PRACTICAL SYNTHETIC PROCEDURES

2,5-Dihydroxyterephthalates, 2,5-Dichloro-1,4-benzoquinone-3,6-dicarboxylates, and Polymorphic 2,5-Dichloro-3,6-dihydroxyterephthalates

Lukas Hintermann,1 Keisuke Suzuki*

Department of Chemistry, Tokyo Institute of Technology, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551, Japan
Fax +81(3)57342788; E-mail: ksuzuki@chem.titech.ac.jp

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Abstract: Reaction of 2,5-dihydroxy(bicyclohexa)-1,4-diene-1,4-dicarboxylates with one equivalent of N-chlorosuccinimide cleanly gives 2,5-dihydroxyterephthalates; reaction with four equivalents of N-chlorosuccinimide gives 2,5-dichloro-1,4-benzoquinone-3,6-dicarboxylates instead. The latter compounds react with sodium dithionite to give 2,5-dichloro-3,6-dihydroxyterephthalates, which will find use in the study of polymorphic phase changes.

Key words: arenes, halogenation, hydroquinones, polymorphism, quinones

Introduction

For synthesizing highly substituted benzene derivatives, cycloaddition or condensation approaches from aliphatic precursors are often more efficient than stepwise aromatic substitutions.2 A good example is the synthetic sequence starting from succinic esters via (a) Claisen condensation to succinylsuccinates1,3, (b) halogenation of 1 to 2,5-dihydroxyterephthalates2 or dichlorobenzoquinones3,5–7 and (c) reduction of 3 to 2,5-dichloro-3,6-dihydroxyterephthalates4 (Scheme 1).5 The latter compounds show ‘chromoisomeric’ behavior due to polymorphism,5,8 and methyl ester4a is a regular subject in spectroscopic,9 crystallographic,10 and theoretical11 studies of polymorphic phase changes, because of its reliable and reproducible generation of a colorless and two yellow polymorphs,8,10 The 2,5-dichloro-1,4-benzoquinone-3,6-carboxylates3 are important intermediates in the synthesis of pigments and colorants themselves,9 or serve as developers in pressure, heat, or light-sensitive colorants for applications in blue-print paper12a or DVD data storage media.12b The direct conversion of 1 into 3 is reported in the literature5,6,9b,c and patents,2 but this reaction using chlorine gas is dangerous and capricious in terms of the yields (ca. 50%)6,7,9b and/or purity of products.9b,c In the course of a total synthesis project, we needed large amounts of 4 and have investigated the classical route from 1 into 3 and into 4.5 These studies led us to find that by replacing chlorine gas with N-chlorosuccinimide and performing the reaction at higher temperatures (ca. 80 °C) in acetic acid, a clean conversion of 1 into 2 or 3 was achieved in a short reaction time. The products 2–4 are useful building blocks for a range of applications and 4a is now an easily accessible demonstration and study object for solvatochromic, chromoisoromeric, and polymorphic behaviors.

Scope and Limitations

While succinylsuccinates1 can be obtained by a double Claisen condensation of dialkyl succinates,3 the esters 1a,b are now commercially available. They are readily transformed to higher esters by thermal transesterification.13,14 We used 4-(dimethylamino)pyridine15 rather than sodium alkoxide14 as a catalyst.13 The synthesis of benzyl ester 1c and (1R)-menthyl ester 1d exemplifies the procedure (Table 1).

The direct chlorination of 1 into 3 using chlorine sometimes gives products containing 2 and 4 as impurities.9b,c We now find that chlorination of 1 with N-chlorosuccinimide in acetic acid is high yielding, selective, and operationally simple. Addition of a single equivalent of N-chlorosuccinimide converts 1 into 2,5-dihydroxyterephthalates2 in high yields (Table 2). This oxidation has previously been performed under less favorable conditions.4

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Table 1 Thermal Transesterification of Succinylsuccinates 1

<table>
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<th>Entry</th>
<th>R</th>
<th>Solvent</th>
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<th>Yield (%)</th>
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<td>1</td>
<td>Bn</td>
<td>o-xylene</td>
<td>1c</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>(1R)-menthyl</td>
<td>1,2-dichlorobenzene</td>
<td>1d</td>
<td>65</td>
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Table 2 2,5-Dihydroxyterephthalates 2 from Succinylsuccinates 1

<table>
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<th>Entry</th>
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<th>Yield (%)</th>
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<td>Me</td>
<td>2a</td>
<td>90</td>
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<tr>
<td>2</td>
<td>1b</td>
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</tr>
<tr>
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<td>1c</td>
<td>Bn</td>
<td>2c</td>
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<td>1d</td>
<td>(1R)-menthyl</td>
<td>2d</td>
<td>87</td>
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</table>

If the first step N-chlorosuccinimide (1 → 2) is followed by addition of another three equivalents of N-chlorosuccinimide to the same pot, the reaction proceeds further to the 2,5-dichlorobenzoquinone esters 3 (Table 3). Notably, benzyl ester 1c reacted without concomitant ring chlorination, and cleavage of the ester alkyl groups was not observed, even under harsh reaction conditions (HCl, 80 °C).

Table 3 2,5-Dichlorobenzoquinones 3 from Succinylsuccinates 1

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
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<td>Me</td>
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<td>Et</td>
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<td>Bn</td>
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<td>78</td>
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<tr>
<td>4</td>
<td>1d</td>
<td>(1R)-menthyl</td>
<td>3d</td>
<td>63</td>
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</table>

Finally, hydroquinones 4 were conveniently obtained by reduction of 2,5-dihalobenzoquinones 3 with aqueous sodium dithionite (Table 4); this procedure gave much cleaner products in comparison with those by the reduction with zinc in acetic acid. Methyl 2,6-dichloro-3,6-dihydroxyterephthalate (4a), an important model compound in the study of polymorphism, was thus readily obtained in 50-g batches. The chlorohydroquinones 4c, d display similar solvatochromism as seen with 4a, b. From the colorless ethanol solution of 4d, a stable colorless solvate 4d·2 EtOH crystallized, whereas solvent-free yellow crystals separated from its greenish dichloromethane solutions.17

Succinylsuccinates 1a and 1b were commercially available; 1b was also synthesized from ethyl succinate. Abbreviations: (1R)-menthyl = (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl.1 H NMR spectra were recorded at 395 MHz in CDCl3 and referenced to internal TMS. 13C NMR spectra were recorded at 99 MHz in CDCl3 and referenced to the solvent signal. Melting points are not corrected, unless noted. All compounds gave elemental analyses (C, H, N) within a ±0.3% range. CAUTION: In the syntheses of 2 and 3, corrosive HCl vapors are released. We usually absorbed these by passing them over (not directly into) a stirred slurry of Ca(OH)2 in H2O.

Dibenzy 2,5-Dihydroxycyclohexa-1,4-diene-1,4-dicarboxylate (1c) In a round-bottomed flask with mounted air-cooled condenser, 1a (5.135 g, 22.5 mmol), BnOH (7.215 g, 66.7 mmol), and DMAP (60 mg) were stirred in o-xylene (10 mL) at 180 °C for 6 h. MeOH vapors were released. The mixture was cooled with vigorous stirring while EtOH (25 mL) was added. After standing at 0 °C and filtration, 1c (7.159 g, 84%) was obtained as faint yellow crystals; mp 167–168 °C.

1H NMR: δ = 3.24 (s, 4 H), 5.24 (s, 4 H), 7.3–7.5 (m, 10 H), 12.15 (s, 2 H). 13C NMR: δ = 28.3, 66.2, 93.2, 128.3, 128.6, 128.9, 135.8, 169.3, 171.4.

Bis[1(1R)-menthyl] 2,5-Dihydroxycyclohexa-1,4-diene-1,4-dicarboxylate (1d) In a round flask with mounted, air-cooled condenser, 1a (2.524 g, 11.06 mmol), (–)(1R)-menthol (5.79 g, 37.05 mmol), and DMAP (0.102 g, 0.83 mmol) in 1,2-dichlorobenzene (5 mL) were heated to 180 °C for 30 min and to 200 °C for 1.5 h. Vapors of MeOH were released. After cooling, MeOH (30 mL) was added with vigorous stirring and the mixture cooled to 0 °C and filtered to give 1d (3.408 g, 65%) as fine yellow needles; mp 146–148 °C.

1H NMR: δ = 0.76 (d, J = 7.0 Hz, 6 H), 0.90 (d, J = 7.0 Hz, 6 H), 0.92 (d, J = 6.6 Hz, 6 H), 0.95–1.20 (m, 6 H), 1.39–1.60 (m, 4 H), 1.65–1.76 (m, 4 H), 1.85 (sept d, J = 7.0, 2.7 Hz, 2 H), 2.00–2.10 (m, 2 H), 3.18 (s, 4 H), 4.80 (td, J = 10.9, 4.4 Hz, 2 H), 12.35 (s, 2 H).
**Diethyl 2,5-Dihydroxyterephthalate (2b)**

To a soln of 1b (12.218 g, 47.68 mmol) in AcOH (85 mL) at 60 °C, NCS (12.3 g, 92.1 mmol) was added in portions and the mixture was stirred at 80 °C for 70 min. More NCS (1.80 g, 13.5 mmol) was added and the mixture was stirred at 90 °C for 2.5 h. The mixture was cooled and the reaction was worked up with AcOH and t-BuOMe. The organic phase was washed with H₂O (3 × 20 mL, 50 mL) and EtOAc. The aqueous phase was acidified with HCl (3 M), dried (Na₂SO₄), and evaporated. The product was recrystallized (hot MeCN, 15 mL) to give 2b (610.2 mg, 77%) as yellow crystals; mp 133–134 °C (Lit.⁴ 133–135 °C).

**Diethyl 2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (3b)**

Following the typical procedure for 3a using 1b (22.40 g, 87.44 mmol) in AcOH (100 mL) with NCS (first 12.3 g, 92.1 mmol, then 30.0 g, 225 mmol) at 80 °C for 70 min. After the second addition, the mixture was stirred at 85 °C for 3 h. The mixture was cooled and filtered and the product was washed with AcOH (2 × 20 mL) and H₂O and dried under high vacuum to give 3b (23.65 g, 84%) as yellow crystals; mp 197–199 °C (Lit.⁵ 195 °C).

**Bis[(1R)-menthyl] 2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (3d)**

A mixture of 1c (3.068 g, 8.065 mmol) and NCS (1.08 g, 8.09 mmol) in AcOH (20 mL) was stirred at 90 °C for 70 min. More NCS (3.63 g, 27.3 mmol) was added and the mixture stirred at 90 °C for 2 h. The mixture was cooled to r.t. with stirring and the product was filtered and washed (MeOH) to give 3c (2.794 g, 78%) as a yellow powder that was sensitive to light; mp 143–148 °C.

**Bis(1R)-menthyl 2,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,4-dicarboxylate (3d)**

A mixture of 1d (2.00 g, 4.2 mmol) and NCS (0.598 g, 4.48 mmol) in AcOH (6 mL) was stirred at 90 °C for 2.5 h. More NCS (1.80 g, 13.5 mmol) was added and the mixture was stirred at 90 °C for 1.5 h. The mixture was cooled and the reaction was worked up with H₂O and t-BuOMe. The organic phase was washed with H₂O (3 ×), dried (Na₂SO₄), and evaporated. The product was recrystallized (hot MeCN, 15 mL) to give 3d (1.257 g, 55%) as yellow needles; a second crop from the mother liquors (183 mg) raised the total yield to 63%; mp 182–183 °C.

**Dimethyl 2,5-Dihydroxyterephthalate (2c)**

To a suspension of 1c (801.8 mg, 2.11 mmol) in AcOH (10 mL) at 60 °C, NCS (296 mg, 2.21 mmol) was added and the mixture was stirred at 80 °C for 70 min. The mixture was then cooled to ca. 10 °C with stirring, filtered, and washed with AcOH (5 mL), H₂O (10 mL) and MeOH (5 mL) to give 2c (660.2 mg, 77%) as yellow crystals; mp 197–199 °C (Lit.⁶ 195 °C).

**Dimethyl 2,5-Dichloro-3,6-dihydroxyterephthalate (4a)**

In a 500-mL round-flask, 3a (20.653 g, 70.47 mmol) was stirred at 0 °C in a mixture of CH₂Cl₂ (120 mL), MeOH (40 mL), H₂O (20 mL), and AcOH (1 mL). A soln of Na₂S₂O₄ (86% content; 21.0 g, 133 mmol) was added and the mixture was stirred at r.t. for 30 min. The heterogeneous (two-phase + solids) mixture was freed from CH₂Cl₂ using CH₂Cl₂/Et₂O. The organic layer was washed with H₂O and MeOH. The organic phase was washed with AcOH (20 mL) and H₂O (50 mL), and then with chilled MeOH. Drying under high vacuum gave 4a (43.503 g, 90%) as yellow crystals; mp 241–243 °C (dec) (Lit.⁶ 243–244 °C).

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Diethyl 2,5-Dichloro-3,6-dihydroxyterephthalate (4b)

To a slurry of 3b (321.5 mg, 1 mmol) in CH₂Cl₂ (5 mL) and AcOH (1 drop), a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (3 mL) was added and the two-phase mixture was stirred at r.t. for 2 h. r-BuOMe (20 mL) and H₂O were added and the organic phase was washed with sat. NaCl (2 ×). The soln was dried (MgSO₄), filtered, and evaporated to give a white solid from the yellow soln. Chromatography (silica gel, EtOAc–hexanes, 1:5) gave 4b (306 mg, 95%) as yellow needles. 1H NMR: δ = 4.15 (t, J = 7.2 Hz, 6 H), 4.50 (q, J = 7.2 Hz, 4 H), 9.34 (s, 2 H).

13C NMR: δ = 14.0, 63.1, 119.2, 119.6, 148.3, 167.0.

Dibenzyl 2,5-Dichloro-3,6-dihydroxyterephthalate (4c)

A soln of 3c (418.5 mg, 0.94 mmol) in CH₂Cl₂ (10 mL) and a soln of Na₂SO₄ (ca. 0.5 mmol) in H₂O (5 mL) were vigorously stirred while MeOH (10 mL) was slowly added, causing a color change from yellow to greenish yellow. After 10 min, the organic solvents (CH₂Cl₂, MeOH) were removed (by rotary evaporation) and the resulting suspension was filtered. The yellow solid was washed with H₂O and dried in air to give 4c (379.6 mg, 90%) as yellow crystalline needles; mp 113–114 °C.

1H NMR: δ = 5.47 (s, 4 H), 7.34–7.51 (m, 10 H), 9.21 (s, 2 H).

13C NMR: δ = 123.7, 124.0 °C (corr.) (Lit. 123 °C). Note: Addition of MeOH or THF will speed up this biphasic reaction.

To a slurry of 3d (177.5 mg, 0.33 mmol) in THF (5 mL), a soln of Na₂S₂O₄ (321.5 mg, 1 mmol) in CH₂Cl₂ (5 mL) and AcOH (2 drops) was added and the biphasic mixture was vigorously stirred. Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise. To a soln of Na₂S₂O₄ (86% content; 256 mg, 1.26 mmol) in H₂O (2 mL) was added a soln of Na₂SO₄ (90 mg, ca. 0.5 mmol) in H₂O (2 mL) was added dropwise.

1H NMR: δ = 0.81 (d, J = 6.9 Hz, 6 H), 0.91 (d, J = 7.0 Hz, 6 H), 0.86–1.00 (m, 2 H), 0.96 (d, J = 6.6 Hz, 6 H), 1.05–1.26 (m, 4 H), 1.50–1.62 (m, 4 H), 1.69–1.80 (m, 4 H), 2.01 (sept d, J = 7.0, 2.6 Hz, 2 H), 2.16–2.24 (m, 2 H), 5.07 (td, J = 10.9, 4.4 Hz, 2 H), 9.28 (s, 2 H).

13C NMR: δ = 15.7, 20.4, 21.7, 22.9, 25.8, 31.3, 33.8, 40.3, 46.8, 77.9, 119.5, 119.8, 148.5, 167.0.

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References