Efficient syntheses of phosphonylated isochromenes by regioselective 6-*endo-dig* addition to carbon-carbon triple bond catalyzed by $Pd(OAc)_2$†‡

Fei Wang,[a] Zhiwei Miao*[a,b] and Ruyu Chen*[a]

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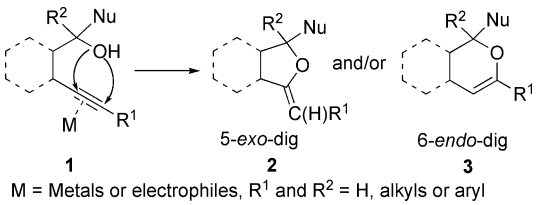
Palladium(II)-catalyzed cycloisomerization of [(2-alkynylphenyl)hydroxymethyl]phosphonates 6 provides an efficient route to phosphonylated isochromenes 7 in THF at room temperature and the reaction proceeded in a regioselective manner leading to the 6-*endo-dig* products 7 in moderate to excellent yields.

Organophosphorus compounds continue to receive widespread attention due to their ubiquity in biological systems and their potential to serve as novel pharmaceuticals.[1] Moreover, recent studies have indicated that heterocyclic analogues containing phosphorus showed interesting bioactivities.[2] Isochromenes are interesting heterocyclic compounds and useful precursors of important heterocyclic derivatives. Some isochromene derivatives have showed interesting pharmacological activity;[3] isochromenes have found application as synthetic intermediates[4] and are potential precursors of isochromanes, whose biological activity is well-known.[5] The cyclization of alkynes containing proximate nucleophilic centers, promoted by organopalladium complexes, is developing into a highly effective strategy for heterocyclic ring construction.[6] Wu has reported the tandem cyclization-addition reaction of 2-alkynylbenzaldehyde with diethyl phosphate catalyzed by AgOTf to afford 1*H*-isochromen-1-ylphosphonates at room temperature in moderate yields. With respect to substrate scope, when a 4-fluorophenyl or butyl group was attached on the triple bond of 2-alkynylbenzaldehyde, the reaction was complicated and no desired product was isolated.[7] Gabriele has already reported several approaches to the Pd(II)-catalyzed synthesis of heterocyclic derivatives starting from acetylenic substrates, by a simple cycloisomerization approach[8] as well as by carbonylative cyclization reactions.[9] Pd(II) can indeed catalyze cycloisomerization methodology with readily available 2-alkynylbenzyl alcohols **1** for the synthesis of (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans and 1*H*-isochromenes (**2** and **3**, respectively, Scheme 1) under neutral conditions.[10]

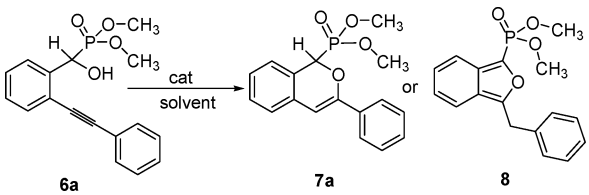
We recently reported the efficient syntheses of (thio)phosphonylated isobenzofurans by tandem nucleophilic addition and regioselective 5-*exo-dig* addition to a carbon-carbon triple bond with a cooperative effect from DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[11] Herein we report the synthesis of phosphonylated isochromenes by regioselective 6-*endo-dig* addition to a carbon-carbon triple bond catalyzed by $Pd(OAc)_2$.



Scheme 1

We started our investigation with dimethyl (2-(2-ethynyl)-phenyl)(hydroxyl)methylphosphonate **6a**, readily available using dimethyl phosphite **4** reacted with *o*-alkynyl benzaldehyde **5** in the presence of triethyl amine in THF at room temperature.[11] This step generally gives yields of the product above 90%. After treatment of this compound with a catalytic amount of palladium(II) acetate (10 mol%) in THF at room temperature, we observed the formation of a product in 90% yield (Table 1, entry 1). Structure elucidation by ^1H, ^{13}C, ^{31}P NMR and mass spectroscopy revealed this compound to be 1*H*-isochromen-1-ylphosphonate **7a**. In this case, only the six-membered endocyclic phosphonylated

Table 1 Screening of the reactions of {[2-(phenylethynyl)phenyl]hydroxymethyl}phosphonate **6a** under different conditions[a]



Entry[a]	Catalyst	Solvent	Yield (**7a**)[d]
1	$Pd(OAc)_2$	THF	90
2	CuI	THF	—
3	CuBr	THF	—
4	$Cu(OAc)_2$	THF	—
5	$Pd(PPh_3)_2Cl_2$	THF	—
6	$AlCl_3$	THF	—
7[b]	$Pd(OAc)_2$	THF	92
8	$Pd(OAc)_2$	CH_2Cl_2	78
9	$Pd(OAc)_2$	DMF	80
10	$Pd(OAc)_2$	Toluene	70
11[c]	DMAP	THF	—
12[c]	Pyridine	THF	—
13[c]	AcOK	THF	—
14[c]	DBU	THF	(**8**) 94

[a] Unless otherwise noted all the reactions were performed with 0.5 mmol of **6a** and 10 mol% catalyst in 5 ml solvent for 5 h at room temperature. [b] 20 mol% of $Pd(OAc)_2$ was used. [c] The amount of base was 2 equiv. of substrate **6a**. [d] Isolated yields.

[a]*State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, China. E-mail: miaozhiwei@nankai.edu.cn; Fax: +86 2350 2351; Tel: +86 2350 4783*
[b]*Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Tsinghua University, Beijing, 100084, China*

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‡ Electronic supplementary information (ESI) available: Detailed description of experimental procedures, full characterization of new compounds **7a-j** shown in Table 2. See DOI: 10.1039/b908313h

isochromenes from 6-*endo-dig*[12] cyclization were obtained, and no five-membered exocyclic products were detected by TLC monitoring. 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.[13] Further screening the reaction of substrates in the presence of a variety of metal catalysts revealed that cyclizations were not observed in the presence of other kinds of catalysts, such as CuI, CuBr, $Cu(OAc)_2$, $Pd(PPh_3)_2Cl_2$ and $AlCl_3$ (Table 1, entry 2–6) and only starting material **6a** was recovered. Increasing the catalyst amount to 20 mol% gave a similar result (92% yield, Table 1, entry 7). Solvent screening showed that THF led to better results than with the other solvents tested, *i.e.* CH_2Cl_2, DMF, and toluene (Table 1, entries 8–10). Thus, the selective synthesis of 6-*endo-dig* 1*H*-isochromen-1- ylphosphonate **7a** from dimethyl (2-(2-ethynyl)phenyl)(hydroxyl)methylphosphonate **6a** was achieved through the use of $Pd(OAc)_2$ and THF as solvent.

In an extension of this work, we also examined the base-induced reaction in order to compare the selectivity of this reaction with that obtained in the Pd-catalyzed process. We found that, using DBU as the base, the reaction of **6a** selectively afforded the isobenzofuran derivative **8**, arising from a 5-*exo-dig* cyclization mode, in 94% yield (Table 1, entry 14).[11] The other nitrogen-containing basic catalysts, such as 4-(*N,N*-dimethyl amino)pyridine (DMAP), pyridine, or AcOK, proved to be ineffective under similar conditions (Table 1, entries 11–12).

Based on the above optimization efforts, we next examined the scope and limitations of the present $Pd(OAc)_2$ catalyzed 6-*endo-dig* cyclization with a series of dialkyl (2-(2-ethynyl)phenyl)-(hydroxyl)methylphosphonate **6**. The application of this methodology to the synthesis of a variety of 1*H*-isochromen-1-ylphosphonates **7** is summarized in Table 2. The reaction of *o*-alkynyl benzaldehyde **5** proceeded smoothly with dialkyl phosphite **4** in the present of Et_3N in THF at room temperature, and gave nearly quantitative yields of dialkyl (2-(2-ethynyl)-phenyl)(hydroxyl)methylphosphonate **6**. As can be seen all the reactions of substrates bearing no further substituent at the benzylic position (R^2 = H) went to completion in the presence of catalytic amounts of $Pd(OAc)_2$ in THF at room temperature within five hours and the six-membered 1*H*-isochromen-1-ylphosphonates **7** were obtained in good to excellent yields (Table 2, entries 2–10). When R^1 was replaced by 4-methylphenyl **6f-g** or 4-fluorophenyl **6h-i**, the reaction was still going very well and the desired products were isolated (Table 2, entries 6–9). The results indicated that an electron-donor group or electron-withdrawing group attached on the aromatic ring of dialkyl (2-(2-ethynyl)phenyl)(hydroxyl)methylphosphonate **6** had no great influence on this cyclization reaction. The reaction of **6j**, bearing a butyl group as R^1, proceeded smoothly to give **7j** in 72% yield (Table 2, entry 10). When *o*-alkynyl acetophenone **5** was employed as the starting material and reacted with dimethyl phosphate **4** to synthesise dimethyl (2-(2-ethynyl)phenyl)(hydroxyl)ethylphosphonate **6k**, no reaction occurred (Table 2, entry 11). Compared with the AgOTf-catalyzed reaction of 2-alkynylbenzaldehyde with diethyl phosphate,[7] our method has the advantage of wider substrate scope (Table 2, entries 8–10). But just as Wu *et al.* mentioned in their work,[7] the corresponding product 1*H*-isochromen-1-ylphosphonate **7** were unstable and easily decomposed at room temperature.

Table 2 Reactions of dialkyl (2-(2-ethynyl)phenyl)(hydroxyl)methyl-phosphonate **6**

Entry[a]	Substrate **4**	**6**	R^1	R^2	Yield of **7** (%)[b]	
1	$H(O)P(OCH_3)_2$	**6a**	Ph	H	**7a**	90
2	$H(O)P(OC_2H_5)_2$	**6b**	Ph	H	**7b**	86
3	$H(O)P(OC_3H_7\text{-}n)_2$	**6c**	Ph	H	**7c**	85
4	$H(O)P(OC_3H_7\text{-}i)_2$	**6d**	Ph	H	**7d**	80
5	$H(O)P(OC_4H_9\text{-}n)_2$	**6e**	Ph	H	**7e**	82
6	$H(O)P(OCH_3)_2$	**6f**	$p\text{-}CH_3C_6H_4$	H	**7f**	85
7	$H(O)P(OC_2H_5)_2$	**6g**	$p\text{-}CH_3C_6H_4$	H	**7g**	81
8	$H(O)P(OCH_3)_2$	**6h**	$p\text{-}FC_6H_4$	H	**7h**	83
9	$H(O)P(OC_2H_5)_2$	**6i**	$p\text{-}FC_6H_4$	H	**7i**	82
10	$H(O)P(OCH_3)_2$	**6j**	$n\text{-}C_4H_9$	H	**7j**	72
11	$H(O)P(OCH_3)_2$	**6k**	Ph	CH_3	—	—

[a] Unless otherwise noted all the reactions were performed with 0.5 mmol of **5** and 10 mol% $Pd(OAc)_2$ in 5 ml solvent at room temperature. [b] Isolated yields.

Formation of **7a** was traced by ^{31}P NMR spectroscopy as shown in Fig. 1. The starting material dimethyl (2-(2-ethynyl)phenyl)(hydroxyl)methylphosphonate **6a** in THF showed a ^{31}P NMR resonance at 23.70 ppm. After $Pd(OAc)_2$ (0.011 g, 10% mol) was added to the solution of **6a**, two new single peaks at 19.73 ppm and 17.72 ppm appeared and assigned as two intermediates of $Pd(OAc)_2$ upon coordination of the triple-bond of **6a** (intermediate **9**) and the intermediate palladium ate complex **11** (Scheme 2). Over time, ^{31}P NMR signals of the starting material gradually disappeared and the signals of **7a** (single peak at 16.60 ppm) increased. $Pd(OAc)_2$ catalyzed the reaction *via* formation of the intermediate **9**, with an active carbon-carbon triple bond. The reaction was almost complete after five hours according to the ^{31}P NMR spectra (Fig. 1).

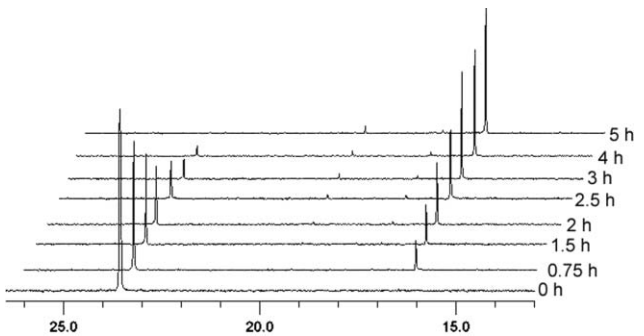
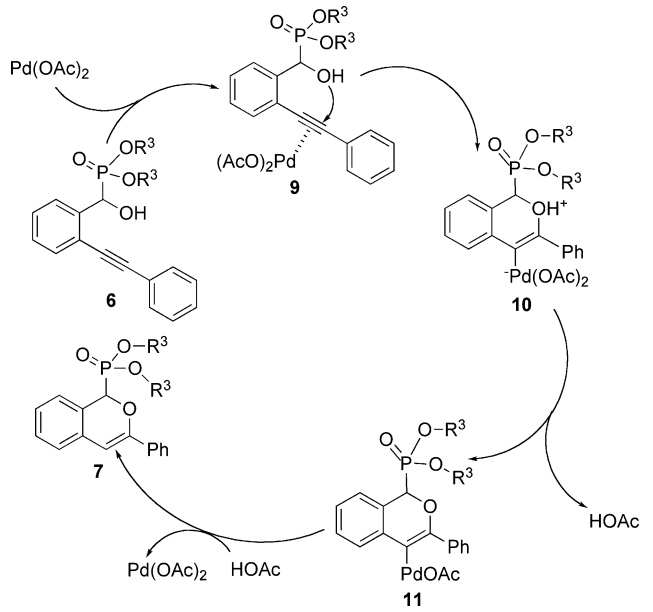


Fig. 1 ^{31}P-NMR stack spectra for the synthesis of **7a** (ppm).

Based on ^{31}P NMR stack spectra (Fig. 1), a plausible mechanism for $Pd(OAc)_2$ catalyzed cyclization reaction of **6** to **7** is outlined in Scheme 2. The process consists of the following key steps: (1) coordination of $Pd(OAc)_2$ to the triple bond of dialkyl (2-(2-ethynyl)phenyl)(hydroxyl)methylphosphonate **6** forming complex **9**,[13] which activates the triple bond toward nucleophilic attack,[14] (2) intramolecular nucleophilic attack of the oxygen atom of the hydroxyl group on the activated carbon-carbon triple bond to afford intermediate **10**, (3) elimination of proton occurs to give complex **11** and AcOH, (4) protonolysis of **11** by AcOH gives the 6-*endo-dig* product **7** with regeneration of $Pd(OAc)_2$.

In conclusion, we have described a general method for the efficient synthesis of phosphonylated isochromenes *via*



Scheme 2

intramolecular 6-*endo-dig* cyclization of dialkyl (2-(2-ethynyl)-phenyl)(hydroxyl)methylphosphonate **6** catalyzed by $Pd(OAc)_2$ in THF at room temperature. The yields obtained were good to excellent in most cases, even though the reaction did not take place in the presence of an alkyl substituent at the benzylic position and the regioselectivity was always 100% favoring 6-*endo-dig* cyclization. The process holds promise as a useful tool for the construction of complex heterocycles phosphonylated isochromenes. Further studies on the mechanistic details and synthetic potential of these cyclizations are in progress.

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