

Favorskii-Type Rearrangement of α,α' -Dihalo Ketones with Sodiomaltonates Leading to Conjugated Enone Derivatives

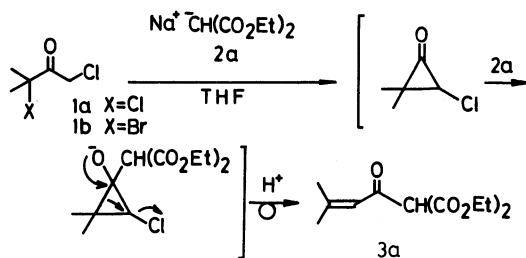
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Synopsis. A new synthetic method of conjugated enones by the use of carbanion-induced Favorskii-type rearrangement is described. The reaction of α,α' -dihalo ketones $R^1R^2(X)CC(O)CH_2X$ with sodiomalonates $Na^+ ^-CH(CO_2R^4)_2$ in THF at 0°C–room temperature gave conjugated enones $R^1R^2C=CHC(O)CH(CO_2R^4)_2$ in 42–66% yields. The reaction can be also adaptable to the enolates of ethyl cyanoacetate or malononitrile to give the corresponding enones.

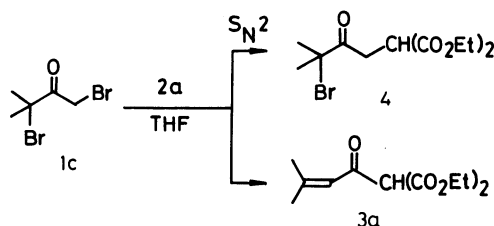
We recently reported that certain α,α' -dihalo ketones caused the Favorskii-type rearrangement by the action of enolate anions derived from β -keto esters¹⁾ and ethyl (diethoxyphosphinyl)acetate,²⁾ giving dihydro-4-pyrones and α -(diethoxyphosphinyl) β -oxo γ,δ -unsaturated esters, respectively. In the previous communication,¹⁾ we simply pointed out that the reaction of 1,3-dichloro-3-methyl-2-butanone (**1a**) with ethyl sodiomalonate (**2a**) gave diethyl (3-methyl-2-butenoyl)malonate (**3a**). Continuous interests to extend the synthetic utility stimulated us to apply the reaction to other α,α' -dihalo ketones and enolate anions.

The reaction of **1a** with two equivalents of **2a** in THF at 0°C–room temperature gave **3a**³⁾ in a 52% yield exclusively (Scheme 1). The yield of **3a** was further improved up to 66% by the use of 3-bromo-1-chloro-3-methyl-2-butanone (**1b**) in place of **1a**. The mechanism for the formation of the unsaturated keto ester is explained in parallel with that described previously.¹⁾

Replacement of the chloro substituent at C-1 by bromine resulted in loss of the product selectivity. Thus the reaction of 1,3-dibromo-3-methyl-2-butanone (**1c**) with **2a** afforded diethyl (3-bromo-3-methyl-2-oxobutyl)malonate (**4**) (43% yield) in addition to the formation of **3a** (49% yield) (Scheme 2). These results



Scheme 1.



Scheme 2.

Table 1. Synthesis of Conjugated Enone Derivatives

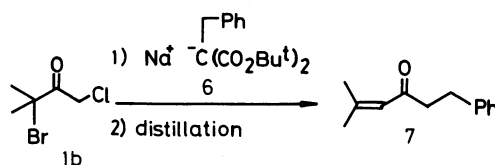
Dihalo ketone	Enolate anion ^{a)}	Product (Yield/%)
		 3b (42)
		 3c (48)
		 3d (53) ^{b)}
		 3e (45)
		 3f (38)
		 3g (59)

a) Sodium salt (NaH, THF). b) A ca. 1:3 mixture of cis- and trans-isomers on the basis of ¹H NMR analysis (see also Ref. 4).

suggest that the Favorskii-type rearrangement and the nucleophilic substitution of **2a** at C-1 occur competitively. The latter reaction would be accelerated in the case of **1c**.

Application of the reaction to the synthesis of various enones **3b–g** is summarized in Table 1. The reaction of 1,3-dichloro-3-methyl-2-pentanone (**1d**) with **2a** gave trans-enone **3d**⁴⁾ predominantly. It is worthwhile to note here that the reaction of **1a** with sodiocyanoacetate (**2d**) also gave **3f**, although the enolate gave only the S_N2 product in the reaction with 3-bromo-3-methyl-2-butanone (**5**).⁵⁾ The difference would come from the ease of abstraction of the C-1 proton of **1a**, **b**, as compared with that of **5**, by the less basic enolate **2d**. The present reaction provides synthetically useful conjugated enone derivatives (**3a–g**) by the use of the Favorskii-type rearrangement.

Furthermore, a similar reaction of **1b** with di-*t*-butyl sodiobenzylmalonate (**6**) afforded 5-methyl-1-phenyl-4-hexen-3-one (**7**) as a result of the decarboxylative decomposition of the Favorskii product in the course of vacuum distillation (Scheme 3).



Scheme 3.

Experimental

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. The bulb-to-bulb distillation was done using a Büchi Kugelrohrföfen at the pressure and the oven temperature indicated. IR spectra were taken on a JASCO A-102 spectrometer. ^1H NMR spectra were measured with a JEOL JNM PMX60-SI spectrometer. Both ^1H NMR (100 MHz) and ^{13}C NMR (25 MHz) spectra were taken on a JEOL FX-100 spectrometer using Me_4Si as an internal standard. HPLC analysis was performed by using Yanagimoto L-2000 apparatus. Elemental analyses were carried out with Yanagimoto MC-2 apparatus. Column chromatography was performed through silica gel (Wakogel C-200). TLCs were done on a silica gel (Kieselgel 60 PF₂₅₄).

Dihalo Ketones. Compound **1c**⁶⁾ was prepared by the bromination (Br_2 , ether) of 3-methyl-2-butanone. Bromo chloro ketone **1b**⁷⁾ as well as dichloro ketones **1a**,⁸⁾ **1d**,⁸⁾ and **1e**⁸⁾ were prepared in a different way from that reported.^{7,8)}

1,3-Dichloro-3-methyl-2-butanone (1a).⁸⁾ Sulfuryl chloride (135 g, 1.0 mol) was added to 3-methyl-2-butanone (34.5 g, 0.41 mol) with stirring at room temperature. After being stirred for 25 h at 40–50 °C, the solution was poured into cold water carefully. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water, dried (CaCl_2), and concentrated under reduced pressure. The residual oil was distilled to give **1a** (44.7 g, 70%): bp 55–59 °C (9 mmHg, 1 mmHg=133.322 Pa).

Dichloro ketones **1d**⁸⁾ and **1e**⁸⁾ were prepared in a similar way in 53 and 40% yields, respectively.

3-Bromo-1-chloro-3-methyl-2-butanone (1b).⁸⁾ A mixture of 3-methyl-2-butanone (9.9 g, 0.115 mol), *N*-bromosuccinimide (20.4 g, 0.115 mol), benzoyl peroxide (2.1 g, 0.0087 mol), and CCl_4 (96 ml) was heated under reflux for 5 h. The mixture was filtered, washed with water and brine, dried (CaCl_2), and then concentrated. The residual oil was subjected to vacuum distillation to give 3-bromo-3-methyl-2-butanone,⁹⁾ (15.9 g, 84%): bp 73–77 °C (93 mmHg). The bromide was then treated with sulfuryl chloride (10.2 g, 0.076 mol) for 11 h at room temperature. Unreacted sulfuryl chloride was removed under reduced pressure. The resulting oil was treated in a manner similar to the foregoing experiment to give **1b** (13.1 g, 68%): bp 90–95 °C (24 mmHg); IR (neat) 1730 cm^{-1} ; ^1H NMR (CCl_4) δ =1.90 (6H, s), 4.53 (2H, s).

Reaction of 1b with Diethyl Sodiomalonate (2a). Synthesis of Diethyl (3-Methyl-2-butenoyl)malonate (**3a**).³⁾ A mixture of diethyl malonate (3.04 g, 19.0 mmol), NaH (457 mg, 19.0 mmol), and THF (25 ml) was heated under reflux for 4 h and then cooled to 0 °C in an ice bath. To the suspension was added a solution of **1b** (1.90 g, 9.52 mmol) and THF (7 ml). After being stirred for 2 h at 0 °C and then for additional 20 h at room temperature, the mixture was acidified with 10% HCl, washed with water, dried (MgSO_4), and then concentrated under reduced pressure. The residual oil was purified by column chromatography (hexane–acetone, 10:1) to give **3a** (1.52 g, 66%). It was subjected to vacuum distillation to afford an analytical sample of **3a**: bp 120–140 °C (1.0 mmHg); IR (film) 1760, 1738, 1697, 1644, 1623 cm^{-1} ; ^1H NMR (CCl_4) δ =1.25 (1.8 H, t, J =7 Hz), 1.28 (1.2 H, t, J =7 Hz), 1.90 (3H, br s), 2.09 (3H, br s), 3.94–4.38 [4.4H, m, ester 2 CH_2 and $\text{CH}(\text{CO}_2\text{Et})_2$], 6.00 (1H, m), 13.47 (0.6 H, s, enol OH).

A similar reaction of dichloro ketone **1a** with **2a** gave **3a** in a 52% yield.

Reaction of 1c with 2a. The crude product was separated by column chromatography (hexane–acetone, 15:1) to give **3a** (49%) and **4** (43%). **4**: IR (neat) 1760–1720 cm^{-1} ; ^1H NMR (CCl_4) δ =1.28 (6H, t, J =7 Hz), 1.88 (6H, s), 3.42 (1H, d, J =8

Hz), 3.43 (1H, d, J =6.5 Hz), 3.77 (1H, dd, J =6.5 and 8 Hz), 4.26 (4H, q, J =7 Hz). Found: C, 44.46; H, 5.87%. Calcd for $\text{C}_{12}\text{H}_{19}\text{O}_5\text{Br}$: C, 44.59; H, 5.92%.

Di-*t*-butyl (3-Methyl-2-butenoyl)malonate (3b): Bp 125–145 °C (3 mmHg); IR (neat) 1730, 1690, 1625 cm^{-1} ; ^1H NMR (CCl_4) δ =1.44 (18H, s), 1.91 (3H, br s), 2.13 (3H, br s), 3.98 (0.8H, s), 6.08 (1H, m), 13.16 (0.2H, s, enol OH). Found: C, 64.26; H, 8.85%. Calcd for $\text{C}_{16}\text{H}_{26}\text{O}_5$: C, 64.41; H, 8.78%.

Diethyl 5-Methyl-3-oxo-4-hexene-2,2-dicarboxylate (3c): Bp 125–145 °C (1.0 mmHg); IR (neat) 1735, 1697, 1623 cm^{-1} ; ^1H NMR (CCl_4) δ =1.27 (6H, t, J =7 Hz), 1.51 (3H, s), 1.94 (3H, br s), 4.18 (4H, q, J =7 Hz), 6.09 (1H, m); ^{13}C NMR (CDCl_3) δ =13.7 (q), 18.0 (q), 20.9 (q), 27.7 (q), 61.7 (t), 66.8 (s), 120.8 (d), 158.1 (s), 168.6 (s), 191.0 (s). Found: C, 60.86; H, 7.72%. Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_5$: C, 60.92; H, 7.87%.

Diethyl (3-Methyl-2-pentenoyl)malonate (3d). The crude product was purified by TLC (hexane–ether, 5:1) to give **3d**:⁴⁾ IR (neat) 1730, 1690, 1620 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.07 (3H, t, J =7 Hz), 1.27 (4.7H, t, J =7 Hz), 1.29 (1.3H, t, J =7 Hz), 1.89 (0.65H, br s, CH_3 of *cis*-**3d**), 2.10 (2.35H, br s, CH_3 of *trans*-**3d**), 2.02–2.72 (2H, m), 3.9–4.4 (4.46H, m, ester 2 CH_2 and OH), 5.95 (1H, m), 12.65 (0.54H, br s, enol OH). Found: C, 60.87; H, 7.62%. Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_5$: C, 60.92; H, 7.87%.

Diethyl (Cyclohexylideneacetyl)malonate (3e). The crude product was purified by TLC (hexane–ether, 5:1) to give **3e**: IR (neat) 1730, 1640, 1560 cm^{-1} ; ^1H NMR (CDCl_3) δ =1.28 (3.3H, t, J =7 Hz), 1.31 (2.7H, t, J =7 Hz), 1.50–2.94 (10H, m), 3.93–4.42 [4.45H, m, ester 2 CH_2 and $\text{CH}(\text{CO}_2\text{Et})_2$], 5.94 (1H, s), 13.42 (0.55H, br s, enol OH). Found: C, 63.72; H, 8.03%. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_5$: C, 63.81; H, 7.85%.

Ethyl 2-Cyano-5-methyl-3-oxo-4-hexenoate (3f). The reaction of **1a** (1.55 g, 0.01 mol) with **2d** [ethyl cyanoacetate (1.94 g, 0.02 mol) and NaH (0.48 g, 0.02 mol) in THF (50 ml)] was done in a similar way. The crude product was purified by column chromatography (hexane–acetone, 5:1) to give **3f** (990 mg, 38%): mp 36–37 °C (CHCl_3); IR (KBr) 3700–3100, 2190, 1660, 1640 cm^{-1} ; ^1H NMR (CD_3COCD_3) δ =1.13 (3H, t, J =7 Hz), 1.86 (3H, br s), 2.10 (3H, br s), 4.16 (2H, q, J =7 Hz), 3.6–4.5 (3H, br s), 6.31 (1H, m). Found: C, 61.49; H, 6.45%. Calcd for $\text{C}_{10}\text{H}_{13}\text{O}_3\text{N}$: C, 61.53; H, 6.71%.

(3-Methyl-2-butenoyl)malononitrile (3g). The reaction of **1a** (1.55 g, 0.01 mol) with **2e** [malononitrile (1.32 g, 0.02 mol) and NaH (0.48 g, 0.02 mol) in THF (40 ml)] was carried out in the usual manner. The crude product was purified by column chromatography (hexane–acetone, 5:1) to give **3g** (0.87 g, 59%): mp 162–163 °C (CHCl_3); IR (KBr) 2220, 2200 1624 cm^{-1} ; ^1H NMR (CD_3COCD_3) δ =2.04 (3H, d, J =0.14 Hz), 2.08 (3H, d, J =1.5 Hz), 6.14 (1H, m), 9.28 (1H, br s, enol OH). Found: C, 64.72; H, 5.46%. Calcd for $\text{C}_8\text{H}_8\text{ON}_2$: C, 64.85; H, 5.44%.

5-Methyl-1-phenyl-4-hexen-3-one (7). The reaction of **1b** (1.99 g, 0.01 mol) with **6** [di-*t*-butyl benzylmalonate¹⁰⁾ (3.06 g, 0.01 mol) and NaH (0.528 g, 0.022 mol) in THF (100 ml)] was carried out in a usual manner. The crude product was subjected to vacuum distillation [bp 150–160 °C (0.3 mmHg)] and purified by column chromatography (hexane–acetone, 20:1) to give **7** (661 mg, 35%): IR (neat) 1693, 1625 cm^{-1} ; ^1H NMR (CCl_4) δ =1.74 (3H, d, J =1.5 Hz), 2.11 (3H, d, J =1.5 Hz), 2.41–3.06 (4H, m), 5.94 (1H, m), 7.09 (5H, br s). Found: C, 82.86; H, 8.61%. Calcd for $\text{C}_{13}\text{H}_{16}\text{O}$: C, 82.94; H, 8.57%.

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