Facile and Efficient Preparation of Alkyl 6-Oxo-1-cyclohexenecarboxylates

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Starting from methyl acetoacetate and its homologues, alkyl 6-oxo-1-cyclohexenecarboxylates have been synthesized in good to high overall yields by two steps.

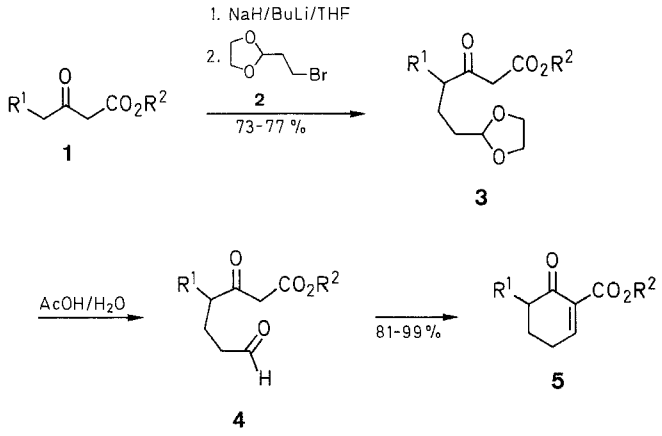
Alkyl 6-oxo-1-cyclohexenecarboxylates **5** have attracted considerable attention as potentially useful synthetic intermediates for the construction of a variety of carbocyclic compounds. Indeed, in the last few years, methyl and ethyl 6-oxo-1-cyclohexenecarboxylates (**5a** and **5b**) have been utilized as Michael acceptors in conjugate addition[1] and as dienophiles for the Diels–Alder reaction, respectively.[2]

The early synthesis of **5b** consisted of bromination of ethyl 2-oxocyclohexanecarboxylate and subsequent dehydrobromination with base[3–5] or heat.[6] However, an ambiguity in the structure assignment of the product derived by the above method was pointed out later on the basis of alternative and unequivocal synthesis of **5b** utilizing an acid-catalyzed cyclization of ethyl 7,7-diethoxy-3-oxoheptanoate, although overall yield was not high.[7] Thereafter it was shown that a two-step sequence consisting of phenylselenenylation of methyl or ethyl 2-oxocyclohexanecarboxylate and succeeding selenoxide elimination efficiently and unambiguously provided the corresponding unsaturated ketoester (**5a** or **5b**).[8] To date, this method is the most reliable preparation of these unsaturated compounds.[1,2]

While the above procedure gave high yields of unsaturated ketoesters (80–90%), it has its own disadvantages, such as the use of expensive and toxic selenenyl compound. In addition, this method seems to be unsuitable for a large scale preparation of **5**.

During the course of our synthetic study of a natural compound, a substantial quantity of *tert*-butyl 6-oxo-1-cyclohexenecarboxylate (**5d**) was required as a starting material. Unexpectedly, a search of the literature revealed no preparation of this useful substrate. In addition, an attempted application of the selenenylation-selenoxide elimination method to *tert*-butyl 2-oxocyclohexanecarboxylate[9] resulted in the formation of a complex mixture, from which **5d** could not be isolated.

These results prompted us to investigate a convenient and general procedure for the synthesis of **5**, and accordingly we report here such a procedure. Synthetic steps number only two from readily available and inexpensive starting materials, and this simplicity made the procedure particularly useful for the laboratory scale preparations of **5**.



1, 3–5	R^1	R^2	1, 3–5	R^1	R^2
a	H	CH_3	**d**	H	*t*-Bu
b	H	Et	**e**	CH_3	CH_3
c	H	*n*-Bu	**f**	$CH_2CH{=}CH_2$	Et

Our method is based on an intramolecular cyclization of formyl β-ketoester **4**; dioxolanyl ketoester **3** derived from the dianion of **1** on alkylation with 2-(2-bromoethyl)-1,3-dioxolane (**2**)[10] would be convertible to **5** on exposure with aqueous acid, since one can expect that the reaction undergoes not only hydrolysis of the acetal group but also subsequent acid-catalyzed intramolecular cyclization of the intermediate **4** generated *in situ*.

Thus, dianions generated from acetoacetic esters **1b–d** and its homologues **1e–f**[11] upon treatment with sodium hydride (1 equiv) followed by butyllithium (1 equiv)[11] in tetrahydrofuran smoothly reacted with **2** to produce corresponding ketoesters (**3b–f**) in good yields (Table).

The second step of this synthesis was successfully carried out by treatment of **3b–f** with 50% aqueous acetic acid at room temperature, thereby providing **5b–f** in excellent yields. Simple filtration of the residue obtained by extractive work-up through a short silica gel column was sufficient to afford **5b–f** of satisfactory quality.[12] It is worthwhile to mention that the reaction conditions used here are compatible even with acid-labile compounds such as **3d** and **3f**.

An attempt to use 2-(2-bromoethyl)-1,3-dioxane[13] in place of **2** for the synthesis of acetal ketoester corresponding to **3** was

Table. β-Ketoesters **3** and Alkyl 6-Oxo-1-cyclohexenecarboxylates **5** Prepared

Product	Yield[a] (%)	bp (°C)/ mbar[b]	Molecular Formula[c] or Lit. bp (°C)/mbar	IR (film)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)
3b	77	67/0.33	$C_{11}H_{18}O_5$ (230.2)	1740, 1710 (br), 1640 (br w)	1.27 (t, 3H, J = 7.0); 1.5–1.9 (m, 4H); 2.6 (m, 2H); 3.43 (s, 2H); 3.90 (m, 4H); 4.19 (q, 2H, J = 7.0); 4.83 (br t, 1H)
3c	75	76/0.33	$C_{13}H_{22}O_5$ (258.3)	1740, 1705, 1650 (br w)	0.94 (t, 3H, J = 6); 1.1–1.9 (m, 8H); 2.60 (m, 2H); 3.42 (s, 2H); 3.90 (m, 4H); 4.15 (t, 2H, J = 6.2); 4.84 (br t, 1H)
3d	73	86/0.13	$C_{13}H_{22}O_5$ (258.3)	1740, 1715, 1645 (br w)	1.45 (s, 9H); 1.5–1.8 (m, 4H); 2.60 (m, 2H); 3.34 (s, 2H); 3.90 (m, 2H); 4.84 (br t, 1H)
3e	75	57/0.15	$C_{11}H_{18}O_5$ (230.2)	1740, 1710, 1645 (br w)	1.13 (d, 3H, J = 6.8); 1.4–2.0 (m, 4H); 2.70 (m, 1H); 3.51 (s, 2H); 3.72 (s, 3H); 3.90 (m, 4H); 4.83 (br t, 1H, J = 4.5)
3f	76	68/0.2	$C_{14}H_{22}O_5$ (270.3)	3050 (w), 1740, 1705, 1640 (br w)	1.25 (t, 3H, J = 7.0); 1.5–1.85 (m, 4H); 2.1–2.4 (m, 2H); 2.7 (m, 1H); 3.45 (s, 2H); 3.90 (m, 4H); 4.18 (q, 2H, J = 7.0); 4.81 (br t, 1H); 4.96 and 5.1 (m, 1H each); 5.5–6.0 (m, 1H)
5b	97	70/0.13	118–122/20[6] 59/0.13[7] 70/0.1[8]	1730, 1710, 1690, 1621 (w)	1.32 (t, 3H, J = 7.0); 1.9–2.2 (m, 2H); 2.4–2.62 (m, 4H); 4.25 (q, 2H, J = 7.0); 7.64 (t, 1H, J = 3.6)
5c	97	63/0.33	$C_{11}H_{16}O_3$ (196.2)	1730, 1705, 1680, 1635 (w), 1615 (w)	0.95 (t, 3H, J = 6); 1.2–1.8 (m, 4H); 1.9–2.2 (m, 2H); 2.3 (m, 4H); 4.22 (t, 2H, J = 6.2); 7.67 (t, 1H, J = 3.6)
5d	81	77/0.13	$C_{11}H_{16}O_3$ (196.2)	1730, 1700, 1680, 1640 (w), 1620 (w)	1.52 (s, 9H); 1.85–2.23 (m, 2H); 2.35–2.6 (m, 4H); 7.52 (t, 1H, J = 3.6)
5e	97	54/0.2	$C_9H_{12}O_3$ (168.2)	1740, 1720, 1690, 1620 (w)	1.17 (d, 3H, J = 6.5); 1.5–2.2 (m, 2H); 2.3–2.64 (m, 3H); 3.80 (s, 3H); 7.61 (td, 1H, J = 3.9, < 1)
5f	99	77/0.2	$C_{12}H_{16}O_3$ (208.2)	3050, 1740, 1710, 1680, 1640 (br w)	1.31 (t, 3H, J = 7.0); 1.6–2.62 (m, 7H); 4.25 (q, 2H, J = 7.0); 4.97 and 5.52 (m, 1H each); 5.5–6.0 (m, 1H); 7.52 (td, 1H, J = 3.9, < 1)

[a] Isolated yield based on **1** for **3**, and **3** for **5**.
[b] Oil bath temperature.
[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.37.
[d] Recorded on a JASCO A-3 spectrophotometer.
[e] Recorded on a JEOL FX90Q spectrometer.

proven to be fruitless since the 1,3-dioxane function was considerably reluctant to undergo hydrolysis under a variety of acidic conditions.

This two-step procedure described above would be a practically useful for the synthesis of **5** because of its simplicity, mild reaction conditions, and high overall yield.

***tert*-Butyl 7,7-(1,2-Ethylenedioxy)-3-oxohexanoate (3d); Typical Procedure:**

To a 50% dispersion of NaH in mineral oil (885 mg, 20.0 mmol) is added THF (50 mL) under N_2, and the suspension is cooled in an ice-water bath. *tert*-Butyl acetoacetate (**1d**; 2.97 g, 18.9 mmol) is added dropwise to the above suspension with stirring over a period of 20 min, and stirring is continued for an additional 15 min. A 1.55 M solution of BuLi in hexane (14.0 mL, 18.8 mmol) is then added dropwise over a period of 15 min. After stirring for 30 min, a solution of bromoacetal **2** (3.74, 20.6 mmol) in THF (2 mL) is added in one lot, and the mixture is allowed to warm slowly to room temperature, and stirring is continued for an additional 3 h. The reaction is quenched with aq. NH_4Cl solution (50 mL) and the product is extracted with Et_2O (3 × 50 mL). The combined ether extract is washed successively with H_2O (70 mL) and brine (50 mL), and dried ($MgSO_4$). Concentration followed by filtration of the residue through a short silica gel column (Merck silica gel 60, 70–230 mesh, 50 g) with the aid of 35% Et_2O in hexane (150 mL) and evaporation of the eluate leaves an oil, which gives **3d** (3.50 g, 73%) as a colorless oil on distillation; yield: 3.5 g (73%); bp 86 °C/0.13 mbar (bath temperature).

***tert*-Butyl 6-Oxo-1-cyclohexenecarboxylate (5d); Typical Procedure:**

A solution of **3d** (1.0 g, 3.87 mmol) and 50% aq. AcOH (50 mL) is stirred at room temperature for 30 h under N_2, and then diluted with H_2O (50 mL). The aqueous solution is saturated with NaCl and extracted with Et_2O (4 × 50 mL). The combined extract is washed successively with sat. $NaHCO_3$ solution (3 × 10 mL), H_2O (100 mL), and brine. Removal of the solvent followed by distillation of the residue affords **5d** (615 mg, 81%) as a colorless oil; yield: 615 mg (81%); bp 67 °C/0.13 mbar (bath temperature).

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