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Rational Synthesis of AB-Type *N*-Substituted Core-Functionalized Naphthalene Diimides (cNDIs)

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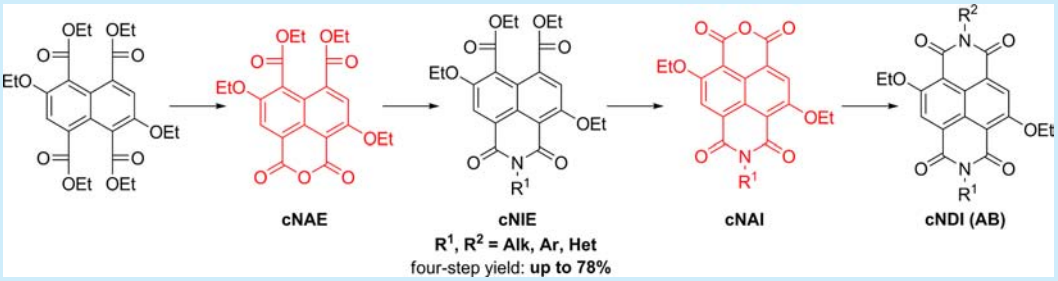
Supporting Information



ABSTRACT: Acid-mediated transformation of tetraethyl 2,6-diethoxynaphthalene-1,4,5,8-tetracarboxylate selectively affords the core-substituted naphthalene-anhydride-ester (cNAE) in quantitative yield. This anhydride can be selectively converted into hetero-*N*-substituted core-functionalized naphthalene diimides (cNDIs) through sequential condensation reactions in the presence of the precursor amine with very high isolated yields over four steps. The approach can be applied to prepare a large variety of heterocyclic, aromatic, and aliphatic heterodiimides.

Thanks to the vigorous organic synthetic developments achieved during recent years, core-substituted naphthalenediimides (cNDIs) now cover an impressive spectrum of structures of tunable properties.[1,2] In particular, the ability of cNDIs bearing electron-donating groups to absorb and fluoresce light through all the visible spectroscopic region[3,4] and of cNDIs equipped with electron-withdrawing groups to display unprecedented π-acidity[5] make these molecular synthons outstanding functional modules for preparing a broad range of materials[6,7] for different applications, such as organic field-effect transistors (OFETs),[8] emissive devices,[9] artificial photosynthetic systems,[4,10] n-type semiconductors,[6,11] and organocatalysis.[12]

Extensive synthetic investigations during recent decades were mainly focused on gaining control over the chemo- and regioselective functionalization of the naphthalene core through aromatic nucleophilic substitution reactions, to prepare a broad range of sophisticated cNDIs derivatives.[2] However, high-yielding, rationally designed, synthetic methodologies for preparing cNDIs featuring different *N*-substituted imidic moieties (AB) have not been developed so far. Whereas homo- (A_2) *N*-substituted NDIs are easily obtained with primary alkyl or aryl amines starting from the precursor core-substituted naphthalenedianhydride (cNDA),[13] AB *N*-substituted cNDIs are typically prepared by statistical condensation reactions of a given cNDA in the presence of a mixture of the two amines.[4,14,15] This synthetic approach yields statistical mixtures of the *N*-substituted cNDIs (the A_2, AB, and B_2 derivatives), the distribution of which depends on the reactivity of the employed amines. Typically, this protocol affords the desired AB *N*-substituted cNDIs in modest yields. The difficulty in accessing large quantities of such *N*-substituted cNDIs is, in our opinion, one of the last synthetic constraints precluding the extensive use of these exceptional chromophores in the development of covalent and noncovalent functional architectures of increased complexity.

Herein we thus describe the first rational synthesis for preparing AB *N*-substituted cNDIs in very high isolated yields. The main precursor for the 2,6-diethoxy NDI is tetraethyl 2,6-diethoxynaphthalene-tetracarboxylate **4**,[4,14] which was prepared following a modified synthetic route (Scheme 1 and Supporting Information (SI)). Bromination (see SI for the details) of commercial NDA **1** with dimethyl dibromohydantoin followed by alkylation with Me_2SO_4 gave tetramethyl 2,6-dibromonaphthalene tetracarboxylate **3** in 36% yield. Subsequent reaction of dibromonaphthalene **3** with EtONa gives diethoxynaphthalene derivative **4** in 84% yield.

As shown in Scheme 1, we found that tetraethyl ester **4** could be selectively transformed into core-substituted naphthalene

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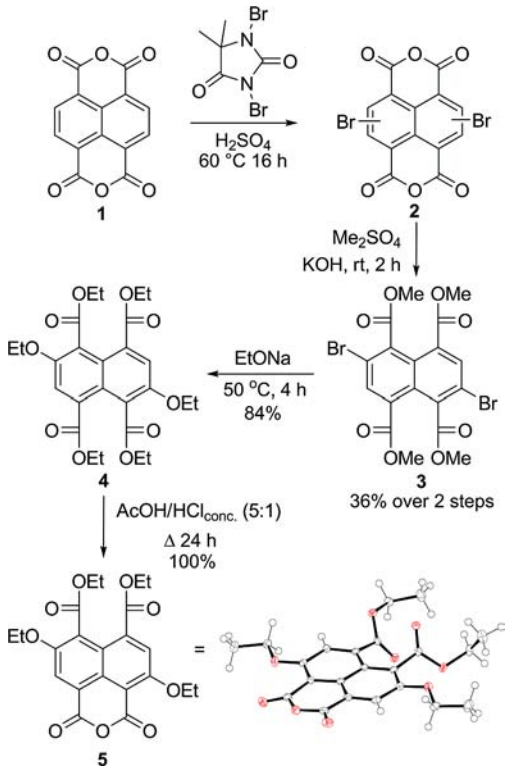
Scheme 1. Synthesis of cNAE 5 and Its ORTEP Representation as Determined by X-ray Diffraction Analysis (Space Group *P*21/*c*)[a]



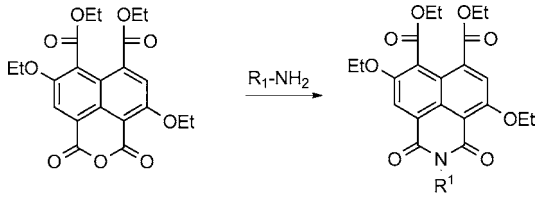
[a]Atomic displacement parameters (223 K) are drawn at the 30% probability level.

monoanhydride (cNAE) **5** under reflux conditions in a 5:1 solution of AcOH and aq. conc. HCl (37%) in 2 h (a quantitative conversion could be obtained after 24 h). cNAE **5** was isolated first as a minor product from the solvolysis reaction of tetraethyl ester **4** in refluxing AcOH in the presence of catalytic amounts of aq. HCl. Suitable single crystals for X-ray crystallography analysis were obtained by recrystallization from hot EtOH. The molecular structure, depicted in Scheme 1, nicely reveals the presence of the anydride and bis-ester functional groups. Remarkably, the same reaction conditions can also be applied for gram-scale synthesis, giving pure product **5** after removal of the solvents. However, reaction of tetraethyl and tetramethyl 2,6-dibromonaphthalene-1,4,5,8-tetracarboxylates in refluxing AcOH with HCl did not afford any monoanhydrides after 24 h, returning only the starting materials in quantitative yields.

Having large quantities of cNAE **5** in hand, we could then undertake the synthesis of a series of core-substituted monoimides (cNIEs) **6** using aliphatic, aromatic, or heterocyclic amines (Table 1).

Refluxing cNAE **5** in EtOH with $BnNH_2$ in the presence of Et_3N afforded cNIE **6a** in 56% yield (tetraester **4** deriving from alcoholysis was also isolated, entry 1). By switching to an aprotic solvent such as 1,4-dioxane, cNIE **6a** was obtained in 87% yield (entry 2). Lower yields were obtained in CH_3CN (entry 3). Interestingly, *n*-$BuNH_2$ in dioxane produced cNIE **6b** in 40% yield (entry 4). Replacement of Et_3N with Hunig's base (diisopropylethylamine, HB) afforded the *N*-alkylated cNIE product in 92% yield after 2 h under reflux (entry 5). Similar results were also obtained with $BnNH_2$ that, in dioxane and in the presence of HB, afforded cNIE **6a** in quantitative yield (entry 6). The condensation reaction with sterically hindered

Table 1. Optimization of the Reaction Conditions for Preparing cNIEs 6a–e[a]



entry	R^1	base	additive	solvent	*t* (°C)	time (h)	yield (%)
1	Bn-	Et_3N	–	EtOH	78	1	**6a** (56)[f]
2	Bn-	Et_3N	–	1,4-dioxane	101	1	**6a** (87)
3	Bn-	Et_3N	–	MeCN	82	1	**6a** (74)
4	*n*-Bu-	Et_3N	–	1,4-dioxane	101	5	**6b** (40)[g]
5	*n*-Bu-	Hunigs base	–	1,4-dioxane	101	2	**6b** (92)
6	Bn-	Hunigs base	–	1,4-dioxane	101	2	**6a** (98)
7	cyclohexyl-	Hunigs base	–	1,4-dioxane	101	24	**6c** (64)
8	cyclohexyl-	Hunigs base	–	mesitylene	165	2	**6c** (34)[h]
9	4-*t*-BuPh-	Hunigs base	–	1,4-dioxane	101	12	**6d** (0)[g]
10	4-*t*-BuPh-	Et_3N[c,d]	benzoic acid[c]	DMF	110	6	**6d** (92)
11	4-*t*-BuPh-	Et_3N[c]	benzoic acid[c]	1,4-dioxane	101	24	**6d** (0)[g]
12	4-*t*-BuPh-	Et_3N	–	DMF	110	24	**6d** (57)
13	Py-4-yl-	Et_3N[c]	benzoic acid[c]	DMF	110	48	**6e** (0)[g]
14	Py-4-yl-	Et_3N[c]	benzoic acid[c]	DMF	150	20	**6e** (0)[h]
15	Py-4-yl-	–	zinc acetate[e]	quinoline	150	12	**6e** (41)
16	Py-4-yl-[b]	–	zinc acetate	quinoline	150	12	**6e** (55)
17	Py-4-yl-	Et_3N[c]	benzoic acid[c]	quinoline	150	12	**6e** (30)

[a]Reaction conditions of NAI **5** (0.23 mmol) with the selected amine (1.1 equiv) in the presence of a base (1.1 equiv) and an acidic additive (1.1 equiv). [b]2.2 equiv. [c]0.6 equiv. [d]Literature conditions.[16] [e]Literature conditions.[17] [f]The product of alcoholysis to tetraester **4** was isolated. [g]Starting material **5** was recovered. [h]Decomposition of starting material **5** was observed.

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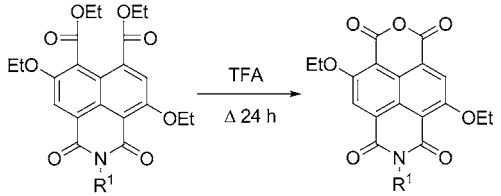
cyclohexylamine in dioxane required a longer time to reach complete conversion. The reaction afforded cNIE **6c** in 64% yield after 24 h under reflux conditions (entry 7). In mesitylene at 165 °C, cNIE **6c** was obtained only in 34% yield (entry 8). An evident decomposition of the starting cNAE material was also observed. When 4-*tert*-butylaniline was used, no conversion was observed after 12 h under the same reaction conditions as those used for the aliphatic amines (entry 9). However, following the protocol developed by Ponomarev and co-workers[16] for the synthesis of *N*-aryl-1,8-naphthalimide, *N*-substituted monoimide cNIE **6d** could be obtained in very high yields (92%) in the presence of Et_3N and benzoic acid in DMF at 110 °C over 6 h (entry 10). cNIE **6d** was also obtained in DMF in the absence of benzoic acid, but with much lower yields (57%) after 24 h at 110 °C (entry 12). Notably, no conversion was observed when cNAE **5** was refluxed in dioxane with 4-*tert*-butylaniline for 24 h (entry 11). Reaction of NAE **5** with 4-amino-pyridine in the presence of Et_3N and benzoic acid gave no conversion even after 48 h in DMF at 110 °C (entry 13). However, by following literature conditions,[17] using $Zn(OAc)_2$ and quinolone gave us desired cNIE **6e** in 41% yield after 12 h at 150 °C (entry 15). Doubling the equivalents of 4-amino-pyridine slightly increased the yield up to 55% (entry 16). Significantly lower yields were obtained in the absence of $Zn(OAc)_2$ (entry 17). From these studies, three optimized preparative imidation methods were thus developed for the alkylic (method **Alk**, entry 5 or 6), aromatic (method **Ar**, entry 10), and heterocyclic (method **Het**, entry 10) imides.

As shown in Scheme 2, the as-produced cNIEs **6** were then quantitatively converted into the corresponding naphthalene

Scheme 2. Conversion of cNIEs 6 into cNAIs 7

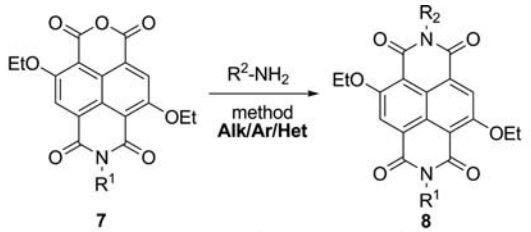


imide anhydrides (cNAIs) **7** after 24 h in neat TFA under reflux. Notably, all the aliphatic, aromatic, and heteroaromatic imides were revealed to be stable under the reaction conditions showing no apparent decomposition.

By following the optimized imidation protocols as described above, precursor cNAIs could be transformed into the corresponding AB *N*-substituted cNDAs. In particular, applying method **Alk** for $BnNH_2$, **Ar** for 4-*tert*-butylaniline, and **Het** for 4-amino-pyridine, we selectively prepared cNDIs **8a**–**c** following two orthogonal synthetic pathways (Scheme 3). Notably, no imide scrambling was observed under any of the employed conditions. It is worth pointing out that while *N*-substituted alkyl and aromatic cNAIs **7a** and **d** display similar reactivity with all the amines, cNAI **7e** reacts with $BnNH_2$ following method **Alk** to give an insoluble product, which we tentatively assigned to an amide-carboxylic intermediate. Further refluxing in AcOH turned out to be necessary to obtain desired cNDI **8b**.

After the optimized reaction conditions were determined, the attention was then focused toward examining the generality of

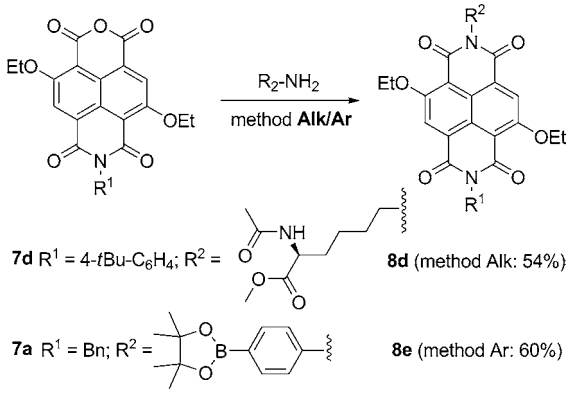
Scheme 3. Synthesis of cNDIs 8x from cNAIs 7x[a]



R1 \ R2	method Alk: Bn-	method Ar: 4-*t*-Bu-Ph-	method Het: Pyrid-4-yl-
Bn-		**8a** (86%)	**8b** (49%)
4-*t*-Bu-Ph-	**8a** (87%)		**8c** (47%)
Pyrid-4-yl-	**8b** (78%)*	**8c** (93%)	

[a]**Method Alk:** Hunig's base, dioxane, 101 °C 2 h; **Method Ar:** Et_3N, benzoic acid, DMF, 110 °C, 6 h; **Method Het:** $Zn(OAc)_2$, quinoline, 150 °C, 12 h; *additional reflux in AcOH for 1 h.

Scheme 4. Imidation of cNAIs 7a, d with N_α-Acetyl-L-lysine Methyl Ester Hydrochloride and 4-Aminobenzeneboronic Acid Pinacol Ester



this methodology, by varying the amine and the cNAI substrates. As outlined in Scheme 4, we also reacted cNIAs with functional amines, such as N_α-Acetyl-L-lysine methyl ester and 4-amino-phenylboronic pinacol ester. By following methods **Alk** and **Ar** for the lysine and phenylboronic ester, respectively, cNAIs **7d** and **7a** were transformed into cNDIs **8d** and **8e** with good yields (Scheme 4).

The synthetic approach proposed here also allowed the preparation of dimeric cNDIs (dcNDIs) **8f**, in which the naphthalene dimide cores are bridged through a 1,4-phenylene spacer. As outlined in Scheme 5, we followed two orthogonal synthetic pathways. In the first avenue, reaction of cNAE **5** with 1,4-phenylenediamine under the conditions of method **Ar** afforded dimeric tetraester **6f** (dcNIE). Solvolysis and condensation of dcNIE selectively afforded dianydride **7f** (dcNDA) that, subjected to the conditions of method **Alk** in the presence of $BnNH_2$, gave dimer cNDIs **8f** (dcNDIs) in 56% yield. Alternatively, dcNDIs **8f** could also be obtained in 78% yield in one reaction step from cNAI **7a** in the presence of 1,4-phenylenediamine following method **Ar**.

In conclusion, we developed the first rational synthesis of hetero-*N*-substituted cNDIs. Three different protocols were established for the preparation of *N*-substituted aliphatic,

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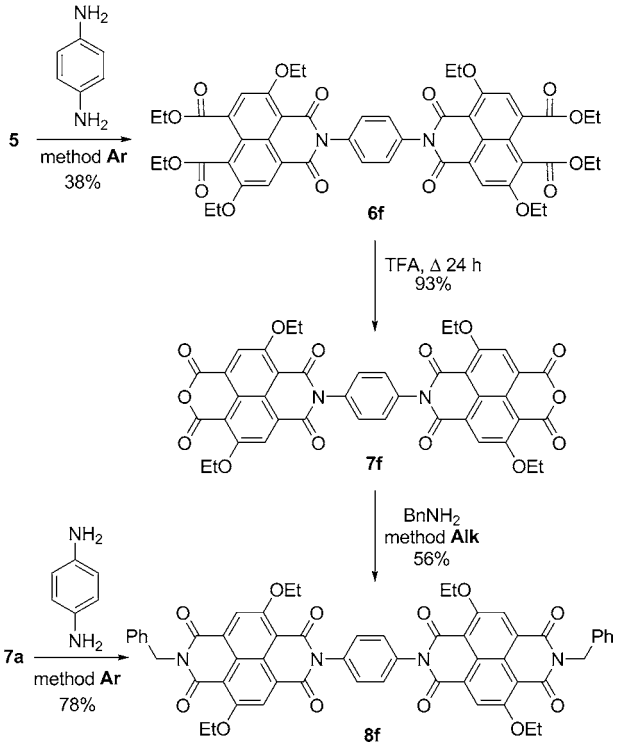
Scheme 5. Synthesis of Dimeric Naphthalenediimide 8f



aromatic, and heteroaromatic imides with exceptionally high yields. The synthetic methodologies were revealed to be compatible with a series of substituents, thus giving access to a great variety of AB *N*-substituted cNDIs in large scales.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all compounds. 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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