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REACTIONS OF CONJUGATED PHENYLAZOALKENES WITH ANIONIC REAGENTS—5

ANTI-PHENYLHYDRAZONE DERIVATIVES

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Abstract—Conjugated phenylazoalkenes add anionic reagents to give 2-substituted *anti*-phenylhydrazones, as demonstrated by ^{1}H NMR spectroscopy and, in some cases, by comparison with authentic samples.

We have previously shown that conjugated phenylazocycloalkenes react with Grignard compounds to give *syn*-phenylhydrazones with the C-2 substituent axially oriented, in accordance with the proposed reaction mechanism.[1-3]

Such a mechanism implies that the C=C–N=N system lies in s-*cis* conformation, that the magnesium coordinates to the nitrogen atom linked to the aromatic ring, and that 1,4 conjugated addition occurs.[2,4]

Some reactions of conjugated arylazoalkenes with anionic reagents are reported for which, however, neither reaction mechanisms nor reaction product structures are proposed.[5]

In these cases it is very unlikely that any coordination occurs between the azoalkene and the reactant, and consequently the anion can attack the azocompound in its more stable s-*trans* conformation. To get a deeper insight into these reactions, we have employed some substrates whose reactivity with Grignard compounds has been already studied.[1,2]

Compound **1**[6] reacts with sodium thiophenate to give the phenylhydrazone **2**[7] identical with the reaction product of ketone **3**[8] and phenylhydrazine and therefore undoubtedly an *anti*-phenylhydrazone.

In the ^{1}H NMR spectrum, the proton geminal to the thiophenyl group in compound **2** gives a signal with a pattern (pseudo triplet, W_H 8 Hz) which indicates that the chair–chair conformational equilibrium is strongly shifted towards the conformer with the C-2 substituent in the axial position. A similar conformational equilibrium due to anomeric effect is found for the ketone **3**.[9] Compound **4**[2] undergoes the same reaction as **1** giving **5**, which is obtained from the trans-ketone **6**[8,9] and phenylhydrazine, and is therefore again the *anti*-phenylhydrazone. The entering group is axially oriented, as revealed by the ^{1}H NMR spectrum of the C-2 geminal proton (pseudo triplet, W_H 8 Hz), in accordance with an antiparallel attack of the reactant.

Continuing our study on the reactivity of conjugated azoalkenes, we employed different nucleophilic reagents, such as sodium ethyl cyanoacetate, malononitrile and diethyl malonate.

Investigations on the reaction products are complicated by the fact that in the ^{1}H NMR spectrum the C-2 proton signals are overlapped by those of the other cycloaliphatic ring protons, therefore preventing us from drawing conclusions on the orientation of the entering group. Compound **1** reacts with sodium ethyl cyano acetate to give the phenylhydrazone **7** which shows the same physicochemical and spectroscopic properties as the product from ketone **8**[10] and phenylhydrazine (Scheme 2). This fact demonstrates that **7** lies in an *anti*-configuration as do compounds **2** and **5**. In this case, however, it is possible that the bulky entering group is equatorially oriented.

Compound **4** also reacts with sodium ethyl cyanoacetate giving the *anti*-phenylhydrazone **9** the ^{1}H NMR spectrum of which is unlike that of the

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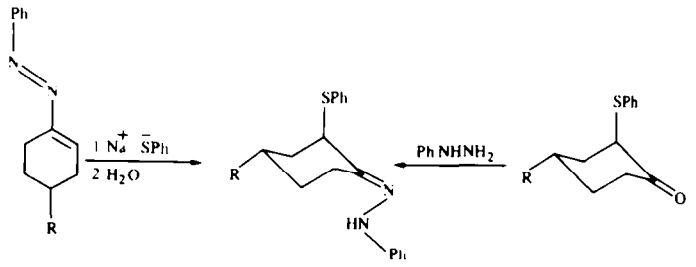
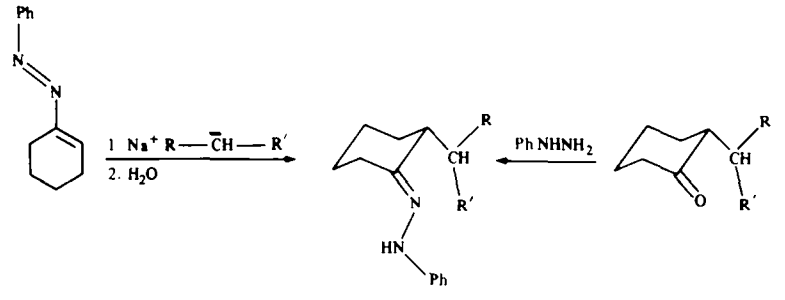


1 R = H **2** R = H **3** R = H
4 R = Bu^t **5** R = Bu^t **6** R = Bu^t

Scheme 1.



1 **7** R = CN R′ = COOEt **8** R = CN R′ = COOEt
12 R = R′ = CN
13 R = R′ = COOEt

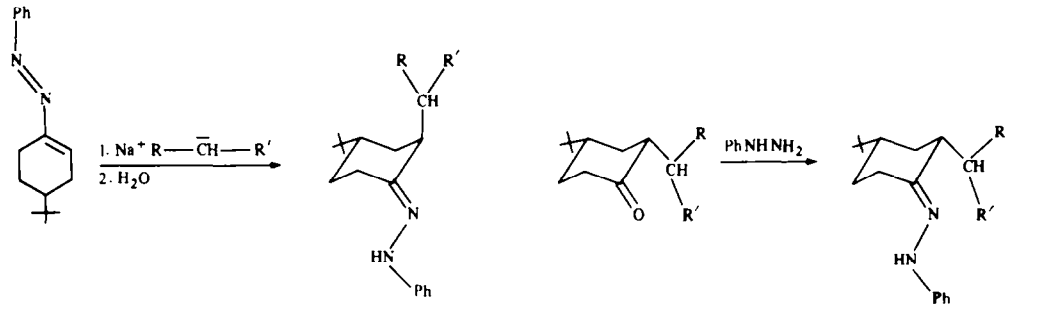
Scheme 2.

product **11**, obtained from the *cis*-ketone **10** and phenylhydrazine (Scheme 3). Since both compounds are *anti*-isomers, the difference between them must be the orientation of the C-2 substituent.

Sodium malononitrile and sodium diethyl malonate were allowed to react with azoalkenes **1** and **4**, leading to the corresponding hydrazones **12**, **13**,[5] **14** and **15** (Schemes 2 and 3). By analogy, we assign to these compounds the structures as in Schemes 2 and 3. Unfortunately, however, we were unable to synthesize the corresponding 2-substituted-cyclohexanones and consequently could not check the structures.

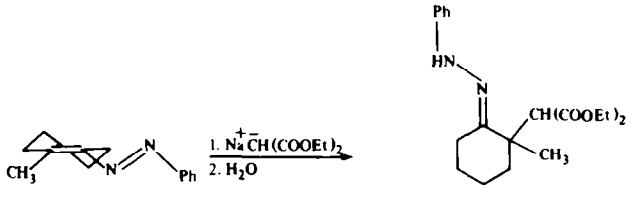
To confirm that azoalkenes lie in s-*trans* conformation when reacting with nucleophiles as above described, compound **16** was examined in which the phenylazo-moiety is forced into the s-*trans* orientation by the presence of the C-2 methyl group. As expected, compound **16** was not attacked by Grignard compounds,[4] whereas reacted with sodium diethyl malonate giving phenylhydrazone **17** (Scheme 4).

The reaction with nucleophilic compounds leading to hydrazone derivative also occurred with open-chain conjugated azoalkenes. Actually phenylazostilbene **18**[11] and sodium ethyl cyano acetate gave the product **19** (Scheme 5), the structure of which was assigned on the basis of its ^{1}H NMR spectrum. In fact the C-1 and C-2 protons give rise to an AB spin system and resonate at δ 4.7 and δ 4.2 respectively.



4 **9** R = CN R′ = COOEt **10** R = CN R′ = COOEt **11** R = CN R′ = COOEt
14 R = R′ = CN
15 R = R′ = COOEt

Scheme 3.



16 **17**

Scheme 4.

Table 1.

Compound	M.p.(°C)[a]	Formula	Analysis(%) Found C	H	N	Required C	H	N	$\bar{\nu}_{max}/cm^{-1}$[b] ν-NH-	ν-C≡N	ν-C=O	ν-C=N-	δ($CDCl_3$)[c]
2	134-135	$C_{18}H_{20}N_2S$	73.2	6.65	9.6	72.95	6.8	9.45	3360				7.9-6.75(11H,m,Ar-H and NH),4.4-4.2 (1H,m,W_H 8Hz,CHSPh),2.7-1.3(9H,m, aliphatic ring H)
5	105-106	$C_{22}H_{28}N_2S$	74.8	8.0	7.7	74.95	8.0	7.95	3360				7.8-6.8(11H,m,Ar-H and NH),4.6-4.4 (1H,m,W_H 8Hz,CHSPh),2.3-1.1(8H,m, aliphatic ring H),0.8(9H,s,$C(CH_3)_3$)
7	173-174	$C_{17}H_{21}N_3O_2$	68.4	6.95	14.2	68.2	7.05	14.0	3350	2240	1710	1630	9.15(1H,s,NH),7.3-6.6(5H,m,Ar-H), 4.35(1H,d,J 5.0Hz,NC-CH-COOEt),4.15 (2H,q,J 7.0Hz,CH_2),3.3-1.4(9H,m, aliphatic ring H),1.2(3H,t,J 7.0Hz,CH_3)
9	165-166	$C_{21}H_{29}N_3O_2$	71.2	8.45	11.6	70.95	8.2	11.8	3330	2250	1720	1630	7.45-6.8(6H,m,Ar-H and NH),4.25(2H, q,J 7.5Hz,CH_2),3.65(1H,d,J 4.5Hz. NC-CH-COOEt),3.5-1.1(8H,m,aliphatic ring H),1.3(3H,t,J 7.5Hz,CH_3),0.9 (9H,s,$C(CH_3)_3$)
11	163-164	$C_{21}H_{29}N_3O_2$	70.8	8.1	11.7	70.95	8.2	11.8	3340	2260	1725	1630	7.45-6.7(6H,m,Ar-H and NH),4.25(2H, q,J 6.0Hz,CH_2),3.6(1H,d,J 4.0Hz, NC-CH-COOEt),3.4-1.1(8H,m,aliphatic ring H),1.3(3H,t,J 6.0Hz,CH_3),0.9 (9H,s,$C(CH_3)_3$)
12	155-156	$C_{15}H_{16}N_4$	71.6	6.35	22.4	71.4	6.4	22.2	3360	2250			8.45(1H,s,NH),7.5-6.6(5H,m,Ar-H), 4.75(1H,d,J 6.0Hz,$CH(CN)_2$),3.4-1.1 (9H,m,aliphatic ring H)
13	138-139	$C_{19}H_{26}N_2O_4$	65.8	7.4	8.0	65.9	7.55	8.1	3330		1750;1710	1640	7.5-6.7(6H,m,Ar-H and NH),4.3(2H, q,J 7.0Hz,CH_2),4.2(2H,q,J 7.0Hz, CH_2),3.95(1H,d,J 10Hz,$CH(COOEt)_2$), 3.3-0.9(9H,m,aliphatic ring H),1.3 (3H,t,J 7.0Hz,CH_3),1.25(3H,t,J 7.0Hz, CH_3)
14	166-167	$C_{19}H_{24}N_4$	73.85	7.65	18.4	74.0	7.85	18.15	3340	2250;2210		1635	7.5-6.8(6H,m,Ar-H and NH),4.35(1H,d, J 6.0Hz,$CH(CN)_2$),3.3-1.1(8H,m,aliphatic ring H),0.9(9H,s,$C(CH_3)_3$)

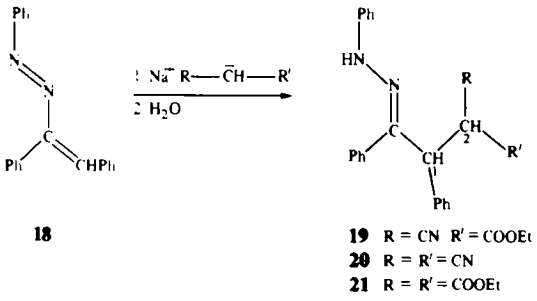
Table 1. (*contd.*)

Compound	M.p.(°C)[a]	Formula	Analysis(%) Found C	H	N	Required C	H	N	$\bar{\nu}_{max}/cm^{-1}$,[b] ν-NH-	ν-C≡N	ν>C=O	ν>C=N-	δ($CDCl_3$)[c]
15	162-163	$C_{23}H_{34}N_2O_4$	68.85	8.7	6.95	68.65	8.5	6.95	3340		1750;1720		7.4-6.8(6H,m,Ar-H and NH),4.3(2H,q, J 7.0Hz,CH_2),4.2(2H,q,J 7.0Hz,CH_2), 3.85(1H,d,J 10Hz,$\underline{CH}(COOEt)_2$),3.6-1.5 (8H,m,aliphatic ring H),1.3(3H,t, J 7.0Hz,CH_3),1.25(3H,t,J 7.0Hz,CH_3), 0.9(9H,s,$C(CH_3)_3$)
17	131-132	$C_{20}H_{28}N_2O_4$	66.4	7.95	7.6	66.65	7.85	7.75	3340		1730;1710		7.5-6.7(6H,m,Ar-H and NH),4.25(2H,q, J 7.5Hz,CH_2),4.2(1H,s,$\underline{CH}(COOEt)_2$), 4.15(2H,q,J 7.5Hz,CH_2),2.9-1.0(3H, m, aliphatic ring H),1.45(3H,s,CH_3), 1.3(3H,t,J 7.5Hz,CH_2-$\underline{CH_3}$),1.25(3H, t,J 7.5Hz,CH_2-$\underline{CH_3}$)
19	94-95	$C_{25}H_{23}N_3O_2$	75.5	5.8	10.4	75.55	5.85	10.55	3340	2250	1740		7.85-6.9(16H,m,Ar-H and NH),4.8-4.1 (2H,m,δ 4.7 C_1-H,δ 4.2 C_2-H,J 7.5Hz), 4.2(2H,q,J 7.5Hz,CH_2),1.2(3H,t, J 7.5Hz,CH_3)
20	146-147	$C_{23}H_{18}N_4$	78.75	5.35	15.75	78.85	5.2	16.0	3340	2260			7.8-6.9(16H,m,Ar-H and NH),4.8-4.3 (2H,m,δ 4.7 C_1-H,δ 4.35 C_2-H,J 9.0Hz)
21	127-128	$C_{27}H_{28}N_2O_4$	72.75	6.3	6.25	72.95	6.35	6.3	3350		1750;1725		7.7-6.9(16H,m,Ar-H and NH),4.7(2H,s, C_1-H and C_2-H),4.3(2H,q,J 7.5Hz,CH_2), 4.0(2H,q,J 7.5Hz,CH_2),1.3(3H,t, J 7.5Hz,CH_3),0.95(3H,t,J 7.5Hz,CH_3)

[a] Crystallized from ethanol.

[b] Nujol. Not all the absorption bands are given.

[c] Compound 5 in C_6D_6; compound 7 in DMSO, compound 12 in $CDCl_3$ and $(CD_3)_2CO$.



18

19 R = CN R' = COOEt
20 R = R' = CN
21 R = R' = COOEt

Scheme 5.

This attribution is confirmed by the ^{1}H NMR analysis of the nitrile derivative **20** in which the C-1 proton shift is at δ 4.7 as in **19**, while the C-2 proton resonates at δ 4.35, due to the different electronegativity of –CN and –COOEt groups.

The ^{1}H NMR spectrum of phenylhydrazone derivative **21** obtained from phenylazostilbene and sodium diethyl malonate reveals the non equivalence of the two ethoxycarbonyl groups and the fortuitous equivalence of the C-1 and C-2 protons.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Jeol JNM 60 HL and on a Brüker WP 80 spectrometer (TMS or DSS as internal standard). IR spectra were recorded with a Perkin–Elmer 297 spectrophotometer. Analytical TLC plates were coated with silica gel G (Merck).

Anti-*phenylhydrazones* (**2**, **5**, **7**, **9**, **11–15**, **17**, **19–21**)

The compound with the activated C–H bonds, ethyl cyanoacetate, malononitrile, diethyl malonate (0.02 mol) was added to Na (0.02 g at) in EtOH (20 ml). After 30 min the appropriate azoalkene (0.01 mol) was added and the mixture was heated at 70–80° with stirring for 3 hr. The solvent was evaporated and the mixture, after the hydrolysis with H_2O, was extracted with ether. The phenylhydrazone, obtained by elimination of the solvent, was crystallized from EtOH.

Compound (**7**) was also synthesized from ketone **8**[10] (0.01 mol) in ether (20 ml) and phenylhydrazine (0.01 mol) at room temperature under stirring for 2–3 hr. The solvent was removed and the compound crystallized.

Compound **11** was prepared from ketone **10** and phenylhydrazine under the same conditions as compound **7**.

All the products were obtained in almost quantitative yield. Physical, analytical, and spectral data are reported in Table 1.

Cis-*ethyl α-cyano-2-oxo-5-t-butylcyclohexaneacetate* (**10**)

This compound was prepared from 2-bromo-4-t-butyl-cyclohexanone[12] (0.01 mol) and sodium cyano acetate (0.01 mol), by the same procedure as compound **8**.[10]

Ketone **10**, which is the main product in the reaction mixture, was purified by column chromatography on extra pure silica gel (Merck 70–230 mesh ASTM, elution with benzene). The compound (0.01 mol) was dissolved in benzene (20 ml) containing p-toluenesulfonic acid (catalytic amount). The solution was refluxed for 72 hr and the ketone was recovered unchanged.

The axial position of the C-1 proton was confirmed by ^{1}H NMR spectral simulation. Colourless oil, b.p. 170–175° (1 mm Hg); (Found: C, 67.70; H, 8.65; N, 5.30; $C_{15}H_{23}NO_3$ requires C, 67.90; H, 8.75; N, 5.30%). δ ($CDCl_3$) 4.35 (2H, q, J 7.0 Hz, CH_2–CH_3), 4.1 (1H, d, J 6.0 Hz, NC–CH–COOEt), 3.45 – 2.95 (1H, m, C_1H), 2.8–1.5 (7H, m, aliphatic ring H), 1.35 (3H, t, J 7.0 Hz, CH_2–CH_3), 1.0 (9H, s, $C(CH_3)_3$). $\bar{\nu}_{max}$ (cm^{-1}, film): 2260 (ᵛCN); 1750, 1720 (ᵛCO ester and ᵛCO).

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