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Procedure for the Rapid Synthesis of the Monomer 1,4-Bis(chloromethyl)-2-(2-ethylhexyloxy)-5methoxybenzene

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Procedure for the Rapid Synthesis of the Monomer 1,4-Bis(chloromethyl)-2-(2-ethylhexyloxy)-5-methoxybenzene

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Abstract: The alkylation of 4-methoxyphenol with 2-ethylhexyl bromide was accelerated by using potassium *tert*-butoxide in dimethylformamide. Subsequent chloromethylation occurred quickly using acetic acid as a cosolvent to give the poly[(2-(2-ethylhexyloxy)-5-methoxy-*p*-phenylene)vinylene] (MEH-PPV) monomer in 61% overall yield on a 2-mol scale.

Keywords: Chloromethylation, conducting polymer, 2-ethylhexyl bromide, MEH-PPV, poly(*p*-phenylvinylene), potassium *tert*-butoxide

Conducting polymers are a new class of semiconducting materials useful for creating optoelectronic devices such as light-emitting diodes^[1,2] and photovoltaic cells.^[3,4] Several projects required a steady supply of the conducting polymer poly[(2-(2-ethylhexyloxy)-5-methoxy-*p*-phenylene)-vinylene] (MEH-PPV)^[5,6] (Fig. 1), and commercial sources were not consistent in regards to price, quality, and molecular weight distribution. Studies regarding our preparation of MEH-PPV will be described elsewhere. The preparation of the MEH-PPV monomer, **2**, has been reported.^[5-9] Here we show a method to prepare **2** quickly and with excellent purity, (Scheme 1).

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Figure 1. MEH-PPV.

The typical conditions for the alkylation of 4-methoxyphenol with 2-ethylhexyl bromide are refluxing in ethanol with potassium hydroxide as base.^[9,10] Using these conditions, the reaction took days to complete. A much faster alkylation took place by using a polar, aprotic solvent and a strong, nonnucleophilic base such as N,N-dimethylformamide and potassium *tert*-butoxide. To make the reaction go to completion, a 1.75-fold excess of potassium *tert*-butoxide and 2-ethylhexyl bromide were added. In this way, the reaction went to completion in 3 h at a 2-mol scale. It is believed that a portion of the 2-ethylhexyl bromide reacts with the base, undergoing dehydrohalogenation and producing an unknown amount of 2-ethylhexene by-product. The product **1** is recovered in 97% yield from the aqueous workup and made analytically pure by reduced pressure distillation.

Typical conditions for chloromethylation include saturation of the reaction mixture with gaseous hydrogen chloride and/or multiple additions of excess paraformaldehyde and aqueous hydrochloric acid.^[11] A serious hazard of chloromethylation under these conditions is the formation of toxic bis(chloromethyl)ether (BCME).^[12,13] It was found that running the chloromethylation of **1** in a mixture of concentrated hydrochloric acid and acetic acid with only 4 equivalents of paraformaldehyde



Scheme 1. Reagents and conditions; (a) KO*t*Bu, DMF, 60 °C; and (b) (CH₂O), conc. HCl, HOAc, 80 °C.

MEH-PPV

gave the bis-chloromethylated product 2 in just 6 h at 80 °C. Although we did not analyze the reaction for BCME, it is most likely present. However, because large excesses of hydrochloric acid and paraformaldehyde were not used, the amount of BCME generated is minimized. The chloromethylation reaction is accelerated because of the acetic acid cosolvent.^[14] The reaction is a two-phase system with the upper phase consisting of the reactant/product and acetic acid. Reaction progress is easily monitored by proton nuclear magnetic resonance, taking an aliquot of the upper phase. The crude product precipitates upon cooling the reaction to room temperature but was difficult to filter in this state, so an extractive workup was necessary. Two recrystallizations from ethanol gave 2 in an analytically pure form in 63% yield. One report^[9] gave a melting point for 2 of 67-68 °C but after multiple recrystallizations of 2 from several solvents (methanol, ethanol, 2-propanol, and 1-butanol) and vacuum drying, a melting point greater than 50 °C was never observed.

EXPERIMENTAL

The melting point was collected on an electrothermal capillary meltingpoint apparatus and is not corrected. All NMR data were collected on a Bruker Avance II 300-MHz spectrometer (¹H at 300 MHz, ¹³C at 75 MHz). NMR data free induction decays (FIDs) were processed using NUTS software from Acorn NMR (Livermore, CA). All ¹H and ³¹C spectra are referenced to tetramethylsilane (TMS). The *N*,*N*-dimethylformamide, 99% (DMF), was purchased from Acros Organics and used as received. All other reagents were purchased from Sigma-Aldrich (Milwaukee) and used as received. Elemental analyses were made by Atlantic Microlab, Inc. (Norcross, GA).

Racemic 1-(2-Ethylhexyloxy)-4-methoxybenzene (1)

A 3-L, three-necked, round-bottomed flask equipped with mechanical stirrer and thermometer was charged with 248 g of 4-methoxyphenol (2 mol) and 1 L of DMF. The mixture was stirred until all the solids dissolved. In one portion, 224 g of KOtBu (2 mol, 1 equiv) was added. After 30 min, all the solids had dissolved, the mixture was a greenish colored solution, and the internal temperature was $50 \,^{\circ}$ C. An addition funnel was equipped and charged with $386 \,^{\circ}$ g of 2-ethylhexyl bromide (2 mol, 1 equiv), which was run into the reaction over $45 \,^{\circ}$ min. Solids began to precipitate shortly after the start of the addition, and the temperature

peaked at 60 °C. After 1 h, the temperature had cooled to 50 °C, and 112 g of KOtBu (1 mol, 0.5 equiv) was added to the reaction. The temperature again rose to 60 °C. The addition funnel was again charged with 193 g of 2-ethylhexyl bromide (1 mol, 0.5 equiv), which was run into the reaction over 30 min. The internal temperature reached 65 °C during the addition. After 1h, a final addition was made of 56g of KOtBu (0.5 mol, 0.25 equiv) followed by 96.5 g of 2-ethylhexyl bromide (0.5 mol, 0.25 equiv) in a similar fashion. After stirring for 3 h, the internal temperature was near rt, and thin-layer chromatography (TLC) showed all the phenol was consumed. Water (1 L) was added to the mixture, and all the solids were allowed to dissolve. The mixture was extracted three times with 1-L portions of Et₂O. The organic extracts were collected and washed once with 500 mL of H₂O followed by 500 mL of brine. The organic phase was dried over 20 g of anhydrous MgSO₄, filtered, and rotary evaporated, leaving a slightly brown liquid. The crude product was distilled at 0.1 torr, discarding all volatiles <90 °C, which contained residual 2-ethylhexyl bromide, to give the title compound (bp 115°C, 0.1 torr) as a colorless liquid (461.5 g, 97%). $\delta_{\rm H}$ (CDCl₃): 6.79 (s, 4H), 3.74 (d, J = 5.7 Hz, 2H), 3.72 (s, 3H), 1.65 (m, 1H), 1.53-1.2 (m 8H), 0.92-0.82 (m, 6H); $\delta_{\rm C}$ (CDCl₃): 153.86, 115.67, 114.83, 71.47, 55.96, 39.71, 30.77, 29.33, 24.10, 23.29, 14.29, 11.32. Elemental analysis calculated for C₁₅H₂₄O₂: C, 76.23; H, 10.24. Found: C, 76.21; H, 10.42.

Racemic 1,4-Bis(chloromethyl)-2-(2-ethylhexyloxy)-5methoxybenzene (2)

Warning! The following reaction must be conducted in a well-ventilated fume hood. Mixtures of formaldehyde and hydrochloric acid are known to generate the human carcinogen bis(chloromethyl)ether.^[12]

A 3-L, round-bottomed flask equipped with mechanical stirrer was charged with 461.5 g of 1 (1.96 mol), 891 mL of glacial HOAc, and 235.2 g of paraformaldehyde (7.84 mol, 4 equiv). The mixture was stirred while 1.1 L conc. HCl was added. An endotherm of 3 °C was observed. A heating mantle was equipped, and the mixture was heated and stirred at 80 °C. Shortly after heating, all the solids dissolved. After 6 h, virtually all the starting material had been consumed by ¹H NMR, and the heating mantle was removed. During cooling to rt, copious white solids precipitated. The mixture was extracted three times with 1.25-L portions of hexanes. The combined extracts were washed twice with 1-L portions of H₂O follow by two washings with 500-mL portions of brine. The organic phase was dried over 20 g of anhydrous MgSO₄, filtered, and rotary evaporated, leaving 630 g of a pale yellow liquid that would slowly solidify at

MEH-PPV

rt into a waxy, white solid. The crude product was kept warm and liquid and transferred to a 5-L round-bottomed flask equipped with mechanical stirrer containing 2 L EtOH. The mixture was stirred and heated until complete dissolution and then allowed to stir until the mixture reached rt. The white precipitate was filtered on a coarse porosity (145- to 175-µm) glass frit. Recrystallization again from 2 L of EtOH and drying (30 °C, 10 torr) overnight gave 403 g (1.2 mol, 63%) of the title compound as a soft, snow-white powder. Mp 45–48 °C. $\delta_{\rm H}$ (CDCl₃): 6.87 (s, 1H), 6.86 (s, 1H), 4.51 (s, 2H), 4.50 (s, 2H), 3.82 (d, J = 5.4 Hz, 2H), 3.79 (s, 3H), 1.69 (m, 1H), 1.56–1.33 (m, 4H), 1.32–1.21 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 9.7 Hz, 3H); $\delta_{\rm C}$ (CDCl₃): 151.21, 151.14, 127.29, 127.10, 114.31, 113.65, 56.56, 41.55, 41.54, 39.86, 30.87, 29.35, 24.27, 23.27, 14.29, 11.45. Elemental analysis calculated for C₁₇H₂₆Cl₂O₂: C, 61.26; H, 7.86. Found: C, 61.39; H, 7.86.

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