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CuX_2-mediated halocyclization of 1,1-difluoro-2,3-allenylphosphonic acid monoesters —synthesis of novel cyclic phosphate mimics

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ABSTRACT

Novel six-membered cyclic phosphate mimics (5-halo-3,3-difluoro-3,6-dihydro-2*H*-1,2-oxaphosphinine 2-oxides) were synthesized via CuX_2 (X = Br, Cl)-mediated halocyclization of 1,1-difluoro-2,3-allenylphosphonic acid monoesters in moderate to good yields with high regio-selectivity. This reaction represents the first example of transition metal-mediated intramolecular cyclization of a P-OH moiety to β-allenylphosphonates with a carbon-carbon double bond.

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1. Introduction

Phosphate-containing molecules play important roles as metabolic intermediates, common regulatory switches for proteins, and a backbone for genetic information in living organisms [1]. However, phosphate moieties are usually considered to be impractical functional groups for drug design because of phosphatase-induced hydrolysis. Hence, hydrolytically stable mimics of naturally occurred phosphates have drawn much attraction recently. Since the pioneering work of Blackburn [2], the isoelectronic and isosteric CF_2/O transposition in phosphate analogues have been viewed as an extraordinarily effective strategy for phosphate mimics. The transposition confers metabolic stability and imparts important features for receptor binding affinity or hydrogen bonding interactions. Thus far, many acyclic difluoromethylenephosphonate derivatives have been studied as potential enzyme inhibitors and useful probes for elucidating biochemical processes [3], however, evaluating cyclic difluoromethylenephosphonates as biological phosphate mimics remains underexplored. To the best of our knowledge, there are few reports in the literature [4] regarding the synthesis of five to seven-membered difluoromethylenephostones, some of which are reported as byproducts or intermediates.

Cyclic phosphate is another kind of bioactive molecule essential to life. Apart from the universal second messenger cyclic AMP and cyclic GMP, other cyclic phosphates detected in diverse biological processes include glucose cyclic phosphodiester, 2′,3′-cyclic phosphodiester nucleotides [5], myo-inositol 1,2-phosphodiester [6], cyclic lysophosphatidic acid [7], and cyclic glycerophosphates [8]. Therefore it is highly desirable to develop a novel general method for producing fluorine—containing cyclic phosphate mimics.

Halocyclization of functionalized allenes, such as 2,3-allenoic acids [9], 2,3-allenoates [10], 2,3-allenamides [11], 1,2-allenylphosphonates acid monoesters [12], and 1,2-allenyl phosphonates [13] with CuX_2 (X = Br, Cl) are well documented. In our previous studies, we have successfully developed efficient methodologies for the synthesis of cyclic difluoromethylenephosphonates via electrophile-promoted cyclization of 1,1-difluoro-2,3-allenylphosphonic acid mono/diesters (Scheme 1, eqn. (1)) [14].

On the basis of above results, we concluded that the reaction of

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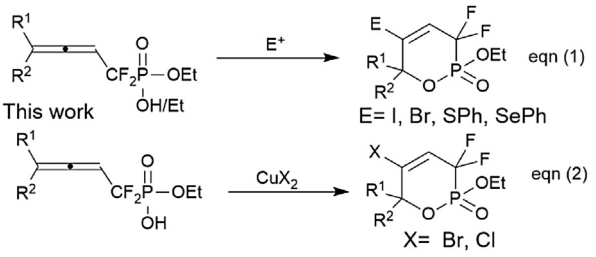


Scheme 1. Cyclization of 1,1-difluoro-2,3-allenylphosphonates.

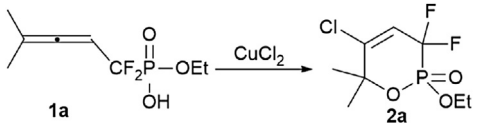
1,1-difluoro-2,3-allenylphosphonic acid monoesters with CuX_2 (X = Br, Cl) could be expected to form cyclic difluoromethylenephosphonates. Herein, we report the successful development of this transformation (Scheme 1, eqn. (2)).

2. Results and discussion

The key starting material (1,1-difluoro-2,3-allenylphosphonic acid monoesters **1**) was readily prepared from hydrolysis of corresponding diethyl phosphonates in aqueous sodium hydroxide solution [14b,15]. To obtain the desired cyclic phosphonates, initial attempt was performed by treating 1,1- difluoro-2,3-allenylphosphonic acid **1a** in N, N- dimethylformamide (DMF) (Table 1, entry 1). Reaction of **1a** with 4 equiv. of $CuCl_2$ in DMF at 80 °C for 6 h smoothly afforded the expected cyclic product **2a** in 38% isolated yield (Table 1, entry 1). To improve the yield, different solvents including N,N-dimethylacetamide (DMA), DMF, acetonitrile, toluene, tetrahydrofuran (THF), dichloromethane and dimethyl sulfoxide (DMSO) (entries 1–7) were employed, and DMA was the most favorable solvent which provided the product in 93% yield based on ^{19}F-NMR (entry 6). Furthermore, the different amount of $CuCl_2$ was also tested. It was found that 4 equiv. of $CuCl_2$ was required to run reaction efficiently. With reducing the amount of $CuCl_2$, the yield of **2a** was decreased and longer reaction time was needed (entries 8–10). Raising the temperature from 80 °C to 90 °C, the yield of **2a** did not increase (entry 15) while the reaction time was shortened. It should be noted that no chlorocyclization product was obtained in the previous research when using N-chlorosuccinimide as an electrophile [14b]. Thus, the most favorable result was obtained when the reaction was carried out in DMA at 80 °C with 4 equiv. of $CuCl_2$.

With the optimized reaction conditions in hand, the scope of reaction was investigated. When replacing $CuCl_2$ with $CuBr_2$, the bromocyclization product **3** was also obtained smoothly from 2,3-allenylphosphonic acid monoester **1**. The reaction time with $CuBr_2$ was relatively shorter than that with $CuCl_2$. In some cases lower temperature favored the $CuBr_2$-mediated cyclization (entries 6, 14). By comparison of the reaction time $CuBr_2$ is more reactive than $CuCl_2$. As shown in Table 2, the reaction was largely influenced by the substitution pattern at the end of allene: 4,4–disubstituted allenylphosphonic acid monoesters gave the cyclization products in moderate to good yields (entries 1–10). When increasing the size of terminal allenyl substitution, the yield was dropped. The bulky *t*-Bu group at 4-carbon (entry 11) showed trace amount of product while corresponding methyl analogue (entry 1) afforded 84% of yield. The low yield could be explained that the bulky moiety blocked the attack of CuX_2 or P-OH to afford transition intermediate. Reaction of 4-monosubstituted substrates with CuX_2 gave low yields (entries 13–18), while no reaction was observed with the 4-nonsubstitued substrate **1j**, which may be due to the lower electron density of mono/non substituted allene and thus lower reactivity toward CuX_2. The reactions were regioselective. In all cases, only six-membered phostones were obtained. It should be noted that two diastereoisomers were formed as a mixture when R^1 was different

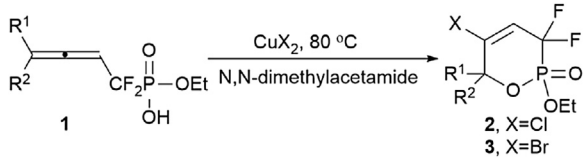
Table 1
Halocyclization of **1a** with $CuCl_2$ under various conditions[a].



Entry	$CuCl_2$ (equiv.)	T (°C)	Solvent	Time (h)	Yield[b](%)
1	4.0	80	DMF	6	38[c]
2	4.0	80	CH_3CN	24	36
3	4.0	80	Toluene	24	NR[d]
4	4.0	reflux	THF	20	Complicated
5	4.0	reflux	CH_2Cl_2	24	NR[d]
6	4.0	80	DMA[e]	4	93
7	4.0	80	DMSO	24	NR[d]
8	1.0	80	DMA	24	43
9	2.0	80	DMA	24	62
10	3.0	80	DMA	12	85
11	5.0	80	DMA	2	88
12	4.0	40	DMA	18	59
13	4.0	60	DMA	12	82
14	4.0	70	DMA	12	84
15	4.0	90	DMA	2	92

[a] Reaction was carried out using **1a** (0.3 mmol) as starting material.
[b] Yield determined via ^{19}F-NMR analysis of the crude mixture using trifluoromethylbenzene as an internal standard.
[c] Isolated yield.
[d] NR = no reaction.
[e] DMA = N,N-dimethylacetamide.

Table 2
Halocyclization of **1** with CuX_2[a].



Entry	**1**	R^1	R^2	Time (h)	**2** (X = Cl)	**3** (X = Br)	Yield[b] (%)
1	**1a**	Me	Me	4	**2a**	-	84
2				0.7	-	**3a**	69
3	**1b**	Et	Et	12	**2b**	-	63
4				2	–	**3b**	76
5	**1c**	-$(CH_2)_4$-		2.5	**2c**	-	68
6				1.5	-	**3c**	60[c]
7	**1d**	-$(CH_2)_5$-		1	**2d**	-	85
8				0.5	–	**3d**	78
9	**1e**	Me	Et	5	**2e**	-	73(52:48)
10				0.5	-	**3e**	74(53:47)
11	**1f**	Me	*t*-Bu	48	**2f**	-	trace
12				5	-	**3f**	54(54:46)
13	**1g**	Me	H	3	**2g**	-	60(42:58)
14				1	-	**3g**	44(50:50)[d]
15	**1h**	*n*-Pr	H	12	**2h**	-	57(44:55)
16				12	-	**3h**	47(41:59)
17	**1i**	*i*-Pr	H	24	**2i**	-	50(35:65)
18				24	-	**3i**	41(38:62)
19	**1j**	H	H	24	**2j**	-	NR[e]
20				24	-	**3j**	NR[e]

[a] Reaction was carried out using **1** (0.3 mmol) and CuX_2 (1.2 mmol).
[b] Isolated yield; ^{1}H-NMR was used to determine the ratios of two isomers.
[c] Reaction was carried out at 50 °C.
[d] Reaction was carried out at 60 °C.
[e] NR = no reaction.

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