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Synthesis of polycyclic phosphonates via an intramolecular Diels-Alder reaction of 2-benzoylbenzalaldehyde and alkenyl phosphites

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Abstract: In this paper, we present a Lewis-acid-promoted reaction of 2-benzoylbenzaldehyde and trialkenyl phosphites, which resulted in the formation of polycyclic phosphonates. The reaction proceeded via nucleophilic attack of trialkenyl phosphite on the carbonyl carbon of 2-benzoylbenzaldehyde. The subsequent intramolecular Diels-Alder reaction led to the formation of the cyclic phosphonate.

Keywords: Intramolecular cycloaddition, Diels-Alder reaction, oxaphosphinane, isobenzofuran, cyclic phosphonate.

Cyclic phosphonates are often utilized as key intermediate reagents (synthetic intermediates) in the preparation of synthetically useful products and biologically active compounds [1,2]. Therefore, the synthesis of these compounds has attracted a great deal of research attention in the fields of synthetic organic, bioorganic, and medicinal chemistry [3-6]. Moreover, the development of new methods for the preparation of cyclic phosphonates has become very important in organic chemistry. For this purpose, the chemistry of isobenzofuran [7,8,9] and the intramolecular Diels-Alder reaction [10,11] are extremely interesting from a theoretical point of view. They represent a possible way to synthesize pharmaceutical candidate compounds, such as natural products and biologically active compounds with complicated structures in only a few short steps [3,12-20]. For example, the synthesis of alkaloid derivatives using Lewis acids has been reported by Yilin et al. [21,22]. Previously, we reported the formation of dialkyl isobenzofuran-1-ylphosphonates by the reaction between *o*-phthalaldehyde and trialkyl phosphites in the presence of a Lewis acid (Scheme 1) [23,24].

In this study, we attempted to apply a Lewis-acid-promoted reaction of aromatic aldehydes and alkenyl phosphites to establish a new method for the one-step synthesis of polycyclic phosphonates.

Unfortunately, the reaction of *o*-phthalaldehyde **1** with triallyl phosphite **2a** or tributenyl phosphite **2b** failed to produce the intramolecular Diels-Alder adducts **4a** and **4b** (Scheme 2). We considered the possibility that isobenzofuran derivatives **3a** and **3b** were formed as intermediates, but decomposed due to their instability under these reaction conditions. Because of the low dienophilicity of the C=C bond of allyl and butenyl groups, the intramolecular Diels-Alder reaction of **3** did not proceed smoothly. On the other hand, adducts **5a** and **5b** were formed from the reaction of **1** with trialkenyl phosphite and *N*-phenylmaleimide via intermediates **3a** and **3b**. However, we considered the possibility to obtain the intramolecular adducts by stabilizing the intermediates **3a** and **3b**.

Considering the previously reported stabilization effect of a phenyl group on the intermediate isobenzofuran-1-ylphosphonate [25], a similar approach was employed in this study. It was expected that the replacement of **1** by 2-benzoylbenzaldehyde **6** would stabilize the intermediates, isobenzofuran derivatives **7a** and **7b**, due to a resonance effect derived from the phenyl group. The intramolecular adduct **9b** (Scheme 3, 31% yield) was generated from the intramolecular Diels-Alder reaction of isobenzofuran derivative **7b** and the subsequent aromatization of the product **8b**. However, these reaction conditions did not yield the intramolecular adduct **9a**. This suggested that the strain of the 5-membered ring in **8a** is stronger than that of the 6-membered ring in **8b**.

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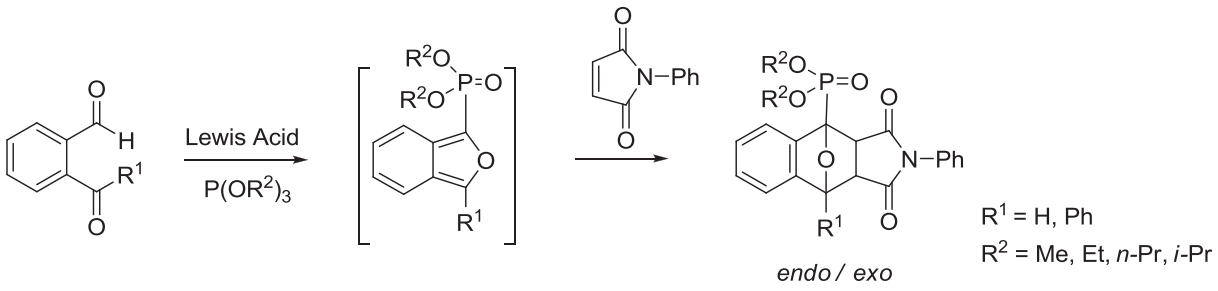
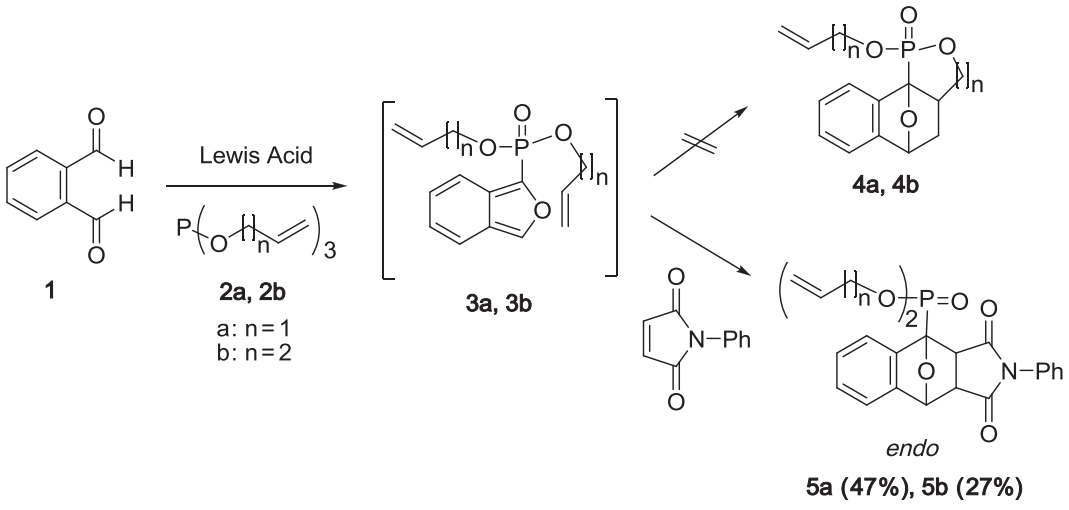
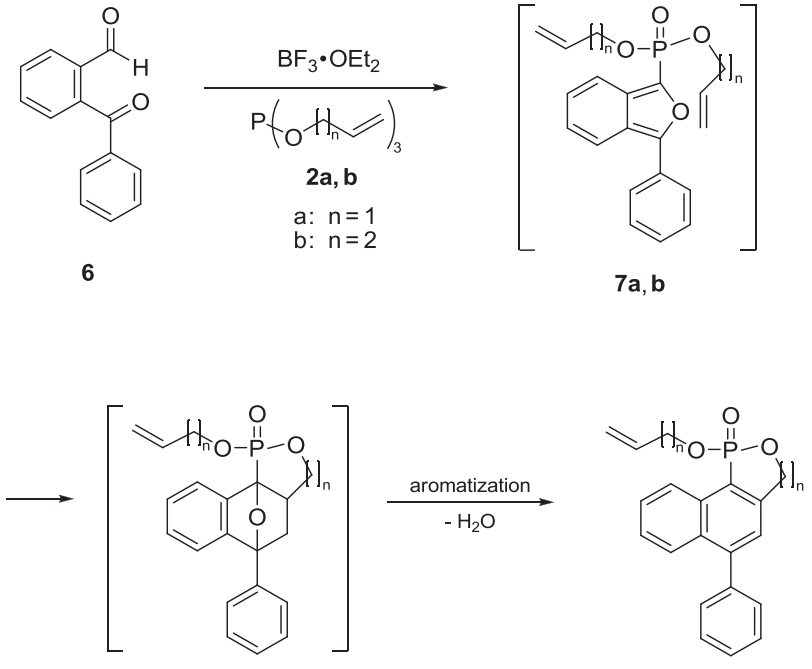


Scheme 1



Scheme 2



Scheme 3

The fact that the yield of the intermolecular adduct **5a** (47%) from triallyl phosphite **2a** was better than that of **5b** (27%) from tributenyl phosphite **2b** (Scheme 2) indicated that the reaction of **2a** proceeded more smoothly than that of **2b** because the allyl cation is more stable than the butenyl cation.

As previously reported, the rate limiting step in the formation of isobenzofuran-1-ylphosphonates is the alkyl group elimination from the trialkyl phosphite [25]. Moreover, the reaction proceeds more easily and the yield is increased when the alkyl group is smaller [Scheme 1, R^1 = H, R^2 = Me (80%), Et (71%), Pr (67%), and *i*-Pr (55%); *endo*/*exo* total yield). Similarly, the yield of polycyclic phosphonates should improve when the butenyl group of the trialkenyl phosphite is converted to a methyl group.

Therefore, dibutenyl methyl phosphite **2c**, where one of the butenyl groups is replaced by a methyl group, was employed in the reaction. This led to an increase in the total yield of the reaction to 67%, with **9b** (48%) being the major product after elimination of the methyl group (Scheme 4).

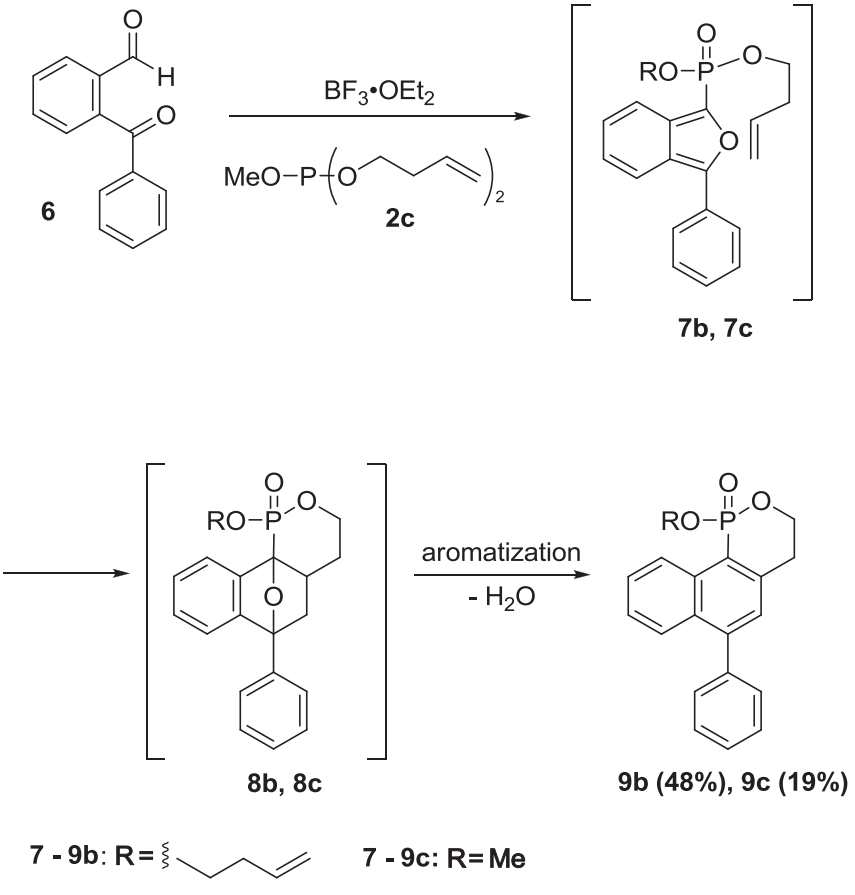
In summary, a new method for the synthesis of polycyclic phosphonates was developed, involving the treatment of 2-benzoylbenzaldehyde **6** with alkenyl phosphites, such as **2b** and **2c**. Polycyclic phosphonates **9b** and **9c** were obtained via an intramolecular cycloaddition in only one step. These reactions provide a new approach to the generation of cyclic phosphonates.

Experimental Details

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Bruker AVANCE III instrument. Tetramethylsilane was employed as an internal standard. The melting points were determined using a Yanako micro melting point apparatus and were uncorrected. High-resolution mass spectra were obtained using a JEOL JMS-T100GCV (EI) and microOTOF-QII (ESI).

General Procedure for the Preparation of Intramolecular Diels-Alder Adducts

BF_3•OEt_2 (1 mmol) was added to a solution of 2-benzoylbenzaldehyde **6** (1 mmol) in acetonitrile (3 mL) at



Scheme 4

Table 1 Yields of intramolecular Diels-Alder adducts **(9a-c)** by the reaction of 2-benzoylbenzaldehyde **(6)** and phosphites **(2a-c)** [a]

Entry	Phosphites	Adducts	Yields[b] (%)
1	**2a**	**9a**	-
2	**2b**	**9b**	31
3	**2c**	**9b, 9c**	48, 19

[a]Reaction conditions: $BF_3 \cdot OEt_2$ and 2-benzoylbenzaldehyde (1 equiv), MeCN, 0 °C, 0.5 h, followed by phosphites (1 equiv), 25 °C, 48 h. [b]Isolated.

0 °C. After stirring at this temperature for 0.5 h, alkenyl phosphite **2b** or **2c** (1 mmol) was added and the mixture was stirred at 25 °C for 48 h. HCl solution was added to quench the reaction, and the organic layer was extracted with CH_2Cl_2, washed with $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel (AcOEt:Hexane = 1:1) to give **9b** or **9c**.

1-(But-3-en-1-yloxy)-6-phenyl-1*H*,3*H*,4*H*-1λ⁵-naphtho[1,2-c][1,2]oxaphosphinin-1-one (9b).

The compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, 1H, *J* = 8.5 Hz), 7.87 (d, 1H, *J* = 8.5 Hz), 7.62 (t, 1H, *J* = 7.4 Hz), 7.43–7.52 (m, 6H), 7.23 (d, 1H, *J* = 5.2 Hz), 5.81 (ddt, 1H, *J* = 17.1, 10.3, 6.8 Hz), 5.13 (d, 1H, *J* = 17.2 Hz), 5.08 (d, 1H, *J* = 10.2 Hz), 4.62-4.68 (m, 2H), 4.29–4.37 (m, 1H), 4.23 (ddd, 1H, *J* = 13.9, 10.0, 6.9 Hz), 3.35–3.43 (m, 1H), 3.14 (ddd, 1H, *J* = 17.2, 7.3, 4.0 Hz), 2.48–2.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3 (d, $^4J_{C,P}$ =3.2 Hz), 142.0 (d, $^2J_{C,P}$ = 6.3 Hz), 139.5, 133.6, 133.4 (d, $^2J_{C,P}$ = 9.8 Hz), 130.9 (d, $^3J_{C,P}$ = 12.2 Hz), 129.7, 128.4, 128.0, 127.8, 127.2 (d, $^3J_{C,P}$ = 14.9 Hz), 127.1 (d, $^3J_{C,P}$ = 5.8 Hz, C-5), 126.8 (C-7), 126.4 (C-8), 120.1 (d, $^1J_{C,P}$ = 174.7 Hz, C-10a), 117.7 (*C*H_2=CH-), 65.9 (d, $^2J_{C,P}$ = 6.0 Hz, CH_2), 65.3 (d, $^2J_{C,P}$ = 7.0 Hz, CH_2), 34.9 (d, $^3J_{C,P}$ = 6.3 Hz, CH_2), 32.3 (d, $^3J_{C,P}$ = 7.1 Hz, C-4). HRMS (EI) Calcd for $C_{19}H_{17}NO_3P$ (M^+): 364.1228. Found: 364.1226.

1-Methoxy-6-phenyl-1*H*,3*H*,4*H*-1λ⁵-naphtho[1,2-c][1,2]oxaphosphinin-1-one (9c).

The compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, 1H, *J* = 8.5 Hz, ArH), 7.87 (d, 1H, *J* = 8.4 Hz, ArH), 7.63 (t, 1H, *J* = 7.7 Hz, ArH), 7.44–7.53 (m, 6H, ArH), 7.24 (d, *J* = 5.2 Hz, 1H, ArH), 4.62 (m, 2H, CH_2), 3.89 (d, 3H, $^3J_{P\text{-}O\text{-}C\text{-}H}$ = 11.4 Hz, CH_3), 3.34–3.41 (m, 1H, CH_2), 3.14–3.21(m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4 (d, $^3J_{C\text{-}P}$ =3.6 Hz, ArC), 142.1 (d, $^2J_{C\text{-}P}$ =6.4 Hz, ArC), 139.5 (ArC), 133.4 (d, $^2J_{C\text{-}P}$ =9.9 Hz, ArC), 130.9 (d, $^3J_{C\text{-}P}$ =12.1 Hz, ArC), 129.7 (ArC), 128.4, 128.0, 127.8, 127.2 (d, $^3J_{C\text{-}P}$ =14.7 Hz, ArC), 126.9 (d, $^3J_{C\text{-}P}$=5.7 Hz, ArC), 126.8 (ArC), 126.4, 120.0 (d, $J_{C\text{-}P}$ = 174.1 Hz, ArC-P), 66.0 (d, $^2J_{C\text{-}O\text{-}P}$ = 5.9 Hz, CH_2), 52.7 (d, $^3J_{C\text{-}O\text{-}P}$ = 6.8 Hz, CH_2), 32.3 (d, $^3J_{C\text{-}O\text{-}P}$ = 7.1 Hz, CH_2). HRMS (EI) Calcd for $C_{19}H_{17}NO_3P$ (M^+): 324.0915. Found: 324.0907.

Bis(but-3-enyl) methyl phosphite (2c).

The compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76–5.85 (m, 2H), 5.06–5.14 (m, 4H), 3.51 (dt, 4H, *J* =7.8, 6.9 Hz), 3.51 (d, 3H, *J* = 10.4 Hz), 2.36–2.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 117.7, 61.7 (d, $^2J_{C,P}$ = 11.7 Hz), 49.0 (d, $^2J_{C,P}$ = 9.3 Hz), 35.6 (d, $^4J_{C,P}$ = 5.0 Hz). HRMS (ESI Negative) Calcd for $C_{19}H_{17}NO_3P$ ($M+H^-$): 205.0994. Found: 205.0637.

Bis(prop-2-enyl) [(3a*R,4*S**,9*S**,9a*R**)-1,3-dioxo-2-phenyl-1,2,3,3a,9,9a-hexahydro-4*H*-4,9-epoxybenzo[f]isoindol-4-yl]phosphonate (*endo*) (5a).**

The compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.61 (m, 1H), 7.34–7.40 (m, 3H), 7.25–7.28 (m, 3H), 6.38–6.42 (m, 2H), 6.02–6.11 (m, 1H), 5.87–5.96 (m, 2H), 5.44–5.49 (m, 1H), 5.28–5.35 (m, 2H), 5.20–5.22 (m, 1H), 4.87–4.98 (m, 2H), 4.64–4.76 (m, 2H), 4.27 (dd, 1H, *J* = 9.0, 8.6 Hz), 4.07 (dd, 1H, *J* = 8.5, 5.8 Hz); ^{13}C NMR (67.80 MHz, $CDCl_3$): δ 172.6, 171.5, 140.7, 140.7, 139.7, 139.6, 132.8, 132.7, 132.4, 132.4, 130.8, 129.0, 128.9, 128.7, 128.6, 126.3, 125.8, 122.1, 121.3, 118.7, 118.5, 86.2 (d, $J_{C,P}$ = 191.3 Hz), 81.6 (d, $^3J_{C,P}$ = 15.4 Hz), 68.5 (d, $^2J_{C,P}$ = 6.0 Hz), 68.0 (d, $^2J_{C,P}$ = 6.2 Hz), 50.7 (d, $^3J_{C,P}$ = 6.6 Hz), 49.7 (d, $^3J_{C,P}$ = 4.4 Hz). HRMS (ESI Negative) Calcd for $C_{24}H_{21}NO_6P$ ($M\text{-}H^+$): 450.1106. Found: 450.1169.

Bis(but-3-enyl) [(3a*R,4*S**,9*S**,9a*R**)-1,3-dioxo-2-phenyl-1,2,3,3a,9,9a-hexahydro-4*H*-4,9-epoxybenzo[f]isoindol-4-yl]phosphonate (*endo*) (5b).**

The compound was obtained as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.58 (m, 1H), 7.33–7.39 (m, 3H), 7.24–7.26 (m, 3H), 6.38–6.41 (m, 2H), 5.81–5.91 (m, 2H), 5.66–5.76 (m, 1H), 5.01–5.20 (m, 4H), 4.47 (dt, 2H, *J* = 6.8, 8.0 Hz, 2H), 4.18–4.29 (m, 3H), 4.05 (dd, 1H, *J* = 5.8, 5.8 Hz), 2.56–2.61 (m, 2H), 2.41 (dt, 2H, *J* = 6.7, 6.7 Hz); ^{13}C NMR (67.80 MHz, $CDCl_3$): δ 172.6, 171.5, 140.8, 140.7, 139.8, 139.8, 133.5, 133.2, 130.8, 129.1, 129.0, 128.8, 128.7, 128.5, 126.3, 122.1, 121.2, 117.9, 117.7, 86.2 (d, $J_{C,P}$ = 191.1 Hz), 81.6 (d, $^3J_{C,P}$ = 15.3 Hz), 67.0 (d, $^2J_{C,P}$ = 6.5 Hz), 66.7 (d, $^2J_{C,P}$ = 6.5 Hz), 50.7 (d, $^3J_{C,P}$ = 6.6 Hz), 49.7 (d, $^3J_{C,P}$ = 4.3 Hz), 35.1 (d, $^3J_{C\text{-}P}$ = 5.5 Hz), 34.8 (d, $^3J_{C,P}$ = 5.8 Hz). HRMS (ESI Negative) Calcd for $C_{26}H_{25}NO_6P$ ($M\text{-}H^+$): 478.1419. Found: 478.1476.

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