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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 9677–9684

Synthesis of triazolyl-alkylphosphonate starting from ω-azidoalkylphosphonates or ω-alkynylphosphonates

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Received 8 June 2007; revised 5 July 2007; accepted 11 July 2007
Available online 15 July 2007

Abstract—1,2,3-Triazolyl-alkylphosphonates are synthesised according to a Huisgen 1,3-dipolar cycloaddition catalysed by copper salts. The cycloaddition of either an alkynylphosphonate with an azidoalkane or an azido-phosphonate with an alkyne is achieved in high yield and regiospecifically. As an illustration of the functionalisation of aromatic ligands by using the catalytic version of the Huisgen reaction, the coupling of 3-ethynyl-1,10-phenanthroline with azidoalkylphosphonate is reported.

1. Introduction

Phosphonate or phosphonic acid's functional groups have been widely used for numerous applications including the design of organic materials,[1] hybrid materials (MOF's),[2] anchoring group for the grafting of organic molecules on the surface inorganic support[3] and applied, for instance, for the design of solar cells.[4] Further, phosphonic acid derivatives have been proven to be efficient as a corrosion inhibitor.[5] These two functional groups are also present in several bio-active compounds,[6] and have been used to design cationic lipids,[7] which have been applied, for instance, as carrier of DNA.[8]

The classical methods used to introduce the phosphate function are based on the phosphorus–carbon bond formation. For instance, the Michaelis–Arbuzov reaction[9] (synthesis of alkylphosphonate) and the Fields reaction (synthesis of aminomethylenephosphonate[10] or phosphonic acid[11]) are two well established methods for this purpose. A complementary approach would consist to construct the targeted polyfunctionalised molecule following a more convergent scheme of synthesis, by the assembly of molecules already functionalised. With such strategy, aiming to incorporate simultaneously into the final molecules a linear spacer ended by a phosphonate functional group, we propose to use bifunctional precursors (ω-alkynylphosphonate or ω-azidoalkylphosphonate) possessing the desired spacer (an alkyl chain).

These precursors will be of great interest to functionalise aromatic ligands with the goal of their immobilisation on the surface of a metal oxide by using methods reported in the literature.[3] The Huisgen reaction (1,3-dipolar cycloaddition reaction between terminal alkyne and an azide[12]), which is characterised by its efficiency and its tolerance towards several functional groups has been selected to construct this convergent scheme of synthesis. Of note, the recent improvements of this reaction, based on the use of a copper (I) catalysis,[13] have been widely reported to produce exclusively one regioisomer the 1,4-disubstituted-1,2,3-triazole.[14,15] In order to apply this coupling reaction for the introduction of linear chains ended by a phosphonate functional group, two strategies, involving either an ω-alkynylphosphonate **A** or an ω-azidophosphonate **B**, can be envisaged (Scheme 1). The synthesis of ω-alkynylphosphonate **A**, necessary for the first approach, can be synthesised according to a methodology recently reported by us[18,19] (Fig. 1). The second strategy needs ω-azidophosphonates **B**, which can be obtained from the methods reported herein or reported in literature. We report in this paper the use of

Keywords: Phosphonate; Azide; Alkyne; Huisgen reaction.
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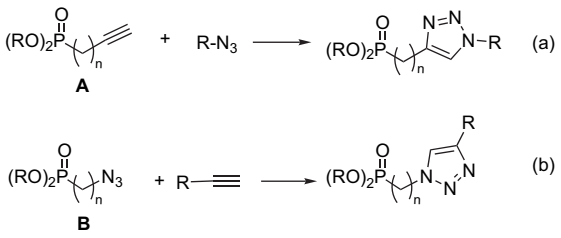
doi:10.1016/j.tet.2007.07.024

both azidophosphonates and alkynylphosphonate as precursors for the Huisgen reaction catalysed by copper salts. The application of this cycloaddition to functionalise a neutral bidentate ligand (1,10-phenanthroline) is also reported. This reaction is also an interesting method to produce azaheterocyclicphosphonates.[20,17]



Scheme 1.

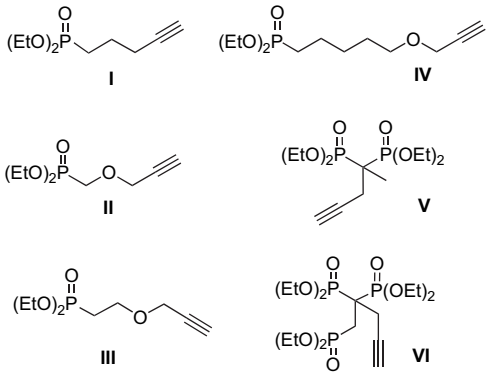


Figure 1.

2. Results and discussion

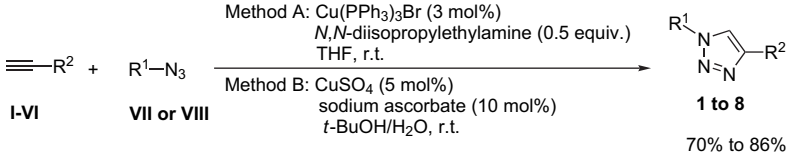
In a first part, we have studied the Huisgen cycloaddition reaction engaging one alkynylphosphonate **I–VI** and an azidoalkane[21,22] **VII** or **VIII**. First of all we have studied the possibility to catalyse the cycloaddition by a copper complex. The method A ($Cu(PPh_3)_3Br$, *N*,*N*-diisopropylethylamine in THF at room temperature)[23] was first evaluated.

As reported into Table 1 (entries 1 and 2) this method was inefficient for these substrates. Then the method B (copper acetate/sodium ascorbate/*t*-BuOH/water[24]), which consists in the generation of Cu^I from Cu^{II} salts by reduction in presence of sodium ascorbate, has been successfully achieved. Indeed, with this method the cycloaddition occurs in high yield and the presence of only one regioisomer is observed (1,4-disubstituted triazole). Moreover, this method has the advantage of not requiring inert atmospheres despite of the instability of the Cu^I oxidation state in the presence of oxygen.[25] Of note, no traces of phosphonate degradation were observed. The reactions were monitored by IR where the azide and the nitrile signatures are characteristic (respectively, 2090 and 2250 cm^{-1}). The steric hindrance at proximity of the alkyne triple bond does not inhibit the cycloaddition reaction (entries 9 and 10) even if the kinetics is decreased (72 h required). Hence the presence of one or more phosphonate group does not interfere with the cycloaddition reaction.

The second way to produce triazolyl phosphonates according to a convergent scheme of synthesis consists to perform the 1,3-dipolar cycloaddition involving the reaction of an azidoalkylphosphonate with an alkyne (**IX** or **X**). The azidoalkylphosphonate (**XII**, **9** or **10**) are readily obtained according to reported methods (**XII**[25]) or from the ω-halogenoalkylphosphonate by reaction with sodium azide (**9** and **10**). The method B (copper acetate/sodium ascorbate/*t*-BuOH/water) was used to achieve these catalysed Huisgen couplings. As reported in Table 2, the yields are good (from 75 to 91%) and the reaction is regiospecific. The regioselectivity of the reaction has been proved by NMR analysis and also, in the case of the compound **11**, by its single-crystal structure. As reported on the ORTEP view of the crystal structure of compound **11** (Fig. 2), the triazole heterocycle ring is substituted in position 1 and 3. Also the co-planarity of the phenyl ring with the triazole heterocycle is noteworthy. Of note, several crystals of compound **11** were tested and all of them possessed the same cell parameters indicating that sample seems to be homogeneous.

To illustrate the functionalisation of a ligand with an alkylphosphonate by using the Huisgen cycloaddition, we have

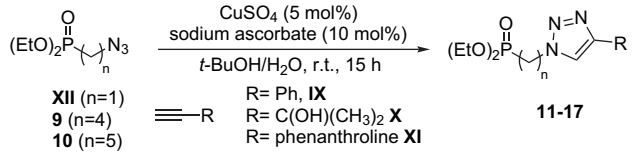
Table 1. 'Click chemistry' reaction with alkynylphosponate **I–VI**



Entry	Alkyne	Azide	R^1	Method	Time (h)	Product yield[a] (%)	Product
1	**I**	**VII**	CH_3–$(CH_2)_{11}$–	A	12	0	
2	**II**	**VII**	CH_3–$(CH_2)_{11}$–	A	12	0	
3	**I**	**VII**	CH_3–$(CH_2)_{11}$–	B	12	88	**1**
4	**II**	**VII**	CH_3–$(CH_2)_{11}$–	B	12	90	**2**
5	**I**	**VIII**	NC–$(CH_2)_4$–	B	12	80	**3**
6	**II**	**VIII**	NC–$(CH_2)_4$–	B	12	83	**4**
7	**III**	**VIII**	NC–$(CH_2)_4$–	B	12	86	**5**
8	**IV**	**VIII**	NC–$(CH_2)_4$–	B	12	82	**6**
9	**V**	**VIII**	NC–$(CH_2)_4$–	B	72	75	**7**
10	**VI**	**VIII**	NC–$(CH_2)_4$–	B	72	70	**8**

[a] Isolated yield.

Table 2. 'Click chemistry' reaction with azidophosphonate



Entry	R	*n*	Azide	Yield[a] (%)	Product
1	Ph	1	**XII**	83	**11**
2	$C(OH)(CH_3)_2$	1	**XII**	85	**12**
3	Ph	4	**9**	84	**13**
4	$C(OH)(CH_3)_2$	4	**9**	75	**14**
5	Ph	5	**10**	91	**15**
6	$C(OH)(CH_3)_2$	5	**10**	82	**16**
7	1,10-Phenanthroline	5	**10**	75	**17**

[a] Isolated yield.

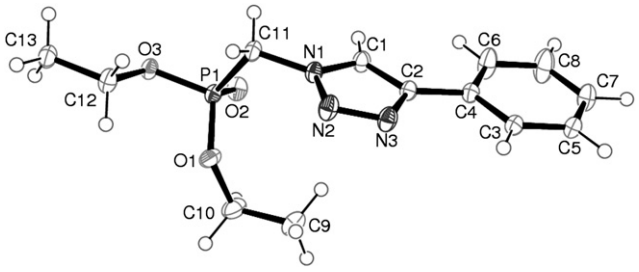


Figure 2. ORTEP diagram (50% ellipsoid) of single-crystal XRD structure of compound **11**. Selected bond length (Å) and angles (°): P1–O2 (1.465), P1–O1 (1.572), P1–O3 (1.570), C2–C4 (1.466), C1–C2 (1.381), C9–C10 (1.494), N1–N2 (1.348), N3–N2 (1.315), C1–N1–N2 (111.09), N1–C11–P1 (113.38), C11–P1–O2 (113.75).

selected the 1,10-phenanthroline, which is a ligand frequently employed in homogeneous catalytic systems.[27] The coupling reaction involves ethynyl-1,10-phenanthroline **XI**[28] (entry 7, Table 2) and the azidopentylphosphonate **10**. The other conditions are similar to those previously reported. The coupling product **17** was isolated in good yield (75%).

3. Conclusion

The 1,3-dipolar cycloaddition Huisgen reactions catalysed by copper sulfate and engaging either an alkyne-phosphonate with an alkyl-azide or an azido-phosphonate with an alkyne are reported. The resulting triazolylalkyl-phosphonates, produced in good yield, are formed regiospecifically. This regiospecificity constitutes a great improvement compared to the thermal cycloaddition reported earlier.[16] Of note, the workup is facilitated because no trace of side product or excess of reactant is present at the end of the reaction. As an illustration of the functionalisation of an aromatic ligand by 1,3-cycloaddition with an azido-phosphonate, 3-ethynyl-[1,10]-phenanthroline has been successfully engaged in this reaction. This convergent method to synthesise phosphonate and poly-phosphonate is readily achieved and the molecules formed are of a great interest for the grafting of organic compounds on the surface of inorganic supports. Noticeably the presence of several phosphonate groups could increase the stability of the grafting.

4. Experimental section

4.1. General methods

Most of the reactions were carried out under nitrogen or argon atmosphere with magnetic stirring and monitored by TLC using silica plates. Synthesised products were purified by distillation or flash column chromatography on silica gel. IR spectra were obtained as solids or neat liquids with a Fourier transform Perkin–Elmer Spectrum One with ATR accessory. Only significant absorptions are listed. The ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded in $CDCl_3$, with a Bruker AC 250 or a Bruker AC 400 spectrometers. The chemical shifts δ are expressed in parts per million, conventional abbreviations are used. Mass spectra were recorded on a QTOF Micro (Waters), ionisation electrospray positive (ESI), lockspray PEG, infusion introduction (5μL/min), source temperature 80 °C, desolvatation temperature 120 °C. Elemental analyses were recorded with an automatic apparatus CHNS-O ThermoQuest. Alkyne-phosphonate **I**–**VI**,[18] azidododecane **VII**,[21a] 4-azidopentane nitrile **VIII**,[28] azido-phosphonate **IX**[26] and 3-ethynyl-1,10-phenanthroline **X**[28] were synthesised following the reported methods.

4.2. General procedure for the Huisgen reaction

In a dry 25 mL round bottom flask were placed alkyne (1.00 equiv), azide (1.00 equiv), copper sulfate (5 mol %), and sodium ascorbate (10 mol %) in 3 mL of a mixture *tert*-butanol/water (50:50). The reaction mixture is stirred at room temperature for 18 h. Water (15 mL) was added and the crude product was extracted with ethyl acetate (3×40 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by chromatography on silica gel (dichloromethane/methanol).

4.3. Huisgen reaction involving ω-alkynylphosphonates

4.3.1. Diethyl 3-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)propylphosphonate 1. General procedure for the Huisgen reaction with 204 mg of diethyl pentynylphosphonate **I** (1 mmol, 1 equiv), 211 mg of azidododecane (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 365 mg of compound **1** as a colourless oil. Yield=88%. IR (neat, ν cm^{-1}): 2924, 2854, 1460, 1230, 1096, 1026, 958. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.96 (t, $^{3}J_{HH}$=7 Hz, 3H, $CH_3(CH_2)_{10}$), 1.20 (br s , 20H, $(CH_2)_{10}CH_2N$), 1.31 (t, $^{3}J_{HH}$=7 Hzs, 6H, CH_3CH_2O), 1.70–2.13 (m, PCH_2CH_2), 2.82 (t, $^{3}J_{HH}$=7 Hz, 2H, $CH_2C{=}CH$), 4.15 (m, 4H, CH_3CH_2OP), 4.32 (t, $^{3}J_{HH}$=7 Hz, 2H, $(CH_2)_{10}CH_2N$), 7.30 (s, 1H, $CH{=}C$). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.9. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 14.1 (s, CH_3), 16.4 (d, $^{3}J_{CP}$=6 Hz, 2×CH_3CH_2O), 22.4 (d, $^{2}J_{CP}$=5 Hz, PCH_2CH_2), 22.6 (s, CH_2CH_3), 25.1 (d, $^{1}J_{CP}$=156 Hz, PCH_2), 26.5 (s, CH_2), 28.9 (s, CH_2), 29.3 (s, CH_2), 29.4 (s, CH_2), 29.5 (s, 2×CH_2), 29.6 (s, 2×CH_2), 30.3 (s, CH_2), 31.9 (s, CH_2), 50.2 (s, CH_2N), 61.5 (d, $^{2}J_{CP}$=7 Hz, 2×CH_3CH_2OP), 120.8 (s, $CH{=}C$), 146.8 (s, $CH{=}C$). MS *m*/*z* (%): 416 (M+H, 47), 388 (37), 360 (15), 250 (100). HRMS

(ES-TOF) calcd for $C_{21}H_{43}N_3O_3P$ M+H 416.3018, found 416.3022.

4.3.2. Diethyl [(1-dodecyl-1*H*-1,2,3-triazol-4-yl)methoxy]-methylphosphonate 2. General procedure for the Huisgen reaction with 206 mg of diethyl (prop-2-ynyloxy)methylphosphonate **II** (1 mmol, 1 equiv), 211 mg of azidododecane (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 400 mg of compound **2** as a colourless oil. Yield=90%. IR (neat, ν cm^{-1}): 2923, 2854, 1466, 1250, 1096, 1022, 964. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (t, $^3J_{HH}$=7 Hz, 3H, CH_3(CH_2)$_{10}$), 1.25 (s_{large}, 20H, (CH_2)$_{10}$CH_2N), 1.35 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 3.82 (d, $^2J_{HP}$=12 Hz, 2H, PCH_2O), 4.29 (m, 4H, CH_3CH_2OP), 4.37 (t, $^3J_{HH}$=7 Hz, 2H, (CH_2)$_{10}$CH_2N), 4.77 (s, 2H, OCH_2C=C), 7.57 (s, 1H, C*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 21.4. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 14.4 (s, *C*H_3), 16.4 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 22.7 (s, *C*H_2CH_3), 26.5 (s, *C*H_2CH_2CH_3), 28.9 (s, *C*H_2CH_2CH_2CH_3), 29.3–30.3 (m, 6×*C*H_2), 31.8 (s, *C*H_2CH_2N$_3$), 50.4 (s, *C*H_2N), 61.4 (d, $^2J_{CP}$=4 Hz, 2×CH_3*C*H_2OP), 63.7 (d, $^1J_{CP}$=168 Hz, P*C*H_2O), 66.2 (d, $^3J_{CP}$=6 Hz, O*C*H_2C=CH), 122.7 (s, *C*H=C), 144.9 (s, CH=*C*). MS *m*/*z* (%): 418 (M+H, 45), 314 (14), 222 (100), 169 (15). HRMS (ES-TOF) calcd for $C_{20}H_{41}N_3O_4P$ M+H 418.2811, found 418.2814.

4.3.3. Diethyl 3-[1-(4-cyanobutyl)-1*H*-1,2,3-triazol-4-yl]-propylphosphonate 3. General procedure for the Huisgen reaction with 204 mg of diethyl pentynylphosphonate **I** (1 mmol; 1 equiv), 124 mg of 5-azidopentane nitrile (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 262 mg of compound **3** as a colourless oil. Yield=80%. IR (neat, ν cm^{-1}): 2246, 1233, 1097, 1022, 956. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.31 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 1.68 (m, 2H, CH_2CH_2CN), 1.81 (m, 2H, PCH_2CH_2), 1.99 (m, 2H, PCH_2), 2.07 (m, 2H, CH_2CH_2N), 2.41 (t, $^3J_{HH}$=7 Hz, 2H, CH_2CN), 2.82 (t, $^3J_{HH}$=7 Hz, 2H, CH_2C=CH), 4.05–4.13 (m, 4H, CH_3CH_2OP), 4.39 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 7.63 (s, 1H, C*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.9. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.7 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 16.9 (s, *C*H_2CN), 22.6 (*C*H_2CH_2CN), 22.7 (d, $^2J_{CP}$=5 Hz, PCH_2CH_2), 25.2 (d, $^1J_{CP}$=140 Hz, P*C*H_2), 26.5 (d, $^3J_{CP}$=17 Hz, PCH_2CH_2CH_2), 29.4 (*C*H_2CH_2N), 49.3 (s, *C*H_2N), 61.8 (d, $^2J_{CP}$=7 Hz, 2×CH_3*C*H_2OP), 119.4 (s, *C*N), 121.4 (s, *C*H=C), 147.4 (s, CH=*C*). MS *m*/*z* (%): 329 (M+H, 65), 301 (100), 273 (32), 255 (68), 227 (62), 163 (90). HRMS (ES-TOF) calcd for $C_{14}H_{26}N_4O_3P$ M+H 329.1718, found 329.1729.

4.3.4. Diethyl {[1-(4-cyanobutyl)-1*H*-1,2,3-triazol-4-yl]-methoxy}methylphoshonate 4. General procedure for the Huisgen reaction with 206 mg of diethyl (prop-2-ynyloxy)-methylphosphonate **II** (1 mmol, 1 equiv), 124 mg of azidopentane nitrile (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 270 mg of compound **4** as a colourless oil. Yield=83%. IR (neat, ν cm^{-1}): 2246, 1246, 1096, 1019, 962. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.34 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 1.70 (m, 2H CH_2CH_2CN), 2.08 (m, 2H, CH_2CH_2N), 2.43 (t, $^3J_{HH}$=7 Hz, 2H, CH_2CN), 3.85 (d, $^2J_{HP}$=9 Hz, 2H, PCH_2O), 4.18 (m, 4H, CH_3CH_2OP), 4.44 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 4.78 (s, 2H, OCH_2C=C), 7.63 (s, 1H, C*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 22.4. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.9 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 17.0 (s, *C*H_2CN), 22.7 (*C*H_2CH_2CN), 29.45 (*C*H_2CH_2N), 49.6 (*C*H_2N), 62.9 (d, $^2J_{CP}$=6 Hz, 2×CH_3*C*H_2OP), 64.5 (d, $^1J_{CP}$=166 Hz, P*C*H_2O), 66.6 (d, $^3J_{CP}$=6 Hz, O*C*H_2C=CH), 119.3 (*C*N), 123.3 (s, *C*H=C), 144.8 (s, CH=*C*). MS *m*/*z* (%): 331 (M+H, 36), 227 (10), 169 (47), 141 (15), 135 (100). HRMS (ES-TOF) calcd for $C_{13}H_{24}N_4O_4P$ M+H 331.1535, found 331.1550.

4.3.5. Diethyl 2-{[1-(4-cyanobutyl)-1*H*-1,2,3-triazol-4-yl]methoxy}ethylphosphonate 5. General procedure for the Huisgen reaction with 220 mg of diethyl (prop-2-ynyloxy)ethylphosphonate **III** (1 mmol, 1 equiv), 124 mg of azidopentane nitrile (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 300 mg of compound **5** as a colourless oil. Yield=86%. IR (neat, ν cm^{-1}): 2247, 1224, 1095, 1021, 957. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.25 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 1.61 (m, 2H, CH_2CH_2CN), 1.99–2.08 (m, 4H, CH_2CH_2N, PCH_2), 2.35 (t, $^3J_{HH}$=7 Hz, 2H, CH_2CN), 3.71 (dt, $^3J_{HP}$=12 Hz, $^3J_{HH}$=7 Hz, 2H, PCH_2CH_2O), 3.99–4.09 (m, 4H, CH_3CH_2OP), 4.35 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 4.57 (s, 2H, OCH_2C=C), 7.59 (s, 1H, C*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 28.6. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.7 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 17.0 (s, *C*H_2CN), 22.7 (*C*H_2CH_2CN), 27.2 (d, $^1J_{CP}$=139 Hz, P*C*H_2), 29.4 (*C*H_2CH_2N), 49.5 (*C*H_2N), 62.1 (d, $^2J_{CP}$=6 Hz, 2×CH_3*C*H_2OP), 64.6 (d, $^3J_{CP}$=6 Hz, O*C*H_2C=CH), 64.8 (s_{large}, PCH_2*C*H_2O), 119.4 (*C*N), 123.0 (s, *C*H=C), 145.4 (s, CH=*C*). MS *m*/*z* (%): 345 (M+H, 70), 289 (26), 183 (100), 155 (36), 135 (73). HRMS (ES-TOF) calcd for $C_{14}H_{26}N_4O_4P$ M+H 345.1692, found 345.1691.

4.3.6. Diethyl 5-{[1-(4-cyanobutyl)-1*H*-1,2,3-triazol-4-yl]methoxy}pentylphosphonate 6. General procedure for the Huisgen reaction with 262 mg of diethyl 5-(prop-2-ynyloxy)pentylphosphonate **IV** (1 mmol, 1 equiv), 124 mg of azidopentane nitrile (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 270 mg of compound **6** as a colourless oil. Yield=82%. IR (neat, ν cm^{-1}): 2246, 1224, 1098, 1023, 957. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.31 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 1.60–1.99 (m, 10H CH_2CH_2CN, PCH_2CH_2CH_2CH_2), 2.09 (m, 2H, CH_2CH_2N), 2.41 (t, $^3J_{HH}$=7 Hz, 2H, CH_2CN), 3.51 (d, $^2J_{HP}$=9 Hz, 2H, CH_2OCH_2C=C), 4.02–4.39 (m, 4H, CH_3CH_2OP), 4.42 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 4.61 (s,

2H, OCH_2C≡C), 7.71 (s, 1H, CH≡C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 32.6. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.8 (d, $^3J_{CP}$=6 Hz, 2×CH$_3$CH$_2$O), 17.0 (s, CH$_2$CN), 21.6 (d, $^2J_{CP}$=5 Hz, CH$_2$CH$_2$PO), 22.7 (CH$_2$CH$_2$CN), 25.5 (d, $^1J_{CP}$=140 Hz, CH$_2$PO), 27.5 (d, $^3J_{CP}$=17 Hz, CH$_2$CH$_2$CH$_2$PO), 29.4 (CH$_2$CH$_2$N), 29.5 (d, $^2J_{CP}$=5 Hz, CH$_2$CH$_2$O), 49.5 (CH$_2$N), 61.8 (d, $^2J_{CP}$=6 Hz, 2×CH$_3C$H$_2$OP), 64.7 (s, CH$_2$O), 70.8 (s, OCH_2C≡CH), 119.4 (CN), 122.8 (s, CH≡C), 146.0 (s, CH≡C). MS *m/z* (%): 387 (M+H, 39), 359 (31), 341 (100), 225 (30). HRMS (ES-TOF) calcd for $C_{17}H_{32}N_4O_4P$ M+H 387.2161, found 387.2152.

4.3.7. Tetraethyl 2-[1-(4-cyanobutyl)-1*H*-1,2,3-triazol-4-yl]-1-methylethyldiphosphonate 7. General procedure for the Huisgen reaction with 340 mg of tetraethyl 1-methylbut-3-ynyldiphosphonate **V** (1 mmol, 1 equiv), 124 mg of azidopentane nitrile (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 350 mg of compound **7** as a colourless oil. Yield=75%. IR (neat, ν cm^{-1}): 2245, 1241, 1096, 1016, 959. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.20 (t, $^3J_{HH}$=7 Hz, 12H, CH_3CH$_2$O), 1.37 (t, $^3J_{HP}$=16 Hz, 3H, CH_3), 1.59 (m, 2H CH_2CH$_2$CN), 1.95 (m, 2H, CH_2CH$_2$N), 2.32 (t, $^3J_{HH}$=7 Hz, 2H, CH_2CN), 3.22 (dt, $^4J_{HH}$=3 Hz, $^3J_{HP}$=15 Hz, 2H, CH_2C≡C), 4.06 (m, 8H, CH$_3$CH_2O), 4.29 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 7.54 (s, 1H, CH≡C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 26.1. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.7 (m, 4×CH$_3$CH$_2$O, CH$_3$), 16.9 (s, CH$_2$CN), 22.6 (s, CH$_2$CH$_2$CN), 29.1 (s, CH$_2$C≡C), 29.4 (s, CH$_2$CH$_2$N), 41.7 (t, $^1J_{CP}$=134 Hz, PCP), 49.2 (s, CH$_2$N), 63.2 (d, $^2J_{CP}$=6 Hz, 4×POCH$_2$), 119.3 (CN), 124.5 (s, CH≡C), 143.0 (s, CH≡C). MS *m/z* (%): 465 (M+H, 28), 419 (100), 391 (59), 363 (24). HRMS (ES-TOF) calcd for $C_{18}H_{35}N_4O_6P_2$ M+H 465.2032, found 465.2021.

4.3.8. Hexaethyl 3-[1-(4-cyanobutyl)-1*H*-1,2,3-triazol-4-yl]propyl-1,2,2-triphosphonate 8. General procedure for the Huisgen reaction with 476 mg of hexaethyl 1-pent-4-ynyl-1,2,2-triphosphonate **VI** (1 mmol, 1 equiv), 124 mg of azidopentane nitrile (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10), R_f=0.5) to afford 420 mg of compound **8** as a colourless oil. Yield=70%. IR (neat, ν cm^{-1}): 2243, 1245, 1092, 1018, 950. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.19–1.30 (m, 18H, CH_3CH$_2$O), 1.60–1.69 (m, 2H CH_2CH$_2$CN), 1.95–1.99 (m, 2H, CH_2CH$_2$N), 2.31–2.44 (m, 4H, CH_2CN, CH_2P), 3.61 (t, $^3J_{HP}$=13 Hz, 2H, CH_2C≡C), 4.07–4.33 (m, 12H, CH$_3$CH_2O), 4.61 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 7.64 (s, 1H, CH≡C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 23.5 (d, $^3J_{PP}$=42 Hz, PCP), 23.8 (d, $^3J_{PP}$=44 Hz, PCP), 26.8 (dd, $^3J_{PP}$=47 Hz, $^3J_{PP}$=44 Hz, CH$_2P$). ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.5–16.0 (m, 6×CH$_3$CH$_2$O, CH$_3$), 17.2 (s, CH$_2$CN), 20.5 (d, $^1J_{CP}$=143 Hz, PCH$_2$), 22.7 (s, CH$_2$CH$_2$CN), 29.5 (s, CH$_2$CH$_2$N), 45.9 (t, $^1J_{CP}$=134 Hz, PCP), 49.3 (s, CH$_2$N), 62.3 (m, 6×POCH$_2$), 119.5 (CN), 125.5 (s, CH≡C), 145.2 (s, CH≡C). MS *m/z* (%): 623 (M+Na, 100), (M+H, 45). HRMS (ES-TOF) calcd for $C_{22}H_{44}N_4O_9P_3$ M+H 601.2321, found 601.2324.

4.4. Typical procedure for the synthesis of azidophosphonates

In a dry 100 mL round bottom flask fitted with a reflux condenser, were placed halogenoalkylphosphonate (1.00 equiv) and sodium azide (1.01 equiv) in 40 mL of DMF. The reaction mixture was heated at reflux for 18 h. After cooling the mixture at room temperature, 15 mL of water was added and the crude product was extracted with ethyl acetate (3×40 mL). The organic phase was then washed with water (3×10 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated and purified by chromatography on silica gel (ethyl acetate).

4.4.1. Diethyl azidobutylphosphonate 9. General procedure for the azidophosphonate with 250 mg of diethyl chlorobutylphosphonate (1.00 equiv, 1.09 mmol), 78 mg sodium azide (1.01 equiv, 1.10 mmol) in 5 mL of DMF yielded 225 mg of colourless oil (88%). IR (neat, ν cm^{-1}): 2096, 1245, 1055, 1027, 959. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.26 (t, $^3J_{HH}$=7 Hz, 6H, 2×CH_3CH$_2$O), 1.58–1.84 (m, 6H, CH_2CH$_2$CH$_2$P), 3.23 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N$_3$), 3.97–4.13 (m, 4H, 2×CH$_3$CH_2O). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.54. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.7 (d, $^3J_{CP}$=6 Hz, 2×CH$_3$CH$_2$O), 20.2 (d, $^3J_{CP}$=17 Hz, CH$_2$CH$_2$CH$_2$P), 25.6 (d, $^1J_{CP}$=155 Hz, CH$_2$PO), 29.7 (d, $^2J_{CP}$=5 Hz, CH$_2$CH$_2$PO), 51.2 (s, CH$_2$N$_3$), 61.9 (d, $^2J_{CP}$=5 Hz, 2×CH$_3C$H$_2$O). MS *m/z* (%): 236 (M+H, 20), 193 (25), 137 (100). HRMS (ES-TOF) calcd for $C_8H_{19}N_3O_3P$ M+H 236.1164, found 236.1169.

4.4.2. Diethyl azidopentylphosphonate 10. General procedure for the azidophosphonate with 1.0 g of diethyl bromopentylphosphonate (1.00 equiv, 3.50 mmol), 230 mg sodium azide (1.01 equiv, 3.53 mmol) in 5 mL of DMF yielded 870 mg of colourless oil (98%). IR (neat, ν cm^{-1}): 2092, 1237, 1022, 955. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.33 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH$_2$O), 1.43–1.78 (m, 8H, (CH_2)$_4$CH$_2$Br), 3.28 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N$_3$), 4.02–4.13 (m, 4H, CH$_3$CH_2O). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 32.00. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.4 (d, $^3J_{CP}$=6 Hz, 2×CH$_3$CH$_2$O), 22.1 (d, $^3J_{CP}$=5 Hz, CH$_2$CH$_2$PO), 25.5 (d, $^1J_{CP}$=141 Hz, CH$_2$PO), 27.9 (d, $^2J_{CP}$=17 Hz, CH$_2$(CH$_2$)$_2$PO), 29.7 (s, CH$_2$CH$_2$N$_3$), 51.1 (s, CH$_2$N$_3$), 61.5 (d, ^{2}J$_{CP}$=7 Hz, 2×CH$_3C$H$_2$O). MS *m/z* (%): 250 (M+H, 10), 207 (25), 179 (29), 165 (100), 151 (41), 137 (79), 125 (43), 111 (44). HRMS (ES-TOF) calcd for $C_9H_{20}NaN_3O_3P$ M+Na 272.1140, found 272.1139.

4.5. Huisgen reaction involving the ω-azidoalkylphosphonates

4.5.1. Diethyl 3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)methylphosphonate 11. General procedure for the Huisgen reaction with 102 mg of ethynylbenzene (1 mmol, 1 equiv), 191 mg of diethyl azidomethylphosphonate **XII** (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: dichloromethane/methanol (90:10),

R_f=0.5) to afford 244 mg of compound **11** as a white solid. After crystallisation in ethyl acetate, a colourless crystal is obtained. Yield=83%. IR (neat, ν cm^{-1}): 2927, 2871, 1223, 1020, 959. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.18 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 4.10 (m, 4H, CH_3CH_2OP), 4.76 (d, $^2J_{HP}$=12 Hz, 2H, PCH_2O), 7.30–7.40 (m, 3H, *m,p*-C*H*), 7.80 (d, $^3J_{HH}$=7 Hz, 2H, *o*-C*H*), 8.05 (s, 1H, NC*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 16.01. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 15.3 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 43.3 (d, $^1J_{CP}$=157 Hz, P*C*H_2), 62.4 (d, $^2J_{CP}$=4 Hz, 2×CH_3CH_2OP), 119.7 (s, N*C*H=C), 124.7 (s, *o-C*), 127.3 (s, *p-C*), 127.8 (s, *m-C*), 129.3 (s, quat-*C*), 147.1 (s, NCH=*C*). MS *m/z* (%): 296 (M+H, 15), 268 (52), 240 (100), 222 (8). HRMS (ES-TOF) calcd for $C_{13}H_{19}N_3O_3P$ M+H 296.1164, found 296.1165.

4.5.2. Diethyl (4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)methylphosphonate 12. General procedure for the Huisgen reaction with 84 mg of 2-methylbut-3-yn-2-ol (1 mmol, 1 equiv), 191 mg of diethyl azidomethylphosphonate **XII** (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The solution was evaporated to dryness in vacuo and 15 mL of water was added. The product was extracted with ethyl acetate (3×25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was washed with 10 mL of diethylether and with 10 mL of dichloromethane to afford 244 mg of compound **12** as a colourless oil. Yield=85%. IR (neat, ν cm^{-1}): 2927, 2871, 1223, 1020, 959. ^1H NMR (400 MHz, DMSO, δ ppm): 1.35 (t, $^3J_{HH}$=7 Hz, 6H, 2×C*H*$_3$CH$_2$O), 1.42 (s, 6H, C*H*$_3$), 3.91–4.00 (m, 4H, CH_3CH_2OP), 5.00 (d, $^2J_{HP}$=12 Hz, 2H, PCH_2N), 7.75 (s, 1H, NC*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 18.67. ^{13}C NMR (62.9 MHz, $CDCl_3$, δ ppm): 16.0 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 30.6 (s, 2×CH_3), 44.4 (d, $^1J_{CP}$=165 Hz, P*C*H_2), 62.4 (d, $^2J_{CP}$=5 Hz, 2×CH_3CH_2OP), 68.2 (s, $C(CH_3)_2OH$), 121.3 (s, N*C*H=C), 155.9 (s, NCH=*C*). MS *m/z* (%): 300 (M+Na, 100), 278 (8), 232 (48). HRMS (ES-TOF) calcd for $C_{10}H_{21}N_3O_4P$ M+H 278.1270, found 278.1282.

4.5.3. Diethyl 4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butylphosphonate 13. General procedure for the Huisgen reaction with 102 mg of ethynylbenzene (1 mmol, 1 equiv), 220 mg of diethyl azidobutylphosphonate **9** (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent dichloromethane/methanol (90:10), R_f=0.5) to afford 284 mg of compound **13** as a colourless oil. Yield=84%. IR (neat, ν cm^{-1}): 2926, 1226, 1024, 965. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.23 (t, $^3J_{HH}$=7 Hz, 6H, C*H*$_3$CH$_2$O), 1.55–1.78 (m), 1.38–1.44 (m, 4H, C*H*$_2$C*H*$_2$P), 1.96–2.07 (m, 1.38–1.44 (m, 2H, C*H*$_2$CH$_2$CH$_2$P), 3.94–4.03 (m, 4H, CH_3CH_2OP), 4.35 (t, $^3J_{HH}$=7 Hz, 2H, C*H*$_2$N), 7.35–7.43 (m, 3H, *m,p*-C*H*), 7.90 (s, 1H, NC*H*=C), 8.05 (d, $^3J_{HH}$=7 Hz, 2H, *o*-C*H*). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.09. ^{13}C NMR (62.9 MHz, $CDCl_3$, δ ppm): 16.4 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 19.6 (d, $^2J_{CP}$=5 Hz, PCH_2CH_2), 24.9 (d, $^1J_{CP}$=172 Hz, P*C*H_2), 30.7 (d, $^1J_{CP}$=15 Hz, P*C*H_2), 49.7 (s, *C*H_2N), 61.6 (d, $^2J_{CP}$=6 Hz, 2×CH_3CH_2OP), 119.6 (s, N*C*H=C), 125.6 (s, *o-C*), 128.1 (s, *p-C*), 128.8 (s, *m-C*), 130.5 (s, quat-*C*), 177.6 (s, NCH=*C*). MS *m/z* (%): 338 (M+H, 22), 193 (100), 165 (63), 137 (54). HRMS (ES-TOF) calcd for $C_{16}H_{25}N_3O_3P$ M+H 338.1634, found 338.1641.

4.5.4. Diethyl 4-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)butylphosphonate 14. General procedure for the Huisgen reaction with 84 mg of 2-methylbut-3-yn-2-ol (1 mmol, 1 equiv), 220 mg of diethyl azidobutylphosphonate **9** (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was washed with 10 mL of diethylether and with 10 mL of dichloromethane to afford 240 mg of compound **14** as a colourless oil. Yield=87%. IR (neat, ν cm^{-1}): 3330, 2950, 2840, 1650, 1120, 1015. ^1H NMR (400 MHz, DMSO, δ ppm): 1.39 (t, $^3J_{HH}$=7 Hz, 6H, C*H*$_3$CH$_2$O), 1.38 (s, 6H, C*H*$_3$), 1.38–1.44 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$P), 3.38–3.97 (m, 4H, CH_3CH_2OP), 4.25 (t, $^3J_{HH}$=7 Hz, 2H, C*H*$_2$N), 5.02 (s, 1H, O*H*), 7.92 (s, 1H, NC*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.73. ^{13}C NMR (62.9 MHz, $CDCl_3$, δ ppm): 16.2 (d, $^3J_{CP}$=7 Hz, 2×*C*H_3CH_2O), 19.0 (d, $^2J_{CP}$=6 Hz, PCH_2CH_2), 23.6 (d, $^1J_{CP}$=160 Hz, P*C*H_2), 30.2 (d, $^1J_{CP}$=15 Hz, $PCH_2CH_2CH_2$), 30.5 (s, 2×CH_3), 48.5 (s, *C*H_2N), 60.9 (d, $^2J_{CP}$=5 Hz, 2×CH_3CH_2OP), 67.0 (s, $C(CH_3)_2OH$), 120.3 (s, N*C*H=C), 155.7 (s, NCH=*C*). MS *m/z* (%): 320 (M+H, 100), 183 (46). HRMS (ES-TOF) calcd for $C_{13}H_{27}N_3O_4P$ M+H 320.1739, found 320.1742.

4.5.5. Diethyl 5-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pentylphosphonate 15. General procedure for the Huisgen reaction with 102 mg of ethynylbenzene (1 mmol, 1 equiv), 249 mg of diethyl azidopentylphosphonate **10** (1 mmol, 1 equiv), 8 mg of copper sulfate (5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography (eluent: ethyl acetate, R_f=0.6) to afford 320 mg of compound **15** as a colourless oil. Yield=91%. IR (neat, ν cm^{-1}): 2931, 1224, 1021, 958. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.24 (t, $^3J_{HH}$=7 Hz, 6H, C*H*$_3$CH$_2$O), 1.60–1.70 (m, 6H, C*H*$_2$C*H*$_2$C*H*$_2$P), 1.91 (m, 2H, C*H*$_2$CH$_2$N), 3.94–4.07 (m, 4H, CH_3CH_2OP), 4.34 (t, $^3J_{HH}$=7 Hz, 2H, C*H*$_2$N), 7.33–7.49 (m, 3H, *m,p*-C*H*), 7.93 (s, 1H, NC*H*=C), 7.95 (d, $^3J_{HH}$=7 Hz, 2H, *o*-C*H*). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.80. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.4 (d, $^3J_{CP}$=6 Hz, 2×*C*H_3CH_2O), 21.9 (d, $^2J_{CP}$=5 Hz, PCH_2CH_2), 25.3 (d, $^1J_{CP}$=172 Hz, P*C*H_2), 27.2 (d, $^3J_{CP}$=15 Hz, $PCH_2CH_2CH_2$), 29.8 (s, *C*H$_2$ CH$_2$N), 50.0 (s, *C*H_2N), 61.5 (d, $^2J_{CP}$=6 Hz, 2×CH_3CH_2OP), 119.5 (s, N*C*H=C), 125.6 (s, *o-C*), 128.0 (s, *p-C*), 128.8 (s, *m-C*), 130.6 (s, quat-*C*), 177.8 (s, NCH=*C*). MS *m/z* (%): 352 (M+H, 18), 207 (58), 179 (67), 151 (100). HRMS (ES-TOF) calcd for $C_{17}H_{27}N_3O_3P$ M+H 352.1790, found 352.1777.

4.5.6. Diethyl 5-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)pentylphosphonate 16. General procedure for the Huisgen reaction with 84 mg of 2-methylbut-3-yn-2-ol (1 mmol, 1 equiv), 249 mg of diethyl azidopentylphosphonate **10** (1 mmol, 1 equiv), 8 mg of copper sulfate

(5 mol %) and 20 mg of sodium ascorbate (10 mol %) in 10 mL of a mixture *t*-BuOH/H_2O (50:50). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was washed with 10 mL of diethylether and with 10 mL of dichloromethane to afford 332 mg of compound **16** as a colourless oil. Yield=82%. IR (neat, ν cm^{-1}): 3380, 2979, 2869, 1217, 1164, 1049, 1021, 959. ^1H NMR (400 MHz, DMSO, δ ppm): 1.27 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 1.29–1.68 (m, 12H, $CH_2CH_2CH_2P$, 2×CH_3), 1.86 (m, 2H, CH_2CH_2N), 3.93–4.15 (m, 4H, CH_3CH_2OP), 4.31 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 8.01 (s, 1H, NC*H*=C). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.73. ^{13}C NMR (62.9 MHz, $CDCl_3$, δ ppm): 16.2 (d, $^3J_{CP}$=6 Hz, 2×CH_3CH_2O), 21.4 (d, $^2J_{CP}$=5 Hz, PCH_2CH_2), 24.2 (d, $^1J_{CP}$=172 Hz, PCH_2), 26.5 (d, $^3J_{CP}$=15 Hz, $PCH_2CH_2CH_2$), 29.2 (s, CH_2CH_2N), 30.6 (s, 2×CH_3), 48.9 (s, CH_2N), 60.7 (d, $^2J_{CP}$=5 Hz, 2×CH_3CH_2OP), 66.9 (s, $C(CH_3)_2OH$), 121.4 (s, NCH=C), 155.2 (s, NCH=C). MS *m*/*z* (%): 356 (M+Na, 33), 270 (100). HRMS (ES-TOF) calcd for $C_{14}H_{28}NaN_3O_4P$ M+Na 356.1715, found 356.1725.

4.5.7. Diethyl 5-[4-(1,10-phenanthrolin-3-yl)-1*H*-1,2,3-triazol-1-yl]pentylphosphonate 17. General procedure for the Huisgen reaction with 50 mg of 3-ethynyl-1,10-phenanthroline **XI** (0.24 mmol, 1 equiv), 61 mg of diethyl 5-azidopentylphosphonate **10** (0.24 mmol, 1 equiv), 2 mg of copper sulfate (5 mol %) and 5 mg of sodium ascorbate (10 mol %) in 3 mL of a mixture *t*-BuOH/H_2O (50:50). The crude product was purified by flash chromatography using a mixture dichloromethane/methanol (80:20) as eluent (R_f=0.4) to afford 90 mg of compound **17** as a colourless oil. Yield=75%. IR (neat, ν cm^{-1}): 1226, 1019, 959. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 1.27 (t, $^3J_{HH}$=7 Hz, 6H, CH_3CH_2O), 1.39–1.76 (m, 6H, $P(CH_2)_3$), 2.06 (m, 2H, CH_2CH_2N), 4.04–4.09 (m, 4H, CH_3CH_2O), 4.45 (t, $^3J_{HH}$=7 Hz, 2H, CH_2N), 7.49 (dd, $^3J_{HH}$=2 Hz, $^3J_{HH}$=3 Hz, H_{10}), 7.81 (m, 2H, H_6, H_7), 8.07 (s, C=C*H*), 8.20 (dd, $^3J_{HH}$=2 Hz, $^4J_{HH}$=2 Hz, H_9), 8.78 (d, $^3J_{HH}$=2 Hz, H_4), 9.15 (d, $^3J_{HH}$=3 Hz, H_{11}), 9.47 (s, H_2). ^{31}P NMR (101.25 MHz, $CDCl_3$, δ ppm): 31.8. ^{13}C NMR (100.8 MHz, $CDCl_3$, δ ppm): 16.8 (d, $^3J_{CP}$=6 Hz, 2×CH_3CH_2O), 22.3 (d, $^3J_{CP}$=5 Hz, CH_2CH_2PO), 25.7 (d, $^1J_{CP}$=141 Hz, CH_2PO), 27.7 (d, $^2J_{CP}$=17 Hz, $CH_2(CH_2)_2PO$), 30.3 (s, CH_2CH_2N), 50.3 (s, CH_2N), 61.9 (d, $^2J_{CP}$=6 Hz, 2×CH_3CH_2O), 120.9 (C=*C*H), 123.4 (C_{10}), 126.3 (C_2), 127.1 (C_6), 127.6 (C_7), 128.9 (C_5), 129.1 (C_8), 132.4 (C_4), 136.4 (C_9), 144.9 (*C*=CH), 145.9 (C_{14}), 146.5 (C_{13}), 148.1 (C_2), 150. 8 (C_{11}). MS *m*/*z* (%): 454 (M+H, 36), 370 (18), 352 (100), 220 (53), 179 (20), 151 (65). HRMS (ES-TOF) calcd for $C_{23}H_{30}N_5O_3P$ M+H 454.2008, found 454.1999.

4.6. X-ray crystallographic determination of 11

Data were collected at 150 K with graphite-monochromatized Mo Kα radiation on a Bruker-Nonius Kappa II diffractometer equipped with a CCD area detector. The crystal structure was solved by direct methods using SHELX97 package.[29] All non-hydrogen atoms were refined anisotropically. All H atoms were calculated and fixed on the heavy atoms in the ideal geometry and subsequently allowed free and refined with isotropic atomic displacement parameters.

4.6.1. Compound 11. $C_{13}H_{18}NO_2$, M=295.27 g/mol, triclinic, space group P-1, a=7.3383(2) Å, b=9.5663(2) Å, c=10.3320(3) Å, α=93.294(1)°, β=98.601(1)°, γ=96.700(1)°, V=710.18(3) Å^3, Z=2, $F(000)$=312, μ=0.205 mm^{-1}, D_c=1.381 g/cm^3. The 26,715 reflections were collected of which 4501 were unique [$R_{(int)}$=0.0244]; 4115 reflections were observed [$I>2\sigma(I)$]. The final refinement gave R_1=0.0358 and wR_2=0.0951 for all reflections. Goodness of fit=1.081, residual electron density in the final Fourier map was 0.458 and −0.367 e/Å^3. CCDC number is 640677.

Acknowledgements

This work has been performed within the 'PUNCHOrga' interregional network (Pôle Universitaire de Chimie Organique). We gratefully acknowledge financial support from the 'Ministère de la Recherche et des Nouvelles Technologies', CNRS (Centre National de la Recherche Scientifique), the 'Région Basse-Normandie' and the European Union (FEDER funding) for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.024.

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