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DIELS-ALDER VERSUS HETERODIENE IN THE REACTION BETWEEN 4-ARYLIDENE-5-PYRAZOLONES AND 2,3-DIMETHYLBUTADIENE: THE EFFECT OF ACID CATALYSIS[1]

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Abstract - The thermal reaction between (E) or (Z)-pyrazolones (1) and 2,3-dimethylbutadiene (2) gave 1,2-dimethyl-5-arylcyclohexen-4-spiro-4' (1'-phenyl-3'-substituted-5'-pyrazolones) (3, 4), from a Diels-Alder reaction, and 4-aryl-2-isopropenyl-2-methyl-5-substituted-7-phenyldihydropyran [3,2-d] pyrazoles (5, 6), from a heterodiene reaction. The effect of the configuration of the starting pyrazolone, as well as that of substituents, on isomer distribution is here discussed.

The reaction can be conveniently catalyzed by different acids. The nature of the pyrazolone- acid complex was investigated by NMR.

The acid influences, dramatically, both the chemoselectivity and the stereoselectivity of the reaction. The effect of the catalyst was rationalized by taking into account both the change of the MOs induced by complexation and steric hindrance of the acid.

When dienes react with α,β-unsaturated carbonyl compounds, the Diels-Alder pathway to cyclohexenes is always preferred to the heterodiene pathway to dihydropyrans.[2]

This occurs both for the simplest model, since the reaction between butadiene and acrolein gives 4-formylcyclohexene and 6-vinyl-Δ 2-dihydropyran in 90% and 0.5% yields respectively,[3] and for more complicated structures, since 2-oxindolil-3-ylidene derivatives react with isoprene to give a regioisomeric mixture of spiro-oxindol-cyclohexenes.[4] Several other examples taken from the literature[5-16] give similar results.

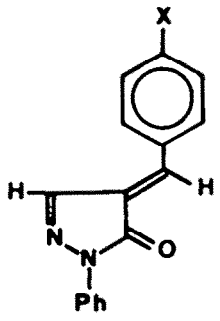
The application of the perturbation equation explains the observed selectivity since the overlap between the C_1 and C_4 coefficients of the butadiene HOMO with the C_3 and C_4 coefficients of the acrolein LUMO gives a larger energy gain than that involving the butadiene coefficients C_1 and C_2 with acrolein O_1 and C_4.[2]

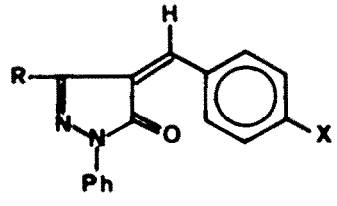
The perturbation theory does not take into account additional factors such as the aromaticity gain of the cycloadducts: therefore, the prediction thus obtained is violated by the reaction of o.quinone methides with butadiene, which only gave 2-vinylchromanes.[17]

A preliminary investigation of the reaction between (E) 4-benzal-1-phenyl-5-pyrazolone (1a) and 2,3-dimethylbutadiene (2) revealed that a mixture of Diels-Alder (3a) and heterodiene adducts (5a) is formed[1] (Scheme 1 and 2).

Here we report the results of a detailed investigation undertaken to evaluate the electronic and configurational factors that affect the reactivity as well as the influence of various catalysts on both reactivity and selectivity.

Scheme 1





1a : X = H
1b X = NO_2
1c X = CN
1d X = OMe
1e X = NMe_2

1f R = Me X = H
1g R = Me X = NO_2
1h R = Me X = NMe_2
1i R = Ph X = H
1l R = Ph X = NO_2
1m R = Ph X = NMe_2

Thermal cycloaddition - The reaction between 2,3-dimethylbutadiene (2) and 4-arylidene-5-pyrazolones (1a-m) (Scheme 1), the latter having:

a) either an (E) (1a-e) or a (Z) configuration (1f-m);

b) either electron-attracting (1b, c, g, l) or electron-releasing substituents (1d, e, h, m) in the arylidene group;

c) different hindering substituents in position 3 (R = H, Me or Ph);

was performed under thermal conditions in benzene.

The low reactivity of the electron-releasing substituted derivatives (1d, e, h, m) required a reaction time of several days at 120°, whereas all other reactions were performed at 80°. A fractional crystallization, together with column chromatography, allowed us to separate 1,2-dimethyl-5-arylcyclohexene-4-spiro-4'(1'-phenyl-5'-pyrazolones) (3, 4) from 4-aryl-2-isopropenyl-2-methyl-7-phenyldihydropyran [3,2-d] pyrazoles (5, 6). (Scheme 2).

The Diels-Alder adducts 4 and the heterodiene adducts 6 were never isolated from pyrazolones with an (E) configuration. From the electron-releasing substituted pyrazolones (1d, e, h, m) only the Diels-Alder adducts were obtained. Table 1 summarizes products and yields obtained under thermal conditions.

Configuration of the adducts 3-6 - Whereas a choice between dienic (3, 4) or heterodienic structures (5, 6) was easily solved by IR and NMR spectroscopy (see experimental), the configuration of 3 and 4 was determined by NMR shift reagent $Eu(fod)_3$ experiments.

When both isomers 3 and 4 were obtained, the (R, S), (or S, R)[18] isomer 3 aromatic protons ortho to X were less deshielded by the lactam carbonyl than those of the (R, R) isomer 4. The H-5 proton of 3, more than that of 4, was deshielded by the lactam carbonyl, but only when R was a methyl group, since a phenyl group also deshielded H-5 in 4. With the aim of eliminating any ambiguity in the configuration of the adducts, the $Eu(fod)_3$ tecnique was used. Since complexation

Scheme 2

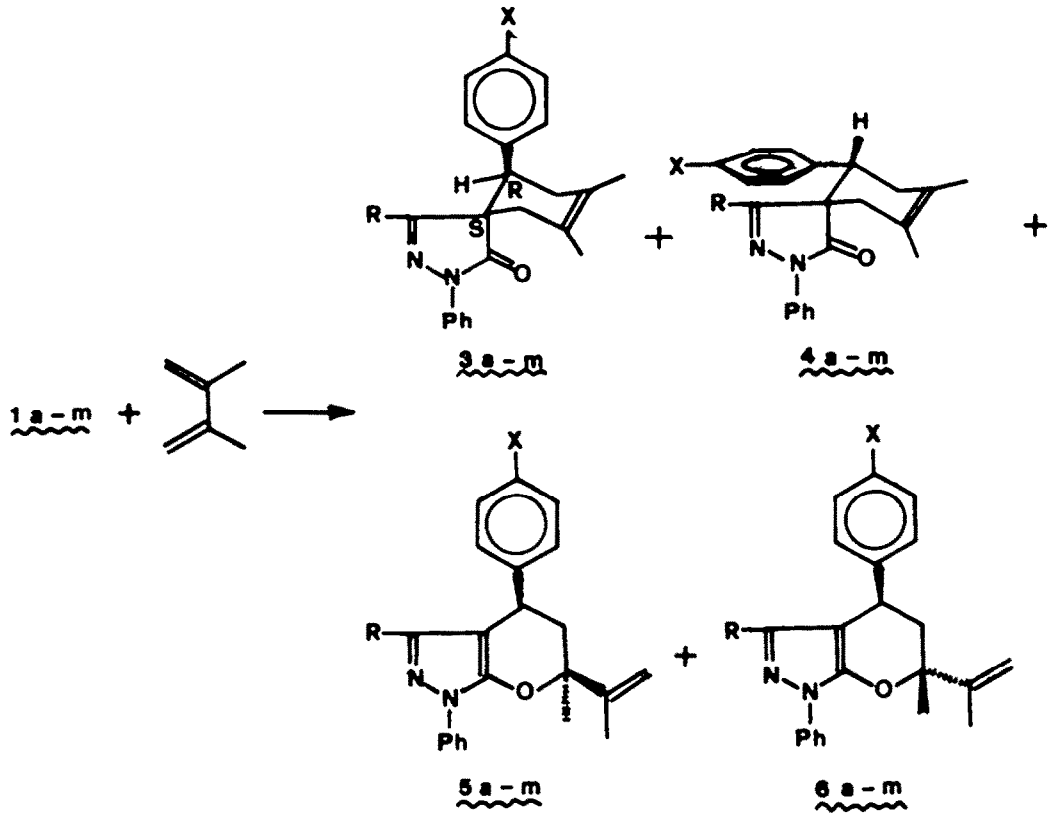


Table 1. Adducts of the thermal reaction between 1 and 2

Pyrazolone	R	X	T°	Time	Adducts yields %			
					3	4	5	6
1a[(a)]	H	H	80	12 h	90	-	10	-
1b	H	NO_2	80	12 h	90	-	10	-
1c	H	CN	80	12 h	90	-	10	-
1d	H	OMe	120	3 d	97	-	-	-
1e	H	NMe_2	120	3 d	90	-	-	-
1f	Me	H	80	2 d	73	14	8	2
1g	Me	NO_2	80	20 h	48	40	6	4
1h	Me	NMe_2	120	10 d	85	9	-	-
1i	Ph	H	80	2 d	40	25	20	10
1l	Ph	NO_2	80	40 h	40	25	20	10
1m	Ph	NMe_2	120	10 d	52	43	-	-

(a) Values taken from ref. 1.

occurred in the carbonyl group, a plot of ρ (molar fraction of the shift reagent) vs $\Delta\delta$ of H-5 gave slopes of about 11-12 for 3 and about 2-3 for 4 respectively.

When a single isomer was obtained from the reaction of 1a–e, the change of the chemical shift of

H-5 induced by $Eu(fod)_3$ gave a correlation of ρ vs $\Delta\delta$, whose slope was 9-10 consistent with the (R, S) configuration of 3a-e.

The configuration of dihydropyran derivatives 5 and 6 was difficult to determine on the basis of spectroscopic data, even if the vinylic protons (in C_6D_6) appear in the form of two broad singlets whose $\Delta\delta$ is in the range 0.30-0.35 ppm for 5 and 0.15-0.20 for 6. The configuration was unambiguously assigned to 5 and 6 since, under more severe thermal conditions, these rearrange stereospecifically to 3 and 4 through a [3.3] sigmatropic shift, which we will describe in detail elsewhere.[19] Thus, 5 had the isopropenyl cis to the 4-aryl group and 6 had these groups in a trans relationship.

Discussion of the thermal results - The first point to be clarified is the reason why electron-releasing substituted pyrazolones (1d, e, h, m) did not yield dihydropyran derivatives.

Whereas at 80°C the adducts 3-6 were stable, at 120°C the dihydropyran derivatives 5,6 underwent the above mentioned [3.3] sigmatropic rearrangement to become spiro-cyclohexen derivatives.[19] Thus we believe that the temperature required to perform these reactions prevented the isolation of dihydropyrans.

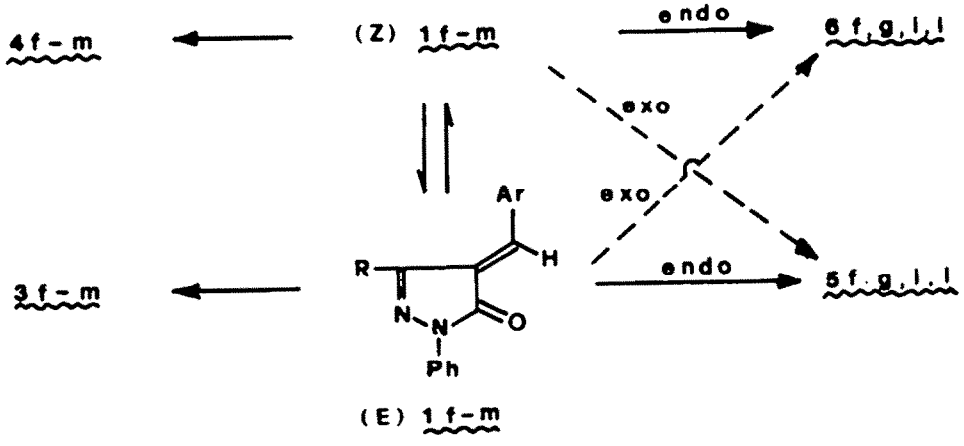
Electron-attracting substituents did not change product composition significantly.

The reactions of 3-H substituted pyrazolones (1a-e) were more stereospecific than any other. This depends on the (E) configuration[20] of these cycloaddends. If the Diels-Alder reactions occurs with retention of the configuration of the dienophile and if the heterodiene reactions occur through an endo transition state (stabilized by non-bonding interactions between the carbon of the carbonyl group and the C-3 center of the butadiene), 3 and 5 are obtained streospecifically.

Furthermore, 1d, e gave only 3d, e. This means that if dihydropyrans are formed, these must have the configuration of 5 since the sigmatropic rearrangement is totally stereospecific.

The reactions of 3-methyl- and 3-phenyl-substituted pyrazolones (1f-m) were non-stereospecific and both diastereoisomers 3 and 4 (and sometimes 5 and 6) were obtained. The (Z) configuration of these cycloaddends[20] should give, as do (E) pyrazolones, cyclohexenes 4 and dihydropyrans 6. If, under the experimental conditions, a (Z)⇌(E) equilibrium occurs and the (E) isomers are more reactive, (as do other cycloadditions of these derivatives),[21] both diastereoisomers are obtained from both a dienic and a heterodienic reactions (Scheme 3).

Scheme 3



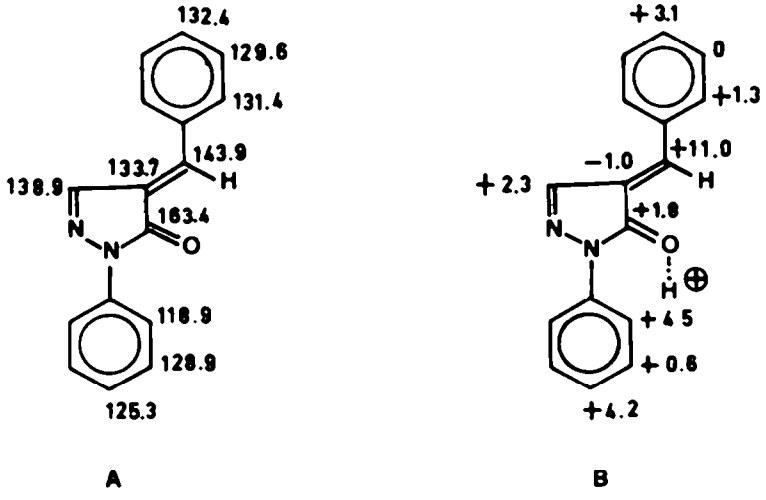
It is known that Lewis acids act not only on the rate but also on both the regioisomeric and stereoisomeric distribution of Diels-Alder reaction.[22] Furthermore, Ismail and Hoffmann[23] found that crotonyl cyanide and 4-methyl-1,3-pentadiene, which did not react under thermal conditions, gave the heterodiene adduct under $AlCl_3$ catalysis.

Before investigating the reactivity of 4-arylidene-5-pyrazolones under acidic catalysis, we studied the nature of the complex between 1 and the catalyst.

Lewis acid-pyrazolone complexes - The nature of the interaction between 4-arylidene-5-pyrazolones and Lewis acids was investigated in (E) isomer **1a** and (Z) isomers **1f**, **i**, changing the nature of the acid which was: H^+ (from CF_3COOH), hard and small-sized, $AlCl_3$, hard but with a large steric hindrance, and $Eu(fod)_3$, soft.

The ^{13}C-NMR spectrum of **1a** was registered at 35°C in both $CDCl_3$ and CF_3COOH, where the protonated species was present. The chemical shift of all carbon atoms and the shift induced in the protonating medium are reported in Scheme 4 (formulae A and B respectively; + means a downfield shift).

Scheme 4



Since the largest variation involved the carbon atom in the β position, as occurs in protonated acrolein,[24] the oxygen atom of the α, β-unsaturated system of **1a** was the site of protonation. This reduced the delocalization of the N-1 lone pair on the phenyl ring, and the shift of its carbon atoms is, moreover, consistent with this assumption. The same trend occurred on the ^{13}C-NMR spectra of **1f**, **i**.

Furthermore, protonation at the oxygen atom did not change the (Z) configuration of **1f**, **i** since the ortho protons of the benzylidene group (strongly deshielded in ^1H-NMR spectra by the carbonyl group -8.48 and 8.46 δ in C_6D_6 respectively-) did not change their chemical shift after the addition of CF_3COOD.

$Eu(fod)_3$ complexation involved the carbonyl group of **1a**, **f**, **i**.

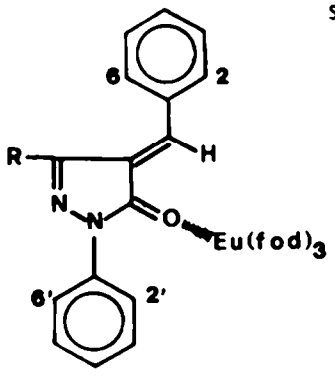
If the variation in the chemical shift for the most significant protons (see Scheme 5) is plotted vs the increasing concentration of $Eu(fod)_3$, the slopes reported in Table 2 are obtained.

The slopes involving H-2' and H-6' (those of the phenyl group in position 1) were significantly

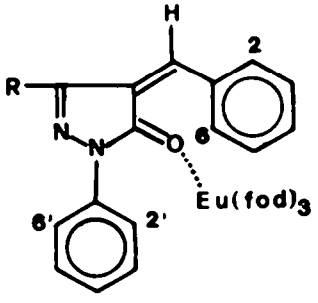
larger for 1a than for 1f, i. If the oxygen atom is the site of complexation, this means that 1a is strongly complexed, whereas the (Z) benzylidene group of 1f, i severely hinders the approach of $Eu(fod)_3$ and the complex is weak.

The configuration of the complexed pyrazolones (Scheme 5) was again (E) for 1a and (Z) for 1f, i. This is suggested by the different slopes of the vinylic proton in 1a and 1f, i. Furthermore, H-2 and H-6 of the benzylidene ring remained deshielded by the carbonyl group in 1f, i and the methyl group of 1f was mainly unchanged.

Scheme 5



1a - $Eu(fod)_3$ complex



1f,i - $Eu(fod)_3$ complexes

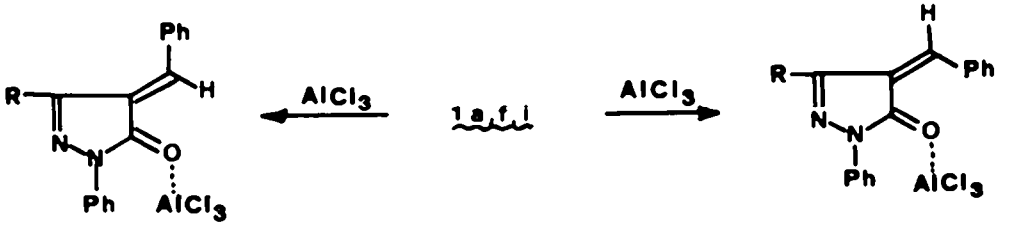
Table 2. Slopes of $\Delta\delta$ vs increasing concentration of $Eu(fod)_3$

Pyrazolone	H benzylidene	2(6)-H	2'(6')-H	R
1a	10.1	a	8.0	3.8
1f	0.6	1.5	1.0	0.5
1i	0.6	1.8	1.1	a

a) not determined

The complexation of 1a, f, i with $AlCl_3$ was followed by ^{1}H-NMR in C_6D_6 solution by adding, initially, 0.5 moles of the Lewis acid and increasing the amount to about 1 : 1 ratio.

Scheme 6



1a,f,i - $AlCl_3$ complexes

1f,i - $AlCl_3$ complexes

Complexation occurred at the oxygen atom as suggested by the upfield shift of the 2',6'-protons.

There is no evidence of a change in configuration for 1a after complexation (Scheme 6) even if the solubility of the $AlCl_3$ complex is very low.

For **1f, i**, the ortho protons of the benzylidene group (H2 and H6) showed both an upfield shift, due to complexation, and a reduced area of their signal, suggesting that part of this signal moved to become overlapped by aromatics. This is a clear sign of a partial change in configuration from (Z) to (E) in the complexed species (Scheme 6), and, as a further sign, the methyl group of **1f** split (the new signal at 1.71 being shielded by the phenyl group in the (E) configuration).

Having in our hands a picture of the effect of the complexation on 4-arylidene-5-pyrazolones, we began to study the effect of Lewis acids on the diene/heterodiene reactions.

Acid-catalyzed cycloadditions - The reaction of **1a** was performed in benzene (unless otherwise stated) in the presence of several acidic catalysts and the results are reported in Table 3.

$AlCl_3$ and $TiCl_4$ (entries 1 and 2) not only increased rate (4 hrs at room temperature) but also changed chemoselectivity as the diene adduct **3a** was the only reaction product. Similar behaviour was found for $Eu(fod)_3$ (entry 3), the only difference being a lower rate due to the softness of the acid.

Chemoselectivity changed dramatically in the reaction with CF_3COOH (entry 5). The reaction was very fast (5 minutes at 0°C) and the main product was the heterodiene adduct **5a**; its stereoisomer **6a** and the diene adduct **3a** were merely minor products. Increased amounts of the heterodiene adduct **5a** were also obtained with para toluensulforic acid and boron trifluoride (entries 6 and 4 respectively).

Nafion H, which is an acidic out-of-phase catalyst (entry 7), did not affect reactivity and the results were comparable to those of the thermal reaction of **1a** (Table 1).

The different behaviour of Lewis ($AlCl_3$ $TiCl_4$) vs protic acids (CF_3COOH, TsOH) prompted us to check the effect of substituents for these two classes of catalyst. The results (entries 8-11 and 12-15 for $AlCl_3$ and CF_3COOH respectively) revealed very low changes except for the reaction of **1e** with $AlCl_3$ (entry 11) where the out-of-phase complex was so stable as to prevent any further reaction. In spite of these disadvantages, after a long reaction time, poor yields of the diene adduct **3e** were obtained.

The dienic adducts obtained from (E) pyrazolones **1a-e** were **3a-e** and they retained the configuration of the starting dienophile. Thus we investigated the acid-catalyzed reaction of (Z) pyrazolones **1f, i** neglecting (because of the trivial results previously obtained) the effect of substituents on the benzylidene ring.

The $AlCl_3$-catalyzed reactions of **1f** and **1i** (entries 16 and 19 respectively) gave diene adducts **3f, i** as the main isomer, **4f, i** being obtained in small amounts only. Thus $AlCl_3$-complexed pyrazolones reacted mainly under the (E) configuration which is always present in the reaction mixture.

The $Eu(fod)_3$ catalyzed reaction of **1f, i** (entries 17 and 20) gave only dienic adducts, **3f, i** being the main isomers. The reactions occurred at room temperature, but, due to weak complexation with a soft acid, they were not fast (10-15 days, compared to the 20 hrs required for **1a**). These $Eu(fod)_3$ complexed pyrazolones reacted mainly under the (E) configuration which is not that of the complexed species.

The CF_3COOH catalyzed reaction of **1f, i** (entries 18 and 21) were again very fast and gave all four isomers. The main dienic and heterodienic adducts were **4f, i** and **6f, i**, both deriving from the (Z) configuration of the protonated pyrazolones.

Table 3. Adducts of the acid-catalyzed reaction between 1 and 2

Entry	Catalyst	Moles of catalyst	Pyrazolone R	X	React. cond. temp. - time	Adducts yields %[a] 3	4	5	6
1[b]	$AlCl_3$	0.3	1a H	H	r.t. - 4 hrs	95	-	-	-
2	$TiCl_4$	0.3	1a H	H	r.t. - 4 hrs	90	-	-	-
3	$Eu(fod)_3$	0.5	1a H	H	r.t. -20 hrs	96	-	-	-
4	BF_3 Et_2O	0.3	1a H	H	r.t. -10 hrs	60	-	21	5
5[b]	CF_3COOH	6.0	1a H	H	0° - 5 min.	35	-	40	5
6	TsOH	0.5	1a H	H	r.t. -20 hrs	56	-	38	<1
7	Nafion H	1 g[d]	1a H	H	r.t. - 7 dd	82	-	15	<1
8	$AlCl_3$	0.3	1b H	NO_2	r.t. - 4 hrs	95	-	-	-
9	$AlCl_3$	0.3	1c H	CN	r.t. - 4 hrs	95	-	-	-
10	$AlCl_3$	0.3	1d H	OMe	r.t. - 4 hrs	95	-	-	-
11	$AlCl_3$	0.3	1e H	NMe_2	r.t. - 3 months	30	-	-	-
12	CF_3COOH	6.0	1b H	NO_2	0° - 5 min	46	-	30	13
13	CF_3COOH	6.0	1c H	CN	0° - 5 min	55	-	32	6
14	CF_3COOH	6.0	1d H	OMe	0° -20 min	46	-	32	7
15	CF_3COOH	6.0	1e H	NMe_2	0° 120 min	41	-	23	<1
16	$AlCl_3$	0.3	1f Me	H	r.t. - 4 hrs	92	3	-	-
17	$Eu(fod)_3$	0.5	1f Me	H	r.t. -15 dd	93	4	-	-
18	CF_3COOH	6.0	1f Me	H	0° - 5 min	12	20	30	37
19	$AlCl_3$	0.3	1i Ph	H	r.t. - 4 hrs	85	10	-	-
20	$Eu(fod)_3$	0.5	1i Ph	H	r.t. -10 dd	62	20	-	-
21	CF_3COOH	6.0	1i Ph	H	0° - 5 min	9	16	22	40

a) given on isolated products b) values taken from ref. 1 c) in CH_2Cl_2 d) per mmol of 1a

Discussion of the results of the acid-catalyzed reactions and conclusions - If the thermal vs the protic-acid-catalyzed reactions are compared, the main differences are a faster rate and an increased yield of the heterodiene adducts in the latter.

A CNDO/2 calculation of 1-phenyl-4-benzylidene-5-pyrazolone (1a) and protonated 1a was performed [25] (Fig. 1). The LUMO is strongly stabilized and therefore the rate of the reaction increased for the lower energy separation between LUMO pyrazolone and HOMO dimethylbutadiene.

The protonation of 1a decreases the LUMO coefficient both at pyrazolone C-4 and at the oxygen atom, but the former more than the latter. This should disfavour more the Diles-Alder than the heterodiene pathway.

The perturbation theory does not take into account steric hindrance of centers involved in cycloadditions. Thus if the oxygen atom is coordinated by $AlCl_3$, $TiCl_4$ or $Eu(fod)_3$, the reaction at this center will be prevented (in spite of favourable MOs factors) and the Diels-Alder pathway will be followed. A lower steric hindrance (BF_3) will give a result that falls between the extremes.

The protic acid-catalyzed reaction of (Z) 4-arylidene-5-pyrazolones (1f,i) gave more heterodiene adducts (5, 6) than Diels-Alder products (3, 4), this in accordance with a FMO control of reactivity. The pyrazolones reacted mainly under the (Z) configuration (yields 4 > 3 and 6 > 5)

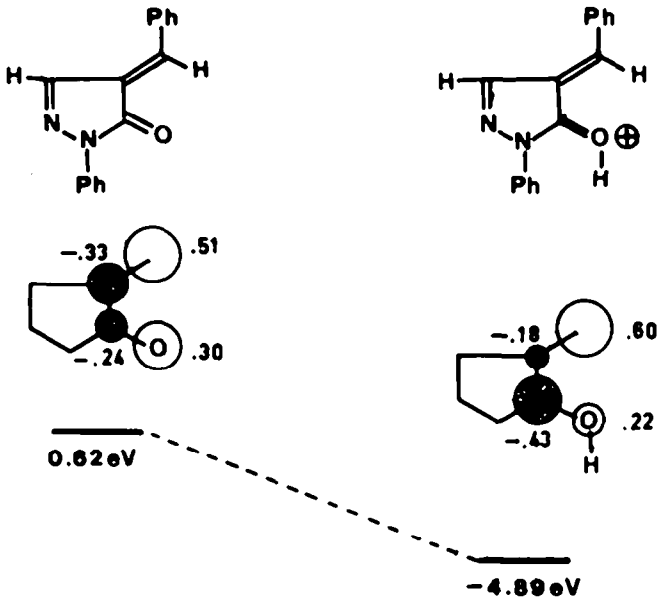


Figure 1. LUMO energy and coefficients of 1a and protonated 1a.

which is consistent with the configuration of the protonated (Z)-pyrazolones that we discussed previously.

The $AlCl_3$-catalyzed reaction of (Z) 4-arylidene-5-pyrazolones (1f, i) gave Diels-Alder adducts 3 and 4 only. Again, this is due to the coordination of the Lewis acid with the oxygen atom which prevented, for steric reasons, any heterodiene pathway. But, as previously shown, coordination with $AlCl_3$ inverted partially the pyrazolone configuration. Therefore, pyrazolones largely reacted under the more reactive (E) configuration, since the yields of 3f, i are significantly larger than those of 4f, i (by a factor of at least 8).

The $Eu(fod)_3$ catalyzed reactions of (Z) pyrazolones, even though the weakly complexed species was again (Z), gave products that derive from an (E) configuration. This result seems at a first glance to be illogical. A possible rationalization lies in the slow rate of the reactions (10-15 days at room temperature) which allowed the equilibrium (Z)$\rightleftharpoons$(E), (already proposed for the thermal reactions-Scheme 3), to be established. This does not occurr in fast reactions (e.g. proton catalyzed - 5 minutes at 0°C).

A final point cannot be omitted. The protic acid-catalyzed reactions of (E) 1a-e gave small, but nevertheless significant, amounts of dihydropyrans 6a-e (entries 5, 6, 12-15).

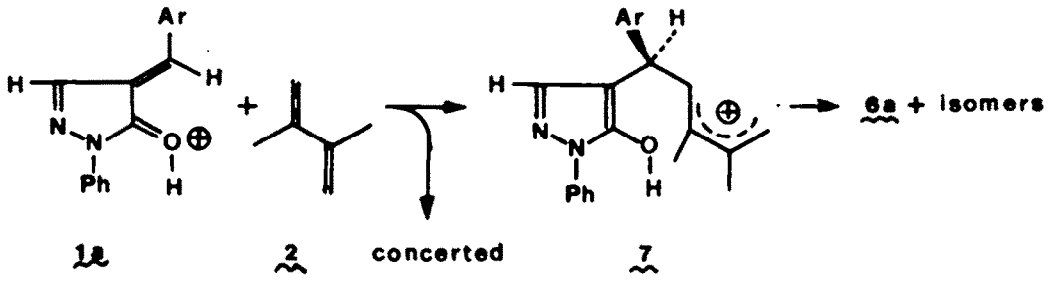
This could be due to a lower endo selectivity of the acid-catalyzed vs the thermal reaction. But this is not supported by FMO data if the coeffcient at the carbon atom of the carbonyl (involved in the secondary non-bonding interaction that gives the endo transition state) is significantly larger in the protonated species than in the non-coordinated one (Fig. 1).

If the acid-catalyzed reaction of 1a with 2 has a significant contribution from the positively-charged intermediate 7 (Scheme 7), its ring closure can explain the formation of 6a.

This two-step mechanism, in competition with the concerted pathway, has sometimes beeen proposed in the literature[26] as an explanation for the formation of some "out-of-the-rule" products of the acid catalyzed Diels-Alder reaction.

In conclusion, acid catalysis in [4+2] cycloaddition is a useful tool to increase rate, to influence stereoisomeric distribution and, at least in these reactions, to change chemoselectivity.

Scheme 7



EXPERIMENTAL

Melting points are uncorrected and were determined by the capillary method on a Tottoli apparatus (Büchi). Elemental analyses were made on Erba CHN analyzer mod. 1106. IR spectra (nujol mulls) were recorded on a Perkin-Elmer 983 spectrophotometer and H- and ^{13}C-NMR spectra on a Bruker WP 80 SY spectrometer ($CDCl_3$ was the solvent, unless otherwise stated, chemical shifts are reported in ppm on the δ scale, coupling constants in Hz).

1-Phenyl-4-aryliden-5-pyrazolones (1a-m) - Prepared in accord with the literature method;[20] for 1c.[27]

Thermal reaction of 1 with 2 - General procedure. A mixture of 1 (2 mmol) and 2 (1.1 ml - 10 mmol) in benzene (10 ml) was heated under the conditions reported in table 1. After the evaporation of the solvent, the adducts were obtained following the procedures reported in table 4.

Table 4

Pyrazolones	Operations required in the order (products separated in the order)
1a - 1e	A (3a-e); B (3a-c, 5a-c)
1f	A (3f); B (4f, 3f and 5, 6f in admixture); C (6f,5f)
1g	B (4g, 3g and 5,6g in admixture); D (6g, 5g)
1h	A (3h); C (4h, 3h)
1i	E (3, 4i and 5, 6i as mixtures); F (4i, 3i); F (6i, 5i)
1l	E (3l, 4l and 5, 6l in admixture); F (6l, 5l)
1m	B (4m, 3m).

A - the residue was ground with a few ml of diisopropylether and the precipitate, after cooling, was filtered off.
B - the mother liquors from A (the crude reaction residue from 1g, m) were column chromatographed (Silicagel Merk 230-400 Mesh, eluant methylenechloride).
C - the mixture from B was chromatographed on a medium pressure liquid chromatograph (Miniprep Jobin Yvon, Silicagel Merk 0.063 mm, eluant cyclohexane/ethylacetate 95:5)
D - as C but the eluant was cyclohexane/diisopropylether 9:1
E - as B but the eluant was methylenechloride/cyclohexane 1:1
F - as C but the eluant was cyclohexane/ethylacetate 98:2.

For these adducts, as well as for those described in this paper, m.p.s. phisical aspect, elemental analyses and IR spectra are reported in table 5; ^{1}H-NMR spectra are reported in tables 6 and 7.

Lewis acid-catalyzed reaction of 1 with 2

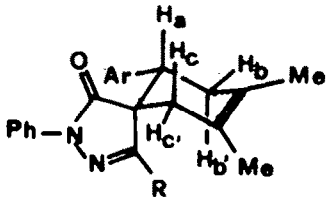
a) $AlCl_3$-catalyzed reaction of 1a-f, i. To a solution of 1a-f,i (2 mmol) in anhydrous benzene (10 ml), $AlCl_3$ (0.08 g - 0.6 mmol) was added. After 1 hr stirring at r.t., 2 (1.1 ml - 10 mmol) was added dropwise and the reaction left under the conditions reported in Table 3. The mixture was poured in $NaHCO_3$ sat. soln., extracted with diethylether, dried over Na_2SO_4 and the solvent was evaporated under vacuum. The adducts were obtained following the procedures reported in Table 4, avoiding operations which involve separation of adducts not obtained in these reactions. From the reaction of 1e, a 40-50% yield of starting pyrazolone was obtained as second fraction, following procedure B.

Table 5. Physical data of compounds 3-6.

Compd	Physical aspect	M.p. (solv.) or B.p.	Elemental analyses	Ir spectra $\nu_{C=O}$ cm^{-1}
3a	White needles	102-103° (a) for $C_{22}H_{22}N_2O$	calc.:C,80.0; H,6.7; N,8.5%	1695
			found: 80.3; 6.8; 8.5	
5a	White needles	113-115° (b)	found: 79.9; 6.7; 8.5	
6a	Oil	100°/0.1 mm Hg	found: 79.9; 6.7; 8.5	
3b	Cream crystals	194-195° (c) for $C_{22}H_{21}N_3O_3$	calc.:C,70.4; H,5.6; N,11.2%	1710
			found: 70.3; 5.7; 11.1	
5b	Cream needles	141-142° (d)	found: 70.3; 5.6; 11.1	
6b	Cream crytstals	131-132° (a)	found: 70.4; 5.8; 11.1	
3c	White platelets	149-150° (e) for $C_{23}H_{21}N_3O$	calc.:C,77.7; H,6.0; N,11.8%	1708
			found: 77.6; 6.0; 11.8	
5c	White chrystals	162-163° (a)	found: 77.6; 5.9; 11.8	
6c	White crystals	123-124° (a)	found: 77.8; 6.1; 11.6	
3d	White needles	110-111° (b) for $C_{23}H_{24}N_2O_2$	calc.:C,76.6; H,6.7; N, 7.7%	1690
			found: 76.7; 6.6; 7.8	
5d	White crystals	131-132° (a)	found: 76.5; 6.6; 7.5	
6d	Oil	100°/0.1 mm Hg	found: 76.9; 6.9; 7.5	
3e	White crystals	147-148° (a) for $C_{24}H_{27}N_3O$	calc.:C,77.2; H,7.3; N,11.2%	1700
			found: 77.3; 7.3; 11.2	
5e	Cream prisms	130-131° (a)	found: 77.4; H,7.4; 11.1	
3f	White needles	126-127° (a) for $C_{23}H_{24}N_2O$	calc.:C,80.2; H,7.0; N,8.1%	1705
			found: 80.1; 7.0; 8.0	
4f	White prisms	115-116° (d)	found: 80.1; 6.9; 8.1	1702
5f	White crystals	98-99° (d)	found: 80.3; 7.1; 8.1	
6f	White crystals	119-121° (a)	found: 80.2; 7.0; 8.2	
3g	Cream crystals	155-156° (d) for $C_{23}H_{23}N_3O_3$	calc.:C,70.9; H,5.9; N,10.8%	1705
			found: 71.1; 6.0; 10.8	
4g	Cream crystals	142-143° (d)	found: 70.9; 6.0; 10.7	1700
5g	Yellowish needles	168-169° (d)	found: 70.6; 5.7; 10.6	
6g	Cream needles	158-159° (d)	found: 70.7; 5.7; 10.6	
3h	White needles	165-167° (d) for $C_{25}H_{29}N_3O$	calc.:C,77.5; H,7.5; N,10.8%	1710
			found: 77.5; 7.5; 10.7	
4h	White needles	158-159° (d)	found: 77.4; 7.5; 10.7	1700
3i	White crystals	167-168° (d) for $C_{28}H_{26}N_2O$	calc.:C,82.7; H,6.4; N, 6.9%	1710
			found: 82.7; 6.4; 6.8	
4i	White crystals	129-130° (d)	found: 82.8; 6.4; 6.9	1710
5i	White crystals	117-119° (b)	found: 82.5; 6.3; 6.7	
6i	White needles	130-132° (b)	found: 82.6; 6.5 6.7	
3j	White needles	183-184° (d) for $C_{28}H_{25}N_3O_3$	calc.:C,74.5; H,5.6; N, 9.3%	1710
			found: 74.4; 5.6; 9.7	
4j	Yellowish needles	193-194° (d)	found: 74.5; 5.6; 9.7	1710
5j	White needles	183-184° (d)	found: 74.6; 5.6; 9.6	
6j	White needles	131-132° (d)	found: 74.6; 5.5; 9.6	
3k	White needles	164-165° (a) for $C_{30}H_{31}N_2O$	calc.:C,80.1; H;6.9; N, 9.4%	1710
			found: 80.1; 7.1; 9.3	
4k	White needles	202-203° (f)	found: 80.1; 7.0; 9.3	1710

a) Diisopropyl ether. b) Petroleum ether 60-80°. c) AcOH. d) EtOH. e) MeOH f) AcOEt

Table 6. ^{1}H-NMR spectra[a] of compounds 3,4.



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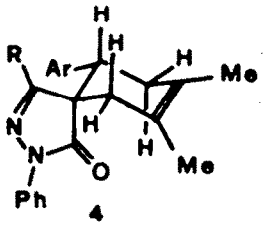

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Compd	H_a[b]	H_b-$H_{b'}$, H_c-$H_{c'}$	Me[d]	R[e]	X[e]	Aromatics[c]
3a	3.4	1.4 -3.1	1.75	7.8		7.0 -7.9
3b	3.55	1.4 -3.1	1.77	7.8		7.0 -8.5
3c	3.4	1.4 -3.1	1.73	7.8		7.0 -7.9
3d	3.32	1.4 -3.0	1.74	7.72	3.68	6.6 -7.8
3e	3.25	1.3 -3.0	1.63	7.68	2.75	6.4 -7.8
3f	3.43	1.4 -3.0	1.75	2.27		6.8 -7.6
4f	3.19	1.4 -3.3	1.75	2.02		6.8 -7.95
3g	3.5	1.45-3.0	1.77	2.27		6.8 -8.2
4g	3.25	1.45-3.5	1.75	2.00		7.0 -8.25
3h	3.37	1.4 -3.0	1.74	2.27	2.83	6.45-7.7
4h	3.1	1.45-3.25	1.74	2.02	2.83	6.4 -7.9
3i	3.4	1.4 -3.25	1.68 1.83	arom		6.7 -7.8
4i	3.75	1.45-3.55	1.75 1.85	arom		6.7 -8.1
3j	3.5	1.4 -3.25	1.74 1.88	arom		6.8 -8.1
4j	3.85	1.35-3.60	1.75 1.80	arom		6.75-8.1
3k	3.35	1.45-3.25	1.70 1.85	arom		6.35-7.9
4k	3.72	1.5 -3.5	1.76 1.82	arom	2.77	6.25-8.15

a) In $CDCl_3$. b) Doubling doublet; broad singlet for 4f, g,h; $J_{ab}+J_{ab'}$, were always in the range 17-18 Hz (values taken in C_6D_6 for 4f, g, h) which indicates a preferred conformation with H_a in the axial position. c) Multiplet. d) One broad singlet for 3a-h, 4f-h; two broad singlets for 3,4i-k. e) Singlet.

b) $TiCl_4$-catalyzed reaction of 1a - $TiCl_4$ (0.07 ml - 0.6 mmol) was added dropwise to a stirred solution of 1a (2 mmol) in anhydrous benzene (10 ml). After 1 hr, 2 (1.1 ml - 10 mmol) was slowly added to the ice-cooled mixture, which was left 4 hrs at r.t. and worked up as described under (a).
c) BF_3-catalyzed reaction of 1a - Fresly distilled BF_3 Et_2O (0.08 ml - 0.3 mmol) was added to 1a (1 mmol) in anhydrous benzene (5 ml) under stirring. After 1 hr, 2 (0.55 ml - 5 mmol) was added dropwise to the ice-cooled mixture, which was then left 10 hrs at r.t.. After a work up as described under (a), the reaction mixture was submitted to procedure B thus obtaining 3a, unreacted 1a ($\leq$ 5%) and a mixture of 5,6a in the order. Pure 6a and 5a were obtained in the order, following procedure C.
d) $Eu(fod)_3$-catalyzed reaction of 1a, f, i. 2 (0.55 ml - 5 mmol) was added to a solution of 1 (1 mmol) in methylenechloride (5 ml) containing $Eu(fod)_3$ (0.516 g - 0.5 mmol) and the reaction mixture was left under the conditions reported in table 3. After evaporation of the solvent, the adducts were obtained following the procedures reported in Table 4.

Protic acid-catalyzed reaction of 1 with 2

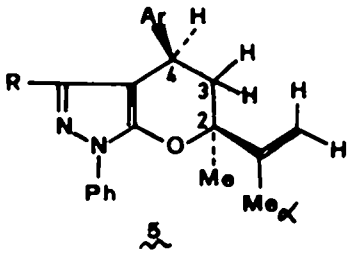
a) CF_3COOH - catalyzed reaction of 1a-f,i - CF_3COOH (0.9 ml - 12 mmol) was added to a solution of 1 (2 mmol) in anhydrous benzene (10 ml) and, under cooling and stirring, 2 (10 mmol) was added dropwise. Stirring was continued untill the colour disappeared, and the reaction mixture was poured into Na_2CO_3 sat. solution, extracted with diethylether, dried over Na_2SO_4 and the solvent evaporated under vacum. Starting from 1a-e, the crude reaction residue was submitted to procedure B

(table 4) obtaining pure **3a-e** and a mixture of **5,6 a-e** in the order. Pure **6a-d** and **5a-d** were obtained (in the order) following procedure D, whereas pure **5e** was obtained by grinding the corresponding mixture with light petroleum ether, cooling and filtering off the precipitate (**6e**, yield 5%, was only detected by NMR in the mother liquors). Starting from **1f, i**, the adducts were obtained following the procedures reported in table 4.

b) p. toluensulfonic acid-catalyzed reaction of **1a**. 2 (5 mmol) was added to a stirred solution of **1a** (1 mmol) and p. toluensulfonic acid (0.086 g - 0.5 mmol) in anhydrous methylenchloride (10 ml) and the mixture was left under the conditions reported in table 3. The reaction mixture was worked up as described under (a) and **6a** was only detected by NMR in the mother liquors of **5a**.

c) Nafion H-catalyzed reaction of **1a** - 2 (5 mmol) was added to a stirred mixture of **1a** (1 mmol) and Nafion 117-H® form (1.0 g, about 0.9 mmol) in anhydrous benzene (10 ml). Stirring was continued at r.t. for 7 days, then the colourless suspension was filtered, the catalyst washed with methylenechloride (2x5 ml), the solvent evaporated and the crude residue was worked up as described under (b).

Table 7. ^{1}H-NMR spectra[a] of compounds 5,6



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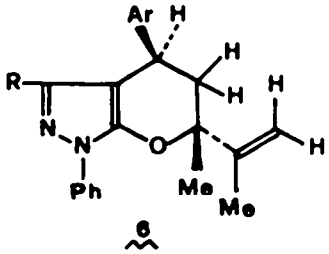

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Compd	H-4[b]	3-CH_2[c]	CH_2 Vinylic[d]		2-Me[e]	Me[d]	R[e]	X[e]	Aromatics[f]
5a	3.78	1.80	5.10	4.80	1.20	1.62	(g)		6.8 -8.3
6a	3.71	1.3- 2.2	4.93	4.72	1.29	1.50	(g)		6.75-8.5
5b	3.66	1.64	5.14	4.84	1.22	1.64	(g)		6.8 -8.4
6b	3.57	1.25-2.0	4.92	4.77	1.30	1.50	(g)		6.7 -8.5
5c	3.55	1.58	5.10	4.8	1.15	1.60	(g)		6.6 -8.4
6c	3.53	1.25-2.0	4.90	4.75	1.28	1.48	(g)		6.65-8.5
5d	3.82	1.85	5.15	4.83	1.25	1.65	7.5	3.42	6.3 -8.4
6d	3.75	1.4 -2.2	4.97	4.77	1.33	1.52	7.4	3.42	6.7 -8.5
5e[h]	3.87	1.92	5.15	4.82	1.25	1.68	7.55	2.58	6.5 -8.4
6e[h]	(i)	(i)	5.0	4.80	1.33	1.55	(i)	2.58	6.5 -8.4
5f	3.77	1.88	5.13	4.80	1.25	1.60	1.97		6.75-8.4
6f	3.75	1.6 -2.25	4.97	4.78	1.33	1.55	1.90		6.8 -8.5
5g	3.65	1.73	5.15	4.82	1.25	1.58	1.88		6.6 -8.5
6g	3.67	1.45-2.15	4.97	4.82	1.35	1.58	1.76		6.6 -8.5
5i	4.11	1.90	5.03	4.69	1.25	1.42	arom		6.8 -8.4
6i	4.13	1.55-2.35	4.97	4.77	1.27	1.57	arom		6.75-8.5
5j	3.94	1.50-1.8	4.97	4.62	1.15	1.29	arom		6.45-8.3
6j	3.95	1.3 -2.1	4.90	4.75	1.30	1.37	arom		6.5 -8.3

(a) In C_6D_6. (b) Doubling doublet; triplet for **5a,e,i,j**; $J_{34}+J_{3,4}$ are in the range 15-17 Hz which indicates a preferred conformation with H_4 in the "pseudo-axial" position. (c) Doublet for **5a-i**; multiplet for **6** and **5j**. (d) Broad singlet.. (e) Singlet. (f) Multiplet. (g) Overlapped by aromatics. (h) Spectrum obtained in admixture with **5e**. (i) Signals overlapped by those of **5a**.

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