THE REACTION OF TRIPHENYLPHOSPHINE WITH 3-METHOXY- AND 3-ACETOXY-4,4,5,5-TETRASUBSTITUTED-1,2-DIOXOLANES

A.L. Baumstark,* P.C. Vasquez and Y.-X. Chen
LBCS, Department of Chemistry, Georgia State University, Atlanta, Georgia 30303

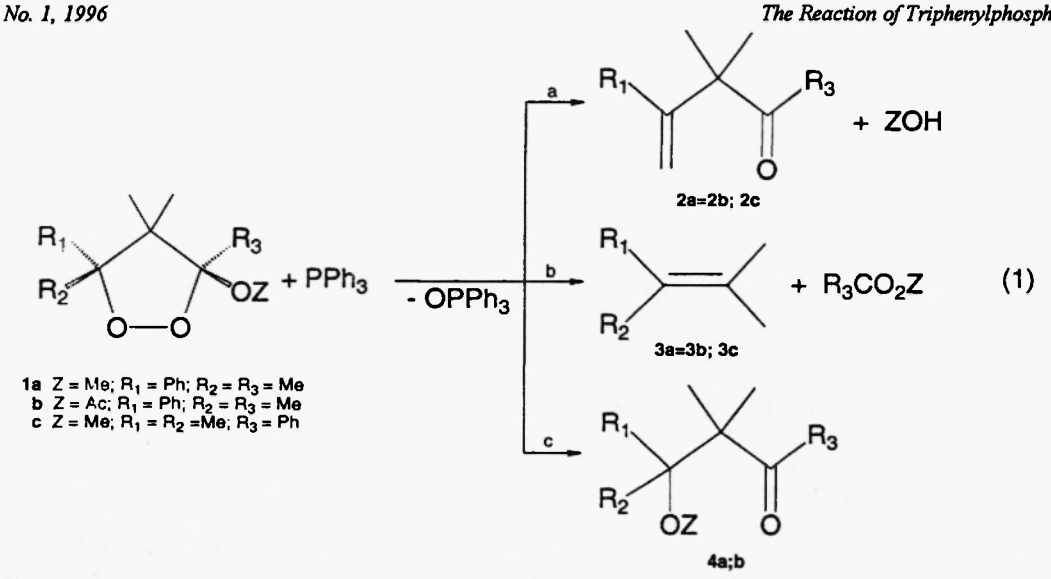
Abstract: The reaction of 3-methoxy-3,4,4,5-tetramethyl-5-phenyl-1,2-dioxolane **1a**, 3-acetoxy-3,4,4,5-tetramethyl-5-phenyl-1,2-dioxolane 1b and 3-methoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane **1c** with triphenylphosphine proceeded sluggishly to yield β,γ-unsaturated ketones **2**, tetrasubstituted alkenes **3** [concomitant yields of methanol or acetic acid (with **2**) and methyl esters or acetic anhydride (with **3**)] and triphenylphosphine oxide as the major products in benzene-d_6. In acetonitrile-d_3, additional products, β-methoxy- or β-acetoxyketones **4** were formed with a corresponding reduction in the yields of **2**. The second order rate constants, k_2, for the reaction of **1a-c** with the phosphine were determined in benzene-d_6; **1b > 1c > 1a**. The k_2 values for **1a**, b in acetonitrile-d_3 were only slightly larger than those found in benzene-d_6. The activation parameters for the reactions of **1a-c** with triphenylphosphine in benzene-d_6 were determined. The results were consistent with initial formation of metastable phosphoranes as the rate-determining step. Subsequent decomposition of the phosphoranes via three ionic routes would account for the observed product distributions.

Introduction

The reactions of phosphines and other trivalent phosphorus compounds with cyclic peroxides including endoperoxides have been found to be useful for peroxide characterization and certain synthetic applications (1). Additionally, these reactions are of mechanistic interest (1,2). Previously, our studies have focused (2) on the reaction of 1,2-dioxetanes with trivalent phosphorus compounds which produce isolable phosphorane intermediates. The reaction of trivalent phosphorus compounds with 1,2-dioxolanes and related compounds has not been investigated extensively. Since triphenylphosphine is readily available, reasonably stable and of moderate reactivity, it is usually the phosphorus compound of choice for exploratory reactions with peroxidic materials. For example, the triphenylphosphine reduction of a prostaglandin endoperoxide model compound, 2,3-dioxabicyclo[2.2.1]heptane, was found (3) to yield a trans-1,3-diol via hydrolysis of an intermediate (phosphorane). The reaction of triphenylphosphine with β-peroxylactones has been studied (4) by Adam as a model system for the Mitsunobu reaction. 3,3-Dimethoxy-1,2-dioxolane and 3-methoxy-1,2-dioxolane were found (5) to yield methyl acrylate and acrolein respectively upon reduction with triphenylphosphine. 3-Hydroxy-1,2-dioxolanes (hemiperketals) have been shown (6) to undergo reaction with triphenylphosphine to yield β-hydroxy-keto compounds. We report here a study of the reaction of triphenylphosphine with 3-methoxy- and 3-acetoxy-4.4,5,5-tetrasubstituted-1,2-dioxolanes (perketals) which provide insights into the mechanisms of phosphorane fragmentation.

Results

The reaction of 3-methoxy-3,4,4,5-tetramethyl-5-phenyl-1,2-dioxolane **1a**, 3-acetoxy-3,4,4,5-tetramethyl-5-phenyl-1,2-dioxolane 1b and 3-methoxy-3-phenyl-4,4,5,5-tetramethyl-1,2-dioxolane **1c** with triphenylphosphine in benzene-d_6 produced β,γ-unsaturated ketones **2**, methanol or acetic acid [co-product with **2**], tetrasubstituted alkenes **3** with concomitant yield of methyl ester or acetic anhydride [for 1b, metastable β-acetoxyketone 4b] and a quantitative yield of triphenylphosphine oxide [rxn 1]. For the reaction of **1a** and 1b,



(1)

the predominant product was the β,γ-unsaturated ketone, **2a**, accounting for roughly 80% of the yield. For **1c**, the yields of **2c** and **3c** were essentially equivalent. The reaction of **1a** and **b** with triphenylphosphine was carried out in acetonitrile-d_3 as solvent. For **1a**, a new product, β-methoxyketone **4a** was obtained with a substantial decrease in the yield of **2a**. The results for **1b** in acetonitrile-d_3, although similar to those obtained in benzene-d_6, also appeared to show a decrease in the yield of **2a** with a corresponding increase in the yield of **4b**. The yields of alkene **3** seemed relatively insensitive to solvent changes. The product yields for the reaction of dioxolanes **1a-c** with triphenylphosphine in benzene-d_6 and acetonitrile-d_3 are summarized in Table 1.

Table 1. Product Yields[a,b] for the Reaction of Triphenylphosphine with Dioxolanes **1a-c** in Benzene-d_6 and Acetonitrile-d_3 at 34 °C

Dioxolane	Solvent	β,γ-Unsaturated ketone, % **2**	Tetrasubstituted alkene, % **3**	ZO-migration products, % **4**
1a	Benzene-d_6	84 ± 4	15 ± 3	0
	Acetonitrile-d_3	41 ± 4	19 ± 4	35 ± 5
1b	Benzene-d_6	74 ± 4	14 ± 3	12 ± 2
	Acetonitrile-d_3	60 ± 3	21 ± 3	19 ± 3
1c	Benzene-d_6	53 ± 4	47 ± 4	0

a) Normalized to remove thermolysis products, determined by ^{1}H NMR spectroscopy. b) Yields of co-products for each type of major organic product are within the range listed. Triphenylphosphine oxide yields are quantitative for all experiments.

The reaction of dioxolanes **1a-c** with one equivalent of triphenylphosphine at 34 °C was very slow, requiring more than ten days for completion for **1a**, several days for **1c** and less than one day for **1b**. Under these reaction conditions, the thermolytic decomposition (7) of **1b** did not compete with reaction 1. However,

thermolysis accounted for 20-25% of the disappearance of **1a** or **1c** under equal molar conditions. A three-to-five-fold excess of phosphine was employed to minimize the extent of thermal decomposition (7) for the latter two cases.

The kinetics of the reaction of dioxolanes **1a-c** with triphenylphosphine was investigated at various temperatures by NMR methodology. In addition, transient upfield signals were observed by ^{1}H NMR spectroscopy, for reactions carried out in benzene-d_6, indicative of the formation of phosphorane intermediates. The reactions showed excellent second-order behavior. At 34°C in benzene-d_6, the following reactivity series was obtained: **1b > 1c > 1a**. The k_2 values for reactions of **1a** and **1b** in acetonitrile-d_3 at 34° were found to be only slightly larger than those obtained in benzene-d_6. The data are listed in Table 2.

Table 2. Second-Order Rate Constants[a] for the Reaction of Dioxolanes **1a-c** with Triphenylphosphine[c] in Benzene-d_6 (and Acetonitrile-d_3).[b]

Dioxolane	Temperature (± 0.2 °C)	k_2 $M^{-1}s^{-1}$
1a	34.0	$1.6 \pm 0.1 \times 10^{-5}$
1a	34.0	$(2.1 \pm 0.1 \times 10^{-5})$[b]
1a	45.3	$4.0 \pm 0.1 \times 10^{-5}$
1a	54.4	$8.5 \pm 0.2 \times 10^{-5}$
1b	22.0	$8.3 \pm 0.7 \times 10^{-5}$
1b	34.0	$1.9 \pm 0.1 \times 10^{-4}$
1b	34.0	$(2.5 \pm 0.1 \times 10^{-4})$[b]
1b	50.0	$4.9 \pm 0.4 \times 10^{-4}$
1b	60.0	$1.0 \pm 0.1 \times 10^{-3}$
1c	22.0	$3.3 \pm 0.2 \times 10^{-5}$
1c	35.8	$8.4 \pm 0.4 \times 10^{-5}$
1c	49.8	$2.6 \pm 0.1 \times 10^{-4}$

a) $[Dioxolane]_0/[Phosphine]_0$ ratio was 1/5 for **1a**; 1/1 for **1b**; and 1/3 for **1c**. b) Rate constants in Acetonitrile-d_3 are in parentheses.

The activation parameters for the reaction of **1a-c** with triphenylphosphine were determined by the Arrhenius method from the data listed in Table 2. The lack of thermal stability and the low reactivity limited the temperature range of the study for compounds **1a** and **1c**. The $\Delta H^{\ddagger}$'s ranged from 15 to 11.5 kcal/mol with $\Delta S^{\ddagger}$'s of -34 to -37 eu. The data are similar to those for the reactions of triphenylphosphine with tetramethyl-1,2-dioxetane [$\Delta H^{\ddagger}$ = 9.6 kcal/mol; $\Delta S^{\ddagger}$ = -27 eu] (8) and with 3-hydroxy-3,4,4,5-tetramethyl-5-phenyl-1,2-dioxolane [$\Delta H^{\ddagger}$ = 15 kcal/mol; $\Delta S^{\ddagger}$ = -22 eu] (6b). The results are listed in Table 3.

Table 3. Activation Parameters for the Reaction of **1a-c** with Triphenylphosphine in Benzene-d_6 at 34 °C

Dioxolane	Ea (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	$\Delta G^{\ddagger}$ (kcal/mol)	k_2 $M^{-1}s^{-1}$
1a	15.6 ± 2.2	15.0	-33.7	25.4	1.6×10^{-5}
1b	12.2 ± 1.1	11.6	-37.2	23.1	1.9×10^{-4}
1c	14.1 ± 2.0	13.5	-33.5	23.8	8.4×10^{-5} (36°)

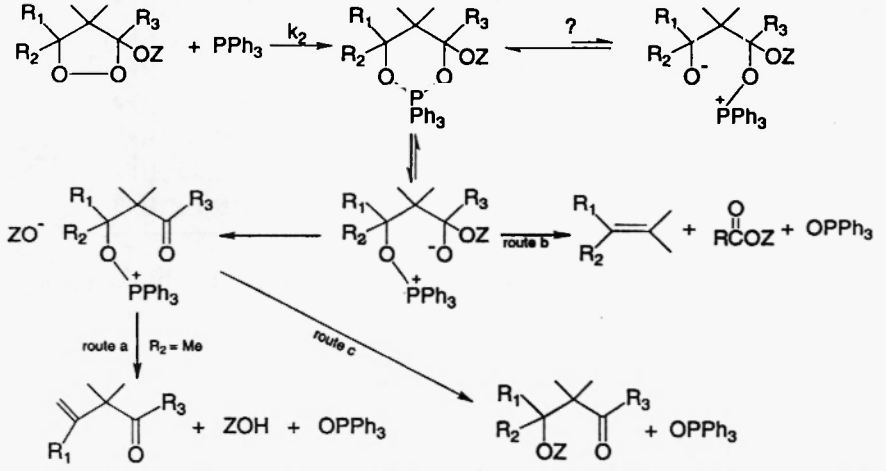
Discussion

The reaction of trivalent phosphorus compounds with a variety of organic peroxides has been shown (2c) to proceed via a biphilic insertion process to generate phosphoranes. The kinetic data for the present case are suggestive of the formation of metastable phosphoranes as the rate-determining step. The observation of transient ^1H NMR signals during the reaction in benzene-d_6 and the insensitivity of k_2 values to a polar solvent are consistent with a biphilic insertion mechanism. The large difference (10-fold increase) in reactivity between **1a** and **1b** is surprising considering the "minor" structural difference (in formally changing Z to acetyl from methyl). This could indicate that the insertion process is not symmetrical. The high $\Delta S^{\ddagger}$ values seem consistent with additional steric requirements.

The reaction of all three dioxolanes with triphenylphosphine in benzene-d_6 produced two major sets of products: β,γ-unsaturated ketones and co-products (route a) and tetrasubstituted alkenes and co-products (route b). In addition, compounds **1a** and **1b** also produced compounds consistent with ZO-migration (route c), the yields of which were solvent dependent. Dioxolane **1c** did not produce methoxy migration products in benzene-d_6. Dioxolane **1a** did not produce a methoxy migration product in benzene-d_6 but in acetonitrile-d_3 it was a major product (35%). Dioxolane **1b** yielded acetoxy migration products both in benzene-d_6 and acetonitrile-d_3 although this was not a major product as for dioxolane **1a**.

The product studies are consistent with three competing routes for fragmentation of the intermediate phosphoranes as shown in Scheme 1. The metastable phosphorane would be expected to undergo heterolytic

Scheme I



cleavage to form phosphonium ion intermediates. Of the two possible P-O bond cleavages, the phosphonium ion with the alkoxy group attached to the same carbon as the OZ group would be the most likely to be formed. This phosphonium ion can undergo a direct fragmentation (route b) to yield alkene, a carbonyl compound and triphenylphosphine oxide. This fragmentation pathway is similar to that proposed[4] for fragmentation of a phosphonium ion intermediate in the β-peroxylactone/triphenylphosphine reaction. Alternatively, the phosphonium ion can undergo loss of ^-OZ to yield a different phosphonium ion intermediate which can undergo an E_2 reaction (route a) to β,γ-unsaturated ketone or a formal substitution process to β-OZ ketone (route c). The pathway shown for route a would also be consistent with the result (5) of Kuczkowski in which α,β-unsaturated carbonyl products were obtained from 3-methoxy substituted 1,2-dioxolanes since position 4 was not blocked. The route c pathway is favored in polar solvents suggesting a process in which triphenylphosphine oxide is lost

from the phosphonium ion followed by capture of $^{-}$OZ to form **4**. In conclusion, the results provide insights into the mechanisms of phosphorane and phosphonium ion fragmentation processes.

Experimental Section

All solvents used for chromatography were of HPLC grade (Aldrich). Benzene-d_6 (1% v/v TMS) was obtained from MSD Isotopes, and acetonitrile-d_3 was obtained from Cambridge Isotope Laboratories. The synthesis and thermolytic studies of 1,2-dioxolane **1a-c** have been reported (7). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL GX-270 MHz NMR spectrometer, in deuterochloroform (Aldrich, 1% v/v TMS). Kinetic experiments were recorded on a Varian EM360L 60 MHz NMR spectrometer. IR spectra were recorded on a Bomem-Michelson 100 FT-IR spectrometer. Combustion analysis was performed by Atlantic Microlab, Atlanta, GA. The GC-MS analysis of reaction products was obtained from a Hewlett Packard 5890 Series II Gas Chromatograph - 5971 Mass Selective Detector.

Kinetic Studies

The kinetic experiments were carried out by the following general procedure. A 0.04 to 0.09 mmol sample of pure 1,2-dioxolane **1a**, b or **c** was weighed into a 5 mm NMR sample tube. 5 μL of anisole (internal standard) and 0.500 mL of perdeuterobenzene were added, followed by 1, 2, 3 or 5 molar equivalents of triphenylphosphine. The sealed NMR tube was placed in a constant temperature bath (T ± 0.2 °C). Reaction progress was followed by monitoring the signal (7) (disappearance, ^{1}H NMR electronic integration) of the most upfield methyl group of the dioxolane vs that of the internal standard. The NMR sample was placed in an ice bath after removal from the constant temperature bath before and after NMR analysis. Reaction time was taken as the composite of time spent in the constant temperature bath. No discoloration was noted. Second order plots were linear for at least two half lives with excellent correlation coefficients (r = 0.99). Variation between duplicate runs was less than 10% of the value of k_2.

Product Studies

The following general procedure was employed for the determination and isolation of the reaction products of 3-ZO-3,4,4,5,5-pentasubstituted-1,2-dioxolanes **1a-c** with triphenylphosphine. A final ^{1}H NMR spectra after complete disappearance of the dioxolane was recorded and the relative peak intensities were determined. The product distribution in the reaction mixture was checked by GC-MS. Volatile products were collected by low temperature distillation under reduced pressure and analyzed by ^{1}H NMR spectroscopy and GC-MS. The non-volatile products were isolated by chromatographic methods (chromatatron) and identified by comparison of physical and spectral (IR, NMR, MS) data with those of authentic samples. The isolated yields were roughly 70-80% of those determined by NMR spectroscopy. Quantitative yields of triphenylphosphine oxide were obtained for all experiments.

From **1a**: Methyl acetate, methanol, and triphenylphosphine oxide were identified by comparison of physical and spectral data with commercial samples (Aldrich). 3,3-Dimethyl-4-phenyl-4-penten-2-one [for **2a** (9), isolated yield 75%, oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.29 (s, 6H), 2.18 (s, 3H), 5.31 (s, 1H), 5.36 (s, 1H), 7.12 (m, 2H), 7.26 (m, 3H); MS 188 (1.3%, 145 (100%)]; and 2-methyl-3-phenyl-2-butene [for **3a** (10), isolated yield 13%, oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.59 (s, 3H), 1.81 (s, 3H), 1.96 (s, 3H), 7.13-7.30 (m, 5H); MS 146 (65%),

131 (100%)] were identified by comparison of spectra data to those in the literature. 4-Methoxy-3,3-dimethyl-4-phenylpentan-2-one **4a** was isolated (27% yield, oil) by chromatography (chromatatron) from the reaction mixture with acetonitrile-d_6 as solvent; ^{1}H NMR ($CDCl_3$) 0.94 (s, 3H), 1.09 (s, 3H), 1.53 (s, 3H), 2.20, (s, 3H), 3.09 (s, 3H), 7.26-7.73 (m, 5H); ^{13}C NMR ($CDCl_3$) 19.4, 21.0, 21.8, 29.4, 50.5, 55.1, 82.5, 127.1, 127.4, 128.2, 140.7, 214.3; IR (neat) 1698 cm^{-1}, 1113 cm^{-1}; MS (EI) 205.2 (0.1%), 189.2 (0.4%), 177.2 (2.2%), 135.1 (100%); MS (CI, isobutane) 221.2 (17.2%), 189.1 (77.5%), 177.1 (8.3%), 135.1 (100.0%); CH analysis: calc. C 76.33, H 9.15; found C 75.94, H, 9.21.

From **1b:** Acetic acid, acetic anhydride and triphenylphosphine oxide were identified by comparison of physical and spectral data to those of authentic samples (Aldrich). 3,3-Dimethyl-4-phenyl-4-penten-2-one [**2a**, 65% isolated yield] and 2-methyl-3-phenyl-2-butene [**3a**, 11 % isolated yield] spectral data were compared to those published in the literature (9,10). 4-Acetyloxy-3,3-dimethyl-4-phenylpentan-2-one **4b** could not be isolated without decomposition (^{1}H NMR in CD_3CN shows singlets at 1.05, 1.10, 1.55, 2.10 and 2.17 ppm); upon evaporation of the solvent acetophenone and 3-methylbutan-2-one were obtained in quantitative yield, presumably through hydrolysis of the acetate followed by retro aldol.

From **1c:** Methylbenzoate, methanol, triphenylphosphine oxide and 2,3-dimethyl-2-butene were identified by comparison of spectral data to those of authentic samples (Aldrich). 2,2,3-Trimethyl-1-phenyl-3-buten-1-one [**2c**, isolated yield 35%, oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 1.39 (s, 6H), 1.73 (m, 3H), 5.00 (m, 1H), 5.10 (m, 1H), 7.33 (m, 2H), 7.41 (m, 1H), 7.98 (m, 2H); MS 188 (4%), 105 (100%)] has been reported previously (9).

Acknowledgment is made to the National Science Foundation (CHE-9017230), SEAS subcontract via CAU (DAAA 15-94-K-0004) and the GSU Research Fund for support of this work.

References

(1) (a) I. Saito, S.S. Nittala in S. Patai (ed): The Chemistry of Functional Groups, Peroxides, Wiley-Interscience , New York, pp. 344-346 (1983); (b) M. Balci,*Chem. Rev. 81*, 91 (1981).

(2) (a) A.L. Baumstark, P.C. Vasquez, *J. Org. Chem. 49*, 793 (1984); (b) A.L. Baumstark in A. Frimer (ed) Singlet Oxygen, Vol. II, CRC Press Uniscience, Boca Raton, FL, pp. 19-25 (1985); (c) P.C. Vasquez, Y.-X. Chen and A.L. Baumstark in *Advances in Oxygenated Processes Vol. 4*, Ed: A.L. Baumstark, Chapt. 7, JAI Press, Greenwich, CT, 1995.

(3) (a) E.L. Clennan, P.C. Heah, *J. Org. Chem. 46*, 4107 (1981); (b) M. Hamberg, J. Svensson, B. Samuelsson, *Proc. Natl. Acad. Sci. USA, 71*, 3400 (1974).

(4) W. Adam, N. Narita and Y. Nishizawa, *J. Am. Chem. Soc. 106*, 1843 (1984).

(5) B.J. Wojciechowski, C.-Y. Chiang and R.L. Kuczkowski, *J. Org. Chem. 55*, 1120 (1990).

(6) (a) H.S. Dang, A.G. Davies and C.H. Schiesser, *JCS, Perkin I 3*, 789 (1990); (b) A.L. Baumstark, P.C. Vasquez and Y.-X. Chen, *Heteroatom Chem. 4*, 175 (1993).

(7) A.L. Baumstark, P.C. Vasquez and Y.-X. Chen, *J. Org. Chem. 59*, 6692 (1994).

(8) A.L. Baumstark and P.C. Vasquez, *J. Org. Chem. 49*, 793 (1984).

(9) A.L. Baumstark and P.C. Vasquez, *J. Heterocycl. Chem. 28*, 113 (1991).

(10) J.E. McMurry, M.P. Fleming, K.L. Kees and L.R. Krepski, *J. Org. Chem. 43*, 3255 (1978).

Received July 14, 1995