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Asymmetric hetero-Diels-Alder reactions. Mechanism of the reaction of alkenyloxazolines with isocyanates

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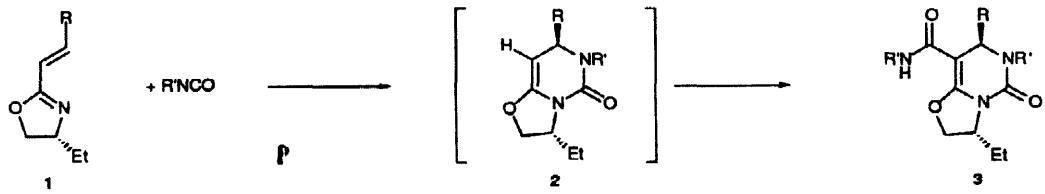
Abstract: Diastereomerically pure oxazolo[3,2-*c*]pyrimidines can be readily prepared by the reaction of alkenyloxazolines with isocyanates. These compounds undergo epimerisation upon prolonged heating. The mechanism of this transformation has been investigated experimentally and computationally.

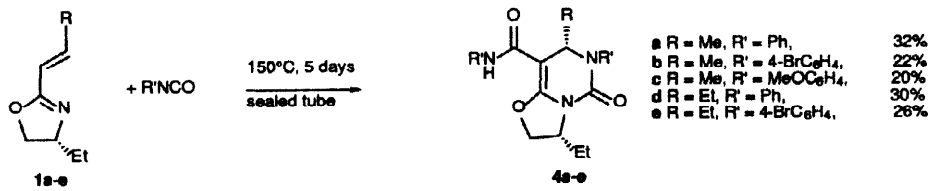
Keywords: Asymmetric synthesis; Diels-Alder reactions;

We recently reported the reaction of alkenyloxazolines **1** with aryl and arylsulfonyl isocyanates as a stereocontrolled entry into the oxazolo[3,2-*c*]pyrimidine ring system present in compounds **3** (**Scheme 1**).[1] This presumably occurs by addition of a second equivalent of isocyanate to compounds **2**. Although the formation of **2** can be written as a concerted hetero-Diels-Alder reaction,[2] we feel that it is far more likely that this reaction takes place in a stepwise manner. Since a computational study on the reactions of aza dienes with ketene also predicts a stepwise pathway,[3] we would now like to present the results of our own computational study in conjunction with some relevant experimental results.



Scheme 1

We had previously noticed that when the reactions were allowed to proceed for extended periods of time at elevated temperatures, an epimerisation took place leading to a 4:1 mixture of diastereoisomers favouring **4** (**Scheme 2**).[4,5] The pure compounds **3** also undergo this isomerisation.



Scheme 2

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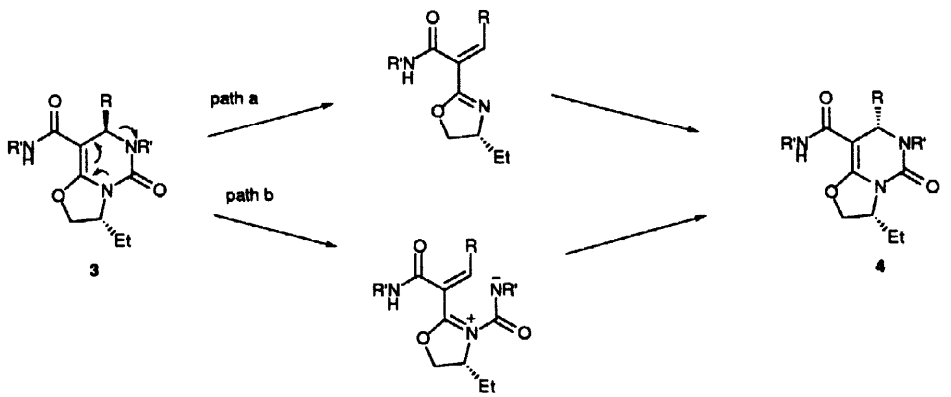
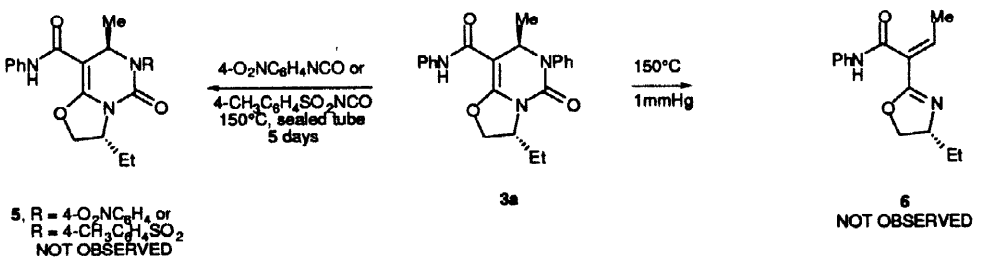
There are two main mechanistic possibilities for this transformation, either extrusion of the isocyanate in the reverse of a hetero-Diels-Alder reaction followed by recombination (**Scheme 3**, path a), or scission of the C-N bond followed by ring closure to give the diastereoisomer (**Scheme 3**, path b).

Reaction of **3a** with 4-nitrophenyl isocyanate or 4-toluenesulfonylisocyanate under appropriate conditions did not lead to formation of mixed products **5**. Similarly heating of **3a** under vacuum showed no evidence for the formation of the alkenyloxazoline **6** (**Scheme 4**). While the lack of such compounds does not rigorously exclude path a, we take this as strong corroboration, and see no reason why the initial formation of **2** should not proceed by a similar pathway.



Scheme 3



Scheme 4

It is not entirely surprising, given the harsh conditions, that this isomerisation is accompanied by some decomposition, although NMR data are fully consistent with the proposed structures, and show the change of stereochemistry quite clearly. The major changes are in the oxazolo ring, suggesting that the conformation of the pyrimidine ring is similar between the two isomers (**Figure 1**).

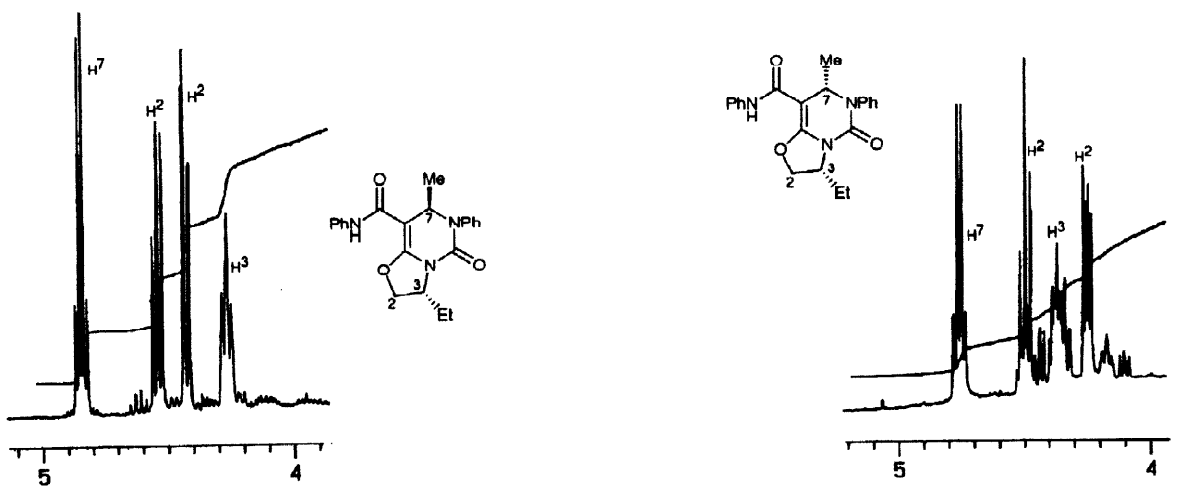
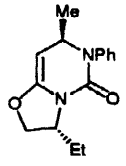


Figure 1

Semi-empirical calculations at the PM3 level[6] estimate the heat of formation of **3a** to be -51.3 kcalmol^{-1} while that of its diastereoisomer **4a** is -52.4 kcalmol^{-1}. From this we can see that the expected ratio of stereoisomers in a thermodynamic mixture is 4:1, exactly as observed! Further calculations showed a similar energy difference for the diastereoisomers **7** and **8**, so that if the first addition of the isocyanate were under thermodynamic control a similar diastereoselectivity would be obtained. We therefore felt that the stereoselectivity in the first step was under kinetic control and set about locating the transition state computationally.



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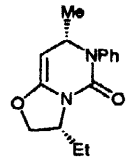

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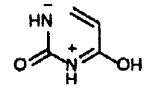
Figure 2

This was again attempted using semi-empirical calculations[7] (MOPAC, PM3 parameterisation using the Cerius2 graphical interface package for preparation of the structures in both cartesian and z-matrix form). The status of structures generated was tested by carrying out a frequency analysis at the same level of theory, minima being recognised by a complete set of positive normal modes and transition states by a single negative (imaginary force constant) mode.

Initial attempts to locate the transition state directly proved less than satisfactory, so the structure was simplified to **9** in which only the heavy atoms involved in the final 6-membered ring, the carbonyl and oxazolo oxygen atoms were included, all unsatisfied bonds being taken up by hydrogen atoms. The location of a transition state for ring closure in this case proved considerably more facile.



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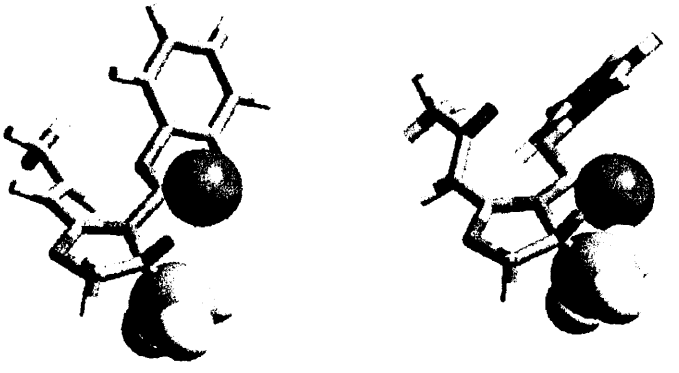
The molecule was then built up from this point in a series of steps: completing the five membered ring (without functionalisation at the 4-position), adding the methyl at the double-bond terminus and finally introducing the *N*-phenyl group. At each stage the preceding transition state structure was used as the basis for modification and the transition state re-optimised. In this way it was possible to arrive at a transition for ring-closure for the proposed stepwise pathway. Finally, transition states leading to the two diastereomeric products were generated by appropriate placement of a methyl group at the 4-position of the oxazoline in place of ethyl (this should be sufficient to study the ring closure leading to the two diastereoisomers without the added complication of the conformations of the ethyl group). The final transition states leading to the 3*R*,7*R* and 3*R*,7*S* products are shown in **Figure 3**. For the 3*R*,7*R* product (observed at lower temperatures/shorter reaction times) the propenyl group is twisted below the plane of the oxazoline ring, so that the isocyanate can approach from above. The transition state leading to the 3*R*,7*S* product is similar, but is of higher energy due to unfavourable interactions between the oxygen of the isocyanate and the substituent at the 4-position of the oxazoline. The space filling representation is used to indicate the isocyanate oxygen and the methyl group at the 4-position of the oxazoline. The final energies of the transition states were calculated to be 6.8 kcalmol^{-1} (3*R*,7*R*) and 9.5 kcalmol^{-1} (3*R*,7*S*). From this we would expect the selectivity to be about 98:2 in favour of the 3*R*,7*R* isomer. Furthermore, since substituents on the methyl group can orient themselves away from the oxygen of the isocyanate, we would not expect a large difference in selectivity in the series methyl, ethyl, 2-propyl. Clearly, since ethyl gives essentially complete selectivity, this will be difficult to probe experimentally, although 2-propyl does give a similar result. Interestingly, the oxazoline with a *gem*-dimethyl group at the 4-position is unreactive towards isocyanates, even at elevated temperatures.

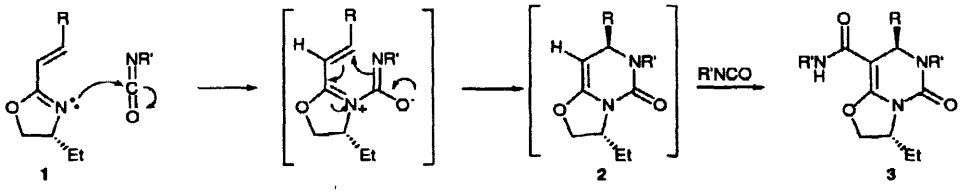
We also investigated the possibility of this reaction being a concerted Diels-Alder reaction, but have so far been unable to locate a transition state.

Clearly the calculations are in good agreement with experimental data, both for the kinetically and thermodynamically controlled reactions. We therefore feel that the reaction proceeds in a stepwise manner as originally proposed (**Scheme 5**).



3R,7R *3R,7S*

Figure 3



Scheme 5

Acknowledgements

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References and Notes

1. M. C. Elliott and E. Kruiswijk, *Chem. Commun.* 1997, 2311; M. C. Elliott, D. E. Hibbs, D. S. Hughes, M. B. Hursthouse, E. Kruiswijk and K. M. A. Malik, *J. Chem. Crystallogr.* 1998, *in press.*

2. For a review of the hetero-Diels-Alder reaction see: L. Tietze and G. Kettschau, *Top. Curr. Chem.*, 1997, **189**, 1.

3. W. M. F. Fabian and G. Kollenz, *J. Phys. Org. Chem.*, 1994, **7**, 1.

4. *Preparation of N8,6-diphenyl-(3R)-ethyl-(7S)-methyl-5-oxo-2,3,6,7-tetrahydrooxazolo[3,2-c]pyrimidine-8-carboxamide* (**4a**): A mixture of phenyl isocyanate (346 mg, 2.90 mmol) and (4*R*)-ethyl-2-(1-propenyl)-4,5-dihydrooxazole (202 mg, 1.45 mmol) were heated in a sealed tube at 150 °C for 65 hours. The residue was purified by column chromatography (eluent 3:1 diethyl ether and hexane) to afford the *title compound* (175 mg, 32%) as a light yellow solid, mp 59 – 61°C (Found: C, 69.73; H, 5.84; N, 10.33. $C_{22}H_{23}N_3O_3$ requires C, 70.01; H, 6.14; N, 11.13%); ν_{max} ($CHCl_3$)/cm^{-1} 3413, 1682, 1652, 1595, 1534 and 694; δ_H (400 MHz; $CDCl_3$) 8.21 (1 H, s, N-H), 7.46 (2 H, d, *J* 8.2, Ar-H), 7.29 (7 H, m, Ar-H), 6.96 (1 H, apparent t, Ar-H), 4.88 (1 H, q, *J* 6.2, Me-C-*H*), 4.57 (1 H, apparent t, *J* 8.1, one of OCH_2), 4.46 (1 H, m, *H*CEt), 4.35 (1 H, dd, *J* 8.2 and 4.5, one of OCH_2), 1.87 - 1.81 and 1.78 - 1.73 (1 H each, m, CH_2), 1.24 (3 H, d, *J* 6.4, CH_3) and 0.90 (3 H, t, *J* 7.4, CH_3); δ_C (100 MHz; $CDCl_3$) 160.9 (C=O), 151.6 (C=O), 149.6 (C), 139.4 (C), 137.6 (C), 128.1 (CH), 127.9 (CH), 126.2 (CH), 126.0 (CH), 122.4 (CH), 119.7 (CH), 83.3 (C), 73.2 (OCH_2), 54.3 (CH), 54.0 (CH), 25.4 (CH_2), 18.1 (CH_3) and 7.8 (CH_3); m/z (EI) 377 (M^+, 21%), 362 (100), 285 (34) and 166 (73).

5. There is a balance between isomerisation and decomposition. The isomerisations must be carried out above the melting point of the pure 3*R*,7*R* isomer (**3a**, 150°C; **3b**, 220°C; **3c**, 140°C; **3d**, 64°C; **3e**, 68°C), although if this is above 150°C decomposition predominates and only a trace of the 3*R*,7*S* isomer can be detected (with the exception of **4b** which can be prepared directly from the alkenyloxazoline at 150°C despite **3b** having a melting point of 220°C).

6. Simple energy minimisations were performed using the semi-empirical package (PM3) in MacSpartan Plus 1.1.7 (Wavefunction Inc.). For each isomer the minimisation was repeated starting at each gauche conformation of the ethyl group in order to be confident that the global minimum had been found.

7. Transition state calculations performed on a Silicon Graphics multiprocessor Origin 2000.