

Selective Reduction of 2-[(Benzoyl)oxy]benzaldehydes without Intramolecular Transesterification

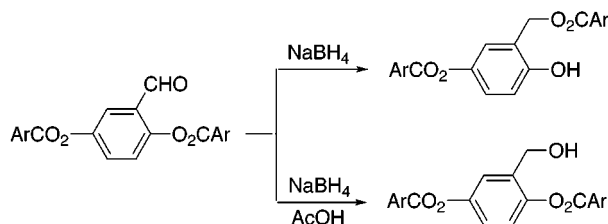
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ABSTRACT

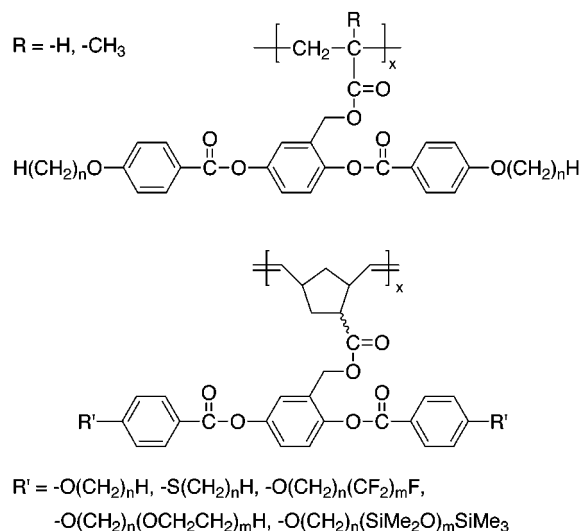


NaBH_4 reduction of 2,5-bis[(4'-(*n*-alkoxy)benzoyl)oxy]benzaldehydes produces primarily the rearranged phenol, which does not generate liquid crystalline phases when laterally attached to a polymer backbone. Rearrangement is prevented by quenching the intermediate benzyl alkoxide with a weak acid. For example, 2,5-bis[(4'-(methoxy)benzoyl)oxy]benzaldehyde is selectively reduced to 2,5-bis[(4'-(methoxy)benzoyl)oxy]benzyl alcohol with less than 5% intramolecular transesterification using 2–3 equiv of NaBH_4 in the presence of 20–30 equiv of acetic acid (1:10 $\text{NaBH}_4/\text{AcOH}$).

A new class of side-chain liquid crystalline polymers (SCLCPs) was synthesized in 1985 with the mesogens laterally attached to the polymer backbone.¹ Most laterally attached SCLCPs are based on 2,5-bis[(4'-(*n*-alkoxy)benzoyl)oxy]aryl mesogens,^{1–8} especially those with a one-carbon benzyl spacer (Scheme 1).^{3–8} Monomers with a one-carbon spacer can be synthesized from the corresponding 2,5-bis[(4'-(*n*-alkoxy)benzoyl)oxy]benzyl alcohols, which were reportedly produced by NaBH_4 reduction of 2,5-bis[(4'-(*n*-alkoxy)benzoyl)oxy]benzaldehydes.³ However, the

first articles³ reported ^1H NMR resonances that were inconsistent with expected spectral data, apparently because

Scheme 1



(1) Hessel, F.; Finkelmann, H. *Polym. Bull.* **1985**, *14*, 375–378.

(2) See, for example: (a) Keller, P.; Hardouin, F.; Mauzac, M.; Achard, M. F. *Mol. Cryst. Liq. Cryst.* **1988**, *155*, 171–178. (b) Bormuth, F. J.; Haase, W. *Liq. Cryst.* **1988**, *3*, 881–891. (c) Cherodian, A. S.; Hughes, N. J.; Richardson, R. M.; Lee, M. S. K.; Gray, G. W. *Liq. Cryst.* **1993**, *14*, 1667–1682.

(3) Zhou, Q. F.; Li, H. M.; Feng, X. D. *Macromolecules* **1987**, *20*, 233–234.

(4) Pugh, C.; Shrock, R. R. *Macromolecules* **1992**, *25*, 6593–6604.

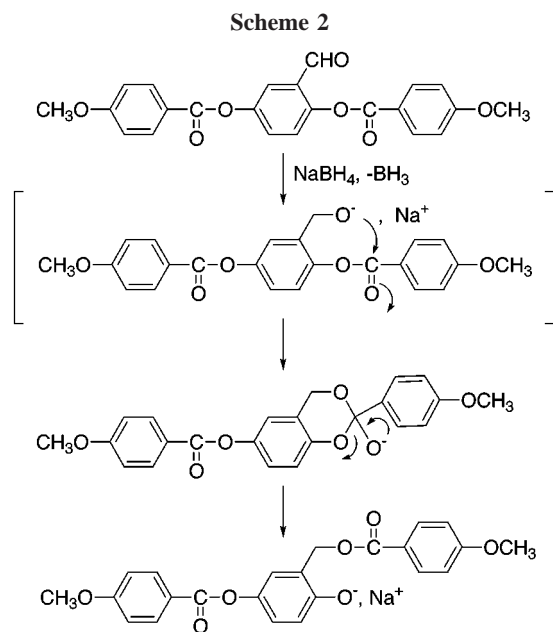
(5) Arehart, S. V.; Pugh, C. *J. Am. Chem. Soc.* **1997**, *119*, 3027–3037.

(6) Pugh, C.; Bae, J.-Y.; Dharia, J.; Ge, J. J.; Cheng, S. Z. D. *Macromolecules* **1998**, *31*, 5188–5200.

(7) Pugh, C.; Malinak, S. M.; Rim, J. B. *ACS Polym. Prepr.* **1999**, *40* (2), 544–545.

(8) Pugh, C.; Thompson, M. J.; Mullins, R. J.; Hwang, J. H. *ACS Polym. Prepr.* **1999**, *40* (2), 536–537.

the reduction produces rearranged phenols,⁴ which do not generate liquid crystalline monomers and polymers.⁴ The rearranged phenols are evidently generated by intramolecular transesterification of the intermediate benzyl alkoxide via a six-membered endo-trig cyclic transition state,⁹ with loss of phenoxide since it is the better leaving group (Scheme 2).



Alternatively, the central aromatic ring can be functionalized with a polymerizable group through a one-carbon spacer by brominating 2,5-bis[4'-(*n*-alkoxy)benzoyloxy]toluenes at the benzylic position, followed by esterification of the resulting benzyl bromides with a carboxylate salt containing the polymerizable group.^{4,5} However, substituents on the mesogen such as siloxanes,⁶ oligo(oxyethylene)s,⁷ and thioether⁸ groups are not stable to bromination. In contrast, the benzyl alcohol route is cleaner and more widely applicable. This paper therefore investigates the possibility of quenching the intermediate benzyl alkoxide with either a proton to generate the less reactive benzyl alcohol or a polymerizable acid chloride to generate stable monomers. Since the neutral benzyl alcohol will also slowly rearrange in solution, the time required for the reduction step must be minimized using a homogeneous reaction, rather than a slower heterogeneous reduction.

With the exception of entries 1 and 12, Table 1 presents the product distribution produced by reduction of 2,5-bis[4'-(methoxy)benzoyloxy]benzaldehyde using NaBH₄ in the presence of a weak protonic acid, a strong protonic acid, and an acid chloride. The reductions were carried out in THF, with a minimum amount of DMSO required to solubilize the benzaldehyde at room temperature. In the absence of an additive (entry 1), reduction using 1 equiv of NaBH₄ is essentially quantitative (99% conversion) in 30 min, but

produces approximately 71% of the rearranged phenol in addition to only 28% of the desired benzyl alcohol. As expected, the low conversion of aldehyde in entries 2 and 3 demonstrates that HCl (aq p*K*_a = -7) reacts with NaBH₄ rather than quench the intermediate benzyl alkoxide. Both the low conversion of aldehyde and the lack of acrylate formation in entry 4 demonstrates that acryloyl chloride also reacts more rapidly than the benzaldehyde with NaBH₄ and is therefore consumed before it quenches the intermediate benzyl alkoxide. Since only 2 equiv of acryloyl chloride were used, 2 equiv of hydride were still available to reduce the resulting aldehyde and benzaldehyde groups.

In contrast, the benzaldehyde reduction proceeds to approximately 90% conversion in the presence of both 1 (entry 5) and 10 equiv (entry 6) of acetic acid (aq p*K*_a = 4.7). In addition, acetic acid prevents formation of all but approximately 10% of the rearranged phenol. However, if the amount of acetic acid is increased to 100 equiv (entry 7), the competing reaction between acetic acid and NaBH₄ becomes significant, and there is insufficient reducing agent present to reduce more than 52% of the benzaldehyde.

Entries 8 and 9 demonstrate that the conversion increases to 99% if the amount of NaBH₄ is increased to 2 equiv relative to the benzaldehyde and that the maximum amount of the benzyl alcohol (94%) is again obtained when the stoichiometry of NaBH₄ and acetic acid is 1:10 (entry 9). Entry 10 confirms that the benzyl alcohol should not remain in solution longer than necessary to complete the reduction or it will slowly rearrange to the corresponding phenol. Entry 11 demonstrates that there is essentially no improvement in the conversion by using 3 equiv of NaBH₄ and 30 equiv of acetic acid, although there is a slight increase in the amount of benzyl alcohol relative to that of the rearranged phenol.

One remaining question is whether this selective formation of the benzyl alcohol is due to quenching of the intermediate benzyl alkoxide by acetic acid or if it is due to reduction by a more selective reducing agent that is generated in situ by reaction of NaBH₄ with acetic acid. For example, aldehydes are chemoselectively reduced in the presence of ketones using 2 equiv of in-situ-generated NaBH(OAc)₃¹⁰ or tetrabutylammonium triacetoxymethylborohydride¹¹ in benzene at 80 °C.

(10) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535–536.

(11) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, 24, 4287–4290.

(12) **Optimized Reduction of 2,5-Bis[4'-(methoxy)benzoyloxy]benzaldehyde** (Entry 11, Table 1). A mixture of 2,5-bis[4'-(methoxy)benzoyloxy]benzaldehyde⁴ (0.50 g, 1.2 mmol) in THF (20 mL) and DMSO (2.0 mL) was heated to dissolve the solids. After cooling, glacial acetic acid (2120 μL, 37 mmol) was added, and the entire solution was immediately added to a slurry of NaBH₄ (0.14 g, 3.7 mmol) in DMSO (1.0 mL). After the solution was stirred at room temperature for 30 min, the reaction mixture was poured into ice-cooled 10% aqueous NaCl (50 mL), and CH₂Cl₂ (25 mL) was added to dissolve the precipitate. The aqueous layer was neutralized with NaHCO₃, and the two layers were separated. The aqueous layer was extracted twice with CH₂Cl₂ (25 mL each). The organic extracts were combined, washed once with 10% aqueous NaCl (30 mL), and dried over Na₂SO₄. After filtration, the solvent was removed in vacuo to yield 0.50 g (100%) of a white solid containing 96% 2,5-bis[4'-(methoxy)benzoyloxy]benzyl alcohol, 3% 2-[(4'-(methoxy)benzoyloxy)methylene]-5-[(4'-(methoxy)benzoyloxy)oxy]phenol, and 1% 2,5-bis[4'-(methoxy)benzoyloxy]benzaldehyde. These values were calculated by comparison of the integrals of the ¹H NMR resonances at 4.65 ppm (s, ArCH₂OH), 5.34 ppm (s, ArCH₂O₂C-), and 10.21 ppm (s, ArCHO). The rearranged phenol is easily

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Table 1. Reduction of 2,5-Bis[(4'-(methoxy)benzoyl)oxy]benzaldehyde^a

entry	reducing agent	additive	time (h)	product composition (%)		
				ArCHO ^b	ArCH ₂ OH ^c	ArOH ^d
1	1 equiv of NaBH ₄	none	0.5	1 ± 2	28 ± 9	71 ± 7
2	1 equiv of NaBH ₄	1 equiv of HCl	0.5	83 ± 5	15 ± 5	2 ± 1
3	1 equiv of NaBH ₄	10 equiv of HCl	0.5	100 ± 0	0 ± 0	0 ± 0
4	1 equiv of NaBH ₄	2 equiv of CH ₂ CHCOCl	0.5	50 ± 14	46 ± 12	4 ± 2
5	1 equiv of NaBH ₄	1 equiv of AcOH	0.5	10 ± 6	79 ± 9	11 ± 4
6	1 equiv of NaBH ₄	10 equiv of AcOH	0.5	7 ± 6	87 ± 5	6 ± 6
7	1 equiv of NaBH ₄	100 equiv of AcOH	0.5	52 ± 12	42 ± 9	6 ± 3
8	2 equiv of NaBH ₄	10 equiv of AcOH	0.5	2 ± 0.4	90 ± 4	8 ± 4
9	2 equiv of NaBH ₄	20 equiv of AcOH	0.5	1 ± 0.2	94 ± 1	5 ± 1
10	2 equiv of NaBH ₄	20 equiv of AcOH	24	1 ± 0.2	89 ± 0.4	10 ± 1
11	3 equiv of NaBH ₄	30 equiv of AcOH	0.5	1 ± 0.2	96 ± 1	3 ± 0.4
12	2 equiv of "NaBH(OAc) ₃ "	none	0.5	80 ± 5	18 ± 4	2 ± 1

^a Each experiment was performed in triplicate with quantitative recovery using 0.5 g of 2,5-bis[(4'-(methoxy)benzoyl)oxy]benzaldehyde in 20 mL of THF and 3.0 mL of DMSO at room temperature for 30 min. ^b Recovered 2,5-bis[(4'-(methoxy)benzoyl)oxy]benzaldehyde. ^c 2,5-Bis[(4'-(methoxy)benzoyl)oxy]benzyl alcohol. ^d Rearranged 2-[(4'-(methoxybenzoyloxy)methylene]-5-[(4''-methoxybenzoyl)oxy]phenol.

In contrast to entries 2–11 of Table 1, entry 12 lists the product composition from first reacting 2 equiv of NaBH₄ with 6.5 equiv of acetic acid at 80 °C for 15 min as in the literature procedure,¹⁰ except that DMSO (1.0 mL) was used as the solvent instead of benzene and the actual reduction was performed at room temperature in THF (20 mL)/DMSO

removed by recrystallization of the benzyl alcohol from ethanol/toluene.⁴ Unreacted benzaldehyde is then removed most easily by first converting the benzyl alcohol to monomer, reacting residual benzaldehyde with *p*-aminophenol, and extracting the resulting imine into 1 M aqueous NaOH followed by passing the monomer through a column of basic activated alumina. ¹H NMR of 2,5-bis[(4'-(methoxybenzoyl)oxy]benzaldehyde: 3.92 (s, OCH₃, 6 H), 7.01 (dd, 4 aromatic H ortho to OCH₃), 7.40 (d, 1 aromatic H meta to CHO), 7.54 (dd, 1 aromatic H para to CHO), 7.78 (d, 1 aromatic H ortho to CHO), 8.18 (dd, 4 aromatic H ortho to CO₂Ar), 10.21 (s, CHO). ¹H NMR of 2,5-bis[(4'-(methoxybenzoyl)oxy]benzyl alcohol: ~2.14 (br s, OH), 3.92 (s, OCH₃, 6 H), 4.65 (s, CH₂OH), 6.99 (dd, 4 aromatic H ortho to OCH₃), 7.21 (s, 2 aromatic H meta and para to CH₂OH), 7.41 (s, 1 aromatic H ortho to CH₂OH), 8.16 (dd, 4 aromatic H ortho to CO₂Ar). ¹H NMR of 2-[(4'-(methoxybenzoyloxy)methylene]-5-[(4''-methoxybenzoyl)oxy]phenol: 3.87 (s, OCH₃), 3.92 (s, OCH₃), 5.34 (s, CH₂O₂CAr), 6.93 (d, 2 aromatic H ortho to OCH₃), 7.02 (m, 2 aromatic H ortho to OCH₃ and 1 aromatic H meta to OH), 7.12 (dd, 1 aromatic H ortho to OH), 7.24 (d, 1 aromatic H ortho to -CH₂-), 8.03 (d, 2 aromatic H ortho to CO₂Ar), 8.19 (d, 2 aromatic H ortho to CO₂Ar), ~8.36 (s, OH).

(2.0 mL). These results should be similar to those of entry 8 if the two experiments involve the same reducing agent(s). However, the resulting "NaBH(OAc)₃" converts only 18% of the benzaldehyde to the benzyl alcohol and a minor amount of the rearranged phenol (2%). This indicates that NaBH₄ reduces the benzaldehyde to the benzyl alkoxide in the optimized reduction¹² and acetic acid quenches the benzyl alkoxide before it rearranges to the corresponding phenol.

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