Synthesis of Novel Phosphorus-Substituted Stable Isoindoles by a Three-Component Coupling Reaction of ortho-Phthalaldehyde, 9,10-Dihydro-9-oxa-10-phosphaphenanthrene 10-Oxide, and Primary Amines

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A three-component coupling reaction of ortho-phthalaldehyde, 9,10-dihydro-9-oxa-10-phosphaphenanthrene 10-oxide, and various primary amines readily afforded novel phosphorus-substituted stable isoindoles in good to excellent yields. The importance of the reversible ring-opening of 9,10-dihydro-9-oxa-10-phosphaphenanthrene 10-oxide by methanolysis in the three-component coupling reaction became apparent.

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Synthesis of Novel Phosphorus-Substituted Stable Isoindoles by a Three-Component Coupling Reaction of \textit{ortho}-Phthalaldehyde, 9,10-Dihydro-9-oxa-10-phosphaphenanthrene 10-Oxide, and Primary Amines

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Abstract A three-component coupling reaction of \textit{ortho}-phthalaldehyde, 9,10-dihydro-9-oxa-10-phosphaphenanthrene 10-oxide, and various primary amines readily afforded novel phosphorus-substituted stable isoindoles in good to excellent yields. The importance of the reversible ring-opening of 9,10-dihydro-9-oxa-10-phosphaphenanthrene 10-oxide by methanolysis in the three-component coupling reaction became apparent.

Key words OPA method, isoindoles, \textit{ortho}-phthalaldehyde, 9,10-dihydro-9-oxa-10-phosphaphenanthrene 10-oxide, primary amines, isoindolin-1-ones, ring-opening, methanolysis

A three-component coupling reaction of \textit{ortho}-phthalaldehyde (OPA), 2-mercaptoethanol, and a primary amine in aqueous alkaline medium is an efficient method of synthesizing isoindole,\textsuperscript{2} an isomer of indole that is also called benzo[c]pyrrole. The analytical method used for primary amines based on the above reaction is known as the OPA method, and it plays an important role in modern amino acid analysis.\textsuperscript{3} It should be noted that the isoindoles obtained by the OPA method are fluorescent compounds ($\lambda_{em}$ = 360 nm, $\lambda_{em}$ = 455 nm), whereas OPA itself is intrinsically nonfluorescent and does not interfere with fluorescence analysis of the resulting isoindoles. However, isoindoles, unlike indoles, are generally unstable and difficult to purify and isolate by silica gel column chromatography, because they are 10π aromatic heterocycles with \textit{ortho}-quinoid-like structures. R. Pino-Rios and M. Solá suggested that the inferior stability of isoindole compared to indole is a result of the decrease in benzene ring aromaticity as a manifestation of the Glidewell-Lloyd rule.\textsuperscript{3} In 2012, a review by C. V. Stevens and co-workers mentioned two strategies for stabilizing isoindoles.\textsuperscript{4} One is to sterically protect the isoindole ring by introducing a bulky substituent, and the other is to lower the highest occupied molecular orbital level of the isoindole ring by introducing an electron-withdrawing group. Recently we reported the synthesis of novel stable isoindoles via the OPA method using bulky C\textsubscript{3}-symmetric primary amines.\textsuperscript{5} As shown in Scheme 1, OPA reacts with O-benzylated tris(hydroxypropyl)aminomethane and a bulky C\textsubscript{3}-symmetric primary amine in the presence of several thiols to afford a novel class of stable and isolable isoindoles. The stability of a series of isoindoles was significantly influenced by the steric protection effect arising from the bulky nature of the C\textsubscript{3}-symmetric primary amine. In a continuation of our interest in the synthesis of stable and isolable novel isoindoles based on the OPA method and their potential for biological activities, we herein report a facile synthesis of phosphorus-substituted stable isoindoles by a three-component coupling reaction of OPA, 9,10-dihydro-9-oxa-10-phosphaphenanthrene 10-oxide (DOPO), and various primary amines. While DOPO is commonly depicted as the aryl arylphophinate structure in the H–P=O form, it is known to undergo tautomerization in solution, resulting in its P–OH form as aryl arylphosphonous acid. Therefore, the phosphorus atom of DOPO exhibits both electrophilic and nucleophilic behaviors.\textsuperscript{5} The resulting isoindoles are presumably stabilized by steric and/or electronic effects due to the phenoxy(phenyl)phosphoryl substituent. To date, the synthesis of phosphorus-substituted stable isoindoles has been limited to the preparation of dialkoxyphosphoryl-substituted isoindoles from the corresponding dialkyl [amino(2-ethynylphenyl)methyl]phosphonates, as reported in the literature.\textsuperscript{7
To prepare novel phosphorus-substituted stable isoindoles, we investigated DOPO as a phosphorus nucleophile instead of the thiol nucleophile in the OPA method. In 1972, T. Saito patented DOPO as a novel class of cyclic organophosphorus compound. It is now a commercially available chemical reagent and known as a typical flame-retardant agent. Table 1 shows the three-component coupling reaction of OPA, HPPA, and 3-pentylamine (1a) in various anhydrous solvents at room temperature in the dark using brown-tinted glassware. The reaction proceeded smoothly in anhydrous MeOH, and DOPO-isoindole 2a was isolated in 70% yield by silica gel column chromatography, as shown in Entry 1. In anhydrous EtOH and i-PrOH, the yields of DOPO-isoindole 2a were 30% and ca. 16%, respectively, with some by-products of isoidolin-1-one 3a (Entries 2 and 3). However, when anhydrous MeCN, CH₂Cl₂ and THF were used (Entries 4–6), the reaction afforded no DOPO-isoindole 2a, and only isoidolin-1-one 3a was obtained in moderate yields.

Table 1 Synthesis of DOPO-isoindole 2a by the three-component coupling reaction of OPA, DOPO, and 3-pentylamine (1a) based on the OPA method

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield of 2a (%)</th>
<th>Yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>30</td>
<td>ca. 8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>i-PrOH</td>
<td>ca. 16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>0</td>
<td>ca. 48&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields.

<sup>b</sup> Small amounts of impurities were included.

DOPO is a hygroscopic white powder and is known to be easily hydrolyzed to 2-(2-hydroxyphenyl)phenylphosphinic acid (HPPA) in open air. But HPPA is reversibly dehydrated to DOPO by drying under reduced pressure during heating as shown in Scheme 2. In 1998, C. S. Wang et al. reported the four-step synthesis of DOPO starting from ortho-phenylenediamine, and the final step was thermal dehydration of HPPA to DOPO by heating from its molten state (106 °C) to 160 °C under reduced pressure. Therefore, it was presumed that reversible alcoholysis proceeded in anhydrous MeOH, EtOH, and i-PrOH to afford methyl 2-(2-hydroxyphenyl)phenylphosphinate (HPPA methyl ester), ethyl 2-(2-hydroxyphenyl)phenylphosphinate (HPPA ethyl ester), and 2-propyl 2-(2-hydroxyphenyl)phenylphosphinate (HPPA 2-propyl ester), respectively (Scheme 2). Since the phosphorus atoms of the ring-opened derivatives of DOPO, such as HPPA methyl ester, HPPA ethyl ester, and HPPA 2-propyl ester, are more nucleophilic than that of DOPO, it is assumed that they readily attacked the monooxime intermediate formed by the reaction of OPA and 3-pentylamine (1a) according to the plausible reaction mechanism of the OPA method. Yasuda et al. reported that DOPO-aldehyde adducts or DOPO-ketone adducts were synthesized without using any bases by the reaction of HPPA with various aldehydes and ketones. This suggests that the phosphorus atom of HPPA is highly nucleophilic.
shown in Figure 1, because they are readily exchanged in deuterated alcohol solvents. Comparing $^1$H NMR spectra of DOPO 30 minutes after dissolution in some deuterated alcohols, the ring-opened derivative formed most rapidly in MeOD-$d_4$, and the formation rate decreased with an increase in the bulkiness of the alcohols. The difference in the formation rate of the ring-opened derivative may be reflected in the yield of the three-component coupling reactions using some alcohols as solvents (Table 1, entries 1–3). Attempts to isolate HPPA methyl ester generated by methanolysis of DOPO in MeOH were not successful, as it readily reverted to DOPO during purification. This is probably due to the relative instability of HPPA methyl ester compared to HPPA.

To examine the scope and limitations of this three-component coupling reaction, various primary amines $1b$–$k$ were subjected to the reaction with OPA and DOPO in anhydrous MeOH as shown in Table 2. To our delight, the reaction with methylamine $1b$, the smallest primary amine, gave the stable DOPO-isoindole $2b$ in 94% yield (Entry 1). Unbranched primary aliphatic amines $1c$–$e$ and branched primary aliphatic amines $1f$–$i$ afforded DOPO-isoindoles $2c$–$i$ in good to excellent yields (Entries 2–8). However, bulky amines such as $1j$ and $1k$ required a higher reaction temperature of 40 °C and reflux, respectively (Entries 9 and 10). All DOPO-isoindoles $2b$–$k$ were found to be stable and were isolable by silica gel column chromatography, similar to DOPO-isoindole $2a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Primary amine $1b$–$k$</th>
<th>Yield of $2b$–$k$ (%)</th>
<th>Yield of $3b$–$k$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$H_2N$–$Me$ ($1b$)</td>
<td>94 ($2b$)</td>
<td>0 ($3b$)</td>
</tr>
<tr>
<td>2</td>
<td>$H_2N$–$Me$ ($1c$)</td>
<td>84 ($2c$)</td>
<td>0 ($3c$)</td>
</tr>
<tr>
<td>3</td>
<td>$H_2N$–$Me$ ($1d$)</td>
<td>67 ($2d$)</td>
<td>0 ($3d$)</td>
</tr>
</tbody>
</table>
In conclusion, we have successfully prepared novel phosphorus-substituted stable isodines, 6-[(2-alkyl-2-1H-isodindol-1-yl)-6H-dibenzo[c,e]1,2]oxaphosphine 6-oxides 2a–k using the OPA method and employing various primary amines 1a–k. The stability of a series of DOPO-isodiones 2a–k may be attributable to the steric and/or electronic effects of the phosphorus substituent derived from DOPO. Notably, the importance of the reversible ring-opening of DOPO by methanolysis in the three-component coupling reaction was also suggested by the detailed examination of the 1H NMR spectral data.

The experimental section has no title; please leave this line here.

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with a JASCO FT/IR-6200 IR Fourier transform spectrometer. 1H NMR (400 MHz) and 13C NMR (125 MHz) spectra were recorded with a Bruker AVANCE 500 spectrometer. A Bruker AV500 spectrometer. Chemical shifts are given in δ values (ppm) using TMS as an internal standard. HRMS (ESI) data were recorded with a Waters LCT Premier spectrometer. Elemental combustion analyses were performed with a J-SCIENCE LAB JM10. All reactions were monitored by TLC employing 0.25 mm silica gel plates (Merck 5715; 60 F254). Flash column chromatography was carried out on silica gel (Sílica Gel P5Q 60B (Fují Silisia Chemical)). Anhydrous EtOH and i-PrOH were used as purchased from FUJIFILM Wako Pure Chemical Corporation. Anhydrous MeOH, MeCN, CH2Cl2, and THF were used as purchased from Kanto Chemical. DOPO was dried under reduced pressure prior to use. All other reagents were used as purchased.

6-[(2-Pentyl-3-yl)-2H-isodindol-1-yl]-6H-dibenzo[c,e]1,2]oxaphosphine 6-Oxide (2a)

To a solution of OPA (51.3 mg, 0.382 mmol) in anhydrous MeOH (1 mL), 3-pentanylamine (1x 48.9 μL, 0.421 mmol) and DOPO (91 mg, 0.421 mmol) were added at 0°C. After stirring in the dark for 3 h at room temperature, the reaction mixture was evaporated in vacuo. The oily residue was purified by flash column chromatography [Silica Gel PSQ 60B: CHCl3–AcOEt (7:1)] to afford isodione 2a (107 mg, 70%) as a white solid; mp 224.0–225.8°C (colorless column, CHCl3–n-hexane).

IR (KBr): 3096, 2946, 2874, 1931, 1821, 1304, 1214, 1120, 906, 758 cm⁻¹.

6-(2-Methyl-2H-isodindol-1-yl)-6H-dibenzo[c,e]1,2]oxaphosphine 6-Oxide (2b)

Yield: 124 mg (94%); pale yellow solid; mp 72.2–74.5°C.

IR (KBr): 3410, 3123, 3053, 2960, 2874, 1968, 1479, 1328, 1230, 1121, 835, 755 cm⁻¹.

IR (KBr): 3409, 3060, 3032, 2955, 1582, 1509, 1477, 1327, 1224, 1119, 899, 862, 789, 755 cm⁻¹.

HRMS (ESI): m/z [M + H]+. calcd for C21H16NO3P: 368.0816; found: 368.0809.

6-(2-Propyl-2H-isodindol-1-yl)-6H-dibenzo[c,e]1,2]oxaphosphine 6-Oxide (2c)

Yield: 120 mg (84%); pale yellow solid; mp 192.4–198.8°C.

IR (KBr): 3410, 3123, 3053, 2960, 2874, 1968, 1479, 1328, 1230, 1121, 935, 755 cm⁻¹.

IR (KBr): 3410, 3123, 3053, 2960, 2874, 1968, 1479, 1328, 1230, 1121, 935, 755 cm⁻¹.

HRMS (ESI): m/z [M + Na]+. calcd for C21H17NO3PNa: 368.0816; found: 368.0809.

6-(2-Phenyl-2H-isodindol-1-yl)-6H-dibenzo[c,e]1,2]oxaphosphine 6-Oxide (2d)

Yield: 109 mg (67%); pale brown solid; mp 57.2–60.0°C.

IR (KBr): 3409, 3060, 2956, 2869, 1931, 1821, 1304, 1214, 1120, 906, 758 cm⁻¹.

6-(2-Heptyl-2H-isodindol-1-yl)-6H-dibenzo[1,2]oxaphosphinine 6-Oxide (2h)

Yield: 141 mg (91%); colorless column (AcOEt): mp 175.2–177.0 °C.

IR (KBr): 3051, 2961, 2944, 2860, 1661, 1926, 1810, 1702, 1448, 1316, 1231, 932, 755 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ = 8.11–8.05 (m, 2H), 7.69–7.60 (m, 4H), 7.57–7.51 (m, 1H), 7.42–7.27 (m, 4H), 7.06–6.95 (m, 2H), 4.66–4.59 (m, 1H), 2.28–2.22 (m, 1H), 1.84–1.58 (m, 6H), 1.21–0.96 (m, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ = 149.2 (d, J_C,P = 6.2 Hz), 133.5 (d, J_C,P = 18.1 Hz), 132.7 (d, J_C,P = 2.5 Hz), 131.0 (d, J_C,P = 12.7 Hz), 130.4, 128.2 (d, J_C,P = 14.5 Hz), 127.4 (d, J_C,P = 136.5 Hz), 125.0 (d, J_C,P = 13.6 Hz), 124.9, 124.4, 124.3, 123.4, 123.0 (d, J_C,P = 10.0 Hz), 121.6 (d, J_C,P = 11.6 Hz), 121.61, 121.0 (d, J_C,P = 6.2 Hz), 121.0, 120.0, 118.4 (d, J_C,P = 8.9 Hz), 105.3 (d, J_C,P = 190.6 Hz), 58.3, 35.7, 35.1, 25.8, 25.3.


6-(2-Cyclohex-2-enyl-2H-isodindol-1-yl)-6H-dibenzo[1,2]oxaphosphinine 6-Oxide (2i)

Yield: 118 mg (85%); white solid; mp 142.8–143.1 °C.

IR (KBr): 3550, 3414, 3112, 3062, 2980, 1637, 1618, 1432, 1237, 906, 758 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ = 8.10–8.04 (m, 2H), 7.69–7.61 (m, 3H), 7.54–7.48 (m, 1H), 7.43–7.33 (m, 3H), 7.32–7.27 (m, 2H), 7.04–6.97 (m, 2H), 5.36 (sept, J = 6.6 Hz, 1H), 1.61 (d, J = 6.6 Hz, 3H), 1.44 (d, J = 6.7 Hz, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ = 149.1 (d, J_C,P = 8.2 Hz), 135.1 (d, J_C,P = 18.1 Hz), 132.7 (d, J_C,P = 2.5 Hz), 130.8 (d, J_C,P = 12.7 Hz), 130.4, 128.3 (d, J_C,P = 14.6 Hz), 127.3 (d, J_C,P = 137.5 Hz), 124.9, 124.7 (d, J_C,P = 12.7 Hz), 124.5, 124.3, 123.5 (d, J_C,P = 10.0 Hz), 122.2 (d, J_C,P = 8.9 Hz), 121.9 (d, J_C,P = 11.8 Hz), 121.7, 120.9 (d, J_C,P = 6.2 Hz), 120.1, 119.7, 105.1 (d, J_C,P = 189.9 Hz), 509, 325, 31.7, 28.8, 26.7, 22.5, 14.0.


6-(2-Isopropyl-2H-isodindol-1-yl)-6H-dibenzo[1,2]oxaphosphinine 6-Oxide (2f)

Yield: 142 mg (96%); white solid: mp 81.2–83.3 °C.

IR (KBr): 3158, 2983, 2231, 1500, 1474, 1402, 1228, 1195, 1117, 891, 757 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ = 8.09–8.05 (m, 2H), 7.84 (d, J = 5.0 Hz, 1H), 7.63–7.58 (m, 5H), 7.43–7.22 (m, 5H), 6.94–6.90 (m, 1H), 6.83–6.77 (m, 2H), 2.09 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz): δ = 149.2 (d, J_C,P = 8.0 Hz), 135.7 (d, J_C,P = 17.2 Hz), 135.0 (d, J_C,P = 5.6 Hz), 135.2, 129.8 (d, J_C,P = 12.7 Hz), 129.0 (d, J_C,P = 141.0 Hz), 128.1 (d, J_C,P = 14.3 Hz), 125.0, 124.5, 124.3, 123.5 (d, J_C,P = 10.0 Hz), 121.2 (d, J_C,P = 12.7 Hz), 122.3 (d, J_C,P = 11.9 Hz), 121.1, 121.07 (d, J_C,P = 6.6 Hz), 121.0 (d, J_C,P = 6.2 Hz), 120.6, 119.3, 104.7 (d, J_C,P = 181.5 Hz), 61.1, 31.8.


6-(2-[tert-Butyl]-2H-isodindol-1-yl)-6H-dibenzo[1,2]oxaphosphinine 6-Oxide (2j)

Yield: 121 mg (81%); white solid; mp 92.5–94.0 °C.

IR (KBr): 3394, 2977, 2879, 1581, 1475, 1401, 1244, 1118, 900, 758 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ = 8.09–8.05 (m, 2H), 7.80 (d, J = 5.0 Hz, 1H), 7.63–7.58 (m, 2H), 7.43–7.22 (m, 5H), 6.94–6.90 (m, 1H), 6.83–6.77 (m, 2H), 2.09 (s, 9H).

¹³C NMR (CDCl₃, 125 MHz): δ = 149.2 (d, J_C,P = 7.9 Hz), 135.8 (d, J_C,P = 17.4 Hz), 135.0 (d, J_C,P = 5.5 Hz), 132.1 (d, J_C,P = 2.6 Hz), 130.2, 129.9 (d, J_C,P = 12.7 Hz), 129.0 (d, J_C,P = 140.9 Hz), 128.1 (d, J_C,P = 15.2 Hz), 125.0, 124.5, 124.3, 123.5 (d, J_C,P = 10.1 Hz), 121.3 (d, J_C,P = 12.8 Hz), 122.3 (d, J_C,P = 12.2 Hz), 122.0 (d, J_C,P = 9.3 Hz), 121.12 (d, J_C,P = 6.0 Hz), 121.07, 120.6, 119.4, 104.6 (d, J_C,P = 186.3 Hz), 64.2, 34.6, 29.7, 29.5, 8.6.

6-{[2-(4,4-Trinmethylocta-2-yl)-2H-isooindol-1-yl]-6H-dibenzof[cd]1,2]oxaphosphinone 6-Oxide (2k)

Yield: 100 mg (63%); white solid; mp 90.0–92.3 °C.

IR (KBr): 3409, 2952, 2901, 1908, 1581, 1475, 1401, 1220, 1118, 895, 757 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ = 8.10–8.05 (m, 2H), 7.86 (d, J = 5.0 Hz, 1H), 7.64–7.59 (m, 2H), 7.42–7.35 (m, 2H), 7.32–7.24 (m, 3H), 6.94–6.90 (m, 1H), 6.81–6.71 (m, 2H), 3.04 (brd, 1H), 2.32 (d, J = 15.4 Hz, 1H), 2.13 (s, 3H), 2.06 (s, 3H), 0.91 (s, 9H).


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References


Supporting Information

for

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$^1$H and $^{13}$C NMR spectra