DOI: 10.1002/adsc.200800484

Efficient Syntheses of (Thio)phosphonylated Isobenzofurans by Tandem Nucleophilic Addition and Regioselective 5-*exo-dig* Addition to Carbon-Carbon Triple Bond: Cooperative Effect to 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)

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Received: August 2, 2008; Published online: November 17, 2008

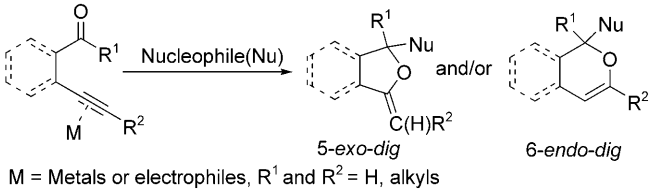
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800484.

Abstract: The tandem nucleophilic addition-cyclization reaction of *o*-alkynylbenzaldehydes or *o*-alkynylacetophenones **2** with dialkyl phosphites or dialkyl phosphonothioates **1** took place very smoothly in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at room temperature. In all cases, the reaction proceeded in a regioselective manner leading to the 5-*exo-dig* products **3** in excellent yields. The phenomenon of a 1,5-sigmatropic hydrogen shift or a 1,5-sigmatropic methyl shift was observed in this reaction depending on the different substituent groups such as R^3 in the *o*-alkynylbenzaldehyde or *o*-alkynylacetophenone **2** substrates.

Keywords: cyclization reaction; 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU); regioselective 5-*exo-dig* addition; tandem nucleophilic addition

Introduction

Organophosphorus compounds continue to receive wide-spread attention due to their ubiquity in biological systems.[1] Isobenzofuran derivatives are useful compounds as building blocks of bioactive compounds and functional materials.[2] In addition, they have reactive diene moieties and can be used for Diels–Alder reactions.[3] Intramolecular ring closure reactions, which can be carried out between the nucleophilic part and carbon-carbon multiple bond in the same molecule, are one of the useful methods for constructing cyclic compounds.[4] Carbonyl groups are of particular interest, since tandem reactions with nucleophiles can occur at this function, broadening the structural panel of the products formed.[5] It is well known that in nucleophile attack processes of acetylenic aldehydes, which have a triple bond as the counterpart, both the '6-*endo-dig*' mode and '5-*exo-dig*' modes are allowed by Baldwin's rule (Scheme 1).[6] In fact, both cyclized products for the 2-ethynylphenyl derivatives have been reported in the literature, for example, indoles,[7] benzo[*b*]furans,[8] isoquinolines,[9] 3-alkylidenephthalides *vs.* 3-substituted isocoumarins,[10] 1-alkylideneisobenzofurans *vs.* 3-substituted 1*H*-2-benzopyrans,[11] and 3-alkylideneisoindoline-1-ones *vs.* 3-substituted isoquinolin-1-ones.[12] Furthermore, Baldwin's rule predicts that both 5-*exo-dig* and 6-*endo-dig* cyclizations are favorable, making selective synthesis difficult in practice (Scheme 1). Therefore, much attention has been paid to the development of a highly regioselective cyclization route.[13] Herein we report a tandem nucleophile attack-intramolecular cyclization reaction of *o*-alkynylbenzaldehyde or *o*-al-



Scheme 1.

kynylacetophenone derivatives with a cooperative effect from DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) that affords (thio)phosphonylated isobenzofuran derivatives in a highly regioselective manner.

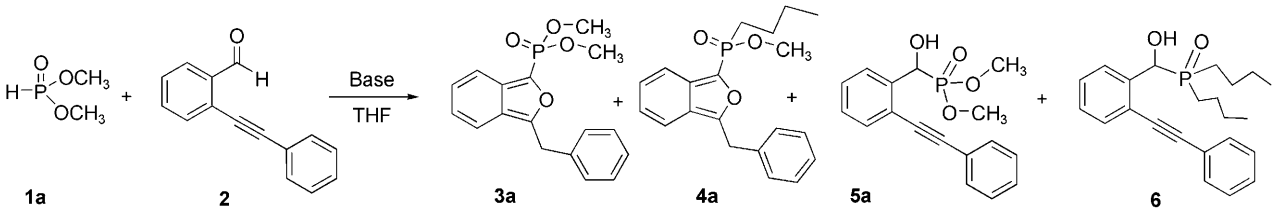
Results and Discussion

A preliminary experiment was conducted using dimethyl phosphite **1a** (0.5 mmol) which was reacted with *o*-alkynylbenzaldehyde **2** (0.5 mmol) in the presence of *n*-butyllithium (*n*-BuLi) (0.5 mmol) in THF at −50 °C (Table 1, entry 3). In this reaction, dimethyl phosphite **1a** was deprotonated by *n*-BuLi and then attacked the *o*-alkynylbenzaldehyde **2**, generating 5-*exo*-*dig* isobenzofuran derivatives **3a** and **4a** in 88% and 12% yields, respectively, as determined by ^{31}P NMR. The result suggests that the reaction time is vital, as both **3a** and **5a** will be generated if the reaction time is below half an hour (Table 1, entries 1 and 2). In order to achieve high yields of this cyclization reaction, we systematically examined the relationship between regioselectivity and solvent. The simple reaction at a ratio **2**:**1**:*n*-BuLi of 1:1:1 in dichloromethane or toluene did not result in thermal cyclization (Table 1, entries 4 and 5).

The transition metal-catalyzed synthesis of various heterocycles *via* cyclization of alkynes possessing a nucleophile in proximity to the triple bond is one of the most important processes in organic synthesis.[14] We examined the reaction of our substrates in the presence of a variety of metal catalysts. Cyclizations were observed in the presence of all kinds of catalysts, whereby CuI, $Pd[P(Ph_3)]_2Cl_2$ and $Pd(OAc)_2$ catalyzed the 5-*exo* cyclization to give the isobenzofuran derivative **3a** in nearly identical yields (Table 1, entries 6–8).

As the metal catalysts did not affect the cyclization, we next focused our attention on the role of the solvent's acidity or basicity in promoting the cyclization modes of **2**. Cyclization was not observed at all in acids such as CF_3COOH, and the only isolated products were **5a** and starting material **2** (Table 1,

Table 1. Optimization of reaction conditions.[a]



Entry	Base[b]	Solvent	Time [h]	Yield [%][c]		
				3a	**4a**	**5a**
1	BuLi	THF[d]	1/4	–	–	>99
2	BuLi	THF[d]	1/2	30	–	70
3	BuLi	THF[d]	20	88	12	–
4	BuLi	CH_2Cl_2[d]	20	–	–	–
5	BuLi	Toluene[d]	20	–	–	–
6	BuLi	THF[e]	20	84	12	6
7	BuLi	THF[f]	20	86	14	–
8	BuLi	THF[g]	20	87	13	–
9	BuLi	THF	20	90	10	–
10	$NaOCH_3$	THF	20	–	–	>99
11	K_2CO_3	THF	20	8	–	92
12	Pyridine	THF	20	–	–	–
13	Et_3N	THF	20	–	–	>99
14	DBU	THF	20	>99	–	–
15	DMAP	THF	20	–	–	>99
16	CF_3COOH	THF	20	–	–	10

[a] Unless otherwise noted all the reactions were performed with 0.5 mmol of **2**, 1.0 mmol dimethyl phosphite **1a** and 1.0 mmol base in 8 mL solvent at room temperature.
[b] When *n*-BuLi was used, the reactions were all performed below −50 °C.
[c] The yields of products were determined from a ^{31}P NMR spectrum of the crude mixture.
[d] All reactions were performed with 0.5 mmol of **2**, 0.5 mmol dimethyl phosphite **1a** and 0.5 mmol base in 8 mL solvent.
[e] 5 mol% of CuI was added.
[f] 5 mol% of $Pd(PPh_3)_2Cl_2$ was added.
[g] 5 mol% of $Pd(OAc)_2$ was added.

entry 16). In contrast, nitrogen-containing basic catalysts, such as 4-(*N,N*-dimethylamino)pyridine (DMAP) and triethylamine, gave only dimethyl [2-(2-phenylethynyl)phenyl](hydroxy)methylphosphonate **5a**, pyridine proved ineffective in the cyclization reaction (Table 1, entry 12). More strongly basic catalysts, such as K_2CO_3, induced the regioselectivity, giving dimethyl 3-benzyl-2*H*-isobenzofuran-1-ylphosphonate **3a** selectively, together with a large amount of **5a** in 92% yield (Table 1, entry 11). Sodium methoxide could only induce product **5a** in nearly quantitative yield. DBU could certainly catalyze the cyclization reaction and produced **3a** with 99% yield. Thus, the selective syntheses of the 5-*exo-dig* isobenzofuran derivative **3a** from *o*-alkynylbenzaldehyde **2** and dialkyl phosphite **1** were achieved through the use of DBU and THF as solvent, respectively.

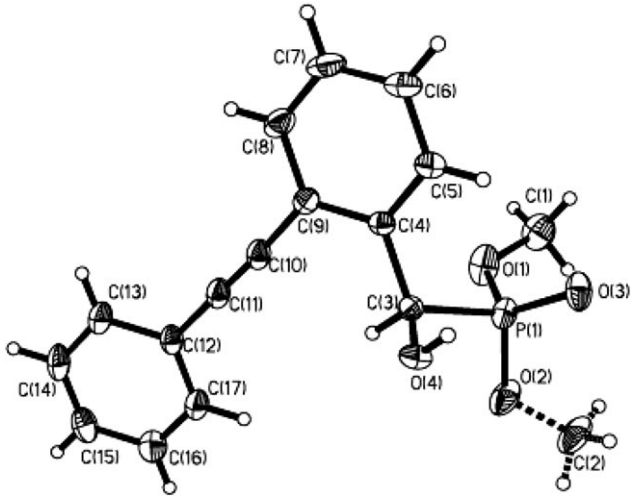


Figure 1. ORTEP diagram of **5a**.

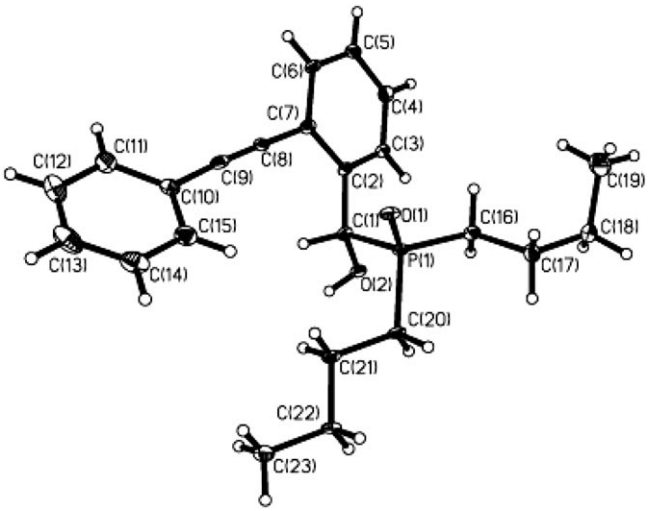


Figure 2. ORTEP diagram of **6**.

In an extension of this work, we also examined the base-induced reaction in order to evaluate the mode of internal cyclization. We found that the base-induced cyclization (*n*-BuLi/THF) of **2** afforded product **3a** in moderate yield with by-products **5a** and **6** in the same reaction. The interesting result is that when the ratio of **2**:**1**:*n*-BuLi was changed to 1:4:4, the only isolated product was the butylated compound **6** (yield 87%) on the phosphorus atom in place of the cyclization. The structures of **5a** and **6** were assigned on the basis of a detailed NMR analysis and firmly established by an X-ray crystallographic study (Figure 1 and Figure 2).[15]

The formation of **3a** was followed by ^{31}P NMR spectroscopy as shown in Figure 3. The starting material dimethyl phosphite **1** in THF showed a ^{31}P NMR signal at 10.61 ppm. After DBU (0.153 g, 1 mmol) had been added to the solution of **1**, a new single peak at 6.56 ppm appeared and was assigned as the deprotonation product of dimethyl phosphate **1**. When *o*-alkynylbenzaldehyde **2** was added to the mixture, the expected nucleophilic addition product was produced (single peaks at 24.68 ppm) in five minutes. As time passed, the ^{31}P NMR signals of the starting material disappeared gradually and the signals of **3a** (single peaks at 1.35 ppm) increased. There is one intermediate that appeared during the synthesis of **3a**. The sig-

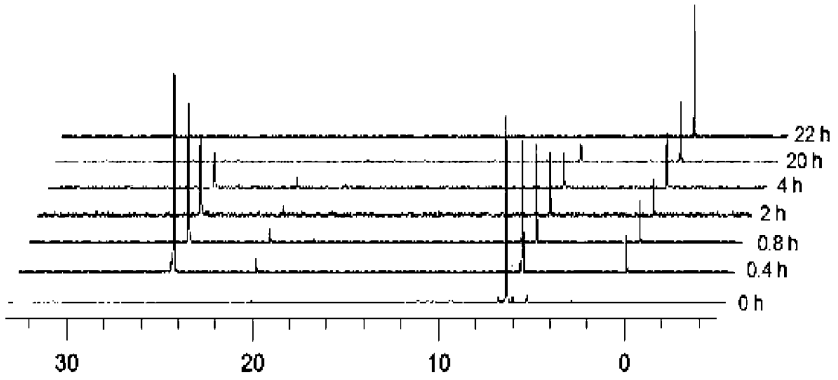
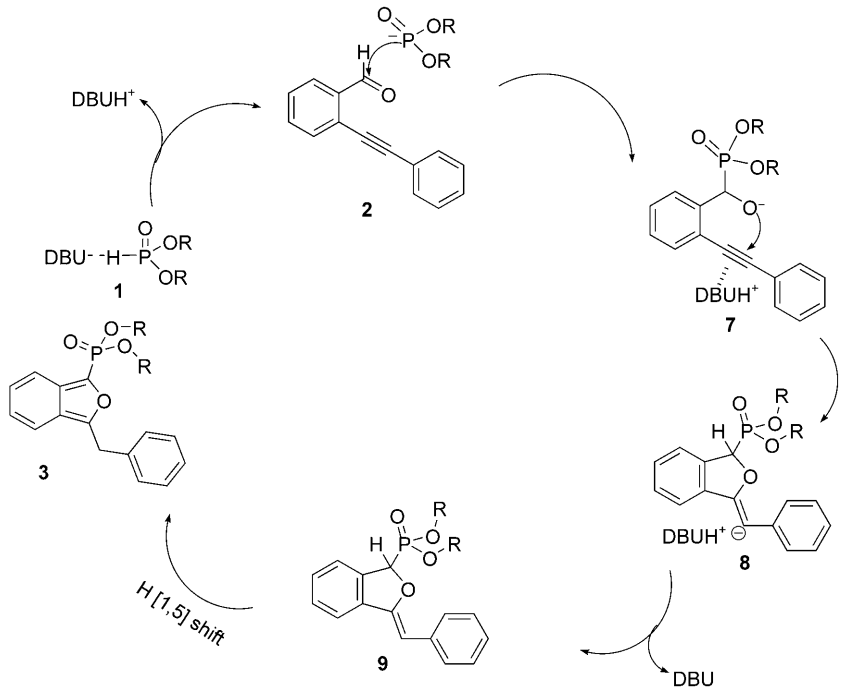


Figure 3. ^{31}P NMR stack spectra for the synthesis of **3a** (ppm).



Scheme 2.

nals at $\delta_P = 20.22$ ppm may belong to intermediate **7** (Scheme 2). DBU accelerates the reaction *via* formation of the intermediate **7**, and activates the carbon-carbon triple bond. The reaction was almost completed after 22 h according to the ^{31}P NMR spectra (Figure 3).

Based on ^{31}P NMR stack spectra (Figure 3), a plausible mechanism for the cooperative effect of DBU on the cyclization reaction of **2** to **3a** is outlined in Scheme 2. The present intramolecular cyclization is most probably initiated by the generation of a phosphonate anion intermediate *via* deprotonation of dialkyl phosphite **1** by DBU. In the meantime, the 5-*exo* cyclization of the oxygen anion to the triple bond would be assisted by the conjugate base of DBU. This is followed by a 1,5-sigmatropic hydrogen shift to afford the alkylidenephthalan derivative **3a**.[16]

In order to prove the 1,5-sigmatropic hydrogen shift to generate the alkylidenephthalan derivative **3a**, 2D NMR HSQC was employed to verify the structure. The cross-peak in the HSQC spectrum of **3a** (Figure 4) between H–$PhCH_2$ and C–$PhCH_2$ atoms confirmed the occurrence of the 1,5-sigmatropic hydrogen shift from **9** to **3** in Scheme 2.

Under the optimized conditions and in the presence of DBU, the 5-*exo-dig* cyclization reaction of *o*-alkynylbenzaldehyde **2** with dialkyl phosphite or dialkyl phosphonothioate **1** exhibits a broad scope. Excellent regioselectivities were obtained and provided good to excellent yields of the desired product **3** for a variety of phosphites and thiophosphites. Dialkyl phosphonothioate **1** exhibited low reactivity and required a longer reaction time, and achieve complete conversion after 32 h (Table 2). When *o*-alkynylacetophenone **2** was used in this nucleophilic addition cyclization reaction, the 1,5-sigmatropic methyl shift products **3h** and **3i** were obtained in moderate yield respectively (Table 2, entry 8 and 9).[17] Compared with the ^{13}C NMR of **3a**, there are also double peaks with chemical shifts at about 90.55 ppm representing $OCP(OCH_3)_2$ and $OCP(OC_2H_5)_2$ in the ^{13}C NMR spectra of **3h** and **3i** with the coupling constants of about 620 Hz, which can represent proof of the 1,5-sigmatropic methyl shift during the reaction. It was found that the use of *o*-alkynylbenzaldehyde led to much better yields than *o*-alkynylacetophenone. The reaction of *o*-alkynylbenzaldehyde **2c**, bearing a butyl group as R^3, with dimethyl phosphite or diethyl phosphite **1**, proceeded smoothly to give **3′a** or **3′b** in good yields (Table 2 entry 10 and 11). In the ^1H NMR spectrum of **3′a** the single peak with a chemical shift of 5.28 ppm represents the existence of an ethene proton, which can prove that there is no 1,5-sigmatropic hydrogen shift during the reaction. Similarly, the trimethylsilyl-substituted **2e** also cyclized in moderate yield. The non-substituted alkyne substrate **2f** can also react with dimethyl phosphite **1** with the aid of DBU in good yield. The reaction of *o*-alkynylacetophenone **2d**, bearing a butyl group as R^3, with dimethyl phosphite **1**, only gave a 50% yield of **3′c** (Table 2 entry 12). An interesting result is that in the reactions of *o*-alkynylbenzaldehyde or *o*-alkynylaceto-

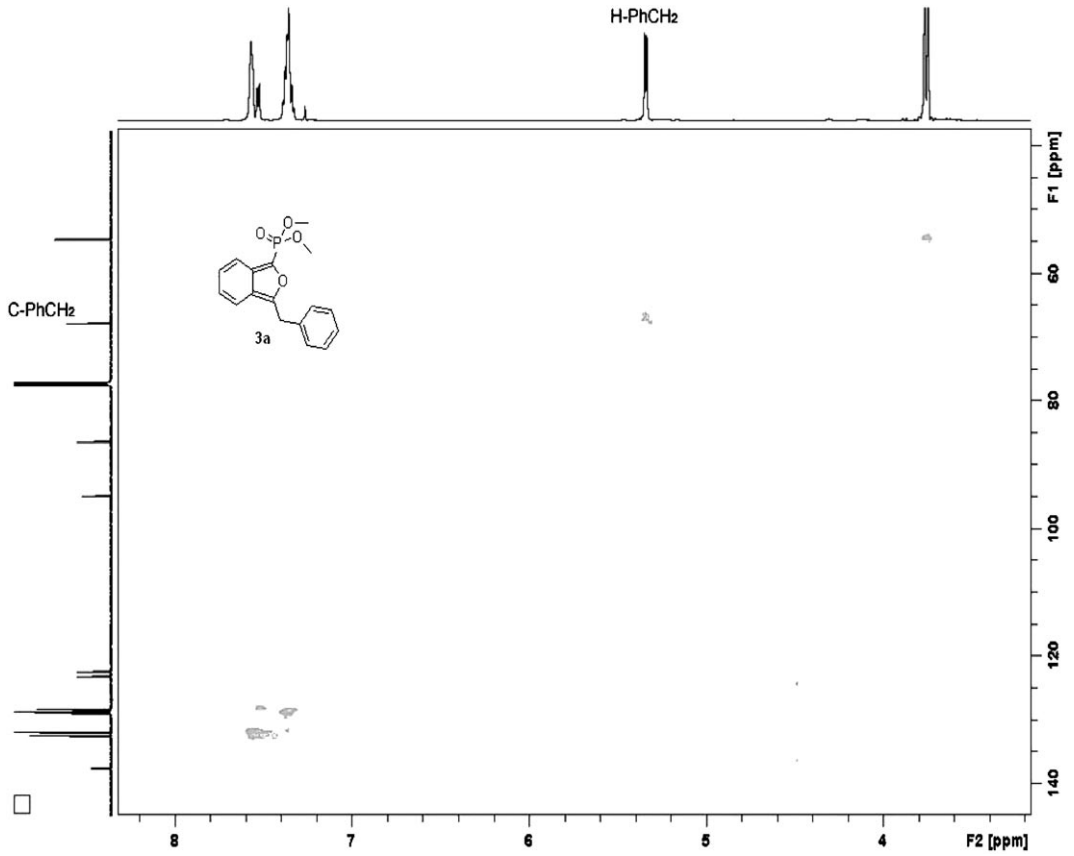
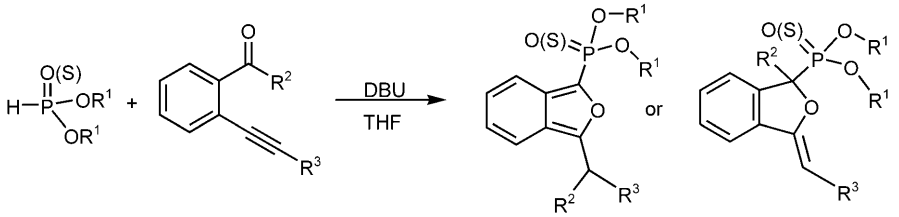


Figure 4. The HSQC spectrum of **3a.**

Table 2. Reactions of dialkyl (thio)phosphite **1** with *o*-alkynylbenzaldehyde or *o*-alkynylacetophenone **2**.



Entry[a]	Substrate **1**	Substrate **2**	R^2	R^3	Temperature [°C]	Product	Yield [%][b]
1	$H(O)P(OCH_3)_2$	**2a**	H	Ph	r.t.	**3a**	98
2	$H(O)P(OC_2H_5)_2$	**2a**	H	Ph	40	**3b**	96
3	$H(O)P(OC_3H_7\text{-}n)_2$	**2a**	H	Ph	40	**3c**	94
4	$H(O)P(OC_3H_7\text{-}i)_2$	**2a**	H	Ph	40	**3d**	91
5	$H(O)P(OC_4H_9\text{-}n)_2$	**2a**	H	Ph	40	**3e**	92
6	$H(S)P(OCH_3)_2$[c]	**2a**	H	Ph	30	**3f**	72
7	$H(S)P(OC_2H_5)_2$[c]	**2a**	H	Ph	35	**3g**	61
8	$H(O)P(OCH_3)_2$	**2b**	CH_3	Ph	40	**3h**	65
9	$H(O)P(OC_2H_5)_2$	**2b**	CH_3	Ph	40	**3i**	60
10	$H(O)P(OCH_3)_2$	**2c**	H	C_4H_9	40	**3′a**	72
11	$H(O)P(OC_2H_5)_2$	**2c**	H	C_4H_9	40	**3′b**	64
12	$H(O)P(OCH_3)_2$	**2d**	CH_3	C_4H_9	60	**3′c**	50
13	$H(O)P(OCH_3)_2$	**2e**	H	Me_3Si	r.t.	**3′d**	54
14	$H(O)P(OCH_3)_2$	**2f**	H	H	r.t.	**3′e**	83

[a] Unless otherwise noted the reactions performed with 0.5 mmol of **2**, 1.0 mmol **1**, 1.0 mmol DBU in 8 mL THF for 20 h.
[b] Isolated yields.
[c] Reaction time is 32 h.

phenone **2**, bearing butyl, trimethylsilyl or hydrogen substituuents as R^3, with dialkyl phosphite **1**, there are no 1,5-sigmatropic hydrogen shift or 1,5-sigmatropic methyl shift products observed.

Conclusions

In conclusion, we have described a general method for the efficient synthesis of isobenzofuran phosphonate or isobenzofuran thiophosphonate derivatives *via* cooperative DBU intramolecular cyclization of *o*-alkynylbenzaldehydes or *o*-alkynylacetophenones and dialkyl phosphite or dialkyl phosphonothioate. The yields are essentially quantitative or very high in most cases, and the regioselectivity was always 100% favoring 5-*exo*-*dig* cyclization. The reaction of *o*-alkynylbenzaldehydes or *o*-alkynylacetophenones **2**, bearing different substituent groups as R^3, with dimethyl phosphite or diethyl phosphite **1**, will furnish dialkyl 1,3-dihydroisobenzofuran-1-ylphosphonates **3** or dialkyl isobenzofuran-1-ylphosphonates **3′**, respectively.

Experimental Section

General Comments

The spectroscopic data of all compounds are given in the Supporting Information.

General Procedure for the Synthesis of (Thio)phosphonylated Isobenzofurans 3

o-Alkynylbenzaldehyde or *o*-alkynylacetophenone **2** (0.5 mmol) in THF (4 mL) was added dropwise to a stirred mixture of dialkyl phosphite or dialkyl phosphonothioate **1** (1.0 mmol) and DBU (0.153 g, 1.0 mmol) in THF (4 mL) at room temperature with TLC (silica gel) monitoring. After 20 h stirring at 40–60 °C (Table 2), the mixture was cooled to room temperature and worked-up with water (5 mL) below 0 °C. The resulting mixture was then extracted by AcOEt and dried with anhydrous sodium sulfate. After concentration, the residue was purified by CC [silica gel, AcOEt/petroleum ether (b.p. 60–90 °C), 1:3] to afford the product **3**.

Acknowledgements

We thank the Committee of Science and Technology of Tianjin (07JCZDJC04800), the Research Foundation for the Doctoral Program of Higher Education of China (20070055042) and Nankai University (J02044 to Z. W. Miao) for financial support.

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[15] CCDC 685563 (**5a**) and CCDC 685564 (**6a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on request to Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U. K. Crystal data for **5a**: empirical formula: $C_{17}O_{17}O_4P$; unit cell parameters: $a=$ 7.599(4) Å, $b=7.866(4)$ Å, $c=29.288(16)$ Å, $\alpha=90°$, $\beta=93.847(9)°$, $\gamma=90°$; space group $P2(1)/C$. Crystal data for **6a:** empirical formula: $C_{46}O_{58}O_4P_2$; unit cell parameters: $a=16.0384(3)$ Å, $b=16.5568(9)$ Å, $c=$ 17.18740(10) Å, $\alpha=74.923(14)°$, $\beta=74.172(14)°$, $\gamma=$ 79.585(17)°; space group P-1.

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