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Rections of 2-Benzoyl-3-chloro-2-cyclohexen-1-ones with Some Organometallic Compounds

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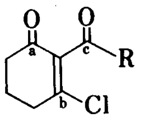
1,2-Addition of organometallic compounds to the C-1 position of 2-benzoyl-3-chloro-2-cyclohexen-1-one is described.

Keywords——organolithium compound; Grignard reagent; 1,2-addition reaction; active site; reactivity of β-diacylvinyl chloride; geometrical isomers; shift reagent

The fact that 2-acyl-3-chloro-2-cyclohexen-1-ones **1a, b** formally have three active sites (sites a, b, and c) toward nucleophiles is of interest. The reactions of 2-acetyl-3-chloro-2-cyclohexen-1-one (**1a**) have been studied extensively by Russian chemists; for instance, the enone **1a** reacted with some weak bases such as CN anion[1] and amines[2] to give the site b substituted compound, with hydride ion[3] to give the site a and c attacked compound, and with strong bases such as carbanions to give complex mixtures.[1] We have studied the reactivity of the 2-benzoyl analog **1b** with amines,[4] stabilized carbanions of active methylene compounds,[5] and carbonyl reagents such as hydroxyamine.[6] All these reactions gave the site b substituted compounds **2** and **3** except for the reaction with the carbonyl reagent. We have now found



1a : $R=CH_3$
1b : $R=C_6H_5$

Fig. 1

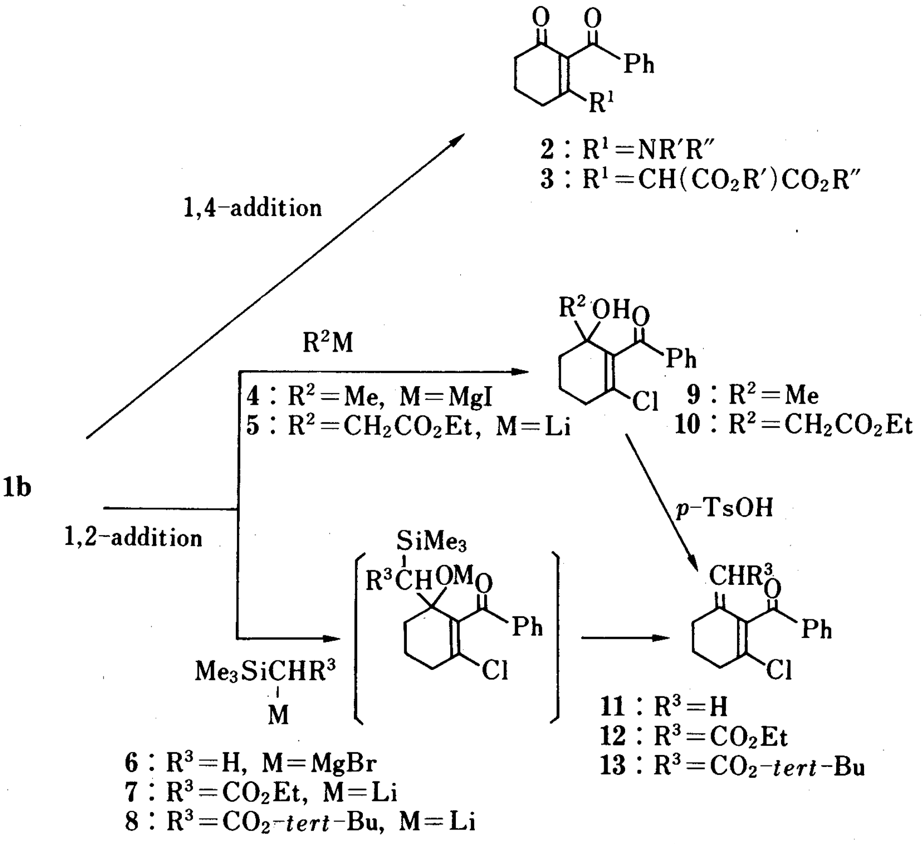
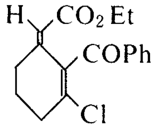
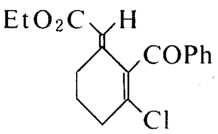
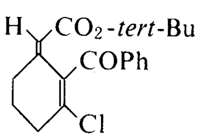
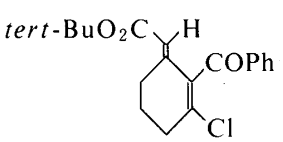


Chart 1

that the organometallic compounds **4**—**8** react with **lb** to give the site a attacked products (**9**—**13**) selectively; these are the first examples of 1,2-addition (site a attack) of carbanions to **1.**

TABLE I. Spectral Data for Geometrical Isomers (*Z* and *E*) of **12** and **13**

Compd. No.	Structure	IR $\nu_{\max}^{CHCl_3}$ cm^{-1}	UV $\lambda_{\max}^{EtOH}$ cm^{-1}	MS *m/z*
12*Z*		1710, 1670, 1620 1270, 1165	260	304(M^+), 259 231(100), 199 195, 171
12*E*		1700, 1670, 1605 1295, 1170	260	304(M^+), 259 231(100), 199 195, 171
13*Z*		1715, 1675, 1630 1605	260	332(M^+), 259 231(100), 195 171, 105
13*E*		1705, 1680, 1620 1610	260	332(M^+), 259 231(100), 195 171, 105

Compd. No.	NMR δ ppm (in $CDCl_3$)	NMR Eu $(fod)_3$[a)]
12*Z*	1.00(3H, t, $J=6.5$ Hz, $OCH_2C\underline{H}_3$)	1.64(3H, t)
	1.8—2.2(2H, m, 5-CH_2)	1.85—2.2(2H, m)
	2.51(2H, m, 6-CH_2)	3.29(2H, m)
	2.70(2H, t, $J=6$ Hz, 4-CH_2)	3.03(2H, t)
	3.78(2H, q, $J=6.5$ Hz, $OC\underline{H}_2CH_3$)	5.31(2H, q)
	5.69(1H, br s, CH=)	8.09(1H, br s, CH=)
	7.3—7.95(5H, m, ArH)	8.0—10.2(5H, m, ArH)
12*E*	1.19(3H, t, $J=6.5$ Hz, $OCH_2C\underline{H}_3$)	1.88(3H, t)
	1.8—2.2(2H, m, 5-CH_2)	1.95—2.35(2H, m)
	2.67(2H, t, $J=6$ Hz, 4-CH_2)	2.86(2H, t)
	3.12(2H, td, $J=6$ and 2 Hz, 6-CH_2)	5.32(2H, td)
	4.09(2H, q, $J=6.5$ Hz, $OC\underline{H}_2CH_3$)	6.62(2H, q)
	5.33(1H, br s, CH=)	7.67(1H, br s)
	7.35—8.0(5H, m, ArH)	7.55—8.6(5H, m)
13*Z*	1.22(9H, s, *tert*-Bu)	1.80(9H, s)
	1.8—2.15(2H, m, 5-CH_2)	1.8—2.15(2H, m)
	2.47(2H, td, $J=6$ and 2 Hz, 6-CH_2)	3.0(4H, br t)
	2.69(2H, t, $J=6.5$ Hz, 4-CH_2)	7.49(1H, br s)
	5.64(1H, br s, CH=)	7.85—9.95(5H, m)
	7.25—7.95(5H, m, ArH)	
13*E*	1.40(9H, s, *tert*-Bu)	1.87(9H, s)
	1.75—2.15(2H, m, 5-CH_2)	1.85—2.25(2H, m)
	2.66(2H, t, $J=6.5$ Hz, 4-CH_2)	2.78(2H, t)
	3.11(2H, td, $J=6$ and 2 Hz, 6-CH_2)	4.0(2H, td)
	5.31(1H, br s, CH=)	6.47(1H, br s)
	7.25—8.0(5H, m, ArH)	7.4—8.35(5H, m)

a) The chemical shifts after addition of 25 mg of Eu$(fod)_3$ are given and all proton signals of these diene isomers were followed by addition of Eu$(fod)_3$ in 5 mg portions.

Treatment of an ether solution of 2-benzoyl-3-chloro-2-cyclohexen-1-one (**1b**)[7] with methylmagnesium iodide (**4**) at 0°C for 1 h provided a 70% yield of the 1,2-addition product **9**. The structure was assigned on the basis of spectral data, mainly from a consideration of the nuclear magnetic resonance (^{1}H-NMR) spectra. The C-6 methylene protons at δ 2.85, ascribed to CH_2CO, shifted to higher field (δ 1.86), ascribed to $CH_2C(CH_3)OH$, after treatment of **1b** with methylmagnesium iodide. Similarly, the lithiated ester (**5**), generated from the reaction of ethyl acetate and lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, reacted with **1b** to give a 50% yield of the 1,2-addition product **10**.

In the case of the organometallic compounds (**6**—**8**) bearing an α-trimethylsilyl group, the silyl-Wittig olefination reaction,[8] which involves an initial 1,2-addition to a carbonyl group, occurred at site a to give the diene derivatives (**11**—**13**) in moderate yields. Thus, trimethylsilylmethylmagnesium bromide (**6**)[9] reacted with **1b** at 0° C for 0.5 h to give the diene **11**. Similarly, the lithiated ester **7**, generated from ethyl trimethylsilylacetate and LDA, reacted with **lb** at −78 °C (15 min) to give a moderate yield of two isomeric dienes, which were separated by column chromatography on silica gel. These products were tentatively assigned as geometrical isomers (**12***Z* and **12***E*) on the basis of the spectral evidence, and this was confirmed by direct comparison of the dienes with authentic samples obtained by the thermal dehydration of **10** in the presence of *p*-TsOH or titanium tetrachloride ($TiCl_4$). The assignmet of these geometrical isomers (**12***Z* and **12***E*) was based on the assumption that the NMR signals due to the C-6 methylene protons of the *E*-isomer should be affected more strongly than those of the *Z*-isomer by addition of a shift reagent, Eu(fod)$_3$, because theethoxycarbonyl group of the *E*-isomer is close to the C-6 methylene protons. The lithiated ester **8**, generated from *tert*-butyl trimethylsilylacetate and LDA, also reacted with **lb** at −78° C (15 min) to give a mixture of the dienes, which were separated by column chromatography on silica gel and assigned as the isomeric dienes (**13***Z* and **13***E*) on the basis of a similar NMR study using Eu(fod)$_3$. The spectral data for these dienes (**12***Z*, **12***E*, **13***Z*, and **13***E*) are summarized in Table I.

The present active carbanions **4**—**8** selectively underwent 1,2-addition (site a attack) to **1b**, although stabilized carbanios gave the 1,4-addition (site b attack)-elimination products.[5] It is likely that the active carbanions react with **lb** at low temperature to give the kinetically controlled products by analogy with the mechanism[10] proposed for the reaction of cyclohex-2-enones with active carbanions at low temperature.

Experimental

All melting points are uncorrected. The infrared (IR) absorption spectra were recorded on a Shimadzu IR-27G spectrometer, and NMR spectra on a Hitachi R-20A (60 MHz) or a Hitachi R-22 (90 MHz) spectrometer (with tetramethylsilane as an internal standard). Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument with a direct inlet system at 70 ev.

Reaction of 2-Benzoyl-3-chloro-2-cyclohexen-1-one (1b) with Methylmagnesium Iodide (4)——A solution of MeMgI (**4**) (2.5 M, 0.2 ml, 0.5 mmol) in ether was added dropwise under argon to a solution of **lb** (65 mg, 0.27 mmol) in ether (8 ml) cooled to 0 °C. The reaction mixture was stirred for 1 h under the same conditions, then partitioned between 10% hydrochloric acid and ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrted *in vacuo*. The residue was subjected to column chromatography on alumina (with chloroform as the eluting solvent) to give a 70% yield (48 mg) of **9** as a syrup; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655, 1640, 1595, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.29 (3H, s, CH_3), 1.5—1.7 (2H, m, CH_2), 1.86 (2H, t, J=7.5 Hz, CH_2), 2.52 (2H, t, J=7 Hz, CH_2), 3.13 (1H, s, OH), 7.7—8.0 (5H, m, ArH). Exact mass calcd for $C_{14}H_{15}ClO_2$: 250.0760. Found: 250.0765.

Reaction of lb with Ethyl Lithioacetate (5)——A solution of *n*-BuLi (1.6 N, 3.2 ml, 5 mmol) was added dropwise under argon to a stirred solution of dry diisopropylamine (0.5 g, 5 mmol) in THF (5 ml) cooled to −78°C. The mixture was stirred for 0.5 h under the same conditions, then used as a THF solution of LDA. Ethyl acetate (446 mg, 5.0 mmol) was added dropwise to the solution of LDA over a few minutes and a solution of **1b** (1.1 g, 4.6 mmol) in THF (4 ml) was then added to the mixture. The whole was stirred at −78°C for 15 min, allowed to warm to room temperature, and stirred overnight. The reaction mixture was quenched with water, then partitioned between 10% hydrochloric acid and ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was subjected to column chromatography on alumina (with chloroform as the eluting solvent) to give a 50% yield of **10** as a syrup. *Anal.* Calcd for $C_{17}H_{19}ClO_4$: C, 63.26; H, 5.93. Found: C, 63.22; H, 5.94. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1695, 1655. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.15 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.7—2.2 (4H, m, $CH_2\times2$), 2.3—2.7 (2H, m, CH_2), 2.63 (1H, d, J=16 Hz, $CH_2\times1/2$), 2.90 (1H, d, J=16 Hz, $CH_2\times1/2$), 4.04 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.48 (1H, s, OH), 7.3—8.2 (5H, m, ArH). MS *m/e*: 324 (M2), 322 (M^+).

Reaction of Ib with Trimethylsilylmethylmagnesium Bromide (6)———A solution of trimethylsilylmethylmagnesium bromide (**6**) (0.7 M, 5 ml, 3.5 mmol) in ether was added dropwise over 5 min to a stirred solution of **Ib** (800 mg, 3.43 mmol) in ether (5 ml) cooled to 0 °C under argon. The reaction mixture was stirred for 0.5 h under the same conditions, allowed to warm to room temperature, and partitioned between 10% hydrochloric acid and ether. The organic layer was washed with brine, dried ($MgSO_4$),and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (with benzene as the eluting solvent) to give a 23% yield (181 mg) of **11** as a syrup; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670, 1625, 1595, 1580. ^{1}H-NMR (10% solution in $CDCl_3$) δ: 1.6—2.2 (2H, m, CH_2), 2.3—2.8 (4H, m, $CH_2\times2$), 4.58 (1H, br s, $CH_2\times1/2$), δ: 4.87 (1H, br s, $=CH_2\times1/2$), 7.3—8.1 (5H, m, ArH). Exact mass calcd for $C_{14}H_{13}ClO$: 232.0653. Found: 232.0643.

Reaction of Ib with Ethhyl Lithiotrimethylsilylacetate (7)———A solution of *n*-BuLi (1.6 N, 6.3 ml, 10 mmol) was added dropwise under argon to a stirred solution of dry diisopropylamine (1.0 g, 10 mmol) in THF (10 ml) cooled to −78 °C. The mixture was stirred for 15 min under the same conditions, and ethyl trimethylsilylacetate (1.6 g, 10 mmol) was added dropwise over 10 min, then a slution of **1b** (1.93 g, 8.2 mmol) in THF (5 ml) was further added. The reaction mixture was stirred for 15 min under the same conditions, allowed to warm to room temperature, quenched with water, and partitioned between 10% hydrochloric acid and ether. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (with benzene as the eluting solvent) to give the *E*-isomer (**12*E***) and *Z*-isomer (**12*E***) in 28% (703 mg) and 17% (425 mg) yields, respectively. **12*E***: syrup. *Anal.* Calcd for $C_{17}H_{17}ClO_3$: C, 67.00; H, 5.62; Cl, 11.63. Found: C, 66.62; H, 5.53; Cl, 11.73. Exact mass calcd. for $C_{17}H_{17}ClO_3$: 304.0866. Found: 304.0867. **12*Z***: syrup. *Anal.* Calcd for $C_{17}H_{17}ClO_3$: C, 67.00; H, 5.62; Cl, 11.63. Found: C, 66.91; H, 5.51; Cl, 12.07. Exact mass calcd for $C_{17}H_{17}ClO_3$: 304.0865. Found: 304.0865.

Thermal Dehydration of 10 to 12*E* and 12*Z*———i) With *p*-TsOH: A solution of **10** (80 mg, 0.25 mmol) and *p*-TsOH (40 mg, 0.23 mmol) in benzene (15 ml) was heated under reflux for 30 min and the mixture was partitioned between benzene (20 ml) and water (5 ml). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (with denzene: ethyl acetate 9: 1 as the eluting solvent) to give **12*E*** and **12*Z*** in 48% and 47% yields, respectively. These products were identical with authentic specimens obtained from the reaction of **Ib** and **7**.

ii) with $TiCl_4$: A solution of $TiCl_4$ (540 mg, 2.84 mmol) in CH_2Cl_2 (2 ml) was added dropwise over 5 min to a cooled and stirred mixture of MeOH (34 mg, 1.07 mmol), acetone (94 mg, 1.63 mmol), H_2O (20 mg, 1.07 mmol) and CH_2Cl_2 (2 ml). Stirring for a few minutes at 0 °C gave a clean yellow solution. A solution of **10** (231 mg, 0.71 mmol) in CH_2Cl_2 (3 ml) was added dropwise to the reaction mixture at room temperature over 15 min and stirring was continued for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between benzene (100 ml) and water (20 ml). Work-up as described above gave a 1: 1 mixture of **12*E*** and **12*Z*** in 74% yield (160 mg). These products were identical with the samples obtained by the thermolysis of **10** in the presence of *p*-TsOH.

Reaction of Ib with *tert*-Butyl Lithiotrimethylsilylacetate (8)———A solution of *n*-BuLi (1.6 N, 6.3 ml, 10 mmol) was added dropwise under argon to a stirred solution of dry diisopropylamine (1.0 g, 10 mmol) in THF (10 ml) cooled to −78°C. The mixture was stirred for 15 min under the same conditions, and *tert*-butyl trimethylsilylacetate (1.88 g, 10 mmol) was added dropwise over 10 min, then a solution of **Ib** (1.8 g, 7.6 mmol) in THF (4 ml) was added. Work-up as described for the reaction of **Ib** with **7** gave **13*E*** and **13*Z*** in 6% (160 mg) and 27% yields (680 mg), respectively. **13*E***: syrup. Exact mass calcd for $C_{19}H_{21}ClO_3$: 332.1179. Found: 332.1180. **13*Z***: mp 102—104°C (from MeOH). *Anal.* Calcd for $C_{19}H_{21}ClO_3$: C, 68.56; H, 6.36. Found: C, 68.34; H, 6.31. Exact mass calcd for $C_{19}H_{21}ClO_3$: 332.1178. Found: 332.1178.

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