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Communication

2-hydroxy-3-(1-(4-vinylbenzyl)imidazol-3-ium-3-yl)propane-1-sulfonate and 3-(4-vinylbenzyl)dimethylammonio)-2-hydroxypropane-1-sulfonate as new zwitterionic monomers

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Abstract: Zwitterionic polymers emerge as very useful materials for applications in antifouling surfaces. The properties of these polymers can be tuned by variation of the chemical structure of the corresponding monomer. In this study, two zwitterionic ammonium sulfonate monomers bearing an hydroxyl function and a styrenic polymerizable groups were prepared in two steps. The two monomers were obtained using 4-vinylbenzyl chloride as the key precursor. The zwitterionic monomers were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and high-resolution mass spectrometry (HRMS). These two monomers enable the preparation of novel zwitterionic polymers with enhanced hydrophilicity due to the presence of a hydroxyl group.

Keywords: monomer; zwitterionic; imidazolium; sulfonate; polymer

1. Introduction

Zwitterionic polymers (or polyzwitterions) exhibit a structure with an equimolar number of anionic and cationic groups on their repeat unit. These polymers are mainly found in two forms with the charges located either on the pendent side chains of the monomer unit or along the polymer backbone (Figure 1) [1,2]. The main application of zwitterionic polymers is the preparation of nonfouling materials and surfaces due to the repelling of bacterial adhesion through polymer hydration [3-5].

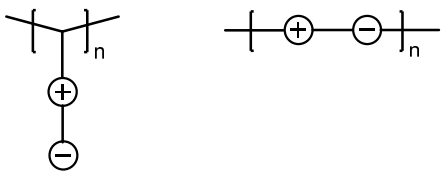

Figure 1. Examples of possible distributions of ionic groups within zwitterionic polymers (schematic representation)

The chemical diversity of zwitterionic polymers comes exclusively from the ionic groups in the monomer. The main cations are obtained by alkylation of a nitrogen or phosphorus atom to generate a quaternary ammonium, pyridinium, imidazolium or phosphonium group. The anion used are carboxylates, sulfonates or phosphates groups. To prepare antifouling surfaces, methacrylate and acrylamide are the most common polymerizable groups used for zwitterionic monomers [2,3]. However, some studies reported the use of a styrenic polymerizable group [6,7]. Very recently, T. Emrick *et al.*

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described the preparation of new zwitterionic monomers using 4-vinylbenzyl sultone as precursor to ammonium sulfonate monomers [6].

In this communication, we describe the synthesis of two styrenic zwitterionic monomers bearing imidazolium or ammonium cation linked to a sulfonate anion. In addition, a hydroxyl function present on each monomer unit could intensify the hydrophilic character of the corresponding polymers and enhance their nonfouling properties.

2. Results and discussion

Recently, our team has developed new efficient approaches to functionalized ionic monomers for their use in epoxy resins [8,9]. Here, we describe a simple two-steps sequence from imidazole or dimethylamine and sodium-3-chloro-2-hydroxypropane-1-sulfonate for the preparation of zwitterionic monomers bearing a styrenic moiety (Scheme 1). In this strategy, we used 4-vinylbenzylchloride as an inexpensive and particularly reactive starting material. Firstly, we added a stoechiometic amount of imidazole in the presence of powdered sodium hydroxide (1 eq) in THF. After 48 h at room temperature, the crude mixture was poured in water and 4-vinylbenzylimidazole **1** was extracted by dichloromethane to give an excellent yield of 96 %. NMR analysis confirmed the alkylation to give the imidazole derivative 1 with no purification required at this step. The quaternarization of the imidazole **1** was performed by reaction with sodium 3-chloro-2-hydroxypropane-1-sulfonate hemihydrate in a mixture of water/methanol (1/1). To optimize this second alkylation, we solubilized the sulfonate in water at room temperature. This aqueous solution was added to imidazole **1** in methanol and the resulting mixture was heated at 90 °C for 72 h. With 1.5 equiv of imidazole **1**, a poor conversion of 60 % is obtained after 72 h. After the reaction, we tested the purification of the crude mixture using Amberlite MB-6113 H^+/OH^- mixed resin. To this end, the crude monomer was precipitated in ethyl acetate and solubilized in water. Then, the mixed-bed ion-exchange resin was added, and the suspension was stirred at room temperature until the disappearance of sodium 3-chloro-2-hydroxypropane-1-sulfonate (followed by ^1H NMR spectroscopy). The resin was filtered, then water was removed under reduced pressure, and finally the residue was dried in vacuo. This protocol afforded a purified product but a significant loss of mass was observed.

In a second study, we used an excess of imidazole **1** to completely consume the 3-chloro-2-hydroxypropane-1-sulfonate and facilitate the purification of the final zwitterion. With 4 equivalents (eq) of imidazole **1**, the conversion reached 95% 72 h at room temperature. The addition of a large excess of imidazole **1** (6 eq) had no influence on the kinetics of this reaction. In both cases, the precipitation of the zwitterionic compound in ethyl acetate led to the pure product in 93% yield. Thermal behavior and stability of this monomer were investigated by TGA. Until 300 °C, the weight loss was negligible. A weight loss equal to 5% was obtained at 357 °C. Using the first derivative of the TGA as a function of temperature, a maximum rate of decomposition was obtained at 385 °C and 482 °C.

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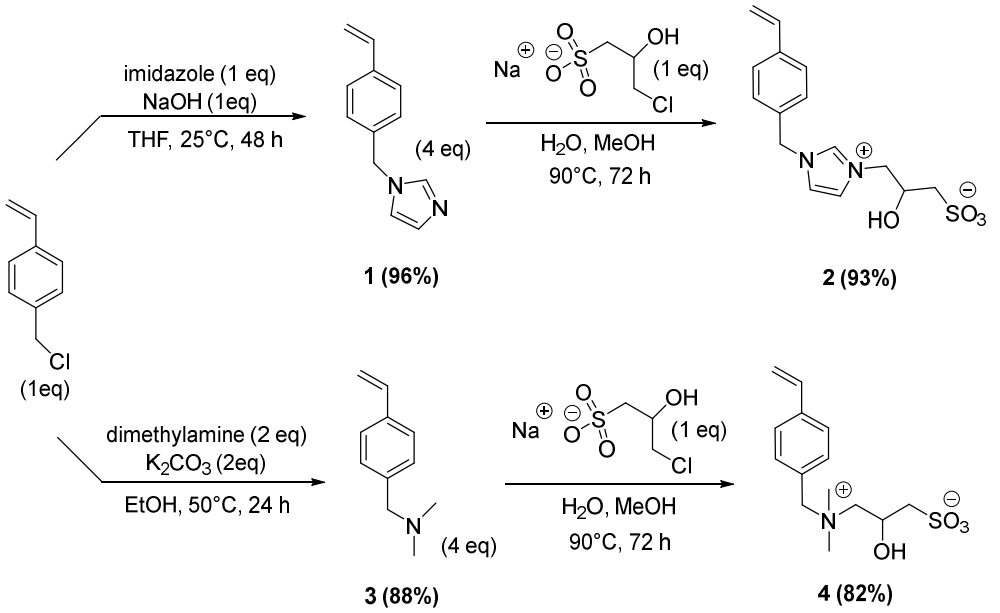

Scheme 1. Synthesis of zwitterionic salts **2** and **4** from 4-vinylbenzylchloride

To complete the previous sequence, we used dimethylamine to provide a new cationic moiety (Scheme 1). This nucleophile is reacted with 4-vinylbenzylchloride to generate tertiary amine **3** in 88% yield. In this case, the amine **3** was purified by column chromatography on silica gel with CH_2Cl_2 /MeOH (90:10) as the eluent. Finally, the zwitterionic compound is synthesized by quaternarization with sodium-3-chloro-2-hydroxypropane-1-sulfonate hemihydrate under similar conditions as previously described in the case of imidazole **1**. The ammonium is isolated by precipitation in acetonitrile and filtration to give the zwitterionic salt **4** in 82% yield.

Various tests of solubility have been carried out with zwitterionic salts **2** and **4**. We used a large number of usual organic solvents such as CH_2Cl_2, MeCN, MeOH and DMF which do not solubilize the two compounds. In DMSO and water, a poor solubility was observed in both cases. To improve the hydrosolubility of these salts, we added NaCl (4 equivalents for **2** and 2 equivalents for **4**) to obtain a homogeneous mixture.

4. Materials and Methods

4.1 Materials.

All reagents were obtained from commercial suppliers and used without further purification: imidazole (TCI), dimethylamine (40 wt% in H_2O, Sigma Aldrich), 4-vinylbenzylchloride (90%, contains 0.1% total stabilizer, Sigma Aldrich), sodium 3-chloro-2-hydroxypropane-1-sulfonate hemihydrate (Alfa Aesar). ^1H NMR and ^{13}C NMR were recorded using 500 Mhz apparatus in an appropriate deuterated solvent ($CDCl_3$, D_2O, DMSO-d_6 from Eurisotop). All chemical shifts δ are reported in parts in ppm (part per million) relative to internal tetramethylsilane and coupling constants (*J*) are indicated in Hertz (Hz). Abbreviations for signal coupling are as follows: s=singlet; d=doublet; dd=doublet of doublets; t=triplet; q=quartet; m=multiplet.

Attenuated total reflection infrared (ATR IR) spectra were recorded using a Perkin Elmer 16 PC FTIR ATR spectrometer.

High resolution mass spectra were recorded on Acquity UPLC H-Class Xevo G2-XS QTof (WATERS) by electrospray ionization (ESI).

Thermogravimetric analyses (TGA) were conducted on Perkin Elmer TGA Pyris 1 with a heating rate of 20 °C/min under a nitrogen atmosphere.

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4.2 Synthesis of imidazole **1**

Imidazole (3.6 g, 50 mmol, 1.0 eq) was solubilized in 50 mL THF and added dropwise to a suspension of NaOH (3.16 g, 50 mmol, 1.0 eq) in THF. The resulting mixture was refluxed for 2 h. After cooling, 4-vinylbenzylchloride (8.03 g, 50 mmol, 1 eq) was slowly added and the reaction mixture was stirred at room temperature for 48 h. The resulting mixture was solubilized in water and the product was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried on $MgSO_4$, filtered and concentrated under reduced pressure to give the 1-(4- vinylbenzyl)imidazole (8.90 g, 96%) which was pure enough to undergo the next step. ^1H and ^{13}C NMR spectra are in agreement with the literature data [10].

4.3 Synthesis of zwitterion **2**

Sodium-3-chloro-2-hydroxypropane-1-sulfonate hemihydrate (1.4 g, 6.7 mmol, 1 eq) was solubilized in H_2O (20 mL) and added to 1-(4-vinylbenzyl)imidazole (5 g, 27 mmol , 4 eq) in MeOH (24 mL). The reaction mixture was stirred at 90 °C for 72 h. The mixture was concentrated under reduced pressure. The product was precipitated in ethyl acetate, filtered and washed with ethyl acetate. The zwitterion was obtained as a white powder (2.02 g, 93%).

^1H NMR (500 MHz, D_2O) δ 3.01 (d, *J* = 6.1 Hz, 2H), 4.18 (dd, *J* = 14.3 and 9.7 Hz, 1H), 4.28-4.31 (m, 1H), 4.39 (dd, *J* = 13.9 and 2.6 Hz, 1H), 5.24 (d, *J* = 11.0 Hz, 1H), 5.28 (s, 2H), 5.77 (d, *J* = 17.7 Hz , 1H), 6.69 (dd, *J* = 17.7 and 11.1 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.38-7.45 (m, 4H), 8.87 (s, 1H).

^{13}C NMR (125 MHz, D_2O) δ 138.5, 136.0, 133.0, 129.0, 127.0, 123.5, 122.4, 115.5, 66.0, 54.01, 53.8, 52.7.

IR (neat) cm^{-1} 3671, 3342, 3086, 2980, 1552, 1410, 1191, 1155, 1039.

HRMS m/z (ESI): calcd, for $C_{15}H_{17}N_2O_4S$ $[M-H]^-$: 321.0909, found: 321.0905.

TGA: $T_{5\%}$ = 357 °C, $T_{20\%}$ = 407 °C and $T_{50\%}$ = 611 °C

4.3 Synthesis of amine **3**

4-vinylbenzylchloride (10 g , 65 mmol , 1.0 eq) was added to a dimethylamine aqueous solution (5.9 g , 131 mmol 2.0 eq) and K_2CO_3 (18.11 g, 131 mmol, 2.0 eq) in ethanol (60 mL). The mixture was degassed with argon and then heated to 50 °C. After 24 h, the solvent was removed under vacuum to obtain the crude product. The amine was purified by silica gel column chromatography with CH_2Cl_2/MeOH (90:10) as the eluent to obtain a colorless liquid (9.3 g, 88%). ^1H and ^{13}C NMR spectra are in agreement with the literature data [11].

4.3 Synthesis of zwitterion **4**

Sodium-3-chloro-2-hydroxypropane-1-sulfonate hemihydrate (1.6 g, 7.8 mmol, 1.0 eq) was solubilized in H_2O (20 mL) and added to *N*-(4- vinylbenzyl)dimethylamine (5 g, 31 mmol, 4.0 eq) in MeOH (20 mL). The reaction mixture was stirred at 90 °C for 72 h. The mixture was concentrated under reduced pressure. The product was precipitated in acetonitrile, filtered and washed with acetonitrile to give zwitterionic salt **4** (1.9 g, 82%) as a white powder.

m.p. = 211 °C

^1H NMR (500 MHz, D_2O) δ 3.01-3.06 (m, 8H), 3.41 (dd, *J* = 13.9 and 9.7 Hz, 1H), 4.39 (dd, *J* = 12.8 and 1.3 Hz, 1H), 4.48 (q, 2H), 4.64-4.67 (m, 1H), 5.32 (d, *J* = 11.3 Hz, 1H), 5.84 (d, *J* = 17.7 Hz, 1H), 6.73 (dd, *J* = 17.4 and 11.0 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H).

^{13}C NMR (125 MHz, D_2O) δ 139.8, 135.8, 1335, 126.7, 126.3, 116.4, 69.6, 67.5, 62.7, 55.3, 50.9, 50.2.

IR (neat) cm^{-1}. 3296, 3027, 2978, 1630, 1480, 1411, 1194, 1165.

HRMS m/z (ESI): calcd. for $C_{14}H_{20}NO_4S$ $[M-H]^-$: 298.1113, found: 298.1109.

5. Conclusions

We have synthesized two styrenic monomers bearing a zwitterionic group (imidazolium or ammonium corresponding to the cationic moiety and sulphonate for the anionic moiety) in association with a hydroxyl function. From 4-vinylbenzylchloride as starting material, salts **2** and **4** were obtained in high overall yield of 89.5% and 72.5% respectively. These monomers can be polymerized by conventional or reversible-deactivation radical polymerizations to produce hydrophilic and/or antifouling materials. They could be used for surface modification in medical equipments (stents, catheter, dental implantology) and micelles preparation for drug delivery systems.

Supplementary Materials: The following supporting informations are available online : copies of the NMR spectra for compounds **1**-**4**, IR spectra for compounds 2 and 4 and TGA curve for compound 2.

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Conflicts of Interest: The authors report no declarations of interest.

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