Dephosphonylation of β-Keto Phosphonates with $LiAlH_4$

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Received September 26, 1995 (Revised Manuscript Received December 8, 1995)

Introduction

β-Keto phosphonates[1] involve a phosphonate group as a regiocontrol element for the alkylation, such as β-keto esters[2] and β-keto sulfones[3] which are useful synthetic intermediates containing a temporary activating group for preparation of regioselective α-alkylated ketones by α-alkylation with subsequent defunctionalization. In contrast to the significant number of applications of β-keto esters and β-keto sulfones in this manner, the method using β-keto phosphonates has not been studied yet, due to the fact that dephosphonylation[4] of β-keto phosphonate is less known.

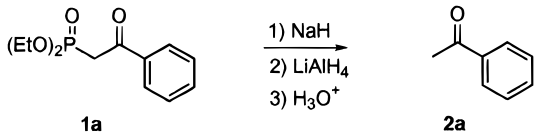
Although various methods or reagents[5,6] have been used to reduce a $C-P^V$ bond into a C−H bond, the known chemical methods for $C-P^V$ cleavage are of limited generality due to the unique substrate requirements. Moreover, there is only one literature[7] reference involving about the C−P bond reduction of β-keto-1-phosphonato esters analogous to β-keto phosphonates. Recently, Denmark[8] pointed out that there was no general method for cleavage of the C−P bond in β-keto phosphonate.

Herein we report a new utility of β-keto phosphonates as building blocks for synthesis of α-alkylated ketones *via* dephosphonylation.

Results and Discussion

We first observed the dephosphonylation of β-keto phosphonate **1a** when the reaction of β-keto phosphonate

Scheme 1



1a **2a**

sodium enolate with $LiAlH_4$ in THF afforded the corresponding ketone **2a** in high yield as shown in Scheme 1.[9]

This observation prompted us to elaborate a general procedure for the preparation of regioselective α-alkylated ketones by the dephosphonylation of the substituted β-keto phosphonates which can be prepared by commonly used methods such as acylation of alkylphosphonate anions[9] and α- or γ-alkylation of β-keto phosphonates.[10,11] The dephosphonylation reaction is rather general as indicated in the Table 1.

β-Aryl-β-keto phosphonates **1a-d** were completely converted into the corresponding ketones without byproducts (**2a-d**). On the other hand, in the case of 1-monosubstituted-β-alkyl-β-keto phosphonates **1e-g** the reaction gave the corresponding ketones in high yields (**2e-g**) along with a small amount of the corresponding alcohols resulting from further reduction. Although complete consumption of the starting materials was observed on reaction of β-alkyl-β-keto phosphonates bearing no substituent at the α-carbon (**1h-j**), the reaction produced the desired ketones **2h-j** in lower yields than in the former cases and side products which could not be identified. Although the use of $LiAlH_4$ in this process was successful, further attempts to find mild and effective reductants for compatibility of a variety of functional groups failed under the same conditions as shown in Table 1 ($LiBEt_3H$, DIBAL-H, $Li(t\text{-}BuO)_3AlH$).

To gain insight about the reaction mechanism, we carried out some experiments using β-keto phosphonates as shown in Scheme 2.

When β-keto phosphonate **1a** was treated with $NaBH_4$ in ethanol, β-keto phosphonate **1a** was smoothly converted to the corresponding β-hydroxy phosphonate **3**. In the case of $LiAlH_4$ in THF, the reaction afforded the complicated mixture **4**. On the other hand, the reaction of β-keto phosphonate **5** involving no α-proton with $LiAlH_4$ gave cleanly the corresponding β-hydroxy phosphonate **6** without dephosphonylated product.

The results of these experiments suggested that dephosphonylation could occur *via* formation of the metal enolate of β-keto phosphonate, and that the complicated mixture **4** might be caused by the action of $LiAlH_4$ as a base as well as a reductant.

In order to investigate further the dephosphonylation reaction, we carried out the following reactions. When reduction of sodium enolate of β-keto phosphonate **1c** with $LiAlD_4$ was followed by quenching with dilute H_2SO_4, the reaction afforded the ketone **2c** containing no deuterium. In the case of using $LiAlH_4$ and deuterated acid, the reaction gave the ketone **2c′**[13] containing two deuteriums as shown in Scheme 3.

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(7) In this case, it was reported as a notable result that during attempted reductions of 2-oxo-1-phosphonato ester to corresponding 2-hydroxy-1-phosphonato ester with various reductants, $Li(t\text{-}BuO)_3AlH$ among them cleaved selectively C−P bond to give the corresponding β-keto ester. However, its mechanism and applications have not been reported. Durrant, G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2582.

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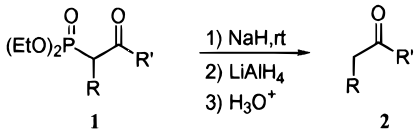
(12) *n*-BuLi was used instead of NaH as a base because the reaction with NaH failed to form the enolate of **1j**.

0022-3263/96/1961-2199$12.00/0

Table 1. Dephosphonylation of Substituted β-Keto Phosphonates[a]

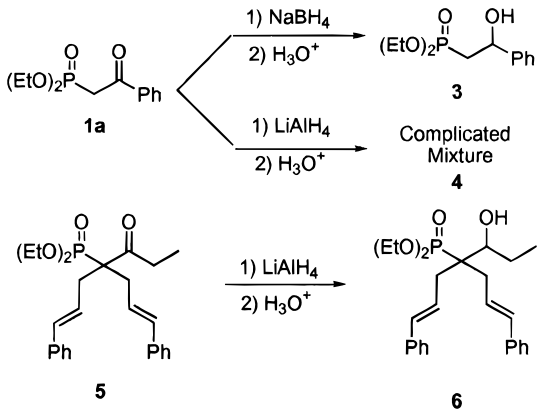


1 2

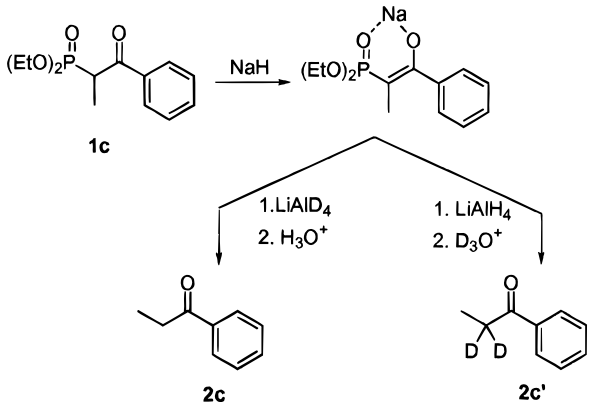
entry (substrate)	R	R′	time, h	products	yield,[b,c] %
1 (**1a**)	H	Ph	<0.2	2a	98
2 (**1b**)	H	4-Cl-Ph	<0.2	2b	97
3 (**1c**)	Me	Ph	<0.2	2c	96
4 (**1d**)	allyl	4-Cl-Ph	<0.2	2d	97
5 (**1e**)	Ph	Me	0.5	2e	89
6 (**1f**)	CH_2Ph	Et	0.5	2f	91
7 (**1g**)	cinnamyl	Et	0.5	2g	87
8 (**1h**)	H	CH_2CH_2Ph	1	2h	57
9 (**1i**)	H	$CH(CH_3)CH_2CH{=}CHPh$	1	2i	72
10 (**1j**[12])[d]	H	$C(CH_3)_2CH2CH{=}CHPh$	1	2j	65

[a] All reactions run in THF and quenched with 10 N sulfuric acid. [b] Yield of isolated, purified products. [c] Solvent was evaporated below 0 °C. [d] *n*-BuLi used instead of NaH.

Scheme 2

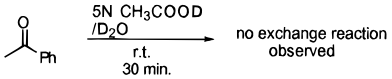


Scheme 3



These results suggest that during the cleavage of the P−C bond, the hydride does not attack the carbon atom linked with phosphorus atom, and that after cleavage of the P−C bond, the intermediate might have dianion character.

(13) Analysis of ^{1}H NMR and ^{13}C NMR spectra indicated dideuterated ketone as the major product along with a small amount of monodeuterated ketone (*ca.* mono:di = 1:9). To investigate the possibility of H−D exchange reaction between D_3O^+ and ketone, the following procedure was carried out.



No deuterized ketone was observed. See supporting information.

In conclusion, we have described the first general example of dephosphonylation of β-keto phosphonates with respect to its simplicity and efficiency. Also these results suggest that the use of β-keto phosphonates as precursors to α-alkylated ketones would complement existing methods used to synthesize alkylated ketones which use β-keto esters and β-keto sulfones.

Further studies on the mechanism and dephosphonylation of other β-carbonyl phosphonates are in progress.

Experimental Section

General Methods. All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. THF was distilled from Na/benzophenone ketyl. ^{1}H-NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ as internal references. Starting materials **1a**−**1i** were synthesized as described in the literature with minor modification.[10−12]

General Procedure for Dephosphonylation of β-Keto Phosphonate 1a. A solution of β-keto phosphonate **1a** (0.256 g, 1 mmol) in anhydrous THF was added *via* syringe to a stirred suspension of NaH and rinsed with hexane (0.027 g, 1.1 mmol) in anhydrous THF at room temperature. After being stirred for 1 h, the resulting enolate was transferred into a stirred solution of $LiAlH_4$ (0.114 g, 3 mmol) in THF at room temperature and stirred for 10 min. The mixture is quenched by transferring it to aqueous 10 N sulfuric acid (10 mL). The solution was extracted with diethyl ether (30 mL x 2). The organic phase was washed with 5% aqueous $NaHCO_3$ and water and then dried over anhydrous $MgSO_4$; the drying agent was filtered off, and the filtrate was evaporated under reduced pressure at below 0 °C. The residue was purified by flash chromatography with ethyl acetate/hexane (10/90) as eluent to give acetophenone (**2a**, 0.118 g, 98%). ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.97−7.91 (m, 2H), 7.56−7.39 (m, 3H), 2.58 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.9, 136.9, 132.9, 121.3, 128.1, 26.3.

4-Chloroacetophenone 2b: obtained as a colorless liquid (0.150 g, 97%) from β-keto phosphonate **1b** (0.291 g, 1 mmol). Reduction time; 10 min. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93−7.84 (m, 2H), 7.46−7.39 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.6, 139.3, 135.2, 129,5 128.7, 26.3.

Propiophenone 2c: obtained as a colorless liquid (0.129 g, 96%) from β-keto phosphonate **1c** (0.291 g, 1 mmol). Reduction time; 10 min. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz ,$CDCl_3$) δ 8.00−7.92 (m, 2H), 7.59−7.38 (m, 3H), 2.99 (q, J = 7.3 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.6, 136.7, 132.6, 128.3, 127.7, 31.5, 8.0.

1-(4-Chlorophenyl)-4-penten-1-one (2d): obtained as a colorless liquid (0.189 g, 97%) from β-keto phosphonate **1d** (0.331 g, 1 mmol). Reduction time; 10 min. Purification by flash

chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 5.97−5.81 (m, 1H), 5.13−4.98 (m, 2H), 3.04 (t, J = 7.3 Hz, 2H), 2.53−2.43 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.0 139.2, 136.9, 135.1, 129.3, 128.7, 128.4, 127.9, 115.3, 37.5, 29.5, 27.9; EIMS *m*/*e* 194 (M^+, 2.1), 141 (41), 139 (100), 113 (10), 111 (24), 75 (7).

1-Phenyl-2-propanone (2e): obtained as a colorless liquid (0.132 g, 89%) from β-keto phosphonate **1e** (0.284 g, 1 mmol). Reduction time; 30 min. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.17 (m, 5H), 3.66 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.9, 134.0, 129.0, 128.3, 126.6, 50.5, 28.6; EIMS *m*/*e* 134 (M^+, 7), 121 (4), 111 (5), 107 (6), 106 (10), 105 (100), 91 (8), 77 (22), 43 (5).

1-Phenyl-3-pentanone (2f): obtained as a colorless liquid (0.147 g, 91%) from β-keto phosphonate **1f** (0.298 g, 1 mmol). Reduction time; 40 min. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23−7.12 (m, 5H), 2.91−2.82 (m, 2H), 2.72−2.63 (m, 2H) 2.35 (q, J = 7.3 Hz, 2H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.1, 140.9, 128.1, 128.0, 125.7, 43.5, 35.7, 29.5, 7.4; EIMS *m*/*e* 162(M^+, 59), 141 (12), 139 (25), 133 (45), 106 (10), 105 (100), 91 (60), 79 (10), 77 (16).

1-Phenyl-1-hepten-5-one (2g): obtained as a colorless liquid (0.164 g, 87%) from β-keto phosphonate **1g** (0.324 g, 1 mmol). Reduction time; 35 min. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.34−7.17 (m, 5H), 6.39 (d, J = 15.9 Hz, 1H), 6.17 (dt, J = 15.8, 6.3 Hz 1H), 2.60−2.37 (m, 6H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.5, 137.3, 130.5, 128.9, 128.3, 126.9, 125.8, 41.7, 35.9, 27.0, 7.6; EIMS *m*/*e* 188 (M^+, 69), 159 (30), 131 (57), 130 (14), 129 (39), 128 (26), 117 (100), 104 (21), 91 (72), 57 (21).

1-Phenyl-3-butanone (2h): obtained as a colorless liquid (0.084 g, 57%) from β-keto phosphonate **1h** (0.284 g, 1 mmol). Reduction time; 1 h. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30−7.17 (m, 5H), 2.93−2.69 (m, 4H), 2.11 (s, 3H);^{13}C NMR (50 MHz, $CDCl_3$) δ 207.7, 140.9, 128.4, 128.1, 126.0, 45.0, 29.9, 29.6; EIMS *m*/*e* 148 (M^+, 100), 133 (22), 115 (11), 105 (88), 91 (58), 77 (18), 65 (6), 51 (5).

5-Methyl-1-phenyl-1-hexen-5-one (2i): obtained as a colorless liquid (0.136 g, 72%) from β-keto phosphonate **1I** (0.324 g, 1 mmol). Reduction time; 1 h. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5H), 6.39 (d, J = 15.8 Hz, 1H), 6.09 (dt, J = 15.7, 7.0 Hz, 1H), 2.68−2.45 (m, 2H), 2.29−215 (m, 1H), 2.12 (s, 3H), 1.11 (d, J = 6.8, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.5, 137.1, 131.8, 128.3, 127.1, 127.0, 125.8, 46.8, 35.9, 28.2, 15.8; EIMS *m*/*e* 188 (M^+, 26), 173 (6), 145 (28), 129 (17), 117 (100), 104 (22), 97 (17), 91 (46), 43 (9).

5,5-Dimethyl-1-phenyl-1-hexen-5-one (2j): obtained as a colorless liquid (0.132 g, 72%) from β-keto phosphonate **1j** (0.338 g, 1 mmol). *n*-BuLi (0.7 mL, 1.6 N solution, 1.1 mmol) was used to form enolate instead of NaH. Reduction time; 1 h. Purification by flash chromatography (ethyl acetate/hexane 10/90). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.14 (m, 5H), 6.38 (d, 1H), 6.06 (dt, 1H), 2.39 (dd, J = 7.4, 1 Hz, 2H), 2.14 (s, 3H), 1.15 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.3, 137.2, 133.0, 128.4, 127.1, 126.1, 125.7, 48.1, 43.0, 25.3, 24.2.; EIMS *m*/*e* 202 (M^+, 9), 188 (5), 117 (100), 105 (6), 91(21), 77(3).

Reduction with $LiAlD_4$ in Scheme 3. According to the general procedure described above, the corresponding enolate of β-keto phosphonate **1c** (1 mmol) was transferred into a stirred solution of $LiAlD_4$ (0.126 g, 3 mmol) in THF at room temperature and stirred for 10 min. Normal workup was followed. The resulting ketone is identical with **2c** (0.124 g, 92%).

Quenching with Deuterated Acid in Scheme 3. According to general procedure described above, the corresponding enolate of β-keto phosphonate **1c** (1 mmol) was transferred into a stirred solution of $LiAlH_4$ (0.114 g, 3 mmol) in THF at room temperature and stirred for 10 min. The mixture is quenched by transferring it to 30% AcOD in D_2O (20 mL). Normal workup gave α,α-d_2-Propiophenone **2c′** (0.095 g, *ca.* mono:di = 1:9, 70%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97−7.93 (m, 2H), 7.54−7.44 (m, 3H), 1.20 (br s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.8, 136.8, 132.7, 128.4, 127.8, 30.9 (quintet, J_{C-D} = 19.0 Hz).

Acknowledgment. This research was supported by Korea Science and Engineering Foundation (KOSEF).

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds in Table 1 and Scheme 3 (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951757P