

A New Synthesis of α,β -Unsaturated Carboxylic Esters. The Condensation of Ethyl Lithiotrimethylsilylacetate with Carbonyl Compounds

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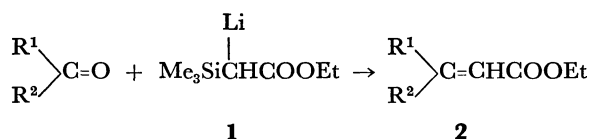
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The key step of the title synthesis involves the conversion of ethyl trimethylsilylacetate to the corresponding enolate, **1**, by treatment with lithium dicyclohexylamide in tetrahydrofuran at -78°C . The condensation of **1** with aldehydes and ketones proceeds smoothly to afford the desired two carbon homologated unsaturated esters in excellent yields. The new process is extended with success to readily-enolizable carbonyl compounds and also to chalcone, which gives no trace of the Michael adduct in the present reaction.

In the conversion of carbonyl compounds to two carbon-homologated α,β -unsaturated carboxylic esters, the most frequently used method is that of Emmons-Wadsworth-Horner olefin synthesis involving the phosphonate carbanions.¹⁾ However, this method has certain limitations with such carbonyl compounds as highly-hindered or readily-enolizable ketones, which are often inert to this type of carbanion,²⁾ and also with enones which are susceptible to the Michael addition.^{1f)}

The present paper will be concerned with a new method for the above transformation using ethyl lithiotrimethylsilylacetate, **1**, which affords α,β -unsaturated carboxylic esters, **2**, exclusively in high yields.



This method is based upon a recent development in silicon-substituted carbanion chemistry, the Peterson olefin synthesis.³⁾ It should be noted, however, that the polarization of the silicon-carbon bond gives rise to a slight anionic character of the carbon, which is much intensified by the directly-attached electron-withdrawing carbonyl group. Ethyl trimethylsilylacetate and similar compounds containing such a SiCH_2CO moiety have been known to undergo a facile heterolysis of the silicon to the carbon bond with diluted acids, alkalis, or even with ethanol.⁴⁾ The activation of the silicon-carbon bond by the ester substituent allows condensations in the presence of a basic catalyst to yield β -trimethylsiloxy-carboxylate.⁵⁾ The previously-proposed mechanism involving ethyl sodiotrimethylsilylacetate has been questioned, and the intermediacy of ethyl sodioacetate has been proposed, the base attack occurring on the silicon atom under the $\text{Si}-\text{CH}_2$ -bond heterolysis to form an ester enolate ion.⁶⁾

Rathke has prepared lithium ester enolates by treating the corresponding esters with lithium *N*-isopropylcyclohexylamide or lithium bis(trimethylsilyl)amide.⁷⁾ This method utilizing the highly-hindered lithium amide has also been successfully applied to the formation of the desired lithium ester enolate, **1**.

The treatment of ethyl trimethylsilylacetate with lithium dicyclohexylamide was performed in dry tetrahydrofuran at -78°C for 10 min. The quenching of the resulting anion, **1**, with water, followed by gas-liquid partition chromatography (glpc) yielded a 95%

recovery of the starting ester. The formation of the **1** anion was further verified by the transformation of carbonyl compounds to the two carbon homologated carboxylic esters in the yields summarized in Table 1.

TABLE 1. CONVERSION OF CARBONYL COMPOUNDS INTO **2** USING ETHYL LITHIOTRIMETHYLSILYLACETATE

$\text{R}^1\text{-CO-R}^2$	Yield of 2 (%) ^{a),b)}	Bp bath temp	<i>E-Z</i> ratio
Benzaldehyde	84	126 °C (2 mmHg)	3 : 1—9 : 1 ^{c),e)}
Nonanal	81	148 °C (2 mmHg)	1 : 1 ^{d)}
Cyclohexanone	95	132 °C (15 mmHg)	—
Cyclododecanone	94	155 °C (2 mmHg)	—
Cyclopentanone	81	120 °C (15 mmHg)	—
Chalcone	86	176 °C (0.5 mmHg)	7 : 3 ^{d),g)}
Acetophenone	63	140 °C (4 mmHg)	2 : 1 ^{d)}
Pinacolone	21	116 °C (12 mmHg)	^{f)}
β -Ionone	82	150 °C (3 mmHg)	3 : 2 ^{d)}

a) All products were characterized by spectroscopic methods and elemental analyses. b) Yields are based on material isolated by chromatography. c) Isomer ratio was variable according to the reaction condition. d) Determined by isolation ratio. e) Determined by glpc. f) The *Z* isomer was undetectable by NMR assay. g) The *E* configuration of C(4)—C(5) double bond is retained.

In Wittig-type reactions, cyclopentanone often fails to give the desired products because of its high degree of enolization.^{2a),c)} Proton-transfer reaction may occur faster than carbonyl addition, with the consequent risk of the isomerization of the resulting α,β -unsaturated esters and/or condensation reactions of the ketone enolate. Nevertheless, we obtain exclusively ethyl cyclopentylideneacetate in a good yield. The reaction mixture must be quenched at -25°C in this case; otherwise, an appreciable amount (as high as 10%) of the isomerized, endo-olefinic β,γ -unsaturated ester is detected by NMR assay.

As expected, however, the condensation of lithium enolate, **1**, with highly-hindered pinacolone gave a poor yield of the desired adduct.

Few examples of the Wittig-Horner reaction of α,β -unsaturated ketones have been recorded. Only chalcone is known to react with the phosphonate carbanions to give a Michael and/or a Wittig-Horner product in low yields.^{1f)} We found that the lithium enolate, **1**, gave solely the expected normal product, ethyl 3,5-diphenylpenta-2,4-dienoate.

β -Ionylideneacetate is one of the important intermediates in the synthesis of vitamin A and its analogs.⁹⁾ The lithium enolate, **1**, proved to react with β -ionone smoothly to give the trienic ester.

In those instances where the formation of both *cis* and *trans* esters were possible, the isomer ratios are as given in Table 1. The stereochemistry was assigned on the basis of the NMR data; the shift values of the vinylic protons were diagnostic (for details, see the Experimental section).¹⁰⁾

Experimental

The IR spectra were determined on a Shimadzu IR-27-G spectrometer; the UV spectra, on a Shimadzu MPS-50-L spectrometer; the mass spectra, on a Hitachi RMU-6L mass spectrometer; the glpc analyses, on a Yanagimoto GCG-550F, and the NMR spectra, on a JEOL C-60-H or Varian EM-360 spectrometer. The chemical shifts are given in δ , with TMS as the internal standard. The analyses were carried out by Mrs. Kiyoko Fujimoto, Prof. Kawanisi's Laboratory and by the staff at the Elemental Analyses Center of Kyoto University. All the experiments were carried out under an atmosphere of dry nitrogen, by preparative thin-layer chromatography (plc) on silica gel PF-254 plates (Merck) with benzene as an eluent, and by preparative column chromatography on silica gel Wakogel C-100 (Wako).

Preparation of Ethyl Trimethylsilylacetate. Ethyl trimethylsilylacetate was prepared by the method of Fessenden⁹⁾ in a 71% yield after distillation; bp 65 °C (68 mmHg).

Generation of Ethyl Lithiotrimethylsilylacetate (1**).** Dicyclohexylamine (365 mg, 2.00 mmol) was dissolved in dry tetrahydrofuran (10 ml). The solution was then cooled to -78 °C and treated with *n*-butyllithium dissolved in hexane (1.35 ml of 1.50 M solution). After it has been stirred for 15 min, a solution of ethyl trimethylsilylacetate (320 mg, 2.00 mmol) in dry tetrahydrofuran (1.0 ml) was added, drop by drop, at -78 °C, and the resulting solution was stirred at the same temperature for 10 min before the subsequent treatments to be described below.

Quenching of Lithium Enolate, **1, with Water.** A solution of **1** prepared from 320 mg (2.00 mmol) of ethyl trimethylsilylacetate was simply quenched with water at -78 °C. A subsequent glpc analysis of the organic layer with tetralin as an internal standard indicated a 95% recovery of the starting ethyl trimethylsilylacetate.

Condensation of Lithium Enolate, **1, with Aldehydes.** To a solution of **1** (1.20 mmol), a solution of the respective aldehyde (1.00 mmol) in dry tetrahydrofuran (1.0 ml) was added, drop by drop, at -78 °C. The reaction mixture was stirred at -78 °C for 1 hr, at -25 °C for 1 hr, and finally at 25 °C for 1 hr. Finely-ground sodium bisulfate monohydrate (0.22 g) was then added, and the mixture was stirred for 10 min. The solid was filtered off, and water was added to the filtrate. This solution was extracted with three 5-ml portions of ethyl acetate. The extracts were combined, dried, and evaporated *in vacuo* to yield an oily product, which was subsequently purified by plc.

Ethyl (*E*) and (*Z*)-Cinnamate were prepared from lithium enolate, **1** (1.20 mmol), and benzaldehyde (108 mg, 1.00 mmol). The crude product was purified by plc, thus furnishing 147 mg (84%) of ethyl cinnamate ((*E*):(*Z*)=8:1). The isomers were separated on a 75 cm \times 3 mm 5% SE 30 on Chromosorb W column at 120 °C.

Ethyl (*E*) and (*Z*)-2-Undecenoate were prepared from **1** and nonanal (142 mg, 1.00 mmol). The resulting oil was chro-

matographed on a silica-gel thin-layer plate. The first band contained ethyl (*Z*)-2-undecenoate (51 mg, 24%): IR (neat) 1724, 1646, 1470, 1418, 1186, 1040, 822 cm⁻¹; NMR (CDCl₃) δ 0.68–1.04 (m, 3H), 1.05–1.75 (m, 12H), 1.24 (t, *J*=7, 3H), 2.57 (br d, 2H), 4.06 (q, *J*=7, 2H), 5.62 (d, *J*=9.3, 1H), 6.05 (d, *J*=9.3 Hz, t, *J*=6.3 Hz, 1H); mass *m/e* (%) 212 (17), 183 (3), 169 (32), 127 (81), 115 (32), 101 (28), 99 (100), 88 (42), 81 (42), 77 (33), 69 (39), 55 (72). The second band was ethyl (*E*)-2-undecenoate (128 mg, 58%): IR (neat) 1724, 1656, 1470, 1270, 1185, 1047, 985 cm⁻¹; NMR (CDCl₃) δ 0.70–1.08 (m, 3H), 1.09–1.85 (m, 12H), 1.28 (t, *J*=7 Hz, 3H), 2.18 (br t, 2H), 4.18 (q, *J*=7 Hz, 2H), 5.74 (d, *J*=15 Hz, 1H), 6.86 (t, *J*=7 Hz, d, *J*=15 Hz, 1H); mass *m/e* (%) 212 (2), 185 (3), 183 (2), 167 (42), 127 (8), 125 (33), 115 (20), 101 (71), 99 (34), 88 (44), 73 (64), 69 (47), 55 (100). (Found: C, 73.7; H, 11.4%).

Condensation of Lithium Enolate, **1, with Ketones.** To a solution of **1** (2.00 mmol), a solution of ketone (1.00 mmol) in dry tetrahydrofuran (1.0 ml) was added, drop by drop, at -78 °C. The resulting mixture was stirred at -78 °C for 1 hr, at -25 °C for 1 hr, and finally at 25 °C for 1 hr. Finely-ground sodium bisulfate monohydrate (0.40 g) was then added, and the mixture was stirred for 10 min. A subsequent work-up yielded an oil, which was purified by silica-gel chromatography, with benzene (plc) or hexane (column) as the eluent.

Ethyl Cyclododecylideneacetate was prepared from **1** (20.0 mmol) and cyclododecanone (1.82 g, 10.0 mmol). The crude product was chromatographed over a 100-g silica gel column, thus furnishing 2.36 g (94%) of ethyl cyclododecylideneacetate as a colorless semisolid; bp 155 °C (bath temp, 2 mmHg); IR (neat) 1720, 1644, 1468, 1444, 1170, 1150, 1036 cm⁻¹; NMR (CCl₄) δ 1.24 (t, *J*=7 Hz, 3H), 1.20–2.00 (m, 18H), 2.21 (br t, *J*=7 Hz, 2H), 2.71 (br t, *J*=7 Hz, 2H), 4.06 (q, *J*=7 Hz, 2H), 5.63 (br s, 1H); mass *m/e* (%) 252 (27), 207 (36), 164 (60), 128 (100). (Found: C, 75.9; H, 11.1%).

Ethyl Cyclohexylideneacetate was prepared from **1** (2.00 mmol) and cyclohexanone (98.0 mg, 1.00 mmol). The liquid thus obtained was purified by plc thus furnishing 159 mg (95%) of ethyl cyclohexylideneacetate as an oil.

Ethyl cyclopentylideneacetate was prepared from cyclopentanone (84 mg, 1.00 mmol), the reaction being quenched by the addition of water at -25 °C. The liquid thus obtained was purified by plc, thus furnishing 125 mg (81%) of ethyl cyclopentylideneacetate as an oil: IR (neat) 1718, 1655, 1377, 1250, 1205, 1125, 1045, 860 cm⁻¹; NMR (CCl₄) δ 1.23 (t, *J*=7 Hz, 3H), 1.50–2.03 (m, 4H), 2.10–3.07 (m, 4H), 4.10 (q, *J*=7 Hz, 2H), 5.70 (s, 1H); mass *m/e* (%) 154 (88), 140 (50), 126 (80), 109 (100), 97 (32), 81 (85), 79 (64), 67 (96); Found: C, 70.3; H, 9.20%. Calcd for C₉H₁₄O₂: C, 70.1; H, 9.15%.

Ethyl 3,5-Diphenylpenta-(2*E*,4*E*) and (2*Z*,4*E*)-dienoate were prepared from **1** (2 mmol) and chalcone (108 mg, 1.00 mmol). The crude oil was purified by plc. The first band contained ethyl 3,5-diphenylpenta-(2*Z*,4*E*)-dienoate (72 mg, 26%): IR (neat) 1715, 1610, 1588, 1275, 1230, 1155, 1100, 1034, 964, 753, 690 cm⁻¹; NMR (CCl₄) δ 1.30 (t, *J*=7 Hz, 3H), 4.26 (q, *J*=7 Hz, 2H), 5.90 (s, 1H), 6.44 (d, *J*=16 Hz, 1H), 7.35 (d, *J*=16 Hz, 1H), 7.36 (m, 10H); UV λ_{max}^{EtOH} 314 nm (ϵ 833); mass *m/e* (%) 278 (18), 249 (3), 233 (11), 205 (100), 190 (8), 178 (6), 165(4), 137 (9), 105 (6), 101 (9), 91 (9), 89 (7), 77 (13). The second band was ethyl 3,5-diphenylpenta-(2*E*,4*E*)-dienoate (168 mg, 60%): IR (neat) 1712, 1610, 1590, 1275, 1230, 1155, 1100, 1034, 965, 753, 690 cm⁻¹; NMR (CCl₄) δ 1.04 (t, *J*=8 Hz, 3H), 4.02 (q, *J*=8 Hz, 2H), 6.06 (s, 1H), 6.33 (d, *J*=14 Hz, 1H), 7.04 (d, *J*=14 Hz,

1H), 7.30 (m, 10H); UV $\lambda_{\text{max}}^{\text{EtOH}}$ 316 nm (ϵ 716); mass m/e (%) 278 (15), 249 (4), 233 (10), 205 (100), 190 (9), 178 (7), 165 (5), 127 (12), 115 (5), 101 (11), 91 (10), 89 (10), 77 (18).

Ethyl (E) and (Z)-3-Phenyl-2-butenolate were prepared from **1** (4 mmol) and acetophenone (240 mg, 2.00 mmol). The crude mixture was chromatographed on a silica-gel plate. The first band consisted of ethyl (E)-3-phenyl-2-butenolate (165 mg, 43%): IR (neat) 1710, 1628, 1447, 1346, 1273, 1170, 1044, 870, 767, 696 cm^{-1} ; NMR (CDCl_3) δ 1.27 (t, $J=7$ Hz, 3H), 2.52 (d, $J=2$ Hz, 3H), 4.13 (q, $J=7$ Hz, 2H), 6.02 (m, 1H), 7.30 (m, 5H); mass m/e (%) 190 (63), 175 (4), 161 (32), 145 (100), 115 (56), 101 (10), 91 (28). The second band was ethyl (Z)-3-phenyl-2-butenolate (74 mg, 20%): IR (neat) 1715, 1640, 1443, 1375, 1230, 1160, 1045, 857, 768, 700 cm^{-1} ; NMR (CDCl_3) δ 1.05 (t, $J=7$ Hz, 3H), 2.12 (d, $J=2$ Hz, 3H), 3.90 (q, $J=7$, 2H), 5.71 (m, 1H), 7.15 (m, 5H); mass m/e (%) 190 (68), 161 (40), 145 (100), 115 (70), 105 (17), 91 (30). A mixture of the (E) and (Z) isomers was analyzed. Found: C, 75.6; H, 7.52%. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$: C, 75.8; H, 7.42%.

Ethyl 3,4,4-Trimethyl-2-pentenoate was prepared from **1** (4.00 mmol) and pinacolone (200 mg, 2.00 mmol). The crude liquid was purified by plc, thus furnishing 67 mg (21%) of ethyl (E)-3,4,4-trimethyl-2-pentenoate: IR (neat) 1717, 1636, 1263, 1180, 1122, 1054, 868 cm^{-1} ; NMR (CDCl_3) δ 1.10 (s, 9H), 1.23 (t, $J=7$, 3H), 2.08 (d, $J=1$, 3H), 4.00 (q, $J=7$, 2H), 5.53 (d, $J=1$, 1H); mass m/e (%) 170 (20), 155 (66), 127 (54), 125 (70), 109 (50), 97 (100), 83 (36), 81 (36), 69 (31), 57 (36), 55 (74). Found: C, 70.7; H, 10.9%. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.5; H, 10.7%.

Ethyl (E) and (Z)- β -Ionylideneacetate were prepared from **1** (4.00 mmol) and β -ionone (384 mg, 2.00 mmol). The crude oil was purified by plc, thus furnishing 430 mg (82%) of ethyl β -ionylideneacetate ((E):(Z)=3:2). The isomers were separated on a 75 cm \times 3 mm 5% SE 30 on Chromosorb W column at 170°. The first peak was ethyl (Z)- β -ionylideneacetate: IR (neat) 1710, 1610, 1450, 1376, 1230, 1155, 1053, 983, 842 cm^{-1} ; NMR (CCl_4) δ 1.06 (s, 6H), 1.24 (t, $J=7$ Hz, 3H), 1.43–2.60 (m, 6H), 1.75 (s, 3H), 2.00 (s, 3H), 4.05 (q, $J=7$, 2H), 5.50 (br s, 1H), 6.42 (d, $J=16$ Hz, 1H), 7.52 (d, $J=16$ Hz, 1H); mass m/e (%) 262 (38), 247 (16), 233 (8), 217 (20), 201 (20), 189 (24), 173 (40), 159 (32), 133 (52), 119 (100), 105 (40), 91 (32). The second peak was ethyl (E)- β -ionylideneacetate: IR (neat) 1710, 1605, 1443, 1366, 1236, 1154, 1047, 970 cm^{-1} ; NMR (CCl_4) δ 1.02 (s, 6H), 1.25 (t, $J=7$ Hz, 3H), 1.44–2.85 (m, 6H), 1.54 (s, 3H), 1.68 (s, 3H), 2.33 (s, 3H), 4.06 (q, $J=7$ Hz, 2H), 5.62 (br s, 1H), 6.00 (d, $J=16$ Hz, 1H), 6.43 (d, $J=16$ Hz, 1H); mass m/e (%) 262 (26), 247 (10), 233 (5), 217 (15), 201 (15), 189 (15), 173 (33), 159 (32), 133 (46), 119 (100), 105 (34), 91 (25). A mixture of the (E) and (Z) isomers was analyzed. Found: C, 78.1; H, 10.1%. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2$: C, 77.8; H, 10.0%.

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