t-BuOK-Induced Cleavage of Dihydrofuran Derivatives: Synthesis of β-(Diethoxyphosphinyl)-β,γ-unsaturated Ketones

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Received May 15, 1995

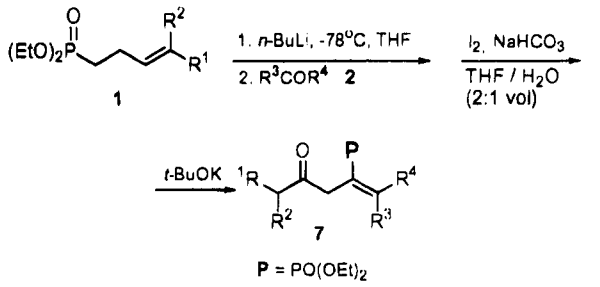
The cleavage of ethers is a widely used reaction in organic synthesis, particularly in the degradation or transformation of natural products and in the manufacture of pharmaceuticals, drugs, and other fine chemicals. Many reagents are capable of cleaving ethers.[1]

During an investigation of the iodocyclization of phosphonates, we have encountered an unusual cleavage of dihydrofuran derivatives leading to the formation of β-(diethoxyphosphinyl)-β,γ-unsaturated ketones **7**. The cleavage of the furan ring in acidic conditions[2] and decomposition of tetrahydrofuran with organolithium[3] have been already studied. To our knowledge, the cleavage of dihydrofuran derivatives with *t*-BuOK is unprecedented. Alkali alkoxides are not generally used to cleave ethers in preparative work, although there are examples in the literature where their ability to do so has been demonstrated.[4] Moreover, this reaction can also be used to prepare β,γ-unsaturated ketones in excellent yields.

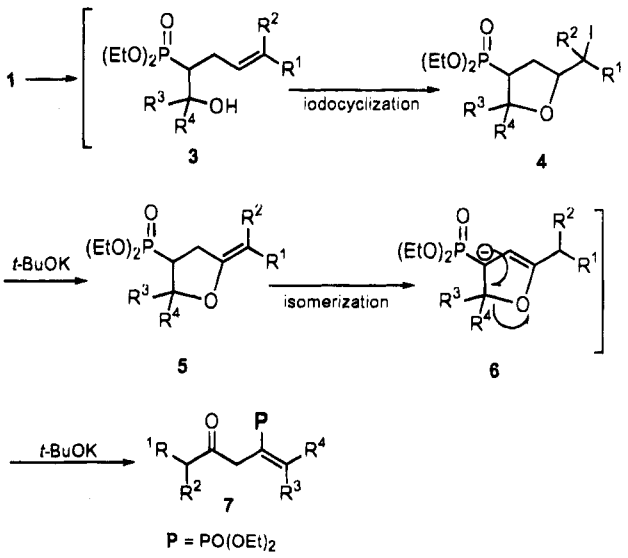
Our initial experiment was performed with an aldehyde by adding it in THF at −78 °C to the lithiated phosphonate generated with *n*-BuLi. The reaction mixture was stirred at room temperature for 30 min under N_2, followed by addition of water, iodine, and $NaHCO_3$. Stereoisomers of **4** did not have to be isolated because all the stereoisomers afforded the same compound **7**. After usual workup, tetrahydrofuran derivative **4** was treated with *t*-BuOK in THF at 0 °C. From this reaction β-(diethoxyphosphinyl)-β,γ-unsaturated ketones **7** were isolated in excellent yield by chromatography (Scheme 1).

While the detailed mechanistic aspects of the ring-cleavage are under investigation, a proposed mechanism is shown in Scheme 2. In the THF:water (2:1 vol) cosolvent system, tetrahydrofuran derivative **4** might form via I_2-induced cyclization.[5] And the dehydroiodination of **4** by *t*-BuOK in anhydrous THF and subsequent basic isomerization might afford dihydrofuran **6**, which then cleaved *in situ* to the product **7**. The results of this reaction are summarized in Table 1. This new method for synthesizing enones works similarly with ketones (Table 1, entries 5, 7, and 8). It was noteworthy that only carbonyl compounds having aryl and vinyl moiety underwent the ring-cleavage reaction. CH_3CHO, $CH_3(CH_2)_5CHO$, $(CH_3)_2CHCHO$, and CH_3COCH_3 did not give the corresponding adduct. This trend suggested that dihydrofuran **6** would tend to cleave into **7** because of the greater stability of the highly conjugated acyclic product **7**. When the reaction was carried out with **8**, none of the desired compound was found probably because **9** does not have an allylic hydrogen.[6] So the cleavage process probably occurred via a deprotonation of the allylic position in compound **6**. When DBU was used in place of *t*-BuOK, the cleavage did not take place. Instead, we obtained dehydroiodinated product **5**. The double bond in product **7** was assigned *E* geometry by NOE experiments.

Scheme 1



Scheme 2



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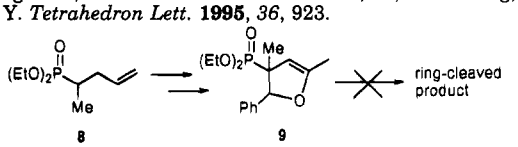

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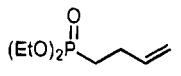
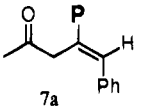
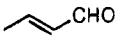
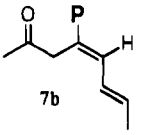
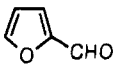
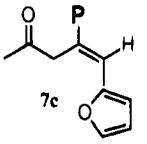
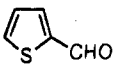
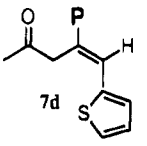
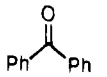
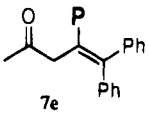
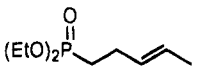
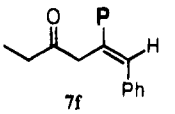
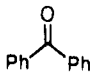
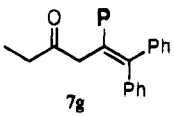
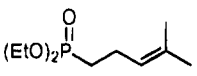
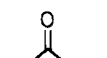
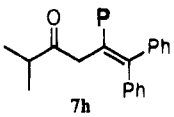
Table 1. *t*-BuOK-Induced Cleavage of Dihydrofuran Derivatives: Synthesis of β-(Diethoxyphosphinyl)-β,γ-unsaturated Ketones

entry	phosphonate	carbonyl	product[a]	yield, %[b]
1	 1a	PhCHO	 7a	95%
2	1a		 7b	93%
3	1a		 7c	92%
4	1a		 7d	87%
5	1a		 7e	88%
6	 1b	PhCHO	 7f	91%
7	1b		 7g	82%
8	 1c		 7h	82%

[a] P = P(O)(OCH$_2$CH$_3$)$_2$. [b] Isolated yield.

In summary, the ring cleavage of dihydrofuran described herein appears to be the first example of this type of reaction that provides a new synthetic method for the β-(diethoxyphosphinyl)-β,γ-unsaturated ketones,[7] which have high versatility and wide potentiality in organic chemistry.[8] Futher studies are planned in our laboratory to demonstrate the utility of this methodology.

Experimental Section

General. 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. Diethyl butenylphosphonates **1** were synthesized as described in the literature with minor modification.[9]

Repesentative Procedure. Preparation of 7a. A solution of diethyl 3-butenylphosphonate (1 mmol) in 5 mL of THF was treated dropwise with a solution of 1.6 M *n*-BuLi (1.1 mmol) in hexane at −78 °C. After stirring for 1 h at this temperature, a solution of benzaldehyde (1.1 mmol) in 5 mL of THF was added dropwise and the reaction mixture was stirred at room temperature for 30 min under N_2, followed by the sequential addition of water (5 mL), iodine (3.3 mmol) and $NaHCO_3$ (1.3 mmol). The mixture was stirred for 2 h at room temperature. To the resultant solution was added saturated sodium thiosulfate, and the mixture was extracted with CH_2Cl_2. Then the combined organic extracts were concentrated and treated with *t*-BuOK in THF at 0 °C. After 30 min, the mixture was quenched with ammonium chloride and extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The mixture was purified by silica gel chromatography using EtOAc as an eluent, which afforded 95% yield.

Tetrahydrofuran Derivative 5a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.30 (dd, 1H, J = 7.3, J = 10.6), 4.30 (m,1H), 3.99−3.88 (m, 5H), 2.92 (m, 2H), 2.59 (m, 2H), 1.14 (t, 6H, J = 7.1); ^{13}C NMR (75 MHz,$CDCl_3$) δ 160.16 (d, J = 12.8), 139.45 (d, J = 3.8), 128.07, 126.09, 82.97 (d, J = 3), 79.93, 81.70 (m), 43.17 (d, J = 150.8), 30.95 (d, J = 2.9), 15.89 (d, J = 6.1).

***(E)*-2-(Diethoxyphosphinyl)-3-phenylprop-2-enyl Methyl Ketone. [*(E)*-Diethyl [1-(2-oxopropyl)-2-phenylethenyl]-phosphonate] (7a):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 24.0), 7.34−7.29 (m, 5H), 4.20−4.04 (m,4H), 3.55 (d, 2H, J = 17.8), 2.24 (s, 3H), 1.49 (t, 6H, J = 7.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.79 (d, J = 1.8), 146.26 (d, J = 11.0), 134.80 (d, J = 22.4), 128.77−126.67 (m), 123.94 (d, J = 180.0), 61.87 (d, J = 5.4), 42.49 (d, J = 9.8), 30.15, 16.1 (d, J = 6.8); HRMS calcd 296.1177, found 296.1188.

(2*E*,4*E*)-2-(Diethoxyphosphinyl)hexa-2,4-dienyl Methyl Ketone. [*(E)*-Diethyl [1-(2-oxopropyl)-2-crotylethenyl]-phosphonate] (7b): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.10−6.95 (m, 1H), 6.10−6.03 (m, 2H), 4.03−3.84 (m, 4H), 3.28 (d, 2H, J = 17.0), 2.09 (s, 3H), 1.75 (d, 3H, J = 3.86), 1.19 (t, 6H, J = 6.91); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.34, 145.76 (d, J = 11.0), 139.65, 125.99 (d, J = 22.1), 118.55 (d, J = 186.1), 61.62 (d, J = 5.3), 41.90 (d, J = 9.8), 29.251, 18.61, 16.08 (d, J = 6.5); HRMS calcd 260.1177, found 260.1183.

***(E)*-2-(Diethoxyphosphinyl)-3-(2-furyl)prop-2-enyl Methyl Ketone. [*(E)*-Diethyl [1-(2-oxopropyl)-2-furylethenyl]-phosphonate] (7c):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34 (d, J = 0.96), 7.22 (d, 1H, J = 23.8), 6.44 (d, 1H, J = 3.3), 6.33−6.31 (m, 1H), 4.83−4.09 (m, 4H), 3.62 (d, 2H, J = 17.5), 2.10 (s, 3H), 1.18 (t, 6H, J = 7.1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.10 (d, J = 3.2), 151.10 (d, J = 26.55), 144.34, 131.72 (d, J = 12.98), 118.50 (d, J = 185.5), 115.69, 111.634, 61.698 (d, J = 5.25), 42.81 (d, J = 7.6), 29.072, 16.49(d, J = 6.6); HRMS calcd 286.0970, found 286.0967.

***(E)*-2-(Diethoxyphosphinyl)-3-(2-thienyl)prop-2-enyl Methyl Ketone. [*(E)*-Diethyl [1-(2-oxopropyl)-2-thienylethenyl]phosphonate] (7d):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, 1H, J = 23.6), 7.37 (d, 1H, J = 4.7), 7.18 (d, 1H, J = 3.48), 7.03−6.98 (m, 1H), 4.12−3.89 (m, 4H), 3.65 (d, 2H, J = 17.8), 2.21 (s, 3H), 1.24 (t, 6H, J = 7.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.43 (d, J = 2.5), 138.19 (d, J = 13.3), 137.53 (d, J = 26.25), 132.27, 128.89, 127.26, 119.25 (d, J = 185.03), 61.85 (d, J = 5.25), 43.27 (d, J = 8.48), 29.61, 16.11 (d, J = 6.5); HRMS calcd 302.0742, found 302.0735.

2-(Diethoxyphosphinyl)-3,3-diphenylprop-2-enyl Methyl Ketone. [Diethyl [1-(2-oxopropyl)-2,2-diphenylethenyl]-phosphonate] (7e): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35−7.10 (m, 10H), 3.90−3.74 (m, 4H), 3.40 (d, 2H, J = 16.4), 2.10 (s, 3H), 1.07 (t, 6H, J = 7.17); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.95 (d, J = 1.35), 158.68 (d, J = 10.3), 141.51, 141.25, 141.05, 140.94, 128.92, 128.90, 128.230, 127.847, 127.655, 127.641, 127.466, 122.61 (d, J = 180.6), 61.49 (d, J = 6.15), 47.03 (d, J = 11.4), 30.04, 15.90 (d, J = 6.9); HRMS calcd 372.1490, found 372.1489.

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(9) Savignac, P.; Brèque, A.; Mathey, F. *Synth. Commun.* **1979**, 487.

(*E*)-2-(Diethoxyphosphinyl)-3-phenylprop-2-enyl Ethyl Ketone. [(*E*)-Diethyl [1-(2-oxobutyl)-2-phenylethenyl]phosphonate] (7f): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, 1H, J = 24.0), 7.34–7.31 (m, 5H), 4.21–4.01 (m, 4H), 3.53 (d, 2H, J = 17.9), 2.56 (q, 2H, J = 7.34), 1.33 (t, 6H, J = 7.0), 1.08 (t, 3H, J = 7.27); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.43, 146.18 (d, J = 11.2), 134.80 (d, J = 22.2), 128.64–128.22 (m), 123.94 (d, J = 180.0), 61.73 (d, J = 5.3), 41.18 (d, J = 9.9), 36.255, 16.0 (d, J = 6.6), 7.517; HRMS calcd 310.1334, found 310.1338.

2-(Diethoxyphosphinyl)-3,3-diphenylprop-2-enyl Ethyl Ketone. [Diethyl [1-(2-oxobutyl)-2-phenylethenyl]phosphonate] (7g): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.08 (m, 10H), 3.88–3.70 (m,4H), 3.36 (d, 2H, J = 16.5), 2.36 (q, 2H, J = 7.28), 1.04 (t, 6H, J = 7.2), 0.97 (t, 3H, J = 7.4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.503, 158.54 (d, J = 10.1), 141.54, 141.28, 141.07, 140.96, 128.85, 128.83, 128.15, 127.74, 127.62, 127.40, 122.64 (d, J = 180.3), 61.39 (d, J = 6.1), 45.85 (d, J = 11.3), 35.82, 15.8 (d, J = 6.9), 7.59; HRMS calcd 386.1647, found 386.1653.

2-(Diethoxyphosphinyl)-3,3-diphenylprop-2-enyl Isopropyl Ketone. [Diethyl [1-(3-methyl-2-oxopropyl)-3,3-diphenylethenyl]phosphonate] (7h): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.08 (m, 10H), 3.94–3.74 (m,4H), 3.47 (d, 2H, J = 16.4), 2.55 (dq, 1H, J = 6.9), 1.07 (t, 6H, J = 7.1), 0.99 (d, 6H, J = 6.9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.82 (d, J = 1.4), 158.72 (d, J = 10.35), 141.72, 141.45, 141.20, 141.10, 128.97, 128.95, 128.24, 127.84, 127.63, 127.62, 127.52, 122.65 (d, J = 180.7), 61.53 (d, J = 5.9), 44.45 (d, J = 10.9), 40.684, 16.199, 15.97 (d, J = 6.9); HRMS calcd 400.1803, found 400.1803.

Dihydrofuran derivative 9: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31–7.26 (m, 5H), 5.87 (d, 1H, J = 21.1), 4.568 (m, 1H), 4.12 (m, 4H), 1.89 (dd, 3H, J = 4.4, J = 1.0), 1.31 (m, 6H), 0.80 (d, 3H, J = 16.6); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.91 (d, J = 12.3), 137.57 (d, J = 7.85), 127.88, 126.63, 98.43 (d, J = 7.4), 85.75 (d, J = 2.4), 62.16 (m), 50.76 (d, J = 151.0), 18.94, 16.47 (d, J = 5.7), 12.697 (d, J = 4.8).

Acknowledgment. We thank the Korea Science and Engineering Foundation for generous support of our research. We are grateful to Dr. Jongki Hong at the Korea Basic Science Center for supplying high resolution mass spectra.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **5a**, **7a–h**, and **9** (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.

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