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First iodocyclization of β-allenic phosphonates: a novel synthesis of α-difluoromethylenephostones

Yun Lin and Jin-Tao Liu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

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Abstract—Six-membered α-difluoromethylenephostones were prepared in moderate to good yields with high regioselectivities under mild conditions from the iodocyclization reaction of diethyl β-allenic α,α-difluorophosphonates using I_2 or ICl as the electrophile.

Recently, increasing focus upon the role and significance of biological phosphoryl transfer in terms of intracellular signal processing has resulted in a heightened interest in hydrolytically stable and effective phosphate analogues. The postulate that the isoelectronic and isosteric CF_2/O transposition in phosphate analogues resulted in especially hydrolytically stable and effective mimics of the corresponding phosphates, originally put forward by Blackburn,[1] has gained notable experimental support. For example, Chambers and O'Hagan demonstrated the electronic and structural similarities between α-difluoromethylenephosphonates and the corresponding phosphates.[2] Danzin and co-workers have noted the superiority of α,α-difluorinated phosphonate bisubstrate analogues (inhibitor of purine nucleoside phosphorylase) over the corresponding nonfluorinated phosphonates.[3]

Up to now a wide range of structurally novel and biologically interesting acyclic α-difluoromethylenephosphonate derivatives have been studied as potential enzyme inhibitors and useful probes for the elucidation of biochemical process.[4] In contrast, evaluation of cyclic α-difluoromethylenephosphonates (phostones) as biological phosphate mimics has never been explored because there are few synthetic methods available to construct such heterocycles. To the best of our knowledge, there are only two papers[5] regarding the formation of five or six-membered α-difluoromethylenephostones as byproducts or intermediates so far.

On the other hand, a series of compounds bearing a cyclic phosphate moiety play vital roles in diverse biological processes. Cyclic phosphates (cPIP) of foremost biological importance are the universal second messenger cyclic AMP and cyclic GMP. Other cyclic phosphates which were detected in biological systems include glucose cyclic phosphodiester,[6] 2′,3′-cyclic phosphodiester nucleotides,[7] riboflavin 4′,5′-cyclic phosphodiester,[8] myo-inositol 1,2-phosphodiester,[9] cyclic glycerophosphates[10] and cyclic lysophosphatidic acid.[11] Recently much attention has been focused on the role of cyclic phosphates in the cellular signal transition.[12] Therefore it is our interest to develop synthetic methodologies for those novel fluorine-containing phostones which might have potential biological activities.

Iodocyclization of an unsaturated carbon–carbon bond has been extensively studied[13] and has been used as a powerful method for the construction of various heterocycles. It is well described that iodocyclization of allenes bearing nucleophiles including N and O in suitable positions not only yielded five to ten-membered heterocycles,[14] but also afforded vinyl iodides which may permit further elaboration to form more complex compounds, and such protocols have been applied to the total synthesis of some natural products. Although a few examples of the electrophilic cyclization of alkenyl phosphates[15] and alkenylphosphonates[16] were reported in the literature including α-allenic phosphonates,[17] similar reaction of β-allenic phosphonates has never

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* Corresponding author. Tel.: +86 21 54925188; fax: +86 21 64166128; e-mail: jtliu@mail.sioc.ac.cn

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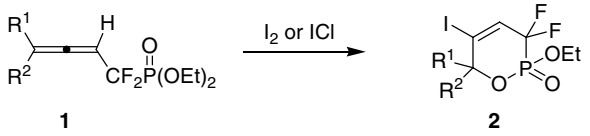
been described so far. In our continuous research on the development of synthetic methodologies for biologically active fluorine-containing compounds, it was found that the iodocyclization of diethyl β-allenic α-difluoromethylenephosphonates (**1**) could be achieved under mild conditions using I_2 or ICl as the electrophile to give six-membered α-difluoromethylenephostones (**2**) in moderate to good yields (Scheme 1). The results are reported in this letter.

The key starting materials **1** were readily prepared according to the reported procedure.[18] Firstly, the reaction of **1a** ($R^1 = R^2 = CH_3$) with 2 equiv of iodine in CH_3CN was examined. To our delight the reaction took place readily at room temperature and the expected cyclization product **2a** was obtained as a white solid in 64% yield after work-up of the reaction mixture. The structure of **2a** was determined by its spectral data as well as X-ray crystallography (Fig. 1).

To improve the yield of cyclization, different conditions were then screened. As shown in Table 1, CH_3CN was a suitable solvent for the reaction and a small amount of water in the reaction mixture favored the cyclization. Furthermore, the reaction was influenced by the amount of iodine and the best result was obtained when 3 equiv of iodine was used (entry 7).

Using optimized conditions, the reaction of other β-allenic phosphonates with iodine or ICl was investigated.[19] The results are summarized in Table 2. In most cases iodine was efficient and the corresponding α-difluoromethylenephostones were obtained in moderate to high yields. The reaction was strongly influenced by the substitution pattern on the allene skeleton: δ, δ-disubstituted allenic phosphonates gave good to excellent yields (entries 1, 3–6), probably caused by the stabilization effect of two alkyl substitutents on the iodonium intermediate formed in the reaction. Bulky groups such as *t*-Bu and Ph at δ-carbon may block the attack of



1 **2**

Scheme 1.

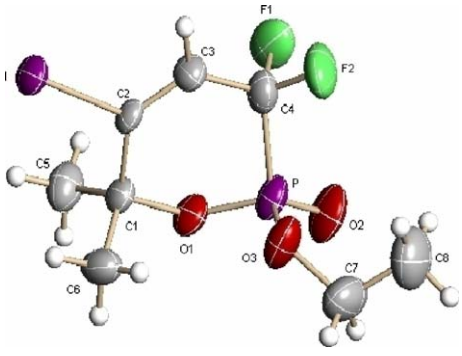
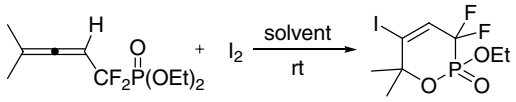


Figure 1. The X-ray crystallographic structure of **2a**.

Table 1. The reaction of **1a** with iodine under different conditions[a]

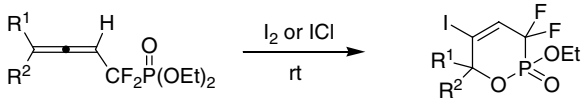


1a **2a**

Entry	I_2 (equiv)	Solvent	Time (h)	Yield[b] (%)
1	2	CH_3CN	3	64
2	2	CH_2Cl_2	6	61
3	2	C_6H_6	6	40
4	2	DMF	6	35
5	2	CH_3CN/H_2O (30:1)	3	70
6	2.5	CH_3CN/H_2O (30:1)	3	75
7	3	CH_3CN/H_2O (30:1)	3	82

[a] The reaction was carried out using 0.5 mmol of **1a** as starting material.
[b] Isolated yield.

Table 2. Synthesis of α-difluoromethylenephostones via iodocyclization of **1**[a]



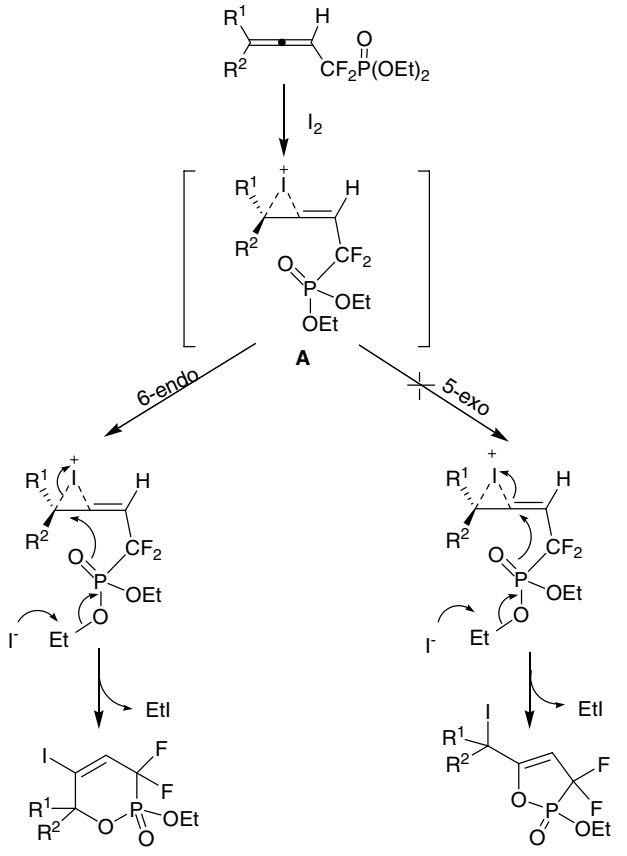
1 **2**

Entry	R^1	R^2	Electrophile	Product	Yield[b] (%)
1	CH_3	CH_3	I_2	**2a**	82
2[c]	CH_3	CH_3	ICl	**2a**	83
3	Et	Et	I_2	**2b**	92
4	–$(CH_2)_5$–		I_2	**2c**	90
5	–$(CH_2)_4$–		I_2	**2d**	81
6	CH_3	Et	I_2	**2e**	91
7	CH_3	*t*-Bu	I_2	**2f**	53
8	CH_3	Ph	I_2	**2g**	64
9	Et	H	I_2	**2h**	25
10[c]	Et	H	ICl	**2h**	80
11[c]	*n*-Pr	H	ICl	**2i**	78
12[c]	*i*-Pr	H	ICl	**2j**	75
13	H	H	I_2	Unstable product	

[a] The reaction was carried out in CH_3CN/H_2O (30:1) at room temperature using 0.5 mmol of **1** and 1.5 mmol of I_2.
[b] Isolated yield based on **1**.
[c] The reaction was carried out using 0.5 mmol of **1** and 0.75 mmol of ICl.

iodine or phosphonyl and make the yield lower. The reaction of δ-monosubstituted allenic phosphonates with iodine gave very low yield (entry 9), however, the desired products **2h**–**2j** could be obtained in moderate yields when stronger electrophile ICl was used in the reaction instead of I_2 (entries 10–12). In the case of terminal allenic phosphonate **1k** ($R^1 = R^2 = H$), the reaction was complicated and the product was not stable enough for isolation.

The reaction was regioselective. In all reactions only six-membered phostones were obtained. In the case of allenic phosphonates with different terminal substitutents, the reaction gave cyclization products as a mixture of two diastereoisomers. The ratios of two isomers were approximately 1:1 with δ, δ-disubstituted allenic phos-



Scheme 2.

phonates (entries 6–8, Table 2) and approximately 2:3 with δ-monosubstituted allenic phosphonates (entries 10–12, Table 2) as indicated by ^{1}H NMR.

A plausible mechanism was proposed for the formation of **2** as illustrated in Scheme 2. The reaction of **1** with iodine gave iodonium **A** and released an iodine anion at the same time. With the assistance of iodine anion, intramolecular nucleophilic attack of oxygen in phosphonyl group on the terminal carbon of allene in the favored *endo* mode afforded the corresponding cyclization product accompanied by the elimination of ethyl iodide.

In conclusion, iodocyclization of β-allenic α-difluoromethylenephosphonates has been achieved under mild conditions for the first time, providing a novel and convenient method for the synthesis of α-difluoromethylenephostones. The presence of vinyl iodide in the resulted fluorine-containing phostones makes it possible to incorporate this novel subunit into other molecules to synthesize various compounds with potential bioactivities. Therefore this strategy opens a new area for the generation of hydrolytically stable and effective cyclic phosphate mimics. Further investigation on the application of this reaction is in progress.

Acknowledgements

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19. Typical procedure for the synthesis of **2**:
Method A: To a solution of **1** (0.5 mmol) in CH_3CN–H_2O (30:1, 6 mL) was added I_2 (1.5 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$ solution. The organic phase was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica gel using petroleum ether/EtOAc as eluent to give the corresponding product **2a**–**2g.**
Method B: This procedure was used for the preparation of **2h**–**2j**. To a solution of **1** (0.5 mmol) in CH_3CN (5 mL) was added ICl (0.75 mmol) in CH_3CN (2 mL), the resulting mixture was stirred in dark under nitrogen at room temperature for 30 min. The reaction mixture was then diluted with EtOAc and washed with 5% aqueous $Na_2S_2O_3$ solution. The organic phase was washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica gel using petroleum ether/EtOAc as eluent to give the corresponding product **2h**–**2j**.
Selected data for **2a**:
Crystal data. $C_8H_{12}F_2IO_3P$, $M = 352.05$, crystal size $0.503 \times 0.408 \times 0.375$ mm, orthorhombic, space group $pbca$, $a = 9.3668$ (8), $b = 11.8779$ (10), $c = 21.8049$ (18)Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90$, $V = 2426.0$ (4) Å^3, $T = 293$ (2) K, $Z = 8$, $D_c = 1.928$ g cm^{-3}, μ(MoKα) = 2.783 mm^{-1}, 13,559 reflections measured, 2762 unique which were used in all calculations. $R_{int} = 0.0947$, $R_1 = 0.0410$. The final $wR(F^2)$ was 0.0487 (all data). (CCDC 602472).
Mp: 90–91°C; IR (KBr) 1623, 1268, 1046, 1005 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56–6.45 (m, 1H), 4.36–4.26 (m, 2H), 1.75 (s, 3H), 1.69 (s, 3H), 1.36 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.6–131.9 (m), 116.3–116.1 (m), 108.6 (td, $J_{C-F} = 254.0$ Hz, $J_{C-P} = 200.0$ Hz), 89.4 (d, $J_{C-P} = 8.0$ Hz), 65.6 (d, $J_{C-P} = 6.0$ Hz), 29.7, 29.4, 16.3 (d, $J_{C-P} = 5.2$ Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.5 (ABdd, $J_{F-F} = 316.6$ Hz, $J_{P-F} = 92.8$ Hz, $J_{H-F} =$ 10.7, 9.0, 8.2, 7.6, 7.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$): δ 1.07–0.12 (m); EIMS m/z (%): 353 (M^++1, 4.78), 244 (34.00), 197 (9.18), 117 (100.00), 97 (52.12), 77 (29.19), 65 (8.49), 51 (11.43), 43 (9.14). Anal Calcd for $C_8H_{12}F_2IO_3P$: C, 27.29; H, 3.44. Found: C, 27.31; H, 3.43.