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Rapid and Mild Synthesis of Functionalized Naphthalenediimides

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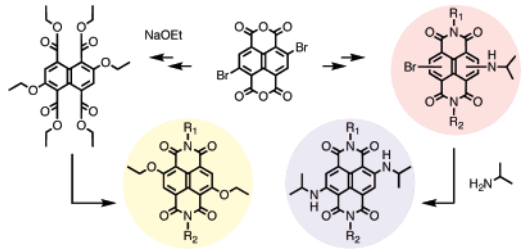
Received November 5, 2007



Core-substituted naphthalenediimides (NDIs) are not often used in functional materials despite excellent properties because the harsh conditions used for their synthesis are incompatible with structural diversity. Here, we report rapid access to blue, red, and yellow NDIs under mild conditions with tolerance toward the additional presence of pertinent functional groups.

As compact, colorizable, organizable, and functionalizable π-acidic n-semiconductors, 2,6-core-substituted 1,4,5,8-naphthalenediimides (NDIs) are exquisite building blocks for advanced functional nanoarchitectures or bioanalytical probes.[1−4] Unlike the colorless NDI without substituents in the core,[5] they are, however, rarely used because their synthesis is inefficient, dangerous, and incompatible with the presence of sensitive functional groups.[2,4] Here, we introduce a general, user-friendly solution to these challenges and provide concise protocols for the rapid, mild, and safer synthesis of blue, red, and yellow NDI fluorophores.

So far, most core-substituted NDIs have been prepared via 2,6-dichloro-1,4,5,8-naphthalenetetracarboxylic dianhydride, *Cl*,*Cl*-NDA **1**. This key intermediate has been synthesized in overall 5−8% yield from commercially available pyrene (**2**) by perchlorination, elimination of HCl, and two steps of oxidation (Scheme 1). The original Vollman procedure has been recently optimized by the Würthner group.[1b,4] Starting from *Cl*,*Cl*-NDA **1**, we prepared the appropriately functionalized blue and red NDIs **3** and **4** for use in the synthesis of a multifunctional photosystem. Namely, the acid-catalyzed imide formation with **1** and the two amines **5** and **6** gave unsymmetrical *Cl*,*Cl*-NDI **7**, which in turn was mono- and, at higher temperature, disubstituted with isopropylamine **8** to give the desired red *N*,*Cl*-NDI **4** and blue *N*,*N*-NDI **3**, respectively.[2,3]

The main difficulty we faced in this approach to NDI fluorophores was the cumbersome synthesis of the *Cl*,*Cl*-NDA **1**. Particularly the excessive use of chlorine gas can be a safety risk in an academic environment without dedicated equipment. Moreover, the known synthetic procedure for the yellow, green-fluorescent *O*,*O*-NDI by similar nucleophilic aromatic substitution[1] was not compatible with the synthesis of *O*,*O*-NDI **9** of interest, because the strong base ethanolate also attacks the protecting groups in *Cl*,*Cl*-NDI **7**.

To bypass the troublesome synthesis of the *Cl*,*Cl*-NDA **1**, we considered using the dibrominated *Br*,*Br*-NDA **10** as in the much better developed syntheses of the homologous perylenediimides (PDIs). The easily accessible *Br*,*Br*-NDA **10** was used previously to introduce carbon substituents (phenyl[1e] and cyano[1d]) into the NDI core. Blue *N*,*N*-NDI has also been synthesized from *Br*,*Br*-NDA **10**,[1b] but the harsh conditions used for this transformation were not compatible with sensitive functional groups. Recent progress with transition-metal-catalyzed methodology[6] suggested that this problem could be addressed.

For a user-friendly, rapid, mild, and safe synthesis of red *N*,*Br*-NDI **11** and blue *N*,*N*-NDI **3**, *Br*,*Br*-NDA **10** was prepared from the commercially available NDA **12** following the reported procedures, using dibromoisocyanuric acid (**13**, Scheme 2).[1b,e] The regioselectivity of bromination at the 2,6 positions was confirmed by the comparison of **3** with the authentic sample,

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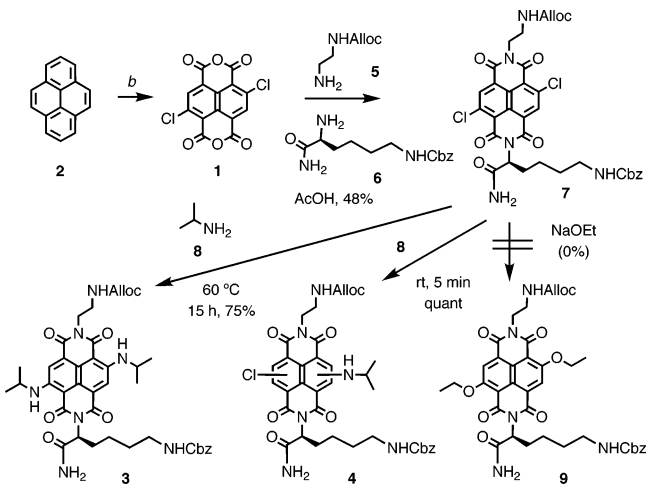
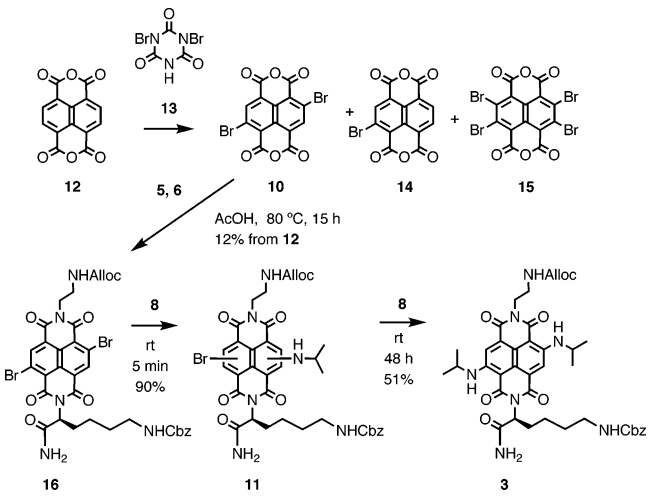
10.1021/jo702392q CCC: $40.75
Published on Web 12/13/2007

SCHEME 1. Summary of the Previous Synthesis of 3 and 4[2,3,a]



[a] Alloc = allyloxycarbonyl. [b]From ref 1b: (1) Cl_2, I_2 (36−38%); (2) KOH (96−97%); (3) fuming HNO_3 (32−45%); (4) fuming HNO_3, conc. H_2SO_4 (45−49%).

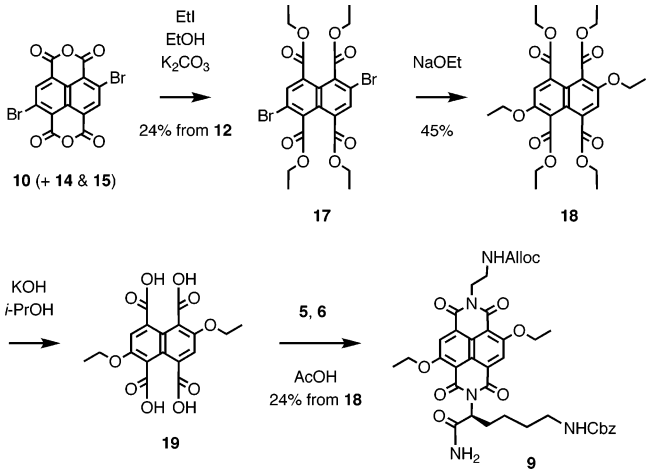
SCHEME 2. Fast, Mild, and Safer Synthesis of *N,N*-NDI 3 and Synthesis of *N,Br*-NDI 11



the observed four imide carbonyl peaks in ^{13}C NMR spectrum of **9**, and the X-ray crystalography of **17** (see the Supporting Information and CCDC-663914). As with the homologous PDIs,[7] it was not possible to separate the *Br,Br*-NDA **10** from other bromination products such as *Br*-NDA **14** or Br_4-NDA **15**.[8] Reaction of this mixture of brominated NDAs with amines **5** and **6** followed by separation from symmetric, monobromo, tetrabromo, and other side products afforded *Br,Br*-NDI **16** in two steps with an overall yield of 12%. This compared very well to obtaining *Cl,Cl*-NDI **7** in five steps with an overall yield of up to 4%.

As with the *Cl,Cl*-NDIs, the first nucleophilic aromatic substitution with isopropylamine **8** proceeded smoothly in 5 min at room temperature to give *N,Br*-NDI **11** as a mixture of the 2,6 and 3,7 trans-isomers. Preliminary results indicated that the spectroscopic properties of *N,Br*-NDI **11** (λ_{ex} 530 nm, λ_{em} 570 nm, Figure S10 in the Supporting Information) are almost identical with those of the previously reported, red, orange-emitting *N,Cl*-NDI **4** (λ_{ex} 530 nm, λ_{em} 570 nm). After screening many conditions including transition metal-catalyzed reactions, we were surprised to find that the second nucleophilic substitution proceeded best in isopropylamine without any additives. After 48 h of reaction at room temperature, the blue target fluorophore **3** was obtained in 51% yield without damage of chirality or the allyloxycarbonyl (Alloc) and Cbz protecting groups. Spectroscopic data of the obtained product **3** were identical with those of the authentic sample, which was previously synthesized from *Cl,Cl*-NDI.[2]

SCHEME 3. Synthesis of *O,O*-NDI 9



To prepare the elusive yellow *O,O*-NDI **9**, it seemed inevitable to make a detour to *O,O*-NDA or its equivalent to avoid damage of the reactive functional groups by the nucleophilic alkoxide (Scheme 3). This strategy is commonly used with the analogous PDI syntheses, where core-substituted anhydrides are prepared by imide formation, nucleophilic core substitution, and saponification.[7] However, attempts to hydrolyze NDIs to NDAs failed because the undesired lactamimide was obtained.[1b] Therefore, we chose to temporarily protect tetraacids as esters.[9] Crude *Br,Br*-NDA **10** was treated with iodoethane in ethanol to give pure 2,6-dibromo-1,4,5,8-naphthalenetetraester (*Br,Br*-NTE) **17** in two steps with an overall yield of 24%. With this substrate, nucleophilic aromatic substitution with ethoxide proceeded without problems. The obtained 2,6-diethoxy *O,O*-NTE **18** could be hydrolyzed with base to give *O,O*-NDA equivalent **19**, which reacted easily with amines **5** and **6** to yield the yellow target fluorophore **9**.

In summary, we disclose rapid, mild, and safe access to blue, red, and yellow NDI fluorophores. The found use of *Br,Br*-NDA greatly simplifies the synthesis of these fluorophores with attractive photo- and electrochemical properties. This result is important because it will stimulate applications of NDI fluorophores in materials sciences and bioanalytics. As far as further improvements are concerned, the expansion to other core substituents, optimization of bromination conditions, as well as

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the screening of metals and ligands for refined C−X coupling reactions appear particularly attractive.

Experimental Section

***N,Br*-NDI 11.** *Br,Br*-NDI **16** (0.14 g, 0.172 mmol, see the Supporting Information) was dissolved in stirred isopropylamine (20 mL). After 5 min at rt, the red solution was evaporated to dryness under reduced pressure. Purification by column chromatography (CH_2Cl_2/MeOH 48:2; R_f 0.4) gave **11** (0.123 g, 90%) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$, N/N = regioisomeric equivalents, Figure S2 in the Supporting Information): δ 10.03/9.99 (d, ^3J(H,H) = 7.6/7.2 Hz, 1H), 8.75/8.67 (s, 1H), 8.31/8.20 (s, 1H), 7.33−7.31 (m, 5H), 6.37 (br s, 1H), 5.89−5.81 (m, 1H), 5.73−5.68/5.68−5.64 (m, 1H), 5.35−5.04 (m, 2H), 5.04 (s, 2H), 4.88 (br s, 1H), 4.54−4.47 (m, 2H), 4.26−4.18 (m, 3H), 3.53 (br s, 2H), 3.19 (br s, 2H), 2.41−2.22 (m, 2H), 1.72 (br s, 2H), 1.62−1.59 (m, 2H), 1.52/1.51 (d, ^3J(H,H) = 7.6/5.6 Hz, 6H); HR-MS (ESI, +ve) calcd for $C_{37}H_{40}BrO_9N_6^+$ 791.2034, found 791.1976.

***N,N*-NDI 3.** A solution of *N,Br*-NDI **11** (8.5 mg, 0.01 mmol) in isopropylamine (1.5 mL) was stirred in a sealed tube at rt for 48 h. The reaction mixture was concentrated in vacuo and the resultant residue was purified by PTLC (CH_2Cl_2/MeOH 48:2; R_f 0.5 with CH_2Cl_2/MeOH 47:3) to give **3** (4.2 mg, 51%) as a blue solid. Analytical and spectroscopic data were as reported previously (Figure S5, Supporting Information).[2a]

***Br,Br*-NTE 17.** A 500 mg sample of *Br,Br*-NDA **10** (1.2 mmol) was suspended in 5 mL of ethanol and 5 mL of ethyl iodide (62 mmol). To this was added K_2CO_3 (1 g, 7.0 mmol). The mixture was refluxed for 6 h by which time the yellow suspension turned gray. The reaction mixture was cooled, evaporated to dryness, redissolved in CH_2Cl_2, and washed with water. The organic layer was then dried over Na_2SO_4 and concentrated to give a gray solid. Purification by column chromatography (CH_2Cl_2; R_f 0.4 with CH_2Cl_2) afforded *Br,Br*-NTE **17** (170 mg, 24% from **12**) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$, Figure S7 in the Supporting Information): δ 8.08 (s, 2H), 4.39 (q, ^3J(H,H) = 7.2 Hz, 4H), 4.36 (q, ^3J(H,H) = 6.9 Hz, 4H), 1.44 (t, ^3J(H,H) = 6.9 Hz, 6H), 1.41 (t, ^3J(H,H) = 7.2 Hz, 6H); MS (ESI) 592 (90, $[M + NH_4^+]$), 529 (95, $[M - OEt]^+$).

***O,O*-NTE 18.** To a freshly prepared solution of NaOEt (8 mL of 2 M) was added drop by drop a solution of *Br,Br*-NTE **17** (240 mg, 0.417 mmol, see the Supporting Information) in 3 mL of dry DMF. The resulting yellow suspension was heated at 50 °C for 4 h. The reaction mixture was quenched with water and then evaporated to dryness in vacuo. The residue was redissolved in water and extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated to give a yellow residue. Purification by column chromatography (petroleum ether/EtOAc 80:20; R_f 0.4 with petroleum ether/EtOAc 80:20) gave *O,O*-NTE **18** (95 mg, 45%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, Figure S8 in the Supporting Information): δ 7.65 (s, 2H), 4.35 (q, ^3J(H,H) = 7.2 Hz, 8H), 4.22 (q, ^3J(H,H) = 6.9 Hz, 4H), 1.43 (t, ^3J(H,H) = 6.9 Hz, 6H), 1.39 (t, ^3J(H,H) = 7.2 Hz, 12H); HR-MS (ESI, +ve) calcd for $C_{26}H_{32}O_{10}Na^+$ 527.1887, found 527.1898.

***O,O*-NDI 9.** *O,O*-NTE **18** (50 mg, 0.13 mmol) was added to 10 mL of a 1 M solution of KOH in 2-propanol. The mixture was refluxed for 14 h and then evaporated to dryness. The obtained residue was dissolved in 5 mL of acetic acid giving a clear yellow solution. To this was added H-Lys(Cbz)-NH_2 **6** (20 mg, 0.13 mmol) and **5** (40 mg, 0.13 mmol) sequentially and the mixture was heated for 12 h at 80 °C. H-Lys(Z)-NH_2 **6** (20 mg, 0.127 mmol) and **5** (40 mg, 0.127 mmol) were added again to the reaction mixture and the mixture was heated for a further 24 h. The reaction mixture was then cooled to rt and diluted with EtOAc (100 mL). The organic layer was washed with 1 M $KHSO_4$ (25 mL × 2), H_2O (25 mL), and brine (25 mL) and finally dried over Na_2SO_4. Solvent was evaporated and the resultant residue was purified by column chromatography (CH_2Cl_2/MeOH 97:3; R_f 0.5 with CH_2Cl_2/MeOH 90:10) affording **9** (23 mg, 24%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, Figure S9 in the Supporting Information): δ 8.33 (s, 1H), 8.24 (s, 1H), 7.28−7.24 (m, 5H), 5.73 (m, 1H), 5.65 (dd, ^3J(H,H) = 9.1 Hz, ^3J(H,H) = 5.3 Hz, 1H), 5.20 (d, ^3J(H,H) = 16.9 Hz, 1H), 5.17 (m, 1H), 5.09 (d, ^3J(H,H) = 10.1 Hz, 1H), 4.96 (s, 2H), 4.85 (t, ^3J(H,H) = 5.1 Hz, 1H), 4.43 (s, 2H), 4.42 (q, ^3J(H,H) = 7.0 Hz, 4H), 4.23 (br s, 2H), 3.49 (m, 2H), 3.14 (m, 2H), 2.38−2.16 (m, 2H), 1.63 (t, ^3J(H,H) = 7.0 Hz, 6H), 1.58−1.48 (m, 2H), 1.46−1.21 (m, 2H); HR-MS (ESI, +ve) calcd for $C_{38}H_{42}O_{11}N_5^+$ 744.2875, found 744.2803.

Acknowledgment. We thank D. Jeannerat, A. Pinto, and S. Grass for NMR measurements, N. Oudry, G. Hopfgartner, P. Perrottet, and the group of F. Gülaçar for MS measurements, and the Swiss NSF for financial support.

Supporting Information Available: Additional experimental procedures, compound characterization data, copies of spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702392Q