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RING TRANSFORMATIONS OF 5-NITROPYRIMIDINE VIA INVERSE DIELS-ALDER REACTIONS[1]

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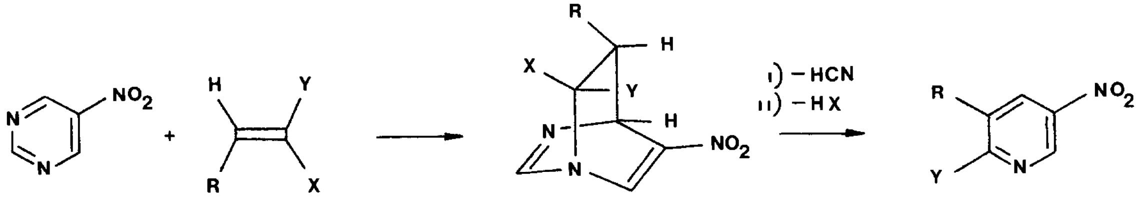
Summary: 5-Nitropyrimidine undergoes inverse Diels-Alder cycloadditions with ketene-N,N-, -O,O-acetals and enamines resulting in pyridine derivatives. The ^{1}H NMR evidence for the 1-N,N-diethylaminopropyne cycloadduct formation is presented

Ring transformations of s-tetrazines proceeding via an inverse electron demand Diels-Alder reaction followed by a retrograde process are well established and have recently been reviewed.[2] Also a number of reports on similar ring transformations of 1,2,4-triazines have appeared in the last decade.[3] However, no example of a Diels-Alder cycloaddition on the pyrimidine ring has been reported so far.

In this communication we wish to show that the pyrimidine ring when activated by a strong electron acceptor as the nitro group is able to undergo [4+2] cycloaddition reactions in which electron-rich ethylenes or acetylenes react as a dienophile and the pyrimidine ring as an electron-deficient diene.

Reaction of 5-nitropyrimidine (1) with ketene-N,N-acetals (2a,b) and ketene-O,O-acetal (2c) results in the formation of pyridine derivatives 3a-c (Scheme 1) No trace of an isomeric product was detected. In case of the reaction of 1 with 3c not the expected 2-methoxy-3-methyl-5-nitropyridine but the corresponding 2-pyridone 3c is formed. Apparently under the condition of the reaction (Table) demethylation has occurred. The structure of the products 3a-c is firmly established by the ^{1}H NMR data, elemental analyses and mass spectrometric data The melting points 3a and 3c are the same as those mentioned in the literature.[4,5]



1 2 a−e 4 3 a−e

a) R=H; X=Y=morpholino
b) R=H; X=Y=piperidino
c) R=CH$_3$; X=Y=OCH$_3$
d) R,Y= (CH$_2$)$_4$; X=morpholino
e) R,Y= (CH$_2$)$_3$; X=pyrrolidino

a) R=H; Y=morpholino
b) R=H, Y=piperidino
c) R=CH$_3$; Y=OH
d) R,Y= (CH$_2$)$_4$
e) R,Y= (CH$_3$)$_3$

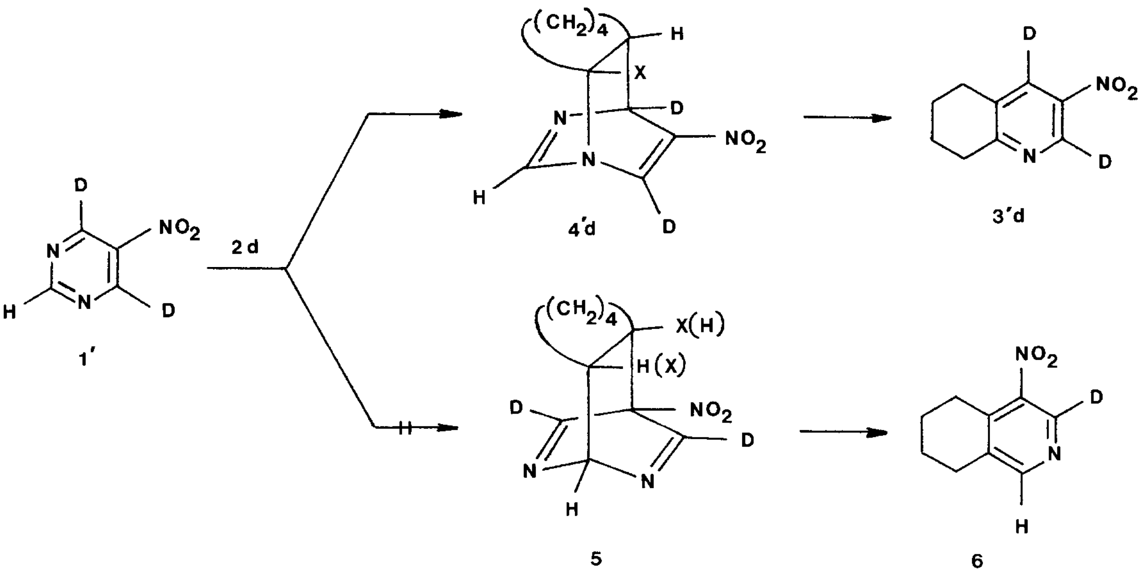
Table. Cycloadducts and Ring Transformation Products obtained by Diels-Alder Cycloaddition on 5-Nitropyrimidine

Starting ethylene or acetylene	Reaction Conditions			Products[9]		mp (°C) (lit.mp)	^{1}H NMR Data in $CDCl_3$ δ (ppm)
	solvent	temp. (°C)	time (h)	registered by ^{1}H NMR	yield[10]		
2a	ethanol	20	2	–[11]	57	143	9.03 (d, H-6, $J_{6,4}$= 2.8 Hz), 8.21 (dd, H-4, $J_{4,3}$ = 9.6 Hz), 6.55 (d, H-3), 3.78 (m, 8H)
			0.25	–	49	(142-143)[4]	
2b	ethanol	20	2	**3b**	52	82-83	8.98 (d, H-6, $J_{6,4}$= 2.8 Hz), 8.14 (dd, H-4, $J_{4,3}$ = 9.5 Hz), 6.52 (d, H-3), 3.70 (m, 4H), 1.67 (m, 6H)
2c	ethanol	78	10	**3c**	17	229-230 (228.5-229.5)[5]	8.47 (d, H-6, $J_{6,4}$ = 2.8 Hz), 8.07 (dq, H-4, $J_{4,methyl}$= 1 Hz), 2.21 (br s,3H)
2d	ethanol	70	2	**3d**	80	71-72	9.13 (d, H-6, $J_{6,4}$ = 2.4 Hz), 8.12 (d, H-4), 2.97 (m, 4H), 1.92 (m, 4H)
2e	ethanol	70	2	**3e**	60	94-95	9.17 (br s,H-6), 8.21 (br s,H-4), 3.10 (m, 4H), 2.30 (m, 2H)
7a	$CDCl_3$	30		**8a**	–	–	7.82 (d, H-2, $J_{2,6}$ = 2 Hz), 6.45 (dq, H-4, $J_{4,6}$ = 1 Hz, $J_{4, methyl}$ = 1 Hz), 4.50 (dd, H-6) 2.01 (d,3H)
	C_6D_6	70	0-3	**8a**	–	–	

From the structure of the products obtained it is evident that the formation of **3a-c** can be described by a [4+2] cycloaddition reaction involving exclusively the 1,4-cycloadduct **4**. This adduct is formed in such a way that the unsubstituted terminus of the alkene becomes attached to the C-4(6) of **1** and the carbon carrying the electronegative groups to N-1(3).

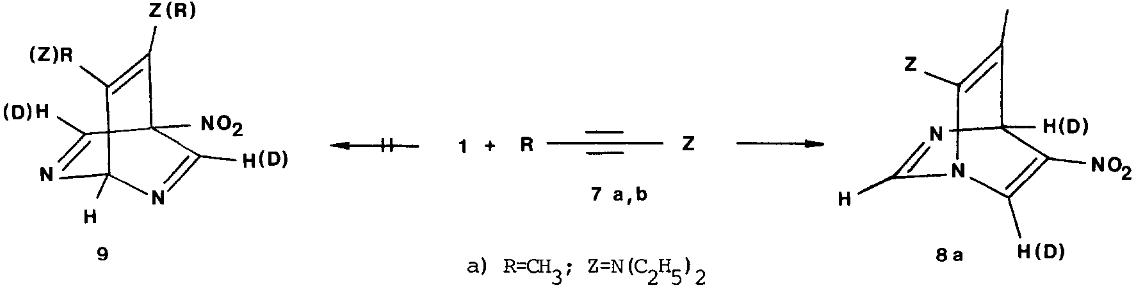
In an extension of this work we also investigated the reaction of **1** with the enamines **2d**,**e**. From these reactions we could isolate the 2,3-annelated cyclohexa- (**3d**) and cyclopenta-5-nitropyridine (**3e**) respectively. To ascertain the structure of these two last-mentioned products we reacted 4,6-dideuterio-5-nitropyrimidine (**1**') with **2d** and found that in the product obtained both deuterio atoms were still present. This result excludes the formation of a 2,5-cycloadduct **5** since it would have led to the tetrahydroisoquinoline derivative **6** having only one deuterium atom (Scheme 2).

From these results one has to conclude that in the reaction of **1** with **2a-e** a Diels-Alder cycloaddition with inverse electron demands takes place involving the 1,4-cycloadduct **4** and not a 2,5-cycloadduct. Thus the reaction is highly regioselective. This 1,4-cycloadduct undergoes a fast elimination of hydrogen cyanide and amine (or alcohol).



In a cycloaddition reaction the rate is known to be determined by separation between the HO orbitals of the alkenes and the LUMO of **1**.[6,7] The observed order of reactivity for the alkenes is decreasing in the series **2a**,**b** > **2d**,**e** > **2c** and is in accordance with qualitative substituent effects on HO orbitals of alkenes[8] Enediamines **2a**,**b** are reactive even at +20°C, but enamines **2d**,**e** react with a perceptible rate only when heated in ethanol. The reaction of **1** with O,O-acetal **2c** requires many hours of heating in ethanol (Table).

N,N-diethylaminopropyne (**7a**) is also reactive with **1** According to ^1H NMR data the cycloadduct **8a** is immediately formed as the sole product when an excess of **7a** is added to a solution of **1** in benzene, chloroform or CCl_4 (Scheme 3, Table). The doublet at 7.82 ppm ($CDCl_3$) was assigned to the H-2 proton of 8a on the base of the product obtained from 4,6-D_2-5-nitropyrimidine (1') and 7a and the procedure of double resonance, being used for the assignment of all other signals (Table). The long-range coupling constant between protons of the methyl group and H-4(^4J=1 Hz) is in agreement with structure 8a and makes opposite orientation of addends or the formation of 9 highly unlikely (Scheme 3).



9

7 a,b

8 a

a) R=CH_3; Z=$N(C_2H_5)_2$

b) R=H; Z=OC_2H_5

The cycloadduct 8a is quite stable in solution, even being heated in benzene for 3 hours, but all attempts to isolate it have failed.

No reaction was observed between 1 and ethoxyethyne (7b).

References and Notes

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9. Satisfactory elemental analyses and appropriate M^+ peaks in mass spectra were obtained for all isolated compounds.
10. By column chromatography on silica gel with chloroform (3b,d,e) or ethanol (3c).
11 Failed to measure because the product 3a is precipitated

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