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GENERATION OF SPECIFICALLY SUBSTITUTED PYRIDINES AND PYRIDONES FROM 2(1H) PYRAZINONES AND ACETYLENES : A FMO DESCRIPTION

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Summary : The title compounds were obtained from reaction of variously substituted 2(1H)pyrazinones with acetylenic derivatives. Experimental evidence points out to a two step mechanism : a Diels Alder cycloaddition followed by immediate decomposition of the adducts into the title products via two competitive retro Diels Alder reactions. The product distribution, which is shown to be highly dependent on the substitution pattern of the reactants, is accounted for by a simple FMO model.

INTRODUCTION.

In a previous paper[1] we reported briefly the Diels-Alder reaction of some substituted 2(1H)-pyrazinones with acetylenic derivatives. The initial adducts were not isolated, but decomposed immediately into specifically substituted 2(1H)-pyridones and/or pyridines (Scheme I). This means that pyrazinones, like 1,2,4-triazines, pyrazines or 1,3-oxazin-6-ones,[2,3] could offer an interesting route towards specifically substituted heterocyclic compounds.

We found indeed that various 3,5-dichloro-2(1H)-pyrazinones 1a-c are easily accessible from α-aminonitriles and oxalyl chloride.[4] Moreover the convertible 3-chlorine substituent can lead to a wide variation of the R^3-substituent. In order to evaluate the synthetic use of pyrazinones we studied in more detail their reactions with some acetylenic derivatives.

RESULTS AND DISCUSSION

In our experiments, 2(1H)-pyrazinones 1 (2.5 mmol) were heated in an excess (2.5 ml) of neat compounds 2-4 under an argon atmosphere at 140°C or at reflux (3). Under these conditions, the intermediate addition compounds of type 5-6 were not observed.

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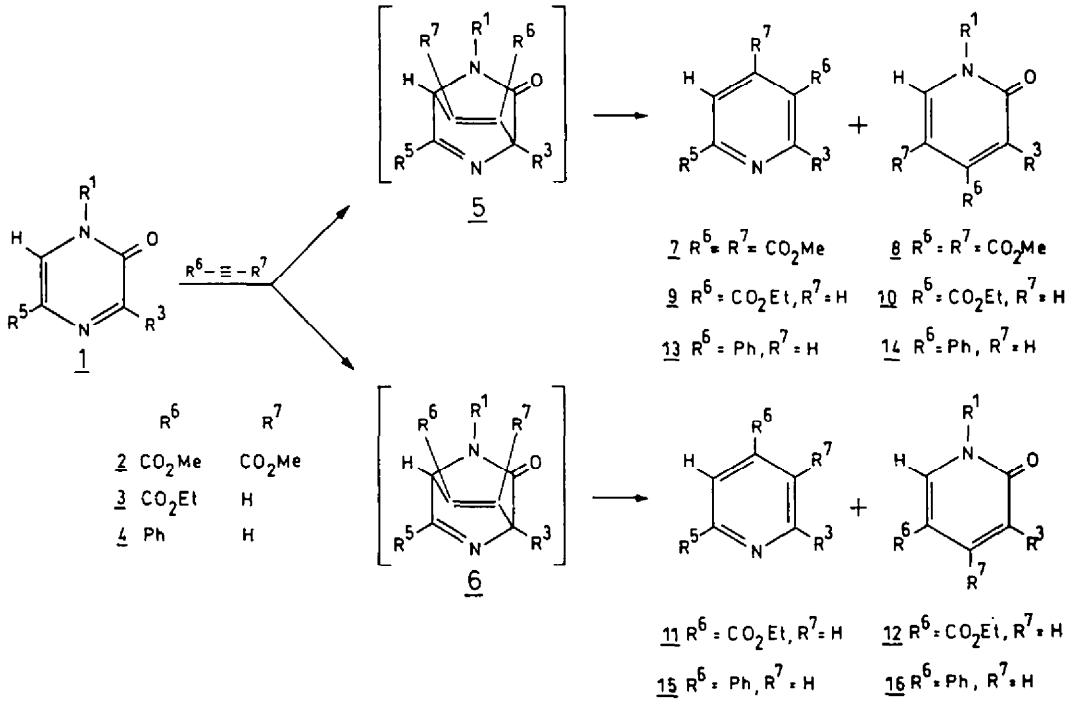

	R⁶	R⁷
2	CO_2Me	CO_2Me
3	CO_2Et	H
4	Ph	H

Pyrazinones 1 + (Adducts 5–6)

	R^1	R^3	R^5
a	Me	Cl	Cl
b	Ph	Cl	Cl
c	pmPh	Cl	Cl
d	Me	OMe	Cl
e	Ph	OMe	Cl
f	pmPh	OMe	Cl
g	Me	CN	Cl
h	Ph	CN	Cl

	R^1	R^3	R^5
i	Ph	OMe	H
j	Ph	Cl	H
k	Oh	CN	H
l	Ph	OMe	Tos
m	Ph	Cl	Tos
n	Me	OMe	NEt_2
o	Ph	OMe	NEt_2

	R^3	R^5
a	Cl	Cl
b	OMe	Cl
c	CN	Cl
d	OMe	H
e	Cl	H
f	CN	H
g	OMe	Tos
h	Cl	Tos
i	OMe	NEt_2

	R^1	R^3
a	Me	Cl
b	Ph	Cl
c	pmPh	Cl
d	Me	OMe
e	Ph	OMe
f	pmPh	OMe
g	Me	CN
h	Ph	CN

(PmPh: p-$MeOC_6H_4$)

Scheme I

Chromatography on silica gel layers yielded only a pyridine and/or pyridone fraction. The identification of these products was readily accomplished by spectroscopic measurements (NMR, IR and MS) and comparison with the spectroscopic data of similar pyridones and pyridines in the literature.[5] The strong lactam carbonyl absorption between 1640-1690 cm^{-1} in the IR-spectra has been used to distinguish between pyridines and pyridones. With dimethyl butynedioate 2 compounds 7, 8 were obtained, whereas mixtures of isomeric pyridines (9, 11 or 13, 15) and pyridones (10, 12 or 14, 16) were obtained with ethyl propynoate 3 or phenyl acetylene 4. These regioisomeric structures and their relative ratio were determined by NMR analysis and in some cases they were isolated. Simple considerations of coupling constant values in the ^{1}H-NMR spectra allowed to distinguish them. Indeed the adjacent ring protons (H and R^7) in the pyridines 9, 13 and in the pyridones 10, 14 show a large coupling constant (≈7.5-8 Hz) in contrast to the low values (≤2.5 Hz) for these protons in the pyridines 11, 15 and the pyridones 12, 16. For example pyridine 9b, obtained from the reaction of pyrazinone 1e with ethyl propynoate 3, exhibits two doublets at 8.15 and 6.95 ppm (J = 7.8 Hz) assignable to the resonances of the "ortho"-protons[6] whereas the two "meta"-protons in the pyridine 11b appear at 7.9 and 6.85 ppm (J = 1 Hz).

We believe that the formation of the pyridines and the pyridones result from two competitive retro Diels-Alder reactions of the intermediate cycloaddition compounds 5,6 which eliminate R^1-N=C=O or R^5-CN, respectively. Experimental results outlined in table I indicate that the regioselectivity and the ratio pyridine/pyridone are strongly dependent on the substituents of the reaction partners. As shown by the amounts of the "ortho" and "meta" products in table I, high to moderate regioselectivity was observed for reactions of phenyl acetylene 4 with pyrazinones 1g,h and 1a,b (entries 25-26 and 10-11; entries 27-28 and 12-13) and for reactions of the electron poor ethyl propynoate 3 with pyrazinones 1d,e and 1j (entries 23-24, 8-9 and 42-43). In these cases the major products were compounds of type 13 ,14 and 9, 10 respectively. These results suggest the predominance of primary cycloadducts of type 5 in the addition step.

Comparison of the ratio pyridine/pyridone obtained from variously substituted pyrazinones indicates that substitution of R^1=Me in the pyrazinones by R^1=Ph or R^1=p-MeOPh leads to an appreciable increase of the pyridine products (entries 2, 17 and 31; 6 and 21). Examination of the entries 2, 33 and 36 reveals a clear preference for the formation of the pyridine derivative when R^5 is chlorine and an exclusive formation of the pyridone derivative when R^5 is Tos or hydrogen. Furthermore, electron withdrawing substituents in position 3 (R^3) of the pyrazinones and/or acetylenic derivatives seem to favour the formation of pyridines. This is shown by the pyridine/pyridone ratios represented in the following sequencies (entries 1, 2, 3 or 4, 6, 8 and entries 1, 4, 10).

The intermediacy of the adducts 5, 6 was deduced from the formation of the thermally stable adducts in the reaction of the pyrazinones 1b, 1e and 1h with ethylenic compounds.[7]

Table I: Product yields and distribution pyridine/pyridone in the reaction of pyrazinones 1 with acetylenes 2, 3 and 4.

Entry	Pyrazinone	Acetylene	Total Yield[a] (%)	Pyridine	Pyridone
1	1h	2	75	97	3
2	1b	2	83	94	6
3	1e	2	92	84	16
4	1h	3	(o)49	78	22
5			(m)46	78	22
6	1b	3	(o)52	64	36
7			(m)29	64	36
8	1e	3	(o)57	44	56
9			(m)12	44	56
10	1h	4	(o)91	77	23
11			(m)8	- [b]	100
12	1b	4	(o)60	75	25
13			(m)15	-	100
14	1e	4	(o)27	51	49
15			(m)9	-	100
16	1g	2	59	44	56
17	1a	2	66	15	85
18	1d	2	82	2	98
19	1g	3	(o)43	30	70
20			(m)42	30	70
21	1a	3	(o)51	-	100
22			(m)26	-	100
23	1d	3	(o)53	-	100
24			(m)9	-	100
25	1g	4	(o)82	2	98
26			(m)9	-	100
27	1a	4	(o)52	-	100
28			(m)17	-	100
29	1d	4	(o)18	-	100
30			(m)7	-	100
31	1c	2	79	96	4
32	1f	2	90	91	9
33	1m	2	68[c]	-	100
34	1l	2	85[c]	-	100
35	1k	2	63	-	100
36	1j	2	74	-	100
37	1i	2	80	-	100
38	1k	3	(o)40	-	100
39			(m)42	-	100
40	1j	3	(o)47	-	100
41			(m)24	-	100
42	1i	3	(o)41	-	100
43			(m)17	-	100

(a) yields were not optimized and the reaction time was 20 minutes for compound 2, 30 minutes for acetylene 3 and 1 hour for compound 4, unless otherwise stated. (o)=R^6 ortho with respect to R^3; (m)=R^6 meta with respect to R^3

(b) not observed

(c) reaction time was 1 hour

Similar adducts were obtained with acetylenic compounds when the reactions were performed at relative low temperature for a long time. Indeed reactions of the pyrazinones 1d and 1e with 2 at 60°C in CH_3CN afforded the corresponding bicyclic adducts as unique products in good yield (see experimental part). The formation of these products was indicated by ^{1}H-NMR measurements on reaction mixtures showing the disappearance of the H-6 signal of the starting pyrazinone and the appearance of the new bridge-head hydrogen signal at upfield shift. Since these compounds bear a quite reactive imidoyl chloride function, they readily underwent hydrolysis leading to the corresponding diones during purification. Nevertheless, isolation of small amounts of each adduct was possible using fast column chromatography. On heating them in a dilute solution in xylene at 140°C, they decomposed to yield the corresponding pyridones and/or pyridines in the same ratio pyridine/pyridone as in the reactions starting from a mixture of the pyrazinone and the acetylenic derivative 2. Furthermore this ratio remained the same during the reaction and no pyrazinone could be observed. This supports the hypothesis that the decomposition of the cycloadducts into pyridones and/or pyridines occurs more readily than the retro Diels-Alder reaction which should regenerate the starting pyrazinones and acetylenic compounds. It seems also that the ratio pyridine/pyridone is a kinetic determined one and directly proportional to the ratio $k_{pyridine}/k_{pyridone}$.

The reactivity of the imidoyl chloride in these butynedioate adducts 5d,e (R^6=R^7=CO_2Me) was further demonstrated by trapping with diethylamine. This yielded the 3-diethylamino derivatives 5n,o (R^6=R^7=CO_2Me) which were isolated by colum chromatography and characterized by spectroscopic measurements. These compounds can be considered as the intermediate adducts from the reaction of compound 2 with the inaccessible 5-diethylamino-2(1H)-pyrazinones 1n,o. Heating compound 5o (R^6=R^7=CO_2Me) in boiling xylene gave exclusively the pyridine derivative 7i, whose spectral data were nearly identical with those of dimethyl 2-methoxy-6-dimethylamino-pyridine-3,4-dicarboxylate.[8] Surprisingly, the same reaction with compound 5n (R^6=R^7=CO_2Me) failed to give retro Diels-Alder products.

A brief study on the effect of changing solvent polarity indicated that yields of pyridines and/or pyridones and the ratio pyridine/pyridone did not change appreciably when either xylene or DMF was used. Even the rate of adduct formation with compound 2 was not changed when toluene was used instead of CH_3CN . (More details are presented in the tables of the experimental section.) This allowed us to exclude an ionic mechanism and to propose concerted pathways in the formation and decomposition of the primary cycloadducts.

As it is well established that the kinetic determined outcome of the Diels-Alder reaction can be interpreted succesfully using the frontier molecular orbital (FMO) method[9], we tried to rationalize the yields and the rate (of the addition step) as a consequence of interactions between the frontier orbitals of the pyrazinone 1 and those of the acetylenic derivatives 2-4. As shown in figure 1, the dominant FMO-interaction in the addition step will be between the HOMO of the pyrazinone and the LUMO of the acetylene 2 or between the

LUMO of the pyrazinone and the HOMO of the acetylene 4. This accounts for the higher reactivity -as deduced from yield data- of the pyrazinone 1d compared to the pyrazinone 1g in the reaction with 2 (Table I, entries 16 and 18) and for the opposite behaviour in the reaction with 4 (Table I, entries 25,26 and 29,30). To some extent it also explains the observed regioselectivity.[1, 10]

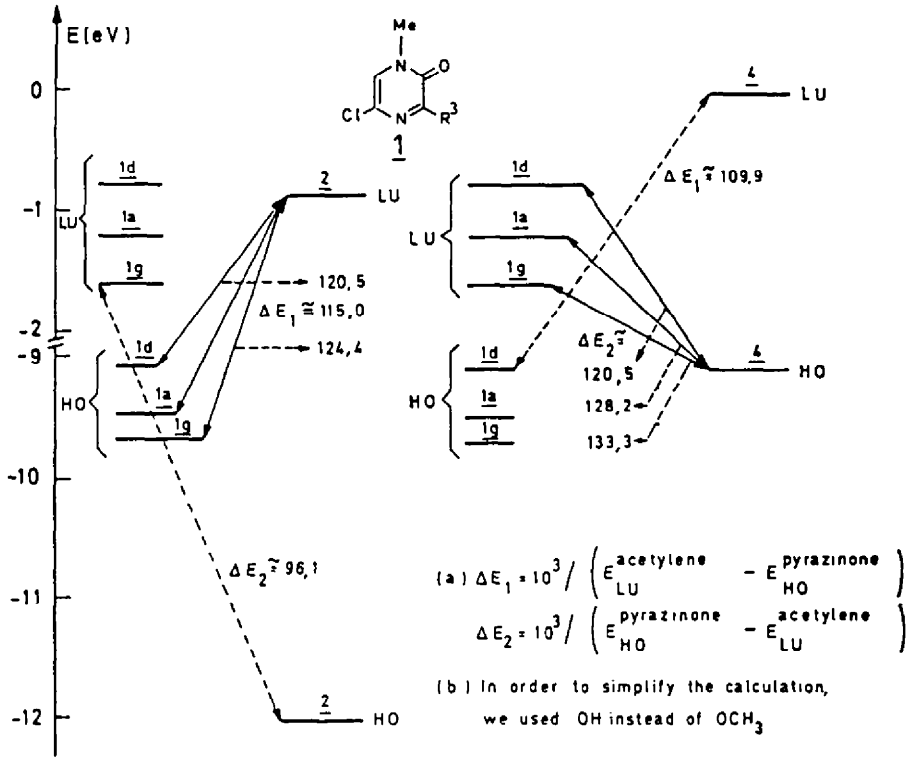

Fig. 1. FMO diagram [(a)] for 2(1H)pyrazinones 1a (R^3 = Cl), 1d (R^3 = OCH3) [(b)], 1g (R^3 = CN) and dimethylbutynoate 2 [(b)] or phenyl acetylene 4.

Using the same approach we also tried to rationalize the decomposition process of the adducts 5,6 as a consequence of interactions between the frontier orbitals of the pyridine or the pyridone and those of R^1-N=C=O or R^5-CN, respectively. The latter approach is grounded on the principle of microscopic reversibility[11], which allows insight in the features of the retro-reaction via a description of the forward reaction. K.N. Houk[12] has pointed out that "FMO-theory can be quantitative when factors other than frontier interactions are constant, or are linearly related to frontier orbital energies". In these cases excellent linear correlations between the log k of the reaction and $1/(E_{LUMO}-E_{HOMO})$

Table II: Values of log $k_{pyridine}/k_{pyridone}$ and $\Delta E^{(a)}$ of the system I (pyridine + R^1-N=C=O) and the system II (pyridone + R^5-CN).

Entry				log k'(b)	System I pyridine+R^1-N=C=O		System II pyridone + R^5-CN	
					ΔE_1	ΔE_2	ΔE_1	ΔE_2
	A: R^1=Ph, R^5=Cl,							
	R^3	R^6	R^7					
1	CN	CO_2Me	CO_2Me	1.51	94.4	138.4	89.6	89.4
2	Cl	"	"	1.19	95.9	134.8	90.9	87.0
3	OMe	"	"	0.75	101.6	129.7	94.5	84.3
4	CN	CO_2Et	H	0.58	96.5	133.7	92.5	87.6
5	CN	H	CO_2Et	0.58	97.0	132.6	91.4	86.4
6	Cl	CO_2Et	H	0.25	98.0	129.5	93.7	85.2
7	Cl	H	CO_2Et	0.25	98.7	127.2	92.9	84.2
8	OMe	CO_2Et	H	-0.31	104.0	123.7	97.4	82.5
9	OMe	H	CO_2Et	-0.31	104.9	122.9	97.3	81.7
	B: R^1=Ph, R^5=Cl, R^6=Ph, R^7=H							
	R^3							
10	CN			0.52	101.2	126.5	95.3	84.2
12	Cl			0.50	102.8	122.4	96.7	82.0
14	OMe			-0.25	109.6	117.4	100.8	79.8
	C: R^1=CH_3, R^3=CN, R^5=Cl,							
	R^6	R^7						
16	CO_2Me	CO_2Me		-0.10	82.7	112.2	89.6	89.4
19	CO_2Et	H		-0.37	84.3	109.1	92.5	87.6
20	H	CO_2Et		-0.37	84.7	108.3	91.4	86.4
25	Ph	H		-1.69	87.9	104.2	95.3	84.2
	D: R^3=R^5=Cl, R^6=R^7=COOMe							
	R^1							
31	pmPh			1.38	96.3	141.4	90.9	87.0
2	Ph			1.19	95.9	134.8	90.9	87.0
17	CH_3			-0.75	83.9	109.8	90.9	87.0
	E: R^3=OCH_3, R^5=Cl, R^6=R^7=COOMe							
	R^1							
32	pmPh			1.00	102.0	135.8	94.5	84.3
3	Ph			0.75	101.6	129.7	94.5	84.3
18	Me			-1.69	88.2	106.4	94.5	84.3

(a) $\Delta E_1 = 10^3/(E^{dienophile}_{LU} - E^{diene}_{HO})$; $\Delta E_2 = 10^3/(E^{diene}_{LU} - E^{dienophile}_{HO})$

Calculations on the parent pyridone show that the energy level of the HOMO and the LUMO do not change appreciably when R^1=Me is substituted by Ph or p-HO-C_6H_4. To simplify the calculations we used R^1=Me instead of Ph or pmPh in the calculations for the pyridone derivatives 8, 10, 12, 14 and 16. Furthermore, we tried to simplify the calculations by utilizing OH instead of OR.

(b) log k'=log $k_{pyridine}/k_{pyridone}$ (deduced from product ratios)

values have been observed.[13] Since all adducts 5,6 are structural very similar, the conditions mentioned above may be fulfilled for the decomposition reaction. As we do not have access to values for $k_{pyridine}$ and $k_{pyridone}$, we assume the ratio pyridine/pyridone equal to the ratio $k_{pyridine}/k_{pyridone}$. This assumption seems reasonable taking account of our experimental results. Values for the energies of the frontier molecular orbitals of the systems involved in the two competitive (retro)Diels-Alder reactions were obtained by performing MNDO calculations.[14] Inspection of the ΔE-values in table II reveals that the reaction of the pyridines with R^1-N=C=O (System I) and the pyridones with R^5-CN (System II) shows the characteristics of a Diels-Alder reaction with inverse and normal electron demand, respectively. In system I, the interaction $LUMO_{pyridine}$-$HOMO_{isocyanate}$ will have the greater contribution to the interaction energy, whereas in system II the interaction $HOMO_{pyridone}$-$LUMO_{cyanate}$ prevails. So, the outcome of the reaction in scheme I will depend to a large extent on the influence of the substituents on the energy levels of the LUMO of the pyridine system and the HOMO of the pyridone system. To substantiate this hypothesis we applied a "stepwise" multiple regression analysis to the log $k_{pyridine}/k_{pyridone}$ and ΔE-values of table II.

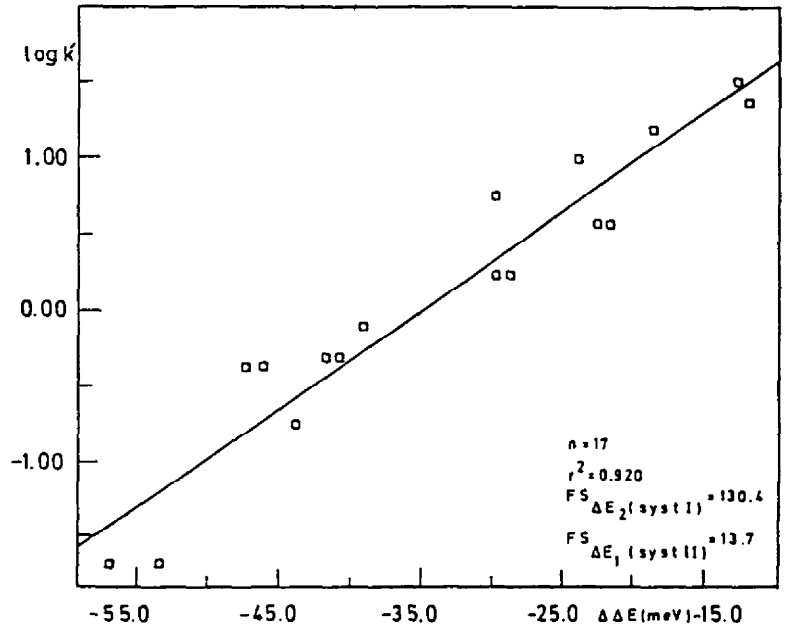

Fig.2 : Plot of log k' (log k pyridine/k pyridone) versus ΔΔE (eq.1)

As shown by figure 2 a good correlation is found between the experimental product distribution (log $k_{pyridine}/k_{pyridone}$) and ΔE_2-values of system I and ΔE_1-values of system II ($r^2_{(n=17)}$=0.920; r is the correlation coefficient and n is the number of data). To obtain this excellent correlation we had to omit the entries 10, 12 and 14 of Table I-II.

In this correlation - numerically represented by equation 1 - the two terms reach significance at the 99% level. For all other combinations of FMO interactions studied in our regression analysis, the correlations found were less satisfactory ($r^2 < 0.90$) and/or did not reach significance even at the 90% level.

$$\log k_{pyridine}/k_{pyridone} = -2.343 + 0.066\ \Delta\Delta E$$

$$\text{with } \Delta\Delta E = \Delta E_{2(\text{system I})} - 1.691\ \Delta E_{1(\text{system II})} \qquad \text{(eq. 1)}$$

It is remarkable how this simple model and both interactions ($\Delta\Delta E$ in eq.1) allow to explain the general features of the product distribution observed for pyrazinones 1 with R^5=Cl. For example, introducing electron withdrawing (Z-)substituents in the pyrazinone and acetylenic derivatives leads to a higher amount of pyridine; this is probably due to an increase of the $LUMO_{pyridine}$-$HOMO_{isocyanate}$ term and a decrease of the $HOMO_{pyridone}$-$LUMO_{cyanate}$ term, since the Z-substituent lowers the LUMO of the pyridine and the HOMO of the pyridone(Table II, A, B and C). Also the increase of the amount of pyridone formed on substitution of the R^1-phenyl or R^1-p-methoxyphenyl group in the pyrazinones by a methyl group, can be accounted for by the corresponding FMO-interactions (Table II,D and E). The lower energy level of the HOMO of methylisocyanate compared to the HOMO of phenyl- or p-methoxyphenylisocyanate gives rise to a decrease of the $LUMO_{pyridine}$-$HOMO_{isocyanate}$ term, while the $HOMO_{pyridone}$-$LUMO_{cyanate}$ term will be virtually unaffected.

Table III: Calculated values of $\log k_{pyridine}/k_{pyridone}$ and $\delta E^{(a)}$ of the system I (pyridine + R^1-N=C=O) and the system II (pyridone + R^5-CN)for model compounds with R^1=Ph; R^3=R^6=R^7=H and varying R^5substituents.

R^5	log k'(b)	System I pyridine+R^1-N=C=O ΔE_1	ΔE_2	System II pyridone+R^5-CN ΔE_1	ΔE_2
NH_2	-1.01	113.5	110.2	96.3	77.4
H	-0.76	106.2	110.7	93.6	75.4
Cl	-0.76	103.6	116.7	98.5	79.2
CN	-1.70	101.6	121.7	114.1	76.6
CO_2H	-2.35	101.6	117.6	118.7	78.5
NO_2	-3.67	95.7	126.3	142.0	68.5

(a) $\Delta E_1=10^3/(E^{dienophile}_{LUMO}-E^{diene}_{HOMO})$; $\Delta E_2=10^3/(E^{diene}_{LUMO}-E^{dienophile}_{HOMO})$; $\Delta E_2=10^3/(E^{diene}_{LUMO}-E^{dienophile}_{HOMO})$. CN, CO_2H, NO_2 model the substituent effect of tosyl since the MNDO method[14] has no appropriate parameters for sulfur if d-orbitals are involved.

(b) $\log k'=\log k_{pyridine}/k_{pyridone}$; calculated values using equation 1

In order to discuss the variation in the product distribution as a consequence of the variation of the substituent R^5 (Table I, entries 1-9 and 33-43), we performed MNDO calculations on a model system (R^1 = Ph; R^3=R^6=R^7=H) as described in table III. We have tried to use equation 1 to derive tendencies for log $k_{pyridine}/k_{pyridone}$ out of the ΔE-values in table III. The calculated log $k_{pyridine}/k_{pyridone}$ values in Table III indicate that substitution of the R^5 substituent equal to Cl by an electron withdrawing group, should favour the formation of the pyridones . Indeed, inspection of the entries 2,3 and 33,34 (Table I) reveals a clear preference for the formation of pyridine derivatives with R^5 equal to Cl, while R^5 equal to tosyl yields exclusively the pyridone derivatives. According to our model, changing R^5 equal to Cl by H or NH_2 should give a rather comparable result as with R^5 = Cl. However, for R^5 = H, pyridone is formed exclusively (compare entries 1-9 with 35-43, table I); for R=NEt_2, only the pyridine is formed as shown by the thermolysis of adduct 5o (R^6=R^7=COOMe). It seems therefore that our model cannot be generalized. Other factors than FMO-interactions may also be involved as suggested by the data from the reaction of the pyrazinones 1b,e,h with phenyl acetylene which do not fit the correlation.

CONCLUSION.

In any event, we can state that the reaction between the pyrazinones 1 and acetylenic derivatives is a general one with the regioselectivity and the mode of decomposition being determined by the substitution pattern of the reaction partners and the intermediate adducts. From a synthetic standpoint it is important to note that pyridines can be expected when using electron poor acetylenes and when starting from pyrazinones bearing a) aryl substituents in position 1, b) electron donating substituents in position 5, c) electron withdrawing substituents in position 3. With contrasting substitution patterns pyridones can be obtained, even exclusively. High regioselectivity is to be expected for pyrazinones with electron donating (attracting) substituents in position 3, reacting with electron poor (rich) acetylenes.

It appears also that the adduct can be isolated if the two modes of decomposition are disfavoured. This has been observed for the thermolysis of 5n. It also accounts for the observation of Sammes et al., who studied the reaction between 1,3-dimethyl-5-ethoxy-2(1H)-pyrazinone and compound 2. They isolated an adduct which was shown to be thermally stable even up to 200°C.[15] A simple FMO model accounts for most of these observations. However to achieve a better understanding, the model needs to be elaborated in more detail, especially by studying the effect of some substituents in position 5 and 6 of the pyrazinone.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 257 spectrophotometer. Mass spectra were taken on a A.E.I.-MS12 (ionization energy 70 eV) apparatus. For the NMR spectra (δ, ppm) a Varian EM-390 and a Bruker WM-250 spectrometer were used. All ^{1}H-NMR spectra were recorded at 90 MHz unless otherwise stated. Analytical and preparative thin layer chromatography was performed using Merck silica gel 60 PF-224 and column chromatography was done using 70-230 mesh silica gel 60 (E.M. Merck) as the stationary phase.

I. SYNTHESIS OF 2(1H)-PYRAZINONES

1. The 3,5-dichloro-2(1H)-pyrazinones 1a-c.

The pyrazinones 1a,b [4] and also 1c were synthesized by cyclization of the corresponding α-aminonitriles in ortho dichlorobenzene with oxalyl chloride at 100°C. The analytical data of compound 1c, which was purified by column chromatography using 5% $CH_3CN/CHCl_3$ as eluent are summarized below

3,5-dichloro-1-paramethoxyphenyl-2(1H)-pyrazinone 1c
Yield : 82%, m.p. (EtOH) : 149°C; IR (KBr) cm^{-1} : 1670 (CO); 1660 (C=N); ^{1}H-NMR ($CDCl_3$) : 7.3 (s, 1H, H_6); 7.15 (m, 4H, ArH); 3.8 (s,3 H, OCH_3); m/z : 270 (M^+, 100); 242 (12.6); 207 (14.2); 134 (6.7). Anal.calcd for $C_{11}H_8Cl_2N_2O_2$: C(48.73); H (2.97); N(10.33). Found : C (48.50); H(2.92); N(10.23).

2. The 5-chloro-3-methoxy-2(1H)-pyrazinones 1d-f

3,5-dichloro-2(1H)-pyrazinone (50 mmol) dissolved in 50 ml of absolute methanol was heated with 50 mmol of NaH in 50 ml of methanol. The reaction mixture was stirred at room temperature during 10 minutes, neutralized with 1N solution of HCl in methanol and evaporated in vacuo. The residue was dissolved in dichloromethane and filtered. The filtrate was evaporated yielding the 3-methoxy derivative in quantitative yield.

5-chloro-3-methoxy-1-methyl-2(1H)-pyrazinone 1d
m.p. (EtOH): 139°C; IR (KBr) cm^{-1} : 1665 (CO); 1605 (C=N); ^{1}H-NMR($CDCl_3$) : 6.93 (s, 1H, H_6); 4.04 (s, 3H, OCH_3); 3.57 (s, 3H, NCH_3); m/z : 174 (M^+, 100); 159 (13); 131 (45). Anal.calcd for $C_6H_7ClN_2O_2$: C (41.28); H (4.04); N (16.04). Found : C(41.37), H (4.14); N (15.92)

5-chloro-3-methoxy-1-phenyl-2(1H)-pyrazinone 1e
m.p. (EtOH) : 117°C; IR (KBr) cm^{-1} : 1670 (CO); 1605 (C=N); ^{1}H-NMR ($CDCl_3$) : 7.15 (m, 5H, Ar-H); 6.95 (s, 1H, H_6); 4.05 (s, 3H, OCH_3); m/z : 236 (M^+, 100); 208 (21); 193 (41.5); 104 (21.3) 77 (82). Anal.calcd for $C_{11}H_9ClN_2O_2$: C (55.83); H (3.83); N(11.84). Found : C (55.62); H (3.90); N (11.61).

5-chloro-3-methoxy-1-paramethoxyphenyl-2(1H)-pyrazinone 1f
m.p. (EtOH) : 138°C; IR (KBr) cm^{-1} : 1670 (CO); 1605 (C=N); ^{1}H-NMR ($CDCl_3$) : 7.15 (m, 4H, ArH); 6.95 (s, 1H, H_6); 4.05 (s, 3H, OCH_3); 3.8 (s, 3H, Ar-OCH_3); m/z: 266 (M^+, 100); 238 (9); 223 (25); 134 (6.3). Anal.calcd for $C_{12}H_{11}ClN_2O_3$: C (54.05); H (4.16); N (10.50). Found : C(54.23); H(4.01); N(10.28).

3. The 5-chloro-3-cyano-2(1H)-pyrazinones 1g-h

A mixture of 3,5-dichloro-2(1H)-pyrazinone (0,1 mol), cuprous cyanide (0,18 mol) and N-methylpyrrolidone (100 ml) was heated for 6 hours at 150°C while being stirred. The black reaction mixture was evaporated in vacuo. The residue was triturated with hot $CHCl_3$ and filtered over charcoal. The filtrate was evaporated. Chromatographic separation of the residue through silica gel column eluting with 5% $CH_3CN/CHCl_3$ gave the title compounds.

5-chloro-3-cyano-1-methyl-2(1H)-pyrazinone 1g
Yield : 68%; m.p. (CH_2Cl_2/hexane) : 110°C; IR (KBr) cm^{-1} : 1670 (CO); 1605 (C=N); 2230 (C≡N); ^{1}H-NMR (DMSO-d_6): 8.6 (s, 1H, H_6); 3.5 (s, 3H, NCH_3); m/z 169 (M^+, 100); 154 (28); 126 (64). Anal.calcd. for $C_6H_4ClN_3O$: C (42.50); H (2.38); N(24.78). Found : C (42.63);

H(2.25); N(24.67).

5-chloro-3-cyano-1-phenyl-2(1H)-pyrazinone 1h

Yield : 72%; m.p. (CH_2Cl_2/hexane) : 160°C; IR (KBr) cm^{-1} : 1675 (CO); 1610 (C=N); 2230 (C≡N); ^{1}H-NMR (DMSO-d_6) : 8.5 (s, 1H, H_6); 7.5 (s, 5H, Ar-H); m/z : 231 (M^+, 100); 203 (92); 142 (45); 77 (90). Anal. calcd for $C_{11}H_6ClN_3O$: C (57.04); H (2.61); N(18.14). Found : C (57.13); H (2.62); N (18.23)

4. 2(1H)-pyrazinones dehalogenated in position 5

a) 3-methoxy-1-phenyl-2(1H)-pyrazinone 1i

A mixture of pyrazinone 1e (500 mg) in 25 ml of methanol and 280 mg of K_2CO_3 was hydrogenated for 1.5 hour in the presence of catalyst (10% Pd/C; 100 mg) at 1 atm.. After removal of the catalyst by filtration, the filtrate was evaporated in vacuo and the residue was dissolved in dichloromethane, washed twice with 20 ml of water and dried over $MgSO_4$. Filtration followed by evaporation gave the title compound in quantitative yield.

m.p. (EtOH) : 151°C; IR (KBr) cm^{-1} : 1660 (CO); 1605 (C=N); ^{1}H-NMR ($CDCl_3$): 7.45 (m, 5H, Ar-H); 6.90 (s, 2H, H_5 and H_6); 4.00 (s, 3H, OCH_3); m/z : 202 (M^+, 31); 174 (10); 77 (100). Anal. calcd for $C_{11}H_{10}N_2O_2$: C (65.34); H (4.98); N(13.85). Found : C(65.23); H(4.91); N(13.72).

b) 3-chloro-1-phenyl-2(1H)-pyrazinone 1j

This compound was obtained from the pyrazinone 1i and phosphoryl chloride by the typical procedure described in the literature for the preparation of 2-chloropyridine from 2-methoxy pyridine[16]. Thus, phosphoryl chloride (0.9 g; 6 mmol) was added dropwise to a solution of pyrazinone 1i (0.609 g, 3 mmol) in DMF (5 ml) with stirring at 0°C followed by heating at 80°C (3 h). It was cooled to 0°C, quenched by adding saturated sodium acetate solution and warmed on water bath for 30 minutes. After cooling, the mixture was extracted with $CHCl_3$ (3 x 10 ml). The organic layer was thoroughly washed with water (3 x 10 ml) and dried over $MgSO_4$. The crude product obtained after removal of the solvent was chromatographed on silica gel. Elution with 5% $CH_3CN/CHCl_3$ gave the title compound which was further purified by recrystallization.

Yield : 85%; m.p. (EtOH) : 225°C; IR (KBr) cm^{-1} : 1665 (CO); 1600 (C=N); ^{1}H-NMR ($CDCl_3$) : 7.4 (m, 5H, Ar-H); 7.2 (s, 2H, H_5 and H_6); m/z : 206 (M^+, 100); 178 (21); 151 (53). Anal. calcd. for $C_{10}H_7ClN_2O$: C (58.13); H (3.41); N (13.56). Found : C(57.96); H(3.44); N(13.38).

c) 3-cyano-1-phenyl-2(1H)-pyrazinone 1k

This compound was prepared from 1j and cuprous cyanide following the typical procedure used for the preparation of 1g and 1h. The product was separated by column chromatrography on silica gel eluting with 5% $CH_3CN/CHCl_3$.

Yield : 66%; m.p. (CH_2Cl_2/hexane) : 156°C; IR (KBr) cm^{-1} : 1665 (CO); 1605 (C=N); 2230 (C≡N); ^{1}H-NMR (DMSO-d_6); 7.35 (s, 2H, H_5 and H_6); 7.4 (s, 5H, Ar-H); m/z : 197 (M^+, 100), 169 (54); 142 (96). Anal. calcd for $C_{11}H_7N_3O$: C (67.00); H(3.58); N(21.31). Found : C(67.11); H(3.60); N(21.18).

5. 3-methoxy and 3-chloro-1-phenyl-5-tosyl-2(1H)-pyrazinone 1l and 1m

Compound 1l (to be published elsewhere) was obtained by cycloaddition of cyanotosylate on 1e, followed by the loss of cyanogen chloride. Compound 1m was obtained from 1l and $POCl_3$ following the typical procedure used for the preparation of 1j. The product was separated by column chromatography on silica gel eluting with 1% $CH_3CN/CHCl_3$.

Yield : 96%; m.p. : 229°C (CH_2Cl_2/hexane); IR (KBr) cm^{-1} : 1690 (CO), 1605 (C=N), ^{1}H-NMR (CDCl3) : 8.2 (s, 1H, H_6); 7.9 (d, 2H, ortho H tosyl); 7.4 (m, 7H, Ar-H and meta H tosyl); 2.4 (s, 3H, CH_3); m/z : 360 (M^+, 27); 296 (27); 268 (31); 261 (26); 77 (100). Anal. calcd for $C_{17}H_{13}ClN_2O_3$: C (56.59); H (3.63); N (7.76). Found : C (56.53); H(3.64); N(7.60).

Table IV : Product yields of pyridines and pyridones from pyrazinones 1 and dimethyl butynedioate 2 (part A), ethyl propynoate 3(part B) and phenyl acetylene 4 (part C).

Pyrazinones	Procedure	Total[a] yield(%)	Pyridine(s) 7 (part A) 9,11 (part B) 13 (part C)	Pyridone(s) 8(part A) 10,12 (part B) 14,16 (part C)
A. 1a	A	66	a(0.066g;10%)	a(0.363g;56%)
1b	A	83	a(0.515g;78%)	b(0.040g; 5%)
1c	A	79	a(0.503g;76%)	c(0.026g; 3%)
1d	A	82	b(0.013g; 2%)	d(0.512g;80%)
1e	A	92	b(0.507g;78%)	e(0.110g;14%)
	B	87[c]	b(0.478g;74%)	e(0.104g;13%)
	B	89[d]	b(0.490g;76%)	e(0.105g;13%)
1f	A	90	b(0.534g;82%)	f(0.069g; 8%)
1g	A	59	c(0.164g;26%)	g(0.207g;33%)
	B	43[e]	c(0.121g;19%)	g(0.150g;24%)
	B	49[e]	c(0.140g;22%)	g(0.169g;27%)
1h	A	75	c(0.464g;73%)	h(0.015g; 2%)
1i	A	80	d -	e(0.634g)
1j	A	74	e -	b(0.597g)
1k	A	63	f -	h(0.490g)
1l	A	85[c]	g -	e(0.676g)
1m	A	68[c]	h -	b(0.547g)
B. 1a	A	77	a -	a(0.415g)
1b	A	81	a(0.286g;52%)[f]	b(0.201g;29%)
1d	A	62	b -	d(0.329g)
1e	A	69	b(0.127g;23%)	e(0.354g;46%)
1g	A	85	c(0.137g;26%)	g(0.306g;59%)
	B	69[c]	c(0.110g;21%)	g(0.246g;48%)
	B	72[d]	c(0.120g;23%)	g(0.252g;49%)
1h	A	95	c(0.395g;75%)	h(0.134g;20%)
1i	A	58	d -	e(0.396)
1j	A	71	e -	b(0.491g)
1k	A	82	f -	h(0.551g)
C. 1a	A	69	a -	a(0.379g)[f]
1b	A	75	a(0.257;46%)[g]	b(0.204g;29%)
1d	A	68[h]	b -	d(0.368g)
	A	25	b -	d(0.135g)
1e	A	79[h]	b(0.110g;20%)[g]	e(0.412g;59%)
	A	36	b(0.049g; 9%)	e(0.188g;27%)
1g	A	91	c -	g(0.473g)
1h	A	99	c(0.375g;70%)[g][i]	h(0.198g;29%)

(a) Yields were not optimized. Reactions were carried out with neat compounds (procedure A) for 30 minutes (parts A,B) or 1 hr (part C) or for 3 to 4 hours (part B) in solvent (procedure B) unless otherwise noted; (b) the by NMR estimated ratios 10/12 were between 1:1 and 2:1, exception made for 1d,e and 1i with respective values 6:1; 5:1 and 6:1; ratios 14/16 were between 1:1 and 4:1, exception made for 1g (14 : 16 ≈ 9:1); (c) reaction performed in xylene; (d) reaction performed in DMF; (e) reaction time was 1 hour; (f) these isomeric compounds were separated and individually characterized; (g) high regioselectivity was observed; (h) reaction time was 4 hrs; (i) product described in the literature, ref.5e.

II. CYCLOADDITION REACTION OF 2(1H)-PYRAZINONES WITH ACETYLENIC COMPOUNDS.

1. Formation of pyridines and 2(1H)-pyridones

General procedure : In neat acetylenic compounds (proced. A) or with solvent (proced. B)

The 2(1H)-pyrazinones (2,5 mmol) were heated with neat acetylenic compounds (2,5 ml) at 140°C under argon atmosphere. The evaporated crude mixtures were examined by ^{1}H-NMR spectroscopy. Products (pyridines and 2(1H)-pyridones) were isolated by preparative TLC with an appropriate solvent system (15% EtOAc/$CHCl_3$; 15 or 25% EtOAC/toluene). When performed in solvent the 2(1H)-pyrazinones (2,5 mmol) and the acetylenic compounds (7,5 mmol) were heated in 25 ml of solvent at 140°C under argon atmosphere. After removal of solvent, the crude reaction mixtures were treated as indicated above. The spectroscopic data and yields of products (recrystallized from CH_2Cl_2/hexane) are given below and in table IV.

Pyridine derivatives

Dimethyl 2,6-dichloro-pyridine-3,4-dicarboxylate 7a
m.p. : 63°C; IR (KBr)cm^{-1}: 1735-1745 (CO ester); ^{1}H-NMR ($CDCl_3$) : 7.8 (s, 1H, H_5); 4,00 (s, 3H, $COOCH_3$); 3.9 (s, 3H, $COOCH_3$); m/z : 263 (M^+, 52); 231 (100). Anal.calcd for $C_9H_7Cl_2NO_4$: C(40.94); H(2.67); N(5.30). Found : C (41.14); H(2.63); N(5.27).

Dimethyl 6-chloro-2-methoxy-pyridine-3,4-dicarboxylate 7b
m.p. 66°C; IR (KBr) cm^{-1} : 1720-1740 (CO ester); ^{1}H-NMR ($CDCl_3$) : 7.35 (s, 1H, H_5); 4.00 (s, 3H, $COOCH_3$), 3.90 (s, 6H, $COOCH_3$ and $-N=C-OCH_3$); m/z : 259 (M^+, 81); 227 (100); 200(95). Anal. calcd for $C_{10}H_{10}ClNO_5$: C (46.26); H (3.88); N(5.39). Found : C (46.25); H (3.82); N(5.31).

Dimethyl 6-chloro-2-cyano-pyridine-3,4-dicarboxylate 7c
m.p. 92.5°C; IR (KBr) cm^{-1} : 1735-1745 (CO ester); 2225 (C≡N); ^{1}H-NMR ($CDCl_3$): 7.9 (s, 1H, H_5); 4.00 (s, 3H, $COOCH_3$); 3.9 (s, 3H, $COOCH_3$); m/z : 254 (M^+, 14); 222 (100). Anal. calcd for $C_{10}H_7ClN_2O_4$: C (47.17); H (2.77); N(11.00). Found : (47.00); H(2.68); N (10.91).

Ethyl 2,6-dichloro-pyridine-3-carboxylate 9a
m.p. : 48°C, (49-50-ref 5b); IR (KBr) cm^{-1} : 1735 (CO ester); ^{1}H-NMR ($CDCl_3$) : 8.15 (d, J=7.5 Hz; 1H, H_4); 7.3 (d, J=7.5 Hz; 1H; H_5); 4.40 (q, 2H, CH_2CH_3); 1.40 (t, 3H, CH_2CH_3); m/z : 219 (M^+,5); 190 (62); 184(36); 173(100).

Ethyl 2,6-dichloro-pyridine-4-carboxylate 11a
m.p. : 63°C; IR (KBr) cm^{-1} : 1740 (CO ester); ^{1}H-NMR ($CDCl_3$): 7.8 (s, 2H, H_3 and H_5); 4.40 (q, 2H, CH_2CH_3); 1.40 (t, 3H, CH_2CH_3); m/z : 219 (M^+, 4); 1.90 (53); 184 (25); 173 (100). Anal. calcd for $C_8H_7Cl_2NO_2$: C (43.67); H (3.21); N (6.37). Found : C(43.52); H(3.11); N(6.45).

Mixture of Ethyl 6-chloro-2-methoxy-pyridine-3 and 4 carboxylate 9b, 11b
IR (neat) : 1740 (CO ester); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : superimposed quartet at 4.40 ppm (CH_2CH_3) and triplet at 1.40 ppm (CH_2CH_3). For 9b : 8.1 (d, J=7.8 Hz; 1H, H_4); 6.95 (d, J=7.8 Hz, 1H, H_5); 4.00 (s, 3H, OCH_3). For 11b : 7.9 (d, J=1 Hz, 1H, H_5); 6.85 (d, J=1Hz, 1H, H_3); 3.95 (s, 3H, OCH_3). Exact mass : 215.0349; Found : 215.0342.

Mixture of Ethyl 6-chloro-2-cyano-pyridine-3 and 4 carboxylate 9c, 11 c
IR (neat) : 2230 (C≡N); 1730 (CO ester); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : superimposed quartet at 4.5 ppm (CH_2CH_3) and triplet at 1.45 ppm (CH_2CH_3). For 9c : 8.4 (d, J=7.5 Hz, H_5); 7.7 (d, J=7.5 Hz, H_4). For 11c : 8.15 (d, J=1.5 Hz, H_5); 8.05 (d, J=1.5 Hz, H_3). Exact mass : 210.0195; found : 210.0202.

2,6-dichloro-3-phenyl-pyridine 13a
m.p. : 92°C; IR (KBr) : no lactam carbonyl absorption. ^{1}H-NMR ($CDCl_3$) : 7.32 (d, J=7.8 Hz, H_5 or H_4); 7.43 (m, 5H, ArH); 7.29 (d, J=7.8 Hz, 1H, H_4 or H_5). m/z : 223 (M^+, 100); 188 (30); 153 (36). Anal. calcd for $C_{11}H_7Cl_2N$: C(58.96); H(3.15); N(6.25). Found : C(59.05); H(3.06); N(6.20).

6-chloro-2-methoxy-3-phenyl-pyridine 13b
m.p. (not recrystallized) : 95°C; IR (KBr) : no lactam carbonyl absorption; ^{1}H-NMR ($CDCl_3$): 7.3 (m, 6H, Ar-H and H_5); 7.9 (d, J=7.5 Hz, 1H, H_4); 3.9 (s, 3H, OCH_3); m/z : 219 (M^+, 100); 184 (33). Exact mass : 219.0451; found : 219.0443.

2(1H)-pyridone derivatives

Dimethyl 3-chloro-1-methyl-2(1H)-pyridone-4,5-dicarboxylate 8a
m.p.:203°C; IR (KBr) cm^{-1} : 1665 (CO lactam); 1715-1740 (CO ester); ^{1}H-NMR ($CDCl_3$): 8.15 (s, 1H, H_6): 4.00 (s, 3H, $COOCH_3$); 3.9 (s, 3H, $COOCH_3$); 3.65 (s, 3H, NCH_3); m/z : 259 (M^+, 91); 244 (39) ; 200 (100). Anal. calcd for $C_{10}H_{10}ClNO_5$: C (46.26); H (3.88); N (5.39). Found : C (46.39); H (3.80); N (5.52)

Dimethyl 3-chloro-1-phenyl-2(1H)-pyridone-4,5-dicarboxylate 8b
m.p. : 175°C; IR (KBr) cm^{-1}: 1680 (CO lactam); 1715-1750 (CO ester); ^{1}H-NMR ($CDCl_3$) : 8.2 (s, 1H, H_6); 7.6-7.3 (m, 5H, Ar-H); 4.00 (s, 3H, $COOCH_3$); 3.9 (s, 3H, $COOCH_3$); m/z : 321 (M^+, 72); 286 (30); 258 (52); 203 (100). Anal. calcd for $C_{15}H_{12}ClNO_5$: C (56.00); H (3.76); N (4.35). Found : C (55.88); H (3.67); N (4.25).

Dimethyl 3-chloro-1-para methoxyphenyl-2(1H)-pyridone-4,5-dicarboxylate 8c
m.p. (not recrystallized) : 143°C; IR (KBr) cm^{-1} : 1660 (CO lactam); 1720-1735 (CO ester); ^{1}H-NMR ($CDCl_3$) : 7.1 (m, 4H, Ar-H); 8.2 (s, 1H, H_6); 4.00 (s, 3H, $COOCH_3$); 3.9 (s, 3H, $COOCH_3$); 3.8 (s, 3H, OCH_3); m/z : 351 (M^+, 89); 316 (100); 292 (7). Exact mass : 351,0509; found : 351.0506.

Dimethyl 3-methoxy-1-methyl-2(1H)-pyridone-4,5-dicarboxylate 8d
m.p. : 174°C; IR (KBr) cm^{-1} : 1670 (CO lactam); 1720-1740 (CO ester); ^{1}H-NMR ($CDCl_3$); 7.8 (5, 1H, H_6); 3.95 (s, 6H, 2 x $COOCH_3$); 3.85 (s, 3H, N=C-OCH_3); 3.60 (s, 3H, NCH_3); m/z : 255 (M^+, 100); 224 (96); 195 (20); 137 (96); 109 (84). Anal. calcd for $C_{11}H_{13}NO_6$: C (51.77), H (5.13), N (5.49). Found : C (51.69); H (5.03); N (5.34)

Dimethyl 3-methoxy-1-phenyl-2(1H)-pyridone-4,5-dicarboxylate 8e
m.p. : 110°C; IR (KBr) cm^{-1} : 1670 (CO lactam); 1730 (CO ester); ^{1}H-NMR ($CDCl_3$); 8.0 (s, 1H, H_6); 7.4 (m, 5H, ArH); 3.95 (s, 6H, $COOCH_3$); 3.85 (s, 3H, OCH_3); m/z : 317 (M^+, 86); 286 (92); 257 (30); 199 (100). Anal. calcd for $C_{16}H_{15}NO_6$: C(60.57); H(4.76); N(4.41). Found : C (60.30); H(4.67); N(4.21)

Dimethyl 3-methoxy-1-paramethoxyphenyl-2(1H)-pyridone-4,5-dicarboxylate 8f
m.p. (not recrystallized) : 125°C; IR (KBr) cm^{-1} : 1665 (CO lactam); 1720-1740 (CO ester); ^{1}H-NMR ($CDCl_3$) : 7.1 (m, 4H, Ar-H); 6.9 (s, 1H, H_6); 4.00 (s, 6H, 2 x $COOCH_3$); 3.95 (s, 6H, N=C-OCH_3); m/z : 347 (M^+, 64); 332 (5); 316 (35); 229 (100). Exact mass : 347.1005; found : 347.1000.

Dimethyl 3-cyano-1-methyl-2(1H)-pyridone-4,5-dicarboxylate 8g
m.p. : 176°C; IR (KBr) cm^{-1} : 1670 (CO lactam); 1720-1740 (CO ester); 2225 (C≡N); ^{1}H-NMR ($CDCl_3$) : 8.35 (s, 1H, H_6) : 4.00 (s, 3H, $COOCH_3$); 3.80 (s, 3H, $COOCH_3$); 3.68 (s, 3H, NCH_3); m/z : 250 (M^+, 89); 235 (47); 191 (100). Anal. calcd for $C_{11}H_{10}N_2O_5$: C (52.80); H (4.03); N (11.20). Found : C (52.61); H(4.10); N(11.12).

Dimethyl 3-cyano-1-phenyl-2(1H)-pyridone-4,5-dicarboxylate 8h
m.p. : 158°C; IR (KBr) cm^{-1} : 1680 (CO lactam); 1720-1745 (CO ester); 2225 (C≡N); ^{1}H-NMR ($CDCl_3$) : 8.4 (s, 1H, H_6); 7.4 (m, 5H, Ar-H); 4.00 (s, 3H, $COOCH_3$); 3.8 (s, 3H, $COOCH_3$); m/z : 312 (M^+, 96); 281 (52); 253 (100). Anal. calcd for $C_{16}H_{12}N_2O_5$: C (61.54); H (3.87); N (8.97). Found : C(61.70); H(3.72); N(9.03)

Mixture of ethyl 3-chloro-1-methyl-2(1H)-pyridone 4 and 5-carboxylate 10a and 12 a
IR (KBr) cm^{-1}: 1665-1670 (CO lactam); 1745 (CO ester), ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds superimposed quartet at 4.30 ppm ($\underline{CH_2}CH_3$) and triplet at 1.35 ppm (CH_2-$\underline{CH_3}$). For 10 a : 7.3 (d, J=7.5 Hz, 1H, H_6); 6.3 (d, J=7.5 Hz, 1H, H_5); 3.55 (s, 3H, NCH_3). For 12a : 8.2 (d, J=2Hz, 1H, H_6); 8.05 (d, J=2Hz, 1H, H_4); 3.65 (s, 3H, NCH_3). Exact mass : 215.0349; found : 215.0346

Mixture of ethyl 3-chloro-1-phenyl-2(1H)-pyridone-4-and 5-carboxylate 10b and 12b
IR (KBr) cm^{-1} : 1640 (CO lactam); 1735 (CO ester); ^{1}H-NMR ($CDCl_3$). For the two isomeric compounds : super imposed quartet at 4.40 ppm ($\underline{CH_2}CH_3$) triplet at 1.40 ppm ($CH_2\underline{CH_3}$) and multiplet at 7.60 ppm. For 10b : 7.35 (d, J=7.5Hz, 1H, H_6); 6.5 (d, J=7.5 Hz, 1H, H_5). For 12b : 8.25 (d, J=1.5 Hz, 1H, H_6); 8.15 (d, J=1.5 Hz, 1H, H_4). Exact mass : 277.0505; found : 277.0501.

Mixture of ethyl 3-methoxy-1-methyl-2(1H)-pyridone-4- and 5-carboxylate 10d and 12d
IR (KBr) cm^{-1} : 1665 (CO lactam); 1735 (CO ester); ^{1}H-NMR ($CDCl_3$); for the two isomeric compounds : superimposed quartet at 4.35 ppm ($\underline{CH_2}CH_3$) and triplet at 1.45 ($CH_2\underline{CH_3}$). For 10d : 7.15 (d, 1H, J=7.5Hz, H_6); 6.35 (d, 1H, J=7.5Hz, H_5); 4.00 (s, 3H, OCH_3); 3.55 (s, 3H, NCH_3). For 12d : 7.45 (d, 1H, J=1.5Hz, H_6); 6.75 (d, 1H, J=1.5Hz, H_4); 3.95 (s, 3H, OCH_3); 3.60 (s, 3H, NCH_3). Exact mass : 211.0844; found : 211.0842.

Mixture of ethyl 3-methoxy-1-phenyl-2(1H)-pyridone-4 and 5-carboxylate 10e and 12e
IR (KBr) cm^{-1} : 1730 (CO ester); 1645 (CO lactam); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : multiplet at 7.4 ppm (ArH); superimposed quartet at 4.40 ppm ($\underline{CH_2}CH_3$) and triplet at 1.38 ($CH_2\underline{CH_3}$). For 10e : 7.12 (d, J=7 Hz, 1H, H_6), 6.38 (d, J=7Hz, 1H, H_5); 4.00 (s, 3H, OCH_3). For 12e : 7.85 (d, J=1.5 Hz, 1H, H_6); 7.3 (d, J=1.5 Hz, 1H, H_4); 4.00 (s, 3H, OCH_3). Exact mass : 273.1001; found : 273.0997.
Mixture of ethyl 3-cyano-1-methyl-2(1H)-pyridone-4 and 5-carboxylate 10g and 12g
IR (KBr) cm^{-1} : 1670 (CO lactam); 1735 (CO ester); 2230 (C≡N); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : superimposed quartet at 4.45 ppm ($\underline{CH_2}CH_3$) and triplet at 1.40 ppm ($CH_2\underline{CH_3}$). For 10g : 8.3 (d, J=7.5 Hz, 1H, H_6); 6.75 (d, J=7.5 Hz, 1H, H_5); 3.55 (s, 3H, NCH_3). For 12g : 8.9 (d, J=2Hz, 1H, H_6); 8.5 (d, 1H, J=2 Hz, 1H, H_4); 3.50 (s, 3H, NCH_3). Exact mass : 206.0691; found : 206.0688.
Mixture of ethyl-3-cyano-1-phenyl-2(1H)-pyridone-4 and 5-carboxylate 10h and 12h
IR (KBr) cm^{-1} : 2225 (C≡N); 1735 (CO ester); 1660 (CO lactam); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : multiplet at 7.5 ppm (ArH); superimposed quartet at 4.4 ppm ($\underline{CH_2}CH_3$) and triplet at 1.45 ppm ($CH_2\underline{CH_3}$). For 10h : 8.2 (d, J=7.5 Hz, 1H, H_6); 6.8 (d, J=7.5 Hz, 1H, H_5). For 12h : 8.5 (s, 2H, H_4 and H_6); exact mass : 268.0847; found : 268.0835.
3-chloro-1-methyl-4-phenyl-2(1H)-pyridone 14a
m.p. : 101°C; IR (KBr) cm^{-1} : 1650 (CO lactam); ^{1}H-NMR ($CDCl_3$): 7.44 (s, 5H, ArH); 7.34 (d, J=7.5 Hz, 1H, H_6); 6.18 (d, J=7.5 Hz, 1H, H_5); 3.68 (s, 3H, NCH_3); m/z : 219 (M^+, 100); 191 (32); 184 (4); 176 (3). Anal. calcd for $C_{12}H_{10}ClNO$: C(65.61); H(4.59); N(6.38). Found : C(65.42); H(4.64); N(6.21).
3-chloro-1-methyl-5-phenyl-2(1H)-pyridone 16a
m.p. : 192°C; IR (KBr) cm^{-1} : 1660 (CO lactam); ^{1}H-NMR ($CDCl_3$) : 7.80 (d, J=2.5 Hz, 1H, H_6); 7.40 (s, 5H, Ar-H); 7.05 (d, J=2.5 Hz, 1H, H_4); 3.69 (s, 3H, NCH_3); m/z : 219 (M^+, 100); 191 (16); 184 (5); 176 (4). Anal. calcd for $C_{12}H_{10}ClNO$: C(65.61); H(4.59); N(6.38). Found : C(65.33); H(4.71); N(6.30).
Mixture of 3-chloro-1,4 and 1,5-diphenyl-2(1H)-pyridone 14b and 16b
IR (KBr) cm^{-1} : 1655-1660 (CO lactam); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : multiplet at 7.5 ppm (ArH). For 14b : 7.4 (d, J=7.5Hz, 1H, H_6); 6.37 (d, J=7.5 Hz, 1H, H_5). For 16b : 7.9 (d, J=2.5 Hz, 1H, H_6); 6.95 (d, J=2.5 Hz, 1H, H_4). Exact mass : 281.0607; found : 281.0601.
Mixture of 3-methoxy-1-methyl-4-phenyl and 5-phenyl-2(1H)-pyridones 14d and 16d
IR (KBr) cm^{-1} : 1655-1665 (CO lactam); 1H-NMR ($CDCl_3$) : for the two isomeric compounds : multiplet at 7.4 ppm (Ar-H). For 14c : 6.95 (d, J=7 Hz, 1H, H_6); 6.20 (d, J=7Hz, 1H, H_5); 3.85 (s, 3H, OCH_3); 3.60 (s, 3H, NCH_3). For 16c : 7.10 (d, J=2 Hz, 1H, H_6); 6.85 (d, J=2 Hz, 1H, H_4); 3.90 (s, 3H, OCH_3); 3.62 (s, 3H, NCH_3). Exact mass : 215.0946; found : 215.0944.
Mixture of 3-methoxy-1,4- and 1,5-diphenyl-2(1H)-pyridone 14e and 16e
IR (KBr) cm^{-1} : 1655-1670 (CO lactam); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : multiplet at 7.45 ppm (Ar-H). For 14e : 7.15 (d, J=7.5 Hz, 1H, H_6); 6.25 (d, J=7.5 Hz, 1H, H_5); 3.85 (s, 3H, $O\underline{CH_3}$). For 16e : 7.18 (d, J=2 Hz, 1H, H_6); 6.90 (d, J=2 Hz, 1H, H_4); 3.90 (s, 3H, OCH_3). Exact mass : 277.1102; found : 277.1091.
Mixture of 3-cyano-1-methyl-4 and 5-phenyl-2(1H)-pyridones 14g and 16g
IR (KBr) cm^{-1} : 2225 (C≡N); 1650-1660 (CO lactam); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : multiplet at 7.55 (Ar-H). For 14g : 7.56 (d, J=7Hz, 1H, H_6); 6.34 (d, J=7 Hz, 1H, H_5); 3.62 (s, 3H, NCH_3). For 16g : 7.76 (d, J=2 Hz, 1H, H_6); 6.82 (d, J=2 Hz, 1H, H_4); 3.65 (s, 3H, NCH_3). Exact mas : 210.0793; found : 210.0795.
Mixture of 3-cyano-1,4 and 1,5-diphenyl-2(1H)-pyridones 14h and 16h
IR (KBr) cm^{-1} : 2225 (C≡N); 1650-1660 (CO lactam); ^{1}H-NMR ($CDCl_3$) : for the two isomeric compounds : multiplet at 7.4 ppm (ArH); For 14h : 7.5 (d, J=7.5 Hz, 1H, H_6); 6.4 (d, J=7.5 Hz, 1H, H_5); For 16h : 8.15 (d, J=2.5 Hz, 1H, H_6); 7.8 (d, J=2.5 Hz, 1H, H_4). Exact mass : 272.0949; found : 272.0935.

2. Reactions of pyrazinones 1a-b, 1d-e and dimethyl butynedioate : formation and thermolysis of bicycloadducts 5

2. a. Cycloaddition

The pyrazinones (2,5 mmol) and dimethyl butynedioate (7.5 mmol) were stirred in dry

acetonitrile (or toluene) at 60°C for 90 hours. The solvent was then removed in vacuo below 60°C. Examination by ^{1}H-NMR spectroscopy of the crude reaction mixtures revealed for each case the presence of the bicycloadduct 5 as unique new product. From the data of table V it appears that the solvent does not influence the rate of the reaction. However, on purification by fast column chromatography, two products were obtained. The first eluted using 15% EtOAc/toluene was the initial adduct 5. The second eluted by more polar solvent system (25% $CH_3CN/CHCl_3$) was by spectroscopic means shown to be the hydrolysed adduct 17 which was characterized in one case of (17e).

Dimethyl 1-methoxy-3,6-dioxo-5-phenyl-2,5-diazabicyclo[2.2.2]octane-7,8-dicarboxylate 17e m.p. (CH_2Cl_2/hexane) : 203°C; IR (KBr)cm^{-1} : 3200-3080 (NH); 1730-1760 (CO ester); 1690-1710 (CO lactam); ^{1}H-NMR (DMSO-d_6); 7.6 (br.s., 1H, NH); 7.5 (m, 5H, ArH); 5.5 (s, 1H, bridge-H); 4.00 (s, 6H, $COOCH_3$); 3.95 (s, 3H, OCH_3); m/z : 360 (M^+, 6); 317 (65); 286 (36); 99 (100). Anal. calcd for $C_{17}H_{16}N_2O_7$: C(56.67); H (4.48); N (7.77). Found : C (56.33); H (4.37); N (7.66).

Table V : Yield and solvent effect in the addition reaction of compounds 1 (2.5 mmol) with dimethyl butynedioate (7.5 mmol).

Pyrazinones	solvent	total yield* (%) of 5a,b,d,e
1a	CH_3CN	45
1b	CH_3CN	55
1b	toluene	51
1d	CH_3CN	75
1e	CH_3CN	80
1e	toluene	75

* the yields obtained - after 90 h reaction at 60°C in 25 ml of solvent - were estimated by ^{1}H-NMR measurements and could be optimalized

2b. reaction of cycloadducts 5d,e with diethylamine : formation of dimethyl 3-diethylamino-1-methoxy-6-oxo-2,5-diazabicyclo[2,2,2]oct-2,7-diene-7,8-dicarboxylate : 5n (R^1 = CH_3) and 5o (-R^1 = Ph)

A solution of diethylamine (0.365 g; 5 mmol) in dioxane (25 ml) was added to the evaporated crude reaction mixture containing adducts 5d and 5e [from a 7-day reaction of dimethyl butynedioate (7.5 mmol) and 2.5 mmol of pyrazinones 1d and 1e in CH_3CN at 60°C.] The mixture was stirred for 10 minutes at room temperature. After removal in vacuo of solvent and excess of diethylamine, the residue was purified by column chromatography. Elution with $CHCl_3$ gave products 5n and 5o characterized spectroscopically :

5n : oil; yield 98%; IR (neat) : 1730-1740 (CO ester); 1690 (CO lactam); ^{1}H-NMR ($CDCl_3$) : 5.5 (s, 1H, H_4); 3.9 (s, 3H, $COOCH_3$); 3.85 (s, 3H, $COOCH_3$); 3.75 (s, 3H, OCH_3); 3.45 (q, 4H, $\underline{CH_2}CH_3$); 2.95 (s, 3H, NCH_3); 1.15 (t, 6H, $CH_2\underline{CH_3}$); m/z : 353 (M^+, 35); 338 (7); 324 (13); 322 (12); 293 (67); 273 (100).
5o : oil yield 0.975 g, 94%; IR (neat) : 1730-1740 (CO ester); 1690 (CO lactam); ^{1}H-NMR ($CDCl_3$) : 7.35 (m, 5H, ArH); 6.05 (s, 1H, H_4); 3.9 (s, 3H, $COOCH_3$); 3.85 (s, 3H, $COOCH_3$); 3.75 (s, 3H, OCH_3); 3.43 (q, 4H, $\underline{CH_2}CH_3$); 1.15 (t, 6H, $CH_2\underline{CH_3}$); m/z: 415 (M^+, 42); 400 (14); 386 (16); 384 (15); 355 (29); 296 (100).

2c. Thermolysis of cycloadducts 5a-b and 5d-e

On heating the adducts 5a,b,d,e at 140°C in dry xylene for 10 minutes complete decomposition into pyridine and/or pyridone was observed. The relative ratios of the latters, determined by ^{1}H-NMR measurements were the same as outlined in table IV (e.g. Pyridine/pyridone ≃ 85:15 in the case of 5e).

2d. Thermolysis of compounds 5n,o

On heating compound 5o (0.415 g; 1 mmol) in boiling xylene complete decomposition into pyridine 7i (0.292 g, 98%) was observed. Its spectral characteristics given below are nearly identical with those of reported dimethyl 2-methoxy-6-dimethylamino-pyridine-3,4-dicarboxylate.[8] However compound 5n was isolated unchanged on heating it under the same conditions.

dimethyl 6-diethylamino-2-methoxy-pyridine-3,4-dicarboxylate 7i
oil; IR (neat) cm^{-1} : 1730-1745 (CO ester); ^{1}H-NMR ($CDCl_3$); 6.29 (s, 1H, H_5); 3.9 (s, 6H, $COOCH_3$); 3.8 (s, 3H, OCH_3); 3.6 (q, 4H, CH_2CH_3); 1.15 (t, 6H, $CH_2\underline{CH_3}$); m/z : 296 (M^+, 65); 281 (100); 267 (25); 265 (42)

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