



Synthesis of CF_3 -containing α -alkynyl- α -aminophosphonates by Sonogashira cross-coupling reaction

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ABSTRACT

An efficient route to new α - CF_3 - α -aminophosphonic acid derivatives bearing an arylalkynyl moiety at the α -carbon atom has been developed. The method is based on palladium-catalyzed cross-coupling of the corresponding α -propargyl (ethynyl) α -aminophosphonates with aryl iodides to afford the aminophosphonic acid derivatives with an internal triple bond that is suitable for further modifications.

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1. Introduction

Unsaturated α -amino acids I (Fig. 1) are very important building blocks in organic and medicinal chemistry, mainly as a result of the diverse reactivity of the multiple bonds and their ability to introduce biologically active functionalities [1]. Thus, they have proved to be extremely useful for a range of transformations, particularly metal-catalyzed functionalizations such as cross-coupling, cycloaddition as well as metathesis-type reactions including acetylene metathesis [2]. Moreover, unsaturated α -amino acids currently play an important role in peptide chemistry due to their facile incorporation into protein structures.

On the other hand, α -amino phosphonic acids and their diesters have found widespread use as analogues of the corresponding α -amino carboxylic derivatives, where the tetrahedral phosphonic acid functionality replaces the planar and less bulky carboxylic acid (Fig. 1).

α -Amino phosphonates have been used as single units and as incorporated into peptides where the phosphonamide moiety can mimic the tetrahedral transition states of enzymatic peptide bond hydrolysis [3]. These structural features cause a unique enzyme response which led to the discovery of new antibacterial agents [4] and inhibitors of protease [5], including HIV-protease.

On the top of this, the introduction of fluorine or fluoroalkyl substituents into biological relevant compounds has become an

important tool in the drug discovery process [6]. Special attention is paid to trifluoromethyl-containing compounds due to the unique properties of the trifluoromethyl group, such as high electro-negativity, electron density, steric hindrance, and hydrophobic character that can profoundly improve the pharmacokinetic profiles of potential drugs [7]. Furthermore, it is known, that the incorporation of α -trifluoromethyl- α -amino acids into strategically important positions of peptides retards proteolytic degradation, induces secondary structure motif, and improves lipophilicity [8] enhancing *in vivo* absorption, thus improving permeability through certain body barriers.

Despite the increasing interest to fluorinated aminophosphonates during the last decade [9] α - CF_3 -substituted α -aminophosphonates with unsaturated groups on α -carbon atom, especially α -alkynyl-containing derivatives, remain a hitherto unknown class of α -aminophosphonic acids.

We have previously described syntheses of α - CF_3 - α -aminophosphonic acid derivatives *via* the addition of sodium acetylidyne or allenylmagnesium bromide to the corresponding highly electrophilic N-Cbz-protected iminophosphonate [10]. α -Alkynyl α - CF_3 -aminophosphonates obtained by this method were further employed in Cu(I)-catalyzed 1,3-dipolar cycloaddition to different organic azides affording the functionalized P-analogous of α - CF_3 -azahistidine (Fig. 2).

Now we wish to disclose an efficient pathway to the novel α - CF_3 - α -aminophosphonate derivatives comprising an arylalkynyl moiety at the α -carbon atom *via* palladium-catalyzed cross-coupling of the corresponding α -propargyl(ethynyl)- α -aminophosphonates with aryl iodides.

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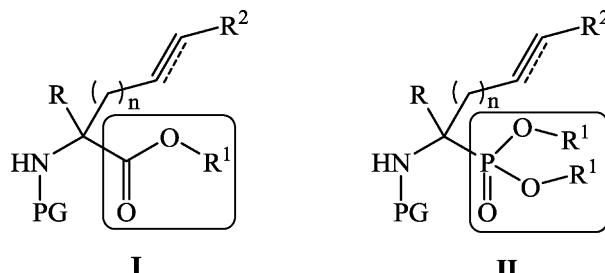


Fig. 1. Unsaturated α -aminocarboxylic and α -aminophosphonic acid derivatives.

2. Results and discussion

The feasibility of the palladium-catalyzed cross-coupling of alkynyl-containing α -CF₃- α -aminophosphonates with aryl halides was initially established by the reaction of propargyl derivative **2** with phenyl iodide. For these purposes, the conditions previously developed for cross-coupling reaction of α -aminocarboxylate analogues [11] were evaluated. Thus, the reaction of **2** with PhI performed at room temperature in DMF, in the presence of PdCl₂(PPh₃)₂ (5 mol%), copper iodide (5 mol%) and an excess of triethylamine (5 equiv.), gave us very poor conversion of starting acetylene for 8 h and just traces of the desired product **4a** (Scheme 1). The monitoring of the reaction was accomplished by TLC and ¹⁹F NMR spectroscopy. The rising of the reaction temperature up to 50 °C slightly increased conversion and **4a** was isolated in yield of 18%.

The variation by the solvents (THF, diethyl ether, and CH₂Cl₂), organic bases (Et₂NH, i-Pr₂NEt), catalysts [PdCl₂(MeCN)₂, Pd(PPh₃)₄], reaction time and temperature did not significantly influence on the conversion. Nevertheless, we were lucky to achieve full conversion performing the reaction in acetonitrile in the presence of PdCl₂(PPh₃)₂ (4 mol%), copper iodide (8 mol%) and 5 equiv. of diisopropylamine as organic base. The reaction was completed for 8 h at ambient temperature to give cross-coupling product **4a** in good yield (62%) after column chromatography.

These conditions have proved to be acceptable for the cross-coupling of α -alkynyl- α -aminophosphonates **1** and **2** with other functional aryl iodides (Table 1). The nature of substituents in benzene ring does not significantly affect the outcome of the process (Table 1). In all studied cases the homo-coupled derivative often observed as a by-product in the related Sonogashira-type reactions (arising from Cu-promoted Glaser coupling [12]) was not detected.

To demonstrate one of the possible synthetic applications of the synthesized CF₃-substituted α -aminophosphonates we performed simultaneous deprotection of amino function and reduction of the internal triple bond by palladium-catalyzed hydrogenation in methanol to afford the corresponding homologous of P-phenylalanine **5** and **6** in excellent yields (Scheme 2).

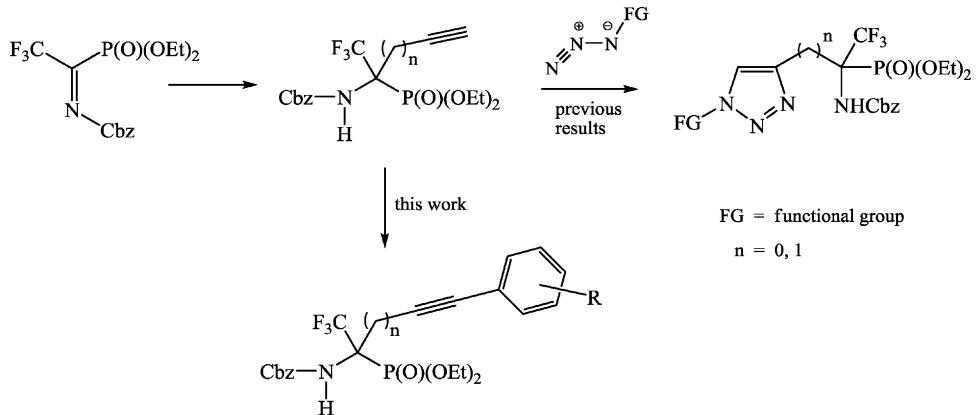
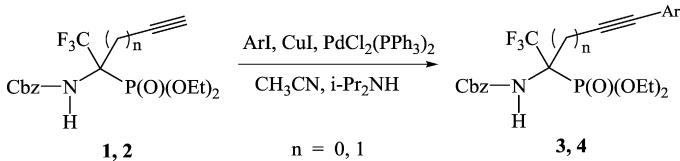
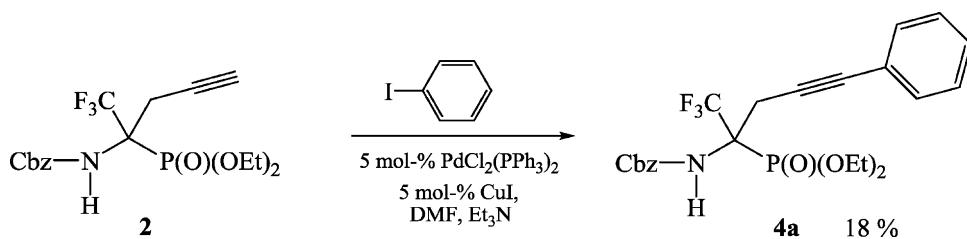


Fig. 2. Synthetic application of α -CF₃- α -alkynyl- α -aminophosphonates.

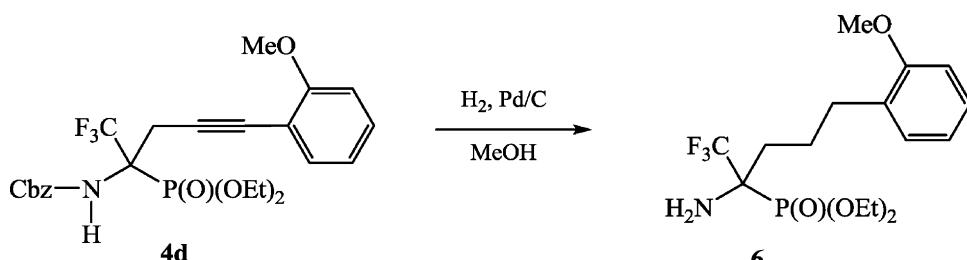
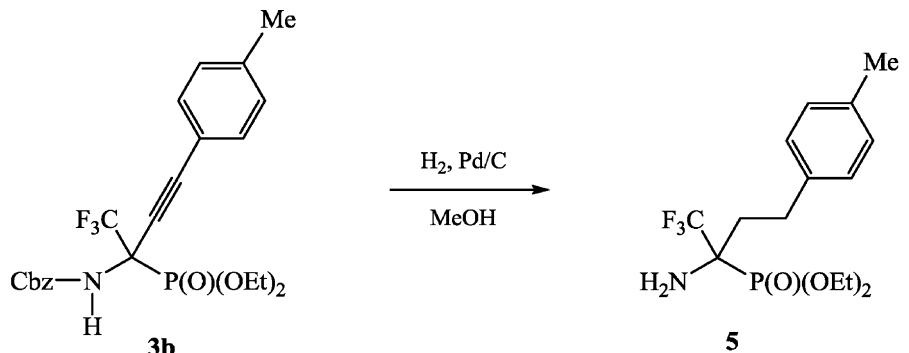
Table 1
Coupling of α -alkynyl- α -aminophosphonates with aryl halides.



Entry	n	Ar	Product	Yield, %
1	0	Ph	3a	65
2	0	4-CH ₃ C ₆ H ₄	3b	53
3	0	4-NH ₂ C ₆ H ₄	3c	48
4	0	4-CH ₃ OC ₆ H ₄	3d	60
5	0	2-CH ₃ OC ₆ H ₄	3e	58
6	1	Ph	4a	62
7	1	4-CH ₃ C ₆ H ₄	4b	57
8	1	4-CH ₃ OC ₆ H ₄	4c	70
9	1	2-CH ₃ OC ₆ H ₄	4d	70
10	1	4-NH ₂ C ₆ H ₄	4e	64
11	1	4-NO ₂ C ₆ H ₄	4f	53



Scheme 1. Reaction of **2** with phenyl iodide.



Scheme 2. Hydrogenation of α -CF₃- α -alkynyl- α -aminophosphonates **3b** and **4d**.

3. Conclusions

In summary, we have developed an efficient pathway to novel α -CF₃-substituted α -amino-phosphonic acid derivatives comprising arylalkynyl moiety at α -carbon atom based on palladium-catalyzed Sonogashira cross-coupling of the corresponding α -propargyl (ethynyl) α -aminophosphonates with aryl iodides. Various N-Cbz-protected aminophosphonates, which might be potentially applicable in the pharmaceutical and biochemical areas, were conveniently obtained in moderate to good yields.

4. Experimental

General: All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. Reactions were performed under an atmosphere of dry argon. Analytical TLC was performed with Merck silica gel 60 F₂₅₄ plates; visualization was accomplished with UV light or spraying with Ce(SO₄)₂ solution in 5% H₂SO₄. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM) and ethyl acetate/petroleum ether as eluent. NMR spectra were obtained with Bruker AV-300, AV-400, or AV-600 spectrometers operating at 300, 400, or 600 MHz, respectively, for ¹H (TMS reference), at 75, 100, or 150 MHz for ¹³C, at 288 MHz for ¹⁹F (CF₃COOH reference), and at 161 MHz for ³¹P (H₃PO₄ reference).

4.1. General procedure for the Sonogashira coupling reaction

In a dry round-bottomed flask, placed under argon, were placed 1.5 equiv. aryl halide, 4 mol% $[\text{PdCl}_2(\text{PPh}_3)_2]$ and copper iodide (8 mol%) in freshly distilled CH_3CN (8 mL). A solution of alkyne (1 equiv.) in diisopropylamine (5 equiv.) was added. The reaction mixture was stirred at room temperature for 12 h. The solution was evaporated to dryness in vacuum, and saturated aqueous ammonium chloride was added. The solution was extracted with dichloromethane. The organic phase was dried with MgSO_4 , filtered, concentrated, and crude product was purified by silica gel column flash chromatography (eluent–dichloromethane/ethyl acetate) to produce compound as yellow oil.

4.1.1. Diethyl [1-[(benzyloxy)carbonyl]amino]-3-phenyl-1-(trifluoromethyl)prop-2-yn-1-yl]phosphonate (3a)

Yield: 50%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.44 (t, $J_{\text{H}-\text{H}} = 7.0$ Hz, 6H, 2CH_3), 4.33–4.51 (m, 4H, OCH_2) 5.19 (d_{AB} , $J_{\text{AB}} = 12.1$ Hz, 1H, CH_2), 5.26 (d_{AB} , $J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.73 (d, $^3\text{J}_{\text{H}-\text{P}} = 7.6$ Hz, 1H, NH), 7.35–7.54 (m, 10H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 5.49 (d, $^3\text{J}_{\text{F}-\text{P}} = 3.0$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 9.55 (q, $^3\text{J}_{\text{P}-\text{F}} = 2.7$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.3 (d, $J = 5.5$ Hz), 56.8 (dq, $J = 33.4$, 149.5 Hz), 65.8 (d, $J = 7.2$ Hz), 66.3 (d, $J = 7.7$ Hz), 67.5, 76.3 (d, $J = 16.0$ Hz), 90.1 (d, $J = 7.7$ Hz), 121.2 (d, $J = 2.7$ Hz), 122.8 (qd, $J = 2.8$ Hz, 286.9 Hz), 128.3, 128.3, 128.5, 129.3, 132.04, 132.05, 135.6, 153.4 ppm. Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{F}_3\text{NO}_5\text{P}$: C, 56.29; H, 4.94; N, 3.98. Found: C, 56.10; H, 4.90; N, 3.90.

4.1.2. Diethyl [1-{{(benzyloxy)carbonyl}amino}-3-(4-methylphenyl)-1-(trifluoromethyl)prop-2-yn-1-yl]phosphonate (3b)

Yield: 53%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.44 (t, $J_{\text{H-H}} = 7.1$ Hz, 6H, 2CH_3), 2.41 (s, 3H, CH_3), 4.35 (m, 4H, OCH_2) 5.19 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.25 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.73 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 7.5$ Hz, 1H, NH), 7.18 (d, $J_{\text{H-H}} = 7.9$ Hz, 2H, ArH), 7.38–7.42 (m, 7H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 5.50 (d, $\text{d}_{\text{J}_{\text{F-P}}} = 3.2$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 9.60 (q, $\text{q}_{\text{J}_{\text{P-F}}} = 2.9$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.3 (m), 22.2, 55.1, 60.2 (dq, $J = 28.1$, 153.8 Hz), 64.2 (m), 66.9, 80.4, 86.0 (d, $J = 6.8$ Hz), 110.2, 111.8, 120.0, 124.2 (qd, $J = 5.7$, 287.7 Hz), 127.8, 128.1, 129.2, 133.1, 135.6, 153.9 (d, $J = 9.1$ Hz), 159.8 ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{NO}_5\text{P}$: C, 57.14; H, 5.21; N, 2.90. Found: C, 57.03; H, 5.17; N, 2.84.

4.1.3. Diethyl [3-(4-aminophenyl)-1-{{(benzyloxy)carbonyl}amino}-1-(trifluoromethyl)prop-2-yn-1-yl]phosphonate (3c)

Yield: 48%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 0.91–0.98 (m, 6H, 2CH_3), 3.36 (br.s., 2H, NH_2), 3.96–4.33 (m, 4H, OCH_2), 4.94 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.00 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 6.17 (d, $J_{\text{H-H}} = 8.4$ Hz, 1H, ArH), 6.24 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 7.8$ Hz, 1H, NH), 7.01–7.14 (m, 5H, ArH), 7.30 (d, $J = 8.2$ Hz, 2H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 6.14 (d, $\text{d}_{\text{J}_{\text{F-P}}} = 3.0$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 10.46 (d, $\text{d}_{\text{J}_{\text{P-F}}} = 2.9$ Hz) ppm. ^{13}C NMR (75.47 MHz, CD_3OD): δ = 15.3 (m), 57.4 (dq, $J = 33.1$, 155.9 Hz), 65.6 (d, $J = 7.7$ Hz), 66.1 (d, $J = 7.7$ Hz), 66.7, 73.7 (d, $J = 14.3$ Hz), 91.5 (d, $J = 7.7$ Hz), 108.6, 114.1, 123.0 (qd, $J = 4.4$, 287.4 Hz), 127.7, 127.8, 128.1, 132.8 (d, $J = 2.2$ Hz), 136.3, 149.4, 154.5 (d, $J = 6.6$ Hz) ppm. Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_5\text{P}$: C, 54.55; H, 4.99; N, 5.78. Found: C, 54.59; H, 5.04; N, 5.75.

4.1.4. Diethyl [1-{{(benzyloxy)carbonyl}amino}-3-(4-methoxyphenyl)-1-(trifluoromethyl)prop-2-yn-1-yl]phosphonate (3d)

Yield: 60%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.31 (t, $J_{\text{H-H}} = 7.0$ Hz, 6H, 2CH_3), 3.74 (s, 3H, OCH_3), 4.25–4.41 (m, 4H, OCH_2), 5.07 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.12 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.64 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 7.8$ Hz, 1H, NH), 6.76–6.84 (m, 2H, ArH), 7.19–7.36 (m, 7H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 5.53 (d, $\text{d}_{\text{J}_{\text{F-P}}} = 2.8$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 9.90 (d, $\text{d}_{\text{J}_{\text{P-F}}} = 2.8$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.0 (m), 55.9, 56.7 (dq, $J = 33.6$, 152.5 Hz), 65.6 (d, $J = 7.4$ Hz), 66.3 (d, $J = 8.0$ Hz), 67.1, 79.6 (d, $J = 16.0$ Hz), 86.8 (d, $J = 8.3$ Hz), 110.4 (d, $J = 3.4$ Hz), 130.5, 134.0 (d, $J = 2.8$ Hz), 135.4, 153.1 (d, $J = 10.6$ Hz), 160.4 (d, $J = 2.0$ Hz) ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{NO}_6\text{P}$: C, 55.31; H, 5.05; N, 2.80. Found: C, 55.27; H, 5.02; N, 2.76.

4.1.5. Diethyl [1-{{(benzyloxy)carbonyl}amino}-3-(2-methoxyphenyl)-1-(trifluoromethyl)prop-2-yn-1-yl]phosphonate (3e)

Yield: 58%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.30 (t, $J_{\text{H-H}} = 7.0$ Hz, 6H, 2CH_3), 3.73 (s, 3H, OCH_3), 4.22–4.34 (m, 4H, OCH_2), 5.06 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.12 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.61 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 7.6$ Hz, 1H, NH), 6.74–6.77 (m, 2H, ArH), 7.19–7.34 (m, 7H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 5.45 (d, $\text{d}_{\text{J}_{\text{F-P}}} = 3.0$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 9.63 (q, $\text{q}_{\text{J}_{\text{P-F}}} = 3.1$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.4 (m), 55.3, 56.9 (dq, $J = 33.7$, 149.2 Hz), 65.7 (d, $J = 7.3$ Hz), 66.3 (d, $J = 7.3$ Hz), 67.5, 74.9 (d, $J = 16.8$ Hz), 77.2, 90.3 (d, $J = 8.8$ Hz), 113.0 (d, $J = 2.9$ Hz), 113.9, 122.9 (dq, $J = 2.9$, 287.2 Hz), 128.3, 128.3, 128.5, 133.6, 133.6, 135.7, 153.4 (d, $J = 10.2$ Hz), 160.4 ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{NO}_6\text{P}$: C, 55.31; H, 5.05; N, 2.80. Found: C, 55.25; H, 5.04; N, 2.77.

4.1.6. Diethyl [1-{{(benzyloxy)carbonyl}amino}-4-phenyl-1-(trifluoromethyl)but-3-yn-1-yl]phosphonate (4a)

Yield: 62%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.38 (t, $J_{\text{H-H}} = 7.1$ Hz, 6H, 2CH_3), 3.49–3.80 (m, 2H, CH_2), 4.25–4.39 (m, 4H,

OCH_2), 5.15 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.24 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.91 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 10.0$ Hz, 1H, NH), 7.32–7.42 (m, 10H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 7.04 (d, $\text{d}_{\text{J}_{\text{F-P}}} = 3.3$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 9.06 (q, $\text{q}_{\text{J}_{\text{P-F}}} = 4.1$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.3 (m), 21.5, 60.9 (dq, $J = 28.7$, 67.5 Hz), 64.6 (m), 67.2, 82.8 (m), 83.9, 123.1, 127.8 (qd, $J = 4.4$, 283.0 Hz), 128.1 (m), 128.1, 128.2, 128.2, 128.5, 131.6, 135.9, 154.2 (d, $J = 9.9$ Hz) ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{NO}_5\text{P}$: C, 57.14; H, 5.21; N, 2.90. Found: C, 57.09; H, 5.18; N, 2.88.

4.1.7. Diethyl [1-{{(benzyloxy)carbonyl}amino}-4-(4-methylphenyl)-1-(trifluoromethyl)but-3-yn-1-yl]phosphonate (4b)

Yield: 30%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.39 (t, $J_{\text{H-H}} = 7.0$ Hz, 6H, 2CH_3), 2.40 (s, 3H, CH_3), 3.45–3.76 (m, 2H, CH_2), 4.25–4.39 (m, 4H, OCH_2), 5.15 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.22 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.79 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 10.2$ Hz, 1H, NH), 7.13 (d, $J_{\text{H-H}} = 7.8$ Hz, 2H, ArH), 7.28–7.42 (m, 7H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 6.99 (s, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 15.84 (q, $\text{q}_{\text{J}_{\text{P-F}}} = 4.4$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.3 (m), 21.4, 21.6, 61.0 (dq, $J = 26.5$, 153.6 Hz), 64.5 (m), 67.2, 81.9 (d, $J = 6.6$ Hz), 84.0, 120.1, 124.4 (qd, $J = 4.4$, 287.4 Hz), 128.1, 128.2, 128.5, 128.9, 131.5, 135.9, 138.1, 154.1 (d, $J = 9.9$ Hz) ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{F}_3\text{NO}_5\text{P}$: C, 57.95; H, 5.47; N, 2.82. Found: C, 58.01; H, 5.44; N, 2.78.

4.1.8. Diethyl [1-{{(benzyloxy)carbonyl}amino}-4-(4-methoxyphenyl)-1-(trifluoromethyl)but-3-yn-1-yl]phosphonate (4c)

Yield: 70%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.37 (t, $J_{\text{H-H}} = 7.1$ Hz, 6H, 2CH_3), 3.43–3.74 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.25–4.37 (m, 4H, OCH_2), 5.13 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.21 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.84 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 10.2$ Hz, 1H, NH), 6.83 (d, $J_{\text{H-H}} = 8.6$ Hz, 2H, ArH), 7.30–7.39 (m, 7H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 7.03 (s, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 15.82 (q, $\text{q}_{\text{J}_{\text{P-F}}} = 4.2$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.3 (m), 21.6, 55.2, 61.0 (dq, $J = 28.7$, 153.1 Hz), 64.5 (m), 67.2, 81.0 (d, $J = 6.6$ Hz), 83.8, 113.8, 115.2, 124.4 (qd, $J = 4.4$, 287.4 Hz), 128.1, 128.2, 128.5, 133.0, 135.9, 154.1 (d, $J = 11.0$ Hz), 159.4 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{F}_3\text{NO}_6\text{P}$: C, 56.14; H, 5.30; N, 2.73. Found: C, 56.17; H, 5.28; N, 2.69.

4.1.9. Diethyl [1-{{(benzyloxy)carbonyl}amino}-4-(2-methoxyphenyl)-1-(trifluoromethyl)but-3-yn-1-yl]phosphonate (4d)

Yield: 70%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.21–1.27 (m, 6H, 2CH_3), 3.34–3.59 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 4.12–4.27 (m, 4H, OCH_2), 5.08 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.3$ Hz, 1H, CH_2), 5.01 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.1$ Hz, 1H, CH_2), 5.86 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 11.3$ Hz, 1H, NH), 6.71–6.79 (m, 2H, ArH), 7.14–7.28 (m, 7H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 6.96 (d, $\text{d}_{\text{J}_{\text{F-P}}} = 3.6$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 15.82 (q, $\text{q}_{\text{J}_{\text{P-F}}} = 4.2$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): δ = 16.0 (m), 22.2, 55.1, 60.2 (dq, $J = 28.1$, 153.8 Hz), 64.2 (m), 66.9, 80.4, 86.0 (d, $J = 6.8$ Hz), 110.2, 111.8, 120.0, 124.2 (qd, $J = 5.7$, 287.7 Hz), 127.8, 128.1, 129.2, 133.1, 135.6, 153.9 (d, $J = 9.1$ Hz), 159.8 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{F}_3\text{NO}_6\text{P}$: C, 56.14; H, 5.30; N, 2.73. Found: C, 56.16; H, 5.28; N, 2.70.

4.1.10. Diethyl [4-(4-aminophenyl)-1-{{(benzyloxy)carbonyl}amino}-1-(trifluoromethyl)but-3-yn-1-yl]phosphonate (4e)

Yield: 50%; oil. ^1H NMR (300.13 MHz, CDCl_3): δ = 1.24 (t, $J_{\text{H-H}} = 7.0$ Hz, 6H, 2CH_3), 3.28–3.59 (m, 2H, CH_2), 3.90 (br.s., 2H, NH_2), 4.10–4.25 (m, 4H, OCH_2), 5.01 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.1$ Hz, 1H, CH_2), 5.08 (d, $\text{d}_{\text{AB}}, J_{\text{AB}} = 12.1$ Hz, 1H, CH_2), 5.67 (d, $\text{d}_{\text{J}_{\text{H-P}}} = 10.5$ Hz, 1H, NH), 6.50 (d, $J_{\text{H-H}} = 8.4$ Hz, 2H, ArH), 7.06 (d, $J_{\text{H-H}} = 8.4$ Hz, 2H, ArH), 7.18–7.27 (m, 5H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): δ = 7.08 (s, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): δ = 15.87 (d, $\text{d}_{\text{J}_{\text{P-F}}} = 3.6$ Hz, 3F, CF_3) ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{NO}_5\text{P}$: C, 57.14; H, 5.21; N, 2.90. Found: C, 57.09; H, 5.18; N, 2.88.

$F = 4.2$ Hz) ppm. ^{13}C NMR (101 MHz, CD_3OD): $\delta = 16.6$ (d, $J = 5.8$ Hz), 23.3, 63.0 (dq, $J = 27.8$, 157.0 Hz), 65.6 (dd, $J = 18.5$, 7.4 Hz), 67.8, 80.2 (d, $J = 8.0$ Hz), 112.7, 114.2, 115.6, 125.8 (qd, $J = 6.2$, 286.3 Hz), 128.9, 128.9, 129.0, 129.4, 131.6, 133.7, 137.9, 149.3, 156.4 (d, $J = 4.9$ Hz) ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_5\text{P}$: C, 55.42; H, 5.26; N, 5.62. Found: C, 55.46; H, 5.24; N, 5.59.

4.1.11. Diethyl [1-*{[(benzyloxy)carbonyl]amino}*-4-(4-nitrophenyl)-1-(trifluoromethyl)but-3-yn-1-yl]phosphonate (4f)

Yield: 46%; oil. ^1H NMR (300.13 MHz, CDCl_3): $\delta = 1.23$ –1.28 (m, 6H, 2 CH_3), 3.40–3.69 (m, 2H, CH_2), 4.08–4.24 (m, 4H, OCH_2), 4.99 (d_{AB}, $J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.10 (d_{AB}, $J_{\text{AB}} = 12.2$ Hz, 1H, CH_2), 5.68 (d, $^3J_{\text{H-P}} = 9.4$ Hz, 1H, NH), 7.19–7.28 (m, 7H, ArH), 7.19–7.28 (m, 6H, ArH), 7.35 (s, 1H, ArH), 8.01 (s, 1H, ArH), 8.04 (s, 1H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): $\delta = 6.84$ (d, $^3J_{\text{F-P}} = 4.0$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): $\delta = 15.41$ (q, $^3J_{\text{P-F}} = 4.2$ Hz) ppm. ^{13}C NMR (75.47 MHz, CDCl_3): $\delta = 16.3$, 21.4, 60.8 (dq, $J = 28.2$, 152.8 Hz), 64.6, 67.3, 82.2, 88.9 (d, $J = 5.8$ Hz), 123.5, 124.3 (dq, $J = 287.2$ Hz), 128.3, 128.3, 128.5, 130.0, 132.3, 135.8, 147.0, 154.1 (d, $J = 10.7$ Hz) ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_7\text{P}$: C, 52.28; H, 4.58; N, 5.30. Found: C, 52.31; H, 4.56; N, 5.27.

4.2. General procedure for hydrogenation of the triple bond

Alkynyl-containing amino ester (0.26 mmol) was dissolved in methanol (10 mL), and palladium on carbon (0.016 mmol, 10%) was added to the solution. The resulting suspension was degassed twice and then stirred under a hydrogen atmosphere for 3 h. The catalyst was filtered off through a Celite plug, and the solvent was removed under reduced pressure to give the pure product.

4.2.1. Diethyl [1-amino-4-(2-methoxyphenyl)-1-(trifluoromethyl)butyl]phosphonate (5)

Yield: 80%; oil. ^1H NMR (300.13 MHz, CDCl_3): $\delta = 1.09$ –1.12 (m, 6H, 2 CH_3), 1.81 (d, $^3J_{\text{H-P}} = 14.1$ Hz, 2H, NH₂), 2.03–2.12 (m, 4H, CH_2), 2.72–2.74 (m, 2H, CH_2), 3.49 (s, 3H, OCH_3), 4.02–4.12 (m, 4H, OCH_2), 6.67 (d, $J_{\text{H-H}} = 8.0$ Hz, 1H, ArH), 6.92 (td, $J_{\text{H-H}} = 1.0$, 7.4 Hz, 1H, ArH), 7.13–7.17 (m, 2H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): $\delta = 5.51$ (d, $^3J_{\text{F-P}} = 4.3$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): $\delta = 20.45$ (q, $^3J_{\text{P-F}} = 4.3$ Hz) ppm. ^{13}C NMR (75.47 MHz, CD_3OD): $\delta = 16.1$ (m), 23.4 (d, $J = 5.5$ Hz), 30.6, 32.7, 54.6, 59.8 (dq, $J = 26.5$, 153.6 Hz), 62.94 (d, $J = 6.6$ Hz), 63.22 (d, $J = 6.6$ Hz), 110.3, 120.4, 126.4 (qd, $J = 8.8$ Hz), 127.2, 129.9, 130.0, 157.6 ppm. Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{F}_3\text{NO}_5\text{P}$: C, 56.67; H, 6.00; N, 2.87. Found: C, 56.69; H, 5.98; N, 2.86.

4.2.2. Diethyl [1-amino-3-(4-methylphenyl)-1-(trifluoromethyl)propyl]phosphonate (6)

Yield: 85%; oil. ^1H NMR (300.13 MHz, CDCl_3): $\delta = 1.16$ (td, $J = 2.3$, 7.0 Hz, 6H, 2 CH_3), 1.85 (br.s., 2H, NH₂), 2.23 (s, 3H, CH_3), 2.30–2.41 (m, 2H, CH_2), 2.98–3.05 (m, 2H, CH_2), 4.04–4.18 (m, 4H, OCH_2), 7.10 (dd, $J_{\text{H-H}} = 7.9$, 21.4 Hz, 4H, ArH) ppm. ^{19}F NMR (282.4 MHz, CDCl_3): $\delta = 5.56$ (d, $^3J_{\text{F-P}} = 4.4$ Hz, 3F, CF_3) ppm. ^{31}P NMR (161.97 MHz, CDCl_3): $\delta = 20.20$ (m) ppm. ^{13}C NMR

(75.47 MHz, CD_3OD): $\delta = 15.4$ (m), 19.7 (m), 28.9, 34.8, 59.6 (dq, $J = 26.5$, 156.4 Hz), 63.7 (d, $J = 7.7$ Hz), 64.0 (d, $J = 6.6$ Hz), 125.9 (qd, $J = 9.9$, 284.1 Hz), 135.3, 138.2 ppm. Anal. Calcd for $\text{C}_{24}\text{H}_{31}\text{F}_3\text{NO}_6\text{P}$: C, 55.70; H, 6.04; N, 2.71. Found: C, 55.73; H, 6.02; N, 2.70.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.07.028.

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