Organosulfur- or Organoselenium-Induced Intramolecular Cycloaddition of β-Allenic α-Difluoromethylenephosphonic Acid Monoesters: Synthesis of Novel Cyclic Phosphate Mimics

Yun Lin,[a,b] Jin-Tao Liu*[a]

[a] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China

[b] College of Chemistry and Environment Science, Nanjing Normal University, 122 Ninghai Road, Nanjing 210097, P. R. of China
Fax +86(21)64166128; E-mail: jtliu@mail.sioc.ac.cn

Received 1 May 2006

Abstract: Novel cyclic phosphate mimics, γ-organosulfur or organoselenium substituted α-difluoromethylenephostones were synthesized in good yields with high regioselectivity under mild conditions by the electrophilic cyclization of β-allenic α-difluoromethylenephosphonic acid monoesters induced by ArSCl or ArSeCl. The reaction represents the first example of an intramolecular addition of phosphonic acid monoesters to β-allenic carbon–carbon double bonds.

Key words: β-allenic α-difluoromethylenephosphonic acid monoester, phosphate mimic, α-difluoromethylenephostone, organoselenium, organosulfur, cyclization

The history of α-difluoromethylenephosphonates as hydrolytically stable natural phosphate mimics dates back to the late 20th century. In 1981, Blackburn[1] first reported that the isoelectronic and isosteric replacement of oxygen by difluoromethylene in phosphate analogues conferred metabolic stability and imparted important features for receptor binding. Since then interest has been growing in the development of general methods for the synthesis of compounds in which the difluoromethylenephosphonate group is borne within a functionalized array. Numerous structurally novel and biologically interesting acyclic α-difluoromethylenephosphonate derivatives have been prepared and studied as potential enzyme inhibitors and useful probes for the elucidation of the biochemical process.[2] In contrast, evaluation of cyclic α-difluoromethylenephosphonates (phostones) as biological phosphate mimics has never been performed because there are few synthetic methods available to construct such kind of heterocycles. [3]

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 detected in biological systems include glucose cyclic phosphodiester,[4] 2′,3′-cyclic phosphodiester nucleotides,[5] riboflavin 4′,5′-cyclic phosphodiester,[6] myo-inositol 1,2-phosphodiester,[7] cyclic lysophosphatidic acid,[8] and cyclic glycerophosphates.[9] Recently much attention has focused on the role of cyclic phosphates in cellular signal transition.[10] Therefore, it is of great significance to develop efficient methods for the synthesis of cyclic α-difluoromethylenephosphonates which might have potential biological activities.

An electrophile-promoted heteroannulation process involving unsaturated compounds bearing a tethered nucleophilic substituent has proven to be an efficient synthetic method toward a large variety of heterocyclic systems.[11] Among them an organosulfur- or organoselenium-induced ring-closure protocol[12] received much attention due to the convenience of the process and the existence of a sulfur/selenium moiety in the product as a potential reaction center for further synthetic transformations.[13]

In this communication, we disclose the first example of organosulfur/organoselenium induced intramolecular addition of phosphonic acid monoesters to β-allenic carbon–carbon double bonds as a convenient method for the synthesis of novel cyclic phosphate mimics, α-difluoromethylenephostones.

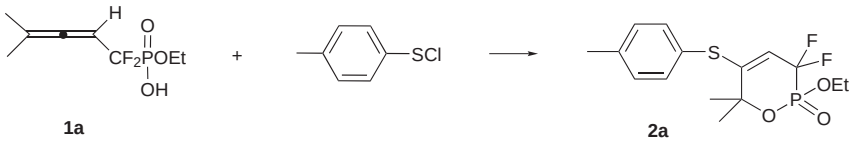
β-Allenic α-difluoromethylenephosphonic acid monoesters **1** were readily prepared from the corresponding diethyl phosphonates by hydrolysis in aqueous sodium hydroxide solution.

The cyclization reaction of **1a** with *p*-MeC_6H_4SCl was first carried out in CH_2Cl_2 at room temperature with a molar ratio of 1:1.5. It was found that the reaction proceeded very fast, giving a white solid after workup. Spectral and elemental analysis showed that it was the desired cyclic product **2a**, but the yield was only 37%. Then the reaction conditions were optimized and the best result was obtained when the reaction was carried out at –30 °C using MeCN as the solvent.

Under the optimized conditions, the reaction of other β-allenic phosphonic acid monoesters with *p*-$CH_3C_6H_4SCl$ was investigated.[14] As shown in Table 2, both δ-monosubstituted and δ,δ-disubstituted β-allenic phosphonic acid monoesters gave the cyclization products in moderate to excellent yields. In the cases of allenic phosphonic acid monoesters with different terminal substituents, the

SYNLETT 2006, No. 14, pp 2227–2230
Advanced online publication: 24.08.2006
DOI: 10.1055/s-2006-948204; Art ID: W09006ST

Table 1 Cyclization of **1a** with *p*-MeC_6H_4SCl under Different Conditions[a]

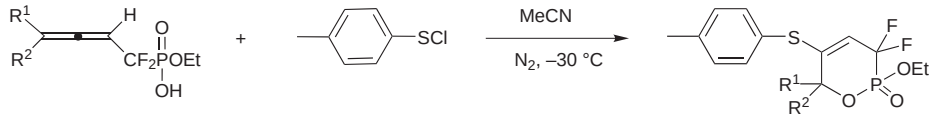


1a **2a**

Entry	Solvent	Additive (1 equiv)	Temperature	Isolated yield (%)
1	CH_2Cl_2	–	r.t.	37
2	MeCN	–	r.t.	77
3	MeCN	Et_3N	r.t.	73
4	MeCN	K_2CO_3	r.t.	74
5	MeCN	–	0 °C	77
6	MeCN	–	–10 °C	78
7	MeCN	–	–30 °C	84

[a] The reaction was carried out with **1a** (0.5 mmol) and *p*-MePhSCl (0.75 mmol).

Table 2 Cyclization of **1** with *p*-MeC_6H_4SCl [a]



1 **2**

Entry	R^1	R^2	Product	Isolated yield (%)
1	Me	Me	**2a**	84
2	Et	Et	**2b**	78
3	-$(CH_2)_5$-		**2c**	49
4	-$(CH_2)_4$-		**2d**	62
5	Me	Et	**2e**	79
6	Me	*t*-Bu	**2f**	59
7	Et	H	**2g**	94
8	*n*-Pr	H	**2h**	89
9	*i*-Pr	H	**2i**	95

[a] The reaction was carried out using **1** (0.5 mmol) and *p*-MeC_6H_4SCl (0.75 mmol).

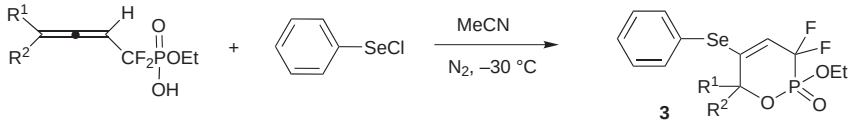
reaction gave cyclic products as a mixture of two diastereoisomers. The ratios of the two isomers were approximately 1:1 (Table 3, entries 5–9) as indicated by ^1H NMR spectroscopy.

Under similar conditions, this protocol could also be successfully applied to the cyclization of **1** with PhSeCl, giving γ-phenylselenium substituted cyclic phosphonates **3**. The results are summarized in Table 3.

The reaction was regioselective. In all cases, only six-membered phostones were obtained and five-membered products, which might be formed by *exo* ring closure were not detected. Based on the above results a plausible mechanism is proposed for the formation of **2** or **3** as illustrated in Scheme 1. The reaction of **1** with ArSCl or ArSeCl gave cyclic intermediate **A** and released a chloride ion. With the assistance of the chloride ion, intramolecular nucleophilic attack of oxygen in the phosphonyl group on the terminal carbon of allene in the favored *endo* mode afforded the corresponding cyclization product.

In conclusion, regioselective organosulfur- or organoselenium-induced intramolecular cycloaddition of β-allenic

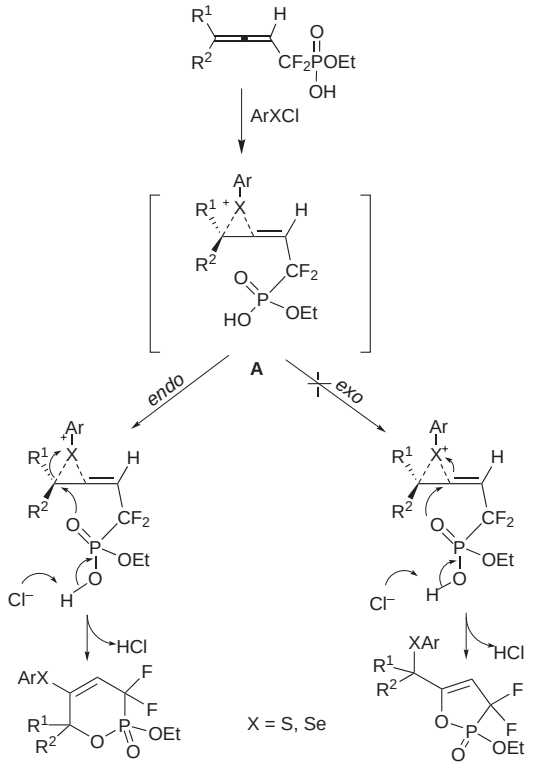
Table 3 Cyclization of **1** with PhSeCl [a]



Entry	R^1	R^2	Product	Isolated yield (%)
1	Me	Me	**3a**	85
2	Et	Et	**3b**	82
3	-$(CH_2)_5$-		**3c**	47
4	-$(CH_2)_4$-		**3d**	87
5	Me	Et	**3e**	86
6	Me	*t*-Bu	**3f**	71
7	Et	H	**3g**	95
8	*n*-Pr	H	**3h**	94
9	*i*-Pr	H	**3i**	93

[a] The reaction was carried out using **1** (0.5 mmol) and PhSeCl (0.75 mmol).

α-difluoromethylenephosphonic acid monoesters was achieved under mild conditions, providing a convenient method for the synthesis of novel cyclic α-difluoromethylenephosphonates. The unique combination of selenium or sulfur with cyclic a-difluoromethylenephosphonates may have interesting biological importance in the construction of cyclic phosphate mimics. Further investigations of this reaction and the properties of those novel fluorine-containing phostones are in progress.



Scheme 1

Acknowledgment

We thank the National Natural Science Foundation of China for financial support (No. 20572124).

References and Notes

(1) (a) Blackburn, G. M.; Brown, D.; Martin, S. J.; Parratt, M. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 181. (b) Blackburn, G. M.; Kent, D. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 913. (c) Blackburn, G. M.; Brown, D.; Martin, S. J. *J. Chem. Res., Synop.* **1985**, 92. (d) Blackburn, G. M.; England, D. A.; Kolkman, F. J. *J. Chem. Soc., Chem. Commun.* **1981**, 930.

(2) (a) Eggenspiller, A.; Berges-Gross, V.; Danzin, C. *Tetrahedron* **1996**, *52*, 177. (b) Kawamoto, A. M.; Campbell, M. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1249. (c) Caplan, N. A.; Pogson, C. I.; Hayes, D. J.; Blackburn, G. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, *3*, 421. (d) Yokomatsu, T.; Hayakawa, Y.; Kihara, T.; Koyanagi, S.; Soeda, S.; Shimeno, H.; Shibuya, S. *Bioorg. Med. Chem.* **2000**, *8*, 2571. (e) Xu, Y.; Prestwich, G. D. *Org. Lett.* **2002**, *4*, 4021. (f) Hum, G.; Lee, J.; Taylor, S. D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3471. (g) Pfund, E.; Lequeux, T.; Masson, S.; Vazeux, M. *Org. Lett.* **2002**, *4*, 843. (h) Yokomatsu, T.; Kato, J.; Sakuma, C.; Shibuya, S. *Synlett* **2003**, 1407. (i) Murano, T.; Yuasa, Y.; Kobayakawa, H.; Yokomatsu, T.; Shibuya, S. *Tetrahedron* **2003**, *59*, 10223. (j) Li, X. F.; Bhandari, A.; Holmes, C. P.; Szardenings, A. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4301. (k) Gautier, A.; Garipova, G.; Salcedo, C.; Balieu, S.; Piettre, S. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 5963.

(3) (a) Thatcher, G. R.; Campbell, A. S. *J. Org. Chem.* **1993**, *58*, 2272. (b) Berkowitz, D. B.; Eggen, M.; Shen, Q. R.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666. (c) Butt, A. H.; Percy, J. M.; Spencer, N. *Chem. Commun*. **2000**, 1691. (d) Marano, T.; Yuasa, Y.; Kobayakawa, H.; Yokomatsu, T.; Shibuya, S. *Tetrahedron* **2003**, *59*, 10223.
(4) Lloir, L. F. *Biochem. Biophys.* **1951**, *33*, 186.
(5) Markham, R.; Smith, J. D. *Biochem. J.* **1952**, *52*, 552.
(6) Forrest, H. S.; Todd, A. R. *J. Chem. Soc.* **1950**, 3295.
(7) Dawson, R. M.; Freinkel, N.; Jungalwala, F. B.; Clarke, N. *Biochem. J.* **1971**, *122*, 605.
(8) Shinitzky, M.; Friedman, P.; Haimovitz, R. *J. Biol. Chem.* **1993**, *268*, 14109.
(9) Friedman, P.; Haimovitz, R.; Markman, O.; Roberts, M. F.; Shinitzky, M. *J. Biol. Chem.* **1996**, *271*, 953.
(10) For recent references, see: (a) Meier, C.; Lorey, M.; Clercq, E. D.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 99. (b) Gypakis, A.; Wasner, H. K. *Biol. Chem.* **2000**, *381*, 1139. (c) Kaur, K.; Lan, M. J. K.; Pratt, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 10436. (d) Liu, Y.; Bruzik, K. S.; Ananthanarayanan, B.; Cho, W. *Bioorg. Med. Chem.* **2003**, *11*, 2471. (e) Wang, P.; Wu, P.; Egan, R. W.; Billah, M. M. *Gene* **2003**, *314*, 15. (f) Fujiwara, Y.; Seboek, A.; Meakin, S.; Kobayashi, T. *J. Neurochem.* **2003**, *87*, 1272. (g) Pelash, A.; Shinitzky, M. *Biochem. Biophys. Res. Commun.* **2004**, *315*, 1045.
(11) Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33.
(12) (a) Ihara, M.; Hags, Y.; Yonekura, M.; Ohsawa, T.; Fukumoto, K. *J. Am. Chem. Soc.* **1983**, *105*, 7345. (b) Mühlstädt, M.; Schubert, C.; Kleinpeter, E. *J. Prakt. Chem.* **1985**, *2*, 270. (c) Berthe, B.; Outurquin, F.; Paulmier, C. *Tetrahedron Lett.* **1997**, *38*, 1393. (d) Brugier, D.; Outurquin, M.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 37. (e) Jana, G.; Viso, A.; Diaz, Y.; Castillon, S. *Eur. J. Org. Chem.* **2003**, 209. (f) Bugarcic, Z. M.; Gavrilovic, M. *Monatsh. Chem.* **2003**, *134*, 1359. (g) Marshall, J.; Wang, X. *J. Org. Chem.* **1990**, *55*, 2995. (h) Ma, S.; Pan, F.; Hao, X.; Huang, X. *Synlett* **2004**, 85. (i) Enchev, D. D. *Heteroat. Chem.* **2005**, *16*, 156.
(13) (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, **1986**. (b) *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; Oxford University: Oxford, **1999**. (c) *Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer: Berlin, **2000**. (d) Oae, S. *Organic Chemistry of Sulfur: Structure and Mechanism*; CRC: London, **1991**. (e) Glass, R. S. *Top. Curr. Chem.* **1999**, *205*, 2.
(14) **Cyclic Products 2 or 3; Typical Procedure**: To a solution of **1** (0.5 mmol) in MeCN (6 mL) in a dry Schlenk tube was slowly added *p*-MeC_6H_4SCl or PhSeCl (0.75 mmol) in MeCN (2 mL) at –30 °C under a N_2 atmosphere. After the reaction was complete (monitored by TLC, ca. 30 min), the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to give product **2** or **3**.
Compound 2a
Mp 54–55 °C. IR (KBr): 1616, 1285, 1116, 1037, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 2 H), 7.28–7.25 (m, 2 H), 5.05–4.92 (m, 1 H), 4.35–4.29 (m, 2 H), 2.40 (s, 3 H), 1.85 (s, 3 H), 1.74 (s, 3 H), 1.38 (t, *J* = 6.6 Hz, 3 H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –101.08 (AB, dd, J_{F-F} = 308.7 Hz, J_{P-F} = 95.6 Hz, J_{H-F} = 11.6, 10.1, 7.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ = –0.58 to –2.54 (m). EIMS: *m*/*z* (%) = 348 (M^+, 29.56), 225 (35.63), 189 (100.00), 117 (56.26), 107 (27.57), 97 (56.06), 77 (58.91). Anal. Calcd for $C_{15}H_{19}F_2O_3PS$: C, 51.72; H, 5.50. Found: C, 51.92; H, 5.49.
Compound 3a
Mp 56–57 °C. IR (KBr): 1621, 1285, 1027, 1001 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 2 H), 7.49–7.28 (m, 3 H), 5.41–5.29 (m, 1 H), 4.37–4.32 (m, 2 H), 1.85 (s, 3 H), 1.75 (s, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –102.16 (AB, dd, J_{F-F} = 311.8 Hz, J_{P-F} = 95.6 Hz, J_{H-F} = 10.2, 8.5, 7.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$): δ = –0.71 to –2.64 (m). EIMS: *m*/*z* (%) = 382 (M^+, 2.47), 381 (14.23), 223 (17.00), 133 (10.31), 117 (100.00), 97 (35.47), 77 (50.49), 65 (10.49), 51 (18.10). Anal. Calcd for $C_{14}H_{17}F_2O_3PSe$: C, 44.11; H, 4.49. Found: C, 44.12; H, 4.60.