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Synthesis of Phosphaisocoumarins via Iodocyclization

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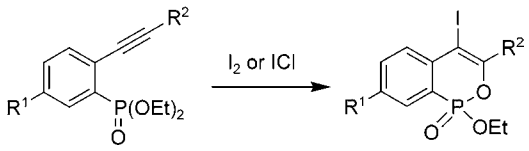
ABSTRACT

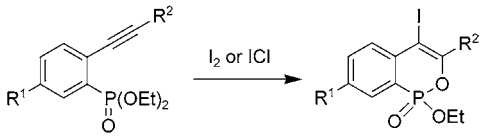


4-Iodophosphaisocoumarins can be prepared in good yield and with high regioselectivity under mild conditions by the reaction of *o*-(1-alkynyl)phenylphosphonates with I_2 or ICl. The present reaction represents the first example of a phosphonate iodocyclization onto a C–C triple bond. The resulting iodides can be further elaborated using palladium-catalyzed coupling reactions.

Isocoumarins are a class of naturally occurring lactones that display diverse bioactivities.[1] Phosphaisocoumarins are phosphorus isocoumarin analogues that also could have bioactivities.[2] Recently, we reported[3] a synthesis of 3-substituted phosphaisocoumarins having no substituent at the 4-position that exploited the Cu(I)-catalyzed cyclization of *o*-(1-alkynyl)phenylphosphonic acid monoesters. In continuation of the above investigation, we recently decided to search for a new procedure that would allow us to synthesize 3,4-disubstituted phosphaisocoumarins.

Iodocyclization of an unsaturated C−C bond with a wide variety of nucleophiles, including N, O, and S nucleophiles, has been extensively studied[4] and has become a powerful method for the construction of various heterocycles. For example, iodocyclization of *o*-(1-alkynyl)benzoic acids or esters[5] is an important way of synthesizing isocoumarins. By way of contrast, only a few examples of the electrophilic cyclization of alkenyl phosphates[6] and alkenylphosphonates[7] are reported in the literature, and to the best of our knowledge, the analogous reaction of phosphates or phosphonates onto a C−C triple bond has never been described thus far. In this paper, we describe the iodocyclization of *o*-(1-alkynyl)phenylphosphonates **1** using I_2 or ICl as the electrophile; this leads to 4-iodophosphaisocoumarins **2** in moderate to excellent yield (Scheme 1). Moreover, not only does our iodocyclization reaction open up a new path for the synthesis of phosphaisocoumarins, but the presence of iodine at the 4-position also permits further elaboration to more complex derivatives.

Scheme 1



1 **2**

The starting alkynes **1** for our approach were readily prepared by the Pd-catalyzed cross-coupling reaction[8] of the

(1) (a) Powers, J. C.; Asgian, J. L.; Ekici, Ö. D.; James, K. E. *Chem. Rev.* **2002**, *102*, 4639 and references therein. (b) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K. I.; Nakajima, S. *Chem. Pharm. Bull.* **1981**, *29*, 2491. (c) Hussain, M. T.; Rama, N. H.; Malik, A. *Indian J. Chem.* **2001**, *40B*, 372. (d) Lee, J. H.; Park, Y. J.; Kim, H. S.; Hong, Y. S.; Kim, K. W.; Lee, J. J. *J. Antibiot.* **2001**, *54*, 463. (e) Whyte, A. C.; Gloer, J. B.; Mallock, D. J. *Nat. Prod.* **1996**, *59*, 765. (f) Shimoda, H.; Matsuda, H.; Yamahara, J.; Yoshikawa, M. *Biol. Pharm. Bull.* **1998**, *21*, 809. (g) Umehara, K.; Matsumoto, M.; Nakamura, M.; Miyase, T.; Kuronagi, M.; Noguchi, H. *Chem. Pharm. Bull.* **2000**, *48*, 566.

(2) (a) Engel, R., Ed. *Handbook of Orgnophosphorus Chemistry*; Marcel Dekker: New York, 1992; Chapter 11. (b) Quin, L. D., Ed. *A Guide to Organophosphorus Chemistry*; John Wiley & Sons: New York, 2000; Chapter 11.

(3) Peng, A.-Y.; Ding, Y.-X. *J. Am. Chem. Soc.* **2003**, *125*, 15006.

(4) See the review: Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33.

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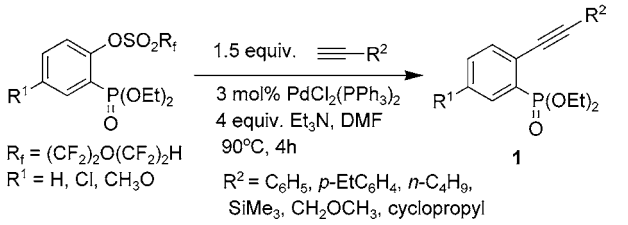
Scheme 2



corresponding aryl perfluoroalkanesulfonates with terminal acetylenes (Scheme 2).

First, we examined the reaction of 2-(phenylethynyl)-phenylphosphonic acid diethyl ester (**1a**) with 2.0 equiv of iodine in several different organic solvents at room temperature. We found that the reaction was highly dependent on the type of solvent used. In CH_3CN and DMF, we did not obtain the desired phosphaisocoumarin **2a** but rather the diiodide **3a** (Figure 1, $R^1 = H$, $R^2 = Ph$) from diiodination

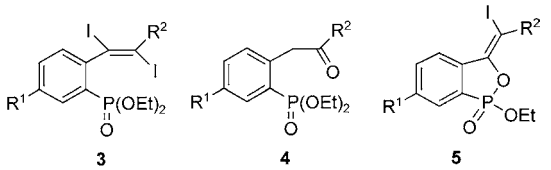
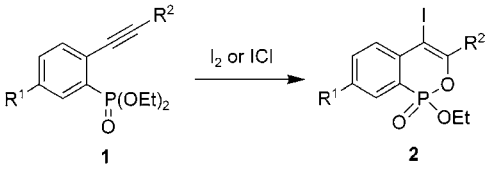


Figure 1.

of the triple bond. However, when the reaction was run in $CHCl_3$ or CH_2Cl_2, the product **2a** was produced in good isolated yield (83 and 80%, respectively) with trace byproducts **3a** and **4a** (as monitored by TLC). When the same reaction was carried out in benzene, **2a** was isolated in 35% yield with 40% recovery of **1a** and 15% of **4a**. Rossi et al.[5a] have isolated a similar ketone byproduct **4** during the iodocyclization of *o*-(arylethynyl)benzoates. The structures of **3a** and **4a** were confirmed by their IR, ^{1}H NMR, and MS spectra. There was no five-membered-ring product **5a** detected in each case.

On the basis of the above results, the iodocyclization of other alkynes **1** with 2.0 equiv of iodine was conducted in $CHCl_3$ at room temperature, and the results are summarized in Table 1. I_2 was efficient in most cases, and a variety of 4-iodophosphaisocoumarins were obtained in good to excellent yields. Functionalities such as chloro and methoxy on the benzene ring were able to withstand the reaction

Table 1. Synthesis of Phosphaisocoumarins via Iodocyclization[a]



entry	R^1	R^2	product	yield (%)[b]
1	H	C_6H_5	**2a**	83
2	H	*n*-C_4H_9	**2b**	70
3	H	H	**2c** + **3c**	4 + 65
4[c]	H	H	**2c**	35
5	Cl	*p*-EtC_6H_4	**2d** + **4d**	64 + 30
6	Cl	C_6H_5	**2e** + **4e**	67 + 25
7	Cl	*n*-C_4H_9	**2f**	64
8	Cl	cyclopropyl	**2g**	76
9	Cl	CH_2OCH_3	**2h**	46
10	Cl	$SiMe_3$	**2i**	0
11[c]	Cl	$SiMe_3$	**2i**	82
12	CH_3O	C_6H_5	**2j**	93

[a] All reactions were conducted at room temperature with 2.0 equiv of I_2 in $CHCl_3$ for 12 h unless otherwise specified.

conditions. Aryl-substituted (entries 1, 5, 6, and 12) and alkyl-substituted (entries 2 and 7−9) alkynes were also well accommodated. However, **1c** (entry 3) gave diiodide **3c** as the major product with very little of the desired product **2c** being formed. A bulky $SiMe_3$ group (**1i**, entry 10) totally halted the reaction, and starting material was completely recovered under these conditions. Use of the strong electrophile ICl instead of I_2 afforded the desired products **2c** and **2i** in moderate yields for **1c** and **1i** (entries 4 and 11). It is also worth mentioning that for the reactions of **1d** and **1e** (entries 5 and 6), the ketone byproducts **4d** and **4e** were isolated in 30 and 25% yields, respectively, which contrasted with the other cases where only small amounts of such byproducts were formed.

The reaction shows high regioselectivity for six-membered-ring phosphaisocoumarins **2**. Five-membered-ring products **5** were never detected under the reaction conditions. The structures of **2** were confirmed by spectroscopic methods (see Supporting Information) and chemically. Thus, the palladium-catalyzed triethylammonium formate reduction[9] of these iodides did not provide **7** but rather compounds of structure **6** (Table 2). It was relatively easy to distinguish the isomers **6** and **7** by ^{1}H NMR spectral analysis of their olefinic proton signal. For example, the olefinic proton of **7b** should couple with the neighboring methylene protons, but this coupling was absent for **6b**. Compound **6c** has two olefinic protons at the 3- and 4-positions resonating at δ 6.76 and 6.09 ppm, respectively, with different coupling constants to phosphorus, which was consistent with the proposed structure. In addition, the structure of **6j** was determined unambiguously by X-ray crystallographic analysis.[3]

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(7) (a) Zhao, Y.-F.; Yan, S.-J.; Zhai, C. *J. Org. Chem.* **1985**, *50*, 2136. (b) Yokomatsu, T.; Shioya, Y.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1997**, *46*, 463.

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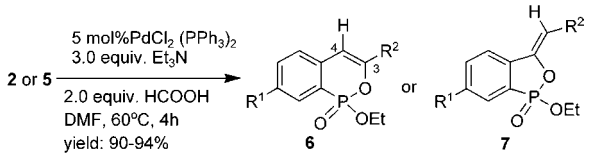
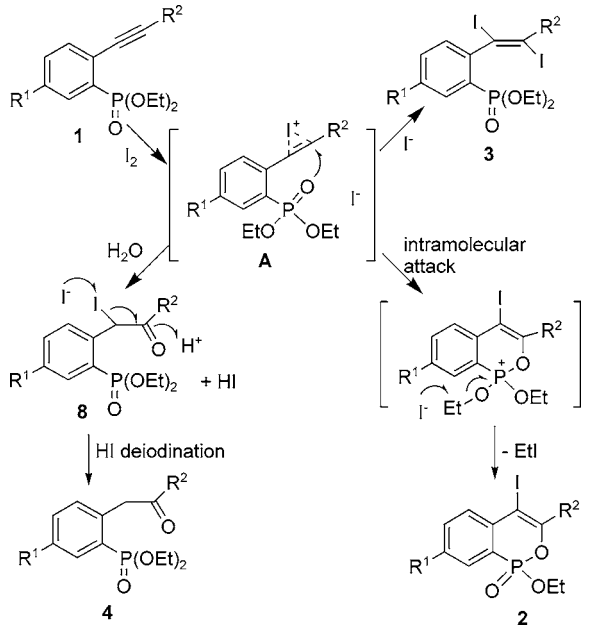
Table 2. ^{1}H NMR Spectral Properties of the Deiodide Products



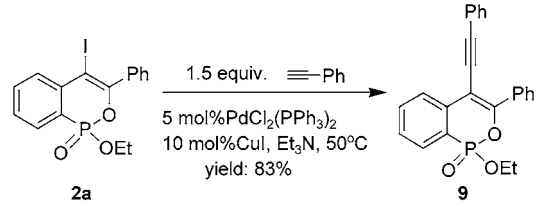
6	R^1	R^2	δ olefinic proton
6a	H	C_6H_5	6.69 (d, $J_{H-P} = 2.1$ Hz)
6b	H	*n*-C_4H_9	5.80 (s)
6c	H	H	6.76 (dd, $J_{H-P} = 18.3$ Hz, $J_{H-H} = 6.0$ Hz, 3-H), 6.09 (dd, $J_{H-H} = 6.0$ Hz, $J_{H-P} = 2.4$ Hz, 4-H)
6j	CH_3O	C_6H_5	6.66 (d, $J_{H-P} = 1.8$ Hz)

Plausible mechanisms for the formation of compounds **2**−**4** are shown in Scheme 3. The desired reaction to form **2** should involve intramolecular nucleophilic attack by the oxygen of the phosphonyl group in an endo mode on the triple bond activated by coordination to I^+ followed by elimination of ethyl iodide.[5b] On the other hand, the iodonium intermediate **A** could also undergo intermolecular attack by I^-, which would lead to compound **3**, or attack by water, which would provide α-iodoketone **7** and HI.[5a] Deiodination of **8** by HI[10] should then produce ketone **4**.

Scheme 3



Scheme 4



The presence of iodine at the 4-position of phosphaisocoumarins allows further structural elaboration, most notably using palladium-catalyzed coupling reactions. For example, when compound **2a** was exposed to Sonogashira coupling conditions[11] with phenylacetylene, the corresponding coupling product **9** was isolated in excellent yield (Scheme 4).

In summary, we have devised a novel strategy for the synthesis of phosphaisocoumarins that proceeds with high regioselectivity; our approach uses the iodocyclization of *o*-(1-alkynyl)phenylphosphonates with I_2 or ICl under mild conditions. The present reaction is the first example of the iodocyclization of phosphonates to a C−C triple bond. The resulting 4-iodophosphaisocoumarins have considerable potential for further elaboration, especially using palladium-catalyzed methods. Further investigation into the scope and limitations of this novel electrophilic cyclization is underway.

Supporting Information Available: Details of experimental procedures as well as compound characterizations for **2** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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