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Synthesis of functionalized poly(vinyl acetate) mediated by alkyne-terminated RAFT agents†

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Two new xanthates with alkyne functionalities were synthesized for the reversible addition fragmentation chain transfer (RAFT) polymerization of vinyl acetate (VAc). The new RAFT agents were fully characterized by ^{1}H and ^{13}C NMR spectroscopy. Unlike the alkyne terminated RAFT agent (AT-X_1) the protected alkyne-terminated RAFT agent (PAT-X_1) was able to conduct the RAFT polymerization of VAc with a good control over the molecular weight (MW) and relatively narrow MW distributions ($Đ$ < 1.4). The linear evolution of M_n with conversion as well as the close agreement between $M_{n,th}$ and $M_{n,GPC}$ values confirmed the controlled features of the RAFT system. It is worth mentioning that the polymer dispersity remained very low ($Đ$ < 1.20) until relatively high monomer conversions (60%) due to the non-activated nature of VAc. The chain end-functionality of the obtained polymers was evaluated by ^{1}H NMR, FTIR-ATR and UV-Vis absorption analysis. The "livingness" of the obtained polymer was confirmed by a successful chain extension experiment. The deprotection of the alkyne functionality in the PVAc, allowed a further copper catalyzed azide–alkyne [3 + 2] dipolar cycloaddition reaction (CuAAC) with an azido terminated-poly(ethylene glycol) (PEG-N_3), to afford PVAc–PEG block-copolymers as a proof-of-concept.

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The reversible deactivation radical polymerization (RDRP) has witnessed enormous improvements during the last two decades.[1–5] For RDRP of activated monomers such as acrylates, methacrylates or styrene, different modifications of atom transfer radical polymerization (ATRP) have successfully been applied.[6–10] However, the development of new RDRP systems that are able to polymerize such non-activated monomers, such as vinyl chloride,[11–13] *N*-vinyl pyrrolidone[14] or vinyl acetate (VAc)[15,16] remains an important challenge. The reversible addition–fragmentation chain transfer (RAFT) polymerization is considered a very effective RDRP method for the polymerization of less activated monomers.[12,17] Other RDRP methods mediated by transition metal catalysts,[18,19] iodine transfer[11,20] or nitroxides[21] have been studied for vinyl chloride and VAc. Recently, some authors reported the use of cobalt complex as organic metallic complexes for the controlled synthesis of poly(vinyl acetate) (PVAc).[22–25] VAc stands out as one of the most studied non-activated vinyl monomers.[26] PVAc has a wide range of industrial applications, from paints to coatings as well as its hydrolyzed derivative, poly(vinyl alcohol) (PVA), that extends its applications to the biomedical field.[27]

The choice of the RAFT agent, is of outmost importance for the success of this RDRP method.[28,29] For non-activated monomers, xanthate mediated RAFT polymerization[30] is one of the most straightforward RDRP strategies to afford optimal control over the polymerization. Due to the high reactivity of the VAc propagating radical, the RAFT agent should have an efficient leaving group, with similar reactivity to the growing macroradical towards the monomer addition. Most of the literature reports, concerning the xanthate mediated RAFT polymerization of VAc, refer the use of methyl(ethoxy carbonyl sulfanyl acetate) (Fig. 1 (Y_1)),[31–33] methyl 2-((ethoxycarbonothiol)thio)propanoate (also known as *O*-ethyl-*S*-(1-methoxy carbonyl) ethyl dithiocarbonate), with 2-propionyl moiety as the leaving group (Fig. 1 (X_1)), for either bulk,[34] solution[35,36] or miniemulsion polymerizations,[33] or very similar RAFT agents.[37,38] Nevertheless, other RAFT agents such as

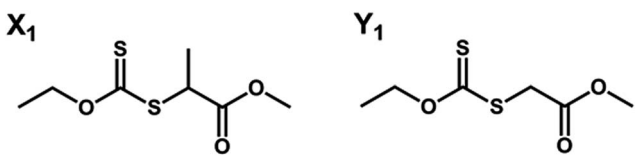

Fig. 1 Schematic representation of the most reported xanthates for the RAFT polymerization of PVAc.

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dithiocarbamates have also been reported for the well-defined polymerization of VAc.[39,40]

The conjugation of polymers through a post polymerization coupling strategy is also a powerful tool in macromolecular engineering to afford new block copolymers with segments that are impossible to link by direct copolymerization. In fact, the single step synthesis of block copolymers is limited to few monomers functionalities, usually with similar chemical and physical properties, or require the use of specific RAFT agents based on a switchable dithiocarbamate moiety that are able to mediate the polymerization of both activated and non-activated monomers.[41] In the case of non-activated monomers, where controlled copolymerization is more difficult, reactions inspired by the "click" coupling approach is a convenient strategy to achieve new polymer architectures, otherwise difficult to access.[42–44] The direct polymerization using a "clickable" functionalized RAFT agent is a common strategy to afford polymers with a specific chain-end functionality, without the need of post-modification procedures.[45] CuAAC reaction between azide and alkyne chain-end functionalities is one of the most explored "click" reaction.[46] Stenzel and co-workers reported the facile synthesis of poly(styrene)-*b*-PVAc block copolymers through a "click" coupling approach from a PVAc synthesized using an azido-xanthate RAFT agent and poly(styrene) synthesized using one alkyne-dithiobenzoate agent.[45] A similar strategy was proposed, by the same group, for the synthesis of comb-like copolymers, from the reaction of an azido functionalized linear PVAc with one alkyne modified methacrylate monomer.[47] The literature involving the use of xanthates with alkyne functionality is very scarce.

To the best of our knowledge, only one reference is available describing the synthesis of (*S*)-2-(propynyl propionate)-*O*-ethyl xanthate, an alkyne terminated RAFT agent, for the controlled synthesis of *N*-vinylpyrrolidone.[48] The aim of the present study was to synthesize new efficient alkyne functionalized xanthate RAFT agents, able to conduct controlled polymerization of vinyl acetate. The present strategy enabled the straightforward preparation of PVAc block copolymers through a simple post polymerization coupling method.

Experimental

Materials

Vinyl acetate (VAc) (≥99%, Aldrich) was purified by passing the monomer through a basic alumina column and then distilled under vacuum (bp 72–73 °C). 2,2′-Azobis(2-methylpropionitrile) (AIBN) (98%, Fluka) was purified by recrystallization from methanol before use. 1,4-Dioxane (99.8%, Acros Organics) was passed through alumina column to remove peroxides and distilled under reduced pressure prior to use. Poly(ethylene glycol) methyl ether ($mPEG_{113}$, MW = 5000 Da) (Aldrich) was dried by azeotropic distillation with toluene. Sodium ascorbate (NaAsc) (≥98%, Sigma), copper(II) sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) (≥98%, Aldrich), methyl 2-bromopropionate (98%, Aldrich), methanol (99.9%, Fisher Scientific), dichloromethane (DCM) (99.99%, Fisher Scientific), potassium ethyl xanthogenate (96%; Aldrich) anhydrous sodium sulfate (≥98%, Fisher Chemical), ethyl acetate (≥99.5%, Fisher Scientific), diethyl ether (99.85%, Fisher Scientific), hexane (99.05%, Fisher Scientific), thionyl chloride (≥99%, Sigma-Aldrich), propargyl alcohol (PA) (99%, Aldrich), triethylamine (≥99%, Sigma-Aldrich), 2-bromopropionic acid (≥99%, Aldrich), 5-trimethylsilyl-4-pentyn-1-ol (96%; Aldrich), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (≥99.0%, Sigma), 4-(dimethylamino)pyridine (≥99%, Aldrich), tetrabutyl ammonium fluoride trihydrate ($TBAF \cdot 3H_2O$) (99%, Acros Organics), sodium azide (99%; Aldrich), tetrahydrofuran (THF) (≥99.9%, Sigma-Aldrich), dimethylformamide (DMF) (≥99.8%; Sigma-Aldrich), deuterated chloroform ($CDCl_3$) (≥99.8%, Euriso-top, +1% TMS) and deuterated DCM (CD_2Cl_2) (≥99.6%, Euriso-top) were used as received. Azido terminated-poly(ethylene glycol) ($mPEG_{113}$-N_3) was synthesized by a nucleophilic substitution of poly(ethylene glycol) methyl ether bromoisobutyrate ($mPEG_{113}$-BiB) (previously synthesized according to the literature procedures[49]) using NaN_3 in DMF (procedure adapted from literature[50]) (see ESI† for detailed synthesis).

Techniques

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DMX-360 (360 MHz for ^1H NMR and 90 MHz for ^{13}C NMR, with a 5 mm manual switching QNP) and a Bruker Avance III spectrometer (400 MHz, with a 5 mm TIX triple resonance detection probe), in a deuterated solvent. Monomer conversions were determined by integration of monomer and polymer peaks using MestRenova software version: 6.0.2–5475. Fourier-transform infrared spectroscopy (FTIR) was performed at 64 scans and with a 4 cm^{-1} resolution between 500 and 3500 cm^{-1}, using a JASCO 4200 FTIR spectrometer, operating in the ATR mode (MKII GoldenGate™ Single Reflexion ATR System). The thermogravimetric analysis (TGA) was carried out on a TGA Q 500 machine (TA Instruments) with a heating ramp set at a constant 10 °C min^{-1}, and covering a temperature range from 25 to 300 °C. High performance gel permeation chromatography (HPSEC) was performed using a Viscotek (ViscotekTDAmax) with a differential viscometer (DV), right-angle laser-light scattering (RALLS, Viscotek), and refractive index (RI) detectors, using column set of a PL 10 μm guard column followed by one MIXED-E PLgel column and one MIXED-C PLgel column. Filtered THF was used as an eluent at a flow rate of 1 mL min^{-1} at 30 °C. The samples were filtered through a polytetrafluoroethylene membrane with 0.2 μm pore before injection and the system was calibrated with narrow PS standards. The d*n*/d*c* of PVAc in THF at 30 °C was determined as 0.0581 (for $\lambda = 670$ nm) using a RUDOLPH RESEARCH J357 Automatic Refractometer (J357-NDS-670-CC). Molecular weight ($M_{n,GPC}$) and dispersity ($Đ$) of synthesized polymers were determined by using either a universal calibration or multidetector analysis (OmniSEC software version: 4.6.1.354). Ultraviolet-Visible (UV-Vis) spectroscopy was carried out using a Jasco V-530 spectrophotometer. The analyses were carried out in $CHCl_3$ in the 250–400 nm range at 25 °C. Absorption spectra were measured from 250 to 400 nm with a resolution of 2.0 nm in a 10 mm UV-cuvette.

Procedures

Synthesis of (*RS*)-*O*-ethyl-*S*-(1-methoxycarbonyl) ethyl-dithiocarbonate (X_1). Methyl 2-bromopropionate (5.13 g, 30.73 mmol) was dissolved in 100 mL of methanol and the solution was cooled down in an ice bath. Potassium ethyl xanthogenate (5.74 g, 34.38 mmol) was then slowly added over a period of 30 minutes. After the complete dissolution of the salt, the reaction mixture was stirred at room temperature during 24 h. The KBr formed was filtered under vacuum, the product was extracted with an ether/hexane mixture (2 : 1 vol%), washed three times with water and dried over anhydrous sodium sulfate. The solvent was evaporated at reduced pressure to give a yellow liquid that was further purified by column chromatography on silica with hexane/ethyl acetate (10 : 1 vol%) as the eluent to give X_1 (4.30 g, 67%). ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 4.6232 (q, 1H, $^3J_{HH} = 7.14$ Hz, diastereotopic –OC*H*HCH$_3$), 4.6199 (q, 1H, $^3J_{HH} = 7.1$ Hz, diastereotopic –OCH*H*CH$_3$), 4.36 (q, 1H, $^3J_{HH} = 7.4$ Hz, –C*H*), 3.73 (s, 3H, –C*H*$_3$), 1.56 (d, 3H, $^3J_{HH} = 7.4$ Hz, –CHC*H*$_3$), 1.40 (t, 3H, $J_{HH} = 7.14$ Hz, –CH$_2$C*H*$_3$).

Synthesis of alkyne-terminated RAFT agent, *O*-ethyl-*S*-(1-propargoxycarbonyl) ethyl-dithiocarbonate (AT-X_1)

2-Bromopropionyl chloride. 4.00 mL of thionyl chloride (5.14 mmol) was slowly added to 4.50 mL of 2-bromopropionic acid (50.00 mmol). A small amount of DMF (10 μL) was used to catalyze the reaction. The mixture was heated to 80 °C and stirred until the complete release of gaseous by-products of the reaction. The product was used without any further purification steps.

(RS)-Propargyl 2-bromopropionate. A solution of PA (2.80 g, 50.00 mmol) and triethylamine (5.06 g, 50.00 mmol) in DCM was cooled down to ~−20 °C with liquid nitrogen. The 2-bromopropionyl chloride was added in portions to the solution. The solution was left off from the cold and kept under stirring until reach the room temperature. The product was washed three times with water and the organic phase was dried under anhydrous sodium sulfate. After solvent evaporation the product was obtained as a light yellow oil (6.98 g, 73%). ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 4.7599 (d, 1H, $^4J_{HH} = 2.5$ Hz, diastereotopic HC≡C–C*H*HO–), 4.7524 (d, 1H, $^4J_{HH} = 2.5$ Hz, diastereotopic HC≡C–CH*H*O–), 4.39 (q, 1H, $^3J_{HH} = 6.9$ Hz, –C*H*–Br), 2.5 (t, 1H, $J_{HH} = 2.5$ Hz, *H*C≡C–), 1.82 (d, 3H, $^3J_{HH} = 6.9$ Hz, –CH$_3$). ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 169.48 (*C*=O), 76.86 (≡*C*–), 75.74 (H*C*≡), 53.40 (*C*H$_2$–O), 39.30 (*C*H–Br), 21.58 (Br–*C*H$_3$).

AT-X_1. Propargyl 2-bromopropionate (4.04 g, 21.13 mmol) was dissolved in 25 mL of PA and the solution was cooled down in an ice bath. Potassium ethyl xanthogenate (3.84 g, 23.92 mmol) was then added to the solution in portions over a period of 30 minutes. After the complete dissolution of the salt, the reaction mixture was stirred at room temperature overnight. The solid KBr was filtered off, the filtrate was extracted with ether/hexane (2 : 1 vol%) and the extract was washed three times with water (500 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated at reduced pressure to give a yellow liquid that was further purified by column chromatography on silica starting with hexane and then hexane/ethyl acetate (10 : 1 vol%) as the eluent to give AT-X_1 as a yellow liquid (2.64 g, 54%). ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) 4.7335 (d, 1H, $^4J_{HH} = 2.4$ Hz, diastereotopic ≡C–C*H*H–O), 4.7321 (d, 1H, $^4J_{HH} = 2.4$ Hz, diastereotopic ≡C–CH*H*–O), 4.6310 (q, 1H, $^3J_{HH} = 7.1$ Hz, diastereotopic C*H*H–CH$_3$), 4.6302 (q, 1H, $^3J_{HH} = 7.1$ Hz, diastereotopic CH*H*–CH$_3$), 4.41 (q, 1H, $^3J_{HH} = 7.4$ Hz, C*H*–CH$_3$), 2.49 (t, 1H, $^4J_{HH} = 2.4$ Hz, C*H*≡C), 1.58 (d, 3H, $^3J_{HH} = 7.4$ Hz, C*H*$_3$–CH), 1.41 (t, 3H, $^3J_{HH} = 7.1$ Hz, C*H*$_3$–CH$_2$). ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) 211.69 (*C*=S), 170.79 (*C*=O), 77.16 (≡*C*–), 75.46 (H*C*≡), 70.44 (*C*H$_2$–CH$_3$), 53.13 (*C*H$_2$–O), 46.83 (*C*H–CH$_3$), 16.68 (*C*H$_3$–CH), 13.73 (*C*H$_3$–CH$_2$) (the peak at 77.16 ppm is overlapped with the solvent peak). ^{13}C NMR (90 MHz, CD_2Cl_2): (ppm) 212.14 (*C*=S), 171.12 (*C*=O), 77.74 (≡*C*–), 75.64 (H*C*≡), 71.14 (*C*H$_2$–CH$_3$), 53.54 (*C*H$_2$–O), 47.14 (*C*H–CH$_3$), 16.96 (*C*H$_3$–CH), 13.97 (*C*H$_3$–CH$_2$).

Synthesis of protected alkyne-terminated RAFT agent (PAT-X_1)

2-(Ethoxycarbonothioylthio)propanoic acid. 4.18 g (27.30 mmol) of 2-bromopropionic acid was dissolved in 40 mL of dry methanol. The solution was cooled down in an ice bath. Potassium ethyl xanthogenate 5.126 g (31.98 mmol) was slowly added to the methanol solution, in portions, over a period of 30 min. After the complete dissolution of potassium ethyl xanthogenate, the ice bath was removed and the reaction proceeded at room temperature for 24 h. The reaction by-product, KBr, was filtered under reduced pressure and the product extracted with an ether/hexane mixture (2 : 1 vol%), washed three times with water and dried over anhydrous sodium sulfate. The product was obtained after the solvent evaporation at reduced pressure. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.00 (s, 1H, –O*H*), 4.6419 (q, 1H, $^3J_{HH} = 7.1$ Hz, diastereotopic C*H*H–CH$_3$), 4.6399 (q, 1H, $^3J_{HH} = 7.1$ Hz, diastereotopic CH*H*–CH$_3$), 4.41 (q, 1H, $^3J_{HH} = 7.47$ Hz, –C*H*–CH$_3$), 1.60 (d, 3H, $^3J_{HH} = 7.4$ Hz, –C*H*$_3$–CH), 1.41 (t, 3H, $^3J_{HH} = 7.1$ Hz, –C*H*$_3$–CH$_2$).

PAT-X_1. In a 200 mL flask, the 2-(ethoxycarbonothioylthio) propanoic acid (0.60 g, 3.10 mmol) was dissolved in 60 mL of dry DCM. 5-Trimethylsilyl-4-pentyn-1-ol (0.68 mL, 3.74 mmol) was added and the mixture was cooled down to 0 °C and bubbled with argon. *N*-(3-Dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydro-chloride (0.78 g, 4.09 mmol) and 4-(dimethylamino)pyridine (5.76 mg, 0.05 mmol) were then added to the solution and the mixture was stirred in the ice bath for more 30 min. The reaction was left at room temperature for 24 h. The RAFT agent was purified by column chromatography on silica with hexane/ethyl acetate (10 : 1 vol%) as the eluent. The PAT-X_1 was obtained as a yellow oil (0.89 g, 86.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.64 (q, 2H, $^3J_{HH} = 7.12$ Hz; C*H*$_2$–CH$_3$), 4.38 (q, 1H, $^3J_{HH} = 7.30$ Hz, –C*H*–CH$_3$), 4.23 (t, 2H, $^3J_{HH} = 6.28$ Hz; C*H*$_2$–O), 2.33 (t, 2H, $^3J_{HH} = 7.05$ Hz; C≡C–C*H*$_2$–), 1.87 (m, 2H, $^3J_{HH} = 6.66$ Hz; –C*H*$_2$–), 1.57 (d, 3H, $^3J_{HH} = 7.14$ Hz, –C*H*$_3$–CH), 1.42 (t, 3H, $^3J_{HH} = 7.13$ Hz, –C*H*$_3$–CH$_2$), 0.14 (s, 9H, (C*H*$_3$)$_3$–Si). ^{13}C NMR (90 MHz, $CDCl_3$) δ (ppm) 212.22 (*C*=S), 171.48 (*C*=O), 105.60 (≡*C*–O), 85.63 (Si–*C*≡), 70.41 (*C*H$_2$–CH$_3$), 64.45 (*C*H$_2$–O), 47.33 (*C*H–CH$_3$), 27.71 (CH$_2$–*C*H$_2$–CH$_2$), 17.01 (≡C–*C*H$_2$–), 16.65 (*C*H$_3$–CH), 13.83 (*C*H$_3$–CH$_2$), 0.22 ((*C*H$_3$)$_3$).

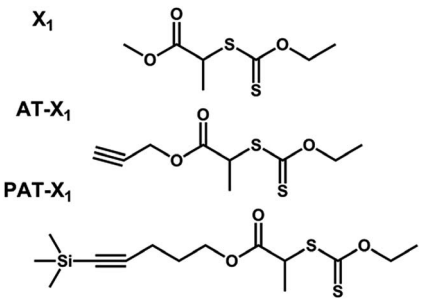

Fig. 2 Structures of RAFT agents synthesized: *O*-ethyl-*S*-(1-methoxycarbonyl) ethyl-dithiocarbonate (X_1), alkyne-terminated RAFT agent (AT-X_1) and protected alkyne-terminated RAFT agent (PAT-X_1).

Typical procedure for the RAFT polymerization of the VAc with [VAc/X_1/AIBN] = 100 : 1 : 0.2 in 1,4-dioxane. VAc (2.02 g, 23.49 mmol), X_1 (48.47 mg, 0.23 mmol), AIBN (7.82 mg, 0.05 mg) and 1.4-dioxane (1.93 mL; previously bubbled with nitrogen for about 10 min) were placed into a 25 mL Schlenk reactor. The reactor was sealed, frozen in liquid nitrogen, and the mixture was deoxygenated with four freeze–vacuum–thaw cycles and purged with nitrogen. The Schlenk reactor was placed in an oil bath at 60 °C with stirring (500 rpm). Different reaction mixture samples were collected during the polymerization through an airtight syringe, purging the side arm of the Schlenk reactor with nitrogen. The collected samples were analyzed by ^{1}H NMR spectroscopy to calculate the monomer conversion and theoretical molecular weight ($M_{n,th}$), and by GPC to determine $M_{n,GPC}$ and $Đ$ of the polymers. The other RAFT polymerizations were carried out employing the same procedure described but using AT-X_1 or PAT-X_1 as the RAFT agents.

Typical procedure for the chain extension of PVAc. A sample of protected alkyne-terminated PVAc (PAT–PVAc) ($M_{n,GPC} = 3.01 \times 10^3$, $Đ = 1.20$) synthesized through a typical RAFT polymerization using the PAT-X_1, and purified by precipitation in cold hexane, was used as macro-RAFT agent in a new RAFT polymerization. Briefly, PAT–PVAc (31.8 mg, 13.4 μmol) was dissolved in 1,4-dioxane (7 mL) and placed into a Schlenk reactor. 360 μL of a stock solution of AIBN (1.1 mg, 6.64 μmol) in 1.4-dioxane was added to the reactor followed by the addition of VAc (4 mL, 46.46 mmol). The reactor was sealed, frozen in liquid nitrogen, and the mixture was deoxygenated with four freeze–vacuum–thaw cycles and purged with nitrogen. The Schlenk reactor was placed in an oil bath at 60 °C with stirring (500 rpm).

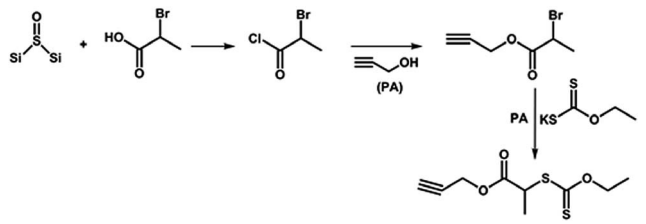

Fig. 3 Schematic representation of the synthesis strategy of alkyne-terminated RAFT agent (AT-X_1).

After 72 h of reaction, a sample was collected and analyzed by GPC.

Typical procedure for PVAc deprotection. A solution of pure protected alkyne terminated PVAc (PAT–PVAc) ($M_{n,GPC} = 6.0 \times 10^3$, $Đ = 1.36$), (0.25 g, 4.20×10^{-2} mmol) in THF (10 mL) was bubbled with nitrogen for about 10 minutes and then cooled down to −20 °C. Then, 2.14 mL of a 0.2 M solution of TBAF·$3H_2O$ (0.43 mmol) was slowly added to the polymer solution. After stirring for 30 minutes at low temperature, the reaction proceeded over night at ambient temperature. The reaction mixture was passed through a silica column to remove the excess of TBAF and the polymer was recovered by precipitation in cold hexane, dried under vacuum and analyzed by ^{1}H NMR.

Coupling reaction between alkyne-terminated PVAc and N_3-PEG. The alkyne-terminated PVAc obtained after the deprotection of the PAT–PVAc (50 mg, 8.33 μmol) and N_3-PEG (55 mg, 10.8 μmol) were dissolved into 5 mL of THF. The mixture was placed in a round-bottom flask equipped with a magnetic stir bar and sealed with a rubber septum. A stock solution of sodium ascorbate (40 mM; 250 μL) in deionized water was added to the solution and the mixture was bubbled with nitrogen for 20 min to remove oxygen. Lastly, a degassed stock solution of $CuSO_4 \cdot 5H_2O$ (13 mM; 250 μL) in deionized water was injected into the flask under nitrogen atmosphere. The reaction was allowed to proceed under stirring at 40 °C for 48 h. The final mixture was passed through an alumina column to remove the copper catalyst and the product precipitated into cold hexanes. The product was analyzed by GPC and FTIR-ATR spectroscopy in order to confirm the success of the coupling reaction.

Results and discussion

Synthesis of the RAFT agents

The use of functionalized RAFT agents avoids further steps involving the modification of the terminals in the polymeric chain structures with chemical groups suitable for further reactions, namely reactions inspired by the "click" coupling strategies. Two different RAFT agents for the polymerization of

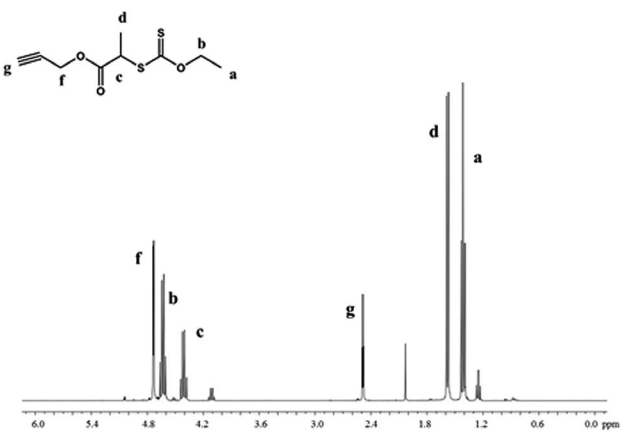

Fig. 4 ^{1}H NMR spectrum in $CDCl_3$ of alkyne-terminated RAFT agent (AT-X_1).

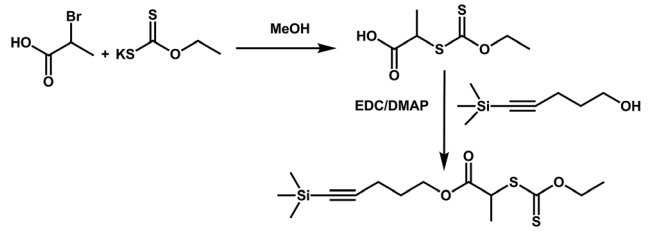

Fig. 5 Schematic representation of the synthesis strategy of protected alkyne-terminated RAFT agent (PAT-X_1).

non-activated monomers were synthesized (AT-X_1 and PAT-X_1), based on *O*-ethyl-*S*-(1-methoxycarbonyl) ethyl-dithiocarbonate xanthate (X_1).[34–36] The structures of the RAFT agents are present in Fig. 2.

X_1 was synthesized through the reaction of potassium ethyl xanthogenate with methyl 2-bromopropionate in methanol according to the similar procedures reported in literature for analogous RAFT agents.[51,52] The success of the reactions was confirmed by ^{1}H NMR (ESI, Fig. S1†). Although the impurities after the synthesis are very small, the purification procedures are crucial to avoid RAFT agent contaminations that could interfere with the success of polymerization.

The synthesis of the AT-X_1 was already been reported by Patel and co-authors for the polymerization of *N*-vinylpyrrolidone.[48]

However, the method reported here is easier, cleaner and more efficient than the aforementioned method that involves the carbodiimide activation. The synthesis of AT-X_1 was carried out into two steps; firstly, the synthesis of the alkyne terminated bromide through the reaction of 2-bromopropionyl chloride and propargyl alcohol (PA), followed by the bromine substitution with the potassium ethyl xanthogenate (Fig. 3). The success of the reaction was confirmed by ^{1}H and ^{13}C NMR spectroscopy (Fig. 4, S2 and S3 (ESI)†). The FTIR-ATR spectra of the AT-X_1 (Fig. S4, ESI†) shows the presence of the characteristic alkyne C≡H stretch vibration at 3300 cm^{-1},[47] and also –C=S and C–S stretching vibrations at 1044 cm^{-1} and 633 cm^{-1}, respectively.

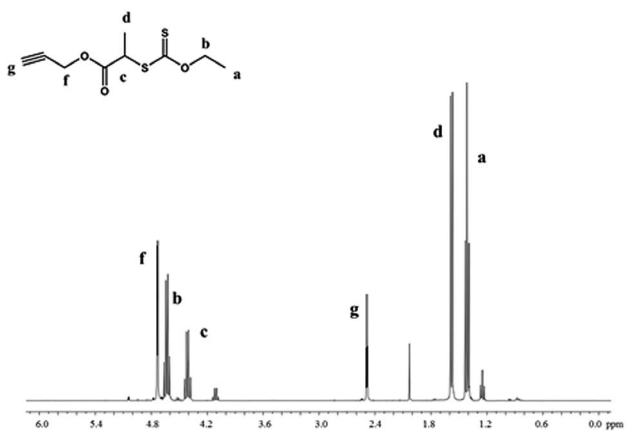

Fig. 6 ^{1}H NMR spectrum in $CDCl_3$ of protected alkyne-terminated RAFT agent (PAT-X_1).

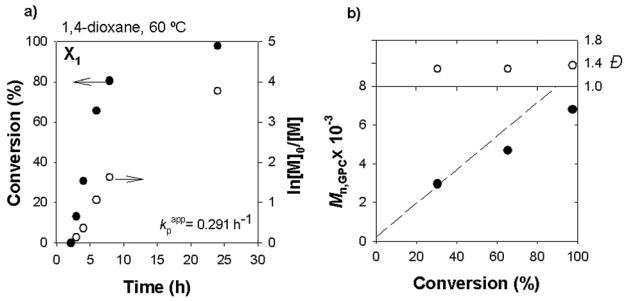

Fig. 7 (a) Kinetic plots of conversion and $\ln[M]_0/[M]$ *vs.* time and (b) plot of number average molecular weights ($M_{n,GPC}$) and dispersity (*Đ*) *vs.* conversion (%) (the dashed line represents the theoretical molecular weight at a given conversion) for RAFT of VAc at 60 °C in 1,4-dioxane using X_1. Reaction conditions: $[VAc]_0/[1,4\text{-dioxane}]_0$ = 1/1 (w/w); $[VAc]_0/[X_1]_0/[AIBN]_0$ = 100/1/0.2 (molar).

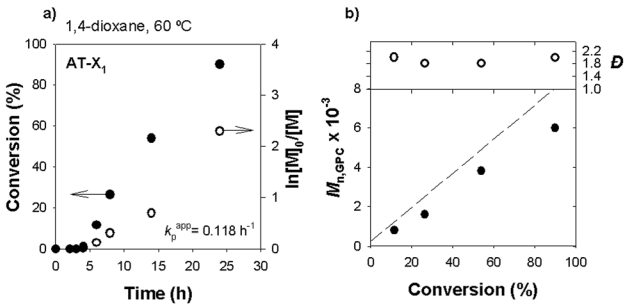

Fig. 8 (a) Kinetic plots of conversion and $\ln[M]_0/[M]$ *vs.* time and (b) plot of number average molecular weights ($M_{n,GPC}$) and dispersity (*Đ*) *vs.* conversion (%) (the dashed line represents the theoretical molecular weight at a given conversion) for RAFT of VAc at 60 °C in 1,4-dioxane using AT-X_1. Reaction conditions: $[VAc]_0/[1,4\text{-dioxane}]_0$ = 1/1 (w/w); $[VAc]_0/[AT\text{-}X_1]_0/[AIBN]_0$ = 100/1/0.2 (molar).

It is known that the alkyne group in the RAFT agent may interfere with the radical polymerization process.[45] In order to evaluate this possibility, the synthesis of new protected RAFT agent (protected alkyne-terminated RAFT agent (PAT-X_1)) using a trimethyl silyl group was envisaged. For the synthesis of the PAT-X_1, 2-(ethoxycarbonothioylthio)propanoic acid, was firstly synthesized through the reaction of potassium ethyl xanthogenate and 2-bromopropionic acid in methanol. The further coupling reaction with 5-trimethylsilyl-4-pentyn-1-ol originates PAT-X_1 (Fig. 5). The success of the reaction was confirmed by ^{1}H NMR (Fig. 6) and ^{13}C NMR (ESI Fig. S5†) (‡[53–55]).

‡ It should be noted that all three target molecules contain a chiral center C*HMeS(CO). It makes geminal methylene protons CHH diastereotopic and causes anisochrony due to unequal magnetic field sensed by these nuclei. The resonance signals of these protons are overlapped in the spectrum of PAT-X_1, whereas the ^{1}H NMR spectra of X_1 and AT-X_1 revealed resolved peaks of each such proton. Therefore, the difference in chemical shifts for these anisochronic protons is 0.0135 ppm for –OC*HH*CH$_3$ in X_1, 0.0014 ppm for CH≡C–C*HH*O– and 0.0009 ppm for –OC*HH*CH$_3$ in AT-X_1. Interestingly, the chemical shift difference of 0.0075 ppm for CH≡C–C*HH*O– diastereotopic protons in propargyl 2-bromopropionate is almost equal to $^4J_{HH}$ coupling constant, thus making a quasitriplet from the two doublets (ESI).

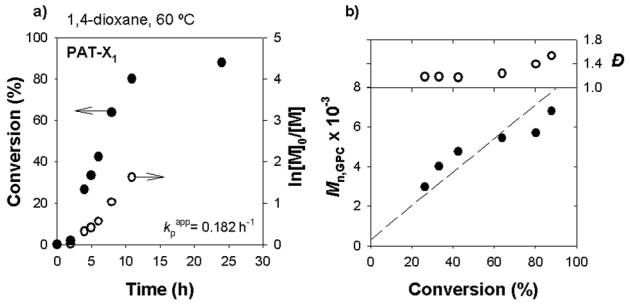

Fig. 9 (a) Kinetic plots of conversion and $\ln[M]_0/[M]$ *vs.* time and (b) plot of number average molecular weights ($M_{n,GPC}$) and dispersity ($Đ$) *vs.* conversion (%) (the dashed line represents the theoretical molecular weight at a given conversion) for RAFT of VAc at 60 °C in 1,4-dioxane using PAT-X_1. Reaction conditions: $[VAc]_0/[1,4\text{-dioxane}]_0$ = 1/1 (w/w); $[VAc]_0/[PAT\text{-}X_1]_0/[AIBN]_0$ = 100/1/0.2 (molar).

Polymerization of VAc using the synthesized RAFT agents

To investigate the ability of the RAFT agents to control the polymerization of non-activated monomers, VAc was used as a model monomer. The polymerization of VAc was carried out using the different xanthates in 1,4-dioxane ($[1,4\text{-dioxane}]_0/[VAc]_0$ = 1/1 (w/w)) at 60 °C and initiated by the AIBN. The ratio of RAFT agent : AIBN was kept at 1 : 0.2. Monomer conversions were calculated using ^{1}H NMR spectroscopy by comparing the integrations of the –C*H* signals on the VAc (δ = 4.50 ppm) with the corresponding signals of the polymer backbone (δ = 4.80). X_1 was used for comparison purposes, since it was already reported for the synthesis of well-defined PVAc.[34–36] Despite the good results obtained when X_1 was used (Fig. 7), the polymer does not have the necessary functionality that would allow further coupling reactions with other molecules or polymers. In the case of X_1, polymer post-modification reactions would be required in order to achieve a specific functionality in the polymer chain-end. In this context, the concept of the direct introduction of the desired functionality in the RAFT agent is preferable.

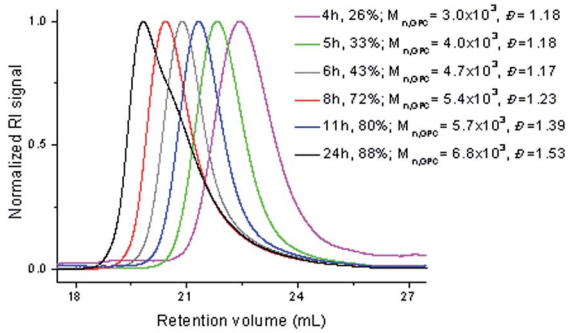

Fig. 10 Evolution of the GPC traces with conversion for the RAFT polymerization of VAc in 1,4-dioxane at 60 °C in the presence of the PAT-X_1. Reaction conditions: $[VAc]_0/[1,4\text{-dioxane}]_0$ = 1/1 (w/w); $[VAc]_0/[PAT\text{-}X_1]_0/[AIBN]_0$ = 100/1/0.2 (molar).

The kinetic data presented in Fig. 7 for the RAFT agent X_1 reveals that the polymer M_n increases linearly with monomer conversion and $Đ$ remain below 1.4 throughout the polymerization. The obtained values are in accordance with similar literature reports for xanthate mediated RAFT polymerizations of Vac in bulk[32] or in ethyl acetate.[35,36]

The AT-X_1 and PAT-X_1 are xanthate molecules with similar structure to X_1 but with a slight variation of the end-group functionality of the leaving group (R group). The protection of the alkyne moiety (PAT-X_1) was performed in order to observe the role of the terminal alkyne in the polymerization course. It is known that the alkyne hydrogen in the end of the leaving group of the RAFT agent may interfere with the radical polymerization.[45] In fact, when X_1 was replaced by AT-X_1, using similar reaction conditions, the homopolymerization of VAc was slower, and larger $Đ$ were observed, as shown in the kinetic data presented in Fig. 8 and GPC traces in Fig. S6 (ESI†).

Fig. 9 presents the kinetic data obtained for the homopolymerization of VAc using the protected-alkyne RAFT agent. The first-order kinetic and the linear evolution of the MW with the conversion indicate a controlled polymerization. It is interesting to notice that below 70% conversion, the $Đ$ values are very low for a non-activated monomer such as VA ($Đ$ < 1.2), but tend to increase for high monomer conversions. For conversions above 80%, the $M_{n,GPC}$ values become smaller than $M_{n,th}$. This observation may be ascribed to irreversible transfer reactions, chain transfer reactions to monomer and polymer, due to the very reactive nature of the VAc propagating radical.[56] This effect is mostly detected in the polymer GPC traces by the presence of a prominent low MW tail (high retention volume) (Fig. 10) and consequent broad MW distributions from moderate to higher monomer conversions. Similar results were already reported for similar RAFT polymerization of VAc (bulk, 60 °C).[57,58] It should be noted the presence of an induction period for the different RAFT agents studied, which could be related with slower reinitiation of the initial RAFT agent.[59] Moreover, several literature reports dealing with the xanthate mediated RAFT polymerization of PVAc reported a similar

Table 1 Kinetic parameters for the RAFT polymerization of VAc using the X_1, AT-X_1 or PAT-X_1 in 1,4-dioxane. Reaction conditions: $[VAc]_0/[1,4\text{-dioxane}]$ = 1/1 (w/w); $[VAc]_0/[RAFT\ agent]_0/[initiator]_0$ = 100/1/0.2

Entry	RAFT agent	Initiator	Temp., °C	Time[a] ,h	Conv.[a], %	k_p^{app}, h^{-1}	$M_{n,th}$[a] × 10^3	$M_{n,GPC}$[a] × 10^3	$Đ$[a]
1	X_1	AIBN	60	24	98	0.291	8.7	6.80	1.4
2	AT-X_1	AIBN	60	24	90	0.118	8.0	6.0	2.0
3	PAT-X_1	AIBN	60	32	96	0.182	8.52	6.69	1.6
4	—	AIBN	60	16	—	—	—	6.06	2.2

[a] Values obtained from the last sample from the kinetic study.

observation.[60,61] Even so, for our novel PAT-X_1, the observed induction period is much smaller. In all cases, the molar mass evolution plots show a discrepancy between the values of $M_{n,th}$ and $M_{n,GPC}$, increasing with conversion. This result may be related with the high concentration of initiator used, which consequently increases the concentration of radicals in the system and promotes irreversible termination reactions. The summary of all experiments performed using the three different RAFT agents is shown in Table 1. The results suggest that only the RAFT agents X_1 and PAT-X_1 were able to conduct a controlled polymerization of VAc with relatively narrow MW distributions, up to high conversions. Despite the high $Đ$ value obtained for the last kinetic point using PAT-X_1, in comparison with the X_1, the kinetic results present in Fig. 9 and 10, indicate that the $Đ$ values tend to increase with reaction conversion. The broad MW distribution observed for the reactions with the alkyne functionalized RAFT agent (AT-X_1) prove the inefficiency of such compound to conduct a controlled polymerization of VAc. On this matter, the $Đ$ values of the PVAc synthesized through RAFT using AT-X_1 or using FRP conditions are similar ($Đ = 2.2$).

Thermogravimetric analysis of the RAFT agents

The thermal behavior of RAFT agents was analyzed by TGA (Fig. 11). The results reveal a single step of mass loss, at relatively low temperatures, for the different RAFT agents synthesized. In order to evaluate the nature of this event, a preparative experiment in a sealed flask under nitrogen was carried out, at 130 °C during 2 h. The comparison of ^{1}H NMR spectra of the RAFT agent before and after the thermal treatment has shown no differences on the peak integrations, which indicates that the mass loss observed in TGA traces are related to volatilization. No significant mass loss was observed after the experiment. Regarding the effect of the structure of R group, the results suggest that the volatilization temperature increases with the following order: PAT-X_1 > AT-X_1 > X_1.

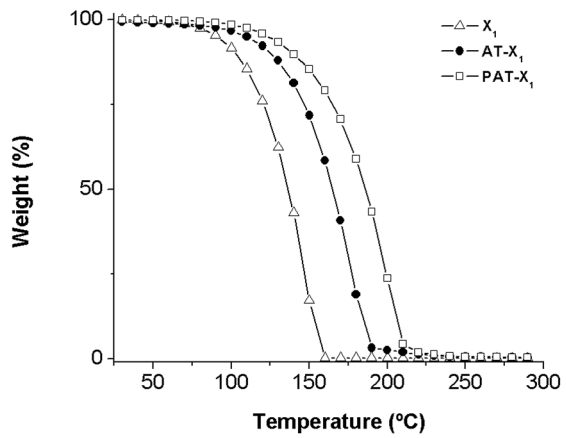

Fig. 11 TGA weight loss curves of X_1, AT-X_1 and PAT-X_1, obtained at a heating rate of 10 °C min^{-1}.

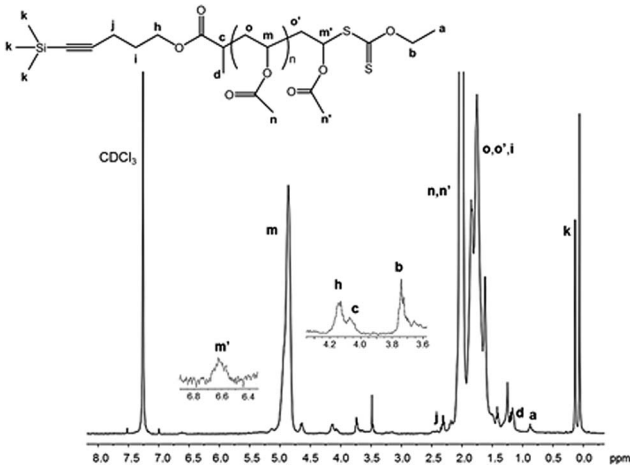

Fig. 12 The ^{1}H NMR spectrum of PVAc synthesized by RAFT using PAT-X_1 ($M_{n,GPC} = 6.0 \times 10^3$; $M_{n,NMR} = 7.56 \times 10^3$, $Đ = 1.36$) in $CDCl_3$.

PVAc chain-end functionality

The chemical structure of the PVAc synthesized by RAFT polymerization was determined with ^{1}H NMR, FTIR-ATR and UV-Vis analysis. Fig. 12 shows the ^{1}H NMR spectrum of a PVAc sample synthesized using the PAT-X_1. The characteristic peaks of the PVAc structure at 1.75 ppm (o, o′, –CH_2–CH–), 2.02 ppm (n, n′, –CH_3), 4.86 ppm (m, –CH$_2$–CH–) and 6.62 ppm (m′, –CH$_2$–CH–S) are in agreement with the data reported in the literature.[37] The retention of RAFT functionality is evidenced by the peaks from the PAT-X_1 at 0.14 ppm (k, –Si(CH_3)$_3$–), 0.88 ppm (a, –CH$_2$–CH_3), 1.17 ppm (d, –CH–CH_3), 2.31 ppm (j, C≡C–CH_2), 3.74 ppm (b, –CH$_2$–CH$_3$), 4.07 ppm (c, –CH–CH$_3$) and 4.15 ppm (h, –CH_2–O–). It should be noted that the ratio between the integral of k and a signals does not correspond to the theoretical value assuming the number of protons from the R and Z groups, respectively. This result may be justified by the unavoidable termination reactions that occur in any radical based polymerization method. It should not be excluded also a possible loss of RAFT chain end functionality during the purification steps.

The preservation of the terminal chains ends during the RAFT reaction can also be accessed by FTIR-ATR analysis. The FTIR-ATR spectra of the PAT-X_1 and the PVAc synthesized using

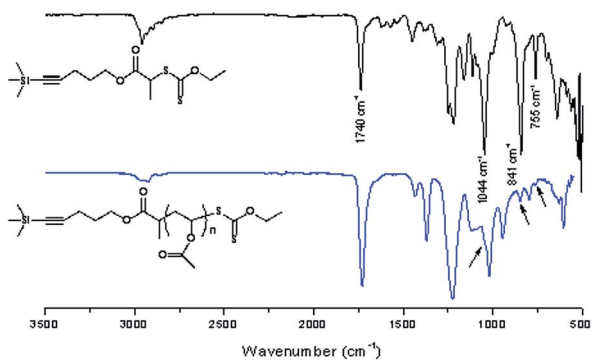

Fig. 13 FTIR-ATR spectra of PAT-X_1 and PAT–PVAc.

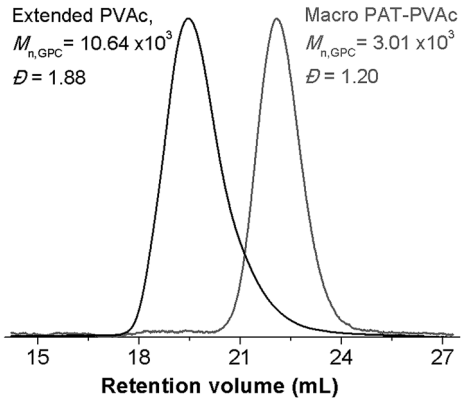

Fig. 14 The GPC traces of PAT–PVAc samples before (on the right) and after chain extension (on the left) experiment.

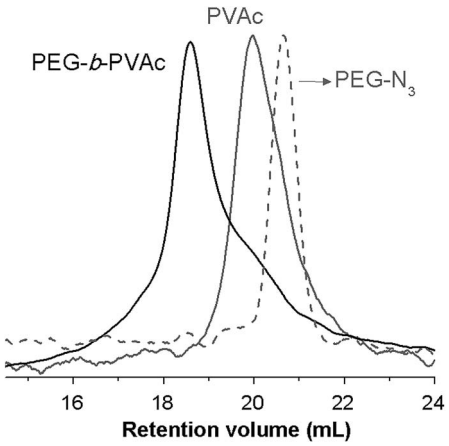

Fig. 16 GPC traces of the RALS signal of the PVAc and PVAc-*b*-PEG copolymer, after the coupling reaction.

the PAT-X_1 is shown in Fig. 13. The bands at 2850–2940 cm^{-1} are associated to both symmetric and asymmetric C–H stretching vibrations. A strong absorption band at 1740 cm^{-1} is related with the –C═O stretching vibration (carbonyl bond of the ester). The characteristic bands of the xanthate group, –C═S and C–S, at 1044 cm^{-1} and 633 cm^{-1} respectively and the characteristic bands of the trimethylsilyl group (–Si–$(CH_3)_3$), at 755 cm^{-1} and 840 cm^{-1} are present in both FTIR-ATR spectra. Ultraviolet-Visible (UV-Vis) spectroscopy has been used as an efficient tool to identify the presence of the characteristic –C═S end-group of polymers prepared by RAFT polymerization. The polymer Z-group can be lost during the polymerization process due to side reactions of the thiocarbonyl groups or due to the inherent termination reactions that occurs during the polymerization.[62] The UV-Vis spectra in $CHCl_3$ of all synthesised PVAc are presented in ESI (Fig. S7†). All samples show an absorption band below 300 nm ascribed to the thiocarbonyl bound, indicating the presence of such groups in the final polymer backbone. This thiocarbonyl group can be further removed or transformed in order to achieve a desired functionality and easily conjugate the polymer with other molecules or polymer segments.[63,64]

Chain extension reaction

The PVAc synthesized through RAFT polymerization ($M_{n,GPC}$ = 3.01 × 10^3, $Đ$ = 1.20) was purified and used as macro-RAFT agent. Fig. 14 shows the complete shift of the molecular weight distribution from a PVAc macroinitiator (macro PAT–PVAc) to a higher MW values (extended PVAc, $M_{n,GPC} = 10.64 \times 10^3$, $Đ$ = 1.88) confirming the "living" nature of the polymer.

Deprotection of PVAc and coupling reaction with N_3-PEG

After the RAFT polymerization of VAc using the PAT-X_1, the protective trimethyl silyl group was removed using TBAF (Fig. 15 (1.2)). The success of the reaction was confirmed by the disappearance of the characteristic trimethyl silyl signal (k) at 0.14 ppm by the ^{1}H NMR spectrum of the unprotected PVAc (Fig. 12 (k) and S8, ESI†).

As a proof of concept an azide terminated PEG (N_3-PEG) was used for the post-polymerization coupling reaction with an alkyne-terminated PVAc (Fig. 15 (1.3)). In fact, this reaction could not be named as "click" reaction since it did not fulfill all of the criteria in the context of macromolecular chemistry.[65] The success of the synthesis of the PEG-*b*-PVAc copolymer was evaluated by GPC and FTIR-ATR spectroscopy. Fig. 16 shows the

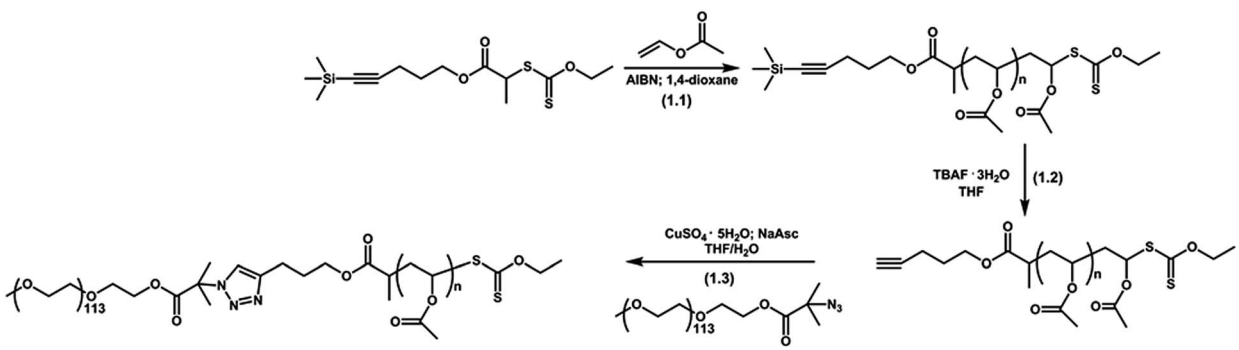

Fig. 15 Schematic representation of the RAFT polymerization of VAc (1.1), PVAc deprotection (1.2) and synthesis of PEG-*b*-PVAc block copolymers by CuAAC reaction (1.3).

clear shift of the molecular weight distribution of the PVAc block towards higher molecular weight values. It should be stressed the presence of a shoulder that based on the GPC traces can be ascribed to the some unreacted PVAc segments. Moreover, the comparison of FTIR-ATR spectra of the homopolymer precursors, N_3-PEG and AT-PVAc with the copolymer PEG-*b*-PVAc (Fig. S9, ESI†), confirms the presence of the characteristic bands from each homopolymer segment in the spectrum of the copolymer and reveals the disappearance of the characteristic azide signal at 2100 cm^{-1}, confirming the success of the coupling reaction.

Conclusions

We reported the synthesis of one protected alkyne containing xanthate RAFT agent, able to efficiently control the polymerization of VAc. The protection of the alkyne moiety in the RAFT agent is crucial to afford a polymerization with a good control over the MW and with low $Đ$. The structural analysis of the PVAc, performed by ^{1}H NMR, FTIR-ATR and UV-Vis experiments reveal the retention of the chain-end functionality. The "living" nature of the PVAc synthesized through RAFT was confirmed by a successful chain extension experiment. After the deprotection of the alkyne end group, the well-defined alkyne-terminated PVAc can be easily conjugated with azido-terminated structures through a CuAAC reaction.

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