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Efficient and Mild Microwave-Assisted Stepwise Functionalization of Naphthalenediimide with α-Amino Acids

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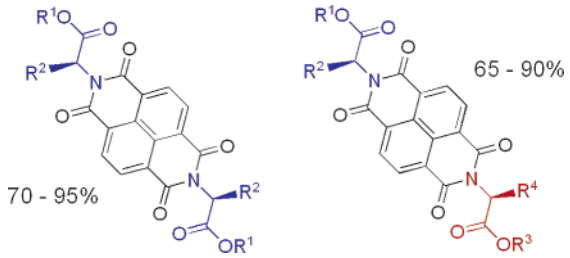

Microwave dielectric heating proved to be an efficient method for the one-pot and stepwise syntheses of symmetrical and unsymmetrical naphthalenediimide derivatives of α-amino acids. Acid-labile side chain protecting groups are stable under the reaction conditions; protection of the α-carboxylic group is not required. The stepwise condensation of different amino acids resulted in high yields of unsymmetrical naphthalenediimides. The reaction proceeds without racemization and is essentially quantitative.

Electron-deficient and electron-rich subunits are common structural motifs in the design of supramolecular architectures including topologically interlocked molecules, molecular devices, and machines.[1] The electron donor−acceptor interaction that arises has been exploited to direct the syntheses of these supramolecules under either thermodynamic or kinetic control. In this respect, the electron-deficient naphthalenediimides and pyromelliticdiimides have been extensively employed by others[2] and us[3] for the preparation of catenanes, rotaxanes and pseudorotaxanes in conjunction with electron-rich dialkoxynaphthalenes and porphyrins. In recent years, some derivatives of naphthalenediimide have enjoyed a new role as building blocks in the synthesis of hetero-oligomers that have the capability to fold, in aqueous solution, into well-defined super-structures.[4] Water-soluble naphthalenediimide derivatives also strongly interact with DNA[5] in a threading mode, and this feature has been exploited for the design of molecular probes.[6] As a part of our ongoing projects, we needed an easy entry to structurally sophisticated naphthalenediimides having additional functional groups for postsynthetic modification. The functionalization of naphthalene tetracarboxylic dianhydride **1** with α-amino acids was an attractive route because of the large diversity of functional groups that could be thus introduced. Despite the well-documented preparation of phthalimido amino acids,[7] the simplest derivatives of α-amino acids featuring an aromatic imide, the literature concerning the structurally related naphthalene and pyromellitic diimides is scant. This is due to the harsh conditions used in the condensation of primary amines with naphthalene- and pyromellitic tetracarboxylic dianhydrides. The published reaction conditions[8] consist of refluxing the two components for prolonged periods of time in high boiling solvents such as DMF, 2-propanol, or pyridine. Although these conditions may be used with free amino acids,[8,9] they may not be compatible with sensitive amines or with protected α-amino acids. We decided to use microwave-induced dielectric heating to reduce the reaction times and to broaden as much as possible the span of the reaction conditions.

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SCHEME 1. General Synthetic Method for the Symmetrical Naphthalinediimine Derivatives 2a−p

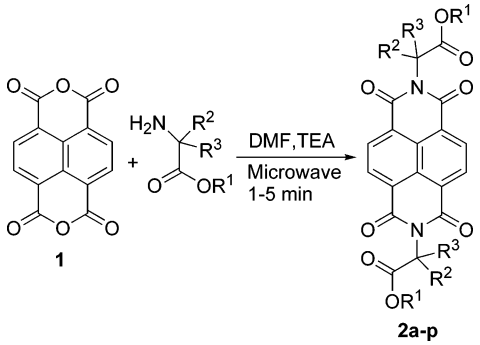

TABLE 1. Condensations of Naphthalene Tetracarboxylic Dianhydride (1) with Protected and Unprotected α-Amino Acids and α-Amino Acid Esters

entry		amino acid	time [min:sec]	yield (%)
1	**2a**	H-Gly-OH	1:00[a]	94
2	(*R*,*R*)-**2b**	H-L-Cys(Trt)-OH	2:20[a]/5:00[b]	95
3	(*S*,*S*)-**2b**	H-D-Cys(Trt)-OH	5:00[b]	86
4	(*R*,*R*)-**2c**	H-L-Cys(Trt)-OMe	5:00[b]	70[c,d]
5	(*S*,*S*)-**2d**	H-L-Ser(Bzl)-OH	2:20[a]	86
6	(*S*,*S*)-**2e**	H-L-Leu-OMe	1:30[a]	95[d]
7	(*S*,*S*)-**2f**	H-L-Phe-OMe	1:50[a]	74[d]
8	(*S*,*S*)-**2g**	H-L-Tyr-OH	3:30[a]	91
9	(*S*,*S*)-**2h**	H-L-His(Trt)-OMe	2:20[a]	73[d]
10	(*S*,*S*)-**2i**	H-L-His(Trt)-OH	5:00[b]	75
11	(*S*,*S*)-**2j**	H-L-Trp-OH	3:10[a]	89
12	(*S*,*S*)-**2k**	H-L-Trp-OMe	3:00[a]	82
13	(*S*,*S*)-**2l**	H-L-Glu(OtBu)-OH	2:40[a]	88
14	(*S*,*S*)-**2m**	H-L-Lys(Boc)-OH	2:40[a]	92
15	(*S*,*S*)-**2n**	H-L-Ala-OH	5:00[b]	84
16	(*S*,*S*)-**2o**	H-L-Arg(Pmc)-OH	5:00[b]	98
17	**2p**	H-Ac6c-OH	20:00[b]	40

[a] Reaction performed at atmospheric pressure with a domestic microwave appliance (800 W) at full power (see Experimental Section, Method A). [b] Reaction performed with a dedicated microwave reactor in pressure tight reaction vessels (see Experimental Section, Method B). [c] Over two steps, starting from H-L-Cys-OMe·HCl. [d] After column chromatography.

The synthesis of the symmetrical naphthalenediimides **2a−p** is outlined in Scheme 1. The derivatives reported in Table 1 were obtained in a pure state after simple workup, and only in a few cases was a purification step necessary. Preliminary experiments were run with a domestic microwave appliance, in an open container and at atmospheric pressure, preventing solvent (DMF) reflux.[10]

Other preparations were run in a dedicated microwave reactor in pressure-resistant, tightly closed reaction vessels. The reactions were carried out at 140 °C for a period of five minutes. In these conditions, the power required to warm the reaction mixture was between 330 and 390 W and the heating process took between 25 and 30 s, followed by pulses of 30−50 W to maintain the reaction mixture at 140 ± 5 °C. To test the viability of this temperature-controlled method with respect to both reaction temperature and reagent concentration, the synthesis of (*R*,*R*)-**2b** was studied at 100 and 140 °C and on 0.2 and 1 g of 1,4,5,8-naphthalenetetracarboxylic dianhydride. All the preparations gave similar results, with (*R*,*R*)-**2b** being obtained in over 90% yields.

(10) A 800 W domestic microwave oven (home appliance); in these conditions and irradiating at full power, the solvent refluxes in about 20 s.

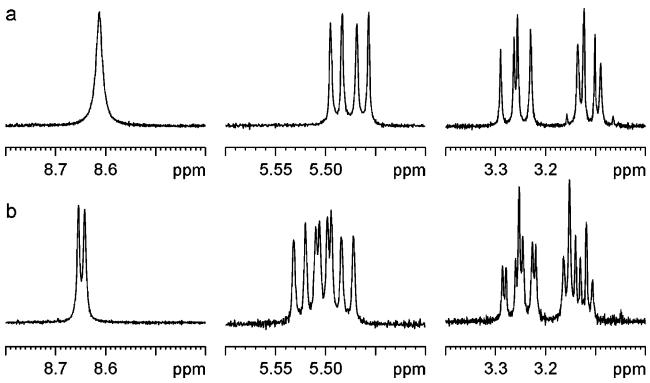

FIGURE 1. (a) Sections of the ^{1}H NMR spectrum of compound (*R*,*R*)-**2b**. (b) Sections of the ^{1}H NMR spectrum of the naphthalene diimide derivative obtained using H-(D,L)-Cys(Trt)-OH. The spectra were recorded at 400 MHz in $CDCl_3$ at 298 K. A Lorentzian/Gaussian window function with LB = −0.3 Hz and GB = 1 was used for resolution enhancement.

To explore the scope of the reaction, both unprotected and protected amino acids were used. We mainly focused on acid-labile protecting groups because of their well-established use for the protection of amino acids in solid-phase synthesis. All the protecting groups tested, trityl (Table 1, entries 2−4, 9, 10), benzyl (5), *tert*-butyl (13), Boc (14), and Pmc (16), were stable under the reaction conditions. No side reactions related to the loss of a protecting group were observed. Remarkably, both free amino acids and amino acid esters could be used without significant differences in the efficiency of the reaction (Table 1, entries 9,10 and 11,12, respectively). This is somewhat surprising because, in these conditions, one may expect self-condensation of amino acid esters to give dipeptides or diketopiperazines and higher oligomers, but such side reactions were never observed. Finally, in the case of unprotected tyrosine, entry 8, the reaction was completely selective for the formation of the symmetrical imide, no formation of esters being detected by ^{1}H NMR and reverse phase HPLC. The synthesis of compound **2p**, where 1-aminocyclohexanecarboxylic acid was used, constitutes a special case in this study as we wanted to test our synthetic protocols on sterically demanding C^α-tetrasubstituted amino acids. The synthesis required longer reaction times due to a combination of the poor solubility of the starting material (H-Ac6c-OH) and steric hindrance imposed by the cyclohexane ring. Compound **2p** was isolated in 40% yield, the lowest observed in this study, along with trace amounts (2%) of the corresponding imide−anhydride derivative, **3** (vide-infra).

We also briefly explored synthetic protocols compatible with the base−labile Fmoc group installed at the N^ϵ nitrogen of lysine. Regrettably, under the standard reaction conditions, complex mixtures were obtained, likely as the result of some Fmoc cleavage.[11] Complex mixtures were obtained as well when arginine methylester and unprotected arginine were reacted using the standard conditions.

(11) In an attempt to solve this problem, the reaction was conducted in the presence of a stoichiometric and substoichiometric amounts of triethylamine, or using the more hindered base, diisopropylethylamine (Hunig's base). Unfortunately, in all the cases, complex mixtures were obtained with no sign of product formation. When no base was added, the reaction was not complete, even after irradiation for 30 min at 140 °C, using the dedicated microwave reactor.

SCHEME 2. General Synthetic Method for the Unsymmetrical Naphthalinediimine Derivatives 4a−d

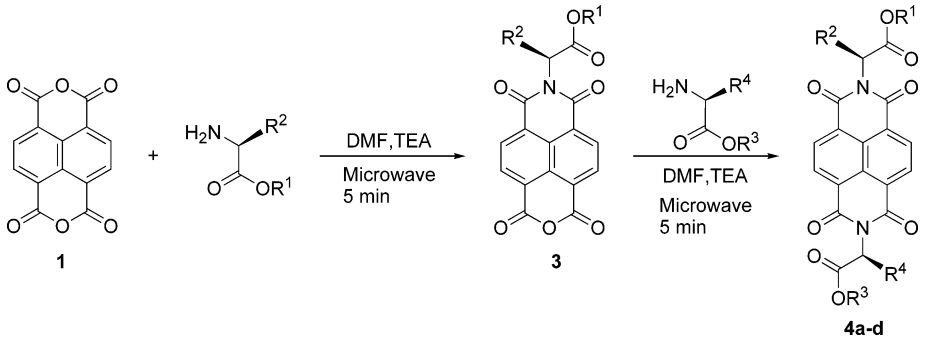

TABLE 2. Stepwise Syntheses of Unsymmetrical L-α-Amino Acid Functionalized Naphthalenediimides[a]

entry		amino acid 1	amino acid 2	yield (%)[b]
1	(*R*,*S*)-**4a**	H-L-Cys(Trt)-OH	H-L-His(Trt)-OH	85[c]
2	(*S*,*S*)-**4b**	H-L-Phe-OMe	H-L-Gln-OH	77
3	(*S*,*S*)-**4c**	H-L-Asp-OMe	H-L-Tyr-OH	90[c]
4	(*S*,*S*)-**4d**	H-L-Ile-OMe	H-L-Trp-OMe	65[d]

[a] Reaction performed with a dedicated microwave reactor in pressure tight reaction vessels. [b] From dianhydride **1**. [c] Determined by ^{1}H NMR on the crude mixture. [d] After column chromatography.

The ^{1}H NMR spectra of compounds **2b−p** display a sharp singlet that broadens at higher concentration[12] for the naphthalenediimide moiety and a single set of signals for the amino acid part. All the materials were also found to be homogeneous by reverse phase HPLC analysis. This indicates that the reaction proceeds without racemization at the α-center.

However, because the two amino acid fragments are quite far apart, one may argue that ^{1}H NMR may not be a reliable method to distinguish between the diastereoisomers of the naphthalenediimide formed upon racemization of the α-centers. To specifically address this point, we used H-(D,L)-Cys(Trt)-OH as the amino acid component in the condensation with anhydride **1**. In this case, three compounds are expected: the symmetrical (*S*,*S*)-**2b** and (*R*,*R*)-**2b** and the unsymmetrical (*S*,*R*)-**2b** in a 1:1:2 ratio. Because the enantiomeric (*S*,*S*)-**2b** and (*R*,*R*)-**2b** cannot be distinguished by NMR, they give a single set of signals that is in a 1:1 ratio with the set for the (*S*,*R*) diastereoisomer. The ^{1}H NMR spectrum in Figure 1 (trace b) clearly illustrates this situation; this is particularly evident when the aromatic protons of the naphthalenediimide are concerned. Trace a shows the ^{1}H NMR spectrum of (*R*,*R*)-**2b** obtained using H-L-Cys(Trt)-OH; its comparison with trace b clearly indicates the absence of any diastereomeric species within the NMR detection limit.

The one-pot procedure for the synthesis of symmetric amino acids derivatives of naphthlenediimides proved to be reliable and efficient, but we were interested in an equally easy route to desymmetrize the dianhydride **1**, obtaining unsymmetrical amino acid functionalized diimides. We thus explored the stepwise method outlined in Scheme 2. To our delight, we found that it is possible to obtain a fairly high yield of unsymmetrical naphthalene diimides with very little contamination by the corresponding symmetrical species. The results of these findings are summarized in Table 2. We speculate that this selectivity is due to the decreased reactivity of intermediate **3** with respect to the unreacted naphthalene dianhydride **1**. In contrast, the standard methods for the synthesis of unsymmetrical naphthalenediimides usually result in almost statistical mixtures. A reasonable explanation for this difference is that in our conditions, the reaction proceeds under kinetic control as a consequence of the dramatic increase of the reaction rate, few minutes against several hours for the reported procedures.

Structural proof for compound **2f** came from single-crystal X-ray diffraction analyses of crystals grown by slow evaporation of an acetone solution and a dichloromethane/acetonitrile mixture. Figure 2 shows the single molecule and packing views of **2f** obtained from acetone. This compound adopts a *C*222(1) space group, where the unit cell contains molecules arranged in parallel fashion, as depicted in Figure 2 (bottom left) when crystallized from acetone, and a *P*1 space group when crystallized from dichloromethane/acetonitrile mixtures (see Supporting Information). Regardless of the solvent used to obtain the single crystals of **2f**, there are two electron donor−acceptor (phenylnaphthalenediimide core) interactions per molecule, each with a different partner. The two aromatic systems are almost parallel, such that the smallest distance between them is 3.32 Å, with the biggest distance being 3.53 Å.

In conclusion, microwave dielectric heating proved to be an efficient and high-yielding method for the syntheses of symmetrical and unsymmetrical amino acid derivatives of naphthalenediimide. The reaction proceeds without racemization at the α-center, and the synthetic conditions are compatible with acid-labile protecting groups. The application of these amino

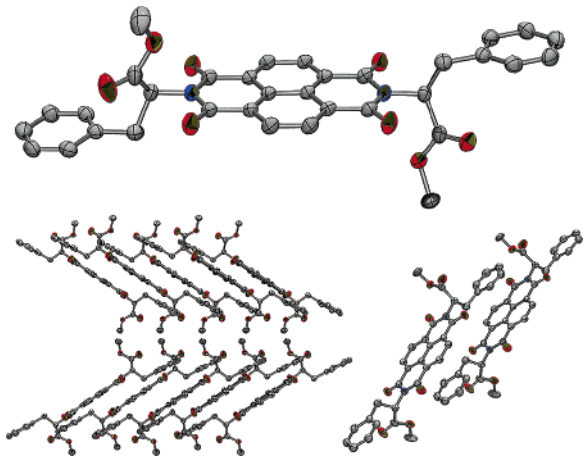

FIGURE 2. Side and crystal packing ORTEP−POVray rendered views of **2f**. The thermal ellipsoids are scaled at 50% probability level. All hydrogen atoms and a disordered solvent molecule (acetone) have been removed for clarity.

(12) Some concentration-dependent changes in chemical shift were also observed.

acid functionalized diimides is under investigation and will be reported in due course.

Experimental Section

Synthesis of Symmetrical Naphthalenediimide Derivatives of α-Amino Acids (2a−p): (A) General Procedure. 1,4,5,8-Naphthalenetetracarboxylic dianhydride (200 mg, 0.746 mmol) and the corresponding α-amino acid derivative (1.491 mmol) were suspended in 20 mL of DMF in a 150-mL Erlenmeyer flask. To this suspension was added 0.2 mL of dry Et_3N. The suspension was sonicated until the mixture became homogeneous. The reaction mixture was heated under microwave irradiation at full power according to the times specified in Table 1, in 4 × 5 s intervals followed by 10 s intervals. During this stage, the reaction mixture was prevented from refluxing (reaction temperature 120−140 °C). The solvent was removed under reduced pressure, and each reaction mixture was worked-up using a suitable method.

(B) General Procedure. 1,4,5,8-Naphthalenetetracarboxylic dianhydride (200 mg, 0.746 mmol) and the corresponding α-amino acid derivative (1.491 mmol) were suspended in 10 mL of DMF in a pressure-tight 20-mL microwave vial. To this suspension was added 0.2 mL of dry Et_3N. The suspension was sonicated until the mixture became homogeneous. The reaction mixture was heated for 5 min at 140 ± 5 °C (direct flask temperature measurement) under microwave irradiation using a dedicated microwave system. The solvent was removed under reduced pressure, and each reaction mixture was worked-up using a suitable method.

Synthesis of Unsymmetrical Naphthalenediimide Derivatives of α-Amino Acids (4a−d). 1,4,5,8-Naphthalenetetracarboxylic dianhydride (200 mg, 0.746 mmol) and the first α-amino acid derivative, amino acid 1 according to Table 2, (0.746 mmol) were suspended in 10 mL of DMF in a pressure-tight 20-mL microwave vial. To this suspension was added 0.1 mL of dry Et_3N. The suspension was sonicated until the mixture became homogeneous. The reaction mixture was heated for 5 min at 140 ± 5 °C (direct flask temperature measurement) under microwave irradiation, using a dedicated microwave system. At this stage, the second α-amino acid derivative (amino acid 2, in Table 2) was added in one portion. An additional 0.1 mL of dry Et_3N was added, and the mixture was sonicated for 30 min. The reaction mixture was heated for an additional 5 min at 140 ± 5 °C (direct flask temperature measurement) under microwave irradiation, using a dedicated microwave system. The solvent was removed under reduced pressure, and each reaction mixture was worked-up using a suitable method.

(7-Carboxymethyl-1,3,6,8-tetraoxo-3,6,7,8-tetrahydro-1*H*-benzo[*lmn*][3,8]phenanthrolin-2-yl)-acetic Acid, 2a. The reaction mixture was concentrated under reduced pressure to a volume of 3 mL and added dropwise to 200 mL of 2.5% aqueous $KHSO_4$ kept under vigorous stirring. The resulting suspension was allowed to coagulate overnight, and the precipitate was collected using a Büchner funnel, washed with water, and dried under vacuum. The product was obtained as a brown-grey powder in 94% yield. mp > 300 °C (Lit:[13] > 390 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 13.19 (bs, 2H), 8.73 (s, 4H), 4.77 (s, 4H); ^{13}C NMR {^{1}H} (100.62 MHz, DMSO-d_6) δ(ppm): 169.1, 162.3, 131.1, 126.4, 126.1, 41.6; HRMS (ESI+) calcd for $C_{18}H_{10}N_2NaO_8$ $[M + Na]^+$ (m/z): 405.0335, found: 405.0329.

(*S*)-4-Carbamoyl-2-[7-((*S*)-1-methoxycarbonyl-2-phenyl-ethyl)-1,3,6,8-tetraoxo-3,6,7,8-tetrahydro-1*H*-benzo[*lmn*][3,8]-phenanthrolin-2-yl]-butyric Acid, (*S*,*S*)-4b. The dark brown oil was taken up into CH_3CN (15 mL). This solution was added under stirring to 75 mL of 1 N HCl. The resulting suspension was allowed to coagulate overnight and was then filtered using a Büchner funnel. The solid was then washed with 100 mL deionized water and dried in vacuo. The product was obtained in the form of a light-brown solid in 77% yield. mp 164−166 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 12.87 (bs, 2H), 8.68−8.67 (d, J = 2.0, 4H), 7.17−7.02 (m, 6H), 6.58 (bs, 1H), 6.03−5.99 (dd, J_1 = 15.0, J_2 = 5.5, 1H), 5.55−5.52 (dd, J_1 = 14.5, J_2 = 4.5, 1H), 3.67 (s, 3H), 3.63−3.58 (dd, J_1 = 19.5, J_2 = 5.5, 1H), 3.36−3.29 (dd, J_1 = 25.0, J_2 = 10.0, 1H), 2.45−2.38 (m, 1H), 2.33−2.24 (m, 1H), 2.19−2.07 (m, 2H); ^{13}C NMR {^{1}H} (100.62 MHz, DMSO-d_6) δ(ppm): 173.4, 170.5, 169.3, 162.3, 162.0, 137.1, 131.4, 131.0, 129.0, 128.2, 126.5, 126.3, 126.0, 125.1, 54.2, 53.2, 52.4, 34.0, 31.6, 23.9; HRMS (ESI+) calcd for: $C_{29}H_{24}N_3O_9$ $[M + H]^+$ (m/z): 558.1513, found: 558.1531.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds, ^{1}H NMR and ^{13}C NMR spectra for compounds **2a**−**p** and **4a**−**d**, X-ray crystallographic data for compound **2f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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