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Asymmetric Diels-Alder Cycloadditions with Acylnitroso Dienophiles Obtained from L-Proline

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Summary. - N-acylnitroso derivatives of L-proline were formed *in situ* from the corresponding hydroxamic acids. They reacted easily with 1,3-cyclohexadiene to give the corresponding diastereoisomeric pairs of Diels-Alder cycloadducts with *d.e.* values ranging from 52 to 68 %.

Diels-Alder cycloadditions, which have been discovered over six decades ago [1,2], play an ever increasing role in contemporary organic synthesis. In particular hetero Diels-Alder reactions are used as pivotal steps in the total synthesis of natural products [2]. Last but not least, asymmetric Diels-Alder reactions have become of primordial interest during the present decade [4-6], this being in great part due to the fact that modern pharmacopoeia requires enantiomerically pure drugs, with the potential advantage of a lower dose and a greater safety, as compared to the corresponding racemates.

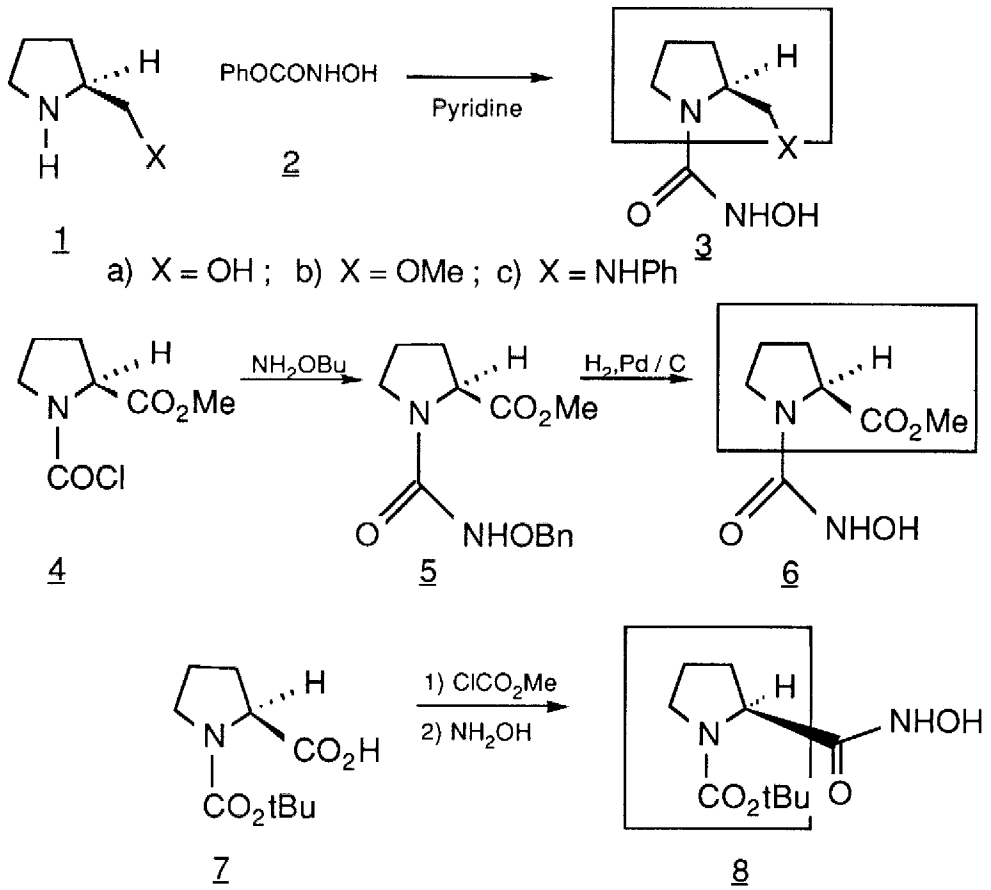
Asymmetric hetero Diels-Alder cycloadditions are of more recent vintage [4-6]. This is particularly true when it comes to Diels-Alder reactions in which optically active acylnitroso dienophiles are involved [7,8]. These latter ones are highly reactive species and can easily be prepared by *in situ* oxidation of the corresponding hydroxamic acids [9]. The few experimental results, which have been published so far with such dienophiles, *e.g.* with acylnitroso derivatives of mandelic acid, show them to lead to cycloadditions having modest *d.e.* values [7,8]. We describe herein some hetero Diels-Alder model reactions between cyclohexadiene and acylnitroso dienophiles **9** which were formed *in situ* from the corresponding L-proline hydroxamic acid derivatives **3a-3c**, **6** and **8** (**Scheme 1**).

Synthesis of some optically active hydroxamic acids. - When using the standard methodology - *i.e.* reaction of hydroxylamine with the corresponding carbamoyl chlorides [7,10] - the L-proline hydroxamic acid derivatives **3a-3c** and **6** could not be prepared in satisfactory yields. The following reaction sequences proved to be of more practical interest for the synthesis of the desired optically active hydroxamic acid derivatives [11] :

- prolinol **1a**, its methyl ether **1b** and the anilino derivative **1c**, when reacted with phenyl N-hydroxycarbamate **2** [12] in pyridine solution, led directly to the corresponding hydroxamic acids **3a-3c** ;

- the carbamoylchloride derivative **4** of methyl prolinate reacted with O-benzyl-hydroxylamine to give **5** ; hydrogenolysis (H_2, Pd/C) of **5** led to **6** ;
- the mixed anhydride of N-t-butoxycarbonylproline **7** reacted with NH_2OH to give **8**.

SCHEME 1



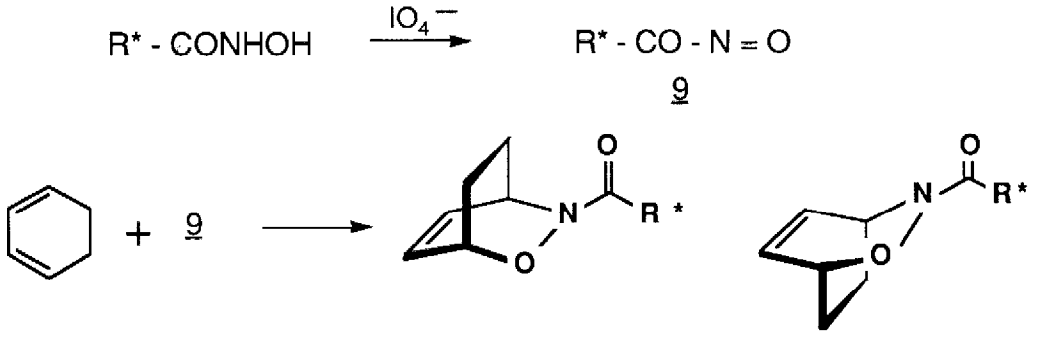
N.B. *The optically active moieties R* of the hydroxamic acids are represented within the rectangles.*

Asymmetric induction. - Addition of the above described optically active hydroxamic acids to stirred solutions of n-Pr_4NIO_4 and of 1,3-cyclohexadiene in $CHCl_3$, led to fast oxidation to the corresponding acylnitroso dienophiles **9** which reacted at once with the diene to give the corresponding cycloadducts. These proved to be, in all instances, pairs of unequal amounts of the expected diastereoisomers **10A/10B** (**Scheme 2**) [11]. The relative amounts (**Table**) of these stereoisomers - but not knowing which is which - were determined by ^{13}C-NMR. From this **Table** it appears clearly that the best *d.e.* value was obtained with the N-acylnitroso

derivative of **3b** (*d.e.* = 68 %), the poorest one with the C-acylnitroso derivative of **8** (*d.e.* = 20 %), albeit in this latter instance the chiral center is nearer the reactive site.

A tentative explanation to account for the difference in magnitude of these various *d.e.* values is as follows : the N-acylnitroso dienophiles are planar urea derivatives, *i.e.* they exhibit a hindered rotation around the N(1)-CO bond ; whereas in the C-acylnitroso derivative of **8** there is free rotation around the C(2)-CO bond (and therefore a lesser asymmetric induction).

SCHEME 2



1) without knowing which is which

Table. - **10A/10B** ratios, and *d.e.* values as obtained when the various acylnitroso dienophiles **9** were reacted with cyclohexadiene (for the formation of dienophiles **9** see **Scheme 2**). Overall yields for the formation of **10A-10B** are indicated in parentheses.

	3a	**3b**	**3c**	**6**	**8**
10A/10B ratios (yields)	76/24 (89)	84/16 (83)	82/18 (79)	77/23 (86)	60/40 (81)
d.e. values	52	68	64	54	20

In similar experiments G.W. Kirby obtained the highest *d.e.* values (*i.e.* 68 % with cyclopentadiene and 59 % with cyclohexadiene) when using the C-acylnitroso derivative of mandelic acid [8]. According to this author the intramolecular hydrogen bond between the secondary OH and the nitroso moiety leads to a stiffening of this dienophile and therefore to higher *d.e.* values, as compared to the corresponding mandelic acid ether derivatives [8]. In the proline series, which we described above, it appears that the intramolecular hydrogen bonding - which according to Kirby should form in **9a** - does not increase the *d.e.* value, as compared to those

dienophiles in which there cannot be any such H-bonding. As a matter of fact **9b** and **9c** (in which there is no H-bonding) lead to higher *d.e.* values (68 % and 64 %, respectively) than **9a** does (52 %).

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References

[1] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **460**, 98 (1928).
[2] Review: H. Wollweber "Diels-Alder-Reaktion", Thieme, Stuttgart (1972); J. Sauer, R. Sustmann, *Angew. Chem.* **92**, 773 (1980); *Angew. Chem. Int. Ed. Engl.* **19**, 779 (1980); M. Petrzilka, J.I. Grayson, *Synthesis* 753 (1981).
[3] D.L. Boger, S.M. Weinreb "Hetero Diels-Alder Methodology in Organic Synthesis", Academic Press, New-York (1987).
[4] P. Wetzel, *Nachr. Chem. Tech. Lab.* **31**, 979 (1983).
[5] W. Oppolzer, *Angew. Chem.* **96**, 840 (1984); *Angew. Chem. Int. Ed. Engl.* **23**, 876 (1984).
[6] K. Krohn , *Nachr. Chem. Tech. Lab.* **35**, 836 (1987).
[7] A. Defoin, H. Fritz, C. Schmidlin, J. Streith, *Helv. Chem. Acta* **70**, 554 (1987).
[8] G.W. Kirby, M. Nazeer, *Tetrahedron Lett.* **29**, 6173 (1988).
[9] G.W. Kirby, *Chem. Soc. Rev.* **6**, 1 (1977).
[10] G. Zinner, G. Isensee, *Arch. Pharmz.* (Weinheim) **307**, 7 (1974).
[11] All new compounds had spectral (NMR, mass) and microanalytical properties in agreement with the structures.
[12] G.M. Steinberg, J. Boger, *J. Org. Chem.* **21**, 660 (1956).

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