

# The Reaction of Pentasubstituted 3-Hydroxy-1,2-Dioxolanes (Hemiperketals) with Trivalent Phosphorus Compounds: Synthesis of $\beta$ -Hydroxy Ketones

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## ABSTRACT

The reaction of a series of 4,4-dimethyl-3,5,5-( $R_3$ ,  $R_2$ ,  $R_1$ )-3-hydroxy-1,2-dioxolanes **1a-d** [**1a** ( $R_1 = R_2 = R_3 = \text{Me}$ ); **1b** ( $R_1 = R_2 = \text{Me}$ ,  $R_3 = \text{Ph}$ ); **1c** ( $R_1 = \text{Ph}$ ,  $R_2 = R_3 = \text{Me}$ ); **1d** ( $R_1 = R_3 = \text{Ph}$ ,  $R_2 = \text{Me}$ )] with trimethyl phosphite or triphenylphosphine produced the  $\beta$ -hydroxy ketones, **2a-d** [( $R_1R_2C(\text{OH})C\text{Me}_2\text{-COR}_3$ ), and the corresponding phosphoryl compounds in high yield. The reactions were slow ( $\sim 24$  hours), requiring excess of the trivalent phosphorus compounds for optimum results. The reaction was found to be of the second order overall, first order in peroxide and in phosphorus reagent. Triphenylphosphine was found to be more reactive than trimethyl phosphite. Formal substitution of a phenyl group for a methyl group on the hemiperketals yielded a reduction of reactivity of  $\sim 2.4$ -fold at the 3-position but an increase in reactivity ( $\sim 1.5$ -fold) at the 5-position. The rate constants for tautomerization of **1c** in benzene were determined. The activation parameters for reaction of **1c** with triphenylphosphine in benzene- $d_6$  were determined [ $\Delta H^\ddagger = 15.0 \pm 1.5$  kcal/mol;  $\Delta S^\ddagger = -21.7$  eu;  $\Delta G^\ddagger = 21.7$  kcal/mol;  $k_{34^\circ} = 2.4 \times 10^{-3}$   $M^{-1} s^{-1}$ ]. The data are consistent with direct insertion of the phosphorus compounds into the peroxide bond to yield phosphorane intermediates. Rapid in-

tramolecular hydrolysis of the intermediates would produce the  $\beta$ -hydroxy ketones and phosphoryl compounds.

The reactions of trivalent phosphorus compounds with cyclic peroxides, especially endoperoxides, are useful for characterization and have synthetic applications [1]. Our previous studies [2] have centered on the reaction of phosphorus compounds with 1,2-dioxetanes to yield phosphoranes via biphilic insertion of the phosphorus into the peroxy bond. The reactions of phosphorus compounds with the 1,2-dioxolane and related ring systems have not been investigated extensively. Clennan and Heah [3a] have reported the reaction of triphenylphosphine with 2,3-dioxabicyclo[2.2.1]heptane (prostaglandin endoperoxide model compound [3b]) to yield a *trans*-1,3-diol via hydrolysis of a phosphorane intermediate. The deoxygenation of  $\beta$ -peroxy lactones has been studied by Adam et al. [4] as a model system for the Mitsunobu reaction. Wojciechowski et al. [5] have shown that 3,3-dimethoxy-1,2-dioxolane and 3-methoxy-1,2-dioxolane yield methyl acrylate and acrolein, respectively, upon treatment with triphenylphosphine. A 3-hydroxy-1,2-dioxolane derivative, synthesized by addition of singlet oxygen to cholest-5-ene-3-one, has been reduced to a  $\beta$ -hydroxy keto compound with triphenylphosphine [6]. Recently, we have developed a new synthetic route [7] for the synthesis of 3-hy-

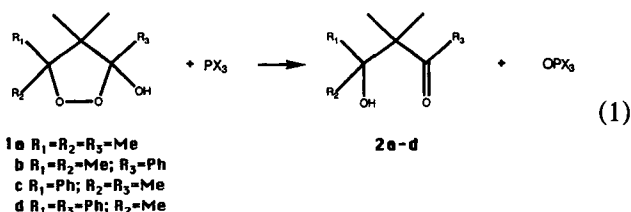
Dedicated to Prof. James Cullen Martin on the occasion of his sixty-fifth birthday.

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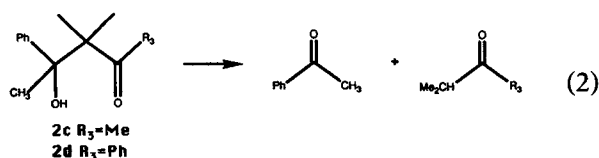
droxy-1,2-dioxolanes. We report a study of the reaction of a series of 4,4-dimethyl-3,5,5-trisubstituted-3-hydroxy-1,2-dioxolanes with trivalent phosphorus compounds to yield highly substituted  $\beta$ -hydroxy ketones.

## RESULTS

The reaction of 4,4-dimethyl-3,5,5-trisubstituted-3-hydroxy-1,2-dioxolanes, **1a–d** (hemiperketals), with trivalent phosphorus compounds produced the corresponding  $\beta$ -hydroxy ketones, **2a–d**, and phosphoryl compounds in greater than 95% yield (Rxn 1). Triphenylphosphine was found to



be more reactive than trimethyl phosphite. The reactions were slow at ambient temperature, requiring  $\sim 1$  day for completion even with an excess of the phosphorus reagents. The process could be carried out conveniently with a large excess of the phosphite in either  $CDCl_3$  or benzene- $d_6$  as solvent. Little or no thermal decomposition of the hemiperketals **1a–d** was noted under these reaction conditions. The  $\beta$ -hydroxy ketones **2a–d** were found to be stable to the conditions. The products were isolated by chromatographic methods and characterized by physical and spectral techniques. Compounds **2c,d** were found to be metastable at room temperature during and after purification, undergoing a "retro-aldol" reaction (Rxn 2) with a  $t_{1/2}$  of 4 hours.



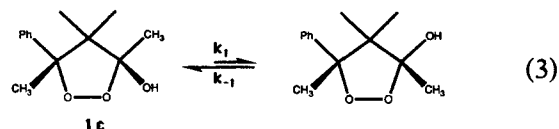
Compounds **2a,b** were found to be stable. Samples of **2a–d** were stored at  $-80^\circ C$  with little or no decomposition.

The kinetics of the reaction of hemiperketals, **1a–d**, with trimethyl phosphite in  $CDCl_3$  at  $22^\circ C$  were measured (Table 1). Since the trimethyl phosphite reduction of **1a–d** was slow, a five- to tenfold excess of the phosphorus reagent was employed. This minimized the loss of hemiperketal due to competing thermal decomposition [9] and resulted in the production of the  $\beta$ -hydroxy ketones in greater than 95% yields. The reactions showed excellent second-order behavior overall. The val-

ues of the second-order rate constants,  $k_2$ , were found to range from  $1.2 \times 10^{-4}$  to  $3.4 \times 10^{-5} M^{-1} s^{-1}$ . Formal substitution of a phenyl for a methyl group on the hemiperketals yielded a reduction of reactivity of  $\sim 2.4$  at the 3-position but a slight increase in reactivity at the 5-position.

The reaction of hemiperketal **1c** with trivalent phosphorus compounds was studied in benzene- $d_6$  (see Table 2). The  $^1H$  NMR data (transient upfield signals) suggested the presence of phosphorane intermediates, but unambiguous identification was not achieved. In all cases,  $\beta$ -hydroxy ketone **2c** and the corresponding phosphoryl compounds were formed as the final products in high yield. Excellent second-order behavior, first order in phosphorus reagent and in peroxide, was observed. At  $34^\circ C$ , the reaction of **1c** with triphenylphosphine was  $\sim 3$ -fold slower in benzene- $d_6$  than in  $CDCl_3$ . In addition, the trimethyl phosphite reduction of **1c** was  $\sim 3.4$ -fold slower than that with triphenylphosphine in benzene- $d_6$  at  $34^\circ C$ . The activation parameters for the reaction of **1c** and triphenylphosphine were determined by the Arrhenius method ( $E_a = 15.6 \pm 1.5$  kcal/mol;  $\Delta H^\ddagger = 15.0$  kcal/mol;  $\Delta S^\ddagger = -21.7$  eu;  $\Delta G^\ddagger = 21.7$  kcal/mol;  $k_{34^\circ} = 2.4 \pm 0.1 \times 10^{-3} M^{-1} s^{-1}$ ).

Hemiperketal **1c** was observed to undergo tautomerization during thermal decomposition and, while in storage [9], presumably via an acyclic intermediate. To assess the possibility that the phosphorus reagents were undergoing reaction with an acyclic intermediate ( $\beta$ -hydroperoxy ketone) rather than the hemiperketal directly, the apparent first-order rate constants ( $k_1$  and  $k_{-1}$ ) for the tautomerization of **1c** in benzene at  $34^\circ C$  were determined (Rxn 3). The values of  $k_1$  and  $k_{-1}$



were found to be  $4.5 \times 10^{-5} s^{-1}$  and  $8.8 \times 10^{-5} s^{-1}$ , respectively. These values are too low to account for the observed kinetic behavior in the presence of the phosphorus compounds and indicate that the phosphorus reagents are undergoing direct reaction with the hemiperketal (closed structure) rather than with a  $\beta$ -hydroperoxy ketone (acyclic structure).

## DISCUSSION

The reduction of hemiperketals with phosphorus reagents should be useful for the synthesis of a variety of highly substituted  $\beta$ -hydroxy aryl and aliphatic ketones.  $\beta$ -Hydroxy ketones, **2a** and **2b**, have been synthesized previously by different methods. Compound **2a** was obtained in 38% yield by the titanium tetrachloride-catalyzed rearrangement of

**TABLE 1** Second-Order Rate Constants and Yields of  $\beta$ -Hydroxy Ketones for the Reaction of Hemiperketals<sup>a</sup> **1a–d** with Trimethylphosphite<sup>b</sup> in  $\text{CDCl}_3$ 

Hemiperketal	$R_1$	$R_2$	$R_3$	Temperature ( $\pm 2^\circ\text{C}$ )	$k_2 \text{ M}^{-1} \text{ s}^{-1}$	$\beta$ -Hydroxy Ketone	Isolated Yield <sup>c</sup> %
<b>1a</b>	Me	Me	Me	22°C	$7.0 \times 10^{-5}$	<b>2a</b>	91
<b>1b</b>	Me	Me	Ph	22°C	$3.4 \times 10^{-5}$	<b>2b</b>	88
<b>1c</b>	Ph	Me	Me	22°C	$1.2 \times 10^{-4}$	<b>2c</b>	87
<b>1d</b>	Ph	Me	Ph	22°C	$4.9 \times 10^{-5}$	<b>2d</b>	74

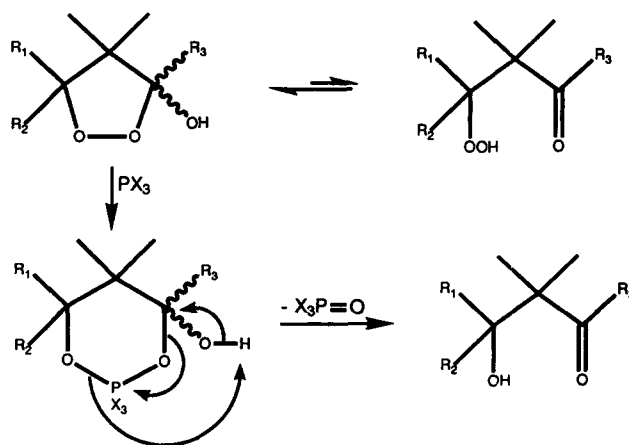
<sup>a</sup> $[1]_0 = 0.14 - 0.28 \text{ M}$ .<sup>b</sup> $[\text{P}(\text{OMe})_3]_0 = 0.30 - 1.10 \text{ M}$ .<sup>c</sup>Yields by <sup>1</sup>H NMR spectroscopy greater than 95%.**TABLE 2** Second-Order Rate Constants for the Reaction of Cyclic Peroxides with Trivalent Phosphorus Compounds ( $\text{PX}_3$ ) in Benzene- $d_6$ 

Peroxide	$\text{PX}_3$	$k_2 \text{ M}^{-1} \text{ s}^{-1}$	$T^\circ\text{C} \pm 0.3^\circ\text{C}$
<b>1c</b>	X = OMe	$7.0 \pm 0.7 \times 10^{-4}$	34.0
<b>1c</b>	X = Ph	$8.6 \pm 0.4 \times 10^{-4}$	22
<b>1c</b>	X = Ph	$2.4 \pm 0.1 \times 10^{-3}$	34.0
<b>1c</b>	X = Ph	$(7.4 \pm 0.3 \times 10^{-3})$	(34.0 in $\text{CDCl}_3$ )
<b>1c</b>	X = Ph	$8.6 \pm 0.4 \times 10^{-3}$	49.8
Tetramethyl-1,2-dioxetane <sup>a</sup>	X = Ph	$1.70 \pm 0.04$	23.9
2,3-Dioxabicyclo[2.2.1]heptane <sup>b</sup>	X = Ph	$9.3 \pm 0.6 \times 10^{-3}$	24

<sup>a</sup>Taken from Ref. [2a].<sup>b</sup>Taken from Ref. [3a].

an epoxy silyl ether [10]. Ketone **2b** was reported as the product of the acid-catalyzed hydrolysis of 2-methoxy-2-phenyl-3,3,4,4-tetramethyloxetane [11]. Substitution ( $R_1$ ,  $R_2$ ) on the  $\beta$ -position can be alkyl and aryl. Attempts to isolate compounds with two  $\beta$ -phenyl groups were unsuccessful (rxn-2 type products were obtained). The production of  $\beta$ -hydroxy keto products by the reduction of **1a–d** with phosphorus compounds is consistent with the results of Dang et al. [6] for the reaction of triphenylphosphine with the hemiperketal formed by singlet oxygen addition to cholest-5-ene-3-one. Similarly, Adam et al. [8] have shown that the triphenylphosphine reduction of 3-hydroxy-6,6-dimethyl-1,2-dioxane produced the  $\gamma$ -hydroxy ketone (4-hydroxy-4-methyl-1-phenyl-1-pentanone) in quantitative yield.

The reaction of **1c** with triphenylphosphine in benzene- $d_6$  at 22°C was approximately tenfold slower than that for 2,3-dioxabicyclo[2.2.1]heptane [3a] at 24°C and approximately 2000-fold slower than that for tetramethyl-1,2-dioxetane [2a] at 23.9°C. The relative reactivity of triphenylphosphine vs. that of trimethyl phosphite was essentially identical to that found in the dioxetane case [2a]. The activation parameter data for the reaction of **1c** with triphenylphosphine showed a large negative  $\Delta S^\ddagger$  value similar to that ( $\Delta S^\ddagger = -27 \text{ eu}$ ) observed [2a] for the tetramethyl-1,2-dioxetane insertion reaction. The results suggest a mechanism (Scheme 1) for the reduction of hemiperketals by

**SCHEME 1**

the trivalent phosphorus compound analogous to that [2] shown for dioxetanes. Biphilic (concerted) insertion of the phosphorus reagent into the peroxy bond would yield a phosphorane intermediate. This phosphorane would undergo intramolecular hydrolysis to yield directly the  $\beta$ -hydroxy ketone and phosphoryl products. The lack of additional (side) products and stability of the  $\beta$ -hydroxy ketone to the reaction conditions appear to rule out phosphonium ion-type intermediates. The effect of formal substitutions of a phenyl for methyl group

on the hemiperketals in the reaction with trimethyl phosphite suggests that the transition state for insertion is not symmetrical.

In conclusion, the reaction of **1a–d** with trivalent phosphorus compounds is a good method for the generation of  $\beta$ -hydroxy ketones and constitutes an alternative approach to the formation of highly substituted aldol adducts.

## EXPERIMENTAL SECTION

All solvents were of reagent grade. Triphenylphosphine (Aldrich) and trimethyl phosphite (Aldrich) were used without further purification. The synthesis of the 3,5,5-trisubstituted-4,4-dimethyl-3-hydroxy-1,2-dioxolanes has been reported [7]. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL GX-270 NMR spectrometer. The  $^1\text{H}$  NMR kinetic runs were carried out on a Varian EM-360 NMR spectrometer. The IR spectra were recorded on a Bomem-Michelson 100-FT-IR spectrometer. Melting points were taken on a Thomas Hoover Uni-melt apparatus and are uncorrected. Combustion analyses were performed by Atlanta Microlabs, Atlanta, GA. The MS data were obtained at the Georgia Institute of Technology, Atlanta, GA.

### Product Studies

The following procedure for the reaction of 3,4,4,5,5-pentamethyl-3-hydroxy-1,2-dioxolane (**1a**) with trimethyl phosphite is representative: to 22 mg (0.14 mmol) of **1a** in 0.5 mL of  $\text{CDCl}_3$  (Aldrich) were added 80  $\mu\text{L}$  (0.68 mmol) of trimethyl phosphite at ambient temperature. After complete disappearance ( $\sim 1$  day) of hemiperketal (monitored by  $^1\text{H}$  NMR spectroscopy), volatile components were removed under reduced pressure at ambient temperature. The residual oily crude products were separated by chromatographic methods (chromatotron: 1/8 in. plates; Silica Gel 60 PF<sub>254</sub> containing gypsum and fluorescent indicator; petroleum ether-diethyl ether 5% step gradient). The  $\beta$ -hydroxy ketone **2a** (3,3,4-trimethyl-3-hydroxy-2-pentanone [10]) was isolated as an oil, 18 mg (0.13 mmol) 91% yield:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.18 (s, 6H), 1.23 (s, 6H), 2.23 (s, 3H), 3.9 (br·s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.5, 25.6, 28.2, 53.2, 74.4, 218.7; IR (neat) 3459.5  $\text{cm}^{-1}$ , 1690.1  $\text{cm}^{-1}$ ; MS, base 57 (EI). For **2b** (1-phenyl-2,2,3-trimethyl-3-hydroxy-1-butanone [11]) oil, 88% isolated yield:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.30 (s, 6H), 1.36 (s, 6H), 4.20 (br·s, 1H), 7.40–7.55 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.2, 25.9, 53.6, 75.2, 126.9, 128.2, 130.6, 140.5, 216; IR (neat) 3459.9  $\text{cm}^{-1}$ , 1663.6  $\text{cm}^{-1}$ ; MS M-1 205, base 149 (EI); M + 1 207 (CI). For **2c** (3,3-dimethyl-4-phenyl-4-hydroxy-2-pentanone) oil, 87% isolated yield:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.14 (s, 3H), 1.19 (s, 3H), 1.60 (s, 3H), 2.08

(s, 3H), 4.36 (br·s, 1H), 7.32 (m, 3H), 7.41 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.7, 22.1, 24.7, 28.9, 53.6, 77.7, 126.9, 127.2, 127.4, 144.1, 218.8; IR (neat) 3458.2  $\text{cm}^{-1}$ , 1687.4  $\text{cm}^{-1}$ ; MS M-1, 2% of base at 105 (EI). Anal calcd C: 75.69, H: 8.80; found C: 75.76, H: 8.83. For **2d** (1,3-diphenyl-2,2-dimethyl-3-hydroxy-1-butanone) mp 84.5–85°C, 74% isolated yield:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.26 (s, 3H), 1.30 (s, 3H), 1.73 (s, 3H), 4.85 (br·s, 1H), 7.10–7.50 (m, 8H), 7.96 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.6, 24.2, 24.8, 54.1, 78.4, 126.4, 127.0, 127.5, 127.6, 127.9, 130.3, 140.6, 144.5, 216.5; IR 3455  $\text{cm}^{-1}$ , 1662.2  $\text{cm}^{-1}$ ; MS, base 105 (EI). Anal calcd C: 80.56, H: 7.51; found C: 80.68, H: 7.53.

### Kinetic Studies

The following procedure for the reaction of hemiperketal **1c** with triphenylphosphine is representative: to 20 mg of **1c** in a new NMR sample tube were added 0.500 mL of benzene- $d_6$  (MSD) containing 5.0  $\mu\text{L}$  of anisole as internal standard. The  $^1\text{H}$  NMR spectrum was recorded, and the signals were integrated vs. internal standard. One equivalent of triphenylphosphine (23.6 mg) was added as the solid, and the solution was maintained at constant temperature (oil bath). The  $^1\text{H}$  NMR spectra were taken at various times, and the signals were integrated vs. internal standard. Samples were placed in an ice bath before and after recording of the  $^1\text{H}$  NMR spectra. Second-order plots of the disappearance of **1c** or appearance of **2c** were linear for at least two half-lives. The reproducibility of the second-order rate constants was better than  $\pm 5\%$  for the reactions carried out in benzene- $d_6$ . The error limits for  $k_2$  in the trimethyl phosphite reactions in  $\text{CDCl}_3$  are larger ( $\pm 20\%$  of value) due to a larger variation in temperature.

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