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Photodecarboxylative benzylations of phthalimides

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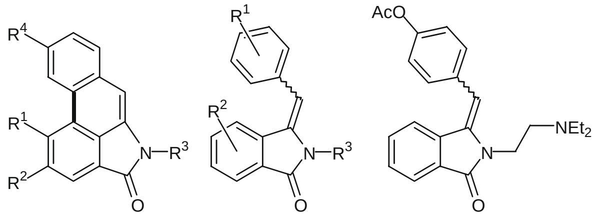
ABSTRACT

Photoadditions of phenylacetates to phthalimides give the corresponding benzylated hydroxyphthalimidines in moderate to high yields of 29–90%. With 2-phenylpropanoate, photoaddition affords a diastereoisomeric mixture in a de of 24% in favour of the *like*-diastereoisomer. L-3-Phenyl lactate and 2-oxo-3-phenylpropanoate both furnish the benzylated product through subsequent loss of formaldehyde and decarbonylation, respectively.

Due to their favourable photophysical and electrochemical properties, phthalimides are superior substrates for photoinduced electron transfer reactions.[1] As an example, the photodecarboxylative (PDC) addition of carboxylates, α-keto carboxylates and heteroatom-substituted carboxylates to phthalimides has been established as a powerful alkylation method.[2] Multi-gram scale alkylations have furthermore, been realised using a 308 nm excimer light source.[3] Of these, the photodecarboxylative benzylation has been applied to the synthesis of open analogues of aristolactams (**I**; Fig. 1).[4,5] Arylmethylene-isoindolin-1-ones (**II**) represent an important class of pharmaceutically active compounds[6] and, as example, the 4-acetoxyphenylmethylene derivative **III** has been shown to exhibit local anaesthetic activity superior to that of procaine.[7]

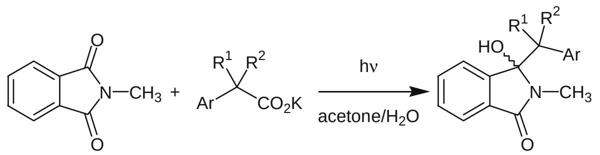
We thus became interested in the photobenzylation of phthalimides as an easy access to novel arylmethylene-isoindolin-1-one precursors. *N*-Methylphthalimide **1** was initially chosen as a model compound for a detailed laboratory study. When **1** was irradiated for 1–5 h in the presence of three equivalents of different potassium phenyl acetates **2a**–**m** in acetone-water (50:50), the corresponding addition products **3a**–**m** were obtained in moderate to high yields of 29–90% (Scheme 1, Table 1).[8] Likewise, vinyl acetate **2n** gave the allylated product **3n** in an acceptable yield of 26%. For all compounds, the characteristic C–OH signals in the ^{13}C NMR spectra were found around 90 ppm. In some cases, the corresponding 'simple' decarboxylation products (-CO_2H↔-H exchange), that is, non-volatile toluene derivatives, were detected in small amounts (<5%) in the crude ^{1}H NMR spectra but no attempt was made to isolate these by-products.

A special case was the irradiation of branched 2-phenylpropanoate **2k** with *N*-methylphthalimide **1** and a diastereoisomeric mixture of *unlike*- and *like*-**3k** was obtained in 90% yield after just two hours of irradiation. The diastereoisomeric ratio was determined



aristolactams (I) **II** **III**

Figure 1. Examples of arylmethylene-isoindolin-1-ones.



1 **2a-m** **3a-m**

Scheme 1. Additions of phenylacetates **2a**–**m** to **1**.

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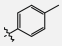
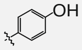
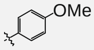
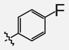
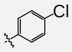
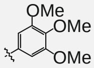
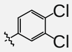
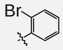
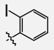
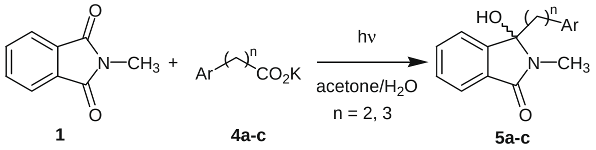
Table 1
Product yields and experimental details for photodecarboxylative benzylations of **1**

	Ar	R^1	R^2	h	3 (%)
a	Ph	H	H	1	80
b		H	H	2	53
c		H	H	6	67/96[a]
d		H	H	4	78
e		H	H	2	36
f		H	H	5	29/56[b]
g		H	H	2	50
h		H	H	3	53
i		H	H	5	35
j		H	H	4	51
k	Ph	Me	H	2	90[c]
l	Ph	Ph	H	3.5	46
m	Ph	Me	Me	3.5	76
n	Vinyl	H	H	5	26

[a] Yield based on a conversion of 70%.
[b] Yield based on a conversion of 52%.
[c] de of 24% in favour of the *like*-diastereoisomer.

for the crude product by integration of baseline-separated signals in the ^{1}H NMR and was found to be 1:1.6 (de of 24%) in favour of the *like*-diastereoisomer. Pure fractions of each diastereoisomer were collected by column chromatography and suitable crystals for X-ray analysis were obtained by recrystallisation (Fig. 2).[9] Interestingly, both compounds formed dimers between different enantiomeric forms via hydrogen bonding.

After five hours of irradiation, the photoreactions involving 3-phenylpropionate (**4a**), 3-(2-methoxyphenyl)propionate (**4b**) and 4-phenylbutanoate (**4c**) furnished the corresponding addition products **5a**–**c** in yields of 67%, 29% and 21% (Scheme 2), respectively. In the case of **4b**, an incomplete conversion of 62% was observed and the 'simple' decarboxylation product 2-ethylanisole was additionally obtained in significant quantity (composition of the crude product: 24% **1**, 40% **5b**, 36% 2-ethylanisole).



Scheme 2. Additions of **4a**–**c** to **1**.

The structure of product **5a** was confirmed by X-ray structure analysis.[10] Remarkably, two molecules of the same enantiomer of **5a** form dimers, which are connected by hydrogen bonding. A pair with the configuration *S* is depicted in Figure 3. The same number of *S*,*S* and *R*,*R* dimers are found in the crystal. Hence, the compound crystallised as a racemate and not as a conglomerate.

Irradiation of **1** in the presence of either potassium L-3-phenyl lactate **6** or sodium 2-oxo-3-phenylpropanoate **7** furnished the benzylated product **3a** in yields of 21% and 52%, respectively (Scheme 3). Hence, decarboxylation is followed by the loss of formaldehyde[11] or decarbonylation, that is, the loss of CO.[12]

The general protocol was furthermore applied to the glycine derivative **8** and the benzylated products **9a** and **b** were isolated in yields of 60% and 63% after four hours and one hour of irradiation (Scheme 4), respectively. Unlike alternative thermal additions (e.g., Grignard reactions[13]), the ester group in the *N*-side chain was tolerated and photoinduced-alkylation occurred regioselectively at the imide chromophore.

The mechanistic scenario for the photoinduced-benzylation is illustrated in Scheme 5.[14] Triplet sensitisation by acetone is followed by a single electron transfer from the carboxylate to the triplet-excited phthalimide (path **A**). Although the oxidation potentials of carboxylates are relatively high (e.g., acetate: $E_{Ox} = 1.54$ V in MeCN, 2.65 V in H_2O vs SCE[15]) both, electron transfer via the excited $^3\pi,\pi^*$ triplet state ($E_{00} = 3.1$ eV) or the higher $^3n,\pi^*$ state ($E_{00} \approx 3.6$ eV), are energetically feasible.[16] Subsequent decarboxylation of the carboxy radical yields the corresponding benzylic radical.[17] Protonation, intersystem crossing and C–C bond formation result in the desired photoaddition products. For 3,4,5-trimethoxyphenyl acetate **2g**, electron transfer has been postulated from the electron-rich aryl group instead (path **B**).[4] Subsequent

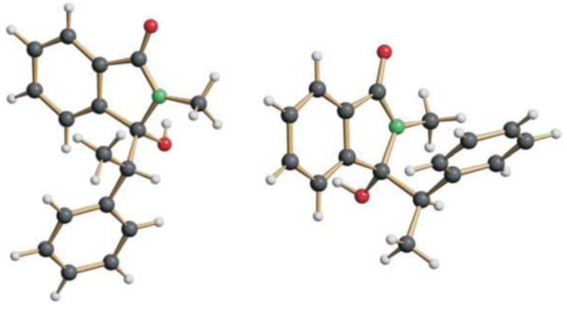


Figure 2. Crystal structures of **ul-3k** and **l-3k**.

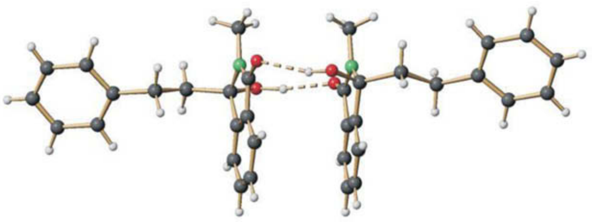
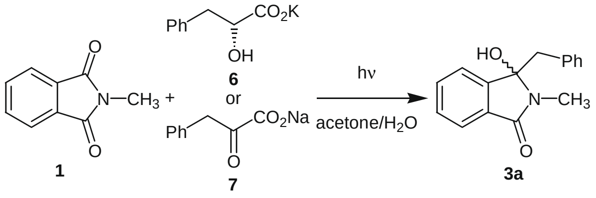
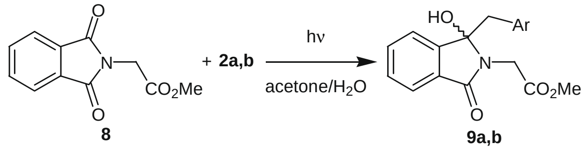


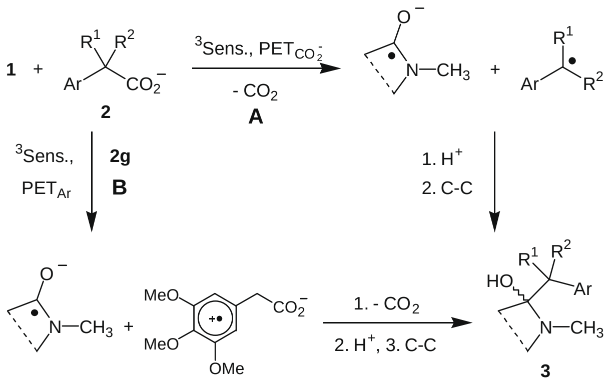
Figure 3. Crystal structure of **5a** (dimer).



Scheme 3. Benzylations of **1** with **6** and **7**.



Scheme 4. Additions of **2a** and **b** to **8**.



Scheme 5. Mechanistic scenario.

loss of carbon dioxide, protonation and C-C bond formation likewise yields the observed addition product. For vinyl acetate **2n** both mechanistic pathways may operate in parallel.[18]

The efficiency of the PDC approach becomes apparent when comparing the benzylation of phthalimides with either toluenes or phenyl acetates, respectively. As reported by Kanaoka et al. photoadditions through hydrogen abstraction give the corresponding benzylated product in low yields and with poor selectivity and conversions.[19] In contrast, the PDC procedure developed rapidly giving the desired benzylation products **3** in moderate to high yields and purities. In addition, the photodecarboxylation protocol utilises simple phenyl acetates **2**. These starting materials are easily accessible in large quantities and with broad structural diversity, and are additionally stable in comparison to reagents used in other *thermal* alkylation methods for example, SmI_2-mediated coupling of organic halides (SmI_2/R–X),[20] addition of organometallic compounds (R–Mg–X or R–Li),[13,21] or alkylation with organic halides using lithium in liquid ammonia (Li/NH_3/R–X),[22] respectively.

In conclusion, phenylacetates efficiently undergo photodecarboxylative benzylations to phthalimides. The procedure offers a versatile access to 3-arylmethylene-isoindolin-1-ones and this application is currently under investigation. In addition, the simple protocol is currently being transferred to 'micro-photochemistry', that is, photochemical transformations in micro-structured devices.[23]

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8. *General irradiation procedure*: *N*-Methylphthalimide (1.5 mmol) was dissolved in acetone (50 mL). A solution of the potassium phenylacetate (4.5 mmol) in water (50 mL) was added, and the mixture was irradiated (Rayonet Photochemical Reactor RPR-200; $\lambda = 300 \pm 20$ nm) at 15–20 °C in a Pyrex Schlenk tube ($\lambda \geqslant 300$ nm) while purging with a slow stream of nitrogen. The progress of the reaction was monitored by TLC analysis or by passing the departing gas stream through a saturated barium hydroxide solution until precipitation of barium carbonate had ceased. Most of the acetone was evaporated and the remaining solution was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. The crude products were purified by column chromatography (eluent:*n*-hexane/EtOAc = 1/1). In some cases, the pure product precipitated during evaporation of acetone and was isolated by vacuum filtration and drying in vacuo instead.Selected physical and spectral data for *3-(4-hydroxybenzyl)-3-hydroxy-2-methy isoindolin-1-one* **3c**: yellow solid, mp 145–148 °C. ^1H NMR (400 MHz, acetone-d_6): $\delta = 3.08$ (s, 3H, NCH_3), 3.25 (d, $^2J = 14.0$ Hz, 1H, CH_2), 3.43 (d, $^2J = 14.0$ Hz, 1H, CH_2), 5.38 (s, 1H, OH), 6.56 (d, $^3J = 8.4$ Hz, 2H, H_{arom}), 6.76 (d, $^3J = 8.4$ Hz, 2H, H_{arom}), 7.44 (m, 1H, H_{arom}), 7.49 (m, 1H, H_{arom}), 7.58 (m, 2H, H_{arom}), 8.20 (s, 1H, OH). ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 23.9$, 42.2, 91.1, 115.3, 122.6, 123.6, 126.2, 129.4, 131.4, 131.8, 133.0, 148.3, 157.0, 166.7. HR-MS (ESI, positive ions): Calcd $[M+H]^+$: 270.11302 for $C_{16}H_{15}NO_3 + H^+$. Found $[M+H]^+$: 270.11273.
9. *Crystal data for* **ul-3k** (CCDC 737177): colourless platelets (from acetone), mp 156–162 °C, $C_{17}H_{17}NO_2$, FW = 267.32 g/mol, triclinic, space group *P*-1; $a = 7.9053(4)$, $b = 8.6707(4)$, $c = 10.7456(5)$ Å; $\alpha = 73.026(2)$, $\beta = 74.305(2)$, $\gamma = 88.757(2)°$; $V = 676.89(6)$ Å^3; $Z = 2$; $d_{calc} = 1.312$ g/cm^3; $R = 0.0425$, $R_w = 0.0842$ for 1945 reflections having $F > 2\sigma(F)$. *Crystal data for* **l-3k** (CCDC 737176): colourless prisms (from acetone), mp 146–152 °C, $C_{17}H_{17}NO_2$, FW = 267.32 g/mol, monoclinic, space group $P2_1/c$; $a = 10.2136(4)$, $b = 10.8771(5)$, $c = 13.3876(6)$ Å; $\beta = 111.297(2)°$; $V = 1385.72(10)$ Å ^{3}; $Z = 4$; $d_{calc} = 1.281$ g/cm^3; $R = 0.0386$, $R_w = 0.0849$ for 2253 reflections having $F > 2\sigma(F)$.
10. *Crystal data for* **5a** (CCDC 737175): colourless prisms (from acetone), mp 65–70 °C, $C_{17}H_{17}NO_2$, FW = 267.32 g/mol, monoclinic, space group $P2_1$; $a = 14.4399(3)$, $b = 28.1060(5)$, $c = 13.4152(2)$ Å; $\beta = 90.1030(10)°$; $V = 5444.52(17)$ Å^3; $Z = 16$; $d_{calc} = 1.304$ g/cm^3; $R = 0.0554$, $R_w = 0.1222$ for 8287 reflections having $F > 2\sigma(F)$.
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