SYNTHESIS OF NOVEL NAPHTHOQUINONE FUSED CYCLIC α-AMINOPHOSPHONATES

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Abstract – The synthesis of a novel quinone fused phosphorus heterocycle, 2-phenoxy-3,4-dihydro-2H-naphtho[2,3-e][1,4,2]oxazaphosphinane-5,10-dione-2-oxides (3a-g), is described for the first time. The products can be obtained easily by one-pot of three-component condensation reaction.

INTRODUCTION

Heterocyclic quinone compounds represent an important class of biologically active molecules. Many quinone analogues containing different heteroatom substituents exhibit the activities through different action and sometimes improve the activities. As a consequence, the molecular framework of a great number of pharmaceuticals and biologically heterocyclic compounds contains a quinone moiety. Nowadays, many heterocyclic quinones containing nitrogen, sulfur or selenium atom have been synthesized, and antitumor activities of these derivatives have been thoroughly studied. However, reports in the literature of the synthesis of quinones condensed with phosphorus heterocycles are rare. On the other hand, N-substituted α-aminoalkane phosphonate derivatives represent a class of compounds that tend to exhibit superior biological activities, including antibacterial, herbicidal, antitumor, and inhibitory activity to enzymes. For several years, we have been investigating the preparation and biological activities of cyclic α-aminophosphonates. As part of our ongoing program aimed at searching for antitumor drugs, we report an easy and versatile method toward the synthesis of some novel cyclic α-aminophosphonates condensed with the naphthoquinone pharmacophore.

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Scheme 1. Synthesis of phosphorus heterocycles (3a-g). Reagents and conditions: (a) NaNO₂, HCl, CH₃OH/H₂O (2/3), 80 °C, 3 h; (b) Na₂S₂O₄, CH₃CH₂OH/H₂O (1/15), rt, 30 min, 78% for two steps; (c) C₆H₅OPCl₂, R₁(CO)R₂, THF, 0 °C to rt, 12h.

RESULTS AND DISCUSSION

The one pot three-component condensation reaction of trivalent phosphorus species, amides, and aldehydes or ketones has been proved facile for the preparation of new phosphorus heterocyclic compounds.⁶⁻⁸ As shown in Scheme 1, the starting material 2-amino-3-hydroxy-1,4-naphthoquinone 2 has been prepared by literature method.⁹ When it was allowed to react with phenyl phosphorodichloridite and ketones or aromatic aldehydes, the target compounds (3a-g) were obtained in 55-82% yields (Table 1). In the case of 3b, we isolated the mixture of two isomers (Figure 1: cis-3b and trans-3b) based on the ³¹P NMR and ¹H NMR (cis/trans 5/2). Unfortunately, they could not be separated by column chromatography. In the cases of 3c-e, the ³¹P NMR of crude product shows single peak. We consider that the cis-isomers are generated preferably because of steric hindrance effects and other trans-isomers have not been formed. The results are similar to our previous reports.⁶,⁷

Table 1. Substituents and yields of phosphorus heterocycles (3a-g)

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>mp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Me</td>
<td>Me</td>
<td>213-215</td>
<td>82</td>
</tr>
<tr>
<td>3b</td>
<td>Me</td>
<td>Et</td>
<td>221-228</td>
<td>75</td>
</tr>
<tr>
<td>3c</td>
<td>Ph</td>
<td>H</td>
<td>229-231</td>
<td>63</td>
</tr>
<tr>
<td>3d</td>
<td>2-NO₂C₆H₄</td>
<td>H</td>
<td>245-247</td>
<td>60</td>
</tr>
<tr>
<td>3e</td>
<td>4-OMeC₆H₄</td>
<td>H</td>
<td>223-225</td>
<td>55</td>
</tr>
<tr>
<td>3f</td>
<td>(CH₂)₄</td>
<td></td>
<td>209-211</td>
<td>67</td>
</tr>
<tr>
<td>3g</td>
<td>(CH₂)₅</td>
<td></td>
<td>205-207</td>
<td>65</td>
</tr>
</tbody>
</table>

a Yield of isomeric mixture.
A possible mechanism for this ring closure reaction is presented in Scheme 2. Reaction of 2-amino-3-hydroxy-1,4-naphthoquinone with phenyl phosphorodichloridite and ketones or aromatic aldehydes would lead to two intermediates (4) and (5), which could undergo ring closure to provide products via the Mannich-type cyclization. The structures of 3a-g were confirmed by $^1$H NMR, $^{31}$P NMR, MS and microanalysis. Compound (3g) was recrystallized from ether and hexane (2:1). An orange single crystal with approximate dimensions of 0.24 mm × 0.20 mm × 0.18 mm was selected for X-Ray crystallographic analysis. The crystal structure of 3g was shown in Figure 2.

In summary, we have synthesized, for the first time, naphthoquinone fused phosphorus heterocycle 2-phenoxy-3,3-disubstituents-3,4-dihydro-2H-naphtho[2,3-e][1,4,2]oxazaphosphinane-5,10-dione-2-oxide. The simple and convenient method could provide valuable routes to various phosphorus heterocycles and enrich the organic and medicinal chemistry of quinones. Future development of exploring antitumor activities of these compounds is in progress.
EXPERIMENTAL

All melting points were determined on a Yanaco apparatus and are uncorrected. NMR spectra were measured on a Bruker AVANCE 300 NMR instrument in CDCl₃ and chemical shifts are expressed as δ. Coupling constants J are given in Hz. Tetramethysilane was used as an internal standard for ¹H NMR, and 85% H₃PO₄ as an external standard for ³¹P NMR spectroscopy. MS were recorded on a Polaris-Q instrument of Thermofinnigan. Elemental analysis was carried out on a Yanaco CHNCORDER MT-3 Analyzer. X-Ray analysis was done on a Bruker SMART 1000 CCD diffractometer with MoKα radiation (λ = 0.71073 Å). Column chromatography was performed using silica gel H (10-40 μm, haiyang chemical Factory of Qingdao). The solvent was dried with sodium and redistilled. Phenyl phosphorodichloridite was synthesized according to the document.¹¹

GENERAL PROCEDURE

2-Amino-3-hydroxy-1,4-naphthoquinone (0.5 g, 2.6 mmol) and phenyl phosphorodichloridite (0.5 g, 2.6 mmol) were dissolved in anhydrous THF (30 mL) with stirring at 0 °C. After 15 minutes, the ketone or aromatic aldehyde (2.6 mmol) was added. The reaction mixture was allowed to warm to rt and was continuously stirred for 12 h. The resulting mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel and eluted with EtOAc/petroleum ether (b.p.: 60–90 °C, 1:1) to afford the analytically pure products.

3,3-Dimethyl-2-phenoxy-3,4-dihydro-2H-naphtho[2,3-e][1,4,2]oxazaphosphinane-5,10-dione 2-oxide (3a)
\[ ^1\text{H NMR} \delta 1.61 (d, J_{PCCH} = 16.4 \text{ Hz}, 3 \text{ H, CH}_3), 1.76 (d, J_{PCCH} = 12.6 \text{ Hz}, 3 \text{ H, CH}_3), 5.41-5.48 (\text{br}, 1 \text{ H, NH}), 7.17-7.35 (m, 5 \text{ H, OPh}), 7.66-8.14 (m, 4 \text{ H, C}_6\text{H}_4); ^{31}\text{P NMR} \delta 8.67; \text{Anal. Calcd for C}_{19}\text{H}_{16}\text{NO}_5\text{P}: \text{C}, 61.79; \text{H}, 4.37; \text{N}, 3.79. \text{Found: C}, 61.55; \text{H}, 4.11; \text{N}, 3.79. \text{MS: } m/z \text{ 369.08 (M\textsuperscript{+}).}
\]

3-Ethyl-3-methyl-2-phenoxy-3,4-dihydro-2\textsuperscript{H}-naphtho[2,3-e][1,4,2]oxazaphosphinine-5,10-dione 2-oxide (3b)

\[ ^1\text{H NMR} \delta \text{cis-3b} 1.23 (t, J = 8.29 \text{ Hz}, 3 \text{ H, CH}_2\text{CH}_3), 1.61 (d, J_{PCCH} = 16.9 \text{ Hz}, 3 \text{ H, CH}_3), 1.94-2.26 (m, 2 \text{ H, CH}_2), 5.43-5.51 (\text{br}, 1 \text{ H, NH}), 7.17-7.32 (m, 5 \text{ H, OPh}), 7.65-8.14 (m, 4 \text{ H, C}_6\text{H}_4); \text{trans-3b} 1.07 (t, J = 6.78 \text{ Hz}, 3 \text{ H, CH}_2\text{CH}_3), 1.71 (d, J_{PCCH} = 15.6 \text{ Hz}, 3 \text{ H, CH}_3), 1.94-2.26 (m, 2 \text{ H, CH}_2), 5.43-5.51 (\text{br}, 1 \text{ H, NH}), 7.17-7.32 (m, 5 \text{ H, OPh}), 7.65-8.14 (m, 4 \text{ H, C}_6\text{H}_4); ^{31}\text{P NMR} \delta \text{cis-3b} 8.37; \text{trans-3b} 8.50; \text{Anal. Calcd for C}_{20}\text{H}_{18}\text{NO}_5\text{P}: \text{C}, 62.66; \text{H}, 4.73; \text{N}, 3.65. \text{Found: C}, 62.55; \text{H}, 4.91; \text{N}, 3.64. \text{MS: } m/z \text{ 383.09 (M\textsuperscript{+}).}
\]

2-Phenoxy-3-phenyl-3,4-dihydro-2\textsuperscript{H}-naphtho[2,3-e][1,4,2]oxazaphosphinine-5,10-dione 2-oxide (3c)

\[ ^1\text{H NMR} \delta 5.09 (d, J_{PH} = 14.1 \text{ Hz}, 1 \text{ H, CH}), 5.96-6.05 (\text{br}, 1 \text{ H, NH}), 7.19-7.42 (m, 10 \text{ H, OPh, Ph}), 7.69-8.18 (m, 4 \text{ H, C}_6\text{H}_4); ^{31}\text{P NMR} \delta 0.71; \text{Anal. Calcd for C}_{23}\text{H}_{16}\text{NO}_5\text{P}: \text{C}, 66.19; \text{H}, 3.86; \text{N}, 3.36. \text{Found: C}, 66.55; \text{H}, 3.91; \text{N}, 3.60. \text{MS: } m/z \text{ 417.08 (M\textsuperscript{+}).}
\]

3-(2-Nitrophenyl)-2-phenoxy-3,4-dihydro-2\textsuperscript{H}-naphtho[2,3-e][1,4,2]oxazaphosphinine-5,10-dione 2-oxide (3d)

\[ ^1\text{H NMR} \delta 4.12 (d, J_{PH} = 13.9 \text{ Hz} 1 \text{ H, CH}), 6.28-6.41 (\text{br}, 1 \text{ H, NH}), 7.21-7.31 (m, 9 \text{ H, OPh, 2-NO}_2\text{C}_6\text{H}_4), 7.52-8.17 (m, 4 \text{ H, C}_6\text{H}_4); ^{31}\text{P NMR} \delta 0.71; \text{Anal. Calcd for C}_{23}\text{H}_{15}\text{N}_2\text{O}_7\text{P}: \text{C}, 59.75; \text{H}, 3.27; \text{N}, 6.06. \text{Found: C}, 59.85; \text{H}, 3.54; \text{N}, 5.98. \text{MS: } m/z \text{ 462.06 (M\textsuperscript{+}).}
\]

3-(4-Methoxyphenyl)-2-phenoxy-3,4-dihydro-2\textsuperscript{H}-naphtho[2,3-e][1,4,2]oxazaphosphinine-5,10-dione 2-oxide (3e)

\[ ^1\text{H NMR} \delta 3.87 (s, 3 \text{ H, OCH}_3) 4.78 (d, J_{PH} = 14.2 \text{ Hz} 1 \text{ H, CH}), 6.32-6.51 (\text{br}, 1 \text{ H, NH}), 7.23-7.38 (m, 9 \text{ H, OPh, 4-MeOC}_6\text{H}_4), 7.71-8.19 (m, 4 \text{ H, C}_6\text{H}_4); ^{31}\text{P NMR} \delta 5.65; \text{Anal. Calcd for C}_{24}\text{H}_{18}\text{NO}_6\text{P}: \text{C}, 64.43; \text{H}, 4.06; \text{N}, 3.13. \text{Found: C}, 64.51; \text{H}, 4.12; \text{N}, 3.51. \text{MS: } m/z \text{ 447.09 (M\textsuperscript{+}).}
\]

2-Phenoxy-4\textsuperscript{H}-spiro{naphtho[2,3-e][1,4,2]oxazaphosphinine-5,10-dione,1'-cyclopentane} 2-oxide (3f)

\[ ^1\text{H NMR} \delta 1.61-2.65 (m, 8 \text{ H, (CH}_2)_4), 5.53-5.61 (\text{br}, 1 \text{ H, NH}), 7.17-7.31 (m, 5 \text{ H, OPh}), 7.66-8.14 (m, 4 \text{ H, C}_6\text{H}_4); ^{31}\text{P NMR} \delta 8.52; \text{Anal. Calcd for C}_{21}\text{H}_{18}\text{NO}_5\text{P}: \text{C}, 63.80; \text{H}, 4.59; \text{N}, 3.54. \text{Found: C}, 63.51; \text{H}, 4.63; \text{N}, 3.49. \text{MS: } m/z \text{ 395.09 (M\textsuperscript{+}).}
\]

2-Phenoxy-4\textsuperscript{H}-spiro{naphtho[2,3-e][1,4,2]oxazaphosphinine-5,10-dione,1'-cyclohexane} 2-oxide (3g)
$^1$H NMR $\delta$ 1.49-2.29 (m, 10 H, (CH$_2$)$_5$), 5.74-5.81 (br, 1 H, NH), 7.18-7.31 (m, 5 H, OPh), 7.65-8.14 (m, 4 H, C$_6$H$_4$); $^{31}$P NMR $\delta$ 7.56; Anal. Calcd for C$_{22}$H$_{20}$NO$_5$P: C, 64.55; H, 4.92; N, 3.42. Found: C, 64.55; H, 5.01; N, 3.39. MS: m/z 409.11 (M$^+$).

REFERENCES (AND NOTES)
10. Crystallographic data were deposited at Cambridge Crystallographic data Center, 12 Union Road, Cambridge CB2 1EZ, UK and are available free from there under the deposition number CCDC 299562.