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The synthesis and fluorescence properties of macromolecular components based on 1,8-naphthalimide derivatives and dimers

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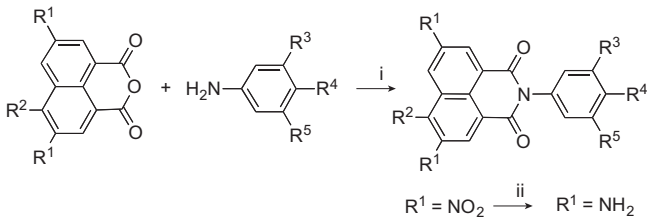
ABSTRACT

A series of novel 1,8-naphthalimide derivatives and dimers possessing reactive carboxylic acid, nitro, amine, or bromide functionality is prepared and their photophysical properties are studied. Those derivatives that contain amine substituents attached directly to the 1,8-naphthalimide unit display intense yellow-green fluorescence.

Derivatives of 1,8-naphthalimide are of interest due to their useful photophysical and biological properties that offer promise for medical applications as free radical scavengers,[1] potential photoredox anticancer agents,[2] fluorescent labels,[3] photosensitizers,[4] and imaging agents.[5–8] Many of these properties are related to their planar shape and optimal size that makes them efficient DNA intercalators.[9–11] In addition, they are particularly attractive as fluorophores as they can demonstrate high quantum yields, good photo-stability and their fluorescence can be tuned throughout a wide spectral range from blue to red.[12] These properties also make 1,8-naphthalimide derivatives ideal for many non-biological applications such as fluorescent pigments and dyes[13] and as components in fluorescent sensors for specific metal cations,[14,15] or pH determination,[16] and within optical switches[17] or organic luminescent devices.[18–20] The attractive properties of the 1,8-naphthalimide chromophore have led to its incorporation into numerous polymeric[21,22] and dendritic[5,23–29] structures so as to tailor solubility, self-association, and molecular size to suit a particular application. Here we describe the synthesis and photophysical properties of 1,8-naphthalimide derivatives that are suitable as building blocks for such macromolecular structures due to additional reactive functionality such as amine, carboxylic acid, or aryl bromide, which is activated toward substitution by amine or aryloxy nucleophiles.[30] Previous reports demonstrate that such substitution at the 4-position can induce a large red-shift to the λ_{max} of the 1,8-naphthalimide chromophore and enhance fluorescence strongly.[30–35]

The novel *N*-phenyl-1,8-naphthalimide derivatives **1**–**9** were synthesized using conventional methodology by refluxing equimolar quantities of 1,8-naphthalic anhydride, 4-bromo-1,8-naphthalic anhydride, or 3,6-dinitro-1,8-naphthalic anhydride with 4-aminobenzoic acid, 5-aminoisophthalic acid or 3,5-diaminobenzoic acid, respectively, in the presence of glacial acetic acid and sodium acetate (Scheme 1, Table 1). Reduction of the nitro substituents of *N*-phenyl-1,8-naphthalimides **2**, **5,** and **8** by a palladium-catalyzed hydrogenation gave amino-containing derivatives **10**–**12** (Scheme 1, Table 1). *N*-Phenyl-1,8-naphthalimide derivatives **1**–**6** were obtained in good yields in high purity by simple flash chromatography or recrystallisation, whereas compounds **7**–**9** were obtained in low yield following chromatographic isolation from by-products, including modest quantities of the 1,3-naphthalimide dimers **13**–**15**. Alternatively, dimers **13**–**15** could be prepared in much higher yield by reacting a twofold excess of 1,8-naphthalic



Scheme 1. The synthesis of 1,8-naphthalimides **1**–**12**. Reagents and conditions: (i) AcOH, NaOAc, reflux, 8–14 h; (ii) H_2, 1 bar, 10% Pd/C, DMF, 25 °C. Table 1 gives substituents R^1–R^5.

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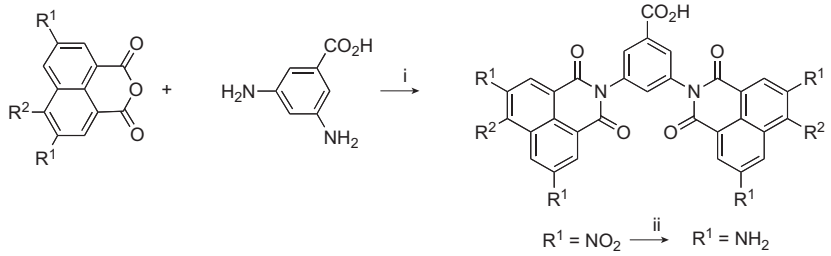
Table 1
Synthetic yields and photophysical properties of 1,8-naphthalimides **1**–**12** (prepared as shown in Scheme 1) and dimers **12**–**16** (prepared as shown in Scheme 2)

Product	R^1	R^2	R^3	R^4	R^5	Yield (%)	λ_{max} abs[a] (nm)	Extinction coefficient[a] (M^{-1} cm^{-1})	λ_{max} emission[a,b] (nm)	RFI[c]	Quantum yield[d] (%)
1	H	H	H	CO_2H	H	92	334	1.4×10^4	383	1.7	—
2	NO_2	H	H	CO_2H	H	93	270	4.4×10^4	341	3.6	—
3	H	Br	H	CO_2H	H	68	342	1.7×10^4	402	1.8	—
4	H	H	CO_2H	H	CO_2H	92	334	1.7×10^4	410	4.4	—
5	NO_2	H	CO_2H	H	CO_2H	95	273	3.2×10^4	419	88	—
6	H	Br	CO_2H	H	CO_2H	85	342	1.6×10^4	408	5.6	—
7	H	H	NH_2	H	CO_2H	43	335	1.3×10^4	422	1.3	—
8	NO_2	H	NH_2	H	CO_2H	12	270	1.2×10^4	455	2.2	—
9	H	Br	NH_2	H	CO_2H	11	342	1.9×10^4	428	1.6	—
10	NH_2	H	H	CO_2H	H	91	440	0.5×10^4	518	198	7.4
11	NH_2	H	CO_2H	H	CO_2H	92	438	0.4×10^4	518	215	10.3
12	NH_2	H	NH_2	H	CO_2H	94	432	0.7×10^4	521	299	16.7
13	H	H	—	—	—	75	335	2.8×10^4	405	2.0	—
14	NO_2	H	—	—	—	71	272	7.6×10^4	342	1.0	—
15	H	Br	—	—	—	67	342	3.4×10^4	401	1.7	—
16	NH_2	H	—	—	—	89	435	1.4×10^4	518	406	22.9

[a] From DMF solution.
[b] Excitation at 438 nm.
[c] RFI = Relative fluorescence intensity normalized with respect to **14**.
[d] Relative to fluoroscein.



Scheme 2. The synthesis of 1,8-naphthalimide dimers **13**–**16**. Reagents and conditions: (i) AcOH, NaOAc, reflux, 8–14 h; (ii) H_2, 1 bar, 10% Pd/C, DMF, 25 °C. Table 1 gives substituents R^1–R^2.

anhydride, 4-bromo-1,8-naphthalic anhydride or 3,6-dinitro-1,8-naphthalic anhydride with 3,5-diaminobenzoic acid (Scheme 2, Table 1). Hydrogenation of dimer **14** gave the amine-containing dimer **16**. All of the compounds demonstrated good solubility in polar aprotic solvents such as DMF or DMSO, but poor solubility in other common solvents including water at pH 7.

The basic photophysical properties of *N*-phenyl-1,8-naphthalimides **1**–**12** and those of the dimers **13**–**16** are listed in Table 1. Of particular note is that the introduction of an electron-donating amine functionality at the 3,6-positions of the naphthalimide unit induces a significant red-shift of ~100 nm in the position of the longest wavelength band (λ_{max} ~520 nm) as demonstrated for *N*-phenyl-1,8-naphthalimides **10**–**12** and dimer **16** (See Supplementary data, Fig. S1). Solutions of these four compounds in DMF also display conspicuous yellow-green fluorescence on excitation at 439 nm (See Supplementary data, Fig. S2). The effect of substitution of the 1,8-naphthalimide core on the relative fluorescence intensity (RFI) of these compounds can be summarized as NH_2 >> Br > H > NO_2. Compounds **10**–**12** and dimer **16** possess clear potential as fluorescent building units for dendritic molecules and polymers, hence, the fluorescence quantum yields Φ_F, for these compounds were measured and found to be in the range 7–23% (Table 1). The red-shifted values for λ_{max} and the intense fluorescence demonstrated by these compounds can be attributed to the presence of the two amines on the 1,8-naphthalimide unit, which can interact with the imide functionality only through cross-conjugation via the π system.[36–38]

For the application of these compounds as building units for dendritic molecules, as cores, branching units or terminal groups, it will be important to maintain the electron-donating ability of the amine groups at the 3,6-positions of the 1,8-naphthalimide units if the intense fluorescence that they induce is to be retained. This could be achieved by attachment of the 1,8-naphthalimide component via the amine or carboxylic acid substituents on the *N*-phenyl unit (e.g., for **1**–**12**: R^3–R^5 = NH_2/CO_2H, or for dimers **13**–**16**: CO_2H). Reactions of the amine substituents on the 1,8-naphthalimide unit derived from monomers **10**–**12** or dimer **16** that will maintain their electron-donating ability (e.g., Michael addition) could also be employed for their incorporation into a dendritic structure. Alternatively, the post-synthetic reduction of the nitro substituents of the 1,8-naphthalimide units derived from components **2**, **5**, **8,** and **14** or aromatic nucleophilic substitution of the bromo-substituent of components derived from 1,8-naphthalimides **3**, **6**, **9,** or **15** could provide amine functionality and able to induce enhanced fluorescence. Preparative studies to explore these strategies are in progress.

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Supplementary data

Supplementary data (full experimental details for the preparation of compounds **1**–**16** and the collection of photophysical data from these materials. UV–vis absorption spectra of these compounds are shown in SI Fig. S1 and the emission spectra of

naphthalimides **10**–**12** and dimer **16** are shown in SI Fig. S2) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.009.

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