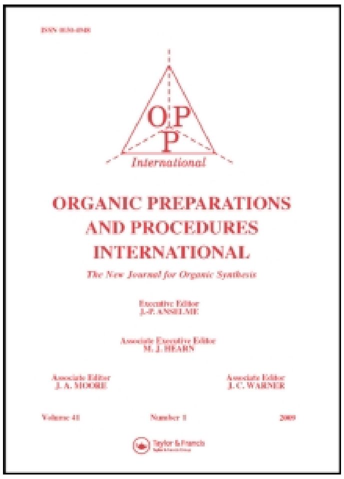

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SYNTHESIS OF 2-AROYL-4-CYANO-4-CARBETHOXY-1,3,5-TRIARYLCYCLOHEXANOLS

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SYNTHESIS OF 2-AROYL-4-CYANO-4-CARBETHOXY-1,3,5-TRIARYLCYCLOHEXANOLS[#]

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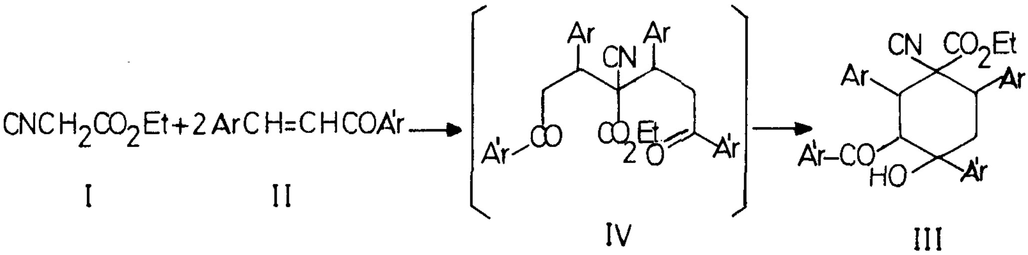
As reported in previous papers,[1-5] the reaction of α,β-unsaturated aromatic ketones bearing a cyano or carbethoxy group in the α-position with active methylene compounds, such as malononitrile or ethyl cyanoacetate, affords δ-cyanoketones which cyclize in the basic medium used for the addition to give a 2-amino-4H-pyran with a cyano or carbethoxy group at positions 3 and 5.

This paper reports the results obtained when chalcones and ethyl cyanoacetate are used as reactants. The reaction proceeds in a very different way and is an useful procedure for the preparation of the new 2-aroyl-4-cyano-4-carbethoxy-1,3,5-triarylcyclohexanols (III) which are obtained in good yield and



are easily isolated in good purity. The ciclohexanols thus obtained are listed in Table 1 together with the microanalytical and physical data.

The formation of cyclohexanols III involves a double Michael addition of ethyl cyanoacetate (I) to two molecules of benzylideneacetophenone (II) to give the bis-adduct IV. This 1,5-diketone undergoes an aldol intramolecular cyclization to the cyclohexanol III which, unlike other cyclic aldols,[6] does not dehydrates spontaneously.

TABLE 1. Physical data of 2-Aroyl-4-cyano-4-carbethoxy-1,3,5-triarylcyclohexanols (III)[a]

Cmpd.	Ar	Ar'	Yield (%)	mp (°C)	Elemental analysis C	H	N	Cl
IIIa	C_6H_5	C_6H_5	64	198-200	79.39	5.86	2.64	
					(79.73)	(5.78)	(2.89)	
IIIb	p-ClC_6H_4	C_6H_5	49	204-206	70.23	4.85	2.34	11.87
					(69.81)	(5.19)	(2.36)	(11.84)
IIIc	C_6H_5	p-ClC_6H_4	47[b]	211-213	70.23	4.85	2.34	11.87
					(70.02)	(4.88)	(2.17)	(11.49)
IIId	p-MeC_6H_4	C_6H_5	59	164-166	79.71	6.28	2.51	
					(79.91)	(6.67)	(2.49)	
IIIe	C_6H_5	p-MeC_6H_4	51	172-173	79.71	6.28	2.51	
					(80.02)	(6.25)	(2.68)	
IIIf	p-$MeOC_6H_4$	C_6H_5	56	184-186	75.00	5.91	2.36	
					(75.39)	(6.03)	(2.43)	
IIIg	C_6H_5	p-$MeOC_6H_4$	49	162-164	75.00	5.91	2.36	
					(75.19)	(5.88)	(2.37)	
IIIh	m-$NO_2C_6H_4$	C_6H_5	50[c]	215-217	67.86	4.68	6.79	
					(68.00)	(4.74)	(7.15)	
IIIi	C_6H_5	p-$NO_2C_6H_4$	48[c]	218-219	67.86	4.68	6.79	
					(68.06)	(4.79)	(7.14)	

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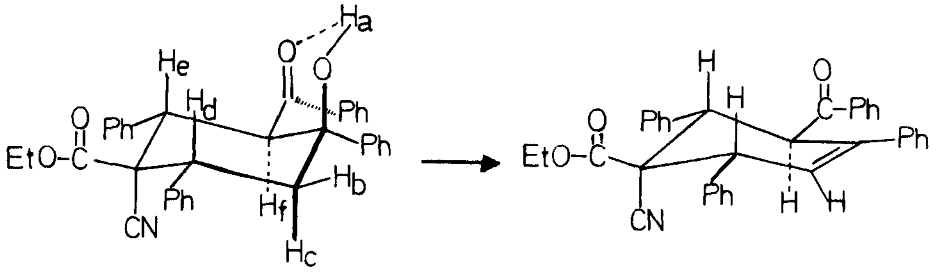
a) Reaction time is 160 hrs unless otherwise stated. b) Reaction time: 30 hrs. c) Reaction time: 20 hrs.

The presence of strongly activating or deactivating substituents in the aromatic rings of the starting compounds does not prevent the reaction and the substituents show little influence on the yield. However, the reaction times are shorter when the aromatic rings bear an electron-withdrawing substituent (Table 1), probably because the Michael addition is easier.

The carbonyl stretching band of cyclohexanols III appears at low wave number (about 1655 cm^{-1}) owing to the formation of an intramolecular hydrogen bond with the hydroxyl group,[7] which gives rise to a broad band at 3300-3500 cm^{-1}. The fact that the position of the hydroxyl and carbonyl bands do not change with the concentration corroborates this intramolecular association. The ^{13}C-NMR spectrum of IIIa shows, besides a carbethoxy carbon at 166.8 ppm and the six aliphatic carbons of the cyclohexane ring, a characteristic singlet of the cyano carbon[9] at 116.97 ppm and a carbonyl carbon at 198.77 ppm, which is in good agreement with the reported value for a hydrogen-bonded carbonyl of an aromatic ketone.[10,11]

The stereochemical configuration of IIIa can be determined from a detailed study of its ^{1}H-NMR spectrum in deuterochloroform. The $CH-CH_2$ moiety is a three spin AMX system corresponding to H_b, H_c and H_d at $\delta_b = 2.25$, $\delta_c = 2.98$ and $\delta_d = 4.35$ ppm (J_{bc} = 13 Hz, J_{cd} = 14.5 Hz, J_{bd} = 3.5 Hz and J_{ac} = 2 Hz); the CH-CH moiety appears as a two spin AB system due to H_e and H_f at $\delta_e = 4.35$ and $\delta_f = 4.94$ ppm (J_{ef} = 12.5 Hz). The carbethoxy group gives rise to a quartet (3.70 ppm) and a triplet at 0.67 ppm (J= 7.5 Hz). The equatorial position of the carbethoxy group, shielded by two phenyl groups, should explain this unusually low chemical shift. The hydroxyl group appears as a doublet at 5.3 ppm (J_{ac}= 2Hz). The intramolecular hydrogen bonding is responsible for the rigid W geometry between H_a and H_c which makes possible the long range coupling observed between these hydrogen atoms. On addition of TFA the hydroxyl signal disappears from the spectrum and the H_a -H_c coupling disappears from the multiplet at 2.98 ppm. Computer spin simulation of the ^{1}H-NMR spectrum of a related structure confirms this long range coupling between an axial hydroxyl hydrogen and a contiguous axial hydrogen, with a coupling constant of 2 Hz.[12]

When IIIa is treated with thionyl chloride in pyridine, dehydration takes place. The carbonyl band of the resulting cyclohexene (V) (vinylic hydrogen at 6.0 ppm in the ^{1}H-NMR spectrum) in which no hydrogen bond exists, shifted 1670 cm^{-1}.



IIIa

V

The unusual dehydration of IIIa to a β,γ-unsaturated ketone rather than an α,β-unsaturated ketone could be accounted for by steric factors. In the α,β-unsaturated ketone, as can be seen in the Dreiding model, the steric hindrance between the benzoyl and the contiguous phenyl groups prevents the conjugation of the ethylenic double bond with either the phenyl group or the benzoyl group. However, conjugation of the double bond with the phenyl group is less hindered in the actually obtained β,γ-unsaturated compound, since the benzoyl group is now not compelled to any degree of conjugation.

EXPERIMENTAL

Melting points were determined with a Buchi apparatus in capillary tubes and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 257 and Perkin-Elmer 580 spectrophotometers. The ^1H-NMR spectra were measured with a Varian T-60A and the ^{13}C-NMR spectra were obtained in a Varian FT-80. A Varian MAT-711 was used for the mass spectra. Microanalysis were performed by Centro Nacional de Química Orgánica de Madrid. The reactions were monitored by TLC, performed on silica gel plates with benzene/ethyl acetate as the eluent. Ethyl cyanoacetate was obtained from Fluka and used without further purification. Benzylideneacetophenone (IIa) was purchased from Merck, IIb was prepared as described by Walther,[13] IIc-IIf were prepared as reported in reference.[14] 4-Nitrobenzylideneacetophenone (IIi) was obtained as described by Weygand.[15] The procedures of Staudinger[16] and Sorge[17] were employed for the preparation of IIg and IIh.

2-Aroyl-4-cyano-4-carbethoxy-1,3,5-triarylcyclohexanols (III). General procedure.- Ethyl cyanoacetate (I) (0.005 mole) and the appropriate benzylideneacetophenone II (0.005 mole) are dissolved in 30 ml of dry ethanol. A few drops of piperidine are added and the mixture is heated to reflux. A few drops of piperidine are added and the mixture is heated to reflux. When TLC shows that the starting materials are exhausted (20-160 hrs), the reaction mixture is allowed to cool to room temperature. The cyclohexanols III precipitate as colorless crystals in good purity and are collected by suction filtration. Further purification is achieved by recrystallization in ethanol. In some cases the precipitation begins during the reflux. The physical, analytical and spectral data of these compounds are summarized in Tables 1 and 2.

6-Benzoyl-4-cyano-4-carbethoxy-1,3,5-triphenylcyclohexene (V). In a two necked flask equipped with a reflux condenser is placed a solution of 0.001 mole of IIIa in the minimal amount of

TABLE 2. Spectroscopic data of 2-Aroyl-4-cyano-4-carbethoxy-1,3,5-triarylcyclohexanols (III).

	NMR[a]								IR[b]	
	ArH (m)	OH (d)	H_f (d)	H_d,H_e (m)	CH_2O (q)	H_c (dt)	H_b (dd)	CH_3 (t)	CO	CN[c]
IIIa[d]	6.80-7.80	5.30	4.94	4.35	3.70	2.98	2.25	0.67	1655	2239[e]
IIIb	6.80-7.50	5.60	4.55	4.05	3.90	3.00	2.00	0.90	1655	2230
IIIc	6.90-7.50	5.70	4.50	4.05	3.90	3.00	2.00	0.85	1660	2240
IIId	6.80-7.50	5.40	4.50	4.05	3.80	3.05	2.05	0.90	1655	2230
IIIe	6.65-7.40	5.40	4.45	4.10	3.75	3.00	2.05	0.80	1660	2250
IIIf	6.45-7.50	5.45	4.50	4.15	3.85	3.05	2.00	0.90	1645	2220
IIIg	6.40-7.40	5.40	4.50	4.15	3.80	3.00	2.00	0.85	1655	2250
IIIh	6.80-8.15	5.75	4.60	4.15	3.90	3.10	2.05	0.90	1645	2230
IIIi	7.00-7.90	6.15	4.60	4.15	3.90	3.10	2.05	0.90	1670	2200

a) Obtained in DMSO-$\underline{d}_6$ unless otherwise stated and reported in δ values against TMS as the internal standard. If the NMR spectra are recorded in crude compounds, contamination with several stereoisomers can be seen in the spectra.

b) Performed as potassium bromide pellets.

c) This band is very weak, as expected for an unconjugated nitrile (see ref. 8) and becomes more intense in concentrated chloroform solution.

d) This spectrum was obtained in deuterochloroform solution.

e) Mass spectrum of compound IIIa: 530(M^+, 3), 529(8), 321(2), 320(2), 210(18), 209(100), 131(10), 105(29), 103(4).

pyridine (∿3ml). Through the second neck, 3 ml of thionyl chloride are added dropwise and with stirring. The reaction mixture is heated to reflux for one hour and the cooled solution is poured into water. The solid that precipitates is collected by filtration in quantitative yield, whased well with water and recrystallized from ethanol. M.p. 175-176 °C.

Anal. Calcd. for $C_{35}H_{29}NO_3$: C, 82.19; H, 5.67; N, 2.74. Found: C, 82.14; H, 5.58; N, 2.87.

IR (potassium bromide pellet): 3040, 3020, 3010, 2980, 2250, 1730, 1670, 1595, 1580, 1495 cm^{-1}. NMR (deuterochloroform): δ 6.80-7.60 (m, 20 H arom.), 6.0 (m, 1 H), 5.50 (m, 1 H), 4.65 (m, 1 H), 4.05 (m, 1 H), 3.70 (q, 2 H, CH_2), 0.75 (t, 3 H, CH_3).

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