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# STEREOCHEMICAL VARIATIONS IN THE DIELS-ALDER REACTIONS OF SILOXYDIENES WITH N,N-DIMETHYL ACRYLAMIDE. A REMARKABLE INFLUENCE OF THE LEWIS ACID CATALYST.‡

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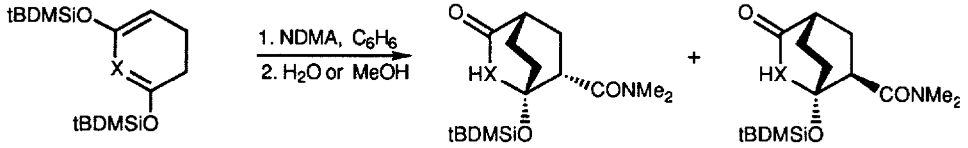
***Abstract*** : Thermal cycloadditions of dienes 1 and 2 with N,N-dimethyl acrylamide proceed with unusual exo selectivity.The stereoselectivity of the corresponding catalysed reactions surprisingly varies with the nature of the catalyst : t-butyldimethylsilyl triflate mainly yields endo adducts whereas Eu(fod)$_3$ gives only exo adducts.

Diels-Alder reactions of 2-azadienes are of great value for the synthesis of pyridines, pyrimidines and piperidines[1,2]. For many applications, the value of these cycloadditions will rely upon the degree of stereochemical control which can be exercised. We recently reported[3] that the reactions of 2-azadienes with *acyclic* dienophiles surprisingly showed a high kinetic exo selectivity whereas the corresponding reactions with *cyclic* dienophiles showed the expected endo preference. This spectacular stereochemical divergence could possibly result from two different reacting conformations of the dienophile, e.g. s-cis for the acyclic series and s-trans for the cyclic series. We have now examined the reactions of dienes 1 and 2 with N,N-dimethyl acrylamide (NDMA) which predominantly exists in the s-cis conformation[4].



1 X=N
2 X=CH

3-endo
4-endo

3-exo
4-exo

tBDM = t-Butyldimethyl

- Scheme 1 -

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‡ Dedicated to Prof. H.G. Viehe on the occasion of his 60th birthday

Thermal reactions of 1 and 2[5] with NDMA were much slower than with the corresponding esters. After hydrolysis or methanolysis of the crude mixtures, compounds 3 and 4 were isolated[6]. In each case, the major isomer resulted from an exo transition state (Scheme 1, Table 1, entries A and B). Endo and exo isomers were separated by flash chromatography. Configurations were established on the basis of $^1$H NMR analyses[7] as previously described for analogous structures[2b].

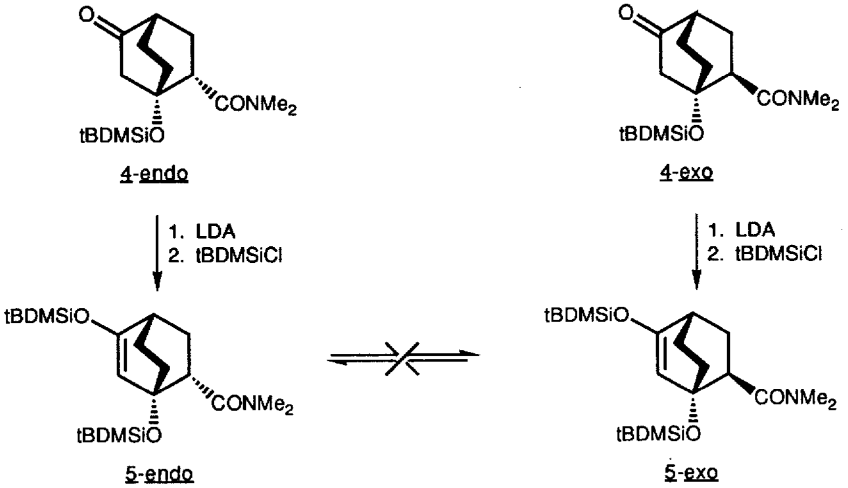
***Table 1 : Reactions of 1 and 2 with N,N-dimethyl acrylamide in benzene***

| Entry | X | Catalyst | Conditions | Yield(%) | Endo : Exo[(e)] |
|---|---|---|---|---|---|
| A | N | no | reflux, 3 days | 53[(b)] | 15 : 85 |
| B | CH | no | 170°C, 6 days[(a)] | 73[(c)] | 30 : 70 |
| C | N | t-$BuMe_2SiOTf$(10%) | 20°C, 1 hr | 92[(b)] | 84 : 16 |
| D | CH | t-$BuMe_2SiOTf$(10%) | 20°C, 30 min | 87[(d)] | 92 : 8 |
| E | N | $Eu(fod)_3$(10%) | reflux, 25 hrs | 80[(b)] | 3 : 97 |
| F | CH | $Eu(fod)_3$(10%) | reflux, 6 days | 82[(c)] | 4 : 96 |

*(a) Reaction performed in a sealed tube; (b) Pure products after methanolysis and flash chromatography; (c) Pure products after hydrolysis with 0.25M HCl and flash chromatography; (d) Pure products after hydrolysis with $H_2O$ and flash chromatography; (e) Determined by capillary gas chromatography or NMR on the crude mixtures.*

A control experiment was performed to establish that no endo-exo equilibration had occured under the reaction conditions. Both 4-endo and 4-exo were converted into the corresponding silyl enol ethers 5 (Scheme 2). No equilibration was observed after 2 days at 170°C (benzene, sealed tube).

These experiments showed that : (a) NDMA yields mainly exo adducts in thermal cycloadditions with 1 and 2 and behaves thus as the other acyclic dienophiles which had been previously studied[2c], (b) aza- and carbadienes 1 and 2 behave similarly. Therefore the lone-pair of the nitrogen atom in diene 1 does not play a significant role in destabilising the endo transition state by electrostatic repulsion. One might also have expected that the presence of an electron-releasing group at C-1 of dienes 1 and 2 would enhance the endo selectivity due to better stabilising secondary orbital interactions. This is clearly not the case. However, electron-releasing groups at C-1 also increase closed-shell repulsions in the endo transition state[8]. We therefore anticipated that the replacement of an amide by a positively charged group in the dienophile would lower the energy of the endo transition states and would thus favour the formation of the endo isomers. This could be easily achieved by running the previous reactions in the presence of a Lewis acid catalyst which reversibly converts a fraction of the amide into the more reactive dienophilic acryliminium salt[9].

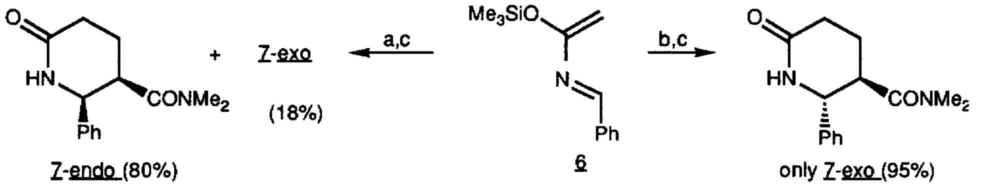


- Scheme 2 -

*t-Butyldimethylsilyl triflate* was found to be an efficient catalyst which does not destroy the highly sensitive dienes 1 and 2. Cycloadditions are completed at room temperature in one hour or less, yields are high and, as anticipated, *a high endo selectivity is observed* (Table 1, entries C and D). Here also, both endo and exo isomers 5 were found to be stable in the presence of t-butyldimethylsilyl triflate for 24 hrs at 20°C. Similar results were obtained using triflic acid : the use of 10% triflic acid as catalyst led to lower chemical yields (55%) but did not affect the endo : exo ratio (90 : 10). On the other hand, when the reaction was performed in the presence of boron trifluoride etherate, the endo-selectivity decreased significantly (endo : exo, 65 : 35).

*Unexpectively, however, when the cycloaddition reaction of 1 and 2 was carried out with $Eu(fod)_3$ as catalyst, virtually complete kinetic exo-selectivity is observed* (Table 1, entries E and F)[10]. This unusual observation is reminiscent of the remarkable influence of the nature of the Lewis acid catalyst on the stereochemistry of condensation of aldehydes with siloxydienes[11].

At this stage, no explanation can yet be offered to these intriguing results which could possibly offer a tool to control endo : exo selectivity in Diels-Alder reactions. While exploring the scope of these preliminary observations, we already found that they apply to the reaction of the open-chain 2-azadiene 6[3] with NDMA (Scheme 3).



a : NDMA,tBDMSiOTf(10%),$CH_2Cl_2$,5 min.,RT b: NDMA,Eu(fod)$_3$(10%),$CH_2Cl_2$,1 day,RT c : MeOH,RT

- Scheme 3 -

The following paper will describe an application of these observations for highly stereoselective asymmetric Diels-Alder reactions.

### *Acknowledgements*

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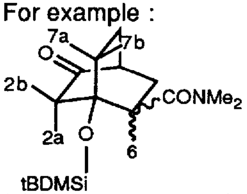
### *References and Notes*

1. Reviews : (a) Boger, D.L. *Tetrahedron* **1983**, 39, 2869. (b) Ghosez, L.; Serckx-Poncin, B.; Rivera, M.; Bayard, Ph.; Sainte, F.; Demoulin, A.; Hesbain-Frisque, A.M.; Mockel, A.; Munoz,L.; Bernard-Henriet, C. *Lect. Het. Chem.* **1985**, 8, 69. (c) Boger, D.L.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis, Academic Press : Orlando, Fl. **1987**.* (d) Barluenga, J. *Bull. Soc. Chim. Belg.* **1988**, 97, 545.
2. Recent papers : (a) Bayard, Ph.; Sainte, F.; Beaudegnies, R.; Ghosez, L. *Tetrahedron Lett.* **1988**, 29, 3799. (b) Rivera, M.; Lamy-Schelkens, H.; Sainte, F.; Mbiya, K.; Ghosez, L. *Tetrahedron Lett.* **1988**, 29, 4573.
3. Bayard, Ph.; Ghosez, L. *Tetrahedron Lett.* **1988**, 29, 6115.
4. Montaudo, G.; Librando, V.; Caccomese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, 95, 6365.
5. Dienes 1 and 2 were prepared by silylation of the dianions derived from glutarimide and 1,3-cyclohexanedione respectively.
6. All new products were characterized by IR, $^1$H NMR, $^{13}$ NMR, elemental analysis and mass spectrometry.
7. For example :



4-exo : $\delta$ 2a = 2,39 ppm $\delta$ 7b = 2.6 ppm $^4J_{6\text{-}2b}$ = 0Hz $^4J_{6\text{-}7a}$ = 1,8Hz

4-endo : $\delta$ 2a = 3,46 ppm $\delta$ 7b = 1.8 ppm $^4J_{6\text{-}2b}$ = 1,7Hz $^4J_{6\text{-}7a}$ = 0Hz

8. (a) Kakushima, H.; Scott, D.G. *Can. J. Chem.* **1979**, 57, 1399. (b) Kakushima, M. *ibid.* **1979**, 57, 2564.
9. (a) Baum, J.S.; Viehe, H.G. *J. Org. Chem.* **1976**, 41, 183. (b) Pouilhes, A.; Kouklovsky, C.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* **1987**, 28, 6183. (c) Jung, M.E.; Vaccaro, N.D.; Buszek, K.R. *Tetrahedron Lett.* **1989**, 30, 1893.
10. 5-Endo was recovered unchanged after prolonged heating at 80°C in the presence of Eu(fod)$_3$.
11. Danishefsky, S.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, 107, 1246.

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