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Photoinduced electron transfer cyclizations of aryl-linked phthalimides

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ABSTRACT

The photochemistry of arene-linked phthalimides incorporating the carboxylate or thioether donor group was investigated. Simple *N*-phthalimidophenyl alkanoates exclusively gave photoreduction (CO_2H/H-exchange) products. In contrast, ω-phthalimido-*meta*-phenoxy carboxylates underwent photodecarboxylative cyclizations in yields of 6–48%. Likewise, catechol-linked derivatives furnished analogue cyclization products in 18–38% yield. Using the photodecarboxylation protocol, macrocyclic target compounds with ring sizes up to 17 could thus be realized. Two model phthalimides containing a thioether branch at the *ortho*-position of the arene-linker gave the analogue seven-membered cyclization products in yields of 28% and 35%, respectively.

The photochemistry of phthalimides has been intensively studied and numerous synthetically useful transformations with high chemical and quantum yields have been developed.[1] Among these, intra- and intermolecular photodecarboxylations (PDC) have been established as simple and efficient alternatives to thermal organometallic reactions.[2] Model reactions were furthermore realized on macro- and micro-scales.[3,4] We have recently described PDC cyclizations of ω-phthalimidoalkynoates to give macrocyclic alkynes with ring-sizes of up to 17.[5] In the recent study, we expanded the portfolio of this reaction and investigated the photochemistry of related arene-linked phthalimides. Despite PDC-type reactions, photoinduced electron transfer (PET) cyclizations of selected thioether-containing compounds were additionally examined.[6]

Simple *N*-phthalimidophenyl carboxylic acids were initially chosen for this study. Irradiations of their corresponding potassium carboxylates **1a**–**e** in aqueous acetone furnished solely the 'simple' decarboxylation (CO_2H/H-exchange) products **2a**–**e** independent of the substitution pattern (Scheme 1, Table 1).[7] The *ortho*- and *meta*-substituted carboxylates **1a** and **1b** gave the highest yields of 62% (**2a**) and 84% (**2b**), respectively, after short irradiation times. As would be expected by the spatial separation of the donor–acceptor couple (CO_2^-/Pht = N) by the rigid arene ring, the *para*-substituted analogue furnished **2c** in only 8% yield after a comparable time period. Consequently, prolonged irradiations were applied for the extended carboxylates **1d** and **1e** and gave improved yields of 28% (**2d**) and 15% (**2e**), respectively. The spectroscopic data of all products matched those reported in the literature. As an example, the terminal CH_3 group in **2e** showed a characteristic triplet at 0.95 ppm in the ^{1}H NMR spectrum.[8]

In our previous investigation we demonstrated that ω-phthalimido-*ortho*-phenoxy carboxylates undergo efficient PDC cyclizations with ring-sizes up to 15 atoms.[9] The corresponding ω-phthalimido-*meta*-phenoxy carboxylates **3a**–**d** were consequently investigated (Scheme 2, Table 2). To compensate for the *meta*-substitution pattern in the ring closure step, longer carbon linkers were specifically introduced. The pentylene (C_5) moiety furnished the 11-membered macrocycle **4a** in a low yield of just 6% together with larger amounts of unidentified decomposition products. Yields steadily increased with increasing chain-length and following this extension strategy, the 16-membered product **4d** was subsequently obtained in 48% yield. While the ^{1}H NMR spectra were rather complex, all cyclization products **4a**–**d** showed the characteristic C–OH signal in their ^{13}C NMR spectra at approximately 93 ppm.[10] In all the cases examined, 'simple' decarboxylation products similar to **2** could be detected, but were not isolated.

Catechol was additionally chosen as a central linker between two flexible carbon chains. Four model compounds, **5a**–**d** were prepared and irradiated under PDC conditions (Scheme 3, Table 3). The 'U-

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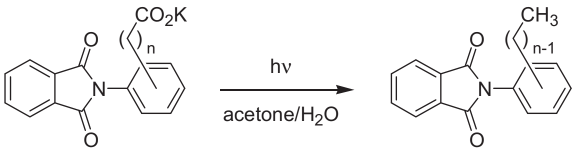


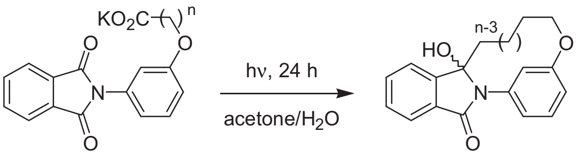
1a-e **2a-e**

Scheme 1. Simple decarboxylation of **1a**–**e**.

Table 1
Experimental details for PDC of **1a**–**e**

Entry	Substitution	*n*	Time (h)	Yield of **2** (%)
1a	*Ortho*	1	1	62[a]
1b	*Meta*	1	2	84
1c	*Para*	1	2	8
1d	*Para*	2	26	28
1e	*Para*	3	24	15

[a] From Ref. 9

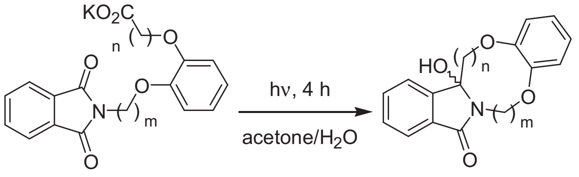


3a-d **4a-d**

Scheme 2. Photodecarboxylative cyclizations of **3a**–**d**.

Table 2
Experimental details for PDC cyclizations of **3a**–**d**

Entry	*n*	Yield of **4** (%)	Ring size
3a	5	6	11
3b	6	18	12
3c	9	38	15
3d	10	48	16

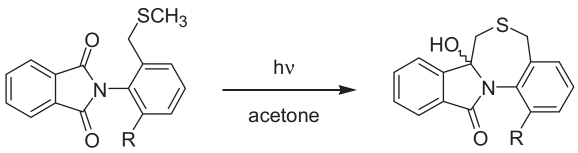


5a-d **6a-d**

Scheme 3. Photodecarboxylative cyclizations of **5a**–**d**.

Table 3
Experimental details for PDC cyclizations of **5a-d**

Entry	*m*	*n*	Yield of **6** (%)	Ring size
5a	4	3	38	13
5b	4	6	25	16
5c	6	3	35	15
5d	8	3	18	17



7a,b **8a,b**

Scheme 4. PET cyclizations of **7a** and **7b**.

Table 4
Experimental details for PET cyclizations of **7a** and **7b**

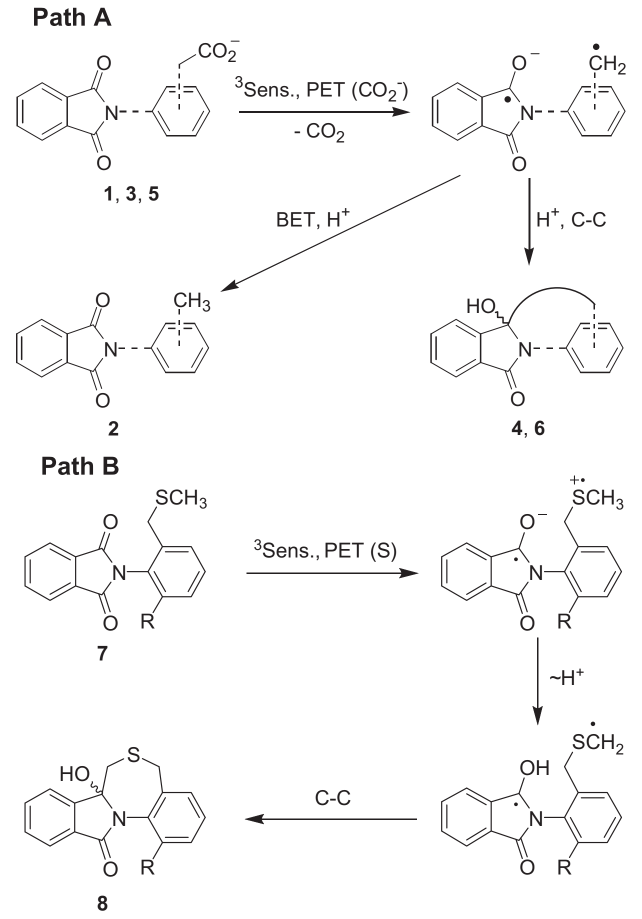
Entry	R	Time (h)	Yield of **8** (%)
7a	H	3	35
7b	*i*-Pr	2	28

shape' of the catechol spacer eases the necessary approach for a successful cyclization. As a result, the cyclization products **6a**–**d** were isolated in moderate yields of 18–38% after just 4 h of irradiation. All compounds showed complex ^{1}H NMR spectra but with distinguished signals for the aromatic isoindolinone group. In their ^{13}C NMR spectra, compounds **6a**–**d** gave characteristic C–OH signals between 90 and 95 ppm.[11] 'Simple' decarboxylation products were again detected but could not be isolated in pure form.

Thioether-containing phthalimides can also be activated photochemically for cyclizations.[6,12] In contrast to the carboxylate systems **3** and **5** described above, the electron-donor moiety remains in the product and is predominantly incorporated into the macrocycle. When the two *ortho*-arene-linked phthalimides **7a** and **7b** were irradiated in acetone for 2–3 h, cyclizations occurred exclusively at the terminal SCH_3-group and the seven-membered products **8a** and **8b** were isolated in yields of 35% and 28%, respectively (Scheme 4, Table 4).[13] In the ^{1}H NMR spectrum, the methylene protons in **8b** showed two sets of doublets at 3.03/3.19 ppm and 3.53/3.89 ppm, respectively.[14] For the *iso*-propyl-containing compound **7b**, cyclization via competing C–H activation was not observed.[15]

The key-step in both mechanistic scenarios (Scheme 5) is an intramolecular electron transfer from the respective donor moiety to the triplet excited phthalimide, the latter populated by sensitization with acetone.[16,17] For all carboxylate containing derivatives **1**, **3** and **5**, electron transfer generates an unstable carboxy radical (path A) which undergoes rapid decarboxylation to the analogous carbon radical. Trapping experiments with electron-deficient alkenes proved the existence of such radicals.[18] In the cases of **3** and **5**, protonation and biradical combination yields the desired cyclization products **4** and **6**, respectively. When cyclization is not possible as with compounds **1**, back electron transfer (BET) provides a carbanion,[19] which is protonated by water to furnish the decarboxylation products **2**.[20] This 'simple' decarboxylation was a minor route for all other carboxylates as well. For substrates **7**, an alternative PET from the thioether results in a radical-ion pair (path B). Proton rearrangement from the terminal SCH_3-group followed by radical combination subsequently gives the cyclization products **8**.[6,12]

In conclusion, the efficiency of PDC cyclizations depended critically on the substitution pattern of the arene and the extent of the linking carbon chain(s). Short chains or remotely positioned carboxylates, as in compounds **1**, solely gave decarboxylation. Extended carbon linkers can, however, compensate the unfavourable *meta*-substitution as demonstrated for substrates **3**. The low yield and high degree of competing decomposition observed during the formation of **4a** suggests that the minimum ring-size for successful cyclization may have been reached for this compound. As for the catechol-linked derivatives **5**, the *ortho*-substitution in combination with the flexible carbon linkers allows for a close contact for electron transfer and cyclization. The notable drop in yields for the larger rings may be caused by steric overcrowding during the necessary biradical approach. Similar effects



Scheme 5. Mechanistic scenarios.

were observed for anthranilic acid based amides and ω,ω-dipeptides.[21,22]

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7. *Typical irradiation procedure*: A mixture of K_2CO_3 (0.13 mmol) and the phthalimide (0.26 mmol) in 100 mL of H_2O/acetone (9:1) was sonicated for 10 min. The clear reaction mixture was subsequently irradiated (Rayonet Photochemical Reactor RPR-208; $\lambda = 300 \pm 20$ nm; ca. 800 W) at 15–20 °C in a Pyrex tube while purging with a constant stream of dry nitrogen. The progress of the reaction was followed by TLC analysis. After a set irradiation time (1–26 h), most of the acetone was evaporated and the remaining mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with 5% $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4 and evaporated to dryness. The products were obtained after column chromatography (SiO_2, *n*-hexane/EtOAc = 1:2).
8. Selected physical and spectral data for *N*-(4-methylphenyl)-phthalimide (**2e**): colourless solid, mp 159–160 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (t, 3H, $J = 8.0$ Hz), 1.64 (m, 2H), 2.62 (t, 2H, $J = 8.0$ Hz), 7.30 (m, 4H), 7.77 (dd, 2H, $J = 3.2, 5.6$ Hz), 7.93 (dd, 2H, $J = 3.2, 5.6$ Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.9$, 31.1, 80.6, 123.9, 126.0, 126.9, 131.7, 134.6, 139.4, 167.2, 176.8 ppm. IR (KBr): $v = 3475$, 3050, 2939, 1771, 1713, 1611, 1518, 1462, 1421, 1386, 1289, 1219, 1175, 1119, 1096, 1081, 1019, 885, 810, 716, 531 cm^{-1}. MS (EI): $m/z = 265$ [M^+], 236, 204, 178, 152, 130, 104, 76.
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10. *Selected physical and spectral data for product* **4d**: colourless solid, mp 138–139 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.51$ (m, 1H), 0.86–1.08 (br m, 11H), 1.38–1.46 (m, 2H), 1.65–1.74 (m, 2H), 1.99–2.03 (m, 2H), 3.34 (br s, 1H), 4.11–4.17 (m, 1H), 4.19–4.52 (m, 1H), 6.85 (d, 1H, $J = 6.4$ Hz), 7.11 (s, 1H), 7.22–7.27 (m, 2H), 7.46 (dd, 1H, $J = 7.2, 7.6$ Hz), 7.52 (d, 1H, $J = 7.6$ Hz), 7.62 (dd, 1H, $J = 7.2, 7.6$ Hz), 7.71 (d, 1H, $J = 7.6$ Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 23.5, 25.5, 25.9, 26.3, 26.7, 27.0, 27.1, 35.5, 67.4, 93.4, 113.8, 114.6, 118.0, 121.6, 123.8, 129.6, 129.7, 131.0, 132.9, 136.5, 146.3, 158.3, 166.7 ppm. IR (KBr): $v = 3244$, 3064, 2923, 2852, 1767, 1746, 1704, 1604, 1495, 1469, 1071, 1014, 894, 884, 791, 718, 700, 635, 593, 531 cm^{-1}. MS (EI): $m/z = 361$ [M^+-H_2O].
11. *Selected physical and spectral data for product* **6b**: colourless solid, mp 183–185 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$–1.53 (br m, 4H), 1.60–1.67 (m, 4H), 1.74–1.84 (br m, 2H), 1.87–1.94 (m, 2H), 2.09–2.21 (m, 2H), 3.25 (s, 1H), 3.29–3.84 (br m, 2H), 3.91–3.95 (m, 2H), 4.04–4.17 (br m, 2H), 6.85–6.90 (m, 4H), 7.42 (dd, 1H, $J = 7.2, 7.6$ Hz), 7.50 (d, 1H, $J = 7.2$ Hz), 7.54 (dd, 1H, $J = 7.2, 7.6$ Hz), 7.64 (d, 1H, $J = 7.6$ Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.9$, 25.6, 26.5, 27.4, 28.1, 28.2, 35.5, 38.5, 67.8, 68.7, 91.4, 112.2, 113.5, 120.6, 120.9, 121.7, 123.2, 129.4, 131.3, 132.1, 146.6, 148.6, 149.0, 167.7 ppm. IR (NaCl): $v = 3422$, 2928, 1685, 1496, 1255, 1051, 824 cm^{-1}. MS (ESI, positive mode): $m/z = 396.22$ $[M+H]^+$.
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13. *Typical irradiation procedure:* A solution of the phthalimide **7** (1 mmol) in 100 mL of acetone was irradiated (Rayonet-Reactor RPR-208; $\lambda = 300 \pm 20$ nm; ca. 800 W) at 15–20 °C in a Pyrex tube while a gentle stream of dry nitrogen was passed through it. The progress of the reaction was followed by TLC analysis. After complete conversion was observed, the acetone was removed by evaporation and the products were isolated by column chromatography (SiO_2, *n*-hexane/EtOAc = 1:2).
14. *Selected physical and spectral data for product* **8b**: yellowish solid, mp 154–155 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.07$ (d, 3H, $J = 6.8$ Hz), 1.21 (d, 3H, $J = 6.8$ Hz), 2.72 (sept, 1H, $J = 6.8$ Hz), 3.03 (d, 1H, $J = 14.3$ Hz), 3.19 (d, 1H, $J = 14.3$ Hz), 3.53 (d, 1H, $J = 18.6$ Hz), 3.75 (s, 1H), 3.89 (d, 1H, $J = 18.6$ Hz), 7.08 (dd, 1H, $J = 1.9, 7.0$ Hz), 7.29 (dd, 1H, $J = 7.0, 7.9$ Hz), 7.33 (dd, 1H, $J = 1.9, 7.9$ Hz), 7.55–7.59 (m, 2H), 7.66 (ddd, 1H, $J = 1.0, 7.5, 7.6$ Hz), 7.91 (d, 1H, $J = 8.2$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.1$, 24.7, 29.1, 35.7, 44.8, 86.0, 121.9, 124.4, 126.1, 126.5, 129.1, 130.1, 131.3, 131.5, 133.1, 139.1, 146.4, 150.4, 167.0 ppm. IR (KBr): $v = 3331$, 3271, 3057, 2952, 2910, 2804, 1689, 1615, 1495, 1467, 1411, 1359, 1237, 1147, 1110, 1089, 1054, 930, 886, 756, 697 cm^{-1}. MS (EI): $m/z = 307$ [M^+-H_2O], 290, 264, 242, 220, 191, 165, 137, 115, 89.
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