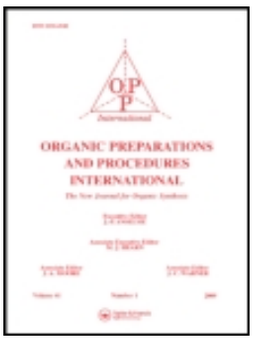

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A Scalable and Efficient Synthesis of 3-Chloro-1,2-propanediol

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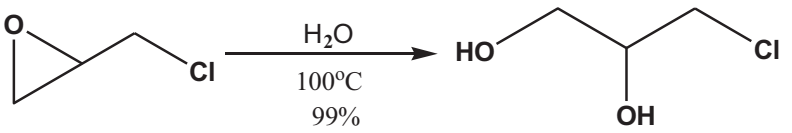
In recent years, environment-friendly and cost effective chemical processes have been and continue to be developed both academically and industrially.[1,2] In this context, the development of simple and efficient synthetic methods that reduce the use of reagents and preferably employ no solvent has attracted much interest.

3-Chloro-1,2-propanediol is an important building block in organic synthesis,[3] and one of its stereoisomers has been used in the synthesis of *linezolid*, a 1,3-oxazolidinone used against antibiotic-resistant *gram*-positive bacteria.[4] This paper reports an eco-friendly, scalable and highly efficient method for the conversion epichlorohydrin to 3-chloro-1,2-propanediol. This procedure involving the addition of water only avoids the use of solvents and acidic or basic conditions to afford 3-chloro-1,2-propanediol in nearly quantitative yield (99%) without the need of purification; no waste is generated.[5] An efficient large scale and optimized preparation is also described (*Scheme 1*).



Scheme 1

The reaction was optimized using 100 mL of epichlorohydrin under various conditions by changing the quantity of water, reaction times, and temperatures, which are critical parameters to obtain the desired product. The amount of water was very important for the isolation step because the removal of a large amount of water (8–15 mol) by distillation under reduced pressure was difficult, requiring a temperature of 100°C and long distillation times (~6 hrs). Distillation under these conditions

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afforded 3-chloro-1,2-propanediol as a yellow oil containing decomposition products. Optimal conditions and yields were obtained using 2.2 molar equivalents of water at 80°C for 3 h under reduced pressure (0.5 mm Hg).

In conclusion, a short, simple, green and an inexpensive industrially practical process for the preparation of 3-chloro-1,2-propanediol was developed. In which the use of solvents, of acidic or basic conditions is avoided. The only reagent used is water and no waste is generated.

Experimental Section

^{1}H NMR spectra were determined in DMSO using a Bruker AC 400 spectrometer at operating at 400 MHz, using TMS as an internal standard. Splitting patterns are as follows: s, singlet; d, duplet; m, multiplet; sl, broad signal. The ^{13}C NMR spectrum was obtained using the same apparatus described above at 100 MHz. Epichlorohydrin was purchased from Sigma-Aldrich and was utilized as the chromatographic standard in TLC analysis. The progress of the reactions was monitored by TLC on 2.0 cm × 4.0 cm aluminum sheets pre-coated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm, eluent: hexane-ethyl acetate (1:1). The chromatograms were visualized using a solution 10% of phosphomolybdic acid in ethanol. Distillation using a vacuum pump (E2M8, EDWARDS, Brazil).

Procedure

A two-phase mixture of epichlorohydrin (473.2 g, 5.11 mol) and water (110.5 g, 6.13 mol) in a 1 L, three-necked flask immersed in an oil bath, equipped with a magnetic stir bar, reflux condenser and a thermometer was stirred at 100°C for 20 h; the progress of the reaction was monitored by TLC (hexane-ethyl acetate 1:1). After this period, an additional amount of water was added (92.0 g, 5.11 mol) and stirring was continued at 100°C for an additional 4 h. Excess water (47 mL) was removed by distillation under reduced pressure (0.5 mm Hg) at 80°C to leave pure (by tlc) 3-chloro-1,2-propanediol (557.0 g, 99%) as a colorless oil.

3-Chloro-1,2-propanediol, colorless oil

^{1}H NMR (400 MHz, DMSO-d_6): δ 5.10 (1H, d, CHO<u>H</u>, exchangeable with D_2O); 4.70 (1H, t, CH_2O<u>H</u>, exchangeable with D_2O); 3.67–3.61 (2H, m, C<u>H</u>$_2$Cl); 3.53–3.48 (1H, m, C<u>H</u>OH); 3.43–3.34 (2H, m, C<u>H</u>$_2$OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 71.1 (CHOH), 62.5 (CH_2OH), 47.0 (CH_2Cl).

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