Notes

Highly Efficient Synthesis of Methyl-Substituted Conjugate Cyclohexenones

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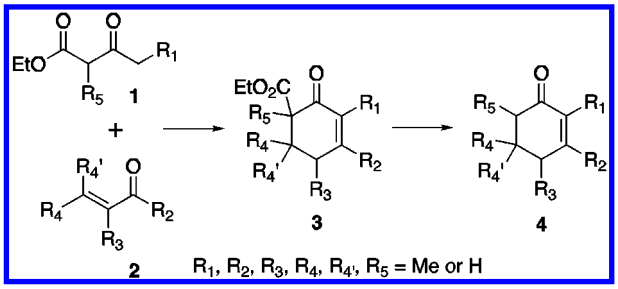
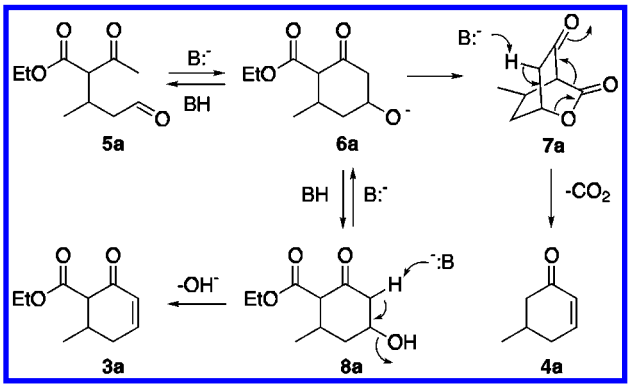
Methyl-substituted conjugate cyclohexenones have widely been used as useful building blocks in the construction of a variety of biologically and/or medicinally important natural products.[1,2] Extensive synthetic efforts have been reported for methyl-substituted conjugate cyclohexenones,[3−12] in which an annulation approach from acyclic precursors constituted a useful entry.[13−15] As shown in Scheme 1, tandem Michael addition−aldol condensation of β-keto esters **1** to conjugate enones (or enals) **2** would produce 6-carbethoxy-2-cyclohexenones **3**,[14] which require saponification and decarboxylation to produce cyclohexenones **4**. However, this sequence may suffer from low yields especially for enones (or enals) with simple substituents (H or Me) due to harsh conditions generally required for the decarboalkoxylation step. Some related annulation procedures have appeared in the literature which facilitated the decarboxylation step by using a metal salt of β-keto acids instead of β-keto esters.[16,17] In an attempt to develop a practical synthetic method of methyl-substituted conjugate cyclohexenones we investigated the base-catalyzed annulation reaction of β-keto esters **1** with conjugate enones (or enals) **2**. We found that by using *t*-BuOK in *t*-BuOH at reflux temperature the decarboalkoxylation smoothly proceeded under this annulation condition to directly produce cyclohexenones **4** in decent yields. Herein, we report the details of our findings.

The reaction of ethyl acetoacetate (**1a**) and crotonaldehyde (**2a**) under *t*-BuOK catalyst (0.25 equiv) in refluxing *t*-BuOH directly produced 5-methyl-2-cyclohexen-1-one (**4a**) in 78% yield. A plausible mechanism of this reaction is shown in Scheme 2. Base-catalyzed Michael addition of **1a** to **2a** affords the tricarbonyl compound **5a**, which then undergoes intramolecular aldol reaction to initially give rise to 3-alkoxycyclohexanone **6a**. This intermediate **6a** would follow two possible modes of reaction sequences, one of which is intramolecular lactonization to produce bicyclic lactone **7a**. Base-catalyzed decarboxylation of **7a** then provides cyclohexenone **4a**. A similar decarboalkoxylation mechanism had been proposed earlier by Stork et al.[18] The other sequence would be protonation of the alkoxy intermediate **6a** followed by dehydration to produce 6-carbethoxy-2-cyclohexenone **3a**. It could be postulated that **4a** should be formed through **3a** by the saponification and decarboxylation sequence. However, that may not be the case under the condition where much less than a stoichiometric amount of OH^- is present. In fact, **3a** did not provide **4a** under KOH catalyst (0.25 equiv) in refluxing *t*-BuOH solvent, which replicated the above reaction condition. The formation of bicyclic lactone **7a** requires syn stereochemical disposition of the alkoxy and the carbethoxy substituents in **6a**, that can be attained through the equilibration between **5a** and **6a**. It seems that the product distribution (**4a** versus **3a**) is determined by the position of the equilibrium between **6a** and **8a**. Under the most basic alcoholic solvent, *t*-BuOH, the equilibrium lies far to alkoxide **6a** to exclusively provide **4a** (78%). When the reaction was conducted under EtONa catalyst (0.25 equiv) in refluxing EtOH, which is a relatively acidic solvent, a substantial amount of the protonated form **8a** existed to give rise to **3a** (38%) along with the decarboalkoxylation product **4a** (37%).

Scheme 1



Scheme 2



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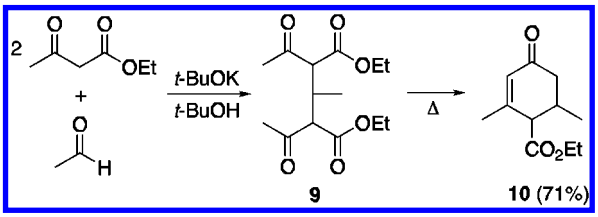
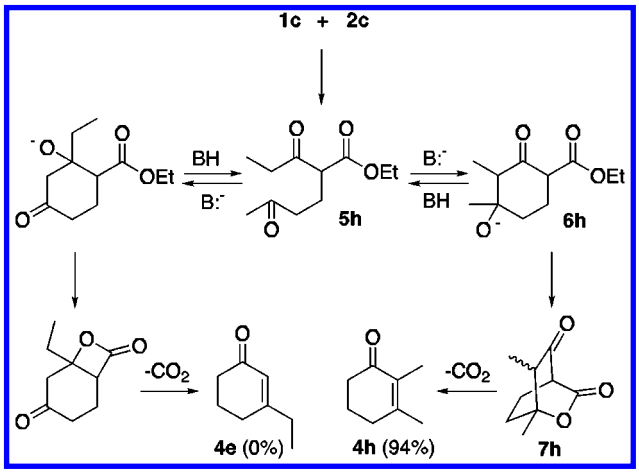
Scheme 3



Scheme 4



The above mechanism was supported by the exclusive formation of 4-carbethoxy-3,5-dimethyl-2-cyclohexen-1-one (**10**) when 2 equiv of ethyl acetoacetate was treated with acetaldehyde in *t*-BuOK/*t*-BuOH condition (Scheme **3**).[19] This reaction presumably proceeded through the intermediate **9** which was formed by the conjugate addition of ethyl acetoacetate to the aldol condensation product of ethyl acetoacetate and acetaldehyde. Since 6-carbethoxy-3,5-dimethyl-2-cyclohexen-1-one was not observed in this reaction, the intermediate **9** must have followed the above proposed decarboalkoxylation process to produce **10**.

We then showed the general applicability of this one-pot process to the preparation of various methyl-substituted conjugate cyclohexenones (Table 1). *β*-Keto esters **1a**−**d** and conjugate enones (or enals) **2a**−**f** were coupled to produce diversely methyl- or ethyl-substituted conjugate cyclohexenones **4a**−**i** in decent yields. For the annulation of *β*-keto esters with α,*β*-unsaturated ketones **2c**, **2d**, and **2e** (entries 3, 4, 5, 7, and 8 in Table 1) two different modes of intramolecular aldol reaction of the initial Michael addition product are possible. These two modes are exemplified for the reaction of **1c** and **2c** (entry 8) in which two different decarboalkoxylation products **4e** and **4h** can be obtained (Scheme 4). Even though the conversion of **4e** into the more stabilized **4h** under the alkaline thermodynamic condition has been reported,[20] this conversion is not possible in *t*-BuOK/*t*-BuOH condition. In fact, the exclusive formation of **4e** by the reaction of **1a** and **2e** in *t*-BuOK/*t*-BuOH condition (entry 5) proves this idea. Since 2,3-dimethyl-2-cyclohexen-1-one (**4h**) was the only product obtained (94% yield), aldol reaction proceeded to produce 3-alkoxy-6-carbethoxycyclohexanone **6h**. It is believed that the neighboring carbethoxy group stabilizes the enolate ion by chelation with the counter metal ion.

Table 1

entry	β-ketoesters	enones (enals)	cyclohexenones	yields[a]
1	**1a**	**2a**	**4a**	78%
2	**1a**	**2b**	**4b**	52%
3	**1a**	**2c**	**4c**	76%
4	**1a**	**2d**	**4d**	75%
5	**1a**	**2e**	**4e**	68%
6	**1b**	**2f**	**4f**	54%
7	**1b**	**2c**	**4g**	60%
8	**1c**	**2c**	**4h**	94%
9	**1d**	**2f**	**4i**	33%

a: Isolated yields after chromatographic separation.

The solvent *t*-BuOH has unique features in this process. First, this protic solvent allows a mild thermodynamic condition where a catalytic amount of base can be used. Second, the solvent is basic enough that the alkoxide ion which is generated from aldol reaction can survive to participate in the decarboalkoxylation process. In conclusion, we have developed a facile and practical one-pot annulation method for various methyl-substi-

(19) The product (a 2.8:1 mixture of stereoisomers), 4-carbethoxy-3,5-dimethyl-2-cyclohexen-1-one (**10**), was confirmed unambiguously after reduction with $NaBH_4$ to 4-carbethoxy-3,5-dimethyl-2-cyclohexen-1-ol (a 2.8:1 mixture of stereoisomers): R_f = 0.13 (2:8 EtOAc:hexanes); IR 3395, 1717, 1173 cm^{-1}; ^{1}H NMR major δ 1.02 (3H, d, J = 6.6 Hz), 1.16 (1H, ddd, J = 9.9, 12.8, 12.8 Hz), 1.28 (3H, t, J = 7.2 Hz), 1.66 (3H, ddd, J = 0.6, 0.7, 1.3 Hz), 1.77 (1H, br s, OH), 1.98−2.12 (2H, m), 2.68 (1H, d, J = 9.9 Hz), 4.20 (2H, q, J = 7.2 Hz), 4.35 (1H, br s), 5.57 (1H, br s); minor δ 1.00 (3H, d, J = 7.0 Hz), 1.69 (3H, br s), 1.72 (1H, br s, OH), 1.83∼1.98 (1H, m), 2.86 (1H, d, J = 5.5 Hz), 4.18 (2H, q, J = 7.1 Hz), 5.64 (1H, br s); ^{13}C NMR major δ 14.3, 20.2, 20.9, 31.5, 40.0, 55.1, 60.6, 67.3, 129.1, 132.7, 174.3; minor δ 14.3, 18.9, 22.2, 30.6, 35.9, 51.2, 60.5, 67.7, 129.6, 133.4, 174.3.

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tuted conjugate cyclohexenones by a series of Michael addition, aldol reaction, and decarboalkoxylation of β-keto esters and conjugate enones (or enals) in the *t*-BuOK/*t*-BuOH system. This highly mild reaction condition allows for simple conjugate enones (or enals) to be used in the annulation reaction without any polymerization. Constructions of bicyclic and heterocyclic compounds using this approach are currently under investigation.

Experimental Section

General. Ethyl 2-methyl-2-propionylacetate (**1d**) was prepared by following the literature procedure.[21,22] All other reagents were obtained from Aldrich Chemical Co. and used as received. Reactions were monitored by GC and TLC on silica gel plates (EM Science, Kieselgel 60, F254). TLC plates were visualized by UV, iodine vapor, and phosphomolybdic acid stain. The column chromatographies were carried out with silica gel 60, 70−230 mesh ASTM supplied by Merck. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively. Chemical shifts are reported in ppm downfield from the internal standard, tetramethylsilane, and coupling constants are given in hertz. Infrared spectra were obtained with CH_2Cl_2 as a solvent. The products, cyclohexenones, were identified by comparison of the spectral data with those reported in the literature. 3-Methyl-2-cyclohexen-1-one and isophorone are commercially available from Aldrich Chemical Co.

General Procedure. To a stirred solution of β-keto ester **1** (1 equiv) and acyclic conjugate enone (or enal) **2** (1 equiv) in *t*-BuOH (1 M) was added a catalytic amount of *t*-BuOK (0.05 equiv) at 0 °C. The reaction mixture was stirred at that temperature for 30 min, and 0.2 equiv of *t*-BuOK was added again. The mixture was then heated at reflux for 20 h. Upon cooling to room temperature, the mixture was quenched with 1 M HCl (10 mL) solution, diluted with a 1:1 mixture of ether and benzene (80 mL), washed with 1 M NaOH solution (20 mL × 3) and brine (20 mL × 2). The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, 1:9−2:8 EtOAc:hexanes).

5-Methyl-2-cyclohexen-1-one (4a).[23−26] The reaction of **1a** (0.91 g, 7 mmol) and **2a** (0.49 g, 7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) provided **4a** (0.60 g, 5.4 mmol) in 78% yield as a light yellow oil.

6-Carbethoxy-5-methyl-2-cyclohexen-1-one (3a). The reaction of **1a** (0.91 g, 7 mmol) and **2a** (0.49 g, 7 mmol) under EtONa (0.25 equiv, 0.12 g, 1.75 mmol) in EtOH (7 mL) produced a 1:1 mixture of **3a** (0.48 g, 2.64 mmol, 38%, a single stereoisomer) and **4a** (0.29 g, 2.66 mmol, 37%) as light yellow oils.

4-Methyl-2-cyclohexen-1-one (4b).[25−28] The reaction of **1a** (0.91 g, 7 mmol) and **2b** (0.49 g, 7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) provided **4b** (0.40 g, 3.64 mmol) in 52% yield as a light yellow oil.

3-Methyl-2-cyclohexen-1-one (4c).[26,29] The reaction of **1a** (0.91 g, 7 mmol) and **2c** (0.49 g, 7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) provided **4c** (0.58 g, 5.29 mmol) in 76% yield as a light yellow oil.

Isophorone (4d).[30] The reaction of **1a** (0.91 g, 7 mmol) and **2d** (0.69 g,7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) provided **4d** (0.73 g, 5.25 mmol) in 75% yield as a light yellow oil.

3-Ethyl-2-cyclohexen-1-one (4e).[20] The mixture of **1a** (0.91 g, 7 mmol) and **2e** (0.59 g, 7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) was stirred at room temperature for 3 h and then heated to reflux for 3 h. After general workup and purification, **4e** (0.59 g, 4.76 mmol) was obtained in 68% yield as a light yellow oil.

6-Methyl-2-cyclohexen-1-one (4f).[4,27,31,32] The reaction of **1b** (1.01 g, 7 mmol) and **2f** (0.39 g, 7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) provided **4f** (0.42 g, 3.78 mmol) in 54% yield as a light yellow oil.

3,6-Dimethyl-2-cyclohexen-1-one (4 g).[4,32] The reaction of **1b** (1.01 g, 7 mmol) and **2c** (0.49 g, 7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) provided **4g** (0.52 g, 4.20 mmol) in 60% yield as a light yellow oil.

2,3-Dimethyl-2-cyclohexen-1-one (4h).[33] The reaction of **1c** (1.01 g, 7.0 mmol) and **2c** (0.49 g, 7.0 mmol) under *t*-BuOK (0.35 g, 3.15 mmol) in *t*-BuOH (7 mL) provided **4h** (0.817 g, 6.58 mmol) in 94% yield as a light yellow oil.

2,6-Dimethyl-2-cyclohexen-1-one (4i).[32,34] The reaction of **1d** (1.20 g, 7 mmol) and **2f** (0.39 g, 7 mmol) under *t*-BuOK (0.20 g, 1.75 mmol) in *t*-BuOH (7 mL) provided **4i** (0.29 g, 2.34 mmol) in 33% yield as a light yellow oil.

4-Carbethoxy-3,5-dimethyl-2-cyclohexen-1-one (10). The reaction of **1a** (2.60 g, 20 mmol) and acetaldehyde (0.44 g, 10 mmol) under *t*-BuOK (0.28 g, 2.50 mmol) in *t*-BuOH (20 mL) provided a 2.8:1 stereoisomeric mixture of **10** (1.39 g, 7.1 mmol) in 71% yield as a light yellow oil.

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Registry No. (supplied by author) **1d**, 759-66-0; **4a**, 7214-50-8; **4b**, 5515-76-4; **4c**, 1193-18-6; **4d**, 78-59-1; **4e**, 17299-34-2; **4f**, 6610-21-5; **4g**, 15329-10-9; **4h**, 1122-20-9; **4i**, 40790-56-5.

Supporting Information Available: Characterization data for cyclohexenones **3a**, **4a**−**i**, and **10**, together with ^{1}H NMR spectra for **3a** and **10** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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