Pergamon

Tetrahedron 54 (1998) 1647–1656

TETRAHEDRON

A Simple Strategy for the Preparation of 4-Aminoquinolines from β-Functionalized Enamines

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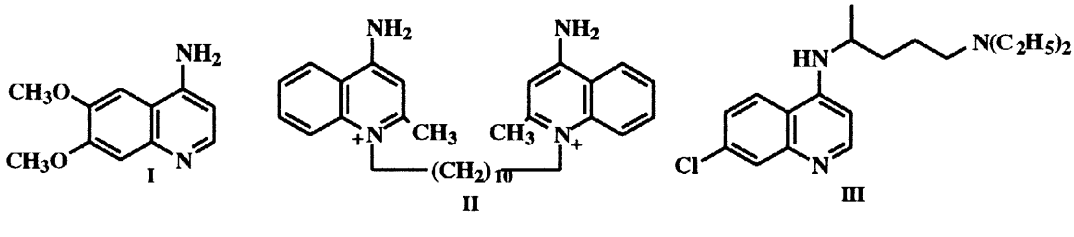
Received 14 October 1997; revised 18 November 1997; accepted 20 November 1997

Abstract: An easy and efficient synthesis of 4-aminoquinolines substituted with a phosphine oxide group in the 3-position **1**, is described. The key step is a heterocyclization of cyano-aryl β-enamino phosphine oxides **4**. The treatment of β-enamines derived from phosphonium salts **7**, with a base afforded phosphazenes **8** and the hydrolysis of these phosphazenes led to the formation of substituted 4-aminoquinolines **9**.

4-Aminoquinoline ring systems represent an important class of compounds[1] which have been shown to have interesting pharmacological properties and so are widely used in medicinal chemistry. Amquisin **I** displays hypotensive activity,[2] while dequalinium analogues **II** are potent and selective K^+ channel blockers[3] and chloroquine **III** is an antimalarial drug, which has remained as a major chemotherapeutic agent for over 40 years[4] (Scheme 1). Likewise, 4-aminoquinolines have been used for the treatment of ulcers and related gastric disorders,[5] as antimalarials,[4] analgesics,[6a] antiinflammatory,[6b] antitumor[6c] and antihypertensive agents,[6d] as non-nucleoside HIV-1 inhibitors and as reversible inhibitors of (H^+/K^+)-ATPase.[5,6f] In this context, we are interested in the design of new aminoquinoline derivatives substituted with a phosphine oxide group. This substituent could regulate important biological functions and could increase the biological activity of these type of compounds, in a similar way to that reported for other pharmaceuticals.[7]

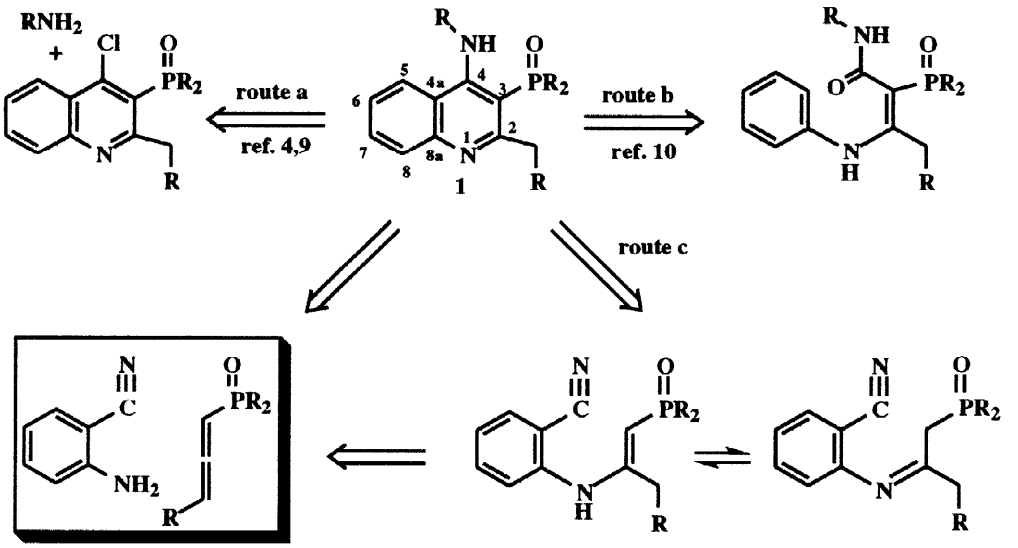


Amquisin **Dequalinium** **Chloroquine**

Scheme 1

0040-4020/98/$19.00
PII: S0040-4020(97)10372-6

While there are many approaches available for quinoline derivatives,[8] synthetic routes to 4-aminoquinolines **1** are relatively few and most of them involve nucleophilic displacement of the chlorine atom of 4-chloroquinoline[1,4,9] (Scheme 2, *route a*). Alternatively, 4-aminoquinolines can be prepared by tandem reactions that involve simultaneous construction of the quinoline ring[1] (carbon-carbon bond formation, C_4-C_{4a}) and introduction of the amino group in the position 4 (Scheme 2, *route b*), as has been recently reported when functionalized β-enamines have been used.[10]



Scheme 2

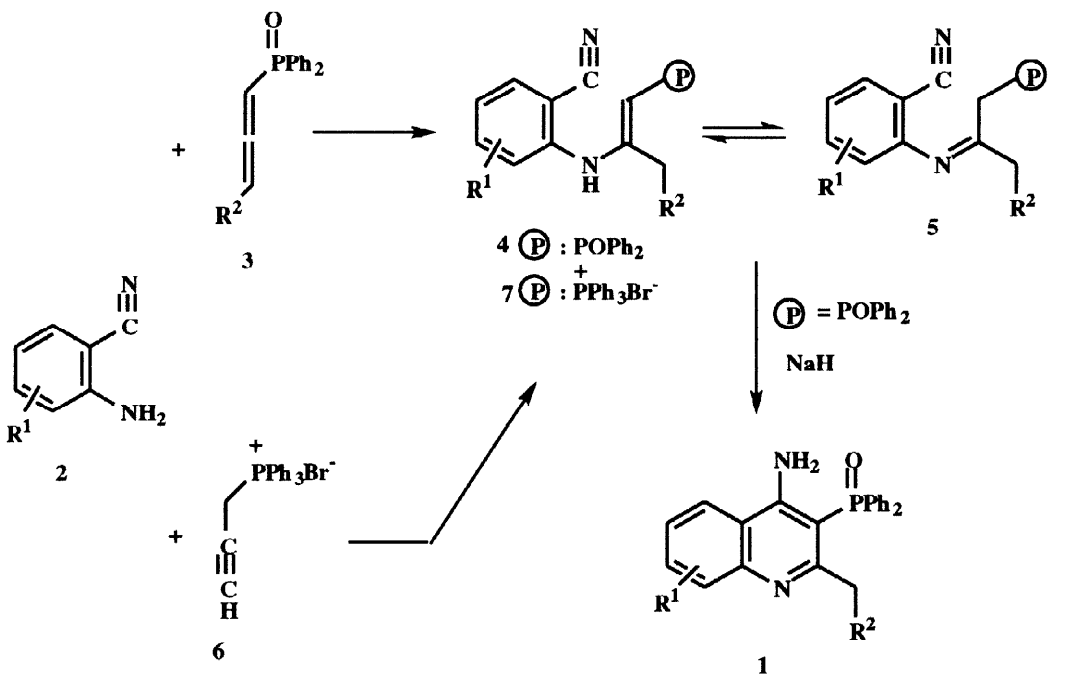
In connection with our interest in the chemistry of phosphazenes[11,12] and phosphorylated enamines we have used these compounds as synthetic intermediates for the preparation of heterocycles.[13] In this context, we have recently described the synthesis of *N*-aryl-4-aminoquinolines[10] from functionalized β-enamines derived from phosphine oxides and phosphonates (Scheme 2, route b). Here we aim to extend the synthetic use of phosphorylated enamines in the preparation of substituted 4-aminoquinolines **1** containing the phosphine oxide group in the 3-position. Retrosynthetically, we envisaged obtaining quinolines **1** by heterocyclization processes involving carbon-carbon bond formation (C_3-C_4) of functionalized imines or enamines containing a cyano group in the *ortho*-position of the aryl group (Scheme 2, route c) and that these key intermediates could be prepared by simple addition of *o*-aminobenzonitrile to allenes derived from phosphine oxides in a similar way to that reported for other amino compounds.[14]

RESULTS AND DISCUSSION

Synthesis of 3-phosphorylated 4-aminoquinolines 1.

The preparation of phosphine oxide derivatives containing a cyano group **4/5** was accomplished easily and in high yields by means of addition of substituted *o*-aminobenzonitriles **2** to phosphine oxide allenes[15] **3** in refluxing acetonitrile (Table 1). Compounds **4/5** were characterized by their spectroscopic data, which indicated that they are isolated as a mixture of *Z*- and *E*-β-enamino compounds **4** (minor products) and the β-

iminophosphine oxides **5** (major compounds), although for our purposes the separation of enamines and imines is not necessary for subsequent reactions. Thus, the *^{31}P-NMR* spectrum for crude compound **4/5a** showed three different absorptions at δ_P 25.6, 28.8 and 29.7 ppm in an approximate isomer ratio 5 : 85 : 10 as evidenced by the relative peak areas for each compound, in which the high-field and the low-field chemical shift corresponds to the *E*-isomer and the *Z*-isomer **4a**. In the *^{1}H-NMR* spectrum of **4a**, the vinylic proton resonates at δ_H 5.02 ppm as a well resolved doublet with coupling constant of $^2J_{PH}$= 17.7 Hz, and the methyl group gives a singlet at δ_H 2.03 ppm, while the *^{13}C-NMR* shows absorptions at δ_C 81.0 ppm ($^1J_{PC}$= 128.8 Hz) and 23.2 ppm ($^3J_{PC}$= 5.4 Hz) assignable to the carbon bonded to phosphorus and the methyl group of the *E*-isomer.[16] Conversely, for **4a** the *Z*-isomer showed clearly different absorptions, namely a doublet at δ_H 4.18 ppm ($^2J_{PC}$= 22.2 Hz) for the vinylic proton as well as a low-field signal for the methyl group at δ_H 2.19 ppm, while in the *^{13}C-NMR* spectrum the absorption of methine carbon is shifted to higher field (δ_C 77.2 ppm) with a lower value of the phosphorus-carbon coupling constant ($^1J_{PC}$= 114.2 Hz) relative to those of the *E*-isomer. Vicinal ^{13}C-^{31}P coupling constant ($^3J_{PC}$= 14.7 Hz) showed that the methyl group and phosphorus atom in the β-enamino compound **4a** are *trans* related.[16] On the other hand, the imine **5a**, for example, showed clearly different absorptions related to the enamine tautomers **4a**, namely a doublet at δ_H 3.56 ppm ($^2J_{PH}$= 15.2 Hz) for the methylene protons as well as a high-field signal for the methyl group at 1.90 ppm, while in the *^{13}C-NMR* spectrum the absorption of methylene carbon is shifted to higher field (δ_C 45.2 ppm) with a lower value of the phosphorus-carbon coupling constant ($^1J_{PC}$= 62.2 Hz) relative to those to the *E*-and *Z*-enamines **4a**.



Scheme 3

Table 1. Preparation of phosphine oxides **4/5** and phosphonium salts **7**.

Entry	Compound	R^1	R^2	Yield (%)[a]	E / Z ratio[b]	m.p. (°C)
1	**4/5a**	H	H	76	5/10/85[c]	117-119
2	**4/5b**	H	Me	78	5/10/85[c]	120-122
3	**7a**	H	H	91	100/0	175-176
4	**7b**	4,5-$(MeO)_2$	H	92	100/0	207-209(d)

[a] Yield of isolated purified product. [b] *E / Z* ratio determined by ^{31}*P-NMR*. [c] *E*-**4** / *Z*-**4** / **5** determined by ^{31}*P-NMR*.

Formation of aminoquinolines **1** were observed when a mixture of the *Z*- and *E*-enamines **4** and the imine-tautomers **5** was used as starting material. Treatment of functionalized phosphine oxides **4/5** with a base such as sodium hydride led to the formation of aminoquinolinylphosphine oxides **1** (Scheme 3) in excellent yield (Table 2, entries 1-3). Spectroscopic data were in agreement with the assigned structure. Mass spectrometry of **1a** showed the molecular ion peak (*m/z* 358, 100 %), while the methyl group gave a ^{1}H resonance at δ_H 2.00 ppm. The formation of substituted quinolines **1** can be assumed to proceed *via* nucleophilic attack of the enamine carbon to the electrophilic nitrile group bonded to the aromatic ring. Compounds **1** can also be obtained in *"one pot"* reaction from the allenes **3** when the mixture of **4** and **5** were directly treated with sodium hydride.

Table 2. Preparation of 4–aminoquinolines **1**, **9** and **12** and iminoquinolines **10**.

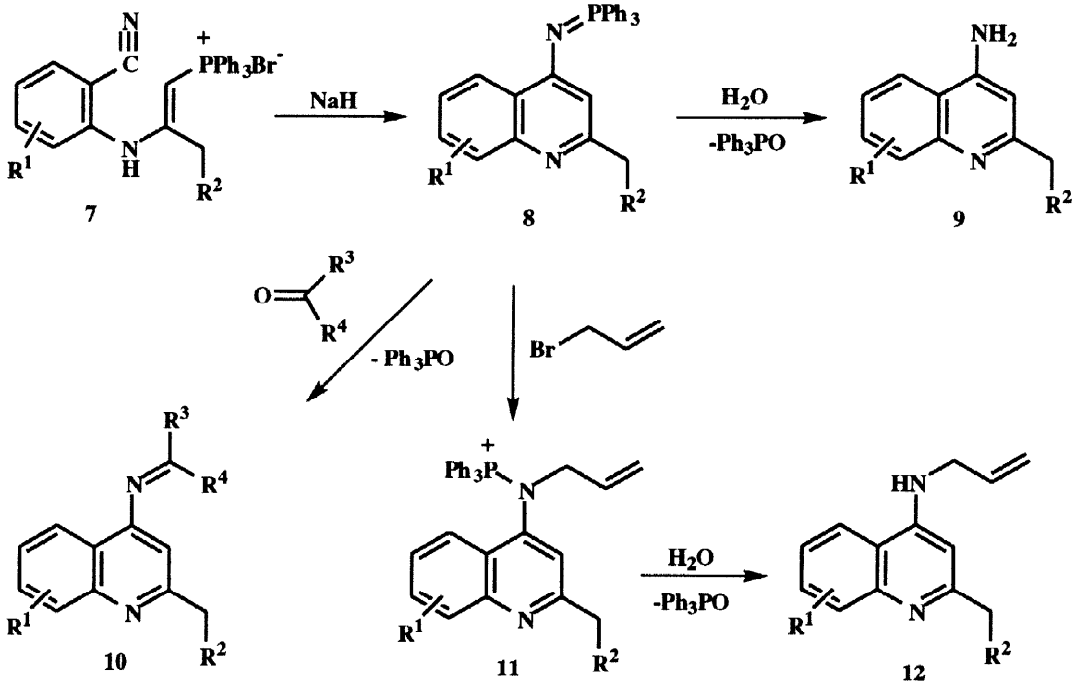
Entry	Comp.	R^1	R^2	R^3	R^4	Yield (%)	m.p. (°C)
1	**1a**	H	H			78[a](71)[b]	135-136
2	**1b**	6,7-$(MeO)_2$	H			79[b]	216-217
3	**1c**	H	Me			78[a]	180-181
4	**9**	H	H			72[c]	163-165[f]
5	**10a**	H	H	*p*-Me-Ph	H	81[d]	98-100
6	**10b**	H	H	CO_2Et	CO_2Et	77[d]	oil[g]
7	**10c**	6,7-$(MeO)_2$	H	3,4-$(MeO)_2$-Ph	H	73[d]	119-121
8	**12**	H	H			86[e]	oil[g]

[a] Yield of isolated product **1** based on **4/5**. [b] Yield of isolated product **1** in "one pot" reaction from **3**. [c] Yield of isolated product **9** based on **7**. [d] Yield of isolated product **10** based on **7**. [e] Yield of isolated product **12** from **11**. [f] **9**: 167-169[17]. [g] Purified by flash chromatography.

Synthesis of 4-aminoquinolines **9** and **12** and iminoquinolines **10**.

This methodology used for the preparation of aminoquinolines **1** can also be applied to the synthesis of 4-aminoquinolines **9** when enamines derived from phosphonium salts **7** were used. Thus, addition of *o*-aminobenzonitriles, to commercially available propargyl phosphonium bromide[18] **6** in refluxing of

acetonitrile (*TLC* control) led to the exclusive formation of *E*-β-enamino phosphonium salts **7** in excellent yield (Scheme 3, Table 1, entries 3-4). Compounds **7** were characterized by their spectroscopic data.



Scheme 4

Treatment of enamines derived from phosphonium salts **7** with sodium hydride gave 4-aminoquinolines **9**. Formation of quinolines **9** could be explained (Scheme 4) through intramolecular nucleophilic attack to the carbon-nitrogen triple bond of phosphorane generated "*in situ*" from β-enaminophophonium salts **7** leading to phosphazene **8** in a similar way to that reported for the intermolecular reaction,[12] hydrolysis of which gave aminoquinoline **9**. Phosphazene intermediates **8**, previously postulated and not detected,[17] proved to be unstable to both distillation and chromatography and were not isolated, but the formation of these compounds in the crude reaction mixture was followed by NMR (^{1}H, ^{13}C, ^{31}P). Additionally, the presence of phosphazenes **8** in the crude reaction mixture was confirmed when they were used "*in situ*" in aza-Wittig reactions and alkylation processes.[11] Reaction of compounds **8** with carbonyl derivatives such as *p*-tolualdehyde, veratraldehyde and diethyl ketomalonate in THF at room temperature gave imino compounds **10** derived from 4-aminoquinolines, while treatment of phosphazene **8** with allyl bromide led to the formation of the aminophosphonium salt **11**, hydrolysis of which gave *N*-substituted 4-aminoquinoline **12**.

In conclusion, we describe an easy and efficient method for the synthesis of 4-aminoquinolines substituted with a phosphine oxide **1** in the 3-position, and 4-aminoquinolines **9** and **12** from readily available starting materials such as *o*-aminobenzonitriles and allenes (see Scheme 2) under mild reaction conditions. 4-Aminoquinolines are useful compounds in medicinal chemistry since these products display a broad range of biological activities and have been widely used as pharmaceuticals.[1-6]

ACKNOWLEDGEMENTS

The present work has been supported by the Dirección General de Investigación Científica y Técnica (DGICYT, PB96-0252) and by the Departamento de Educación, Universidades e Investigación del Gobierno (GV, PI-96/36). J. García thanks the Ministerio de Educación y Ciencia for a Predoctoral Fellowship.

EXPERIMENTAL SECTION

General. Melting points were determined with a Buchi SPM-20 apparatus and are uncorrected. Analytical *TLC* was performed on 0.25 mm silica gel plates (Merck). Visualization was accomplished by *UV* light and iodine. All solvents used in reactions were freshly distilled from appropriate drying agents before use: *THF* (sodium benzophenone ketyl) acetonitrile *(P_2O_5)*; chloroform *(P_2O_5)*. All other reagents were recrystallized or distilled as necessary. Column (flash) chromatography was carried out on silica gel (Merck, 70-230 mesh). Mass spectra were obtained on a Hewlett Packard 5890 spectrometer. Infrared spectra were taken on a Nicolet IRFT Magna 550 spectrometer. *^{1}H-NMR* spectra were recorded on a Varian 300 MHz spectrometer using tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal reference in *$CDCl_3$* solutions. *^{13}C-NMR* spectra were recorded at 75 MHz with chloroform (77.0 ppm) as an internal reference in *$CDCl_3$* solutions. *^{31}P-NMR* spectra were recorded at 120 MHz with 85% phosphoric acid as an external reference. Elemental analyses were performed in a Leco CHNS-932 instrument. Chemical shifts are given in ppm *(δ)*; multiplicities are indicated by s (singlet), d (doublet), dd (double-doublet), t (triplet) q (quadruplet) or m (multiplet). Coupling constants, *J*, are reported in hertz. Infrared spectra *(IR)* were obtained as neat liquids, or as solids in *KBr*. Peaks are reported in cm^{-1}. Mass spectra *(EI)* were obtained with a ionization voltage of 70 eV. Data are reported in the form m/z (intensity relative to base = 100). All reactions were performed in oven (125 °C) or flame-dried glassware under an inert atmosphere of dry N_2.

General Procedure for the Preparation of the β-Enamino 4 - and/or β-Iminophosphine Oxides 5. A dry flask, 100-ml, 2-necked, fitted with a dropping funnel, gas inlet, and magnetic stirrer, was charged with 1.2 g (5 mmol) of allenediphenylphosphine oxide[15] **3** (R^2=H), or 1.27 g (5 mmol) of 1,2-butadienyldiphenylphosphine oxide[15] **3** ($R^2 = CH_3$), and 25 mL of acetonitrile. A solution (5 mmol) of amine and 10 mL of acetonitrile was added over 10 min. The mixture was stirred and refluxed until *TLC* indicated the disappearance of the phosphine oxide **3** (48 h). The mixture was concentrated and the crude product was purified by recrystallization (hexane / CH_2Cl_2).

***Z*- and *E*-β-*N*-*o*-Cyanophenylaminoprop-1-enyldiphenylphosphine oxide (4a) and β-*N*-*o*-cyanophenyliminopropyl-diphenylphosphine oxide (5a)**. 1360 mg (76 %) of **4a/5a** as a white solid. Data for **4a**: mp 116-118 °C; *^{1}H-NMR* (300 MHz) **4a**: 2.03 and 2.19 (s, 3H, *E*- and *Z*-CH_3), 3.67 (s, 1H, NH), 4.18 (d, 1H, $^2J_{PH}$= 22.2 Hz, *Z*-CH), 5.02 (d, 1H, $^2J_{PH}$= 17.7 Hz, *E*-CH), 6.29-7.76 (m, 14H, arom). **5a**: 1.90 (s, 3H, CH_3), 3.56 (d, 2H, $^2J_{PH}$= 15.2 Hz, CH_2-P), 6.29-7.76 (m, 14H, arom); *^{13}C-NMR* (75 MHz) **4a**: 19.9 (d, $^3J_{PC}$= 14.7 Hz, *Z*-CH_3), 23.2 (d, $^3J_{PC}$= 5.4 Hz, *E*-CH_3), 77.2 (d,$^1J_{PC}$= 114.2 Hz, *Z*-C-P), 81.0 (d,$^1J_{PC}$= 128.8 Hz, *E*-C-P), 110.1-136.1 (C-arom and CN), 156.7 (=C-N). **5a**: 21.3 (CH_3), 45.2 (d, $^1J_{PC}$= 62.2 Hz, CH_2-P), 110.1-136.1 (C-arom and CN), 165.2 (=C-N); *^{31}P-NMR* (120 MHz). **4a**: 25.6 (*E*-isomer), 29.7 (*Z*-

isomer). **5a**: 28.8; *IR (KBr)* 3190, 3152, 2227, 1521, 1177 cm^{-1}; *MS* (EI) 358 (M^+, 10). Anal. Calcd for $C_{22}H_{19}N_2OP$: C, 73.74; H, 5.31; N, 7.82. Found: C, 73.66; H, 5.36; N, 7.75.

***Z*- and *E*-β-*N*-*o*-Cyanophenylaminobut-1-enyldiphenylphosphine oxide (4b) and β-*N*-*o*-cyanophenyliminobutyl-diphenylphosphine oxide (5b).** 1451 mg (78 %) of **4b/5b** as a white solid. Data for **4b**: mp 124-126 °C; *^{1}H-NMR* (300 MHz) **4b**: 1.03 and 1.06 (t, 3H, $^3J_{HH}$= 7.1 Hz, *E*- and *Z*-CH_3), 2.29-2.44 (m, 2H, CH_2), 4.33-4.87 (m, 2H, NH and *E*- and *Z*-CH), 6.29-7.91 (m, 15H, arom). **5b**: 0.98 (t, 3H, $^3J_{HH}$= 7.0 Hz, CH_3), 2.62 (q, 2H, $^3J_{HH}$= 7.0 Hz, CH_2), 3.42 (d, 2H, $^2J_{PH}$= 14.8 Hz, CH_2-P), 6.29-7.91 (m, 15H, arom); *^{13}C-NMR* (75 MHz) **4b**: 10.6 and 12.1 (CH_3), 28.4 (CH_2), 78.0 (d, $^1J_{PC}$= 113.7 Hz, *Z*-CH), 81.2 (d, $^1J_{PC}$= 129.2 Hz, *E*-CH), 110.2-132.1 (C-arom and CN), 159.0 (=C-N). **5b**: 7.9 (CH_3), 27.1 (CH_2), 48.2 (d, $^1J_{PC}$= 61.6 Hz, CH_2-P), 110.2-132.1 (C-arom and CN), 167.7 (C=N); *^{31}P-NMR* (120 MHz) **4b**: 25.9 (*E*-isomer), 30.0 (*Z*-isomer). **5b**: 28.1; *IR (KBr)* 3230, 3143, 2213, 1523, 1221 cm^{-1}; *MS* (EI) 372 (M^+, 33). Anal. Calcd for $C_{24}H_{21}N_2OP$: C, 77.42; H, 5.65; N, 7.53. Found: C, 77.56; H, 5.72; N, 7.65.

General Procedure for the Preparation of the β-Aminoprop-1-enylphosphonium Bromides 7. A dry flask, 100-ml, 2-necked, fitted with a dropping funnel, gas inlet, and magnetic stirrer, was charged with 1.9 g (5 mmol) of propargyltriphenylphosphonium bromide **6** and 25 mL of acetonitrile. A solution (5 mmol) of amine and 10 mL of acetonitrile was added over 10 min. The mixture was stirred and refluxed until *TLC* indicated the disappearance of phosphonium salt (48 h). The mixture was concentrated and the crude product was triturated with diethyl ether.

***E*-β-*N*-*o*-Cyanophenylaminoprop-1-enylphosphonium bromide (7a).** 2270 mg (91 %) of **7a** as a white solid. Data for **7a**: mp 175-176 °C; *^{1}H-NMR* (300 MHz) 2.09 (s, 3H, CH_3), 4.15 (d, 1H, $^2J_{PH}$= 14.8 Hz, CH), 7.31-7.98 (m, 19H, arom), 10.72 (s, 1H, NH); *^{13}C-NMR* (75 MHz) 21.5 (CH_3), 63.5 (d, $^1J_{PC}$= 118.8 Hz, CH), 109.6-140.4 (C-arom and CN), 163.9 (=C-N); *^{31}P-NMR* (120 MHz) 16.9; *IR (KBr)* 3138, 2985, 2220, 1514, 1242, 1103 cm^{-1}; *MS* (EI) 418 (M^+-HBr, 19). Anal. Calcd for $C_{28}H_{24}N_2PBr$: C, 67.33; H, 4.81; N, 5.61. Found: C, 67.41; H, 4.79; N, 5.76.

***E*-β-*N*-2-Cyano-4,5-dimethoxyphenylaminoprop-1-enylphosphonium bromide (7b).** 2570 mg (92 %) of **7b** as a yellow solid. Data for **7b**: mp 207-209 °C; *^{1}H-NMR* (300 MHz) 2.06 (s, 3H, CH_3), 3.88 (s, 3H, CH_3-O), 3.98 (s, 3H, CH_3-O), 4.20 (s_{broad}, 1H, CH-P), 6.99-7.77 (m, 17H, arom), 10.52 (s, 1H, NH); *^{13}C-NMR* (75 MHz) 21.4 (CH_3), 55.9 (CH_3-O), 56.1 (CH_3-O), 62.9 (d, $^1J_{PC}$= 119.3 Hz, CH-P), 100.2-153.3 (C-arom and CN), 163.6 (=C-N); *^{31}P-NMR* (120 MHz) 16.8; *IR (KBr)* 3409, 2932, 2210, 1513, 1093 cm^{-1}; *MS* (EI) 478 (M^+-HBr, 13). Anal. Calcd for $C_{30}H_{28}N_2O_2PBr$: C, 64.40; H, 5.01; N, 5.02. Found: C, 64.51; H, 5.13; N, 4.93.

General Procedure for the Preparation of the 4-Aminoquinolines 1. A dry flask, 100-ml, 2-necked, fitted with a dropping funnel, gas inlet, and magnetic stirrer, was charged with NaH (3 mmol) and *$CHCl_3$* (20 mL). A solution of a mixture of β-enaminophosphine oxides **4** and β-iminophosphine oxides **5** (3 mmol) in *$CHCl_3$* (10 mL) was then added. The mixture was stirred and refluxed until *TLC* indicated the disappearance of the compounds **4/5**. The mixture was diluted with water (30 mL) and extracted with *CH_2Cl_2* (3 x 15 mL). The *CH_2Cl_2* layers were washed with water (2 x 20 mL). The combined organic layers were dried over *$MgSO_4$*, filtered, and concentrated. The crude product was purified by flash-chromatography on silica gel (hexane/ethyl acetate, 1/1). Quinolines can also be obtained in "one pot" reaction: A solution of 3 mmol of allenes **3** and *o*-aminobenzonitrile **2** in acetonitrile was stirred and refluxed (~3 days), treated with NaH and heated until formation of **1** (*TLC* control). The quinoline **1** was purified as described above.

3-Diphenylphosphoryl-2-methyl-4-aminoquinoline (1a). 795 mg (78 %) of **1a** as a white solid. Data for **1a**: mp 135-136 °C; *^{1}H-NMR* (300 MHz) 2.00 (s, 3H, CH_3), 7.42-7.86 (m, 16H, arom and NH_2); *^{13}C-NMR* (75 MHz) 28.4 (CH_3), 95.4 (d, *$^1J_{PC}$*= 102.8 Hz, C-P), 117.4-159.3 (C-arom); *^{31}P-NMR* (120 MHz) 40.1; *IR (KBr)* 3430, 3350, 3024, 1646, 1217 cm^{-1}; *MS* (EI) 358 (M^+, 74). Anal. Calcd for $C_{22}H_{19}N_2OP$: C, 73.74; H, 5.31; N, 7.82. Found: C, 73.67; H, 5.46; N, 7.73.

3-Diphenylphosphoryl-2-methyl-6,7-dimethoxy-4-aminoquinoline (1b). 990 mg (79 %) of **1b** as a white solid. Data for **1b**: mp 216-217 °C; *^{1}H-NMR* (300 MHz) 1.92 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 6.31-8.12 (m, 14H, arom and NH_2); *^{13}C-NMR* (75 MHz) 29.5 (CH_3), 55.2 (CH_3), 55.8 (CH_3), 100.1 (d, *$^1J_{PC}$*= 107.0 Hz, C-P), 117.9-159.9 (C-arom); *^{31}P-NMR* (120 MHz) 40.0; *IR (KBr)* 3370, 3191, 1640, 1440, 1150 cm^{-1}; *MS* (EI) 418 (M^+, 30). Anal. Calcd for $C_{24}H_{23}N_2O_3P$: C, 68.90; H, 5.50; N, 6.70. Found: C, 69.02; H, 5.58; N, 6.61.

3-Diphenylphosphoryl-2-ethyl-4-aminoquinoline (1c). 870 mg (78 %) of **1c** as a white solid. Data for **1c**: mp 180-181 °C; *^{1}H-NMR* (300 MHz) 0.55 (t, 3H, *$^3J_{HH}$*= 7.2 Hz, CH_3), 2.36 (q, 3H, *$^3J_{HH}$*= 7.2 Hz, CH_2), 7.26-7.87 (m, 16H, arom and NH_2); *^{13}C-NMR* (75 MHz) 12.6 (CH_3), 33.1 (CH_2), 94.8 (d, *$^1J_{PC}$*= 103.2 Hz, C-P), 117.3-163.7 (C-arom); *^{31}P-NMR* (120 MHz) 40.5; *IR (KBr)* 3383, 3218, 2953, 1639, 1229 cm^{-1}; *MS* (EI) 372 (M^+, 47). Anal. Calcd for $C_{23}H_{21}N_2OP$: C, 74.19; H, 5.64; N, 7.53. Found: C, 74.08; H, 5.51; N, 7.61.

Reaction of phosphonium salts 7 with sodium hydride. Sodium hydride (3 mmol) was added to a solution of phoshonium salts **7** (3 mmol) in acetonitrile (20 mL). The reaction mixture was refluxed and stirred under nitrogen for 3 days to give the phosphazenes **8**. The reaction product is unstable to distillation or chromatography and therefore was not isolated and used for the following reactions, without further purification.

2-Methyl-4-triphenylphosphoiminoquinoline 8a. Data for **8a**:*^{1}H-NMR* (300 MHz) of crude reaction mixture: 2.11 (s, 3H, CH_3), 6.33-7.90 (m, 14H, arom); *^{13}C-NMR* (75 MHz) of crude reaction mixture: 28.7 (CH_3), 115.0-161.3 (C-arom); *^{31}P-NMR* (120 MHz) 14.7.

2-Methyl-6,7-dimethoxy-4-triphenylphosphoiminoquinoline 8b. Data for **8b**:*^{1}H-NMR* (300 MHz) of crude reaction mixture: 1.99 (s, 3H, CH_3), 3.79 (s, 3H, CH_3-O), 3.84 (s, 3H, CH_3-O), 6.77-7.83 (m, 14H, arom); *^{13}C-NMR* (75 MHz) of crude reaction mixture: 28.5 (CH_3), 55.9 (CH_3-O), 56.5 (CH_3-O), 118.1-154.3 (C-arom); *^{31}P-NMR* (120 MHz) 14.2.

Aza-Wittig reaction of *N*-quinolinyl phosphazenes 8 with carbonyl compounds. Synthesis of iminoquinolines 10. A solution of carbonyl compunds (3 mmol) in anhydrous *THF* (20 mL) was added dropwise to a solution of phosphazene **8** generated "*in situ*" from β-enaminophosphonium bromide **7**. The mixture was stirred at room temperature until *TLC* indicated the disappearance of phosphazene **8**. The mixture was diluted with 30 mL water and extracted with *CH_2Cl_2* (3 x 15). The *CH_2Cl_2* layers were washed with water. The combined organic layers were dried over *$MgSO_4$*, filtered and concentrated. The crude product was purified by flash-chromatography on silica gel (hexane).

***Syn*- and *anti*-2-methyl-4-(*p*-methylphenylimino)quinoline 10a**. 632 mg (81 %) of **10a** as a yellow solid. Data for **10a**: mp 98-100 °C; *^{1}H-NMR* (300 MHz) 2.10 and 2.34 (s, 3H, CH_3), 2.38 and 2.52 (s, 3H, CH_3), 6.40-7.83 (m, 10H, arom and H-C=N); *^{13}C-NMR* (75 MHz) 16.7 (CH_3), 21.4 (CH_3), 117.3-154.5 (C-arom), 167.5 and 168.6 (C=N); *IR (KBr)* 3038, 2979, 1630, 1222 cm^{-1}; *MS* (EI) 260 (M^+, 32). Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.08; H, 6.15; N, 10.78. Found: C, 83.19; H, 6.21; N, 10.87.

***Syn*- and *anti*-2-methyl-4-(diethoxycarbonylimino)quinoline 10b**. 725 mg (77 %) of **10b** as a yellow oil. Data for **10b**: R_f = 0.80 (ethyl acetate); *^{1}H-NMR* (300 MHz) 1.16-1.34 (m, 6H, CH_3), 1.94 and 2.04 (CH_3), 5.90 and 5.93 (s, 1H, C_3-H), 6.74-7.62 (m, 4H, arom); *^{13}C-NMR* (75 MHz) 13.8 and 14.0 (CH_3), 18.4 and 20.6 (CH_3), 59.2 and 62.0 (CH_2), 118.0-152.6 (C-arom), 167.4 and 168.2 (C=O), 173.2 (C=N); *IR* (*KBr*) 3162, 2972, 1730, 1273 cm^{-1}; *MS* (EI) 314 (M^+, 56). Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.97; H, 5.73; N, 8.92. Found: C, 64.88; H, 5.61; N, 9.03.

***Syn*- and *anti*-2-methyl-6,7-dimethoxy-4-(3,4-dimethoxyphenylimino)quinoline 10c**. 801 mg (73 %) of **10c** as a yellow solid. Data for **10c**: mp 119-121; *^{1}H-NMR* (300 MHz) 2.13 and 2.49 (s, 3H, CH_3), 3.87, 3.89, 3.90 and 3.91 (s, 3H, CH_3-O), 6.38 (s, 1H, C_3-H), 6.84-7.77 (m, 7H, arom and H-C=N); *^{13}C-NMR* (75 MHz) 16.2 and 22.8 (CH_3), 55.4, 55.5, 55.6, 55.7 and 55.9 (CH_3-O), 110.2-153.0 (C-arom), 167.5 and 168.7 (C=N); *IR* (*KBr*) 2959, 1595, 1508, 1260 cm^{-1}; *MS* (EI) 366 (M^+, 36). Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.85; H, 6.01; N, 7.65. Found: C, 68.96; H, 6.11; N, 7.58.

Reaction of phosphazene 8a with allyl bromide. Synthesis of *N*-allyl-*N*-(2-methyl-4-aminoquinolinyl)phosphonium bromide 11. Allyl bromide (3 mmol) was added to a solution in acetonitrile (20 mL) of phosphazene **8a** generated "*in situ*" from β-enaminophosphonium bromide **7a**. The mixture was stirred until ^{31}P-NMR indicated the disappearance of phosphazene. The mixture was concentrated and the crude product was triturated with diethyl ether to afford 1358 mg (84%) of **11** as a yellow solid. Data for **11**: mp 214-217 °C; *^{1}H-NMR* (300 MHz) 2.53 (s, 3H, CH_3), 4.86-5.30 (m, 4H, =CH_2 and N-CH_2), 6.13 (m, 1H, =CH), 7.29-8.91 (m, 20H, arom); *^{13}C-NMR* (75 MHz) 22.6 (CH_3), 51.4 (CH_2-N), 109.7 (d, $^3J_{PC}$= 12.8 Hz, =CH), 117.5 (=CH_2), 125.1-164.2 (C-arom); *^{31}P-NMR* (120 MHz) 16.5; *IR* (*KBr*) 3436, 3045, 1587, 1487, 1441 cm^{-1}; *MS* (EI) 458 (M^+-HBr, 15). Anal. Calcd for $C_{31}H_{28}N_2PBr$: C, 69.01; H, 5.19; N, 5.20. Found: C, 69.13; H, 5.02; N, 5.31.

Synthesis of 2-methyl-4-allylaminoquinoline 12. Hydrolysis of *N*-allyl-*N*-(2-methyl-4-aminoquinolinyl)phosphonium bromide 11. A 1 M aqueous solution of HCl (10 mL) was added to a solution of **11** (1078 mg, 2 mmol) in methanol (20 mL). The mixture was stirred until *TLC* indicated the disappearance of compound **11** (12 h). The mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The CH_2Cl_2 layers were washed with water (2 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford an oil that was chromatographed on silica gel to give 321 mg (81%) of **12** as a yellow oil (R_f = 0.2, ethyl acetate). Data for **12**: *^{1}H-NMR* (300 MHz) 2.57 (s, 3H, CH_3), 3.71 (m, 2H, N-CH_2), 4.98-5.21 (m, 3H, =CH and CH_2), 6.17 (s, 1H, NH), 6.53 (s, 1H, C_3-H), 7.40-7.95 (m, 4H, arom); *^{13}C-NMR* (75 MHz) 29.6 (CH_3), 53.8 (CH_2-N), 103.2-161.9 (C-arom); *IR* (*KBr*) 3415, 3002, 1440, 1277 cm^{-1}; *MS* (EI) 198 (M^+, 35). Anal. Calcd for $C_{13}H_{14}N$: C, 78.79; H, 7.07; N, 7.08. Found: C, 78.87; H, 7.15; N, 6.90.

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