

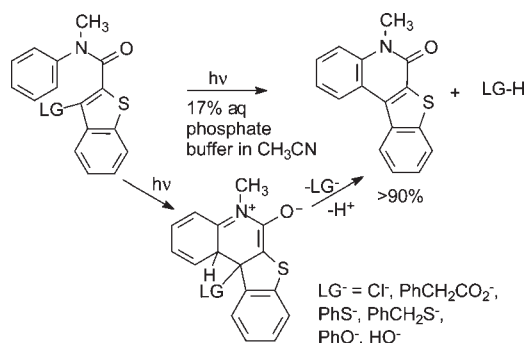
# Photochemical Eliminations Involving Zwitterionic Intermediates Generated via Electrocyclic Ring Closure of Benzothiophene Carboxanilides

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Leaving groups such as carboxylate, thiolate, and phenolate are expelled via zwitterionic intermediates produced upon photochemical electrocyclic ring closure of benzothiophene carboxanilides in the triplet excited state. Chemical yields generally exceed 90%, while quantum yields vary with basicity of the released leaving group.

Photochemical electrocyclic ring closure of  $\alpha,\beta$ -unsaturated anilides is thought to produce intermediates that have zwitterionic character (Scheme 1).<sup>1–4</sup> Such zwitterionic intermediates as **2** should be capable of expelling leaving group anions ( $\text{LG}^-$ ), such as carboxylate and

phenolate groups,<sup>5,6</sup> which represent functionality present in numerous biomolecules. The expectation is that the photochemistry could constitute the basis for the design of a new class of “cage” compounds, which are generally used in biological applications for the photolytic generation of locally high concentrations of biological substrates in cells and tissue.<sup>7</sup>

Our recent study used a photochemical electrocyclic ring closure to generate zwitterionic intermediates from acrylic anilides.<sup>3</sup> The photochemical electrocyclization was 8–10% efficient with respect to light utilization. However, the leaving groups were evidently not expelled directly from the putative zwitterionic intermediate, unlike Scheme 1, but instead

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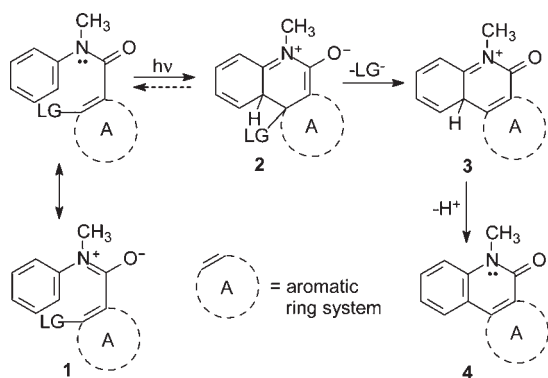
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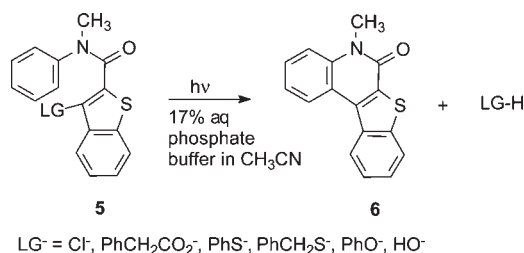
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Scheme 1



Scheme 2



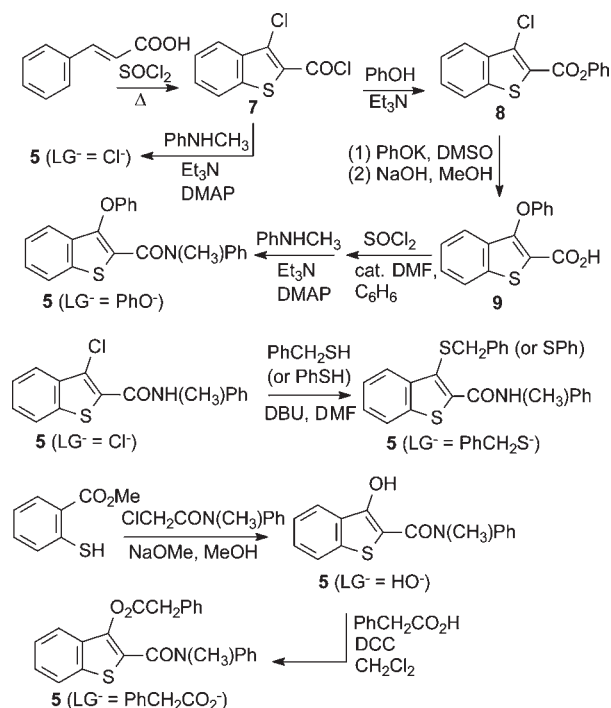
were eliminated from an enolate formed upon deprotonation of the zwitterion.<sup>3b</sup>

This deprotonation step had to compete with a 1,5-H shift in the zwitterionic intermediate that gave a product, which retained the leaving group, and thus, leaving group expulsion did not represent 100% of the reaction. Furthermore, the quantum yields for leaving group release appeared to be controlled by the competition between deprotonation and 1,5-H shift and were largely independent of leaving group basicity.<sup>3b</sup>

We sought to replace the acrylamide moiety with an aromatic ring system (ring A in Scheme 1) so that expulsion of LG<sup>-</sup> from the zwitterionic intermediate would potentially have a greater likelihood of competing with the deprotonation and 1,5-H shift pathways. A previous study<sup>8</sup> showed that the incorporation of a benzothiophene ring system as ring A in Scheme 1 led to high yields of electrocyclic ring closure. Therefore, we studied the benzothiophene carboxanilide **5**, which incorporates various LG<sup>-</sup>s at the C-3 position of such a benzothiophene ring system (Scheme 2). We now report evidence in support of leaving group expulsions that occur directly from a zwitterionic intermediate, generated photochemically via electrocyclic ring closure of benzothiophene carboxanilide **5**.

Benzothiophene carboxanilides bearing leaving groups at C-3 can be synthesized from either the 3-hydroxy

Scheme 3



derivative **5** (LG<sup>-</sup> = HO<sup>-</sup>) or from the 3-chloro compound **5** (LG<sup>-</sup> = Cl<sup>-</sup>) (Scheme 3). The latter compound is synthesized via acylation of *N*-methylaniline with **7**, which is produced by refluxing cinnamic acid with SOCl<sub>2</sub>.<sup>9</sup> After conversion of **7** to the phenyl ester, the C-3 chloro group can also be substituted by phenolate anion to obtain **9**,<sup>10</sup> which then is readily converted into amide **5** (LG<sup>-</sup> = PhO<sup>-</sup>). Various thiolates are capable of directly displacing the C-3 chloride in amide **5** (LG<sup>-</sup> = Cl<sup>-</sup>) under mild conditions.<sup>11</sup> Carboxylate groups such as PhCH<sub>2</sub>CO<sub>2</sub><sup>-</sup> are introduced via DCC coupling with the 3-hydroxy compound **5** (LG<sup>-</sup> = HO<sup>-</sup>), obtained via an alkylation and subsequent Dieckmann condensation.

Direct photolyses of 10<sup>-2</sup> M benzothiophene carboxanilides **5** in 20–30% H<sub>2</sub>O containing 100 mM phosphate buffer (pH 7) in CH<sub>3</sub>CN with unfiltered light from a 450 W medium pressure mercury lamp were taken to essentially complete conversion. Nearly quantitative expulsion of the leaving groups was observed in most cases. Product yields were determined by <sup>1</sup>H NMR spectroscopy for similar small scale runs performed with samples prepared in deuterated solvents (Table 1). The cleavage coproduct in all cases was **6**. No other photoproducts were observed by NMR spectroscopy of the photolyzates for any of the LG<sup>-</sup>s.

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Quantum yields at 310 nm for LG<sup>-</sup> expulsion and formation of **6** decreased with increasing basicity of LG<sup>-</sup> (Table 1), contrary to what was observed in our earlier study of acrylanilide electrocyclizations. The dependence of  $\Phi$  on LG<sup>-</sup> basicity is consistent with a mechanism, whereby photochemical electrocyclic ring closure results in formation of a ground state intermediate, which expels the

leaving group (Scheme 1). The zwitterion **2** would be a plausible ground state intermediate in such LG<sup>-</sup> expulsions. However, in order for the quantum yields to decrease with increasing LG<sup>-</sup> basicity, there must be a pathway that competes with the LG<sup>-</sup> expulsion. In Scheme 1 the competing pathway is considered to be ring-opening of the zwitterionic intermediate to regenerate the photochemical reactant; i.e., the cyclized imminium ion moiety of **2** would be a good internal leaving group.

The photochemistry of **5** occurs in the triplet excited state. Quantum yields decrease, when photolyses are conducted in air-saturated solvent, and 1,3-pentadiene (a triplet excited state quencher) is effective at quenching the photo-reaction. The triplet multiplicity is further supported by the observation of a significant heavy atom effect. Photolysis of 6-bromobenzothiophene carboxanilide **10** at 310 nm in 17% H<sub>2</sub>O containing 100 mM phosphate buffer in dioxane at pH = 7 under N<sub>2</sub> gives **11** with  $\Phi = 0.32$  (Scheme 4), whereas, without the 6-bromo substituent,  $\Phi = 0.23$  for **5** (LG<sup>-</sup> = Cl<sup>-</sup>) under similar conditions. The heavy atom in this case is expected to promote intersystem crossing and thus increase the quantum yield for the triplet photo-reaction.

In the quenching by 1,3-pentadiene, linear Stern–Volmer quenching plots are obtained for LG<sup>-</sup> = PhCH<sub>2</sub>CO<sub>2</sub><sup>-</sup> and PhO<sup>-</sup> (Figure 1A). The slopes ( $k_q\tau$ ) for these plots are essentially the same, within experimental error. The lifetime of the triplet excited state  $\tau$  is found to be  $932 \pm 41$  and  $830 \pm 122$  ns for LG<sup>-</sup> = PhCH<sub>2</sub>CO<sub>2</sub><sup>-</sup> and PhO<sup>-</sup>, respectively. For the calculation of  $\tau$ , the solvent was taken as acetonitrile, for which  $k_q = 2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ , although the photolyses at 310 nm were actually conducted with 17% H<sub>2</sub>O containing 100 mM phosphate buffer in CH<sub>3</sub>CN as the solvent.

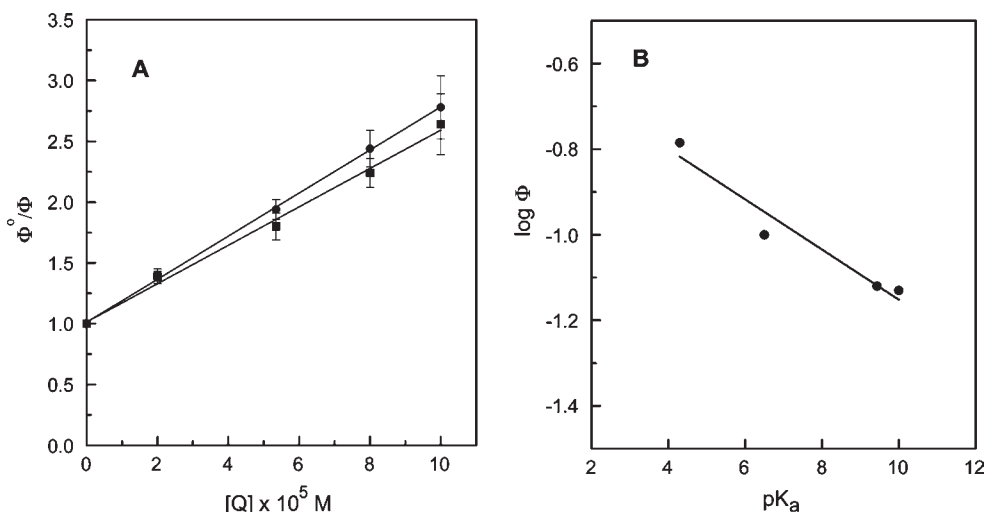
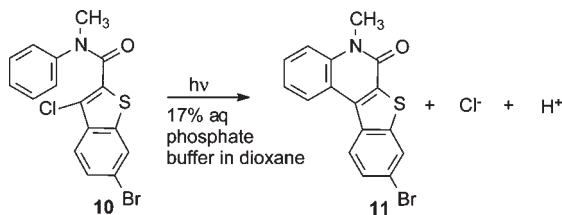
In terms of the mechanism, it is evident that the singlet excited state intersystem crosses to generate the triplet

**Table 1.** Yields and Quantum Yields<sup>a,b</sup>

reactant, LG <sup>-</sup>	LG-H, %	product <b>6</b> , %	$\Phi$
Cl <sup>-</sup>	nd <sup>c</sup>	100	0.23
PhCH <sub>2</sub> CO <sub>2</sub> <sup>-</sup>	95	99	0.16
PhS <sup>-</sup>	nd <sup>c</sup>	91 <sup>d</sup>	0.10
PhO <sup>-</sup>	96	99	0.074
PhCH <sub>2</sub> S <sup>-</sup>	91	98	0.076
HO <sup>-</sup>	nd	93	0.007

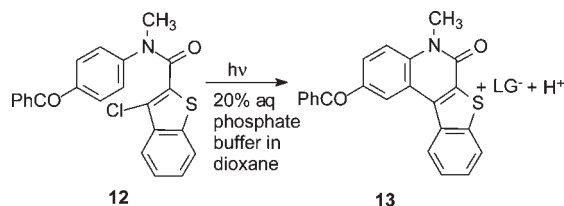
<sup>a</sup>The solvent was 20–30% D<sub>2</sub>O containing 100 mM phosphate buffer (pD = 7) in CD<sub>3</sub>CN for chemical yields, whereas 17% H<sub>2</sub>O containing 100 mM phosphate buffer in CH<sub>3</sub>CN was used for quantum yields. <sup>b</sup>Yields were determined by NMR with DMSO as the integration standard. For the quantum yields photolysates were extracted by CHCl<sub>3</sub> and concentrated prior to NMR analyses. <sup>c</sup>Not determined. <sup>d</sup>7.2% unreacted starting material was present.

**Scheme 4**



**Figure 1.** (A) Stern–Volmer plots for the quenching of **5** (LG<sup>-</sup> = PhCH<sub>2</sub>CO<sub>2</sub><sup>-</sup>, ●) and **5** (LG<sup>-</sup> = PhO<sup>-</sup>, ■) by 1,3-pentadiene as triplet quencher in 17% H<sub>2</sub>O containing 100 mM phosphate buffer in CH<sub>3</sub>CN. (B) Plot of log  $\Phi$  vs pK<sub>a</sub> of the LG<sup>-</sup> conjugate acid.

**Scheme 5**



excited state, which cyclizes with a rate constant  $1/\tau = \text{ca. } 10^6 \text{ s}^{-1}$ . The plot of  $\log \Phi$  vs  $\text{p}K_a$  (LG-H) (Figure 1B) shows that quantum yields vary primarily with  $\text{LG}^-$  basicity. Significant scatter in such a plot would be expected, considering the rather different  $\text{LG}^-$ s being correlated. Figure 1A,B are consistent with lifetimes of the reacting excited state and intersystem crossing efficiencies that are not overly sensitive to variation of  $\text{LG}^-$ ; i.e., the  $\text{LG}^-$ s do not strongly affect either  $\Phi_{\text{isc}}$  or  $\tau$ . A reasonable conclusion is that quantum yields vary primarily with  $\text{LG}^-$  basicity, which controls the rate of the  $\text{LG}^-$  expulsion step in competition with ring-opening of intermediate **2** to regenerate the starting material.

Preliminary work was done to extend the absorption of **5** to longer wavelengths by introducing a benzoyl group at the C-4 position of the *N*-phenyl group. *N*-Methyl 4-aminobenzophenone was acylated by **7** to furnish **12** with a C-3 chloro group. Direct photolysis of  $10^{-2} \text{ M}$  **12** in 20%  $\text{H}_2\text{O}$  containing 100 mM phosphate buffer in  $\text{CH}_3\text{CN}$  using a 450 W medium pressure mercury lamp under  $\text{N}_2$  produced a nearly quantitative yield of **13** upon photoelectrocyclization with loss of  $\text{LG}^- = \text{Cl}^-$  (Scheme 5). To resolve solubility problems with photoproduct **13**, the aq  $\text{CH}_3\text{CN}$  was replaced with dioxane for the quantum yield

determinations. The quantum yield of **12** at 365 nm was  $\Phi = 0.15$  in  $\text{N}_2$  saturated 20%  $\text{H}_2\text{O}$  containing 100 mM phosphate buffer in dioxane.

In this study we have shown that the benzothiophene carboxanilides have considerable potential for use as cage compounds in biological applications. A variety of leaving groups, which are straightforwardly incorporated at the C-3 position of the benzothiophene ring system by standard synthetic procedures, are photochemically expelled completely without formation of side products, and the quantum efficiencies for  $\text{LG}^-$  expulsion vary with basicity of the  $\text{LG}^-$  over the range 0.007–0.2. The approximate dependence of  $\log \Phi$  on the  $\text{p}K_a$  of the leaving group conjugate acid suggests that the  $\text{LG}^-$  expulsion competes with ring-opening of the zwitterionic intermediate to regenerate starting material. The electrocyclic ring closure to form the zwitterionic intermediate occurs in the triplet excited state. The plan is to introduce other, longer wavelength chromophoric groups by replacing the *N*-phenyl group of the anilide. Our initial step in this direction is the introduction of a benzophenone chromophore, which allows photolyses to be conducted at 365 nm.

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**Supporting Information Available.** Experimental procedures for the synthesis of **5** ( $\text{LG}^- = \text{Cl}^-$ ,  $\text{PhCH}_2\text{CO}_2^-$ ,  $\text{PhS}^-$ ,  $\text{PhCH}_2\text{S}^-$ ,  $\text{PhO}^-$ ,  $\text{HO}^-$ ), **8–10**, and **12**). Experimental procedures for photolyses, quantum yield determinations, and isolation and characterization of photoproducts **6**, **11**, and **13**. Spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.