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X=Y-ZH Systems as Potential 1,3-Dipoles. Activation of the ZH Proton in Imines

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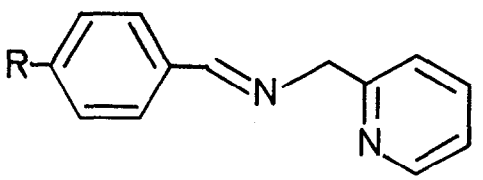
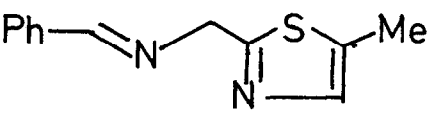
Summary. A range of substituents is capable of inducing thermal 1,3-dipole formation in imines (>C=N-CH<) by activation of the CH proton as shown by trapping experiments with dipolarophiles.

We have demonstrated the ability of imines of α-amino acids[1] and their esters[2] to generated 1,3-dipoles under thermal activation in both polar and non-polar solvents.[1,2] Dipole formation is strongly catalysed by Lewis and Bronsted acids[1,3] and imines are particular examples of the general X=Y-ZH system.[4] The ease of dipole formation in imines is influenced by the basicity of the central Y (nitrogen) atom and the pKa of the ZH (CH) proton.[5]

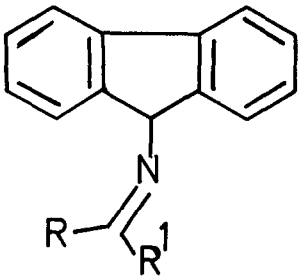
We now report that activation of the ZH proton is not limited to carboxyl, ester or nitrile.[6] Thus the pyridyl-(1), thiazolyl-(2), fluorenyl-(3) and dibenzotropyl-(4) imines and the lactams (5b,c) and thiolactone (5a) all undergo cycloaddition to dipolarophiles under thermal activation in good yield.



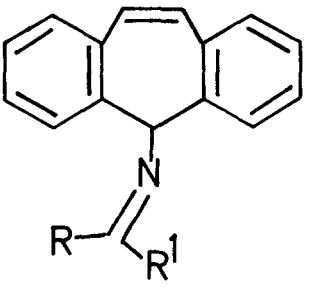
(1)



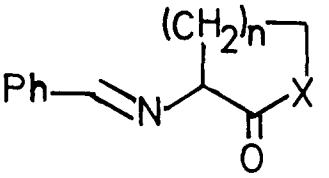
(2)



(3) a. $R=R^1$= 9-fluorenyl
b. R=H, R^1= Ph

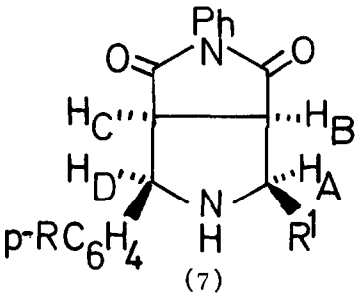


(4) a. $R=R^1$= 9-fluorenyl
b. R=H, R^1= Ph



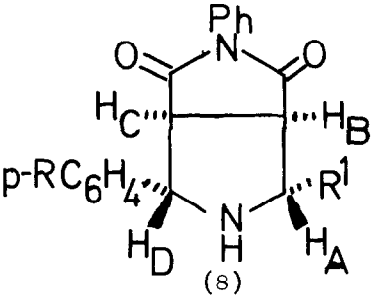
(5) a. X=S, n=1
b. X=NH, n=2
c. X=NH, n=3

Thus the pyridyl imines (1) react (boiling toluene, 2-10h) with N-phenyl maleimide (6) to give a mixture of two adducts (7) and (8) arising from endo- and exo-transition states (Table) involving a 1,3-dipole with configuration (9). An analogous 1:1 endo-exo product mixture is obtained from (2) and (6).



(7)

a. R^1= 2-pyridyl
b. R^1= 2-(5-methylthiazolyl)



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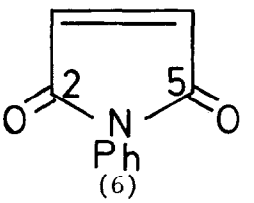

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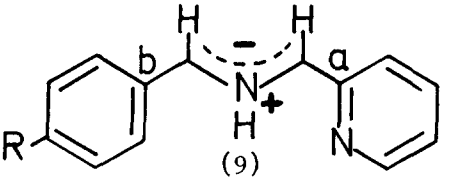


(9)

Table. Endo-exo (7a:8a) isomer ratios in cycloadditions of (1) with (6)

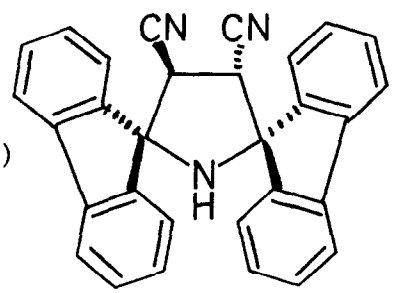
R	Ratio (7a:8a)	Yield %
NMe_2	0.9:1	70
OMe	1.2:1	72
H	1.1:1	82
CF_3	1.9:1	66
CN	2:1	80
NO_2	2.5:1	60

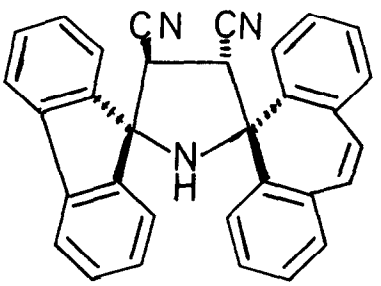
Huckel M.O. calculations[7] indicate a decrease in attractive secondary orbital interactions [HOMO(9) - LUMO(6)] which favour the endo transition state as R is varied from NO_2 to NMe_2. These interactions involve C_a and C_b of (9)

and C(2) and C(5) of (6). Appropriate blank experiments on separated pairs of isomers (7a) and (8a) show they do not interconvert under the reaction conditions. Stereochemical assignments are based on NOE difference spectroscopy. Thus for (7b; R=H) irradiation ($CDCl_3$) of H_B causes an enhancement of the signals for H_A (8.8%) and H_C (7.4%) whilst irradiation of H_C causes an enhancement of the signals for H_B (9.2%) and H_D (7%). Similar experiments on (8b; R=H) resulted in enhancements of H_C (11%) and H_A (2.7%) when H_B is irradiated and enhancements of H_B (14%) and H_D (1.9%) when H_C is irradiated.

The imines (3a) and (4a) undergo analogous cycloadditions to give spiro-adducts. Thus (3a) reacts with fumaronitrile (xylene, 110°, 20h) to give (10; 75%), and (4a) similarly (xylene, 110 , 48h) gives (11; 80%). Similar cyclo adducts are given by (3b) and (4b). The lactams (5b,c) undergo cycloaddition with a range of dipolarophiles, e.g. (5b) reacts (toluene, 110°, 1.15h) with dimethyl fumarate to give the endo-adduct (12; 82%) together with a trace of the corresponding exo-adduct. The thiolactone (5a) spontaneously dimerises to (13) and cycloadditions are conducted by thermally cracking (13) (retro-1,3-dipolar cycloaddition) in the presence of a dipolarophile.[8] Thus (13) and acenaphthylene react (xylene, 120°, 5dy) to give a 3.4:1 mixture of endo- and exo-adducts (14). Finally, the imine (15) derived from pyridoxal and pyridoxylamine reacts (acetonitrile, 100°, 20h) to give (16; 72%).

(10)





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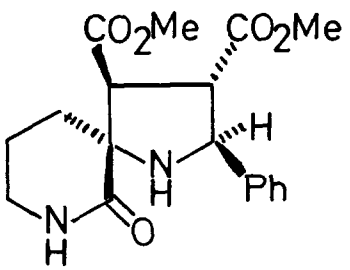

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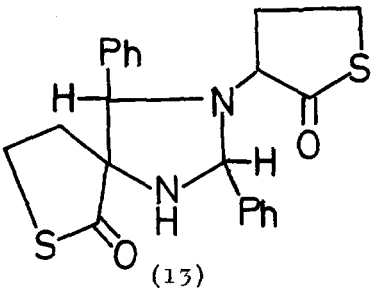

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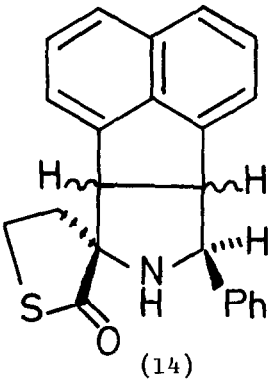

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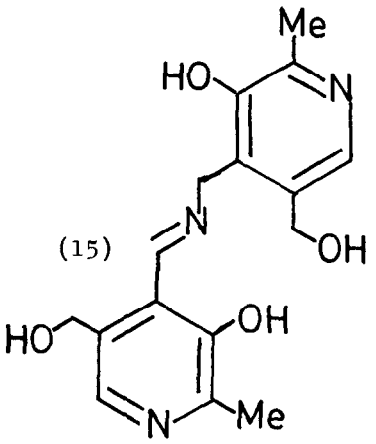

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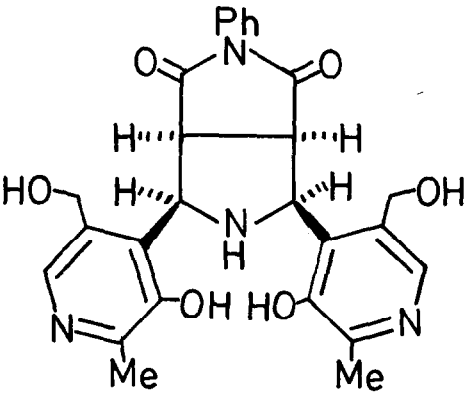

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