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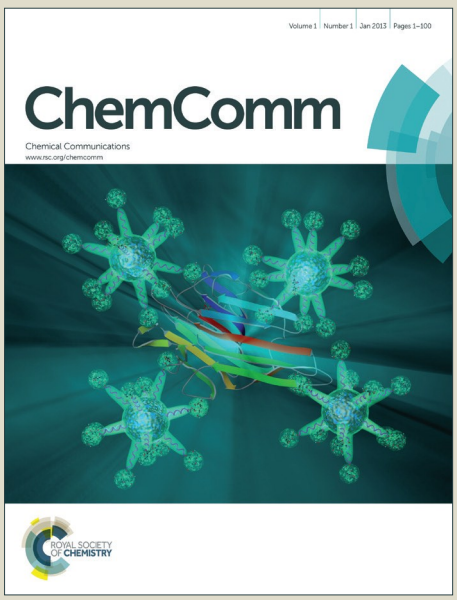

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Synthesis and structures of stable phosphorus zwitterions derived from mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates†

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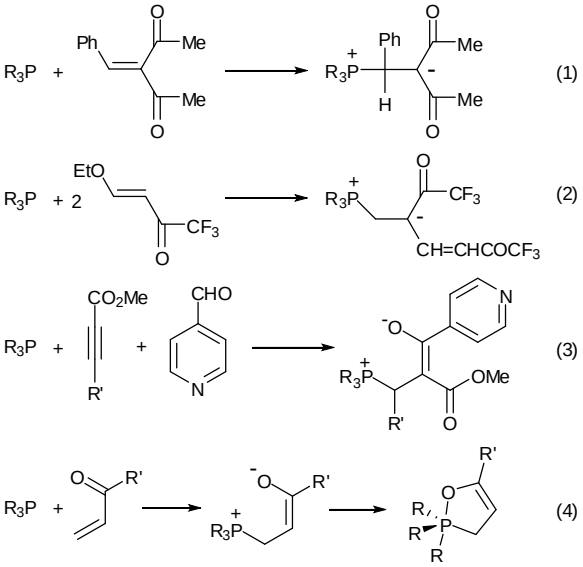
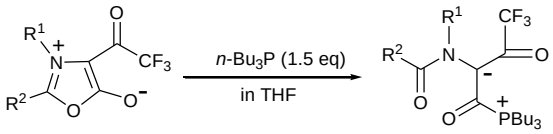
Trialkyl phosphites were evaluated as phosphorus nucleophiles for addition to mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (1), thereby producing tetravalent phosphorus zwitterions (2) in good yields. The structure of 2 was determined to be a tetravalent phosphonium enolate in a single crystal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

In organic chemistry, tetravalent phosphonium zwitterions are difficult to isolate because phosphorus atoms have multiple valance structures.[1] Several research groups have attempted to isolate stable tetravalent phosphonium zwitterions. To date, Ramirez et al.[2] in 1968, Zhu et al.[3] in 2005, and Kwon et al.[1] in 2007 have reported their isolation and molecular structures in the addition reactions of 3-benzylidene-2,4-pentanedione with phosphonate or phosphine [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_3P and their conversion to furan derivatives[4a] or other heterocycles[4b-d] 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 phosphines 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 (munchnones) **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_3P.



1a-g **2a-g**

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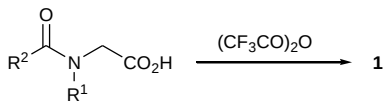
through cyclodehydration by trifluoroacetic anhydride followed by trifluoroacetylation at the C-4 position of an intermediary mesoionic 1,3-oxazolium-5-olate.[12]



When 1 mmol of **1** and 1.5 mmol of Bu_3P 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 PBu_3, P(*t*-Bu)$_3$, PCy_3, and PPh_3, PBu_3 was found to be the only successful reagent. We speculate that PPh_3, P(t-Bu)$_3$, and P(C_6H_{11})$_3$ are too sterically hindered and not sufficiently nucleophilic toward the mesoionic ring. On the other hand, PBu_3 is less sterically hindered and functions as a better nucleophile.[8]

Triethyl phosphite $(EtO)_3P$ and diethyl phosphite $(EtO)_2P(=O)H$ 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.

Table 1. Reactions of **1** with PBu_3[a]

Entry	1	R^1	R^2	Time (h)	Yields of **2** (%)
1	**a**	Ph	4-BrC_6H_4	4	**2a** (72)
2	**b**	Me	4-BrC_6H_4	4	**2b** (74)
3	**c**	Ph	Ph	3	**2c** (93)
4	**d**	Me	Ph	4	**2d** (89)
5	**e**	Ph	Me	2.5	**2e** (86)
6	**f**	Bn	Ph	6.5	**2f** (89)
7	**g**	Ph	*t*-Bu	5	**2g** (95)

[a] Isolated yields.

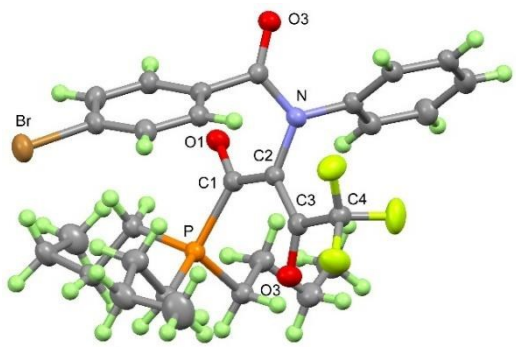


Figure 1. Ortep Drawing of **2a** (50% Probability)

As shown in Table 1 (entries 1-7), mesoionic **1a-g** bearing either alkyl or aryl substituents at the C2 or N3 positions all functioned well, giving zwitterions **2a-g** in fair to excellent yields. Zwitterionic compounds **2** may be stored for several months at room temperature without changing.

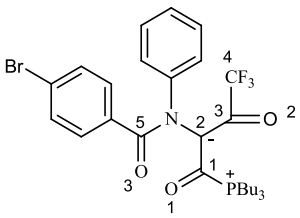
The zwitterionic structure of **2** was fully characterized in a single crystal X-ray diffraction analysis and using spectral methods.

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.

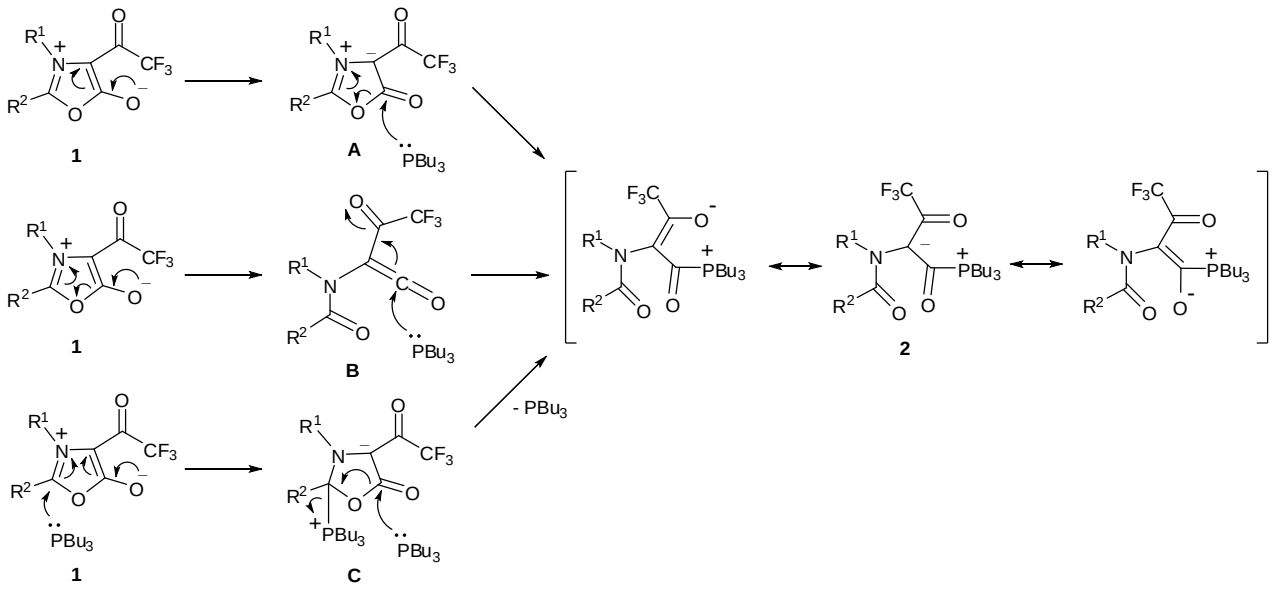
No vibrational frequencies around 1700 cm^{-1} corresponded to C=O stretches and indicated a decrease in the C=O bond order, consistent with π-electron delocalization through the keto-enol system.[1, 3] The carbonyl stretching frequency of the acetyldiethylmethylphosphonium iodide ($Et_2MeP^+COMe\ I^-$) was previously reported to be 1707 cm^{-1}.[15] The broadening of lines, which is typical for betaines in general, was observed in the ^{13}C NMR spectra of *N*-phenyl derivatives (**2a, c, e**).[16]

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



2a

Bond length (Å)		Bond angle (°)		Dihedral angle (°)	
P-C1	1.883	P-C1-C2	123.52	C3-C2-C1-O1	168.99
C1-C2	1.427	P-C1-O1	112.42	C3-C2-C1-P	12.14
C2-C3	1.410	O1-C1-C2	124.05	C1-C2-C3-O2	6.05
C3-C4	1.553	C1-C2-C3	122.05	C1-C2-C3-C4	176.77
C1-O1	1.245	C1-C2-N	115.89	O1-C1-C2-N	3.14
C3-O2	1.247	C3-C2-N	121.58	N-C2-C3-C4	11.55
C5-O3	1.231	C2-C3-O2	124.98	N-C2-C1-P	175.73
C2-N	1.445	O2-C3-C4	114.23		
C5-N	1.377	C2-C3-C4	120.73		



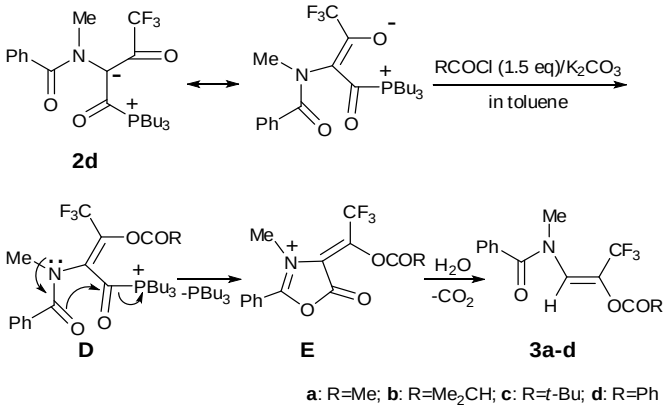
Scheme 1. Proposed mechanism for the formation of products **2**.

^{13}C NMR signals of the central 1,3-diketone unit in **2d** appeared characteristically at δ 121.6 (d, $^{2}J_{C\text{-}P}$=62.3 Hz), 173.3 (d, $^{1}J_{C\text{-}P}$=47.9 Hz), and 173.9 (qd, $^{2}J_{C\text{-}F}$=31.9 Hz, $^{3}J_{C\text{-}P}$=3.6 Hz) ppm.[17]

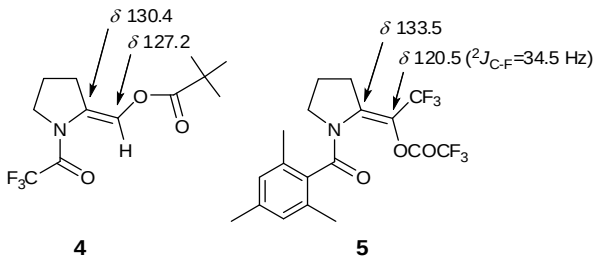
The ^{31}P NMR signals of **2** were observed at 27.5-29.7 ppm. Based on previous findings, an acylphosphonium ($Bu_3P^+COMe\ Cl^-$) derived from acetyl chloride and PBu_3 gave rise to a signal at 28.8 ppm in the ^{31}P NMR spectrum.[18]

The mechanism underlying this reaction has not yet been elucidated in detail; however, the three possibilities described below are outlined in Scheme 1. Bu_3P attacks the tautomeric intermediate **A** to give the resonance-stabilized zwitterionic compounds **2**. Bu_3P 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_3P. Bu_3P acts as a nucleophilic trigger and forms the zwitterionic intermediate **C**, which is attacked by a second Bu_3P to give the ring opening product **2** concomitant with the re-generation of Bu_3P.

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_2CO_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 oxazolium-5-ones **E**. The intermediates **E** undergo hydrolysis followed by decarboxylation to give the enol esters **3** (Scheme 2). ^{13}C NMR signals of the double bond in **3a** appeared at δ 120.7 (q, $^{2}J_{C\text{-}F}$=37.4 Hz) and 126.1 ppm, which are consistent with those for the enol esters **4**[20] and **5**[21], as shown in Scheme 3.



Scheme 2. Proposed mechanism for the formation of **3**.



Scheme 3. ^{13}C-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 PBu_3-catalyzed homodimerization of ketoketenes.[8] 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.

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17 **Compound 2d**: Yellow crystals, 89% yield. mp 113–115 °C (AcOEt/hexane). IR (KBr) ν_{max}: 2954, 2942, 2873, 1639, 1541, 1423, 1330, 1230, 1219, 1178, 1131, 943, 867, 705 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 and 0.96 (t, *J* = 7.4 Hz, 9H, CH_3), 1.15–1.29 (m, 6H, CH_2), 1.47–1.68 (m, 6H, CH_2), 1.96–2.14 (m, 6H, PCH_2) 3.05 and 3.18 (s, 3H, NCH_3), 7.20 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.26 (t, *J* = 7.1 Hz, 1H, Ar*H*), 7.32–7.39 (m, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.2, 19.9 (d, $^1J_{C-P}$ = 45.0 Hz, PCH_2), 23.8 (d, $^2J_{C-P}$ = 15.2 Hz, *C*H_2), 24.3 (d, $^3J_{C-P}$ = 4.3 Hz, *C*H_2), 37.4 and 40.3, 118.4 (q, $^1J_{C-F}$ = 290.3 Hz, *C*F_3), 121.6 (d, $^2J_{C-P}$ = 62.3 Hz, N*C*), 126.5 and 127.0, 127.3 and 128.1, 128.8 and 129.4, 136.8 and 137.8, 173.3, (d, $^1J_{C-P}$ = 47.9 Hz, P*C*O), 173.9 (qd, $^2J_{C-F}$ = 31.9 Hz, $^3J_{C-P}$ = 3.6 Hz, CF_3*C*O), 173.9 ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ 29.2 ppm. MS *m/z*: 473 (M^+, 4.4), 271 (100). HRMS (EI) for $C_{24}H_{35}F_3NO_3P$ (M^+): Calcd, 473.2307. Found, 473.2286.
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