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A FACILE SYNTHESIS OF SUBSTITUTED 1,8-NAPHTHYRIDINES BASED ON THE AZA-WITTIG/ELECTROCYCLIC RING CLOSURE STRATEGY

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Abstract – Several new 1,8-naphthyridine derivatives (**7**) and (**8**) has been synthesized *via* an aza-Wittig reaction. Iminophosphoranes, 2-ethoxy-3-cyano-5-(2-ethoxycarbonyl)-4-phenyl-6-[(triphenylphosphoranilidene)amino]pyiridine (**4**) and 2-ethoxy-3-cyano-5-(2-cyanovinyl)-4-phenyl-6[(triphenylphosphoranilidene)-amino]pyridine (**5**), easily obtained from the 2-chloro-5-cyano-6-ethoxy-4-phenylpyridine-3-carboxaldehyde (**1**), react with heterocumumulenes such as aromatic isocyanates to give directly the title compounds in an aza-Wittig/electrocyclic ring closure process. The yields were from 60% to 97%.

Nitrogen-containing heterocycles are of broad pharmaceutical interest and this justifies continuing efforts in the development of structure-activity relationship in this series and of new synthetic strategies.[1] There is an enormous interest in the synthesis of new heterocyclic rings stimulated by recent reports that showed antitumor activity in a wide range of heterocyclic compounds isolated from marine organisms.[2]

The naphthyridines and their derivatives exhibit various types of biological activity, and the organic chemistry has been frequently reviewed.[3] 1,8-Naphthyridine are important scaffolds in many compounds with pharmacological applications,[4] and their anti-allergy, antibacterial, antihypertensive and anti-inflammatory properties have been reported.[5] Since the discovery of the first therapeutically useful antibacterial quinolone, nalidixic acid, numerous derivatives have been prepared in search of improved antibacterial activities.[6] The resurgence of interest in quinolones, naphthyridones and related compounds has resulted in an enormous account of research on new structural modifications to improve the overall spectrum of antibacterial activity, bioavailability and safety. Detailed structure-activity relationships have been reviewed.[7] Different series of naphthyridine derivatives which possessed excellent broad-spectrum

activity against Gram-positive and Gram-negative bacteria as well as good pharmacokinetic properties have been prepared and are used clinically.[8] Nevertheless a number of these compounds have quite often exhibited other properties which caused toxicity and preclude their clinical use.[9]

On the other hand, 1,8-napthyridines are also known to be good bidentate ligands in organometallic complexes. 1,8-Napthyridine (napy) and its simplest 2-substituted and 2,7-disubstituted derivatives may act as monodentate and bidentate ligands, resembling the behavior of the carboxylate ligands.[10] Special interest was focused on the photochemistry and redox properties of mononuclear ruthenium complexes.[11] Moreover, novel multidendate dinucleating ligands based on the 1,8-napthyridine skeleton have been prepared with the aim of mimicking the coordination environment of dinuclear metalloenzymes and diiron-containing, redox-active proteins.[12] Finally, dinuclear ruthenium complexes with the 1,8-naphthyridine ligand are stable and active catalysts for the oxidation of alcohols and the epoxidation of alkenes.[13]

Recently, in the course of a study aimed at the discovery of new compounds to combat scuticociliatosis, our results demonstrate that substituted naphthyridines are new antiprotozoals active against *Philasterides dicentrarchi*, the causative agent of scuticiciliatosis in farmed turbot and Black Sea bass-bream.[14] Consequently, the establishment of a facile and regioselective construction of these fundamental heterocyclic skeletons is important.

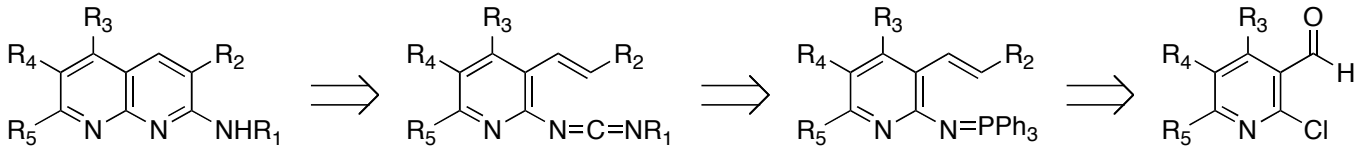
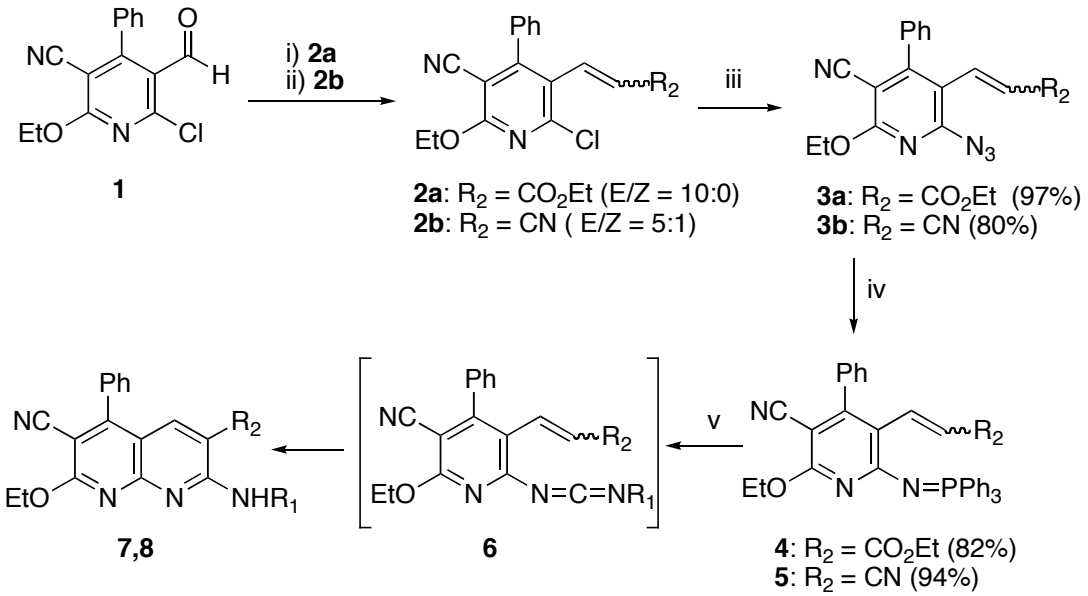


Figure 1. General retrosynthetic pathway for synthesis of the substituted 1,8-naphthyridines

In this context, the aza-Wittig reaction of iminophosphoranes with heterocumulenes, e.g. carbon dioxide, carbon disulfide, and isocyanates, or isothiocyanates is a very useful reaction in synthetic heterocyclic chemistry. The aza-Wittig reaction has become one of the most important synthetic methods for constructing novel C=N, N=N, and S=N double bonds containing compounds, especially in modern nitrogen heterocyclic synthesis. In recent years, there has been a significant interest in the preparation and reactivity of *N*-heteroaryliminophosphoranes because of their promising potential as building blocks for the construction of nitrogen-containing heterocycles compounds, and many interesting heterocyclization reactions involved functionalized iminophosphoranes have been reviewed.[15] Consequently, improvements that increase the efficiency or enlarge its applicability are desirable, and the discovery of novel functionalized iminophosphoranes bearing a moiety able to react with the aza-Wittig product is important in this respect.[16]

Recently, in the course of our studies directed toward the synthesis of fused heterocycles, we have reported the synthesis of fused pyrimidines based on the tandem aza-Wittig heterocumulene-mediated annulation strategy.[17] Work in our laboratories has been recently concerned with the synthesis of 1,8-naphthyridines, pyridothienopyrimidines and pyridothienotriazines, with the aim of evaluating their antiprotozoal activity.[14] As a continuation of our search for new biologically active heterocycles, we now report a new and facile approach to the synthesis of properly substituted 1,8-naphthyridine derivatives, centered on the aza-Wittig reaction of iminophosphoranes with heterocumulenes. Our general approach to the synthesis of poly-functionalized 1,8-naphthyridine derivatives (Figure 1) is centered on the aza-Wittig reaction of iminophosphoranes with heterocumulenes to give a 1,3,5-hexatriene moiety containing a carbon atom at one end and cumulated double bond at the other, which subsequently undergoes the stepwise formation of the pyridine ring following the aza-Wittig/electrocyclic ring closure strategy.



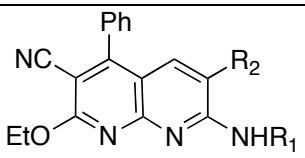
Scheme 1. Synthesis and structure of substituted 1,8-naphthyridines (**7**) and (**8**).

The starting iminophosphoranes (**4** and **5**) for the intermolecular aza-Wittig reaction followed by electrocyclization sequence were conveniently prepared from 2-chloro-5-cyano-6-ethoxy-4-phenylpyridine-3-carboxaldehyde **(1)** (Scheme 1). This compound can be directly and efficiently obtained by substitutive deamination [*tert*-butyl nitrite and anhydrous copper(II) chloride in dry acetonitrile] of 2-amino-3-formylpyridine derivative.[18] Carboxaldehyde (**1**) reacted with an equimolecular quantity of (carboxymethylene)triphenyl phosphorane to give good yield of 2-chloro-3-vinylpyridine (**2a**). Only *E*-isomer was obtained: the ^{1}H NMR spectrum of **2a** includes two characteristic doublets (δ = 5.84 and 7.43

ppm, with J = 16.1 Hz) from a *trans*-configuration of the double bond, in addition to the set of signals due to the phenyl and ethoxy groups. While, the ^{13}C NMR spectrum showed signals at δ = 126.3 and 136.9 ppm to the vinyl carbons. The attempted Wittig reaction with (cyanomethyl)triphenylphosphorane to yield **2b** resulted in non-selectivity to give a mixture of *E* and *Z* isomers (*E*:*Z* = 5:1 according to its NMR spectrum) in 75%.

Compounds (**2**) react with sodium azide in dimethyl sulfoxide at room temperature to give the 2-azido-3-vinylpyrimidines (**3a**) and (**3b**) in 98% and 83% yield, respectively. The preparation of the desired key iminophosphoranes (**4**) and (**5**) was accomplished very easily through the classical Staudinger reaction[19] of 2-azidopyrimidines (**3a**) and (**3b**) with triphenylphosphine in dry methylene chloride at room temperature in good yields.

Table 1. Physicochemical data for 1,8-naphthyridines (**7a-d**) and (**8a-d**)



Compound[a]	R_1	R_2	mp (ºC)	Yield (%)	Molecular formula[b]
7a	C_6H_5	CO_2Et	259-261	83[c]	$C_{26}H_{22}N_4O_3$
7b	4-Me-C_6H_4	CO_2Et	250-252	93[c]	$C_{27}H_{24}N_4O_3$
7c	4-Cl- C_6H_4	CO_2Et	299-301	80[c]	$C_{26}H_{21}ClN_4O_3$
7d	4-MeO- C_6H_4	CO_2Et	203-205	87[c]	$C_{27}H_{24}N_4O_4$
8a	C_6H_5	CN	302-304	60[d]	$C_{24}H_{16}N_5O$
8b	4-Me- C_6H_4	CN	280-282	63[d]	$C_{25}H_{19}N_5O$
8c	4-Cl- C_6H_4	CN	276-278	85[d]	$C_{24}H_{16}ClN_5O$
8d	4-MeO- C_6H_4	CN	218-220	60[d]	$C_{25}H_{19}N_5O_2$

[a] All spectra data were consistent with the assigned structures.

[b] All compounds analyzed for C, H, N; analytical results are within 0.4% of theoretical values.

[c] Purified by flash chromatography using dichloromethane as eluent.

[d] Recrystallized from ethanol/CH_2Cl_2

The reaction of the iminophosphoranes 2-ethoxy-3-cyano-5-(2-ethoxycarbonyl)-4-phenyl-6-[(triphenylphosphoranilidene)amino]pyridine (**4**) and 2-ethoxy-3-cyano-5-(2-cyanovinyl)-4-phenyl-6-[(triphenylphosphoranilidene)amino]pyrimidine **(5**) with aromatic isocyanates, in dry toluene at reflux temperature, gave triphenylphosphine oxide and the corresponding functionalized 1,8-naphthyridines (**7a-d**) and (**8a-d**), respectively.

Presumably, the mechanisms of these conversions involve initial aza-Wittig reaction between the iminophosphorane and the isocyanate to give a carbodiimide (**6**) as highly reactive intermediate, which easily undergoes electrocyclic ring closure followed by [1,3-*H*] shift to afford the final substituted 1,8-naphthyrines (**7**) and (**8**) in good yields (60-93%). This assumption is supported by the isolation of the intermediate carbodiimides in aza-Wittig/electrocyclic-ring closure process.[17, 20]

The structure of compounds (**7**) and (**8**), shown in Table 1, was consistent with their elemental analyses and spectral data. The mass spectra showed the expected molecular ion peak and the NH group of all 1,8-naphthyiridine derivatives showed a strong absorption band at υ = 3200-3300 cm^{-1} in the IR spectra. Moreover, IR spectra of compounds (**7a-d**) showed one strong absorption band at υ = 1690-1700 cm^{-1} due to the carbonyl group. In the ^{1}H NMR spectra, the characteristic chemical shifts of the amino group are found at δ = 7.65-10.70 ppm and those of H-5 at δ = 8.03-8.48 ppm as singlets, while the ^{13}C NMR spectra showed a signal at δ = 141.8-143.6 ppm due to the C-5 carbon. On the other hand, ^{13}C NMR spectra of compounds (**7a-d**) showed a signal at δ = 114.5-115 ppm and compounds (**8a-d**) two signals at δ = 114.2–115.4 due to the one or two cyano groups, respectively. Complete information about the NMR, IR and MS spectra is presented in the EXPERIMENTAL.

The above method demonstrate that the tandem aza-Wittig/electrocyclization strategy provides a new entry to a variety of substituted 1,8-naphthyridines. Advantages of the present method are: easy availability of starting materials, good yields in the iminophosphorane preparation as well as in the cyclization step, and experimental simplicity of the synthetic procedure. Due to the easily accessible and versatile starting materials, this method has the potential in the synthesis of many biologically and pharmaceutically active naphthyridine derivatives, because dinucleating ligands based on 2,7-disubstituted 1,8-naphthyridines are the nitrogen analogues of the carboxylate ligands, which bridge the catalytic centres in metallohydrolases that perform the hydrolysis of biologically important substrates as DNA, RNA, and peptides by the cooperation between two metal centers.[21]

EXPERIMENTAL

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin-Elmer 783 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Brucker AC 200F instrument at room temperature. MS spectra were obtained on a VG QUATTRO spectrometer. The silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the silica gel 60 (230-400 mesh) employed for flash chromatography were purchased from Merck. Microanalyses for, C, H, and N were performed by the elemental analyses general service of the University of A Coruña.

2-Chloro-5-cyano-6-ethoxy-3-(2-ethoxycarbonyl)-4-phenylpyridine (**2a**):

A mixture of **1** (0.30 g, 1.05 mmol) and (ethoxycarbonylmethylene)triphenylphosphorane (0.41 g, 1.17 mmol) in DMF (6 mL) was stirred at rt for 14 h. Water (10 mL) was added and the aqueous phase was extracted with ether (3x50 mL) and the organic layer was dried over anhydrous sodium sulfate and filtered. Concentration to dryness yielded a crude material which was purified by flash chromatography using CH_2Cl_2/hexane (2:1, v/v) as eluent to yield **2a** (0.28 g, 75%): mp 104-106 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3000, 2220 (CN), 1705 (CO), 1650, 1590, 1560. MS (EI, *m/z* %) = 358 (M^+ + 2, 6), 356 (M^+, 15), 321 (33), 311 (17), 293 (58), 283 (82), 265 (92), 255 (100), 191 (86), 164 (84). ^{1}H NMR ($CDCl_3$) δ = 1.23 (t, 3H, *J* = 7.2 Hz, CH_3); 1.49 (t, 3H, *J* = 7.0 Hz, CH_3); 4.15 (q, 2H, *J* = 7.2 Hz, OCH_2); 4.57 (q, 2H, *J* = 7.0 Hz, OCH_2); 5.84 (d, 1H, *J* = 16.1 Hz, H-2'); 7.43 (d, 1H, *J* = 16.1 Hz, H-1'); 7.24-7.52 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3); 14.2 (CH_3); 60.7 (CH_2); 64.8 (CH_2); 97 (**C**-CN); 112.8 (CN); 121.9 (C-3); 126.3 (C-2'); 128.6, 129.0, 130,1, 134.2 (C_6H_5), 136.9 (C-1'); , 158.2 (C-Cl), 162.6, 165.8 (CO). *Anal*. Calcd for $C_{19}H_{17}N_2O_3Cl$: C, 63.96; H, 4.80; Cl, 9.94; N, 7.85. Found: C, 63.75; H, 4.86; Cl, 10.14; N, 7.74.

2-Chloro-5-cyano-3-(2-cyanovinyl)-6-ethoxy-4-phenylpyridine (**2b**):

To a mixture of **1** (0.30 g, 1.05 mmol) and (cyanomethyl)triphenylphosphonium chloride (0.42 g, 1.25 mmol) in dry THF (20 mL) triethylamine (0.17 mL, 1.26 mmol) was added, and the mixture was stirred at rt for 20 h. The solvent was evaporated and the resulting solid was purified by flash chromatography using CH_2Cl_2/hexane/AcOEt (5:20:1,) as eluent to give an *E* and *Z* mixture (5:1) of **2b** (0.25 g, 77%): mp 120-122 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3000, 2220 (CN), 2210 (CN), 1620, 1550, 1540, 1450, 1420. MS (EI, *m/z* %) = 311 (M^+ + 2, 7), 309 (M^+, 51), 282 (42), 280 (100), 254 (37), 246 (39), 217 (45) 191 (60), 180 (60), 164 (73). ^{1}H NMR ($CDCl_3$): *E* isomer: δ = 1.49 (t, 3H, *J* = 7.1 Hz, CH_3); 4.69 (q, 2H, *J* = 7.1 Hz, OCH_2); 5.33 (d, 1H, *J* = 17.1 Hz, H-2'), 7.20 (d, 1H, *J* = 16.1 Hz, H-1'); 7.23-7.58 (m, 5H, C_6H_5); *Z* isomer: 5.56 (d, 1H, *J* = 11.2 Hz, H-2'); 6.97 (d, 1H, *J* = 11.2 Hz, H-1'). *Anal*. Calcd for $C_{17}H_{12}N_3OCl$: C, 65.92; H, 3.90; Cl, 11.45; N, 13.57. Found: C, 65.75; H, 3.86; Cl, 11.69; N, 13.44.

2-Azido-5-cyano-6-ethoxy-3-(2-ethoxycarbonyl)-4-phenylpyridine (**3a**):

To a well-stirred solution of sodium azide (0.05 g, 0.76 mmol) in DMSO/AcOH(20:1, v/v)(2 mL) was added the 2-chloro-4-cyano-5-ethoxy-3-(2-ethoxycarbonyl)-4-phenylpyridine (**2a**) (0.18 g, 0.50 mmol) and the reaction mixture was stirred at rt for 4 h. The precipitate obtained was filtered off and recrystallized from acetone to yield **3a** (0.18 g, 98%): mp 158-160 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3000, 2220 (CN), 2190, 2175 (N_3), 1710 (CO), 1640, 1550, 1500. MS (EI, *m/z* %) = 363 (M^+ + 2, 2), 335 (M^+ - N_2, 43), 307 (26), 311 (17), 288 (11), 261 (66), 248 (17), 235 (100), 234 (59), 206 (52). ^{1}H NMR ($CDCl_3$) δ = 1.24 (t, 3H, *J* = 7.1 Hz, CH_3); 1.49 (t, 3H, *J* = 7.1 Hz, CH_3); 4.15 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.59 (q, 2H, *J* = 7.1 Hz, OCH_2); 6.44 (d, 1H, *J* = 16.6 Hz, H-2'); 7.24 (d, 1H, *J* = 16.6 Hz, H-1'); 7.23-7.52 (m, 5H, C_6H_5). *Anal*. Calcd for $C_{19}H_{17}N_5O_3$: C, 62.80; H, 4.72; N, 19.27. Found: C, 62.93; H, 4.57; N, 19.18.

2-Azido-5-cyano-3-(2-cyanovinyl)-6-ethoxy-4-phenylpyridine (**3b**):

To a stirred solution of sodium azide (0.06 g, 0.97 mmol) in DMSO/AcOH(20:1, v/v) (2 mL) was added the *E* and *Z* mixture (5:1) of 2-chloro-4-cyano-5-ethoxy-3-(2-cyanovinyl)-4-phenylpyridine **2b** (0.20 g, 0.64 mmol) and the reaction mixture was stirred at rt for 1 h. The precipitate obtained was filtered off and purified by flash chromatography using CH_2Cl_2/hexane/AcOEt (5:20:1) as eluent to give **3b** (0.18 g, 84%): mp 156-158 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3000, 2220 (CN), 2210 (CN), 2150, 2140 (N_3), 1610, 1550, 1400. MS (EI, *m/z* %) = 316 (M^+, 28), 288 (M^+ - N_2, 37), 287 (52), 260 (100). ^{1}H NMR ($CDCl_3$): δ = 1.50 (t, 3H, *J* = 7.1 Hz, CH_3); 4.60 (q, 2H, *J* = 7.1 Hz, OCH_2); 6.10 (d, 1H, *J* = 17.0 Hz, H-2'); 6.91 (d, 1H, *J* = 17.0 Hz, H-1'); 7.19-7.56 (m, 5H, C_6H_5). ^{13}C NMR): δ = 14.3 (CH_3); 64.2 (CH_2); 89.7 (**C**-CN); 94.1 (CN); 101.6 (C-2'); 111.6, 113.8 (CN); 118,1; 128.5, 129.3, 130.3, 133.7, 135.5 (C_6H_5); 141.3 (C-1'), 159.5, 163.1 ppm. *Anal.* Calcd for $C_{17}H_{12}N_6O$: C, 64.55; H, 3.82; N, 26.57. Found: C, 64.75; H, 3.86; N, 26.44.

2-Ethoxy-3-cyano-5-(2-ethoxycarbonyl)-4-phenyl-6-[(triphenylphosphoranilidene)amino]pyridine (**4**)

A mixture of **3a** (0.70 g, 1.93 mmol) and triphenylphosphine (0.56 g, 2.12 mmol) in CH_2Cl_2 (4 mL) was stirred at rt for 6 h. Concentration to dryness yielded a crude material, which was recrystallized from ethanol/acetone to yield **4** (0.94 g, 82%): mp 189-191 ºC. IR (KBr, cm^{-1}) ν = 3000, 2220 (CN), 1700 (CO), 1640, 1560, 1540, 1500, 1450. MS (EI, *m/z* %) = 597 (M^+, 10), 524 (100), 496 (9), 262 (25). ^{1}H NMR ($CDCl_3$) δ = 0.95 (t, 3H, *J* = 7.1 Hz, CH_3); 1.25 (t, 3H, *J* = 7.1 Hz, CH_3); 3.48 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.13 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.21 (d, 1H, *J* = 15.6 Hz, H-2'); 7.25-7.79 (m, 21H, C_6H_5 + H-1') ppm. ^{13}C NMR ($CDCl_3$) δ = 14.4 (CH_3), 59.7 (CH_2), 62.1 (CH_2), 84.9 (**C**-CN); 113.4, 113.8, 117.0, 119.2 (C-2'), 128.0, 128.5, 128.7, 128.9, 130.0, 132.3, 132.7, 132.9, 136.6, 140.4 (C-1'), 157.8, 162.4, 163.6, 163.7, 168.6 (CO) ppm. ^{31}P NMR ($CDCl_3$) δ = 18.56 ppm. *Anal.* Calcd for $C_{37}H_{32}N_3O_3P$: C, 74.86; H, 5.40; N, 7.03. Found: C, 74.75; H, 5.56; N, 7.14.

2-Ethoxy-3-cyano-5-(2-cyanovinyl)-4-phenyl-6-[(triphenylphosphoranilidene)amino]pyridine (**5**)

A mixture of **3b** (0.12 g, 0.38 mmol) and triphenylphosphine (0.12 g, 0.42 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 7 h. Concentration to dryness yielded a crude material, which was purified by flash chromatography using CH_2Cl_2/hexane/AcOEt (5:20:1, v/v) to yield **5** (0.19 g, 94%): mp 227-229 ºC (EtOH). IR (KBr, cm^{-1}) ν = 2210 (CN), 1600, 1550, 1540, 1530, 1490, 1440. MS (EI, *m/z* %) = 550 (M^+, 26), 549 (37), 521 (17), 510 (9), 473 (9), 262 (47), 183 (100). ^{1}H NMR ($CDCl_3$) δ = 0.93 (t, 3H, *J* = 7.1 Hz, CH_3); 3.45 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.12-7.72 (m, 22H, C_6H_5 + H-1'+ H-2') ppm. ^{13}C NMR ($CDCl_3$) δ = 14.2 (CH_3), 62.4 (CH_2), 85.7, 88.8 (**C**-CN), 96.0 (CN); 112.4 (C-1'), 112.8, 116.5 (CN), 120.8, 127.5, 128.7, 128.8, 129.1, 129.5, 132,5, 132,7, 136.0, 145.9 (C-2'), 153.0, 158.0, 162.2 ppm. ^{31}P NMR ($CDCl_3$) δ = 20.95 ppm. *Anal.* Calcd for $C_{35}H_{27}N_4OP$: C, 76.35; H, 4.94; N, 10.18. Found: C, 76.43; H, 4.76; N, 10.44.

3-Cyano-2-ethoxy-6-ethoxycarbonyl-4-methyl-1,8-naphthyridines (**7a-d**); General Procedure:

To a stirred solution of iminophosphorane (**4**) (0.1 g, 0.16 mmol) in dry toluene (6 mL) was added the appropriate aromatic isocyanate (0.82 mmol) under argon. After the reaction mixture was refluxed for 2.5-6 h (TLC monitored), the solvent was removed off under reduced pressure and the resulting solid was purified by flash chromatography using CH_2Cl_2 as eluent.

3-Cyano-2-ethoxy-6-ethoxycarbonyl-4-phenyl-7-*N*-phenylamino-1,8-naphthyridine (**7a**) (86%): mp 259-261 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3200 (NH), 2210 (CN), 1690 (CO), 1610, 1600, 1580, 1550. MS (EI, *m/z* %) = 438 (M^+, 43), 437 (100), 391 (12), 363 (32), 335 (19). ^{1}H NMR ($CDCl_3$) δ = 1.31 (t, 3H, *J* = 7.1 Hz, CH_3); 1.53 (t, 3H, *J* = 7.1 Hz, CH_3); 4.34 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.75 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.15-7.95 (m, 10H, $2C_6H_5$); 8.47 (s, 1H, H-5); 10.66 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$) δ = 14.0 (CH_3), 14.4 (CH_3), 61.9 (CH_2), 64.1 (CH_2), 95.0 (**C**-CN), 109.3, 111.0, 114.5 (CN), 121.1, 124.0, 128.9, 129.0, 129.4, 130.2, 133.1, 138.7 (C_6H_5), 141.9 (C-5), 156.4, 158.4, 164.9, 166.5 (CO). *Anal.* Calcd for $C_{26}H_{22}N_4O_3$: C, 71.22; H, 5.06; N, 12.78. Found: C, 71.15; H, 5.26; N, 12.74.

3-Cyano-2-ethoxy-6-ethoxycarbonyl-4-phenyl-7-*N*-(4-methylphenyl)amino-1,8-naphthyridine (**7b**) (93%): mp 250-252 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3300 (NH), 3000, 2220 (CN), 1700 (CO), 1610, 1600, 1580, 1550. MS (EI, *m/z* %) = 452 (M^+, 50), 451 (100), 405 (10), 377 (20), 349 (19). ^{1}H NMR ($CDCl_3$) δ = 1.31 (t, 3H, *J* = 7.1 Hz, CH_3); 1.52 (t, 3H, *J* = 7.1 Hz, CH_3); 2.37 (s, 3H, CH_3); 4.34 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.74 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.22, 7.78 (AA'XX' system, 4H, *J* = 8.3 Hz, C_6H_4); 7.45-7.62 (m, 5H, C_6H_5); 8.45 (s, 1H, H-5); 10.57 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$) δ = 14.0 (CH_3), 14.4 (CH_3), 20.9 (CH_3), 61.8 (CH_2), 64.0 (CH_2), 94.6 (**C**-CN), 109.2, 110.8, 115.0 (CN), 121.3, 128.8, 129.4, 129.5, 130.1, 133.2, 133.6, 136.1 (C_6H_5 + C_6H_4), 141.8 (C-5), 156.5, 158.4, 164.9, 166.5 (CO). *Anal.* Calcd for $C_{27}H_{24}N_4O_3$: C, 71.67; H, 5.35; N, 12.38. Found: C, 71.75; H, 5.46; N, 12.24.

3-Cyano-2-ethoxy-6-ethoxycarbonyl-4-phenyl-7-*N*-(4-chlorophenyl)amino-1,8-naphthyridine (**7c**) (80%): mp 299-301 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3250 (NH), 2990, 2210 (CN), 1700 (CO), 1610, 1580, 1560. MS (EI, *m/z* %) = 474 (M^+ + 2, 24), 473 (M^+ + 1, 46), 472 (M^+, 68), 471 (100), 425 (11), 397 (24), 371 (16). ^{1}H NMR ($CDCl_3$) δ = 1.32 (t, 3H, *J* = 7.1 Hz, CH_3); 1.54 (t, 3H, *J* = 7.1 Hz, CH_3); 4.34 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.75 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.37, 7.89 (AA'XX' system, 4H, *J* = 8.8 Hz, C_6H_4); 7.33-7.90 (m, 5H, C_6H_5); 8.48 (s, 1H, H-5); 10.70 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$) δ = 14.0 (CH_3), 14.4 (CH_3), 62.0 (CH_2), 64.2 (CH_2), 95.2 (**C**-CN), 109.2, 111.1, 114.8 (CN), 122.2, 128.9, 129.4, 130.2, 133.0, 137.3 (C_6H_4 + C_6H_5), 141.9 (C-5), 156.2, 158.1, 158.5 (C-Cl), 165.0, 166.4 (CO). *Anal.* Calcd for $C_{26}H_{21}N_4O_3Cl$: C, 66.03; H, 4.48; Cl, 7.50; N, 11.85. Found: C, 65.95; H, 4.59; Cl, 7.78; N, 11.64.

3-Cyano-2-ethoxy-6-ethoxycarbonyl-4-phenyl-7-*N*-(4-methoxyphenyl)amino-1,8-naphthyridine (**7d**) (87%): mp 203-205 ºC (EtOH). IR (KBr, cm^{-1}) ν = 3250 (NH), 2990, 2210 (CN), 1700 (CO), 1600, 1580, 1550. MS (EI, *m/z* %) = 469 (M^+ + 1, 30), 468 (M^+, 100), 467 (82), 421 (12), 393 (13), 365 (15). ^{1}H NMR

($CDCl_3$) δ = 1.31 (t, 3H, *J* = 7.1 Hz, CH_3); 1.51 (t, 3H, *J* = 7.1, CH_3); 3.84 (s, 3H, OCH_3); 4.34 (q, 2H, *J* = 7.1 Hz, OCH_2); 4.74 (q, 2H, *J* = 7.1 Hz, OCH_2); 6.96, 7.80 (AA'XX' system, 4H, *J* = 9.0 Hz, C_6H_4); 7.45-7.64 (m, 5H, C_6H_5); 8.45 (s, 1H, H-5); 10.51 (br s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$) δ = 14.0 (CH_3), 14.4 (CH_3), 55.5 (OCH_3), 61.8 (CH_2), 64.0 (CH_2), 109.2, 115.0 (CN), 114.2, 122.8, 128.8, 129.4, 129.5, 130.1, 133.2 (C_6H_5 + C_6H_4), 141.8 (C-5), 156.5, 158.5, 166.5 (CO). *Anal.* Calcd for $C_{27}H_{24}N_4O_4$: C, 69.22; H, 5.16; N, 11.96. Found: C, 69.05; H, 5.16; N, 12.04.

3,6-Dicyano-2-ethoxy-4-methyl-1,8-naphthyridines (**8a-d**); General Procedure:

To a stirred solution of iminophosphorane (**5**) (0.15 g, 0.27 mmol) in dry toluene (6 mL) was added the appropriate aromatic isocyanate (1.36 mmol) under argon and the reaction mixture was heated at reflux for 3-8 h (TLC monitored). After cooling, the precipitate obtained was filtered off and recrystallized from ethanol/CH_2Cl_2.

3,6-Dicyano-2-ethoxy-4-phenyl-7-*N*-phenylamino-1,8-naphthyridine (**8a**) (60%): mp 302-304 ºC. IR (KBr, cm^{-1}) ν = 3280 (NH), 2220 (CN), 1610, 1600, 1580, 1550. MS (EI, *m/z* %) = 391 (M^+, 62), 390 (96), 362 (100), 189 (10), 182 (18). ^1H NMR ($CDCl_3$) δ = 1.53 (t, 3H, *J* = 7.1 Hz, CH_3); 4.76 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.12-7.83 (m, 11H, NH + $2C_6H_5$); 8.06 (s, 1H, H-5) ppm. ^{13}C NMR ($CDCl_3$) δ = 14.3 (CH_3), 64.5 (CH_2), 95.2 (**C**-CN), 96.3 (**C**-CN), 111.2, 114.3 (CN), 115.4 (CN), 121.3, 125.2, 129.1, 129.3, 130.6, 132.4, 137.4 (C_6H_5), 143.6 (C-5), 155.8, 157.8, 165.1. *Anal.* Calcd for $C_{24}H_{16}N_5O$: C, 73.64; H, 4.38; N, 17.89. Found: C, 73.75; H, 4.56; N, 17.62.

3,6-Dicyano-2-ethoxy-4-phenyl-7-*N*-(4-methylphenyl)amino-1,8-naphthyridine (**8b**) (63%): mp 280-282 ºC. IR (KBr, cm^{-1}) ν = 3330 (NH), 2210 (CN), 1640, 1600, 1580, 1560. MS (EI, *m/z* %) = 405 (M^+, 85), 376 (100), 253 (16), 239 (19), 189 (34), 173 (14). ^1H NMR ($CDCl_3$) δ = 1.52 (t, 3H, *J* = 7.1 Hz, CH_3); 2.38 (s, 3H, CH_3); 4.73 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.14-7.68 (m, 10H, NH + C_6H_5 + C_6H_4); 8.03 (s, 1H, H-5) ppm. ^{13}C NMR ($CDCl_3$) δ = 14.3 (CH_3), 21.0 (CH_3), 64.5 (CH_2), 95.1 (**C**-CN), 96.1 (**C**-CN), 111.1, 114.3 (CN), 115.4 (CN), 121.6, 129.1, 129,2, 129.8, 130.5, 132.0, 132.5, 134.8, 135.1, 135.4 (C_6H_5), 143.6 (C-5), 155.6, 157.8, 165.0. *Anal.* Calcd for $C_{25}H_{19}N_5O$: C, 74.06; H, 4.72; N, 17.27. Found: C, 73.85; H, 4.86; N, 17.44.

3,6-Dicyano-2-ethoxy-4-phenyl-7-*N*-(4-chlorophenyl)amino-1,8-naphthyridine (**8c**) (85%): mp 276-278 ºC. IR (KBr, cm^{-1}) ν = 3330 (NH), 2220 (CN), 1630, 1580, 1550, 1490. MS (EI, *m/z* %) = 427 (M^+ + 2, 29), 426 (M^+ + 1, 45), 425 (M^+, 87), 424 (88), 398 (35), 396 (100). ^1H NMR ($CDCl_3$) δ = 1.54 (t, 3H, *J* = 7.1 Hz, CH_3); 2.38 (s, 3H, CH_3); 4.75 (q, 2H, *J* = 7.1 Hz, OCH_2); 7.37-7.80 (m, 10H, NH + C_6H_5 + C_6H_4); 8.07 (s, 1H, H-5) ppm. ^{13}C NMR ($CDCl_3$) δ = 14.3 (CH_3), 64.6 (CH_2), 95.1 (**C**-CN), 96.1 (**C**-CN), 111.4, 114.2 (CN), 115.3 (CN), 122.5, 129.1, 129,3, 130.2, 130.6, 132.3, 136.0 (C_6H_5), 143.6 (C-5), 155.2, 157.5, 158.0 C-Cl). *Anal.* Calcd for $C_{24}H_{16}N_5OCl$: C, 67.69; H, 3.79; Cl, 8.32; N, 16.44. Found: C, 67.85; H, 3.86; Cl, 8,10; N, 16.27.

3,6-Dicyano-2-ethoxy-4-phenyl-7-*N*-(4-methoxyphenyl)amino-1,8-naphthyridine (**8d**) (60%): mp 218-220 ºC. IR (KBr, cm^{-1}) ν = 3300 (NH), 2210 (CN), 1600, 1580, 1550. MS (FAB, *m/z* %) = 422 [(MH^+, 47)], 394 (26), 367 (13), 291 (100), 288 (11). ^{1}H NMR ($CDCl_3$) δ = 1.51 (t, 3H, *J* = 7.1 Hz, CH_3); 3.85 (s, 3H, OCH_3); 4.73 (q, 2H, *J* = 7.1 Hz, OCH_2); 6.98, 7.64 (AA'XX' system, 4H, *J* = 9.3 Hz, C_6H_4); 7.40-7.64 (m, 6H, NH + C_6H_5); 8.03 (s, 1H, H-5) ppm. *Anal*. Calcd for $C_{25}H_{19}N_5O_2$: C, 71.25; H, 4.54; N, 16.62. Found: C, 71.55; H, 4.86; N, 16.24.

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REFERENCES

1. R. J. Ife, T. H. Brown, P. Blurton, D. J. Keeling, C. A. Leach, M. L. Meeson, M. E. Parsons, and J. Theobald, *J. Med. Chem*., 1995, **38**, 2763.
2. (a) S. E. Kane, *Adv. Drug Res*., 1996, **28**, 181 (b) M. L. Bourguet-Kondraki, M. T. Martin, and M. Guyot, *Tetrahedron Lett*., 1996, **37**, 3447 (c) M. Kobayashi, Y.-J. Chen, S. Aoki, Y. In, T. Ishida, and I. Kitagawa, *Tetrahedron,* 1995, **51**, 3727 (d) K. L. Jr. Rinehart, J. Kobayashi, G. C. Harbour, J. Gilmore, M. Mascal, T. G. Holt, L. S. Shield, and F. Lafargue, *J. Am. Chem. Soc*., 1987, **109**, 3378 (e) Y. Take, Y. Inouye, S. Nakamura, H. S. Allaudeen, and A. Kubo, *J. Antibiot*., 1989, **42**, 107.
3. (a) W. W. Paudler and T. J. Kress, *Adv. Heterocycl. Chem.,* 1970, **11**, 123. (b) H. C. Van der Plas, M. Wozniak, and H. J. W. Van den Kaak, *Adv. Heterocycl. Chem.,* 1983, **33**, 96. (c) W. W. Paudler and R. M. Sheets, *Adv. Heterocycl. Chem.,* 1983, **33**, 147. (d) P. A. Lowe, 'Naphthyridines, Pyridoquinolines and Similar Compounds. In Comprehensive Heterocyclic Chemistry', ed. by A. R. Katritzky and C. W. Rees, Pergamon, Oxford, UK, 1984, Vol. 2, pp. 582-628. (e) S. P. Stanforth, 'Bicyclic 6-6 Systems: Two Heteroatoms 1:1. In Comprehensive Heterocyclic Chemistry II', ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Elsevier, Oxford, UK, 1996, Vol. 7, pp. 527-555. (f) V. P. Litvinov, S. V. Roman, and V. D. Dyachenko, *Russ. Chem. Rev.,* 2000, **69**, 201, *ibid.,* 2001, **70**, 299.
4. (a) K. Chen, S. Kuo, M. Hsieh, and K. Anthoner, *J. Med. Chem*., 1997, **40**, 3049. (b) M. Dadawneh, C. Manera, C. Mori, G. Saccomanni, and P. L. Ferrarini, *Farmaco,* 2002, **57**, 631. (c) H. Misbahi, P. Brouant, A. Hever, A. M. Molnar, K. Wolfard, G. Spengler, H. Mefetah, J. Molnar, and J. Barbe, *Anticancer Res.,* 2002, **22**, 2097. (d) J. T. Leonard, R. Gangadhar, S.K. Gnanasam, S. Ramachandran, M. Saravanan, and S. K. Sridhar, *Biol. Pharm. Bull.,* 2002, **25**, 798. (e) S. P. Stanforth, in *Bicyclic 6-6-Systems: two Heteroatoms 1:1*. Comprehensive Heterocyclic Chemistry, ed. by A. R. Katritzky,

C. W. Rees, and E. F. V. Scriven, Vol. 7. Elsevier Science, London, 1996, p. 558.

5. H. Egawa, A. Miyamoto, Y. Minamida, H. Nishimura, H. Okada, H. Uno, and J. Matsumoto, *J. Med. Chem.,* 1984, **27**, 1543. (b) K. K. Shibamori, H. Egawa, T. Miyamoto, Y. Nishimura, A. Itokawa, J. Nakano, and J. Matsumoto, *Chem. Pharm. Bull.,* 1990, **38**, 2390. (c) D. Bouzard, P. Di Cesare, M. Essiz, J. P. Jacquet, B. Ledoussal, P. Remuzon, R. E. Kessler, and J. Fung-Tomc, *J. Med. Chem.,* 1992, **35**, 518. (d) A. J. Corraz, S. L. Dax, N. K. Dunlap, N. H. Georgopapadakou, D. D. Keith, D. L. Pruess, P. L. Rossman, R. Then, J. Unowsky, and C. Wei, *J. Med. Chem.,* 1992, **35**, 1828.
6. (a) D. T. W. Chu and P. B. Fernandes, *Adv. Drug Res.,* 1991, **21**, 39, and references cited. (b) P. A. Lowe, *Comp. Heterocycl. Chem. 1st edn.* 1984, **2**, 581, and references cited therein.
7. L. A. Mitscher, P. V. Devasthale, and R. M. Zavod, 'The Quinolones', ed. by G. G. Crumpin, Springer Verlag, London, 1990, pp. 115-146.
8. (a) Y. Jinjo, H. Kondo, M. Taguchi, Y. Inoue, F. Sakamoto, and G. Tsukamoto, *J. Med. Chem.,* 1994, **37**, 2791 and references therein. (b) Y. Kimura, S. Atarashi, K. Kawakami, K. Sato, and I. Kayakawa, *J. Med. Chem.,* 1994, **37**, 3344 and references cited therein.
9. D. Bouzard in 'Antibiotics and Antiviral Compounds', ed. by K. Krohn, H. A. Kirst, and H, Maag, VCH, Weinheim, 1993, pp. 187-193.
10. M. A. Ciriano and L. A. Oro, 'Pyridopyridine Ligands. In Comprehensive Coordination Chemistry II. From Biology to Nanotechnology', ed. by J. A. McCleverty and T. J. Meyer, Elsevier, Oxford, UK, 2004, Vol. 1, pp. 55-61 and references cited therein.
11. R. J. Staniewicz and D. G. Hendricker, *J. Am. Chem. Soc.,* 1977, **99**, 6581.
12. C. He and S. J. Lippard, *Tetrahedron,* 2000, **56**, 8245.
13. (a) A. E. M. Boelrijk, M. M. van Velzen, T. X. Neenan, J. Reedijk, H. Kooijman, and A. L. Spek, *J. Chem. Soc. Dalton Trans.,* 1995, 2465. (b) A. E. M. Boelrijk, T. X. Neenan, and J. Reedijk, *J. Chem. Soc., Dalton Trans.,* 1997, 4561.
14. (a) J. M. Quintela, C. Peinador, L. González, R. Iglesias, I. Paramá, F. Alvarez, M. L. Sanmartín, and R. Riguera, *Eur. J. Med. Chem.,* 2003, **38**, 265. (b) A. Paramá, R. Iglesias, F. Alvarez, J. M. Leiro, J. M. Quintela, C. Peinador, L. González, R. Riguera, and M. L. Sanmartín, *Dis. Aquat. Org.,* 2004, **62**, 97.
15. S. Eguchi, T. Okano, and T. Okawa, *Recent Res. Dev. Org. Chem.*, 1997, **1**, 337. (b) P. Molina and M. J. Vilaplana, *Synthesis,* 1994, 1197. (c) N. I. Gussar, *Russ. Chem. Rev.,* 1991, **60**, 146. (d) H. Wamhoff, G. Richardt, and S. Stölben, *Adv. Heterocycl. Chem.*, 1995, **64**, 159. (d) S. Eguchi, Y. Matsushita, and K. Yamashita, *Org. Prep. Proceed. Int.,* 1992, **24**, 209.
16. For some references, see. (a) P. Molina, M. Alajarín, and P. Sánchez-Andrada, *J. Org. Chem.,* 1994, **59**, 7306 (b) M. Nitta, T. Akei, and Y. Iino, *J. Org. Chem.,* 1994, **59**, 1309 (c) H. Wamhoff, C.

Bamberg, S. Herrmann, and M. Nieger, *J. Org. Chem.,* 1994, **59**, 3985 (d) A. R. Katritzky, J. Jiang, and P. Steel, *J. Org. Chem.,* 1994, **59**, 4551. (e) M.-W. Ding, S.-J. Yang, and J. Zhu, *Synthesis,* 2004, 75 and references cited therein. (f) H.-Q. Wang, Z.-J. Liu, L.-M. Yang, and M.-W. Ding, *J. Heterocycl. Chem.,* **2004**, 41, 393. (g) T. Okawa and S. Eguchi, *Tetrahedron,* 1998, **54**, 5853. (h) P. Molina, P. M. Fresneda, and S. Delgado, *Synthesis,* 1999, 326 (i) Ch. Shi, Q. Zhang, and K. K. Wang, *J. Org. Chem.,* 1999, **64**, 925. (j) T. Saito, T. Ohkubo, H. Kuboki, M. Maeda, K. Tsuda, T. Karakasa, and S. Satsumabayashi, *J. Chem. Soc., Perkin Trans. 1,* 1998, 986. (k) M. Takahashi and D. Suga, *Synthesis,* 1998, 986.

17. (a) D. Vázquez, C. Peinador, and J. M. Quintela, *Tetrahedron,* 2004, **60**, 275, and references cited therein. (b) R. Alvarez-Sarandés, C. Peinador, and J. M. Quintela, *Tetrahedron,* 2001, **57**, 5413 and references cited.
18. V. Ojea, C. Peinador, and J. M. Quintela, *Synthesis,* 1992, 798.
19. H. Staudinger and J. Meyer, *Helv. Chim. Acta,* 1919, **2**, 635.
20. P. Molina, A. Arqués, M. V. Vinader, J. Becher, and K. Brondum, *J. Org. Chem.,* 1988, **53**, 4654.
21. (a) C. He, A. M. Barrios, D. Lee, J. Kuzelka, R. M. Davydof, and S. J. Lippard, *J. Am. Chem. Soc.,* 2000, **122**, 12683. (b) C. He, J. L. DuBois, B. Hedman, K. O. Hodgson, and S. J. Lippard, *Angew. Chem., Int. Ed.,* 2001, **40**, 1484. (c) C. He and S. J. Lippard, *J. Am. Chem. Soc.,* 2000, **122**, 184.