Tetrahedron Letters,Vol.27,No.22,pp 2509-2512,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

DIELS-ALDER REACTIONS OF THE HETERODIENE SYSTEM IN 2(1H)-PYRAZINONES

M. Tutonda, D. Vanderzande, J. Vekemans, S. Toppet and G. Hoornaert*

Department of Chemistry, K.U.Leuven
Celestijnenlaan 200 F, 3030 Leuven, Belgium

Abstract. Variously substituted 2(1H-pyrazinones react with acetylenic derivatives to give specifically substituted pyridones or pyridines. The observed selectivity can be explained in terms of HO-LU interactions for the reagents and two competitive retro Diels-Alder reactions of the primary bicycloadducts. With cyanotosylate as dienophile no pyrimidone derivative but a new 2(1H)-pyrazinone is obtained.

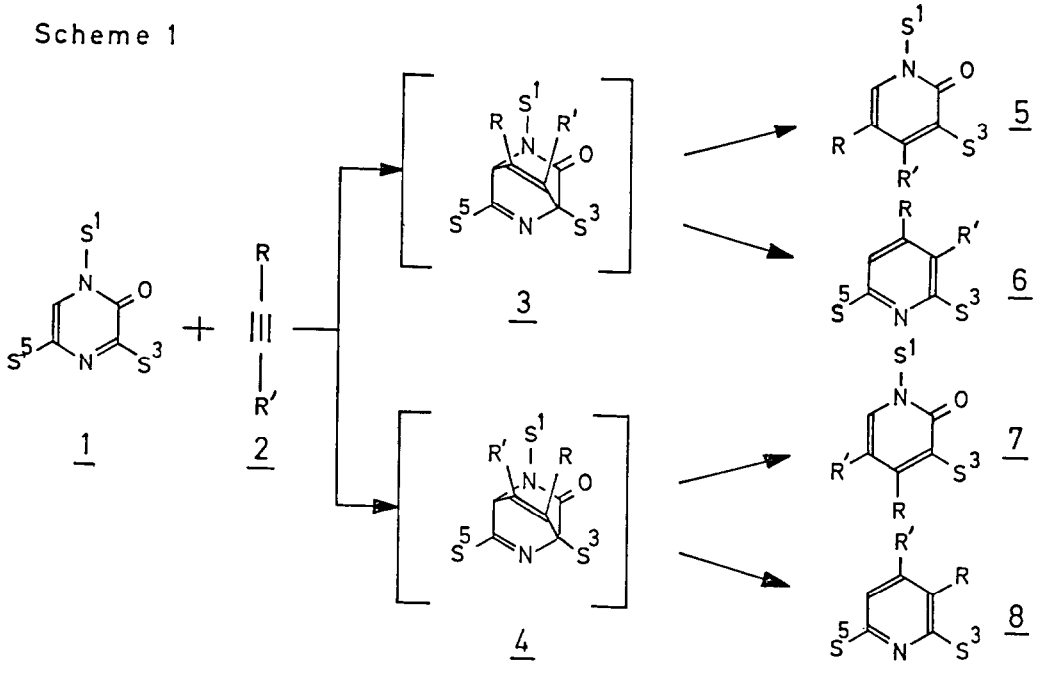
The Diels-Alder reactions of acyclic or cyclic azadienes with dienophiles offer an interesting method for the synthesis of heterocyclic compounds[1]. Especially in connection with 2-azabutadiene systems, we mention reactions of the open chain moiety bearing ether or amine groups at positions 1 or 3[2]; another pathway is offered by the Diels-Alder reactions of 2-substituted-4-methyl-1,3-oxazin-6-ones[3] and of some pyrazine derivatives[4,5].

Our interest in the Diels-Alder reactions of 2(1H)pyrazinones 1 with dienophiles relates to the easy formation of 3,5 dichloro-2(1H)-pyrazinones from α-aminonitriles and oxalyl chloride[6]. Moreover these compounds contain a convertible 3-Cl group and a variable substitution pattern of pyrazinones 1 and dienophiles would allow for a wide range of structural and functional variation in the adducts. In order to evaluate their synthetic use, we studied the regioselectivity of adduct formation and the mode of its decomposition. The scarce literature data[4,5] on the behaviour of suchlike adducts do not allow for a general statement.

We could prove the versatility of the Diels-Alder addition by the reactions of electron poor and electron rich ethylenic and acetylenic compounds. With ethylenic compounds, a mixture of regioisomeric and stereoisomeric adducts was obtained in high yield on heating styrene or methyl acrylate with variously substituted 2(1H)-pyrazinones 1a-c. To get further information on the regioselectivity of these reactions, we focussed our attention on experiments with acetylenic compounds. Whereas the adducts obtained with ethylenic compounds are thermally stable, those expected with acetylenic compounds decompose to give pyridones or pyridines by a retro Diels-Alder reaction (Scheme 1).

As is shown in table 1, the reactivity and regioselectivity in these reactions with variously substituted 2(1H)-pyrazinones 1 and acetylenic dienophiles 2 together with the mode of decomposition of the intermediate addition compounds 3-4, strongly depend on the substituents. In our experiments, pyrazinones 1 (1 mmole) were heated in an excess (1 ml) of neat compounds 2 under argon atmosphere at 140°C or at reflux (2b). The evaporated reaction mixture was chromatographed on silica gel plates to yield a pyridone and a pyridine fraction containing compounds 5, 7 respectively 6, 8. The regioisomeric products could be separated in

Scheme 1



	S^1	S^3	S^5		R	R'
1a	Ph	CN	Cl	2a	H	Ph
1b	Ph	Cl	Cl	2b	H	CO_2Et
1c	Ph	OMe	Cl	2c	CO_2Me	CO_2Me
1d	CH_3	CN	Cl			
1e	Ph	CN	H			

TABLE 1. Diels-Alder reactions of variously substituted 2(1H)-pyrazinones 1a-e and acetylenic derivatives 2a-c

Pyrazinones	Acetylenic Compounds	total yield (%)	Reaction time (h)	Ratio* (3/4)	Ratio 6,8 / 5,7
1a	2a	99	1/2	10:1	2.5 : 1
1b	2a	75	1	4:1	1.6 : 1
1c	2a	36	1	3:1	0.55: 1
1a	2b	95	1/2	1:1	3.7 : 1
1c	2b	69	1/2	5:1	0.5 : 1
1a	2c	75	1/3	-	30 : 1
1e	2c	63	1/3	-	0.05: 1
1b	2c	83	1/3	-	15 : 1
1c	2c	92	1/3	-	5.5 : 1
1d	2c	59	1/3	-	0.8 : 1

* The ratio 3/4 was calculated from the amount of regioisomeric pyridones and pyridines

some reactions. In most cases the intermediate addition compounds were not observed. Spectroscopic evidence for an addition compound was obtained only in the reaction of 1-methyl-3,5-dichloro-2(1H)-pyrazinone with dimethyl butynedioate. Isolation of structure 3, 4 (S^1 = Me, $S^3 = S^5$ = Cl, R = R' = CO_2Me) was possible when the reaction was performed at 60°C for a long time. On heating, it decomposed to yield the corresponding pyridone and pyridine; no pyrazinone of type 1 was observed. The ^1H nmr data allow to assign the regioisomeric structures of both pyridines and pyridones. The adjacent ring protons in pyridines 5 and pyridones 6 show a large coupling constant (∿ 7,5-8 Hz) in contrast to the low value (≤ 2.5 Hz) for pyridones 7 and pyridines 8.

The rate of the reaction for compounds 1a-c with phenylacetylene 2a and ethyl propynoate 2b change in a similar way (1a > 1b > 1c) as observed qualitatively for dienophilic ethylene derivatives. However from table 1 it appears that the order of reactivity is inversed in the case of the reactions with dimethyl butynedioate 2c: the 3-methoxy derivative 1c is more reactive than the 3-cyano derivative 1a. This behaviour seems to be explained by a rate determining addition process involving predominantly the interactions of the LUMO of the azadiene systems of 1a,b with the HOMO of phenylacetylene and of the HOMO of the azadiene systems 1a-c with the LUMO of dimethyl butynedioate. Simple frontier orbital considerations point out that both interactions must probably be taken into account for most other cases. The regioselectivity derived from the calculated ratio 3/4 is generally in agreement with simple calculations. They predict the high regioselectivity for the reactions 1a-2a and 1c-2b which are characterized by predominant LU-HO respectively HO-LU interactions.

We believe that the formation of the pyridines 6, 8 and the pyridones 5, 7 result from two competitive retro Diels-Alder reactions of the intermediates 3, 4. Competition between the elimination of S^5CN or $S^1N{=}C{=}O$ would be governed by the frontier orbitals of the pyridone 5, 7 or the pyridine 6, 8 and those of S^5CN or $S^1N{=}C{=}O$ respectively. The ratios pyridine : pyridone in table 1 can be accounted for by simple HMO calculations (table 2). They indicate that for the pair pyridone $-S^5CN$ the interaction $HO_{pyridone}\text{-}LU_{S^5CN}$ is predominant and for the pair pyridine-$S^1N{=}C{=}O$, the interaction $LU_{pyridine}\text{-}HO_{S^1N=C=O}$ seems to be more favoured.

TABLE 2. Energy-gap values (β) of the interactions Pyridone-S^5CN and pyridine-$S^1N{=}C{=}O$ from simple HMO calculations[8].

Pyrazinones	Acetylenic derivatives	Interactions Pyridines-$S^1N{=}C{=}O$		Interactions Pyridones-S^5CN	
		HO/LU	LU/HO	HO/LU	LU/HO
1a	2c	1.75	1.01	1.48	1.84
1b	2c	1.72	1.05	1.44	1.95
1c	2c	1.63	1.06	1.39	1.96
1d	2c	1.89	1.41	1.49	1.96

In this way electron poor substituents of both starting pyrazinones and acetylenic derivatives could favour the interaction of the LU of the pyridine with the HO of $S^1N{=}C{=}O$. These substituents would also disfavour the interaction of the HO of the pyridone with the LU of S^5CN.

This accounts for the observed increase (Table 1) of the ratio pyridine : pyridone when 2c is used instead of 2b,a as dienophiles; equally the sequency 1a > 1b > 1c can be interpreted. The higher energy for the HO of phenyl isocyanate compared with the HO of methyl isocyanate[8] can explain why more pyridine is formed when 1a instead of 1d reacts with 2c. The exclusive formation (ratio < 0.05) of pyridone in reaction of 1e with 2c in comparison with the ratio (>30) for 1a could be accounted for by the higher energy of the LU of ClCN in comparison with that of HCN . If the two modes of decomposition are disfavoured, the adduct would be isolable as has been the case in the reaction of 1,3-dimethyl-5-methoxy 2(1H)pyrazinone with dimethyl butynedioate.[5]

In a qualitative way we also studied the reaction of the heterodienophile cyanotosylate with compound 1c. Only one product was obtained and its nmr data allowed us to assign it the 3-methoxy-1 phenyl-5-tosyl-2(1H)-pyrazinone structure. The ^{13}C nmr of the isolated product agrees well with the literature data of 2(1H)-pyrazinones[6]. The doublet ($^{1}J_{C-H}$ = 190Hz) at 126.2 ppm of C-6 excludes the alternative 5-methoxy-3-phenyl-6-tosyl-4(3H)-pyrimidone structure in which the C-2 should absorb at lower field as in the corresponding 3-methyl-4 (3H)-pyrimidone[9] where it appears at 151.6 ppm.

In conclusion, we can state that reactions between pyrazinones and acetylenic derivatives is a general one with the substitution pattern governing the regioselectivity of the addition step and the mode of decomposition of the addition product. Pyridines seem to be expected with the electron poor acetylene derivatives, conjugated or electron rich substituents in position 1 and electron poor substituents in position 3 of the pyrazinones. Further experimental results about the cycloaddition of various 5- or 6-substituted 2(1H)-pyrazinones and more advanced calculations are needed to improve predictions about the selective formation of specifically substituted pyridines, pyridones or other heterocycles.

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(Received in UK 14 April 1986)