Tetrahedron: Asymmetry Vol. 2, No. 12, pp. 1173-1176, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Asymmetric Diels-Alder Reactions of a Nitroso Compound derived from D-Bornane-10,2-Sultam

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(*Received* 26 *September* 1991)

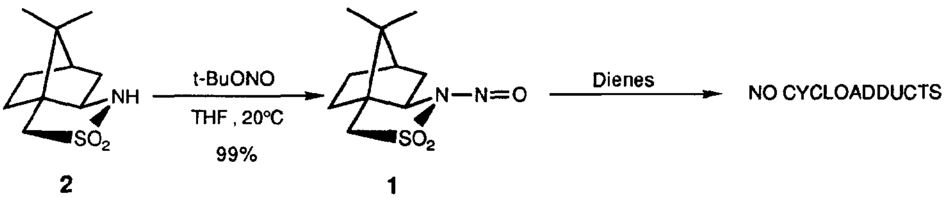
Key words : oxyamination, nitroso compounds, cycloaddition, D-bornane-10,2-sultam

Abstract : Acylnitroso dienophile **3** derived from D-bornane-10,2-sultam undergoes cycloaddition with high yields and complete facial selectivity to cyclopentadiene and cyclohexadiene. When the nitroso group is attached to the sultam nitrogen, it is no longer reactive in Diels-Alder reactions.

The asymmetric oxyamination of dienes is a useful route towards enantiomerically pure amino alcohols and amino acids. Excellent results have been obtained with simple dienes and α-chloronitroso dienophiles derived from epiandrosterone or D-mannose.[1] However these dienophiles are not compatible with more reactive and sensitive dienes (e.g. 2-azadienes).[2] For this purpose carbamoylnitroso dienophiles derived from 2,5-disubstituted pyrrolidines with C_2 symmetry are superior : they undergo cycloaddition in high yields and excellent facial selectivities to various dienes including the highly sensitive 2-azadienes.[3,4]

In an extension of this work, we present preliminary results on the Diels-Alder reactions of nitroso compounds derived from D-bornane-10,2-sultam, a readily accessible chiral auxiliary which has proven to be extremely effective as a stereodirecting group.[5]

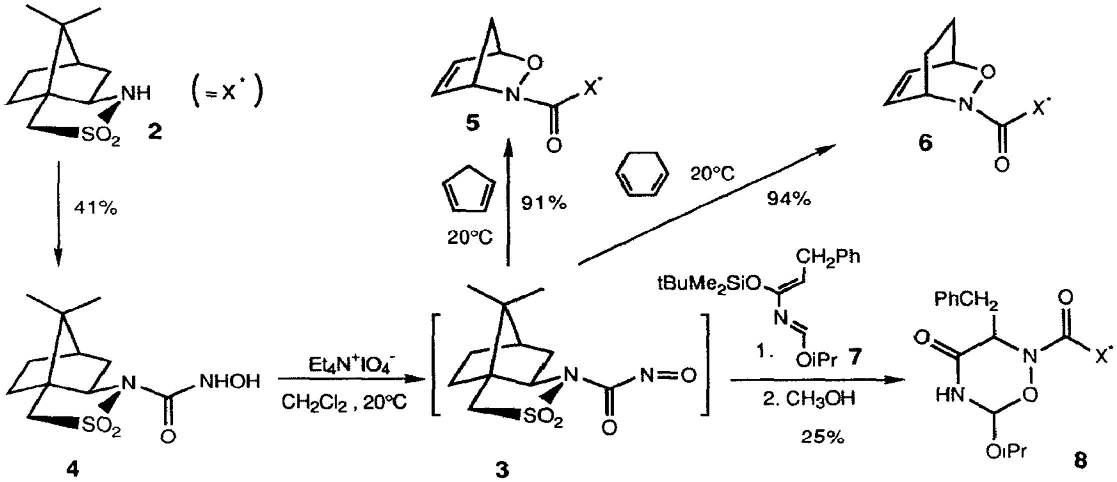
We have first examined the stable, crystalline N-nitrososultam **1** which was readily prepared by nitrosation of commercially available sultam **2** (Scheme 1).



Scheme 1

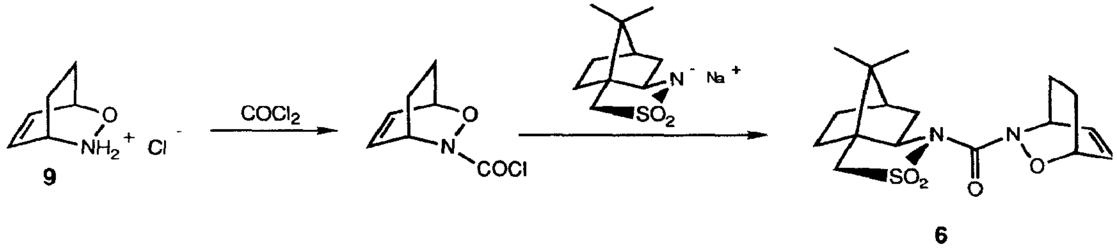
Compound **1** did not undergo Diels-Alder reactions with dienes such as cyclopentadiene or cyclohexadiene. It thus appears that the sultam group does not activate the N = O functionality towards electron-rich dienes. We also found that **1** was unreactive towards an electron-deficient diene such as ethyl sorbate.

We therefore decided to examine nitroso compound **3** in which the nitroso group should be strongly activated by the carbonyl group. Sultam **2** was transformed into hydroxamic acid **4** (unoptimized yield 41 %) (Scheme 2). The unstable nitroso compound **3** had to be generated *in situ* by the classical procedure using a solution of tetraethylammonium periodate in dichloromethane at room temperature. In the presence of a five-fold excess of cyclopentadiene or cyclohexadiene, adducts **5** or **6** were obtained in excellent yields and better than 98 % ee.[6] The ^{1}H NMR spectra of the crude reaction mixtures showed only one set of signals. On the other hand an independently prepared mixture of both diastereoisomers showed well-separated signals.[7]



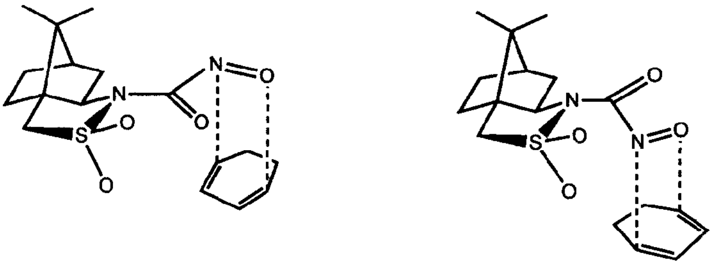
Scheme 2

The absolute configuration of **6** was established by independent synthesis from the known (1R, 4S) oxazine **9** (Scheme 3).[8]



Scheme 3

The facial diastereoselectivity observed in the cycloadditions is consistent with transition state models **A** or **B** (Scheme 4). Transition state **A** results from an *endo* approach of the diene from the less-hindered side of the dienophile in a *syn-syn* conformation around the -SO_2N-CO and CO-NO bond. Transition state **B** results from an *exo* approach of the diene from the less-hindered side of the dienophile in an *anti-syn* conformation. The choice of these reacting conformations results from the predictions of ab initio LCAO-SCF-MO calculations[9] using the MINI1 basis set of Huzinaga.[10] The calculations predict that the *syn-syn* fully optimized conformer is 1.3 kcal higher in energy than the anti-syn optimized conformer. Conformational analysis shows that these two conformers are 19.7 and 34.5 kcal more stable than the *syn-anti* and *anti-anti* conformers respectively. However, inspection of molecular models suggests that in transition state **B** the large SO_2 group could interact with the approaching diene. This could not be the case in transition state **A** which should therefore be preferred. This transition state would also be closer to the one postulated by Oppolzer[5] for catalytic hydrogenation or Lewis acid catalyzed Diels-Alder reactions of the corresponding acrylic derivatives. Furthermore, an "endo approach" of diene and nitroso dienophile would be in agreement with what has been previously observed for other chiral acylnitroso compounds.[3]



A **B**

Scheme 4

The ready availability of the new chiral nitroso dienophile in both enantiomeric forms and the high facial selectivities observed *without addition of Lewis acids* should make the method very attractive for the asymmetric oxyamination of dienes. However it will probably be useful only with less functionalized dienes. Indeed we found that the reaction of **3** with a highly reactive diene such as 2-azadiene **7** gave a low yield of adduct **8** which could not be separated from the many products of the reaction mixture. Therefore, at present, only carbamoylnitroso compounds derived from 2,5-disubstituted pyrrolidines possessing C_2 symmetry can be considered as general and efficient reagents for the oxyamination of dienes.

Acknowledgements

Financial support from the University of Louvain (assistantship to V. G.) and from the Ministère de l'Education et de la Recherche Scientifique de la Communauté Française de Belgique (Action Concertée 86/91-84) is gratefully acknowledged.

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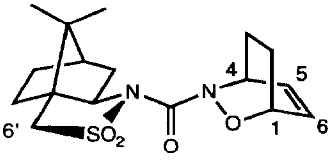
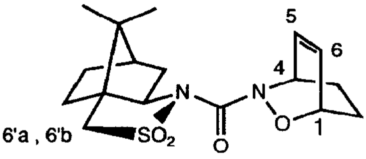
6. All new products have been characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis.
7. For example : **6a** δ H6 = 6.60, δ H5 = 6.39, δ H6' = 3.39 (s)
   6b δ H6 = 6.69, δ H5 = 6.54, δ H6'a = 3.36, δ H6'b = 3.34 (AB)



6a



6b

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