Tetrahedron Letters 52 (2011) 1101–1104

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of a series of monomeric styrene sulfobetaine precursors

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ARTICLE INFO

Article history:
Received 3 November 2010
Revised 17 December 2010
Accepted 22 December 2010
Available online 7 January 2011

Keywords:
Sulfobetaine
Monomeric precursor
Styrene derivative

ABSTRACT

Procedures for the synthesis of five sulfobetaine monomers as styrene derivatives are given. The five molecules form a homologous row differing in the distance between the inner quaternary amine and the outer sulfonic acid from one methylene group to five methylene groups. Syntheses are achieved by a sequence of nucleophilic substitutions starting from commercially available precursors.

Zwitterionic molecules of the sulfobetaine type are frequently utilized in different fields of chemistry. They are applied as zwitterionic surfactants[1] or as surface modificators.[2] They can also be attached to silica or polymeric backbones and serve as stationary phases in zwitterionic hydrophilic interaction chromatography (ZIC-HILIC)[3,4] or for solid phase extraction.[5,6]

For these applications sulfobetaines containing polymerizable functional groups are essential. Methacrylate derivatives are of interest as the polymers obtained there from[7] can be used on membranes to prevent fouling[8] or they can be attached to titanium alloys to reduce thrombogenicity.[9]

A parameter which is not often considered, despite a profound effect on the chemical and physical properties of the molecules, is the distance between the ammonium and the sulfonate group. Weers et al. investigated a few zwitterionic tensides with spacers varying the distance between the charged groups.[10] They found that the distance between the charges has an enormous influence on the critical micellar concentration and on the hydrophilicity of the molecules.

To investigate these effects on zwitterionic ion chromatography (ZIC) separations, we have prepared a row of homologous monomeric zwitterionic precursors as styrene derivatives. The structures of these molecules are given in Figure 1. By applying a grafting reaction, these precursors can be attached to a polymeric backbone and used for ZIC and ZIC-HILIC separations.[4]

Syntheses of monomeric zwitterionic precursors were achieved by subsequent nucleophilic substitutions involving two or three reaction steps for all five molecules. For the sulfobetaines **1** and **2** having one and two methylene groups between the charged functional groups, a tertiary amine carrying a sulfonic acid was prepared first. This amine can then be used for the substitution of chloride from 4-vinylbenzylic chloride (Schemes 1 and 2).

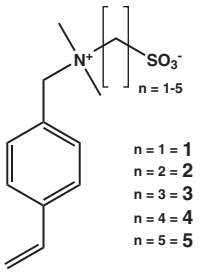
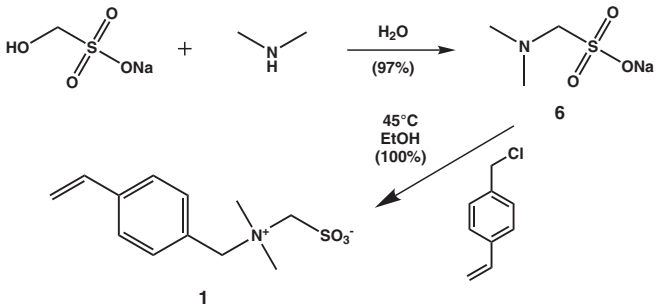


Figure 1. Structure of the synthesized sulfobetaine monomers.



Scheme 1. Synthesis of 4-vinylbenzyl-dimethylammonio methanesulfonate **1**.

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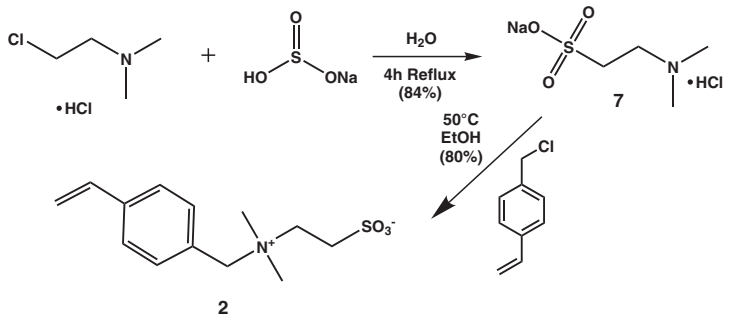
doi:10.1016/j.tetlet.2010.12.100

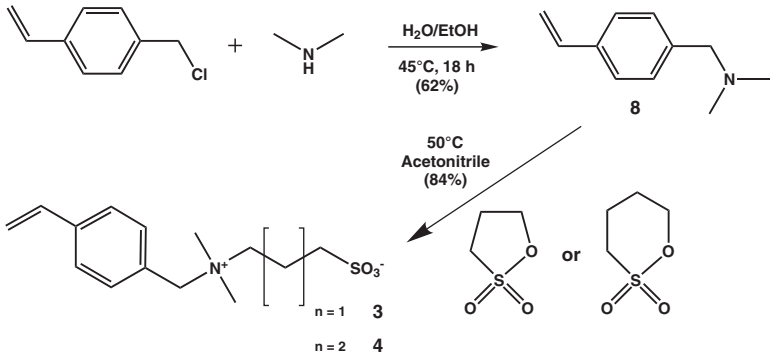


Scheme 2. Synthesis of 4-vinylbenzyl-dimethylammonio ethanesulfonate **2**.

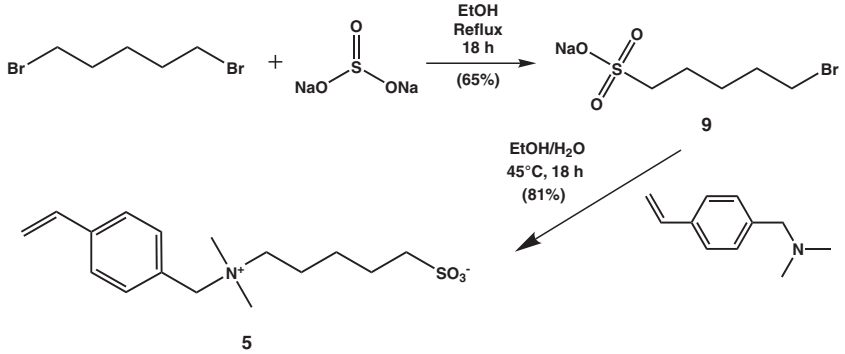
N,*N*-Dimethylamino methanesulfonate **6** was prepared according to a procedure published by King and Skonieczny[11] starting from sodium hydroxymethanesulfonate and an aqueous solution of *N*,*N*-dimethylamine. The reaction is carried out at room temperature yielding 97% of the desired product. The product is slowly added to a cooled solution of 4-vinylbenzyl chloride in ethanol under nitrogen atmosphere and heated to 45 °C for 24 h leading to 4-vinylbenzyl-dimethylammonio methanesulfonate **1** in quantitative yields.[12]

Preparation of the molecule with two methylene groups between the amine and the sulfonic acid proceeds via a different path beginning with the tertiary amine 2-chloro-*N*,*N*-dimetylethylamine hydrochloride. According to a procedure by Palmi et al.[13] the tertiary amine is sulfonated using sodium metabisulfite giving *N*,*N*-dimethyltaurine hydrochloride **7** in 84% yield. The yield can be increased from the reported 58–84% by preparing the sodium salt instead of the free sulfonic acid. The lower yield in literature procedure is likely to be due to the loss of product during work-up. The excess sodium metabisulfite is removed using a strongly acidic cation exchange resin in the H^+-form. 4-Vinylbenzyl-dimethylammonio ethanesulfonate **2** is prepared by slowly adding the sulfonate to a cooled solution of 4-vinylbenzyl chloride in ethanol under nitrogen atmosphere and heating the mixture to 50 °C for 18 h.[14] Due to the reduced reactivity of hydrochlorides, ammonium hydroxide has to be added to the mixture to increase reaction rates. The final reaction gives 80% yield.

The molecules **3**–**5** are synthesized in a slightly different way by nucleophilic reaction of 1,3-propanesultone, 1,4-butanesultone, and 5-bromopentane-1-sulfonate with 4-vinylbenzyl-*N*,*N*-dimethylamine **8** (Schemes 3 and 4). For these molecules better yields and more efficient synthesis routes are obtained when the amination of 4-vinylbenzyl-chloride was carried out as the first reaction step. The amination is achieved by slowly adding an aqueous solution of *N*,*N*-dimethylamine to 4-vinylbenzyl chloride in ethanol under nitrogen atmosphere. Possibly due to the formation of the less reactive *N*,*N*-dimethylamine hydrochloride the product **8** can only be obtained in 62% yield. Even increasing the amount of *N*,*N*-dimethylamine added to a constant amount of 4-vinylbenzyl



Scheme 3. Synthesis of 4-vinylbenzyl-dimethylammonio propanesulfonate **3** and 4-vinylbenzyl-dimethylammonio butanesulfonate **4**.



Scheme 4. Synthesis of 4-vinylbenzyl-dimethylammonio pentanesulfonate **5**.

chloride does not improve yields. Fortunately *N*,*N*-dimethylamine hydrochloride precipitates from 4-vinylbenzyl-*N*,*N*-dimethylamine **8** when the solvent is removed and can be easily be filtrated from the product. Analogous formations of *N*,*N*-dimethylamine hydrochloride can be observed during the reaction of 5-bromopentane-1-sulfonate with *N*,*N*-dimethylamine. Therefore the preparation of 4-vinylbenzyl-*N*,*N*-dimethylamine **8** is carried out as the first step, because both educts are commercially available and reasonably priced.

The final synthetic steps leading to **3** and **4** follow the polymer analogous reaction described by Jiang and Irgum[15] (Scheme 3). Compound **3** has already been prepared and used for polymerization by McCormick and Shen before.[16,17] The sultone rings are opened in a nucleophilic substitution by 4-vinylbenzyl-*N*,*N*-dimethylamine **8** forming both charged groups. Yields for both of these reactions are 84%.[18]

The molecule having five methylene groups between the amine and the sulfonic acid is prepared by the reaction of 5-bromopentane-1-sulfonate **9** with 4-vinylbenzyl-*N*,*N*-dimethylamine **8**. 5-Bromopentane-1-sulfonate **9** is generated in a separate reaction step (Scheme 4) according to a procedure by Fujii and Cook.[19] An excess of 1,5-dibromopentane in ethanol/water (100:30) is heated to reflux and a solution of sodium sulfite in water is slowly added to the stirred solution. The unwanted reaction of both halides of one molecule with sodium sulfite is thus effectively prevented. The reaction yields 65%. The sulfonate is then added to a solution of 4-vinylbenzyl-*N*,*N*-dimethylamine **8** in ethanol/water under nitrogen atmosphere and heated to 45 °C for 18 h giving **5** with 81% yield.[20]

To ensure the composition of the prepared products, the counter ions of the sulfobetaine monomers **1**–**5** are determined using anion exchange chromatography and the CHN-values from combustion elemental analysis. While the molecules **1**, **2**, and **5** are present with sodium and chloride (**1** and **2**) or sodium and bromide (**5**) as counter ions for the charged functional groups, the molecules **3** and **4** do not show any counter ions. This observation can easily be explained by looking at the synthesis routes. Sulfobetaines **1**, **2**, and **5** are prepared using nucleophilic substitutions of halides by tertiary amines. The used sulfonic acids were present as sodium salts. In contrast, the sulfobetaines **3** and **4** are synthesized from sultones. The quaternary amine and the sulfonic acid are prepared in one step by a ring opening nucleophilic substitution thus excluding the presence of further anions or cations in solution.

In conclusion simple synthetic routes for the preparation of a homologous row of sulfobetaine monomers as styrene derivatives could be found. All synthesized molecules have been successfully used for polymerization reactions. They were attached to highly porous highly crosslinked PS/DVB core materials with particle sizes of 4.6 μm by a grafting reaction.[21,4] Thereby zwitterionic stationary phases with exchange capacities in the range 50–250 μmol/g PS/DVB were prepared and used in zwitterionic ion chromatography.[4,22]

Acknowledgment

This work was supported by Metrohm AG, Herisau, Switzerland.

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12. *Synthesis of 4-vinylbenzyl-dimethylammonio methanesulfonate* **1**: Under a nitrogen atmosphere 2.82 ml of 4-vinylbenzyl chloride (0.020 mol, 1.0 equiv) are dissolved in 20 ml of ethanol and cooled to 273 K. 3.22 g of *N*,*N*-dimethylamino methanesulfonate **6** (0.020 mol, 1.0 equiv) in 50 ml ethanol/water (1:1) are slowly added over a period of 15 min. The reaction mixture is heated to 45 °C for 24 h, then the solvent is removed. The product is washed with acetonitrile to give 6.26 g (0.020 mol, 100%) of **1** as a colorless powder. ^{1}H NMR (300 MHz, D_2O): 7.57 (m, 4H, CH_{aromat}); 6.81 (dd, 1H, ^3J = 11.0 and 17.7 Hz, CH_{olefin}); 5.93 (d, 1H, ^3J = 17.7 Hz, CH_{trans}); 5.40 (d, 1H, ^3J = 11.0 Hz, CH_{cis}); 4.73 (s, 2H, $CH_{2,benzyl}$); 4.41 (s, 2H, CH_2); 3.26 (s, 6H, 2 × CH_3). ^{13}C NMR (75 MHz, D_2O): 140.0 (C_q); 135.7 (CH_{olefin}); 133.5 (2 × CH_{aromat}); 126.8 (2 × CH_{aromat}); 125.9 (C_q); 116.4 ($CH_{2,olefin}$); 72.5 (CH_2); 69.2 ($CH_{2,benzyl}$); 51.0 (2 × CH_3). Anal. Calcd for $C_{12}H_{17}ClNNaO_3S$: C, 45.9; H, 5.5; N, 4.5. Found: C, 44.8; H, 5.7; N, 4.0.
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18. *General procedure for the synthesis of 4-vinylbenzyl-dimethylammonio propanesulfonate* **3** *and 4-vinylbenzyl-dimethylammonio butanesulfonate* **4**: Under a nitrogen atmosphere 3.22 g of 4-vinylbenzyl-*N*,*N*-dimethylamine **8** (0.020 mol, 1.0 equiv) are dissolved in 100 ml of acetonitrile and 1 equiv of the sultone (1,3-propanesultone or 1,4-butanesultone) is added. The reaction mixture is heated to 323 K for 48 h, then the solvent is removed. The products are washed with acetonitrile to give 5.40 g of **3** (0.017 mol, 84%) or 5.1 g of **4** (0.017 mol, 85%) as colorless powders.
Data for 4-vinylbenzyl-dimethylammonio propanesulfonate **3**: ^{1}H NMR (300 MHz, D_2O): 7.55 (m, 4H, CH_{aromat}); 6.82 (dd, 1H, ^3J = 11.0 and 17.7 Hz, CH_{olefin}); 5.93 (d, 1H, ^3J = 17.7 Hz, CH_{trans}); 5.40 (d, 1H, ^3J = 11.0 Hz, CH_{cis}); 4.48 (s, 2H, $CH_{2,benzyl}$); 3.43 (m, 2H, NCH_2); 3.03 (s, 6H, 2 × CH_3); 2.96 (t, 2H, ^3J = 7.4 Hz, SCH_2); 2.30 (m, 2H, –CH_2–). ^{13}C NMR (75 MHz, D_2O): 139.8 (C_q); 135.7 (CH_{olefin}); 133.2 (2 × CH_{aromat}); 126.5 (2 × CH_{aromat}); 126.3 (C_q); 116.3 ($CH_{2,olefin}$); 67.8 ($CH_{2,benzyl}$); 62.3 (NCH_2); 49.5 (2 × CH_3); 47.3 (SCH_2); 18.3 (CH_2). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.3; H, 7.5; N, 4.9%. Found: C, 58.5; H, 7.4; N, 4.8%.
Data for 4-vinylbenzyl-dimethylammonio butanesulfonate **4**: ^{1}H NMR (300 MHz, D_2O): 7.54 (m, 4H, CH_{aromat}); 6.81 (dd, 1H, ^3J = 11.0 and 17.7 Hz, CH_{olefin}); 5.92 (d, 1H, ^3J = 17.7 Hz, CH_{trans}); 5.39 (d, 1H, ^3J = 11.0 Hz, CH_{cis}); 4.44 (s, 2H, $CH_{2,benzyl}$); 3.29 (m, 2H, NCH_2); 3.00 (s, 6H, 2 × CH_3); 2.96 (t, 2H, ^3J = 7.6 Hz, SCH_2); 2.02 (m, 2H, –CH_2–); 1.78 (m, 2H, –CH_2–). ^{13}C NMR (75 MHz, D_2O): 139.8 (C_q); 135.7 (CH_{olefin}); 133.2 (2 × CH_{aromat}); 126.7 (2 × CH_{aromat}); 126.5 (C_q); 116.3 ($CH_{2,olefin}$); 67.6 ($CH_{2,benzyl}$); 63.4 (NCH_2); 50.0 (2 × CH_3); 49.6 (SCH_2); 21.1 (CH_2); 21.0 (CH_2). Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.6; H, 7.8; N, 4.7. Found: C, 58.5; H, 7.9; N, 4.3.
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20. *Synthesis of 4-vinylbenzyl-dimethylammonio pentanesulfonate* **5**: Under a nitrogen atmosphere 6.0 g of 5-bromopentane-1-sulfonate **9** (0.024 mol, 1 equiv) are dissolved in 60 ml of ethanol/water (1:1) and cooled to 273 K. 3.87 g of 4-vinylbenzyl-*N*,*N*-dimethylamine **8** (0.024 mol, 1.0 equiv) are added in one portion. The reaction mixture is heated to 318 K for 18 h, then the solvent is removed. The product is washed with acetonitrile to give 7.19 g (0.019 mol, 81%) of **5** as a colorless powder. ^{1}H NMR (300 MHz, D_2O): 7.76 (m, 4H, CH_{aromat}); 6.95 (dd, 1H, ^3J = 11.0 and 17.7 Hz, CH_{olefin}); 6.09 (d, 1H, ^3J = 17.7 Hz, CH_{trans}); 5.56 (d, 1H, ^3J = 11.0 Hz, CH_{cis}); 4.72 (s, 2H, $CH_{2,benzyl}$); 3.53 (m, 2H, NCH_2); 3.26 (s, 6H, 2 × CH_3); 3.03 (m, 2H, SCH_2); 2.14 (m, 2H, NCH_2CH_2); 1.97 (m, 2H, SCH_2CH_2); 1.70 (m, 2H, CH_2). ^{13}C NMR (75 MHz,

D_2O): 139.8 (C_q); 135.7 (CH_{olefin}); 133.2 ($2 \times CH_{aromat}$); 126.7 ($2 \times CH_{aromat}$); 126.5 (C_q); 116.3 ($CH_{2,olefin}$); 67.6 ($CH_{2,benzyl}$); 63.4 (NCH_2); 50.0 ($2 \times CH_3$); 49.6 (SCH_2); 21.1 (CH_2); 21.0 (CH_2). Anal. Calcd for $C_{16}H_{25}BrNNaO_3S$: C, 46.4; H, 6.1; N, 3.4. Found: C, 47.6; H, 5.8; N, 3.1.

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