Tetrahedron Letters 52 (2011) 6623–6626

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient syntheses of 3-phosphorylquinolin-4-ones and 3-phosphoryl-1,8-naphthyridin-4-ones

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ARTICLE INFO

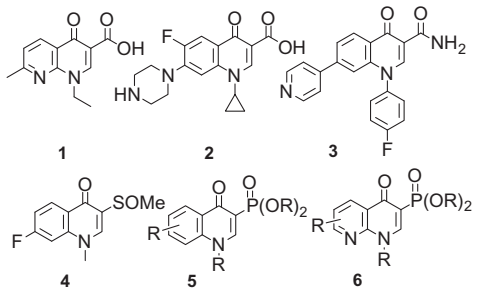
Article history:
Received 1 August 2011
Revised 15 September 2011
Accepted 30 September 2011
Available online 6 October 2011

Keywords:
Quinolinones
Naphthyridinones
3-Diethoxyphosphorylquinolin-4-one
3-Diethoxyphosphoryl-1,8-naphthyridin-4-one

ABSTRACT

A series of 3-diethoxyphosphorylquinolin-4-ones and 3-diethoxyphosphoryl-1,8-naphthyridin-4-ones containing various substituents at N-1 and C-7 was synthesized in a four-step reaction sequence starting from readily available ethyl 2-chlorobenzoates or ethyl 2-chloronicotinates and diethyl methylphosphonate. Selected quinolinone and naphthyridinone products were transformed into free mono and diacids.

Nitrogen-containing heterocycles are a very important class of organic compounds which are widely used in medicinal and/or synthetic chemistry.[1] Particularly interesting from a biological point of view are 3-carboxyquinolin-4-ones and 3-carboxy-1,8-naphthyridin-4-ones which are well known antibacterial agents.[2] Nalidixic acid (**1**) and ciprofloxacin (**2**) are good examples. Also, quinolin-4-ones substituted at position 3 by electron-withdrawing functionalities such as amide or sulfinyl groups possess desirable biological activities; quinolin-4-one **3** was found to have strong antiviral activity[3] and flosequinan (**4**) has been used as a drug for the treatment of congestive heart failure.[4]



In continuation of our research on phosphorylated oxa- and aza-heterocycles,[5] we became interested in developing a general and efficient approach to phosphorus analogs of 3-carboxyquinolin-4-ones and 3-carboxy-1,8-naphthyridin-4-ones of general structure **5** and **6**, wherein the carboxyl group is replaced by a phosphoryl group. These compounds are important for two reasons. Firstly, it is well known that the phosphoryl group can mimic the tetrahedral intermediates formed in enzymatic reactions involved in carboxyl group metabolism.[6] Therefore, the replacement of a carboxyl group with a phosphoryl moiety can produce biologically active analogs which might inhibit key enzymes or interact with receptors which normally bind the corresponding original compounds.[7] Secondly, phosphorylated quinolinones **5** and naphthyridinones **6** are potentially useful synthetic intermediates. For example, they can act as Michael acceptors. Consequently, the addition of nucleophiles to these compounds and subsequent Horner–Wadsworth–Emmons olefination might give access to 3-alkylidenequinolin-4-ones and 3-alkylidenenaphthyridin-4-ones containing an α-alkylidenecarbonyl moiety. Many natural and synthetic heterocycles possessing this structural motif display cytotoxic, anti-inflammatory, antimicrobial, and other biological activities.[5a–c,e,8]

Several procedures for the synthesis of 3-phosphorylquinolinon-4-ones have been described so far. 2-Amino-3-diethoxyphosphoryl-quinolin-4-ones were prepared by condensation of isatoic anhydrides[9] or 2,4-benzoxazin-1-ones[10] with phosphonoacetonitrile. 3-Dialkoxyphosphoryl-1-methylquinolin-4-ones were synthesized in a four-step reaction sequence starting from the Arbuzov reaction of 2-nitrophenacyl bromide and trialkyl phosphites.[11] In turn, preparation of 6-substituted-4-hydroxy-2-trifluoromethyl-

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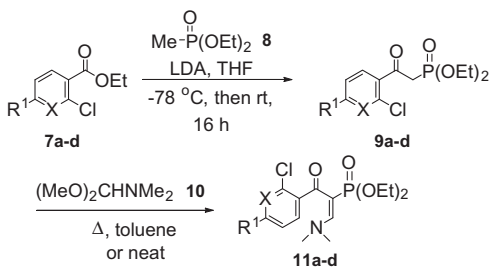
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.09.144

quinolines was accomplished by the reaction of trifluoroacetimidoyl chlorides with phosphonoacetates in the presence of NaH, followed by intramolecular cyclization.[12] Finally, condensation of ethyl 2-aminobenzoate with β-ketophosphonates or β-ketophosphine oxides followed by intramolecular cyclization was employed in the preparation of 2-substituted-3-phosphorylquinolin-4-ones.[13] The synthesis of 3-phosphoryl-1,8-naphthyridin-4-ones **6** has not been reported so far.

Herein we present a convenient and general approach to 3-diethoxyphosphorylquinolin-4-ones **13a–f** and 3-diethoxyphosphoryl-1,8-naphthyridin-4-ones **13g–j**. Treatment of ethyl 2-chlorobenzoates **7a,b**[14a] or ethyl 2-chloronicotinates **7c,d**[14b] with diethyl methylphosphonate (**8**)[15] in the presence of LDA gave, after standard work-up and purification by column chromatography, 2-oxo-2-(2-chlorophenyl)ethylphosphonates **9a,b** or 2-oxo-2-(2-chloro-3-pyridyl)ethylphosphonates **9c,d**, respectively, in good to excellent yields (Table 1). In the next step the enamine functionality was introduced to phosphonates **9** using dimethylformamide–dimethyl acetal (DMFDMA) (**10**).[16] Heating of 2-oxo-2-phenylethylphosphonates **9a,b** with DMFDMA (**10**) in toluene at 110 °C for 4.5 h, followed by purification by column chromatography furnished diethyl 1-dimethylaminomethylidene-2-oxo-2-phenylphosphonates **11a,b** in excellent yields (Table 1).[17] Disappointingly, applying the same procedure on 2-oxo-2-pyridylethylphosphonate (**9c**) provided diethyl 1-dimethylaminomethylidene-2-oxo-2-pyridylphosphonate (**11c**) in a low 43% yield. However, we were pleased to observe that heating both substrates at 80 °C for 2 h without solvent gave the expected pyridylphosphonate **11c** in almost quantitative yield. The same procedure worked well for the synthesis of pyridylphosphonate **11d**. However, our efforts to purify compounds **11c,d** were unsuccessful. During column chromatography, in the presence of traces of water, these compounds decomposed. Analysis of the ^{31}P and ^{1}H NMR spectra of the eluted material revealed the presence of starting phosphonates **9c** or **9d** along with other compounds, which were difficult to identify. For this reason compounds **11c,d** were used as such in the next step. Phosphonates **11a–d** were obtained as single *E* isomers. The $^{3}J_{HP}$ coupling constants, determined from the ^{1}H NMR spectra, and which fell into the range 14.8–15.3 Hz proved diagnostic being typical for the *cis*-relationship between the phosphoryl group and vinyl hydrogen.[18]

Table 1
Synthesis of 2-oxoethylphosphonates **9a–d** and 1-dimethylaminomethylidene-2-oxophosphonates **11a–d**



Compound	X	R^1	Yield[a] of **9** (%)	Yield of **11** (%)
a	CH	Cl	79	89[a]
b	CH	F	77	95[a]
c	N	H	80	~95[b]
d	N	Me	85	~95[b]

[a] Yield of pure isolated product.
[b] Yield of crude product estimated by ^{31}P NMR spectroscopy.

Inspection of the ^{1}H NMR spectra of **11a–d** revealed that the *N*,*N*-dimethyl groups appeared as two broad singlets. However, when a sample of **11a** in $CDCl_3$ was heated gradually to 60 °C, one sharp singlet (3.19 ppm) for both methyl groups was formed. The coalescence temperature for the *N*,*N*-dimethyl groups was reached at ca. 28 °C. We also tried to determine the rotational barrier around the enamine double bond. However, after heating the sample in DMSO-d_6 to 120 °C and cooling to room temperature, no additional signals were evident. Likewise, cooling a sample of **11a** to −60 °C resulted in sharp singlets for the *N*,*N*-dimethyl group (3.39 ppm and 2.98 ppm) but no additional signals in both the ^{1}H and ^{31}P NMR spectra were found. These results support the conclusion that the *E* isomer is more stable than the *Z* isomer. A likely explanation is the strong steric interaction between the diethoxyphosphoryl and dimethylamino groups which destabilize the *Z* isomer. Similar results were obtained in variable temperature NMR experiments performed on diethyl 1-dimethylamino-3-oxobut-1-en-2-ylphosphonate.[19] For this compound the coalescence temperature for *N*,*N*-dimethyl groups was −6 °C. However, it was possible to determine the *E*/*Z* isomer ratio (*E*/*Z* = 93/7) because separate signals due to the vinyl protons of the *E*- and *Z*-isomers appeared in the ^{1}H NMR spectrum when the sample was cooled to −33 °C.

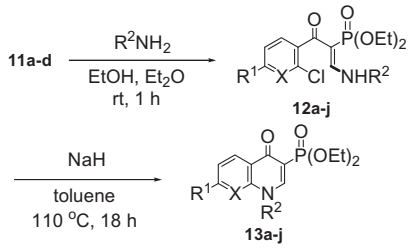
The synthesis of a wide range of alkyl- or arylaminovinylphosphonates **12a–j** was accomplished by stirring dimethylaminovinylphosphonates **11a–d** with the appropriate primary amine at room temperature (Table 2). Usually 1.0–1.5 equiv of the amine was added. However, when the reaction was performed with highly volatile methyl or ethyl amine addition of 10 equiv of these reagents was necessary to obtain satisfactory yields. Substitution of the dimethylamino group in **11a–d** proceeded smoothly under these conditions, providing vinylphosphonates **12a–j** in excellent yields as mixtures of *E* and *Z* isomers in the ratios given in Table 2.[20] It is noteworthy that the products **12a–j** were formed as *E*/*Z* mixtures, whereas substrates **11a–d** appeared as single *E* isomers. A likely explanation is the greater steric interaction between the diethoxyphosphoryl group and tertiary dimethylamine group in **11a–d** in comparison to the secondary amine group present in products **12a–j**.

Aminovinylphosphonates **12a–j** were next subjected to an intramolecular nucleophilic aromatic substitution by heating in boiling toluene in the presence of NaH. Standard work-up and purification by column chromatography gave the expected 3-diethoxyphosphorylquinolin-4-ones **13a–f** or 3-diethoxyphosphoryl-1,8-naphthyridin-4-ones **13g–j** in excellent yields (Table 2).[21] The structures of the final products and the intermediates were confirmed by IR, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy and elemental analysis.

Finally, we demonstrated that quinolinones and naphthyridinones **13** could be easily transformed into the corresponding mono and diacids using classic techniques (Scheme 1). Thus, treatment of **13c** or **13h** with trimethylbromosilane followed by solvolysis in ethanol furnished diacids **14c** or **14h** in 96% and 95% yields, respectively.[22] Also, transformation of **13c** or **13h** into monoacids **15c** or **15h** was performed in boiling 2-butanone in the presence of LiBr. Standard work-up and purification by crystallization from CH_2Cl_2/hexane gave the expected monoacids in excellent 98% and 96% yields, respectively.[23]

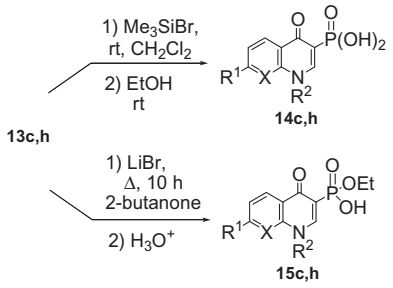
In conclusion, this new protocol facilitates considerably the synthesis of diversified 3-diethoxyphosphorylquinolin-4-ones **13a–f** and 3-diethoxyphosphoryl-1,8-naphthyridin-4-ones **13g–j**. The synthetic pathway starts from readily available 2-chlorobenzoates or 2-chloronicotinates and enables efficient introduction of various alkyl or aryl substituents on the N-1 nitrogen atom. Formation of the intermediate vinylphosphonates **11a–d** as *E* isomers was rationalized on the basis of the steric effect between the diethoxyphosphoryl and dimethylamine groups. Effective transformation of the

Table 2
Synthesis of aminovinylphosphonates **12a–j**, 3-diethoxyphosphorylquinolin-4-ones **13a–f** and 3-diethoxyphosphoryl-1,8-naphthyridin-4-ones **13g–j**



Compound	X	R^1	R^2	Equiv of R^2NH_2	**12**		**13** Yield[b] (%)
					E/*Z*[a]	Yield[b] (%)	
a	CH	Cl	*c*-Hex	1.0	65:35	80	93
b	CH	Cl	Ph	1.5	45:55	94	85
c	CH	Cl	Me	10.0	55:45	97	80
d	CH	Cl	(*R*)-Ph(Me)CH	1.0	60:40	92	84
e	CH	Cl	(*S*)-Ph(Me)CH	1.0	60:40	97	86
f	CH	F	Me	10.0	55:45	98	83
g	N	H	Me	10.0	75:25	81	76
h	N	H	*c*-Hex	1.0	65:35	86	89
i	N	H	Ph	1.2	60:40	74	88
j	N	Me	Et	10.0	70:30	82	92

[a] Determined from integration of the ^{31}P NMR spectra.
[b] Yield of pure isolated product.



Scheme 1. Synthesis of diacids **14c**,**h** and monoacids **15c**,**h**.

final phosphonates **13** into phosphonic diacids **14** or monoacids **15** was also demonstrated. Further investigations to elaborate the scope of this methodology and to show the synthetic utility of the products obtained are currently in progress in our laboratory.

Acknowledgment

This work was financed by the Ministry of Science and Higher Education (Project No. N N204 005736).

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17. *Typical procedure for the preparation of phosphonates **11a**,**b***: A solution of **9a** (3.25 g, 10.0 mmol) and DMFDMA (1.43 g, 12.0 mmol) in dry toluene (40 mL) was heated at 110 °C for 4.5 h. The crude mixture was diluted with toluene (20 mL) and the solvent removed. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 100:1), to give pure **12a** (3.38 g, 89%), as a yellow solid; mp = 78–80 °C. ^{31}P NMR (63 MHz, $CDCl_3$) δ 22.76. ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (t, 6H, $^3J_{H-H}$ = 7.1 Hz, 2 × CH_3CH_2O); 3.03 (br s, 3H, CH_3N); 3.27 (br s, 3H, CH_3N); 3.80–4.00 (m, 4H, 2 × CH_2O); 7.22 (dd, 1H, $^3J_{H-H}$ = 8.2 Hz, $^4J_{H-H}$ = 2.0 Hz, *CH*); 7.34 (d, 1H, $^3J_{H-H}$ = 8.2 Hz, *CH*); 7.37 (d, 1H, $^4J_{H-H}$ = 2.0 Hz, *CH*); 7.73 (d, 1H, $^3J_{H-P}$ = 15.3 Hz, *CH*CP). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 14.24 (d, $^3J_{C-P}$ = 7.1 Hz, 2 × CH_3CH_2O); 41.29 (br s, CH_3N); 46.08 (br s, CH_3N); 59.71 (d, $^2J_{C-P}$ = 5.7 Hz, 2 × CH_2O); 91.89 (d, $^1J_{C-P}$ = 193.7 Hz, *C*P); 124.26 (s, CH_{Ar}); 127.48 (s, CH_{Ar}); 129.07 (s, CH_{Ar}); 130.54 (s, *C*C(O)); 133.57 (s, *C*Cl); 137.67 (s, *C*Cl); 159.92 (d, $^2J_{C-P}$ = 16.9 Hz, *CH*CP); 186.46 (d, $^2J_{C-P}$ = 12.2 Hz, *C*(*O*)). IR: 1056, 1244, 1636, 3070 cm^{-1}. Anal. calcd for $C_{15}H_{20}Cl_2NO_4P$: C, 47.39; H, 5.30; N, 3.68. Found: C, 47.63; H, 5.21; N, 4.01.

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20. *Typical procedure for the preparation of vinylphosphonates* ***12a–j***: A solution of **11a** (3.04 g, 8.0 mmol) and cyclohexylamine (0.79 g, 8.0 mmol) in a mixture of EtOH and Et_2O (2/1, 45 mL) was stirred at rt for 1 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:1), to give pure **12a** (2.78 g, 80%), as a yellow solid; mp = 124–126 °C. ^{31}P NMR (63 MHz, $CDCl_3$) δ 22.02 (*Z*), 22.52 (*E*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, 6H, $^3J_{H-H}$ = 7.0 Hz, 2 × CH_3CH_2O, *E*); 1.33 (t, 6H, $^3J_{H-H}$ = 7.0 Hz, 2 × CH_3CH_2O, *Z*); 1.21–2.04 (m, 10H, 5 × CH_2, *E*, *Z*); 3.00–3.14 (m, 1H, *CH*NH, *Z*); 3.22–3.40 (m, 1H, *CH*NH, *E*); 3.79–4.00 (m, 4H, 2 × CH_2O, *E*); 4.04–4.20 (m, 4H, 2 × CH_2O, *Z*); 7.20–7.31 (m, 3H, CH_{Ar}, *E*, *Z*); 7.40–7.70 (m, 1H, *CH*CP, *E*); 7.95 (d, 1H, $^3J_{H-H}$ = 14.0 Hz, $^3J_{H-P}$ = 11.5 Hz, *CH*CP, *Z*); 9.42–9,55 (m, 1H, *NH*, *Z*); 11.00–11.15 (m, 1H, *NH*, *E*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 15.89 (d, $^3J_{C-P}$ = 7.1 Hz, 2 × CH_3CH_2O, *E*); 16.15 (d, $^3J_{C-P}$ = 6.7 Hz, 2 × CH_3CH_2O, *Z*); 24.11 (s, CH_2, *Z*); 24.28 (s, CH_2, *E*); 24.87 (s, CH_2, *E*, *Z*); 33.36 (s, CH_2, *Z*); 33.46 (s, CH_2, *E*); 57.91 (s, *CH*NH, *Z*); 58.80 (s, *CH*NH, *E*); 61.30 (d, $^2J_{C-P}$ = 5.4 Hz, 2 × CH_2O, *E*); 62.28 (d, $^2J_{C-P}$ = 5.1 Hz, 2xCH_2O, *Z*); 92.66 (d, $^1J_{C-P}$ = 206.8 Hz, *C*P, *E*); 92.97 (d, $^1J_{C-P}$ = 183.6 Hz, *C*P, *Z*); 125.66–139.21 (6 × C_{Ar}, *E*, *Z*); 161.15 (d, $^2J_{C-P}$ = 19,0 Hz *CH*CP, *E*); 161.99 (d, $^2J_{C-P}$ = 10.0 Hz *CH*CP, *Z*); 189.49 (d, $^2J_{C-P}$ = 8.7 Hz, *C*(*O*), *Z*); 191.84 (d, $^2J_{C-P}$ = 15.8 Hz, *C*(*O*), *E*). IR: 1056, 1232, 1624, 3070 cm^{-1}. Anal. calcd for $C_{19}H_{26}Cl_2NO_4P$: C, 52.55; H, 6.03; N, 3.23. Found: C, 52.26; H, 6.29; N, 3.11.
21. *Typical procedure for the preparation of 3-diethoxyphosphorylquinolin-4-ones* ***13a–f*** *or 3-diethoxyphosphoryl-1,8-naphthyridin-4-ones* ***13g–j***: NaH (0.22 g, 9.0 mmol) was added to a solution of **12a** (2.60 g, 6.0 mmol) in dry toluene (30 mL) at rt. The mixture was heated for 18 h at 110 °C. Next, H_2O (10 mL) was added and the aqueous layer was extracted with toluene (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 100:1), to give **13a** (2.23 g, 93%), as a yellow solid; mp = 116–118 °C. ^{31}P NMR (63 MHz, $CDCl_3$) δ 17.29. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21–2.20 (m, 10H, 5 × CH_2); 1.36 (t, 6H, $^3J_{H-H}$ = 7.1 Hz, 2 × CH_3CH_2O); 4.11–4.35 (m, 5H, 2 × CH_2O, *CH*); 7.39 (dd, 1H, $^3J_{H-H}$ = 8.6 Hz, $^4J_{H-H}$ = 1.7 Hz, CH_{Ar}); 7.53 (d, 1H, $^4J_{H-H}$ = 1.7 Hz, CH_{Ar}); 8.42 (d, 1H, $^3J_{H-H}$ = 8.6 Hz, CH_{Ar}); 8.45 (d, 1H, $^3J_{H-P}$ = 13.8 Hz, *CH*CP). ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.59 (d, $^3J_{C-P}$ = 6.6 Hz, 2 × CH_3CH_2O); 23.32 (s, CH_2); 24.00 (s, 2 × CH_2); 30.71 (s, 2 × CH_2); 57.86 (s, *CH*); 60.82 (d, $^2J_{C-P}$ = 5.8 Hz, 2xCH_2O); 106.64 (d, $^1J_{C-P}$ = 193.6 Hz, *C*P); 113.19 (s, CH_{Ar}); 123.51 (s, CH_{Ar}); 124.52 (d, $^3J_{C-P}$ = 10.7 Hz, *C*C(O)); 127.57 (s, CH_{Ar}); 137.57 (s, *C*Cl); 138.97 (s, *C*N); 144.90 (d, $^2J_{C-P}$ = 18.3 Hz, *CH*CP); 173.38 (d, $^2J_{C-P}$ = 3.8 Hz, *C*(*O*)). IR: 1031, 1256, 1636, 3072 cm^{-1}. Anal. calcd for $C_{19}H_{25}ClNO_4P$: C, 57.36; H, 6.33; N, 3.52. Found: C, 57.15; H, 6.56; N, 3.78.
22. *Phosphonic diacids* ***20*** *were prepared according to the literature procedure*: McKenna, C. S.; Schidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, 739. For example: product **14c** was isolated as a brown solid, mp = 207–209 °C. ^{31}P NMR (63 MHz, $CDCl_3$ + CF_3COOH) δ 11.62. ^{1}H NMR (250 MHz, $CDCl_3$ + CF_3COOH) δ 4.41 (s, 3H, CH_3N); 7.88 (d, 1H, $^3J_{H-H}$ = 8.9 Hz, CH_{Ar}); 8.03 (s, 1H, CH_{Ar}); 8.55 (d, 1H, $^3J_{H-H}$ = 8.9 Hz, CH_{Ar}); 9.27 (d, 1H, $^3J_{H-P}$ = 10.8 Hz, *CH*CP). ^{13}C NMR (101 MHz, $CDCl_3$ + CF_3COOH) δ 44.30 (s, CH_3N); 106.29 (d, $^1J_{C-P}$ = 190.3 Hz, *C*P); 117.55 (s, CH_{Ar}); 119.26 (d, $^3J_{C-P}$ = 10.8 Hz, *C*C(O)); 127.59 (s, CH_{Ar}); 130.82 (s, CH_{Ar}); 141.02 (s, *C*Cl); 145.18 (s, *C*N); 152.73 (d, $^2J_{C-P}$ = 15.5 Hz *CH*CP); 171.55 (d, $^2J_{C-P}$ = 4.6 Hz, *C*(*O*)). IR: 1040, 1127, 1612 cm^{-1}. Anal. calcd for $C_{10}H_9ClNO_4P$: C, 43.90; H, 3.32; N, 5.12. Found: C, 43.74; H, 3.51; N, 4.89.
23. *Phosphonic monoacids* ***15*** *were prepared according to the literature procedure*: Krawczyk, H. *Synth. Commun.* **1997**, *27*, 3151–3161. For example: product **15c** was isolated as a white solid, mp = 199-202 °C. ^{31}P NMR (63 MHz, $CDCl_3$) δ 14.01. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (t, 3H, $^3J_{H-H}$ = 7.1 Hz, CH_3CH_2O); 4.00 (s, 3H, CH_3N); 4.10 (dq, 2H, $^3J_{H-H}$ = 7.1; $^3J_{H-P}$ = 7.1, CH_2O); 7.45 (dd, 1H, $^3J_{H-H}$ = 8.7 Hz, $^4J_{H-H}$ = 1.6 Hz, CH_{Ar}); 7.53 (d, 1H, $^4J_{H-H}$ = 1.6 Hz, CH_{Ar}); 8.28 (d, 1H, $^3J_{H-H}$ = 8.7 Hz, CH_{Ar}); 8.63 (d, 1H, $^3J_{H-P}$ = 12.2 Hz, *CH*CP). ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.33 (d, $^3J_{C-P}$ = 6.9 Hz, CH_3CH_2O); 41.74 (s, CH_3N); 62.09 (d, $^2J_{C-P}$ = 5.7 Hz, CH_2O); 109.19 (d, $^1J_{C-P}$ = 181.0 Hz, *C*P); 116.10 (s, CH_{Ar}); 123.47 (d, $^3J_{C-P}$ = 10.7 Hz, *C*C(O)); 126.42 (s, CH_{Ar}); 128.25 (s, CH_{Ar}); 140.00 (s, *C*Cl); 140.94 (s, *C*N); 150.90 (d, $^2J_{C-P}$ = 16.1 Hz *CH*CP); 176.22 (d, $^2J_{C-P}$ = 5.1 Hz, *C*(*O*)). IR: 1043, 1590, 1621 cm^{-1}. Anal. calcd for $C_{12}H_{13}ClNO_4P$: C, 47.78; H, 4.34; N, 4.64. Found: C, 47.52; H, 4.29; N, 4.43.