Selective Synthesis of 3-Methylene-2,3-dihydrofurans or 1,2,4-Trisubstituted Furans via Tandem Reactions of Allenic Ketones with α-Chloro β-Keto Esters or Ketones

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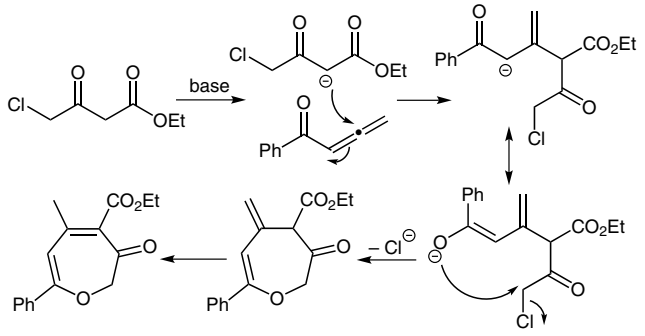
Abstract: Novel and efficient synthesis of functionalized furan derivatives have been developed in this paper. Promoted by K_2CO_3, allenic ketones underwent tandem reactions with 2-chloroacetoacetate or 3-chloropentane-2,4-dione to afford 3-methylene-2,3-dihydrofurans with high efficiency under remarkably mild conditions. When the same substrates were treated with potassium carbonate and triphenylphosphine, on the other hand, 1,2,4-trisubstituted furans could be obtained in good yields.

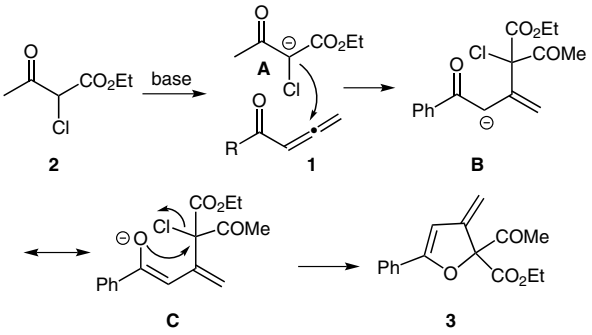
Key words: allenic ketones, furan derivatives, phosphine catalysis, tandem reactions

The development of efficient and novel synthetic strategies by employing functionalized allenes as versatile synthetic intermediates has become a hot topic in organic synthesis.[1] As a continuation of our study in this field, we have recently developed a selective synthesis of oxepin-3(2*H*)-ones via base-promoted tandem reaction of 1,2-allenic ketone with 4-chloroacetoacetate (Scheme 1).[2]



Scheme 1 Synthesis of oxepin-3(2*H*)-one via tandem reaction of 1,2-allenic ketone with 4-chloroacetoacetate

Inspired by the above results, we envisioned a new synthetic pathway toward 3-methylene-2,3-dihydrofuran (**3**) via a cascade reaction of 1,2-allenic ketone **1** with 2-chloroacetoacetate (**2**) as shown in Scheme 2. It is well known that 2,3-dihydrofurans belong to an important class of compounds which show a wide range of biological activity and form the basic structure of many natural products, such as aflatoxins and others.[3] Notwithstanding their importance, simple and efficient synthetic methods toward 2,3-dihydrofurans without using transition-metal catalysts are still highly desirable.[4]



Scheme 2 Proposed synthesis of 3-methylene-3-dihydrofuran via a cascade reaction of 1,2-allenic ketone with 2-chloroacetoacetate

To check the feasibility of our proposed preparation of **3**, 1-phenylbuta-2,3-dien-1-one (**1a**) and ethyl 2-chloroacetoacetate (**2a**) were treated with K_2CO_3 in THF at room temperature for two hours. To our delight, ethyl 2-acetyl-3-methylene-5-phenyl-2,3-dihydronpuran-2-carboxylate (**3aa**) was obtained in a yield of 75%.

Then, a number of solvents (CH_2Cl_2, EtOAc, toluene, DMSO, and MeCN), different bases (Na_2CO_3, $NaHCO_3$, LiOH, and NaOH) were tested. It was found that the highest yield could be obtained when the reaction was run in MeCN at room temperature for one hour in the presence of one equivalent of K_2CO_3. With the optimized reaction conditions, the scope of the synthesis of **3** was then studied with a series of substituted 1,2-allenic ketones **1a**–**e** and α-halogenated active methylene compounds **2a**,**b**. Representative results are shown in Table 1.[5] It turned out that both 1-aryl- (Table 1, entries 1–3, 5) and 1-phenylethyl-substituted (Table 1, entry 4) 1,2-allenic ketones underwent this tandem reaction smoothly to afford the corresponding 3-methylene-2,3-dihydrofurans **3** in good yields. It was noted that the electronic nature of substituents does not show an obvious effect on the yield of **3** (Table 1, entries1–3). On the other hand, the retarding effect of sterics on this reaction is illustrated in Table 1, entry 6

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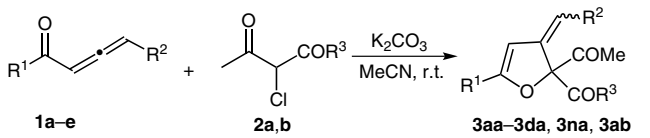
where 1,2-allenic ketone bearing a substituent on the terminal position of the allenic unit gave the corresponding product in lower yield.

Table 1 Synthesis of Substituted 2,3-Dihydrofurans **3**[a]



Entry	R^1, R^2	R^3	Yield of **3** (%)[b]
1	**1a** Ph, H	**2a** OEt	**3aa** 85
2	**1b** 4-BrC_6H_4, H	**2a** OEt	**3ba** 82
3	**1c** 4-MeC_6H_4, H	**2a** OEt	**3ca** 86
4	**1d** $PhCH_2CH_2$, H	**2a** OEt	**3da** 81
5	**1a** Ph, H	**2b** Me	**3ab** 83
6	**1n** Ph, Me	**2a** OEt	**3na** 54

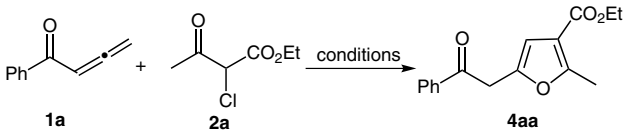
[a] Reaction conditions: **1** (1.5 mmol), **2** (1.65 mmol), K_2CO_3 (1.5 mmol), MeCN (5 mL), r.t., 1 h.
[b] Isolated yield.

Recently, phosphine-catalyzed cycloaddition reactions of allenoates or their surrogates as a nucleophile with various electrophiles have emerged as a versatile platform for the synthesis of valuable five- and six-membered cyclic structures.[1k,m,6] We noticed that in the formation of 3-methylene-2,3-dihydrofurans **3**, allenic ketones **1** were actually acting as an electrophile while 2-chloroacetoacetate (**2**) was acting as a nucleophile. If treated with phosphine, on the other hand, allenic ketones are expected to be transformed into a nucleophilic intermediate[6] to undergo a nucleophilic reaction with 2-chloroacetoacetate (**2**). To explore the possible reactivity of allenic ketones with 2-chloroacetoacetate under the promotion of phosphine, the mixture of **1a** (1 mmol), **2a** (1.1 mmol), Ph_3P (0.1 mmol), and K_2CO_3 (1 mmol) in toluene was stirred at room temperature for 0.5 hours. It turned out that the reaction gave a yellow solid product, which was identified as a polysubstituted furan **4aa** based on its NMR and HRMS spectra.

Furans represent an important class of heterocycles since they occur in a multitude of natural products[7] and possess a broad spectrum of biological and pharmaceutical properties.[8] Furthermore, they are also versatile building blocks in synthetic organic chemistry.[9] Although many synthetic routes for their preparation have been developed, this field is still far from being solved and the development of efficient ways to construct furan molecules from readily available starting materials under mild conditions remains an important goal.[10] This urged us to optimize the above process to develop it into an efficient and general protocol for the preparation of functionalized furans.

For this purpose, the amount of phosphine, different bases, and solvents were screened and their effects on this reaction are summarized in Table 2. Firstly, it showed that the amount of Ph_3P has a remarkable effect on this reaction (Table 2, entries 1–4). In the absence of Ph_3P, no formation of **4aa** was observed. With 0.1 or 0.2 equivalents of Ph_3P, the yield of **4aa** was very low. With 0.5 equivalents of Ph_3P, a yield of 65% could be obtained (Table 2, entry 4). Further increase in the dosage of Ph_3P did not improve the reaction obviously (Table 2, entry 5). It was also demonstrated that 1,4-diazabicyclo[2,2,2]-octane (DABCO) and Me_3P did not perform as well in terms of catalytic activity as Ph_3P for this reaction (Table 2, entries 7 and 8). Subsequently, the effect of different solvents was also examined. Among the solvents studied, toluene turned out to be the most efficient (Table 2 entries 9–11). With toluene as solvent, other bases, such as Na_2CO_3, KOH, LiOH, or $NaHCO_3$, were also tried. They gave lower yields of **4aa** than K_2CO_3 (Table 2, entries 12–15).

Table 2 Optimization Studies for the Formations of **4aa**[a]



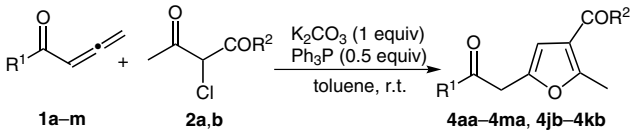
Entry	Base	Catalyst (equiv)	Solvent	Yield (%)[b]
1	K_2CO_3	–	toluene	trace
2	K_2CO_3	Ph_3P (0.1)	toluene	15
3	K_2CO_3	Ph_3P (0.2)	toluene	20
4	K_2CO_3	Ph_3P (0.5)	toluene	65
5	K_2CO_3	Ph_3P (1.0)	toluene	66
6	–	Ph_3P (0.5)	toluene	25
7	K_2CO_3	DABCO(0.5)	toluene	27
8	K_2CO_3	Me_3P(0.5)	toluene	24
9	K_2CO_3	Ph_3P (0.5)	CH_3Cl	26
10	K_2CO_3	Ph_3P (0.5)	THF	14
11	K_2CO_3	Ph_3P (0.5)	MeCN	10
12	Na_2CO_3	Ph_3P (0.5)	toluene	40
13	KOH	Ph_3P (0.5)	toluene	34
14	LiOH	Ph_3P (0.5)	toluene	30
15	$NaHCO_3$	Ph_3P (0.5)	toluene	15

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), base (1.0 mmol), solvent (5 mL), r.t., 1.5 h.
[b] Isolated yield.

With the optimized conditions in hands, the scope and generality for the synthesis of 1,2,4-trisubstituted furans was investigated.[11] It turned out that both 1-aryl (Table 3, entries 1–10, 13, and 14) and 1-benzyl- (Table 3, entries 11 and 15) or 1-phenylethyl-substituted (Table 3, entries 12 and 16) 1,2-allenic ketones underwent this tandem re-

action smoothly to afford the desired furan in moderate to good yields. Functional groups such as F, Cl, Br, CH_3O, and CF_3 are well tolerated. Clearly, the electronic nature of substituents on the aromatic ring shows an obvious effect on the yield of **4aa**. Substrates with an electron-donating group gave better yields (Table 3, entries 6, 7, 9, and 10) than that with an electron-withdrawing group (Table 3, entries 2–5, 8). Promisingly, this transformation could be extended to 3-chloropentane-2,4-dione (**2b**), though the yields of the corresponding products were lower (Table 3, entries 14–16).

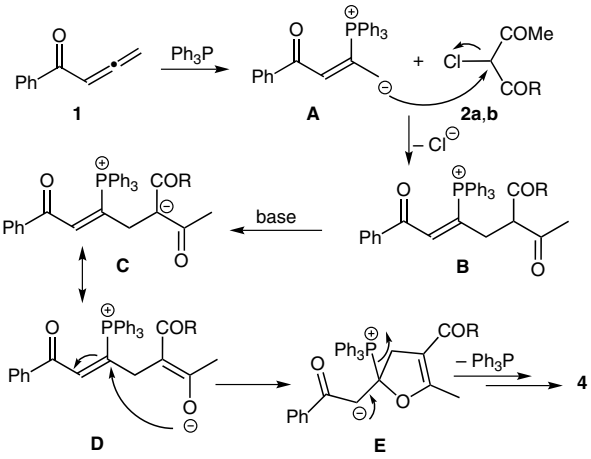
Table 3 Synthesis of Substituted Furans **4**[a]



Entry	R^1	R^2	Yield of **4** (%)[b]
1	**1a** Ph	**2a** OEt	**4aa** 65
2	**1b** 4-FC_6H_4	**2a** OEt	**4ba** 58
3	**1c** 4-ClC_6H_4	**2a** OEt	**4ca** 52
4	**1d** 4-BrC_6H_4	**2a** OEt	**4da** 53
5	**1e** 4-CNC_6H_4	**2a** OEt	**4ea** 40
6	**1f** 4-MeC_6H_4	**2a** OEt	**4fa** 82
7	**1g** 4-$MeOC_6H_4$	**2a** OEt	**4ga** 80
8	**1h** 3-BrC_6H_4	**2a** OEt	**4ha** 45
9	**1i** 3-MeC_6H_4	**2a** OEt	**4ia** 74
10	**1j** 2-$MeOC_6H_4$	**2a** OEt	**4ja** 72
11	**1k** Bn	**2a** OEt	**4ka** 83
12	**1l** $PhCH_2CH_2$	**2a** OEt	**4la** 88
13	**1m** furan-2-yl	**2a** OEt	**4ma** 42
14	**1j** 2-$MeOC_6H_4$	**2b** Me	**4jb** 40
15	**1k** Bn	**2b** Me	**4kb** 42
16	**1l** $PhCH_2CH_2$	**2b** Me	**4lb** 44

[a] Reaction conditions: 1 (1.5 mmol), 2 (1.65 mmol), Ph_3P (0.75 mmol), K_2CO_3 (1.5 mmol), toluene (5 mL), r.t., 1.5 h.
[b] Isolated yield.

Based on the above observations, a plausible mechanistic pathway for the formation of **4** is proposed in Scheme 3. Firstly, nucleophilic addition of triphenylphosphine onto allenic ketone **1** results in a phosphonium intermediate **A**. Then, **A** undergoes an intermolecular C-nucleophilic substitution with **2** to afford **B**, which is then deprotonated to give a zwitterionic intermediate **C**. Intermediate **C** can readily isomerize to its tautomer **D**. Compound **D** undergoes a 5-*exo*-*trig* process to produce the furan intermediate **E**. Subsequent expulsion of the phosphine catalyst from **E** furnishes **4**.



Scheme 3 Plausible pathway for the formation of **4**

In summary, we have established a highly selective, convenient, and practical method to synthesize 2,3-dihydrofurans or 1,2,4-trisubstituted furans from the tandem reaction of 1,2-allenic ketones with α-chloro β-keto esters or ketones under the promotion of potassium carbonate or a combination of triphenylphosphine and potassium carbonate at room temperature. With advantages such as readily available acyclic substrates, free of expensive catalysts/reagents, and extremely mild reaction conditions, the methods developed herein should be important applications in heterocyclic chemistry and related areas.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(5) **Typical Procedure for the Preparation of Compounds 3aa–da,na,ab – Exemplified with 3aa (Table 1, Entry 1)**
To a flask containing 1-phenylbuta-2,3-dien-1-one (**1a**, 1 mmol) and ethyl 2-chloroacetoacetate (**2**, 1.1 mmol) in MeCN (3 mL) were added anhydrous K_2CO_3 (1.0 mmol). The solution was stirred at r.t. for 1 h. The reaction then was quenched with aq NH_4Cl and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried, filtered, and concentrated under vacuum. The residue was purified by column chromatography over silica gel using EtOAc–PE (1:15, v/v) as eluent to give **3aa** (68%).

2-Acetyl-3-methylene-5-phenyl-2,3-dihydrofuran-2-carboxylate (3aa, Table 1, Entry 1)
Eluent: EtOAc–PE (1:15), yellow oil; yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.68 (m, 2 H), 7.42–7.38 (m, 3 H), 6.07 (s, 1 H), 5.18 (s, 1 H), 5.12 (s, 1 H), 4.29 (q, *J* = 6.8 Hz, 2 H), 2.31 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.0, 166.1, 161.1, 144.7, 129.9, 129.1, 128.8, 128.6, 125.6, 104.9, 101.9, 94.1, 62.5, 25.1, 14.013. ESI-HRMS: *m/z* calcd for $C_{16}H_{17}O_4$ $[M + H]^+$: 273.1127; found: 273.1137.

Ethyl 2-Acetyl-5-(4-bromophenyl)-3-methylene-2,3-dihydrofuran-2-carboxylate (3ba, Table 1, Entry 2)
Eluent: EtOAc–PE (1:15); yellow oil; yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.53 (m, 4 H), 6.06 (s, 1 H), 5.20 (s, 1 H), 5.14 (s, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 2.30 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 166.0, 160.0, 144.3, 131.9, 128.0, 127.1, 124.0, 105.7, 102.5, 94.1, 62.7, 25.1, 14.0. ESI-HRMS: *m/z* calcd for $C_{16}H_{16}BrO_4$ $[M + H]^+$: 351.0232; found: 351.0237.

Ethyl 2-Acetyl-3-methylene-5-*p*-tolyl-2,3-dihydrofuran-2-carboxylate (3ca, Table 1, Entry 3)
Eluent: EtOAc–PE (1:15); yellow oil; yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.4 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 6.02 (s, 1 H), 5.51 (s, 1 H), 5.08 (s, 1 H), 4.29 (t, *J* = 6.8 Hz, 2 H), 2.38 (s, 3 H), 2.31 (s, 3 H), 1.30 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 166.2, 161.4, 144.8, 140.2, 129.3, 126.4, 125.6, 104.3, 101.1, 94.0, 62.5, 25.1, 25.5, 14.0. ESI-HRMS: *m/z* calcd for $C_{17}H_{19}O_4$ $[M + H]^+$: 287.1283; found: 287.1280.

Ethyl 2-Acetyl-3-methylene-5-(3-oxo-3-phenylpropyl)-2,3-dihydrofuran-2-carboxylate (3da, Table 1, Entry 4)
Eluent: EtOAc–PE (1:15); yellow oil; yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 2 H), 7.22–7.20 (m, 3 H), 5.38 (s, 1 H), 4.99 (s, 1 H), 4.95 (s, 1 H), 4.31–4.25 (m, 2 H), 2.96–2.91 (m, 2 H), 2.70–2.66 (m, 2 H), 2.23 (s, 3 H), 1.38 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 166.2, 165.1, 144.6, 140.4, 128.5, 128.4, 128.3, 126.4, 103.1, 102.9, 94.1, 62.5, 32.6, 30.0, 24.9, 14.0. ESI-HRMS: *m/z* calcd for $C_{19}H_{21}O_5$ $[M + H]^+$: 329.1389; found: 329.1383.

1,1′-(3-Methylene-5-phenyl-2,3-dihydrofuran-2,2-diyl)diethanone (3ab, Table 1, Entry 5)
Eluent: EtOAc–PE (1:15); yellow oil; yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.69 (m, 2 H), 7.44–7.42 (m, 3 H), 6.08 (s, 1 H), 5.13 (s, 1 H), 5.03 (s, 1 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 160.9, 144.0, 130.0, 129.1, 128.8, 128.7, 127.0, 125.4, 104.4, 102.3, 99.0, 25.5. ESI-HRMS: *m/z* calcd for $C_{15}H_{15}O_3$ $[M + H]^+$: 243.1021; found: 243.1027.

1,1′-(3-Ethylidene-5-phenyl-2,3-dihydrofuran-2,2-diyl)diethanone (3na, Table 1, Entry 6)
Eluent: EtOAc–PE (1:15); yellow oil; yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.69 (m, 2 H), 7.42–7.36 (m, 3 H), 6.18 (s, 1 H), 5.51 (q, *J* = 7.6 Hz, 1 H), 4.31–4.23 (m, 2 H), 2.29 (s, 3 H), 1.85 (d, *J* = 7.2 Hz, 3 H), 1.29 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 166.7, 159.6, 136.9, 129.5, 128.6, 125.4, 116.2, 98.6, 93.8, 62.4, 25.1, 15.4, 14.0. ESI-HRMS: *m/z* calcd for $C_{16}H_{17}O_3$ $[M + H]^+$: 257.1178; found: 257.1183.

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(11) **Typical Procedure for the Preparation of Compounds 4aa–ma,jb–kb – Exemplified with 4aa (Table 3, Entry 1)**
To a flask containing 1-phenylbuta-2,3-dien-1-one (**1a**, 1 mmol) and triphenylphosphine (0.5 mmol) in toluene (5 mL) were added ethyl 2-chloroacetoacetate (**2**, 1.1 mmol) and anhydrous K_2CO_3 (1.0 mmol). The solution was stirred at r.t. for 1.5 h. The reaction then was quenched with aq NH_4Cl and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried, filtered, and concentrated under vacuum. The residue was purified by column chromatography over silica gel using EtOAc–PE (1:30, v/v) as eluent to give **4aa** (65%).

Ethyl 2-Methyl-5-(2-oxo-2-phenylethyl)furan-3-carboxylate (4aa, Table 3, Entry 1)
Eluent: EtOAc–PE (1:30); yellow syrup; yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.0 Hz, 2 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 6.49 (s, 1 H), 4.24 (s, 2 H), 4.24 (q, *J* = 7.6 Hz, 2 H), 2.52 (s, 3 H), 1.30 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6, 164.0, 158.8, 146.2, 136.0, 133.6, 128.8, 128.5, 114.5, 109.3, 60.1, 38.0, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{16}H_{17}O_4$ $[M + H]^+$: 273.1127; found: 273.1130.

Ethyl 5-[2-(4-Fluorophenyl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4ba, Table 3, Entry 2)
Eluent: EtOAc–PE (1:30); yellow solid; yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 2 H), 7.313–7.308 (m, 1 H), 7.15–7.11 (m, 2 H), 6.49 (s, 1 H), 4.24 (q, *J* = 7.6 Hz, 2 H), 4.21 (s, 2 H), 2.52 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1, 167.2, 164.7, 164.0, 158.9, 146.0, 133.8, 133.6, 132.4, 132.4, 132.1, 131.3, 131.2, 128.8, 128.6, 128.6, 128.5, 116.0, 115.8, 114.5, 109.4, 60.1, 38.0, 14.4, 13.8. ESI-HRMS: m/z calcd for $C_{16}H_{16}FO_4$ $[M + H]^+$: 291.1033; found: 291.1037.

Ethyl 5-[2-(4-Chlorophenyl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4ca, Table 3, Entry 3)
Eluent: EtOAc–PE (1:30); yellow solid; yield: 52%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.8 Hz, 2 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 6.49 (s, 1 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 4.22 (s, 2 H), 2.52 (s, 3 H), 1.31 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5, 164.0, 159.0, 145.8, 140.1, 134.3, 123.0, 129.1, 114.5, 109.5, 60.1, 38.1, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{16}H_{16}ClO_4$ $[M + H]^+$: 307.0737; found: 307.0742.

Ethyl 5-[2-(4-Bromophenyl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4da, Table 3, Entry 4)
Eluent: EtOAc–PE (1:30); yellow solid; yield: 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 6.47 (s, 1 H), 4.23 (q, *J* = 6.8 Hz, 2 H), 4.20 (s, 2 H), 2.51 (s, 3 H), 1.29 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6, 163.9, 158.9, 145.8, 134.7, 132.1, 130.1, 128.8, 114.5, 109.5, 60.1, 38.0, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{16}H_{16}BrO_4$ $[M + H]^+$: 351.0232; found: 351.0237.

Ethyl 5-[2-(4-Cyanophenyl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4ea, Table 3, Entry 5)
Eluent: EtOAc–PE (1:10); white solid; yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H), 6.51 (s, 1 H), 4.27 (s, 2 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 2.53 (s, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 163.9, 159.1, 145.0, 138.9, 132.7, 129.0, 117.8, 116.8, 114.6, 109.8, 60.2, 38.4, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}NO_4$ $[M + H]^+$: 298.1079; found: 298.1083.

Ethyl 2-Methyl-5-(2-oxo-2-*p*-tolylethyl)furan-3-carboxylate (4fa, Table 3, Entry 6)
Eluent: EtOAc–PE (1:15); white solid; yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 6.47 (s, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 4.20 (s, 2 H), 2.51 (s, 3 H), 2.38 (s, 3 H), 1.29 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3, 164.1, 158.8, 146.4, 144.5, 133.5, 129.4, 128.7, 114.4, 109.2, 60.0, 37.9, 21.7, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{17}H_{19}O_4$ $[M + H]^+$: 287.1283; found: 287.1289.

Ethyl 5-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4ga, Table 3, Entry 7)
Eluent: EtOAc–PE (1:10); white solid; yield: 80%. ^{1}H NMR (400 MHz, CD_3OD and DMSO-d_6): δ = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.09 (d, *J* = 8.8 Hz, 2 H), 6.53 (s, 1 H), 4.38 (s, 2 H), 4.28 (q, *J* = 6.8 Hz, 2 H), 3.92 (s, 3 H), 2.55 (s, 3 H), 1.35 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 164.1, 163.8, 158.4, 148.0, 130.9, 129.1, 114.2, 114.0, 108.9, 60.0, 55.2, 37.3, 13.8, 12.3. ESI-HRMS: *m/z* calcd for $C_{17}H_{19}O_5$ $[M + H]^+$: 303.1232; found: 303.1236.

Ethyl 5-[2-(3-Bromophenyl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4ha, Table 3, Entry 8)
Eluent: EtOAc–PE (1:30); white solid; yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.36 (t, *J* = 8.4 Hz, 1 H), 6.50 (s, 1 H), 4.26 (q, *J* = 7.6 Hz, 2 H), 4.23 (s, 2 H), 2.54 (s, 3 H), 1.32 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 164.0, 159.0, 145.5, 137.7, 136.4, 131.6, 130.4, 127.1, 123.1, 114.5, 109.6, 60.1, 38.1, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{16}H_{16}BrO_4$ $[M + H]^+$: 351.0232; found: 351.0237.

Ethyl 2-Methyl-5-(2-oxo-2-*m*-tolylethyl)furan-3-carboxylate (4ia, Table 3, Entry 9)
Eluent: EtOAc–PE (1:15); yellow oil; yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.77 (m, 2 H), 7.37–7.26 (m, 2 H), 6.48 (s, 1 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 4.22 (s, 2 H), 2.53 (s, 3 H), 2.40 (s, 3 H), 1.31 (t, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 164.0, 158.7, 146.3, 138.6, 136.2, 134.3, 129.0, 128.6, 125.8, 114.5, 109.3, 60.0, 38.0, 21.3, 14.3, 13.7. ESI-HRMS: *m/z* calcd for $C_{17}H_{19}O_4$ $[M + H]^+$: 287.1283; found: 287.1289.

Ethyl 5-[2-(2-Methoxyphenyl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4ja, Table 3, Entry 10)
Eluent: EtOAc–PE (1:10); white solid, yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.71 (m, 1 H), 7.47–7.42 (m, 1 H), 6.99–6.93 (m, 2 H), 6.43 (s, 1 H), 4.26 (s, 2 H), 4.23 (q, *J* = 6.8 Hz, 2 H), 3.89 (s, 3 H), 2.51 (s, 3 H), 1.29 (t, *J* = 6.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.5, 164.1, 158.7, 158.4, 147.3, 134.1, 130.8, 127.2, 120.8, 114.3, 111.6, 108.8, 59.9, 55.5, 42.6, 14.3, 13.7. ESI-HRMS: *m/z* calcd for $C_{17}H_{19}O_5$: $[M + H]^+$: 303.1232; found: 303.1236.

Ethyl 2-Methyl-5-(2-oxo-3-phenylpropyl)furan-3-carboxylate (4ka, Table 3, Entry 11)
Eluent: EtOAc–PE (1:15); white solid; yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 3 H), 7.17–7.15 (m, 2 H), 6.43 (s, 1 H), 4.25 (q, *J* = 6.8 Hz, 2 H), 3.73 (s, 2 H), 3.67 (s, 2 H), 2.51 (s, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.8, 163.9, 158.8, 145.9, 133.6, 129.4, 128.8, 127.2, 114.5, 109.4, 60.0, 49.1, 41.2, 14.3, 13.7. ESI-HRMS: *m/z* calcd for $C_{17}H_{19}O_4$ $[M + H]^+$: 287.1283; found: 287.1288.

Ethyl 2-Methyl-5-(2-oxo-4-phenylbutyl)furan-3-carboxylate (4la, Table 3, Entry 12)
Eluent: EtOAc–PE (1:15); colorless oil; yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2 H), 7.20–7.15 (m, 3 H), 6.43 (s, 1 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 2.89 (t, *J* = 7.2 Hz, 2 H), 2.79 (t, *J* = 7.2 Hz, 2 H), 2.53 (s, 3 H), 1.33 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.8, 164.0, 158.9, 146.0, 140.7, 133.9, 133.7, 128.5, 128.4, 126.2, 114.5, 109.3, 60.1, 43.5, 42.2, 29.6, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{18}H_{21}O_4$ $[M + H]^+$: 301.1440; found:

301.1446.

Ethyl 5-[2-(Furan-2-yl)-2-oxoethyl]-2-methylfuran-3-carboxylate (4ma, Table 3, Entry 13)

Eluent: EtOAc–PE (1:10); yellow solid; yield: 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 1.2 Hz, 1 H), 7.26–7.25 (m, 1 H), 6.56–6.55 (m, 1 H), 6.50 (s, 1 H), 4.25 (q, *J* = 6.8 Hz, 2 H), 4.10 (s, 2 H), 2.52 (s, 3 H), 1.31 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.5, 164.1, 158.9, 151.9, 147.0, 145.6, 118.3, 114.5, 112.6, 109.4, 60.1, 37.8, 14.4, 13.8. ESI-HRMS: *m/z* calcd for $C_{14}H_{15}O_5$ $[M + H]^+$: 263.0919; found: 263.0915.

2-(4-Acetyl-5-methylfuran-2-yl)-1-(2-methoxyphenyl)-ethanone (4jb, Table 3, Entry 14)

Eluent: EtOAc–PE (1:30); white solid; yield: 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.76 (m, 1 H), 7.51–7.47 (m, 1 H), 7.03–6.97 (m, 2 H), 6.43 (s, 1 H), 4.30 (s, 2 H), 3.93 (s, 3 H), 2.54 (s, 3 H), 2.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6, 194.4, 158.8, 157.8, 147.3, 134.3, 130.9, 126.9, 122.2, 120.9, 111.6, 108.7, 59.9, 55.6, 42.6, 29.2, 14.5. ESI-HRMS: *m/z* calcd for $C_{16}H_{17}O_4$ $[M + H]^+$: 273.1127; found: 273.1125.

1-(4-Acetyl-5-methylfuran-2-yl)-3-phenylpropan-2-one (4kb, Table 3, Entry 15)

Eluent: EtOAc–PE (1:10) yellow oil; yield: 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 3 H), 7.18–7.17 (m, 2 H), 6.39 (s, 1 H), 3.76 (s, 2 H), 3.70 (s, 2 H), 2.52 (s, 3 H), 2.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 194.1, 158.1, 145.8, 133.4, 129.5, 128.9, 127.3, 122.3, 109.2, 49.4, 41.0, 29.2, 14.4. ESI-HRMS: *m/z* calcd for $C_{16}H_{17}O_3$ $[M + H]^+$: 257.1178; found: 257.1184.

1-(4-Acetyl-5-methylfuran-2-yl)-4-phenylbutan-2-one (4lb, Table 3, Entry 16)

Eluent: EtOAc–PE (1:10); yellow oil; yield: 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2 H), 7.21–7.15 (m, 3 H), 6.38 (s, 1 H), 3.64 (s, 2 H), 2.90 (t, *J* = 7.6 Hz, 2 H), 2.81 (t, *J* = 8.0 Hz, 2 H), 2.53 (s, 3 H), 2.36 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.7, 194.1, 158.1, 145.9, 140.7, 128.6, 128.4, 126.3, 122.3, 109.1, 43.7, 42.1, 29.6, 29.2, 14.4. ESI-HRMS: *m/z* calcd for $C_{17}H_{19}O_3$ $[M + H]^+$: 271.1334; found: 271.1341.

