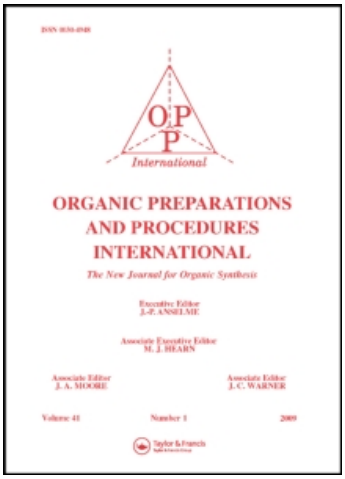

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CONVENIENT PREPARATION OF A NEW ZWITTERIONIC TOSYLATE

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CONVENIENT PREPARATION OF A NEW ZWITTERIONIC TOSYLATE

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(07/08/03)

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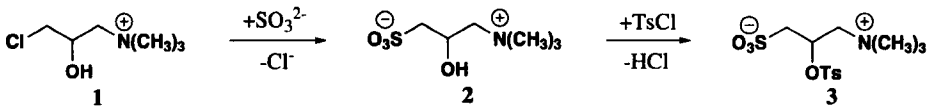
In the context of our studies with water soluble and amphiphilic phosphines,[1] we undertook the synthesis of a new asymmetric and zwitterionic tosylate because it is an attractive compound for the preparation of new functionalized phosphines. The goal was to obtain an asymmetric tosylate that contains two ionic groups of different charge in the same molecule. This new compound could be an excellent synthon to prepare asymmetric water soluble ligands[2] that can be useful in asymmetric catalysis.[3]

Thus, racemic (±)(3-chloro-2-hydroxypropyl)trimethylammonium chloride (**1**) was chosen as a starting compound because pure enantiomers are accessible and inexpensive, and an anionic group can easily be introduced. Compound **1** is mainly used in the preparation of partially cationized derivatives of polymers such as cellulose and starch.[4] The enantiomeric form (S)-(-)-(3-chloro-2-hydroxypropyl)trimethylammonium chloride has been used in the resolution of racemic bis-β-naphthol compounds[5] and in the synthesis of carnitine.[6] However, as far as we know, compound **1** has not been used in the synthesis of water-soluble or asymmetric ligands. In order to explore this possibility, we synthesized the new zwitterionic tosylate 2-tosyloxy-3-trimethylammonium-1-propanesulfonate (**3**) in two steps as shown in the *Scheme*.

The alcohol **2** has been used in the separation of proteins and in biochemical studies[7] and has been prepared *via* the reaction between 3-chloro-2-hydroxy-1-propanesulfonic acid with trimethylamine[8]. We synthesized this compound by reaction of **1** with sodium sulfite in water at reflux for 8 hours. Although recrystallization of this mixture from water/methanol did not allow complete removal of sodium chloride from **2**, this did not constitute a problem because the NMR spectrum showed that no other organic compounds were present in the mixture and sodium chloride did not interfere in the next step. Although it does not exhibit any appreciable solubility in organic solvents, a suspension of the zwitterionic alcohol **2** in tetrahydrofuran reacted with tosyl chloride after addition of an aqueous solution of NaOH, as shown in the *Scheme*. This method led to an 85% yield of the zwitterionic tosylate **3**, which is more soluble in organic solvents than **2** and can be recrystallized in methanol. It was characterized by NMR and IR data. As expected,



1 2 3

its NMR spectrum shows a shift of signals of C2 and the hydrogen atom bound to this atom compared to their positions in **2**.

This work shows that it is possible to prepare zwitterionic tosylates from zwitterionic alcohols by means of the reaction with tosyl chloride although the ionic alcohol is virtually insoluble in organic solvents.

EXPERIMENTAL SECTION

All reactions were performed under nitrogen by standard Schlenk tube techniques. The NMR spectra were recorded by the *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona* on a Bruker AC250 instrument. All chemical shifts are reported in ppm and are referenced with respect to residual protons in the solvents for ^{1}H spectra and to solvent signals for ^{13}C spectra. Infrared spectra were recorded on a Perkin-Elmer FT-2000. Elemental analyses were determined on a Carlo Erba CHN EA-1108 by the *Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona.*

(±) 2-Hydroxy-3-trimethylammonium-1-propanesulfonate (2).- To a solution of (±) (3-chloro-2-hydroxypropyl)trimethylammonium chloride (22.8 g, 0.12 mol) in water (50 mL), was added dropwise a solution of sodium sulphite (15.5 g, 0.12 mol) in water (75 mL) at room temperature with stirring. Then, water (50 mL) was added and the mixture was heated to reflux for 8 hrs. Next, this solution was evaporated to dryness in vacuum with heating (50-60°C). The white solid which was obtained was dissolved in the minimum quantity of hot water (40-50 mL), and methanol was added (400-500 mL) until a white solid crystallized. The mixture was cooled at 4°C for 6-8 hours and the solid was collected and dried under vacuum to yield 36.6 g of a mixture of **2** and NaCl (59% purity on the basis of elemental analysis, which represents a chemical yield of 91%).

IR (KBr): 1204(s) and 1171(s) cm^{-1} (n_{S-O}, SO_3^-). ^{1}H NMR (D_2O): δ 3.36 (b, CH_2S, 2H), 3.43 (s, $N(CH_3)_3$, 9H), 3.77 (b, CH_2N, 2H), 4.85 (b, CH, 1H). $^{13}C\{^{1}H\}$ NMR (D_2O): δ 54.9 ($N(CH_3)_3$), 55.5 (CH_2S), 63.5 (CH), 69.9 (CH_2N).

(±) 2-Tosyloxy-3-trimethylammonium-1-propanesulphonate (3).- Tosyl chloride (10.6 g, 0.055 mol) was added to a stirred suspension of **2** (33.9 g of the mixture of **2** and NaCl obtained above, 0.1 mol) in tetrahydrofuran and the resulting mixture was cooled to 15°C. Then, a solution of 5N NaOH (30 mL) was added dropwise over 20 min. under continuous stirring. Next, a second portion of tosyl chloride was added (10.6 g, 0.055 mol) and NaOH 5N (30 mL) was added as described above. At this point, all insoluble solids were dissolved and two liquid phases were formed. This mixture was stirred for 3h below 15°C and the pH was maintained between neutral or slightly basic by addition of small quantities of the 5N sodium hydroxide solution. The resulting solution was evaporated to dryness under vacuum and a white solid was obtained. This solid was dissolved in hot methanol (200 mL), filtered hot and under suction to remove NaCl and

allowed to cool to room temperature. The solid which crystallized was collected and dried under vacuum to yield 30.2 g (85%) of white crystalline solid, mp. 245°C (dec.). IR (KBr): 1209(s) and 1171(s) cm^{-1} (ν_{S-O}, SO_3^-). ^1H NMR (D_2O): δ 2.25 (s, CH_3-C_{aryl}), 2.83 (b, CH_2S, 2H), 3.00 (s, $N(CH_3)_3$, 9H), 3.76 (b, CH_2N, 2H), 5.22 (b, CH, 1H), 7.33 (d, J = 8.1 Hz, Ph), 7.70 (d, J = 8.4 Hz, Ph). $^{13}C\{^1H\}$ NMR (D_2O): δ 21.8 (CH_3-C_{aryl}), 55.0 ($N(CH_3)_3$), 68.8 (CH_2N), 73.4 (CH), 52.9 (CH_2S), 128.9/131.6/132.0/148.8 (Ph).

Anal. Calcd. for $C_{13}H_{21}NO_6S_2$: C, 44.43; H, 6.02; N, 3.99; S, 18.25. Found: C, 44.41; H, 5.73; N, 3.88; S, 18.00.

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