

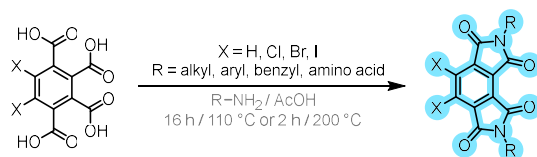
Improved syntheses of halogenated benzene-1,2,3,4-tetracarboxylic diimides

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Supporting Information Placeholder



- generalizable solution-phase method, 21 examples
- up to 93% isolated yields, highest when X = halogen
- microwave conditions succeed for sterically big R
- computational and experimental mechanistic insights

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 the direct reaction of benzene-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, and that S_NAr reactivity is only observed when excess amine is used. The halogenated diimides described here are attractive building blocks for organic materials chemistry.

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 pyrene (PDI) (Figure 1a) have received significant research attention because of their facile syntheses and amenability to derivatization at both the core and imide N positions.^{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 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 activity¹⁴ and near-IR absorptions.¹⁵

We recently began exploring the *ortho*-diimide structural isomer of the well-known pyromellitic diimide, which is known as mellophanic diimide (MDI),^{16–19} 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). Core dichlorinated N,N'-dihexyl MDI (Cl₂-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.^{20,21} 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.²² With these observations in mind, we set out to establish generalizable synthetic methods for obtaining differently halogenated MDI derivatives.

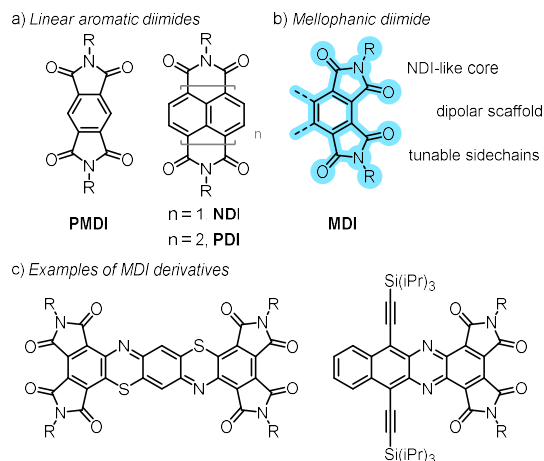


Figure 1. Structural formulas of a) pyromellitic diimide (PMDI), naphthalene diimide ($n = 1$, NDI), and perylene diimide ($n = 2$, PDI), b) mellophanic diimide (MDI), and c) heteroacene MDI derivatives that are near-IR absorbing electron acceptors.

Results and Discussion. Conventionally, aromatic diimides are synthesized by condensation between the relevant aromatic cyclic dianhydride and an amine, a process which 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 (Fig 2a).¹⁸ 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. Inspired by the mellitic triimide synthesis developed by Rose et. al,²³ we were previously able to obtain N,N'-dihexyl-4,5-dichloro-MDI (**Cl₂-MDI-Hex**) after the 3-day solid-state dehydration of an ammonium carboxylate salt (Fig. 2b).²⁰ 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 not successful with more sterically demanding amines. As a result of further synthetic exploration, here we report our findings that the direct solution-phase reaction between benzene-1,2,3,4-tetracarboxylic acids and primary amines is a widely generalizable method for synthesizing MDI derivatives of a variety of N substitutions and core halogenations (Fig. 3c).

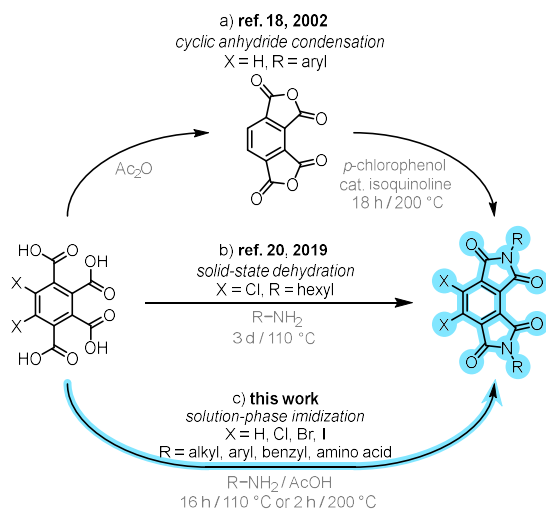


Figure 2. The historical development of synthetic methods for the preparation of MDI compounds began with a) conventional imidization of a dianhydride precursor, then b) solid-state dehydration of ammonium carboxylate salts to obtain dichlorinated MDIs, and presented here, c) the direct solution-phase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

Synthesis. The commercially available 1,2,3,4-tetramethylbenzene was chlorinated,²⁰ brominated,²⁴ or iodinated²⁵ following literature procedures to yield intermediates **1-X** (X = Cl, Br, or I) which were then subjected to exhaustive oxidation by 10 eq. of KMnO₄ in tBuOH/H₂O (1/1 v/v) to provide the halogenated benzene-1,2,3,4-tetracarboxylic acids. Although many KMnO₄ methylarene 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 KMnO₄ required to achieve full oxidation and furthermore is less prone to exotherm during the addition of KMnO₄. 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.

Although we initially followed our previously developed solid-state dehydration protocol for synthesizing **3-X-R**, 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 CH₂Cl₂. Although the reaction byproducts are often polar and soluble enough in AcOH to be removed during the filtration process, additional purification can be easily achieved by passing the crude product mixture through a SiO₂ column.

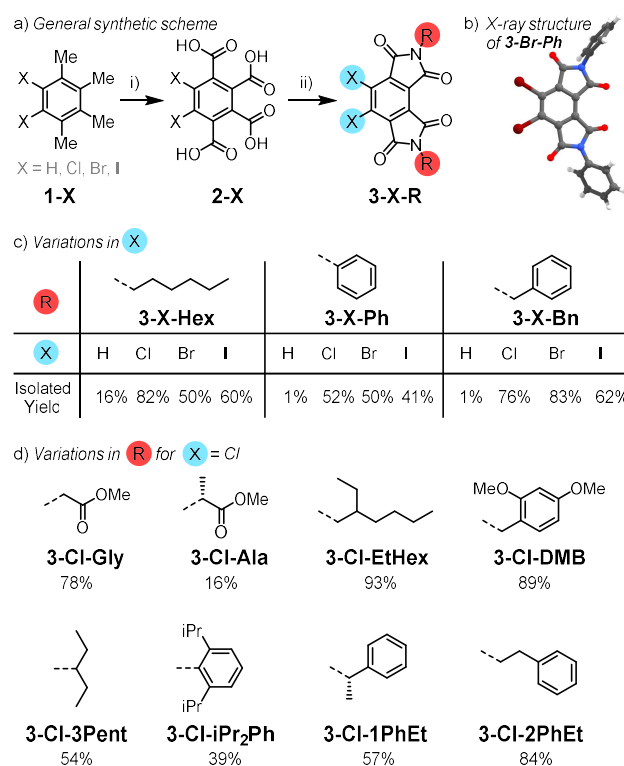


Figure 3. a) Synthetic pathway for the preparation of **3-X-R** compounds. i) 10 eq. KMnO₄ / tBuOH / H₂O; ii) RNH₂ / AcOH. b) Single crystal X-ray structure of **3-Br-Ph**. c) Table of isolated yields for a variety of **3-X-R** compounds with a focus on variation in X. Reaction conditions: 0.1 M **2-X** in AcOH, 2.1 equiv R-NH₂, 110 °C, 16 hr.

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 (Figure 3b). 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.^{26,27} Attempts to perform imidization with 6-amino-1-hexanol,

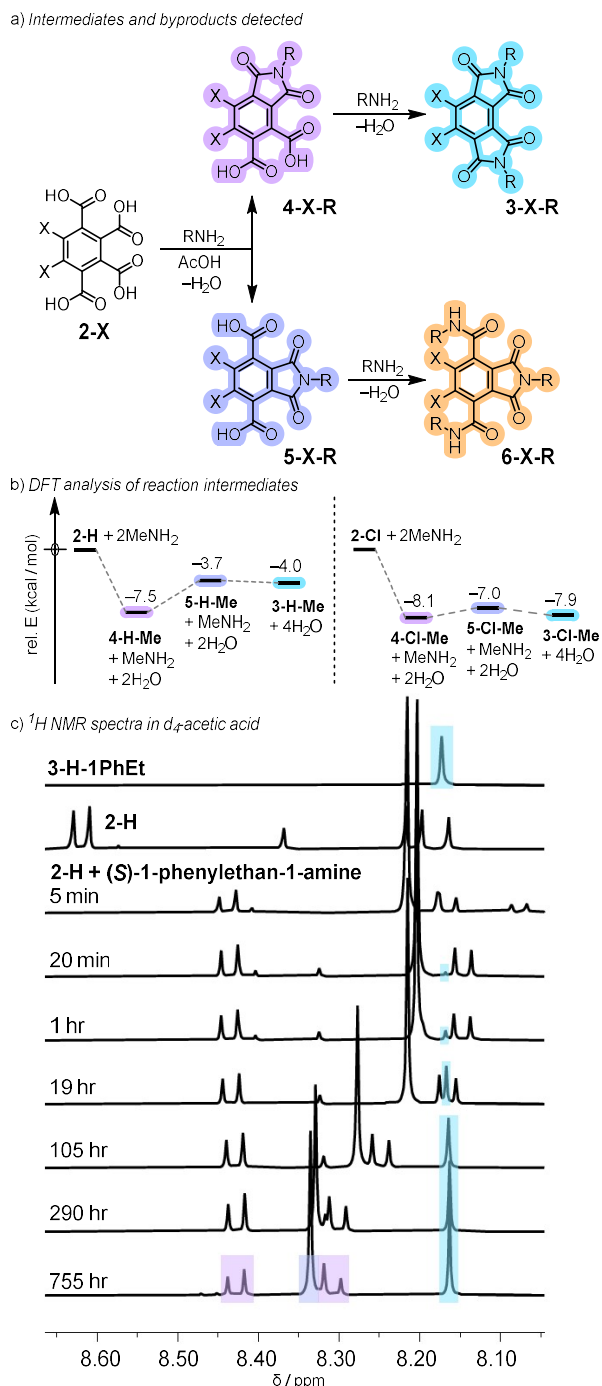


Figure 5. a) A simplified schematic of reaction intermediates and by-products during the formation of **3-X-R**. b) A comparison of DFT-calculated energies for X = H or Cl and R = Me in implicit AcOH solvent (M062X / 6-31G(d)). c) ¹H NMR time-course study of the reaction between **2-H** and (*S*)-1-phenylethan-1-amine in d₄-acetic acid at 110 °C, focused on the aromatic region.

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 density functional theory calculations (M062X/6-31G(d)) with implicit acetic acid solvent to evaluate the energy landscape of the reaction for the reaction between methylamine and either **2-H** or **2-Cl**. 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 0.3 kcal/mol. Although these calculations do not account for the added complexities of mixed anhydride formation or R group identity, they do correlate with our experimental findings that **3-X-R** formation is higher yielding when X = halogen. Taken together, it is reasonable to posit that the statistical advantage of monophthalimide formation balances against substrate-specific energetic differences to influence overall conversion into MDI products.

In conclusion, 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 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 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.

ASSOCIATED CONTENT

Supporting Information

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Author Contributions

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

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