A New Convenient Synthesis of Phosphoranylideneaminoquinones from Isoxazolequinones

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The reaction of [2,1]benzisoxazole-4,7-quinones **1** and naphth[2,3-*c*]isoxazole-4,9-quinone **4** with phosphines leads to phosphoranylideneaminoquinones **2** and **5**, respectively, in good to excellent yields.

Compounds containing a heterocyclic moiety fused to the quinone system are of considerable interest because of a range of biological activities, as well as for their versatile chemistry.[1]

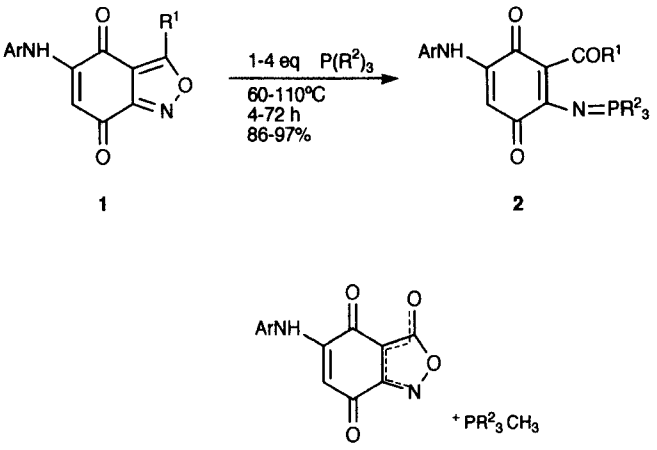
We reported a simple preparation of substituted [2,1]benzisoxazole-4,7-quinones **1** and naphth[2,3-*c*]isoxazole-4,9-quinone **4** starting from readily accessible 2-carboxy-1,4-benzo- and naphthohydroquinones.[2] In the light of recent developments, these products are versatile intermediates for the preparation of sulfoximidoquinones,[3] highly functionalized alkylidenebutenolides[4,5] and *N*-alkylisoxazolequinones,[5] among others.

The cleavage of the N–O bond of the isoxazole ring with various reagents is a well-known reaction.[6] Thus, the addition of triphenylphosphine to benzisoxazole to give (2-acylphenyl)iminotriphenylphosphoranes has been reported.[7] However, few examples of the preparation of phosphoranylideneaminoquinones are described.[8] Iminophosphorane mediated synthesis of heterocyclic ring systems has developed remarkably in recent years[9,10] and the preparation of functionalized iminophosphoranes is therefore an expanding topic.[9,11]

We report herein a convenient method for the synthesis of phosphoranylideneaminobenzo- and naphthoquinones **2** and **5** which consists of the reaction of benzisoxazolequinones **1** and naphthisoxazolequinone **4**, respectively, with phosphines.

The reaction of 5-arylamino-3-methoxy[2,1]benzisoxazole-4,7-quinones **1** with triphenylphosphine and tributylphosphine in dry toluene affords the corresponding phosphoranylideneaminoquinones **2a–d** in almost quantitative yields (Scheme 1).

The lower reactivity of triphenylphosphine made necessary the use of an excess of the reagent. Heating of the reaction mixtures above 60 °C is not advisable because of the thermal instability of isoxazolequinones.[4,5] If the reaction is carried out in more polar solvents such as chloroform, or with high excess of the phosphine, which is linked to an increase of the medium polarity, a mixture of **2** and the corresponding phosphonium salt **3** is also obtained. This side reaction becomes almost quantitative if tributylphosphine and chloroform are used. The formation of **2** suggests a mechanism in which a vinylogous methoxycarbonylnitrene form **B** (Scheme 2) of the isoxazolequinone **A** attacks the unshared electron pair on the phosphorus atom of the corresponding phosphine. In more polar solvents the form **A** becomes important, acting as a methylating agent to give also compounds **3**.



1 **2** **3**

1,2,3	R^1	Ar	R^2
a	OCH_3	C_6H_5	Ph
b	OCH_3	p-BrC_6H_4	Ph
c	OCH_3	C_6H_5	nBu
d	OCH_3	p-BrC_6H_4	nBu
e	CH_3	C_6H_5	Ph

Scheme 1

The polar character of the O–Me bond of **A** (Scheme 2) could be responsible for the efficient migration of the methyl group to yield **3**.[3]

Table 1. Iminophosphoranes **2** and **5**

Product[a]	Reaction Conditions				mp (°C)	Yield (%)[c]
	Temp. (°C)	Phosphine (mmol)	Concentration (10^{-3} M)[b]	Time (h)		
2a	60	4	50	9	255–60	97
2b	60	4	50	8	238	96
2c	60	1	0.3	4	90	89
2d	60	1	0.3	4	125–30	87
2e	110	4	50	60	173–75	93
5a	60	2	1.5	96	122	67
5b	60	1	0.3	8	syrup	89

[a] Satisfactory microanalyses obtained: C ±0.25, H ±0.27, N ±0.17.
[b] Concentration of phosphine in dry toluene.
[c] Yield of pure isolated product.

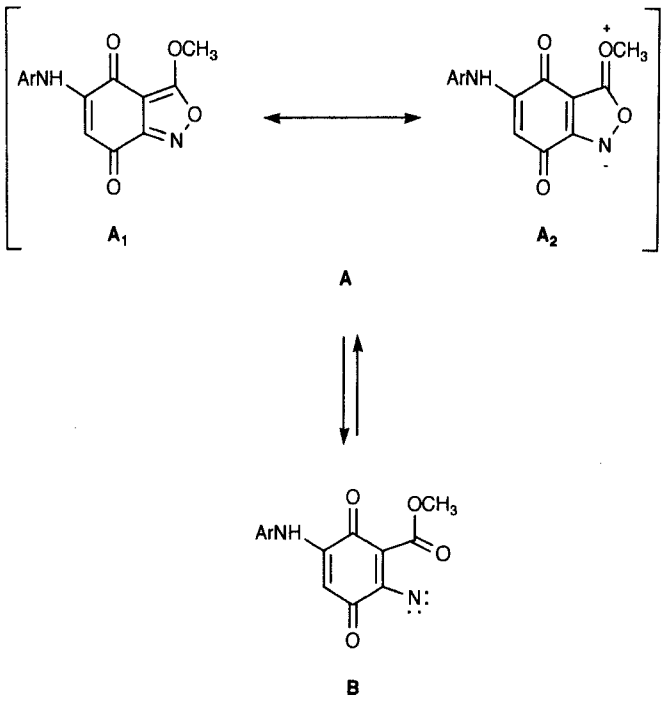
Table 2. Spectral Data of Iminophosphoranes **2** and **5**

Compound	IR ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ	^{13}C NMR ($CDCl_3$) δ, J (Hz)	^{31}P NMR ($CDCl_3$) δ (ppm)	MS-EI m/z (%)
2a	3340, 3090, 1740, 1650, 1600, 1540	8.21 (s, 1H, NH), 7.8–7.1 (m, 20H, arom), 5.81 (s, 1H, CH=), 4.00 (s, 3H, OCH_3)	177.56 (^{P-C}J = 11, C-1), 175.63 (C-4), 167.58 (CO), 158.18 (^{P-C}J = 8.5, C-2), 147.07 (C-5), 137.15 (C-1′), 132.17 (^{P-C2}J = 10.5), 131.51 (^{P-C4}J = 2.9), 129.92 (^{P-C1}J = 105), 129.21 (C-3′), 128.27 (^{P-C3}J = 11), 125.46 (C-4′), 122.54 (C-2′), 113.29 (^{P-C}J = 24, C-3), 94.81 (C-6), 51.71 (OCH_3)	16.65	532 (22, M^+), 262 (100)
2b	3260, 3090, 1740, 1650, 1590, 1520	8.15 (s, 1H, NH), 7.8–7.0 (m, 19H, arom), 5.77 (s, 1H, CH=), 4.00 (s, 3H, OCH_3)	177.74 (^{P-C}J = 8.5, C-1), 175.47 (C-4), 167.47 (CO), 157.95 (^{P-C}J = 8.5, C-2), 146.68 (C-5), 136.48 (C-1′), 132.15 (^{P-C2}J = 8), 132.07 (C-3′), 131.57 (^{P-C4}J = 2.9), 129.74 (^{P-C1}J = 104.5), 128.29 (^{P-C3}J = 13.5), 124.02 (C-4′), 118.24 (C-2′), 113.51 (^{P-C}J = 24, C-3), 95.32 (C-6), 51.71 (OCH_3)	16.79	612, 610 (42, M^+), 262 (100)
2c	3220, 2940, 2860, 1720, 1605, 1570	8.31 (s, 1H, NH), 7.4–7.1 (m, 5H, arom), 5.86 (s, 1H, CH=), 3.83 (s, 3H, OCH_3), 2.1–1.9 (m, 6H, CH_2), 1.8–1.2 (m, 12H, CH_2), 0.95 (t, 9H, CH_3)	179.78 (^{P-C}J = 8.5, C-1), 174.15 (C-4), 167.76 (CO), 159.28 (^{P-C}J = 8.5, C-2), 148.12 (C-5), 137.36 (C-1′), 129.32 (C-3′), 125.59 (C-4′), 122.68 (C-2′), 112.14 (^{P-C}J = 24.5, C-3), 94.66 (C-6), 51.37 (OCH_3), 27.51, 26.08 (^{P-C1}J = 64.5), 24.08, 23.63 (^{P-C2}J = 4), 24.02 (^{P-C3}J = 27.5), 13.49 (CH_3)	36.17	472 (56, M^+), 440 (100)
2d	3300, 3000, 2910, 1735, 1635, 1600	8.29 (s, 1H, NH), 7.5–7.1 (m, 4H, arom), 5.86 (s, 1H, CH=), 3.83 (s, 3H, OCH_3), 2.1–1.9 (m, 6H, CH_2), 1.8–1.2 (m, 12H, CH_2), 0.95 (t, 9H, CH_3)	180.01 (^{P-C}J = 13.5, C-1), 174.00 (C-4), 167.69 (CO), 159.06 (^{P-C}J = 8, C-2), 147.73 (C-5), 136.59 (C-1′), 132.39 (C-3′), 124.14 (C-4′), 118.43 (C-2′), 112.28 (^{P-C}J = 22, C-3), 95.14 (C-6), 51.39 (OCH_3), 27.46, 26.00 (^{P-C1}J = 63.5), 24.09, 23.65 (^{P-C2}J = 4), 24.04 (^{P-C3}J = 27.5), 13.49 (CH_3)	36.36	552, 550 (37, M^+), 76 (100)
2e	3330, 3090, 1750, 1645, 1625, 1520	8.17 (s, 1H, NH), 7.7–7.1 (m, 20H, arom), 5.74 (s, 1H, CH=), 2.57 (s, 3H, CH_3)	201.48 (CO), 177.80 (^{P-C}J = 9, C-1), 176.41 (C-4), 158.52 (^{P-C}J = 8.5, C-2), 147.23 (C-5), 137.25 (C-1′), 132.10, 131.91 (^{P-C2}J = 9.5), 131.50 (^{P-C4}J = 2.9), 130.11 (^{P-C1}J = 104.5), 129.26 (C-3′), 128.35 (^{P-C3}J = 13.5), 125.52 (C-4′), 122.54 (C-2′), 120.20 (^{P-C}J = 24, C-3), 94.92 (C-6), 32.07 (CH_3)	17.84	516 (20, M^+), 262 (100)
5a	3060, 1730, 1670, 1595, 1535, 1500	8.3–7.2 (m, 19H, arom), 4.01 (s, 3H, OCH_3)	181.44 (^{P-C}J = 8, C-1), 180.48 (C-4), 168.13 (CO), 153.61 (^{P-C}J = 13.5, C-2), 136.16, 135.94 (C-4a, C-8a), 134.33 (C-6, C-7), 132.56, 132.07 (^{P-C2}J = 8.5), 132.22, 128.54 (^{P-C3}J = 11.5), 131.86 (^{P-C4}J = 2.8), 130.09 (^{P-C1}J = 104.5), 126.46, 126.07 (C-5, C-8), 121.76 (^{P-C}J = 22.5, C-3), 52.19 (OCH_3)	30.89	491 (36, M^+), 277 (100)
5b	2960, 2930, 2870, 1725, 1675, 1530	8.3–7.2 (m, 4H, arom), 3.87 (s, 3H, OCH_3), 2.1–1.9 (m, 6H, CH_2), 1.8–1.2 (m, 12H, CH_2), 0.95 (t, 9H, CH_3)	183.70 (^{P-C}J = 8.5, C-1), 180.37 (C-4), 168.13 (CO), 153.76 (^{P-C}J = 8.5, C-2), 136.16, 135.81 (C-4a, C-8a), 134.50 (C-6, C-7), 126.57, 126.17 (C-5, C-8), 120.14 (^{P-C}J = 19, C-3), 51.70 (OCH_3), 27.54, 26.26 (^{P-C1}J = 55.5), 24.16 (^{P-C2}J = 13.5), 23.66 (^{P-C3}J = 7.5), 13.50 (CH_3)	32.56	431 (22, M^+), 372 (100)

Table 3. Phosphonium salts **3** and **6**

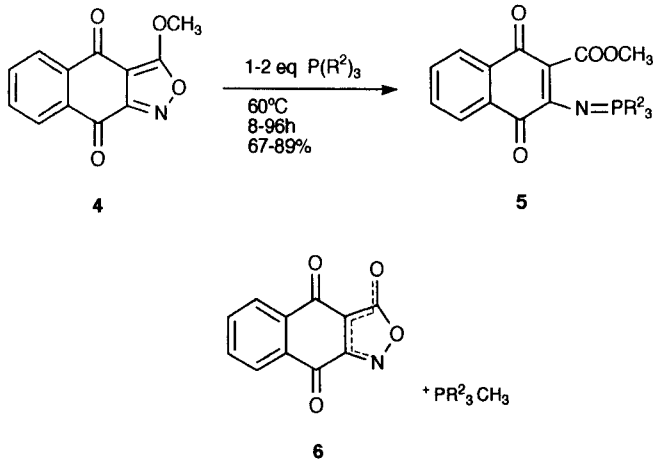
Product	Ratio **2**(**5**) : **3**(**6**)[a]	Yield (%)[b]	mp (°C)	^1H NMR δ, J (Hz)
3a	2 : 1	29	80–81	9.04 (s, 1H, NH), 8.2–7.1 (m, 20H, arom), 5.70 (s, 1H, CH=), 3.13 (d, 3H, ^{H-P}J = 13.4, CH_3)[c]
3b	2 : 1	28	163–164	9.04 (s, 1H, NH), 7.9–7.3 (m, 19H, arom), 5.70 (s, 1H, CH=), 3.13 (d, 3H, ^{H-P}J = 13.4, CH_3)[c]
3c	1 : 15	40	74–76	8.23 (s, 1H, NH), 7.4–7.1 (m, 5H, arom), 6.04 (s, 1H, CH=), 2.4–2.1 (m, 6H, CH_2), 1.94 (d, 3H, ^{H-P}J = 13.4, CH_3), 1.8–1.4 (m, 12H, CH_2), 0.93 (t, 9H, CH_3)[d]
3d	1 : 15	45	104–108	8.22 (s, 1H, NH), 7.5–7.1 (m, 4H, arom), 6.00 (s, 1H, CH=), 2.4–2.2 (m, 6H, CH_2), 1.94 (d, 3H, ^{H-P}J = 13.4, CH_3), 1.8–1.4 (m, 12H, CH_2), 0.93 (t, 9H, CH_3)[d]
6a	1 : 2	30	180–182	8.1–7.2 (m, 19H, arom), 3.1 (d, 3H, ^{H-P}J = 13.4, CH_3)[d]
6b	1 : 4	41	76–78	8.1–7.1 (m, 4H, arom), 2.4–2.2 (m, 6H, CH_2), 1.94 (d, 3H, ^{H-P}J = 13.4, CH_3), 1.8–1.4 (m, 12H, CH_2), 0.93 (t, 9H, CH_3)[d]

[a] Analyzed by ^1H NMR
[b] Yield of pure isolated product
[c] In DMSO-d_6
[d] In $CDCl_3$



Scheme 2

Iminophosphoranequinone **2e** is prepared in the same way from **1e** in quantitative yield. In this case the formation of phosphonium salt is not possible. The lower reactivity of **1e** in comparison with **1a,b** indicates a stronger N–O bond in the former case. This is in good agreement with previous data obtained for both compounds.[5] On the other hand, the higher thermal stability of **1e** allows the heating of the reaction mixture to reduce the reaction times.



5,6	R^2
a	Ph
b	nBu

Scheme 3

The reaction of 3-methoxynaphth[2,3-*c*]isoxazole-4,9-quinone **4** with triphenyl- and tributylphosphine in the same conditions affords the corresponding phosphoranylideneaminoquinones **5** in good yields (Scheme 3). In chloroform the phosphonium salts **6** are also obtained.

Triphenylphosphine derivatives **2a,b,e** and **5a** can be purified by standard column chromatography. However tributylphosphine compounds **2c,d** and **3b** are very sensitive to silica gel and undergo acid-catalyzed cleavage to give 2-amino-5-anilino-3-carbomethoxy-1,4-benzoquinone and 2-amino-3-carbomethoxy-1,4-naphthoquinone, respectively.

In summary, the reactions of aliphatic and aromatic phosphines with isoxazolequinones offers the first general synthetic approach to functionalized phosphoranylideneaminoquinones in excellent yields. The method has considerable advantages compared with the azido route to iminophosphoranequinones,[8] not only for the better yield, but also for the versatility and functionalization possibilities of the starting isoxazolequinones. The syntheses of new heterocyclic quinones from these iminophosphoranes are presently under investigation.

Melting points were determined on a Büchi 504392 (S) apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY spectrometer with TMS as internal standard, and ^{31}P NMR were recorded on a Bruker AMX 300 spectrometer with H_3PO_4 as internal standard. MS spectra were recorded on Hewlett-Packard 5985 and Hitachi Perkin-Elmer RMU-6MG (70 eV, EI mode instruments).

Phosphoranylideneaminoquinones 2 and 5; General Procedure:
A solution of the appropriate isoxazolequinone **1** or **4** (1 mmol) and the corresponding phosphine (1–4 mmol) in dry toluene was stirred at 60–110 °C under an argon atmosphere as indicated in each case (Table 1), and the course of the reaction was followed by TLC. When the reaction was complete (Table 1), the solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel using CH_2Cl_2/acetone as eluent (**2a,b,e** and **5a**) or recrystallized from toluene/hexane (**2c,d** and **5b**). The yields of **2** and **5** varied from 67–97 % (Table 1). Mp and spectra data are given in Tables 1 and 2, respectively.

Phosphonium Salts 3 and 6:
A solution of the appropriate isoxazolequinone **1** or **4** (1 mmol) and the corresponding phosphine (2 mmol) in $CHCl_3$ (100 mL) was stirred at reflux temperature under argon for 4–6 h. The solvent was evaporated under reduced pressure and the residue was analyzed by ^1H NMR spectroscopy showing to be a mixture of **2** and **3**, or **5** and **6**, respectively. The ratio **2(5)**:**3(6)** are given in Table 3. Pure compounds **3** and **6** were obtained by recrystallization of the reaction products from $CHCl_3$/EtOAc. The compounds are very hygroscopic. Mp and ^1H NMR details are given in Table 3.

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