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# Notes

## Details Concerning the Chloromethylation of Soluble High Molecular Weight Polystyrene Using Dimethoxymethane, Thionyl Chloride, and a Lewis Acid: A Full Analysis

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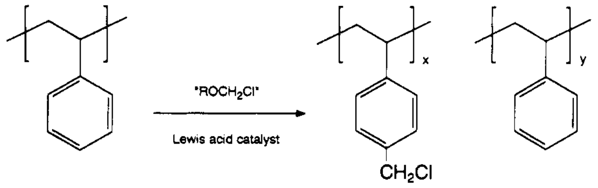
### Introduction

The chloromethylation of polystyrene is a valuable procedure that was established nearly four decades ago by Pepper, Paisley, and Young (eq 1).[1] Chloromethylated polystyrene is the starting point for the synthesis of polymer-bound reagents for organic synthesis,[2] ion-exchange resins,[3] and the very famous Merrifield peptide synthesis.[4] Several variations for the chloromethylation of polystyrene have been developed.[5] The primary driving force behind most procedures has been to replace the very toxic and highly volatile chloromethyl methyl ether (CME).[6] Most chloromethylation procedures have focused on either cross-linked polystyrene or low molecular weight soluble polystyrene.



(1)

$(x/1.00)100 = \%$ modification
$x + y = 1.00$

The purpose of this work is threefold. In ref 5 of this paper we have supplied a complete and up-to-date review of the chloromethylation procedures available to the polymer chemist. The second aspect to this paper is to present full details and characterize a practical chloromethylation of *soluble high molecular weight polystyrene* using safe and commercially available reagents. The third and more minor aspect, but certainly important, is to provide a safe chloromethylating procedure which will be easily identified in a literature search by workers in the field.

### Results and Discussion

To start the chloromethylation procedure polystyrene is dissolved in dimethoxymethane (~4 h). Treatment of the dimethoxymethane/polystyrene solution with thionyl chloride cleanly afforded CME and dimethyl sulfite in ~1 h. The products were characterized by both proton and carbon NMR spectroscopy. There was no spectroscopic evidence for the accumulation of (MeO)SOCl in the reaction, only formation of dimethyl sulfite.[7] Any water or methanol in the dimethoxymethane was found to react very quickly with the thionyl chloride to afford gaseous products (i.e., $SO_2$ and HCl) or dimethyl sulfite. At this point in the reaction CME has been generated cleanly and is now ready for addition of the Lewis acid catalyst. Either a zinc(II) chloride (ether) or tin(IV) chloride (dichloromethane) solution was used to introduce the appropriate Lewis acid catalyst.

We have contrasted the performance of the zinc(II) and tin(IV) Lewis acid catalysts in Figure 1. From the plot it is evident that the tin(IV) catalyst starts out very active and then after 24 h tends to parallel the zinc(II) catalyst in performance. The zinc(II) catalyst performs equally well at 30 and 40 °C, with the latter being more practical for higher degrees of chloromethylation.

The chloromethylated polymers remained tractable and colorless materials. There was a distinct increase in viscosity of polymer solutions (same concentration) concomitant with modification values over 15–20%. After chloromethylation values of 8% or greater, we did not observe a $T_g$ for the polymers at or above ambient temperature. It is also noteworthy to mention that using the tin catalyst at 40 °C resulted in gelation within 1 h after addition of the catalyst. This polymer was not characterized and was assumed to be significantly cross-linked.[8]

The chloromethylated polymers were characterized by carbon NMR spectroscopy. Using the procedure of Ford and Yacoub,[9] we searched for $CH_2OH$ groups (a possible side product of polymer workup) and cross-linking by careful examination of the $^{13}C$ NMR spectrum for the polymeric products. No signal in the $^{13}C$ NMR spectrum at $\delta$ 65.1 corresponding to the hydroxymethyl group was observed. Furthermore, FT-IR and elemental analysis (i.e., C, H, and Cl% summed to 100%) data were consistent with a hydroxy-free polymer. We also submitted chloromethylated samples for metal analysis and found no detectable amount of zinc (<22 ppm). A comparative analysis of the $^{13}C$ NMR data for the polystyrene starting material and chloromethylated samples showed a line broadening consistent with some cross-linking in the chloromethylated samples (e.g., high polystyrene, $\delta$ 40.4, half-height width = 28 Hz; chloromethylated sample, $ZnCl_2$ at 40 °C, 24 h, $\delta$ 39.2, half-height width = 37 Hz). GPC data show an increase in the polydispersion from 1.53 to 1.72 (34% modification). The $M_n$ showed a slight decrease (~4%) with an increase in $M_w$.

We attempted to use the above chloromethylation conditions on *tert*-butylbenzene. Using the tin(IV) Lewis acid catalyst and employing heat (~50 °C) for several days afforded no detectable amount of chloromethylation. We had hoped this experiment would permit us to determine the selectivity (or lack of selectivity) for para substitution. It is somewhat puzzling why the procedure does not work on the benzene derivative. The observation that indeed CME is generated in the above procedure leads us to believe the para selectivity is similar to that of previous chloromethylation procedures.

### Concluding Remarks

A complete procedure for the chloromethylation of *soluble high molecular weight polystyrene* has been described as well as complete characterization of the

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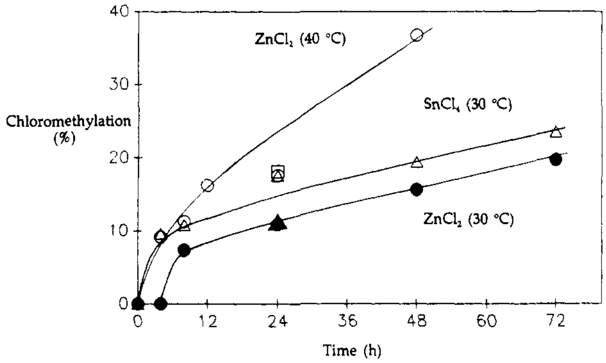

**Figure 1.** Plot showing chloromethylation versus reaction time. Reaction conditions are labeled with the Lewis acid catalyst and reaction temperature employed. For details concerning reactant quantities, see the Experimental Section. The box at $t$ = 24 h represents a chloromethylation experiment with a 100% increase in the $ZnCl_2$ (40 °C) catalyst (i.e., 0.08 mmol/g of polymer). The filled triangle at $t$ = 24 h is for a chloromethylation experiment with a 100% increase in both dimethoxymethane and thionyl chloride.

polymer products. The in situ generation of CME is a safe and very efficient alternative to handling CME directly. This procedure uses inexpensive and commercially available reagents which do not require any special handling or purification techniques. The soluble chloromethylated high polymers were shown to be slightly cross-linked but remained tractable and colorless up to 37% modification. Furthermore, the chloromethylated polymers produced through this procedure do not contain polymer-bound hydroxymethyl groups.

## Experimental Section

**General Procedures.** All manipulations of compounds and solvents were carried out by using standard Schlenk techniques. The high molecular weight polystyrene ($M_n$ = 280 000 as indicated by Aldrich), dimethoxymethane, thionyl chloride, and tin(IV) chloride (1.0 M in $CH_2Cl_2$) were obtained from Aldrich and used as received. The zinc(II) chloride solution (0.94 M in diethyl ether) was prepared by the usual method,[10] and the molarity was determined gravimetrically. The $^1H$ NMR spectra were obtained at 270 MHz using a JEOL 270 FT-NMR spectrometer and $Me_4Si$ as the internal standard. The $^{13}C$ NMR spectra were obtained on a JEOL 270 FT-NMR (67.8 MHz for carbon) with the $CDCl_3$ resonance assigned to 77.00 ppm. Polymer analyses were performed with Perkin-Elmer TGA7 and DSC7 equipment. Elemental analyses were performed at Atlantic Microlab Inc., Norcross, GA, and Galbraith Laboratories, Inc., Knoxville, TN.

**General Chloromethylation Procedure.** A Schlenk flask was charged with a stir bar and polystyrene (5.00 g). The flask was flushed with nitrogen, and dimethoxymethane (25 mL, 0.28 mol) was added. After the polystyrene was completely dissolved (~4 h), the mixture was cooled to 0 °C, the flask was equipped with a mineral oil bubbler, and then thionyl chloride (9.2 mL, 0.13 mol) was added (*Caution*: choromethyl methyl ether, a potent carcinogen,[6] is generated in situ at this point). The reaction was allowed to warm and stir at ambient temperature for 45 min and then cooled to 0 °C. The appropriate Lewis acid catalyst was added (0.04 mmol/g of polymer) and then the mixture was placed in an oil bath already at the desired reaction temperature. Aliquots (2 mL) of the reaction mixture were removed and precipitated into methanol (~10 mL). The polymer was filtered, redissolved in $CHCl_3$, and reprecipitated into methanol (2 times). The filtrates were all combined and disposed of as chlorinated waste. The purified polymer was then dried under vacuum at 60 °C and analyzed for chlorine to determine the extent of chloromethylation.

**Polymer Analysis by DSC.** The starting high polystyrene was subjected to DSC analysis (nitrogen atmosphere, ramp 10 °C/min, hermetically sealed aluminum pans). We observed the $T_g$ at 108 °C and $T_m$ at 250 °C (lit. from Aldrich: $T_g$ = 100 °C and $T_m$ = 240 °C). Analysis of various chloromethylated samples by DSC at temperatures ranging from −60 to +220 °C did not display a measurable $T_g$. However, in some samples of lower chloromethylation (<8%) a *very weak* $T_g$ (~110 °C) was observed.

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## References and Notes

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(6) For a reference delinating some of the toxic effects of CME, see: Weiss, W. *J. Occup. Med.* **1976**, *18*, 194.

(7) Both proton and carbon NMR data showed only formation of CME and $(MeO)_2SO$. This was confirmed by comparison to authentic samples of both compounds.

(8) Formation of insoluble chloromethylated polymer (i.e., cross-linked) has been a longstanding problem with chloromethylation procedures, especially so where high percent modifications are sought (see ref 1).

(9) Ford, W. T.; Yacoub, S. A. *J. Org. Chem.* **1981**, *46*, 819.

(10) Introduction of the $ZnCl_2$ as an ether solution was found to be very advantageous, and in fact addition of solid $ZnCl_2$ caused local gelling of the solution. We made our $ZnCl_2$ solution from predried and fused $ZnCl_2$ and distilled ether (over $CaH_2$ and under $N_2$). Even with these precautions we found insoluble material [presumably $Zn(OH)_2$] persisted after 24 h of stirring. The insoluble material was removed by filtration through Celite.

**Registry No.** $CH_2(OMe)_2$, 109-87-5; $SOCl_2$, 7719-09-7; $SnCl_4$, 7646-78-8; $ZnCl_2$, 7646-85-7; polystyrene, 9003-53-6.