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Improved Syntheses of Halogenated Benzene-1,2,3,4-Tetracarboxylic Diimides

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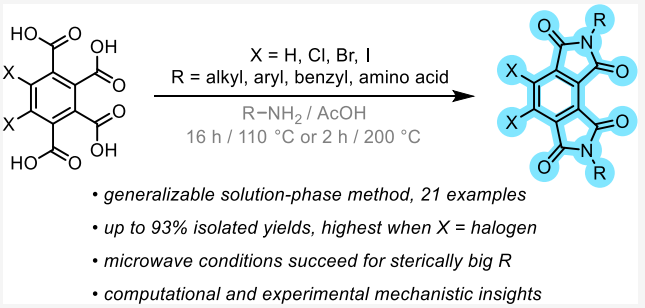
ABSTRACT: The preparation of halogenated benzene-1,2,3,4-tetracarboxylic diimide derivatives is challenging because of the possibility of competitive incorrect cyclizations and S_NAr reactivity. Here, we demonstrate that bypassing traditional cyclic anhydrides and instead directly reacting dihalobenzene-1,2,3,4-tetracarboxylic acids with primary amines in acetic acid solvent successfully provides a range of desirable *ortho*-diimide products in good yields. Furthermore, we demonstrate that sterically challenging *N*-derivatizations can be readily achieved under microwave reactor conditions. The halogenated diimides described here are attractive building blocks for organic materials chemistry.



INTRODUCTION

Aromatic diimides, also known as bis(dicarboximide)s, are the linchpin of a diversity of organic materials encompassing vivid pigments and dyes,[1−3] thermally robust polymers,[4] and n-type electronic materials.[5,6] The electron-withdrawing nature of the cyclic imides lends itself to the creation of n-type semiconducting materials.[3] The annulation of aromatic rings with cyclic imides tends to lead to more significant LUMO-lowering effects than HOMO-lowering effects, thus resulting in red-shifted bandgaps and absorption profiles. Aromatic diimides derived from benzene (PMDI), naphthalene (NDI), and perylene (PDI) (Figure 1a) have received significant research attention because of their facile syntheses and amenability to derivatization.[7−10] While changes in *N*-functionalization are often exploited for tuning solid-state packing behavior and solubility profiles,[11−13] core modification through substitution and metal-mediated cross-coupling reactions of halogenated aromatic diimides[14,15] results in fine control over energy levels and electronic structure.[7,10] In recent years, researchers have developed new strategies for incorporating cyclic imides onto a growing number of aromatic scaffolds, resulting in interesting redox activity[16] and near-IR absorptions.[17]

We recently began exploring the *ortho*-diimide structural isomer of the well-known pyromellitic diimide, which is known as mellophanic diimide (**MDI**),[18−21] and have discovered that it has significant potential as a building block in the construction of compounds with properties of interest to organic materials chemists (Figure 1b,c). Although MDI is slightly less electron accepting than PMDI,[22,23] its geometry enables synthetic possibilities unavailable to the sterically constrained[24] PMDI core. Core dichlorinated *N,N′*-dihexyl

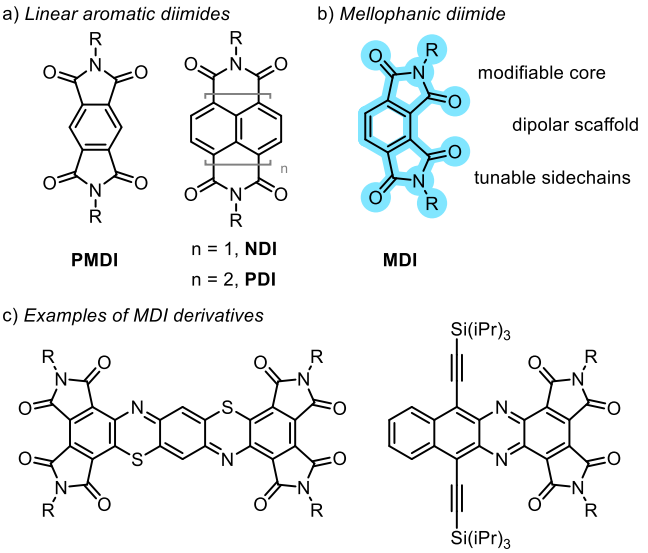


Figure 1. Structural formulas of (a) pyromellitic diimide (PMDI), naphthalene diimide (n = 1, NDI), and perylene diimide (n = 2, PDI), (b) mellophanic diimide (MDI), and (c) heteroacene MDI derivatives that are near-IR absorbing electron acceptors.

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MDI (**Cl_2-MDI-Hex**), for example, readily undergoes both S_NAr and Pd-catalyzed substitutions with aromatic ortho dinucleophiles to lead to a range of highly chromophoric and electron-accepting hetero- and azaacene structures.[23,25] The development of MDI as a building block is further attractive because it is derived from 1,2,3,4-tetramethylbenzene, which is a byproduct of durene synthesis and a constituent of petroleum extract that has no significant industrial use.[26] With these observations in mind, we set out to establish generalizable synthetic methods for obtaining differently halogenated MDI derivatives.

RESULTS AND DISCUSSION

Conventionally, aromatic diimides are synthesized by condensation between the relevant aromatic cyclic dianhydride and an amine, a process that proceeds through an amide-carboxylic (amic) acid intermediate. Extending this approach to the synthesis of ortho aromatic diimides such as mellophanic diimide, however, is complicated by the possibility of incorrect cyclizations to yield 3,6-dicarboxyphthalimide byproducts. Two strategies were identified by Fang et al. for overcoming this challenge: (1) room-temperature amic acid formation followed by acetic anhydride-mediated dehydration and (2) high-temperature equilibration of the reaction mixture to reach the MDI thermodynamic product (Figure 2a).[20]

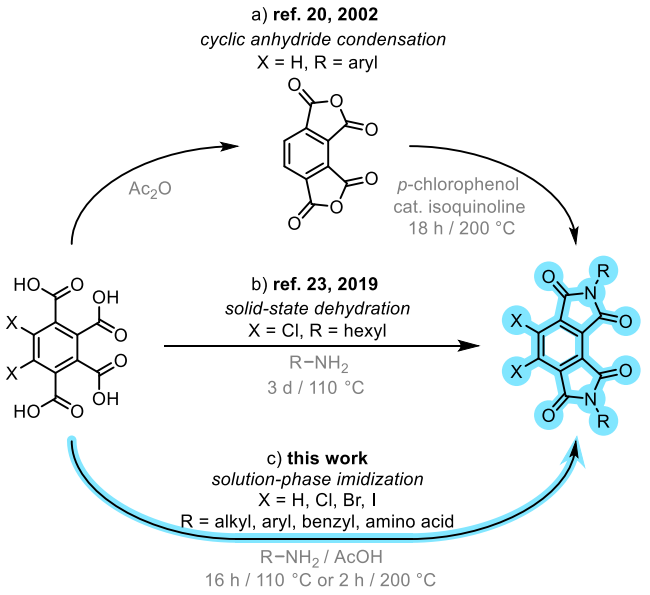

Figure 2. The historical development of synthetic methods for the preparation of MDI compounds began with (a) conventional imidization of a dianhydride precursor, then (b) solid-state dehydration of ammonium carboxylate salts to obtain dichlorinated MDIs, and presented here, (c) the direct solution-phase condensation of tetracarboxylic acids with amines.

While both of these methods were successful for synthesizing *N,N′*-diaryl MDI compounds, we found that they could not be reliably extended toward either *N,N′*-dialkyl- or core-chlorinated MDIs because of competing nucleophilic aromatic substitution reactions and significant 3,6-dicarboxyphthalimide formation, particularly in solvents such as DMF and THF. Inspired by the mellitic triimide synthesis developed by Rose et al.,[27] we were previously able to obtain *N,N′*-dihexyl-4,5-dichloro-MDI (**Cl_2-MDI-Hex**) after the 3-day solid-state dehydration of an ammonium carboxylate salt (Figure 2b).[23] In further explorations, however, we found that this solid-state method could not be consistently extrapolated to differently halogenated benzene tetracarboxylic acids, and furthermore was unsuccessful with more sterically demanding amines. Here, we report our findings that the direct solution-phase reaction between benzene-1,2,3,4-tetracarboxylic acids and primary amines in an acetic acid solvent is a generalizable method for synthesizing MDI derivatives of a variety of imide substitutions and core halogenations (Figure 2c).

Synthesis. The commercially available 1,2,3,4-tetramethylbenzene was chlorinated,[23] brominated,[28] or iodinated[29] following literature procedures to yield intermediates **1-X** (X = Cl, Br, or I), which were then subjected to exhaustive oxidation by 10 eq. of $KMnO_4$ in tBuOH/H_2O (1/1:v/v) to provide the halogenated benzene-1,2,3,4-tetracarboxylic acids **2-X** (Figure 3a). Although many $KMnO_4$ methylarene

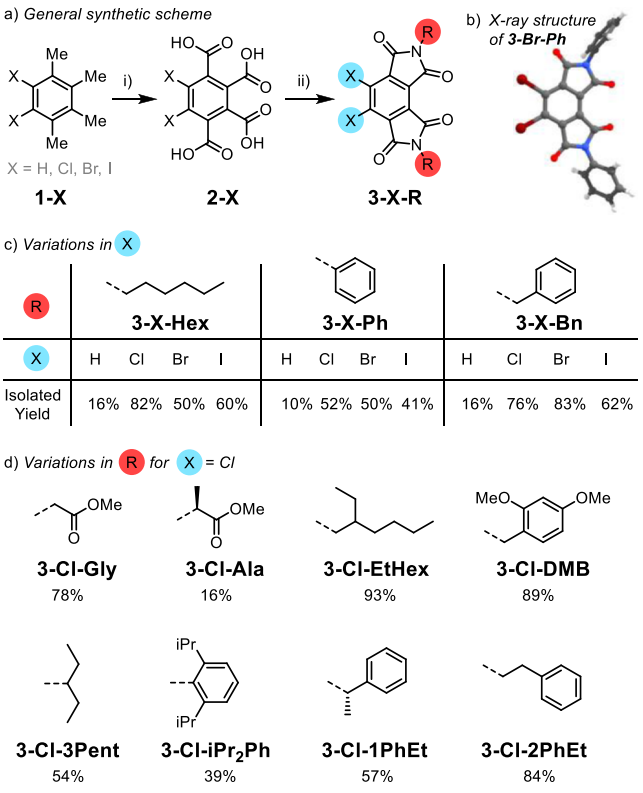

Figure 3. (a) Synthetic pathway for the preparation of **3-X-R** compounds. (i) 10 eq. $KMnO_4$/tBuOH/H_2O; (ii) RNH_2/AcOH. (b) Single crystal X-ray structure of **3-Br-Ph**. (c) Table of isolated yields for a variety of **3-X-R** compounds with a focus on variation in X. Reaction conditions: 0.1 M **2-X** in AcOH, 2.1 equiv *R*–NH_2, 110 °C, 16 h.

oxidation procedures use pyridine as a co-solvent to improve reactant solubility, we have found that the use of tBuOH co-solvent reduces the equivalents of $KMnO_4$ required to achieve full oxidation and furthermore is less prone to exotherm during the addition of $KMnO_4$. Complete removal of reaction solvent prior to acidification of the carboxylate intermediate is important for avoiding the formation of *t*-butyl ester impurities. Our largest scale oxidation (20.0 g, 98.5 mmol of **1-Cl**) proceeded smoothly to provide the tetraacid **2-Cl** in 85% isolated yield.

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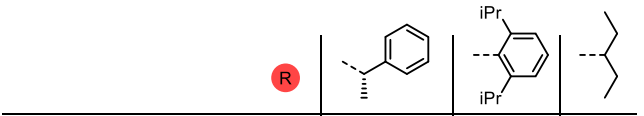
Although we initially followed our previously developed solid-state dehydration protocol for synthesizing **3-X-R** compounds, we were motivated by inconsistent yields and long reaction times to investigate a solution-phase method. Unexpectedly, simply heating the tetraacids **2-X** with primary amines in acetic acid solvent followed, if necessary, by the precipitation of products with the addition of water or MeOH to the reaction mixture, provided MDIs **3-X-R** in up to 93% isolated yield. In some cases, a small amount of additional product can be recovered by extraction of the aqueous filtrate with CH_2Cl_2. Although the reaction byproducts are often polar and soluble enough in AcOH to be removed during the filtration process, the crude material can easily be further purified by passing the crude product mixture through a SiO_2 column.

This method is successful with a variety of amines and there is no discernible trend between the identity of the halogen and the reaction yield. Hexylamine, aniline, and benzylamine react smoothly with **2-X** (X = Cl, Br, and I) in good yields to produce a suite of **3-X-R** compounds. Single crystal X-ray data for **3-Br-Ph** confirms the MDI constitution of the products (Figures 3b, S1−S6). It is notable, as will be discussed below, that yields tend to be higher for the halogenated **3-X-R** compounds than the non-halogenated ones. Amino acid methyl esters can also be readily converted into MDIs, which suggests they may be interesting building blocks for self-assembling small molecules.[30,31] Attempts to perform imidization with 6-amino-1-hexanol, however, resulted in complex mixtures as a consequence of acetate ester formation with the free alcohol. With these results in hand, we attempted to install more sterically demanding *N*-groups such as branched alkyl chains and 2,6-dialkylaryl groups since these are commonly used by organic materials chemists to manipulate crystal packing and solubility. Although 2-ethylhexylamine reacted readily with **2-H** to yield **3-H-EtHex**, imidization of **2-H** with the more sterically hindered nucleophiles such as (*S*)-1-phenylethan-1-amine and 2,6-diisopropylaniline proved to be more recalcitrant. We were unable to isolate any products after applying our standard reaction method, and heating (*S*)-1-phenylethan-1-amine with **2-H** for 3 days at 110 °C resulted in only 11% formation of **3-H-1PhEt**. These low yields for sterically hindered amines were also found when attempting these same reactions using our older solid-state approach (Figure 4).

To overcome this slow reaction rate, we turned to microwave reaction conditions. Gratifyingly, reacting **2-Cl** and (*S*)-1-phenylethan-1-amine at 200 °C for 24 h led to a 58% isolated yield for **3-H-1PhEt**. Under these forcing conditions, an important consideration is whether nucleophilic aromatic substitution (S_NAr) reactions at the aryl halides start to take place when X = halogen. In our trials, we did not observe significant levels of S_NAr reactivity when 2.1 equiv of amine was reacted with tetraacid **2-Cl**.

Mechanistic Insights. Our first attempted synthesis of **3-H-1PhEt** under microwave conditions was performed at 200 °C for 2 h of reaction time and resulted in an 11% isolated yield. Both running the reactions for longer (200 °C for 24 h) or with more equivalents of nucleophile (12 equiv. amine, 200 °C for 2 or 24 h) improved the isolated yield, to 58 and 46%, respectively. It is worth noting that the excess amine approach is not feasible under microwave conditions when X = halogen because of the competitive S_NAr reactions. From a mechanistic perspective, these observations suggest that in AcOH solvent,



	X	H	Cl	Cl	Cl
Solid-state Heating	110 °C / 3 d	-	1%	9%	4%
Conventional Heating (0.1 M in AcOH)	110 °C / 16 hr	0%	57%	39%	54%
Microwave Heating (0.1 M in AcOH)	200 °C / 2 hr	11%	42%	66%	70%
	200 °C / 24 hr	58%	-	-	-
	200 °C / 2 hr excess amine	46%	-	-	-
	200 °C / 24 hr excess amine	48%	-	-	-

Figure 4. Comparison of isolated yields for imidizations between **2-X** and sterically demanding amines under varying reaction conditions.

the reaction is likely taking place under overall equilibrating conditions. To gain more insight into the reaction process, we performed a ^{1}H NMR time-course study of the reaction between **2-H** and (*S*)-1-phenylethan-1-amine in d_4-acetic acid at 110 °C. The core aromatic signals provide a convenient signal for tracking the formation of new species. Upon dissolving only **2-H**, the ^{1}H NMR spectrum reflects the presence of a complex mixture of anhydrides corresponding to intermediates with or without symmetry around the central benzene ring. Although we cannot rule out the cyclic anhydride formation, we believe that mixed acetic anhydride formation is more likely based on the solubility of the reaction intermediates and the results of density functional theory (DFT) calculations (see below). Upon addition of the amine and heating for 5 min, a number of different intermediates are detected by ^{1}H NMR spectroscopy, and the formation of the desired MDI product is first observable after 20 min of reaction time. After 19 h, the mixture resolves itself into being primarily four species, three with symmetry around the benzene core and one without. After 11 days of reaction time, the desired product constitutes only 18% of the product mixture, which highlights the value of microwave reaction conditions for achieving higher yields on a reasonable time scale. The NMR spectrum of the reaction after a total of 31.5 days at 110 °C shows that the product distribution reaches a roughly 1:1:1 ratio of **3-H-1PhEt**, **4-H-1PhEt**, and **5-H-1PhEt** (Figures 5a,b and S7).

We were able to tentatively assign the structure of the reaction intermediates by performing column chromatography on incomplete reaction mixtures and analyzing the filtrates collected during reaction workups. Of these, the most notable intermediates are dicarboxyphthalimides **4-X-R** and **5-X-R**, which correspond to the asymmetric and symmetric phthalimide possibilities, respectively, for monophthalimide formation between the tetraacids **2-X** and an amine (Figure 5a). It is again worth noting that during the reaction, however, it is difficult to rule out whether mixed acetic acid anhydride derivatives are the dominant species. Liquid chromatography mass spectrometry analysis of crude reaction mixtures corroborates the ^{1}H NMR and preparatory observations of **4-X-R** and **5-X-R** as the primary reaction byproducts, but also reveal one other identifiable product corresponding to a diamidophthalimide species **6-X-R**. The analogous diamido

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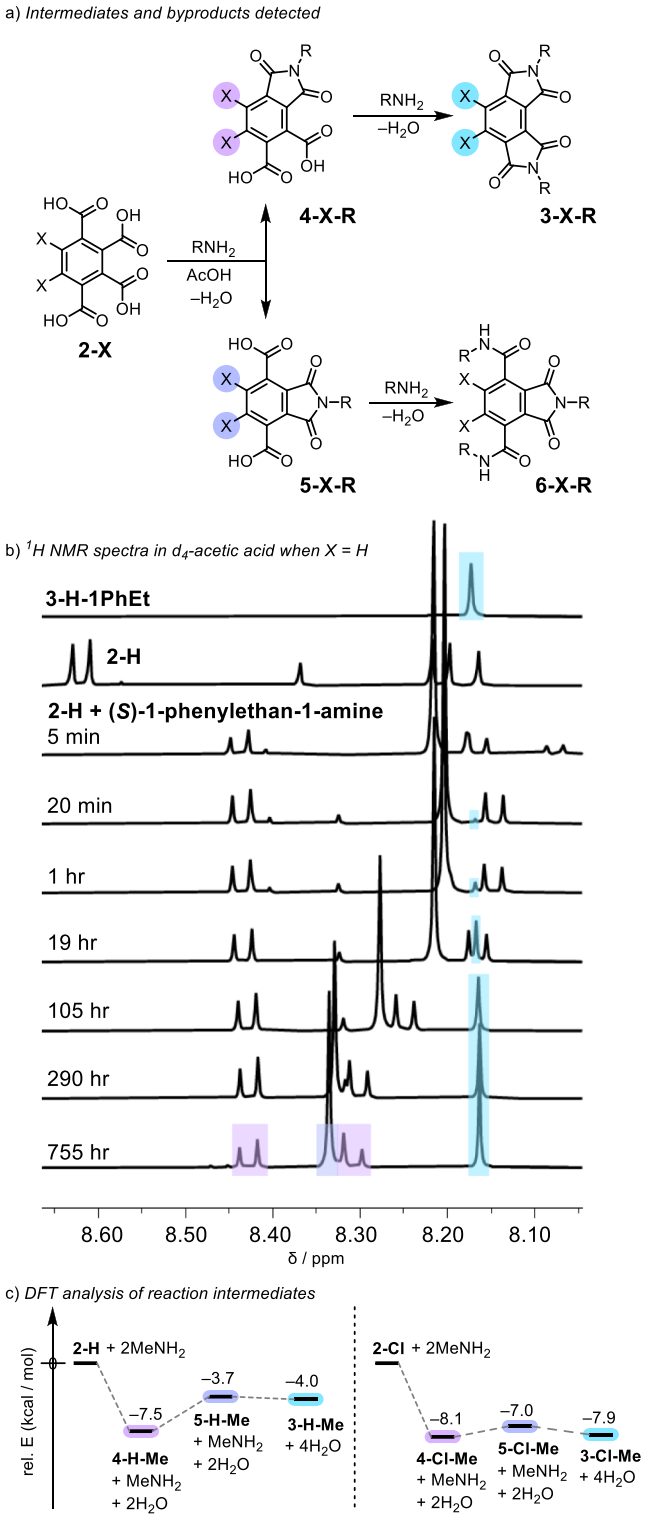

Figure 5. (a) A simplified schematic of reaction intermediates and byproducts during the formation of **3-X-R**. (b) ^{1}H NMR time-course study of the reaction between **2-H** and (*S*)-1-phenylethan-1-amine in d_4-acetic acid at 110 °C, focused on the aromatic region. The highlighted region corresponds to X = H in part a. (c) A comparison of DFT-calculated energies for X = H or Cl and R = Me in an implicit AcOH solvent [M062X/6-31G(d)].

derivative of **4-X-R** should be more likely to proceed to cyclize into **3-X-R** and thus is less likely to be observed.

From a purely statistical perspective, intermediates **4-X-R** and **5-X-R** should be formed in a 3 to 1 ratio because both the 1- and 2-carboxamide derivatives of **2-X** can dehydrate into intermediate **4-X-R**, while only the 2-carboxamide can cyclize into intermediate **5-X-R**. To add context to our understanding, we performed DFT calculations [M062X/6-31G(d)] with implicit acetic acid solvent to evaluate the energy landscape of the reaction between methylamine and either **2-H** or **2-Cl** (Figure 5c). In both cases, the formation of the less symmetric **4-X-Me** is thermodynamically favorable compared to the formation of **5-X-Me**. Interestingly, the transformation of **4-H-Me** into **3-H-Me** is found to be an uphill process by 3.5 kcal/mol, while the analogous conversion of **4-Cl-Me** into **3-Cl-Me** costs only 0.2 kcal/mol. Although these calculations do not account for R group identity, they do correlate strongly with our experimental findings that **3-X-R** formation is higher yielding when X = halogen. We further evaluated the energies of anhydrides formed from compounds **4-X-Me** and **5-X-Me** to determine whether these intermediates might contribute to reaction selectivity. The two possible mixed monoacetic anhydride derivatives of **4-X** are more stable than the analogous anhydrides of **5-X** by ∼5 kcal/mol when X = H and ∼3 kcal/mol when X = Cl (Figure S10,11). Additionally, the cyclic anhydride derivatives of **4-X** are higher in energy than the monoacetic anhydrides. Taken together, we posit that energetic and statistical preference for the formation of the asymmetric **4-X-R** intermediate, in addition to the relatively lower energy of mixed anhydride intermediates, drives conversion into MDI products.

Finally, we sought to understand whether there are any mechanistic differences between imidizations using cyclic dianhydrides as the reaction partner with the primary amine versus our approach of using tetracarboxylic acids as the electrophile. When **2-H** and mellophanic dianhydride (**7-H**) were separately dissolved in d_4-acetic acid with the assistance of heating (1 min in a 110 °C heating block), the aromatic regions of the resulting ^{1}H NMR spectra are qualitatively the same (Figure 6a). This finding shows that the same intermediate species are formed preferentially in the course of the reaction. In an effort to identify these species, we again turned to DFT calculations. Of the 16 different possible anhydrides that can be formed when **2-X** is reacted with AcOH (Figures S10 and 11), four are relatively lower in energy for both X = H and Cl. We, therefore, hypothesize that the spectra in Figure 6a can be explained as a mixture of **2-H** with **2-H-1Ac1**, **2-H-1Ac2**, **8-H**, and **9-H**.

With this combined experimental and computational evidence, we are empowered to conclude that it is unnecessary to perform the extra synthetic step of preparing dianhydride precursors because their relative instability in acetic acid solvent results in solvolysis. This efficiency is particularly relevant for researchers targeting the preparation of novel aromatic diimides for which anhydride precursors are not commercially available.

■ CONCLUSIONS

We have developed methods for the preparation of a wide range of 5,6-dihalobenzene-1,2,3,4-bis(dicarboximides) from the direct solution-phase condensation of benzene-1,2,3,4-tetracarboxylic acids and primary amines in an acetic acid solvent. The preparation of compounds with sterically demanding groups at the N atoms of the imides can be achieved readily under microwave conditions. Experimental

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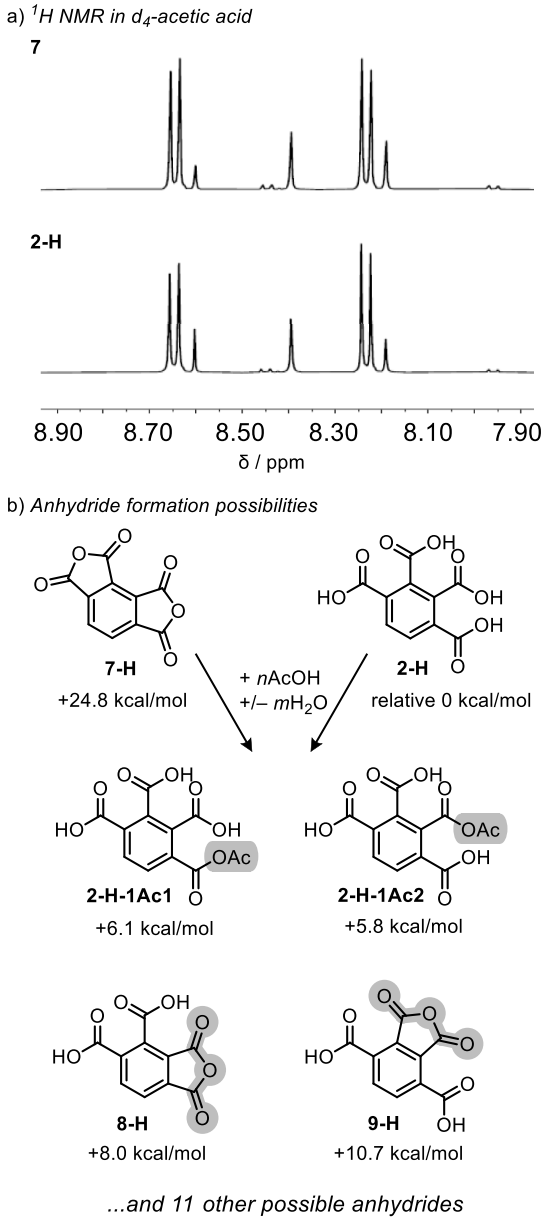

Figure 6. (a) ^{1}H NMR of dianhydride **7** and tetraacid **2-H** dissolved in d_4-acetic acid. (b) Scheme showing the four most stable anhydrides, as predicted by DFT calculations, that are formed upon dissolving either **7** or **2-H** in AcOH.

and computational studies suggest that the reaction can take place under equilibrium conditions that are favored both statistically and thermodynamically to yield the desired *ortho*-diimide compounds instead of the symmetric dicarboxyphthalimide. Importantly, it is possible to avoid perturbing the aryl halide positions under these reaction conditions, which sets the stage for exploring a broad range of chemistries available for producing imide-decorated aromatic compounds with tailored form and function.

EXPERIMENTAL SECTION

General Information. Reagents were purchased from TCI Chemicals or Sigma-Aldrich and used as supplied. Microwave reactions were performed in sealed vials using a Biotage Initiator+ equipped with an auto-sampler. The reactor is equipped with an IR-sensor for temperature monitoring. Column chromatography was performed using a Teledyne Isco Combiflash Rf$^+$ and Silicycle SiliaSep or Teledyne Isco flash cartridges (normal phase, 40−63 μm, 60 Å). ^{1}H NMR and ^{13}C NMR spectra were collected on a Bruker Avance III 400 MHz and referenced to residual solvent as the internal standard ($CDCl_3$: ^{1}H-7.26 ppm and ^{13}C-77.16 ppm, Acetone-d_6: 1*H*-2.05 ppm and ^{13}C-29.84 ppm). High-resolution ESI-MS data were collected on a Thermo Scientific Orbitrap Velos (University of Minnesota, Masonic Cancer Center). IR spectra were collected on a Thermo Fisher Nicolet iS10 FTIR Spectrometer. Phase changes/melting points were determined by differential scanning calorimetry (DSC) using a TA Instruments Discovery DSC25.

Synthesis of 2-X Compounds. Compound **2-Cl** was prepared following literature procedures.[23]

Synthesis of 2-Br (5,6-Dibromobenzene-1,2,3,4-tetracarboxylic Acid). Setup: A 500 mL three-neck flask equipped with a magnetic stir bar and a water-cooled condenser was charged with **1-Br**[32] (8.29 g, 28.12 mmol, 1 equiv), tBuOH (60 mL), and H_2O (60 mL). Subsequently, $KMnO_4$ (22.22 g, 140.60 mmol, 5 equiv) was added in one batch to the reaction mixture. The open necks were sealed with glass stoppers, the condenser was left open, and the reaction mixture was then refluxed gently using an aluminum bead heating bath with vigorous stirring until the purple color of the solution faded, indicating complete consumption of $KMnO_4$. The reaction flask was removed from the heating bath and then more $KMnO_4$ (22.22 g, 140.60 mmol, 5 equiv) was added. The reaction mixture was refluxed gently with vigorous stirring for 16 h, at which point it was observed that the solution was still purple in color. Workup: Before cooling to room temperature, EtOH (10 mL) was added to quench the remaining $KMnO_4$. Once the purple color of $KMnO_4$ disappeared, the reaction mixture was hot filtered to remove the MnO_2 byproduct. The solvents were distilled off by rotary evaporation, and the residue was further dried in a vacuum oven at 60 °C for an hour. The residue was then carefully redissolved in a small amount of water and concentrated HCl was added drop-wisely until a solution with pH < 2 was achieved. The excess concentrated HCl and H_2O were removed by rotary evaporation to yield a white solid, consisting of what we presume to be a mixture of product and KCl. The solid was dried in vacuum at 60 °C overnight. Acetone (100 mL) was added to the residue and the mixture was stirred vigorously to break up the solid aggregates and extract the product. The insoluble inorganic material was removed by vacuum filtration, and the filtrate was evaporated to yield a brown solid that was found to be analytically pure **2-Br** (9.26 g, 22.49 mmol, 80% yield). Characterization: ^{13}C{^{1}H} NMR (101 MHz, Acetone-d_6); δ 166.33, 166.10, 139.53, 132.44, 126.09. HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_{10}H_3Br_2O_8$, 410.8180; found, 410.8152. IR spectrum (solid), ν, cm^{-1}: 1693; 1437; 1240. mp 186.92 °C.

Synthesis of 2-I (5,6-Diiodobenzene-1,2,3,4-tetracarboxylic Acid). Setup: A 500 mL three-neck flask equipped with a magnetic stir bar and a water-cooled condenser was charged with **1-I**[29] (9.65 g, 25.00 mmol, 1 equiv), tBuOH (40 mL), and H_2O (80 mL). Subsequently, $KMnO_4$ (19.75 g, 125.00 mmol, 5 equiv) was added in one batch to the reaction mixture. The open necks were sealed with glass stoppers, the condenser was left open, and the reaction mixture was then refluxed gently using an aluminum bead heating bath with vigorous stirring until the purple color of the solution faded, indicating complete consumption of $KMnO_4$. The reaction flask was removed from the heating bath and then more $KMnO_4$ (11.85 g, 75.00 mmol, 3 equiv) was added. The reaction mixture was refluxed gently with vigorous stirring for 16 h, at which point it was observed that the solution was still purple in color. Workup: Before cooling to room temperature, EtOH (15 mL) was added to quench the remaining $KMnO_4$. Once the purple color of $KMnO_4$ disappeared, the reaction mixture was hot filtered to remove the MnO_2 byproduct. The solvents were distilled off by rotary evaporation and further dried in a vacuum oven at 60 °C for an hour. The residue was then carefully redissolved in a small amount of water and the concentrated HCl (8.3 mL, 5 equiv) drop-wisely. The solution was stirred for 10 min before another batch of concentrated HCl (8.3 mL, 5 equiv) was added

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drop-wisely to obtain a solution with pH < 2. The excess concentrated HCl and H_2O were removed by rotary evaporation to yield a white solid, consisting of what we presume to be a mixture of product and KCl. The solid was dried in vacuum at 60 °C overnight. Acetone (100 mL) was added to the residue and the mixture was stirred vigorously to break up the solid aggregates and extract the product. The insoluble inorganic material was removed by vacuum filtration, and the filtrate was evaporated to yield a brown solid that was found to be **2-I** (7.16 g, 20.11 mmol, 57% yield), containing a small amount of unoxidized impurities. Characterization: $^{13}C\{^1H\}$ NMR (101 MHz, Acetone-d_6); δ 168.21, 166.41, 143.41, 132.01, 112.94. HRMS (ESI) m/z: $[M - H]^-$ calcd for $C_{10}H_3I_2O_8$, 504.7923; found, 504.7895. IR spectrum (solid), ν, cm^{-1}: 1692; 1435; 1233; 1165; 1122; 898; 599. mp 183.85, 199.19 °C (two peaks observed).

Synthesis of 3-X Compounds. *General Procedures.* To synthesize the dihalogenated mellophanic diimides (**X_2-MDI-R**), all reactions required a tetracid, an amine, and acetic acid as solvents. Reactions were run at a 0.1 M concentration of **2-X** in AcOH to ensure optimal dehydration of carboxylic acids to imides. Generally, **2-X** (100 mg) was dissolved in glacial acetic acid at a 0.1 M concentration. Then, the amine of choice (R = phenyl, benzyl, hexyl, etc.) was added to the reaction vessel. The reaction mixture was stirred at 120 °C for 12 h. Then, precipitates formed upon cooling of the reaction mixture, or by the addition of anti-solvent, were collected by vacuum filtration. Products were characterized by ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry.

Setup. Setup A: A round-bottom flask equipped with a magnetic stir bar, charged with AcOH. The reaction flask was heated using an aluminum bead bath.

Setup B: A 2- or 5 mL microwave vial equipped with a magnetic stir bar was charged with AcOH. The vial was heated in a microwave reactor.

Workup. Workup A: The crude reaction mixture was cooled to room temperature with stirring and the resulting precipitate was collected via vacuum filtration, using MeOH rinses as needed to maximize product recovery.

Workup B: The crude reaction mixture was cooled to room temperature with stirring. Because no precipitates were observed, an anti-solvent (MeOH or H_2O) was added to precipitate the product, which was then collected via vacuum filtration.

Workup C: Additional crops of the product were collected from the filtrate after completing Workup A.

Purification. Purification A: The reaction mixture was cooled to room temperature on stirring; however, no solid precipitate formed even upon the addition of H_2O. The crude reaction mixture was extracted using CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was dried over $MgSO_4$, volatiles removed by rotary evaporation, and the residue purified by column chromatography on SiO_2 (CH_2Cl_2).

Purification B: Solid isolated from Workup A or B yielded the impure product (determined via NMR), so the crude solid was purified by column chromatography on SiO_2 (CH_2Cl_2).

Synthesis of 3-H-Hex (2,7-dihexylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.100 g, 0.395 mmol, 1 equiv) of **2-H** was dissolved with stirring and heating at 120 °C in 3.9 mL of AcOH. Upon complete dissolution, (109 μL, 0.825 mmol, 2.1 equiv), hexylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 4.0 mL of DI H_2O; however, no solid precipitate formed so, Purification A was utilized to yield **3-H-Hex**, a pale white solid (0.025 g, 0.064 μmol, 16.3% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 8.18 (s, 2H), 3.75 (t, 4H), 1.69 (p, J = 7.1 Hz, 4H), 1.38–1.23 (m, 12H), 0.91–0.84 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 166.7, 164.4, 137.7, 128.2, 38.9, 31.5, 28.5, 26.6, 22.6, 14.1. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{22}H_{28}N_2O_4$, 384.2055; found, 384.2053. IR spectrum (solid), ν, cm^{-1}: 1705; 1368; 1068; 726. mp 191.11 °C.

Synthesis of 3-Cl-Hex (4,5-Dichloro-2,7-dihexylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (1.01 g, 3.13 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at120 °C in 31 mL of AcOH. Upon complete dissolution, (860 μL, 6.51 mmol, 2.1 equiv), hexylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup A was followed alongside Workup C using MeOH as a rinse with no additional purification steps to yield **3-Cl-Hex**, a white solid (1.16 g, 2.56 mmol, 81.9% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 3.75 (t, J = 7.3 Hz, 4H), 1.75–1.65 (m, 4H), 1.36–1.28 (m, 12H), 0.98–0.79 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.0, 162.4, 137.0, 133.7, 127.6, 39.3, 31.4, 28.3, 26.6, 22.6, 14.1. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{22}H_{26}Cl_2N_2O_4$, 452.1275; found, 452.1254. IR spectrum (solid), ν, cm^{-1}: 1710; 1399; 1356; 1092; 736. mp 160.31 °C.

Synthesis of 3-Br-Hex (4,5-dibromo-2,7-dihexylpyrrolo[3,4-e]-isoindole-1,3,6,8(2*H*,7*H*)-tetraone):

Setup: Following steps from Setup A, (0.101 g, 0.245 mmol, 1 equiv) of **2-Br** was dissolved with stirring and heating at 120 °C in 2.5 mL of AcOH. Upon complete dissolution, (62 μL, 0.51 mmol, 2.1 equiv), hexylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup A was followed with no additional purification steps to yield **3-Br-Hex**, a pale-yellow solid (0.133 g, 0.122 mmol, 49.7% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 3.79–3.72 (m, 4H), 1.70 (t, J = 7.1 Hz, 4H), 1.42–1.19 (m, 12H), 0.96–0.80 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.4, 162.4, 135.7, 129.7, 128.3, 39.4, 31.4, 28.3, 26.6, 22.6, 14.1. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{22}H_{26}Br_2N_2O_4$, 542.0244; found, 542.0249. IR spectrum (solid), ν, cm^{-1}: 1710; 1403; 1350; 1083; 737. mp 168.51 °C.

Synthesis of 3-I-Hex (2,7-Dihexyl-4,5-diiodopyrrolo[3,4-e]-isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (1.01 g, 1.99 mmol, 1 equiv) of **2-I** was dissolved with stirring and heating at 120 °C in 19.8 mL of AcOH. Upon complete dissolution, (550 μL, 0.416 mmol, 2.1 equiv), hexylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup C was followed using EtOH rinse with no additional purification steps to yield **3-I-Hex**, a pale-yellow solid (0.764 g, 1.20 mmol, 60.3% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 3.76 (t, J = 7.3 Hz, 4H), 1.71 (q, J = 7.4 Hz, 4H), 1.38–1.25 (m, 12H), 0.92–0.84 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 165.1, 162.3, 139.0, 128.6, 115.9, 39.5, 31.4, 28.2, 26.6, 22.6, 14.1. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{22}H_{26}I_2N_2O_4$, 635.9987; found, 635.9961. IR spectrum (solid), ν, cm^{-1}: 1710; 1395; 1335; 734. mp 160.75 °C.

Synthesis of 3-H-Ph (2,7-diphenylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.049 g, 0.191 mmol, 1 equiv) of **2-H** was dissolved with stirring and heating at 120 °C in 2.0 mL of AcOH. Upon complete dissolution, (38 μL, 0.42 mmol, 2.1 equiv.), aniline was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 3 mL of DI H_2O alongside Purification B to yield **3-H-Ph**, a pale white solid (0.007 g, 19.5 μmol, 10.2% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 8.39 (s, 2H), 7.60–7.41 (m, 10H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 165.5, 163.0, 137.8, 131.2, 129.4, 129.3, 128.9, 128.6, 126.6. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{22}H_{12}N_2O_4$, 368.0803; found, 368.0802. IR spectrum (solid), ν, cm^{-1}: 1721; 1366; 1140; 1097; 726; 717; 683; 622. mp 284.51 °C.

Synthesis of 3-Cl-Ph (4,5-Dichloro-2,7-diphenylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (1.02 g, 3.16 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 30 mL of AcOH. Upon complete dissolution, (595 μL, 6.52 mmol, 2.1 equiv), aniline was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup A was followed alongside Workup C using MeOH as a rinse with no additional purification steps to yield **3-Cl-Ph**, a white solid (0.7107 g, 1.63 mmol, 51.5% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 7.59–7.50 (m, 4H), 7.50–7.42 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 162.9, 161.1, 138.1, 133.6, 130.9, 129.5, 129.1, 127.6, 126.6. HRMS

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(ESI) *m/z*: $[M]^-$ calcd for $C_{22}H_{10}Cl_2N_2O_4$, 436.0023; found, 436.0002. IR spectrum (solid), ν, cm^{-1}: 1727; 1713; 1393; 1365; 1123; 739; 731; 715; 688. mp 298.1 °C.

Synthesis of 3-Br-Ph (4,5-Dibromo-2,7-diphenylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (1.01 g, 2.45 mmol, 1 equiv) of **2-Br** was dissolved with stirring and heating at 120 °C in 24 mL of AcOH. Upon complete dissolution, (466 μL, 5.10 mmol, 2.1 equiv), aniline was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup A was followed with no additional purification steps to yield **3-Br-Ph**, a pale-yellow solid (0.643 g, 0.122 mmol, 49.9% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 7.59−7.49 (m, 4H), 7.51−7.42 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 163.3, 161.1, 135.6, 131.0, 130.9, 129.5, 129.1, 128.3, 126.6. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{22}H_{10}Br_2N_2O_4$, 525.8992; found, 525.8979. IR spectrum (solid), ν, cm^{-1}: 1731; 1717; 1382; 1357; 1125; 737; 728; 710; 691; 627. mp 335.66 °C.

Synthesis of 3-I-Ph (4,5-Diiodo-2,7-diphenylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.102 g, 0.201 mmol, 1 equiv) of **2-I** was dissolved with stirring and heating at 120 °C in 2.0 mL of AcOH. Upon complete dissolution, (38 μL, 0.42 mmol, 2.1 equiv), aniline was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup C was followed using a MeOH rinse with no additional purification steps to yield **3-I-Ph**, a yellow-brown solid (0.051 g, 0.008 mmol, 40.5% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 7.57−7.50 (m, 4H), 7.49−7.42 (m, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.0, 161.1, 138.9, 131.1, 129.4, 129.1, 128.6, 126.6, 117.5. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{22}H_{10}I_2N_2O_4$, 619.8735; found, 619.8713. IR spectrum (solid), ν, cm^{-1}: 1711; 1374; 1126; 736; 726; 707; 691; 627. mp 350.23 °C.

Synthesis of 3-H-Bn (2,7-dibenzylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.051 g, 0.199 mmol, 1 equiv) of **2-H** was dissolved with stirring and heating at 120 °C in 2.0 mL of AcOH. Upon complete dissolution, (45 μL, 0.41 mmol, 2.1 equiv) benzylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using a MeOH rinse to yield **3-H-Bn,** a white solid (0.0122 g, 0.031 mmol, 15.5% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 8.17 (s, 2H), 7.50−7.42 (m, 4H), 7.35−7.23 (m, 6H), 4.89 (s, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 166.2, 163.9, 137.7, 135.7, 129.2, 128.9, 128.7, 128.5, 128.3, 42.5. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{24}H_{16}N_2O_4$, 396.1116; found, 396.1103. IR spectrum (solid), ν, cm^{-1}: 1709; 1388; 729; 698; 626. mp 214.56, 224.99 °C (two peaks observed).

Synthesis of 3-Cl-Bn (2,7-Dibenzyl-4,5-dichloropyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.101 g, 0.312 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 3.1 mL of AcOH. Upon complete dissolution, (71 μL, 0.650 mmol, 2.1 equiv), benzylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup A was followed with no additional purification steps to yield **3-Cl-Bn**, a white solid (0.111 g, 0.239 mmol, 76.4% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 7.49−7.42 (m, 4H), 7.36−7.25 (m, 6H), 4.88 (s, 4H)·$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 163.6, 162.0, 137.3, 135.3, 133.7, 129.3, 129.0, 128.5, 127.6, 42.8. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{24}H_{14}Cl_2N_2O_4$, 464.0336; found, 464.0319. IR spectrum (solid), ν, cm^{-1}: 1728; 1715; 1338; 734; 696. mp 234.16, 246.52 °C (two peaks observed).

Synthesis of 3-Br-Bn (2,7-Dibenzyl-4,5-dibromopyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.100 g, 0.245 mmol, 1 equiv) of **2-Br** was dissolved with stirring and heating at 120 °C in 2.5 mL of AcOH. Upon complete dissolution, (56 μL, 0.51 mmol, 2.1 equiv), benzylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup A was followed with no additional purification steps to yield **3-Br-Bn**, a pale-yellow solid (0.111 g, 0.201 mmol, 82.7% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 7.50−7.43 (m, 4H), 7.36−7.26 (m, 6H), 4.89 (s, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.0, 161.9, 135.7, 135.3, 130.1, 129.4, 129.0, 128.5, 128.3, 42.9. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{24}H_{14}Br_2N_2O_4$, 553.9305; found, 553.9305. IR spectrum (solid), ν, cm^{-1}: 1724; 1706; 1383; 1340; 1325; 1128; 726; 736; 694; 624; 613. mp 246.07 °C.

Synthesis of 3-I-Bn (2,7-Dibenzyl-4,5-diiodopyrrolo[3,4-e]-isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup:Following steps from Setup A, (0.100 g, 0.201 mmol, 1 equiv) of **2-I** was dissolved with stirring and heating at 120 °C in 2.0 mL of AcOH. Upon complete dissolution, (46 μL, 0.42 mmol, 2.1 equiv), benzylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup C was followed using a MeOH rinse with no additional purification steps to yield **3-I-Bn**, a pale yellow solid (0.080 g, 0.124 mmol, 61.6% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 7.51−7.43 (m, 4H), 7.36−7.25 (m, 3H), 4.90 (s, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.7, 161.9, 139.0, 135.3, 129.4, 129.0, 128.6, 128.5, 116.3, 43.0. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{24}H_{14}I_2N_2O_4$, 647.9048; found, 647.9043. IR spectrum (solid), ν, cm^{-1}: 1719; 1710; 1386; 1343; 738; 723; 694. mp 295.44 °C.

Synthesis of 3-Cl-Gly (Dimethyl 2,2′-(4,5-dichloro-1,3,6,8-Tetraoxo-1,3,6,8-tetrahydropyrrolo[3,4-e]isoindole-2,7-diyl)-diacetate). Setup: Following steps from Setup A, (0.0504 g, 0.156 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 1.6 mL of AcOH. Upon complete dissolution, (40 mg, 0.319 mmol, 2.1 equiv), glycine methyl ester hydrochloride was added. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 2 mL of DI H_2O with no additional purification steps to yield **3-Cl-Gly**, a white solid (0.052 g, 0.121 mmol, 77.7% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 4.51 (s, 4H), 3.79 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 166.9, 163.0, 161.3, 137.9, 133.9, 127.6, 53.2, 39.6. HRMS (ESI) *m/z*: $[M + OH]^-$ calcd for $C_{16}H_{11}Cl_2N_2O_9$, 444.9847; found, 444.9817. IR spectrum (solid), ν, cm^{-1}: 1721; 1230; 1132; 742. mp 198.1 °C.

Synthesis of 3-Cl-Ala (Dimethyl 2,2′-(4,5-dichloro-1,3,6,8-Tetraoxo-1,3,6,8-tetrahydropyrrolo[3,4-e]isoindole-2,7-diyl) (2*S*,2′*S*)-dipropionate). Setup: Following steps from Setup A, (0.0526 g, 0.163 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 1.6 mL of AcOH. Upon complete dissolution, (42.8 mg, 0.307 mmol, 2.1 equiv), alanine methyl ester hydrochloride was added. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 2 mL of DI H_2O with no additional purification steps to yield **3-Cl-Ala**, a white solid (0.012 g, 0.027 mmol, 16.4% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 5.04 (q, *J* = 7.4 Hz, 2H), 3.76 (s, 6H), 1.73 (d, *J* = 7.4 Hz, 6H)·$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 169.3, 163.0, 161.4, 133.6, 127.5, 53.3, 48.6, 15.1, 15.0. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{18}H_{14}Cl_2N_2O_8$, 456.0133; found, 456.0102. IR spectrum (solid), ν, cm^{-1}: 1728; 1715; 1373; 1157; 781; 737. mp 163.41 °C.

Synthesis of 3-Cl-EtHex (4,5-Dichloro-2,7-bis(2-ethylhexyl)-pyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.110 g, 0.340 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 3.0 mL of AcOH. Upon complete dissolution, (120 μL, 0.733 mmol, 2.1 equiv), 2-ethylhexylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 2 mL of DI H_2O alongside Purification B to yield **3-Cl-EtHex**, a white solid (0.089 g, 0.32 mmol, 92.8% yield).

Characterization: ^1H NMR (400 MHz, $CDCl_3$); δ 3.68−3.61 (m, 4H), 1.85 (p, *J* = 6.5 Hz, 2H), 1.31 (tq, *J* = 11.5, 6.6 Hz, 16H), 0.96−0.82 (m, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.3, 162.7, 137.0, 133.6, 127.5, 43.1, 38.3, 30.7, 28.7, 24.1, 23.1, 14.2, 10.5. HRMS (ESI) *m/z*: $[M]^-$ calcd for $C_{26}H_{34}Cl_2N_2O_4$, 508.1901; found,

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508.1873. IR spectrum (solid), ν, cm^{-1}: 1709; 1399; 135; 1091; 736. mp 75.4, 136.43, 382.64 °C (three broad peaks observed).

Synthesis of 3-Cl-DMB (4,5-Dichloro-2,7-bis(2,4-dimethoxybenzyl)pyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: Following steps from Setup A, (0.075 g, 0.232 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 2.3 mL of AcOH. Upon complete dissolution, (110 μL, 0.730 mmol, 2.1 equiv), 2,4-dimethoxybenzylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 2 mL of DI H_2O with no additional purification steps to yield **3-Cl-DMB**, a white solid (0.122 mg, 0.208 mmol, 89.4% yield).

Characterization: ^{1}H NMR (400 MHz, DMSO); δ 7.09 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 2.4 Hz, 2H), 6.44 (dd, J = 8.4, 2.4 Hz, 2H), 4.69 (s, 4H), 3.79 (s, 6H), 3.73 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO); δ 163.7, 162.1, 160.2, 157.6, 134.1, 133.6, 128.9, 127.6, 115.3, 104.5, 98.3, 55.6, 55.2, 36.9. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{28}H_{22}Cl_2N_2O_8$, 584.0759; found, 584.0725. IR spectrum (solid), ν, cm^{-1}: 1713; 1437; 1278; 1253; 1214; 1175; 1133; 1078; 997. mp 344.82 °C.

Synthesis of 3-Cl-3Pent (4,5-Dichloro-2,7-di(pentan-3-yl)-pyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup 1: Following steps from Setup A, (0.109 g, 0.336 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 3.2 mL of AcOH. Upon complete dissolution, (76 μL, 0.65 mmol, 2.1 equiv), 3-aminopentane was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 2 mL of DI H_2O with no precipitate formation. Thus, Purification A was followed to yield **3-Cl-3Pent**, a white-beige solid (0.077 g, 0.182 mmol, 54.0% yield).

Characterization: ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.12 (tt, J = 10.3, 5.2 Hz, 2H), 2.08 (ddq, J = 14.7, 10.1, 7.4 Hz, 4H), 1.80 (dqd, J = 14.7, 7.4, 5.2 Hz, 4H), 0.87 (t, J = 7.4 Hz, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.4, 162.9, 137.0, 133.2, 127.3, 57.2, 25.2, 11.3. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{20}H_{22}Cl_2N_2O_4$, 424.0962; found, 424.0932. IR spectrum (solid), ν, cm^{-1}: 1713; 1345; 1080; 739; 527. mp 106.76, 122.82, 126.86 °C (three peaks observed).

Setup 2: Following steps from Setup B, (0.051 g, 0.157 mmol, 1 equiv) of **2-Cl** was added alongside 1.6 mL of AcOH and (38 μL, 0.326 mmol, 2.1 equiv) 3-aminopentane. The reaction was then sealed and reacted in the Microwave Reactor at 200 °C for 2 h. Workup and Purification: Workup B was followed using 2.0 mL of DI H_2O with no additional purification steps to yield **3-Cl-3Pent**, a yellow solid (0.047 g, 0.111 mmol, 70.4% yield).

Characterization: ^{1}H NMR (400 MHz, $CDCl_3$); δ 4.12 (tt, J = 10.2, 5.2 Hz, 2H), 2.09 (ddq, J = 14.7, 10.1, 7.4 Hz, 4H), 1.81 (dqd, J = 14.7, 7.5, 5.2 Hz, 4H), 0.87 (t, J = 7.4 Hz, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 164.5, 162.9, 137.0, 133.2, 127.4, 57.2, 25.2, 11.3. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{20}H_{22}Cl_2N_2O_4$, 424.0962; found, 424.0932. IR spectrum (solid), ν, cm^{-1}: 1713; 1345; 1080; 739; 527. mp 106.76, 122.82, 126.86 °C (three peaks observed).

Synthesis of 3-Cl-iPr$_2$Ph (4,5-Dichloro-2,7-bis(2,6-diisopropylphenyl)pyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup 1: Following steps from Setup A, (0.101 g, 0.313 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 3.2 mL of AcOH. Upon complete dissolution, (123 μL, 0.100 mmol, 2.1 equiv), 2,6-diisopropylaniline was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 2 mL of DI H_2O with no additional purification steps to yield **3-Cl-iPr$_2$Ph**, a white solid (0.073 g, 0.121 mmol, 38.6% yield).

Setup 2: Following steps from Setup B, (0.053 g, 0.164 mmol, 1 equiv) of **2-Cl** was added alongside 1.6 mL of AcOH and (62 μL, 0.329 mmol, 2.1 equiv) 2,6-diisopropylaniline. The reaction was then sealed and reacted in the microwave reactor at 200 °C for 2 h. Workup and Purification: Workup B was followed using 2.0 mL of DI H_2O with no additional purification steps to yield **3-Cl-iPr$_2$Ph**, a yellowish-white solid (0.066 g, 0.108 mmol, 65.9% yield).

Characterization: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.53–7.45 (m, 2H), 7.34–7.27 (m, 4H), 2.69 (hept, J = 7.0 Hz, 4H), 1.20 (d, J = 6.9 Hz, 12H), 1.17 (d, J = 6.8 Hz, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 163.8, 161.6, 147.1, 138.1, 133.9, 130.8, 127.8, 126.2, 124.3, 29.6, 24.4, 24.2. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{34}H_{34}Cl_2N_2O_4$, 604.1901; found, 604.1862. IR spectrum (solid), ν, cm^{-1}: 1730; 1356; 1130; 802; 741; 676. mp 320.22 °C.

Synthesis of 3-Cl-1PhEt (4,5-Dichloro-2,7-bis((*S*)-1-phenylethyl)pyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup 1: The following steps from Setup A, (0.103 g, 0.319 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 3.0 mL of AcOH. Upon complete dissolution, (79 μL, 0.627 mmol, 2.1 equiv), *S*-methylbenzylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 2 mL of DI H_2O with no additional purification steps to yield **3-Cl-1PhEt**, a white solid (0.089 g, 0.181 mmol, 56.7% yield).

Characterization: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.55–7.47 (m, 4H), 7.36–7.21 (m, 6H), 5.61 (q, J = 7.3 Hz, 2H), 1.94 (d, J = 7.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 163.7, 162.2, 139.1, 137.1, 133.4, 128.8, 128.4, 127.9, 127.5, 51.1, 17.2. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{26}H_{18}Cl_2N_2O_4$, 492.0649; found, 492.0621. IR spectrum (solid), ν, cm^{-1}: 1714; 1331; 738; 697. mp 106.81 °C.

Setup 2: The following steps from Setup B, (0.052 g, 0.161 mmol, 1 equiv) of **2-Cl** was added alongside 5.2 mL of AcOH and (41 μL, 0.325 mmol, 2.1 equiv) *S*-methylbenzylamine. The reaction was then sealed and reacted in the microwave reactor at 200 °C for 2 h. Workup and Purification: Workup B was followed using 5.0 mL of DI H_2O with no additional purification steps to yield **3-Cl-1PhEt**, a pale white solid (0.033 g, 0.067 mmol, 41.6% yield).

Characterization: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.55–7.39 (m, 4H), 7.39–7.22 (m, 6H), 5.60 (q, J = 7.3 Hz, 2H), 1.94 (d, J = 7.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 163.7, 162.1, 139.1, 137.1, 133.4, 128.8, 128.3, 127.9, 127.5, 126.6, 51.1, 17.2. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{26}H_{18}Cl_2N_2O_4$, 492.0649; found, 492.0621. IR spectrum (solid), ν, cm^{-1}: 1714; 1331; 738; 697. mp 106.81 °C.

Synthesis of 3-Cl-2PhEt (4,5-Dichloro-2,7-diphenethylpyrrolo[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: The following steps from Setup A, (2.0 g, 6.18 mmol, 1 equiv) of **2-Cl** was dissolved with stirring and heating at 120 °C in 60 mL of AcOH. Upon complete dissolution, (1.63 mL, 13.0 mmol, 2.1 equiv), 2-ethylphenylamine was added via micropipette. The reaction was then stirred for 18 h. Workup and Purification: Workup B was followed using 30 mL of DI H_2O with no additional purification steps to yield **3-Cl-2PhEt**, a white solid (2.55 g, 5.18 mmol, 83.7% yield).

Characterization: ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.34–7.20 (m, 10H), 4.04–3.95 (m, 4H), 3.06–2.98 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 163.7, 162.1, 137.4, 137.1, 133.6, 128.92, 128.86, 127.5, 127.1, 40.4, 34.3. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{26}H_{18}Cl_2N_2O_4$, 492.0649; found, 492.0625. IR spectrum (solid), ν, cm^{-1}: 1711; 1361; 1345; 1186; 741; 730. mp 208.75 °C.

Synthesis of 3-H-1PhEt (2,7-bis((*S*)-1-phenylethyl)pyrrolo-[3,4-e]isoindole-1,3,6,8(2*H*,7*H*)-tetraone). Setup: The following steps from Setup B, (0.052 g, 1.99 mmol, 1 equiv) of **2-H** was added alongside 2.0 mL of AcOH and (45 μL, 0.41 mmol, 2.1 equiv) benzylamine. The reaction was then sealed and reacted in the microwave reactor at 200 °C for 24 h. Workup and Purification: Workup B was followed using 2.0 mL of DI H_2O with no additional purification steps to yield **3-H-1PhEt**, a pale white solid (0.050 g, 0.118 mmol, 57.7% yield).

Characterization: ^{1}H NMR (400 MHz, $CDCl_3$); δ 8.11 (s, 2*H*), 7.55–7.48 (m, 4*H*), 7.36–7.22 (m, 5*H*), 5.61 (q, J = 7.4 Hz, 2H), 1.94 (d, J = 7.4 Hz, 6*H*). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$); δ 166.3, 164.1, 139.6, 137.5, 128.7, 128.5, 128.3, 128.2, 127.8, 50.7, 17.4. HRMS (ESI) m/z: $[M]^-$ calcd for $C_{26}H_{20}N_2O_4$, 424.1429; found, 424.1411. IR spectrum (solid), ν, cm^{-1}: 1708; 1339; 730; 696. mp 229.62 °C.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01241.

Thermal ellipsoid plot; stick depiction of the unit cell; stick depiction of the two unique molecules; overlay of the coordinates; π-dimer interplanar separations; unit cell; crystallographic data; bond lengths; bond angles; torsion angles; and $^{1}H/^{13}C$ NMR spectra (PDF)

Computed Cartesian coordinates (ZIP)

Accession Codes

CCDC 2145273 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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