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Stable Tetravalent Phosphonium Enolate Zwitterions

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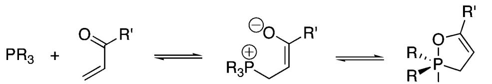
Phosphine-catalyzed reactions of electron-deficient alkenes have emerged as powerful tools for the preparation of biologically and medicinally useful compounds.[1,2] Common to these transformations is the generation of a putative dipolar phosphonium enolate through the addition of a tertiary phosphine to an electrophilic alkene. Focusing on the use of allenoates as substrates, we have explored the various reactions available for the key zwitterionic intermediates and have developed new methods for the syntheses of tetrahydropyridines, dihydropyrroles, dioxanes, and pyrones.[3] In those studies, the reaction pathways of the proposed intermediates could be controlled by varying the nature of the electrophile[4] or the structure of the initial zwitterionic adduct by using a bulky phosphine.[3d] Although this approach has proved fruitful, leading to the discovery of an array of new reactions, we and others have never directly observed any of the conjectured zwitterionic intermediates.[5] Given the pivotal mechanistic roles played by phosphonium enolate intermediates, knowledge of their structures and reactivities will greatly benefit the further development of phosphine-catalyzed reactions. Herein, we report the syntheses of stable tetravalent phosphonium enolates through simple one-pot, three-component processes and the X-ray crystallographic characterization of these dipolar intermediates.

Structural studies of tetravalent phosphonium zwitterions are complicated by the ability of their phosphorus atoms to adopt multiple valence structures. In particular, β-phosphonium enolates arising from the addition of trivalent phosphines to α,β-unsaturated carbonyl compounds are unstable and exist mainly as isomeric pentavalent phosphoranes (eqs 1 and 2).[6] For this reason, whereas a number of 1,2-λ^5-oxaphospholenes have been characterized well,[7] direct observation of tetravalent phosphonium enolates has remained an elusive goal, even though the mechanistic implications for various phosphine-catalyzed processes would be immense.[8]



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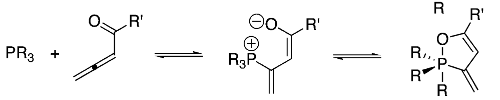

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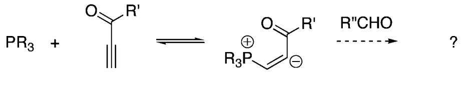

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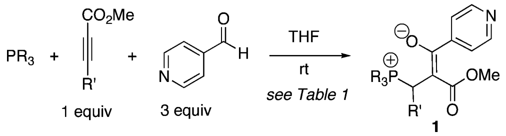
Following our interest in the chemistry of vinyl phosphonium enolates (eq 2) vis-à-vis that of alkyl derivatives (eq 1),[2,3] we pondered the reactivity of a further type of vinyl phosphonium zwitterion: one derived from an electron-deficient alkyne (eq 3). We were particularly intrigued to examine its potential to undergo addition to an aldehyde—and to determine the structure of any such adduct. We were pleased to find that the three-component coupling reaction of PMe_3, methyl phenylpropiolate, and 4-pyridinecarboxaldehyde proceeded smoothly in THF at room temperature to provide yellow crystals of a 1:1:1 adduct **1a** (R = Me; R′ = Ph) in 83% yield (eq 4 and Table 1). The ^1H, ^{13}C, and ^{31}P NMR spectral data of **1a** suggested a dipolar structure. Most notably, the ^{31}P NMR spectrum exhibited a diagnostic signal for tetravalent phosphorus at +16.0 ppm (entry 1).[9] The reaction of PBu_3 provided a similar dipolar adduct **1b** (^{31}P NMR: $\delta = +32.2$ ppm) in 91% yield under otherwise identical reaction conditions (entry 2). This reaction proved to be a general one for a range of methyl propiolates of varying steric and electronic nature (entries 2−5).



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(4)

The X-ray crystallographic data for **1a** reveal that the phosphorus atom exists in a tetrahedral geometry and does not bond covalently with the enolate oxygen atom, as evidenced by the P1−O5 distance of 2.821 Å (Figure 1).[10,11] The C3−C4 and C4−O5 bonds (1.393 and 1.271 Å, respectively) both possess partial double bond character, with the negative charge dispersed mainly between the C3 and O5 atoms. Although the carbomethoxy group appears to contribute to the delocalization of the negative charge only to a small degree, as indicated by the C3−C6 and C6−O7 bond lengths (1.440 and 1.230 Å, respectively), its near in-plane orientation with the enolate (C4−C3−C6−O7 dihedral angle: 175.74°) suggests a possible means of stabilization of the dipolar structure.

The crystals of **1b** and **1f** contained pairs of conformationally distinct non-interacting zwitterions in each unit cell. The distances between the P1 and O5 atoms in the pair of **1b** zwitterions (2.947 and 2.941 Å, respectively) reflect the increased steric bulk around the phosphorus center of **1b** relative to that in **1a**. Again, the negative charge is localized on each C3−C4−O5 enolate moiety. In fact, in one of the two conformations, the ester is twisted out of conjugation from the enolate (C4−C3−C6−O7 dihedral angle: 146.84°; Table 1, entry 2). The more electron-deficient phosphonium center in **1f** resides closer to the oxygen atom than that in **1a**, despite the increased steric bulk around the phosphorus atom (P1−O5 distances in **1f**: 2.597 and 2.620 Å, respectively).

Our X-ray crystallographic analyses of **1a**, **1b**, and **1f** provide the first direct experimental proof of the tetravalency of phosphorus atoms in phosphonium enolate zwitterions; previously, evidence for their structures was implied from NMR and IR spectroscopic data.[8] We construe that the presence of electron-donating alkyl groups on the phosphonium centers in our zwitterions decreases their impetus for conversion to pentavalent phosphoranes. Indeed, a number of stable oxaphospholenes have been isolated containing three aryl substituents on pentavalent phosphorus atoms.[12] Accordingly, we turned our attention to zwitterionic systems containing one or more aryl substituents on their phosphorus atoms. We isolated zwitterions **1f** and **1g** from the reactions of PMe_2Ph with methyl phenylpropiolate and $PMePh_2$ with methyl propiolate, respectively (Table 1, entries 6 and 7). The reaction of $PMePh_2$

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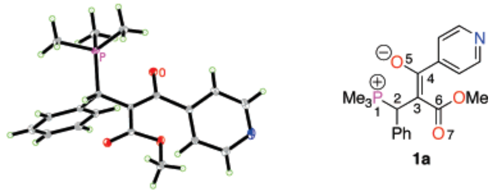
Table 1. Synthesis and Structural Data of Phosphonium Enolate Zwitterions **1**

entry	phosphine	R′	time (h)	temp	yield[a] (%)	product	δ_P (ppm)	P⁺–O⁻ distance (Å)	C4–C3–C6–O7 dihedral angle
1	PMe_3	Ph	12	rt	83	**1a**	+16.0	2.821	175.74°
2	PBu_3	Ph	6	rt	91	**1b**[b]	+32.3	2.947 & 2.941	146.84 & 174.63°
3	PBu_3	H	0.5	rt	95	**1c**	+32.4	NA	NA
4	PBu_3	CH_3	5.5	rt	33	**1d**	+35.8	NA	NA
5	PBu_3	CO_2Me	1	rt	84	**1e**	+36.2	NA	NA
6	PMe_2Ph	Ph	12	rt	81	**1f**[b]	+17.4	2.597 & 2.620	2.95 & 175.29°
7	$PMePh_2$	H	12	rt	77	**1g**	+22.4	NA	NA
8	$PMePh_2$	Ph	72	80 °C[c]	0	**1h**	+16.5	NA	NA
9	PPh_3	Ph	168	80 °C[c]	no reaction	NA	NA	NA	NA
10	PPh_3	H	168	80 °C[c]	no reaction	NA	NA	NA	NA

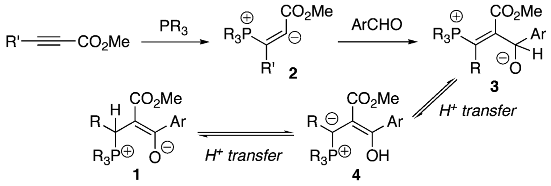
[a] Isolated yield. [b] Crystals of **1b** and **1f** contained two zwitterions per unit cell; tabulated data are presented for each molecule. [c] Sealed tube.



1a

Figure 1. ORTEP depiction of **1a** (50% thermal ellipsoids).

Scheme 1. Proposed Mechanism for the Formation of **1**



with methyl phenylpropiolate did produce a zwitterion that was observable in solution (NMR spectroscopy) but not isolable (entry 8). In contrast, the reactions of PPh_3 did not provide any detectable zwitterions (entries 9 and 10).[13] These results are consistent with our hypothesis that electron-releasing alkyl substituents on the phosphonium center play a critical role in stabilizing phosphonium enolate zwitterions.

We propose that zwitterion **1** is formed through conjugate addition of the phosphine to the propiolate and subsequent nucleophilic addition of the vinyl anion **2** to 4-pyridinecarboxaldehyde (Scheme 1).[14] The resulting zwitterion **3**, upon proton transfer, forms the ylide **4**. Another proton-transfer process affords the zwitterion **1**.[15]

This paper describes the synthesis of stable phosphonium enolate zwitterions, which have been proposed as intermediates in Morita−Baylis−Hillman (MBH) reactions, through novel three-component coupling reactions between tertiary phosphines, alkynoates, and aldehydes. We report, for the first time, the isolation and X-ray crystallographic characterization of such phosphonium enolate zwitterions, establishing the tetravalent nature of their phosphorus atoms unequivocally. These structures, which stand in contrast to those of the well-established pentavalent 1,2-λ^5-oxaphospholenes, might explain the instability and high reactivity of phosphonium enolate zwitterions in MBH-type reactions. Our future efforts will focus on exploring the synthetic utility of zwitterions **1** and on extending this study to novel catalytic processes involving phosphonium enolates.

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Supporting Information Available: Representative experimental procedures and spectral data for all new compounds (PDF). Crystallographic data for compounds **1a**, **1b**, and **1f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Trace amounts (0.5−7%) of a product containing two units from 4-pyridinecarboxaldehyde and one from methyl propiolate were isolated from several of the reactions. The formation of this product can be rationalized from consideration of our proposed mechanism; see the Supporting Information for details.

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