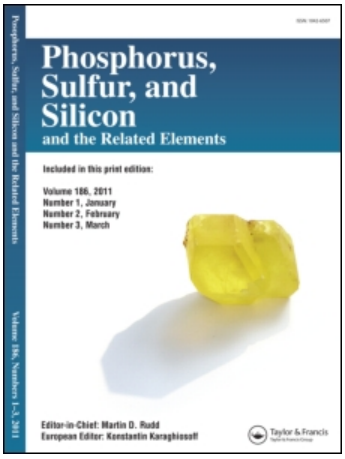

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OXIDATIONS OF TRIETHYL α-PHOSPHONOACRYLATE. EPOXIDATION TO TRIETHYL α-PHOSPHONOACRYLATE OXIDE BY HYPOCHLORITE AND FORMATION OF TRIETHYL DIHYDROXYPHOSPHONOACETATE WITH RuO_4-PERIODATE

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Oxidation of the methylidene double bond in triethyl α-phosphonoacrylate **2** by O_3, catalytic RuO_4 (RuO_2/NaOCl, RuO_2/$NaIO_4$) and stoichiometric RuO_4 was investigated as a route to α-oxygenated phosphonoacetate derivatives. Ozonation of **2** gave a mixture of products containing, in one experiment, triethyl phosphonoglyoxylate **1** as a minor (<5%) component. Efforts to prepare ethylidene compounds analogous to **2** (as alternative ozonation substrates) using known routes for synthesis of corresponding diethyl oxomalonate derivatives were unsuccessful. Treatment of **2** in biphasic H_2O/CCl_4 with catalytic RuO_4 using NaOCl as co-oxidant or with NaOCl alone produced a novel epoxide product, triethyl α-phosphonoacrylate oxide (**7**) in up to 79% isolated yield. When NaOCl was replaced with $NaIO_4$ as the RuO_2 reoxidant (H_2O/$CHCl_3$), the major reaction product in the aqueous phase was identified by ^{13}C and ^{31}P NMR as triethyl dihydroxyphosphonoacetate **8**, the hydrate of the ketone **1**. Reaction of **2** with stoichiometric RuO_4 in CCl_4 did not provide **1**. A convenient modification in the synthesis of **2** is also described, and its ^{13}C and ^{31}P NMR spectra are reported.

Key words: Oxidation; epoxide; sodium hypochlorite; sodium periodate; ruthenium tetroxide; triethyl α-phosphonoacrylate oxide; dihydroxyphosphonoacetate.

INTRODUCTION

Phosphonates are versatile molecules with applications in areas ranging from agricultural chemistry to medicinal and radiopharmaceutical chemistry.[1,2] Our current interest in phosphonates capable of selectively inhibiting viral nucleic acid polymerases[3–5] or displaying other bioactivities[6] led us to investigate synthesis of α-oxygenated phosphonoacetates such as triethyl oxophosphonoacetate (triethyl phosphonoglyoxylate) **1** from triethyl α-phosphonoacrylate **2**, using several reagents known to cleave oxidatively carbon-carbon double bonds in alkenes. We previously communicated the first well-documented[§] preparation of **1** via oxygen-transfer from propylene oxide to the α-carbene of triethyl phosphonoacetate.[8] Our present work demonstrates by NMR a RuO_4-catalyzed conversion of **2** to the hydrate of **1** by aqueous periodate, and also has resulted in isolation of a novel, H_2O-compatible epoxide derived from **2**.

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§An early report[7] of the preparation of **1** from reaction of triethyl phosphite with ethyl oxalyl chloride has not been substantiated.[8]

EXPERIMENTAL

All solvents were analytical grade. Triethyl phosphonoacetate, ruthenium dioxide and sodium periodate were purchased from Aldrich Chemical Co., Milwaukee, WI. Sodium hypochlorite solution (5.25%) was purchased in the form of commercial bleach from a local market. Authentic **1** was prepared by the literature procedure.[8] NMR spectra were recorded on a Bruker WP-270SY spectrometer, operating at 270.13 MHz (^{1}H), 109.35 MHz (^{31}P), and 67.92 MHz (^{13}C). In NMR studies of periodate oxidation experiments, a Bruker AM360 spectrometer was used at 90.56 MHz (^{13}C) and 145.78 MHz (^{31}P). NMR sample solutions were 10% w/v in $CDCl_3$. ^{1}H and ^{13}C chemical shifts were referenced to solvent peaks ($CHCl_3$ and $CDCl_3$, respectively) and are reported relative to external tetramethylsilane. ^{31}P NMR chemical shifts are reported relative to external 85% H_3PO_4. The ^{1}H NMR δ and J parameters for the nonequivalent epoxy CH_2 protons of **7** were determined using an Excel ver. 3.0 spreadsheet and the standard formula for an ABX system.[9] IR spectra of neat liquid films (NaCl discs) were measured on a Perkin-Elmer 281 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mass spectral measurements were obtained at 20 eV on a VG 7070 high-resolution MS instrument at the University of California, Riverside.

Triethyl α-Phosphonoacrylate **2**. The procedure of Semmelhack et al.[10] for preparing **2** from triethyl phosphonoacetate and formaldehyde has the disadvantage of specifying piperidine, currently a substance controlled by the U.S. Drug Enforcement Administration, as the basic reagent. We found that freely purchased 2,6-dimethylpiperidine can replace piperidine. Thus, paraformaldehyde (1.93 g; 64 mmol), 2.6-dimethylpiperidine (0.8 g; 7.4 mmol) and methanol (50 ml) were heated to reflux under N_2 for 2 h. The mixture was allowed to cool to room temperature, and triethyl phosphonoacetate (12.2 g; 54 mmol) was added. The mixture was refluxed overnight and evaporated under reduced pressure. The residue was twice dissolved in benzene, and re-evaporated. ^{31}P NMR evaluation indicated complete conversion of starting material (δ 20.6) to the adduct product (δ 19.7). The final residue was distilled in vacuo from 1.0 ml H_3PO_4, giving **2**: bp 99–102°C, 0.02 mm Hg (6.75 g, 53%; lit.[10] 48%). Product purity was verified by IR and ^{1}H NMR.[10] The ^{13}C and ^{31}P NMR spectra of this compound have not been reported previously: ^{13}C{^{1}H} NMR: δ = 13.7 (s, CH_3[CO]); 15.8 (d, $^3J_{CP}$ = 6 Hz, CH_3[PO]); 61.1 (s, CH_2[CO]); 62.3 (d, $^2J_{CP}$ = 6 Hz, CH_2[PO]); 133.3 (d, $^1J_{CP}$ = 188 Hz, $C{=}CH_2$); 142.6 (d, $^2J_{CP}$ = 4 Hz, $C{=}CH_2$); 163.4 ppm (d, $^2J_{CP}$ = 17 Hz, C=O). ^{31}P{^{1}H} NMR: δ = 12.0 ppm (s).

Attempted Syntheses of β-Substituted Phosphonoacrylates

Attempted Synthesis of Triethyl Ethylidenephosphonoacetate **3** *by Reaction of Triethyl Phosphonoacetate, Acetaldehyde and 2,6-Dimethylpiperidine*. Triethyl phosphonoacetate (22.4 g; 100 mmol), acetaldehyde (5.72 g; 130 mmol), and 2,6-dimethylpiperidine (2.68 g; 20 mmol) were heated in a sealed tube at 100°C for 36 h. The tube was opened at 0°C. No evidence for formation of the desired product was observed (^{31}P NMR).

Attempted Synthesis of **3** *by Reaction of Triethyl Phosphonoacetate, Acetaldehyde and Acetic Anhydride*. In an adaptation of the method of Fones[11] for the synthesis of diethyl ethylidenemalonate from diethyl malonate, a round-bottomed flask was equipped with a thermometer, a condenser (0°C, circulating bath) and an N_2 adapter. The flask was charged with triethyl phosphonoacetate (13.8 g; 62 mmol), acetaldehyde (5.9 g; 0.13 mol) and acetic anhydride (10.8 g; 106 mmol). After 12 h at reflux, no significant reaction was evident (^{31}P NMR).

Attempted Synthesis of Triethyl Isopropylidenephosphonacetate **4** *by Reaction of Triethyl Phosphonoacetate, Acetone and 2,6-Dimethylpiperidine*. Triethyl phosphonoacetate (13.8 g; 62 mmol), acetone (5.05 g; 81 mmol) and 2,6-dimethylpiperidine (2.10 g; 21 mmol) were refluxed as described above for 12 h without significant reaction (^{31}P NMR).

Ozonation of **2**

The procedure of Jung et al.[12] for the conversion of diethyl ethylidenemalonate **5** to diethyl oxomalonate **6** was adapted. An O_2 cylinder was connected (with tygon tubing via a calcium sulfate drying tower) to a Wellsbach ozone generator. The outlet of the generator was attached to a subsurface addition tube, placed in a 100 mL three-necked round-bottomed flask equipped with a reflux condenser. The condenser outlet was connected to two aqueous KI traps in series. The O_2 was turned on and the reaction flask charged with **2** (10 g in 50 mL CH_2Cl_2). The system was purged with O_2 for 30 min as the reaction flask was cooled to −78°C in a dry ice/acetone bath. The ozonator pressure was adjusted to 8 psi, and the flow rate set at 2 linear ft/min. During ozonation (95 V), the initially colorless reaction mixture became greenish yellow, then deep blue. After 2 h, the ozonator was turned off and the reaction flask was purged with O_2 for 15 min. During this time a 100 mL three-necked round-bottomed flask

equipped with a magnetic stirrer, a reflux condenser leading to a nitrogen bubbler, and an addition funnel was charged with Me_2S (8 g; 0.13 mol). The "ozonide" solution was then added (N_2) with stirring over 10 min. After further stirring overnight, the solvent was removed in vacuo, leaving a greenish-yellow oil whose ^{31}P NMR spectrum showed multiple resonances, dominated by a peak at δ = 0.2 ppm. In one run, a small peak (<5%) at δ = −2.8 ppm was observed, that shifted to δ = 14 ppm on addition of methanol. Formation of the product with δ = −2.8 ppm, tentatively‖ identified as **1**,[8] was not observed in several other runs. After ozonation as described above, the "ozonide" was also quenched using PPh_3 at 25°C and −78°C and using Me_2S at 78°C, with similar results.

RuO_4/Hypochlorite Oxidations of **2**

dl-Triethyl α-Phosphonoacrylate Oxide **7**. A 1 L flask was charged with CCl_4 (alternatively, $CHCl_3$) (250 mL) and 5.25% sodium hypochlorite solution (400 mL; 282 mmol). RuO_2 (11 mg; 0.08 mmol) was added, and observed to immediately oxidize to RuO_4[13] (yellow organic phase). A small portion of **2** was added with vigorous shaking, causing the color of the reaction mixture to change briefly to black; when the mixture again became yellow, more alkene was added in the same manner. After 10 min, addition of alkene was complete (10 g; 42 mmol) and the two phases were separated. The organic layer was treated with isopropanol (1 mL), then filtered through Celite, dried ($MgSO_4$), re-filtered, and evaporated under reduced pressure. The pale brown, oily residue was distilled under reduced pressure to give 7.49 g (71%) of the product as a colorless oil, bp 92–94°C (0.002 mm). ^1H NMR: δ = 1.20 (m, 9H, CH_3); 3.06, 3.14, tot. 2H (ABX, $^1J_{HH}$ = 6.5 Hz, $^1J_{HP}$ = 4 Hz, C_α-CH_2); 4.03 (m, 6H, CH_2O). ^{13}C NMR: δ = 13.4 ppm (q, $^1J_{CH}$ = 127 Hz, CH_3[CO]); 15.8 (broad q, $^1J_{CH}$ = 125 Hz, CH_3[PO]); 50.0 (d, $^1J_{CP}$ = 206 Hz, C_α-CH_2); 50.5 (t, $^1J_{CH}$ = 183 Hz, C_α-CH_2); 61.8 (t, $^1J_{CH}$ = 148 Hz, CH_2[CO]); 63.3 (t, broad, $^1J_{CH}$ = 146 Hz, CH_2[PO]); 165.8 ppm (d, $^2J_{CP}$ = 22 Hz, C=O). $^{13}C\{1H\}$ NMR: δ = 13.4 (s, CH_3[CO]); 15.8 (d, $^3J_{CP}$ = 6 Hz, CH_3[PO]); 50.0 (d, $^1J_{CP}$ = 206 Hz, C_α-CH_2); 50.5 (s, C_α-CH_2); 61.8 (s, CH_2[PO]); 63.3 (d, $^2J_{CP}$ = 7 Hz, CH_2[PO]); 165.8 ppm (d, $^2J_{CP}$ = 22 Hz, C=O). $^{31}P\{1H\}$ NMR: δ = 14.8 ppm (s). IR: included peaks at 3043 (w), 2990 (ms), 1740 (s), 1320 (sh, s), 1285 (sh, s), 1255 (s), 1060–1010 (b, s) cm^{-1}. Anal. calcd for $C_9H_{17}O_6P$: C 42.86; H 6.79. Found: C 42.52; H 6.49. Mass spectrum $(M + 1)^+$: *m/e* 253.084. Reqd. for $^{12}C_9$ $^1H_{18}$ $^{16}O_6$ ^{31}P: *m/e* 253.084. When the reaction was performed identically omitting the RuO_2 (and isopropanol and Celite steps), a product was isolated (8.77 g, 79%) that was spectroscopically indistinguishable from **7** prepared as described above.

RuO_4/Periodate Oxidation of **2**

Detection of Triethyl Dihydroxyphosphonoacetate (Triethyl Phosphonomesoxylate) **8**. $RuO_2 \cdot H_2O$ (10 mg; 0.07 mmol) and $NaIO_4$ (99%; 1.3 g; 6.0 mmol) were mixed with EtOH-free, freshly distilled $CHCl_3$ and H_2O (2 mL each) at 25°C for 10 min. After further addition of each solvent (3 mL), stirring was continued until the organic layer showed the characteristic yellow color of RuO_4 (ca. 10 min), whereupon **2** (0.60 g; 2.5 mmol) was added, causing a color change to black. Stirring was continued until the color became olive green (75 min). After filtration to remove a grayish solid, the liquid layers were separated and analyzed by ^{31}P NMR. In the spiking experiment to identify **8**, 0.15 g authentic **1** was added directly to the NMR tube containing the aqueous sample aliquot. Parallel oxidation reactions containing twofold more $NaIO_4$, and containing 1.3 g of $NaIO_4$ but omitting the ruthenium oxide, were carried out in the same manner. Further ^{31}P NMR analysis was conducted at intervals of 1 and 3 days. In a scaled-up experiment, $RuO_2 \cdot H_2O$ (100 mg; 0.7 mmol), $NaIO_4$ (99%; 12.4 g; 57 mmol) were reacted at 25°C in $CHCl_3$ and H_2O (50 mL each) until the organic layer became yellow, whereupon **2** (6 g; 25 mmol) was added (black). After 75 min of stirring, the yellow color returned and the mixture was worked up as described above. The aqueous layer (^{31}P NMR showed predominantly **8**) was treated with 200 mL EtOH, filtered, and evaporated at reduced pressure. The residual oil (4.2 g) was analyzed by ^{13}C and ^{31}P NMR (the latter showed evidence that **8** had decomposed by about 40% during work-up, and no further attempt to isolate the compound was made). In a control experiment with RuO_2 omitted from the oxidation mixture, conversion of **2** to **8** was not observed (^{31}P NMR).

Stoichiometric Oxidation of **2** *with Excess RuO_4*. $RuO_2 \cdot H_2O$ (0.5 g, 3.3 mmol) was suspended in CCl_4 (40 mL), and 5.25% NaOCl (300 mL, 212 mmol) was added. After stirring for 1 h, the layers were separated, and the bright yellow organic layer was dried ($MgSO_4$) and filtered. A 10 mL aliquot was treated with **2** (100 mg, 0.42 mmol). ^{31}P NMR analysis revealed the formation of multiple phosphorus-containing products, with ^{31}P chemical shifts between 0 and 20 ppm, none of which corresponded to **1** or **7**. When authentic **1** (100 mg) was added to a 10 mL aliquot of the RuO_4 reagent, the mixture immediately turned black, and ^{31}P NMR revealed a mixture of eight phosphorus-containing products

‖Authentic **1** was not available at the time these experiments were performed.

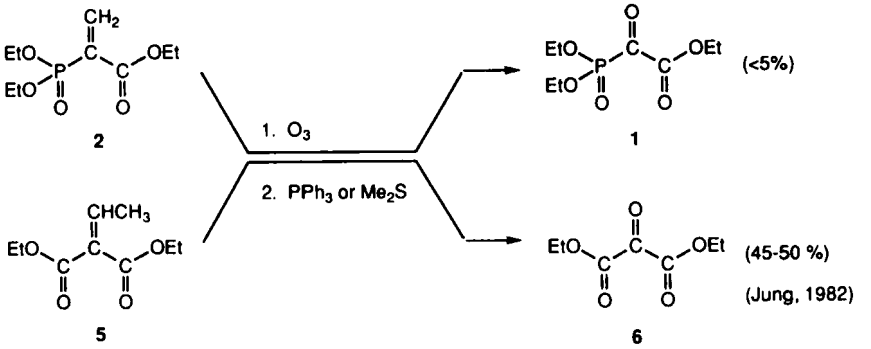
within the same chemical shift range. However, when a 10 mL aliquot of the reagent was combined with authentic **8** (100 mg) in 10 mL H_2O, the organic layer remained yellow. A ^{31}P NMR spectrum of the aqueous layer confirmed that the hydrate was stable in contact with the ruthenium reagent under these biphasic conditions.

RESULTS AND DISCUSSION

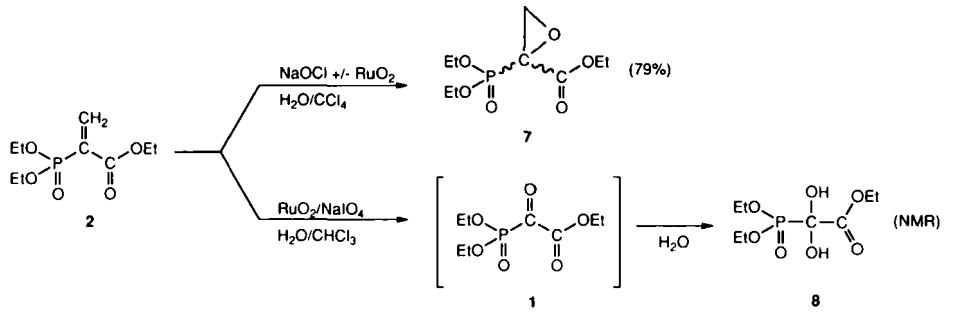
Initially, we examined ozonolysis of **2** in dichloromethane at −78°C as a route to **1**. Ozonolysis of the structurally related ethylidenemalonate ester **5**, using triphenyl phosphine (PPh_3) to decompose the ozonide, has been shown to provide the oxomalonate analogue of **1**, **6**, in 45–50% yield.[12] However, PPh_3 or Me_2S work-up of the presumptive intermediate from ozonation of **2** at two different temperatures gave mixtures of several unidentified phosphorus-containing products but little (one experiment) or no **1** detectable by ^{31}P NMR.

Abnormal ozonolyses, which are not uncommon with α,β-unsaturated carbonyl compounds, are usually deviant in the ozonide generation step.[14] The possibility that ozonolysis of a β-substituted α-phosphonoacrylate might proceed more satisfactorily was not pursued because acetaldehyde (to prepare triethyl ethylidenephosphonoacrylate, **3**) or acetone (to prepare the triethyl isopropylidenephosphonoacrylate, **4**) could not be readily substituted for formaldehyde in the method used to synthesize **2**. Triethyl phosphonoacetate also failed to react with acetic anhydride and acetaldehyde to form **4** under conditions that[11] transform diethyl malonate and acetaldehyde into the corresponding ethylidenemalonate derivative **5**.

Our unpromising preliminary results with ozonation of **2** led us to examine an alternative oxidant, ruthenium tetroxide (RuO_4), which, as stated in Courtney's monograph,[13] "almost invariably" oxidizes alkenes to carbonyl compounds, including refractory alkenes unsuccessfully oxidized by ozone, osmium tetroxide, or chromium trioxide.[13,15,16] The reagent is generally used catalytically, the alkene substrate being dissolved in a compatible organic solvent combined with aqueous sodium hypochlorite or sodium periodate as a co-oxidant, which generates the RuO_4 in situ from RuO_2.[17] As alkene oxidation proceeds, the Ru^{IV} formed is continuously reoxidized to Ru^{VIII} by the NaOCl or $NaIO_4$. With H_2O-soluble alkene derivatives, the RuO_2/NaOCl reagent has been used in monophasic aqueous oxidations, but due to the limited solubility of **2** in H_2O, we employed biphasic conditions. When **2** was treated with RuO_4 made in situ from RuO_2 (RuO_2/NaOCl)



SCHEME I



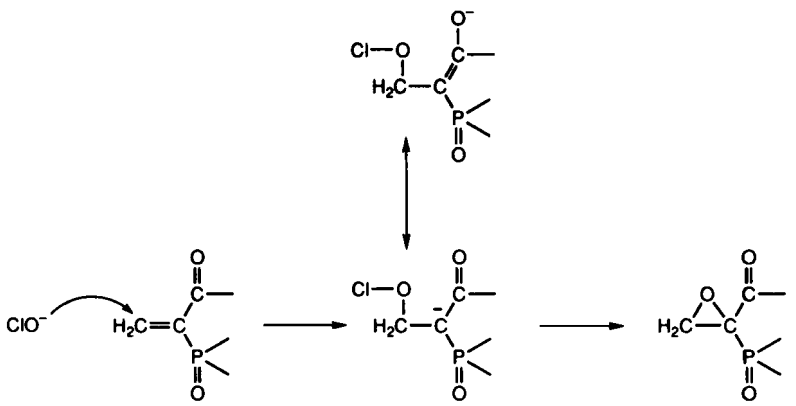
SCHEME II

in a two-phase (CCl_4/H_2O) reaction mixture, ^{31}P NMR analysis of the organic layer revealed a single peak (δ = 15 ppm in $CDCl_3$). This product was not, however, **1** which has δ = −2.4 ppm in $CDCl_3$ and which would be in any case be expected to hydrate and pass into the aqueous layer under the reaction conditions.[8] Analysis of the isolated product by ^{13}C NMR showed, in addition to peaks assignable to ethyl C—C—O—P and C—C—O—C=O, a C_α doublet with $^1J_{CP}$ = 206 Hz and a C_β triplet with $^1J_{CH}$ of 183 Hz, both near δ = 50 ppm with C_β at slightly lower field, consistent with a 2,2-disubstituted epoxide.[9,18] The proton vs. phosphorus spin-spin couplings were verified by a ^1H-decoupled ^{13}C NMR spectrum. For comparison, ethylene oxide has $^1J_{CH}$ = 176 Hz,[18] indicating somewhat greater s character in the C—H bonds of the product oxirane ring. The ^1H spectrum supported the above assignments, and included an AB multiplet, further split into a doublet (attributed to a $^3J_{HP}$ of 4 Hz). The IR spectrum, combustion analysis and high resolution MS of the product confirmed its identity as *dl*-triethyl α-phosphonoacrylate oxide (*dl*-ethyl 2-(diethoxyphosphinyl)-2,3-epoxypropenoate; *dl*-ethyl 2-(diethoxyphosphinyl)-2-oxiranecarboxylate) **7** (Scheme II). This previously undescribed compound has the substructural element of an α-oxiranyl phosphonate in common with the antibiotic fosfomycin.[19] Of particular note is its stability in contact with H_2O.

The formation of an epoxide product during RuO_4 oxidation of an alkene has been claimed in at least one instance, involving a steroidal conjugated diene.[20] However, when oxidation of **2** was repeated omitting RuO_2, **7** was again obtained, in slightly higher yield. Epoxidation of α,β-unsaturated ketones by NaOCl has been described previously,[20] although the usual reagent for epoxidation of double bonds conjugated with electron-withdrawing groups is alkaline H_2O_2 or a hydroperoxide.[21] A possible two-step mechanism explaining formation of **7** would begin with nucleophilic Michael β-addition of the hypochlorite anion to **2** followed by ring closure, as shown in Scheme III. A similar mechanism has been proposed for epoxidation of α,β-unsaturated substrates by hydroperoxyl anion.[21]

As conversion of **2** to its epoxide could thus be ascribed to a direct reaction with the hypochlorite co-oxidant,¶ we reattempted the catalytic RuO_4 oxidation of **2** using $NaIO_4$ (2.2 eq.) in place of NaOCl. The organic phase of the resulting mixture

¶Aqueous NaOCl (one phase) also smoothly converts tetraethyl ethylidene-1,1-bis(phosphonate) to the corresponding epoxide in good yield.[22,23] The latter compound was recently prepared by another method.[24]



SCHEME III

showed only ^{31}P NMR peaks (<19 ppm) attributable to starting material (δ 12.5), but the aqueous phase contained major ^{31}P NMR-active components at δ 18 (27%), δ 14.5 (58%), and δ 1.1 ppm (15%). The second product was identified as triethyl dihydroxyphosphonoacetate **8**, the hydrate of the ketone **1**, by spiking the NMR sample with authentic **1** and retaking the spectrum. As mentioned already, **1** hydrates rapidly and quantitatively in contact with H_2O[8]; the hydrate **8** is not extractable from H_2O into $CHCl_3$ or CCl_4.[8] When the reaction mixture was allowed to remain overnight at room temperature (pH 2.5–2.8), the ^{31}P NMR peak assigned to **8** decreased (to 25%), while the peak near 1 ppm increased to 48% and the peak at 18 ppm remained unchanged (27%). At the end of 3 days, **8** was no longer detectable in the mixture, apparently having been converted entirely to the species resonating at 1 ppm. When the equivalents of $NaIO_4$ were doubled, ^{31}P NMR analysis immediately after reaction showed the presence of only two products, **8** (63%) and the product at 1 ppm (37%). After one day, the relative proportions of the two peaks were 14% and 86%, respectively. An essential role for the oxidized ruthenium catalyst in the reaction was confirmed by a control experiment using $NaIO_4$ alone, which produced no **8**. A scaled-up reaction containing all components was also carried out. ^{13}C NMR analysis of the oily residue obtained from work-up of the aqueous phase confirmed the presence of **8** (characteristic α-carbon signal of **8** at δ = 93 ppm ($^1J_{CP}$ = 200 Hz); and ethyl group resonances).[8] During the work-up, which involved precipitation of iodate salts by EtOH followed by evaporation on a rotary evaporator, the relative amount of **8** present decreased from 80% to about 50%, indicating partial decomposition. In control experiments with RuO_2 omitted from the oxidation mixture, conversion of **2** to **8** was not observed (^{31}P NMR).

To establish the importance of using aqueous, biphasic catalytic oxidation conditions, the reaction was repeated using a stoichiometric amount of preformed (NaOCl) RuO_4 in CCl_4 alone. Visual evidence of oxidation (yellow → black)[††] was seen, and ^{31}P NMR analysis revealed partial conversion of the starting phosphonate

††RuO_2 is black, RuO_4 is a brilliant yellow, thus, a catalytic RuO_4 oxidation is known to be complete when a yellow color persists in the reaction mixture.[13]

ester to several phosphorus-containing products; however, none were identifiable as **1**. Further investigation revealed that authentic **1** was partly degraded when exposed to the same concentration of RuO_4 in anhydrous CCl_4. However, exposure of an aqueous solution of **8** (prepared directly from **1**) to the same reagent (generated in CCl_4 from NaOCl) produced no evidence of reaction (^{31}P NMR; no change in color from yellow to black). It may be that the hydrate is inherently more stable to RuO_4 than the ketone, but the hydrate may also be protected from decomposition because it partitions into the aqueous layer, while the ruthenium reagent,[8] already present at a much lower concentration in the catalytic biphasic system than in the stoichiometric monophasic system, largely partitions into the organic phase.

It thus appears likely that the RuO_4 oxidation of **2** proceeds 'normally' in the biphasic $NaIO_4$ system, cleaving the $C_\alpha{=}C_\beta$ bond to form **1** (possibly via an intermediate which gives the peak at 18 ppm), which then immediately adds H_2O to its α-ketone carbonyl group, giving **8**‡‡ (Scheme III). In the acidic reaction mixture, **8** partly decomposes at 25°C to give the phosphorus-containing fragment which has a ^{31}P NMR peak at 1 ppm. This peak, which appears as a pentet with $J \approx 7$ Hz, could arise from diethyl phosphate, formed under the oxidizing conditions of the acidic reaction mixture via P—C bond scission in **8**§§.

SUMMARY

In conclusion, **1** was not reliably obtained from ozonation of **2**, which proved refractory under conditions that gave satisfactory alkene → ketone conversion with the diethyl malonate system,[12] pointing up limitations in using the chemistry of the latter to inform reactions of corresponding phosphonoacetate derivatives. Oxidation under biphasic conditions in the presence of a catalytic amount of RuO_4 provides different products, depending on the choice of co-oxidant. Using NaOCl, the catalyst can be dispensed with, and the $C_\alpha{=}C_\beta$ bond, instead of undergoing complete cleavage, is epoxidized to form the interesting 2-phosphono 2-carboxy oxirane triester **7**. The stability of this compound in contact with H_2O suggests that the reactivity of its epoxide ring with more powerful nucleophiles, e.g. as may occur in enzymes, should be explored.

Electron deficiency in the conjugated alkene substrate should favor β-addition of nucleophiles while decreasing its reactivity to electrophilic attack by RuO_4. As a result, in the case of **2** the choice of co-oxidant is critical: with the nucleophilic oxidant OCl^-, direct epoxidation to **7** predominates, whereas with non-nucleophilic IO_4^-, normal oxidative cleavage proceeds, the α-keto phosphonoacetate intermediate **1** being immediately transformed into the corresponding α,α-dihydroxy derivative **8** by the H_2O solvent component.

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‡‡The RuO_4-periodate reagent also cleaves the alkene double bond in the bisphosphonate ester corresponding to **2**: cf. Note[9]. The rhodium-promoted propylene oxide oxygen-transfer reaction used to synthesize **1** from the corresponding α-diazo derivative[8] has not proven useful for synthesis of α-keto bisphosphonate esters.[25] However, we have recently succeeded in preparing these ketones by a different route.[26]

§§This assignment was supported by a spiking experiment.

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