Cyclic Dimerization of Ethyl 1-Arylethylidenecyanoacetates with Grignard Reagents

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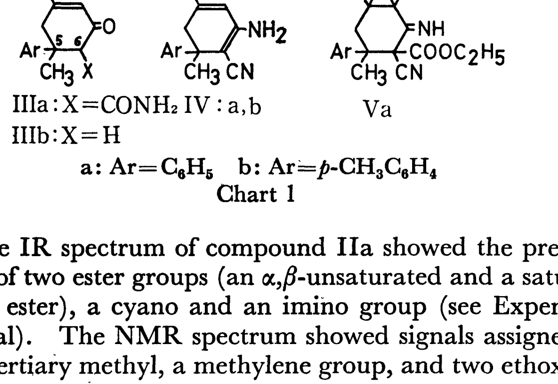
The treatment of ethyl 1-arylethylidenecyanoacetates (I) with Grignard reagents, especially mesitylmagnesium bromide, gave ethyl 2,4-diaryl-5-cyano-5-ethoxycarbonyl-6-imino-4-methyl-1-cyclohexenecarboxylates (II), a dimer of I.

The preparation of ethyl *t*-alkylcyanoacetate by the conjugate addition of Grignard reagents to ethyl 1-alkylethylidenecyanoacetate has been reported.[1] The treatment of ethyl 1-arylethylidenecyanoacetate (I)[2] with isopropylmagnesium bromide yielded ethyl 3-aryl-2-cyano-3-isopropylbutanoate and an unknown yellow compound II, which is a dimeric product. It was found that ester I reacted with mesitylmagnesium bromide (MesMgBr) to give only the same unknown dimeric product. Other Grignard reagents also yielded the dimeric product, as shown in Table 1. The structure of the dimeric product was assumed to be ethyl 2,4-diaryl-5-cyano-5-ethoxycarbonyl-6-imino-4-methyl-1-cyclohexenecarboxylate (II) on the basis of the mechanism of base-catalyzed dimerization shown in Chart 1.

Table 1. Yield (%) of Dimer II

I	RX for RMgX				
	MeI	EtBr	*i*-PrBr	*t*-BuCl	MesBr
Ia	6.1	5.8	21.3	1.9	30.2
Ib	1.8	6.1	42.7	3.5	52.4



I : a,b

II : a,b

IIIa:X=CONH$_2$ IV : a,b Va

IIIb:X=H

a: Ar=C_6H_5 b: Ar=*p*-$CH_3C_6H_4$

Chart 1

The IR spectrum of compound IIa showed the presence of two ester groups (an α,β-unsaturated and a saturated ester), a cyano and an imino group (see Experimental). The NMR spectrum showed signals assigned to a tertiary methyl, a methylene group, and two ethoxy groups (see Experimental).

Compound IIa was stable for refluxing in conc. hydrochloric acid; however, the treatment of IIa with an acetic acid-concd hydrochloric acid solution under reflux gave white crystals (IIIa). The IR spectrum showed no absorption band due to the ester, cyano, and imino groups, but carbonyl bands due to α,β-unsaturated ketone and an amide group were observed. The UV spectrum showed an absorption maximum at 293 nm characteristic of 3-phenyl-2-cyclohexenone systems.[3] The above results, therefore, indicate that the imino group of compound IIa was hydrolyzed with the simultaneous hydrolytic decarboxylation of two ethoxycarbonyl groups.

The NMR spectrum of IIIa showed the presence of a vinyl, a tertiary methyl, a methylene (ABX-type), a methine (singlet), and an amide proton (see Experimental). The methine singlet due to H-6 indicates the presence of two groups (phenyl and methyl) on C-5. Therefore, the amide group is located on C-6.

From these data, compound IIIa was assigned to 6-carbamoyl-5-methyl-3,5-diphenyl-2-cyclohexenone.

The alkaline hydrolysis of IIa with potassium hydroxide in boiling ethylene glycol afforded pale yellow crystals (IVa). The IR spectrum showed the presence of an amino and a cyano group, and the NMR spectrum revealed signals due to the ABX system, in which the AB pattern of methylene appeared at δ 2.94 and the X part (a vinylic proton) at 6.02. From the results, IVa was assigned to 2-amino-6-methyl-4,6-diphenyl-1,3-cyclohexadienecarbonitrile.

The oxidation of IIa with alkaline hydrogen peroxide in acetone gave epoxide (Va). The epoxidation of the double bond caused the shift of the UV absorption band of a conjugated system to that of a simple aromatic system (see Experimental).

IIb was assigned to ethyl 5-cyano-5-ethoxycarbonyl-6-imino-4-methyl-2,4-di(*p*-tolyl)-1-cyclohexenecarboxylate from spectral analysis (see Experimental).

In contrast with the acid hydrolysis of IIa, IIb gave a product (IIIb) with the simultaneous loss of carbonyl groups. The analogy in the ring system was supported by the UV spectrum (λ_{max} 296 nm).[4]

IIb gave 2-amino-6-methyl-4,6-di(*p*-tolyl)-1,3-cyclo hexadienecarbonitrile (IVb) by alkaline hydrolysis.

The epoxidation of IIb gave no crystalline products.

Experimental

All melting points are uncorrected. Unless otherwise noted, UV, IR, and NMR spectra were measured in 95% ethanol, chloroform, and deuteriochloroform (with TMS as an internal standard), and presented in λ_{max} nm (log ε), ν_{max} cm^{-1}, and δ ppm, respectively. The instruments used for the measurements are a Cary 14 recording spectrophotometer, a JASCO model DS-402G infrared spectrophotometer, and a JEOLCO model

C-60 spectrometer.

Materials. Ethyl 1-phenylethylidenecyanoacetate (Ia) was prepared according to the method of McElvain and Clemens,[5] bp 149.5—153 °C/3 Torr (lit,[5] 135—160 °C/0.35 Torr); Ethyl 1-(*p*-tolyl)ethylidenecyanoacetate (Ib) was prepared accoding to the methob of Cope,[6] bp 122—123 °C/3.5×10^{-3} Torr (lit,[6c] 160—170 °C/10 Torr).

Reaction of Ethyl 1-Arylethylidenecyanoacetate (I) with Grignard Reagent. To a Grignard solution, prepared from 2.92 g (0.12 mol) of magnesium, 0.12 mol of alkyl halide, and 22 ml of absolute ether, was added 0.1 mol of I in 30 ml of refluxing absolute ether over a period of 20 min. The mixture was refluxed under stirring for 1 hr and then left to stand overnight. An excess of the Grignard reagent was decomposed by the addition of aqueous ammonium chloride. The reaction mixture was extracted with ether and the ethereal extract was dried. After removal of the solvent, the residue dissolved in ethanol was treated with active carbon, and cooled with ice. The resulting yellow crystals were washed with cold ethanol, and recrystallized from ethanol to give II. The filtrate was concentrated *in vacuo* and analyzed by chromatography on silica gel. Elution with benzene-ethyl acetate (10: 1, v/v) gave yellow crystals (II). Combined II was recrystallized from 50% ethanol (the yield is indicated in the yield table). A pure sample was obtained after several recrystallizations.

a) IIa: Mp 134.5—135.0 °C. IR: 3400 (=NH), 2221 (C≡N), 1746, 1706 (C=O), and 1626 (C=C). UV: 240 (4.05) and 324 (3.97). NMR: 0.75 (t, 3H, $J=7$ Hz), 1.31 (t, 3H, $J=7$ Hz), 1.70 (s, 3H), 3.08 (ABq, 2H, $J=18$ Hz, $\nu_0\delta=8.7$ Hz), 3.88 (q, 2H, $J=7$ Hz), 4.27 (q, 2H, $J=7$ Hz), and 6.95—7.61 (m, 11H, 2 Ph and =NH). Found: C, 72.70; H, 6.01; N, 6.37%. Calcd for $(C_{13}H_{13}O_2N)_2$: C, 72.54; H, 6.09; N, 6.51%.

b) IIb: Mp 149.0—150.0 °C. IR: 3405 (=NH), 2219 (C≡N), 1741, 1702 (C=O), and 1617 (C=C). UV: 246 (4.07) and 336 (4.03). NMR: 0.80 (t, 3H, $J=7$ Hz), 1.29 (t, 3H, $J=7$ Hz), 1.65 (s, 3H), 2.30 (s, 6H), 3.01 (ABq, 2H, $J=17$ Hz, $\nu_0\delta=10.5$ Hz), 3.87 (q, 2H, $J=7$ Hz), 4.21 (q, 2H, $J=7$ Hz), and 6.80—7.37 (m, 9H). Found: C, 73.33; H, 6.57; N, 5.94%. Calcd for $(C_{14}H_{15}O_2N)_2$: C, 73.34; H, 6.59; N, 6.11 %.

Acid Hydrolysis of II. A mixture of 1 g of II, 10 ml of acetic acid and 5 ml of conc. hydrochloric acid was boiled under reflux for 13 hr. Carbon dioxide was evolved during the reaction. The reaction mixture was concentrated under reduced pressure. The residue dissolved in ether was washed with saturated aqueous sodium bicarbonate and the solvent was distilled off. The residue dissolved in benzene was analyzed by chromatography on silica gel and eluted with benzene. Elution with benzene gave white crystals, which, after recrystallization from ethanol, gave a pure sample (III).

a) IIIa: Yield 80 mg, mp 181.0—181.5 °C. IR (KBr disk): 3382, 3164 (NH_2), 1686 (amide I), 1632 (C=O), and 1600 (C=C). UV: 293 (4.22) and 255^{sh} (4.01). NMR (DMSO-d_6, JEOLCO PS-100 spectrometer): 1.51 (s, 3H), 3.38 (ABX, 2H, $J_{AB}=18.5$ Hz, $J_{BX}=2$ Hz, $\Delta\nu_{AB}=12$ Hz), 3.91 (s, 1H), 6.30 (d, 1H, $J=2$ Hz), 7.32 (s, 2H), 7.54 (m, 5H), and 7.77 (m, 5H). Found: C, 78.47; H, 6.28; N, 4.39%. Calcd for $C_{20}H_{19}O_2N$: C, 78.66; H, 6.27; N, 4.59%.

b) IIIb: Yield 450 mg, mp 105.0—106.5 °C. IR: 1655 (C=O) and 1607 (C=C). UV: 296 (4.29), 217^{sh} (4.22), and 231^{sh} (4.00). NMR (CCl_4): 1.41 (s, 3H), 2.28 (s, 3H), 2.36 (s, 3H), 2.59 (d, 2H, $J=9$ Hz), 2.89 (d, 2H, $J=6$ Hz), 6.21 (s, 1H), 7.06 (m, 4H), and 7.24 (m, 4H). Found: C, 87.12; H, 7.81%. Calcd for $C_{21}H_{22}O$: C, 86.85; H, 7.64%.

Alkaline Hydrolysis of II. A mixture of 1 g of II, 4.3 g (76.6 mmol) of potassium hydroxide and 280 ml of ethylene glycol was refluxed for 3 hr. The reaction mixture was poured into cold water, and extracted with ether. The ethereal extract was washed with saturated aqueous sodium chloride, dried and evaporated producing pale yellow crystals.

a) IVa: Yield 230 mg, mp 158.0—159.0 °C. Several recrystallizations from ethanol gave a pure sample, mp 158.5—159.0 °C. IR: 3399, 3490 (NH_2), 2193 (C≡N), 1645, and 1621 (C=C). UV: 271 (4.20) and 358 (4.06). NMR: 1.61 (s, 3H), 2.94 (ABX, 2H, $J_{AB}=17$ Hz, $J_{AX}=1.8$ Hz, $\Delta\nu_{AB}=14.4$ Hz), 4.51 (s, 2H), 6.02 (d, 1H, $J_{AX}=1.8$ Hz), and 7.30 (m, 10H). Found: C, 83.95; H, 6.53; N, 9.95%. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78%.

b) IVb: Yield 800 mg, mp 171.5—174.5 °C. Several recrystallizations from ethanol gave a pure sample, mp 174.0—175.0 °C. IR: 3490, 3399 (NH_2), 2190 (C≡N), 1642, and 1620 (C=C). UV: 275 (4.20) and 358 (4.05). NMR: 1.62 (s, 3H), 2.25 (s, 3H), 2.32 (s, 3H), 2.92 (ABX, 2H, $J_{AB}=17$ Hz, $J_{AX}=1.8$ Hz, $\Delta\nu_{AB}=14.4$ Hz), 4.44 (s, 2H), 6.02 (d, 1H, $J_{AX}=1.8$ Hz), and 7.00—7.40 (m, 8H). Found: C, 84.20; H, 7.24; N, 8.95%. Calcd for $C_{22}H_{22}N_2$: C, 84.04; H, 7.05; N, 8.91%.

Hydrogen Peroxide Oxidation of IIa. To a mixture of 1 g (2.33 mmol) of IIa, 25 ml of 30% hydrogen peroxide and 35 ml of acetone was added 3 ml of 10% aqueous sodium carbonate at room temperature over a period of 20 min. The mixture was heated in a water bath for 3 min and then left to stand for two days. The excess of hydrogen peroxide was decomposed by the addition of aqueous sodium thiosulfate. The reaction mixture was evaporated under reduced pressure, and then cooled with ice-water. The resulting white crystals were recrystallized several times from 50% aqueous ethanol to give a pure sample, mp 157.5—158.0 °C, yield 300 mg. IR: 3425 (=NH), 2227 (C≡N), 1751, and 1718 (C=O). UV: 266 (4.13). NMR: 0.72 (t, 3H, $J=7$ Hz), 1.31 (t, 3H, $J=7$ Hz), 1.70 (s, 3H), 2.59 (ABq, 2H, $J=15$ Hz, $\nu_0\delta=21.3$ Hz), 3.75 (q, 2H, $J=7$ Hz), 4.22 (q, 2H, $J=7$ Hz), 6.47 (m, 1H), and 7.07—7.44 (m, 10H). Found: C, 70.07; H, 5.89; N, 6.37%. Calcd for $C_{26}H_{26}O_5N_2$: C, 69.94; H, 5.87; N, 6.27%.

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