Tetrahedron Vol. 40. No. 24, pp. 5263 to 5267, 1984
Printed in the U.S.A.

0040-4020/84 $3.00 + .00

REACTIONS OF CONJUGATED PHENYLAZOALKENES WITH ALIPHATIC AMINES. *SYN*- AND *ANTI*-PHENYLHYDRAZONE DERIVATIVES

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(*Received in UK* 24 *January* 1984)

Abstract—Conjugated phenylazoalkenes react with aliphatic amines to give mixtures of *syn*- and *anti*-phenylhydrazones, the composition of which is solvent dependent. A mechanism for these reactions is proposed. The structures of the products were determined by spectroscopic methods.

It is known that conjugated phenylazoalkenes react with Grignard compounds furnishing phenylhydrazones in the *syn* configuration,[1-4] whereas with anionic reagents they give *anti* isomers.[5] In the case of phenylazocycloalkenes the attack of the reactant at C-2 of the aliphatic residue always occurs in the axial mode.

Only one reaction of a conjugated azoalkene with an aliphatic amine has been reported.[6,7] The reaction in methanol, gives a single phenylhydrazone, while in tetrahydrofuran (THF) it furnishes a mixture of isomeric phenylhydrazones.

The aim of the present paper is to investigate: (i) the role of the solvent in the distribution of the isomers; (ii) the kinetic or thermodynamic control of the reactions; (iii) the reaction mechanisms and the relative stereochemistry.

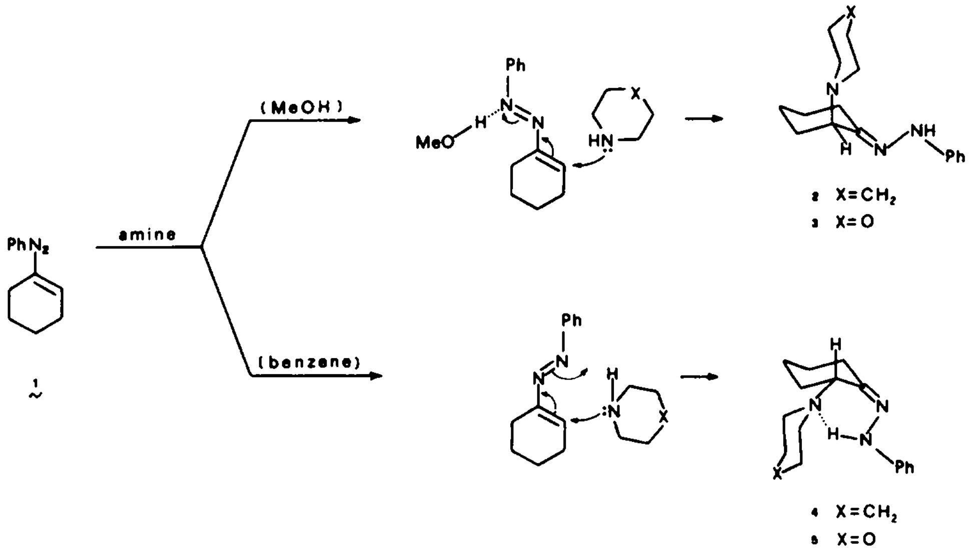
We have therefore considered the reaction of 1-phenylazocyclohexene (**1**) with piperidine in three different solvents, methanol, THF, and benzene. The percentages of *syn*- and *anti*-phenylhydrazones thus obtained are reported in Table 1. Formation of the *anti* isomer is favoured in the polar solvent, while the *syn* isomer largely predominates in the apolar solvent. Similar results are obtained from 1-phenylazocyclohexene (**1**) and morpholine (Table 1). All reactions were carried out in refluxing solvent for 6 hr.

The dependence of the product distribution upon the solvent can be explained as follows. If we admit that the polar protic solvent can solvate the phenylazoalkene in its more stable *s-trans* conformation, as depicted in Scheme 1, then the *anti*-phenylhydrazone is formed. On the other hand, in an apolar solvent, a concerted 1,4-addition of the amine to the substrate in the *s-cis* conformation would occur giving the *syn*-phenylhydrazone (Scheme 1). Mixed products are obtained in an aprotic moderately polar solvent, such as THF.

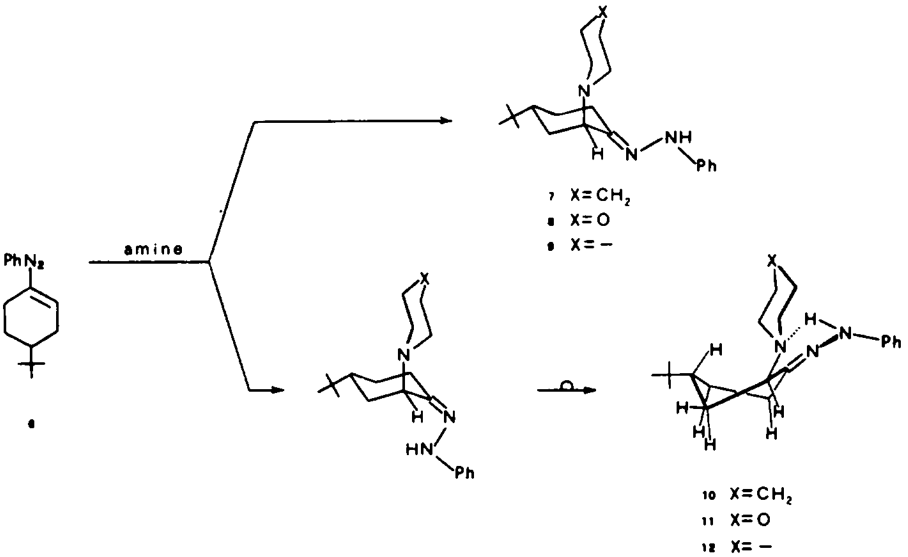
Attempted equilibration of compounds **2–5**, under

Table 1.

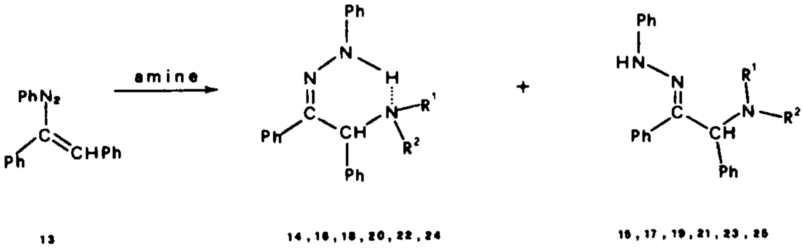
Azocompound	Amine	Phenylhydrazones	Solvent	Percentage of isomers syn	 anti
1	piperidine	2,4	MeOH	0	100
			THF	20	80
			C_6H_6	70	30
1	morpholine	3,5	MeOH	2	98
			THF	30	70
			C_6H_6	80	20
6	piperidine	7,10	MeOH	2	98
			THF	15	85
			C_6H_6	20	80
6	morpholine	8,11	MeOH	5	95
			THF	20	80
			C_6H_6	35	65
6	pyrrolidine	9,12	MeOH	0	100
			THF	20	80
			C_6H_6	30	70



Scheme 1.



Scheme 2.



14, 15 $R^1,R^2 = (CH_2)_5$
16, 17 $R^1,R^2 = (CH_2)_2\text{—}O\text{—}(CH_2)_2$
18, 19 $R^1,R^2 = (CH_2)_4$
20, 21 $R^1 = R^2 = Et$
22, 23 $R^1 = H$, R^2 = n-propyl
24, 25 $R^1 = H$, $R^2 = Ph\text{—}CH_2$

Scheme 3.

Table 2.

Azocompound	Amine	Phenylhydrazones	Solvent	Percentage of isomers <u>syn</u>	<u>anti</u>
13	piperidine	14,15	MeOH	50	50
			THF	75	25
			C_6H_6	90	10
13	morpholine	16,17	MeOH	35	65
			THF	80	20
			C_6H_6	95	5
13	pyrrolidine	18,19	MeOH	25	75
			THF	75	25
			C_6H_6	80	20
13	diethylamine	20,21	MeOH	95	5
			THF	85	15
			C_6H_6	98	2
13	<u>n</u>-propylamine	22,23	MeOH	45	55
			THF	75	25
			C_6H_6	98	2
13	benzylamine	24,25	MeOH	25	75
			THF	70	30
			C_6H_6	60	40

Table 3.

Compound	M.p.(°C)[a]	Formula	Analysis(%) Found C	H	N	Required C	H	N	ν -NH-/cm^{-1} [b]	
2	116-118	$C_{17}H_{25}N_3$	75.3	9.25	15.5	75.25	9.3	15.5	3360	
4	90-91		75.2	9.35	15.4					3150
3	127-128	$C_{16}H_{23}N_3O$	70.1	8.45	15.3	70.3	8.5	15.35	3360	
5	105-106		70.3	8.4	15.5				3360	3190
7	154-156	$C_{21}H_{33}N_3$	76.85	10.1	12.7	77.0	10.15	12.85	3360	
10	111-112		77.2	10.25	12.65				3360	3150
8	162-163	$C_{20}H_{31}N_3O$	72.7	9.3	12.6	72.9	9.5	12.75	3360	
11	65-66		72.85	9.45	12.8				3360	3180
9	133-134	$C_{20}H_{31}N_3$	76.55	9.8	13.3	76.65	9.95	13.4	3360	
12	oil		76.7	10.1	13.4				3360	3150
14	138-139	$C_{25}H_{27}N_3$	81.1	7.2	11.3	81.25	7.35	11.35		3140
15	oil		81.2	7.3	11.25				3330	
16	133-135	$C_{24}H_{25}N_3O$	77.45	6.7	11.15	77.6	6.8	11.3		3150
17	116-117		77.5	6.65	11.35				3340	
18	153-154	$C_{24}H_{25}N_3$	80.9	7.2	11.75	81.1	7.1	11.8		3150
19	82-83		81.25	7.0	11.65				3330	
20	100-102	$C_{24}H_{27}N_3$	80.6	7.55	11.5	80.65	7.6	11.75		3120
21	63-65		80.5	7.4	11.7				3330	
22	79-80	$C_{23}H_{25}N_3$	80.4	7.25	12.2	80.45	7.35	12.25	3320	3140
23	oil		80.6	7.45	12.1				3330	
24	121-122	$C_{27}H_{25}N_3$	82.8	6.3	10.55	82.85	6.45	10.75	3325	3150
25	112-113		82.7	6.55	10.8				3340	

[a] The solid compounds were crystallized from EtOH.

[b] In CCl_4 solution.

the experimental conditions of formation, failed. This indicates a kinetically-controlled distribution of the products (**2**–**5**).

The structures of phenylhydrazones **2**–**5** are unambiguously inferred from the ^{1}H NMR spectra of the C-2 protons and the N$\underline{H}$ protons. In the compounds **2** and **3** the C-2 protons are equatorially oriented (δ 3.0–2.85, W_H 7.5 Hz, and δ 3.0–2.75, W_H 7.5 Hz, respectively), while in **4** and **5** they are axial (δ 3.6–3.2, W_H 18 Hz, and δ 3.6–3.2, W_H 15 Hz, respectively). Moreover, because of the intramolecular hydrogen bond NH—–N, well evident in the IR spectra, the N$\underline{H}$ protons are more deshielded in the *syn* isomers.

To get further insight into the stereochemistry of these reactions, 1-phenylazo-4-*t*-butylcyclohexene (**6**) was allowed to react with piperidine, morpholine and pyrrolidine. The results of these reactions are reported in Table 1.

Both *syn*- and *anti*-phenylhydrazones are formed by axial attack of the amine on the azoalkene **6**. In the ^{1}H NMR spectra of the *syn*-isomers (**10**–**12**) the C-2 protons show signals with W_H values remarkably smaller (10.5, 13.0 and 7.5 Hz respectively) than those of the corresponding products **4** and **5** (18.0 and 15.0 Hz). Furthermore, the IR spectra reveal a weak intramolecular hydrogen bond. These data are consistent with a twist-boat conformation for the *syn*-phenylhydrazones **10**–**12** (Scheme 2).

The *anti*-isomers **7**–**9** show spectroscopic features similar to those of compounds **2** and **3**.

No equilibration was observed for compounds **7**–**12** under their formation conditions.

The reaction with aliphatic amines, leading to a mixture of *syn*- and *anti*-phenylhydrazones, takes place also with open-chain conjugated azoalkenes. For example, phenylazostilbene (**13**)[8] reacts with aliphatic amines in methanol, THF, and benzene as solvent (Scheme 3). The results are listed in Table 2.

Phenylhydrazones **16**–**19** and **22**–**25** are derived from kinetically-controlled reactions since again no equilibration was observed. However, the *anti*-isomers **15** and **21** do isomerize to the corresponding *syn* derivatives (**14** and **20**). The conversion of **15** into **14**, methanol refluxing for 6 hr with piperidine, proceeds to 30–40%, while **21** in the same refluxing

Table 4.

Compound	δ ($CDCl_3$)
2	7.6-6.7(m,6H,Ar-H and N$\underline{H}$);3.0-2.85 (m,1H,W_H7.5Hz,C$\underline{H}$-N);2.85-1.1(m,18H, aliphatic ring H)
4	11.05(s,1H,N$\underline{H}$);7.4-6.5(m,5H,Ar-H); 3.6-3.2(m,1H,W_H18Hz,C$\underline{H}$-N);2.8-1.2 (m,18H,aliphatic ring H)
3	7.5-6.6(m,6H,Ar-H and N$\underline{H}$);3.9-3.4 (m,4H,CH_2-O-CH_2);3.0-2.75(m,1H,W_H 7.5Hz,C$\underline{H}$-N);2.75-1.1(m,12H,aliphatic ring H)
5	10.35(s,1H,N$\underline{H}$);7.6-6.7(m,5H,Ar-H); 4.1-3.6(m,4H,CH_2-O-CH_2)3.6-3.2(m,1H, W_H15Hz,C$\underline{H}$-N);2.4-1.0(m,12H,aliphatic ring H)
7	7.55-6.7(m,6H,Ar-H and N$\underline{H}$);3.0-2.75(m,1H,W_H6Hz,C$\underline{H}$-N);2.7-1.0(m, 17H,aliphatic ring H);0.85(s,9H, $C(CH_3)_3$)
10	9.5(s,1H,N$\underline{H}$);7.6-6.7(m,5H,Ar-H); 3.75-3.4(m,1H,W_H10.5Hz,C$\underline{H}$-N);2.8-1.2(m,17H,aliphatic ring H)0.9(s, 9H,$C(CH_3)_3$)
8	7.55-6.8(m,6H,Ar-H and N$\underline{H}$);4.0-3.5(t,4H,CH_2-O-CH_2);3.05-2.8(m,1H, W_H7.0Hz,C$\underline{H}$-N);2.8-1.1(m,11H,CH_2-N and aliphatic ring H);0.9(s,9H, $C(CH_3)_3$)
11	8.35(s,1H,N$\underline{H}$);7.6-6.6(m,5H,Ar-H); 3.95-3.2(m,5H,CH_2-O-CH_2 and C$\underline{H}$-N, W_H14Hz);2.8-1.05(m,11H,CH_2-N-CH_2 and aliphatic ring H);0.9(s,9H, $C(CH_3)_3$)
9	7.5-6.7(m,6H,Ar-H and N$\underline{H}$);3.05-2.8(m,1H,W_H7.5Hz,C$\underline{H}$-N);3.8-1.1 (m,15H,aliphatic ring H);0.9(s, 9H,$C(CH_3)_3$)
12	7.6-6.7(m,6H,Ar-H and N$\underline{H}$);3.6-3.35(m,1H,W_H7.5Hz,C$\underline{H}$-N);2.9-1.2(m,15H,aliphatic ring H); 0.9(s,9H,$C(CH_3)_3$)
14	12.9(s,1H,N$\underline{H}$);8.0-6.8(m,15H,Ar-H); 4.7(s,1H,C$\underline{H}$-Ph);2.7-2.25(m,4H, CH_2-N-CH_2);1.9-1.4(m,6H,aliphatic ring H)
15	7.6-6.7(m,16H,Ar-H and N$\underline{H}$);4.35(s, 1H,C$\underline{H}$-Ph);2.75-2.35(m,4H,CH_2-N-CH_2); 1.8-1.5(m,6H,aliphatic ring H)
16	12.5(s,1H,N$\underline{H}$);8.0-6.8(m,15H,Ar-H); 4.7(s,1H,C$\underline{H}$-Ph);4.0-3.6(m,4H,aliphatic ring H);2.8-2.3(m,4H,aliphatic ring H)
17	7.6-6.8(m,16H,Ar-H and N$\underline{H}$);4.35(s, 1H,C$\underline{H}$-Ph);3.95-3.6(m,4H,aliphatic ring H);2.85-2.5(m,4H,aliphatic ring H)
18	12.65(s,1H,N$\underline{H}$);8.0-6.8(m,15H,Ar-H); 4.75(s,1H,C$\underline{H}$-Ph);2.85-2.4(m,4H, aliphatic ring H);2.1-1.5(m,4H, aliphatic ring H)
19	7.8-6.8(m,16H,Ar-H and N$\underline{H}$);4.4(s,1H, C$\underline{H}$-Ph);3.1-2.4(m,4H,aliphatic ring H);2.2-1.6(m,4H,aliphatic ring H)
20	12.75(s,1H,N$\underline{H}$);8.0-6.8(m,15H,Ar-H); 5.1(s,1H,C$\underline{H}$-Ph);3.1-2.5(q,4H,J 7.5 Hz,C$\underline{H}_2$Me);1.2-0.8(t,6H,J 7.5Hz,CH_3)
21	7.7-6.7(m,16H,Ar-H and N$\underline{H}$);4.85(s, 1H,C$\underline{H}$-Ph);3.1-2.6(q,4H,J 7.5Hz, C$\underline{H}_2$Me);1.25-0.8(t,6H,J 7.5Hz,CH_3)
22	12.65(s,1H,N$\underline{H}$-Ph);7.9-6.7(m,15H, Ar-H);5.25(s,1H,C$\underline{H}$-Ph);2.95-2.55 (t,2H,C$\underline{H}_2$Et);1.9-1.2(m,3H,C$\underline{H}_2$Me and N$\underline{H}$-CH_2);1.1-0.7(t,3H,CH_3)
23	7.5-6.6(m,16H,Ar-H and N$\underline{H}$-Ph);4.7 (s,1H,C$\underline{H}$-Ph);2.9-2.2(m,3H,N$\underline{H}$-C$\underline{H}_2$); 2.0-1.2(m,2H,C$\underline{H}_2$Me);1.1-0.7(t,3H,CH_3)
24	12.5(s,1H,N$\underline{H}$-Ph);7.9-6.7(m,20 H,Ar-H); 5.4(s,1H,C$\underline{H}$-Ph);3.9(d,2H,J 3.0Hz, CH_2);1.9(s,1H,N$\underline{H}$-CH_2)
25	7.6-6.7(m,21H,Ar-H and N$\underline{H}$-Ph);4.75(s, 1H,C$\underline{H}$-Ph);3.95(s,2H,CH_2);2.5(s,1H,N$\underline{H}$-CH_2)

solvent for 6 hr with diethylamine is completely isomerized to **20**. This behaviour of compounds **15** and **21** appears unusual and requires further investigation.

EXPERIMENTAL

^{1}H NMR spectra were recorded with JEOL JNM 60 HL and Bruker WP 80 spectrometers (TMS as internal standard). IR spectra were recorded with a Perkin–Elmer 225 spectrophotometer. Analytical tlc plates were coated with silica gel G (Merck).

Syn *and* Anti-*Phenylhydrazones* (**2–5**, **7–12**, **14–25**)

The appropriate amine (0.03 mol) was added to the azoalkene (0.01 mol) in methanol, THF, or benzene (30 ml). The mixture was refluxed for 6 hr. The solvent was evaporated and the isomers percentage was estimated by tlc and then quantitatively determined by ^{1}H NMR. The products were isolated by column chromatography on highly pure silica gel (Merck 70–230 mesh ASTM, eluting with benzene). The solid compounds were crystallized from EtOH.

Equilibration attempts were performed by addition of a few drops of the appropriate amine to the phenylhydrazone derivative (0.001 mol) in methanol, THF, or benzene (10 ml). The mixture was heated for 6 hr.

All the products were obtained in almost quantitative yield. Physical, analytical, and spectral data are reported in Tables 3 and 4.

Acknowledgements—The authors wish to thank Dr. Adriano Bigotto for the IR spectra and the IR interpretation, and Mr. Luciano Stoppari for the ^{1}H NMR spectra. This work was supported by a grant from the C.N.R., Rome.

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