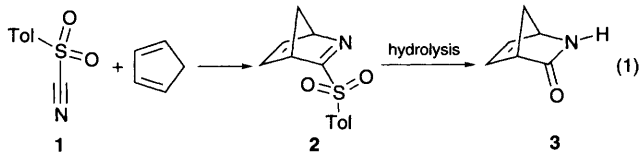
# Unusual mechanism of hydrolysis of the tosyl cyanide–cyclopentadiene adduct to the lactam 2-azabicyclo[2.2.1]hept-5-en-3-one

**Paul E. Morgan,[a] Ray McCague[b] and Andrew Whiting*[a]**

[a] *Department of Chemistry, Faraday Building, U.M.I.S.T., PO Box 88, Manchester, UK M60 1QD*
[b] *Chiroscience Ltd., Cambridge Science Park, Milton Road, Cambridge, UK CB4 4WE*

**Hydrolysis of the cycloaddition product derived from tosyl cyanide and cyclopentadiene was investigated using $^{18}O$ label incorporation experiments; thus, sulfonyl imine 2 was transformed into $^{18}O$ labelled lactam 3 with $^{18}O$ labelled acetic acid, which is consistent with the intervention of intermediate 6 during the hydrolysis.**

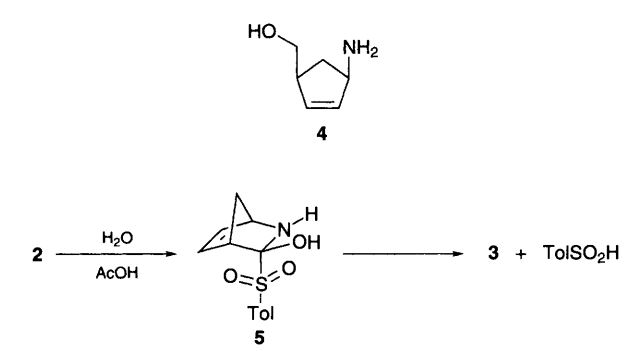
Nitriles have been used as reactive dienophiles for a wide range of hetero-Diels–Alder reactions.[1] In particular, tosyl cyanide **1** has been useful for the construction of several pyridine and hydropyridine analogues.[2,3] This includes reaction with cyclopentadiene [eqn. (1)] to give 2-azabicyclo[2.2.1]hept-5-en-3-one (γ-lactam **3**) after hydrolysis of the initially formed cycloadduct **2**.[4] Recently, lactam **3** has become important for the synthesis of several carbocyclic nucleosides based upon derivatives of **4**.[3b,5]




**1** **2** **3**

As part of a program examining new methods for the asymmetric control of hetero-Diels–Alder reactions, we examined the reaction of tosyl cyanide **1** and cyclopentadiene in the presence of various Lewis-acid catalysts.[6] The yields obtained of lactam **3** from these reactions were highly dependant upon the work-up conditions employed. A study was therefore undertaken to ascertain exactly what mechanism was operative in the conversion of **2** to **3**, since this clearly would be relevant not only to system **2**, but to other sulfonyl cyanide cycloadducts. Here we report the probable mechanism for the conversion of **2** to **3**, as determined by use of $^{18}O$ labelling experiments.

The accepted mechanism for the conversion of **2** to **3** involves the addition of water across the sulfonyl imine function of **2** in the presence of acetic acid, to give tetrahedral intermediate **5**, which might be expected to cleave at the C–N bond to relieve ring strain. However, if structure **5** intervenes in the hydrolysis of **2**, subsequent collapse would involve expulsion of tolyl sulfinic acid to afford lactam **3**[3b] (Scheme 1). It was assumed therefore that the effect of the acetic acid was purely to protonate imine **2**, *i.e.* to catalyse addition of water across the imine function (affording **5**).



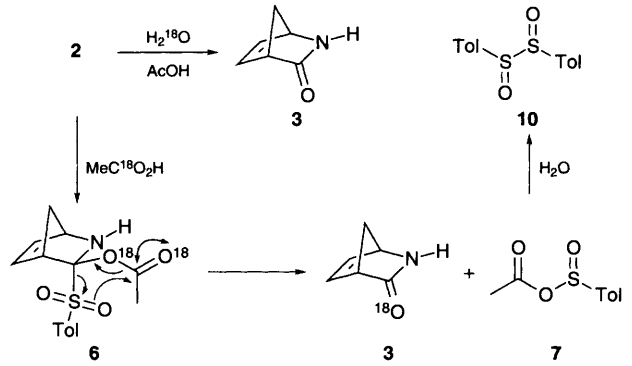

**Scheme 1**

In contrast, several attempts to hydrolyse adduct **2** (directly from the reaction mixture of tosyl cyanide **1** and cyclopentadiene) with water alone or in the presence of base (NaOH) were unsuccessful. However, addition of acetic acid[3b] results in rapid and clean conversion of **2** to **3**, whether in the presence or absence of water.

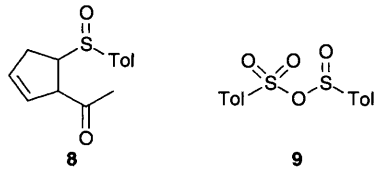
To probe this matter further, hydrolysis of adduct **2** was carried out both with acetic acid in $^{18}O$ labelled water and with $^{18}O$ labelled acetic acid alone in $CDCl_3$. It was found to our surprise that the $^{18}O$ label was not incorporated in lactam **3** using acetic acid in $^{18}O$ labelled water, but was incorporated[7] into the carbonyl group of lactam **3** using the $^{18}O$ labelled acetic acid in $CDCl_3$ (Scheme 2). The insoluble byproduct from the reaction was removed by filtration and identified by mass spectrometry as a mixture of acetyl tolyl sulfinate **7** and an addition product of **7** with cyclopentadiene, probably possessing structure **8**.[8] This was not our expectation, since the byproduct originally reported[3b] for this reaction was tosyl tolyl sulfinate **9**; however this was not unambiguously characterised.

None of the experiments carried out in these laboratories have resulted in the isolation of **9** to date. Indeed, hydrolysis of the crude filtrate, *i.e.* a mixture of **7** and **8**, results in the sole isolation of compound **10**.[9] Whilst it is possible that **10** results from **9** by disproportionation, it is perhaps more likely that it derives directly from tolyl sulfinic acid[9] after hydrolysis of product **7**.

Overall, these results may be interpreted as outlined in Scheme 2, *i.e.* electron deficient imine **2** reacts rapidly with




**Scheme 2**




**8** **9**

acetic acid to give a transient† tetrahedral intermediate **6**. Elimination of acetoxy tolyl sulfinate **7** provides lactam **3**. The lactam **3** is therefore produced because of the unusual properties of sulfur; being able to readily reduce from $S^{VI}$ to $S^{IV}$, as demonstrated by the elimination of **7** from intermediate **6** (Scheme 2).

We thank the EPSRC for a studentship to (P. M.) and Chiroscience for additional funding.

## Footnote

† Acetic acid adduct **6** can not be observed by NMR. Addition of acetic acid to **2** results in immediate conversion to **3**.

## References

1 D. L. Boger and S. N. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Organic Chemistry Monographs; vol. 47, Academic Press, San Diego, 1987; A. I. Meyers, in *The chemistry of the cyano group*, ed. S. Patai and Z. Rappoport, Interscience, London, 1970, pp. 356.

2 U. Rüffer and E. Breitmair, *Synthesis*, 1989, 623; S. M. Weinreb and R. R. Smith, *Tetrahedron*, 1982, **38**, 3087; A. M. Van Leusen and J. C. Jagt, *Tetrahedron Lett.*, 1970, 971; P. G. Pews, E. B. Nyquist and F. P. Corson, *J. Org. Chem.*, 1970, **35**, 4096.

3 (*a*) J. C. Jagt and A. M. Van Leusen, *Recl. Trav. Chim. Pays-Bas*, 1973, **82**, 1343; (*b*) *J. Org. Chem.*, 1974, **39**, 564; (*c*) S. Daluge and R. Vince, *J. Org. Chem.*, 1978, **43**, 2311.

4 Although we have not experienced problems with adduct **2** [see ref. 3(*b*)], we have had reports that **2** can undergo exothermic decomposition when in an impure state and being collected by filtration (C. F. Palmer, unpublished observations). However, the pure adduct does not appear to be unstable. Probably residues from the reaction, in combination with air, are responsible for the exothermic decomposition process. *Selected data* for **2**: δ (300 MHz, $CDCl_3$) 2.15 (2 H, ABq, *J* 8 Hz, sep. 40 Hz, $CH_2$), 2.46 (3 H, s, $CH_3$), 4.42 (1 H, m, HCC=N), 5.39 (1 H, m, HC=N), 6.80 (2 H, m, HC=CH), 7.37 and 7.78 (each 2 H, d, *J* 9 Hz, ArH's).

5 S. J. C. Taylor, A. G. Sutherland, C. Lee, R. Wisdom, S. Thomas, S. M. Roberts and C. Evans, *J. Chem. Soc., Chem. Commun.*, 1990, 1120; C. F. Palmer, K. P. Parry and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1991, 485; C. F. Palmer, K. P. Parry, S. M. Roberts and V. Sik, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2051; 1992, 1021.

6 R. McCague, P. E. Morgan and A. Whiting, unpublished results.

7 Lactam **3** was identical in all spectroscopic and analytical aspects to that reported;[3] *selected data* for **3**: *m/z* (CI, $NH_3$) 127 (50%, M + $NH_4^+$) and 110 (100, M + $H^+$). For $^{18}O$ labelled lactam **3**; *m/z* (CI, $NH_3$) 129 (75, $^{18}M$ + $NH_4^+$), 127 (12, M + $NH_4^+$), 112 (100, $^{18}M$ + $H^+$) and 110 (25, M + $H^+$). Accurate mass measurement of this peak gave *m/z* 112.0650. Calc. for $C_6H_8N\ ^{18}O$, 112.0648.

8 Evidence for the production of acetoxy tolyl sulphinate **7** was based on mass spectral analysis of the insoluble product: *m/z* (FAB) 197 ($M^+$ − H). The other major by-product detected in the crude filtrate was consistent with the addition product of cyclopentadiene and acetyl sulphinate, *i.e.* **8** or an isomer thereof; *m/z* (FAB) 249 ($M^+$ + H), 205 ($M^+$ + H − $C_2H_3O$). Other minor products were also detected which were consistent with the fact that sulphinate **7** undergoes disproportionation.

9 H. S. Hertz, B. Cockson and A. R. Seidle, *J. Org. Chem.*, 1977, **42**, 2508.

*Received, 24th May 1996; Com. 6/03616C*