

# Photodegradation of aryl sulfonamides: *N*-tosylglycine

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Continuing uncertainty about pathways and consequences of the photolability of aryl sulfonamides is partly resolved by the results of comprehensive product analysis in the photolysis of aqueous *N*-tosylglycine, which indicate that intramolecular electron or hydrogen transfer (according to conditions) promote the widely reported S–N cleavage and reveal the nature of subsequent and competing processes.

Aryl sulfonamides are of topical interest photochemically for two reasons: as photolabile pharmaceutical compounds<sup>1</sup> and as photolabile protected amines, peptides and proteins, the latter attracting continuing study<sup>2</sup> despite subsequent results<sup>3</sup> detracting from their early promise.<sup>4</sup> Regulatory demands for increasingly detailed stability data<sup>5</sup> contrast with rudimentary knowledge of the photochemistry of existing sulfonamide drugs, and prompt increasing attention to those in development. The variable and generally unsatisfactory results of attempted photodeprotections have been attributed to side reactions that can be reduced in some cases by structural modification<sup>3</sup> or the addition of further reagents,<sup>6</sup> but remain largely unknown.

In a continuing study of the photochemistry of peptide derivatives,<sup>7,8</sup> we have monitored products during the photolysis of aqueous *N*-tosylglycine (**1**) and, observing a high mass balance early in the reaction, are able to propose a sequence of events that both explains the product distributions and implicates processes that may direct photolytic outcomes with other aryl sulfonamides.

Photolyses were carried out under nitrogen with 10<sup>-2</sup> mol dm<sup>-3</sup> aqueous solutions of *N*-tosylglycine, either unadjusted (pH 3) or adjusted to pH 9 with NaOH, in quartz tubes and using a carousel surrounding a 400 W medium pressure mercury arc as previously described.<sup>7</sup> Products were identified by diagnostic chromatographic comparison with standards and quantified by HPLC<sup>9</sup> (formaldehyde and glyoxylic acid as DNP derivatives; glycine as AccQ.Tag<sup>®</sup> derivative by fluorescence detection<sup>10</sup>) and gas electrode analysis (CO<sub>2</sub> and NH<sub>3</sub>).<sup>7</sup>

The data in Table 1 are consistent with the sequence of reactions in Scheme 1 (shown for 7% reaction at pH 9), which also accords collectively with several earlier observations of

sulfonamide photochemistry reported separately.<sup>3</sup> Reaction (i) indicates a cyclic abstraction of H–C<sub>α</sub> and reaction (ii) suggests β-homolysis of a bond known to be involved in the π→π\* state of analogous carboxamides<sup>11</sup> and dimerization of the comparatively stable amido-methylene radical.<sup>7</sup> The major route, reaction (iii), reflects the known behaviour of excited aryl sulfonamides as electron acceptors,<sup>12</sup> and generates an intermediate from which observed products are derived by loss of CO<sub>2</sub> alone [reaction (iv)] or with concomitant S–N cleavage [reaction (vi)], and, more speculatively, *via* cyclizations and hydrolysis [reactions (v) and (vii)]. Such processes would require particular orbital alignments, so product distribution would be determined largely by the conformations available in the short-lived intermediates.

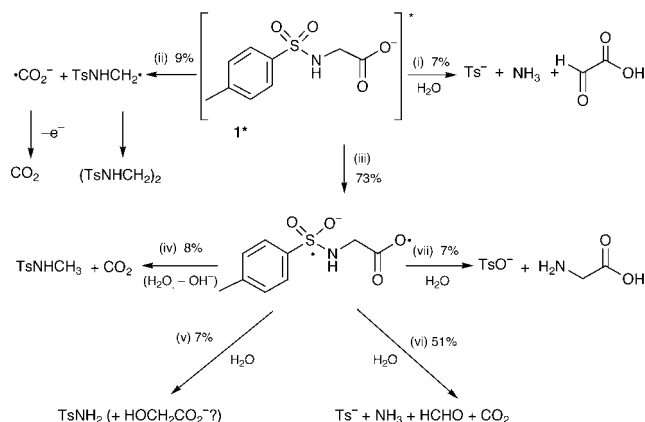
The percentage assigned to each route in Scheme 1 corresponds with the observed yield values of uniquely associated products. The accumulated values implicated for coproducts formed in more than one route [CO<sub>2</sub> (68%), NH<sub>3</sub> (58%) and TsH (58%)] are in fair agreement with those observed, and would be more so if the value for HCHO reflected some losses, directly or indirectly, by the unassigned reducing capacity available from reaction (ii). The latter would, in any case, account for loss of some material and this is incorporated in the mass balance data of Table 1. Scheme 1 is also supported by product correlations (*e.g.* TsH vs. NH<sub>3</sub>, *r*<sup>2</sup> = 0.998, slope 1.1; TsH vs. HCHO + glyoxylic acid, *r*<sup>2</sup> = 0.984, slope = 0.9) and by the main differences in outcome when the substrate is not ionized. In that case, lower yields of principal products by reaction (iii) are consistent with the need for H-atom transfer,<sup>13</sup> making other pathways, including reactions (i) and (ii), slightly more competitive. The lack of TsNHCH<sub>3</sub> and the enhanced yield of TsOH may be associated with the inability to generate the sulfonyl group directly in reactions (iv) and the easier hydrolysis anticipated for the protonated intermediate in reactions (vii), respectively. While quantitation at 20% conversion is intrinsically more accurate, the scope for complication by secondary processes is increased. The data remain consistent with Scheme 1, however.

It would appear from these results that electron or hydrogen-atom transfer to the sulfonyl group will be prominent in the photochemistry of aryl sulfonamides, with β-homolysis a

**Table 1** Product distributions (mol%) in the photolysis of *N*-tosylglycine

Product	7% reaction <sup>a</sup>		20% reaction <sup>b</sup>	
	pH 3	pH 9	pH 3	pH 9
NH <sub>3</sub>	47	49	50	49
CO <sub>2</sub>	34	80	32	87
TsH <sup>c</sup>	28	68	31	62
HCHO	29	51	29	35
OHCCO <sub>2</sub> H	13	7	8	4
TsOH	19	7	6	3
H <sub>3</sub> N <sup>+</sup> CH <sub>2</sub> CO <sub>2</sub> <sup>-</sup>	13	— <sup>d</sup>	8	—
TsNH <sub>2</sub>	5	7	3	5
TsNHCH <sub>3</sub>	0	8	1	6
(TsNHCH <sub>2</sub> ) <sub>2</sub> <sup>e</sup>	14	9	8	5
Mass balance <sup>f</sup>	80	>90	60	60

<sup>a</sup> Error < ± 4. <sup>b</sup> Error < ± 2. <sup>c</sup> Standard: Li salt (98%), Sigma-Aldrich Ltd. <sup>d</sup> Not measured. <sup>e</sup> Standard tosylation of diamine, mp 161 °C (lit., 160 °C). <sup>f</sup> According to Scheme 1 (see text); error < ± 11 and < ± 6 at 7 and 20% reaction, respectively.



**Scheme 1**

significant competing process. The availability of diverse pathways subsequently suggests that a search among such derivatives for photoremoveable protecting groups is unlikely to be productive and that their use for this purpose may be best pursued with cathodic deprotection strategies in mind.<sup>14</sup> The photochemical strategy is flawed by the capacity of the oxidized component of the charge-separated intermediates to promote highly competitive alternative degradation.

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