Synthesis of ω-Phosphonated Poly(ethylene oxide)s Through the Combination of Kabachnik–Fields Reaction and ''Click'' Chemistry

Thi Thanh Thuy N'Guyen,[1] Karima Oussadi,[1,2] Véronique Montembault,[1] Laurent Fontaine[1]

[1]LUNAM Université, Institut des Molécules et Matériaux du Mans, Equipe Méthodologie et Synthèse des Polymères, UMR CNRS 6283, Université du Maine, Avenue O. Messiaen, 72085 Le Mans Cedex 9, France
[2]Université des Sciences et de Technologie Mohamed Boudiaf, BP 1505, Oran El M'Naouar 31000, Algeria
Correspondence to: L. Fontaine (E-mail: laurent.fontaine@univ-lemans.fr)

Received 13 July 2012; accepted 27 September 2012; published online 19 October 2012
DOI: 10.1002/pola.26399

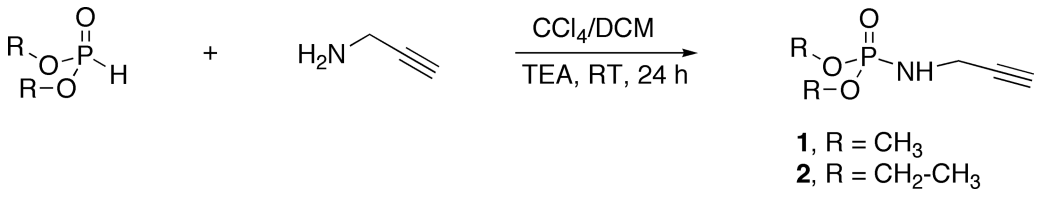
ABSTRACT: The synthesis of new ω-phosphonic acid-terminated poly(ethylene oxide) (PEOs) monomethyl ethers was investigated by the combination of Atherton–Todd or Kabachnik–Fields reactions and the "click" copper-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes. The Atherton–Todd route fails to give the corresponding phosphonic acid-terminated PEOs due to competitive cleavage of the P—N bond during the dealkylation step. In contrast, the Kabachnik–Fields route leads with very good yields to ω-phosphonic acid-PEO through "click" reaction of azido-PEO onto dimethyl aminopropargyl phosphonate prepared by Kabachnik–Fields reaction between propargylbenzylimine and dimethyl phosphonate, followed by acidic hydrolysis. The reported methodology, precluding the use of anionic polymerization of ethylene oxide, leads to novel well-defined phosphonic acid-terminated PEOs from commercially available products in good yields. Moreover, such a strategy can be adapted to anchor phosphonic acid functionality onto a wide range of polymers. © 2012 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 51: 415–423, 2013

KEYWORDS: aminophosphonates; Atherton–Todd reaction; "click" chemistry; functionalization of polymers; Kabachnik–Fields reaction; MALDI; modification; poly(ethylene oxide); synthesis; water-soluble polymers

INTRODUCTION Phosphorus-containing polymers have attracted attention because of their broad application areas.[1–4] Polyphosphonates and polyphosphates are known as fire-retardant additives,[5] adhesion promoters and corrosion inhibitors,[2] and chelating agents.[6–8] Phosphorus-based polymers can also be employed for various biomedical applications[9,10] such as drug delivery,[11–16] tissue engineering,[17] and dental applications.[18–20]

Poly(ethylene oxide) (PEO)—also referred to as poly(ethylene glycol) (PEG) for structures bearing hydroxyl end-groups—is a neutral, non-toxic, hydrophilic synthetic polymer which has found numerous applications.[21] It has emerged as the polymer of choice for use in pharmaceutical, biotechnical, and biomedical applications. Because of those interesting properties, the range of PEO-based polymers has been expanded, including complex structures of graft copolymers with PEO side chains,[22–24] and PEO oligomers with tailored functionalities at the chain-ends.[25] Some specific applications require heterobifunctional PEOs with distinct reactive functional groups at the ends of the polymer chain.[26–32] One of the most commonly used functionalized derivatives of PEO is methoxy-terminated PEO (mPEG) which can serve as the building block for preparation of various heterobifunctional PEOs.[25] PEO is also one of the most widely used coatings for magnetic nanoparticles because of its low cytotoxicity, hydrosolubility, and ability to mask foreign substrates from the immune system.[33] A number of PEO end-functionalized with various organophosphorus groups have been investigated,[34–39] especially in view of the ability of organophosphates to bind to a wide range of metal oxide surfaces.[40–43] Nevertheless, only a few efficient syntheses of phosphorylated end-functionalized PEOs have been reported in the literature up to now. Besides esterification of mPEG using $POCl_3$ followed by partial hydrolysis,[35–38] phosphorus end-functionalized PEOs were prepared via radical addition reactions[44,45] and Michael addition.[46] Phosphonated PEOs were prepared by Mosquet et al.[47] and by Shephard et al.[36] through Moedritzer–Irani reaction.[48] Phosphonated PEOs have mainly found applications as steric stabilizers for colloidal suspensions,[47] and for coating metallic nanoparticles.[34–36,46] In this context, this report describes the combination of Atherton–Todd reaction[6,8,12,13,16,49] and of Kabachnik–Fields reaction[7,50–52] together with "click" chemistry[53] for the straightforward synthesis of mPEGs containing an ω-phosphonyl functional group which are potential candidates for a wide range of uses, including stabilization and dispersion of metallic nanoparticles.[34–42]

Additional Supporting Information may be found in the online version of this article



SCHEME 1 Synthesis of propargyl phosphoramidates **1** and **2**.

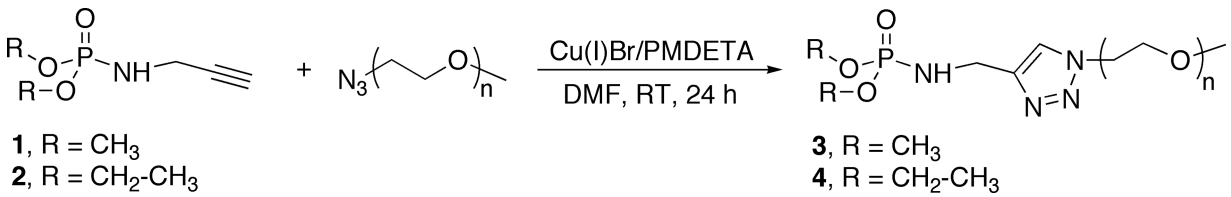
RESULTS AND DISCUSSION

Atherton–Todd Route

Propargyl phosphoramidates bearing a dialkyl phosphonate group, that is dimethyl prop-2-ynylphosphoramidate (**1**) and diethyl prop-2-ynylphosphoramidate (**2**), were synthesized via Atherthon–Todd reaction according to Scheme 1. The reaction of diethyl phosphonate with *N*-propargylamine was carried out according to a literature procedure,[54] leading to **2** in 55% yield after distillation. The same procedure was used to generate the new compound **1**, which was obtained in a modest 22% yield after recrystallization of the crude solid product from hexane:dichloromethane. ^{1}H, ^{13}C, and ^{31}P NMR (see Supporting Information Figs. S1 and S2), as well as high resolution mass spectrometry, confirmed the successful synthesis of compounds **1** and **2**.

The "click" coupling reactions were performed between **1** or **2** and azido-terminated PEO monomethyl ether 2000 (PEO—N_3) as shown in Scheme 2. PEO—N_3 was synthesized by mesylation of hydroxyl-terminated PEO monomethyl ether, followed by nucleophilic substitution using sodium azide according to a literature procedure.[23] The "click" reactions were carried out in *N,N*-dimethylformamide (DMF) at room temperature for 24 h using a stoichiometric ratio between PEO—N_3 and alkynyl groups in the presence of a catalytic amount of Cu(I)Br with *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (PMDETA) as the ligand. The phosphonate-terminated PEO monomethyl ethers **3** and **4** (Scheme 2) were purified by precipitation into diethyl ether.

^{1}H NMR spectra of **2** and **4** clearly indicated the shift of the alkyne proton at 2.25 ppm (e, Supporting Information Fig. S2) to 7.70 ppm [e, Supporting Information Fig. S3(A)] as well as the shift of the methylene group next to the alkyne functionality at 3.68 ppm (d, Supporting Information Fig. S2) to 4.22 ppm [d, Supporting Information Fig. S3(A)], which correspond to the protons linked to the formed triazole ring. Completion of the reaction was confirmed by the ratio of integrations of peaks assigned to the CH_3 protons of diethyl phosphonate groups [a at 1.31 ppm, Supporting Information Fig. S3(A)] to the proton of the triazole ring [e at 7.70 ppm, Supporting Information Fig. S3(A)] that gave a 6:0.96 ratio. The same conclusions could be drawn from the reaction between **1** and PEO—N_3 [Supporting Information Fig. S3(B)]. Moreover, the matrix-assisted laser desorption and ionization time of flight (MALDI-TOF) mass spectra (Fig. 1) confirmed the expected structures. As an example, the MALDI-TOF mass spectrum of **4** [Fig. 1(A)] showed a single series of peaks separated by $m/z = 44.04$, the molecular weight of the PEO repeat unit (calculated value = 44.0262 g mol^{-1}). The peak at $m/z = 1900.15$ corresponds to a polymer of 37 PEO units ionized by a sodium atom, with a methyl group at one chain-end and a triazole diethylphosphoramidate group —CH_2—NH—P(O)$(OEt)_2$ at the other chain-end (calculated value = 1900.06 g mol^{-1}). The last step for obtaining phosphonic acid-terminated PEO monomethyl ether consists in the deprotection of the phosphonates in a multi-step one-pot procedure. The established methodology to remove the ester protecting groups of phosphonates involving the use of trimethylsilyl bromide (TMSBr) has been used (Scheme 3).[55] This transformation has been characterized by ^{31}P NMR (Supporting Information Fig. S4), with a shielding of the signal of the P(O) group from 10.86 ppm [Supporting Information Fig. S4(A)] to 1.22 ppm [Supporting Information Fig. S4(B)], which is consistent with values reported in the literature for aminophosphonic acids.[56] ^{1}H NMR spectrum (Supporting Information Fig. S5) also confirmed the total disappearance of the signals due to the CH_3 of the dimethylphosphonate group and a shielding of the CH_2 connecting the phosphoramide group from 4.22 to 4.37 ppm. The MALDI-TOF mass spectrum of the resulting product (Fig. 2) shows a single series of peaks separated by $m/z = 44.10$, the molecular weight of the PEO repeat unit (calculated value = 44.0262 g mol^{-1}). Nevertheless, the peak at $m/z = 1956.08$ corresponds to a polymer of 41 PEO units ionized by a potassium atom, with a methyl group at one chain-end and a triazole aminomethyl group at the other chain-end (calculated value = 1956.11 g mol^{-1}). This means that the P—N bond of **3** (and **4**) is susceptible to TMSBr cleavage, as



SCHEME 2 Synthesis of phosphonate-terminated PEO monomethyl ethers **3** and **4**.

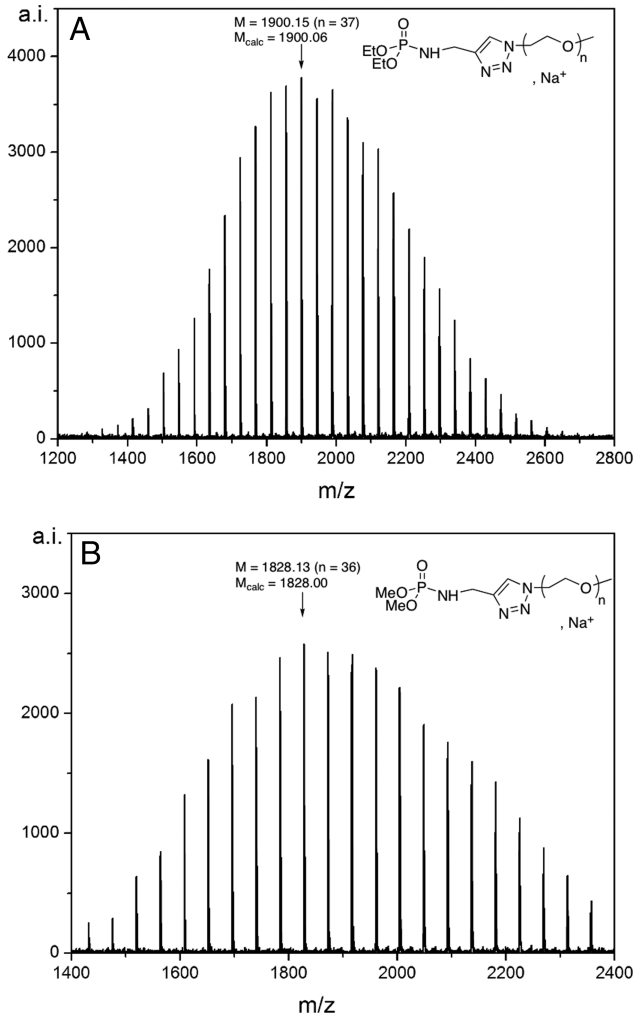


FIGURE 1 MALDI-TOF mass spectra of (A) diethylphosphonate-terminated PEO monomethyl ether (**4**) and (B) dimethylphosphonate-terminated PEO monomethyl ether (**3**); matrix: DCTB, NaTFA.

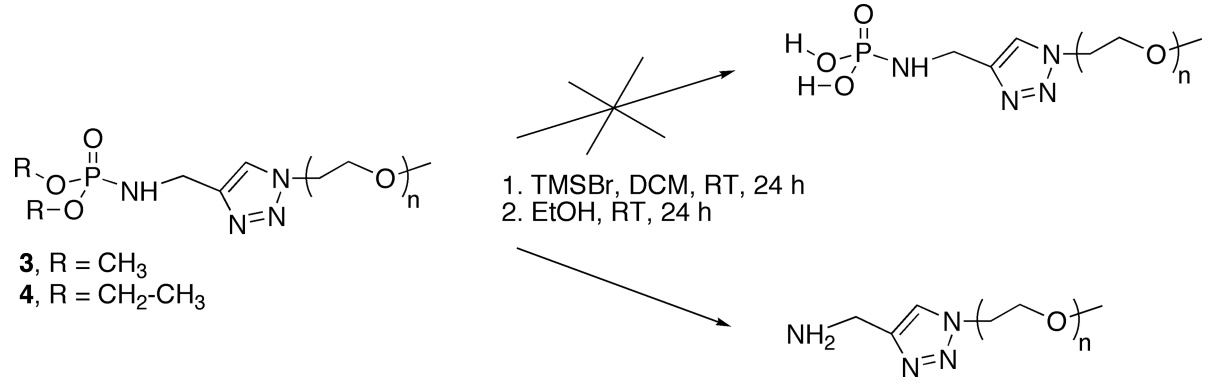
evidenced by MALDI-TOF mass spectrometry, and as already observed with phosphoramide esters generated from secondary amines.[56] These results prompt us to use another strategy to prepare ω-phosphorylated PEO by introducing a robust P—C bond between the phosphoryl moiety and the PEO chain using the Kabachnik–Fields reaction.[7,50–52]

Kabachnik–Fields Route

Propargyl aminophosphonate **6** was synthesized through Kabachnik–Fields reaction[51,52] in a two-step procedure (Scheme 4) according to a literature protocol.[57] In the first step, *N*-benzylideneprop-2-yn-1-amine (**5**) was synthesized from benzaldehyde and *N*-propargylamine in 77% yield.[58] In the second step, imine **5** was reacted with dimethyl phosphite under solvent-free and catalyst-free conditions for 8 h at 60–80 °C to afford dimethyl phenyl(prop-2-ynylamino)methylphosphonate (**6**) in a very good 85% yield after silica gel column chromatography. The structure of **6** was confirmed by IR, ^{1}H, ^{13}C, ^{31}P spectroscopy, and mass spectrometry. The ^{1}H NMR spectrum of **6** [Supporting Information Fig. S7(A)] showed the disappearance of the signal arising from the CH=N group of imine **5** at 8.56 ppm [Supporting Information Fig. S6(A)] and concomitant appearance of a new peak at 4.39 ppm ascribed to the CH(P) proton of **6**. Moreover, the ^{31}P NMR spectrum of **6** [Supporting Information Fig. S7(B)] showed a singlet at 25.06 ppm, in the region expected for aminophosphonate derivatives.[59–61]

Typical "click" coupling reaction between PEO—N_3 2000 and 5000 and **6** (Scheme 5) was then successfully performed in DMF solvent at room temperature for 24 h under the conditions reported above. The phosphonate-terminated PEO monomethyl ethers **7a** (from PEO—N_3 2000) and **7b** (from PEO—N_3 5000) were purified by precipitation into diethyl ether.

Figure 3 shows the ^{1}H NMR spectrum of dimethylphosphonate-terminated PEO **7a** (see Supporting Information Fig. S8 for **7b**). A set of new peaks was clearly observed at 7.61 ppm typical of the methine proton of the triazole ring, at 3.52–3.72 ppm typical of the protons for the ethylene oxide units, at 3.38 ppm for the methoxy protons, at 4.52 ppm for the —(triazole)—CH_2CH$_2$(OCH$_2$CH$_2$)$_{44}$OCH$_3$, and at 3.86 ppm for the —(triazole)—CH$_2$CH_2(OCH$_2$CH$_2$)$_{44}$OCH$_3$ protons. Concomitant shielding of the CH linked to the phosphorus from 4.39 ppm [H_5, Supporting Information Fig. S7(A)] to 4.12 ppm (H_5, Fig. 3) also confirmed that the desired reaction had taken place. Furthermore, integrations of the newly



SCHEME 3 Reaction of phosphonate-terminated PEO with TMSBr.

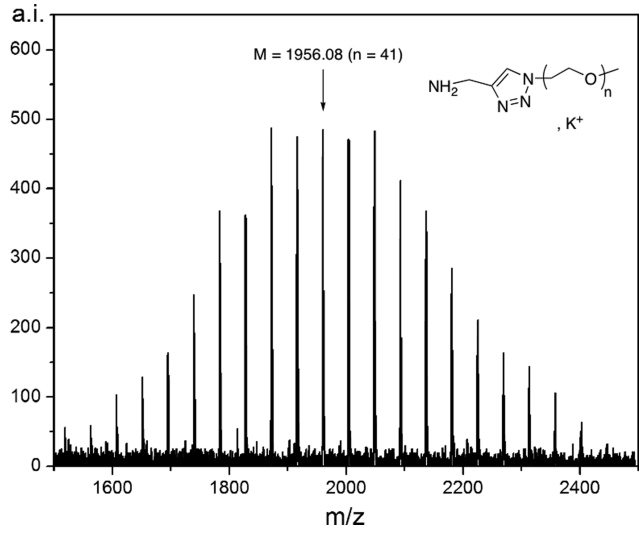


FIGURE 2 MALDI-TOF mass spectrum of the product resulting from the attempted dealkylation reaction of **3** using TMSBr; matrix: α-cyano-4-hydroxycinnamic acid, KTFA.

five-membered triazole ring proton (H_9, Fig. 3) peak and the methoxy-terminal PEO protons (H_{13}, Fig. 3) peak gave a 3:1 ratio, indicating almost quantitative "click" transformation. Moreover, the MALDI-TOF characterization of **7a** sample (Fig. 4) fully corroborates the results of ^{1}H NMR analysis. Only one population is observed with a peak-to-peak mass increment of 44.04 g mol^{-1} corresponding to the molecular weight of the PEO repeat unit (calculated value = 44.0262 g mol^{-1}). Each signal of this series is assignable to the dimethylphosphonate-terminated PEO monomethyl ether **7a**. For instance, the peak at m/z = 2066.19 is assigned to species with a degree of polymerization of 42 ionized by a sodium atom, with a methyl group at one end and a dimethylphosphonyl group at the other chain-end (calculated value = 2066.11 g mol^{-1}).

The dimethylphosphonate-terminated PEO monomethyl ethers **7a,b** were then converted to their phosphonic acid homologues **8a,b** according to (i) the previous methodology involving the use of TMSBr and (ii) using acidic hydrolysis (Scheme 6). ^{1}H NMR and ^{31}P NMR spectroscopy (Supporting Information Fig. S9) both confirmed a total conversion of the ester groups into phosphonic acid by the disappearance of the CH_3 signal at 3.80 ppm and by a shift of the P signal from 25.52 ppm to 13.29 ppm for **8a**. Furthermore, the FTIR spectrum showed the appearance of a new broad absorbance band at 3100 cm^{-1}, which confirmed the formation of phosphonic acid chain-end. To provide direct evidence for the phosphonic acid-terminated PEO structure obtained, MALDI-TOF analysis of **8a** was carried out, as shown in Figure 5. The MALDI-TOF mass spectrum of the resulting product recorded in negative ion mode shows only one series of peaks, which show a regular interval of 44.08 g mol^{-1} for the molar mass that corresponds to the ethylene oxide unit. In addition, the peak at m/z = 2174.92 corresponds to a deprotonated polymer of 43 PEO units, with a methyl group at one chain-end and a phosphonic acid at the other chain-end (calculated value = 2174.21 g mol^{-1}). Similar results were obtained for **8b**.

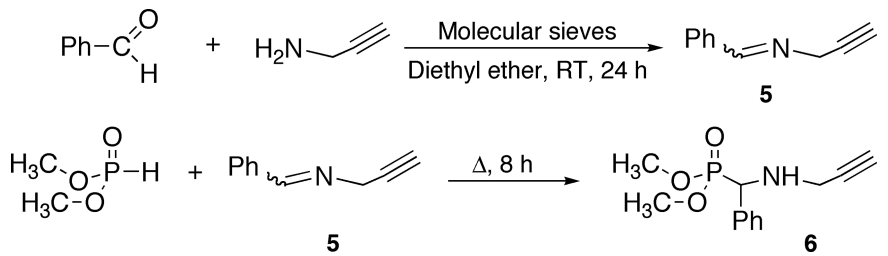
EXPERIMENTAL

Materials

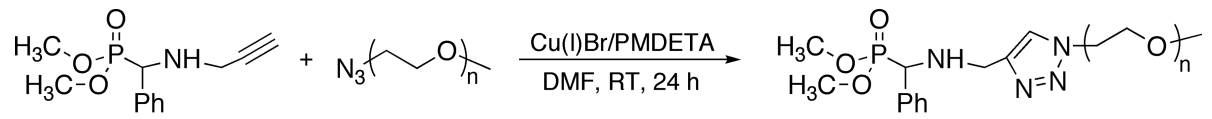
Triethylamine (b.p.$_{760\ \mathrm{Torr}}$ = 86 °C) was distilled over CaH_2 and was stored at −4 °C after purification. Diethyl phosphite (b.p.$_{0.2\ \mathrm{Torr}}$ = 50 °C) and dimethyl phosphite (b.p.$_{0.2\ \mathrm{Torr}}$ = 40 °C) were distilled in vacuum before use. PEO monomethyl ether (PEO—OH) 2000 ($M_{n\ \mathrm{NMR}}$ = 2010 g mol^{-1}) and PEO-OH 5000 ($M_{n\ \mathrm{NMR}}$ = 4600 g mol^{-1}) were heated at 120 °C for 3 h under nitrogen atmosphere to remove excess water before use. Azido-terminated PEO monomethyl ethers (PEO—N_3 2000 and 5000)[23] and *N*-benzylideneprop-2-yn-1-amine (**5**)[58] were synthesized according to literature procedures. All other chemicals were purchased from commercial sources and used without further purification.

General Characterization

NMR spectra were recorded on a Bruker Avance 400 spectrometer using deuterated chloroform or methanol as the solvent and tetramethylsilane, 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) and H_3PO_4 as a reference for ^{1}H, ^{13}C, and ^{31}P nuclei, respectively. Coupling constants and chemical shifts are reported in hertz and in parts per million (ppm), respectively. FTIR spectra were recorded using a Nicolet avatar 370 DTGS spectrometer in transmittance mode. High resolution mass spectra (HR-MS) were recorded on a Waters-Micromass® GCT Premier™ (GC, CI+, methane) using a HP 6890 GC apparatus equipped with a chromatographic column of 25 m, diameter 250 μm, thickness 0.25 μm. The sample was warmed at a temperature of 40 °C for 5 min and then further heated at a heating rate of 10 °C min^{-1} up to 220 °C. HR-MS were recorded on Waters-Micromass GCT Premier spectrometers. MALDI-TOF mass spectrometry



SCHEME 4 Synthesis of propargylaminophosphonate **6**.



6 **7a-b**

SCHEME 5 Synthesis of phosphonate-terminated PEO monomethyl ethers **7a** (from PEO—N_3 2000) and **7b** (from PEO—N_3 5000).

analysis was performed on a Bruker Biflex III MALDI-TOF instrument equipped with nitrogen laser operating at 337 nm, a 2 GHz sampling rate digitizer, pulsed ion extraction source and reflectron. The laser pulse width is 3 ns and maximum power is 200 mJ. Spectra were recorded in the linear mode or negative mode with an acceleration voltage of 19 kV and delay of 200 ns. One hundred single shot acquisitions were summed to give the spectra and the data were analyzed using Bruker XTOF software. Samples were run in α-cyano-4-hydroxycinnamic acid (HCCA) or 2-[(*2E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) as the matrix doped with sodium trifluoroacetate (NaTFA), potassium trifluoroacetate (KTFA), or sodium iodide as the cationizing agent.

General Procedure for the Synthesis of Propargylphosphoramidates via Atherton–Todd Reaction

A solution of di(m)ethyl phosphite (0.05 mol) in carbon tetrachloride (15 mL) was added dropwise to a mixture of *N*-propargylamine (2.75 g, 0.05 mol), triethylamine (6.06 g, 0.06 mol), carbon tetrachloride (10 mL), and dichloromethane (25 mL) under stirring. The mixture was stirred at room temperature for 24 h, poured into dichloromethane (50 mL) and then extracted with water (3 × 10 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed by evaporation.

Dimethyl Prop-2-ynylphosphoramidate 1

The resulting solid was purified by recrystallization from hexane:dichloromethane to afford **1** (1.8 g; 22%) as a beige powder. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.73 (s, 6H, C*H*$_3$), 3.66 (d, J = 4.35 Hz, 2H, NH—C*H*$_2$), 3.33 (s, 1H, N*H*), 2.29 (t, J = 2.46 Hz, 1H, C≡ C*H*). ^{13}C NMR ($CDCl_3$, 100.62 MHz), δ (ppm): 81.27 (d, J = 5.84 Hz, *C*—CH), 71.20 (s, C≡*C*H), 53.08 (d, J_{P-C} = 5.29 Hz, *C*H$_3$), 30.78 (s, NH—*C*H$_2$). ^{31}P NMR ($CDCl_3$, 161.96 MHz), δ (ppm): 10.64. FTIR (cm^{-1}): 3221 (ν_{N-H}); 2955 and 2851 (ν_{C-H}); 2110 ($\nu_{C\equiv C}$); 1220 ($\nu_{P=O}$); 1182 (ν_{P-O-C}); 1103, 1033, and 990 (ν_{P-N-C}). HR-MS (CI). Calcd for $C_5H_{10}NO_3P$ + H^+: 164.0477. Found: 164.0480.

Diethyl Prop-2-ynylphosphoramidate 2

Purification by distillation under reduced pressure (b.p.$_{0.3\ Torr}$ = 75 °C) afforded **2** (5.25 g; 55%) as a clear colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.05 (s, 1H, N*H*), 4.08 (m, 4H, POC*H*$_2$CH$_3$), 3.68 (d, J = 4.59 Hz, 2H, NH—C*H*$_2$), 2.25 (q, J = 4.96 Hz, 1H, C≡C*H*), 1.33 (t, J = 4.03 Hz, 6H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100.62 MHz), δ (ppm): 81.50 (d, J = 5.29 Hz, *C*≡CH), 70.70 (s, C≡*C*H), 61.91 (d, J_{P-C} = 5.31 Hz, POC*H*$_2$), 30.28 (s, NH—*C*H$_2$), 15.77 (d, J_{P-C} = 7.37 Hz, *C*H$_3$). ^{31}P NMR ($CDCl_3$, 161.96 MHz), δ (ppm): 8.25. FTIR (cm^{-1}): 3226 (ν_{N-H}); 2994 and 2908 (ν_{C-H}); 2115 ($\nu_{C\equiv C}$); 1635 (ν_{N-H}); 1229 ($\nu_{P=O}$); 1166 (ν_{P-O-C}); 1116, 1029, and 970 (ν_{P-N-C}). HR-MS (CI). Calcd for $C_7H_{14}NO_3P$ + H^+: 192.0790. Found: 192.0790.

Dimethyl Phenyl(prop-2-ynylamino)methylphosphonate 6

Imine **5** (7 mmol) and dimethyl phosphite (0.77 g; 7 mmol) were placed in a 100-mL round-bottom flask equipped with a magnetic stirrer, a reflux condenser, and a dropping funnel. The reaction mixture was heated for 8 h at 80 °C. The α-aminophosphonate was purified by silica gel column chromatography eluted with ethyl acetate:acetonitrile, 80:20, to give pure **6** as a yellow oil. Yield: 85%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.48 (d, J = 6.43 Hz, 2H, H_1); 7.39–7.26 (m, 3H, H_2 & H_3); 4.39 (d, J = 4.09 Hz, 1H, C*H*—P); 3.65 (m, 6H,

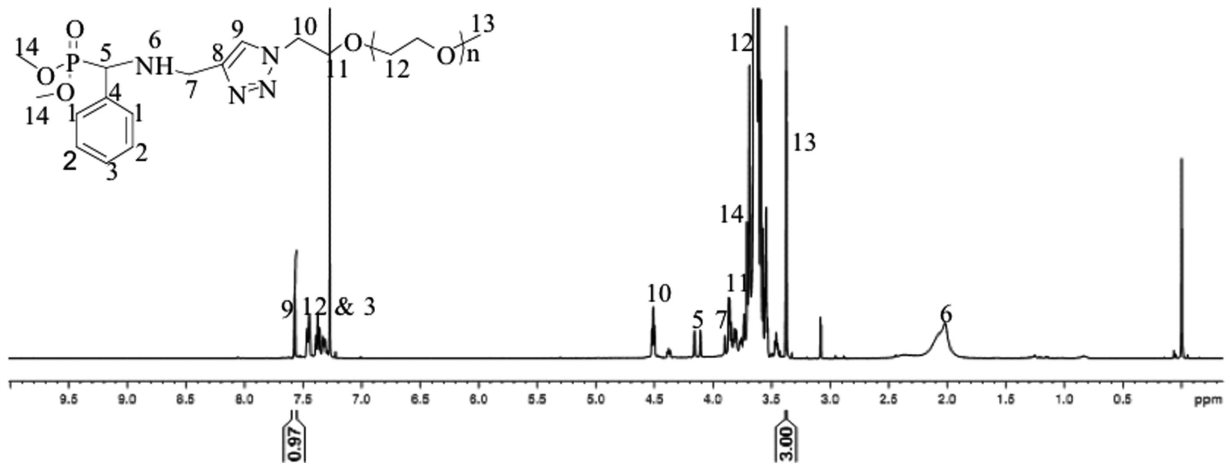


FIGURE 3 ^{1}H NMR spectrum of dimethylphosphonate-terminated PEO monomethyl ether **7a**; solvent: $CDCl_3$.

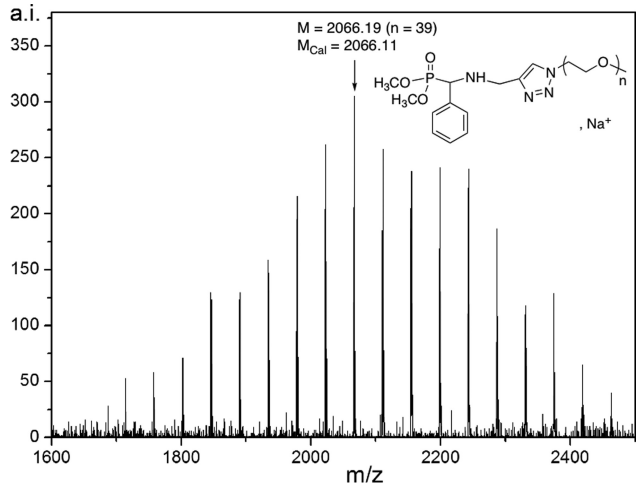


FIGURE 4 MALDI-TOF mass spectrum of dimethylphosphonate-terminated PEO monomethyl ether **7a**; matrix: DCTB, KTFA.

CH_3); 3.31 (m, 2H, CH_2); 2.24 (s, N*H*); 2.29 (q, J = 2.01 Hz, 1H, C≡C*H*). ^{13}C NMR ($CDCl_3$, 100.62 MHz), δ (ppm): 133.78 (d, J = 6.25 Hz, C_4); 128.37 (d, J = 6.03 Hz, C_3); 128.17 (d, J = 2.59 Hz, C_1); 127.83 (d, J = 3.15 Hz, C_2); 80.28 (*C*≡CH); 71.93 (C≡*C*H); 58.23 (d, J = 5.63 Hz, *C*H$_3$); 53.61 (t, J = 4.51 Hz, *C*HP); 35.87 (d, J = 19.14 Hz, N—*C*H$_2$). ^{31}P NMR ($CDCl_3$, 161.96 MHz), δ (ppm): 25.06. IR (ν, cm^{-1}): 3431 (ν_{N-H}); 2126 ($\nu_{C\equiv C}$); 1248 ($\nu_{P=O}$); 1146 (ν_{P-O-C}). HRMS (CI—H$^+$). Calcd for $C_{12}H_{17}NO_3P$ + H$^+$: 255.0946. Found: 255.0817.

General Procedure for the Synthesis of Phosphonate-Terminated PEO Monomethyl Ethers via "click" Coupling Reaction

In a typical experiment, azido-terminated PEO monomethyl ether (0.5 mmol), phosphonate derivative (0.5 mmol), and *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDETA; 0.1 g, 0.6 mmol) were charged to a dry Schlenk tube along with degassed DMF (5 mL). The tube was sealed with a rubber septum and subjected to six freeze–pump–thaw cycles. This solution was then cannulated under nitrogen into another Schlenk tube, previously evacuated and filled with nitrogen, containing Cu(I)Br (0.023 g, 0.16 mmol) and a stir bar. The resulting solution was subsequently stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (50 mL) and then washed with 3 × 100 mL of an aqueous ethylenediamine tetraacetate solution (0.03 mol/L) to remove the catalyst. The organic layer was dried over $MgSO_4$ and filtered. The resulting phosphonate-terminated PEO monomethyl ethers were isolated by precipitation into diethyl ether.

Dimethylphosphonate-Terminated PEO Monomethyl Ether 3

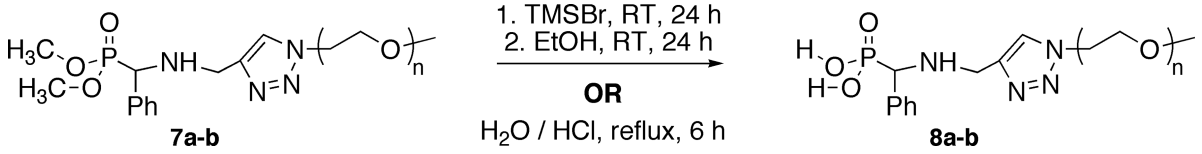
White powder. Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.70 (s, 1H, triazole), 4.53 (t, J = 5.33 Hz, 2H, $N_{triazole}$—C*H*$_2$—CH$_2$—O), 4.22 (d, J = 4.82 Hz, 2H, NH—C*H*$_2$), 3.87 (t, J = 5.53 Hz, 2H, $N_{triazole}$—CH$_2$—C*H*$_2$—O), 3.72 (s, 6H, P(O)O—C*H*$_3$), 3.60–3.68 (m, 172H, C*H*$_2$—C*H*$_2$—O), 3.38 (s, 3H, O—C*H*$_3$), 2.17 (s, 1H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 146.95 (*C*=C—$N_{triazole}$), 128.92 (C=*C*—$N_{triazole}$), 72.05 (*C*H$_2$—O—CH$_3$), 70.69 (—*C*H$_2$—O), 69.24 ($N_{triazole}$—CH$_2$—*C*H$_2$—O), 58.65 (*C*H$_3$—O), 53.15 (d, J_{P-C} = 5.5 Hz, P(O)O—*C*H$_3$), 50.34 ($N_{triazole}$—*C*H$_2$—CH$_2$—O), 36.75 (N—*C*H$_2$). ^{31}P NMR ($CDCl_3$, 161.96 MHz), δ (ppm): 10.86. FTIR (cm^{-1}): 2882 (ν_{C-H}); 1466 ($\nu_{C=C\ triazole}$); 1240 ($\nu_{P=O}$); 1146 (ν_{P-O-C}); 1101 (ν_{P-N-C}).

Diethylphosphonate-Terminated PEO Monomethyl Ether 4

White powder. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.70 (s, 1H, triazole), 4.53 (t, J = 5.77 Hz, 2H, $N_{triazole}$—C*H*$_2$—CH$_2$—O), 4.22 (t, J = 5.03 Hz, 2H, NH—C*H*$_2$), 4.06 (q, J = 4.86 Hz, 4H, P(O)OC*H*$_2$CH$_3$), 3.87 (t, J = 5.26 Hz, 2H, $N_{triazole}$—CH$_2$—C*H*$_2$—O), 3.52–3.73 (m, 172H, C*H*$_2$—C*H*$_2$—O), 3.38 (s, 3H, O—C*H*$_3$), 2.16 (s, 1H, N*H*), 1.31 (t, J = 7.71 Hz, 6H, P(O)O—CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 146.83 (*C*=C—$N_{triazole}$), 122.75 (C=*C*—$N_{triazole}$), 71.56 (*C*H$_2$—O—CH$_3$), 70.39 (—*C*H$_2$—O), 69.25 ($N_{triazole}$—CH$_2$—*C*H$_2$—O), 61.96 (d, J_{P-C} = 5.6 Hz, P(O)O—*C*H$_2$CH$_3$), 58.95 (*C*H$_3$—O), 50.35 ($N_{triazole}$—*C*H$_2$—CH$_2$—O), 36.72 (N—*C*H$_2$), 15.93 (d, J_{P-C} = 7.2 Hz, P(O)O—CH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$, 161.96 MHz), δ (ppm): 8.31. FTIR (cm^{-1}): 2882 (ν_{C-H}); 1466 ($\nu_{C=C\ triazole}$); 1240 ($\nu_{P=O}$); 1146 (ν_{P-O-C}); 1103 (ν_{P-N-C}).

Dimethylphosphonate-Terminated PEO Monomethyl Ether 7a (from PEO—N_3 2000)

Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.61 (s, 1H, triazole); 7.46 (d, J = 7.01 Hz, 2H, H_1); 7.38–7.26 (m, 3H, H_2 & H_3); 4.52 (t, J = 3.89 Hz, 2H, $N_{triazole}$—C*H*$_2$—CH$_2$—O); 4.12 (d, J = 2.89 Hz, 1H, *CH*P); 3.94 (d, J = 5.60 Hz, 2H, NH—C*H*$_2$); 3.86 (t, J = 4.86 Hz, 2H, $N_{triazole}$—CH$_2$—C*H*$_2$—O); 3.80 (s, 6H, P(O)O—C*H*$_3$); 3.52–3.72 (m, 172H, C*H*$_2$—C*H*$_2$—O); 3.38 (s, 3H, O—C*H*$_3$); 2.08 (s, 1H, N*H*). ^{13}C NMR (100.62 MHz, $CDCl_3$), δ (ppm): 145.73 (*C*=C—$N_{triazole}$); 134.86 (C_4); 128.94 (C_3); 128.12 (C_1); 127.98 (C_2); 123.08 (C=*C*—$N_{triazole}$); 71.95 (*C*H$_2$—O—CH$_3$); 70.95 (*C*H$_2$—O—CH$_2$); 69.55 ($N_{triazole}$—CH$_2$—*C*H$_2$—O); 60.36 (*C*HP); 59.04 (O—*C*H$_3$); 53.58 (P(O)O—*C*H$_3$); 50.21 ($N_{triazole}$—*C*H$_2$—CH$_2$—O); 42.53 (N—*C*H$_2$). ^{31}P NMR ($CDCl_3$, 161.96 MHz), δ (ppm): 25.52. IR (ν, cm^{-1}): 3436 (ν_{N-H}); 2883 (ν_{C-H}); 1466 ($\nu_{C=C\ triazole}$); 1242 ($\nu_{P=O}$); 1148 (ν_{P-O-C}).



SCHEME 6 Synthesis of phosphonic acid-terminated PEO monomethyl ethers **8a,b**.

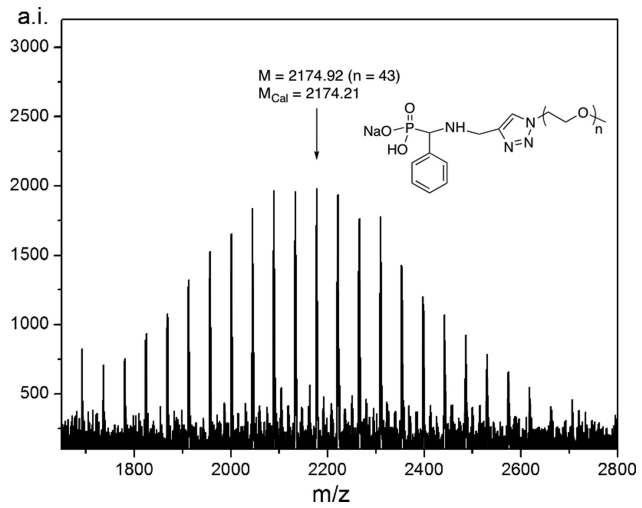


FIGURE 5 MALDI-TOF mass spectrum of phosphonic acid-terminated PEO monomethyl ether **8a**; matrix: DCTB, sodium iodide.

Dimethylphosphonate-Terminated PEO Monomethyl Ether 7b (from PEO—N_3 5000)

Brown powder. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.58 (s, 1H, triazole); 7.45 (s, 1H, H_1); 7.40–7.33 (m, 3H, H_2 & H_3); 4.52 (t, J = 5.07 Hz, 2H, $N_{triazole}$—CH_2—CH_2—O); 4.14 (m, 1H, *CH*P); 3.86 (m, 8H, $N_{triazole}$—CH_2—CH_2—O, P(O)OCH_3); 3.82–3.49 (m, 172H, CH_2—CH_2—O); 3.46 (t, J = 4.68 Hz, 2H, NH—CH_2); 3.38 (s, 3H, O—CH_3); 2.50 (s, 1H, N*H*). ^{13}C NMR (100.62 MHz, CD_3OD), δ (ppm): 145.69 (*C*=C—$N_{triazole}$); 135.10 (C_4); 128.70 (C_3); 128.12 (C_1); 125.46 (C_2); 123.04 (C=*C*—$N_{triazole}$); 71.92 (CH_2—O—CH_3); 70.55 (*C*H_2—O—CH_2); 69.50 ($N_{triazole}$—CH_2—*C*H_2—O); 60.31 (*C*HP); 59.01 (O—*C*H_3); 53.64 (P(O)O—*C*H_3); 45.56 ($N_{triazole}$—*C*H_2—CH_2—O); 42.49 (N—*C*H_2). ^{31}P NMR (CD_3OD, 161.96 MHz), δ (ppm): 25.47.

Amino-Terminated PEO Monomethyl Ether from 3

Yellow oil. Yield: 69%. ^{1}H NMR (400 MHz, CD_3OD), δ (ppm): 8.30 (s, 1H, triazole), 4.64 (t, J = 5.5 Hz, 2H, $N_{triazole}$—C*H*$_2$—CH_2—O), 4.37 (d, J = 4.6 Hz; 2H, NH—C*H*$_2$), 3.90 (t, J = 5.5 Hz, 2H, $N_{triazole}$—CH_2—C*H*$_2$—O), 3.74–3.56 (m, 172H, C*H*$_2$—C*H*$_2$—O), 3.38 (s, 3H, O—C*H*$_3$), 2.36 (s, 1H, N*H*). ^{13}C NMR (100 MHz, CD_3OD), δ (ppm): 141.98 (*C*=C—$N_{triazole}$), 123.69 (C=*C*—$N_{triazole}$), 71.91 (*C*H_2—O—CH_3), 70.55 (—*C*H_2—O), 69.37 ($N_{triazole}$—CH_2—*C*H_2—O), 59.04 (*C*H_3—O), 50.26 ($N_{triazole}$—*C*H_2—CH_2—O), 34.15 (N—*C*H_2).

General Procedure for the Cleavage of Dimethylphosphonate-Terminated PEO Monomethyl Ethers Using TMSBr

A solution of the dialkylphosphonate-terminated PEO monomethyl ether (0.05 mmol) in 5 mL of DCM was added to a 100-mL two-necked flask equipped with a stir bar, a nitrogen inlet, and a dropping funnel. The solution was stirred at room temperature under nitrogen and a solution of TMSBr (0.48 g, 3.2 mmol) in 5 mL of dichloromethane (DCM) was added dropwise via the dropping funnel. The reaction mixture was stirred for 24 h at room temperature. At the end of the reaction, the large excess of bromosilane and DCM were removed by evaporation under low pressure. After the total elimination of bromosilane, ethanol (50 mL) was added to the flask and the stirring was continued for 24 h at room temperature. Ethanol was removed under reduced pressure to obtain the phosphonic acid-terminated PEO monomethyl ether.

General Procedure for Dimethylphosphonate-Terminated PEO Monomethyl Ether Hydrolysis

In a 50-mL round-bottom flask equipped with a reflux condenser and a stir bar was placed the dimethylphosphonate-terminated PEO monomethyl ether (0.05 mmol) in 5 mL of HCl 20%. The solution was stirred and refluxed at 90 °C for 6 h. Then the mixture was evaporated *in vacuo* to dryness. The crude phosphonic acid-terminated PEO monomethyl ether was dried at room temperature *in vacuo* for 24 h.

Phosphonic Acid-Terminated PEO Monomethyl Ether 8a

Brown powder. Yield: 90%. ^{1}H NMR (400 MHz, CD_3OD), δ (ppm): 8.13 (s, 1H, triazole); 7.60 (m, 2H, H_1); 7.56–7.47 (m, 3H, H_2 & H_3); 4.63 (t, J = 4.96 Hz, 2H, $N_{triazole}$—CH_2—CH_2—O); 4.38 (m, 1H, *CH*P); 3.90 (t, J = 5.21 Hz, 2H, NH—CH_2); 3.81 (t, J = 5.61 Hz, 2H, $N_{triazole}$—CH_2—CH_2—O); 3.70–3.52 (m, 172H, CH_2—CH_2—O); 3.36 (s, 3H, O—CH_3); 2.21 (s, 1H, N*H*). ^{13}C NMR (100.62 MHz, CD_3OD), δ (ppm): 141.25 (*C*=C—$N_{triazole}$); 131.71 (C_4); 130.83 (C_3); 130.32 (C_1); 129.57 (C_2); 125.57 (C=*C*—$N_{triazole}$); 80.43 (*C*H_2—O—CH_3); 73.65 (*C*H_2—O—CH_2); 67.62 ($N_{triazole}$—CH_2—*C*H_2—O); 58.32 (*C*HP); 58.12 (O—*C*H_3); 54.76 ($N_{triazole}$—*C*H_2—CH_2—O); 37.07 (N—*C*H_2). ^{31}P NMR (CD_3OD, 161.96 MHz), δ (ppm): 13.29. IR (ν, cm^{-1}): 3346 (ν_{OH}); 2884 ($\nu_{C—H}$); 1466 ($\nu_{C=C,\ triazole}$); 1240 ($\nu_{P=O}$).

Phosphonic Acid-Terminated PEO Monomethyl Ether 8b

Brown powder. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.15 (s, 1H, triazole); 7.60 (s, 1H, H_1); 7.54–7.47 (m, 3H, H_2 & H_3); 4.62 (t, J = 4.82 Hz, 2H, $N_{triazole}$—CH_2—CH_2—O); 4.40 (m, 1H, *CH*P); 3.90 (t, J = 5.08 Hz, 2H, $N_{triazole}$—CH_2—CH_2—O); 3.80–3.48 (m, 172H, CH_2—CH_2—O); 3.45 (t, J = 4.68 Hz, 2H, NH—CH_2); 3.35 (s, 3H, O—CH_3); 2.88 (s, 1H, N*H*). ^{13}C NMR (100.62 MHz, CD_3OD), δ (ppm): 142.35 (*C*=C—$N_{triazole}$); 134.46 (C_4); 132.54 (C_3); 131.87 (C_1); 130.39 (C_2); 127.86 (C=*C*—$N_{triazole}$); 72.96 (*C*H_2—O—CH_3); 71.56 (*C*H_2—O—CH_2); 70.16 ($N_{triazole}$—CH_2—*C*H_2—O); 62.43 (*C*HP); 58.86 (O—*C*H_3); 44.73 ($N_{triazole}$—*C*H_2—CH_2—O); 41.96 (N—*C*H_2). ^{31}P NMR (CD_3OD, 161.96 MHz), δ (ppm): 13.29.

CONCLUSIONS

The present study investigated the combination of Atherton–Todd reaction, on the one hand, and the Kabachnik–Fields reaction, on the other hand, together with "click" copper-catalyzed 1,3-dipolar cycloaddition of azides and terminal alkynes for introducing a phosphonic acid group at the chain-end of PEO monomethyl ethers. Well-defined dialkylphosphonate-terminated PEO monomethyl ethers were successfully obtained from commercially available products in good yields using the Atherton–Todd route. However, the established methodology to remove the ester protecting

groups of phosphonates involving the use of TMSBr led to P—N bond cleavage, as demonstrated by MALDI-TOF MS analysis. In contrast, the Kabachnik–Fields route afforded ω-phosphonic acid-functionalized PEOs with good yields from commercially available products. This work also conducted structural analyses, including ^{1}H, ^{13}C, ^{31}P NMR, and MALDI-TOF MS, to confirm the structures of the so-obtained polymers. The versatile strategy reported in this work can be used to introduce a phosphonic acid group at the chain-end of the wide range of polymers bearing an azido end-group that are nowadays attainable. By varying the nature of the aldehyde used in this strategy, virtually any functional group can be inserted into the so-obtained ω-phosphonic acid-functionalized PEOs. The resulting end-functionalized polymers could be used in a variety of applications, including biomedical applications for linking and coating for metal oxide nanoparticles.

ACKNOWLEDGMENTS

Authors thank Jean-Claude Soutif and Emmanuelle Mebold for MALDI-TOF mass spectrometry analyses. T.T.T.N. thanks the Ministry of Education and Training, Vietnam; K.O. thanks the Algerian Ministry of Foreign Affairs.

REFERENCES AND NOTES

1 David, G.; Negrell-Guirao, C.; Iftene, F.; Boutevin, B.; Chougrani, K. *Polym. Chem.* **2012,** *3*, 265–274.

2 Maiti, S.; Banerjee, S.; Palit, S. K. *Prog. Polym. Sci.* **1993,** *18*, 227–261.

3 Penczek, S.; Pretula, J.; Kaluzynski, K. *Biomacromolecules* **2005,** *6*, 547–551.

4 Oussadi, K.; Montembault, V.; Belbachir, M.; Fontaine, L. *J. Appl. Polym. Sci.* **2011,** *122*, 891–897.

5 Lu, S. Y.; Hamerton, I. *Prog. Polym. Sci.* **2002,** *27*, 1661–1672.

6 Fontaine, L.; Derouet, D.; Chairatanathavorn, S.; Brosse, J. C. *React. Polym.* **1993,** *19*, 47–54.

7 Ménard, L.; Fontaine, L.; Brosse, J. C. *React. Polym.* **1994,** *23*, 201–212.

8 Fontaine, L.; Derouet, D.; Chairatanathavorn, S.; Brosse, J. C. *Eur. Polym. J.* **1995,** *31*, 109–120.

9 Monge, S.; Canniccioni, B.; Graillot, A.; Robin, J. *J. Biomacromolecules* **2011,** *12*, 1973–1982.

10 Wang, Y. C.; Yuan, Y. Y.; Du, J. Z.; Yang, X. Z.; Wang, J. *Macromol. Biosci.* **2009,** *9*, 1154–1164.

11 Zhao, Z.; Wang, J.; Mao, H. Q.; Leong, K. W. *Adv. Drug Deliv. Rev.* **2003,** *55*, 483–499.

12 Brosse, J. C.; Derouet, D.; Fontaine, L.; Chairatanathavorn, S. *Makromol. Chem.* **1989,** *190*, 2339–2345.

13 Brosse, J. C.; Fontaine, L.; Derouet, D.; Chairatanathavorn, S. *Makromol. Chem.* **1989,** *190*, 2329–2338.

14 Fontaine, L.; Derouet, D.; Brosse, J. C. *Eur. Polym. J.* **1990,** *26*, 857–863.

15 Fontaine, L.; Derouet, D.; Brosse, J. C. *Eur. Polym. J.* **1990,** *26*, 865–870.

16 Fontaine, L.; Marbœuf, C.; Brosse, J. C.; Maingault, M.; Dehaut, F. *Macromol. Chem. Phys.* **1996,** *197*, 3613–3621.

17 Suzuki, S.; Whittaker, M. R.; Grondahl, L.; Monteiro, M. J.; Wentrup-Byrne, E. *Biomacromolecules* **2006,** *7*, 3178–3187.

18 Moszner, N.; Salz, U.; Zimmermann, J. *Dent. Mater.* **2005,** *21*, 895–910.

19 Catel, Y.; Degrange, M.; Le Pluart, L.; Madec, P. J.; Pham, T. N.; Chen, F.; Cook, W. D. *J. Polym. Sci. Part A: Polym. Chem.* **2009,** *47*, 5258–5271.

20 Catel, Y.; Besse, V.; Zulauf, A.; Marchat, D.; Pfund, E.; Pham, T. N.; Bernache-Assolant, D.; Degrange, M.; Lequeux, T.; Madec, P. J.; Le Pluart, L. *Eur. Polym. J.* **2012,** *48*, 318–330.

21 Harris, J. M. Poly(Ethylene Glycol): Chemistry and Biotechnical and Biomedical Applications; Plenum Press: New York, **1972.**

22 Oussadi, K.; Montembault, V.; Fontaine, L. *J. Polym. Sci. Part A: Polym. Chem.* **2011,** *49*, 5124–5128.

23 Le, D.; Montembault, V.; Soutif, J. C.; Rutnakornpituk, M.; Fontaine, L. *Macromolecules* **2010,** *43*, 5611–5617.

24 Zhang, S.; Li, A.; Zou, J.; Lin, L. Y.; Wooley, K. L. *ACS Macro. Lett.* **2012,** *1*, 328–333.

25 Thompson, M. S.; Vadala, T. P.; Vadala, M. L.; Lin, Y.; Riffle, J. S. *Polymer* **2008,** *49*, 345–373.

26 Li, J.; Kao, W. J. *Biomacromolecules* **2003,** *4*, 1055–1067.

27 Mongondry, P.; Bonnans-Plaisance, C.; Jean, M.; Tassin, J. F. *Macromol. Rapid Commun.* **2003,** *24*, 681–685.

28 Zeng, F.; Allen, C. *Macromolecules* **2006,** *39*, 6391–6398.

29 Parrish, B.; Breitenkamp, B.; Emrik, T. *J. Am. Chem. Soc.* **2005,** *127*, 7404–7410.

30 Hiki, S.; Kataoka, K. *Bioconjugate Chem.* **2010,** *21*, 248–254.

31 Raynaud, J.; Absalon, C.; Gnanou, Y.; Taton, D. *Macromolecules* **2010,** *43*, 2814–2823.

32 Li, Z.; Chau, Y. *Bioconjugate Chem.* **2011,** *22*, 518–522.

33 Laurent, S.; Forge, D.; Port, M.; Roch, A.; Robic, C.; Vander Elst, L.; Muller, R. N. *Chem. Rev.* **2008,** *108*, 2064–2110.

34 Qi, L.; Seghal, A.; Castaing, J.-C.; Chapel, J.-P.; Fresnais, J.; Berret, J. F.; Cousin, F. *ACS Nano* **2008,** *2*, 879–888.

35 Tromsdorf, U. I.; Bruns, O. T.; Salmen, S. C.; Beisiegel, U.; Weller, H. *Nano Lett.* **2009,** *9*, 4434–4440.

36 Shephard, J. J.; Dickie, S. A.; McQuillan, A. J. *Langmuir* **2010,** *26*, 4048–4056.

37 Liu, X. L.; Fan, H. M.; Yi, J. B.; Yang, Y.; Choo, E. S. G.; Xue, X. M.; Fan, D. D.; Ding, J. *J. Mater. Chem.* **2012,** *22*, 8235–8244.

38 Na, H. B.; Lee, I. S.; Seo, H.; Park, Y. I.; Lee, J. H.; Kim, S. W.; Hyeon, T. *Chem. Commun.* **2007,** 5167–5169.

39 Basly, B.; Felder-Flesch, D.; Perriat, P.; Billotey, C.; Taleb, J.; Pourroy, G.; Begin-Colin, S. *Chem. Commun.* **2010,** *46*, 985–987.

40 White, M. A.; Johnson, J. A.; Koberstein, J. T.; Turro, N. J. *J. Am. Chem. Soc.* **2006,** *128*, 11356–11357.

41 Boyer, C.; Bulmus, V.; Priyanto, P.; Teoh, W. Y.; Amal, R.; Davis, T. P. *J. Mater. Chem.* **2009,** *19*, 111–123.

42 Boyer, C.; Priyanto, P.; Davis, T. P.; Pissuwan, D.; Bulmus, V.; Kavallaris, M.; Teoh, W. Y.; Amal, R.; Carol, M.; Woodward, R.; St Pierre, T. *J. Mater. Chem.* **2010,** *20*, 255–265.

43 Quéffelec, C.; Petit, M.; Janvier, P.; Knight, D. A.; Bujoli, B. *Chem. Rev.* **2012,** *112*, 3777–3807.

44 Essahli, M.; Ganachaud, F.; In, M.; Boutevin, B. *J. Appl. Polym. Sci.* **2008,** *108*, 483–490.

45 Traina, C. A.; Schwartz, J. *Langmuir* **2007,** *23*, 9158–9161.

46 Goff, J. D.; Huffstetler, P. P.; Miles, W. C.; Pothayee, N.; Reinholz, C. M.; Ball, S.; Davis, R. M.; Riffle, J. S. *Chem. Mater.* **2009,** *21*, 4784–4795.

47 Mosquet, M.; Chevalier, Y.; Brunel, S.; Guicquero, J. P.; Le Perchec, P. *J. Appl. Polym. Sci.* **1997,** *65*, 2545–2555.

48 Moedritzer, K.; Irani, R. R. *J. Org. Chem.* **1966,** *31*, 1603–1607.

49 Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945,** 660–663.

50 Kabachnik, M. I.; Medve, T. Y. *Dokl. Akad. Nauk. SSSR* **1952,** *83*, 689–692; Kabachnik, M. I.; Medve, T. Y. *Chem. Abstr.* **1953,** *47*, 2724b.

51 Fields, E. K. *J. Am. Chem. Soc.* **1952,** *74*, 1528–1531.

52 Zefirov, N. S.; Matveeva, E. D. *Arkivoc* **2008,** 1–17.

53 Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001,** *40*, 2004–2021.

54 Zwierzak, A. *Synthesis* **1982,** *11*, 920–922.

55 McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M. C. *Tetrahedron Lett.* **1977,** *18*, 155–158.

56 Kishore Kumar, G. D.; Saenz, D.; Lokesh, G. L.; Natarajan, A. *Tetrahedron Lett.* **2006,** *47*, 6281–6284.

57 Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, J. *Bioorg. Med. Chem.* **1996,** *4*, 1693–1701.

58 Metcalf, B.; Casara, P. *Tetrahedron Lett.* **1975,** *16*, 3337–3340.

59 Kraicheva, I.; Bogomilova, A.; Tsacheva, I.; Momekov, G.; Troev, K. *Eur. J. Med. Chem.* **2009,** *44*, 3363–3367.

60 Maier, L.; Diel, P. J. *Phosphorus Sulfur Silicon Relat. Elem.* **1991,** *57*, 57–64.

61 Cottier, L.; Descotes, G.; Lewkowski, J.; Skowronski, R. *Phosphorus Sulfur Silicon Relat. Elem.* **1996,** *116*, 93–100.