Convenient One-Pot Methods for the Construction of Cyclohexyl Rings at the α-Methylene Moieties of Ketones, Esters, Lactones, and Nitriles through a Michael Addition–Dieckmann Cyclization Sequence

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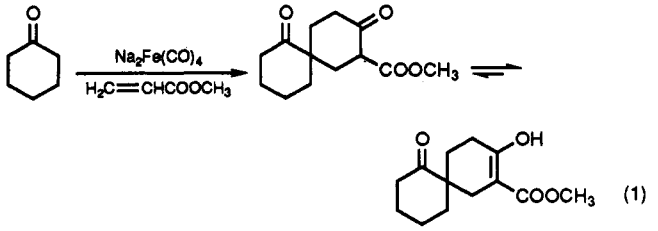
In the course of an investigation[1-3] on the utilization of the super nucleophile,[4] $[Fe(CO)_4]^{2-}$, we have observed that it readily reacts with cyclohexanone and methyl acrylate under ambient conditions to give the product with a cyclohexyl ring constructed on the active methylene moiety (eq 1).

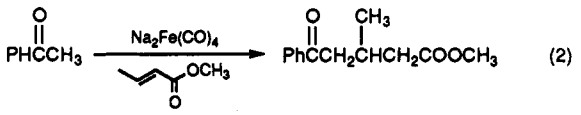


(1)

We have found that the transformation is a general one, and several other ketones, esters, and nitriles can be converted to the corresponding cyclic products (Table I). The reactions were carried out using 10 mmol of the organic substrate, 20 mmol of $Na_2Fe(CO)_4$, and 20 mmol of methyl acrylate in THF (40 mL). Higher yields (~15% greater) were obtained using 40 mmol of $Na_2Fe(CO)_4$.

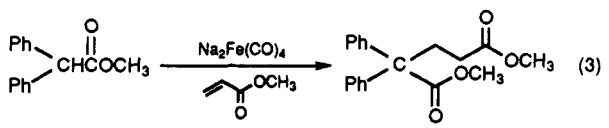
The transformation can be rationalized by the sequence of reactions involving double Michael additions[5] followed by Dieckmann cyclization[6] through enolate intermediates.[7]

We have observed that the reaction in the case of acetophenone using methyl crotonate gives only the corresponding monoalkylated product (eq 2). Also, an



(2)

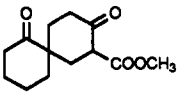
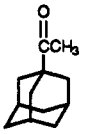
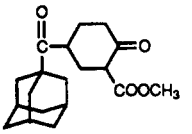
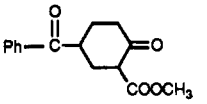
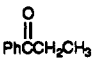
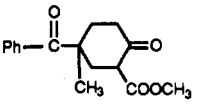
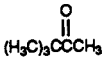
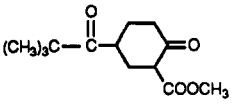
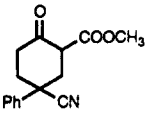
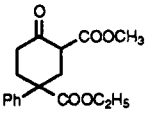
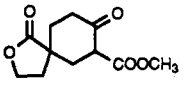
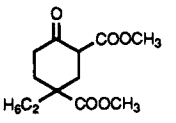
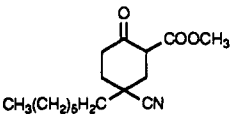
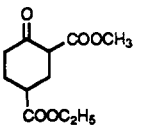
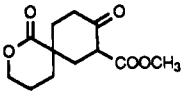
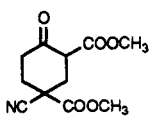
α-methine derivative gives the corresponding alkylated product as expected (eq 3).



(3)

If this transformation goes through the enolate intermediate, then there is a possibility to achieve this using

Table I. Synthesis of Cyclic β-Keto Esters from Active Methylene Compounds and Methyl Acrylate Using $Na_2Fe(CO)_4$ and NaOMe

no.	substrate	product[a]	yield[b] (%) A	B
1			53	42
2			49	45
3			58	55
4			43	42
5			48	40
6	$PhCH_2CN$		62	56
7	$PhCH_2COOC_2H_5$		59	52
8			55	50
9	$CH_3(CH_2)_2COOCH_3$		48	41
10	$CH_3(CH_2)_7CN$		49	45
11	$CH_3COOC_2H_5$			40
12				48
13	$NCCH_2COOCH_3$			54

[a] The products were identified by the spectral data (IR, ^1H NMR, ^{13}C NMR). Mass spectral data (EI) were obtained for products in entries (1–3 and 6–8). For entries (2 and 6–8) elemental analyses (see Experimental Section) were also obtained. [b] Yields of the products were calculated from the amount of substrate (ketones, esters, nitriles, and lactones) used. A: Yields of the products obtained using $Na_2Fe(CO)_4$. B: Yields of the products obtained using NaOMe.

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other more readily accessible bases such as alkoxides. Surprisingly, to our knowledge, no such general transformations have been reported.[8]

We have observed that the same cyclic products are obtained when sodium methoxide is utilized in place of $Na_2Fe(CO)_4$ (Table I). Again, the transformation is a general one and the cyclic products are obtained in 40-56% yields. Also, the reaction of benzyl cyanide with methyl crotonate gives only the monoalkylated Michael addition product; no cyclic product was formed. It is of interest to note that the reaction of excess benzyl cyanide with acrylonitrile in the presence of Na/CH_3OH has been reported to give the α-phenyl glutaronitrile. The reaction with methyl acrylate also gives the corresponding monoalkylated product under these conditions.[9]

The cyclic product obtained in the reaction of cyclohexanone and acrylate has been previously prepared through a two-step sequence for utilization in the synthesis of some biologically active compounds.[10] The simple, general, one-pot methods described here for the construction of a cyclohexyl ring at the α-methylene position of carbonyl and nitrile substrates will be useful for such applications.

Experimental Section

All reactions were carried out under a dry nitrogen atmosphere. All transfers and manipulations of compounds were carried out under nitrogen atmosphere. Tetrahydrofuran was freshly distilled over benzophenone–sodium. $Fe(CO)_5$ supplied by Fluka Switzerland was used. Commercially available ketones, esters, nitriles, and lactones were used in the experiments.

All melting points reported are uncorrected and were determined using a Buchi-510 capillary point apparatus. Infrared spectra were recorded on Perkin-Elmer IR spectrophotometer Model 257 with polystyrene as reference. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL-FX-100 spectrometer with chloroform-*d* as a solvent and TMS as reference (δ = 0 ppm). Elemental analyses were performed on a Perkin-Elmer elemental analyzer Model 240C. Column chromatography was carried out using ACME's silica gel (100–200 mesh).

Reaction of Cyclohexanone and Methyl Acrylate in the Presence of $Na_2Fe(CO)_4$. To a suspension of $Na_2Fe(CO)_4$ [prepared using $Fe(CO)_5$ (4.32 g, 22 mmol), Na (1.02 g, 44 mmol), and naphthalene (2.04 g, 16 mmol)] in THF (50 mL) was added cyclohexanone (0.98 g, 10 mmol) and the mixture stirred for 1 h under a N_2 atmosphere. To this mixture was added methyl acrylate (1.72 g, 20 mmol), and the mixture was further stirred for 12 h at 25 °C. It was poured into acetone (40 mL) containing $CuCl_2$ (5.38 g, 40 mmol) to decompose the iron carbonyl. Water (40 mL) was added, and the organic phase was separated. The aqueous phase was saturated with NaCl and extracted with ether (2 × 40 mL). The combined organic extract was washed with H_2O (20 mL) and brine (30 mL), dried, and concentrated. The residue was subjected to column chromatography. Hexane eluted naphthalene, and 4% ethyl acetate in hexane eluted cyclic β-keto ester 1 (53%, 1.26 g) IR (neat) 1610, 1650, 1700 cm^{-1}; ^1H NMR δ ppm 1.62–2.58 (m, 14H), 2.84 (m, 1H), 3.72 (s, 3H); ^{13}C NMR δ ppm 20.2, 25.1, 27.2, 27.8, 29.1, 36.6, 37.7, 46.5, 50.7, 94.5, 170.3, 172.1, 213.7; MS (EI) *m/e* 238 (M^+, 80).

The above procedure was followed for other substrates (Table I, entries 2–10). The physical constants and spectral data obtained are summarized below.

2: yield 49% (1.56 g); mp 85 °C; IR (neat) 1615, 1650, 1700 cm^{-1}; ^1H NMR δ ppm 1.64–2.48 (m, 22H), 3.08 (m, 1H), 3.71 (s, 3H); ^{13}C NMR δ ppm 25.3, 26.2, 28.0, 28.6, 36.7, 37.8, 38.1, 39.5, 47.2, 51.5, 96.7, 171.3, 172.3, 217.1; MS (EI) *m/e* 318 (M^+, 20). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.69; H, 8.17. Found: C, 71.32; H, 8.37.

3: yield 58% (1.51 g); IR (neat) 1610, 1650, 1705 cm^{-1}; ^1H NMR δ ppm 1.65–2.64 (m, 7H), 3.32 (m, 1H), 3.62 (s, 3H), 7.74–7.94 (m, 2H), 7.22–7.50 (m, 3H); ^{13}C NMR δ ppm 24.1, 25.0, 28.0, 40.8, 51.0, 96.0, 128.0, 128.4, 132.8, 135.6, 171.0, 172.3, 201.8; MS (EI) *m/e* 260 (M^+ 60).

4: yield 43% (1.44 g); IR (neat) 1610, 1650, 1700 cm^{-1}; ^1H NMR δ ppm 1.40 (s, 3H), 1.64–1.98, 2.04–2.40 (m, 6H), 3.02 (m, 1H), 3.60 (s, 3H), 7.28–7.48 (m, 3H), 7.52–7.64 (m, 2H); ^{13}C NMR δ ppm 24.1, 26.1, 30.7, 32.1, 46.2, 51.0, 95.6, 127.2, 127.9, 130.8, 138.1, 171.0, 172.3, 207.3.

5: yield 48% (1.22 g); IR (neat) 1610, 1650, 1700 cm^{-1}; ^1H NMR δ ppm 1.04–1.20 (m, 9H), 1.64–2.60 (m, 7H), 2.84 (m, 1H), 3.64 (s, 3H); ^{13}C NMR δ ppm 25.0, 25.4, 25.8, 28.0, 39.8, 44.3, 50.8, 96.1, 170.7, 172.2, 216.9.

6: yield 62% (1.60 g); mp 95 °C; IR (KBr) 1600, 1650, 2230 cm^{-1}; ^1H NMR δ ppm 2.10–3.11 (m, 6H), 3.76 (s, 3.76 (s, 3H), 7.22–7.60 (m, 5H), 12.20 (s, 1H); ^{13}C NMR δ ppm 27.1, 31.4, 34.8, 41.1, 51.7, 95.1, 122.2, 125.7, 128.6, 129.3, 139.4, 170.8, 172.2; MS (EI) *m/e* 257 (M^+, 40). Anal. Calcd for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.09; H, 5.97; N, 5.26.

7: yield 59% (1.8 g); IR (neat) 1600, 1640, 1710 cm^{-1}; ^1H NMR δ ppm 1.21 (t, 3H), 2.10–3.11 (m, 8H), 3.70 (s, 3H), 7.21–7.30 (m, 5H); ^{13}C NMR δ ppm 13.8, 26.5, 29.3, 30.6, 48.9, 51.3, 52.1, 60.8, 95.9, 125.8, 127.2, 128.6, 141.4, 171.3, 172.5, 174.8; MS (EI) *m/e* 304 (M^+, 10). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.1; H, 6.62. Found: C, 67.5; H, 6.66.

8: yield 55% (1.26 g); mp 92 °C; IR (KBr) 1620, 1720 cm^{-1}; ^1H NMR δ ppm 1.56–2.68 (m, 9H), 3.80 (s, 3H), 4.36 (t, 2H); ^{13}C NMR δ ppm 25.5, 27.6, 29.4, 32.8, 41.0, 51.4, 65.1, 94.7, 170.7, 172.7, 180.5; MS (EI) *m/e* 226 (M^+, 25). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.39, H, 6.24. Found: C, 57.89; H, 6.23.

9: yield 48% (1.16 g); IR (neat) 1600, 1650, 1730 cm^{-1}; ^1H NMR δ ppm 0.90 (t, 3H), 1.51 (q, 2H), 1.90–2.51 (m, 6H), 3.4 (s, 3H), 3.6 (s, 3H); ^{13}C NMR δ ppm 13.2, 17.9, 27.1, 32.6, 35.6, 51.3, 51.6, 125.8, 138.0, 167.0, 173.1, 179.5.

10: yield 49% (1.36 g); IR (neat) 1640, 1730, 2200 cm^{-1}; ^1H NMR δ ppm 0.96 (t, 3H), 1.40 (m, 10H), 1.71 (m, 2H), 2.3–2.8 (m, 4H), 3.76 (s, 3H); ^{13}C NMR δ ppm 13.5, 16.5, 22.2, 25.0, 26.9, 28.2, 28.6, 31.3, 32.5, 51.0, 119.5, 125.4, 128.2, 166.2, 172.7.

Reaction of Cyclohexanone with Methyl Acrylate in the Presence of NaOMe. To a suspension of NaOMe (1.08 g, 20 mmol) in THF (40 mL) was added cyclohexanone (0.98 g, 10 mmol) and the mixture stirred for 1 h at 25 °C under nitrogen atmosphere. To this solution was added methyl acrylate (1.72 g, 20 mmol) and the resulting solution further stirred for 10 h at 25 °C. The resulting mixture was poured into dilute HCl (15 mL), the organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phase was washed successively with H_2O (20 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated. The residue was subjected to column chromatography. The cyclic β-keto ester 1 (1.01 g, 42%) was eluted using 4% ethyl acetate in hexane.

Similar procedure was followed for other substrates (Table I). The physical constants and the spectral data of cyclic β-keto esters (Table I, entries 1–10) were found to be similar to that obtained using $Na_2Fe(CO)_4$. The data for other cyclic β-keto esters (entries 11–13) obtained in the reaction using NaOMe are summarized below.

11: yield 40% (0.90 g); IR (neat) 1600, 1640, 1730 cm^{-1}; ^1H NMR δ ppm 1.20 (t, 3H), 2.40–2.71 (m, 6H), 3.65 (s, 3H), 4.10 (q, 2H); ^{13}C NMR (45 °C) δ ppm 13.9, 25.7, 27.4, 29.4, 46.1, 51.2, 51.8, 59.1, 77.4, 95.2, 170.8, 172.5, 175.0; ^{13}C NMR (25 °C) 13.9, 25.6, 27.1, 32.6, 32.9, 38.8, 51.2, 51.6, 60.1, 60.5, 98.0, 117.3, 125.4, 125.7, 136.5, 138.8, 163.4, 172.1, 174.2.

12: yield 48% (1.16 g); IR (neat) 1620, 1720 cm^{-1}; ^1H NMR δ ppm 1.50–2.81 (m, 10H), 3.70 (s, 3H), 4.31 (t, 2H); ^{13}C NMR δ ppm 20.2, 25.1, 28.9, 30.1, 31.6, 40.6, 51.6, 70.0, 94.6, 170.5, 172.7, 175.8.

13: yield 54% (1.36 g); IR (neat) 1610, 1650, 1730, 2220 cm^{-1}; ^1H NMR δ ppm 2.10–2.91 (m, 6H), 3.75 (s, 3H), 3.82 (s, 3H); ^{13}C NMR δ ppm 25.7, 28.0, 30.1, 42.2, 51.8, 53.8, 93.7, 118.3, 168.6, 170.1, 171.7.

(8) However, it has been briefly mentioned that the lactone enolate derived from butyrolactone on treatment with cinnamates yields the corresponding cyclic β-keto esters in 35–55% yield: Brimacombe, J. S.; Haque, Z. U.; Murray, A. W. *Tetrahedron Lett.* **1974**, 4087.

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Reaction of Acetophenone and Methyl Crotonate in the Presence of $Na_2Fe(CO)_4$. To a suspension of $Na_2Fe(CO)_4$ [prepared using $Fe(CO)_5$ (4.32 g, 22 mmol), Na (1.02 g, 44 mmol), and naphthalene (2.04 g, 16 mmol)] in THF (50 mL) was added acetophenone (1.21 g, 10 mmol) and the mixture stirred for 1 h under a N_2 atmosphere. To this mixture was added methyl crotonate (2.00 g, 20 mmol), and the mixture was further stirred for 12 h at 25 °C. The resulting mixture was poured into acetone (40 mL) containing $CuCl_2$ (5.38 g, 40 mmol) to decompose the iron carbonyl. Water (40 mL) was added, and the organic phase was separated. The aqueous phase was saturated with NaCl and extracted with ether (2 × 40 mL). The combined organic extract was washed with H_2O (20 mL) and brine (30 mL), dried, and concentrated. The residue was subjected to column chromatography. Hexane eluted naphthalene, and 4% ethyl acetate in hexane eluted ester 14 (50%, 1.10 g): IR (neat) 1680, 1740 cm^{-1}; ^1H NMR δ ppm 0.96–1.08 (d, 3H), 2.24–3.04 (m, 5H), 3.64 (s, 3H), 7.32–7.56 (m, 3H), 7.84–7.98 (m, 2H); ^{13}C NMR δ ppm 19.8, 26.5, 40.5, 44.5, 51.1, 127.9, 128.4, 132.7, 136.8, 172.6, 198.8.

Reaction of Methyl 1,1-Diphenylacetate and Methyl Acrylate in the Presence of $Na_2Fe(CO)_4$. To a suspension of $Na_2Fe(CO)_4$ [prepared using $Fe(CO)_5$ (4.32 g, 22 mmol), Na (1.02 g, 44 mmol), and naphthalene (2.04 g, 16 mmol)] in THF (50 mL) was added methyl 1,1-diphenylacetate (2.26 g, 10 mmol) and the mixture stirred for 1 h under a N_2 atmosphere. To this mixture was added methyl acrylate (1.72 g, 20 mmol), and the mixture was further stirred for 12 h at 25 °C. The resulting mixture was poured into acetone (40 mL) containing $CuCl_2$ (5.38 g, 40 mmol) to decompose the iron carbonyl. Water (40 mL) was added, and the organic phase was separated. The aqueous phase was saturated with NaCl and extracted with ether (2 × 40 mL). The combined organic extract was washed with water (20 mL) and brine (30 mL), dried, and concentrated. The residue was subjected to column chromatography. Hexane eluted naphthalene, and 4% ethyl acetate in hexane eluted ester (15) (80%, 1.25 g): IR (neat) 1710, 1730 cm^{-1}; ^{13}C NMR δ ppm 30.4, 33.1, 51.4, 52.3, 59.6, 127.1, 128.1, 128.8, 142.2, 173.7, 174.3. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.05; H, 6.45. Found: C, 73.0; H, 6.49.

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Supplementary Material Available: ^{13}C NMR spectra (25 MHz, $CDCl_3$) of compounds 1–15 (16 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.