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Synthesis of versatile TIPNO-based alkoxyamines

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ABSTRACT

The versatile chloromethyl TIPNO-based alkoxyamine was efficiently transformed into other valuable functionalised TIPNO-based alkoxyamines such as amino alkoxyamines which are interesting initiators for block copolymers and bisalkoxyamines in good yield and in two steps at the most. One bisalkoxyamine has allowed to prepare well-defined polystyrene-*b*-poly(*n*-butyl acrylate)-*b*-polystyrene symmetrical triblock copolymer. The last representative example of such alkoxyamines is a styrenic alkoxyamine which was copolymerized with styrene to afford branched polystyrene. Finally, for the first time branched poly(*n*-butyl acrylate) by nitroxide mediated radical polymerization was obtained and was a efficient macroinitiator of styrene, which indicates that the radical polymerization mediated by this styrenic alkoxyamine is living.

1. Introduction

Since its discovery [1,2], nitroxide mediated radical polymerization (NMRP) has been improved especially with the emergence of the nitroxides of second generation [3–11] whose s are versatile initiators/mediators of NMRP as they provide the control of molecular weight, polydispersity and end-group functionality during polymerization of almost all vinylic monomers polymerizable by a radical process. The C–O bond of an alkoxyamine is a relative robust bond except under strong oxidative [12], reductive conditions [13] or when it is heated during polymerization [1]. Therefore, the chemistry of alkoxyamines has been developed: many functionalized alkoxyamines designed for applications such as organic electronics [14], homogenous catalysis [15], surface modification [16–20] or biomolecule conjugation [21,22] are today described. Such alkoxyamines have allowed, combined with the livingness of the NMRP process to synthesize well-defined macromolecular architectures [23–25] such as multifunctional macromolecules [26], dynamic covalent polymers [27], nanogels [28], polymer brushes [29], block copolymers [30–40], graft [41] polymers, star polymers [42,43], hyperbranched polymers [44], networks [45] and micelles [46] or core-crosslinked nanoparticles [47]. In this context, we wish to describe in this work, the synthesis of nine new functionalized alkoxyamines based on 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide [3], also called TIPNO. The well known chloromethyl TIPNO-based alkoxyamine [21] was the versatile brick that has afforded efficiently and in two steps at the most all alkoxyamines, which is a serious advantage compared with the previously described synthesis of alkoxyamines. Carbamate alkoxyamines were synthesized and were transformed into amine alkoxyamines that are valuable initiators for the preparation of block copolymers for example. By phase transfer catalysis, bisalkoxyamines, the more useful initiators for the synthesis of symmetrical triblock copolymers were also obtained and were successfully used for the controlled synthesis of a polystyrene-*b*-poly(*n*-butyl acrylate)-*b*-polystyrene. Finally, a styrenic alkoxyamine was especially prepared and during styrene polymerization has yielded well defined styrene macromonomers at low conversion and branched polystyrenes for higher conversion. Moreover the polymerization of *n*-butyl acrylate initiated by this polymerizable alkoxyamine was controlled and living and for the first time, it was possible to prepare branched poly(*n*-butyl acrylate) by NMRP. The potential of this polymerizable alkoxyamine is interesting as its polymerization by other controlled radical polymerizations such as ATRP and RAFT, combined with NMRP should afford in a controlled way other valuables macromolecular architectures such as random graft copolymers.

2. Experimental

2.1. General considerations

^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on Bruker AC 200 MHz or ARX 250 MHz instruments. Proton and carbon chemical shifts are reported using the resonance of the deuterated solvent as internal standard. Elemental analyses were performed by the Service Central d'Analyses of the CNRS. Chemical ionisation (CI, ammonia or methane) and electronic

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ionisation (EI) mass spectra were obtained with a JMS-700 spectrometer. All reagents and chemicals were obtained from commercial suppliers without further purification excepted when indicated. Styrene (99%; Acros) was distilled in vacuo and stored at −4 °C. Acrylic acid (99.5%) was purchased from Acros and used without further purification. Ethyl acetate (99%), triphenylphosphine (98%), formaldehyde (37 wt.% in water), lithium aluminium hybride powder (95%), sodium borohydride (>98%), methylamine solution (2 *M* in tetrahydrofuran) di-*tert*-butyldicarbonate (97%), sodium azide, sodium hydride (60% dispersion in mineral oil), Jacobsen's catalyst (98%), *tert*-butylamine, hydrogen peroxide (35 wt.% in water), di-*tert*-butyl peroxide (99%), trifluoroacetic acid (99%) and tri-*n*-butyl phosphine (95%) were all obtained from Acros Organics. Zinc powder (99%) was purchased from ABCR. 4-vinylbenzyl chloride (technical, 90%, Aldrich), tetrabutyl ammonium bromide (98%) and tetrabutyl ammonium iodide (98%) were used as received from Aldrich. Tri-*n*-butyl phosphine was distilled *in vacuo* immediately before use. Ethanol, dichloromethane (CH_2Cl_2) and toluene (>99%) were purchased from VWR. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under N_2 from sodium benzophenone, DMF was distilled from CaH_2. Silica gel for column chromatography was Merck Kieselgel 60. Column chromatographic separations were carried out using Merck silica gel 60 (230–400 mesh) or alumina when it is indicated.

Size exclusion chromatography (SEC) was performed at 40 °C with two columns (PSS SDV, linear MU, 8 × 300 mm; bead diameter, 5 μm; separation limits, 400 to 2×10^6 g · mol^{-1}). The eluent was THF at a flow rate of 1 mL · min^{-1}. A differential refractive index detector (LDC Analytical refracto-Monitor IV) was used and molar mass distributions were derived from a calibration curve based on polystyrene (PS) standards from Polymer Standards Service. The monomer conversion for styrene polymerization was determined by gravimetry after drying the polymer samples under vacuum for 48 h.

The following derivatives, 2,2,5-trimethyl-4-phenyl-3-azahexane-3-oxyl (TIPNO) **2** [3], 2,2,5-trimethyl-3-(1-(4′-chloromethyl)phenylethoxy)-4-phenyl-3-azahexane **4** [49], O-[1-(4-azidomethyl-phenyl)-ethyl]-N-*tert*-butyl-N-(2-methyl-1-phenyl-propyl)-alkoxyamine **11** [55], Mn(Salen)Cl **3** [49], methylcarbamic acid *tert*-butyl ester **5** [57] were synthesized according to literature procedures.

2.2. Synthesis and characterisation of TIPNO-based alkoxyamines

2.2.1. 2-Methyl-2-nitropropane [48] (*1*)

A solution of *tert*-butylamine (52 mL, 0.5 mol) and $Na_2WO_4 \cdot 2H_2O$ (4 g) in 20 mL of water was cooled in an ice bath. Hydrogen peroxide (150 mL of a solution at 35%) was added dropwise with stirring. The first 100 mL was added so that the temperature of the reaction mixture was kept between 15 °C and 20 °C by cooling the mixture in the ice bath and by adding ice in small portions. Methanol (100 mL) was then added to the reaction mixture and the peroxide addition was continued at 25–35 °C. At the end of the addition (Caution!: the temperature was still increasing and the ice addition was repeated if the temperature was exceeding 60 °C), the solution is stirred at room temperature during the night. The product was extracted with dichloromethane (200 mL). The organic layer was dried over magnesium sulfate and distilled at atmospheric pressure to give 30.3 g (58% yield) of **1**. Bp = 126–127 °C. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.51 ppm (s, 9H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 84.86 (*t*Bu), 27.53 ppm (CH_3).

2.2.2. 2,2,5-Trimethyl-3-(1′-p-(t-butyloxycarbonylmethyl-amidomethylphenyl)-ethoxy)-4-phenyl-3-azahexane (*6*)

First procedure: To a stirred solution of methylcarbamic acid *tert*-butyl ester **5** (0.527 g, 4.026 mmol) in DMF (10 mL) cooled to 0 °C, under N_2 atmosphere, sodium hydride (0.161 g, 4.026 mmol) was added. After stirring for 2 h at room temperature, chloromethyl **4** (1 g, 2.684 mmol) dissolved in DMF (10 mL) was added to the reaction mixture dropwise at 0 °C. The reaction mixture was warmed to room temperature and allowed to stir for additional 24 h. The excess of sodium hydride was slowly quenched with ice–water (5 mL) until the solution turned clear. The reaction mixture was diluted with water (50 mL) and extracted with diethyl ether (2 × 150 mL). The combined organics were washed with brine and dried over $MgSO_4$, concentrated. The crude product was purified by column chromatography (10:90: EtOAc/pentane) to provide the alkoxyamine **6** as a yellow oil (1.124 g, 89%).

Second procedure: To a solution of the vinyl carbamate **7** (1.12 g, 4.53 mmol) and 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide, 1 (1 g, 4.54 mmol), in 1:1 toluene/ethanol (27 mL) was added [N,N′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato] manganese(III) chloride (430 mg, 0.614 mmol) followed by di-*tert*-butyl peroxide (0.664 g, 4.54 mmol) and sodium borohydride (0.343 g, 9.02 mmol). The reaction mixture was then stirred at room temperature for 12 h, evaporated to dryness, and partitioned between dichloromethane (150 mL) and brine (150 mL). The combined organics were dried over $MgSO_4$, concentrated. The crude product was purified by column chromatography (10:90: EtOAc/pentane) to provide the alkoxyamine **6** as a yellow oil (1.09 g, 51%).

^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.19–7.05 (m, 18H, aromatic), 4.83 (q + q, 2H, CH–O), 4.35 and 4.31 (each s, 4H, CH_2–N), 3.34 (d, 1H, *J* = 10.6 Hz, CH–N), 3.20 (d, 1H, *J* = 10.6 Hz, CH–N), 2.73 (s, 6H, CH_3–N), 2.25 (two m, 2H, CH–*iPr*), 1.54 (d, 3H, *J* = 6.6 Hz, C**H**$_3$–CH–O), 1.46 (d, 3H, *J* = 6.6 Hz, C**H**$_3$–CH–O), 1.40 (s, 9H, *t*Bu–O), 1.23 (d, 3H, *J* = 6.2 Hz, C**H**$_3$–*iPr*), 0.96 (s, 9H, *t*Bu), 0.81 (d, 3H, *J* = 6.2 Hz, C**H**$_3$–*iPr*), 0.69 (s, 9H, *t*Bu), 0.46 (d, 3H, *J* = 6.6 Hz, C**H**$_3$–*iPr*), 0.11 ppm (d, 3H, *J* = 6.6 Hz, C**H**$_3$–*iPr*).

^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.82 (C=O), 144.62, 143.96, 142.38, 142.16, 136.98, 130.88, 127.94, 127.31, 127.24, 127.13, 126.32, 126.13 (aromatic), 83.13, 82.51 (CH–O), 79.53 (*t*Bu–O), 72.14, 72.00 (CH–N), 60.53, 60.35 (*t*Bu–N), 52.37, 51.62 (CH_2–N), 33.85 (CH_3–N), 31.94, 31.49 (CH–*iPr*), 28.41, 28.33, 28.19 (*t*Bu), 24.55, 22.93, 22.20, 21.94, 21.13, 20.95 ppm (CH_3). MS (CI, NH_3): *m*/*z* (%) 469 (M+2, 100). Anal. Calcd for $C_{29}H_{43}N_2O_3$ C, 74.5; H, 9.2; N, 6. Found C, 75.03; H, 9.57; N, 5.50.

2.2.3. 4-(Vinylbenzyl) methylcarbamic acid tert-butyl ester (*7*)

To a stirred solution of methylcarbamic acid *tert*-butyl ester **5** (6.62 g, 27.6 mmol) in DMF (60 mL) cooled to 0 °C, under N_2 atmosphere, sodium hydride (0.66 g, 27.6 mmol) was added. After stirring for 2 h at room temperature, vinyl benzyl chloride (3.6 mL, 23 mmol) dissolved in DMF (20 mL) was added to the reaction mixture dropwise at 0 °C. The reaction mixture was warmed to room temperature and allowed to stir for additional 48 h. The excess of sodium hydride was slowly quenched with ice–water (5 mL) until the solution turned clear. The reaction mixture was diluted with water (100 mL) and extracted with diethyl ether (2 × 200 mL). The combined organics were washed with brine and dried over $MgSO_4$, concentrated. The crude product was purified by column chromatography (10:90: EtOAc/pentane) to provide **7** as an oil (2.669 g, 47%).

^{1}H NMR (200 MHz, $CDCl_3$, δ): 7.34 (d, 2H, *J* = 8 Hz, aromatic); 7.16 (d, 2H, *J* = 8 Hz, aromatic), 6.67 (dd, 2H, *J* = 17.5 Hz, 11 Hz, –C**H**=CH_2), 5.70 (d, 1H, *J* = 17.5 Hz, –CH=C**H**$_2$, *trans*), 5.2 (d, 1H, *J* = 11 Hz, –CH=C**H**$_2$, *cis*), 4.38 (s, 2H, CH_2–N), 2.80 (s, 3H, CH_3–N), 1.46 ppm (s, 9H, *t*Bu). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 155.65 (C=O), 137.57, 136.4, 136.28, 127.31, 126.21 (4 **C**H–aromatic and **C**H=CH_2), 113.49 (CH=**C**H_2), 79.46 (*t*Bu), 52.15 (**C**H_2–N), 33.70 (**C**H_3–N), 28.30 ppm (*t*Bu). EIMS: *m*/*z* (%) 247 (M, 100).