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Epoxidation of phosphinoyl alkenes with hydrogen peroxide

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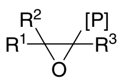
Abstract—The epoxidation of alkenylphosphorus compounds with hydrogen peroxide was systematically studied, revealing that while alkenylphosphine oxides failed to produce the corresponding epoxides, alkenylphosphonates, or phosphinates having a phenyl group at α-position reacted with H_2O_2/K_2CO_3 or alkenylphosphonic acids or phosphinic acids having an aliphatic group at α- or β-positions reacted with $H_2O_2/Na_2WO_4/Et_3N$ to produce high yields of the corresponding epoxides.

Phosphinoyl epoxides **1** are an important class of compounds in bioorganic chemistry. For example, fosfomycin ($R^2 = Me$; $R^1 = R^3 = H$; $[P] = P(O)(OH)_2$) is a famous antibiotic, which is widely used clinically.[1] They are also important synthetic intermediates for the preparation of various bioactive compounds.[2] A straightforward method for their preparation is the direct epoxidation of the corresponding alkenyl phosphorus compounds.[3] Thus, epoxidation of some alkenyl phosphorus compounds with NaOCl,[4] carboxylic peracid,[5] CF_3CO_3H,[6] dioxirane,[7] ^{t}BuOOH,[8] etc.[9] have been reported. However, a systematic investigation on the epoxidation of alkenyl phosphorus compounds (phosphonates, phosphinates, and phosphine oxides) has not been performed, partly due to the lack of these chemicals. For example, the epoxidation of alkenylphosphinates is not known. Hydrogen peroxide H_2O_2 is a clean oxidant.[10] The epoxidation of alkenyl phosphinoyl compounds using H_2O_2, however, is rather limited.[11] We have recently developed a catalytic method for the selective preparation of alkenylphosphorus compounds.[12] Now we wish to report a systematic study on the epoxidation of these phosphorus compounds with H_2O_2 (Scheme 1), revealing that the epoxidation is strongly structure depending.



1, [P] = a phosphinoyl (P(O)) group

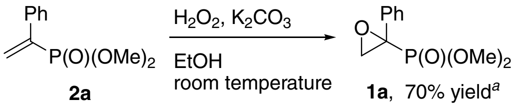
2: [P] = $P(O)(OMe)_2$
3: [P] = $P(O)(OH)_2$
4: [P] = $P(O)Ph_2$
5: [P] = P(O)Ph(OEt)
6: [P] = P(O)Ph(OH)

2′: [P] = $P(O)(OMe)_2$
3′: [P] = $P(O)(OH)_2$
4′: [P] = $P(O)Ph_2$
5′: [P] = P(O)Ph(OEt)
6′: [P] = P(O)Ph(OH)

a: R = Ph, **b**: R = *n*-C_6H_{13}, **c**: R = H

Scheme 1. A series of alkenylphosphorus compounds.

The epoxidation of alkenylphosphonic acids and their esters with H_2O_2 was investigated first. In the case of the *gem*-alkenes (**2**), we found that dimethyl (1-phenylethenyl)phosphonate (**2a**; $[P] = P(O)(OMe)_2$, R = Ph) could be successfully epoxidized by a mixture of 30% H_2O_2 (8.8 equiv) and K_2CO_3 (1 equiv) in EtOH at room temperature to give the desired epoxide in 70% yield (Scheme 2).[11a–e,13] Similar reactions using other bases such as NaOH, $NaHCO_3$, and Et_3N did not give satisfactory results.



NaOH, none^b; $NaHCO_3$, none^c; Et_3N, none^c

Scheme 2. Epoxidation of dimethyl (1-phenylethenyl)phosphonate. Conditions: **2a** (1 mmol), base (1 mmol), 30% aqueous H_2O_2 (1 mL, 8.8 mmol), EtOH (1 mL), room temperature, 16 h: (a) determined by ^{31}P NMR; (b) $EtOCH_2CH(Ph)P(O)(OMe)_2$ was formed quantitatively; (c) no reaction.

Keywords: Phosphinoyl epoxide; Epoxidation; Hydrogen peroxide.

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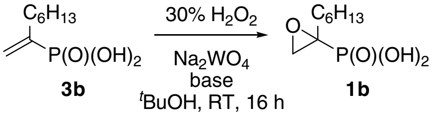
Surprisingly, when the Ph group of **2a** was replaced by an alkyl group *n*-C_6H_{13} (**2b**; [P] = P(O)(OMe)$_2$, R = *n*-C_6H_{13}), the epoxidation did not proceed at all under similar reaction conditions. Compound **2b** remained unchanged even after heating at 60 °C for 2 days. This difference in reactivity between **2a** and **2b** might be due to the electron-donating character of *n*-C_6H_{13} and the lack of its ability for stabilizing the intermediate anion formed via the nucleophilic attack of HOO^- to the double bond.[11a–e,13]

Since a tungstate is a common catalyst for the epoxidation of electron-rich alkenes with H_2O_2,[14] we thought that this tungstate-catalyzed epoxidation should be applicable to that of **2b**. Disappointingly, however, this strategy did not work at all. Remarkably, however, instead of **2b**, when its corresponding phosphonic acid (**3b**; [P] = P(O)(OH)$_2$, R = *n*-C_6H_{13}) was employed as the substrate, the epoxidation proceeded efficiently. Thus, **3b** reacted with 1 equiv of 30% aqueous H_2O_2 in the presence of Na_2WO_4 (1 mol %) and a catalytic amount of Et_3N (0.5 equiv) at room temperature to give the corresponding epoxide in 93% yield (Table 1, run 11). The reaction is highly affected by the amounts of tungstate, Et_3N and H_2O_2 used as shown in Table 1. For example, when an equimolar ratio of Et_3N was employed (run 5), the epoxidation became sluggish, although a similar reaction using 20 mol % tungstate catalyst and 1 equiv of Et_3N gave 99% yield of **1b** (run 1). On the other hand, reducing the amount of Et_3N to 0.1 mol equiv lowers the yields of **1b**, particularly in cases when less H_2O_2 was employed (compare runs 6, 9, and 11 with runs 7, 10, and 12). High loadings of the tungstate catalyst did not always give good results. As the loading of tungstate increased (>5 mol %), the yields of **1b** decreased (runs 2–4), probably due to the decomposition of the epoxide formed. It is noted again that this tungstate can catalyze the epoxidation of phosphonic acids but not their esters, that is, a similar treatment of **2b** resulted in a complete recovery of the substrate.[15]

Table 1. Epoxidation of **3b** with H_2O_2[a]



Run	Na_2WO_4 (mol %)	Et_3N (equiv)	H_2O_2 (equiv)	Conversion[b] (%)	Yield[b] (%)
1	20	1	9	100	99
2	20	0.5	9	100	5
3	10	0.5	9	100	15
4	5	0.5	9	100	44
5	1	1	9	7	0
6	1	0.5	9	100	83
7	1	0.1	9	99	75
8	1	0.05	9	82	33
9	1	0.5	4	95	73
10	1	0.1	4	97	26
11	***1***	***0.5***	***1***	***94***	***93***
12	1	0.1	1	92	57

[a] Conditions: **3b** (0.5 mmol) in ^{t}BuOH (0.5 mL), room temperature, 16 h.

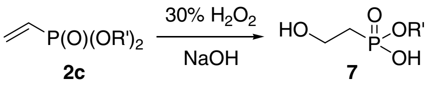
[b] The conversion of the starting material and the yield of the product were determined by ^{31}P NMR.

The reactions of the *trans*-alkenes **2′** did not completely comply with the reaction patterns of their corresponding *gem*-alkene counterparts **2**. Thus, no epoxidation took place with dimethyl (2-phenylethenyl)phosphonate (**2′a**; [P] = P(O)(OMe)$_2$, R = Ph) and dimethyl (1-octenyl)phosphonate (**2′b**; [P] = P(O)(OMe)$_2$, R = *n*-C_6H_{13}) under the reaction conditions of Scheme 2.[16] For these substrates, the $H_2O_2/Na_2WO_4/Et_3N$ system (Table 1) was also not effective. Although the tungstate catalyzed epoxidation of phosphonic acid **3′b** ([P] = P(O)(OH)$_2$, R = *n*-C_6H_{13}) under the reaction conditions of Table 1 (run 11) could produce (2-hexyloxiranyl)phosphonic acid (**1b′**) in 97% yield,[17] a similar reaction with **3′a** ([P] = P(O)(OH)$_2$, R = Ph) gave a complicated mixture.

Finally, unsubstituted vinylphosphonate **2c** ([P] = P(O)(OEt)$_2$, R = H) reacted quite differently (Scheme 3). Thus, diethyl vinylphosphonate under the reaction conditions of Scheme 2 (H_2O_2/base) only gave a trace amount of epoxide. The main product (up to 87% yield) was, interestingly, a monoester of hydroxyethylphosphonic acid **7**.[18] Changing the solvent to MeOH, ^{i}PrOH, ^{t}BuOH, H_2O, THF, and acetone, or changing the base to K_2CO_3, NaOMe, NaOEt, NaO^{t}Bu, Ca(OH)$_2$, $CaCO_3$, and CaO, all gave a similar result.

Phosphinates **5**–**6′** display a similar reaction pattern to their phosphinates counterparts. Thus, ethyl phenyl-(1-phenylethenyl)phosphinate (**5a**; [P] = P(O)Ph(OEt), R = Ph), *but not 2-octenylphosphinate* (**5b**; [P] = P(O)-Ph(OEt), R = *n*-C_6H_{13}), was successfully epoxidized under the conditions of Scheme 2 to give 70% yield of phenyl(1-phenyloxiranyl)phosphinate (**1c**) as a 1:1 diastereomeric mixture.[19] To the best of our knowledge, this is the first synthesis of such a phosphinyloxirane. In a similar manner, treatment of alkenylphosphinic acids having a α-*n*-C_6H_{13} (**6b**) or β-*n*-C_6H_{13} group (**6′b**) under the conditions of $H_2O_2/Na_2WO_4/Et_3N$ system (Table 1, run 11) gave the corresponding epoxides **1d** and **1′d** in 62% and 71%, respectively. However, similar to phosphonic acids, β-Ph phosphinic acid **6′a** did not give the corresponding epoxide by the treatment with $H_2O_2/Na_2WO_4/Et_3N$.[20]

In sharp contrast to these alkenylphosphonates and alkenylphosphinates, alkenyl phosphine oxides (**4** and **4′**; [P] = P(O)Ph$_2$, R = Ph or *n*-C_6H_{13}) did not react with H_2O_2 under similar reaction conditions. The unsubsti-



Yield: R = Me, 72%; R = Et, 87%; R = *i*-Pr, 65%

Scheme 3. Conditions: **2c** (1 mmol), NaOH (1 mmol), 30% H_2O_2 (1 mL, 8.8 mmol), EtOH (1 mL), room temperature, 20 h.

tuted diphenylvinylphosphine oxide did not afford the corresponding epoxide either.

In summary, the epoxidation of alkenylphosphorus compounds with H_2O_2 is highly affected by the substituents of the phosphorus compounds. By using H_2O_2/K_2CO_3, epoxidation takes place efficiently with alkenylphosphonates or phosphinates having a phenyl group at α-position (**2a** and **5a**, R = Ph), and by using H_2O_2/Na_2WO_4/Et_3N, epoxidation takes place efficiently with alkenylphosphonic acids[21] or phosphinic acids having an aliphatic group at α- or β-positions (**3b**, **3′b**, **6b**, and **6′b**, R = *n*-C_6H_{13}). Alkenylphosphine oxides did not produce the corresponding epoxides under similar conditions. These results, to some extent, resemble the early observations on the epoxidation of α,β-unsaturated carbonyl compounds,[15] which deserve future mechanistic exploration.

Acknowledgements

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Supplementary data

Detailed experimental procedures and copies of ^{1}H and ^{13}C spectra of the phosphinoyl epoxides. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.11.083.

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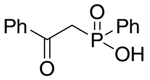
15. Similar tungstate catalyzed epoxidation of α,β-unsaturated carboxylic acids with H_2O_2 is known to be affected by a lot of factors such as pH (the addition of a base) and concentration, under which a complex of different tungstate species exhibiting different catalytic activities are believed to be produced (a) Payne, G. B.; Williams, P. H. *J. Org. Chem.* **1959**, *24*, 54; (b) Kirshenbaum, K. S.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1979; (c) Shi, H.-C.; Chen, G.; Wang, X.-Y.; Zhang, Z.-G. *J. Mol. Catal. A: Chem.* **2004**, *216*, 29.
16. The difference of the reactivity between **2a** and **2′a** may be due to the fact that the resulting anionic intermediate generated by the addition of HO_2^- could be more stabilized in case of **2a**. However, a steric effect may be also contributing since DFT calculations (HF/6-311G(2d,p)//B3LYP/6-31G(d) level of theory) showed lower LUMO of **2′a** (1.96 eV) than that of **2a** (2.58 eV) which excludes the possibility of lacking of electrophilicity of **2′a**.
17. Retention of the *trans* configuration during present reaction was confirmed on the basis of $^3J_{HH}$ value (∼3 Hz) of two adjacent oxirane ring protons on the products, which are typical of *trans*-substituted phosphoryl oxiranes (Ref. 7b) (see Supplementary data).
18. It was noted, however, that in the absence of H_2O_2 no reaction took place between **2c** and NaOH, indicating that H_2O_2 is necessary for the formation of **7** under the present conditions. Thus, the β-addition of HOO^- to the carbon–carbon double bond must proceed. The intermediate might be unstable or decomposed before the oxirane ring was formed. Vinylphosphonic acid could be epoxidized in the presence of a tungstate salt (40% yield).

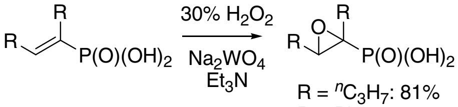
19. The ^{31}P NMR spectrum of the product in $CDCl_3$ displays two peaks at δ 32.8 and 35.7 with an integral ratio of 1:1 (see Supplementary data).
20. Instead, ketone **8** was obtained.



8

Although a pinacol type rearrangement of epoxyphosphonates to the aldehydes via phosphorus migration mediated by an acid or heat is known (Churi, R. H.; Griffin, C. E. *J. Am. Chem. Soc.* **1966**, *88*, 1824), we assume that **8** was formed directly from the oxidation of the alkene. Transition metal-catalyzed oxidation of alkenes to ketones with H_2O_2 is well known (Ref. 14).

21. The trisubstituted alkenes (*trans*-phosphinic acids) are also successfully epoxidided to the corresponding oxiranes under the conditions of run 11 Table 1.



R = $^{n}C_3H_7$: 81%
R = Ph: 87%