Photodecarboxylative Cyclizations of ω-Phthalimido-para-phenoxy Carboxylates

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The chemistry of electronically-excited phthalimides is dictated by electron and/or hydrogen transfer reactions. The photochemistry of phthalimides has been intensively studied, and numerous synthetically useful transformations with high chemical and quantum yields have been developed. Among the synthetic applications, intra- and intermolecular photodecarboxylation (PDC) of ω-phthalimidoalkyl carboxylates has been developed by Griesbeck and co-workers as a versatile pathway to medium- and large-ring heterocycles. Model reactions were further realized on macro- and micro-scales. We recently described PDC cyclizations of ω-phthalimidoalkynoates to produce macrocyclic alkynes with ring-sizes up to 17. In recent study, we expanded the portfolio of this reaction and investigated the photochemistry of related aryl-linked phthalimides in Scheme 1. Based on these approaches, we demonstrated that ω-phthalimido-ortho/meta-phenoxy carboxylates efficiently underwent PDC cyclizations. While the yields of ω-phthalimido-ortho-phenoxy carboxylates steadily decreased with increasing chain-length and the maximum yield of the 6-membered product was obtained in 75%, the yields of meta-phenoxy carboxylates steadily increased with increasing chain-length and the extended 16-membered product was subsequently obtained in 48% yield.

As an extension of our work, we were interested in using para-substituted aryl carboxylates with a linker between the phthalimide chromophore and terminal phenyl carboxylic acid. The U-shaped geometry of the central skeleton should favor close contact geometry between the two active ends of the molecule, preferably for large ring systems. In this paper, we describe the photochemistry of several ω-phthalimido-para-alkoxy phenyl carboxylic acids (4a-c) differing in internal carbon-chain lengths (Scheme 2).

Syntheses of ω-Phthalimido-para-alkoxy Phenyl Acetic Acids. ω-Phthalimido-para-alkoxy phenyl acetic acids (4a-c) containing an alkyl chain were prepared by the formation of an ether-linkage to investigate the relationship between ring size and yield through intramolecular PDC cyclization. To compensate for the para-substitution pattern in the ring closure step, longer carbon linkers were specifically introduced. The derivatives 4a-c were prepared from 4-hydroxy-phenyl acetate as described in Scheme 2. Coupling of 4-hydroxyphenyl acetate and the corresponding 1,ω-dibromo-alkanes produced 2a-c in moderate yields of 52-56%. Treatment of 2a-c with potassium phthalimide in DMF yielded compound 3a-c in good yields of 72-89%. Subsequent
hydrolysis with conc. HCl/H$_2$O/acetone at reflux afforded the desired ω-phthalimido-para-alkoxy phenyl acetic acids (4a-c) as colorless solids in 68-83% yield.

**Photolyses of ω-Phthalimido-para-alkoxy Phenyl Acetic Acids.** ω-Phthalimido-para-alkoxy phenyl acetic acids (4a-c) were deprotonated with potassium carbonate (K$_2$CO$_3$) prior to photolysis. Photolyses were performed with the corresponding potassium salts of 4a-c in acetone/water mixtures (9:1,v/v) using a Rayonet photoreactor equipped with low pressure mercury lamps (phosphor coated with an emission maximum at ca. 300 nm; 800 W). Irradiations were stopped after 4 h and thin layer chromatography (TLC) analyses of the crude reaction mixtures indicated conversion rates greater than 90%.

Photolysis of ω-phthalimido-para-alkoxy phenyl acetic acid (4a) resulted in the cyclization product 5a in 19% isolated yield (Scheme 2). In CDCl$_3$, the $^1$H-NMR spectra showed multi-signals for the N-CH$_3$ groups between 3.41 and 3.47 ppm. The benzylic proton attached beside hydroxyl carbon gave a singlet at 3.48 ppm, which was unambiguously assigned. In the $^{13}$C-NMR spectrum, the newly formed C-OH group showed a characteristic resonance at 90.7 ppm. Although the simple decarboxylation product was not observed in the crude product, NMR and TLC analysis indicated several other by-products in a total amount of ca. 5-10%. However, none of these by-products could be isolated in a sufficient amount and purity. Likewise, compounds 4b and 4c produced the corresponding cyclization products 5b and 5c, respectively. The isolated yield for the 18-membered ring 5c was high with 46%, whereas the smaller ring-system 5b had a decreased isolated yield of 37%, as summarized in Table 1. The amounts of unreactive starting material were estimated below 5-10%. Additionally, several by-products were detected in total amounts of ca. 5-10% in the crude reaction mixtures by TLC or NMR analysis. Yields of 5 steadily increased with increasing chain-length and following this extension strategy, the 18-membered product 5c was subsequently obtained in 46% yield. The structural assignments of the photoproducts were based on the spectroscopic data. The complex multiplet between 6.8 and 7.8 ppm further revealed the asymmetry of the aromatic ring, corroborating the structure of the cyclization product. While the $^1$H-NMR spectra were rather complex, all cyclization products 5a-c showed the characteristic C-OH signal in their $^{13}$C-NMR spectra at approximately 90 ppm. In all three cases, the $^{13}$C-NMR spectra showed clear resonances at 90.65 (5a), 90.63 (5b) and 90.38 ppm (5c), respectively, corresponding to quaternary C-OH carbons. The GC/MS spectrum showed molecular ion peaks. The spectral data of the cyclization products are consistent with carbon-carbon bond formation between the phthalimide carbonyl carbon and α-carbon of potassium carboxylates.

**Mechanistic Interpretations.** When the geometric disadvantages of the linking para-linked long chain compounds were cooperative by an elongated chain, photocyclization products were obtained in good yields (19-46%). The efficiency of the cyclization increases with increasing carbon-chain length. The key-step in the mechanistic scenario (Scheme 3) is an intramolecular electron transfer from the respective donor moiety to the triplet excited phthalimide, populated by sensitization with acetone. For carboxylate 4, electron transfer generates an unstable carboxy radical that undergoes rapid decarboxylation to the analogous carbon radical. Subsequently, protonation and biradical combination yields the desired cyclization product 5. When cyclization is not possible, back electron transfer (BET) provides a carbanion, which is protonated by water to produce the decarboxylation product 6.

In conclusion, ω-phthalimido-para-phenoxy carboxylates (4a-c) underwent photodecarboxylative macrocyclizations in reasonable yields of 19-46%. The optimal yield of intramolecular cyclization was obtained from the substrate (4c) to form an 18-membered ring. The photocyclization efficiency increases with increasing carbon-chain length, probably due to the good chance that they would collide. Therefore, we concluded that the efficiency of PDC cyclizations depended critically on the substitution pattern of the arene and the linking carbon-chain lengths between electron-donor and acceptor. The extended carbon linker in the para-substitution arene must compensate for the unfavorable para-substitution to allow for close contact for electron transfer and cyclization.

**Experimental Section**

**General Procedures.** All starting materials and reagents were purchased from Aldrich Chemical Co. and used without further purification. Solvents used for synthesis (acetone, nitrile, DMF, hexane, and ethyl acetate) were purified *via* literature methods. Twice-distilled water and reagent grade acetone were used for the photoreactions.

Melting points were obtained on a Buchi 510 melting point apparatus.

Table 1. Experimental details for the PDC cyclizations of 4a-c

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>Ring size</th>
<th>Yield of 5 (%)</th>
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<tbody>
<tr>
<td>4a</td>
<td>3</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>4b</td>
<td>5</td>
<td>16</td>
<td>37</td>
</tr>
<tr>
<td>4c</td>
<td>7</td>
<td>18</td>
<td>46</td>
</tr>
</tbody>
</table>

*Isolated yields.*
point apparatus and were uncorrected. NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 MHz \(1^1H\) and 100 MHz \(13^C\)-frequencies) using tetramethylsilane (TMS) or the solvent residual peak as an internal standard. CDC\(_1\), was stored over K\(_2\)CO\(_3\) to remove trace amounts of acid. Chemical shifts \(\delta\) are given in ppm and coupling constants \(J\) in Hz. The chemical shifts for the acid protons of 1a-c were not observed (> 10 ppm). MS spectra were determined on a V. G. Autospec-Ultima (EL, 70 eV) instrument. Fourier-transform infrared (FT-IR) spectra were recorded on a Bomem MB-100 series FT-IR spectrophotometer (KBr disc or film). Photochemical reactions were performed in Pyrex vessels (\(\lambda > 280 \text{ nm}\)) using a Rayonet photochemical reactor equipped with 3000 Å lamps (\(\lambda = 300 \pm 10 \text{ nm}\); ca. 800 W).

**Synthesis of Methyl Bromoehexyloxy Phenyl Acetate (2a):** The mixture of methyl 4-hydroxyphenyl acetate (1) (1.00 g, 6.02 mmol), K\(_2\)CO\(_3\) (1.00 g, 7.22 mmol), and KI (catalyst) in dry acetonitrile (25 mL) were added to 1,6-dibromohexane (1.1 mL, 7.22 mmol) and stirred in a 80-90 °C oil bath for 12 h. After completing the reaction by monitoring on thin layer chromatography (TLC), the solvent was evaporated. The resulting mixture was diluted with ethyl acetate, washed with water, dried over MgSO\(_4\) and the solvent was evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1) to produce 2a (1.08 g, 55%) as a colorless oil. \(^1H\)-NMR (400 MHz, CDC\(_1\)) \(\delta 1.49-1.50\) (m, 4H), 1.78 (t, 2H, \(J = 6.7 \text{ Hz}\)), 1.89 (t, 2H, \(J = 7.2 \text{ Hz}\)), 3.41 (t, 2H, \(J = 6.6 \text{ Hz}\)), 3.56 (s, 2H), 3.68 (s, 3H), 3.94 (t, 2H, \(J = 6.3 \text{ Hz}\)), 6.83 (d, 2H, \(J = 8.6 \text{ Hz}\)), 7.17 (d, 2H, \(J = 8.1 \text{ Hz}\)); \(^13^C\)-NMR (100 MHz, CDC\(_1\)) \(\delta 25.3, 27.9, 29.1, 32.7, 33.7, 40.2, 51.9, 67.7, 114.5, 125.8, 130.1, 158.0, 172.1.

**Methyl Bromomctoxy Phenyl Acetate (2b):** The reaction of methyl 4-hydroxyphenyl acetate (1) (1.00 g, 6.02 mmol), K\(_2\)CO\(_3\) (1.00 g, 7.22 mmol), KI (catalyst), and 1,8-dibromooctane (1.32 mL, 7.22 mmol) in dry acetonitrile (25 mL) was performed as described for the preparation of 2a to produce 2b (1.13 g, 52%) as a colorless oil. \(^1H\)-NMR (400 MHz, CDC\(_1\)) \(\delta 1.35-1.45\) (m, 8H), 1.76 (t, 2H, \(J = 7.2 \text{ Hz}\)), 1.85 (t, 2H, \(J = 7.3 \text{ Hz}\)), 3.40 (t, 2H, \(J = 6.8 \text{ Hz}\)), 3.55 (s, 2H), 3.67 (s, 3H), 3.92 (t, 2H, \(J = 6.5 \text{ Hz}\)), 6.83 (d, 2H, \(J = 8.1 \text{ Hz}\)), 7.16 (d, 2H, \(J = 8.3 \text{ Hz}\)); \(^13^C\)-NMR (100 MHz, CDC\(_1\)) \(\delta 25.9, 28.1, 28.7, 29.1, 29.2, 32.8, 33.9, 40.3, 51.9, 67.9, 114.5, 125.7, 130.05, 158.1, 172.1.

**Methyl Bromodecethoxy Phenyl Acetate (2c):** The reaction of methyl 4-hydroxyphenyl acetate (1) (1.00 g, 6.02 mmol), K\(_2\)CO\(_3\) (1.00 g, 7.22 mmol), KI (catalyst), and 1,8-dibromooctane (1.63 mL, 7.22 mmol) in dry acetonitrile (25 mL) was performed as described for the preparation of 2a to produce 2c (1.30 g, 56%) as a colorless oil. \(^1H\)-NMR (400 MHz, CDC\(_1\)) \(\delta 1.30-1.44\) (m, 12H), 1.74-1.86 (m, 4H), 3.40 (t, 2H, \(J = 6.8 \text{ Hz}\)), 3.55 (s, 2H), 3.67 (s, 3H), 3.92 (t, 2H, \(J = 6.6 \text{ Hz}\)), 6.83 (d, 2H, \(J = 8.6 \text{ Hz}\)), 7.16 (d, 2H, \(J = 8.8 \text{ Hz}\)); \(^13^C\)-NMR (100 MHz, CDC\(_1\)) \(\delta 25.6, 27.8, 28.1, 28.3, 28.9, 29.0, 29.1, 32.4, 33.2, 33.6, 39.9, 51.5, 67.5, 114.1, 125.3, 129.7, 157.7, 171.8.

**Synthesis of \(\omega\)-Phthalimido-para-hexyloxy Phenyl Acetic Acid (4a):** A solution of 3a (1.14 g, 2.90 mmol) in acetone/H\(_2\)O/HCl (40:28:12, v/v/v) (30 mL) was stirred in a 60-65 °C oil bath for 5 h. After completing the reaction by monitoring on TLC, the solvent was evaporated. The resulting mixture was diluted with ethyl acetate, washed with water, dried over MgSO\(_4\) and the solvent was evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1:1) to produce 4a (0.92 g, 83%) as a white solid. mp 116-118 °C; FT-IR (KBr, cm\(^{-1}\)) 3462, 3227, 2940, 1773, 1613, 1362, 800; \(^1H\)-NMR (400 MHz, CDC\(_1\)) \(\delta 1.40-1.78\) (m, 8H), 3.57 (s, 2H), 3.69 (t, 2H, \(J = 7.3 \text{ Hz}\)), 3.92 (t, 2H, \(J = 6.4 \text{ Hz}\)), 6.82 (d, 2H, \(J = 8.3 \text{ Hz}\)), 7.15 (d, 2H, \(J = 8.9 \text{ Hz}\)), 7.70 (dd, 2H, \(J = 3.4, 3.4 \text{ Hz}\)), 7.83 (dd, 2H, \(J = 3.4, 3.4 \text{ Hz}\)); \(^13^C\)-NMR (100 MHz, CDC\(_1\)) \(\delta 25.7, 26.6, 28.6, 29.1, 37.9, 40.3, 52.0, 67.7, 114.5, 123.1, 125.7, 130.1, 132.0, 133.7, 158.0, 168.3, 172.2.

**Notes**

Photolysis of 4a: Potassium carbonate (K$_2$CO$_3$) (17.9 mg, 0.13 mmol) was dissolved in 2 mL of water. A solution of 4a (100 mg, 0.26 mmol) in 100 mL of an acetic acid/H$_2$O (9:1, v/v) solution was added. The mixture was stirred for 30 min and concentrated (300 mm) in 4 h while purging with a slow stream of N$_2$ gas. The solution was evaporated and extracted with chloroform, washed with water, dried over MgSO$_4$ and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 1:1) to produce 5a (17.0 mg, 19%), mp 182-184 °C; 1$^H$-NMR (400 MHz, CDCl$_3$) $\delta$ 0.31-1.69 (m, 8H), 2.56-2.76 (m, 2H), 3.48 (s, 2H), 4.14-4.37 (m, 2H), 6.94 (d, 2H, J = 3.8 Hz), 6.99 (d, 1H, J = 8.3 Hz), 7.10 (d, 2H, J = 5.8 Hz), 7.46 (t, 1H, J = 7.1 Hz), 7.59 (2H, J = 5.9 Hz), 7.68 (d, 1H, J = 7.1 Hz), 7.79 (d, 1H, J = 8.1 Hz); 1$^C$-NMR (100 MHz, CDCl$_3$) $\delta$ 22.3, 25.6, 26.5, 26.8, 28.0, 41.3, 44.4, 67.3, 90.7, 116.3, 117.7, 121.4, 123.2, 127.9, 129.5, 130.4, 131.3, 131.5, 132.2, 148.7, 157.5, 168.0; Mass (m/z) 337 (M$^+$), 319, 230, 160, 108.

Photolysis of 4b: The reaction of K$_2$CO$_3$ (16.9 mg, 0.12 mmol) in 2 mL of water and 4b (100 mg, 0.24 mmol) in 100 mL of an acetic acid/H$_2$O (9:1, v/v) solution was performed as described for the photolysis of 4a to produce 5b (33.0 mg, 37%), mp 171-173 °C; 1$^H$-NMR (400 MHz, CDCl$_3$) $\delta$ 0.78-1.37 (m, 8H), 1.53-1.76 (m, 4H), 2.70-2.81 (m, 2H), 3.48 (s, 2H), 4.23-4.33 (m, 3H), 6.84-7.10 (m, 3H), 7.48 (t, 1H, J = 7.1 Hz), 7.57 (d, 2H, J = 7.3 Hz), 7.62 (d, 1H, J = 6.8 Hz), 7.72 (d, 1H, J = 7.2 Hz); 1$^C$-NMR (100 MHz, CDCl$_3$) $\delta$ 22.3, 25.6, 26.5, 26.8, 28.0, 41.3, 44.4, 67.3, 90.6, 116.3, 117.7, 121.4, 123.2, 127.9, 129.5, 130.4, 131.3, 131.5, 132.2, 148.6, 157.4, 168.0; Mass (m/z) 365 (M$^+$), 281, 207, 107.

Photolysis of 4c: The reaction of K$_2$CO$_3$ (15.7 mg, 0.01 mmol) dissolved in 2 mL of water and 4c (100 mg, 0.22 mmol) in 100 mL of an acetonitrile/H$_2$O (9:1, v/v) solution was performed as described for the photolysis of 4a to produce 5c (41.0 mg, 46%), mp 182-184 °C; 1$^H$-NMR (400 MHz, CDCl$_3$) $\delta$ 0.87-1.76 (m, 16H), 2.77-2.85 (m, 2H), 3.08-3.15 (m, 2H), 3.48 (s, 2H), 3.59-4.17 (m, 2H), 6.80 (d, 2H, J = 3.8 Hz), 7.11 (d, 2H, J = 8.1 Hz), 7.31 (d, 1H, J = 7.9 Hz), 7.47 (t, 1H, J = 7.1 Hz), 7.59 (d, 2H, J = 7.3 Hz), 7.62 (d, 1H, J = 6.8 Hz), 7.72 (d, 1H, J = 7.2 Hz); 1$^C$-NMR (100 MHz, CDCl$_3$) $\delta$ 24.0, 25.8, 27.1, 27.5, 27.6, 27.7, 27.8, 28.6, 40.6, 43.8, 66.7, 90.4, 116.3, 117.7, 121.4, 123.2, 127.9, 129.5, 130.4, 131.3, 131.5, 132.2, 148.6, 157.4, 168.0; Mass (m/z) 393 (M$^+$), 305, 207, 107.

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