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The Stereoselective Synthesis of β-Haloenol Phosphates—A Reinvestigation of the Reaction of α-Haloketones with Diethyl Phosphite

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ABSTRACT: *A new pathway for the reaction involving an α-haloketone and a dialkyl phosphite has been suggested, It offers a highly stereoselective synthetic procedure leading to β-haloenol phosphates in one-pot reactions that take place in good yields. However, normal Pudovik reaction products were formed when the reaction was carried out using a relatively small amount of base.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 55–59, 1999

INTRODUCTION

Enol phosphates are a class of important organic compounds, and various efforts have been made in the preparation of bioactive enol phosphates. Some are a kind of potent insecticide that has wide fields of application. Recently, Stowell and Widlaucks [1] reported the synthesis of enol phosphates having a leaving group at the 1-position that can inactivate phosphatase. Similarly, β-haloenol phosphates, during the course of an enzyme-catalyzed hydrolysis, can give rise to an intermediate that would undergo a rapid chemical rearrangement to a highly reactive compound, an α-haloketone, which is a powerful alkylating agent in the active site of the enzymes. Thus, such a molecular structure would be valuable for the design of mechanism-based inactivators of phosphatase.

The reaction of an α-haloacetophenone with diethyl phosphite is very interesting and extremely complex [2]. The reaction of an α-bromoketone with a dialkyl phosphite gives mainly a ketophosphonate via the Michaeles–Becker pathway. However, an α-chloroketone generally follows the Pudovik pathway to give a "Perkow-type" product [3] that is the result of attack of the phosphorus atom on the carbon of the carbonyl group rather than at the halogen leaving site. Treatment of an α-chloroalkyl aryl ketone with a dialkyl phosphite in the presence of a very small amount of base at a temperature below 30°C leads to a dialkyl hydroxymethylphosphonate in good yield, and this is transformed into an epoxyphosphonate and the isomeric vinyl phosphate when a higher concentration of base is used, or at an elevated temperature. The relative proportion of the epoxyphosphonate and vinyl phosphate depend insignificantly on the polarity of the reaction medium. At this time, we wish to report on the stereoselective syntheses of β-haloenol phosphates by the action of α-haloketones on diethyl phosphite via the Atherton–Todd route. This is the third pathway of this reaction matrix as shown in Scheme 1.

RESULTS AND DISCUSSION

Selectivity of the reaction usually depends on the relative reactivity of two functional groups, but other

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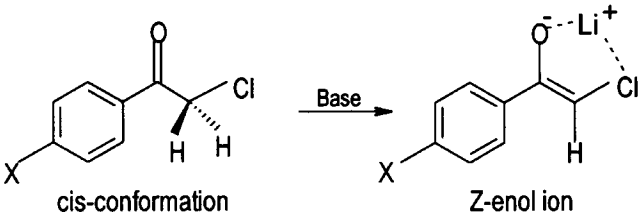
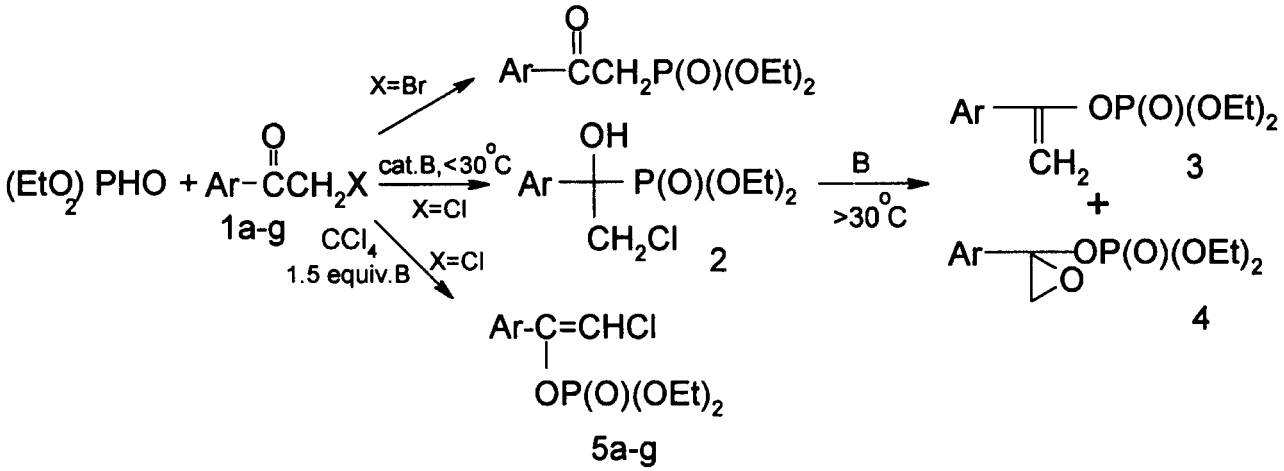
factors can also have a major influence on selectivity. Thus, we can control the selectivity of a given reaction by manipulating several factors. In this article, the reaction of an α-haloketone with diethyl phosphite was studied in the presence of base and carbon tetrachloride. At $-60°C$, α-haloacetophenone, $LiN(SiMe_3)_2$, carbon tetrachloride, and diethyl phosphite were mixed in THF. At low temperature, the substitution or addition reaction was very slow, the Michaelis–Becker or Pudovik reaction did not occur, and therefore, α-haloacetophenones and phosphite were first deprotonated. Thus, a phosphite anion attacked carbon tetrachloride only to give an intermediate diethyl phosphorochloridate. Reactions then followed the Atherton–Todd pathway to form β-haloenol phosphates (Scheme 2) in good yields, as shown in Table 1.

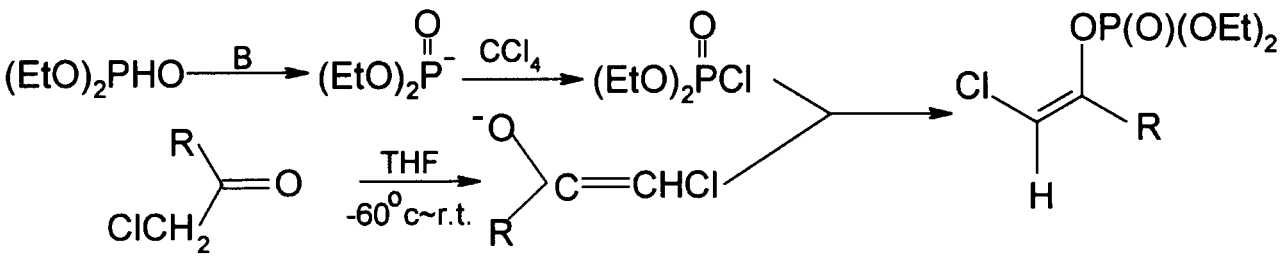
We found that all of the α-haloacetophenones listed in Table 1, except for compound **1e**, formed *Z* isomers under the given conditions in a highly stereoselective manner. The structures of the products were assigned on the basis of ^{1}H-NMR spectral analysis; the spectrum did not show the vinyl proton peak of the *E* isomer and the methylene peaks of three Perkow-type products in comparison with the spectra of pure samples and the data in references. TLC monitoring did not show the presence of other products. In each case, this analysis was carried out on the crude product prior to purification by chromatography. The stereoselectivity can be rationalized by the CIPE hypothesis (complex-induced proximity effect) [4]. The more stable *cis*-conformation of α-chloroacetophenone, which had been confirmed by infrared spectroscopy [5], and the chelation between lithium and chlorine atom favored the formation of the *Z*-enol ion that led to the formation of predominantly *Z*-isomeric β-haloenol phosphates, shown as follows.



However, 2,2′,4′-trichloroacetophenone was an exception. Infrared spectroscopy [6] had confirmed that the gauche conformation of 2,2′,4′-trichloro-

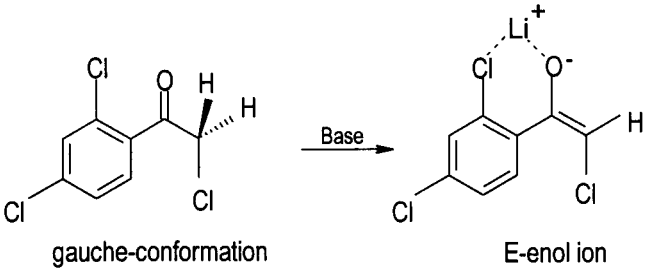


SCHEME 1



SCHEME 2

acetophenone **1e** is predominant in an apolar solvent, and, at the same time, the chelation between lithium and the 2-chloro atom in the benzene ring would also decrease the chelation of the lithium ion with chlorine atom at the α-carbon atom. In the case of 2,3′,4′-trichloro-acetophenone (**1f**), the chlorine being substituted at the 3-position of the benzene ring, only the *Z* isomer was obtained, which supports the concept of the chelate effect between the lithium ion with the chlorine atom at the 2-position of the benzene ring in the former example (**1e** of Table 1).



The temperature effect on the isomeric proportion *Z*/*E* of the products **5e** was examined. Under −60°C, the abstraction of an α-hydrogen was kinetically controlled leading to the formation of more *E*-enol ion that would result in the formation of more of the *E*-isomeric product. With an increase of the reaction temperature, the proportion of the *Z* isomer increased, as shown in Table 2. Thus, the *Z* enol should be thermodynamically more stable than the *E* enol.

TABLE 1 The Preparation of β-Chloroenol Phosphates

NO	*Y*(*Ar*= *Y-phenyl*)	*Yield* (%)[a]	*Z:E*[b]
1a	4-methoxy	55	>95:5
1b	4-methyl	60	>95:5
1c	H	65	>95:5
1d	4-choloro	66	>95:5
1e	2,4-dichloro	76	1:2
1f	3,4-dichloro	63	>95:5
1g	4-nitro	20	>95:5

[a]Isolated yield.
[b]The *E*/*Z* ratios were determined by ^{1}H-NMR analyses of the vinyl proton peaks of reaction products in the crude reaction mixture.

TABLE 2 The Temperature Effect on *Z*/*E* of **5e**

Reaction Temperature (°*C*)	*Yield* (%)	*Z:E*
−60	76	1:2
−30	68	1:1
20	62	4:3

The *Z*/*E* ratio was determined by ^{1}H-NMR analysis of the vinyl proton peak of **5e** in the crude product.

The reaction carried out in the presence of NaH as the base had a similar result.

We also studied the effect of the amount of the base on the reaction of 2,2′,4′-trichloro-acetophenone to observe the relationship with other possible reaction pathways. When the amount of the base was decreased, the Perkow-type dichloro enol phosphate (**3e,** Ar = 2,4-dichlorophenyl) was obtained, which was formed via a Pudovik reaction. With a decrease in the amount of base, the proportion of this product increased, as shown in Table 3. Because partial enolization of an α-haloketone did not facilitate the formation of the β-chloroenol phosphate product, the competitive Pudovik route, catalyzed by the base, occurred.

From Table 1, it can be seen that α-chloro-4-nitro-acetophenone yielded relatively small amounts of product. When the reaction was carried out by use of NaH as a base, only 7.5% of the chloroenol phosphate **5e** was detected, but the vinyl phosphate **3g** was found. Under the same conditions, α-bromo-4-nitro-acetophenone gave epoxy-phosphonate **4g** (Ar = 4-nitrophenyl). This can be attributed to the strong electron-withdrawing effect of the nitro group, and thus, the phosphite anion attacked the carbonyl carbon in the first place.

Aliphatic α-chloroketones underwent the same reaction. The two examples shown in Table 4, α-chlorocyclohexanone (**6**) and 1-chloro-1-phenylacetone (**7**), illustrate the generality. The fact that compound (**7**) gave two structural isomers (**7a** and **7b**) may be attributed to the existence of two kinds of lithium enolates [7], one of which resulted in two stereoisomers, **7a-*Z*** and **7a-*E***. When NaH was used as the base, the ratio of the *Z* isomer in the product increased.

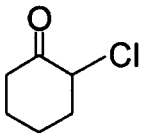
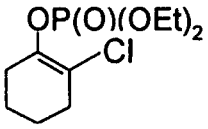
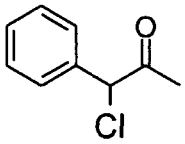
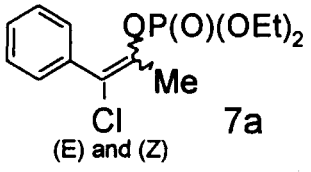
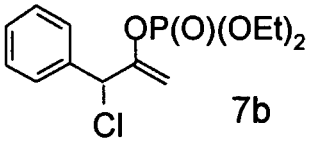
In summary, the reaction of α-haloketones with dialkyl phosphites have three possible pathways: the Michaeles–Becker reaction, the Pudovik reaction, and the Atherton–Todd reaction as reported in this article. The third way offers stereoselective syntheses of β-haloenol phosphates in a one-pot type of reaction. The new procedure employed a readily available phosphorylation procedure. In comparison with this procedure, the starting materials, β-hal-

TABLE 3 The Effect of Base on the Reaction of **1e**

1e:*Base*	*Todd Product* :	*Pudovik Product* (**3e**)
1:1.5	100	0
1:1.0	17	15
1:0.5	11	26

The ratio was determined by ^{1}H-NMR analysis of the vinyl proton peak of **5e** and methylene peak of **3e** in the crude product.

TABLE 4 The Reaction of Aliphatic Ketone with Diethyl Phosphite

NO	Substrate	Product	Base	Yields [a] (%)	Product [b] 7aE:7aZ:7b
6			$LiN(SiMe_3)_2$	70	
7		 7a (E) and (Z) +  7b	$LiN(SiMe_3)_2$	62	11:22:14
			NaH	58	1 : 5 : 0

[a]Isolated yield.
[b]The ratios were determined by ^{1}H-NMR analyses of the methyl and methylene peaks of reaction products in the crude product.

oenol phosphates, were prepared by the Michaelis–Becker method, α-dichloroketones were prepared only with difficulty, and the reaction stereoselectivity was unsatisfactory.

EXPERIMENTAL

Materials

2-Chloro-4′-methylacetophenone [8], 2-chloro-4′-methoxylacetophenone [8], 2-chloro-2′,4′-trichloroacetophenone [9], 2,3′,4′-trichloroacetophenone [9], and 2-chloro-4′-nitroacetophenone [10] were prepared according to the literature procedures. 2-Chlorocyclohexanone [11] and 1-chloro-1-phenylacetone [12a] were prepared by treatment of the corresponding ketone with $SOCl_2$. 2-Bromo-4′-nitroacetophenone was obtained by treatment of the corresponding acetophenone with bromine at room temperature [12b]. All the precursor compounds were characterized by ^{1}H-NMR spectroscopy and physical constants (purity > 95%). 2-Chloroacetophenone and 2-chloro-4′-chloro-acetophenone are available commercially (purity > 98%), diethyl phosphite (purity > 99%) was purchased from FLUKA company and distilled prior to use. Carbon tetrachloride was dried over anhydrous Na_2SO_4. THF was treated by the ketyl derived from sodium and benzophenone.

Instrumentation

Mass spectra were taken on a Finnigan-MATB 430 spectrometer. ^{1}H-NMR spectra were recorded on a FX-90Q instrument in CCl_4 with TMS as an external standard. Microanalyses were performed on a Rapid CHN-O-S analyzer.

GENERAL PROCEDURE

A multinecked round-bottomed flask was charged with $Li[N(SiMe_3)_2]$ (1.5 mL, 1.0 M solution in THF) and anhydrous THF (5 mL). The mixture was stirred under a nitrogen atmosphere and cooled to -60°C. A solution of α-haloketone (1.0 mmol) in THF was added slowly. After the mixture had been stirred for 30 minutes, diethyl phosphite (1.2 mmol) in CCl_4 was added dropwise. Then the temperature of the resulting mixture was allowed to rise to room temperature. When the reaction was complete as monitored by TLC (about 1.5 h after addition of diethyl phosphite), the reaction mixture was neutralized with acetic acid and then filtered. The filtrate was washed with water, dried over Na_2SO_4, and concen-

trated in vacuum to give an oil. The proportion of isomers was determined by NMR spectroscopy. The pure product was obtained after chromatography on silica gel using petroleum ether and ethyl acetate as eluent. The *E* and *Z* isomers were not separated generally. The known compounds were identified in agreement with the literature data, and only the ^{1}H-NMR data are reported here.

2-Chloro-1-(4-methoxylphenyl)vinyl Diethyl Phosphate (**5aZ**) *[13].* ^{1}H NMR δ: 1.39 (t, 6H), 3.90 (s, 3H), 4.19 (m, 6H), 6.00 (s, 1H), 7.17 (m, 4H).

2-Chloro-1-(4-methylphenyl)vinyl Diethyl Phosphate (**5bZ**) *[13].* ^{1}H NMR δ: 1.26 (t, 6H), 4.06 (m, 4H), 6.04 (s, 1H), 7.19 (m, 4H).

2-Chloro-1-phenylvinyl Diethyl Phosphate (**5cZ**) *[14].* ^{1}H NMR δ: 1.24 (t, 6H), 4.06 (m, 4H), 6.15 (s, 1H), 7.32 (m, 5H).

2-Chloro-1-(4-chlorophenyl)vinyl Diethyl Phosphate (**5dZ**) *[15].* ^{1}H NMR δ: 1.25 (t, 6H), 4.10 (m, 4H), 6.20 (s, 1H), 7.36 (m, 4H).

2-Chloro-1-(2,4-dichlorophenyl)vinyl Diethyl Phosphate (**5eZ** *and* **E**) *[16].* ^{1}H NMR δ: 1.26 (t, 6H), 4.00 (m, 4H), 5.84, 6.40 (*Z* and *E*, s, 1H), 7.28 (m, 3H).

2-Chloro-1-(3,4-dichlorophenyl)vinyl Diethyl Phosphate (**5fz**) *[13].* ^{1}H NMR δ: 1.43 (t, 6H), 4.26 (m, 4H), 6.32 (s, 1H), 7.57 (m, 3H).

2-Chloro-1-(4-nitrophenyl)vinyl Diethyl Phosphate (**5gZ**) *[13].* ^{1}H NMR δ: 1.34 (t, 6H), 4.15 (m, 4H), 6.43 (s, 1H), 7.92 (m, 4H).

1-(2,4-Dichlorophenyl)vinyl Diethyl Phosphate (**3e**, *Ar = 2,4-Dichlorophenyl*) *[17].* ^{1}H NMR δ: 1.30 (t, 6H), 4.10 (m, 4H), 5.01 (t, 1H, $J_{HCH} = J_{POCCH} = 2$ Hz), 5.38 (t, 1H), 7.35 (m, 3H).

The Reaction of 2-Halo-4′-nitroacetophenone with Diethyl Phosphite with NaH as Base

The reaction of 2-chloro-4′-nitroacetophenone followed the general procedure using NaH as base and gave **5g** 7.5% and **3g** 38%. 2-Bromo-4′-nitroacetophenone formed **4g** 40%.

1-(4-Nitro-phenyl)vinyl Diethyl Phosphate (**3g**, *Ar = 4-nitrophenyl*) *[18].* ^{1}H NMR δ: 1.37 (t, 6H), 4.16 (m, 4H), 5.40 (m, 2H), 7.95 (d-d, 4H). MS (m/z, %): 302 (M + 1, 100.00), 155 (44.00), 127 (14.77).

Diethyl 1-(4-Nitrophenyl)-epoxyphosphonate (**4g**, *Ar = 4-Nitrophenyl*). ^{1}H NMR δ: 1.3 (q, 6H), 2.78 (t, 1H, $J_{HCH} = J_{POCCH} = 5$ Hz), 3.41 (t, 1H), 4.12 (m, 4H), 7.32–8.18 (m, 2H). $C_{12}H_{16}NO_6P$ (301.26): calcd C, 47.84; H, 5.36; found: C, 47.90; H, 5.40. MS (m/z, %): 302 (M + 1, 78.64), 285 (8.93), 274 (46.41), 245 (44.81), 228 (9.70), 150 (100.00), 134 (17.66), 121 (16.64), 89 (28.27), 65 (25.37).

2-Chloro-1-cyclohexen-1-yl Diethyl Phosphate (**6**) *[19].* ^{1}H NMR δ: 1.50 (t, 6H), 1.91 (m, 4H), 2.55 (m, 4H), 4.28 (m, 4H).

1-Methyl-2-phenyl-2-chlorovinyl Diethyl Phosphate (**7a**). ^{1}H NMR δ: 1.23 (t, 6H), 2.08, 2.33 (*E* and *Z*, s, 3H), 4.25 (m, 4H), 7.30 (s, 5H). $C_{13}H_{18}ClO_4P$ (304.73): calcd C, 51.23; H, 5.96; found: C, 51.60; H, 6.14. MS (m/z, %): 305 (M + 1, 1.81), 269 (2.82), 213 (8.00), 155 (100.00), 149 (4.38), 127 (37.64), 115 (43.63), 105 (7.63), 99 (38.15), 81 (9.02).

1-(α-Chloro-benzyl)vinyl Diethyl Phosphate (**7b**). ^{1}H NMR δ: 1.23 (t, 6H), 4.25 (m, 4H), 4.85 (s, 1H), 5.09 (t, 1H $J_{HCH} = J_{POCCH} = 2$ Hz), 5.46 (t, 1H), 7.30 (m, 5H). MS (m/z, %): 304 (M, 19.52), 269 (22.89), 241 (7.74), 213 (20.87), 155 (100.00), 127 (33.67), 115 (92.60), 99 (50.50), 81 (14.14), 44 (10.10).

REFERENCE

[1] J. K. Stowell, T. S. Widlauski, *J. Am. Chem. Soc., 116,* 1994, 789.

[2] N. D. Kimpe, R. Verhé: *The Chemistry of α-Haloketone, α-Haloaldehydes and α-Haloimines*, Wiley, Chichester (1988).

[3] A. Meisters, J. M. Swan, *Aust. J. Chem., 18,* 1965, 168; M. A. Ruveda, S. A. DeLicastro, *Tetrahedron, 28,* 1972, 6012.

[4] P. Beak, A. Basn, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res., 29,* 1996, 552.

[5] L. J. Bellamy, L. C. Thomas, R. L. Williams, *J. Chem. Soc.,* 1956, 3704; P. R. Olivato, S. A. Guerrero, R. R. Hase, *J. Chem. Soc. Perkin Trans., 2,* 1990, 465.

[6] P. J. Krueger, *Can. J. Chem., 51,* 1973, 1363; L. J. Bellamy, R. G. Scamehoru, *J. Chem. Soc.,* 1957, 4294; L. J. Bellamy, L. C. Thomas, R. L. Williams, *J. Chem. Soc.,* 1956, 3704.

[7] F. G. Bordwell, R. G. Scamehorn, *J. Am. Chem. Soc., 90,* 1968, 6751.

[8] F. Kunckell, *Ber., 30,* 1897, 577; F. Tutin, *J. Chem. Soc., 97,* 1910, 2500.

[9] Okada, Masayaki, *Jpn. Kokai Tokkyo Koho JP, 63,* 115839[88,115839].

[10] P. Truitt, R. Stead, L. M. Long, W. J. Middleton, *J. Am. Chem. Soc., 71,* 1949, 3511.

[11] E. W. Warnhoff, D. G. Martin, W. S. Johonson, *Org. Syn. Coll., 4,* 162.

[12] (a) F. G. Bordwell, R. G. Scamehorn, *J. Am. Chem.*

Soc., 90, 1968, 6751; (b) J. W. Baker, *J. Chem. Soc.,* 1931, 2416.
[13] A. Preiss, H. Luthardt, H. Deuther, *J. Prakt. Chemie, 324,* 1982, 461.
[14] I. J. Borowitz, K. C. Yee, R. K. Crouch, *J. Org. Chem., 38,* 1973, 1713.
[15] Malionowski, *Henryk. Organika, 96,* 1977.
[16] A. Zwiersak, B. Sledzinski, L. Cieslak, *Pr. Inst. Przem. Org., 6,* 1974, 85.
[17] Y.-P. Sun, E. R. Johnson, *J. Econ. Entomol., 65(3),* 1972, 629.
[18] R. D. Frampton, T. T. Tidwell, V. A. Young, *J. Am. Chem. Soc., 94,* 1972, 1271.
[19] T. V. Kim, Zh. M. Ivanova, Yu. G. Gololobov, *Zh. Obshch. Khim., 48,* 1978, 1967.