Synthesis of 6-Substituted 3-(Alkoxycarbonyl)-5-aryl-α-pyrones

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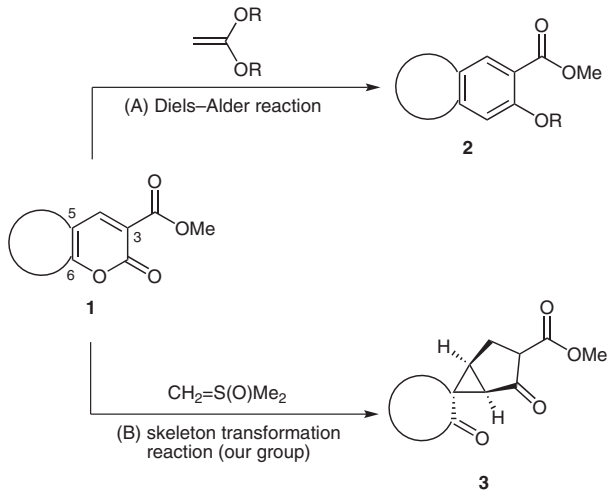
Abstract: An efficient synthesis of 6-substituted 3-(alkoxycarbonyl)-5-aryl-α-pyrones is reported. This methodology consists of the successive manipulation of an addition–elimination reaction between benzyl ketone derivatives and dimethyl methoxymethylenemalonate, and an acid-catalyzed condensation reaction. The synthesis is applicable to various 5-*p*-substituted-aryl 6-substituted α-pyrones and good to excellent yields were obtained over two steps from benzyl ketone derivatives that were easily prepared from phenylacetic acid by the Negishi coupling or the Claisen decarboxylation reaction.

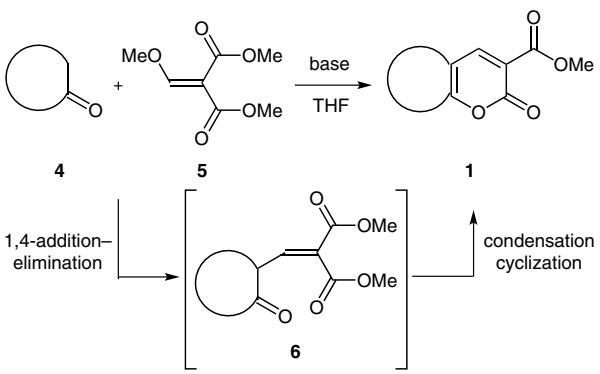
Key words: α-pyrone, heterocycles, 1,4-addition, condensation, ketones

The α-pyrone (2*H*-pyran-2-one) ring system is found in various natural products[1] and pharmacologically active compounds, such as non-peptidic HIV-1 protease inhibitors.[2] Furthermore, α-pyrones that contain conjugated dienes and ester groups have found use as reliable building blocks.[3]



Scheme 1 Reactivity of α-pyrone with an electron-withdrawing group at the 3-position

The introduction of an electron-withdrawing group at the 3-position of α-pyrone plays an important role in the reactivity of α-pyrone. α-Pyrone **1** with an electron-withdrawing group at the 3-position is a good substrate for the inverse-electron-demand Diels–Alder reaction, forming aromatic compound **2** (Scheme 1).[4] Moreover, we have recently reported the skeleton transformation reaction of α-pyrone **1** into bicyclo[3.1.0]hexane derivative **3** using dimethyl sulfoxonium methylide [H_2C=S(O)Me_2].[5] In the course of our study, we were interested in the reactivity of 5-aryl-α-pyrone derivative as the reaction substrate under skeleton transformation reaction conditions. Although several methods for the synthesis of α-pyrones with an electron-withdrawing group in the 3-position have been reported,[6] as far as we know, there are few reports of the synthesis of 5-aryl-α-pyrone derivatives with an electron-withdrawing group in the 3-position.[6b,7] Herein, we report an efficient synthesis of 6-substituted 3-(alkoxycarbonyl)-5-aryl-α-pyrones through successive manipulations.



Scheme 2 Synthesis of α-pyrone via 1,4-addition–elimination and condensation–cyclization

One of the most convenient and reliable methods for the synthesis of α-pyrone **1** is the condensation–cyclization reaction between cyclic ketone **4** and dimethyl methoxymethylenemalonate (**5**)[8] under basic conditions (Scheme 2).[4,9] In this case, the enolate of cyclic ketone **4** displaces the terminal methoxy group of **5** by a 1,4-addition–elimination reaction to yield adduct **6**. Then, **6** is subjected to lactonization to form α-pyrone **1** in one step. We applied Boger and Mullican's method[9] to cyclic ketones to obtain the desired compounds in good yields.[5] Next, we applied this method to the synthesis of 5-aryl-α-pyrones. Instead of cyclic ketone **4**, acyclic benzyl ketone derivative **7a** was treated with dimethyl methoxymethylenemalonate (**5**)[8] using lithium diisopropylamide or lithium hexamethyldisilazanide in tetrahydrofuran. Unfortunately, desired product **8a** was obtained in 28% and 32% yields, respectively (Table 1, entries 1 and 2). The addition of 5 Å molecular sieves enhanced the product yield to 60% (entry 3). However, when the reaction conditions used in Table

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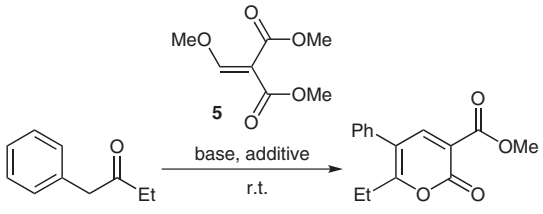
1, entry 3 were applied to the synthesis of 5-*p*-substituted-aryl α-pyrones **8b**–**f**, either no product was obtained or product was obtained in low yield (Scheme 3). From this disappointing outcome, we assumed that further condition optimization was necessary to obtain useful methodology for the synthesis of α-pyrones **8b**–**f**. To obtain the desired products **8a**–**f** in good yields, the reaction must proceed via thermodynamically controlled enolates of **7a**–**f**, which are formed by deprotonation at the α-position between the phenyl group and the carbonyl group in **7a**–**f** with a base. It was considered that lithium hexamethyldisilazanide, a relatively bulky base, was unsuitable for this reaction. Thus, we selected conditions that used sodium hydride at room temperature so that the reaction would proceed via thermodynamically controlled enolates of **7a**–**f**. Although a complex mixture was obtained under the conditions in which sodium hydride was employed instead of lithium hexamethyldisilazanide (Table 1, entry 4), changing the solvent from tetrahydrofuran to dimethyl sulfoxide increased the yield of the reaction intermediates **9** and **10** (Figure 1), and **8a** was obtained in 7% yield after purification (entry 5). Reaction intermediates **9** and **10** were suggested to be formed by the addition reaction between **7a** and **5** without further condensation–cyclization reaction under basic conditions. The flexibility of intermediates **9** and **10**, which were produced from acyclic ketone **7a**, would be disadvantageous for the cyclization compared with the case using cyclic ketone **4**. Thus, we explored the optimum conditions in which reaction intermediates **9** and **10** would be converted into the desired product **8a**.

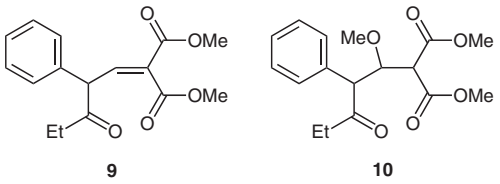
Table 1 Optimization of Conditions



7a **8a**

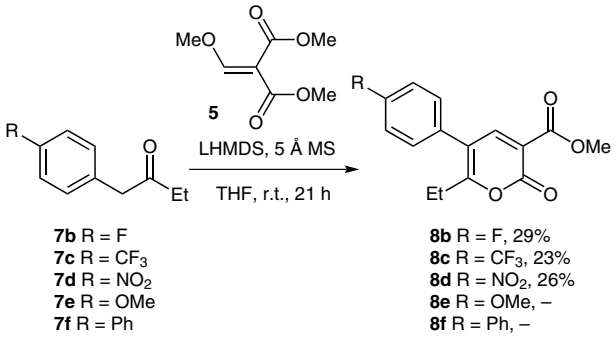
Entry	Base	Additive	Solvent	Time (h)	Yield[a] (%)
1	LDA[b]	–	THF	22	28
2	LHMDS[c]	–	THF	24	32
3	LHMDS[c]	5 Å MS	THF	21	60
4	NaH[d]	5 Å MS	THF	21	complex
5	NaH[d]	5 Å MS	DMSO	22	7[e,f]
6	NaH[d]	5 Å MS	DMSO	22	80[g]

[a] Isolated yield unless otherwise indicated.
[b] The enolate was prepared from **7a** with LDA at –78 °C to –5 °C.
[c] The enolate was prepared from **7a** with LHMDS at 0 °C.
[d] The enolate was prepared from **7a** with NaH at r.t.
[e] Determined by ^{1}H NMR.
[f] Compounds **9** and **10**, which are noncyclized intermediates, were also obtained in 70% and 3% yields, respectively.
[g] The crude mixture was refluxed with AcOH for 16 h.



9 **10**

Figure 1 Noncyclized intermediates **9** and **10**

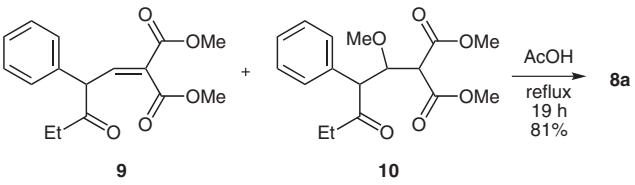


7b R = F
7c R = CF_3
7d R = NO_2
7e R = OMe
7f R = Ph

8b R = F, 29%
8c R = CF_3, 23%
8d R = NO_2, 26%
8e R = OMe, –
8f R = Ph, –

Scheme 3 Disappointing results of 5-*p*-substituted aryl-α-pyrone synthesis under conditions specified in Table 1, entry 3

The acid-catalyzed condensation cyclization is a classic strategy for the construction of an α-pyrone ring system. In 1902, Buchner and Schroder reported the acid-catalyzed condensation cyclization of a synthetic intermediate using hydrochloric acid that furnished 5-alkyl-α-pyrone-6-carboxylic acid.[10] Other groups reported the synthesis of α-pyrone derivatives under acidic conditions.[11] Our preliminary study revealed the applicability of acid-catalyzed condensation cyclization using acetic acid (Scheme 4).[12,13] A mixture of reaction intermediates **9** and **10** was heated under reflux in acetic acid for 19 hours, and the two spots of **9** and **10** on a TLC plate converged to form an almost single spot of α-pyrone **8a**. To summarize the results, after the formation of a thermodynamically controlled enolate in the reaction of benzyl ketone derivative **7a** with sodium hydroxide in dimethyl sulfoxide at room temperature, malonate **5** was added in the presence of 5 Å molecular sieves, and the resulting crude mixture was refluxed in acetic acid. This was followed by purification by silica gel column chromatography to give the desired α-pyrone **8a** in 80% yield in two steps through successive manipulations with one purification (entry 6).



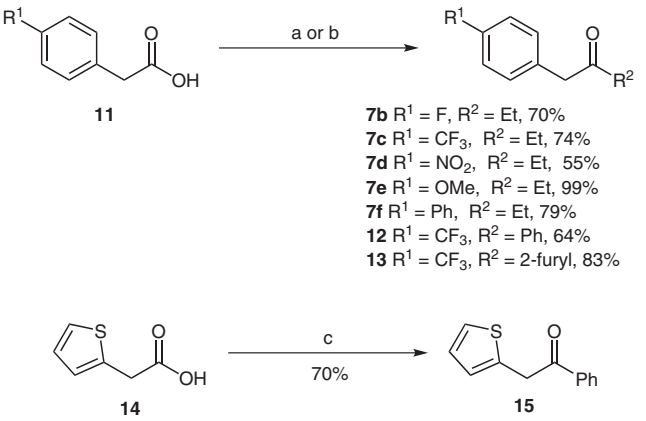
9 **10**

9/**10** = 5:1

Scheme 4 Preliminary study of acid-catalyzed condensation cyclization

In order to establish the generality of the synthesis of α-pyrone, benzyl ketone derivatives **7b**–**f**, **12**, **13**, and **15** as

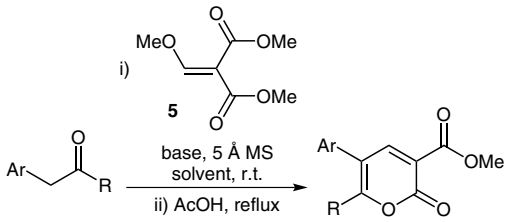
substrates were prepared from commercially available phenylacetic acids **11**, as shown in Scheme 5. Benzyl ethyl ketone derivatives **7b–f** containing such substituents as F, CF_3, NO_2, OMe, and Ph at the *para* position of the benzene ring were prepared by Negishi coupling.[14] In the cases of aryl benzyl ketone derivatives **12** and **13**, the Claisen decarboxylation reaction[15] was employed. With the Claisen decarboxylation reaction, thiophene-2-acetic acid (**14**) could be also converted into the corresponding ketone derivative **15**.



Scheme 5 Synthesis of benzyl ketone derivatives. *Reagents and conditions*: (a) 1. $(COCl)_2$, DMF (cat.), CH_2Cl_2, r.t., 1 h; 2. $Pd(PPh_3)_4$, Et_2Zn, benzene, r.t., 14–20 h for **7b–f**; (b) R^2CO_2Me, NaHMDS, THF, DMF, –10 °C, 3.5 h for **12** and **13**; (c) $PhCO_2Me$, NaHMDS, THF, DMF, –10 °C, 3.5 h.

The scope and limitations of α-pyrone synthesis are summarized in Table 2. The introduction of an electron-withdrawing (F, CF_3, NO_2) or an electron-donating (Ph, OMe) group to the *para* position of the phenyl group was acceptable, giving the corresponding α-pyrones **8b–f** in moderate yields (entries 1–5). α-Pyrones **8g** and **8h** having isopropyl and butyl groups at the 6-position were also synthesized in good yields, 90% and 79%, respectively (entries 6 and 7). In the cases of α-pyrones having aryl groups at the 6-position (entries 8–11), the lithium hexamethyldisilazanide and tetrahydrofuran system was used instead of the sodium hydride and dimethyl sulfoxide system to furnish the corresponding α-pyrones **8i–l** in moderate to good yields, because the substrates contained only one deprotonation position at the α-position of carbonyl groups and there was no problem about selectivity for the formation of enolates. In fact, the lithium hexamethyldisilazanide and tetrahydrofuran system was favorable for the synthesis of α-pyrone **8j**, which was obtained in higher yield using this system (77%) than using sodium hydride and dimethyl sulfoxide (58%) (entry 9). In this synthesis method, heterocycles were accommodated at the 5- or 6-position. Benzyl furyl ketone **13** was converted into α-pyrone **8k** in 75% yield, which contained a furan moiety at

Table 2 Scope and Limitations



Entry	Substrate	Ar	R	Base, solvent	Product	Yield[a] (%)
1	**7b**	4-FC_6H_4	Et	NaH, DMSO	**8b**	68
2	**7c**	4-$F_3CC_6H_4$	Et	NaH, DMSO	**8c**	65
3	**7d**	4-$O_2NC_6H_4$	Et	NaH, DMSO	**8d**	66
4	**7e**	4-$MeOC_6H_4$	Et	NaH, DMSO	**8e**	73
5	**7f**	4-PhC_6H_4	Et	NaH, DMSO	**8f**	57
6	**7g**	Ph	*i*-Pr	NaH, DMSO	**8g**	90
7	**7h**	Ph	Bu	NaH, DMSO	**8h**	79
8	**7i**	Ph	Ph	LHMDS, THF	**8i**	85
9	**12**	4-$F_3CC_6H_4$	Ph	LHMDS, THF NaH, DMSO	**8j**	77 58
10	**13**	4-$F_3CC_6H_4$	2-furyl	LHMDS, THF	**8k**	75
11	**15**	2-thienyl	Ph	LHMDS, THF	**8l**	57

[a] Isolated yield.

the 6-position (entry 10). 5-(2-Thienyl)-α-pyrone **8l** was also accessible in moderate yield (entry 11).

In conclusion, we have developed an efficient procedure for the synthesis of 6-substituted 3-(alkoxycarbonyl)-5-aryl-α-pyrones. Our method produced α-pyrone derivatives in moderate to good yields in two steps through successive manipulations of the addition–elimination reaction by using the sodium hydride and dimethyl sulfoxide or lithium hexamethyldisilazanide and tetrahydrofuran systems and acid-catalyzed condensation–cyclization in acetic acid. This method allowed the easy incorporation of a range of substituents into the benzene ring in the 5-position and 6-position of the α-pyrone. Benzyl ketone derivatives, substrates of the α-pyrone synthesis, were easily prepared from the corresponding phenylacetic acid derivatives via the Negishi coupling reaction or the Claisen decarboxylation reaction. The reactivities of these 3-(alkoxycarbonyl)-5-aryl-α-pyrones will be reported in due course.

All commercial reagents were used without further purification. Melting points were measured with a Yanaco MP micro-melting point apparatus and are uncorrected. NMR spectra were measured on Jeol AL-270 (^{1}H: 270 MHz) and Varian Inova 400NB (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometers with TMS as internal standard. IR spectra were recorded with a Shimadzu FTIR-8400. A JEOL JMS-GC mate spectrometer was used for low-resolution and high-resolution electron ionization MS (LR-EIMS and HR-EIMS). Silica gel 60N (Kanto Chemical Co., Inc.) was used for column chromatography.

1-(4-Fluorophenyl)butan-2-one (7b); Typical Procedure for the Negishi Coupling Reaction[14]

Oxalyl chloride (0.943 mL, 11.0 mmol) was added to a solution of 2-(4-fluorophenyl)acetic acid (1.00 g, 6.49 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction was initiated by the addition of 5 drops of DMF. After 30 min at 0 °C, the mixture was allowed to warm to r.t. and stirred for an additional hour. The solvents were evaporated and the residue was dissolved in benzene (15 mL). Then, $Pd(PPh_3)_4$ (300 mg, 0.260 mmol) was added. After cooling to 0 °C, 1.06 M Et_2Zn in *n*-hexane (6.12 mL, 6.49 mmol) was added dropwise and the mixture was stirred at r.t. for 15 h. After quenching by the addition of water, the mixture was filtered over a Celite® pad and the filtrate was extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:1) to give **7b** (704 mg, 70%) as a colorless liquid.

IR ($CHCl_3$): 1717, 1510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.2 Hz, 3 H), 2.48 (q, *J* = 7.2 Hz, 2 H), 3.67 (s, 2 H), 6.98–7.04 (m, 2 H), 7.14–7.19 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 35.3, 48.7, 115.5 (d, $^2J_{C,F}$ = 21.2 Hz, 2 C), 130.1 (d, $^4J_{C,F}$ = 3.1 Hz), 130.9 (d, $^3J_{C,F}$ = 8.0 Hz, 2 C), 161.9 (d, $^1J_{C,F}$ = 244.0 Hz), 208.7.

MS (EI): *m*/*z* (%) = 166 (M^+, 10.3), 109 (38.5), 57 (100.0).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}FO$: 166.0794; found: 166.0790.

1-[4-(Trifluoromethyl)phenyl]butan-2-one (7c)

Following the typical procedure for **7b** using 2-[4-(trifluoromethyl)phenyl]acetic acid (1.00 g, 4.90 mmol) gave **7c** as a white amorphous solid; yield: 787 mg (74%).

IR ($CHCl_3$): 1714 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.2 Hz, 3 H), 2.51 (q, *J* = 7.2 Hz, 2 H), 3.76 (s, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 35.7, 49.1, 124.1 (q, $^1J_{C,F}$ = 270.6 Hz), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, 2 C), 129.3 (q, $^2J_{C,F}$ = 23.3 Hz), 129.8 (2 C), 138.3, 207.7.

MS (EI): *m*/*z* (%) = 216 (M^+, 5.0), 159 (52.5), 109 (27.7), 57 (100.0).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{11}F_3O$: 216.0762; found: 216.0765.

1-(4-Nitrophenyl)butan-2-one (7d)

Following the typical procedure for **7b** using 2-(4-nitrophenyl)acetic acid (1.00 g, 5.52 mmol) gave **7d** as yellowish prisms; yield: 584 mg (55%); mp 47–51 °C (*n*-hexane).

IR ($CHCl_3$): 1716, 1607, 1348 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.4 Hz, 3 H), 2.55 (q, *J* = 7.4 Hz, 2 H), 3.83 (s, 2 H), 7.37 (br d, *J* = 9.0 Hz, 2 H), 8.19 (br d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 36.0, 48.9, 123.7 (2 C), 130.4 (2 C), 141.7, 147.0, 206.9.

MS (EI): *m*/*z* (%) = 193 (M^+, 3.4), 137 (23.6), 57 (100.0).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}NO_3$: 193.0739; found: 193.0733.

1-(4-Methoxyphenyl)butan-2-one (7e)[16]

Following the typical procedure for **7b** using 2-(4-methoxyphenyl)acetic acid (3.00 g, 18.1 mmol) gave **7e** as a yellowish liquid; yield: 3.18 g (99%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.3 Hz, 3 H), 2.46 (q, *J* = 7.3 Hz, 2 H), 3.62 (s, 2 H), 3.80 (s, 3 H), 6.84–6.89 (m, 2 H), 7.10–7.15 (m, 2 H).

1-(Biphenyl-4-yl)butan-2-one (7f)[17]

Following the typical procedure for **7b** using 2-(biphenyl-4-yl)acetic acid (1.00 g, 4.71 mmol) gave **7f** as a yellowish solid; yield: 831 mg (79%).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.3 Hz, 3 H), 2.52 (q, *J* = 7.3 Hz, 2 H), 3.74 (s, 2 H), 7.22–7.60 (m, 9 H).

1-Phenyl-2-[4-(trifluoromethyl)phenyl]ethanone (12);[18] **Typical Procedure for Claisen Decarboxylation Reaction**[15]

To a solution of 2-[4-(trifluoromethyl)phenyl]acetic acid (200 mg, 0.980 mmol) and methyl benzoate (0.120 mL, 0.980 mmol) in DMF was added 1.1 M NaHMDS in THF (3.60 mL, 3.96 mmol) at –10 °C over 1 min. The mixture was stirred at –10 °C for 3.5 h. To the resulting mixture was added sat. aq NH_4Cl and extraction was carried out with EtOAc (3 ×). The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:1) to give **12** (165 mg, 64%) as a white solid.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 4.36 (s, 2 H), 7.37–7.63 (m, 7 H), 8.00–8.04 (m, 2 H).

1-(2-Furyl)-2-[4-(trifluoromethyl)phenyl]ethanone (13)

Following the typical procedure for **12** using 2-[4-(trifluoromethyl)phenyl]acetic acid (204 mg, 1.00 mmol) gave **13** as colorless prisms; yield: 211 mg (83%); mp 120–122 °C (*n*-hexane).

IR (KBr): 1676, 1468 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12 (s, 2 H), 6.57 (dd, *J* = 1.8, 3.6 Hz, 1 H), 7.26 (dd, *J* = 0.8, 3.6 Hz, 1 H), 7.43 (br d, *J* = 8.0 Hz, 2 H), 7.59 (br d, *J* = 8.0 Hz, 2 H), 7.62 (dd, *J* = 0.8, 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.9, 112.6, 118.0, 124.1 (q, $^1J_{C,F}$ = 262.2 Hz), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, 2 C), 129.3 (q, $^2J_{C,F}$ = 32.2 Hz), 129.9 (2 C), 137.9, 146.8, 152.2, 185.6.

MS (EI): *m*/*z* (%) = 254 (M^+, 5.3), 95 (100.0).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_9F_3O_2$: 254.0554; found: 254.0559.

1-Phenyl-2-(2-thienyl)ethanone (15)
Following the typical procedure for **12** using thiophene-2-acetic acid (**14**, 1.00 g, 7.03 mmol) gave **15** as a white amorphous solid; yield: 1.00 g (70%).

IR ($CHCl_3$): 1686, 1599 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.490 (br s, 1 H), 4.493 (br s, 1 H), 6.93–6.95 (m, 1 H), 6.97 (dd, *J* = 3.2, 5.0 Hz, 1 H), 7.23 (dd, *J* = 1.6, 5.0 Hz, 1 H), 7.46–7.50 (m, 2 H), 7.58 (tt, *J* = 1.4, 7.6 Hz, 1 H), 8.01–8.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.4, 125.1, 126.8, 126.9, 128.6 (2 C), 128.7 (2 C), 133.4, 135.5, 136.1, 196.0.

MS (EI): *m*/*z* (%) = 202 (M^+, 27.8), 105 (100.0), 97 (20.5), 77 (70.9).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{10}O_4S$: 202.0452; found: 202.0449.

Methyl 6-Ethyl-2-oxo-5-phenyl-2*H*-pyran-3-carboxylate (8a); Typical Procedure for 6-Substituted 3-(Alkoxycarbonyl)-5-aryl-α-pyrones
To a stirred suspension of 1-phenylbutan-2-one (**7a**, 1.00 mL, 6.68 mmol) and 5 Å MS (508 mg) in DMSO (20 mL) was added NaH (60% in oil, 294 mg, 7.35 mmol) in one portion at r.t. and the mixture was stirred for 1 h. Dimethyl methoxymethylenemalonate (**5**, 1.40 g, 8.02 mmol) in DMSO (10 mL) was added at r.t. and the mixture was stirred for 22 h. After acidification with aq 1 M HCl to pH 4 in an ice water bath, the mixture was filtered over Celite® pad and the filtrate was extracted with Et_2O (3 ×). The combined organic layer was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated in vacuo to give the crude material as a yellow oil (2.27 g). The crude material was dissolved in AcOH (40 mL) and the solution was refluxed (oil bath temp: 135 °C). After 16 h, the mixture was concentrated in vacuo to afford the crude product as an orange oil. The crude product was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 3:1) to give **8a** (1.38 g, 80%) as a pale yellow oil.

IR ($CHCl_3$): 1761, 1744, 1709, 1541 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.6 Hz, 3 H), 2.60 (q, *J* = 7.6 Hz, 2 H), 3.91 (s, 3 H), 7.24–7.49 (m, 5 H), 8.23 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 25.5, 52.6, 113.7, 117.9, 128.3, 128.8 (2 C), 129.0 (2 C), 134.7, 152.6, 158.0, 164.0, 169.9.

MS (EI): *m*/*z* (%) = 258 (M^+, 100.0), 197 (79.4), 173 (90.2), 115 (52.3).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{14}O_4$: 258.0892; found: 258.0901.

Methyl 6-Ethyl-5-(4-fluorophenyl)-2-oxo-2*H*-pyran-3-carboxylate (8b)
Following the typical procedure for **8a** using **7b** (389 mg, 2.52 mmol) gave **8b** as a yellowish oil; yield: 473 mg (68%, 2 steps).

IR ($CHCl_3$): 1763, 1742, 1711, 1541 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.6 Hz, 3 H), 2.56 (q, *J* = 7.6 Hz, 2 H), 3.91 (s, 3 H), 7.12–7.18 (m, 2 H), 7.21–7.26 (m, 2 H), 8.18 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 25.5, 52.7, 113.8, 116.1 (d, $^2J_{C,F}$ = 21.6 Hz, 2 C), 116.9, 130.6 (d, $^3J_{C,F}$ = 8.4 Hz, 2 C), 130.7, 152.4, 157.9, 162.6 (d, $^1J_{C,F}$ = 247.4 Hz), 164.0, 170.0.

MS (EI): *m*/*z* (%) = 276 (M^+, 100.0), 248 (46.7), 233 (42.0), 191 (92.5).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{13}FO_4$: 276.0798; found: 276.0796.

Methyl 6-Ethyl-2-oxo-5-[4-(trifluoromethyl)phenyl]-2*H*-pyran-3-carboxylate (8c)
Following the typical procedure for **8a** using **7c** (521 mg, 2.41 mmol) gave **8c** as a pale yellow amorphous solid; yield: 513 mg (65%, 2 steps).

IR ($CHCl_3$): 1765, 1742, 1713, 1545 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.6 Hz, 3 H), 2.60 (q, *J* = 7.6 Hz, 2 H), 3.92 (s, 3 H), 7.41 (dd, *J* = 0.6, 8.7 Hz, 2 H), 7.73 (dd, *J* = 0.6, 8.7 Hz, 2 H), 8.20 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 25.6, 52.8, 114.2, 116.6, 123.8 (q, $^1J_{C,F}$ = 270.5 Hz), 126.0 (q, $^3J_{C,F}$ = 4.0 Hz, 2 C), 129.3 (2 C), 130.7 (q, $^2J_{C,F}$ = 32.6 Hz), 138.4, 151.8, 157.6, 163.8, 170.2.

MS (EI): *m*/*z* (%) = 326 (M^+, 100.0), 298 (63.3), 283 (49.6), 241 (61.8).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{13}F_3O_4$: 326.0766; found: 326.0769.

Methyl 6-Ethyl-5-(4-nitrophenyl)-2-oxo-2*H*-pyran-3-carboxylate (8d)
Following the typical procedure for **8a** using **7d** (1.02 g, 5.29 mmol) gave **8d** as yellowish prisms; yield: 1.06 g (66%, 2 steps); mp 132–135 °C (*n*-hexane–EtOAc).

IR (KBr): 1753, 1709, 1599, 1547, 1524 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.4 Hz, 3 H), 2.61 (q, *J* = 7.4 Hz, 2 H), 3.92 (s, 3 H), 7.48 (dt, *J* = 2.2, 9.0 Hz, 2 H), 8.20 (s, 1 H), 8.33 (dt, *J* = 2.2, 9.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 25.7, 52.8, 114.4, 115.9, 124.2 (2 C), 129.9 (2 C), 141.3, 147.7, 151.2, 157.2, 163.6, 170.4.

MS (EI): *m*/*z* (%) = 303 (M^+, 100.0), 275 (84.0), 260 (39.7), 218 (62.4).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{13}NO_6$: 303.0743; found: 303.0741.

Methyl 6-Ethyl-5-(4-methoxyphenyl)-2-oxo-2*H*-pyran-3-carboxylate (8e)
Following the typical procedure for **8a** using **7e** (1.03 g, 5.78 mmol) gave **8e** as a yellowish oil; yield: 1.21 g (73%, 2 steps).

IR ($CHCl_3$): 1759, 1740, 1709, 1611, 1541 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.6 Hz, 3 H), 2.60 (q, *J* = 7.6 Hz, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 6.95–6.99 (m, 2 H), 7.16–7.20 (m, 2 H), 8.20 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 25.5, 52.6, 55.3, 113.6, 114.3 (2 C), 117.5, 126.8, 130.0 (2 C), 152.9, 158.1, 159.6, 164.1, 169.7.

MS (EI): *m*/*z* (%) = 288 (M^+, 85.5), 256 (35.5), 227 (100.0), 203 (57.1).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{16}O_5$: 288.0997; found: 288.0996.

Methyl 5-(Biphenyl-4-yl)-6-ethyl-2-oxo-2*H*-pyran-3-carboxylate (8f)
Following the typical procedure for **8a** using **7f** (1.09 g, 4.85 mmol) gave **8f** as a yellowish foam; yield: 920 mg (57%, 2 steps).

IR ($CHCl_3$): 1761, 1740, 1709, 1541 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.6 Hz, 3 H), 2.66 (q, *J* = 7.6 Hz, 2 H), 3.91 (s, 3 H), 7.32–7.50 (m, 5 H), 7.60–7.69 (m, 4 H), 8.27 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 25.8, 52.9, 114.0, 117.8, 127.3 (2 C), 127.9 (2 C), 128.0, 129.1 (2 C), 129.5 (2 C), 133.8, 140.3, 141.5, 152.8, 158.3, 164.3, 170.2.

MS (EI): *m*/*z* (%) = 334 (M^+, 91.8), 273 (100.0), 249 (32.5).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{18}O_4$: 334.1205; found: 334.1203.

Methyl 6-Isopropyl-2-oxo-5-phenyl-2*H*-pyran-3-carboxylate (8g)

Following the typical procedure for **8a** using 3-methyl-1-phenylbutan-2-one (**7g**, 1.00 mL, 5.94 mmol) gave **8g** as a pale yellow foam; yield: 1.45 g (90%, 2 steps).

IR ($CHCl_3$): 1763, 1740, 1709, 1526 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 6 H), 2.95–3.05 (m, 1 H), 3.90 (s, 3 H), 7.23–7.27 (m, 2 H), 7.39–7.48 (m, 3 H), 8.19 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (2 C), 30.6, 52.6, 113.7, 116.9, 128.3, 128.8 (2 C), 129.0 (2 C), 134.8, 152.7, 158.0, 164.0, 172.8.

MS (EI): *m*/*z* (%) = 272 (M^+, 66.4), 229 (100.0), 197 (65.3), 173 (71.1).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{16}O_4$: 272.1048; found: 272.1050.

Methyl 6-Butyl-2-oxo-5-phenyl-2*H*-pyran-3-carboxylate (8h)

Following the typical procedure for **8a** using 1-phenylhexan-2-one (**7h**, 1.00 mL, 5.45 mmol) gave **8h** as a yellowish oil; yield: 1.23 g (79%, 2 steps).

IR ($CHCl_3$): 1763, 1744, 1711, 1526 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.4 Hz, 3 H), 1.24–1.33 (m, 2 H), 1.64–1.72 (m, 2 H), 2.57 (t, *J* = 7.8 Hz, 2 H), 3.91 (s, 3 H), 7.23–7.27 (m, 2 H), 7.38–7.47 (m, 3 H), 8.21 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 22.3, 29.6, 31.7, 52.7, 113.6, 118.4, 128.3, 128.9 (2 C), 129.0 (2 C), 134.8, 152.6, 158.1, 164.1, 169.3.

MS (EI): *m*/*z* (%) = 286 (M^+, 100.0), 229 (42.3), 215 (63.3), 197 (59.3), 173 (63.8).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{18}O_4$: 286.1205; found: 286.1207.

Methyl 2-Oxo-5,6-diphenyl-2*H*-pyran-3-carboxylate (8i); Typical Procedure

To a stirred suspension of 1,2-diphenylethanone (**7i**, 1.00 g, 5.10 mmol) and 5 Å MS (500 mg) in THF (5 mL) was added 1.0 M LHMDS in THF (5.10 mL, 5.10 mmol) dropwise at 0 °C and the mixture was stirred for 30 min at 0 °C. Dimethyl methoxymethylenemalonate (**5**, 977 mg, 5.61 mmol) in THF (3 mL) was added at 0 °C and the mixture was stirred for 19 h at r.t. After acidification with aq 1 M HCl to pH 4 in an ice-water bath, the mixture was filtered over Celite® pad and the filtrate was extracted with Et_2O (3 ×). The combined organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 3:1) to give a mixture of **8i** and reaction intermediates (1.80 g, **8i**/reaction intermediate, 1.0:1.6).

The mixture of **8i** and reaction intermediates (1.44 g, 4.04 mmol) was dissolved in AcOH (30 mL) and the solution was refluxed (oil bath temp: 135 °C). After 24 h, the mixture was concentrated in vacuo. The crude product was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 3:1) to give **8i** (1.06 g, 85%, 2 steps) as yellowish prisms; mp 167–170 °C (THF–*n*-hexane).

IR (KBr): 1786, 1744, 1703, 1541, 1489 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 7.20–7.43 (m, 10 H), 8.35 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.7, 114.2, 117.9, 128.3 (2 C), 129.12 (2 C), 129.14 (3 C), 129.5 (2 C), 131.0, 131.1, 135.3, 153.6, 157.4, 162.7, 164.0.

MS (EI): *m*/*z* (%) = 306 (M^+, 100.0), 278 (46.1), 105 (29.6).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{14}O_4$: 306.0892; found: 306.0884.

Methyl 2-Oxo-6-phenyl-5-[4-(trifluoromethyl)phenyl]-2*H*-pyran-3-carboxylate (8j)

Following the typical procedure for **8i** using **12** (100 mg, 0.378 mmol) without column chromatography (silica gel) before refluxing in AcOH gave **8j** as a yellow amorphous solid; yield: 109 mg (77%, 2 steps).

IR ($CHCl_3$): 1763, 1751, 1713, 1537, 1518 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H), 7.28–7.44 (m, 7 H), 7.62 (br d, *J* = 8.0 Hz, 2 H), 8.33 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.9, 114.6, 116.5, 123.8 (q, $^1J_{C,F}$ = 270.9 Hz), 126.1 (q, $^3J_{C,F}$ = 3.6 Hz, 2 C), 128.6 (2 C), 129.5 (2 C), 129.6 (2 C), 130.5 (q, $^2J_{C,F}$ = 32.6 Hz), 130.7, 131.5, 139.1, 152.8, 157.0, 163.5, 163.8.

MS (EI): *m*/*z* (%) = 374 (M^+, 87.3), 346 (81.6), 315 (16.2), 259 (17.2), 105 (100.0).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{13}F_3O_4$: 374.0766; found: 374.0760.

Methyl 6-(2-Furyl)-2-oxo-5-[4-(trifluoromethyl)phenyl]-2*H*-pyran-3-carboxylate (8k)

Following the typical procedure for **8i** using **13** (150 mg, 0.589 mmol) without column chromatography (silica gel) before refluxing in AcOH gave **8k** as yellow prisms; yield: 161 mg (75%, 2 steps); mp 163–166 °C (*n*-hexane–EtOAc).

IR ($CHCl_3$): 1767, 1753, 1709, 1562, 1529, 1502 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 6.50 (dd, *J* = 1.6, 3.6 Hz, 1 H), 6.94 (dd, *J* = 0.8, 3.6 Hz, 1 H), 7.38 (dd, *J* = 0.8, 1.6 Hz, 1 H), 7.46 (br d, *J* = 8.0 Hz, 2 H), 7.72 (br d, *J* = 8.0 Hz, 2 H), 8.21 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 112.8, 113.2, 114.3, 117.8, 123.9 (q, $^1J_{C,F}$ = 230.9 Hz), 125.7 (q, $^3J_{C,F}$ = 3.8 Hz, 2 C), 129.7 (2 C), 130.7 (q, $^2J_{C,F}$ = 32.6 Hz), 138.5, 145.5, 146.6, 152.8, 153.1, 156.0, 163.7.

MS (EI): *m*/*z* (%) = 364 (M^+, 100.0), 336 (73.4), 95 (84.5).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{11}F_3O_5$: 364.0558; found: 364.0563.

Methyl 2-Oxo-6-phenyl-5-(2-thienyl)-2*H*-pyran-3-carboxylate (8l)

Following the typical procedure for **8i** using **15** (590 mg, 2.92 mmol) without column chromatography (silica gel) before refluxing in AcOH gave **8l** as pale yellow needles; yield: 515 mg (57%, 2 steps); mp 114–116 °C (*n*-hexane–EtOAc).

IR ($CHCl_3$): 1761, 1744, 1713, 1541, 1526, 1489 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 6.94 (dd, *J* = 1.2, 3.6 Hz, 1 H), 7.01 (dd, *J* = 3.6, 5.2 Hz, 1 H), 7.31–7.35 (m, 3 H), 7.42 (tt, *J* = 1.2, 7.6 Hz, 1 H), 7.51–7.54 (m, 2 H), 8.37 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 111.4, 114.1, 127.2, 127.7, 128.0, 128.4 (2 C), 129.3 (2 C), 131.0, 131.4, 136.1, 153.5, 157.0, 163.4, 163.8.

MS (EI): *m*/*z* (%) = 312 (M^+, 100.0), 284 (33.1), 105 (68.1), 77 (32.9).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{12}O_4S$: 312.0456; found: 312.0453.

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