

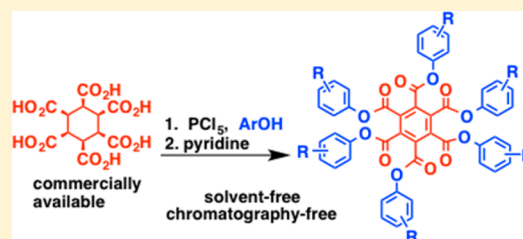
Access to Aryl Mellitic Acid Esters through a Surprising Oxidative Esterification Reaction

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S 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 cyclohexane-to-benzene conversions under relatively mild, metal-free conditions.



Numerous synthetic methods are known to make alkyl esters of mellitic acid,^{1–5} but aryl esters of mellitic acid have not been reported to date. We are interested in aryl esters of mellitic acid because of their possible use as scaffolds for fast-releasing domino self-immolative linkers,⁶ 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.⁷

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*-

Table 1. Optimization of Reaction Conditions

temp (°C)	PCl ₅ (equiv)	time (step 1, step 2, step 3) ^a (h)	yield (isolated %)
130	6	1, 4, 2	49
130	9	1, 4, 2	31
130	12	1, 4, 2	63
130	12	1, 1, 1	45
130	12	24, 24, 24	52
130	18	1, 4, 2	0
100	12	1, 4, 2	58
160	12	1, 4, 2	47

^astep 1 = PCl₅ digestion; step 2 = addition of phenol; step 3 = addition of pyridine.

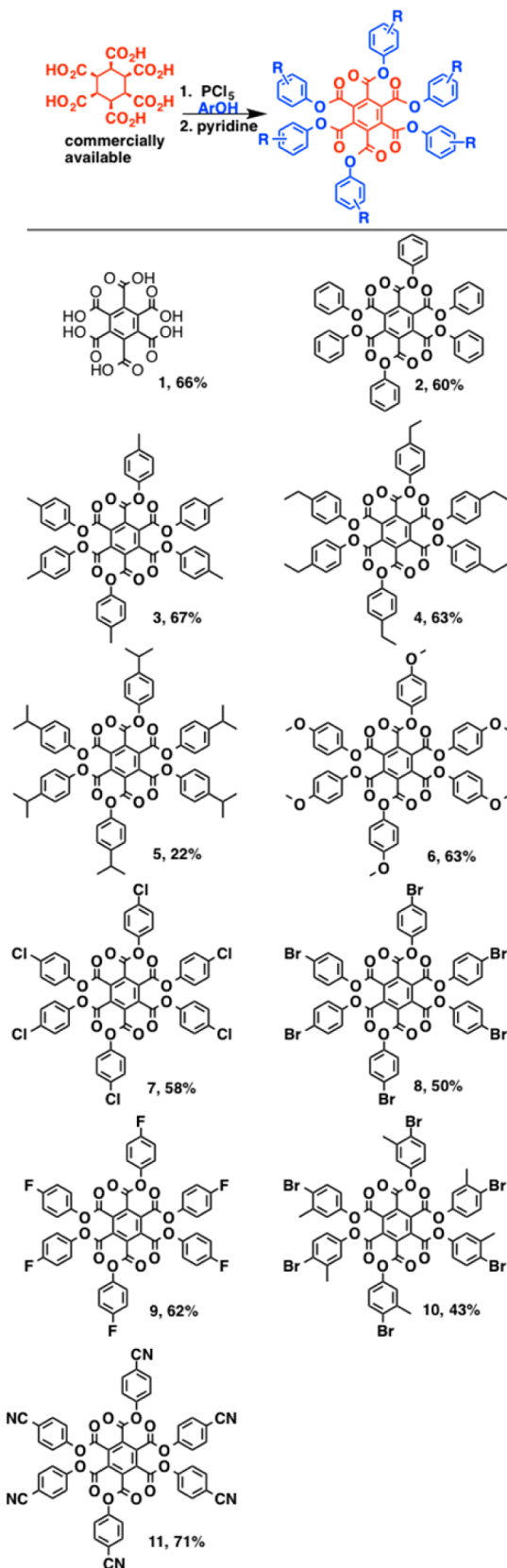
methoxy phenol, alkyl phenols) as well as some electron-poor phenols (halophenols, cyanophenol) with some exceptions. Using our standard conditions, 4-nitrophenol, 2,2'-bisphenol, 4-phenylphenol, 4-acetamidophenol, 4-*tert*-butylphenol, and 1- and 2-naphthol failed to yield the corresponding mellitic 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

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Scheme 1. Scope of Oxidative Esterification

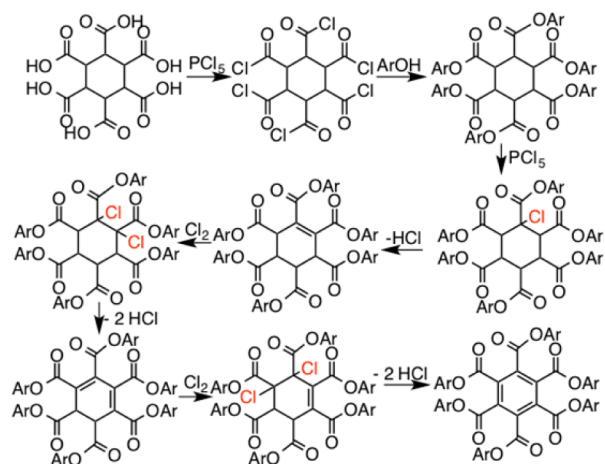


specific to the 1,2,3,4,5,6-cyclohexanecarboxylic acid scaffold. Subjecting 1,3,5-cyclohexanetricarboxylic acid (*all-cis*) and 1,2-cyclohexanedicarboxylic acid (both *cis* and *trans*) leads to typical esterification with no oxidation of the cyclohexane

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-cyclohexanecarboxylic 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-cyclohexanecarboxylic 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 stereochemistry of the starting material. Reacting the *all-trans*-1,2,3,4,5,6-cyclohexanecarboxylic 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,⁸ 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 2. Plausible Mechanism of Oxidative Esterification Reaction



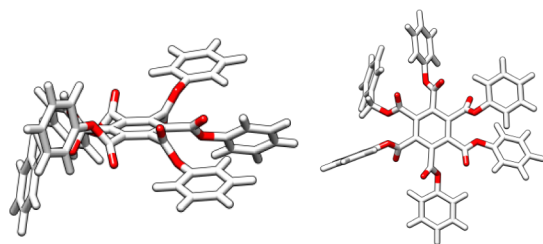


Figure 1. Density functional theory (B3LYP/6-31G(d)) computed structure of **2** showing paddlewheel-like arrangement of the aryl rings: left, side view; right, top view.

In conclusion, we have developed a simple procedure to access previously unknown aryl mellitic acid esters via a novel oxidative esterification reaction. This approach has obvious synthetic advantages as the reaction is carried out via a solvent-free, one-pot digestion and has a washing workup that avoids chromatography. This reaction is novel because oxidations of cyclohexane rings to benzene typically require high temperatures in excess of 200 °C and a metal catalyst, whereas this reaction is performed in the absence of metal and at comparatively low temperatures. Aryl mellitic acid esters may prove to be useful in domino self-immolative linkers or as the cores of structurally interesting dendrimers.

EXPERIMENTAL SECTION

General Procedure. Aryl mellitic acid esters were prepared by using PCl_5 (1.794 g, 8.6 mmol) and 1,2,3,4,5,6-cyclohexanhexacarboxylic acid (0.250 g, 0.7 mmol). This mixture was digested for 1 h at 130 °C. Various phenols were then added in excess 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 allowed to continue refluxing for 2 h. Pyridine was distilled off, and the product was filtered and washed with cold methanol or acetone. The target product was characterized by ^1H NMR, ^{13}C NMR, and HRMS.

Mellitic Acid (1). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then water (10 mL) was added to the reaction mixture, which was heated at the same temperature for 4 h. Water was removed using a rotary evaporator, leaving a white solid in the flask that contained mellitic acid and phosphoric acid byproduct, which made purification and yield determination difficult. To find the percent yield, the mellitic acid/byproduct mixture was derivatized by esterification to methyl ester of mellitic acid using a known procedure⁹ which has a yield of 81% (verified independently by us). The yield from starting material to the mellitic acid methyl ester was 0.291 g (54%). From this, we could determine that the reaction to form mellitic acid **1** affords 0.162 g (66%). ^{13}C NMR (150 MHz): δ (ppm) 169.3, 133.7.

Mellitic Acid Hexaphenyl Ester (2). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then, phenol (2.703 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 allowed to continue refluxing for 2 h. Pyridine was distilled off, the reaction mixture was filtered, and the solid product was washed with cold methanol to afford 0.341 g (60%) of the product as a yellow amorphous solid. Mp: 230.5–231.5 °C. ^1H NMR (600 MHz): δ (ppm) 7.35 (t, J = 7.0 Hz, 2H), 7.28 (t, J = 7.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H). ^{13}C NMR (150 MHz): δ (ppm) 163.2, 150.4, 134.5, 129.8, 127.0, 121.4. HRMS (ESI) m/z : $[\text{M} + \text{H}_2\text{O}]^+$ calcd for $\text{C}_{48}\text{H}_{32}\text{O}_{13}$ 816.1843, found 816.2109.

Mellitic Acid Hexa(4-methylphenyl) Ester (3). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic acid (0.250 g, 0.7 mmol) and digested for 1 h at 130 °C. Then 4-methylphenol (*p*-cresol, 3.105 g, 28.7 mmol) was added to reaction

mixture, which as 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 methanol to afford 0.429 g (67%) of the product as a white amorphous solid. Mp: 248.0–249.0 °C. ^1H NMR (600 MHz): δ (ppm) 7.14 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (150 MHz): δ (ppm) 163.5, 148.2, 136.6, 134.5, 130.3, 121.1, 21.1. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{54}\text{H}_{42}\text{NaO}_{12}$ 905.2574, found 905.2526.

Mellitic Acid (Hexa-4-ethylphenyl) Ester (4). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic 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 (q, J = 8.0 Hz, 2H), 1.24 (t, J = 8.0 Hz, 3H). ^{13}C 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 : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{60}\text{H}_{54}\text{NaO}_{12}$ 989.3513, found 989.3520.

Mellitic Acid (Hexa-4-isopropylphenyl) Ester (5). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic 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, and the reaction mixture was filtered, the solid product was washed with cold methanol to afford 0.169 g (22%) of the product as a yellow amorphous solid. Mp: 201.0–203.5 °C. ^1H NMR (600 MHz): δ (ppm) 7.18 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 2.91 (m, 1H), 1.25 (s, 6H). ^{13}C 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 : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{66}\text{H}_{66}\text{NaO}_{12}$ 1073.4452, found 1073.4460.

Mellitic Acid (Hexa-4-methoxyphenyl) Ester (6). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic 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 the solid product was washed with cold methanol to afford 0.442 g (63%) of the product as a white amorphous solid. Mp: 223.0–223.5 °C. ^1H NMR (600 MHz): δ (ppm) 7.05 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (150 MHz): δ (ppm) 163.6, 158.1, 143.9, 134.5, 122.2, 114.8, 55.8. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{54}\text{H}_{42}\text{O}_{18}\text{Na}$ 1001.2263, found 1001.2291.

Mellitic Acid (Hexa-4-chlorophenyl) Ester (7). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic 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 the solid product was washed with cold acetone to afford 0.423 g (58%) of the product as a white amorphous solid. Mp: > 260 °C. ^1H NMR (600 MHz): δ (ppm) 7.34 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H). ^{13}C NMR (150 MHz): δ (ppm) 162.7, 148.6, 134.4, 132.9, 130.1, 122.5. Anal. Calcd for $\text{C}_{48}\text{H}_{24}\text{Cl}_6\text{O}_{12}$: C, 57.29; H, 2.39. Found: C, 57.05; H, 2.18%.

Mellitic Acid (Hexa-4-bromophenyl) Ester (8). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanhexacarboxylic 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 the 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): δ (ppm) 7.49 (d, $J = 9.0$ Hz, 2H), 6.97 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR (150 MHz): δ (ppm) 162.6, 149.1, 134.4, 133.1, 122.9, 120.6. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{48}\text{H}_{24}\text{Br}_6\text{NaO}_{12}$ 1294.6204, found 1294.6212.

Mellitic Acid (Hexa-4-fluorophenyl) Ester (9). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanehexacarboxylic 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 0.404 g (62%) of the product as a white amorphous solid. Mp: 210.0–210.5 °C. ^1H NMR (600 MHz): δ (ppm) 7.17 (m, 2H), 7.12 (m, 2H). ^{13}C NMR (150 MHz): δ (ppm) 163.1, 161.8, 160.2, 146.0, 134.5, 122.7, 116.8. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{48}\text{H}_{24}\text{F}_6\text{NaO}_{12}$ 929.1070, found 929.1066.

Mellitic Acid (Hexa-3-methyl-4-bromophenyl) Ester (10). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanehexacarboxylic 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: 201.5–202.5 °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). ^{13}C 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 $\text{C}_{54}\text{H}_{36}\text{Br}_6\text{O}_{12}\text{Na}$: C, 46.98; H, 2.61. Found: C, 46.96; H, 2.44.

Mellitic Acid (Hexa-4-cyanophenyl) ester (11). PCl_5 (1.794 g, 8.6 mmol) was added to 1,2,3,4,5,6-cyclohexanehexacarboxylic 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 0.494 g (71%) of the product as a light brown 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). ^{13}C NMR (150 MHz): δ (ppm) 161.9, 152.8, 134.4, 134.4, 122.1, 117.5, 112.0. HRMS (ESI) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{34}\text{H}_{24}\text{N}_6\text{NaO}_{12}$ 971.1350, found 971.1347.

■ ASSOCIATED CONTENT

📄 Supporting Information

Copies of ^1H NMR, ^{13}C 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

- (1) Cadierno, V.; Garcia-Garrido, S. E.; Gimeno, J. *J. Am. Chem. Soc.* **2006**, *128*, 15094.
- (2) Geny, A.; Agenet, N.; Iannazzo, L.; Malacria, M.; Aubert, C.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1810.

- (3) Kotha, S.; Khedkar, P. *Eur. J. Org. Chem.* **2009**, 730.
- (4) Saino, N.; Amemiya, F.; Tanabe, E.; Kase, K.; Okamoto, S. *Org. Lett.* **2006**, *8*, 1439.
- (5) Takeuchi, R.; Nakaya, Y. *Org. Lett.* **2003**, *5*, 3659.
- (6) Mahoney, K. M.; Goswami, P. P.; Winter, A. H. *J. Org. Chem.* **2013**, *78*, 702.
- (7) Yamasaki, N.; Inoue, Y.; Yokoyama, T.; Tai, A.; Ishida, A.; Takamuku, S. *J. Am. Chem. Soc.* **1991**, *113*, 1933.
- (8) Berger, U.; Dannhardt, G.; Wiegrebe, W. *Arch. Pharm. (Weinheim)* **1984**, *317*, 488.
- (9) Ranganathan, S.; Muraleedharan, K. M.; Chandrashekhara Rao, C. H.; Vairamani, M.; Karle, I. L.; Gilardi, R. D. *Chem. Commun. (Cambridge)* **2001**, 2544.