Favorskii-Type Rearrangement of α,α′-Dihalo Ketones with Sodiomalonates Leading to Conjugated Enone Derivatives

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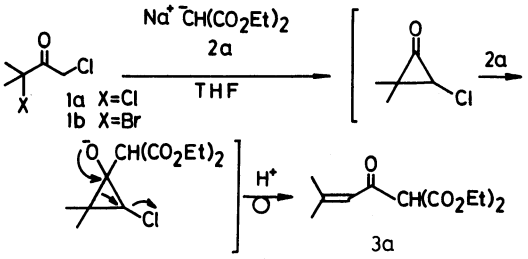
Synopsis. A new synthetic method of conjugated enones by the use of carbanion-induced Favorskii-type rearrangement is described. The reaction of α,α′-dihalo ketones $R^1R^2(X)CC(O)CH_2X$ with sodiomalonates $Na^+ {}^-CR^3(CO_2R^4)_2$ in THF at 0 °C—room temperature gave conjugated enones $R^1R^2C{=}CHC(O)CR^3(CO_2R^4)_2$ in 42—66% yields. The reaction can be also adaptable to the enolates of ethyl cyanoacetate or malononitrile to give the corresponding enones.

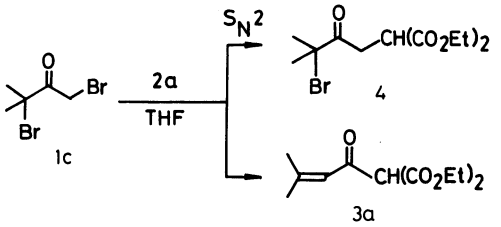
We recently reported that certain α,α′-dihalo ketones caused the Favorskii-type rearrangement by the action of enolate anions derived from β-keto esters[1] and ethyl (diethoxyphosphinyl)acetate,[2] giving dihydro-4-pyrones and α-(diethoxyphosphinyl) β-oxo γ,δ-unsaturated esters, respectively. In the 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

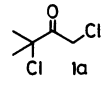
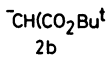
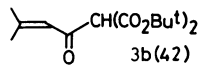
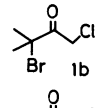
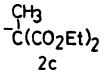
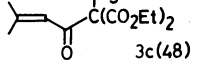
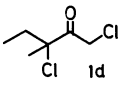
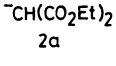
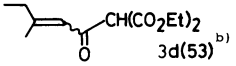
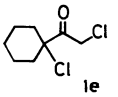
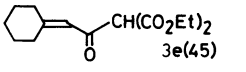
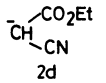
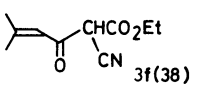
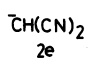
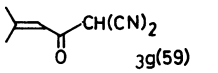


Scheme 1.



Scheme 2.

Table 1. Synthesis of Conjugated Enone Derivatives

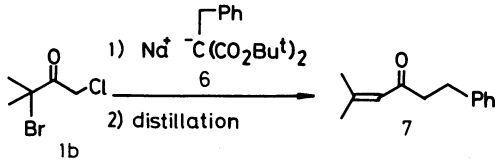
Dihalo ketone	Enolate anion[a]	Product (Yield/%)
 1a	 2b	 3b(42)
 1b	 2c	 3c(48)
 1d	 2a	 3d(53)[b]
 1e	2a	 3e(45)
1a	 2d	 3f(38)
1b	 2e	 3g(59)

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 Kugelrohrofen at the pressure and the oven temperature indicated. IR spectra were taken on a JASCO A-102 spectrometer. ^{1}H NMR spectra were measured with a JEOL JNM PMX60-SI spectrometer. Both ^{1}H 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 PF_{254}).

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}; ^{1}H 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}; ^{1}H NMR (CCl_4) δ=1.25 (1.8 H, t, J=7Hz), 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 $CH(CO_2Et)_2$], 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}; ^{1}H 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 $C_{12}H_{19}O_5Br$: 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}; ^{1}H 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 $C_{16}H_{26}O_5$: 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}; ^{1}H 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 $C_{13}H_{20}O_5$: 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}; ^{1}H 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 $C_{13}H_{20}O_5$: 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}; ^{1}H 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 $CH(CO_2Et)_2$], 5.94 (1H, s), 13.42 (0.55H, br s, enol OH). Found: C, 63.72; H, 8.03%. Calcd for $C_{15}H_{22}O_5$: 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}; ^{1}H 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 $C_{10}H_{13}O_3N$: 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}; ^{1}H 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 $C_8H_8ON_2$: 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 benzylmalonate[10] (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}; ^{1}H 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 $C_{13}H_{16}O$: C, 82.94; H, 8.57%.

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