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Photochemical electrocyclization of α,β-unsaturated anilides to give zwitterionic intermediates which eliminate carboxylate and phenolate leaving groups

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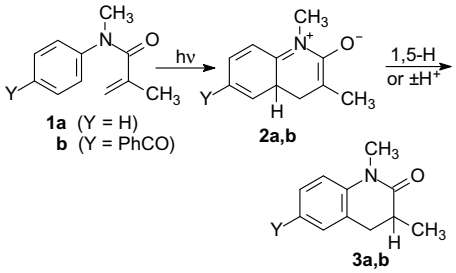
ABSTRACT

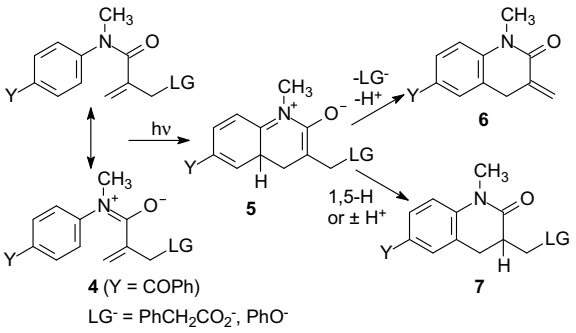
α,β-Unsaturated anilides bearing allylic leaving groups undergo photochemical electrocyclic ring closure to produce zwitterionic intermediates which eliminate carboxylate and phenolate leaving groups.

Photolysis of the α,β-unsaturated anilide **1a** produces the six-membered ring lactam **3a** (Scheme 1).[1,2] The mechanism is thought to involve a photochemically allowed conrotatory ring closure to afford a zwitterionic intermediate[1–4] which rearranges to the lactam photoproduct via a 1,5-H shift and/or a series of proton transfer steps via an enol (Scheme 1).[5] The potential intermediacy of a zwitterionic species makes this reaction of interest, because recent studies have shown that similar zwitterionic intermediates, generated photochemically from α-keto amides, eliminate carboxylate and phenolate leaving groups attached to the position α to the keto group in the reactants.[6,7]



Scheme 1.

As shown in Scheme 2, an analogous elimination reaction can be envisioned from the zwitterionic intermediate **5**, which would be generated via excited state electrocyclization of α,β-unsaturated anilides **4** which incorporate leaving groups (LG^-) at the allylic position of the methacrylamide group. The elimination of LG^- from **5** may compete with either 1,5-H shift or protonation of the enolate moiety by protic solvent. If the elimination is the major process, anilides similar to **4** would offer the potential advantage of having a modular, modifiable aniline group as the chromophore. It is noteworthy that the aniline group is a common structural motif in highly absorbing organic dyes. Incorporating such chromophores into cage compounds similar to **4** could thus



Scheme 2.

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provide a strategy for the photorelease of biologically active leaving groups using long wavelength light. Photoactive cage compounds are important, because they provide the most practical means for rapidly activating biomolecules for triggering biological processes for studies under physiological conditions.[8,9] Photochemically removable protecting groups are also used in the synthesis of biopolymers, in photolithography, and in the fabrication of oligonucleotide arrays.[9,10]

In this Letter, we demonstrate that the release of leaving groups is the predominate photoreaction of *para*-benzoyl substituted anilides **4** (Y = PhCO) (Scheme 2).[11] Moreover, the *para*-benzoyl group in anilide **4** has the advantage of substantially shifting light absorption to relatively long wavelengths such that the photolyses can be routinely performed at 365 nm (ε 120 L mol^{-1} cm^{-1}), which makes this cage system potentially useful for practical biological applications. The details of these findings are described herein.

Photolysis (>300 nm) of **4** ($LG^- = PhCH_2CO_2^-$) in an air-saturated solution of 50% D_2O in CD_3CN containing 0.1 M phosphate buffer at pD 7 resulted in the release of phenylacetic acid in 71% yield and the formation of the α-methylene lactam **6**[12] in 53% yield at 94% conversion according to ^{1}H NMR analyses of the photolysate. These products were accompanied by a 25% yield of lactam **7**[13] which retained the leaving group (Scheme 2). During the photolysis the yield of **6** became progressively less than the yield of the released carboxylic acid, evidently due to secondary photolysis (Fig. 1).

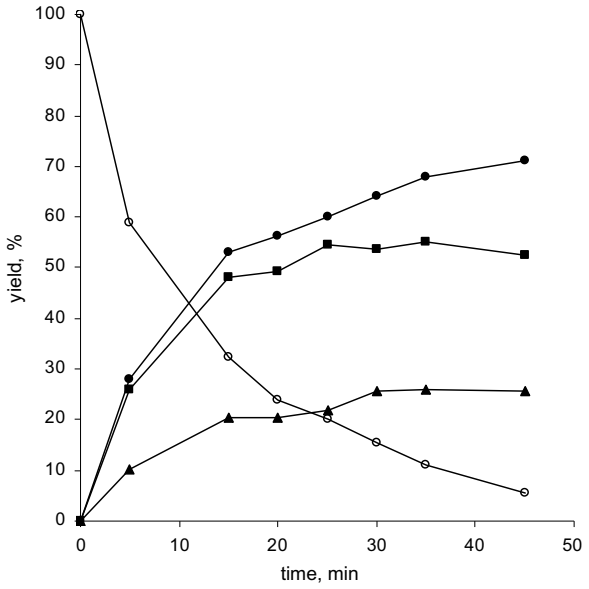

Figure 1. Plot of yield versus time for photolysis of **4** in 50% D_2O containing buffer in CD_3CN at pD 7 from ^{1}H NMR analyses. Symbols correspond to unreacted **4** (○), released $PhCH_2CO_2H$ (●), elimination coproduct **6** (■), and lactam **7** ($LG^- = PhCH_2CO_2^-$), ▲).

Control experiments showed no indication of a 'dark' solvolytic release of carboxylic acid from **4** or **7** ($LG^- = Ph_2CO_2^-$) in 50% D_2O in CD_3CN containing 0.1 M phosphate buffer at pD 7 at room temperature for over a period of a week.

Changing the leaving group to phenolate in **4** ($LG^- = PhO^-$) led to mainly photolytic elimination to give 45% of **6**, 20% of lactam **7** ($LG^- = PhO^-$), and 36% unreacted starting material in 50% D_2O in CD_3CN containing 0.1 M phosphate buffer at pD 7 (Scheme 2). Interestingly, however, in the nonpolar solvent C_6D_6 the photoelimination product **6** was not observed and instead, lactam **7** ($LG^- = PhO^-$)[14] was formed as the sole product in 85% yield, together with 10% unreacted starting material. These results with $LG^- = PhO^-$ are consistent with the involvement of a ground state intermediate, such as **5**, which can partition between products **6** and **7**, depending upon the solvent polarity.

Such behavior of **5** ($LG^- = PhO^-$) has been observed previously in the case of α-keto amides bearing phenolic leaving groups,[7b] for which the zwitterionic intermediate predominantly eliminates the phenolate leaving group in polar or aqueous solvents, but cyclizes to give significant amounts of product retaining the phenolic group in nonpolar solvents.

The zwitterionic intermediate **5** is thought to be formed via photochemical electrocyclic ring closure in the excited state. The quantum efficiency for this ring closure step would not be expected to be affected significantly by the basicity of the remote leaving group attached to the methacrylamide group. This is evidenced by the similarity in total quantum yields for products **6** + **7** determined for **4** ($LG^- = PhCH_2CO_2^-$), **4** ($LG^- = PhO^-$), and for comparison, **1b** (Y = PhCO), which has no leaving group (Table 1) and gives only **3b** upon photolysis. These quantum yields argue against expulsion of the leaving group directly in a short-lived excited state, since the quantum yields would then be expected to decrease with increasing leaving group basicity. For the same reason, the quantum yields would not be consistent with a reversible ring closure step.

The reactive excited state responsible for the photochemistry of **1b** and **4** is the singlet excited state, according to the following quenching studies. The involvement of the triplet excited state, produced via rapid intersystem crossing, would be expected on the basis of the very weak fluorescence ($\Phi < 0.01$) for **1b**, as has been reported for other aminobenzophenone derivatives.[15] However, the quantum yields for products are unaffected by the presence of 10^{-2} M 2-naphthalene sulfonate (an efficient triplet quencher) in 50% buffer in CH_3CN (Table 1). In the case of **1b** we find that comparable concentrations of the 2-naphthalene sulfo-

Table 1
Quantum yields for **1b**, **4** ($LG^- = PhCH_2CO_2^-$), and **4** ($LG^- = PhO^-$)

Reactant	Solvent	Additive	Φ[a,b]	
			6	**7**
4 ($LG^- = PhCH_2CO_2^-$)	Buffer[c]	None	0.069	0.018
	Buffer[c]	0.011 M 2-NPS[d]	0.075	0.021
4 ($LG^- = PhO^-$)	Buffer[c]	None	0.061	0.016
	C_6H_6	None	0	0.10
1b	Buffer[c]	None	na[e]	0.077 (**3b**)[e]
	Buffer[c]	0.012 M 2-NPS[d]	na[e]	0.070 (**3b**)[e]
	20% aq CH_3CN	0.15 M *trans*-piperylene	na[e]	0.10 (**3b**)[e]

[a] Determined at 365 nm as an average of two or more independent determinations using ferrioxalate as the actinometer.
[b] Products quantified by HPLC analyses using an internal standard.
[c] Solvent was 50% water containing 0.10 M phosphate buffer in CH_3CN.
[d] Sodium 2-naphthalenesulfonate.
[e] Only product **3b** is observed without a leaving group.

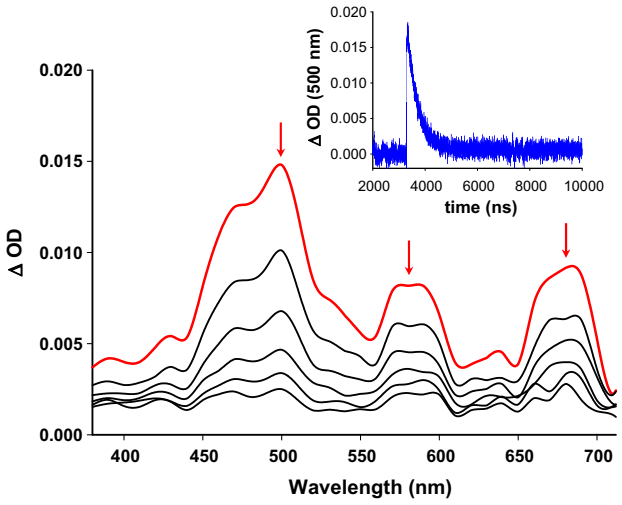

Figure 2. Transient triplet absorption spectrum produced upon laser flash photolysis of 2.5 mM **1c** in 50% aq CH_3CN containing 0.1 M phosphate buffer following 10 ns laser excitation at 355 nm. The spectral bands at 500 nm, 580 nm, and 670 nm showed identical decay lifetimes (τ = 335 ns).

nate strongly quench a transient absorption (Fig. 2) attributable to the triplet excited state.[16] Such quenching, which likely involves energy transfer, occurs at close to diffusion controlled rate, with a bimolecular rate constant of $k_q = 3.77 \times 10^9\ M^{-1}\ s^{-1}$, according to the linear Stern–Volmer plot. We therefore conclude that the photochemistry of **1b** and **4** derives from the singlet excited state. Although the triplet excited state is observed in the laser flash photolyses, its triplet yield is not especially high, as energy transfer to effect trans-cis isomerization of 0.15 M *trans*-piperylene[17] gives $\Phi_{isc} = 0.20$ in benzene and 0.15 in 10% aq CH_3CN, while the reaction of **1b** is unquenched by the piperylene such that Φ (**3b**) = 0.10.

In conclusion, methacrylanilides with allylic leaving groups photolytically release phenylacetic acid and phenol to form an α-methylene lactam in aqueous buffer with a quantum yield of ca. 0.06–0.07. The minor product is a lactam which retains the leaving group, and the elimination from the postulated intermediate, zwitterion **5**, effectively competes with the formation of the minor lactam. The overall quantum yield for the reaction is governed by the efficiency for the singlet excited state electrocyclic ring closure step.

Acknowledgments

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Supplementary data

Detailed experimental procedures for the synthesis of **4** ($LG^- = PhCH_2CO_2^-$, PhO^-), synthesis of **7** ($LG^- = PhCH_2CO_2^-$), isolation of **6** and **7** (LG^- = PhO^-), and NMR spectra for **4** ($LG^- = PhCH_2CO_2^-$, PhO^-), **6**, and **7** ($LG^- = PhCH_2CO_2^-$, PhO^-). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.079.

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11. (a) According to a previous report,[11b] *para*-substituted derivatives **1b** are capable of overcoming a strongly adverse polar solvent effect on the photochemistry to give high yields of lactams as photoproducts, whereas **1a**,[1] which lacks the *para*-benzoyl group, was photochemically unreactive in polar or protic solvents such as CH_3CN or alcohols.; (b) Nishio, T.; Tabata, M.; Koyama, H.; Sakamoto, M. *Helv. Chim. Acta* **2005**, *88*, 78–86.
12. The spectral data for **6** were as follows: ^1H NMR ($CDCl_3$) δ 3.44 (s, 3H), 3.78 (s, 2H), 5.53 (s, 1H), 6.19(s, 1H), 7.03 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.58 (t, J = 8.0 Hz 1H), 7.68–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$) 30.3, 34.2, 114.1, 124.0, 124.3, 128.5, 129.5, 129.9, 130.6, 132.0, 132.4, 135.2, 137.9, 143.5, 165.1, 195.6. When stored as a solid, compound **6** slowly reacts in the dark to give unknown products which show broad peaks in the ^1H NMR spectrum. The 'dark' reaction substantially slows when **6** is stored as a dilute solution in 50% buffer in CH_3CN.
13. Pure lactam **7** ($LG^- = PhCH_2CO_2^-$), mp 77–79 °C, was obtained by acylating lactam **7** (LG^- = HO^-), produced upon photolysis of **4** (LG^- = HO^-) in benzene, followed by chromatographic separation from a small amount of **6** and unreacted starting material. The spectral data for **7** (LG^- = HO^-) were as follows: ^1H NMR ($CDCl_3$) δ 2.68–2.85 (m, 3H), 3.33 (s, 3H), 3.55 (s, 2H), 4.28 (dd, J = 5.20, 8.40 Hz, 1H), 4.50 (dd, J = 3.33, 8.40 Hz, 1H), 6.96 (d, J = 6.33 Hz, 1H), 7.12–7.24 (m, 5H), 7.43 (t, J = 5.52 Hz, 2H), 7.54 (t, J = 5.56 Hz, 2H), 7.69 (m, 2H); ^{13}C NMR ($CDCl_3$) 28.3, 30.1, 40.0, 41.4, 63.5, 114.4, 124.9, 127.4, 128.6, 128.8, 129.5, 130.0, 130.2, 130.8, 132.3, 132.5, 134.0, 138.0, 143.8, 169.7, 171.6, 195.6.
14. Chromatography of the photolysate on silica gel eluting with 10% ethyl acetate in hexane gave NMR pure **7** (LG^- = PhO^-) as a colorless oil. The spectral data were as follows: ^1H NMR ($CDCl_3$) δ 2.99–3.12 (m, 2H), 3.26 (dd, J = 11.6, 21.3 Hz, 1H), 3.44 (s, 3H), 4.19 (dd, J = 7.6, 9.6 Hz, 1H), 4.50 (dd, J = 3.7, 9.6 Hz, 1H), 6.95 (m, 3H), 7.07 (d,J = 8.2 Hz, 1H), 7.29 (t, J = 7.6 Hz, 2H), 7.50 (t, J = 8.0 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.75–7.79 (m, 4H); ^{13}C NMR ($CDCl_3$) 28.8, 30.2, 40.6, 66.8, 114.3, 114.8, 121.3, 125.4, 128.5, 129.7, 130.0, 130.3, 130.7, 132.3, 132.5, 138.0, 144.0, 158.8, 170.2, 195.7.
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