

Reactions of Conjugated Arylazocycloalkenes with Grignard Reagents. Part 3.¹ A Convenient Synthesis of 2,6-Diaryl- and 2-Alkyl-6-aryl-cyclohexanones

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A synthesis of the title compounds with the substituents at C-2 and C-6 *trans* to each other is described. 2-Arylcyclohexanones were converted into 1-phenylazo-6-arylcyclohexenes, which by reaction with Grignard reagents led to *trans*-2,6-diaryl- and *trans*-2-alkyl-6-aryl-cyclohexanone phenylhydrazones. These compounds by oxidative hydrolysis furnished the corresponding *trans*-ketones, which were readily epimerised into the more stable *cis*-isomers.

IN continuing our studies on the reactions of conjugated arylazocycloalkenes with Grignard reagents,^{1,2} we have examined the possibility of using these reactions as a novel entry into 2,6-diaryl- and 2-alkyl-6-aryl-cyclo-

hexanones. To our knowledge there is little reported in the literature on these compounds,³⁻⁷ which could be interesting intermediates in the synthesis of particular drugs⁸ and diterpenoid alkaloids.⁵

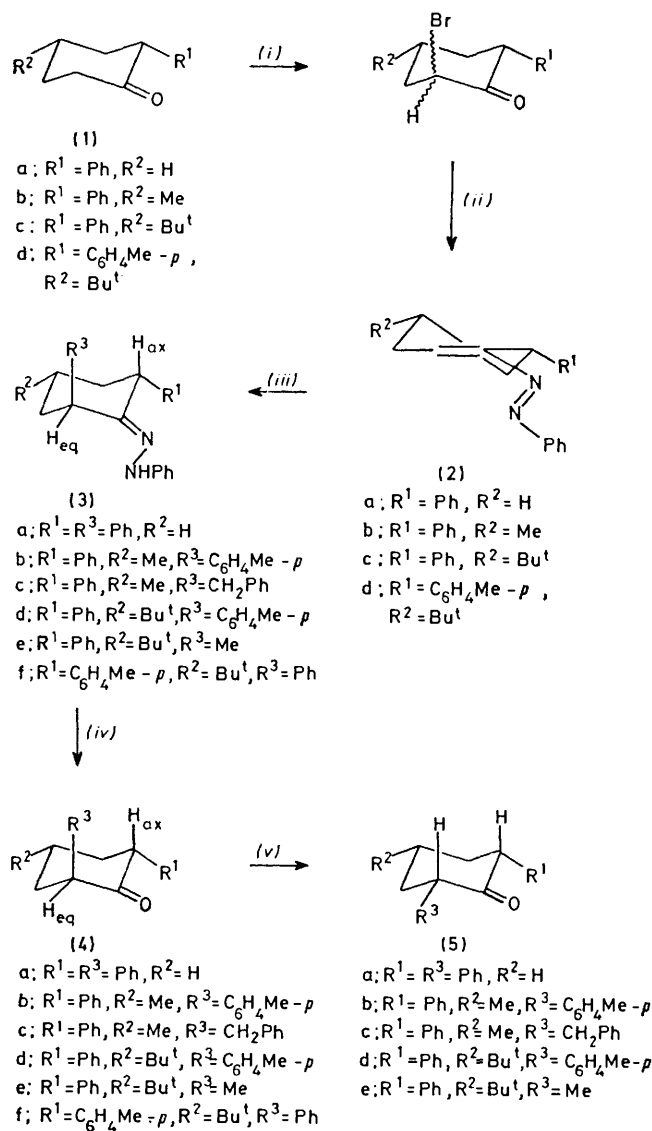
We have previously reported a general synthesis of 2-alkyl- and 2-aryl-cyclohexanones (1),¹ for which the aforementioned Grignard reactions were the key steps. As an extension of this work we now describe a convenient synthesis (75–80% yield) of 2,6-diaryl- and 2-alkyl-6-aryl-cyclohexanones (4) with the two substituents *trans*, starting from ketones (1) through the reaction sequence depicted in the Scheme.

RESULTS AND DISCUSSION

According to the reaction mechanism previously reported² for the conjugated addition of a Grignard reagent to arylazocyclohexenes, the hydrazones (3) must have the *syn*-configuration with respect to the entering group R³ which, in turn, will have axial orientation. The stereochemistry at C-2 and C-6 of the hydrazones (3a, b, d, and f) was determined by ¹H n.m.r. spectral analysis. Compound (3a) shows two well-resolved signals corresponding to an equatorial [δ 4.2, $W_{\frac{1}{2}}$ 9.5 Hz] and an axial [δ 3.65, $W_{\frac{1}{2}}$ 17 Hz] benzylic proton, respectively; similar spectral features are displayed by compounds (3b, d, and f) (see Table 2).

Little information can be drawn from the ¹H n.m.r. spectrum of (3c), since the signal for the proton geminal to the CH₂Ph group is overlapped by those of benzylic protons of the same group. The hydrazone (3e) could not be isolated because of its easy auto-oxidation into the 1-hydroperoxy-1-phenylazo-derivative. However, the structures of (3c and e) can be assigned by analogy with those of the similar compounds (3a, b, d, and f).

The stereochemistry of the substituted cyclohexanones (4) must be the same as that of the corresponding hydrazone (3), as regards the relative configurations of C-2, C-4, and C-6. In fact, compounds (4) are obtained from (3) under non-epimerising hydrolytic conditions.^{1,9} The *trans* relationship between the substituents at C-2 and C-6 was evident from the ¹H n.m.r. spectral data of (4e and f). Compound (4e) shows a signal [δ 3.55, $W_{\frac{1}{2}}$ 16 Hz] for an axial benzylic proton and a doublet [δ 1.15, J 7.5 Hz] typical of an axial methyl group. Compound (4f) exhibits two distinct signals corresponding to an



SCHEME (i) Br₂(CCl₄); (ii) PhNHNH₂-pyridine; (iii) R³MgX; (iv) NaIO₄ (pH 7); (v) pyrrolidine (dilute MeOH)

TABLE 1
Physical, analytical, and spectral data of arylazocyclohexenes (2a—d)

Compound (2a)	M.p. (°C) 105—106 (ethanol)	Formula C ₁₈ H ₁₈ N ₂	Analysis (%)						λ_{\max} , ^a /nm	δ (CDCl ₃)
			Found			Required				
			C	H	N	C	H	N		
(2a)	105—106 (ethanol)	C ₁₈ H ₁₈ N ₂	82.5	6.7	10.8	82.4	6.9	10.7	434	7.8—7.0 (11 H, m, Ar-H and vinyl H), 4.4 (1 H, m, <i>W</i> ₁ 13.5 Hz, <i>CHPh</i>), 3.0—1.3 (6 H, m, aliphatic ring H)
(2b)	99—100 (ethanol)	C ₁₉ H ₂₀ N ₂	82.3	6.95	10.3	82.55	7.3	10.15	432	7.7—6.8 (11 H, m, Ar-H and vinyl H), 4.1 (1 H, m, <i>W</i> ₁ 17 Hz, <i>CHPh</i>), 2.6—0.8 (5 H, m, aliphatic ring H), 1.0 (3 H, d, <i>J</i> 5.5 Hz, Me)
(2c)	117—119 (ethanol)	C ₂₂ H ₂₆ N ₂	82.5	8.15	8.85	82.95	8.25	8.8	436	7.5—6.9 (11 H, m, Ar-H and vinyl H), 4.0 (1 H, m, <i>W</i> ₁ 20 Hz, <i>CHPh</i>), 2.7—0.8 (5 H, m, aliphatic ring H), 0.95 (9 H, s, <i>CMe</i> ₃)
(2d)	118—119 (methanol)	C ₂₃ H ₂₈ N ₂	83.1	8.1	8.75	83.1	8.5	8.45	433	7.5—6.9 (10 H, m, Ar-H and vinyl H), 4.0 (1 H, m, <i>W</i> ₁ 20 Hz, <i>CHAr</i>), 2.7—0.8 (5 H, m, aliphatic ring H), 2.2 (3 H, s, <i>ArMe</i>), 0.9 (9 H, s, <i>CMe</i> ₃)

^a N=N band (*n*- π^*).

equatorial [δ 3.95, *W*₁ 9 Hz] and an axial [δ 3.65, *W*₁ 18 Hz] benzylic proton, respectively.

The ¹H n.m.r. spectra of (4a—d) did not enable the C-2 and C-6 protons to be distinguished (see Table 3); however, unambiguous confirmation of the stereochemistry of ketones (4) was achieved by their base-catalysed equilibration into the more stable all-*cis*-isomers (5).

EXPERIMENTAL

¹H N.m.r. spectra were recorded with a JEOL JNM 60 HL spectrometer (SiMe₄ as internal standard) and i.r. spectra with a Perkin-Elmer 257 spectrophotometer. U.v. spectra were determined for solutions in 95% ethanol with a Perkin-Elmer 124 spectrophotometer. Analytical t.l.c.

plates were coated with silica gel G (Merck). Arylazocyclohexenes were purified by column chromatography on alumina (Merck) (elution with light petroleum, b.p. 40—70 °C). Cyclohexanones were purified by column chromatography on extra pure silica gel (Merck; 70—230 mesh ASTM) (elution with benzene).

Arylazocyclohexenes (2a—d).—A solution of bromine (0.01 mol) in CCl₄ (15 ml) was added dropwise and with stirring to a solution of cyclohexanone (1a—d)¹ in 20 ml of the same solvent, maintaining the temperature at 0—5 °C. The reaction mixture was washed with water until neutral, dried (Na₂SO₄), and evaporated. To the oily residue pyridine (0.01 mol) was added and the temperature was kept at 70 °C for 2 min. The reaction mixture was cooled at room temperature, treated with THF (3 ml), and poured with stirring into a solution of phenylhydrazine (0.01 mol) in THF (20 ml) cooled at 0 °C. Stirring was continued for 3 h.

TABLE 2
Physical, analytical, and spectral data of cyclohexanone phenylhydrazones (3a—d, and f)

Compound	M.p. (°C)	Formula	Analysis (%)						δ (CDCl ₃)
			Found			Required			
			C	H	N	C	H	N	
(3a)	145—146 (ethanol)	C ₂₁ H ₂₄ N ₂	84.3	7.45	8.45	84.65	7.1	8.25	7.5—6.5 (16 H, m, Ar-H and NH), 4.2 (1 H, m, <i>W</i> ₁ 9.5 Hz, <i>H</i> _{eq}), 3.65 (1 H, m, <i>W</i> ₁ 17 Hz, <i>H</i> _{ax}), 2.6—1.4 (6 H, m, aliphatic ring H)
(3b)	113—115 (ethanol)	C ₂₆ H ₂₈ N ₂	84.5	7.45	7.9	84.75	7.65	7.6	7.6—6.5 (15 H, m, Ar-H and NH), 4.2 (1 H, m, <i>W</i> ₁ 8.5 Hz, <i>H</i> _{eq}), 3.7 (1 H, m, <i>W</i> ₁ 17.5 Hz, <i>H</i> _{ax}), 2.6—0.6 (5 H, m, aliphatic ring H), 2.35 (3 H, s, <i>ArMe</i>), 0.95 (3 H, d, <i>J</i> 5 Hz, Me)
(3c)	99—101 (ethanol)	C ₂₆ H ₂₈ N ₂	84.5	7.75	7.55	84.75	7.65	7.6	7.5—6.1 (16 H, m, Ar-H and NH), 3.7 (1 H, m, <i>W</i> ₁ 17.5 Hz, <i>H</i> _{ax}), 3.5—2.7 (3 H, m, <i>CH</i> ₂ <i>Ph</i> and <i>H</i> _{eq}), 2.5—0.8 (5 H, m, aliphatic ring H), 1.0 (3 H, d, <i>J</i> 6 Hz, Me)
(3d)	Oil	C ₂₆ H ₃₄ N ₂	84.5	8.25	6.85	84.85	8.35	6.8	7.9—6.4 (15 H, m, Ar-H and NH), 4.2 (1 H, m, <i>W</i> ₁ 7 Hz, <i>H</i> _{eq}), 3.6 (1 H, m, <i>W</i> ₁ 17.5 Hz, <i>H</i> _{ax}), 2.9—0.7 (5 H, m, aliphatic ring H), 2.25 (3 H, s, <i>ArMe</i>), 0.85 (9 H, s, <i>CMe</i> ₃)
(3f)	Oil	C ₂₉ H ₃₄ N ₂	84.6	8.55	6.5	84.85	8.35	6.8	7.9—6.4 (15 H, m, Ar-H and NH), 4.3 (1 H, m, <i>W</i> ₁ 7 Hz, <i>H</i> _{eq}), 3.6 (1 H, m, <i>W</i> ₁ 18 Hz, <i>H</i> _{ax}), 2.9—0.7 (5 H, m, aliphatic ring H), 2.35 (3 H, s, <i>ArMe</i>), 0.85 (9 H, s, <i>CMe</i> ₃)

TABLE 3
Physical, analytical, and spectral data of cyclohexones (4a—f)

Compound (4a) ^b	M.p. (°C)	Formula	Analysis (%)				$\nu_{\max.}$ $^{\circ}/\text{cm}^{-1}$	$\delta(\text{CDCl}_3)$
			Found		Required			
			C	H	C	H		
(4a)	Oil	$\text{C}_{18}\text{H}_{18}\text{O}$	86.2	7.4	86.35	7.25	1 710 ^c	7.65—6.8 (10 H, m, Ar-H), 3.85 (2 H, m, $W_{\frac{1}{2}}$ 13 Hz, <i>CHPh</i>), 2.7—1.3 (6 H, m, aliphatic ring H)
(4b)	Oil	$\text{C}_{20}\text{H}_{22}\text{O}$	85.9	7.75	86.3	7.95	1 710 ^c	7.6—6.6 (9 H, m, Ar-H), 4.0—3.4 (2 H, m, H_{eq} and H_{ax}), 2.9—0.8 (5 H, m, aliphatic ring H), 2.25 (3 H, s, <i>ArMe</i>), 0.95 (3 H, d, <i>J</i> 5.5 Hz, Me)
(4c)	Oil	$\text{C}_{20}\text{H}_{22}\text{O}$	86.1	7.75	86.3	7.95	1 705 ^c	7.4—6.9 (10 H, m, Ar-H), 4.0—3.5 (1 H, m, $W_{\frac{1}{2}}$ 17.5 Hz, H_{ax}), 3.4—2.8 (3 H, m, CH_2Ph and H_{eq}), 2.5—0.8 (5 H, m, aliphatic ring H), 0.95 (3 H, d, <i>J</i> 6 Hz, Me)
(4d)	Oil	$\text{C}_{23}\text{H}_{28}\text{O}$	86.3	8.9	86.2	8.8	1 715 ^c	7.5—6.9 (9 H, m, Ar-H), 4.1—3.4 (2 H, m, H_{eq} and H_{ax}), 2.4—0.7 (5 H, m, aliphatic ring H), 2.3 (3 H, s, <i>ArMe</i>), 0.95 (9 H, s, CMe_3)
(4e)	Oil	$\text{C}_{17}\text{H}_{24}\text{O}$	83.7	9.85	83.55	9.9	1 715 ^c	7.8—6.7 (5 H, m, Ar-H), 3.55 (1 H, m, $W_{\frac{1}{2}}$ 16 Hz, H_{ax}), 2.65 (1 H, m, <i>CHMe</i>), 2.4—0.7 (5 H, m, aliphatic ring H), 1.15 (3 H, d, <i>J</i> 7.5 Hz, Me), 0.9 (9 H, s, CMe_3)
(4f)	125—127 (methanol)	$\text{C}_{23}\text{H}_{28}\text{O}$	86.1	8.65	86.2	8.8	1 715 ^d	7.7—6.7 (9 H, m, Ar-H), 3.95 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, H_{eq}), 3.65 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, H_{ax}), 3.0—0.9 (5 H, m, aliphatic ring H), 2.3 (3 H, s, <i>ArMe</i>), 1.0 (9 H, s, CMe_3)

^a C=O stretch. ^b Ref. 7. ^c Liquid film. ^d Nujol.

The products were obtained in 90—95% yield. Physical, analytical, and spectral data are reported in Table 1.

Cyclohexanone Phenylhydrazones (3a—d and f).—The reactions of arylazocyclohexenes (2a—d) (0.01 mol) were carried out with the Grignard reagents (PhMgBr, *p*-tolyl-MgBr, PhCH₂MgCl, and MeMgI) (0.025 mol) in anhydrous ether with stirring at room temperature for 3 h. The mixtures were hydrolysed with aqueous 20% ammonium chloride. The organic layers, after washing with water until neutral, drying, and evaporation of the solvent, gave the products (3a—d and f) in almost quantitative yield. Physical, analytical, and spectral data for (3a—d and f) are reported in Table 2. Compound (3e) easily underwent auto-oxidation furnishing *1-hydroperoxy-1-phenylazo-2-methyl-4-*t*-butyl-6-phenylcyclohexane*, m.p. 138—139 °C (from light petroleum) (Found: C, 75.6; H, 8.2; N, 7.35.

$\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2$ requires C, 75.4; H, 8.25; N, 7.65%); δ 7.65—6.9 (10 H, m, Ar-H), 4.0 (1 H, m, $W_{\frac{1}{2}}$ 17 Hz, *CHPh*), 3.45 (1 H, s, OH), 2.85 (1 H, m, *CHMe*), 2.5—1.2 (5 H, m, aliphatic ring protons), 1.4 (3 H, d, *J* 7.5 Hz, Me), and 0.95 (9 H, s, CMe_3); $\lambda_{\max.}$ 407 nm (N=N bond, $n-\pi^*$).

Cyclohexanones (4a—f).—The phenylhydrazone (3a—d, and f) (0.005 mol) was dissolved in methanol (50—70 ml) and hydrolysed at pH 7 with sodium periodate as previously described for *trans*-2,4-disubstituted cyclohexanones.¹ Compound (4e) was obtained in the same way from the Grignard reaction mixture of (2c) with MeMgI, without isolating the hydrazone (3e). Compounds (4a—f) were obtained in quantitative yield. Physical, analytical, and spectral data are reported in Table 3.

Cyclohexanones (5a—e).—The compounds were obtained in almost quantitative yield from the isomers (4a—f) by

TABLE 4
Physical, analytical, and spectral data for cyclohexanones (5a—e)

Compound	M.p. (°C)	Formula	Analysis (%)				$\nu_{\max.}$ $^{\circ}/\text{cm}^{-1}$	$\delta(\text{CDCl}_3)$
			Found		Required			
			C	H	C	H		
(5a) ^b	123—124 (light petroleum)	$\text{C}_{18}\text{H}_{18}\text{O}$	86.4	7.2	86.35	7.25	1 710 ^c	7.55—6.4 (10 H, m, Ar-H), 3.75 (2 H, m, $W_{\frac{1}{2}}$ 17 Hz, <i>CHPh</i>), 2.5—1.6 (6 H, m, aliphatic ring H)
(5b)	108—109 (methanol)	$\text{C}_{20}\text{H}_{22}\text{O}$	86.1	7.95	86.3	7.95	1 715 ^c	7.5—6.8 (9 H, m, Ar-H), 3.8 (2 H, m, $W_{\frac{1}{2}}$ 17 Hz, <i>CHAR</i>), 2.7—0.9 (5 H, m, aliphatic ring H), 2.25 (3 H, s, <i>ArMe</i>), 1.05 (3 H, d, <i>J</i> 6 Hz, Me)
(5c)	87—88 (methanol)	$\text{C}_{20}\text{H}_{22}\text{O}$	86.35	7.8	86.3	7.95	1 710 ^c	7.6—6.8 (10 H, m, Ar-H), 3.75 (1 H, m, $W_{\frac{1}{2}}$ 18 Hz, <i>CHPh</i>), 3.2—2.6 (2 H, m, CH_2Ph), 2.6—0.7 (6 H, m, aliphatic ring H), 0.95 (3 H, d, <i>J</i> 6 Hz, Me)
(5d)	167—169 (methanol)	$\text{C}_{23}\text{H}_{28}\text{O}$	85.9	8.75	86.2	8.8	1 710 ^c	7.5—7.0 (9 H, m, Ar-H), 3.8 (2 H, m, $W_{\frac{1}{2}}$ 17.5 Hz, <i>CHAR</i>), 2.6—0.9 (5 H, m, aliphatic ring H), 2.3 (3 H, s, <i>ArMe</i>), 0.95 (9 H, s, CMe_3)
(5e)	71—72 (methanol)	$\text{C}_{17}\text{H}_{24}\text{O}$	83.25	9.75	83.55	9.9	1 720 ^c	7.6—7.0 (5 H, m, Ar-H), 3.6 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, <i>CHPh</i>), 3.0—0.7 (6 H, m, aliphatic ring H), 1.05 (3 H, d, <i>J</i> 6.5 Hz, Me), 0.95 (9 H, s, CMe_3)

^a C=O stretch. ^b Refs. 3, 4, and 7. ^c Nujol.

equilibration in basic medium.¹ Physical, analytical, and spectra data are reported in Table 4.

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