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STEREOCHEMICAL ASPECTS OF BASE-PROMOTED REACTIONS OF o-ALKENYL SUBSTITUTED ARYLHYDRAZONOYL CHLORIDES WITH TRIPHENYLPHOSPHINE

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Abstract—The title arylhydrazonoyl chlorides treated with Et_3N and PPh_3 give arylazomethylenetriphenylphosphoranes and, in some cases, products of intramolecular cyclization (cyclopropacinnolines and benzodiazepines). A high concentration of base and a polar solvent accelerate all the observed reactions. In the presence of PPh_3 a low reaction temperature and a non polar solvent favour the formation of the phosphoranes over the cyclization reaction. The steric configuration of phosphoranes and cyclopropacinnolines is determined by the relative stability of the two isomers.

It is known that arylhydrazonoyl halides react with PPh_3 in the presence of Et_3N to give the corresponding arylazomethylenetriphenylphosphoranes.[1,2] When an α-β unsaturated substituent is *ortho* to the hydrazo group the intermolecular reaction with PPh_3 is favoured over the alternative intramolecular cyclization,[3] which had never been observed, even as side reaction, when the reaction with PPh_3 was carried out in CH_3CN at room temperature.[4]

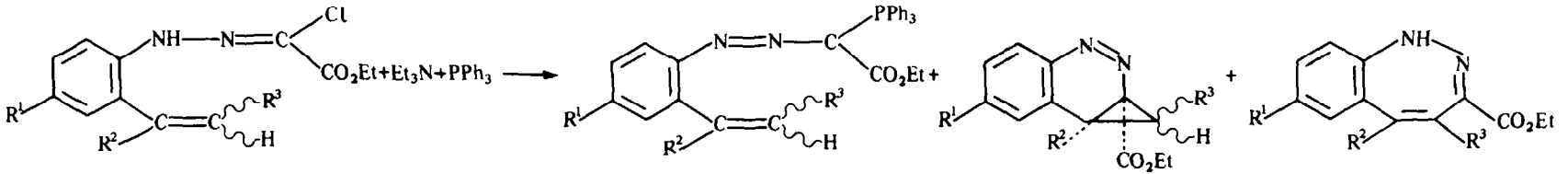
We wanted to check if the synthesis and some thermal reactions[4] of the arylazomethylenetriphenylphosphoranes carrying an o-alkenyl substituent were influenced by the configuration around the double bond of the olefinic group. Compounds (**1a**)*Z*, (**1b**)*E* and (**1b**)*Z* reacted with PPh_3 and Et_3N in the conditions previously described[2] affording a high yield of the corresponding phosphoranes, but compound (**1a**)*E* showed anomalous behaviour. Indeed, with an equimolar amount of PPh_3 and a small excess of Et_3N it gave only a 30% of a phosphorane (**2a**) identical with that obtained from the *Z* isomer, together with a 20% of *endo*-Me cyclopropacinnoline (**3a**) and a 33% of benzodiazepine (**4a**). The unexpected low reactivity towards PPh_3 and the unexpected steric configuration of both phosphorane and cyclopropacinnoline isolated from the reaction mixture prompted us to study the reaction of hydrazonoyl chlorides (**1a**) and (**1b**), *E* and *Z*, with Et_3N with or without PPh_3. This paper is concerned with factors which influence competition between the intermolecular reaction with PPh_3 and the intramolecular cyclization, and with the stereochemistry of both reactions.

It appears that the intermolecular reaction with PPh_3 competes with the intramolecular cyclization, but in some cases does not overcome it completely, even in the presence of a large excess of PPh_3. It appears also that the use of CH_3CN as solvent strongly accelerates all the examined reactions, allowing them to be carried out at room temperature instead than at 80° as in C_6H_6. The reaction temperature and also the nature of the solvent play an important role in product distribution. In fact in the case of (**1a**) the formation of phosphorane is favoured at room temperature and in benzene solution while at 80° the intramolecular cyclization predominates. It had already been noticed that cyclopropacinnolines are not thermally stable, and rearrange on heating to other products.[3-6] We have now observed that cyclopropacinnolines (**3a**) (*endo*-Me) and (**3b**) both *endo* and *exo*-phenyl, on refluxing in C_6H_6, rearrange to the corresponding benzodiazepines (**4a, b**), and this rearrangement is not influenced by the presence of Et_3N.

Moreover, in the case of (**3b**), the *endo* and *exo*-phenyl isomers, in solution, interconvert to a 7:3 equilibrium mixture, independently on the presence of base. The reactions of hydrazonyl chlorides (**1a, b**) *E, Z* with PPh_3, as well as their intramolecular cyclizations are all accelerated by a high concentration of Et_3N. But the most striking features of these reactions are that from the *E* and *Z* isomers of hydrazonoyl chlorides (**1a**) one isolates only one cyclopropacinnoline, the *endo*-Me isomer, and the *Z* phosphorane. In one case (see Table 1) the NMR spectrum of the crude product mixture, taken just after the complete conversion of (**1a**)*E*, showed also a quartet at 5.12 ppm which may be reasonably attributed to phosphorane (**2a**)*E*. In solution this quartet slowly decreased and finally disappeared, while that of the *Z* isomer at 5.40 ppm increased. The attribution of the signal at 5.40 ppm to the *Z* isomer and of that at 5.12 ppm to the *E* isomer has been made by analogy with chlorohydrazones (**1a**)*E* and *Z*. All attempts to isolate the phosphorane (**2a**) failed.

The results reported in Table 1 show, once again,[7] the complexity of behaviour of the hydrazonoyl chlorides (**1**) in base promoted reactions. Nevertheless, the reaction patterns indicated in Scheme 1 might account for the observed results. A high base concentration and the use of a polar solvent should accelerate the formation of the nitrile imine (**5**), which is the first step of all the observed reactions. The cyclic dipolar species (**6**), generated by 1,7-electrocyclic rearrangement of the first formed nitrile imine (**5**), represents the common intermediate of cyclopropacinnolines and benzodiazepines; indeed cyclopropacinnoline formation is favoured over that of benzodiazepine on kinetic grounds, i.e. in CH_3CN as solvent, which is polar and in which the reaction

Table 1.



(1) **(2)** **(3)** **(4)**

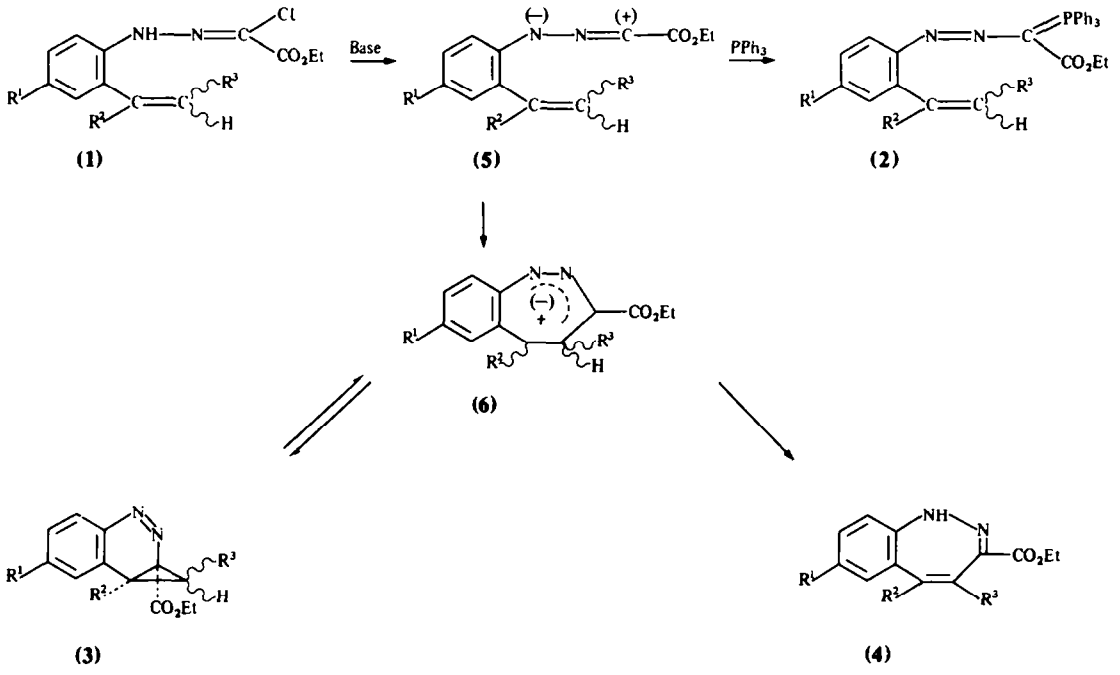
a: $R^1=Cl, R^2=Ph, R^3=Me$; b: $R^1=R^2=H, R^3=Ph$

	REACTANTS		REACTION CONDITIONS			OVERALL YIELD %	PRODUCTS RATIO				
(1)	Et_3N moles/mole(1)	PPh_3 moles/mole(1)	Solvent	Temp. °C	Time		(2)	conf.	(3)	conf.	(4)
aE	1.5	3	CH_3CN	r.t.	11h	91[c]	71	Z	8	Me endo	26
"	5	3	"	"	1h	100[d]	70	E+Z	22	"	8
"	5	3	C_6H_6	"	20 days	85[d]	71	Z	-		29
"	5	3	"	80	4h	100[d]	25	Z	-		75
"	1.5	-	CH_3CN	r.t.	14h	100[d]	-		32	Me endo	68
"	5	-	"	"	1,5h	100[d]	-		25	"	75
"	5	-	C_6H_6	80	5h	88[c]	-		-		100
aZ	1.5	3	CH_3CN	r.t.	7h	95[c]	100	Z	-		-
"	5	3	"	"	1h	100[c]	85	"	15	Me endo	-

"	5	3	C_6H_6	"	20 days	75[d]	100	"	-		-
"	5	3	"	80	4h	100[d]	57	"	38	Me endo	5
"	1.5	-	CH_3CN	r.t.	1 day	100[d]	-		97	"	3
"	5	-	"	"	45 min	98[d]	-		100	"	
"	5	-	C_6H_6	80	7h	98	-		91		9
bE	1.5	3	CH_3CN	r.t.	20 min	95[c]	100	E	-		-
"	5	3	"	"	10 min	95[c]	100	"	-		-
"	1.5	-	"	"	20 min	100[d]	-		91(9)	Ph eso(endo)	-
"	5	-	C_6H_6	80	1h	100[d]	-		40(50)	" "	10
"	5	-	CH_3CN	r.t.	10 min	100[d]	-		90(10)	" "	-
"	5	3	C_6H_6	"	48h	95	100	E	-		-
bZ	1.5	3	CH_3CN	r.t.	2h	89[c]	100	Z	-		-
"	5	3	"	"	45 min	90[c]	100	Z	-		-
"	1.5	-	"	"	2h	100[d]	-		92(8)	Ph endo(eso)	-
"	5	-	C_6H_6	80	4h	100[d]	-		20(10)	" "	70

c = YIELDS ON ISOLATED PRODUCTS

d = YIELDS CALCULATED FROM NMR SPECTRUM OF THE CRUDE REACTION MIXTURE



Scheme 1.

operates at lower temperatures. The interconversion of *endo* and *exo*-phenyl cyclopropacinnolines (**3b**) may be explained by assuming that the heterocyclic ring in the intermediate (**6**) flips at a rate comparable with that of the formation of the 3,5 bond. The trapping of the dipolar species (**6**) by 1,3-reaction with $N_3^{(-)}$ in phase transfer conditions has been reported.[7]

But the synthesis of the phosphoranes does not go through the intermediacy of the cyclic dipole (**6**); phosphoranes are formed directly on reaction of PPh_3 with nitrile imines (**5**), and PPh_3 seems to be completely unreactive towards the cyclic dipole (**6**). When *exo*-phenyl cyclopropacinnoline (**3b**) was reacted with 3 mol PPh_3 there was interconversion to a 3:7 mixture of *exo* and *endo*-phenyl cyclopropacinnoline (**3b**), at the same rate as in the absence of PPh_3.

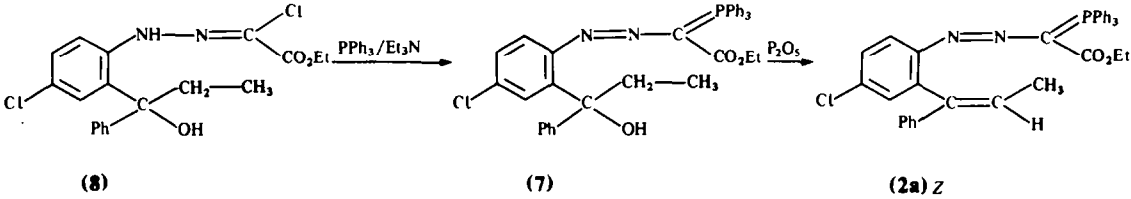
The competition between the intermolecular reaction with PPh_3 and the intramolecular cyclization, in the cases where it has been observed, appears to be influenced by temperature and solvent polarity. The temperature effect may reflect a lower activation enthalpy for the formation of the phosphorane with respect to that of the cyclic species (**6**), according to the general trend observed when bimolecular and monomolecular reactions are compared.

The solvent effect on products distribution can be accounted for by the larger charge separation involved in the formation of (**6**) with respect to that of the phosphorane.

In the case of (**1a**) only the *Z* phosphorane could be isolated, both from the *Z* and *E*(**1a**) isomers, possibly because the *Z* form is much more stable than the *E* isomer: this statement is consistent with the above reported alterations in the NMR spectrum of the crude reaction mixture from (**1a**)*E*, PPh_3, and Et_3N, and is also consistent with the fact that only the *Z* isomeric phosphorane (**2a**) is obtained on dehydration of the hydroxy phosphorane (**7**) by P_2O_5, while in the same conditions the corresponding chlorohydrazone (**8**) gives both *E* and *Z* isomers, with the former one in major quantity[7] (Scheme 2).

Phosphorane (**2a**)*E*, which should be first formed in the reactions of (**1a**)*E* with PPh_3, should then turn into its *Z* isomer. This transformation should be made possible by charge delocalization on a very large portion of the molecule of phosphoranes (**2**), which might considerably lower the rotational barrier around the olefinic bond.

Phosphoranes (**2a**)*E* and (**2b**)*E* and *Z* have been subjected to thermal treatment, in order to make the phosphoranyl moiety to react with the *o*-alkenyl group. All the phosphoranes were rather stable to elevated temperatures and only reacted at about 110° at a reasonable rate (24–34 h) to give in high yield the corresponding benzodiazepines, thus preventing the



Scheme 2.

Table 2. Physical, spectral, and analytical data of new compounds

Comp.	M.P.(°C)	Cryst. solv.	ν_{max}(Nujol),cm^{-1}	δ ($CDCl_3$)	Elemental analysis % Found (required)		
					C	H	N
(7)	200-202	EtOH	3120 (V. broad), 1680	0.9 (3Hm), 1,1 (3H,t, J 7) , 2.25 (2Hm), 4.2 (2H,q, J 7), 6.35-7.8 (23H,m), 9.0 (1H, br,s)	72.21 (71.55)	5.54 (5.48)	4.48 (4.51)
(2a)Z	172-174	C_6H_6-light petroleum	3025, 1665	1.0(6H, t , J 7), 4.05 (2H,q , J 7), 5.40(1H, q ,J 7) , 6.6-7.65 (23H,m)	72.95 (73.60)	5.40 (5.31)	4.59 (4.64)
(2b)E	182-183	C_6H_6-light petroleum	1670	1.1 (3H, t,J 7),4.15 (2H, q, J 7), 6.5-7.8 (26H,m)	77.35 (77.87)	5.56 (5.59)	4.99 (5.05)
(2b)Z	176-178	C_6H_6-light petroleum	1670	1.1 (3H, t,J 7), 4.15 (2H,q, J 7) , 5.67 (1H, d,J 13.5), 5.77 (1H,d, J 13.5), 6.6-7.73 (24H, m)	77.27 (77.87)	5.54 (5.59)	5.01 (5.05)

observation of any possible influence of the configuration around the double bond on their cyclization reaction; on the other hand the stereochemistry plays an important role in determining the nature and the stereochemistry of the products of the reaction between nitrile imines and PPh_3.

EXPERIMENTAL

M.ps were taken with a Büchi apparatus and are uncorrected. NMR and IR spectra were recorded with a Varian EM-90 and a Perkin–Elmer 377 instrument, respectively. Chemical shifts are given as δ values, in ppm (Me_4Si as internal standard). M.ps (crystallization solvent), spectral and analytical data for all new compounds are collected in Table 2.

Arylazomethylenetriphenylphosphorane (**7**)

Arylhydrazonoylchloride (**8**) (3.14 g) was suspended into a soln of PPh_3 (4.17 g) in CH_3CN (110 cm³). A soln of Et_3N (2.23 cm³) in CH_3CN (10 cm³) was slowly added during 3 h under stirring. The mixture, stirred overnight, became clear and did not contain any hydrazonoyl chloride (**8**) (TLC silica gel; eluant C_6H_6–EtOAc 1:1). After evaporation of the solvent under reduced pressure, the residue was washed several times with light petroleum, then with water and dried at room temp. to give 4.5 g of (**7**) as a yellow solid.

Dehydration of phosphorane (**7**)

To a soln of phosphorane (**7**) (1 g) in C_6H_6 (50 cm³), P_2O_5 (3g) was added. The mixture was stirred overnight at room temp and then poored on ice. NaOH pellets were added to make the mixture strongly alkaline. The organic layer was separated and the aqueous layer was extracted several times with Et_2O. The collected organic solns were dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. An NMR spectrum of the crude reaction mixture (0.8g) revealed the presence of some unreacted phosphorane (**7**) but no signals which could be reasonably attributed to (**2a**)*E* isomer.

Reactions of hydrazonoyl chlorides (**1**) *with* PPh_3 *and* Et_3N

(a) *In CH_3CN.* To a solution of hydrazonoyl chloride (**1**) ($3 \cdot 10^{-3}$ moles) and PPh_3 ($9 \cdot 10^{-3}$ moles) in CH_3CN (100 cm³), Et_3N was added under stirring at room temperature in the ratios indicated in Table 1. Reaction progress was monitored by TLC (silica gel; eluant Et_2O–light petroleum 1:1). When (**1**) was completely reacted, the solvent was evaporated under reduced pressure at room temperature. The residue was taken up with water and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and the solvent evaporated at room temperature. The residue was examined by NMR as crude mixture and its components were separated by column chromatography (silica gel; eluant Et_2O–light petroleum–Et_3N 1:1:0.1). Phosphoranes (**2**) were not eluted by the above solvents but were recovered by extruding the silica gel at the top of the column, extracting it several times with CH_2Cl_2 and evaporating the solvent at reduced pressure.

(b) In C_6H_6 the reactions were carried out as in CH_3CN, at room temperature or at reflux (see Table 1). The solution was extracted with water and dried over Na_2SO_4; the solvent was evaporated at reduced pressure and the residue was examined by NMR and column chromatographed, above.

Reactions of hydrazonoyl chlorides (**1**) *with* Et_3N

The reactions were carried out in CH_3CN or in C_6H_6 as described in the preceding section, without adding PPh_3. Reactant ratios, reaction temperatures and times are reported in Table 1.

Thermal treatment of phosphoranes

Phosphoranes (**4**) ($1.7 \cdot 10^{-3}$ moles) were refluxed in toluene (30 cm³) and the reactions progress was monitored by TLC (silica gel; eluant Et_2O–light petroleum 1:1). Below 110° the reactions were very slow and even at this temperature the complete conversion of phosphoranes required from 24h ((**2a**)*Z*) to 34h ((**2b**)*E* and *Z*). Toluene was evaporated at reduced pressure and the reaction products (PPh_3 and benzodiazepines) were separated by column chromatography (silica gel; eluant Et_2O–light petroleum 1:1). Benzodiazepines were recovered in yields from 85% (**4a**) to 90% (**4b**).

Thermal treatment of cyclopropacinnolines

Cyclopropacinnolines (**3**) ($1.4 \cdot 10^{-4}$ moles) were refluxed in C_6H_6 (20 cm³). Reactions progress was monitored by TLC (silica gel; eluant Et_2O–light petroleum 1:1). At complete conversion the solvent was evaporated at reduced pressure and the residue, examined by NMR showed the benzodiazepines to be practically pure. The conversion of (**3a**) required 40h, while that of (**3b**), both *endo* and *exo*-phenyl, was complete in 6h. The above reactions, carried out in the presence of Et_3N (7.10^{-4} moles) gave the same results in the same times.

Isomerization of endo and exo-phenyl cyclopropacinnolines (**3b**)

A solution of *exo*-Ph cyclopropacinnoline (**3b**) (30 mg) in C_6D_6 (0.5 cm³) was left at room temperature. NMR spectra recorded every 24h showed a steady transformation into the *endo*-Ph isomer. After 9 days there was a 7:3 equilibrium mixture of the *endo* and *exo*-Ph isomers, which did not change any more in the following days. The same behaviour was observed in the presence of DABCO (30 mg) whose NMR signals do not interfere with those of cyclopropacinnolines. In $CDCl_3$ the same transformation required 7 days. The *endo*-Ph isomer isomerized to the same 7:3 mixture in the same time.

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