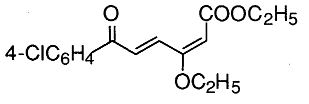
Novel Annulation of 6-Aryl-3-ethoxy-6-hydroxy-2,4-hexadienoates to 5-Benzoyl-3-ethoxycyclopent-2-en-1-ones under Basic Conditions

Tomikazu Kawano, Md. Saiful Islam, Jae-Seung Jeong, and Ikuo Ueda*
The Institute of Scientific and Industrial Research, Osaka University, 8-1, Mihogaoka, Ibaraki, Osaka 567

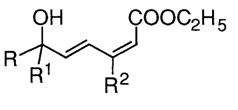
(Received April 21, 1997; CL-970298)

Reaction of 6-aryl-3-ethoxy-6-hydroxy-2,4-hexadienoates with potassium hydroxide in ethanol gave 5-benzoyl-3-ethoxycyclopent-2-en-1-ones in moderate yields.

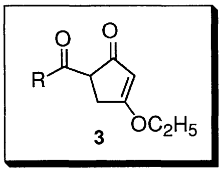
In relation to the total synthesis of biologically active natural products such as prostaglandins or various kinds of terpenes, a significant number of methods for the construction of the cyclopentenone ring have been developed.[1] Recently, we have reported the construction of a cyclopentenone ring by [3+2]-annulation between bifunctional carbonyl compounds and 2-ethoxy-2-propenylidenetriphenylphosphoranes or 2-oxo-propylidenetriphenylphosphoranes.[2] Among them, 6-oxo-3-ethoxy-2,4-hexadienoates (**1**) and its 6-hydroxy derivatives (**2a**), which were prepared from 4-chlorophenylglyoxal monohydrate and 2-ethoxy-2-propenylidenetriphenylphosphoranes,[2d] have been shown to be useful intermediates for the synthesis of heterocyclic compounds such as 2*H*-pyrans, 2*H*-pyran-2-ones, 2-oxo-1,2,5,6-tetrahydropyridines and furans.[3] We herein report synthesis of 5-benzoyl-3-ethoxycyclopent-2-en-1-ones (**3**) by reaction of 6-aryl-3-ethoxy-6-hydroxy-2,4-hexadienoates (**2**) with potassium hydroxide in ethanol.



1



2a: $R=4\text{-}ClC_6H_4$, $R^1=H$, $R^2=OC_2H_5$



3

When **2a** was treated with two equimolar amounts of potassium hydroxide in ethanol at room temperature for 24 h, a colorless crystalline product (mp 120.5-121.5 °C) was obtained as plates in 42% yield after recrystallization from a mixture of hexane and ethyl acetate. Elemental analysis and mass spectral data show it to have the composition $C_{14}H_{13}ClO_3$. The IR spectrum shows strong absorption bands at 1680 cm^{-1} due to a benzoyl carbonyl group and 1700 cm^{-1} due to a carbonyl group of the cyclopentenone skeleton, respectively. In the ^1H-NMR spectrum, two signals at 8.08 (d, 2H, J = 8.6 Hz) and 7.47 (d, 2H, J = 8.6 Hz) ppm were assigned to four aromatic protons and two signals observed at 4.11 (q, 2H, J = 7.0 Hz) and 1.45 (t, 3H, J = 7.0 Hz) ppm were assigned to methylene and methyl protons of the ethoxy group. The signal observed at 5.20 (s, 1H) ppm was assigned as an olefinic proton located in the cyclopentenone ring. Two signals observed at 2.72 (dd, 1H, J = 7.0 and 16 Hz) and 3.34 (dd, 1H, J = 2.6 and 16 Hz) ppm were assigned to the methylene protons, and the signal observed at 4.58 (dd, 1H, J = 2.6 and 7.0 Hz) ppm was assigned to the methine proton adjacent to the methylene protons on the basis of the coupling constants observed. These spectral data indicate its structure to be 5-(4-chlorobenzoyl)-3-ethoxycyclopent-2-en-1-one (**3a**),[4] which was confirmed unambiguously by a single-crystal X-ray analysis.[5] Crystals of **3a** were obtained by crystallization from a mixture of hexane and ethyl acetate, and the result of X-ray crystallographic analysis is depicted in Figure 1.[6]

Table 1. List of substrate **2** and product **3**

	Substrate 2			Product 3	
	R	R^1	R^2	(Yield /%)	
2a	$4\text{-}ClC_6H_4$	H	OC_2H_5	**3a**	42
2b	$4\text{-}ClC_6H_4$	CH_3	OC_2H_5		-[a]
2c	$4\text{-}ClC_6H_4$	H	H		-
2d	$3\text{-}ClC_6H_4$	H	OC_2H_5	**3d**	30
2e	$2,4\text{-di-}ClC_6H_4$	H	OC_2H_5	**3e**	41
2f	$4\text{-}CH_3C_6H_4$	H	OC_2H_5	**3f**	48
2g	$4\text{-}CH_3OC_6H_4$	H	OC_2H_5	**3g**	43
2h	$4\text{-}NO_2C_6H_4$	H	OC_2H_5		-
2i	2-Thienyl	H	OC_2H_5	**3i**	44
2j	CH_3	H	OC_2H_5		-
2k	Adamantyl	H	OC_2H_5		-

[a] - : not detected

As shown in Table 1, similar treatment of **2d-2g**, **2i** with potassium hydroxide gave the corresponding cyclopentenones (**3d-3g**, **3i**). The yields for this reaction, which were isolated and unoptimized, ranged from 30% to 48%. Our limited studies

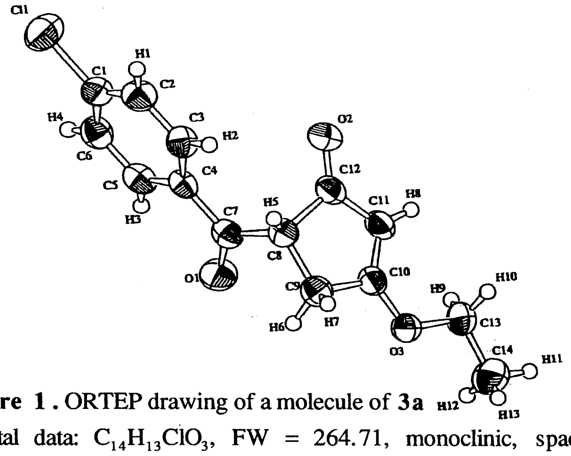
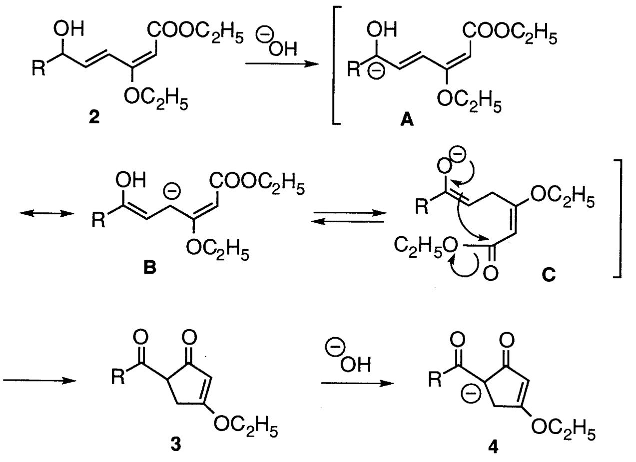


Figure 1. ORTEP drawing of a molecule of **3a**

Crystal data: $C_{14}H_{13}ClO_3$, FW = 264.71, monoclinic, space group $P2_1/n$ (#14), a = 6.575(2), b = 10.530(2), c = 18.323(1) Å, β = 92.45(1)°, V = 1267.3(4) $Å^3$, Z = 4, D_{calc} = 1.39 g/cm^3, unique reflections = 1832 ($I>3\sigma(I)$), R = 0.043, R_w = 0.047.

showed that suitable substrates for this cyclization were **2a**, **2d**-**2g**, **2i** with ethoxy and aryl groups at the 3- and 6-positions of the 6-hydroxy-2,4-hexadienoate except for **2h**. For **2b** with disubstituents at the 6-position and **2c** without ethoxy group at the 3-position, the reactions failed to occur. Reaction of **2j** and **2k** with alkyl group instead of aryl group at the 6-position proceeded to afford polar material(s) without the formation of the desired products.



Scheme 1.

On the basis of above observations, this cyclization can be illustrated in Scheme 1. First, **2** reacts with the hydroxide ion to give a carbanion intermediate **A** which is transformed to an anion **B**. This anion is converted to an intermediate **C** which is cyclized to afford **3**. The formation of the stable anion **4** may be the driving force for the cyclization.

In summary, we have developed a convenient synthetic method for direct construction of 5-benzoyl-3-ethoxycyclopent-2-en-1-ones from 6-aryl-3-ethoxy-2,4-hexadienoates, which were easily prepared from arylglyoxal monohydrates and stable [3-ethoxycarbonyl-2-ethoxy-2-propenylidene]triphenylphosphorane, under basic conditions. We also disclosed the importance of 6-aryl-3-ethoxy-2,4-hexadienoates as synthetic intermediates for the construction of a 3-ethoxycyclopent-2-en-1-one ring.

The authors are indebted to the Material Analysis Center of ISIR for the elemental analyses.

References and Notes

1 a) T. -L. Ho, in "*Carbocycle Construction in Terpene Synthesis*," VCH Publisher: New York (1988). b) T. Hudlicky, F. Rulin, T. C. Lovelace, and J. W. Reed, in "*Studies in Natural Products Chemistry* ," ed by A. Rahman, Elsevier: Amsterdam (1989), Vol. 3, p.3.

2 a) M. Hatanaka, Y. Himeda, and I. Ueda, *Tetrahedron Lett.*, **32**, 4521 (1991). b) M. Hatanaka, R. Imashiro, and I. Ueda, *Chem. Lett.*, **1992**, 2253. c) M. Hatanaka, Y. Tanaka, Y. Himeda, and I. Ueda, *Tetrahedron Lett.*, **34**, 4837 (1993). d) M. Hatanaka, Y. Himeda, R. Imashiro, Y. Tanaka, and I. Ueda, *J. Org. Chem.*, **59**, 111 (1994). e) Y. Himeda, M. Hatanaka, and I. Ueda, *J. Chem. Soc., Chem. Commun.*, **1995**, 449. f) M. Hatanaka, Y. Himeda, Y. Tanaka, and I. Ueda, *Tetrahedron Lett.*, **36**, 3211 (1995). g) M. Hatanaka, Y. Tanaka, and I. Ueda, *Tetrahedron Lett.*, **36**, 3719 (1995). h) Y. Himeda, I. Ueda, and M. Hatanaka, *Chem. Lett.*, **1996**, 71. i) Md. S. Islam, T. Kawano, M. Hatanaka, and I. Ueda, *Tetrahedron Lett.*, **37**, 5735 (1996).

3 T. Kawano, T. Ogawa, Md. S. Islam, and I. Ueda, *Tetrahedron Lett.*, **36**, 7685 (1995). b) Y. Tanaka, T. Kawano, Md. S. Islam, H. Nishioka, M. Hatanaka, and I. Ueda, *Chem. Pharm. Bull.*, **44**, 885 (1996).

4 All new compounds showed the expected spectral properties and gave satisfactory elemental analyses. **3g**: mp 118.5-120.0 °C. (colorless needles from hexane-ethyl acetate). ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.11 (d, 2H, J = 8.9 Hz), 6.98 (d, 2H, J = 8.9 Hz), 5.21 (s, 1H), 4.60 (dd, 1H, J = 2.6, 6.9 Hz), 4.10 (q, 2H, J = 7.3 Hz), 3.89 (s, 3H), 3.32 (ddd, 1H, J = 1.4, 2.6, 17 Hz), 2.73 (ddd, 1H, J = 1.3, 17, 7.0 Hz), 1.45 (t, 3H, J = 7.0 Hz), IR (KBr) ν: 1700, 1680 cm^{-1}. MS m/z: 260 (M$^+$). Anal Found: C, 68.77; H, 5.80%. Calcd for $C_{15}H_{16}O_4 1/8H_2O$: C, 68.62; H, 6.24%.

5 RASA software was employed for the entire structure analysis.

6 ORTEP-II was employed for drawing the molecular structure, C. K. Johnson, "ORTEP Report ORNL-5138," Oak Ridge National Laboratory, Tennessee (1976).