Heteroatom Chemistry
Volume 18, Number 4, 2007

A Simple and Convenient Procedure for the Synthesis of Naphthoquinone Fused Cyclic α-Aminophosphoryl Chloride

Bin Wang, Zhiwei Miao, and Ruyu Chen

State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

Received 10 March 2006; revised 29 May 2006

ABSTRACT: *The synthesis of a novel quinone fused phosphorus heterocycle, 2-chloro-3,3-disubstituents-3,4-dihydro-2H-naphtho[2,3-e][1,4,2]-oxazaphosphinane-5,10-dione 2-oxide (**3a–g**), was described for the first time. These compounds, which have a readily leaving group Cl, can serve as intermediates of many quinone fused phosphorus heterocycles. The structures of **3a–g** were characterized by using common spectroscopic methods. According to the X-ray structure of **3a**, these compounds may be used as DNA-intercalators.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:359–362, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20306

INTRODUCTION

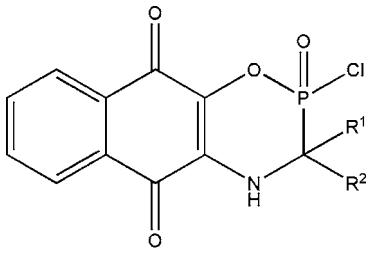
The quinone structure is common in numerous natural products that are associated with antitumor, antibacterial, antimalarial, and antifungal activities [1]. A variety of heterocyclic quinones with different heteroatom substituents could exhibit the activities through different action and sometimes improve the activities [2–5].

On the other hand, organophosphorus compounds continue to receive widespread attention due to their ubiquity in biological systems [6,7] and their potential to serve as novel pharmaceuticals [8–13]. α-Aminophonic acids and their derivatives have often exhibited biochemical activity similar to that of naturally occurring carboxylic acids and their derivatives [14–16]. In the literature, many heterocyclic quinones with nitrogen, sulfur, or selenium atom have been synthesized, and antitumor activities of these derivatives have been thoroughly studied [17–20]. However, only a few examples of quinone condensed with phosphorus heterocycles have been reported [21,22].

Recently, combination chemotherapy has been adopted to combat cancer. By introducing two groups with different mechanisms of action into one molecular, the new structure obtained containing two functional groups would also be beneficial in the treatment of cancer. As a part of our ongoing efforts for the preparation of biologically active phosphorus heterocycles [23,24], we decided to explore the synthesis of some novel cyclic α-aminophonate, α-aminophonic acid, and α-aminophonic amide condensed with the naphthoquinone pharmacophore. In the course of synthesis of target compounds mentioned above, we found that the structure **A** with different substituents at 3-position, 2-chloro-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,4,2]oxazaphosphinane-5,10-dione 2-oxide, is a key precursor of many compounds (Fig. 1).

For molecular **A**, Cl serves as a leaving group and facilitates the attacking of a variety of nucleophilic reagents, thus effectively forming various

Correspondence to: Ruyu Chen; e-mail: binwang@mail.nankai.edu.cn.



R^1, R^2 = Alkyl, Ph, H

A

FIGURE 1 Naphthoquinone condensed with phosphorus heterocycle.

substituted phosphorylated heterocycles. On this basis, we now report an easy and versatile method toward the synthesis of these important intermediates.

RESULTS AND DISCUSSION

The 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 [25,26]. As shown in Scheme 1, the starting material 2-amino-3-hydroxy-1,4-naphthoquinone **2** has been prepared by the literature method [27]. When it was allowed to react with phosphorus trichloride and ketones or aromatic aldehydes, the target compounds **3a–g** were obtained in 45–67% yields from compound **2** (Table 1). In the case of **3b**, we isolated two isomers (*cis*-**3b** and *trans*-**3b**, ratio 1:1) by further column chromatography. In the cases of **3c, 3d**, and **3e**, only one isomer was isolated.

Compared with other reported phosphorus agents in this type of ring-closing reaction, such as $PhPCl_2$ [26], $ROPCl_2$ [24], $(RO)_2PCl$ [28], and H_2PO_2Me [29], PCl_3 is common and commercially available. Moreover, the products obtained can be readily derived. The structures of **3a–g** were confirmed by ^1H NMR, ^{31}P NMR, MS and microanalysis (Tables 2 and 3).

TABLE 1 Substituents and Yields of Phosphorus Heterocycles **3a–g**

Product	*R^1*	*R^2*	*Yield[a] (%)*
3a	Me	Me	67
3b	Me	Et	55[b]
3c	Ph	H	58
3d	2-$NO_2C_6H_4$	H	63
3e	4-$OMeC_6H_4$	H	45
3f	$(CH_2)_4$		62
3g	$(CH_2)_5$		60

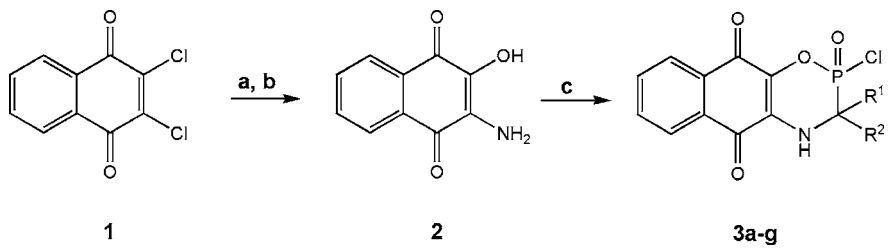
[a]Yield from 2-amino-3-hydroxy-1,4-naphthoquinone **2**.
[b]Total yield of geometric isomers.

Compound **3a** was recrystallized from ether and hexane (2:1). An orange single crystal with approximate dimensions of 0.26 mm × 0.14 mm × 0.12 mm was selected for X-ray crystallographic analysis [30].

The cytotoxic mechanism of the quinone derivatives has been extensively studied, and one possible mechanism of action has been suggested as a DNA topoisomerase inhibitor via DNA-intercalation, or reducing quinone moiety by oxidoreductase [31–35]. According to the protocol reported previously, the DNA-intercalating molecule must have a planar tricyclic or tetracyclic ring with a length of 3–4 Å and a width of 6–8 Å. It must also have a *p*-conjugated quinone containing nitrogen as this enables hydrogen bonding with DNA [36,37].

The X-ray structure of 2-chloro-3,3-dimethyl-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,4,2]oxazaphosphinane-5,10-dione 2-oxide **3a** shown in Fig. 2, illustrated that N1 and O3 are almost coplanar with the quinonyl ring, while P1 and C11 are at the opposite side. The dihedral angle of naqthoquinonyl ring and six-member phosphorus heterocycle was 8.4°. The distances between each atom of right-side phosphorus heterocycle and the plane of naqthoquinone were shown in Table 4.

It can be found that the three rings are approximately coplanar. On the other hand, the distance of



1 **2** **3a-g**

SCHEME 1 Synthesis of phosphorus heterocycles (**3a–g**). Reagents and conditions. (a) $NaNO_2$, HCl, CH_3OH/H_2O (2/3), 80°C, 3 h; (b) $Na_2S_2O_4$, CH_3CH_2OH/H_2O (1/15) room temperature, 30 min, 78% for two steps; (c) PCl_3, $R^1(CO)R^2$, THF, 0°C to room temperature,12 h.

TABLE 2 The Synthesis of Naphthoquinone Fused Cyclic α-Aminophosphoryl Chloride 3

Product	*mp (°C)*	*^{31}P NMR ($CDCl_3$/H_3PO_4)*	*MS (M^+)*	*Found/Calcd*		
				C (%)	*H (%)*	*N (%)*
3a	211–213	26.0	311	49.97/50.10	3.56/3.56	4.28/4.49
3b	232–234[a]	25.6/26.2	325	52.00/51.63	4.12/4.02	4.30/4.30
3c	196–198	7.03	359	56.45/56.76	3.08/3.08	3.85/3.89
3d	245–247	6.23	404	50.37/50.45	2.45/2.49	6.91/6.92
3e	213–215	8.01	389	55.51/55.47	3.42/3.36	3.45/3.59
3f	195–197	24.0	337	53.21/53.35	3.78/3.88	4.12/4.15
3g	201–203	26.1	351	54.64/54.64	4.23/4.30	4.11/3.98

[a]Two isomers show no difference in melt point.

P1 and C8, P1 and C9, C11 and C8, and C11 and C9, is 7.489 Å, 7.632 Å, 7.523 Å, and 7.368 Å, respectively. These results are consistent with the conditions prescribed for intercalator species. Above characters of novel qunione–phosphorus heterocycles will be useful in the study of structure–activity relationship.

In conclusion, we have synthesized, for the first time, naphthoquinone fused phosphorus heterocycles 2-chloro-3,3-disubstituents-3,4-dihydro-2*H*-naphtho[2,3-*e*][1,4,2]oxazaphosphinane-5,10-dione 2-oxides by three-component condensation reaction. The method could provide valuable routes to various phosphorus heterocycles and enrich the organic and medicinal chemistry of quinones. Future developments include preparation of various substituted phosphorylated quinonyl heterocycles and exploring their activities. Results will be reported in due course.

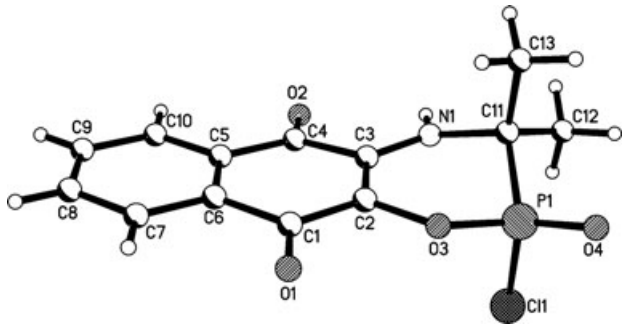


FIGURE 2 Single crystal structure of **3a**.

TABLE 3 ^{1}H NMR Data of the Synthesized Phosphorus Heterocycles **3a–g**

Product	*^{1}H NMR ($CDCl_3$/TMS), δ, J (Hz)*
3a	1.67 (d, $^3J_{PCCH} = 17.3$ Hz, 3H, CH_3), 1.78 (d, $^3J_{PCCH} = 20.5$ Hz, 3H, CH_3), 5.45–5.53 (br, 1H, NH), 7.70–8.19 (m, 4H, C_6H_4)
3b	*cis*:1.14 (t, $J = 7.04$ Hz, 3H, CH_2CH_3), 1.57 (d, $^3J_{PCCH} = 15.6$ Hz, 3H, CH_3), 1.65–1.98 (m, 2H, CH_2CH_3), 5.21–5.43 (br, 1H, NH), 7.70–8.19 (m, 4H, C_6H_4) *trans*: 1.23 (t, $J = 7.04$ Hz, 3H, CH_2CH_3), 1.61 (d, $^3J_{PCCH} = 15.6$ Hz, 3H, CH_3), 2.01–2.23 (m, 2H, CH_2CH_3), 5.21–5.43 (br, 1H, NH), 7.70–8.19 (m, 4H, C_6H_4)
3c	4.88 (d, $^2J_{PH} = 17.5$ Hz, 1H, CH), 5.85–5.93 (br, 1H, NH), 7.40–7.50 (m, 5H, C_6H_5), 7.66–8.12 (m, 4H, C_6H_4)
3d	4.11 (d, $^2J_{PH} = 15.8$ Hz, 1H, CH), 5.65–5.73 (br, 1H, NH), 7.23–7.35 (m, 4H, C_6H_4), 7.55–8.17 (m, 4H, C_6H_4)
3e	3.91 (s, 3H, OCH_3), 5.84–5.89 (br, 1H, NH), 7.27–7.35 (m, 4H, C_6H_4), 7.55–8.20 (m, 4H, C_6H_4)
3f	1.60–2.67 (m, 8H, $(CH_2)_4$), 5.48–5.57 (br, 1H, NH), 7.70–8.18 (m, 4H, C_6H_4)
3g	1.58–2.62 (m, 10H, $(CH_2)_5$), 5.52–5.60 (br, 1H, NH), 7.70–8.19 (m, 4H, C_6H_4)

EXPERIMENTAL

Instruments and Reagents

All melting points were determined on a Yanaco apparatus and are uncorrected. NMR spectra were measured on a Bruker AVANCE 300 NMR instrument in $CDCl_3$ and chemical shifts are expressed as δ. Coupling constants J are given in Hz. Tetramethylsilane was used as an internal standard for ^{1}H NMR, and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. Mass spectra were recorded on a Polaris-Q instrument of Thermofinnigan. Elemental analysis was carried out on a Yanaco

TABLE 4 Distances of Atoms to the Plane of Naphthoquinonyl Ring[a] (Å)

P1	*C11*	*N1*	*O3*	*C2*	*C3*
0.2531	0.5497	0.1518	0.0232	0.0130	0.0658

[a]Equation of least-squares plane of naphthoquinonyl ring: $6.753x - 6.675y + 3.306z - 1.5771 = 0$.

CHNCORDER MT-3 Analyzer. X-ray analysis was done on a Bruker SMART 1000 CCD diffractometer with MoKα radiation ($\lambda = 0.71073$ 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.

*General Procedure for the Synthesis of 2-Chloro-3,3-disubstituents-3,4-dihydro-2H-naphtho[2,3-e][1,4,2]oxazaphosphinane-5,10-dione 2-oxide (**3a–g**)*

Equivalent of 2-amino-3-hydroxy-1,4-naphthoquinone **2** and phosphorus trichloride were dissolved in anhydrous THF with stirring at 0°C. Fifteen minutes later, ketone or aromatic aldehyde (1 equiv) was added. The reaction mixture was allowed to warm to room temperature and was continuously stirred for 12 h. The resulting mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel, eluting with EtOAc/petroleum ether (bp 60–90°C, 1:1) to afford analytically pure product (for compound **3b**, separating the two isomers by further column chromatography, EtOAc/Hexane 1/5).

ACKNOWLEDGMENTS

This work was supported by Nankai University: J 02044.

REFERENCES

[1] Wakelin, I.; Waring, M. J. In Comprehensive Medicinal Chemistry; Sammes, P. G. (Ed.); Pergamon: Oxford, 1990; Vol. 2, pp. 725–791.
[2] Hayashi, T.; Smith, F. T.; Lee, K. H. J. Med Chem 1987, 30, 2005.
[3] Schellhammer, C. W.; Petersen, S.; Domagk, G. Naturwissenschaften 1959, 46, 81.
[4] Cone, R.; Hasan, S. K.; Lown, J. W.; Morgan, A. R. Can J Biochem 1976, 54, 219.
[5] Yamashita, Y.; Kawada, S.; Fujii, N.; Nakano, H. Cancer Res 1990, 50, 5841.
[6] Westheimer, F. H. Science 1987, 235, 1173.
[7] Seto, H.; Kuzuyama, T. Nat Prod Rep 1999, 16, 589.
[8] Lejczak, B.; Dus, D.; Kafarski, P. Anti-Cancer Drug Des 1990, 5, 351.
[9] Colvin, O. M. Curr Pharm Des 1999, 5, 555.
[10] Boyd, V L.; Zon, G.; Himes, V. L.; Stalick, J. K.; Mighell, A. D.; Secor, H. V. J. Med Chem 1980, 23, 372.
[11] Misiura, K.; Kinas, R. W.; Stec, W. J.; Kusnierczyk, H.; Radzikowski, C.; Sonoda, A. J. Med Chem 1988, 31, 226.
[12] Mader, M. M.; Bartlett, P. A. Chem Rev 1997, 97, 1281.
[13] Kafarski, P.; Lejczak, B. Anticancer Agents Curr Med Chem 2001, 1, 301.
[14] Oleksyszyn, J. In Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity; Kukhar, V. P.; Hudson, H. R. (Eds.); John Wiley & Sons: Chichester, 2000; pp. 537–558.
[15] Peyman, A. In Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity, Kukhar, V. P.; Hudson, H. R. (Eds.); John Wiley & Sons: Chichester, 2000, pp. 559–578.
[16] Markwell, R. In Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity, Kukhar, V. P.; Hudson H. R. (Eds.); John Wiley & Sons: Chichester, 2000, pp. 597–620.
[17] Schulz, W. G.; Skibo, E. B. J. Med Chem 2000, 43, 629.
[18] Gomez-Monterrey, I.; Santelli, G.; Campiglia, P.; Califano, D.; Falasconi, F.; Pisano, C.; Vesci, L.; Lama, T.; Grieco, P.; Novellino, E. J. Med Chem 2005, 48, 1152.
[19] Huang, L. J.; Kuo, S. C.; Perng, C. Y.; Chao, Y. H.; Wu, T. S.; Mcphail, A. T.; Mauger, A.; Cheng, H. H.; Lee, K. H. Bioorg Med Chem Lett 1998, 8, 2763.
[20] Ryu, C. K.; Han, J. Y.; Jung, O. J.; Lee, S. K.; Lee, J. Y.; Jeong, S. H. Bioorg Med Chem Lett 2005, 15, 679.
[21] Boulos, L. S.; Arsanious, M. H. N. Tetrahedron 1997, 53, 3649.
[22] Boulos, L. S. Abd-El-Malek, H. A. Heteroatom Chem 1999, 10, 488.
[23] Wang, B.; Miao, Z. W.; Huang, Y.; Chen, R. Y. Heterocycles 2006, 68, 2123.
[24] Wang, B.; Miao, Z. W.; Huang, Y.; Chen, R. Y. Heteroatom Chem (in press).
[25] Wang, B.; Wang, J.; Miao, Z. W.; Chen, R. Y. Chinese J. Struct. Chem. 2006, 25, 1129.
[26] Chen, R. Y.; Feng, K. S. Phosphorus, Sulfur Silicon Relat Elem 1993, 75, 123.
[27] Podrebarac, E. G.; Cheng, C. C. J Am Chem Soc 1970, 35, 281.
[28] Dimukhametov, M. N.; Bajandina, E. V.; Davydova, E. Y.; Dobrynin, A. B.; Guvaidullin, A. T.; Litvinov, I. A.; Zyablikovoa, T. A.; Alfonsov, V. A. Heteroatom Chem. 2003, 14, 56.
[29] Cristau, H. J.; Monbrun, J.; Tillard, M.; Pirat, J. L. Tetrahedron Lett 2003, 44, 3183.
[30] Crystallographic data was deposited at Cambridge Crystallographic data Center, 12 Union Road, Cambridge CB2 1EZ, UK and is available from there under the deposition number CCDC 290940.
[31] Denny, W. A.; Bagulet, B. C. In Molecular Aspects of Anticancer Drug-DNA Interactions, 2nd ed; Waring, M. J.; Neidle, S. (Eds.); Macmillan: London, 1994; p 270.
[32] Pommier, Y.; Capranico, G.; Orr, A.; Kohn, K. W. Nucleic Acids Rep 1991, 19, 5973.
[33] Fosse, P.; Rene, B.; Le Bret, M.; Paoletti, C.; Saucier, J. M. Nucleic Acids Rep 1991, 19, 2861.
[34] Lin, A. J.; Lillis, B. J.; Sartorelli, A. C. J. Med Chem 1975, 18, 917.
[35] Beall, H. D.; Liu, Y.; Siegel, D.; Bolton, E. M.; Gibson, N. W.; Ross, D. Biochem Pharmacol 1996, 51, 645.
[36] Moore, M. H.; Hunter, W. N.; d'Estaintot, B. L.; Kennard, O. J. Mol Biol 1989, 206, 693.
[37] Pindur, U.; Haber, M.; Sattler, K. J. Chem Educ. 1993, 70, 263.