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Facile Synthesis of Phosphorylated Azides in Ionic Liquids and Their Use in the Preparation of 1,2,3-Triazoles

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ABSTRACT: *The facile general synthetic route to azidoalkylphosphonates by the nucleophilic substitution reaction in a series of bromoalkylphosphonates was elaborated, using 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) as a recyclable reaction medium. These azidoalkylphosphonates were used as intermediates for copper(I)-catalyzed regioselective 1,3-dipolar cycloaddition with a variety of alkynes to afford 4-substituted (1H-1,2,3-triazol-1-yl)alkylphosphonates as potential drug candidates.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:293–300, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20420

INTRODUCTION

Modern drug discovery requires the identification and optimization of synthetic routes to specifically acting low-molecular weight molecules. That is why simple methods that can quickly and easily generate large libraries of compounds have emerged and are more and more used [1]. The so-called "click" methodology recently introduced by Sharpless et al. [2] is one of these methods based on reactions that are of wide scope, give high yields, and use highly energetic reactants to form irreversible carbon–heteroatom bonds. The Huisgen 1,3-dipolar cycloaddition of azides with terminal alkynes perfectly illustrates this kind of reactions. The discovery of catalytic properties of copper(I), which allows high rate and control of regioselectivity of this cycloaddition to give 1,4-disubstituted 1,2,3-triazoles, stimulated the investigations in this field over the last 5 years. The above methodology of 1,2,3-triazole ring formation has been successfully used for the synthesis of a wide range of novel biologically active compounds including triazole-linked glycoconjugates [3] and glycopeptides [4], 1,2,3-triazole-modified nucleic acids [5], 1,2,3-triazole-containing dendrimers [6], and nucleoside analogs [7]. It should be noted that despite the 1,2,3-triazole structural moiety does not occur in nature a wide range of compounds containing this functionality have exhibited diverse biological activities [8] such as anti-HIV [9],

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anti-epileptic [10], and antimicrobial [11] and act as selective β_3-adrenergic receptor agonists [12].

At the same time, it is well recognized that organophosphorus compounds also exhibit different types of bioactivity and, therefore, form an important series of compounds in the search for new drugs [13]. Phosphorylated compounds may be used as prodrugs to improve drug delivery to particular targets, and solubility of drugs could be modified by attaching phosphorus groups; for example, phosphorylation significantly increases the solubility of steroidal drugs in water. Therefore, phosphorylated 1,2,3-triazoles possessing the advantages both of triazole and phosphonate moieties may be useful as potential drug candidates.

Despite a few azidoalkylphosphonates obtained by traditional substitution of an appropriate leaving group were previously described in the literature [14], until now they did not attract much attention in synthetic and medicinal chemistry in general and in the synthesis of phosphorylated 1,2,3-triazoles via 1,3-dipolar cycloaddition with azides in particular. To the best of our knowledge, the above approach was used only for the synthesis of a phosphorylated analog of ribavirin [15] and for the transformation of bromoethylphosphonate to 4-carbomethoxy-1,2,3-triazole by a two-step one-pot procedure using the polymer-supported azide [16].

We believe that the fewer number of publications concerning the reactivity of ω-azidoalkyl phosphonates may be related to the fact that their synthesis had no general character, sometimes required rather drastic reaction conditions and resulted in the target compounds with poor yields. At the same time, it is well known that room temperature ionic liquids (RTILs), due to their potential for recyclability, ability to dissolve a variety of organic, inorganic, and metal complex materials, and promote a variety of chemical transformations, are of interest in chemistry in the search for green alternatives to traditional organic solvents [17]. Phosphorus-containing ILs (phosphonium salts having different anions and imidazolium hexafluorophosphates) are of special importance [18]. However, successful examples of ILs applications as activating media for organophosphorus synthesis are rather scare and restricted to the Wittig–Horner [19], Arbuzov [20], and Kabachnik–Fields [21] reactions and the esterification of phosphonic(phosphinic) acids by triethyl(methyl) orthoacetate [22]. A few numbers of publications in this area may be explained by easy dealkylation of phosphorus esters observed in a variety of ILs [20] instead of desired reactions involving other functionalities in the molecules. Nevertheless, the proper choice of IL in use gives the possibility to avoid such drawback.

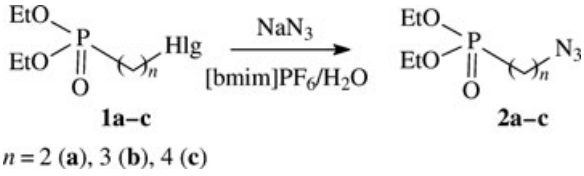
Taking into account that some RTILs, namely [bmim][PF_6], [bmim][NTf_2], and [hpyr][NTf_2], are an efficient promoting medium for nucleophilic displacement reactions [23] to give the corresponding substituted products with a considerable increase in conversion comparing the reactions performed in traditional solvents, we investigated the possibility of using ILs as promoting reaction media for the synthesis of azidoalkylphosphonates by azide/halogen exchange.

In this communication, we report the general facile route to azidoalkylphosphonates based on our recent results and demonstrate their application in the synthesis of phosphorylated triazoles.

RESULTS AND DISCUSSION

The transformation of bromoalkylphosphonates **1a–c** to the corresponding azides **2a–c** was found to give the best results in terms of both conversion and reaction rate in [bmim][PF_6] compared with [bmim][NTf_2]. When the [bmim][PF_6]/H_2O system was applied, the reaction proceeded smoothly at room temperature to give the desired compounds in 95%–98% yield and no side products including dealkylated phosphonous acids were observed in these reactions (Scheme 1). The time required for the complete azide **2a–c** formation strongly depends on the alkylene chain length in the starting substrate. For the less reactive 2-bromoethylphosphonate **1a**, it took about 5 days (120 h) to afford **2a** in 95% yield, whereas in the case of **1b** ($n = 3$) and **1c** ($n = 4$) similar high-yielding results were obtained over 40 h and 48 h, respectively.

Increasing the reaction temperature to 80°C resulted in a reduction in the reaction time up to 2 h for **1a** and to about 30 min for more reactive **1b,c**. Nevertheless, diethyl(bromomethyl)phosphonate **1d** ($n = 1$) did not undergo azide/halide exchange neither under prolonged reaction time at room temperature nor under elevated temperature. The workup procedure involved the removal of the aqueous phase, extraction with Et_2O (twice), and evaporation of the combined ether extract to result in the desired azides **2a–c** in the yield of 95%–98% as slightly yellowish oils having purity more than 98% according the ^{1}H NMR data. The ^{31}P NMR spectrum of



1a–c **2a–c**

$n = 2$ (**a**), 3 (**b**), 4 (**c**)

SCHEME 1

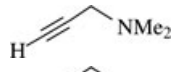
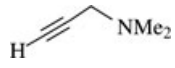
azido-substituted phosphonate **2a** shows a singlet at δ ~26.9 ppm, whereas the signals for compounds **2b,c** were slightly downfield shifted (ca. 31 ppm). The IR spectra of **2a–c** (KBr) show characteristic absorption bands at 1244–1248 (P=O) and 2098–2104 cm^{-1} (N_3).

Using **1b** as a starting representative example, we demonstrated that [bmim]PF_6 can be recycled and reused at least five times without any decrease in activity. Moreover if the first reaction cycle provided the desired **2b** in the yield of 97% (purity ca. 98%), the isolated yield and purity were even higher (quantitative yield, >99% purity) for subsequent reaction cycles. The only limitation was a slight reduction in the volume of IL phase, arising from its partial solubility in water and diethyl ether (cf. [19b]).

Therefore, [bmim]PF_6 ionic liquid can be successfully used as a reaction medium for the synthesis of phosphonates bearing azide functionality, providing the facile route to such compounds.

The azidoalkylphosphonates **2a–c** obtained were tested as substrates for Cu(I)-catalyzed 1,2,3-triazole formation. A few procedures were suggested for reactions of such type in the literature, namely direct introduction of catalytic amount of Cu(I) salt (CuI, CuBr, etc.) into the reaction system in conjugation with organic or inorganic base [24] or the catalyst can be generated in situ by the reduction of Cu(II) salts, usually in organo-aqueous systems [25]. Estimating all these variants, we concluded that the latter procedure (method A, see Experimental part) was the most suitable in the case of the simplest alkynes **3a–c** (Scheme 2). When the starting substrates were used in equimolar amounts, the conversion was more than 90% (according to the ^{31}P NMR data of the reaction mixtures) under the above-mentioned conditions. Using a small excess of alkyne led to an increase in the yield of crude product to 95%–96% (69%–86% after purification). Minor impurities presented the starting reactants, and copper complexes formed both by starting and final phosphonates. At the same time, in experiments performed with direct introduction of Cu(I) catalysts (methods B and C) the yields of individual compounds **4a–f** decreased up to 48%–63%.

TABLE 1 Reaction of **2a–c** with Alkynes via Scheme 2

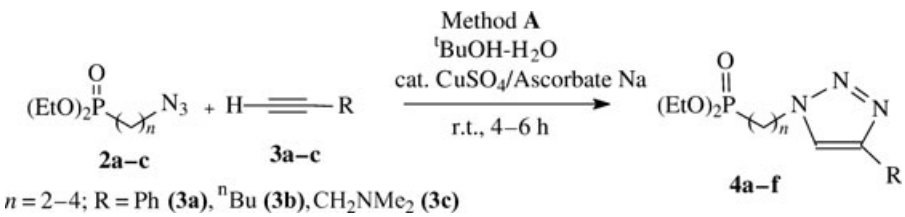
Entry	*Azide*	*n*	*Alkyne*	*Product*	*Yield*[a]
1	**2a**	2	Ph—≡—H	**4a**	69
2	**2b**	3	Ph—≡—H	**4b**	75
3	**2b**	3	^{n}Bu—≡—H	**4c**	74
4	**2c**	4	^{n}Bu—≡—H	**4d**	71
5	**2b**	3		**4e**	79
6	**2c**	4		**4f**	86

[a]Isolated yields after purification by column chromatography.

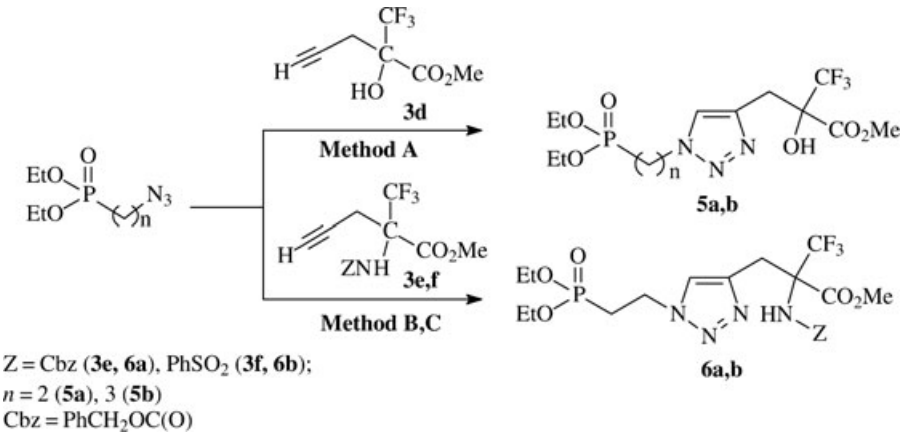
To impart better lipophilic and biodegradable properties that are advantageous in medicinal chemistry [26] to phosphorylated triazoles, propargyl-substituted CF_3-containing alcohol **3d** [27a] and protected amino acids **3e,f** [27b] were also used in the above-mentioned cycloaddition (Scheme 3).

In the reaction with the unsaturated alcohol **3d,** the reaction performed using the method A gave the desired compounds **5a,b** in the yields of 77%–78%, whereas for the synthesis of **6a,b** CuI was used as a catalyst either in the same *t*-BuOH/H_2O medium under elevated temperature (method B) or in THF solution (method C). Comparing the yields for **6b** we may mention that organoaqueous media provided better yields of the products.

Phosphorylated triazoles **4–6** were isolated mostly as colorless oils (only the hydroxyl-substituted product **5a** was isolated as a white solid). In the ^{31}P spectra, the signals of the compounds of 1,2,3-triazole series were observed practically in the same regions as those for their azido-containing precursors **2a–c**. The structures of the compounds obtained were unambiguously confirmed by IR and ^{1}H and ^{13}C NMR spectra, containing characteristic sets of signals of the corresponding structures.



SCHEME 2



SCHEME 3

CONCLUSION

In summary, we reported a new examples of ILs' application as activating media for organophosphorus synthesis and demonstrated that 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) is a suitable recyclable medium for efficient synthesis of azidoalkylphosphonates being useful intermediates for the synthesis of phosphorylated 1,3,2-triazoles via coupling with a variety of alkynes. Biological tests of compounds **4–6** are under investigation.

EXPERIMENTAL

NMR spectra were recorded with a Bruker Avance-300 spectrometer (^{1}H, 300.13; ^{31}P, 121.49; and ^{13}C, 75.47 MHz) and a Bruker Avance-400 spectrometer (^{1}H, 400.13; ^{31}P, 161.97; and ^{13}C, 100.61 MHz) using residual proton signals of deuterated solvent as an internal standard (^{1}H, ^{13}C) and H_3PO_4 (^{31}P) as an external standard. The ^{13}C NMR spectra were registered using the *J*MODECHO mode; the signals for the C atom bearing odd and even numbers of protons have opposite polarities. IR spectra were recorded on a Fourier spectrometer "Magna-IR750" (Nicolet), with a resolution of 2 cm^{-1}, 128 scans. The assignment of the absorption bands in IR spectra was made according to [28]. Mass spectrometry was performed on a tandem Finnigan LCQ Advantage instrument using positive mode. Analytical TLCs were performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or spraying with $Ce(SO_4)_2$ solution in 5% H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 digital melting point apparatus and were uncorrected.

The starting ω-bromoalkylphosphonates **1a–c** were obtained via an Arbuzov reaction of the corresponding α,ω-dihalogenoalkanes with triethylphosphite according to [29], [30] and [31] for $n = 2$, 3, and 4, respectively. Propargyl-substituted fluorinated alcohol **3d** and protected amino acids **3f,e** were obtained via the processes reported by one of us previously, based on the Grignard reagent addition to high-electrophilic methyl trifluoropyruvate and its imines [27].

*General Procedure for the Synthesis of ω-Azidoalkylphosphonates (**2a–c**)*

A solution of sodium azide (10.0 mmol, 2 eq.) in water (1.0 mL) was added to a vigorously stirred solution (~1200 rpm) of ω-bromoalkyl)diethylphosphonate **1** (5.0 mmol) in [bmim]PF_6 (1 mL) at room temperature. The resulting two-layer mixture was stirred over 120 h ($n = 2$), 48 h ($n = 3$), and 40 h ($n = 4$) at room temperature or over 2 h ($n = 2$) and 30 min ($n = 3.4$) at 80°C, whereas the reaction course was followed by ^{31}P NMR. The upper water layer was decanted, the residue was extracted with diethyl ether (10 × 3 mL), and the combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo to give the desired products, which were used in the next reaction without further purification. Similar results were obtained using 0.1 mol of the starting substrate **1a–c**, indicating the possibility of further scaling up if necessary.

For the recycling experiments, the next portion of bromopropylphosphonate **1b** was added to the residue from the previous cycle followed by a solution of NaN_3 in water and the procedure was repeated as described. The spectral data for the product obtained were identical to

those for the sample from the previous cycle. ω-Azidoalkylphosphonates **2a–c** were used in the reactions of 1,2,3-triazole formation without further purification.

*Diethyl 2-azidoethylphosphonate (**2a**).* Yield 94% (purity 96%). ^{31}P NMR (121 MHz, $CDCl_3$): δ 26.88. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 6H, CH_3, $^3J_{H-H} = 7.1$ Hz), 2.04 (dt, 2H, PCH_2, $^2J_{P-H} = 18.6$ Hz, $^3J_{H-H} = 7.7$ Hz), 3.52 (dt, 2H, NCH_2, $^3J_{P-H} = 7.8$ Hz, $^3J_{H-H} = 7.7$ Hz), 4.07–4.11 (m, 4H, OCH_2). IR (thin film) ν (cm^{-1}): 965, 1028 and 1057 (P—O—C), 1248 (P=O), 2103 (N_3), 2910, 2933, 2984, 3472. EMS: *m/z* calcd for $C_6H_{14}N_3O_3P$: 207.17 $[M]^+$; found: 208.2 $[M + H]^+$.

*Diethyl 2-azidopropylphosphonate (**2b**).* Yield 97% (purity 95%). ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.93. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, 6H, CH_3, $^3J_{H-H} = 7.1$ Hz), 1.82–1.98 (m, 4H, $P(CH_2)_2$), 3.43 (t, 2H, NCH_2, $^3J_{H-H} = 6.4$ Hz), 4.12–4.17 (m, 4H, OCH_2). IR (thin film) ν (cm^{-1}): 962, 1027, and 1054 (P—O—C), 1244 (P=O), 2101 (N_3), 2874, 2913, 2935, 2983, 3874. EMS: *m/z* calcd for $C_7H_{16}N_3O_3P$: 221.2 $[M]^+$; found: 222.0 $[M + H]^+$.

*Diethyl 2-azidobutylphosphonate (**2c**).* Yield 98% (purity 100%). ^{31}P NMR (121 MHz, $CDCl_3$): δ 31.37. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 and 1.32 (2t, 3H + 3H, CH_3, $^3J_{H-H} = 7.0$ Hz), 1.66–1.75 (m, 6H, $P(CH_2)_3$), 3.23–3.32 (m, 2H, NCH_2), 4.04–4.08 (m, 4H, OCH_2). IR (thin film) ν (cm^{-1}): 962, 1028 (P—O—C), 1055, 1244 (P=O), 2098 (N_3), 2829, 2874, 2916, 2982, 3465. Anal Calcd. for $C_8H_{18}N_3O_3P$: C, 40.85; H, 7.71; N, 17.86; P 13.17. Found: C, 40.70; H, 7.52; N 17.97; P, 12.86.

*General Procedures for the Synthesis of 4-Substituted 1,2,3-Triazoles (**4–6**)*

Method A. A solution of azidophosphonate **2** (1.0 mmol), sodium ascorbate (0.3 mmol), and 0.5 mol% copper(II) sulfate pentahydrate (0.05 mmol) in a mixture of *t*-BuOH-H_2O (1:1 ratio) (2 mL) was added to a solution of the corresponding acetylene **3** (1.0 mmol) in a mixture of *t*-BuOH-H_2O (3 mL). The reaction mixture was stirred at room temperature for 4–6 h until the completion of the reaction monitored by TLC. After evaporation of the mixed solvent under reduced pressure, water (2 mL) was added to a residue. Then the aqueous mixture was extracted with ethyl acetate (2 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash chromatography on silica gel eluting by EtOAc-hexane (1.5:1). In the case of hydrophilic aminomethyl-substituted products **4e,f**, the reaction mixture was evaporated to dryness, acetonitrile was added to a residue, the precipitated copper salts were filtered off, and the filtrate was evaporated, and purified by column chromatography.

Method B. To a solution of the corresponding acetylene **3** (1.0 mmol) in the mixture of *t*-BuOH-H_2O (1:1 ratio) (3 mL), a solution of azide **2** (2.0 mmol) and CuI (0.1 mmol) in the mixture of *t*-BuOH-H_2O (1:1 ratio) (2 mL) was added. The reaction mixture was stirred for 8 h at 80–90°C until the completion of the reaction monitored by TLC. Then, water (15 mL) was added to a reaction mixture and the aqueous layer was extracted with methylene chloride (3 × 15 mL). The organic layer was dried over $MgSO_4$, evaporated, and the residue was purified by flash chromatography on silica gel using acetone–hexane (1.5:1) as an eluent.

Method C. A solution of the corresponding acetylene **3** (1.0 mmol) in anhydrous THF (2 mL) was added dropwise to a solution of CuI (1.0 mmol) in anhydrous THF (2 mL). To the reaction mixture, DIPEA (*N*,*N*-diisopropylethylamine) was added (10 mmol), followed by dropwise addition of azide **2** (1.5 mmol) solution in anhydrous THF (2 mL) within 10 min. The reaction mixture was stirred at room temperature for 6–7 h until the completion of the reaction monitored by TLC. The reaction mixture was subsequently neutralized with 1 N HCl (15 mL), diluted with H_2O (5 mL), and extracted with ether (3 × 15 mL). The organic layer was dried over $MgSO_4$, evaporated, and the residue was purified by flash chromatography on silica gel using acetone–hexane (1.5:1) as an eluent.

*Diethyl 2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethylphosphonate (**4a**).* Method A: oil, yield 69%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.78. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, 6H, CH_3, $^3J_{H-H} = 7.1$ Hz), 2.38 (dt, 2H, PCH_2, $^2J_{P-H} = 7.6$ Hz, $^3J_{H-H} = 7.7$ Hz), 3.97–4.04 (m, 4H, OCH_2), 4.58 (dt, 2H, NCH_2, $^3J_{P-H} = 7.5$ Hz, $^3J_{H-H} = 7.7$ Hz), 7.23 (t, 1H, CH=, $^4J_{H-H} = 7.3$ Hz), 7.23 (t, 2H, Ph, $^3J_{H-H} = 7.1$ Hz), 7.67–7.78 (m, 3H, Ph). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 16.32 (d, CH_3, $^3J_{P-C} = 6.0$ Hz), 27.14 (d, PCH_2, $^1J_{P-C} = 141.4$ Hz), 44.57 (CH_2N), 62.15 (d, $POCH_2$, $^2J_{P-C} = 6.6$ Hz), 120.31 (HC=), 125.64 (o-C in Ph), 128.17 (p-C in Ph), 128.83 (m-C in Ph), 130.45 (ipso-C in Ph), 144.53 (Ph—C=). IR (thin layer) ν (cm^{-1}): 697, 768, 974, 1028, and 1030 (P—O—C), 1240 (br) (P=O), 1610 (weak) (C=C), 2907, 2983, 3464 (br). Calcd. for

$C_{14}H_{20}N_3O_3P$: C, 54.36; H, 6.52; N, 13.59. Found: C, 54.27; H, 6.61; N, 13.38.

*Diethyl 3-(4-phenyl-1H-1,2,3-triazol-1-yl)propylphosphonate (**4b**).* Method A: oil, yield 75%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.04. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 6H, CH_3, $^3J_{H-H} = 7.1$ Hz), 1.67 (m, 2H, CH_2), 2.20 (m, 2H, CH_2, $^3J_{H-H} = 7.2$ Hz), 3.97–4.08 (m, 4H, OCH_2), 4.44 (t, 2H, NCH_2, $^3J_{H-H} = 6.9$ Hz), 7.26 (t, 1H, CH=, $^4J_{H-H} = 7.5$ Hz), 7.35 (t, 2H, Ph, $^3J_{H-H} = 7.6$ Hz), 7.76 (d, 3H, Ph, $^3J_{H-H} = 8.5$ Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 16.44 (d, CH_3, $^3J_{P-C} = 6.0$ Hz), 22.46 (d, PCH_2, $^1J_{P-C} = 143.4$ Hz), 23.70 (d, $PCH_2\underline{C}H_2$, $^2J_{P-C} = 4.3$ Hz), 49.98 (d, CH_2N, $^3J_{P-C} = 14$ Hz), 61.81 (d, $POCH_2$, $^2J_{P-C} = 6.3$ Hz), 119.99 (H$\underline{C}$=), 125.66 (o-C in Ph), 128.16 (p-C in Ph), 128.84 (m-C in Ph), 130.51 (ipso-C in Ph), 143.58 (Ph-C=). IR (thin layer) ν (cm^{-1}): 697, 768, 964, 1030, and 1048 (P—O—C), 1230 and 1251 (P=O), 1610 (weak) (C=C), 2907, 2982, 3454 (br). Calcd for $C_{15}H_{22}N_3O_3P$: C, 55.72; H, 6.86; N, 13.00. Found: C, 55.54; H, 6.94; N, 12.77.

*Diethyl 3-(4-butyl-1H-1,2,3-triazol-1-yl)propyl)-phosphonate (**4c**).* Method A: light-yellow oil, yield 74%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.0. ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, 3H, CH_3, $^3J_{H-H} = 7.3$ Hz), 1.24 (t, 6H, CH_3, $^3J_{H-H} = 7.0$ Hz), 1.32 (m, 2H, CH_2), 1.56–1.68 (m, 4H, CH_2), 2.21 (m, 2H, PCH_2), 2.64 (t, 2H, CH_2, $^3J_{H-H} = 7.5$ Hz), 3.99–4.05 (m, 4H, OCH_2), 4.36 (t, 2H, NCH_2, $^3J_{H-H} = 6.7$ Hz), 7.30 (br.s, 1H, CH). Calcd for $C_{15}H_{22}N_3O_3P$: C, 55.72; H, 6.86; N, 13.00. Found: C, 55.54; H, 6.94; N, 12.77.

*Diethyl 3-(4-butyl-1H-1,2,3-triazol-1-yl)butylphosphonate (**4d**).* Method A: light-yellow oil, yield 71%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 31.0. ^1H NMR (300 MHz, $CDCl_3$): δ 0.68 (t, 3H, CH_3, $^3J_{H-H} = 7.2$ Hz), 1.13 (t, 6H, CH_3, $^3J_{H-H} = 7.0$ Hz), 1.13–1.15 (m, 2H, CH_2), 1.36–1.39 (m, 4H, CH_2), 1.51–1.54 (m, 2H, PCH_2), 1.72–1.79 (m, 2H, PCH_2), 2.45 (t, 2H, CH_2, $^3J_{H-H} = 7.4$ Hz), 3.76–3.85 (m, 4H, OCH_2), 4.10 (br, 2H, NCH_2), 7.12 (s, 1H, CH). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 13.18 ($\underline{C}H_3(CH_2)_3$), 15.80 (d, $\underline{C}H_3CH_2O$, $^3J_{P-C} = 5.8$ Hz), 18.99 (d, $PCH_2\underline{C}H_2$, $^2J_{P-C} = 4.7$ Hz), 21.63 ($\underline{C}H_2CH_3$), 24.22 (d, PCH_2, $^1J_{P-C} = 141.6$ Hz), 24.68 (=$CCH_2\underline{C}H_2$), 30.15 (d, $P(CH_2)_2\underline{C}H_2$, $^3J_{P-C} = 15.3$ Hz), 30.94 ($\underline{C}H_2C$=), 48.78 (CH_2N), 61.81 (d, $POCH_2$, $^2J_{P-C} = 6.6$ Hz), 120.06 (H$\underline{C}$=),147.67 (Bu-C=). Calcd for $C_{14}H_{28}N_3O_3P$: C, 52.98; H, 8.89; N, 13.24. Found: C, 52.65; H, 8.64; N, 12.97.

*Diethyl 3-{4-[(dimethylamino)methyl]-1H-1,2,3-triazol-1-yl}propylphosphonate (**4e**).* Method A: oil, yield 79%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.03. ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 6H, CH_3, $^3J_{H-H} = 7.1$ Hz), 1.60–1.68 (m, 2H), 2.06–2.18 (m, 2H, PCH_2), 2.54 (s, 6H, NCH_3), 3.93–4.06 (m, 4H, OCH_2), 4.37 (c, 2H, NCH_2), 7.94 (br.s, 1H, CH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 16.28 ($\underline{C}H_3CH_2$), 22.36 (d, PCH_2, $^1J_{P-C} = 143.1$ Hz), 23.48 (d, $PCH_2\underline{C}H_2$, $^2J_{P-C} = 4.3$ Hz), 42.58 (CH_3N), 50.05 (d, $N\underline{C}H_2CH_2$, $^3J_{P-C} = 16.4$ Hz), 51.87 (NCH_2), 61.68 (d, $POCH_2$, $^2J_{P-C} = 6.6$ Hz), 125.85 (CH_2—N—$\underline{C}$=), 139.02 (N=N—C=). Calcd for $C_{12}H_{25}N_4O_3P$: C, 47.36; H, 8.28; N, 18.41. Found: C, 46.94; H, 8.05; N, 18.11.

*Diethyl 3-{4-[(dimethylamino)methyl]-1H-1,2,3-triazol-1-yl}butylphosphonate (**4f**).* Method A: oil, yield 86%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.86. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 6H, CH_3, $^3J_{H-H} = 7.0$ Hz), 1.48–2.50 (3 br. overlapped m, 12H, $P(CH_2)_3 + N(CH_3)_2$), 3.45–3.58 (m, 2H, NCH_2CH_2), 3.95–4.12 (m, 4H, OCH_2), 4.32 (c, 2H, NCH_2), 7.47 (br.s, 1H, CH). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 16.41 ($\underline{C}H_3CH_2$), 19.60 ($PCH_2\underline{C}H_2$), 24.83 (d, PCH_2, $^1J_{P-C} = 141.9$ Hz), 30.54 (d, $P(CH_2)_2\underline{C}H_2$, $^3J_{P-C} = 14.6$ Hz), 42.58 (CH_3N), 44.82 ($N\underline{C}H_2CH_2$), 49.60 (NCH_2), 61.47 (d, $POCH_2$, $^2J_{P-C} = 6.6$ Hz), 122.44 (CH_2—N—$\underline{C}$=), 145.09 (N=N—C=). Calcd for $C_{12}H_{25}N_4O_3P \cdot 2H_2O$: C, 44.06; H, 8.82; P, 8.74. Found: C, 44.05; H, 8.05; P, 8.66.

*Methyl 2-({1-[2-(diethoxyphosphoryl)ethyl]-1H-1,2,3-triazol-4-yl}methyl)-3,3,3-trifluoro-2-hydroxypropanoate (**5a**).* Method A: white solid, yield 78%, mp 84–86°C. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.58. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (two t, 6H, CH_3, $^3J_{H-H} = 7.08$ Hz), 2.29–2.40 (m, 2H, —CH_2), 3.18 and 3.52 (AB-system, 1H + 1H, $CH_2C(OH)$, $^2J_{H-H} = 14.85$ Hz), 3.82 (s, 3H, OCH_3), 3.98–4.08 (m, 4H, OCH_2), 4.41 (s, 1H, OH), 4.47–4.57 (m, 2H, $N\underline{C}H_2CH_2$), 7.51 (s, 1H, CH). ^{19}F NMR (282 MHz, $CDCl_3$): δ –0.63 (s, CF_3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 16.27 (CH_3CH_2), 27.03 (d, PCH_2, $^1J_{P-C} = 141.4$ Hz), 28.99 ($\underline{C}H_2C$=), 44.46 (CH_2N), 54.15 (OCH_3), 62.16 (d, $POCH_2$, $^2J_{P-C} = 6.3$ Hz), 77.18 (d, $\underline{C}(OH)CF_3$, $^2J_{F-C} = 29.3$ Hz), 123.28 (q, CF_3, $^1J_{F-C} = 286.2$ Hz), 123.85 (CH=), 139.95 ($CH_2\underline{C}$=), 169.13 (CO). IR (KBr) ν (cm^{-1}): 976, 1033 (P—O—C), 1065, 1152, 1180, 1227 (P=O), 1731 (C=O), 3204 (br.OH). Calcd for $C_{13}H_{21}F_3N_3O_6P$: C, 38.74; H, 5.21; N, 10.43; P, 7.68. Found: C, 38.70; H, 5.21; N, 10.28; P, 7.53.

*Methyl 2-({1-[3-(diethoxyphosphoryl)propyl]-1H-1,2,3-triazol-4-yl}methyl)-3,3,3-trifluoro-2-hydroxypropanoate (**5b**).* Method A: oil, yield 77%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 30.04. ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, 6H, CH_3, $^2J_{H-H} = 7.1$ Hz), 1.61 (appar. dt, 2H, $PCH_2C\underline{H}_2$, $^3J_{H-H} = 8.0$ Hz,

$^3J_{P-H} = 12.7$ Hz), 2.06–2.21 (m, 2H, PCH_2), 3.19 and 3.52 (AB-system, 1H + 1H, $CH_2C(OH)$, $^2J_{H-H} = 14.6$ Hz), 3.78 (s, 3H, OCH_3), 4.00–4.06 (m, 4H, OCH_2), 4.37 (t, 2H, NCH_2, $^3J_{H-H} = 6.9$ Hz), 4.99 (br.s, 1H, OH), 7.55 (s, 1H, CH). ^{19}F NMR (282 MHz, $CDCl_3$): δ –0.56 (s, CF_3). IR (KBr) ν (cm^{-1}): 976, 1028 (P—O—C), 1050 (C—O—C), 1136, 1188, 1228 (P=O), 1753 (C=O), 3202 (br.OH). Calcd for $C_{14}H_{23}F_3N_3O_6P$: C, 40.32; H, 5.51; N, 10.08. Found: C, 40.32; H, 5.51; N, 9.84.

*Methyl 2-{[(benzyloxy)carbonyl]amino}-2-({1-[2-(diethoxyphosphoryl)ethyl]-1H-1,2,3-triazol-4-yl}methyl)-3,3,3-trifluoropropanoate (***6a***)*. Method C: oil, yield 50%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.18. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, 6H, CH_3, $^2J_{H-H} = 7.08$ Hz), 2.31–2.42 (dt, 2H, CH_2, $^3J_{H-H} = 7.5$ Hz, $^2J_{P-H} = 18.7$ Hz), 3.97 (s, 3H, OCH_3), 4.09–4.17 (m, 4H, OCH_2), 3.71 and 4.23 (AB-system, 1H + 1H, CH_2, $^2J_{H-H} = 14.61$ Hz), 4.42–4.55 (m, 2H, NCH_2), 5.05 and 5.21 (AB-system, 1H + 1H, $CH_2C(CF_3)$, $^2J_{H-H} = 12.2$ Hz), 6.32 (s, 1H, NH), 7.32 (s, 1H, CH), 7.42 (s, 5H, Ph). ^{19}F NMR (282 MHz, $CDCl_3$): δ 3.66 (s, CF_3). EMS: *m/z* Calcd for $C_{21}H_{28}F_3N_4O_7P$: 537.1 $[M + H]^+$; found: 537.0 $[M + H]^+$, 493 $[M + H\text{-}OEt]^+$.

*Methyl 2-({1-[2-(diethoxyphosphoryl)ethyl]-1H-1,2,3-triazol-4-yl}methyl)-3,3,3-trifluoro-2-[(phenylsulfonyl)amino]propanoate (***6b***)*. Method B: oil, yield 62%. Method C: oil, yield 32%. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.43. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, 6H, CH_3, $^2J_{H-H} = 7.1$ Hz), 2.47 (dt, 2H, PCH_2, $^3J_{H-H} = 7.8$ Hz, $^2J_{P-H} = 18.7$ Hz), 3.70 and 4.02 (AB-system, 1H + 1H, $CH_2C(NH—)$, $^2J_{H-H} = 14.6$ Hz), 3.97 (s, 3H, OCH_3), 4.12–4.22 (m, 4H, OCH_2), 4.63–4.67 (m, 2H, NCH_2), 6.27 (s, 1H, NH), 7.51–7.62, 7.86–7.87 (m, 5H, Ph). ^{19}F NMR (282 MHz, $CDCl_3$): δ 5.42 (s, CF_3). EMS: *m/z* calcd for $C_{19}H_{26}F_3N_4O_7PS$: 543.1 $[M + H]^+$; found: 543.0 $[M + H]^+$, 515 $[M + H\text{-}2Et]^+$.

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