A practical synthesis of diethyl 1-[(alkylamino)(cyano)methyl]vinylphosphonates

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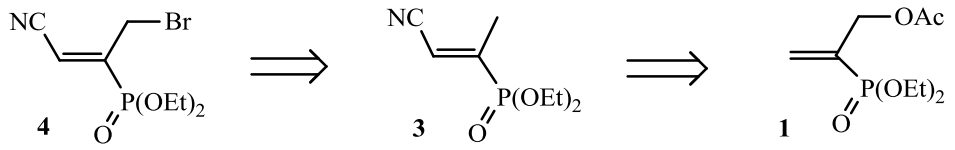
Abstract

A simple, convenient and highly stereoselective synthesis of diethyl *(E)*-1-(bromomethyl)-2-cyanovinylphosphonate **4** is described. The product would be a useful substrate for the synthesis of diethyl 1-[(alkylamino)(cyano)methyl]vinylphosphonates **5** *via* allylic rearrangement S_N2 -type mechanism.

Keywords: Functionalized allyl bromide, vinyl phosphonate, DABCO, allylamine

Introduction

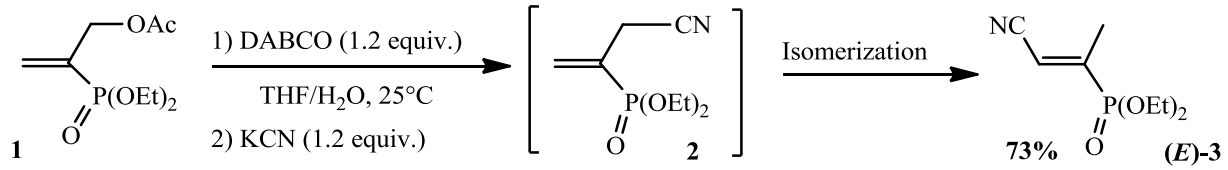
α-Functionalized acrylic compounds are the most attractive organic synthons in the synthesis of diverse functional molecules. Their high reactivity makes them versatile starting materials for the synthesis of some biological active compounds.[1,2] Indeed, allyl bromides constitute the core structures of numerous natural products[3-5] and biologically active compounds.[5-8] Considering the increased importance of bromomethylated compounds[9-14] and in connection with our research projects[15-18] on the utility of allyl bromides, we report here a novel synthetic method of diethyl (*E*)-1-(bromomethyl)-2-cyanovinylphosphonate **(*E*)-4** from diethyl 1-(acethoxymethyl) vinylphosphonate **1**. We propose the protocol as a two-step synthesis involving, first, a successive S_N2 -S_N2 reaction of 1,4-diazabicyclo[2.2.2]octane (DABCO), then KCN[18,19] on the functional allyl acetate **1**, followed by the radical brominating reaction of the β-cyanophosphonate **(*E*)-3** leading to the corresponding allyl bromide **(*E*)-4** as shown in the retrosynthetic way (Scheme 1).



Scheme 1. Retrosynthetic analysis.

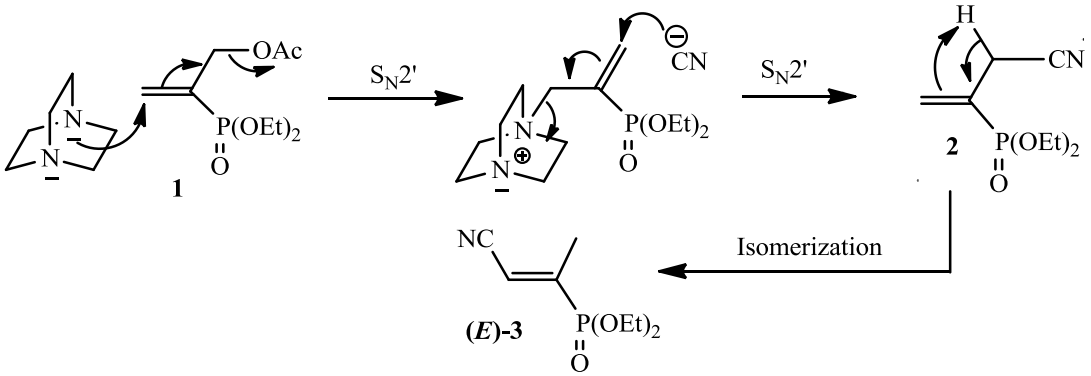
Results and Discussion

Allyl acetate **1** has been obtained by standard acetylation of diethyl 1-(hydroxymethyl) vinylphosphonate.[20] The reaction of **1** with DABCO (1.2 equiv.) in a mixture of THF-H_2O (3:1) under stirring at room temperature furnished a quaternary ammonium salt whose reaction with KCN (1.2 equiv.) generates the allyl cyanide **2** which undergoes a spontaneous isomerization offering the possibility to isolate, after usual workup, the phosphonate **(*E*)-3** in good yield (73%) (Scheme 2).



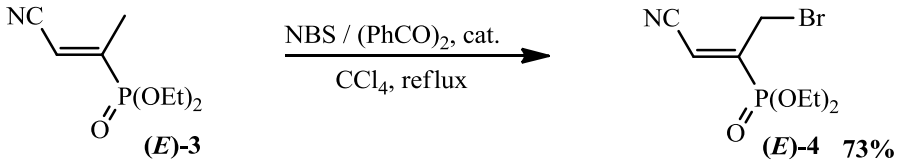
Scheme 2. Synthesis of diethyl 2-cyano-1-methylvinylphosphonate **(*E*)-3**.

Regarding the formation of **(*E*)-3**, the plausible mechanism reported in the scheme 3, indicates that this β-cyanophosphonate could be the product of two successive S_N2 -S_N2 reactions on the acetate **1**, then cyanide ions on the quaternary ammonium intermediate, leading to the vinyl phosphonate **2** which spontaneously rearranges on its positional isomer **(*E*)-3** (Scheme 3).



Scheme 3. Proposed mechanism for the synthesis of β-cyanovinylphosphonate **(*E*)-3.**

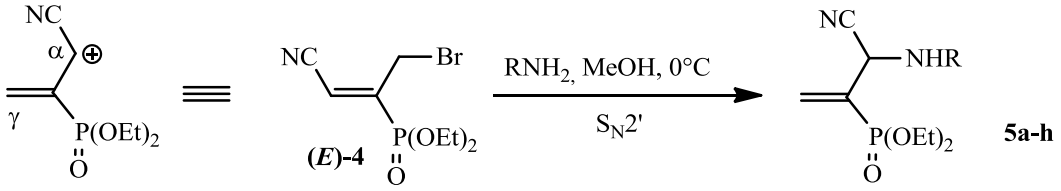
The selective bromination of the new β-cyanovinylphosphonate **(*E*)-3** *via* the use of N-bromosuccinimide (NBS)[21] in the presence of catalytic amount of benzoyl peroxide in carbon tetrachloride (CCl_4) at reflux, leads only to the *E* isomer of the expected diethyl *(E)*-1-(bromomethyl)-2-cyanovinylphosphonate **(*E*)-4** in good yield (Scheme 4).



Scheme 4. Synthesis of allyl bromide **(*E*)-4** from nitrile **(*E*)-3** *via* radical brominating reaction.

For both compounds **(*E*)-3** and **(*E*)-4**, the preferred configuration being *E* as confirmed by two-dimensional NMR (NOESY). Indeed, there is no correlation between the ethylenic proton (6.09 ppm) and those of methyl group (1.29 ppm) for the allyl nitrile **3**, then the vinylic proton (6.26 ppm) and those of CH_2Br (4.18 ppm) in the case of the allyl bromide **(*E*)-4**. This result may justify the geometry of each synthetic intermediate **(*E*)-3** and **(*E*)-4** in order to achieve the synthesis of functional allylamines **5**. Due to the synthetic importance of allyl bromide **(*E*)-4,** we believe that these adducts could be used in one step synthesis of a new family of functionalized allylamines **5**. It should be noted that these compounds might be effective precursors in organic synthesis[22], including biologically active products such as *Streptogramin* antibiotics,[23] alkaloids[24] and antifungal chemotherapeutic agents,[25] and in several naturally occurring compounds.[26-32]

Because of the importance of functionalized allylamines[17,18, 33-36] and their applications, we report herein a simple and economical method for their synthesis from the reaction coupling of allyl bromide **(*E*)-4** with various primary amines in methanol at 0 °C. As reported in our previous works,[18,33] allyl bromide **(*E*)-4** could be considered as an allyl cation equivalent which reacts with a variety of nucleophiles including primary amines. Thus, the regioselectivity and the abnormal (S_N2) substitution product can be explained by the increased electrophilicity of γ-carbon of **(*E*)-4** leading to a new family of diethyl 1-[(alkylamino)(cyano)methyl]vinylphosphonates **5 a-h** in moderate yields (Scheme 5, Table 1).



Scheme 5. Conversion of allyl bromide **(*E*)-4** into allylamines **5**.

Table 1. Synthesis of diethyl 1-[(alkylamino)(cyano)methyl]vinylphosphonates **5 a-h**

Product	R	Time (h)	Yield (*) (%)
5 a	$C_6H_5CH_2$	2	61
5 b	p-$MeOC_6H_4CH_2$	1.5	56
5 c	i-Pr	4	45
5 d	c-C_6H_{11}	4	50
5 e	p-$ClC_6H_4CH_2$	3	54
5 f	C_6H_5CHMe	2.5	66
5 g	n-Bu	3	48
5 h	p-$FC_6H_4CH_2$	2	74

(*) Yields refer to the pure isolated products characterized by ^1H, ^{13}C NMR.

Conclusion

We developed a simple and reliable two step synthetic way to prepare a new multifunctional allyl bromide **(*E*)-4** which can be efficiently converted into allylamines **5**. We believe that the simplicity of the protocol and the importance of new Michael acceptors **5** isolated and their useful applications in organic synthesis would make this method very convenient.

Experimental Section

General Procedures. ^1H-NMR and ^{13}C-NMR spectra were recorded on Bruker AMX 300 spectrometer working at 300 MHz, 121 MHz and 75 MHz respectively for the proton, ^{31}P and ^{13}C with $CDCl_3$ as the solvent and TMS as the internal standard. The chemical shifts (δ) and coupling constants *(J)* are, respectively, expressed in parts per million (ppm) and Hertz (Hz). All NMR spectra were acquired at room temperature. Assignments of proton (^1H-NMR) and carbon (^{13}C-NMR) signals were secured by DEPT 135 and HMBC experiments. Multiplicity of peaks is indicated by the following: s, singlet; d, doublet; t, triplet; dt, doublet of triplets; q, quartet; dq, doublet of quartets; br, board; m, multiplet. The elementary analyses (C, H, N) were performed on a Perkin-Elmer 240 B microanalyser. All reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F254, Merck) eluting with the solvents indicated, visualized by a 254 nm UV lamp and aqueous potassium permanganate solution. For column chromatography, Fluka Kieselgel 70-230 mesh was used.

Diethyl 1-(acethoxymethyl) vinylphosphonate (1). To a mixture of diethyl 1-(hydroxymethyl) vinylphosphonate (20 mmoles), acetic anhydride (60 mmoles) in 80 mL of anhydrous ether cooled at 0 °C under stirring in nitrogen atmosphere, was added a drop of concentrated sulfuric

acid. After completion of the reaction, the mixture was hydrolyzed with ice water and extracted with ether (3x20 mL). The organic layers were washed successively with sodium hydroxide solution (1.5 M) and brine until neutral pH then dried over $MgSO_4$ and concentrated in vacuo. After evaporating of the solvent, the oily residue obtained was distilled under reduced pressure to obtain the allyl acetate **1**. Colorless oil. Yield: 75%, b.p. 98 °C/0.6 mmHg; ^{1}H-NMR (300 MHz, $CDCl_3$) : 6.14 (d, 1H, $^3J_{HP}$= 24 Hz, =CH); 5.96 (d, 1H, $^3J_{HP}$= 31 Hz, =CH); 4.67 (d, 2H, $^3J_{HP}$= 9 Hz, OCH_2); 4.05 (dq, 4H, *J*= 6.75 Hz, *J*= 6.75 Hz, $2OCH_2$); 2.05 (s, 3H, CH_3); 1.27 (t, 6H, *J*= 6 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): 170.1 (s, C=O); 134.6 (d, =C, $^1J_{CP}$= 176.3 Hz); 130.9 (d, $=CH_2$, $^2J_{CP}$= 17 Hz); 62.8 (d, $2OCH_2$, $^2J_{CP}$= 18 Hz); 62.1 (d, OCH_2, $^2J_{CP}$= 6 Hz); 20.7 (CH_3); 16.2 (d, $2CH_3$, $^3J_{CP}$= 6 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :15.8.

Diethyl (*E*)-2-cyano-1-methylvinylphosphonate (3). To a mixture of diethyl 1-(acethoxymethyl) vinylphosphonate **1** (5mmol) in 20 mL of (THF/H_2O) (3:1) was added 1,4-diazabicyclo[2.2.2]octane (DABCO) (6 mmol). The reaction mixture was stirred at room temperature until the DABCO salt was formed, then KCN (6 mmol) was added. After stirring for 2 hours, the reaction was completed as monitored by TLC. After addition of saturated solution of NH_4Cl (10 mL), the mixture was extracted with ether (3x20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was separated by chromatography on silica gel (Hexane-AcOEt, 2:8) providing the nitrile **(*E*)-3**. Yellow liquid. Yield: 73%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 6.09 (d, 1H, $^3J_{HP}$= 21 Hz, =CH); 4.07 (dq, 4H, *J*= 7.5 Hz, *J*= 7.5 Hz, $2OCH_2$); 2.13 (d, 3H, $^3J_{HP}$= 15 Hz, CH_3); 1.29 (t, 6H, *J*= 7.5 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): 151.3 (d, =C, $^1J_{CP}$= 174.7 Hz); 114.5 (d, CN, $^3J_{CP}$= 31.5 Hz); 110.8 (d, =CH, $^2J_{CP}$= 18.7 Hz); 62.9 (d, $2OCH_2$, $^2J_{CP}$= 6 Hz); 17.5 (d, CH_3, $^2J_{CP}$= 7.5 Hz); 16.2 (d, $2CH_3$, $^3J_{CP}$= 6 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :13.9. Anal. Calcd for $C_8H_{14}NO_3P$ (203.17) C, 47.29; H, 6.95; N, 6.89%. Found: C, 47.06; H, 6.86; N, 6.79%.

Diethyl *(E)*-1-(bromomethyl)-2-cyanovinylphosphonate (4). To a solution of 0.5 g of diethyl 2-cyano-1-methylvinylphosphonate **(*E*)-3** (2.5 mmoles) in 10 mL of anhydrous carbon tetrachloride was added 1.11g of NBS (6.25 mmoles) and 0.01g of benzoyl peroxide. The reaction mixture was stirred at reflux under nitrogen atmosphere for 8 hours. After cooling, the mixture was filtered and the solvent was removed in vacuo and the obtained residue was purified by column chromatography (Hexane-AcOEt, 6:4). Yellow-orange liquid. Yield: 73%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 6.26 (d, 1H, $^3J_{HP}$= 18 Hz, =CH); 4.18 (d, 2H, $^3J_{HP}$= 17.1 Hz, CH_2Br); 4.13 (m, 4H, $2OCH_2$); 1.31 (t, 6H, *J*= 7.5 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): 150.3 (d, =C, $^1J_{CP}$= 179.3 Hz); 114.6 (d, =CH, $^2J_{CP}$= 18 Hz); 113.3 (d, CN, $^3J_{CP}$= 28.5 Hz); 63.5 (d, $2OCH_2$, $^2J_{CP}$= 8 Hz); 23.5 (d, CH_2Br, $^2J_{CP}$= 8.2 Hz); 16.2 (d, $2CH_3$, $^3J_{CP}$= 6.7 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :11.2. Anal. Calcd for $C_8H_{13}BrNO_3P$ (282.07) C, 34.06; H, 4.65; N, 4.97%. Found: C, 33.89; H, 4.59; N, 4.90%.

Procedure for the synthesis of diethyl 1-[(alkylamino)(cyano)methyl]vinylphosphonates (5 a-h). To a solution of allyl bromide **(*E*)-4** (0.7g, 2.25 mmol) in 5 mL of absolute methanol was added dropwise primary amine (4.5 mmol). The reaction mixture was stirred at 0 °C for 1.5-

4 hours, then the mixture was concentrated and the methanol was removed under reduced pressure. The liquid obtained was purified by column chromatography (Hexane-AcOEt, 1:1).

Diethyl 1-[(benzylamino)(cyano)methyl]vinylphosphonate (5a). Yellow liquid. Yield: 61%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 7.27 (m, 5H, H aromatic); 6.30 (d, 1H, $^{3}J_{HP}$= 15 Hz, =CH); 6.15 (d, 1H, $^{3}J_{HP}$= 6 Hz, =CH); 4.42 (d, 1H, $^{3}J_{HP}$= 9 Hz, CHCN); 4.05 (m, 4H, $2OCH_2$) ; 3.86 (AB, 2H, *J*=12 Hz, CH_2N); 1.91 (br, s, 1H, NH); 1.22 (t, 6H, *J*= 7.5 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): 137.7, 128.5, 128.3, 127.6, (C aromatic) ; 134.4 (d, =C, $^{1}J_{CP}$= 183 Hz) ; 133.2 (d, $=CH_2$, $^{2}J_{CP}$= 7.5 Hz) ; 117.1 (d, CN, $^{3}J_{CP}$= 12 Hz) ; 62.7 (d, $2OCH_2$, $^{2}J_{CP}$= 8.25 Hz) ; 51.4 (d, CHCN, $^{2}J_{CP}$= 15 Hz); 51.1 (CH_2N); 16.2 (d, $2CH_3$, $^{3}J_{CP}$= 6 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :14.5. Anal. Calcd for $C_{15}H_{21}N_2O_3P$ (308.31) C, 58.43; H, 6.87; N, 9.09%. Found: C, 58.15; H, 6.79; N, 9.20%.

Diethyl 1-[(cyano)(4-methoxybenzylamino)methyl]vinylphosphonate (5b). Orange liquid. Yield: 56%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 7.20 (d, 2H, *J*= 6 Hz, H aromatic); 6.78 (d, 2H, *J*= 6 Hz, H aromatic); 6.30 (d, 1H, $^{3}J_{HP}$= 18 Hz, =CH); 6.15 (d, 1H, $^{3}J_{HP}$= 9 Hz, =CH); 4.39 (d, 1H, $^{3}J_{HP}$= 9 Hz, CHCN); 4.06 (dq, 4H, *J*= 7.5 Hz, *J*= 7.5 Hz, $2OCH_2$); 3.8 (AB, 2H, *J*=12 Hz, CH_2N); 3.72 (s, 1H, OCH_3); 1.95 (br, s, 1H, NH); 1.24 (t, 6H, *J*= 6 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): 167.6, 130.1, 129.7, 129.6, 113.9, (C aromatic) ; 134.4 (d, =C, $^{1}J_{CP}$= 183 Hz) ; 133.1 (d, $=CH_2$, $^{2}J_{CP}$= 7.5 Hz); 117.1 (d, CN, $^{3}J_{CP}$= 12.75 Hz); 62.6 (d, $2OCH_2$, $^{2}J_{CP}$= 8.25 Hz); 55.2 (OCH_3); 51.3 (d, CHCN, $^{2}J_{CP}$= 16.5 Hz); 50.4 (CH_2N); 16.2 (d, $2CH_3$, $^{3}J_{CP}$= 6.75 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :14.6. Anal. Calcd for $C_{16}H_{23}N_2O_4P$ (203.17) C, 56.80; H, 6.85; N, 8.28%. Found: C, 56.52; H, 6.75; N, 8.16%.

Diethyl 1-[(cyano)(isopropylamino)methyl]vinylphosphonate (5c). Yellow liquid. Yield: 45%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 6.35 (d, 1H, $^{3}J_{HP}$= 24 Hz, =CH); 6.20 (d, 1H, $^{3}J_{HP}$= 3 Hz, =CH); 4.54 (d, 1H, $^{3}J_{HP}$= 9 Hz, CHCN); 4.13 (dq, 4H, *J*= 7.5 Hz, *J*= 7.5 Hz, $2OCH_2$); 3.15 (sept, 1H, *J*= 6.2 Hz, CHN); 1.90 (br, s, 1H, NH); 1.34 (t, 6H, *J*= 7.5 Hz, $2CH_3$); 1.25 (d, 6H, *J*= 6 Hz, $2CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): 131.7 (d, =C, $^{1}J_{CP}$= 183 Hz); 128.7 (d, $=CH_2$, $^{2}J_{CP}$= 7.5 Hz); 117.9 (d, CN, $^{3}J_{CP}$= 12.75 Hz); 62.8 (d, $2OCH_2$, $^{2}J_{CP}$= 14 Hz); 49.2 (d, CHCN, $^{2}J_{CP}$= 15.75 Hz); 42.4 (CHN); 25.8 ($2CH_3$); 16.3 (d, $2CH_3$, $^{3}J_{CP}$= 6.75 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :14.4. Anal. Calcd for $C_{11}H_{21}N_2O_3P$ (260.12) C, 50.76; H, 8.13; N, 10.76%. Found: C, 50.52; H, 8.03; N, 10.63%.

Diethyl 1-[(cyano)(cyclohexylamino)methyl]vinylphosphonate (5d). Yellow liquid. Yield: 50%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 6.35 (d, 1H, $^{3}J_{HP}$= 23 Hz, =CH); 6.25 (d, 1H, $^{3}J_{HP}$= 3 Hz, =CH); 4.48 (d, 1H, $^{3}J_{HP}$= 11 Hz, CHCN); 4.10 (m, 4H, $2OCH_2$); 3.14 (m, 1H, CHN); 1.86 (m, 4H, $2CH_2$); 1.68 (m, 4H, $2CH_2$); 1.58 (br, s, 1H, NH); 1.24 (t, 6H, *J*= 7.0 Hz, $2CH_3$); 1.17 (m, 2H, CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): 134.7 (d, =C, $^{1}J_{CP}$= 181 Hz); 132.6 (d, $=CH_2$, $^{2}J_{CP}$= 7.5 Hz); 117.9 (d, CN, $^{3}J_{CP}$= 12.75 Hz); 61.9 (d, $2OCH_2$, $^{2}J_{CP}$= 14.25 Hz); 49.9 (d, CHCN, $^{2}J_{CP}$= 15.75 Hz); 48.0 (CHN); 29.7 ($2CH_2$); 23.8 ($2CH_2$) ; 21.3 (CH_2); 16.2 (d, $2CH_3$, $^{3}J_{CP}$= 6 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) : 14.4. Anal. Calcd for $C_{14}H_{25}N_2O_3P$ (300.33) C, 55.99; H, 8.39; N, 9.33%. Found: C, 55.78; H, 8.29; N, 9.20%.

Diethyl 1-[(4-chlorobenzylamino)(cyano)methyl]vinylphosphonate (5e). Yellow liquid. Yield: 54%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 7.28 (m, 4H, H aromatic); 6.40 (d, 1H, $^{3}J_{HP}$= 15 Hz, =CH_2); 6.25 (d, 1H, $^{3}J_{HP}$= 9 Hz, =CH_2); 4.49 (d, 1H, $^{3}J_{HP}$= 12 Hz, CHCN); 4.14 (dq, 4H, *J*= 6 Hz, *J*= 6 Hz, 2OCH_2); 3.9 (AB, 2H, *J*=12 Hz, CH_2N); 1.71 (br, s, 1H, NH); 1.32 (t, 6H, *J*= 7.5 Hz, 2CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): 136.2, 133.1, 130.9, 128.7 (C aromatic) ; 134.4 (d, =C, $^{1}J_{CP}$= 172.5 Hz) ; 133.4 (d, =CH_2, $^{2}J_{CP}$= 9.75 Hz); 116.9 (d, CN, $^{3}J_{CP}$= 12.7 Hz) ; 62.8 (d, 2OCH_2, $^{2}J_{CP}$= 7.5 Hz) ; 51.5 (d, CHCN, $^{2}J_{CP}$= 16.5 Hz) ; 50.3 (CH_2N); 16.3 (d, 2CH_3, $^{3}J_{CP}$= 6.75 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :14.4. Anal. Calcd for $C_{15}H_{20}ClN_2O_3P$ (342.75) C, 52.56; H, 5.88; N, 8.17%. Found: C, 52.31; H, 5.79; N, 8.92%.

Diethyl 1-[(cyano)(1-phenylethylamino)methyl]vinylphosphonate (5f). Green liquid. Yield: 66%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 7.33 (m, 5H, H aromatic); 6.33 (d, 1H, $^{3}J_{HP}$= 12 Hz, =CH); 6.22 (d, 1H, $^{3}J_{HP}$= 9 Hz, =CH); 4.16 (d, 1H, $^{3}J_{HP}$= 3 Hz, CHCN); 4.14-4.05 (massif, 5H, 2OCH_2 + CHN); 2.02 (br, s, 1H, NH); 1.41 (d, 3H, *J*= 6 Hz, CH_3); 1.31 (t, 6H, *J*= 6 Hz, 2CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): 134.7 (d, =C, $^{1}J_{CP}$= 182.2 Hz); 133.8 (d, =CH_2, $^{2}J_{CP}$= 7.5 Hz) ; 142.5, 128.7, 127.7, 126.9 (C aromatic) ; 117.3 (d, CN, $^{3}J_{CP}$= 11.25 Hz) ; 62.5 (d, 2OCH_2, $^{2}J_{CP}$= 14.2 Hz) ; 56.7 (CHN) ; 50.2 (d, CHCN, $^{2}J_{CP}$= 15.75 Hz) ; 24.7 (CH_3); 16.2 (d, 2CH_3, $^{3}J_{CP}$= 6.75 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :14.5. Anal. Calcd for $C_{16}H_{23}N_2O_3P$ (322.33) C, 59.62; H, 7.19; N, 8.69%. Found: C, 59.33; H, 7.09; N, 8.56%.

Diethyl 1-[(butylamino)(cyano)methyl]vinylphosphonate (5g). Yellow liquid. Yield: 48%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 6.33 (d, 1H, $^{3}J_{HP}$= 18 Hz, =CH); 6.23 (d, 1H, $^{3}J_{HP}$= 3 Hz, =CH); 4.52 (d, 1H, $^{3}J_{HP}$= 10.20 Hz, CHCN); 4.15 (dq, 4H, *J*= 7.35 Hz, *J*= 7.35 Hz, 2OCH_2) ; 2.78, 2.65 (2m, 2H, CH_2N); 1.90 (br, s, 1H, NH); 1.42 (m, 4H, 2CH_2); 1.35 (t, 6H, *J*= 6 Hz, 2CH_3); 0.92 (t, 3H, *J*= 7.5 Hz, CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): 134.3 (d, =C, $^{1}J_{CP}$= 183 Hz); 132.7 (d, =CH_2, $^{2}J_{CP}$= 7.5 Hz); 117.3 (d, CN, $^{3}J_{CP}$= 11.25 Hz); 62.6 (d, 2OCH_2, $^{2}J_{CP}$= 7.5 Hz); 52.5 (CH_2N); 52.3 (d, CHCN, $^{2}J_{CP}$= 15.5 Hz); 32.9 (CH_2); 20.2 (CH_2) ; 16.3 (d, 2CH_3, $^{3}J_{CP}$= 6.75 Hz); 13.8 (CH_3); ^{31}P-NMR (121 MHz, $CDCl_3$) :14.4. Anal. Calcd for $C_{12}H_{23}N_2O_3P$ (274.29) C, 52.54; H, 8.45; N, 10.21%. Found: C, 52.29; H, 8.34; N, 10.07%.

Diethyl 1-[(cyano)(4-fluorobenzylamino)methyl]vinylphosphonate (5h). Yellow liquid. Yield: 74%, ^{1}H-NMR (300 MHz, $CDCl_3$) : 7.35 (dd, 2H, *J*= 9 Hz, $^{4}J_{H\text{-}F}$= 5.7 Hz, H aromatic); 7.02 (t, 2H, $^{3}J_{H\text{-}H}$= $^{3}J_{H\text{-}F}$= 9 Hz, H aromatic); 6.37 (d, 2H, $^{3}J_{HP}$= 21 Hz, =CH); 6.27 (d, 2H, $^{3}J_{HP}$= 6 Hz, =CH); 4.49 (d, 1H, $^{3}J_{HP}$= 9 Hz, CHCN); 4.12 (q, 4H, *J*= 6 Hz, 2OCH_2); 3.91 (AB, 2H, *J*=12 Hz, CH_2N); 2.07 (br, s, 1H, NH); 1.33 (t, 6H, *J*= 7.5 Hz, 2CH_3); ^{13}C-NMR (75 MHz, $CDCl_3$): 162.3 (d, C aromatic, $^{1}J_{CF}$= 243.75 Hz,); 134.5 (d, =C, $^{1}J_{CP}$= 182.2 Hz) ; 133.6 (C aromatic); 133.2 (d, =CH_2, $^{2}J_{CP}$= 7.5 Hz); 130.1 (d, C aromatic, $^{3}J_{CF}$= 7.5 Hz,); 117 (d, CN, $^{3}J_{CP}$= 12 Hz) ; 115.4 (d, C aromatic, $^{2}J_{CF}$= 21 Hz,); 62.7 (d, 2OCH_2, $^{2}J_{CP}$= 7.5 Hz) ; 51.5 (d, CHCN, $^{2}J_{CP}$= 15.75 Hz) ; 50.3 (CH_2N); 16.3 (d, 2CH_3, $^{3}J_{CP}$= 6.75 Hz); ^{31}P-NMR (121 MHz, $CDCl_3$) :14.54; ^{19}F-NMR (282 MHz, $CDCl_3$) :-114.91. Anal. Calcd for $C_{15}H_{20}FN_2O_3P$ (326.11) C, 55.21; H, 6.18; N, 8.59%. Found: C, 54.93; H, 6.10; N, 8.48%.

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