

An Unusual Solvent Effect in an Intramolecular Diels–Alder Reaction

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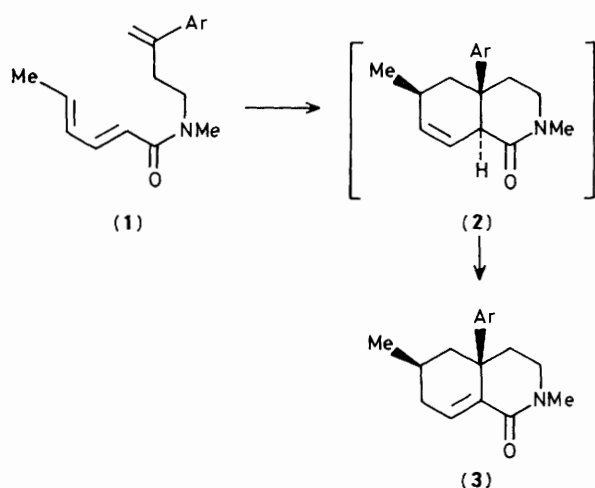
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The intramolecular Diels–Alder reaction of triene (**1**) gives different products depending on the solvent.

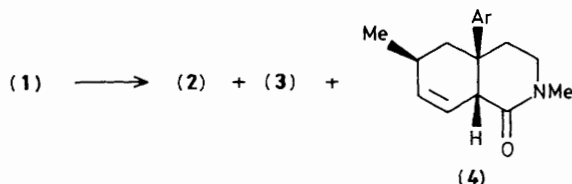
We recently reported the intramolecular Diels–Alder reaction of triene (**1**) in dimethyl sulphoxide (DMSO) at 185 °C which gave the α,β -unsaturated lactam (**3**) *via* conjugation of the carbon–carbon double bond of the initially formed adduct (**2**) (Scheme 1).¹ During further investigation of this reaction as an approach to biologically-active 4a-aryldecahydro-

isoquinolines, we have carried out this reaction in toluene and observed the formation of a different range of products. We now report the results of these investigations.

Heating the triene (**1**) in toluene at 185–190 °C for 24 hours gave a mixture of 3 products along with approximately 10% of recovered starting material (Scheme 2). The major product,



Scheme 1. Ar = 3-methoxyphenyl.

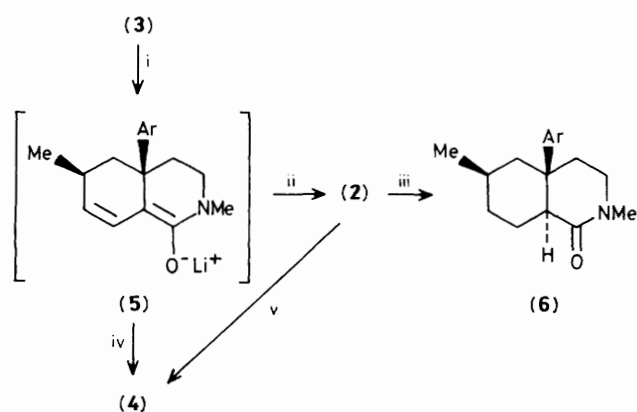


Scheme 2

isolated in 56% yield, was identified as the β,γ -unsaturated bicyclic lactam (4)[†] with the *cis*-ring junction. The second product, isolated in 15% yield, was the α,β -unsaturated lactam (3) previously the major product of the cycloaddition carried out in DMSO. The third product, isolated in between 2 and 5% yield, was the β,γ -unsaturated bicyclic lactam (2)[†] with the *trans*-ring junction. Clearly, product (4) violates a basic tenet of the concerted (4 + 2) cycloaddition reaction, that the stereochemistry of the diene is retained.

The structures of the two new products (4) and (2) were proved in the following manner. The ¹H n.m.r. spectrum of (4) showed a pair of multiplets each integrating for 1 proton at δ 5.6–5.8 confirming the presence of the β,γ -unsaturated lactam system but giving no information concerning the stereochemistry. However, treatment of the α,β -unsaturated lactam (3) with an excess of lithium hexamethyldisilazide followed by quenching with acetic acid gave the β,γ -unsaturated lactam (2) with the *trans*-ring junction (Scheme 3). That the ring junction is *trans* was apparent from the ¹H n.m.r. spectrum (δ 0.3, 3H, doublet, C-6 methyl group) and by hydrogenation to give the saturated lactam (6), a known compound.¹ Treatment of (3) with an excess of lithium hexamethyldisilazide followed by quenching with methanol led to the *cis*-ring junction β,γ -unsaturated lactam (4) only.² That (4) has the *cis*-ring junction was confirmed by a doublet integrating for 3 protons at δ 0.95 in the ¹H n.m.r. spectrum.¹

These results suggest that kinetic quenching of the dienolate (5) in the presence of an excess of a weakly basic anion (acetate) gives the *trans*-ring junction whereas in the presence of a more basic anion (methoxide) epimerisation of the adduct (2) to give the thermodynamically more stable *cis*-fused

Scheme 3. Reagents and conditions: i, LiN(SiMe₃)₃, THF, 0°C; ii, AcOH; iii, Pd/C, H₂, EtOH; iv, MeOH; v, LiOMe, THF, 20°C.

adduct (4) occurs. This has been confirmed in a separate experiment by epimerisation of (2) with one equivalent of lithium methoxide in tetrahydrofuran (THF) to give (4) in 87% yield.

The isolation of the new products (2) and (4) from the Diels–Alder reaction of (1) in toluene requires some comment. The Diels–Alder reaction in both DMSO and toluene must give the *trans*-fused β,γ -unsaturated lactam (2) as the initial product. In DMSO this subsequently rearranges *via* the dienol or the dienolate to the thermodynamically-preferred α,β -unsaturated lactam (3). There are several reported examples in which the double bond of the initially formed cycloaddition product has migrated into conjugation with a carbonyl group.³ In toluene, this same intermediate (2) prefers to reprotonate at the α -position to give the β,γ -unsaturated lactam (4). The fact that this has the *cis*-ring junction indicates that deprotonation and reprotonation occur several times allowing formation of the thermodynamically-preferred ring junction (*vide infra*). Indeed, a recent report explains the loss of stereochemistry of the dienophile in an intramolecular Diels–Alder reaction as a subsequent epimerisation of the kinetic product to give the more stable ring junction stereochemistry.⁴ In the case of (4), a similar loss of stereochemistry is observed but in the diene portion of the substrate. Such allylic rearrangements have been shown, even in protic media, to involve varying degrees of intramolecular proton transfer.⁵ It is possible that the ion-pair formed upon deprotonation of (2) is tighter in toluene and thus favours internal return⁶ *i.e.* α -reprotonation with epimerisation at this position. In DMSO, a looser ion-pair exists and γ -reprotonation leading to conjugated lactam (3) predominates.

The existence of this unusual solvent effect has been confirmed by heating the pure β,γ -unsaturated lactam (4) in DMSO under the conditions of the Diels–Alder reaction. A high yield of α,β -unsaturated lactam (3) was isolated. This transformation cannot occur *via* the reverse Diels–Alder reaction of (4) as this would lead not to triene (1) but to its (*E,Z*)-stereoisomer. Similarly, heating of the *trans*-fused β,γ -unsaturated lactam (2) in DMSO leads to almost pure α,β -unsaturated lactam (3) whereas in toluene a 25:1 mixture of *cis*-fused β,γ -unsaturated lactam (4) and α,β -unsaturated lactam (3) was isolated.

Our original observation that the Diels–Alder reaction of (1) proceeds entirely through the *endo*-transition state is confirmed and the change in product distribution is clearly a solvent effect on the subsequent transformations of the initial cycloaddition product.

[†] All new compounds gave satisfactory spectroscopic and analytical data.

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References

- 1 S. Handa, K. Jones, C. G. Newton, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 1362.
 - 2 V. Snieckus, J. A. Oakleaf, M. T. Thomas, and A. Wu, *Tetrahedron Lett.*, 1978, **19**, 1645.
 - 3 S. F. Martin, S. A. Williamson, R. P. Gist, and M. Smith, *J. Org. Chem.*, 1983, **48**, 5170.
 - 4 P. Magnus, C. Walker, P. R. Jenkins, and K. A. Meneer, *Tetrahedron Lett.*, 1986, **27**, 651.
 - 5 D. J. Cram and R. T. Uyeda, *J. Am. Chem. Soc.*, 1964, **86**, 5466.
 - 6 D. J. Cram, 'Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965, p. 154.
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