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# DIELS-ALDER VERSUS HETERODIENE REACTION: THE EFFECT OF ACID CATALYSIS.

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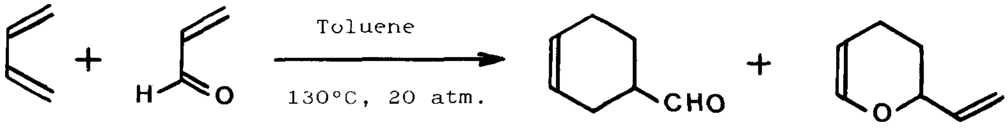
Summary: The difference between thermal, $AlCl_3$- and $CF_3COOH$-catalyzed reaction of (E)-4-benzal-1-phenyl-5-pyrazolone and 2,3-dimethylbutadiene is discussed in terms of Diels-Alder *versus* heterodiene reactivity.

A $4\pi+2\pi$ cycloaddition between a diene and an $\alpha,\beta$-unsaturated carbonyl compound can lead either to a cyclohexene, *via* a Diels-Alder reaction, or to a vinyldihydropyran *via* an heterodiene reaction.[1]

In the absence of additional factors (*e.g.* the aromaticity gain of *o*.quinone methides[2]), a simple application of the perturbation equation rationalizes[1] the strong preference observed[3] in the reaction between butadiene and acrolein to give 4-formylcyclohexene (90%) rather than 6-vinyl-Δ2-dihydropyran (0.5%) (Scheme 1).

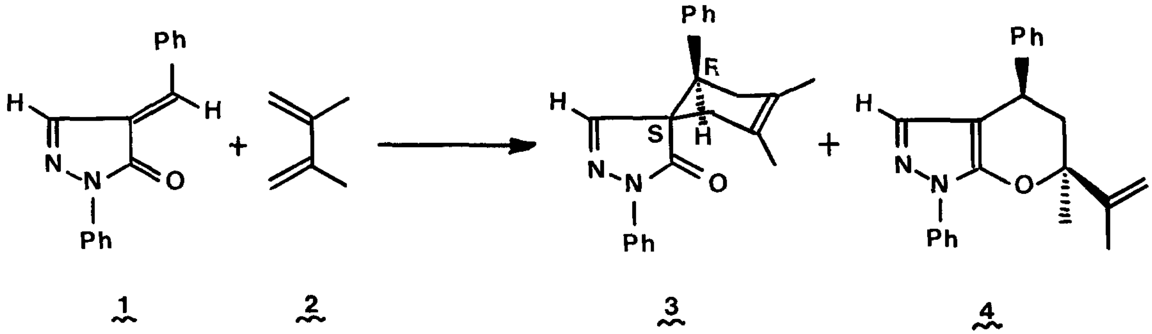
Scheme 1



Similar results were obtained in the heterocyclic field: *e.g.* when 2-oxoindolin-3-ylidene derivatives were allowed to react with isoprene,[4] a regioisomeric mixture of spiro-oxindolcyclohexenes was the only reaction product.

In this paper we wish to report the results of the reaction between (E)-4-benzyliden-1-phenyl-5-pyrazolone (1)[5] and 2,3-dimethylbutadiene (2). In refluxing benzene the reaction occurred in nearly quantitative yield with the formation of two products: **3** and **4** in the ratio 90:10. A fractional crystallization together with a column chromatography allowed us to separate 1,2-dimethyl-5-phenylcyclohexene-4-spiro-4'(1'-phenyl-5'-pyrazolone) (**3**) and 2-isopropenyl-2-methyl-4,7-diphenyldihydropyran[3,2-d]pyrazole (**4**)[6] (Scheme 2).

Scheme 2



The configuration[7] of **3** was (4S,5R) as derived by NMR shift reagent (Eu fod$_3$) experiments, whereas that of **4** was assigned as (2S,4R) from its stereospecific rearrangement to **3** under more severe thermal conditions which we will describe in detail elsewhere. This suggests that endo t.s. (stabilized by secondary non-bonding interactions) was strongly preferred in the heterodiene reaction.

It is known that Lewis acids act strongly on rate, regioisomeric and stereoisomeric distribution of the Diels-Alder reaction.[8] In addition to this, recently Ismail and Hoffmann[9] found that crotonyl cyanide and 4-methyl-1,3-pentadiene did not react under thermal conditions but gave the heterodiene adduct when the reaction was performed in the presence of AlCl$_3$.

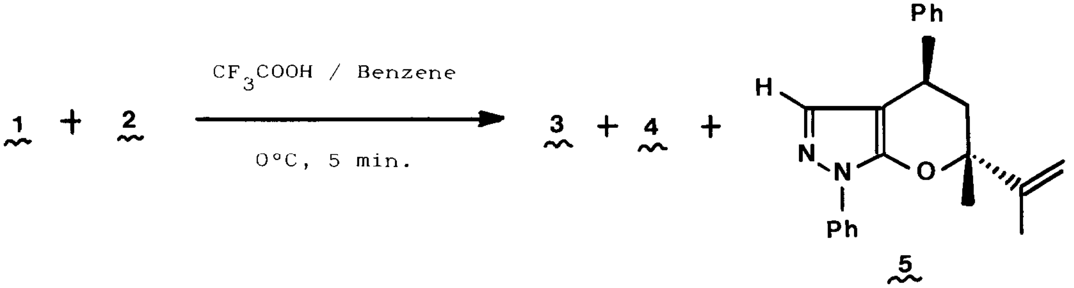
When the reaction of **1** and **2** was run with a catalytic amount of anhydrous AlCl$_3$ in benzene, a 95% yield of **3** was obtained and **4** was not found in the reaction mixture (Scheme 3).

Scheme 3

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{r.t., 4 hrs}]{\mathrm{AlCl_3}\ /\ \text{Benzene}} \mathbf{3}$$

Having unearthed this significant effect of the Lewis-acid catalysis on the chemoselectivity of the reaction, we explored a new acidic condition. In the presence of trifluoroacetic acid excess, the reaction between 1 and 2 was accomplished in benzene at 0° within a few minutes and, to our surprise, three products were isolated. 4 became the main product since this and 3 were obtained in 40 and 35% respectively, but a new product (5) was isolated in a 5% yield which was the (2S,4S) isomer of 4 (Scheme 4).

Scheme 4



To affect significantly both the rate and the ratio of isomers, an excess of $CF_3COOH$ must be used since minor amounts of catalyst gave only small variations. Table 1 summarizes products and yields obtained under the different experimental conditions.

Table 1. Adducts of the reaction between 1 and 2.[a]

| Catalyst | Equivs.[b] of Catalyst | T (°C) | Time | Overall[c] yield % | Relative product[d] yields % 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|
| none | - | 80 | 12 hrs | 100 | 90 | 10 | - |
| $AlCl_3$ | 0.3 | 25 | 4 hrs | 95 | 100 | - | - |
| $CF_3COOH$ | 1.0 | 25 | 3 hrs | 96 | 74 | 24 | 2 |
| $CF_3COOH$ | 6.0 | 0 | 5 min | 85 | 44 | 50 | 6 |

a) Ratio 2:1=5, benzene was the solvent. b) Based on pyrazolone. c) Of Crystallized products. d) All isolated adducts are primary reaction products as they are stable under the reaction conditions.

Different Lewis acids were found to influence the regioisomer distribution of the Diels-Alder reaction.[10,11] For the first time the above reported results show that different acids can induce a variation on the reaction chemoselectivity, this variation involving a choice between Diels-Alder and heterodiene reactions.

To rationalize the above reported results, more detailed experiments are required, mainly to detect the site of the acid coordination in 1. At least either the oxygen atom of the $\alpha,\beta$-unsaturated carbonyl system or the nitrogen atom in position 2 could be involved.

It is known that coordination of acrolein with an acid results in a significant decrease in its LUMO $C\alpha$ coefficient.[12] Thus if this is taken as a model for **1**, the lowering of the carbon coefficient in position 4 should disfavour the Diels-Alder reaction, as happens with the trifluoroacetic acid-catalysis.

These considerations neglect the steric requirements of the reaction. Hence if coordination results in a severe steric hindrance of one end of the heterodiene system, in spite of the more favourable frontier term, the overall effect will favour the Diels-Alder reaction, as happens with the aluminium trichloride-catalysis.

It is much more difficult to represent the effect on the reaction sites of the coordination of nitrogen. Thus calculations are being run to test also if soft and hard acids can coordinate different sites of **1**.

Furthermore new substrates are planned with a view to eventual future perspectives and evaluations of the meaning of the formation of **5** in the trifluoroacetic acid-catalyzed reaction.[13]

References and notes

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