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Hydroxyethylation of Tiron with Ethylene Oxide

by P. Szczeciński

Warsaw University of Technology, Faculty of Chemistry,
Noakowskiego 3, 00-664 Warszawa, Poland
E-mail: przemsz@ch.pw.edu.pl

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An efficient method for the preparation of disodium 4,5-bis(2-hydroxyethoxy)-1,3-benzenedisulfonate in reaction between Tiron (disodium 4,5-dihydroxy-1,3-benzenedisulfonate) and ethylene oxide under mild conditions is described. The influence on the reaction of the molar ratio of reagents used, temperature and different divalent metal salts as catalysts, is discussed.

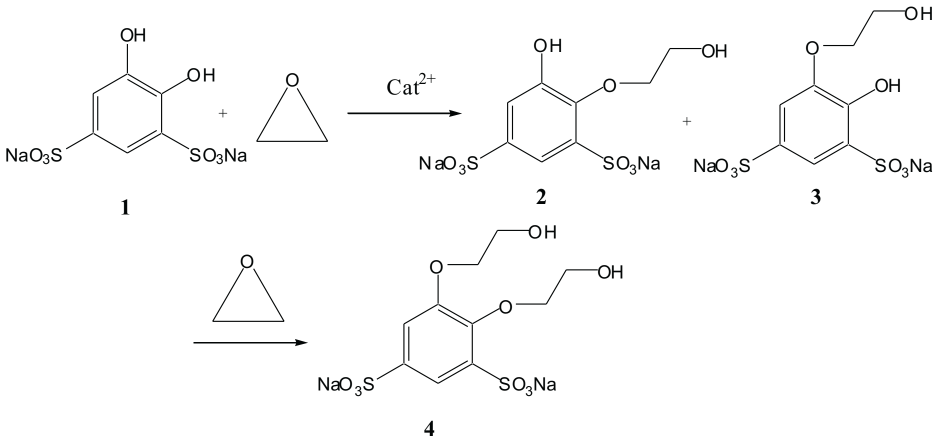
Key words: ethylene oxide, Tiron, hydroxyethylation of phenols

A survey of the methods of hydroxyethylation of phenols revealed that most frequently 2-halogenoethanols [1–7], ethylene carbonate [8] or ethylene oxide [9–15] were used as hydroxyethylating agents. The reactions were performed at elevated temperatures and, in the case of the last reactant, they often required the use of high pressure. Our goal was to adapt a procedure, to prepare bis-hydroxyethylated derivative of Tiron not contaminated with poly-ethoxylated by-products in reaction with ethylene oxide under mild conditions. This compound is interesting because, taking into account its functional groups, it could be used in syntheses of water soluble polyesters. We paid our attention to the method described in [15], in which 1,2-bis(2-hydroxyethoxy)benzene was obtained from catechol and ethylene oxide in a water solution at room temperature and with the use of calcium chloride catalyst. The pilot experiment indicated that in the conditions applied for catechol, **1** reacts much slower and that substantial amount of the products of ethylene oxide hydrolysis and polymerization is formed. A gradual precipitation of water insoluble calcium salt of **3** was also observed (see Scheme 1). Therefore, we decided to optimise the reaction conditions to obtain the highest possible reaction yield and to assure satisfying purity of the product. It was also interesting to check if other divalent metal salts may be used as catalysts and if the method can be applied to hydroxyethylation of other dihydroxybenzene derivatives.

RESULTS AND DISCUSSION

The course of the reaction is:

Scheme 1



To find the optimal proportions of reactants several experiments in a few grams scale at room temperature have been carried out, in which different molar ratios of ethylene oxide and/or calcium chloride *vs.* **1** have been used. The progress of the process was monitored by ^{1}H NMR spectra. The integral intensities of appropriate aromatic signals were used for the determination of quantitative composition of reacting mixture. From obtained results the following conclusions can be drawn: The volume of the reaction mixture is determined mainly by solubility of **1**; almost saturated solutions have been used in all experiments. The higher molar ethylene oxide/**1** or calcium chloride/**1** ratios the higher the reaction rate. On the other hand, a large excess of ethylene oxide leads to the formation of substantial amount of ethylene glycol and poly-ethoxyalcohols as by-products, causing the separation and purification of **4** more difficult. Similarly, high calcium chloride/**1** ratio is undesired as it intensifies the formation of calcium salt of **3**. Even at the largest excesses of both ethylene oxide and calcium chloride used, it has taken nine days to reach full conversion of **1**.

Because the time of the reaction was unacceptable long, it was decided to perform this process at elevated temperature. At 50°C the conversion of **1** was completed after 24 h and the inside pressure was still low enough to use a glass vessel. All other observations were very similar to those drawn from room temperature experiments. On the basis of the investigations described above, optimal reaction parameters have been chosen. The elaborated procedure (see Experimental) was proved to be efficient for the synthesis of **4** on laboratory scale.

Another goal was to investigate the catalytic properties of calcium salts other than chloride as well as salts of other divalent metals. The following salts have been tested: calcium bromide, iodide, acetate and nitrate, strontium, magnesium and barium chlorides, magnesium sulfate and barium nitrate. Both barium salts appeared to be useless, as they form with compound **1** salts insoluble in water, immediately after mixing. Applying a molar equivalent of different salts instead of calcium chloride, several experiments were performed following procedure described for preparation of **4** (see Experimental). The mixtures after reaction were analyzed by ^{1}H NMR to determine the molar percentage of compound **4**. Magnesium sulfate and calcium nitrate were found to be poor catalysts. In the case of the former salt, the reaction mixture comprised only 29% of compound **4** and 18% of unreacted substrate **1**. In the case of calcium nitrate the respective values were 13% and 37%. All other salts investigated gave at least as good results as that for calcium chloride.

Finally, the procedure has been checked for hydroxyethylation of other phenol derivatives. It was successfully applied for preparation of disodium 4,6-bis(2-hydroxyethoxy)-1,3-benzenedisulfonate and 2-(2-hydroxyethoxy)-5-sulfobenzoic acid. Unexpectedly, hydroxyethylation of 2,5-dihydroxybenzoic acid gave only mono 5-substituted product. Prolongation of the reaction time or/and rising the temperature as well as changing of the pH of the reaction mixture led to an oily, difficult to separate mixture of compounds, whose proton NMR spectrum showed the presence of several -OCH_2CH_2- groups. The reaction between Tiron and propylene oxide has been also carried out. Though it was slower, its course was identical as in the case when ethylene oxide was used. Proton NMR data of above mentioned products are given in Experimental.

EXPERIMENTAL

All NMR spectra were recorded in D_2O (50 mg/ml) solutions using a Varian Gemini 2000 spectrometer operating at 4.7 T. Sodium 3-(trimethylsilyl)propane sulfonate was used as an internal chemical shift reference for proton and carbon spectra (δ_{CH_3} = 0 ppm).

Disodium 4,5-bis(2-hydroxyethoxy)benzene-1,3-disulfonate (4). The solution of 100 g (0.25 mol) of compound **1** and 4 g (0.035 mol) of $CaCl_2$ in 320 mL of water was placed in a 2 l round-bottomed, one neck, flask and cooled to 2℃. Ethylene oxide (200 ml, 176 g, 4.0 mol) cooled to *ca.* –10°C was poured into the flask and the neck was tightly closed. The flask was placed in a thermostated oil bath and heated at 50℃ for 24 h. Then, after being cooled in icy water, it was opened and equipped with a distillation set containing a gas trap cooled with solid carbon dioxide. The mixture was heated in a water bath at 60℃ and the excess of ethylene oxide was distilled off. The remaining content of the flask was filtered. The insoluble in water, mono-hydroxyethylated product was washed with a small amount of water and dried in air at 90℃. Yield – 17.8 g. The filtrate was evaporated to dryness using a rotary evaporator (90°C, 30 mmHg). The residue, thick oil, was diluted with 100 ml of methanol, warmed up to the boiling point, cooled and left for 3 h at room temperature. White crystals were filtered, washed with 10 ml of methanol and dried in air at 90℃ for 10 h and then under reduced pressure (0.3 mmHg) at 170°C for 3 h. Yield 89 g (70%). The combined methanol solutions were diluted with 300 ml of acetone and left for the time needed for the separated oil to solidify (3 h). The second batch of the product was filtered, washed twice with 15 ml of methanol and dried as above. White crystals (11 g) with a pale violet shadow were obtained. The filtrate, after removing the solvents (90°C, 30 mmHg), gave 30 g of oil composed mainly of ethylene glycol.

The product **4** is very good soluble in water and DMSO. It is insoluble in alcohols, ethers, acetone and haloalkanes. A sample was crystallized from small amount of water. Anal.: for $C_{10}H_{12}Na_2O_{10}S_2$: calcd. C, 29.85%; H, 3.01%. Found: C, 29.85%, H, 2.94%; ^{1}H NMR (pH 8.4): 7.84 (d, 1H, H_2, $J_{H2,H6}$ = 2.0 Hz), 7.64 (d, 1H, H_6), 4.40 (m, 2H), 4.27 (m, 2H), 4.00 (m, 2H), 3.94 (m, 2H). Aliphatic proton signals are triplet-like multiplets of intensity of 2H each. Decouplig experiment revealed that first and last of them form one and second and third the other AA′BB′ spin system; ^{13}C NMR (pH 8.4): 154.78, 150.13, 140.62, 138.70, 120.11, 117.27, 78.11, 73.29, 63.90, 62.71.

4-Hydroxy-5-(2-hydroxyethoxy)benzene-1,3-disulfonate (3). The synthesis was carried out in a few grams scale using 1 mol of $CaCl_2$ per 1 mol of **1**. All other conditions were identical as those for synthesis of **4**. The solid precipitated during reaction, after being filtered, washed with water and methanol, appeared to be a mono hydroxyethylated derivative of Tiron, only slightly contaminated with ethylene glycol. The liquid part of the reaction mixture comprised mainly ethylene glycol and a trace of **4**. Obtained product contains calcium ions but its exact cationic composition has not been investigated. On the basis of proton coupled ^{13}C NMR spectrum the product was proved to be a salt of 4-hydroxy-5-(2-hydroxyethyl)benzene-1,3-disulfonic acid. It is soluble in water at low pH. ^{1}H NMR (pH 1.4): 7.77 (d, 1H, H_2, $J_{H2,H6}$ = 2.2 Hz), 4.26, 4.00 (two triplet-like multiplets of intensity of 2H each); ^{13}C NMR (pH 1.4): 149.91, 148.83, 136.14, 130.64, 120.10. 115.37, 73.27, 62.64.

Disodium 4,6-bis(2-hydroxyethoxy)-1,3-benzenedisulfonate. ^{1}H NMR (pH 9.5): 8.20 (s, 1H, H_2), 6.85 (s, 1H, H_5), 4.33, 3.98 (triplet-like multiplets of intensity of 4H each); ^{13}C NMR (pH 9.5): 162.39, 131.73, 124.80, 102.60, 73.86, 62.70.

Sodium salt of 2-(2-hydroxyethoxy)-5-sulfobenzoic acid. ^{1}H NMR: 7.97 (d, 1H, H_6, $J_{H4,H6}$ = 2.4 Hz), 7.23 (dd, 1H, H_4, $J_{H4,H3}$ = 8.9 Hz), 7.00 (d, 1H, H_3), 4.05, 3.72 (triplet-like multiplets of intensity of 2H each); ^{13}C NMR: 170.04, 160.41, 135.98, 132.41, 129.81, 120.54, 114.83, 71.48, 60.62.

5-Hydroxy-2-(2-hydroxyethoxy)benzoic acid. ^{1}H NMR (acetone-d_6): 7.36 (d, 1H, H_6, $J_{H4,H6}$ = 3.2 Hz), 7.17 (dd, 1H, H_4, $J_{H4,H3}$ = 9.0 Hz), 6.88 (d, 1H, H_3).

Disodium 4,5-bis(2-hydroxypropoxy)-1,3-disulfonate. ^{1}H NMR: 7.65 (d, 1H, H_2, $J_{H2,H6}$ = 2.2 Hz), 7.44 (d, 1H, H_6), 4.3–3.8 (m, 6H, CH_2+CH), 1.12, 1.04, 1.03 (doublets of intensities 6:3:3, respectively, CH_3 of two diastereomers).

SUMMARY

The method described allows to hydroxyethylate Tiron under mild conditions giving a product of high purity and with a good yield. The formation of polyethoxylated products has not been observed in any of the cases investigated. A part of the results was patented [16].

REFERENCES

1. Bermudez J.L. Campo C., Sinisterra J.V. and Llama E.F., *Tetrahedron Lett*., **38**, 4137 (1997).
2. Tsotinis A., Calogeropoulou Th., Koufaki M., Souli Ch., Balzarini J., DeClercq E. and Makriyannis A., *J. Med. Chem*., **39**, 3418 (1996).
3. Kawashima Y., Kameo K., Kato M., Hasegawa M., Tomisawa K., Hatayama K., Hirono S. and Morigochi I., *Chem. Pharm. Bull*., **40**, 774 (1992).
4. Smith R.A., *J. Am. Chem. Soc*., **62**, 994 (1940).
5. Halasz A., *Bull. Soc. Chim. Franc*., **8**, 170 (1941).
6. Roithner E., *Monatsh. Chem*., **15**, 674 (1894).
7. Bentley W.H., Haworth E. and Perkin W.H., *J. Chem. Soc*., **69**, 164 (1896).
8. Yoshino T., Inaba S. and Ishido Y., *Bull. Chem. Soc. Jpn*., **46**, 553 (1973).
9. Patat F., Cremer E. and Bobleter O., *J. Polymer Sci*., **12**, 489 (1954).
10. Patat F., Cremer E. and Bobleter O., *Monatsh. Chem*., **83**, 322 (1952).
11. Bobleter O., *Monatsh. Chem*., **87**, 483 (1956).
12. Becker B. and Barthell E., *Monatsh. Chem*., **77**, 80 (1947).
13. Eichinger P.C.H., Bowie J.H. and Hayes R.N., *J. Am. Chem. Soc*., **111**, 4224 (1989).
14. Nakayama H. and Yamashita K., DE Patent No. 4 110 363 A1. *C.A*., **116**, 140215n.
15. Parsons D.G., *J. Chem. Soc., Perkin Trans. 1*, **6**, 1193 (1984).
16. Pevere V., Szczeciński P., Desmurs J.-R., Galliot J.-C., Lartigue-Peyrov F., PCT Int. Appl. WO 9954,292 (1999); *C.A*., **131**, 300820w, (1999).