The Favorskii-type Rearrangement of 3-Bromo-β-ionone with Sodium Ethoxide

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Synopsis. The reaction of 3-bromo-β-ionone with sodium ethoxide afforded ethyl 4-(2,6,6-trimethyl-2-cyclohexenylidene)butyrate by a Favorskii-type rearrangement, accompanied by double-bond migration, while with sodium phenoxide or diethyl amine, substitution products were primarily obtained.

In the course of studies of the nucleophilic substitution of 3-bromo-β-ionone (**1**) with the sodiomalonic ester, we have found that the major product thus obtained was an ester with a loss of ketone carbonyl. The preparation of esters from α-halo ketones by the action of bases is known as the Favorskii rearrangement,[1] but there have been no reports on the rearrangement of halo ketones having the halogen atom separated from the carbonyl group by conjugated double bonds. For examining this new type of Favorskii rearrangement in more detail, we conducted the reaction of **1** with several kinds of bases and discussed the reaction mechanism.

The reaction of **1** with sodium ethoxide gave a straight chain ester and 3-ethoxy-β-ionone in the ratio of *ca.* 10:1 (Table 1, Exptl No. 1). The same ester was also obtained when **1** was subjected to the usual conditions of malonic-ester synthesis in ethanol (No. 4), while the reactions with diethyl sodiomalonate in tetrahydrofuran (No. 3), phenoxide (No. 5), or diethyl amine (No. 6) in ethanol gave only substitution products. The UV and ^{1}H-NMR spectra of the ester indicated that the double bond conjugated to the carbonyl group no longer exists; the IR spectrum also indicated the disappearance of the *trans*-double bond, and other analytical results identified the structure of the ester (**8**).

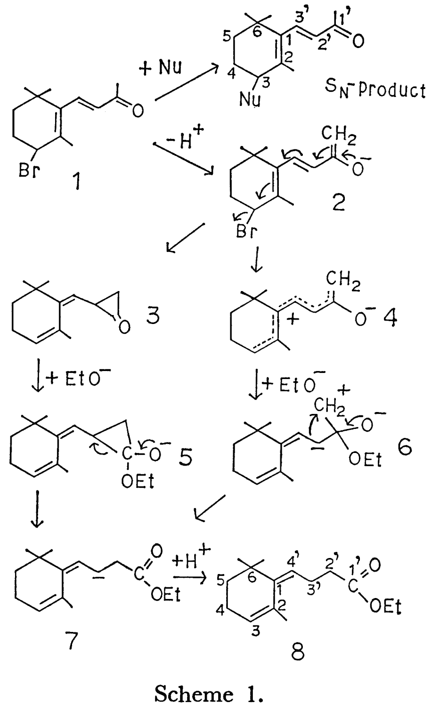
The initial step of the Favorskii rearrangement of α-halo ketones with bases was considered to be a proton abstraction; the resulting enolate anion induces the production of a cyclopropanone or a zwitterion to form a commonly α-branched ester.[2] This suggests that the enolate anion (**2**) might undergo the ejection of bromine with concerted or subsequent double-bond migration by an internal S_N2'-type displacement.[3] The opening of the cyclopropanone ring (**3**) or rearrangement of the zwitterion (**4**) by the attack of the ethoxide ions should give a more stable carbanion. The carbanion in **7** is more stable than the α-branched methylide intermediate because of the resonance stabilization with conjugated double bonds as well as its secondary character, thereby leading to ethyl 4-(2,6,6-trimethyl-2-cyclohexenylidene)butyrate (**8**) as the principal product.

The rate of nucleophilic substitution might be slow at the 3-position of the ring with a boat conformation due to the steric hindrance by the 2,6,6-trimethyl groups, whereas the rearrangement by the removal of enolic hydrogen is facilitated by the presence of the conjugated double bonds at the α-position. Thus, sodium ethoxide in even a minor amount may remove the enolic hydrogen to give the rearrangement intermediate in spite of the unfavorable equilibrium between sodium ethoxide and diethyl sodiomalonate in ethanol; the resulting intermediate (**3** or **4**) might be very unstable and might react easily with excess ethanol as the solvent to form the ethyl ester. The acidity of the enol-tautomer in **1** might not be so large as those of acyclic α-halo ketones[4] and α-haloarylalkyl ketones;[5] therefore, the formation of the enolate anion did not occur with weak bases, but substitution products were primarily formed.

Table 1. The reaction of 3-bromo-β-ionone with nucleophiles

Exptl No.	Nucleophile[a)]	Solvent	Reaction product: Rearrangement	Reaction product: Substitution
1	EtONa	EtOH	81%	8%
2	EtONa[b)]	EtOH	72	16
3	$NaCH(COOEt)_2$	THF	0	82
4	$NaCH(COOEt)_2$	EtOH	52	32[c)]
5	PhONa	EtOH	0	87
6	Et_2NH	EtOH	0	88

a) Two equivalents for 3-bromo-β-ionone. b) Equimolar amount. c) Substitution product with diethyl sodiomalonate.



Scheme 1.

Experimental

The infrared, ultraviolet, ^{1}H-NMR, ^{13}C-NMR, and mass spectra were obtained using Hitachi 215, Hitachi 200-10, JEOL-PMX 60, JEOL-FX 90Q, and Hitachi RMU-6MG spectrometers respectively. Elemental analyses were conducted using a Perkin Elmer 250 instrument.

3-Bromo-*β*-ionone(**1**) was prepared with *β*-ionone and *N*-bromosuccinimide in carbon tetrachloride.[6] Since the brominated compound was presumed to be unstable, the crude product after the filtration of succinimide was used for the next process without purification.[7] ^{1}H-NMR(CCl$_4$): δ=1.08(s, 6-Me$_2$), 1.62(m, 5-H$_2$), 1.85(s, 2-Me), 2.13(d, J=6 Hz, 4-H$_2$), 2.20(s, 1′-Me), 4.61(br s, 3-H), 6.05(d, J=16 Hz, 2′-H), 7.15(d, J=17 Hz, 3′-H).

Ethyl 4-(2,6,6-Trimethyl-2-cyclohexenylidene)butyrate (8): A solution of **1** (4.2 g, 15.6 mmol) in carbon tetrachloride (8 ml) was added to freshly prepared ethanolic sodium ethoxide (31.2 mmol in 40 ml) at room temperature. The mixture was stirred overnight and then poured into water (100 ml). The product was extracted with ether and the organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give an orange oil. It was chromatographed over a silica-gel column (Wako C-300) with ether in hexane (2% v/v) to give **8** in an 81% yield based on **1**. Bp 110—112 °C/0.7 mmHg. UV$_{\mathrm{max}}$(CHCl$_3$): 242 nm. IR(CHCl$_3$): 1725 cm^{-1} (ester). ^{1}H-NMR(CDCl$_3$): δ=1.01 (s, 6H, 6-Me$_2$), 1.33 (t, J=8 Hz, ester-CH$_3$), 1.2—1.6 (m, 5-H$_2$), 1.9—2.1 (m, 4-H$_2$), 2.03 (s, 2-Me)), 2.2—2.6 (m, 4H, 2′-H$_2$, 3′-H$_2$), 4.21 (q, 2H, J=7 Hz, ester-CH$_2$), 5.25 (t, 1H, J=5 Hz), 5.55 (t, 1H). ^{13}C-NMR(CDCl$_3$): δ=14.1(ester-CH$_3$), 23.6 (2-Me), 24.4 (3′), 27.5 (6-Me$_2$), 27.9 (6), 35.3(4), 35.4(2′), 37.0(5), 60.0 (ester-CH$_2$), 120.4(3), 127.9(4′), 131.6(2), 145.2(1), 172.9 (1′). MS, *m/e*(rel intensity): 236 (M$^+$, 18.7), 88 (100). Found: C, 75.62; H, 10.20%. Calcd for C$_{15}$H$_{24}$O$_2$: C, 76.21; H, 10.24%.

Malonic Ester Synthesis Applied to 1 in Ethanol: Diethyl sodiomalonate was prepared with diethyl malonate (37.4 mmol) and sodium ethoxide (31.2 mmol) in ethanol (50 ml) at 55 °C for 30 min. The reaction conditions were similar to those used for **8**. The reaction product was chromatographed over a silica-gel column with ether in hexane (2%) to give **8** in a 52% yield, subsequent elution with ether in hexane (50%) gave 3-[bis(ethoxycarbonyl)methyl]-*β*-ionone in a 32% yield. UV$_{\mathrm{max}}$(CHCl$_3$): 291 nm. IR (CHCl$_3$): 1725(ester), 1660(ketone), 970(CH:CH) cm^{-1}. ^{1}H-NMR(CDCl$_3$): δ=1.05 (s, 6H, 6-Me$_2$), 1.28 (t, 6H, J=7 Hz, ester-CH$_3$), 1.7—2.0 (m, 4,5-H$_2$, 3-H), 1.74(s, 2-Me), 2.2(s, 3H, 1′-Me), 3.78(d, 1H, J=5 Hz, 3-CH), 4.23(q, 4H, J=7 Hz, ester-CH$_2$), 6.10(d, 1H, J=17 Hz, 2′-H), 7.31(d, 1H, J=17 Hz, 3′-H). ^{13}C-NMR(CDCl$_3$): δ=13.9 (ester-CH$_3$), 19.8(4), 21.7(2-Me), 26.9(1′-Me), 27.9, 28.8(6-Me$_2$), 34.3(6), 37.0(3), 41.4(5), 53.7(3-CH), 60.9, 61.1(ester-CH$_2$), 131.9(2), 133.0(3′), 139.6(1), 143.2(2′), 168.0, 168.8(ester C=O), 197.9(1′). MS, *m/e*: 350(M$^+$, 3), 55(100). Found: C, 69.00; H, 8.75%. Calcd for C$_{20}$H$_{30}$O$_5$: C, 68.54; H, 8.62%.

Nucleophilic Substitution with Sodium Phenoxide: A mixture of **1** (15.6 mmol) and sodium phenoxide (32 mmol) in ethanol (30 ml) was stirred overnight at room temperature and then poured into a cold 5% aqueous sodium hydroxide solution. The reaction product was extracted with ether, and the organic layer was washed with a 2% aqueous sodium hydroxide solution and water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Subsequent silica gel chromatography afforded 3-phenoxy-*β*-ionone (hexane–ether, 9:1) in an 87% yield. UV$_{\mathrm{max}}$(CHCl$_3$): 285, 275$^{\mathrm{sh}}$ nm. IR(CHCl$_3$): 1660(ketone), 995(phenoxy), 970(CH:CH) cm^{-1}. ^{1}H-NMR(CDCl$_3$): δ=4.48(t, 1H, 3-H), 6.17(d, 1H, J=17 Hz, 2′-H), 6.9—7.7(m, 6H, phenyl, 3′-H). ^{13}C-NMR (CDCl$_3$): δ=18.8(4), 24.1(2-Me), 27.1, 27.4(6-Me$_2$), 28.8 (1′-Me), 34.5(5), 34.6(6), 75.7(3), 116, 121.0, 129.5(*o*-, *p*-, and *m*-phenyl carbon), 131.3(2), 133.2(3′), 140.9(1), 142.3 (2′), 158.5 (3-O-C), 198.0(1′). MS, *m/e*: 284(M$^+$, 2.9), 191(100). Found: C, 79.87; H, 8.56%. Calcd for C$_{19}$H$_{24}$O$_2$: C, 80.24; H, 8.50%.

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7) The purity was checked by ^{1}H-NMR.