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DIELS-ALDER REACTIONS OF 2-AZADIENES. DIASTEREOSELECTIVE SYNTHESES OF 2-AZABICYCLO[2.2.2]OCTAN-2-ONES AND OF 2,3,4-SUBSTITUTED CYCLOHEXANONES.

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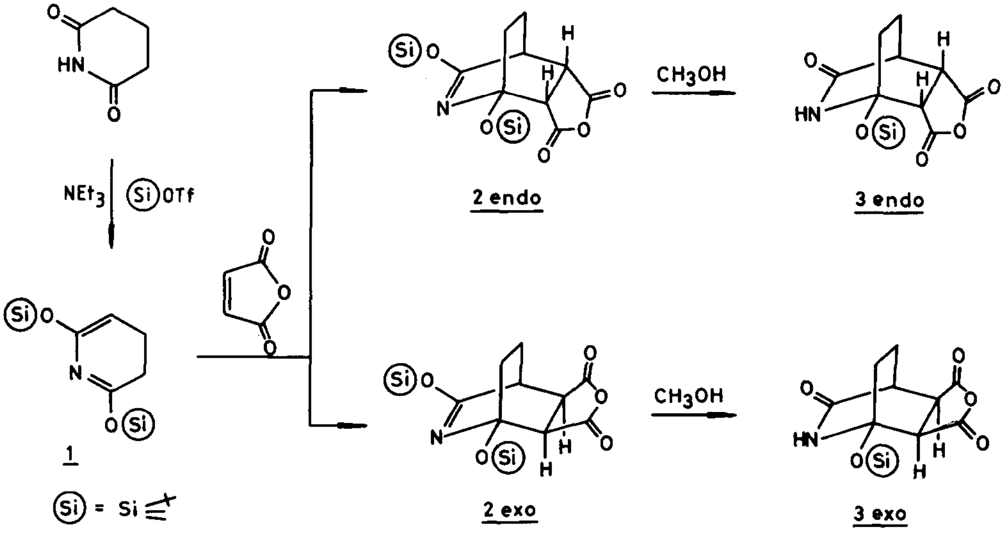
Summary : Glutarimide is readily disilylated to yield the cyclic 2-azadiene 1 which reacts with open-chain dienophiles with surprisingly high exo-selectivity. The resulting 2-azabicyclo[2.2.2]octan-3-ones are stereoselectively transformed into substituted cyclohexanones.

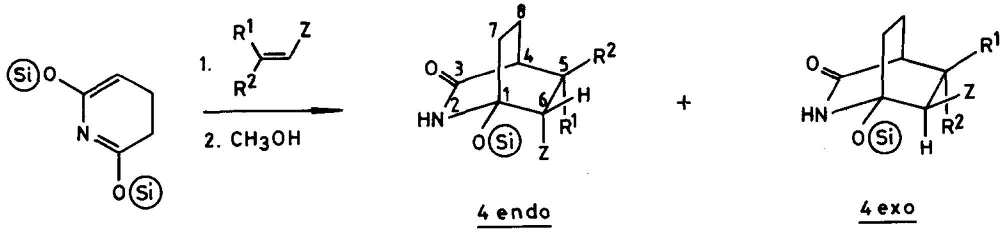
The Diels-Alder reaction of activated 1- and 2-azadienes is a powerful method for the synthesis of nitrogen-containing six-membered rings with a defined substitution pattern[1,2].

We have recently prepared the new cyclic 2-azadiene 1 by silylation of glutarimide (Scheme 1). Compound 1 is a colourless liquid which is purified by distillation. It can be kept in the refrigerator for several months without substantial change. Compound 1 readily reacted with maleic anhydride at 0°-20°C to yield a mixture of endo and exo adducts 2 endo and 2 exo. Upon treatment with methanol at room temperature, the most labile silyl group was cleaved and compounds 3 endo and 3 exo were obtained in 70% yield (endo:exo 4:1)[3].



Scheme 1

Surprisingly, the reaction of 1 with open-chain dienophiles took place with a high exo-diastereoselectivity (Scheme 2, Table 1). Methanolysis of the crude adducts yielded compounds 4 exo and 4 endo which were readily separated by flash chromatography. Configurations were established on the basis of the values[4] of coupling constants $^3J_{H_5-H_6}$ and $^4J_{H_6-H_7}$. This was further confirmed by an X-ray crystal structure analysis in the case of 4d (exo)[5].



Scheme 2

Table 1 : Reactions of 1 with Open-chain Dienophiles

	Z	R^1	R^2	Conditions$^{a)}$	Yield of 4$^{b)}$ (%)	Endo:Exo$^{c)}$
a	$COCH_3$	H	H	60°C, 5hrs	55	14 : 86
b	CN	H	H	60°C, 48hrs	73	10 : 90
c	CO_2CH_3	H	H	60°C, 72hrs	74	8 : 92
d	CO_2CH_3	CO_2CH_3	H	60°C, 10days	67	0 : 100
e	CO_2CH_3	H	CO_2CH_3	60°C, 35hrs	84	0 : 100
f	CO_2CH_3	H	CH_3	120°C, 21hrs	67	3 : 97

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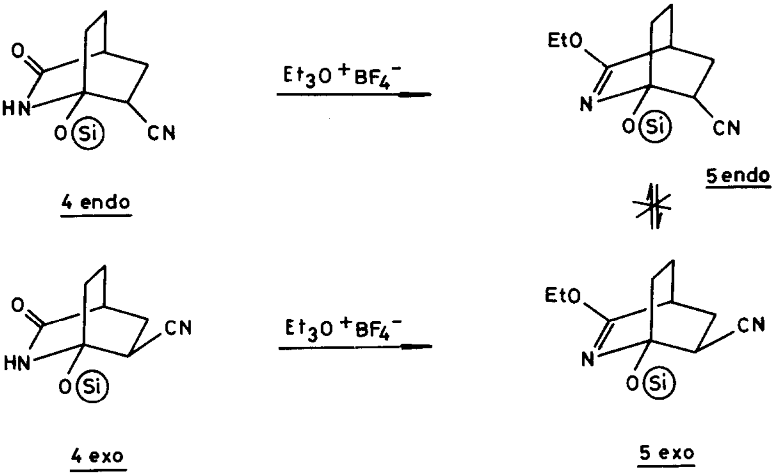
a) Cycloadditions in benzene; b) Mixture of endo- and exo-isomers after chromatography;
c) Determined on the crude adducts.

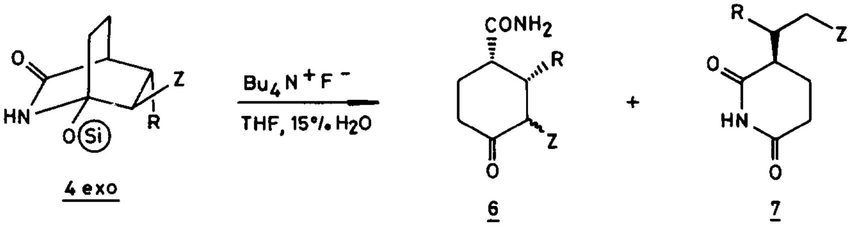
It was shown that this high exo-preference was not the result of a thermodynamic equilibrium. Both endo- and exo-isomers of 4b were converted into the corresponding iminoethers[6] 5 endo and 5 exo (Scheme 3). It was expected that 5 endo and 5 exo would behave as the corresponding O-silyl iminoethers which could not be prepared by silylation of 4 endo and 4-exo[7]. Both 5 endo and 5 exo were found to be stable under the conditions used for the cycloaddition. Furthermore they remained unchanged even after 2 days at 120 °C. This unusual exo-selectivity thus appears to be the result of kinetic control.

We also found that compounds 4 exo could readily be transformed into substituted cyclohexanones 6. Treatment of 4 exo with tetrabutylammonium fluoride in THF containing 15% H_2O caused the cleavage of the C-N bond when Z = CO_2CH_3. Derivatives of cyclohexanone 6 were obtained in good yields (Scheme 4).



Scheme 3

When Z is a stronger electron-withdrawing group such as $COCH_3$, cleavage of the C-C bond was observed and a substituted glutarimide 7a was obtained. We also found that the amount of H_2O in THF exercises a significant effect on the ratio 6:7. Yields of 6 were lower with 5% of H_2O.



	Z	R		
a.	$COCH_3$	H	0%	79%
c.	CO_2CH_3	H	86%	0%
e.	CO_2CH_3	CO_2CH_3	78%	0%
f.	CO_2CH_3	CH_3	79%	10%

Scheme 4

The chemistry described above demonstrates the utility of 2-azadiene 1 for the stereoselective synthesis of substituted 2-azabicyclo[2.2.2]octanes. It also provides a novel and stereoselective route towards polysubstituted cyclohexanones which should become a useful complement to existing methods. An intriguing feature of the cycloaddition reactions with 1 is their pronounced exo-stereoselectivity. We are presently studying the structural factors controlling these unusual stereoselectivities.

Acknowledgment

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References and Notes

1. Reviews : D.L. Boger, Tetrahedron 1983, 39, 2869; L. Ghosez, B. Serckx-Poncin, M. Rivera Ph. Bayard, F. Sainte, A. Demoulin, A.M. Hesbain-Frisque, A. Mockel, L. Munoz and C. Bernard-Henriet, Lect. Het. Chem. 1985, 8, 69; D. Bellus, Lect. Het. Chem. 1987, 9, 65.
2. Recent papers :
   1-aza-1,3 dienes :
   B. Serckx-Poncin, A.M. Hesbain-Frisque and L. Ghosez, Tetrahedron Lett. 1982, 23, 3261; Y.S. Cheng, A.T. Lupo, F.W. Fowler, J. Am. Chem. Soc. 1983, 105, 7696; M. Komatsu, S. Takamatsu, M. Uesaka, S. Yamamoto, Y. Ohshiro, T. Agawa, J. Org. Chem. 1984, 49, 2691; Y.C. Hwang, F.W. Fowler, J. Org. Chem. 1985, 50, 2719; M. Ihara, T. Kirihara, K. Fukumoto, T. Kametani, Heterocycles 1985, 23, 1097.
   2-aza-1,3 dienes :
   A. Demoulin, H. Gorissen, A.M. Hesbain-Frisque and L. Ghosez, J. Am. Chem. Soc. 1975, 97, 4409; R. Gompper, U. Heinemann, Angew. Chem. Int. Ed. Engl. 1981, 20, 296; F. Sainte, B. Serckx-Poncin, A.M. Hesbain-Frisque and L. Ghosez, J. Am. Chem. Soc. 1982, 104, 1428; M.M. Ito, Y. Nomura, Y. Takeushi, S. Tomoda, Bull. Chem. Soc. Jpn. 1983, 56, 641; J. Barluenga, M. Tomas, A. Ballesteros, V. Gotor, J. Chem. Soc. Chem. Commun. 1987, 1195.
3. All new products were characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis or mass spectrometry.
4. Examples : 4d(exo), $^{3}J_{H_5-H_6}$ = 12.03 Hz and $^{4}J_{H_6-H_7}$ = 1.95 Hz; 4d(endo), $^{3}J_{H_5-H_6}$ = 11.18 Hz and $^{4}J_{H_6-H_7}$ =0 Hz; 4e(exo), $^{3}J_{H_5-H_6}$ =6.29 Hz and $^{4}J_{H_6-H_7}$= 2.37 Hz.
5. We thank Drs J.P. Declercq, B. Tinant and Prof. M. Van Meerssche for the cristallographic studies.
6. W. Kantlehner, Adv. Org. Chem. 1979, 9, part 2, 181-277.
7. D.L. Birkoffer, D.A. Ritter, Angew. Chem. Int. Ed. Engl. 1965, 4, 5, 417.

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