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DIHYDROPYRANS FROM 1,4-CYCLOADDITION OF ENAMINES TO ARYLMETHYLENEPYRAZOLONES. POLAR CHARACTER OF THE THERMAL REARRANGEMENT OF THE RESULTING CYCLOADDUCTS.

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Abstract

The inverse electron demand hetero-Diels-Alder reaction of arylmethylenepyrazolones with enamines results in the selective formation of 3,4-dihydro-2H-pyran derivatives. These cycloadducts under thermodynamic conditions, are transformed via the zwitterion, which can be captured in the presence of tetracyanoethylene (TCE), as the more stable Michael-type adducts. The zwitterion could also be the intermediate for the cyclic adducts.

Introduction

Hetero-Diels-Alder reaction with inverse electron demand between α,β-unsaturated carbonyl compounds and appropriate dienophiles is an attractive route for the synthesis of 3,4-dihydro-2H-pyran derivatives[1]. This reaction has been successfully extended to a lot of heterodiene systems[2-4] and the products obtained have always implied a 1,4-cycloaddition. This reaction

appears to be a powerful and versatile approach to the synthesis of dihydropyrans fused to pyrazoles.

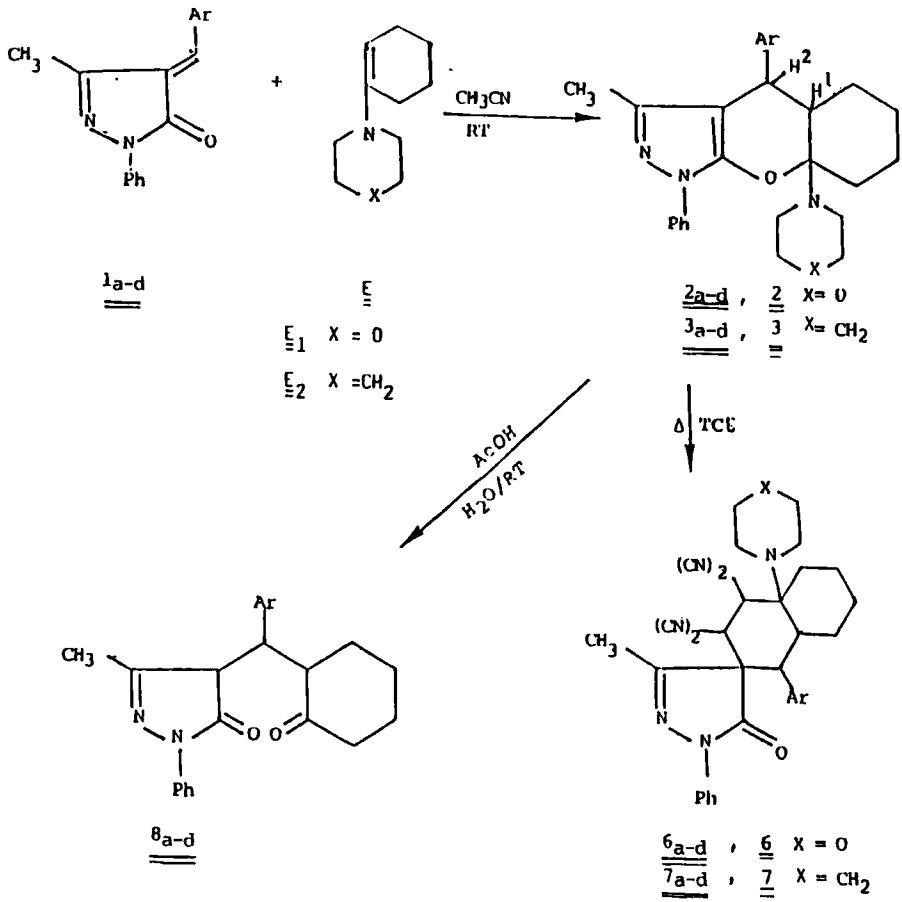
We have found[4] that the α,β-unsaturated system of arylmethylenerhodanines reacts with enamines undergoing 1,4-cycloaddition. In order to extend the applicability of the reaction, we now wish to report the results of the reaction of some 4-arylidene-3-methyl-1-phenyl-5-pyrazolones 1_{a-d}, another type of α,β-unsaturated carbonyl heterocyclic compound containing a lactam carbonyl group, with enamines.

Results and Discussion

The reaction of 1_{a-d} with excess enamine E_1 or E_2 in CH_3CN at 20 °C led to the formation of a colourless solid, the analytical data of which agreed well with 1:1 adducts (Scheme 1). The structures of the adducts 2_{a-d} and 3_{a-d} have been assigned through spectroscopic data.

The IR spectra showed a band at 1600 cm^{-1}, attributable to the enol ether double bond[3], suggesting that 1,4-cycloaddition had taken place. The carbonyl bands were missing, indicating the absence of both cyclobutane derivatives and alkylated enamines (Table 1).

The main features of the ^1H NMR spectra are reported in Table 2. All other protons of the base and of the aromatic rings showed the appropriate chemical shift values. The large values for the coupling constant



1a-d

E

E1 X = O

E2 X = CH_2

2a-d , 2 X= O

3a-d , 3 X= CH_2

8a-d

6a-d , 6 X = O

7a-d , 7 X = CH_2

a Ar = $C_6H_4.NO_2$-p

b = $C_6H_4.Cl$-p

c = Ph

d = $C_6H_4.OCH_3$-p

(Scheme 1)

Table 1: Spectroscopic data (KBr cm^{-1})

Compd.	νC=O lactam	νC=C enamine	νC=C dihydropyran	νC=C exocyclic
1a	1680	-	-	1620
2a	-	-	1605	-
3a	-	-	1600	-
4a	1700	-	-	-
5a	1700	-	-	-
1b	1675	-	-	1615
2b	-	-	1610	-
3b	-	-	1600	-
4b	1700	1630	-	-
5b	1700	-	-	-
1c	1675	-	-	1610
2c	-	-	1600	-
3c	-	-	1600	-
4c	1700	1625	-	-
5c	1705	-	-	-
1d	1675	-	-	1615
2d	-	-	1605	-
3d	-	-	1600	-
4d	1700	1630	-	-
5d	1705	-	-	-
6b*	1700	-	-	-
8a	1680	-	-	-

* cyano group absorbed at 2220 cm^{-1}.

of the dihydropyran protons, compared agreeably with similarly condensed dihydropyran derivatives[5-7], are the most diagnostic feature in the ^1H NMR spectra.

The proposed orientation of the cycloaddition was confirmed by hydrolytic cleavage of the adducts 2_{a-d} and

Table 2a: ^1H NMR spectra $\delta(CDCl_3)$ ppm and TMS internal standard.

a:

Compd.	H^2	H^1	CH_2-OCH_2	CH_2-N-CH_2	CH_2	aromatic protons
2a		4.9(b)*	3.6(m)	2.7(m)	0.9-2.2(m)	7.2-8.2(m)
2b	4.1(d) J=10Hz	2.4(m)	3.7(m)	2.9(m)	1.8(m)	7.1-8.0(m)
2c		4.8(b)	3.6(m)	2.6(m)	0.9-2.1(m)	7.1-7.8(m)
2d	4.0(d) J=9Hz	2.3(m)	3.7	2.9(m)	1.8(m)	6.9-8.0(m)

* b = broad

b:

Compd.	CH_2-N-CH_2	CH_2	H_2	aromatic proton	Note
3a	2.4(s)	0.9-1.9(m)	5.0(d) J=4Hz	7.2-8.2 (m)	CH_3 and H_1
3b	2.3(b)	0.8-1.9(m)	4.9(d)	7.2-8.0(m)	overlaped
3c	2.3(b)	0.7-2.0(m)	4.9(d) J=4Hz	7.0-8.0(m)	with protons
3d*	2.3(s)	0.7-2.0(m)	4.8(d) J=4Hz	6.9-8.0(m)	of enamine

* OCH_3 appears at = 3.8(s).

c:

Compd.	Morpholine protons	cyclohexene protons	=CH
4a	3.3 and 3.7(b)	0.9-2.3(m)	-
4b	3.6(b)	1.3-3.7(m)	6.1(m)
4c	3.6(b)	0.9-2.2(m)	5.4(m)
4d	3.5 and 3.7(b)	7.0-2.3(m)	4.9(m)
6b	3.8(s)	-	-

d:

Compd.	piperidine protons	cyclohexene protons	N=C-CH_3
5a	2.6(b)	0.8-2.0(m)	2.3(s)
5b	2.5(b)	0.8-2.0(m)	2.2(s)
5c	2.4(b)	0.7-2.0(m)	2.2(s)
5d	2.3(b)	0.6-1.9(m)	2.0(s)

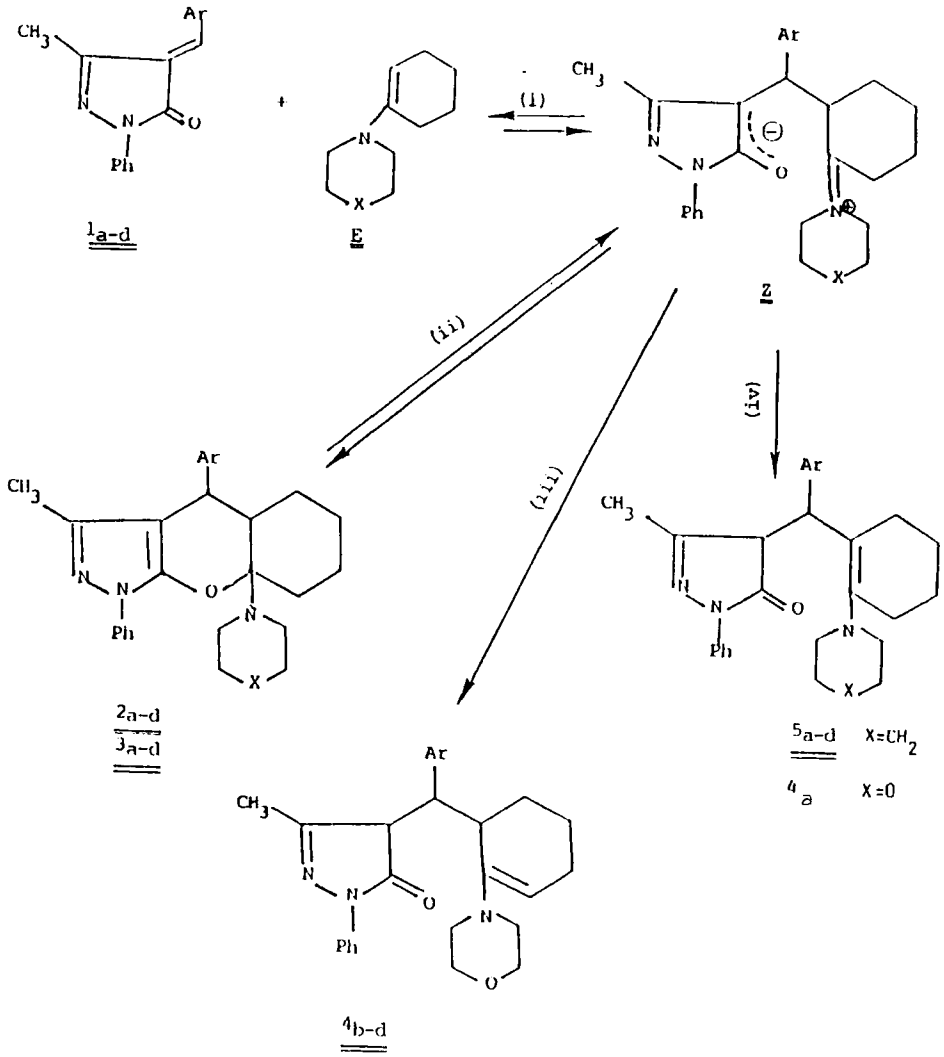
3_{a-d} under mild conditions in dilute acetic acid for 1/2 h; the (open-chain) pyrazolone derivatives 8_{a-d} (Scheme 1) being obtained. In this polar medium the formation of the dipolar intermediate should be favoured[8].

The dihydropyran derivatives 2_{a-d} and 3_{a-d} are thermally unstable, ring opening occurs on refluxing in acetonitrile and the corresponding open-chain Michael-type products 4_{a-d} and 5_{a-d} are obtained (Scheme 2). The IR spectra showed strong bands at 1670 cm^{-1} and 1640 cm^{-1}, due to the carbonyl group and the enamine double bond, respectively (Table 1). The ^1H NMR spectra showed no vinyl proton signals for 5_{a-d} while a triplet at δ = 4.95 ppm due to an enamine vinyl proton from 4_{b-d} was observed (Table 2). These results are interesting since the thermal rearrangement of dihydropyran to alkylated enamine has previously been reported by Ristaliti et al.[9] and Tacconi et al.[10].

Treating the dihydropyran adducts 2_{a-d} and 3_{a-d} with tetracyanoethylene (TCE) under the same experimental conditions as used for their ring cleavage, led to good yields of the adducts 6_{a-d} and 7_{a-d}; the elementary analyses of which are consistent with 1:1 adducts (Scheme 1). These results demonstrate the presence of a zwitterionic intermediate in the decomposition of the dihydropyran adducts through a two-step pathway, already proposed by Fleming[11].

The reaction of enamines E_1 and E_2 with arylmethylenepyrazolones 1_{a-d} can proceed via a two-step mechanism with the formation of a zwitterionic intermediate Z from which the different products 2, 3, 4 and 5 are generated (Scheme 2). A similar mechanism has already been suggested for the reaction leading to dihydropyrans. Alternatively, the formation of dihydropyrans could be regarded as a Diels-Alder-like reaction, occurring with a one-step mechanism (concerted reaction). The subsequent thermal rearrangement of the dihydropyrans[10] to Michael-type adducts should proceed via the zwitterion Z. The two-step mechanism appears to be the most reasonable[12] for the cycloaddition of enamines to dienes[8,12,13].

If a two-step mechanism is also operative for the formation of dihydropyrans 2 and 3, these as well as the Michael-type adducts 4 and 5 originate from the same dipolar intermediate Z (Scheme 2) formed in the first step (i) of the process. At room temperature step (ii) can be regarded as irreversible. Therefore, since under these conditions the main products of these reactions, namely dihydropyran adducts, are the thermodynamically less stable, the reactions are kinetically controlled and the product distribution will depend on the transition states of the steps (ii-iv). Consequently, the formation from Z of the cycloadducts 2 and 3, which implies only a charge neutralization, should be energe-



(Scheme 2)

tically favoured over the formation of the Michael-type adducts 4 and 5 requiring proton abstraction from the 2- and 6-positions of the cyclohexene ring of Z. On this basis, at room temperature the kinetically controlled reaction product is still the dihydropyran adduct but, this, under thermodynamic conditions, is transformed through the zwitterion to the more stable Michael adduct. This latter compound therefore becomes the final product of the reaction between the arylmethylenepyrazolones 1_{a-b} and enamines E_1 and E_2.

conclusion:

In this reaction, the 1,4-cycloadducts are the primary reaction products which can undergo thermal rearrangement via a dipolar intermediate which can be captured in the presence of (TCE), to Michael-type adducts as final products. This conversion is considered further proof of the polar character of the cycloaddition with enamines.

Experimental

GENERAL PROCEDURES:

a. Reaction of 1 with enamines E_1 and E_2.

To a stirred solution of 1 (1.0 equiv.) in acetonitrile, the enamine E_1 or E_2 (1.2 equiv.) was added. The mixture was stirred for (4-12 h) at room temperature (20 °C). After evaporation of the acetonit-

rile at room temperature under reduced pressure, the residue was ground with cold petroleum ether. The corresponding adduct was obtained in high yield.

b.Hydrolytic Cleavage:-

0.3 mmole of the cycloadduct was added to a cooled and stirred mixture of AcOH (6 ml) and H_2O (1 ml). Stirring and cooling were continued for 1/2 h then the precipitate 8 was filtered and washed with a large amount of water.

c.Thermal Rearrangement of Dihydropyrans:-

The dihydropyran was dissolved in acetonitrile at room temperature and the solution was refluxed for 40-100 hrs. The adducts 2_{a-d}, 3_{a-d} were completely decomposed and their NMR and IR-spectra were found identical with the spectra of the corresponding Michael-type adducts.

d. Reaction of Dihydropyrans With (TCE):-

To a stirred solution of TCE (1.0 equiv.) in acetonitrile, was added the cycloadduct (1.0 equiv.). The solution was stirred and refluxed under the same conditions of thermolysis of the cycloadduct.

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