Favorskii-Type Rearrangement of α,α'-Dihalo Ketones Induced by Enolates of (Diethoxyphosphinyl)acetic Esters and Its Application to the Synthesis of α,α'-Divinyl Ketones

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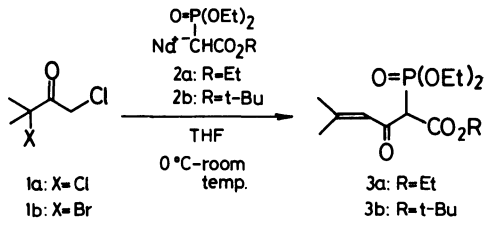
Synopsis. A Favorskii-type rearrangement of 1,3-dihalo-3-methyl-2-butanone with enolate of ethyl (diethoxyphosphinyl)acetate or *t*-butyl (diethoxyphosphinyl)acetate gave ethyl 2-(diethoxyphosphinyl)-5-methyl-3-oxo-4-hexenoate (**3a**) or its *t*-butyl ester (**3b**). Compound **3b** was applied to the preparation of (*E*)-5-methyl-1-(*p*-tolyl)-1,4-hexadien-3-one and diethyl (4-methyl-2-oxo-3-pentenyl)phosphonate, which are the important intermediates for natural product syntheses.

Recently, we have made considerable efforts[1a-d] to extend the base of the Favorskii rearrangement[2] to carbanions such as enolates of malonic ester and (phenylsulfonyl)acetic ester. In a preceding paper,[1d] we reported that sodium enolates of β-keto esters reacted with 1,3-dihalo-3-methyl-2-butanone to give dihydro-4-pyrone derivatives via the Favorskii-type rearrangement. In this paper, we elucidate that the reaction is adaptable to enolates of (diethoxyphosphinyl)acetic esters, giving α-(diethoxyphosphinyl) β-keto esters (**3a,b**) in good yields. Products having a phosphinyl-functionality were utilized for the preparation of α,α'-divinyl ketones.

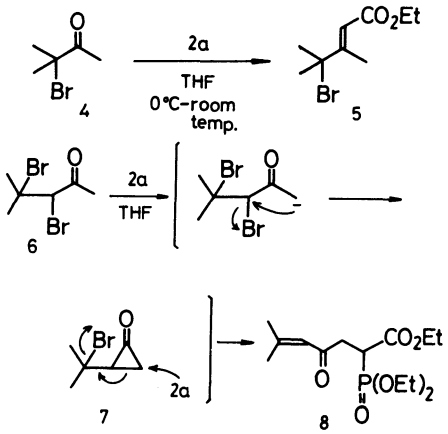
A reaction of 1,3-dichloro-3-methyl-2-butanone (**1a**) with sodium enolate of ethyl (diethoxyphosphinyl)-acetate (**2a**) in THF at room temperature gave ethyl 2-(diethoxyphosphinyl)-5-methyl-3-oxo-4-hexenoate (**3a**) in 42% yield (Scheme 1). The yield was improved up to 79% by using 3-bromo-1-chloro-3-methyl-2-butanone (**1b**). The *t*-butyl ester **3b** was similarly obtained in 36% yield from **1a** or in 81% yield from **1b**. The reaction can be explained in parallel with that described previously.[1d]



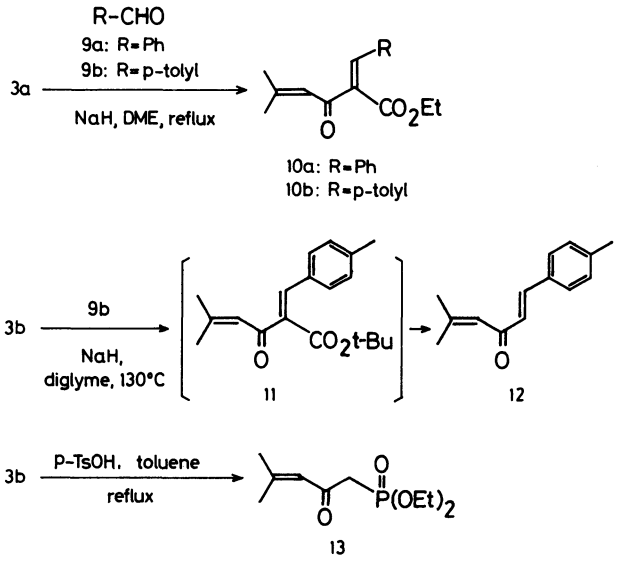
Scheme 1.

Attempts to apply the above reaction to 3-bromo-3-methyl-2-butanone (**4**) and 3,4-dibromo-4-methyl-2-pentanone (**6**) resulted in giving **5** (43% yield) and **8** (41% yield), respectively (Scheme 2). The formation of **8** suggests to us that the enolate **2a** may attack C-3 methylene carbon, instead of the carbonyl carbon, of the cyclopropanone intermediate **7**, which is produced under the basic conditions in a manner similar to the conventional Favorskii rearrangement.[2] It is interesting that the mode of the ring cleavage[3] of **7** is in marked contrast to that of the Favorskii rearrangement although a further investigation is required to confirm the mechanism.

The Horner–Wadmorth–Emmons reaction of sodium



Scheme 2.



Scheme 3.

enolate derived from **3a** with benzaldehyde (**9a**) was carried out in refluxing 1,2-dimethoxyethane (DME), giving α-benzylidenation product **10a** in 31% yield[4] (Scheme 3). A similar reaction with *p*-tolualdehyde (**9b**) gave **10b** in only 17% yield.[4] On the other hand, sodium enolate derived from **3b** was allowed to react with aldehyde **9b** at an elevated temperature (130 °C) in diglyme to give (*E*)-5-methyl-1-(*p*-tolyl)-1,4-hexadien-3-one (**12**) in 47% yield. In this case, deesterification of **11** may have occurred thermally[5] in the course of the reaction. Furthermore, the treatment of **3b** with a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene gave (4-methyl-2-oxo-3-pentenyl)-phosphonate (**13**) in 78% yield. Compounds **12** and **13** are the important intermediates for the syntheses of *ar*-turmerone[1d,6] and related sesquiterpenes.[7]

Experimental

IR spectra were taken on a JASCO Model A-102 spectrometer. ^{1}H NMR spectra (60 MHz) were measured with a JEOL Model JNM-60 SI spectrometer by using Me_4Si as an internal standard. Preparative TLC was carried out on silica gel (Kieselgel 60 PF_{254}, Merck A. G. Darmstadt).

Materials: 1,3-Dichloro-3-methyl-2-butanone (**1a**)[8] was prepared by chlorination of 3-methyl-2-butanone with 2.4 equiv of sulfuryl chloride. 3-Bromo-3-methyl-2-butanone (**4**)[9] was prepared by bromination of the starting ketone with *N*-bromosuccinimide. 3-Bromo-1-chloro-3-methyl-2-butanone (**1b**)[10] was obtained by chlorination of **4** with sulfuryl chloride. (Diethoxyphosphinyl)acetates **2a**[11] and **2b**[12] were prepared by the reported procedures.

Ethyl 2-(Diethoxyphosphinyl)-5-methyl-3-oxo-4-hexenoate (3a). To a suspension of NaH (48 mg, 2 mmol) in THF (6 ml) was added a solution of ethyl (diethoxyphosphinyl)-acetate (448 mg, 2 mmol) in THF (2 ml); stirring was continued at room temperature for 2 h. To this was added **1b** (199 mg, 1 mmol) with stirring during an additional 48 h at room temperature. The mixture was poured into water and acidified with 10% HCl. The organic layer was extracted with ether, washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC on silica gel (hexane–acetone, 3:1) to give 242 mg (79%) of **3a**: IR (neat) 1740, 1693, 1620, and 1555 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.32 (9H, t, *J*=7 Hz), 1.96 (3H, d, *J*=1.5 Hz), 2.14 (3H, d, *J*=1.2 Hz), 3.74—4.36 (6.77H, m), 6.32 (0.77H, m), 6.79 (0.23H, m), 14.65 (0.23H, br s, enol OH). Found: C, 50.87; H, 7.64%. Calcd for $C_{13}H_{23}O_6P$: C, 50.98; H, 7.57%.

A similar reaction of **1a** with **2a** gave **3a** in 42% yield.

***t*-Butyl 2-(Diethoxyphosphinyl)-5-methyl-3-oxo-4-hexenoate (3b).** A similar reaction of **1a** and **1b** with sodium enolate of *t*-butyl (diethoxyphosphinyl)acetate (**2b**) gave **3b** in 36% and 81% yields, respectively. **3b**: IR (neat) 1730, 1690, 1620, and 1555 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.31 (6H, t, *J*=7 Hz), 1.45 (9H, s), 1.93 (3H, br s), 2.09 (3H, br s), 3.67—4.36 (4.8H, m), 6.30 (0.2H, m), 6.73 (0.8H, m), 13.90 (0.2H, br s, enol OH). Found: C, 53.97; H. 8.06%. Calcd for $C_{15}H_{27}O_6P$: C, 53.89; H, 8.18%.

Ethyl (*E*)-4-Bromo-3,4-dimethyl-2-pentenoate (5):[13] 43% yield after purification by column chromatography (hexane–ether, 30:1); IR (neat) 1725 and 1640 cm^{-1}, ^{1}H NMR (CCl_4) δ=1.28 (3H, t, *J*=7 Hz), 1.93 (6H, s), 2.36 (3H, s), 4.11 (2H, q, *J*=7 Hz), 5.85 (1H, m).

Ethyl 2-(Diethoxyphosphinyl)-6-methyl-4-oxo-5-heptenoate (8). To a mixture of mesityl oxide (98.1 mg, 1.0 mmol), $NaHCO_3$ (35 mg, 0.42 mmol), and ether (1 ml), was added bromine (159 mg, 1.0 mmol) dropwise; the mixture was stirred for 2 h. The resulting ether solution of 3,4-dibromo-4-methyl-2-pentanone (**6**)[14] was slowly introduced to a suspension of **2a** which was prepared from ethyl (diethoxyphosphinyl)acetate (448 mg, 2.0 mmol) and NaH (48 mg, 2 mmol) in THF (2 ml) in a manner similar to that described above. After being stirred for 21 h at room temperature, the usual work up of the mixture gave 128 mg (41%) of **8** after purification by preparative TLC (hexane–acetone, 4:1; twice development, R_f=0.16—0.26). **8**: IR (neat) 1740, 1695, and 1625 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.28, 1.30, 1.32 (each with 3H, t, *J*=7 Hz), 1.88 (3H, br s), 2.10 (3H, br s), 2.7—3.7 (3H, m), 4.13 (6H, q, *J*=7 Hz), 6.02 (1H, m). Found: C, 52.43; H, 7.93%. Calcd for $C_{14}H_{25}O_6P$: C, 52.50; H, 7.87%.

Ethyl 2-Benzylidene-5-methyl-3-oxo-4-hexenoate (10a). To a suspension of NaH (72 mg, 3 mmol) in DME (3 ml) was added a solution of ester **3a** (918 mg, 3 mmol) and benzaldehyde (**9a**) (501 mg, 3.6 mmol) in DME (4 ml). The mixture was stirred for 1 h at room temperature and then for an additional 3 h under reflux. It was poured into water and acidified with 10% HCl. The organic layer was extracted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was purified by preparative TLC (hexane–acetone, 3:1) to give 240 mg (31%) of **10a**: IR (neat) 1720, 1705, 1672, and 1618 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.30 (3H, t, *J*=7 Hz), 1.84 (2.2H, br s), 1.95 (0.8H, br s), 2.17 (3H, br s), 4.20 (2H, q, *J*=7 Hz), 5.92 (0.7H, m), 6.20 (0.3H, m), 7.26 (5H, m), 7.40 (0.3H, s), 7.47 (0.7H, s). Found: C, 74.46; H, 6.94%. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02%.

Ethyl 5-Methyl-3-oxo-2-(*p*-tolylmethylene)-4-hexenoate (10b). A similar reaction of **3a** with *p*-tolualdehyde (**9b**) gave **10b** (17%): IR (neat) 1719, 1670, and 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.27 (3H, t, *J*=7 Hz), 1.83 (1.7H, s), 1.94 (1.3H, s), 2.18 (3H, br s), 2.33 (3H, s), 4.21 (1.1H, q, *J*=7 Hz), 4.28 (0.9H, q, *J*=7 Hz), 6.02 (0.56H, m), 6.27 (0.44H, m), 6.9—7.4 (4H, m), 7.43 (0.44H, s), 7.51 (0.56H, s). Found: C, 75.16; H, 7.34%. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%.

(*E*)-5-Methyl-1-(*p*-tolyl)-1,4-hexadien-3-one (12). A similar reaction of enolate of **3b** with **9b** was carried out in diglyme at 130 °C for 16 h. The crude product was purified by preparative TLC (hexane–acetone, 3:1) to afford **12** (47%), whose ^{1}H NMR spectral data were identical with those reported.[6]

Diethyl (4-Methyl-2-oxo-3-pentenyl)phosphonate (13). A mixture of **3b** (131 mg, 0.39 mmol), *p*-toluensulfonic acid (40 mg, 0.23 mmol), and toluene (3 ml) was stirred for 3.5 h under reflux. The cooled mixture was washed with aqueous $NaHCO_3$ and water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried ($MgSO_4$) and then concentrated. Distillation of the crude product [bp 100—105 °C (0.3 mm Hg) (1 mmHg=133.322 Pa)] gave **13** (89 mg, 78%): IR (neat) 1680, 1620, and 1255 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.33 (6H, t, *J*=7 Hz), 1.93 (3H, br s), 2.13 (3H, br s), 2.88 (2H, d, *J*=22 Hz), 3.97 and 4.11 (each with 2H, q, *J*=7 Hz), 6.20 (1H, m). Found: C, 59.25; H, 9.53%. Calcd for $C_{10}H_{19}O_2P$: C, 59.39; H, 9.47%. These spectral data are consistent with those of the corresponding dimethyl ester.[6a]

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