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Synthesis of 1*H*-isochromen-1-ylphosphonates via AgOTf-catalyzed reaction of 2-alkynylbenzaldehyde with diethyl phosphite

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ABSTRACT

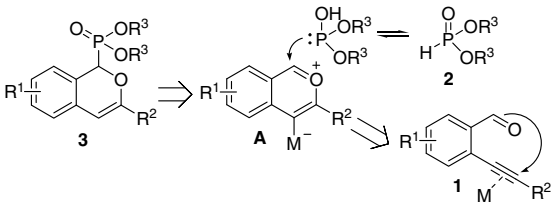
Tandem cyclization–addition reaction of 2-alkynylbenzaldehyde with diethyl phosphite catalyzed by AgOTf at room temperature was developed, which afforded the desired 1*H*-isochromen-1-ylphosphonates in moderate to good yields.

Due to their ubiquity in biological systems[1] and their potential to serve as pharmaceuticals,[2] considerable attention has been paid to organophosphorus compounds. Moreover, recent studies have indicated that many heterocycle analogues containing phosphorus showed interesting bioactivities. For instance, phosphacoumarins showed good inhibitory activity against SHP-1.[3] Meanwhile, as a privileged fragment, 1*H*-isochromene is a ubiquitous subunit in many natural products with remarkable biological activity.[4] Because of the importance of organophosphorus compound and 1*H*-isochromene, our continuous interest in natural product-like compounds[5] led us to devote our efforts for the development of efficient methods for the synthesis of phosphorus-contained 1*H*-isochromene molecules, with a hope of finding more active hits or leads for our particular biological assays.[6] Herein, we would like to disclose our preliminary results for the synthesis of 1*H*-isochromen-1-ylphosphonates via AgOTf-catalyzed reaction of 2-alkynylbenzaldehyde with diethyl phosphite.

Significant research has been reported utilizing cyclization and cycloisomerization of *o*-alkynylbenzaldehydes and related substrates.[7–11] For instance, Yamamoto and others have reported numerous approaches starting from 2-alkynylbenzaldehyde to afford putative metal-'ate' dipolar intermediates that may be reacted further to afford a variety of structures.[7] We also found that *o*-alkynylbenzaldehyde could be utilized in multi-component reactions for the construction of 1,2-dihydroisoquinoline scaffold.[5a,e]

Prompted by these results, we envisioned that the scaffold of 1*H*-isochromen-1-ylphosphonate **3** might be generated via tandem cyclization–addition reaction of 2-alkynylbenzaldehyde **1** with diethyl phosphite **2** under suitable conditions in the presence of metal catalysis (Scheme 1). Retro-synthetically, the cyclization involving metal catalysis is believed to proceed via the formation of the metal-complex, which renders the electrophilicity of the alkyne moiety. This triggers intermolecular attack of the nucleophile, which gives rise to the cyclic vinyl metal species that upon protonolysis will yield the desired 1*H*-isochromen-1-ylphosphonate **3** and the metal-cation, which can then enter again the catalytic cycle.

To verify the practicability of the projected route as shown in Scheme 1, the reaction was initially studied with 2-alkynylbenzaldehyde **1a**, which was selected as suitable substrate for reaction development (Table 1). This compound could be easily accessed via palladium-catalyzed Sonogashira coupling reactions of 2-bromobenzaldehyde with phenylacetylene.[10e] At the outset, various Lewis acids were screened and the results are shown in Table 1. No reaction occurred when copper(I) iodide was employed as



Scheme 1.

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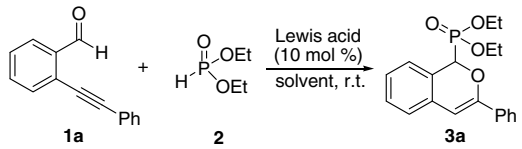
Table 1
Screening conditions for reaction of alkynylbenzaldehyde **1a** with diethyl phosphite **2**



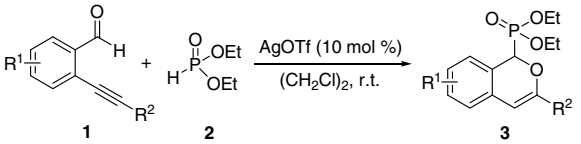
1a **2** **3a**

Entry	Lewis acid	Solvent	Yield[a] (%)
1	CuI (10 mol %)	$(CH_2Cl)_2$	—
2	$Cu(OTf)_2$ (10 mol %)	$(CH_2Cl)_2$	29
3	AgOTf (10 mol %)	$(CH_2Cl)_2$	82
4	$PdCl_2$ (10 mol %)	$(CH_2Cl)_2$	20
5	$Zn(OTf)_2$ (10 mol %)	$(CH_2Cl)_2$	—
6	$Yb(OTf)_3$ (10 mol %)	$(CH_2Cl)_2$	—
7	$Dy(OTf)_3$ (10 mol %)	$(CH_2Cl)_2$	—
8	$FeCl_3$ (10 mol %)	$(CH_2Cl)_2$	—
9	$In(OTf)_3$ (10 mol %)	$(CH_2Cl)_2$	—
10	AgOTf (10 mol %)	THF	66
11	AgOTf (10 mol %)	Toluene	79
12	AgOTf (10 mol %)	DMF	—
13	AgOTf (10 mol %)	DMSO	—
14	AgOTf (10 mol %)	MeCN	—
15	AgOTf (10 mol %)	Acetone	14
16	AgOTf (5 mol %)	$(CH_2Cl)_2$	80

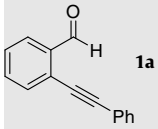
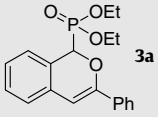
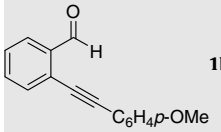
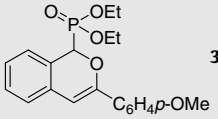
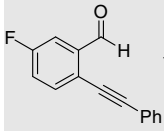
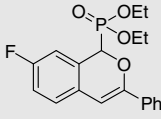
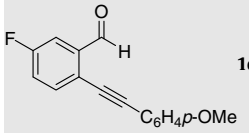
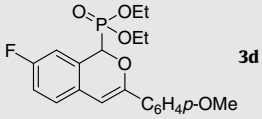
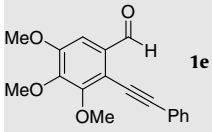
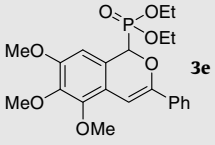
[a] Isolated yield based on 2-alkynylbenzaldehydes **1a**.

catalyst for the reaction of 2-alkynylbenzaldehyde **1a** with diethyl phosphite at room temperature in 1,2-dichloroethane (Table 1, entry 1). To our delight, we observed the formation of desired 1*H*-isochromen-1-ylphosphonate **3a** when the catalyst was replaced by copper(II) triflate, albeit in low yield (29%, Table 1, entry 2). Further investigation revealed that this result could be dramatically improved when silver triflate was utilized in the reaction, and the corresponding product was afforded in 82% yield (Table 1, entry 3). It is well-known that silver(I) salts have mild Lewis acidity and have been used as catalysts in organic synthesis. Among these salts, AgOTf is one of the most popular reagents for inducing transformations, which take advantage of its affinity for halogen and sulfur functional groups, and carbon–carbon unsaturated bonds rather than oxygen functional groups.[11] Following an extensive investigation, we observed that the yields were inferior when other Lewis acids [$PdCl_2$, $Yb(OTf)_3$, $Zn(OTf)_2$, $In(OTf)_3$, $Dy(OTf)_3$, $FeCl_3$] were employed in the reaction (Table 1, entries 4–9). These results indicated that AgOTf was the most efficient catalyst for this kind of transformation. Solvent screening demonstrated that 1,2-dichloroethane was the solvent of choice. Other solvents such as THF, toluene, MeCN gave unsatisfactory results (Table 1, entries 10–15). Similar yield was observed when the catalytic amount of AgOTf was reduced to 5 mol % (Table 1, entry 16). However, prolonged reaction time was necessary for completion of the reaction.

Table 2
AgOTf-catalyzed tandem addition–cyclization reaction of alkynylbenzaldehydes **1** with diethyl phosphite **2**[12,a]

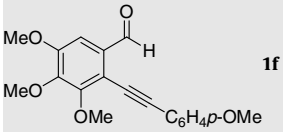
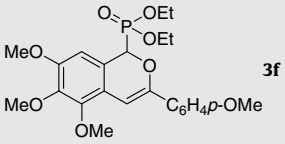
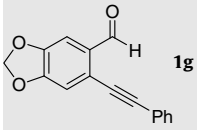
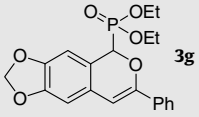
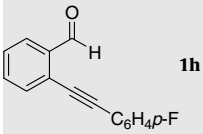
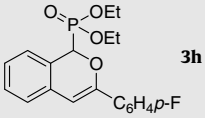
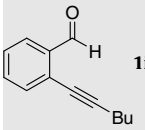
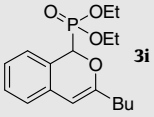
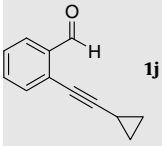
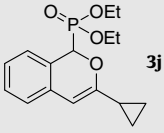


1 **2** **3**

2-Alkynylbenzaldehyde	Product	Yield[b] (%)
 **1a**	 **3a**	82 (12 h)
 **1b**	 **3b**	75 (12 h)
 **1c**	 **3c**	44 (12 h)
 **1d**	 **3d**	45 (5 h)
 **1e**	 **3e**	88 (4 h)

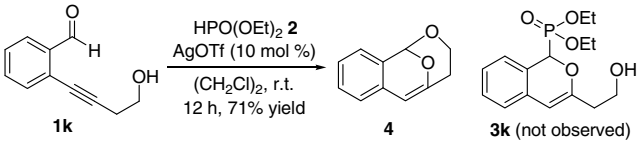
(*continued on next page*)

Table 2 (*continued*)

2-Alkynylbenzaldehyde	Product	Yield[b] (%)
 **1f**	 **3f**	74 (7 h)
 **1g**	 **3g**	87 (7 h)
 **1h**	 **3h**	—[c] (12 h)
 **1i**	 **3i**	—[c] (12 h)
 **1j**	 **3j**	—[c] (12 h)

[a] Reaction conditions: alkynylbenzaldehydes **1** (0.20 mmol), diethyl phosphite **2** (0.24 mmol), AgOTf (10 mol %), DCE (2.0 mL), rt.
[b] Isolated yield based on 2-alkynylbenzaldehydes **1**.
[c] The reaction was complicated and no desired product was isolated.

To test the effectiveness of the silver(I) triflate catalytic system, a range of *o*-alkynylbenzaldehydes **1** were examined using the preliminary optimized reaction conditions (1,2-dichloroethane as the solvent, 10 mol % of AgOTf, room temperature, overnight), and the results are summarized in Table 2. Complete conversion and moderate to good isolated yields were observed for most cases utilized. For instance, 75% yield of 1*H*-isochromen-1-ylphosphonate **3b** was obtained for the reaction of 2-alkynylbenzaldehyde **1b** with diethyl phosphite. Inferior results were displayed when substrates with electron-withdrawing groups attached on the aromatic ring of 2-alkynylbenzaldehyde were employed. The results indicated that the electron-withdrawing group attached on the aromatic ring of 2-alkynylbenzaldehyde might presumably decrease the nucleophilicity of oxygen in carbonyl group, since intermediate **A** would be formed during the reaction process. For example, 44% or 45% yield of product **3c** or **3d** was generated, respectively when fluoro-substituted 2-alkynylbenzaldehydes **1c** and **1d** were employed in the reaction. 2-Alkynylbenzaldehyde **1e** reacted with diethyl phosphite leading to the corresponding product **3e** in 88% yield. A similar yield (87%) was observed when substrate **1g** was utilized in the reaction. In this kind of transformation, the R^2 group attached on the triple bond is crucial. When R^2 was replaced by 4-fluorophenyl (**1h**), butyl (**1i**), or cyclopropyl group (**1j**), the reaction was complicated and no desired product was isolated. Although the mechanism for this messy outcome is not clear, we reasoned that it might be due to the instability of the corresponding product since compounds **3a–g** were also unstable and easy to be deteriorated at room temperature. Interestingly, reaction of substrate **1k** under silver-catalyzed conditions proceeded well to afford acetal product **4** in 71% yield and the desired product **3k** was not detected at all (Scheme 2). In this transformation, diethyl phosphite did not involve and only intramolecular addition occurred.



Scheme 2.

In summary, we have described AgOTf-catalyzed tandem addition–cyclization reaction of 2-alkynylbenzaldehyde with diethyl phosphite, which provide a facile and efficient protocol to facilitate the concise synthesis of 1*H*-isochromen-1-ylphosphonate derivatives. We also observed the intramolecular addition of substrate **1k** to generate acetal compound **4**. Introducing enantioselectivity in the scaffold and screening for biological activity of these small molecules are under investigation in our laboratory, and the results will be reported in due course.

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12. *General procedure for AgOTf-catalyzed tandem addition–cyclization reaction of alkynylbenzaldehydes* ***1****with diethyl phosphite* ***2***: A mixture of alkynylbenzaldehydes **1** (0.20 mmol), diethyl phosphite **2** (0.24 mmol), and AgOTf (0.02 mmol, 10 mol %) in 1,2-dichloroethane (2.0 mL) was stirred at room temperature under nitrogen atmosphere overnight. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2×10 mL). The extracts were evaporated in vacuo, followed by purification on silica gel affording the product 1*H*-isochromen-1-ylphosphonates **3**. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.12 (t, J = 6.8 Hz, 3H), 1.27 (t, J = 6.8 Hz, 3H), 3.82–3.96 (m, 2H), 4.05–4.12 (m, 2H), 5.75 (d, J = 12.2 Hz, 1H), 6.32 (s, 1H), 7.05 (d, J = 7.3 Hz, 1H), 7.16 (t, J = 6.8 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 7.30–7.38 (m, 3H), 7.73 (d, J = 7.3 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 16.3, 62.6, 63.2, 63.3, 74.4 (d, J_{CP} = 159.2 Hz), 100.4, 123.9, 124.1, 125.1, 125.7, 125.8, 126.7, 128.1, 128.8, 130.9, 131.0, 133.7, 151.7; ^{31}P NMR (161 MHz, $CDCl_3$) δ 17.93. MS (ESI): m/z 343 (M^+-H); HRMS calcd for $C_{19}H_{21}O_4P$ (M^+-H): 343.1099, found: 343.1117. Compound **3b**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.14 (t, J = 7.1 Hz, 3H),1.29 (t, J = 6.8 Hz, 3H), 3.82 (s, 3H), 4.09–4.11 (m, 4H), 5.73 (d, J = 12.2 Hz, 1H), 6.21 (s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 7.3 Hz, 1H), 7.15 (d, J = 6.4 Hz, 1H), 7.20–7.24 (m, 2H), 7.68 (d, J = 9.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 16.4, 55.2, 62.5 63.2, 74.6 (d, J_{CP} = 158.3 Hz), 99.0, 113.6, 123.8, 123.9, 125.7, 125.8, 126.4, 126.5, 126.7, 128.8, 131.4, 151.8, 160.3; ^{31}P NMR (161 MHz, $CDCl_3$) δ 18.10. MS (ESI): m/z 375 (M^++H); HRMS calcd for $C_{20}H_{23}O_5P$ (M^++H): 375.1361, found: 375.1378. Compound **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.19 (t, J = 7.4 Hz, 3H), 1.31 (t, J = 6.8 Hz, 3H), 3.95–4.03 (m, 2H), 4.09–4.15 (m, 2H), 5.70 (d, J = 13.2 Hz, 1H), 6.30 (s, 1H), 6.95–7.05 (m, 3H), 7.34–7.40 (m, 3H), 7.72 (d, J = 6.8 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 16.4, 62.8, 63.3, 74.2 (d, J_{CP} = 161.1 Hz), 99.7, 113.3 (d, J = 20.4 Hz), 115.6 (d, J = 20.7 Hz), 125.1, 125.5 (d, J = 7.6 Hz), 126.3 (d, J = 7.6 Hz), 127.3, 128.3, 128.9, 133.6, 151.3, 161.5 (d, J = 246.0 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 17.25. MS (ESI): m/z 363 (M^++H); HRMS calcd for $C_{19}H_{20}FO_4P$ (M^++H): 363.1161, found: 363.1179. Compound **3d**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.18 (t, J = 6.6 Hz, 3H), 1.30 (t, J = 6.6 Hz, 3H), 3.83 (s, 3H), 3.92–4.15 (m, 4H), 5.68 (d, J = 13.2 Hz, 1H), 6.19 (s, 1H), 6.90 (d, J = 7.2 Hz, 2H), 6.92–7.00 (m, 3H), 7.66 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 55.3, 62.8, 63.3, 74.3 (d, J_{CP} = 159.2 Hz), 98.2, 113.2 (d, J = 22.9 Hz), 113.7, 115.6 (d, J = 21.9 Hz), 125.1, 126.0 (d, J = 7.8 Hz), 126.3, 126.7, 127.7, 151.3, 160.3, 161.3 (d, J = 246.9 Hz); ^{31}P NMR (161 MHz, $CDCl_3$) δ 17.47. MS (ESI): m/z 393 (M^++H); HRMS calcd for $C_{20}H_{22}FO_5P$ (M^++H): 393.1267, found: 393.1291. Compound **3e**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.14 (t, J = 6.8 Hz, 3H), 1.35 (t, J = 6.8 Hz, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.92–4.17 (m, 4H), 5.67 (d, J = 11.7 Hz, 1H), 6.55 (s, 1H), 6.66 (s, 1H), 7.31–7.38 (m, 3H), 7.74 (d, J = 7.3 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 16.3, 29.5, 30.1, 56.0, 60.8, 61.2, 61.6, 62.5, 63.2, 74.1 (d, J_{CP} = 158.3 Hz), 94.9, 105.6, 118.0, 119.7, 124.9, 128.1, 128.4, 134.0, 142.2, 147.9, 150.0, 152.3; ^{31}P NMR (161 MHz, $CDCl_3$) δ 19.10. MS (ESI): m/z 457 (M^++Na); HRMS calcd for $C_{22}H_{27}O_7P$ (M^++Na): 457.1392, found: 375.1410. Compound **3f**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.15 (t, J = 7.2 Hz, 3H),1.33 (t, J = 7.2 Hz, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 3.92–4.15 (m, 4H), 5.65 (d,J = 11.6 Hz, 1H), 6.42 (s, 1H), 6.65 (d, J = 1.6 Hz,1H), 6.90 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.5, 55.2, 56.1, 60.9, 61.3, 62.6, 63.3, 73.3, 74.2 (d, J_{CP} = 158.3 Hz), 105.7, 113.6,118.4, 119.5, 126.5, 126.8, 142.2, 147.8, 150.1, 152.0, 160.0;^{31}P NMR (161 MHz, $CDCl_3$) δ 18.14.MS (ESI): m/z 465 (M^++H); HRMS calcd for $C_{23}H_{29}O_8P$ (M^++H): 465.1678, found: 465.1679. Compound **3g**: ^{1}H NMR (400 MHz, $CDCl_3$): 1.18 (t, J = 7.2 Hz, 3H),1.31 (t, J = 7.2 Hz, 3H), 3.99–4.13 (m, 4H), 5.64 (d,J = 11.2 Hz, 1H), 5.94 (dd, J = 5.9 Hz, J = 1.5 Hz, 2H), 6.23 (s, 1H), 6.58 (s, 1H), 6.77 (s, 1H), 7.32– 7.37 (m, 3H), 7.71 (d, J = 6.8 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3, 16.4, 29.6, 30.2, 61.7, 62.6, 63.3, 74.5 (d, J_{CP} = 159.2 Hz), 100.7, 101.1, 104.9, 106.9, 117.4, 125.0, 125.6, 128.3, 128.7, 133.7, 146.4, 148.0, 150.5; ^{31}P NMR (161 MHz, $CDCl_3$) δ 18.44. MS (ESI): m/z 411 (M^++Na); HRMS calcd for $C_{20}H_{21}O_6P$ (M^++Na): 411.0973, found: 411.0991. Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51–2.53 (m, 2H), 3.73–3.76 (m, 1H), 4.60–4.62 (m, 1H), 5.77 (s, 1H), 6.00 (s, 1H), 6.97 (d, J = 7.3 Hz, 1H), 7.17–7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4, 63.5, 97.5, 102.9, 123.5, 125.7, 125.9, 126.6, 129.1, 130.4, 150.4. MS (ESI): m/z 175 (M^++H); HRMS calcd for $C_{11}H_{10}O_2$ (M^++H): 175.0759, found: 175.0757.