efficiently with a wide range of 2-pyridyl-substituted α-hydroxy ketones, affording the corresponding products in moderate to high yields (**3ba**–**ia**). It was found that sterically less bulky α-hydroxy ketones were favorable to the reaction. When the substrates contain bulky alkyl groups (**1f**) or phenyl group (**1g**) on the alkyl chain adjacent to the hydroxyl group, lower yields were observed. However, cyclohexyl- and cyclopentyl-substituted substrates worked well to furnish the spirocyclic products in high yields (**3ha** and **3ia**). Pleasingly, 3-pyridyl-, 4-pyridyl-, and 2-quinolinyl-substituted α-hydroxy ketones underwent the reaction to generate the corresponding products **3ja**, **3ka**, and **3la** in 35%, 62%, and 76% yields, respectively. When aromatic α-hydroxy ketones containing different substituents at the para-, meta-, and ortho-positions of the aromatic ring were examined for the reaction, we found that the reactivity of this type of compounds is quite sensitive to both electronic and steric factors. Hence, the substrates bearing electron-withdrawing substituents at the para- or meta-position of the phenyl ring, such as **1m**–**o**, were compatible with the reaction, and were efficiently transformed into the corresponding products in good to high yields (**3ma**–**oa**). When the ortho-position-substituted substrate, 2-methyl-4-(2-nitrophenyl)but-3-yn-2-ol (**1p**), was employed, only a trace amount of product was observed. Furthermore, the reaction with the substrates bearing electron-neutral or electron-donating groups on the aromatic ring failed to yield even a trace of the desired products, and increasing the temperature just led to the decomposition of the substrates.

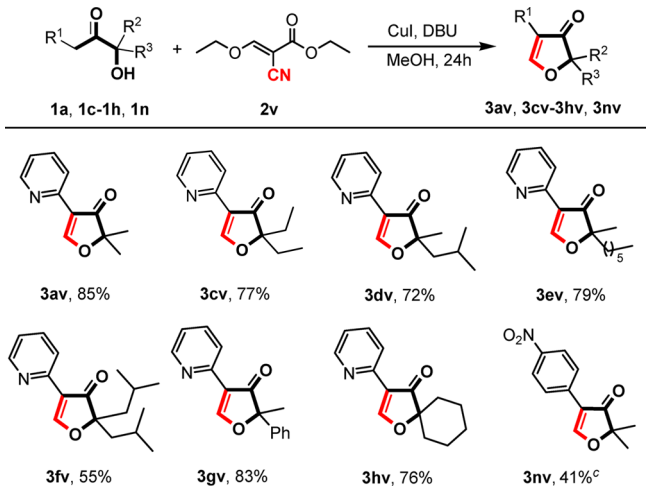
Table 3. Substrate Scope of α-Hydroxy Ketones[a,b]



[a]Reaction conditions: α-hydroxy ketone (0.25 mmol), **2a** (0.30 mmol), CuI (0.05 mmol), DBU (0.125 mmol), H_2O (0.5 mmol), MeOH (1 mL), 100 °C, 24 h. [b]Isolated yields. [c]The reaction was carried out at 120 °C. [d]The reaction was carried out at 140 °C.

Surprisingly, when we treated **1a** under the optimized reaction conditions with ethyl (ethoxymethylene)cyanoacetate (**2v**), which is a versatile building block in organic synthesis,[13] none of the desired products was observed. However, a 2,2,4-trisubstituted 3(2*H*)-furanone derivative, 2,2-dimethyl-4-(pyridin-2-yl)furan-3(2*H*)-one (**3av**), was isolated in 85% yield. It is very interesting because in this transformation, nitrile **2v** just provides a carbon atom for the assembly of **3av**. Because the reaction provides a facile access to 2,2,4-trisubstituted 3(2*H*)-furanones, which are often difficult to synthesize by the methods already reported,[6−10] we decided to further investigate this reaction by using various α-hydroxy ketones (Table 4). It was found that the results are quite similar to those presented in Table 3. Thus, 2-pyridiyl-substituted α-hydroxy ketones could be efficiently converted into the corresponding products (**3av** and **3cv**–**hv**) in moderate to high yields. But for phenyl-substituted substrates, only those containing electron-withdrawing groups could be tolerated. For example, α-hydroxy ketone **1n** could take part in the reaction at a higher

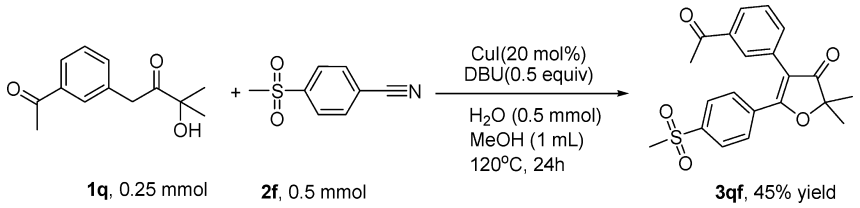
Table 4. Synthesis of Various 2,2,4-Trisubstituted 3(2*H*)-furanones[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2v** (0.30 mmol), CuI (0.05 mmol), DBU (0.125 mmol), H_2O (0.5 mmol), MeOH (1 mL), 100 °C, 24 h. [b]Isolated yields. [c]The reaction was carried out at 120 °C.

DOI: 10.1021/acs.joc.5b00356
J. Org. Chem. 2015, 80, 4957−4965

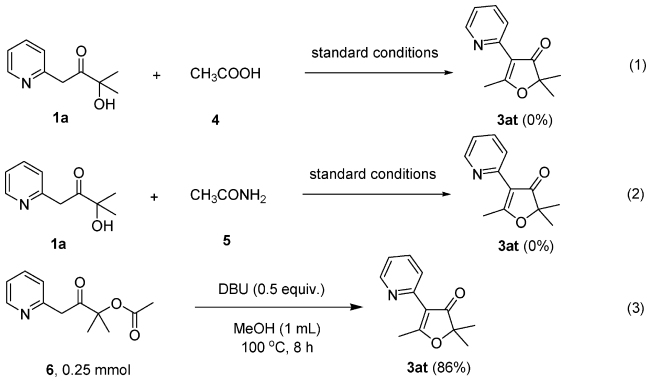
Scheme 1. Synthesis of 3qf



temperature (120 °C), giving rise to the desired product **3nv** in 41% yield.

Furthermore, we applied our method to the synthesis of 4-(3-acetylphenyl)-2,2-dimethyl-5-(4-(methylsulfonyl)phenyl)-furan-3(2*H*)-one (**3qf**), a potent selective COX-2 inhibitor, which was previously prepared by Shin and co-workers through a multistep procedure.[2d,e] Satisfyingly, just by mixing the commercially available nitrile **2f** and **1q** in wet methanol in the presence of CuI and DBU at 120 °C, the desired product **3qf** could be obtained in 45% yield after 24 h (Scheme 1). This example highlights the advantages of our protocol in the construction of highly functionalized 3(2*H*)-furanones in terms of step economy and simple operation.

For a deeper understanding of the reaction mechanism, several experiments were conducted. First, the reaction of acetic acid (**4**) with **1a** under standard conditions was investigated. However, the desired product **3at** was not observed (eq 1).



Furthermore, acetamide (**5**) could not react with **1a** under the same conditions as well (eq 2). These results reveal that neither carboxylic acid nor amide is the intermediate of the reaction, although it is well-known that nitriles can undergo hydration to generate the corresponding amides or carboxylic acids.[14] However, treatment of 2-methyl-3-oxo-4-(pyridin-2-yl)butan-2-yl acetate (**6**) with 0.5 equiv of DBU in methanol at 100 °C for 8 h led to **3at** (86%, eq 3), indicating that compound **6** might be the intermediate for the formation of **3at**.[15]

As for the reaction of ethyl (ethoxymethylene)cyanoacetate (**2v**), we suppose that under our reaction conditions, hydrogen cyanide might be formed through the cleavage of the C(sp^2)–CN bond of **2v**,[16] and then the in situ-generated HCN reacts with α-hydroxy ketones to furnish the corresponding products. To prove our hypothesis of the formation of HCN during the reaction, we used indicator paper to detect the putative HCN under different reaction conditions. As can be seen from Table 5, when the combination of **2v**, CuI, DBU, H_2O, and MeOH was heated at 100 °C for 3 h, the indicator paper turned rose-red, indicating that HCN was generated in situ (entry 1). Moreover, in the absence of CuI or DBU, the mixture did not produce any detectable HCN (entries 2–4). These results

Table 5. Detection of HCN by Indicator Paper[a]

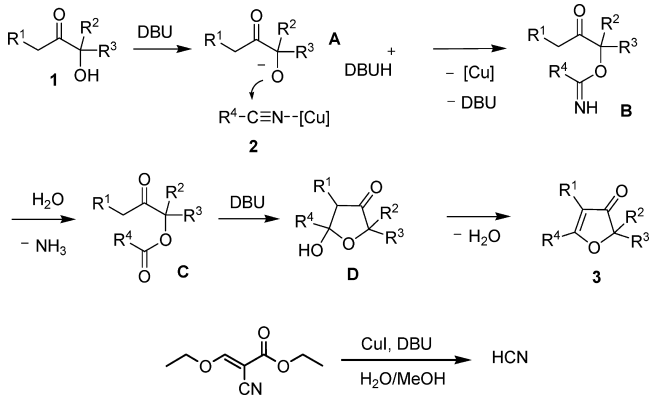
entry	2v	CuI	DBU	H_2O	MeOH	rose-red
1	×	×	×	×	×	+
2	×	×		×	×	–
3	×		×	×	×	–
4	×			×	×	–

[a]Reaction conditions: **2v** (0.30 mmol), CuI (0.05 mmol), DBU (0.125 mmol), H_2O (0.5 mmol), MeOH (1 mL). The mixture was heated under 100 °C for 3 h. "–" means negative result; "+" means positive result.

indicated that the cooperation of CuI and DBU played a key role in the in situ formation of HCN.

On the basis of the above-described observations and previous reports,[14] a plausible mechanism is illustrated in Scheme 2, which is consistent with the one we previously

Scheme 2. Proposed Reaction Mechanism



proposed.[10] Initially, an oxy anion species **A** is formed from α-hydroxy ketones **1** in the presence of DBU, which subsequently undergoes a nucleophilic attack to the carbon–nitrogen triple bond of the nitrile **2** under the assist of copper catalyst, generating ester intermediate **C** via **B**. Then, the base-promoted intramolecular Claisen condensation takes place to give intermediate **D**, which undergoes dehydration to afford the final product **3**. As for the mechanism of the reaction of ethyl (ethoxymethylene)cyanoacetate (**2v**), hydrogen cyanide is formed in situ from **2v** in the presence of CuI and DBU and then reacts with α-hydroxy ketones by following the steps described above to furnish the corresponding products. However, the mechanism of the formation of HCN from **2v** in detail is unclear yet.

CONCLUSION

In summary, we have successfully developed a facile and versatile protocol for the straightforward construction of a wide range of highly substituted 3(2*H*)-furanones via a copper-

DOI: 10.1021/acs.joc.5b00356
J. Org. Chem. 2015, 80, 4957–4965

catalyzed [4 + 1] annulation between α-hydroxy ketones and nitriles. Especially, the reaction of ethyl (ethoxymethylene)-cyanoacetate provides an easy entry to 2,2,4-trisubstituted 3(2*H*)-furanones, which are difficult to obtain by the methods already reported. The mechanism of the transformation was also discussed. The important features of the present methodology include the use of readily available substrates and cheap catalysts, wide substrate scope, high functional group tolerance, and an easy workup procedure. Further investigation of the pharmacological properties of the compounds synthesized herein and the application of ethyl (ethoxymethylene)cyanoacetate as a HCN equivalent for the synthesis of nitriles are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded by using a 400 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm, respectively, and $CDCl_3$ is used as a solvent with TMS as the internal standard. Mass spectra were recorded on a gas chromatograph−mass spectrometer. The data of HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with an infrared spectrometer. Melting points were determined with a digital melting point measuring instrument. Compounds **1a−p** were synthesized according to the literature procedures.[11] Other substrates were commercially purchased and used without further purification.

*General Procedure for the Preparation of 3(2H)-Furanones (**3**).* To a 15 mL dried Schlenk tube were added the mixture of α-ketols (0.25 mmol), nitriles (0.30 mmol), CuI (0.05 mmol), DBU (0.125 mmol), H_2O (0.5 mmol), and methanol (1 mL) successively. The Schlenk tube was then sealed and heated at the selected temperature under magnetic stirring for 24 h. After the reaction was completed, the mixture was concentrated in vacuum and the crude residue was separated by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1 to 10:1) to give the desired products **3**.

*5-(4-Acetylphenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3aa**).* Brown oil (65.3 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.4 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 2 H), 7.80−7.74 (m, 3H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.26−7.23 (m, 1 H), 2.62 (s, 3 H), 1.60 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 197.3, 179.2, 149.6, 149.5, 139.3, 136.6, 134.0, 129.1, 127.9, 124.8, 122.7, 114.5, 88.0, 26.7, 23.3. IR (KBr): 2979, 2930, 1690, 1600, 1386, 1265, 1173, 1061, 905, 744, 607 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{19}H_{17}NNaO_3$ [M + Na]$^+$: 330.1101; found 330.1104.

*Methyl 4-(5,5-Dimethyl-4-oxo-3-(pyridin-2-yl)-4,5-dihydrofuran-2-yl)benzoate (**3ab**).* Brown oil (62.9 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.7 Hz, 1 H), 8.02 (d, *J* = 8.5 Hz, 2 H), 7.79−7.72 (m, 3 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.26−7.20 (m, 1 H), 3.93 (s, 3 H), 1.59 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 179.3, 166.2, 149.7, 149.5, 136.6, 133.9, 132.9, 129.2, 128.8, 124.8, 122.6, 114.5, 88.0, 52.4, 23.3. IR (KBr): 3057, 2981, 1726, 1696, 1603, 1474, 1386, 1280, 1173, 1109, 1062, 906, 775, 707, 610 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{19}H_{18}NO_4$ [M + H]$^+$: 324.1230; found 324.1226.

*4-(5,5-Dimethyl-4-oxo-3-(pyridin-2-yl)-4,5-dihydrofuran-2-yl)-benzonitrile (**3ac**).* Light yellow solid (55.8 mg, 77%), mp: 129−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 7.80−7.75 (m, 1 H), 7.70−7.59 (m, 3 H), 7.25 (s, 1 H), 1.59 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 178.0, 149.4, 149.2, 136.7, 134.1, 131.8, 129.4, 124.7, 122.9, 118.0, 115.1, 99.9, 88.1, 23.2. IR (KBr): 2981, 2931, 2230, 1696, 1601, 1474, 1387, 1258, 1170, 1063, 905, 848, 796, 749, 611 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{18}H_{15}N_2O_2$ [M + H]$^+$: 291.1128; found 291.1123.

*2,2-Dimethyl-4-(pyridin-2-yl)-5-(4-(trifluoromethyl)phenyl)furan-3(2H)-one (**3ad**).* Light yellow solid (43.2 mg, 52%), mp: 105−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.5 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 7.77 (td, *J* = 7.8, 1.6 Hz, 1 H), 7.63−7.60 (m, 3 H), 7.24 (dd, *J* = 6.8, 5.5 Hz, 1 H), 1.59 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 178.8, 149.5, 136.7, 133.4 (d, *J* = 32.5 Hz), 133.3 (d, *J* = 1.2 Hz), 129.2, 125.1 (q, *J* = 3.8 Hz), 124.7, 123.6 (d, *J* = 271 Hz), 122.7, 114.4, 88.0, 23.3. IR (KBr): 2982, 2934, 1699, 1608, 1476, 1388, 1324, 1172, 1131, 1066, 906, 850, 796, 763, 612 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{18}H_{15}F_3NO_2$ [M + H]$^+$: 334.1049; found 334.1051.

*2,2-Dimethyl-5-(4-nitrophenyl)-4-(pyridin-2-yl)furan-3(2H)-one (**3ae**).* Brown solid (62.1 mg, 80%), mp: 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 3.5 Hz, 1 H), 8.22 (d, *J* = 8.7 Hz, 2 H), 7.91 (d, *J* = 8.7 Hz, 2 H), 7.79 (t, *J* = 7.7 Hz, 1 H), 7.66 (d, *J* = 7.8 Hz, 1 H), 7.27−7.25 (m, 1 H), 1.60 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 177.8, 149.4(9), 149.4(5), 149.1, 136.7, 135.89, 130.0, 124.6, 123.2, 123.0, 115.2, 88.3, 23.3. IR (KBr): 2981, 2932, 2216, 1699, 1591, 1523, 1350, 1268, 1172, 1063, 905, 855, 795, 698, 609 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{15}N_2O_4$ [M + H]$^+$: 311.1026; found 311.1027.

*2,2-Dimethyl-5-(4-(methylsulfonyl)phenyl)-4-(pyridin-2-yl)furan-3(2H)-one (**3af**).*[17] Yellow solid (74.5 mg, 87%), mp: 138−139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.2 Hz, 1 H), 7.98−7.90 (m, 4 H), 7.82−7.74 (m, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.28−7.21 (m, 1 H), 3.07 (d, *J* = 1.1 Hz, 3 H), 1.60 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 178.1, 149.4, 149.2, 143.0, 136.7, 135.0, 129.7, 127.1, 124.6, 122.9, 114.9, 88.1, 44.3, 23.2. IR (KBr): 2981, 2929, 1697, 1620, 1385, 1319, 1151, 1063, 961, 770, 554 cm^{-1}. MS (EI) *m*/*z*: 343, 342(100), 314, 263, 194, 178, 151, 121, 89, 76.

*5-(4-Fluorophenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ag**).* Light yellow solid (45.9 mg, 65%), mp: 94−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.57 (m, 1 H), 7.79−7.71 (m, 3 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.26−7.21 (m, 1 H), 7.08−7.02 (m, 2 H), 1.58 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 179.4, 165.0 (d, *J* = 254 Hz), 150.0, 149.4, 136.8, 131.3 (d, *J* = 9.0 Hz), 126.0 (d, *J* = 3.2 Hz), 125.0, 122.5, 115.5 (d, *J* = 22.0 Hz), 113.0, 87.8, 23.3. IR (KBr): 2981, 2930, 1695, 1608, 1509, 1474, 1412, 1386, 1260, 1234, 1155, 1063, 906, 845, 747, 609 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{15}FNO_2$ [M + H]$^+$: 284.1081; found 284.1084.

*5-(4-Chlorophenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ah**).* Light yellow solid (54.4 mg, 73%), mp: 137−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.5 Hz, 1 H), 7.76 (td, *J* = 7.7, 1.5 Hz, 1 H), 7.66 (d, *J* = 8.7 Hz, 2 H), 7.57 (d, *J* = 7.8 Hz, 1 H), 7.34 (d, *J* = 8.7 Hz, 2 H), 7.23 (dd, *J* = 6.9, 5.5 Hz, 1 H), 1.58 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 179.3, 149.9, 149.5, 138.4, 136.7, 130.2, 128.5, 128.3, 124.9, 122.6, 113.5, 87.8, 23.3. IR (KBr): 2980, 2931, 1696, 1614, 1472, 1384, 1234, 1175, 1092, 1063, 906, 838, 794, 744, 609 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{15}ClNO_2$ [M + H]$^+$: 300.0786; found 300.0787.

*5-(4-Bromophenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ai**).* Light yellow solid (48.9 mg, 57%), mp: 130−131 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.3 Hz, 1 H), 7.75 (t, *J* = 7.7 Hz, 1 H), 7.59−7.56 (m, 3 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 7.26−7.18 (m, 1 H), 1.57 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 179.3, 149.9, 149.5, 136.6, 131.5, 130.3, 128.7, 126.9, 124.8, 122.6, 113.6, 87.8, 23.3. IR (KBr): 2979, 2930, 1695, 1613, 1491, 1382, 1256, 1174, 1064, 1011, 905, 793, 609 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{15}BrNO_2$ [M + H]$^+$: 344.0281; found 344.0278.

*5-(4-Iodophenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3aj**).* Light yellow solid (52.8 mg, 54%), mp: 125−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.2 Hz, 1 H), 7.74 (m, 3 H), 7.56 (d, *J* = 7.9 Hz, 1 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 7.26−7.20 (m, 1 H), 1.57 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 179.5, 149.9, 149.5, 137.5, 136.6, 130.2, 129.3, 124.8, 122.6, 113.7, 99.4, 87.8, 23.3. IR (KBr): 2977, 2928, 1694, 1610, 1470, 1400, 1282, 1173, 1062, 1007, 905, 764, 609 cm^{-1}. HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{15}INO_2$ [M + H]$^+$: 392.0142; found 392.0145.

*2,2-Dimethyl-5-phenyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ak**).*[10] Yellow oil (35.0 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 3.6 Hz, 1 H), 7.74 (t, *J* = 7.4 Hz, 1 H), 7.68 (d, *J* = 7.4 Hz, 2 H), 7.53 (d, *J* = 7.8 Hz, 1 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 7.24−7.19 (m, 1 H), 1.58 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 180.5, 150.3, 149.6, 136.5, 132.1, 129.8, 128.8, 128.2,

DOI: 10.1021/acs.joc.5b00356
J. Org. Chem. 2015, 80, 4957−4965

124.9, 122.4, 113.4, 87.7, 23.3. MS (EI) m/z: 265 [M^+], 264 (100), 222, 179, 151, 105, 77, 43.

5-(4-Methoxyphenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3al**). Brown oil (22.2 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 4.1 Hz, 1 H), 7.74 (t, J = 7.6 Hz, 1 H), 7.68 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.24−7.19 (m, 1 H), 6.85 (d, J = 8.7 Hz, 2 H), 3.83 (s, 3 H), 1.57 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 180.1, 162.8, 150.7, 149.5, 136.5, 125.1, 122.2, 122.1, 113.7, 112.1, 87.4, 55.4, 23.4. IR (KBr): 2978, 2930, 1691, 1606, 1512, 1473, 1387, 1261, 1182, 1063, 906, 840, 763, 591 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{18}H_{18}NO_3$ [M + H]$^+$: 296.1281; found 296.1289.

5-(3-Acetylphenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3am**). Brown oil (42.9 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.3 Hz, 1 H), 8.36 (s, 1 H), 8.08 (d, J = 7.8 Hz, 1 H), 7.91 (d, J = 7.8 Hz, 1 H), 7.79 (t, J = 7.7 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 1 H), 7.25−7.24 (m, 1 H), 2.51 (s, 3 H), 1.61 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 197.0, 179.5, 149.8, 149.3, 137.0, 136.8, 133.1, 131.4, 130.4, 129.1, 128.6, 124.9, 122.7, 113.8, 88.0, 26.5, 23.3. IR (KBr): 2980, 2931, 1691, 1614, 1471, 1427, 1384, 1252, 1172, 1063, 907, 794, 592 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{19}H_{17}NNaO_3$ [M + Na]$^+$: 330.1101; found 330.1095.

3-(5,5-Dimethyl-4-oxo-3-(pyridin-2-yl)-4,5-dihydrofuran-2-yl)-benzonitrile (**3an**). Brown solid (44.0 mg, 61%), mp: 81−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.5 Hz, 1 H), 8.11 (s, 1 H), 7.99 (d, J = 8.0 Hz, 1 H), 7.83−7.76 (m, 2 H), 7.68 (d, J = 7.9 Hz, 1 H), 7.52 (t, J = 7.9 Hz, 1 H), 7.28−7.26 (m, 1 H), 1.61 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 177.8, 149.4, 149.1, 136.8, 134.9, 132.9, 132.5, 131.4, 129.0, 124.6, 123.0, 117.9, 114.3, 112.7, 88.1, 23.3. IR (KBr): 2981, 2931, 2232, 1700, 1620, 1472, 1386, 1291, 1159, 1064, 910, 796, 749 cm^{-1}. HRMS-EI (m/z): calcd for $C_{18}H_{15}N_2O_2$ [M + H]$^+$: 291.1128; found 291.1124.

5-(3-Fluorophenyl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ao**). Light yellow solid (38.7 mg, 55%), mp: 76−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 2.0 Hz, 1 H), 7.76 (t, J = 7.7 Hz, 1 H), 7.56 (d, J = 7.7 Hz, 1 H), 7.47 (t, J = 10.0 Hz, 2 H), 7.35−7.30 (m, 7.9 Hz, 1 H), 7.26−7.21 (m, 1 H), 7.20−7.16 (m, 1 H), 1.58 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 178.8, 162.2 (d, J = 246.6 Hz), 149.8, 149.6, 136.6, 131.8 (d, J = 8.1 Hz), 129.8 (d, J = 8.0 Hz), 124.9, 124.7 (d, J = 3.1 Hz), 122.6, 119.0 (d, J = 21.2 Hz), 115.8 (d, J = 23.8 Hz), 114.0, 87.8, 23.2. IR (KBr): 2980, 2931, 1697, 1583, 1471, 1386, 1284, 1219, 1159, 1063, 963, 911, 786, 705, 615 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{17}H_{15}FNO_2$ [M + H]$^+$: 284.1081; found 284.1087.

5-(Benzo[d][1,3]dioxol-5-yl)-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3aq**). Yellow oil (30.7 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 4.4 Hz, 1 H), 7.76 (t, J = 7.7 Hz, 1 H), 7.54 (d, J = 7.9 Hz, 1 H), 7.32 (dd, J = 8.3, 1.5 Hz, 1 H), 7.23 (dd, J = 6.8, 5.5 Hz, 1 H), 7.16 (d, J = 1.4 Hz, 1 H), 6.78 (d, J = 8.3 Hz, 1 H), 6.00 (s, 2 H), 1.56 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 179.7, 151.1, 150.3, 149.4, 147.6, 136.8, 125.2, 124.6, 123.5, 122.4, 112.3, 108.8, 108.2, 101.7, 87.5, 23.3. IR (KBr): 3460, 2979, 2929, 1692, 1597, 1448, 1386, 1240, 1155, 1038, 909, 788, 744, 615 cm^{-1}. HRMS EI (m/z): calcd for $C_{18}H_{16}NO_4$ [M + H]$^+$: 310.1074; found 310.1069.

2,2-Dimethyl-4-(pyridin-2-yl)-5-(pyridin-3-yl)furan-3(2H)-one (**3ar**). Brown solid (38.5 mg, 58%), mp: 140−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 1.5 Hz, 1 H), 8.69 (dd, J = 4.8, 1.4 Hz, 1 H), 8.54 (d, J = 4.7 Hz, 1 H), 8.07 (dt, J = 8.0, 1.9 Hz, 1 H), 7.77 (td, J = 7.8, 1.8 Hz, 1 H), 7.66 (d, J = 7.9 Hz, 1 H), 7.34 (dd, J = 8.0, 4.9 Hz, 1 H), 7.23 (ddd, J = 7.4, 4.9, 1.0 Hz, 1 H), 1.59 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 178.2, 152.3, 149.8, 149.5, 149.4, 136.7, 136.0, 127.0, 124.5, 122.9, 122.8, 114.3, 88.0, 23.3. IR (KBr): 2980, 2929, 1697, 1614, 1469, 1386, 1262, 1175, 1064, 903, 746, 707, 612 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{16}H_{15}N_2O_2$ [M + H]$^+$: 267.1128; found 267.1126.

2,2-Dimethyl-4-(pyridin-2-yl)-5-(1H-pyrrol-2-yl)furan-3(2H)-one (**3as**). Brown solid (14.7 mg, 23%), mp: 91−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.11 (s, 1 H), 8.74 (d, J = 8.2 Hz, 1 H), 8.60 (d, J = 3.4 Hz, 1 H), 7.80 (t, J = 7.8 Hz, 1 H), 7.25−7.19 (m, 3 H), 6.45−6.44 (m, 1 H), 1.53 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 173.6, 150.9, 146.4, 137.4, 125.0, 124.5, 122.7, 121.1, 116.2, 111.5, 105.5, 86.2, 23.7. IR (KBr): 2980, 2927, 1678, 1576, 1512, 1428, 1275, 1209, 1136, 1069, 748, 616 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{15}H_{15}N_2O_2$ [M + H]$^+$: 255.1128; found 255.1127.

2,2,5-Trimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3at**).[10] Yellow oil (36.8 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 3.1 Hz, 1 H), 8.02 (d, J = 8.0 Hz, 1 H), 7.69 (t, J = 7.7 Hz, 1 H), 7.19−7.06 (m, 1 H), 2.71 (s, 3 H), 1.46 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 188.2, 150.7, 148.8, 136.2, 122.4, 121.3, 112.2, 87.8, 23.1, 17.8. MS (EI) m/z: 203 [M^+] (100), 188, 160, 117, 90, 78, 63, 43.

5-Butyl-2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3au**).[10] Yellow oil (41.0 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.4 Hz, 1 H), 8.00 (d, J = 8.0 Hz, 1 H), 7.69 (td, J = 7.9, 1.6 Hz, 1 H), 7.12 (dd, J = 6.9, 5.3 Hz, 1 H), 3.21−3.14 (t, J = 7.6 Hz, 2 H), 1.75−1.67 (m, 2 H), 1.47−1.37 (m, 8 H), 0.93 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5, 191.8, 150.7, 148.8, 136.2, 122.5, 121.3, 111.7, 87.6, 30.4, 28.4, 23.1, 22.4, 13.7. IR (KBr): 2960, 2931, 2870, 1693, 1601, 1480, 1395, 1280, 1162, 1110, 1008, 798, 745, 591 cm^{-1}. MS (EI) m/z: 245 [M^+], 230, 216(100), 202, 188, 160, 146, 130, 117, 89, 78.

5,5′-(1,4-Phenylene)bis(2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one) (**3ac′**). Light yellow solid (82.3 mg, 73%), mp: 183−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.1 Hz, 2 H), 7.74 (td, J = 7.8, 1.7 Hz, 2 H), 7.68 (s, 4 H), 7.56 (d, J = 7.9 Hz, 2 H), 7.25−7.19 (m, 2 H), 1.57 (s, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 179.2, 149.8, 149.5, 136.6, 133.0, 128.6, 124.8, 122.6, 114.3, 87.9, 23.3. IR (KBr): 2980, 2930, 1695, 1607, 1473, 1383, 1253, 1177, 1063, 905, 792, 741, 610 cm^{-1}. HRMS EI (m/z): calcd for $C_{28}H_{25}N_2O_4$ [M + H]$^+$: 453.1809; found 453.1810.

5,5′-(1,3-Phenylene)bis(2,2-dimethyl-4-(pyridin-2-yl)furan-3(2H)-one) (**3an′**). Brown oil (89.1 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.4 Hz, 2 H), 8.23 (s, 1 H), 7.81 (dd, J = 7.9, 1.6 Hz, 2 H), 7.73 (td, J = 7.7, 1.7 Hz, 2 H), 7.54 (d, J = 7.9 Hz, 2 H), 7.34 (t, J = 7.9 Hz, 1 H), 7.23−7.18 (m, 2 H), 1.55 (s, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 179.1, 149.8, 149.4, 136.5, 132.2, 130.1, 129.2, 128.0, 124.8, 122.5, 113.8, 87.7, 23.3. IR (KBr): 2979, 2931, 1696, 1618, 1473, 1380, 1259, 1161, 1064, 1092, 907, 745, 691, 611 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{28}H_{25}N_2O_4$ [M + H]$^+$: 453.1809; found 453.1810.

5-(4-Acetylphenyl)-2-ethyl-2-methyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ba**). Brown oil (63.3 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.4 Hz, 1 H), 7.94 (d, J = 8.3 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H), 7.75 (t, J = 7.7 Hz, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.25−7.21 (m, 1 H), 2.62 (s, 3 H), 2.04−1.93 (m, 2 H), 1.56 (s, 3 H), 0.98 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 197.3, 179.8, 149.6, 149.5, 139.2, 136.5, 133.9, 129.0, 127.9, 124.7, 122.6, 115.9, 90.7, 30.3, 26.7, 21.6, 7.5. IR (KBr): 2974, 2935, 1689, 1600, 1387, 1266, 1175, 1071, 847, 746, 603 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{20}H_{20}NO_3$ [M + H]$^+$: 322.1438; found 322.1436.

5-(4-Acetylphenyl)-2,2-diethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ca**). Brown oil (71.9 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.8 Hz, 1 H), 7.95 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.75 (td, J = 7.7, 1.3 Hz, 1 H), 7.58 (d, J = 7.5 Hz, 1 H), 7.22 (dd, J = 7.4, 5.0 Hz, 1 H), 2.61 (s, 3 H), 1.99 (q, J = 7.4 Hz, 4 H), 0.95 (t, J = 7.4 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 197.2, 180.6, 149.5, 149.5, 139.3, 136.5, 133.9, 128.9, 127.9, 124.6, 122.6, 117.4, 93.7, 29.2, 26.7, 7.3. IR (KBr): 2972, 2940, 1689, 1600, 1505, 1407, 1266, 1171, 1072, 994, 942, 848, 747, 601 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{21}H_{22}NO_3$ [M + H]$^+$: 336.1594; found 336.1595.

5-(4-Acetylphenyl)-2-isobutyl-2-methyl-4-(pyridin-2-yl)furan-3(2H)-one (**3da**). Brown oil (73.1 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.7 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 2 H), 7.83−7.73 (m, 3 H), 7.59 (d, J = 7.9 Hz, 1 H), 7.27−7.19 (m, 1 H), 2.61−2.60 (m, 3 H), 1.96−1.80 (m, 3 H), 1.55 (s, 3 H), 0.98 (dd, J = 8.6, 6.3 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 197.3, 179.4, 149.7, 149.5, 139.2, 136.6, 134.0, 129.0, 127.9, 124.7, 122.6, 115.4, 90.7, 45.4, 26.7, 24.2, 23.5, 22.3. IR (KBr): 2957, 2871, 1690, 1600, 1473, 1386, 1266, 1172, 1041, 845, 744, 605 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{22}H_{24}NO_3$ [M + H]$^+$: 350.1751; found 350.1748.

5-(4-Acetylphenyl)-2-hexyl-2-methyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ea**). Brown oil (78.1 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.3 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 2 H), 7.81 (d, J = 8.2 Hz,

DOI: 10.1021/acs.joc.5b00356
J. Org. Chem. 2015, 80, 4957−4965

2 H), 7.76 (t, J = 7.7 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.26−7.20 (m, 1 H), 2.61 (s, 3 H), 1.98−1.89 (m, 2 H), 1.56 (s, 3 H), 1.37−1.20 (d, J = 16.8 Hz, 8 H), 0.85 (t, J = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 197.3, 179.7, 149.6, 149.5, 139.3, 136.6, 134.0, 129.0, 127.9, 124.7, 122.6, 115.7, 90.5, 37.2, 31.5, 29.2, 26.7, 23.0, 22.5, 22.0, 13.9. IR (KBr): 2958, 2856, 1690, 1600, 1408, 1265, 1174, 1042, 846, 747, 607 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{24}H_{28}NO_3$ [M + H]$^+$: 378.2064; found 378.2060.

*5-(4-Acetylphenyl)-2,2-diisobutyl-4-(pyridin-2-yl)furan-3(2H)-one (**3fa**).* Brown oil (56.9 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1 H), 7.94 (d, J = 8.4 Hz, 2 H), 7.84−7.75 (m, 3 H), 7.60 (d, J = 7.4 Hz, 1 H), 7.21−7.27 (m, 1 H), 2.61 (s, 3 H), 1.97−1.91 (m, 2 H), 1.86−1.79 (m, 4 H), 0.94 (dd, J = 7.6, 6.4 Hz, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 197.3, 179.9, 165.4, 149.7, 149.5, 139.3, 136.7, 134.0, 129.0, 128.0, 124.8, 122.7, 93.7, 45.5, 26.7, 24.3, 24.0. IR (KBr): 2958, 2871, 1690, 1600, 1472, 1385, 1265, 1168, 1091, 747, 602 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{25}H_{30}NO_3$ [M + H]$^+$: 392.2220; found 392.2219.

*5-(4-Acetylphenyl)-2-methyl-2-phenyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ga**).* Brown solid (64.5 mg, 70%), mp: 133−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.3 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H), 7.75 (t, J = 7.7 Hz, 1 H), 7.65−7.61 (m, 2 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.41−7.37 (m, 2 H), 7.35−7.30 (m, 1 H), 7.25−7.22 (m, 1 H), 2.63 (s, 3 H), 1.96 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 197.3, 179.6, 149.4, 149.3, 139.5, 138.0, 136.7, 133.7, 129.2, 128.7, 128.3, 128.0, 124.9, 124.6, 122.8, 114.6, 89.5, 26.7, 24.9. IR (KBr): 3059, 2929, 1687, 1600, 1382, 1265, 1157, 1072, 930, 748, 699, 604 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{24}H_{20}NO_3$ [M + H]$^+$: 370.1438; found 370.1430.

*2-(4-Acetylphenyl)-3-(pyridin-2-yl)-1-oxaspiro[4.5]dec-2-en-4-one (**3ha**).* Brown oil (78.1 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.3 Hz, 1 H), 7.94 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 7.75 (td, J = 7.8, 1.6 Hz, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.22 (dd, J = 6.8, 5.4 Hz, 1 H), 2.61 (s, 3 H), 1.95−1.70 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 197.2, 179.0, 149.7, 149.4, 139.1, 136.4, 134.1, 129.0, 127.8, 124.7, 122.5, 115.1, 31.9, 26.6, 24.4, 21.7. IR (KBr): 2938, 2859, 1684, 1600, 1386, 1266, 1224, 1123, 1059, 954, 919, 846, 747, 605 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{22}H_{22}NO_3$ [M + H]$^+$: 348.1594; found 348.1590.

*2-(4-Acetylphenyl)-3-(pyridin-2-yl)-1-oxaspiro[4.4]non-2-en-4-one (**3ia**).* Brown solid (62.4 mg, 75%), mp: 89−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.3 Hz, 1 H), 7.93 (d, J = 8.2 Hz, 2 H), 7.81−7.72 (m, 3 H), 7.60 (d, J = 7.8 Hz, 1 H), 7.25−7.21 (m, 1 H), 2.61 (s, 3 H), 2.25−2.14 (m, 2 H), 2.13−1.98 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 197.3, 179.4, 149.8, 149.6, 139.2, 136.6, 134.1, 129.1, 127.9, 124.8, 122.6, 115.9, 98.0, 37.6, 26.7, 25.7. IR (KBr): 2965, 2927, 1688, 1599, 1386, 1264, 1171, 748, 605 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{21}H_{20}NO_3$ [M + H]$^+$: 334.1438; found 334.1434.

*5-(4-Acetylphenyl)-2,2-dimethyl-4-(pyridin-3-yl)furan-3(2H)-one (**3ja**).* Brown oil (26.8 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 28.5 Hz, 2H), 7.96 (d, J = 7.9 Hz, 2H), 7.72 (d, J = 6.8 Hz, 3H), 7.36 (s, 1H), 2.62 (s, 3H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 197.0, 177.7, 174.5, 149.6, 148.3, 139.4, 137.1, 133.5, 128.5, 128.5, 123.7, 111.4, 26.7, 23.3. IR (KBr): 2926, 2853, 1690, 1614, 1387, 1266, 1167, 1062, 740, 604 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_3$ [M + H]$^+$: 308.1281; found 308.1281.

*5-(4-Acetylphenyl)-2,2-dimethyl-4-(pyridin-4-yl)furan-3(2H)-one (**3ka**).* Brown oil (46.8 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 2H), 7.98 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.28 (s, 2H), 2.64 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 197.0, 178.6, 149.7, 139.6, 138.2, 133.3, 128.7, 128.4, 123.8, 112.0, 88.4, 26.7, 23.2. IR (KBr): 2981, 2928, 2854, 1692, 1598, 1390, 1266, 1168, 1054, 831, 605 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_3$ [M + H]$^+$: 308.1281; found 308.1282.

*5-(4-Acetylphenyl)-2,2-dimethyl-4-(quinolin-2-yl)furan-3(2H)-one (**3la**).* Yellow solid (67.5 mg, 76%), mp: 116−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.19 (m, J = 8.5 Hz, 1H), 7.95−7.86 (m, 5H), 7.84 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 2.60 (s, 3H), 1.64 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 197.3, 179.8, 150.3, 147.9, 139.3, 136.5, 134.0, 129.6, 129.3, 129.0, 127.8, 127.5, 127.3, 126.7, 122.4, 114.8, 88.1, 26.7, 23.3. IR (KBr): 3061, 2980, 2928, 1690, 1595, 1507, 1386, 1265, 1176, 1058, 834, 754, 605 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{23}H_{20}NO_3$ [M + H]$^+$: 358.1438; found 358.1446.

*Methyl 4-(2-(4-Acetylphenyl)-5,5-dimethyl-4-oxo-4,5-dihydrofuran-3-yl)benzoate (**3ma**).* Yellow solid (61.6 mg, 68%), mp: 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 2 H), 7.93 (d, J = 8.4 Hz, 2 H), 7.71 (d, J = 8.4 Hz, 2 H), 7.39 (d, J = 8.3 Hz, 2 H), 3.93 (s, 3 H), 2.61 (s, 3 H), 1.59 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 197.1, 177.5, 166.8, 139.3, 134.4, 133.7, 129.9, 129.3, 129.3, 128.7, 128.3, 113.9, 87.8, 52.1, 26.7, 23.3. IR (KBr): 2981, 2953, 1723, 1690, 1596, 1386, 1274, 1189, 1111, 1051, 961, 845, 787, 603 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{22}H_{20}NaO_5$ [M + Na]$^+$: 387.1203; found 387.1198.

*5-(4-Acetylphenyl)-2,2-dimethyl-4-(4-nitrophenyl)furan-3(2H)-one (**3na**).* Brown solid (70.2 mg, 80%), mp: 117−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.18 (m, 2 H), 7.98 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 2.63 (s, 3 H), 1.61 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 196.9, 178.4, 147.0, 139.7, 136.6, 133.3, 130.0, 128.7, 128.5, 123.8, 112.8, 88.4, 26.7, 23.3. IR (KBr): 2981, 2931, 1690, 1601, 1516, 1386, 1344, 1267, 1168, 1051, 852, 734, 603 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{20}H_{17}NNaO_5$ [M + Na]$^+$: 374.0999; found 374.0992.

*5-(4-Acetylphenyl)-2,2-dimethyl-4-(3-nitrophenyl)furan-3(2H)-one (**3oa**).* Brown oil (65.6 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.16 (m, 2 H), 7.96 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 7.8 Hz, 1 H), 7.55 (t, J = 7.8 Hz, 1 H), 2.62 (s, 3 H), 1.61 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 197.0, 177.9, 148.5, 139.6, 135.4, 133.3, 131.5, 129.7, 128.6, 128.5, 124.3, 122.6, 112.7, 88.2, 26.7, 23.3. IR (KBr): 3084, 2982, 2932, 1689, 1598, 1530, 1386, 1348, 1266, 1169, 1055, 843, 729, 607 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{20}H_{17}NNaO_5$ [M + Na]$^+$: 374.0999; found 374.1000.

*2,2-Dimethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3av**).* Brown oil (40.3 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 8.52 (d, J = 4.2 Hz, 1 H), 8.07 (d, J = 7.9 Hz, 1 H), 7.69 (td, J = 7.8, 1.5 Hz, 1 H), 7.19−7.13 (m, 1 H), 1.49 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 176.1, 149.4, 149.3, 136.6, 122.2, 120.4, 116.7, 90.6, 23.0. IR (KBr): 3460, 2981, 2930, 1697, 1610, 1477, 1381, 1192, 1068, 885, 794, 745, 618, 509 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{11}H_{12}NO_2$ [M + H]$^+$, 190.0863; found 190.0862.

*2,2-Diethyl-4-(pyridin-2-yl)furan-3(2H)-one (**3cv**).* Yellow oil (42.0 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1 H), 8.52 (d, J = 4.4 Hz, 1 H), 8.10 (d, J = 7.9 Hz, 1 H), 7.68 (t, J = 7.7 Hz, 1 H), 7.19−7.11 (m, 1 H), 1.89 (q, J = 7.5 Hz, 4 H), 0.86 (t, J = 7.4 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.72, 177.38, 149.2, 136.6, 122.1, 120.3, 119.6, 96.6, 28.8, 7.2. IR (KBr): 3060, 2979, 2934, 1764, 1692, 1610, 1472, 1375, 1243, 1186, 1055, 905, 793, 745, 619 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{13}H_{16}NO_2$ [M + H]$^+$: 218.1176; found 218.1177.

*2-Isobutyl-2-methyl-4-(pyridin-2-yl)furan-3(2H)-one (**3dv**).* Yellow oil (41.8 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 8.52 (d, J = 4.4 Hz, 1 H), 8.09 (d, J = 7.9 Hz, 1 H), 7.68 (t, J = 7.7 Hz, 1 H), 7.19−7.10 (m, 1 H), 1.85−1.68 (m, 3 H), 1.45 (s, 3 H), 0.94 (d, J = 6.2 Hz, 3 H), 0.90 (d, J = 6.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 176.4, 149.4, 149.3, 136.6, 122.2, 120.4, 117.7, 93.4, 45.1, 24.2, 24.0, 23.5, 22.3. IR (KBr): 3060, 2959, 2929, 1764, 1695, 1610, 1474, 1371, 1243, 1186, 1053, 791, 620 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{14}H_{18}NO_2$ [M + H]$^+$: 232.1332; found 232.1336.

*2-Hexyl-2-methyl-4-(pyridin-2-yl)furan-3(2H)-one (**3ev**).* Yellow oil (51.5 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1 H), 8.52 (d, J = 4.2 Hz, 1 H), 8.09 (d, J = 7.9 Hz, 1 H), 7.69 (t, J = 7.7 Hz, 1 H), 7.19−7.11 (m, 1 H), 1.89−1.76 (m, 2 H), 1.45 (s, 3 H), 1.30−1.17 (m, 8 H), 0.85 (t, J = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 176.6, 149.3, 149.2, 136.7, 122.2, 120.4, 117.8, 93.3, 36.7, 31.5, 29.2, 22.8, 22.5, 21.9, 14.0. IR (KBr): 3503, 2930, 2860, 1764, 1695, 1610, 1474, 1374, 1243, 1180, 1053, 793, 620 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{16}H_{21}NNaO_2$ [M + Na]$^+$: 282.1464; found 282.1467.

*2,2-Diisobutyl-4-(pyridin-2-yl)furan-3(2H)-one (**3fv**).* Yellow oil (37.0 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1 H), 8.52 (d, J = 4.4 Hz, 1 H), 8.11 (d, J = 7.9 Hz, 1 H), 7.69 (t, J = 7.7 Hz, 1

DOI: 10.1021/acs.joc.5b00356
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H), 7.20−7.12 (m, 1 H), 1.86−1.80 (m, 2 H), 1.73−1.69 (m, 4 H), 0.91 (d, J = 5.9 Hz, 6 H), 0.86 (d, J = 5.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 176.9, 149.4, 149.3, 136.7, 122.2, 120.4, 119.4, 96.5, 45.3, 24.3, 23.9, 23.7. IR (KBr): 3060, 2957, 2873, 1694, 1611, 1472, 1361, 1244, 1183, 1095, 890, 790, 747, 620 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{17}H_{23}NNaO_2$ [M + Na]$^+$, 296.1621; found 296.1624.

*2-Methyl-2-phenyl-4-(pyridin-2-yl)furan-3(2H)-one (**3gv**).* Brown oil (52.5 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s, 1 H), 8.52 (d, J = 4.4 Hz, 1 H), 8.05 (d, J = 7.9 Hz, 1 H), 7.66 (t, J = 7.7 Hz, 1 H), 7.54 (d, J = 7.9 Hz, 2 H), 7.39−7.30 (m, 3 H), 7.18−7.11 (m, 1 H), 1.86 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 176.5, 149.3, 149.1, 137.3, 136.6, 128.6, 128.3, 124.5, 122.3, 120.5, 117.0, 92.0, 24.5. IR (KBr): 3060, 2984, 2928, 2855, 1704, 1612, 1476, 1356, 1243, 1180, 1051, 793, 747, 698, 618 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{16}H_{13}NNaO_2$ [M + Na]$^+$: 274.0838; found 274.0842.

*3-(Pyridin-2-yl)-1-oxaspiro[4.5]dec-2-en-4-one (**3hv**).* Light yellow solid (43.9 mg, 76%), mp: 100−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 8.51 (d, J = 4.5 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 7.67 (t, J = 7.7 Hz, 1 H), 7.21−7.08 (m, 1 H), 1.83−1.74 (m, 5 H), 1.72−1.65 (m, 4 H), 1.44−1.35 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 176.2, 149.5, 149.2, 136.6, 122.1, 120.5, 117.3, 92.6, 31.8, 24.4, 21.6. IR (KBr): 3060, 2991, 2935, 2858, 1764, 1691, 1610, 1475, 1376, 1243, 1055, 919, 790 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{14}H_{15}NNaO_2$ [M + Na]$^+$, 252.0995; found 252.0997.

*2,2-Dimethyl-4-(4-nitrophenyl)furan-3(2H)-one (**3nv**).* Yellow solid (23.5 mg, 41%), mp: 176−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1 H), 8.23 (d, J = 8.1 Hz, 2 H), 7.90 (d, J = 8.2 Hz, 2 H), 1.50 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 173.5, 146.6, 136.0, 125.6, 124.0, 114.8, 90.2, 23.0. IR (KBr): 3358, 2991, 2922, 2851, 1763, 1680, 1601, 1510, 1379, 1243, 1055, 850, 744, 745, 623, 504 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{12}H_{11}NNaO_4$ [M + Na]$^+$: 256.0580; found 256.0576.

*4-(3-Acetylphenyl)-2,2-dimethyl-5-(4-(methylsulfonyl)phenyl)-furan-3(2H)-one (**3qf**).*[2e] Brown solid (43.2 mg, 45%), mp: 190−191 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 3 H), 7.90 (s, 1 H), 7.82 (d, J = 8.4 Hz, 2 H), 7.52−7.46 (m, 2 H), 3.08 (s, 3 H), 2.58 (s, 3 H), 1.60 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 197.7, 175.8, 143.1, 137.7, 134.7, 133.9, 129.7, 129.2, 129.2, 128.0, 127.5, 114.6, 87.9, 44.2, 26.6, 23.2. MS (EI) m/z: 384[M$^+$], 283, 199, 183 (100), 137, 121, 103, 76, 65.

*Procedure for the Preparation of 2-Methyl-3-oxo-4-(pyridin-2-yl)butan-2-yl Acetate (**6**).* To a stirred solution of 3-hydroxy-3-methyl-1-(pyridin-2-yl)butan-2-one (**1a**) (1 mmol), pyridine (1.4 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (0.1 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was slowly added acetic anhydride (1.5 mmol). The mixture was warmed to room temperature. After being stirred overnight, the reaction was quenched with 2 M aqueous HCl, and the product was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine. Then the organic phase was dried over $MgSO_4$, concentrated by rotary evaporation, and separated by column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) as eluent to give the desired product **6** (143.7 mg, 65% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.3 Hz, 1 H), 7.66 (td, J = 7.7, 1.8 Hz, 1 H), 7.33 (d, J = 7.8 Hz, 1 H), 7.18 (ddd, J = 7.4, 5.0, 0.9 Hz, 1 H), 4.02 (s, 2 H), 2.11 (s, 3 H), 1.54 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 170.6, 154.7, 148.8, 136.5, 124.7, 121.9, 83.8, 45.0, 23.4, 21.1. IR (KBr): 2991, 2935, 2360, 1732, 1592, 1372, 1257, 1148, 914, 746 cm^{-1}. HRMS-ESI (m/z): calcd for $C_{12}H_{15}NNaO_3$ [M + Na]$^+$: 244.0944; found 244.0941.

Procedure for the Detection of HCN by Indicator Paper. Picrate paper was prepared by wetting filter paper with a solution of sodium bicarbonate (5.0 g) and picric acid (0.5 g) in water (100 mL). After drying the paper, it was cut into strips and inserted into a 2 mL plastic vial with a number of holes. To a 15 mL dried Schlenk tube were added the mixture of ethyl (ethoxymethylene)cyanoacetate (**2v**, 0.3 mmol), CuI (0.05 mmol), DBU (0.125 mmol), H_2O (0.5 mmol), and methanol (1 mL) successively. The plastic vial was placed above the reaction mixture. The Schlenk tube was then sealed and heated in oil bath at 100 °C for 3 h. The test paper in the plastic vial turned rose-red, indicating the existence of HCN.[18]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all synthesized compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00356.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21172078), the National Basic Research Program of China (973 Program) (2011CB808600), the Guangdong Natural Science Foundation (10351064101000000), and the Fundamental Research Funds for the Central Universities (2013ZM0061) for financial support.

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DOI: 10.1021/acs.joc.5b00356
J. Org. Chem. 2015, 80, 4957−4965