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Synthesis and structures of stable phosphorus zwitterions derived from mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates†

Ryosuke Saijo, a Hidemitsu Uno, b Shigeki Mori c and Masami Kawase a,*

Trialkyl phosphites were evaluated as phosphorus nucleophiles for addition to mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (1), thereby producing tetravalent phosphorus zwitterions (2) in good yields. The structure of 2 was determined to be a tetravalent phosphonium enolate in a single crystal X-ray analysis.

In organic chemistry, tetravalent phosphonium zwitterions are difficult to isolate because phosphorus atoms have multiple valence structures. Several research groups have attempted to isolate stable tetravalent phosphonium zwitterions. To date, Ramirez et al. 1 in 1968, Zhu et al. in 2005, and Kwon et al. in 2007 have reported their isolation and molecular structures in the addition reactions of 3-benzylidene-2,4-pentanedione with phosphate or phosphate [eqn (1)], 2 in the reactions of EtOCH=CHCOCF 3 with PBu 3 [eqn (2)], 3 and in the three-component coupling reactions between tertiary phosphines, alkynoates, and aldehydes [eqn (3)]. 1 Lin et al. 4 have also reported the isolation and molecular structures of some zwitterions isolated in the addition reaction of Michael acceptors and Bu 3 P and their conversion to furan derivatives 4a or other heterocycles 4b-4d via an intramolecular Wittig reaction. These zwitterions are stabilized by the resonance of carbanions.

Phosphine-promoted reactions are increasingly becoming synthetically useful for the preparation of biologically and medicinally useful compounds. 5 In many reported reactions, nucleophilic phosphites react with π-acceptors, such as electron-deficient olefins, 6 acetylenes, 7 ketenes, 8 allenes, 9 and azodicarboxylate, 10 resulting in the formation of phosphonium zwitterionic intermediates in the first step of the reaction. However, structural studies on tetravalent phosphonium zwitterion intermediates are challenging because phosphonium ions are unstable and sometimes cyclize to pentavalent phosphoranes when γ-alkoxide groups are present [eqn (4)]. 11

In the course of our studies on the reactions of mesoionic 1,3-oxazolium-5-olates (munchrones) 1, 12 we discovered a new route that allows for the isolation of tetravalent phosphonium zwitterions 2 in good yields via the reaction of 1 and Bu 3 P.

We herein describe the synthesis and X-ray crystallographic characterization of phosphonium enolate (acylphosphonium) zwitterions 2, unequivocally establishing the tetravalent nature of their phosphorus atoms.

The mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates 1 were easily prepared from N-acyl-N-alkyl-α-amino acids in one step.

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a Faculty of Pharmaceutical Sciences, Matsuyama University, 4-2 Bunkyo-cho, Matsuyama, Ehime 790-8578, Japan. Fax: +81 89 9267162; Tel. +81 89 9267098; E-mail: kawase@cc.matsuyama-u.ac.jp
b Department of Chemistry and Biology, Graduate School of Science and Engineering, Ehime University, Matsuyama, 790-8577, Japan.

c Advanced Research Support Center, Ehime University, Matsuyama, 790-8577, Japan.

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through cyclodehydration by trifluoroacetic anhydride followed by trifluoroacetylation at the C-4 position of an intermediary mesionic 1,3-oxazolium-5-olate.¹²

When 1 mmol of 1 and 1.5 mmol of Bu₃P were mixed in THF, the reaction proceeded well at room temperature. After the mixture was stirred for 2.5-6.5 h, a TLC analysis showed that the starting material 1 disappeared completely. Following the evaporation of the solvent and purification by silica gel column chromatography eluted with AcOEt-hexane (1:2), the pure product 2 was obtained in a good yield. The reaction could proceed in other solvents, such as toluene, 1,2-dichloroethane and DMF, but the conversion was slightly low. Table 1 shows the results.

Among the trialkyl or triaryl phosphines tested such as PBu₃, P(t-Bu)₃, PCy₃, and PPh₃, PBu₃ was found to be the only successful reagent. We speculate that PPh₃, P(t-Bu)₃, and P(C₆H₅)₃ are too sterically hindered and not sufficiently nucleophilic toward the mesionic ring. On the other hand, PBu₃ is less sterically hindered and functions as a better nucleophile.⁸

Triethyl phosphate (EtO)₃P and diethyl phosphate (EtO)₂P(OH) were also evaluated as P-nucleophiles for addition to 1d.⁸ In these reactions, the starting material (1d) was not recovered and several materials were detected by TLC, none of which were characterized.

As shown in Table 1 (entries 1-7), mesionic 1a-g bearing either alkyl or aryl substituents at the C2 or N3 positions all performed well, giving zwitterions 2a-g in fair to excellent yields. Zwitterionic compounds 2 were stable for several months at room temperature without changing. The zwitterionic structure of 2 was fully characterized in a single crystal X-ray diffraction analysis and using spectral methods.

An X-ray single crystal investigation of compound 2a revealed a tetravalent phosphonium enolate structure (Fig. 1).¹³ Some selected bond lengths and angles are listed in Table 2. These results revealed that the two C1-C2 (1.427 Å) and C2-C3 (1.410 Å) bonds have the double-bond characteristic, compared to the normal values for C=C (1.34 Å) and C-C (1.54 Å), and the two carbonyl bonds C1=O1 (1.245 Å) and C3=O2 (1.247 Å) are slightly longer than a normal carbonyl bond length (1.23 Å).¹⁴ This equalization is typical for highly delocalized keto-enol systems.¹⁴

The atoms O1, C1, C2, C3, and O2 are nearly co-planar (the dihedral angles of C1-C2-C3-O2 and C3-C2-C1-O1 are 6.05° and 168.99°, respectively). These results indicate that the anion is fully dislocated, which stabilizes its resonance structure. The distance between P and O2 is 2.88 Å, which is smaller (shorter) than their corresponding van der Waals contact of 3.32 Å (van der Waals radius for P=1.80 Å and O=1.52 Å), resulting in negligible interactions.

No vibrational frequencies around 1700 cm⁻¹ corresponded to C=O stretches and indicated a decrease in the C=O bond order, consistent with π-electron delocalization through the keto-enol system.¹⁻³ The carbonyl stretching frequency of the acetyldiethylmethylyphosphonium iodide (Et₂MeP⁺COMe⁻) was previously reported to be 1707 cm⁻¹.¹⁵ The broadening of lines, which is typical for betaines in general, was observed in the ¹³C NMR spectra of N-phenyl derivatives (2a, c, e).¹⁶

Table 1. Reactions of 1 with PBu₃

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R¹</th>
<th>R²</th>
<th>Time (h)</th>
<th>Yields of 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>Ph</td>
<td>4-BrC₆H₄</td>
<td>4</td>
<td>2a (72)</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>Me</td>
<td>4-BrC₆H₄</td>
<td>4</td>
<td>2b (74)</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>Ph</td>
<td>Ph</td>
<td>3</td>
<td>2c (93)</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>Me</td>
<td>Ph</td>
<td>4</td>
<td>2d (89)</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>Ph</td>
<td>Me</td>
<td>2.5</td>
<td>2e (86)</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>Bn</td>
<td>Ph</td>
<td>6.5</td>
<td>2f (89)</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>Ph</td>
<td>t-Bu</td>
<td>5</td>
<td>2g (95)</td>
</tr>
</tbody>
</table>

Table 2. Selected bond lengths and angles of compound 2a

<table>
<thead>
<tr>
<th>Bond length (Å)</th>
<th>Bond angle (°)</th>
<th>Dihedral angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-C1</td>
<td>1.883</td>
<td>P-C1-C2</td>
</tr>
<tr>
<td>C1-C2</td>
<td>1.427</td>
<td>P-C1-O1</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.410</td>
<td>O1-C1-C2</td>
</tr>
<tr>
<td>C3-C4</td>
<td>1.553</td>
<td>C1-C2-C3</td>
</tr>
<tr>
<td>C1-O1</td>
<td>1.245</td>
<td>C1-C2-N</td>
</tr>
<tr>
<td>C3-O2</td>
<td>1.247</td>
<td>C3-C2-N</td>
</tr>
<tr>
<td>C5-O3</td>
<td>1.231</td>
<td>C2-C3-O2</td>
</tr>
<tr>
<td>C2-N</td>
<td>1.445</td>
<td>C2-C3-C4</td>
</tr>
<tr>
<td>C5-N</td>
<td>1.377</td>
<td>C2-C3-C4</td>
</tr>
</tbody>
</table>

Figure 1. Ortep Drawing of 2a (50% Probability)
13C NMR signals of the central 1,3-diketone unit in 2d appeared characteristically at $\delta$ 121.6 (d, $^2J_{C-P}=62.3$ Hz), 173.3 (d, $^1J_{C-P}=47.9$ Hz), and 173.9 (qd, $^2J_{C-P}=31.9$ Hz, $^3J_{C-P}=3.6$ Hz) ppm.

The 31P NMR signals of 2 were observed at 27.5-29.7 ppm. Based on previous findings, an acylphosphonium (Bu$_3$P$^+$COMe Cl$^-$) derived from acetyl chloride and PBu$_3$ gave rise to a signal at 28.8 ppm in the 31P NMR spectrum.17

The mechanism underlying this reaction has not yet been elucidated in detail; however, the three possibilities described below are outlined in Scheme 1. Bu$_3$P attacks the tautomeric intermediate A to give the resonance-stabilized zwitterionic compounds 2. Bu$_3$P attacks a ketene intermediate B to give the compounds 2 because mesoionic 1 is in equilibrium with the ketene in which the ketene carbonyl is attacked by Bu$_3$P. Bu$_3$P acts as a nucleophilic trigger and forms the zwitterionic intermediate C, which is attacked by a second Bu$_3$P to give the ring opening product 2 concomitant with the re-generation of Bu$_3$P.

Acylphosphonium zwitterions 2 were reacted with acyl chloride and the novel formation of trifluoromethylated enol esters 3 was observed (Scheme 2). Thus, the reaction of the zwitterion 2d and an acid chloride such as acetyl chloride, isobutyryl chloride, pivaloyl chloride, or benzoyl chloride in the presence of K$_2$CO$_3$ in toluene occurred at 80 °C, giving the trifluoromethylated enol esters 3 in moderate yields (23-62%).19 Zwitterions 2 are multifunctional compounds with one nucleophilic enol and one electrophilic acyl group, and, thus, may undergo acylation at the enol oxygen to give the intermediate D, which may then cyclize to afford oxazolidin-5-ones E. The intermediates E undergo hydrolysis followed by decarboxylation to give the enol esters 3 (Scheme 2). 13C NMR signals of the double bond in 3a appeared at $\delta$ 120.7 (q, $^2J_{C-C}=37.4$ Hz) and 126.1 ppm, which are consistent with those for the enol esters 4 and 5, as shown in Scheme 3.

Scheme 1. Proposed mechanism for the formation of products 2.

Scheme 2. Proposed mechanism for the formation of 3.

Scheme 3. 13C-NMR data for 4 and 5.
Conclusions

The first example of a novel class of acylphosphonium enolates has become readily available in good yields. We herein isolated and characterized some stable acylphosphonium zwitterions that were some of the key intermediates in the PBu₃-catalyzed homodimerization of ketoketenes. The observation that the title compounds of this study, the acylphosphonium zwitterions 2, are easily obtained, even at room temperature, indicates that the specific chemistry of these neutral derivatives of acylphosphonium cations will be developed.

Notes and references

13. The structure of 2a was confirmed by X-ray analysis (CCDC no. 1440729).
17. Compound 2d: Yellow crystals, 69% yield. mp 113-115 °C (ACOEt/hexane). IR (KBr) νmax: 2954, 2942, 2873, 1639, 1541, 1423, 1330, 1230, 1219, 1178, 1131, 943, 867, 705 cm⁻¹. 1H NMR (500 MHz, CDCl₃) δ 0.89 and 0.96 (t, J = 7.4 Hz, 9H, CH₃), 1.51–1.29 (m, 6H, CH₂), 1.47–1.68 (m, 6H, CH₂), 1.96–2.14 (m, 6H, PCH₂), 3.05 and 3.18 (s, 3H, NCH₃), 7.20 (t, J = 7.5 Hz, 2H, ArH), 7.26 (t, J = 7.1 Hz, 1H, ArH), 7.32–7.39 (m, 2H, ArH) ppm. 13C NMR (126 MHz, CDCl₃) δ 13.2, 19.9 (d, 1JCP = 45.0 Hz, PCH₂), 23.8 (d, 2JCP = 15.2 Hz, CH₂), 24.3 (d, 3JCP = 4.3 Hz, CH₂), 37.4 and 40.3, 118.4 (q, 1JCP = 290.3 Hz, CF₃), 121.6 (d, 2JCP = 62.3 Hz, NC), 126.5 and 127.0, 127.3 and 128.1, 128.8 and 129.4, 136.8 and 137.8, 173.3, (d, 3JCP = 47.9 Hz, POC), 173.9 (q, 3JCP = 31.9 Hz, CF₃CO), 173.9 ppm. 31P NMR (202 MHz, CDCl₃) δ 29.2 ppm. MS m/z: 473 (M⁺, 44), 271 (100). HRMS (EI) for C₁₂H₂₃F₃NO₃P (M⁺): Calcd, 473.2307. Found, 473.2286.
19. Full details of the reaction of 2 with acid chlorides will be reported elsewhere.