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Access to Aryl Mellitic Acid Esters through a Surprising Oxidative Esterification Reaction

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Supporting Information

ABSTRACT: A serendipitously discovered oxidative esterification reaction of cyclohexane hexacarboxylic acid with phosphorus pentachloride and phenols provides one-pot access to previously unknown aryl mellitic acid esters. The reaction features a solvent-free digestion and chromatography-free purifications and demonstrates the possibility of cyclohexaneto-benzene conversions under relatively mild, metal-free conditions.

Numerous synthetic methods are known to make alkyl esters of mellitic acid,¹⁻³ but aryl esters of mellitic acid have not been reported to date. We are interested in aryl esters, because of their possible use as scaffolds for fast-releasing domino self-immolative linkers,⁴ but they are also structurally interesting paddlewheel motifs that may find use as the cores of hexagonally branched dendrimers. Additionally, some hindered mellitic acid esters are of interest for their anomalous fluorescence behavior.⁵

Perhaps unsurprisingly given the absence of all methods to prepare these structures in the literature, all our attempts to prepare aryl mellitic acid esters via its acid chloride or through direct esterification of mellitic acid with standard coupling reagents (DCC/DMAP, PyBOP, CDI, etc.) were unsuccessful. In contrast, alkyl esters of mellitic acid can be made easily through these methods. The sterically hindered nature of these aryl esters may explain why they are difficult to prepare via direct methods. Fortunately, we serendipitously discovered a surprising oxidative esterification reaction by digesting all-cis-1,2,3,4,5,6-cyclohexanehexacarboxylic acid with phosphorus pentachloride and phenols that leads to the ring-oxidized aryl mellitic acid esters in one pot. The aryl esters can be purified through washing procedures, avoiding chromatography.

The reaction optimization, which was performed using p'-methoxyphenol, included variation of following parameters: equivalents of PCl₅, temperature, and time for each reaction step (Table 1). It was found that 12 equiv of PCl₅ (2 equiv per acid moiety) results in the best yield for solvent-free digestion at 130 °C. Addition of pyridine in the final step was used in all cases except for the synthesis of mellitic acid, where addition of water led to product in the absence of pyridine.

The reactions to prepare the aryl mellitic acid esters are one-pot, solvent-free reactions that can be performed under air and give products that can be purified by washing procedures to free the aryl mellitic acid esters from byproducts (typically P(OAr)₃ and pyridine). As can be seen in Scheme 1, the reaction can tolerate both electron-rich phenols (e.g., p'-methoxy phenol, alkyl phenols) as well as some electron-poor phenols (halophenols, cyanophenol) with some exceptions. Using our standard conditions, 4-nitrophenol, 2,2'-bisphenol, 4-phenylphenol, 4-acetamidophenol, 4-tert-butylphenol, and 1- and 2-naphthol failed to yield the corresponding mellitic acid ester in significant quantities. Additionally, it was possible to use alkyl alcohols instead of phenols, but we observed some conversion of the alcohols to the alkyl chlorides during the PCl₅ digestion step and the alkyl esters of mellitic acid are difficult to separate from the P(OR)₃ byproduct. Given that there are numerous methods to make alkyl esters of mellitic acid via standard procedures, we did not pursue these oxidative alkyl esterification reactions further. Further, we note that reaction with water instead of a phenol led to mellitic acid as an inseparable mixture with phosphoric acid. Thus, the mellitic acid was converted to its methyl ester to determine the reaction yield in this one case (see the Experimental Section for details).

Mechanistic Considerations. A few additional experiments shed some light on the mechanism of this remarkable oxidative esterification reaction. First, the reaction appears to be

<p>| Table 1. Optimization of Reaction Conditions |</p>
<table>
<thead>
<tr>
<th>temp (°C)</th>
<th>PCl₅ (equiv)</th>
<th>time (step 1, step 2, step 3)* (h)</th>
<th>yield (isolated %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>6</td>
<td>1, 4, 2</td>
<td>49</td>
</tr>
<tr>
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<td>1, 4, 2</td>
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</tr>
<tr>
<td>160</td>
<td>12</td>
<td>1, 4, 2</td>
<td>47</td>
</tr>
</tbody>
</table>

*step 1 = PCl₅ digestion; step 2 = addition of phenol; step 3 = addition of pyridine.
specific to the 1,2,3,4,5,6-cyclohexanehexacarboxylic acid scaffold. Subjecting 1,3,5-cyclohexanetricarboxylic acid (all-cis) and 1,2-cyclohexanedicarboxylic acid (both cis and trans) leads to typical esterification with no oxidation of the cyclohexane ring to benzene. Second, given that addition of phenols to the acid chloride of mellitic acid leads to no esterification, it is likely that esterification occurs prior to ring oxidation. In contrast, esterification of the acid chloride of 1,2,3,4,5,6-cyclohexanehexacarboxylic acid with phenols proceeds to give the cyclohexane hexaester in normal fashion, possibly due to a more flexible cyclohexane ring leading to less steric hindrance between the aryl esters. Finally, subjecting the hexaaryl ester of 1,2,3,4,5,6-cyclohexanehexacarboxylic acid to the reaction conditions leads to oxidation of the cyclohexane to the benzene ring, lending support to the possibility of esterification followed by oxidation. Additionally, the mechanism is indifferent to the stereochmistry of the starting material. Reacting the all-trans-1,2,3,4,5,6-cyclohexanehexacarboxylic acid leads to essentially identical yields as the all-cis stereoisomer (although the all-cis stereoisomer is available commercially, leading to our preference to using that stereoisomer as the starting material). As to the oxidation mechanism itself, one possibility is that it follows an α chlorination/elimination mechanism. PCl₅ is known to be in an equilibrium with PCl₃ and Cl₂ at elevated temperatures, so Cl₂ may play a role in the oxidation process. It may be the case that the contiguous adjacent acid groups in the starting material allow for milder α chlorination. We tested the importance of Cl₂ in the oxidation by performing the same reaction with PCl₃ (which lacks the ability to form Cl₂) and obtained esterified product that was not ring oxidized. This experiment implicates Cl₂ as the likely oxidant in this reaction. Isolated yields are not affected by running the reaction under air or argon, suggesting molecular oxygen is not playing a role in the oxidation mechanism. We also considered that pyridine might play a role in the oxidation mechanism (e.g., by forming N-chloropyridinium), but given that mellitic acid can be formed by addition of water instead of a phenol without adding pyridine, this possibility seems to be less likely. Additionally, without pyridine we obtain the product esters, albeit in somewhat diminished yields. The combination of these experiments led us to suggest the mechanism shown in Scheme 2.

Although we were unable to obtain X-ray quality crystals of the esters, density functional theory computations (B3LYP/6-31G(d)) on 2 suggest the phenyl rings adopt an interesting paddlewheel-like structure to minimize strain. See Figure 1.

Scheme 1. Scope of Oxidative Esterification

Scheme 2. Plausible Mechanism of Oxidative Esterification Reaction

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Note

Water was removed using a rotary evaporator, leaving a white solid in the reaction mixture, which was heated at the same temperature for 4 h.

**Mellitic Acid (Hexa-4-ethylphenyl) Ester (4).** PCl5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanexehexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-ethylphenol (3.508 g, 28.7 mmol) was added to reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and solid product was washed with cold methanol to afford 0.435 g (63%) of the product as a beige amorphous solid. Mp: 189.0–190.0 °C. 1H NMR (600 MHz): δ (ppm) 7.16 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 2.65 (g, J = 8.0 Hz, 2H), 1.24 (t, J = 8.5 Hz, 3H). 13C NMR (150 MHz): δ (ppm) 163.4, 148.4, 142.9, 134.5, 129.1, 121.1, 28.5, 15.7. HRMS (ESI) m/z: [M + Na]+ calcd for C46H32NaO12 899.3513, found 899.3520.

*Mellitic Acid (Hexa-4-isopropylphenyl) Ester (5).** PCl5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanexehexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-isopropylphenol (3.911 g, 28.7 mmol) was added to reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and solid product was washed with cold methanol to afford 0.435 g (63%) of the product as a beige amorphous solid. Mp: 210.0–210.5 °C. 1H NMR (600 MHz): δ (ppm) 7.43 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 2.91 (m, 1H), 1.25 (s, 6H). 13C NMR (150 MHz): δ (ppm) 163.4, 148.4, 147.5, 134.5, 127.6, 121.1, 33.8, 24.1. HRMS (ESI) m/z: [M + Na]+ calcd for C48H34NaO12 1073.4452, found 1073.4460.

*Mellitic Acid (Hexa-4-methoxyphenyl) Ester (6).** PCl5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanexehexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-methoxyphenol (3.565 g, 28.7 mmol) was added to reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and solid product was washed with cold methanol to afford 0.442 g (63%) of the product as a yellow amorphous solid. Mp: 183.0–183.5 °C. 1H NMR (600 MHz): δ (ppm) 7.47 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H). 13C NMR (150 MHz): δ (ppm) 153.6, 158.1, 143.9, 134.5, 122.2, 114.8, 55.8. HRMS (ESI) m/z: [M + Na]+ calcd for C48H34O12Na 1101.2263, found 1101.2291.

*Mellitic Acid (Hexa-4-chlorophenyl) Ester (7).** PCl5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanexehexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-chlorophenol (3.692 g, 28.7 mmol) was added to reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and solid product was washed with cold methanol to afford 0.442 g (63%) of the product as a yellow amorphous solid. Mp: > 260 °C. 1H NMR (600 MHz): δ (ppm) 7.34 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H). 13C NMR (150 MHz): δ (ppm) 162.2, 148.6, 134.4, 132.9, 120.1, 122.5. Anal. Calcd for C48H32Cl2O12: C, 57.29; H, 2.18%. Found: C, 57.05; H, 2.18%.

*Mellitic Acid (Hexa-4-bromophenyl) Ester (8).** PCl5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanexehexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-bromophenol (4.968 g, 28.7 mmol) was added to reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and solid product was washed with cold acetone to afford 0.453 g (50%) of the product as a beige amorphous solid. Mp: > 260 °C. 1H NMR (600 MHz):
Mellitic Acid (Hexa-4-fluorophenyl) Ester (9). PCl₅ (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanecarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-fluorophenol (3.219 g, 28.7 mmol) was added to the reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and the solid product was washed with cold acetone to afford 0.494 g (71%) of the product as a white amorphous solid. Mp: 210.5 °C. ¹H NMR (600 MHz): δ (ppm) 7.17 (m, 2H), 7.12 (m, 2H). ¹³C NMR (150 MHz): δ (ppm) 163.1, 161.8, 160.2, 146.0, 134.5, 122.7, 116.8. HRMS (ESI) m/z: [M + Na]⁺ calcd for C₄₈H₂₄Br₆NaO₁₂ 1294.6204, found 1294.6212.

Mellitic Acid (Hexa-3-methyl-4-bromophenyl) Ester (10). PCl₅ (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanecarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 3-methyl-4-bromophenol (5.371 g, 28.7 mmol) was added to reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off and the reaction mixture was filtered and solid product was washed with cold acetone to afford 0.416 g (43%) of the product as a beige amorphous solid. Mp: 202.5 °C. ¹H NMR (600 MHz): δ (ppm) 7.53 (d, J = 8.5 Hz, H), 6.97 (d, J = 8.5 Hz, H), 6.85 (dd, H), 2.31 (s, 3H). ¹³C NMR (150 MHz): δ (ppm) 163.1, 161.8, 160.2, 146.0, 134.5, 122.7, 116.8. HRMS (ESI) m/z: [M + Na]⁺ calcd for C₄₈H₂₄F₆NaO₁₂ 929.1070, found 929.1066.

Mellitic Acid (Hexa-4-cyanophenyl) Ester (11). PCl₅ (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanecarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-cyanophenol (3.421 g, 28.7 mmol) was added to reaction mixture, which was heated at the same temperature for 4 h followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and the solid product was washed with cold acetone to afford 0.404 g (62%) of the product as a beige amorphous solid. Mp: > 260 °C. ¹H NMR (600 MHz): δ (ppm) 7.70 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H). ¹³C NMR (150 MHz): δ (ppm) 162.7, 149.1, 140.1, 134.4, 133.6, 123.4, 122.9, 120.1, 23.2. Anal. Calcd for C₅₄H₃₆Br₆O₁₂Na: C, 46.98; H, 2.44. Found: C, 46.96; H, 2.44.

ASSOCIATED CONTENT

Supporting Information
Copies of ¹H NMR, ¹³C NMR, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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REFERENCES