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HETERODIENE SYNTHESES—X[1]

REACTION OF ARYLIDENE-PYRAZOLONES AND -ISOXAZOLONES WITH DIHYDROPYRAN: NATURE OF THE TRANSITION STATE

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Abstract—Dihydropyran reacts easily with the α, β-unsaturated carbonyl system of heterocyclic rings (pyrazoles or isoxazoles) in accordance with a 1,4-cycloaddition.

The stereochemistry of the addition is followed and the two-step character of the reaction mechanism is shown.

Pursuing our research on the cycloaddition between arylidene-pyrazolones or -isoxazolones and vinylethers[2], we wish to report the results obtained with dihydropyran, a cyclic ether little studied as a partner in (4 + 2) cycloadditions.[3]

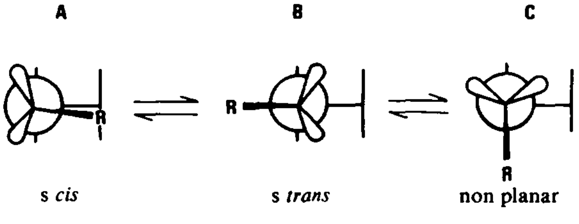
Previously reported reactions of β-substituted acyclic vinylethers have shown that a steric control occurs in the transition state.[2c] This, and the retention of stereochemistry of the starting ether in the adduct, lead us to propose a concerted transition state with asynchronous bond formation and consequently a partial character of nucleophilic attack for the formation of the C_3—C_4 bond.

No evidence for a two step reaction with loss of the configuration of the starting ether has been shown.

The nucleophilic character, under the same substrates, depends upon the degree of resonance arising from the overlap of the π-orbital of the double bond with the oxygen lone pair *p*-orbital.

Various methods have been proposed to estimate the contribution of the polar form: mainly, relationship between the electronic density of the β-C atom and the NMR spectral parameters, obtained from estimation of the chemical shift values of the β-ethylenic protons[4a, b], or relationship with C^{13} chemical shift of the β-C atom.[5]

A recent MO calculation[6] infers that the degree of overlap of orbitals, hence the resonance, depends upon the conformation of the vinylether whose significant rotamers are s.*cis* (A), s.*trans* (B) (both planar) and a non-planar form (C) (Scheme 1).



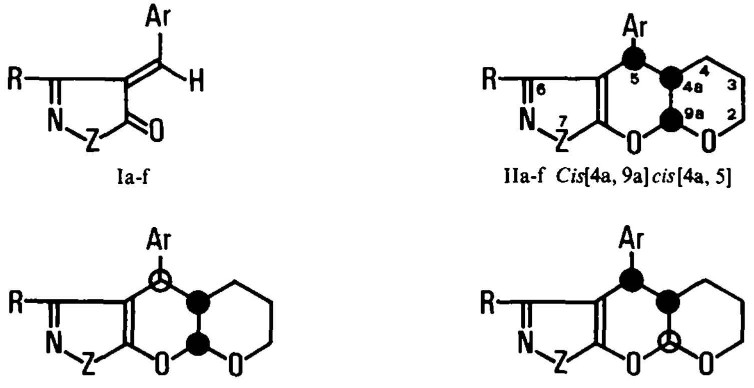
Scheme 1

We have therefore considered an ether, dihydropyran, which is forced into a conformation (half-chair[7] or sofà[8]) similar to s.*cis* (A).

The reaction was performed, whatever the substrate, with an excess of dihydropyran as solvent and the reaction mixtures were warmed in sealed tubes at 120° over an oil-bath.

We isolated mixtures of isomers with different distribution, but the overall yield was in the range 60–80%.

Chromatographic separations, fractional crystallizations or both techniques together (Experimental) gave the pure adducts the IR spectra of which lacked a CO band and suggested a 1,4-cycloaddition as reaction mode. Thus tetrahydropyran [3′, 2′: 5, 6] dihydropyran [2, 3-c] pyrazoles and tetrahydropyran [3′, 2′: 5, 6] dihydropyran [3, 2-d] isoxazoles are obtained from pyrazolones and isoxazolones respectively (Scheme 2).



Ia-f

IIa-f *Cis*[4a, 9a]*cis*[4a, 5]

IIIa-f *cis*[4a, 9a]*trans*[4a, 5]

IVb, f *trans*[4a, 9a]*cis*[4a, 5]

I, II, IIIa: Z = N-Ph; R = H; Ar = Ph
I, II, III, IVb: Z = N-Ph; R = Me; Ar = Ph
I, II, IIIc: Z = N-Ph; R = Ph; Ar = Ph
I, II, IIId: Z = N-Ph; R = Ph; Ar = p.MeOPh
I, II, IIIe: Z = N-Ph; R = Ph; Ar = p.ClPh
I, II, III, IVf: Z = 0; R = Ph; Ar = Ph

SCHEME 2

The investigation of the structures was monitored by NMR, which is in general complex; nevertheless a few signals can be assigned easily: the doublet of the anomeric proton H_{9a} and the doublet of the benzylic proton H_5, even if partially overlapped by the signals of the tetrahydropyran methylene to the O atom (H_2), can be assigned as the doublet collapses to a singlet when H_{4a} is irradiated.

A small $|^4J|$ coupling ($\sim$0·3 Hz) sometimes broadens H_5 and H_{9a} probably due to coupling with other protons which lie in a mutual equatorial position; however the correct assignment of the long range coupled protons is rather difficult owing to the multiplicity of the protons and the complexity of the signals involved.

The main NMR spectroscopic parameters for each derivative are reported in Table 1*.

If we assume, and nothing suggests the contrary, that our adducts prefer the same conformation[9] as the adducts from acyclic ethers, i.e. the dihydropyran fragment is in

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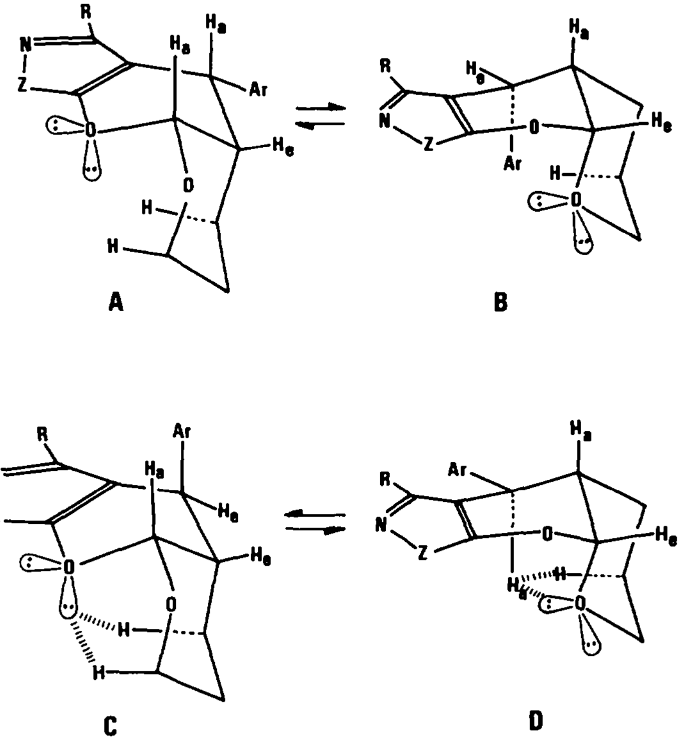
* Chemical shifts are reported in ppm on the δ scale, coupling constants in cps; $CDCl_3$ was the solvent and TMS the internal standard.

TABLE 1

Compd	H_{9a} J_{4a9a}	H_{4a} (decoupl.)	H_5 J_{4a5}	H_2	H_3–H_4	R	R′	Aromatic protons
IIa	D 5·78 1·5	M 2·1	D 4·40 5·5	M 3·8–4·1	M 1·0–1·9	overlapped by aromatics		M 7·1–8·0
IIIa	D 5·44 1·5	M 2·1	D 3·88 3·25	M 3·7–4·1	M 1·2–2·0	overlapped by aromatics	—	M 7·0–8·1
IIb	D 5·68 1·5	M 2·1	D 4·32 6·0	M 3·7–4·2	M 1·3–2·0	Me S 1·79	—	M 7·1 8·0
IIIb	D 5·43 1·5	M 2·0	D 3·77 2·25	M 3·7–4·2	M 1·5–2·0	Me S 1·92	—	M 7·0–8·0
IVb	D 5·06 8·75	M 2·0	D 3·89 6·0	M 3·7–4·1	M 1·2–2·0	Me S 1·90	—	M 7·0–8·0
IIc	D 5·80 1·5	M 2·2	D 4·66 6·1	M 3·6–4·3	M 0·9–1·8	Aromatics	—	M 6·9–8·1
IIIc	D 5·50 1·5	M 2·1	D 3·96 1·2	M 3·6–4·0	M 1·4–1·9	Aromatics	—	M 7·0–8·1
IId	D 5·77 1·5	M 2·2	D 4·60 6·0	M 3·6–4·3	M 0·9–1·8	Aromatics	OMe S 3·63	M 6·4–8·1
IIId	D 5·51 1·5	M 2·1	D 3·95 1·2	M 3·7–4·1	M 1·4–2·0	Aromatics	OMe S 3·76	M 6·7–8·2
IIe	D 5·79 1·5	M 2·2	D 4·71 6·2	M 3·6–4·2	M 1·0–1·8	Aromatics	—	M 6·9–8·1
IIIe	D 5·47 1·5	M 2·1	D 3·99 1·2	M 3·6 4·2	M 1·4 2·1	Aromatics	—	M 7·0 8·1
IIf	D 5·86 1·5	M 2·1	D 4·54 6·0	M 3·6–4·1	M 1·0–1·8	Aromatics	—	M 6·8–7·5
IIIf	D 5·55 1·5	M 2·1	D 3·83 1·2	M 3·6 4·1	M 1·6 2·0	Aromatics	—	M 7·0–7·6
IVf	D 5·12 8·8	M 2·05	D 3·93 5·4	M 3·6–4·1	M 1·3–2·0	Aromatics	—	M 6·9–7·6

a flexible half-chair form and that the fused pyran ring adopts a chair conformation, for *cis* fused rings the structure will be an equilibrium between two conformers: A and B when the aryl group is *cis*, C and D when it is *trans* (Scheme 3).



Scheme 3

Since H_{9a}/H_{4a} *cis* coupling always has a value of about 2 $Hz^{2c, 10}$, we believe that all the described adducts, apart from IVb and IVf, have the required character: J_{4a9a} *trans* in fact should be an axial/axial coupling.

The presence of isomers with the same [4a, 9a] stereochemistry must therefore be due to the different configuration of the aryl group in the 4-position.

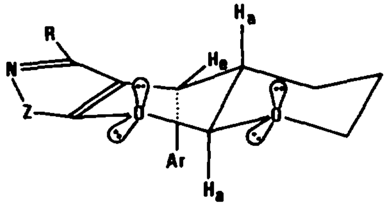
Since in many previously considered similar adducts J_{4a5} *cis* always has a value of about 6·5 $Hz^{2c, 10}$, within the preferred conformation[9], we assign this configuration to the isomers IIa–e. Consequently other isomers will have a J_{4a5} *trans*, but the low value for IIIc–e indicates it must have a fully equatorial/equatorial character, i.e. in the equilibrium C $\rightleftharpoons$ D, C must be the preferred conformation.

This preference can be rationalized as due to strong steric interactions: a "*gauche* butane" (D) versus a "*gauche* propyl ether" (C) interaction[11] and the steric interaction already shown between the equatorial aryl group and the phenyl group at 6 on the heterocyclic ring[9].

If this is true, one of the factors against D must decrease for R = Me and = H. As a matter of fact J_{4a5} has a value of 2·25 in IIIb and 3·25 Hz in IIIa, and this shows the increased axial/axial contribution.

We have not yet considered isomers IV which, despite the low yield, are of considerable importance.

The large value of J_{4a9a} is in accordance with an axial/axial *trans* coupling[2c], therefore we can assign to these adducts a *trans* junction between the two pyran rings. In this case, as for *trans* decalins[12], *trans* fusion makes the structure rigid and allows to determine the configuration of the 5 position. Since H_{4a} is fixed in the axial position, a *trans* J_{4a5} should be an axial/axial coupling: the observed value is too small for this but perfectly reasonable for a *cis* value. The configuration (E) (Scheme 4) can therefore be assigned to IVb and IVf, having phenyl group in the axial position.



E

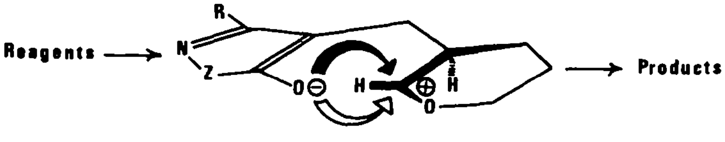
Scheme 4

Since each isomeric product is perfectly stable under the reaction conditions*, these *trans* [4a, 9a] adducts are kinetically-controlled products too.

DISCUSSION

The stereochemistry of the adducts allows us to infer the reaction mechanism.

The nucleophilic attack of the dihydropyran on the α,β-unsaturated carbonyl system gives rise to a discrete intermediate, probably of zwitterionic character, whose subsequent closure occurs, at least in two cases, with loss of the original *cis* configuration (Scheme 5).



Scheme 5

To our knowledge, this is the first example of a (4 + 2) cycloaddition of unsaturated carbonyl compounds and vinylethers occurring through an intermediate whose presence is demonstrated.

The low value of the ratio of the isomers with loss of configuration to those with retention of configuration, indicates the high degree of "memory"[13] which the intermediate has of its origin when the ring closure occurs and this might justify the retention of configuration in the other cases. However this low value could also mean that these cycloadditions with vinylethers lie in a border region where the

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* The adducts can be equilibrated under acidic conditions as will be reported in a forthcoming paper.

TABLE 2

Compd	Type of separation	Yield	m.p. (solvent)	Physical state	Elemental analysis	
IIa	Col. Chrom. Cy/AcOEt 90:10	52%	165-6° (dIPE)	Soft colourless needles	for $C_{21}H_{20}N_2O_2$	found: C, 76·30; H, 6·16; N, 8·22 calc: C, 75·88; H 6·07; N, 8·43%
IIIa	Col. Chrom. Cy/AcOEt 90:10	32%	118-9° (dIPE)	Small colourless prisms	for $C_{21}H_{20}N_2O_2$	found: C, 76·30; H, 6·15; N, 8·58 calc: C, 75·88; H, 6·07; N, 8·43%
IIb	Fract. Cryst. EtOH	42%	211-2° (EtOH)	Soft solourless needles	for $C_{22}H_{22}N_2O_2$	found: C, 76·31; H, 6·62; N, 8·10 calc: C, 76·27; H, 6·40; N, 8·09%
IIIb	Fract. Cryst. EtOH	23%	128-9° (EtOH)	Colourless needles	for $C_{22}H_{22}N_2O_2$	found: C, 75·98; H, 6·41; N, 7·85 calc: C, 76·27; H, 6·40; N, 8·09%
IVb[a]	Col. Chrom. Cy/AcOEt 90:10	2%	194-5° (dIPE)	Colourless prisms	for $C_{22}H_{22}N_2O_2$	found: C, 75·91; H, 6·53; N, 7·94 calc: C, 76·27; H, 6·40; N, 8·09%
IIc	Col. Chrom. Cy/PhH 50:50	26%	181-2° (Cy)	Small white crystals	for $C_{27}H_{24}N_2O_2$	found: C, 79·76; H, 5·94; N, 6·94 calc: C, 79·38; H, 5·92; N, 6·86%
IIIc	Col. Chrom. Cy/PhH 50:50	47%	204-5° (EtOH)	Small white crystals	for $C_{27}H_{24}N_2O_2$	found: C, 79·60; H, 5·93; N, 6·82 calc: C, 79·38; H, 5·92; N, 6·86%
IId	Col. Chrom. Cy/AcOEt 95:5	29%	200-1° (EtOH)	Soft white needles	for $C_{28}H_{26}N_2O_3$	found: C, 76·24; H, 6·08; N, 6·36 calc: C, 76·69; H, 5·98; N, 6·39%
IIId	Col. Chrom. Cy/AcOEt 95:5	53%	226-7° (EtOH)	Soft white needles	for $C_{28}H_{26}N_2O_3$	found: C, 76·46; H, 6·02; N, 6·42 calc: C, 76·69; H, 5·98; N, 6·39%
IIe	Col. Chrom. Cy/PhH 50:50	32%	245 6° (EtOH)	Small white crystals	for $C_{27}H_{23}N_2O_2Cl$	found: C, 72·74; H, 5·27; N, 6·42; Cl, 8·03 calc: C, 73·21; H, 5·22; N, 6·32; Cl, 8·01%
IIIe	Col. Chrom. Cy/PhH 50:50	53%	203-4° (EtOH)	Soft colourless needles	for $C_{27}H_{23}N_2O_2Cl$	found: C, 73·20; H, 5·22; N, 6·33; Cl, 8·35 calc: C, 73·21; H, 5·22; N, 6·32; Cl, 8·01%
IIf	Col. Chrom. Cy/AcOEt 88:12	15%	190-1° (EtOH)	Soft white needles	for $C_{21}H_{19}NO_3$	found: C, 75·98; H, 5·81; N, 4·33 calc: C, 75·65; H, 5·74; N, 4·20%
IIIf	Col. Chrom. Cy/AcOEt 88:12	39%	185-6° (EtOH)	Small colourless prisms	for $C_{21}H_{19}NO_3$	found: C, 75·40; H, 5·80; N, 4·27 calc: C, 75·65; H, 5·74; N, 4·20%
IVf[b]	Col. Chrom. Cy/AcOEt 88:12	6%	203-4° (EtOH)	Soft colourless needles	for $C_{21}H_{19}NO_3$	found: C, 75·43; H, 5·73; N, 4·29 calc: C, 75·65; H, 5·74; N, 4·20%

[a] Small amounts (about 0·2%) of red prisms (m.p. 131-2°-dIPE) can sometimes be isolated from the reaction mixture, but the structure of this product seems to be far from the present topic.

[b] Small amounts (0·8%) of white crystals (m.p. 170-1°-EtOH) can be isolated from the reaction mixture by col. chrom. The mass spectrum of this product shows it to be an adduct. If/dihydropyran 1:2 (m/e = 417), $\nu_{c=o}$ = 1750 cm^{-1}, but the NMR spectrum seems inconsistent with a 2 + 2 + 2 cycloadduct.

concept of synchronous, concerted or asynchronous reaction loses a discrete meaning and indicates only the predominant character of the reaction.

It is reasonable to assume that the predominant character of two-step reaction of the above reported cycloaddition, under our experimental conditions, depends upon the increased nucleophilicity of the dihydropyran in comparison to the previously reacted acyclic β-substituted vinylethers.

Calculations of the theoretical π indexes by the CNDO/2 method have recently shown that the charge density on the β-carbon atom is increased when a s.*cis* conformation is adopted[6] and the value for a s.*cis* β-methylethoxyethylene is not far from row values obtained for β-methylsubstituted enamines[14].

Therefore demonstration of the existence of an intermediate for a cycloaddition with dihydropyran is not astonishing if we consider that an intermediate has been invoked[15] in cycloadditions with enamines.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra (nujol mulls) run on a Perkin–Elmer 257 spectrophotometer. NMR spectra run on a Perkin–Elmer R-12 spectrometer by Dr. A. Gamba Invernizzi. Microanalyses were performed by Dr. L. Maggi Dacrema.

General procedure. A mixture of arylidene-pyrazolone or isoxazolone I (0·003 mole) and dihydropyran (5·0 ml) was warmed in a sealed tube over an oil-bath for a period of about 200 hr at 120°. After this time the colour of the starting material disappeared and the mixture became a brown viscous soln. The excess dihydropyran was evaporated under reduced pressure and the black-brown tar was chromatographed over a silica gel column (eluant: cyclohexane-AcOEt 70/30). The colourless mixture of adducts was collected, the overall yield was determined and the composition of the mixture was monitored by NMR. The isomers were separated by column chromatography (silica gel—eluant: Cy-AcOEt 9/1 or Cy-PhH 1/1) or, when mixtures were still obtained, by fractional crystallization.

The characterization of the isomers is reported in Table 2.

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