

Studies on the Condensation Products of 1,3-Diaryl-2-propen-1-one with Ethyl cyanoacetate

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Summary: Michael condensation of 3', 4'-dimethylbenzalacetophenone (I) with ethyl cyanoacetate in the presence of ammonium acetate leads to the formation of 6-(3,4-dimethylphenyl)-2-hydroxy-4-phenyl nicotinonitrile (II), 6-(3,4-dimethylphenyl)-1,2-dihydro-4-phenyl-2-oxonicotinonitrile (III) and ethyl 2-amino-6-(3,4-dimethylphenyl)-4-phenyl nicotinate (IV). The reaction of II with alkyl halides, phosphorus oxychloride and Grignard reagents gives the 2-alkoxy-(VI), 2-chloro-(VII) and the 3-acyl-(IX)-derivatives. Reactions of VII with amines and hydrazine hydrate, IXb with hydrazine hydrate, hydroxylamine hydrochloride and thiourea, III with ethyl bromoacetate, phosphorus oxychloride, and Grignard reagent and IV with acetyl chloride are described.

It is known that ethyl cyanoacetic ester reacts with chalcones to give at high temperature, in the presence of ammonium acetate the corresponding pyridones and/or the corresponding amino piperidine derivatives.¹⁻⁴

In the present investigation the author reinvestigated the same procedure using chalcone (I) produced from 3,4-dimethylphenyl acetophenone with benzaldehyde to obtain the corresponding mixture of 6-(3,4-dimethylphenyl)-2-hydroxy-4-phenyl nicotinonitrile (II), 6-(3,4-dimethylphenyl)-1,2-dihydro-4-phenyl-2-oxonicotinonitrile (III) and ethyl 2-amino-6-(3,4-dimethylphenyl)-4-phenyl-nicotinate (IV), respectively. Compounds II and III show the carbonyl stretching frequency* at 1670-1650, NH and OH frequency at 3060-2920 and the C≡N frequency at 2227-2225, the infrared spectrum of IV showed bands attributable for CO (1690), C=N (1620) and NH (3420).

When the reaction was carried out in benzene, only the 3-cyano-4,6-diaryl-2-oxo-1,2,3,4-tetrahydropyridine derivative (V) was isolated. The reaction involved is the Michael addition and cyclization without dehydrogenation. In favour of this assumption is the fact that II can be prepared from V by heating at 120-150°. The infrared spectrum of V exhibited characteristic absorption bands for NH and OH (3106-2985), C≡N (2227) and CO (1962).

The alkylation⁵⁻⁶ of pyridone II was investigated. Thus treatment of the potassium salt of II with alkyl

halides, namely, methyl iodide, benzyl chloride or ethyl bromoacetate gave 2-methoxy-(VIa), 2-benzyloxy-4,6-diaryl nicotinonitriles (VIb) and (3-cyano-4,6-diaryl-2-pyridyl)oxyacetic acid, ethyl ester (VIc). The structure of these 2-alkoxy pyridines was supported by their spectral data. Their IR showed strong bands characteristic of C≡N (2230-2220), C=N (1592-1590) and the absence of OH, NH and CO groups. VIc showed also the ester group (1755). The PMR (CDCl₃) spectrum[†] of VIc showed signals at 7.88-6.8(9H,m,ArH + -CH), 5.1(2H,s,OCH₂), 4.31(2H,q,CH₂ of ethyl), 2.38 (6H, s,ArCH₃), 1.28(3H,t,CH₃ of ethyl).

When II was treated with phosphorus oxychloride⁷ the 2-chloro-4,6-diaryl nicotinonitrile VII was obtained. Treatment of the tetrahydropyridone derivative V with phosphorus oxychloride resulted in the replacement of hydroxyl group by chlorine accompanied by dehydrogenation and formation of VII. The IR spectrum of VII was devoid of νC=O. The PMR (CDCl₃) showed signals at 7.89-6.82 (9H,m,ArH+ -CH), 2.5(3H,s,CH₃), 2.38 (3H,s,CH₃). Treatment of VII with sodium methoxide⁸ gave VIa, identical with that obtained by methylation of II.

The well-known⁹ reactivity of 2-halogen substituents in the pyridine nucleus prompted a study of the replacement of the chlorine atom with amines. Thus, treatment of VII with methylamine or allylamine gave VIIIa and b, respectively. The infrared spectra of VIII showed bands at 2225 and 1650 attributable to ν C≡N

[†] ν_{max} in cm⁻¹ and PMR chemical shifts in δ, ppm throughout the paper.

and ν C=N.

Compound VII reacted also with hydrazine hydrate in absolute ethanol to give the 2-hydrazino derivative VIIIc.

The behaviour of pyridone II was also investigated towards Grignard reagents. Thus, treatment of II with methyl- or ethyl-magnesium iodide yielded the 3-acyl-2(IH)-pyridone IXa and b, respectively. The IR spectra of IX revealed a strong absorption band at 1700-1690 attributable to acyl carbonyl group. The PMR (CDCl₃) of IXb showed signals at 8.18-6.6 (10H,m,ArH+—CH=+NH), 2.65(2H,q,CH₂ of ethyl), 2.32(6H,s,ArCH₃) 0.98(3H,t,CH₃ of ethyl).

Compound (IXb) underwent condensation with hydrazine hydrate in boiling ethanol to give the substituted 1H-pyrazolo [3,4-b] pyridine (X). The IR spectrum of X showed characteristic bands around 1620, 1505 and 3360 attributable to C=N, and NH respectively.

Reaction of IXb with hydroxylamine hydrochloride in boiling pyridine produced substituted isoxazolo [5,4-b] pyridine (XI). The IR spectrum of XI showed band at 1618 attributable to ν C=N.

Condensation of IXb with thiourea gave substituted 2-thiono-1H-pyrido-[2,3-d] pyrimidine (XII). The IR showed bands characteristic of NH, C=N and C=S.

When the second adduct III was subjected to alkaline hydrolysis yields the decarboxylated product XIII. Its IR showed bands characteristic of C=O (1590) and NH (3020).

The reaction of III with POCl₃ takes place via the lactim form to give the 2-chloro-6-(3,4-dimethylphenyl)-4-phenyl nipecotonitrile (XIV). The IR spectrum showed bands at 2220 for C \equiv N and at 160 for C=N.

Also when the potassium salt of III reacts with ethyl bromoacetate afforded the o-alkylation product (XV). The IR spectrum showed the characteristic ester group at 1750.

Action of ethyl magnesium iodide in dry ether on III yielded the corresponding 3-acyl derivative XVI. Its IR spectrum showed the characteristic acyl carbonyl group at 1700.

When the third adduct IV was subjected to alkaline hydrolysis, it yields the decarboxylated product XVII. The structure of XVII was confirmed from its insolubility in bicarbonate solution and from the IR spectrum

which showed the absence of band attributable to carbethoxy group and the presence of bands attributable for C=N (1620) and NH (3420).

Reaction of IV with acetyl chloride to give the corresponding anilide derivative XVIII.

Experimental

Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Beckman spectrophotometer. PMR spectra were run on a Varian A-60 using TMS as internal standard.

Reaction of I with ethyl cyanoacetate without a solvent: Formation of II-IV -

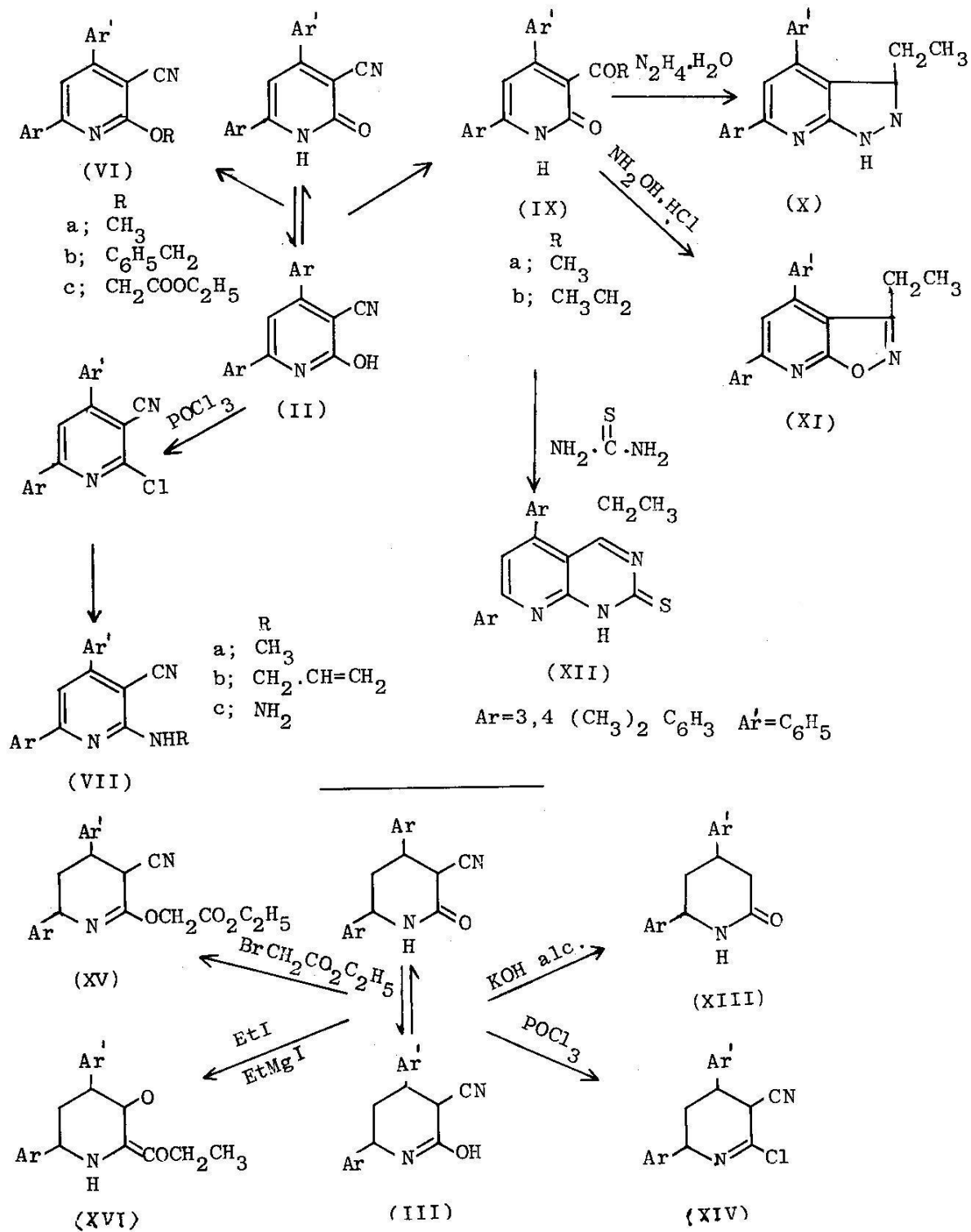
A mixture of ethyl cyanoacetate (0.03 mol), I (0.03 mol) and ammonium acetate (0.24 mol) was heated at 160-70° in an oil-bath for 8 hr. The reaction mixture was cooled and the yellow oil obtained was washed with water, and by fractional crystallization using light petrol (60-80°C), ethanol and acetic acid, compounds IV, III and II were separated as yellow crystals respectively.

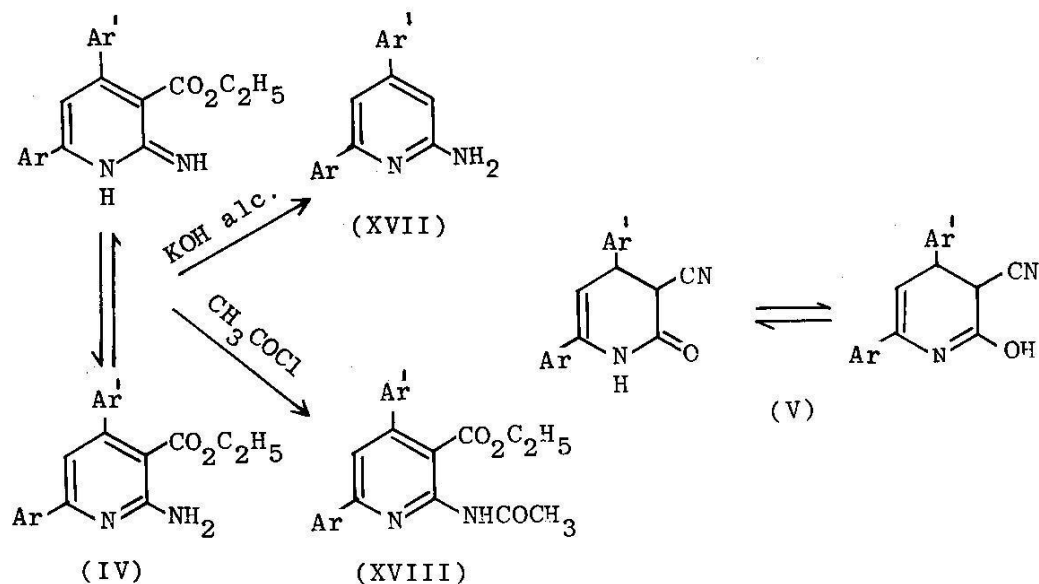
Reaction of I with ethyl cyanoacetate in benzene: Formation of V-

A mixture of ethyl cyanoacetate (0.05 mol), I (0.05 mol), and ammonium acetate (0.04 mol) in 40 ml of benzene was refluxed for 8 hr. Water was added to the reaction mixture, and, after it had stood overnight, a crystalline matter was precipitated. The solid was treated with a small amount of dilute methanol to remove the unchanged chalcone, then crystallized from the suitable solvent to give V.

Alkylation of II and III: Formation of VIa-c and XV-

A mixture of II or III (0.01 mol), anhydrous potassium carbonate (0.03 mol), dimethyl sulfate, benzyl chloride or ethyl bromoacetate (0.03 mol) and dry acetone (50 ml) was refluxed for 20 hr. After removing the excess solvent the products were crystallized from the proper solvent to give compounds VIa-c and XV, respectively.





Action of phosphorus oxychloride on II, V or III: Formation of VII and XIV—

A suspension of II, V or III (1 g) and phosphorous oxychloride (5 ml) was heated on a water bath for 2 hr. The reaction mixture was poured gradually onto crushed ice. The solid which separated was filtered off and crystallized from the suitable solvent to give VII and XIV, respectively.

Reaction of 2-chloro-4,6-diarlylnicotinonitrile VII with sodium methoxide: Formation of VIa—

A solution of VII (1 g) in methanol (20 ml) was treated with sodium methoxide (prepared, by dissolving 0.23 g sodium in 10 ml methanol) and refluxed for 5 hr, then allowed to cool. The solid obtained upon dilution of the reaction mixture with water was filtered off and crystallized from the proper solvent to give VIa.

Reaction of VII with amines: Formation of VIII a and b

A suspension of VII (0.5 g) and the appropriate amine (methyl-amine or allylamine) (4 ml) was refluxed for 2 hr and allowed to cool. The reaction mixture was triturated with cold ethanol and the solid so obtained, was crystallized from the proper solvent to give VIIIa and b, respectively.

Action of hydrazine hydrate on VII and IXb: Formation of VIIIc and X—

A solution of VII or IXb (0.01 mol) and hydrazine hydrate (0.01 mol) in absolute ethanol (30 ml) was refluxed for 4 hr. The products obtained after concentration and cooling were crystallized from suitable solvents to give VIIIc and X, respectively.

Action of Grignard reagents on II and III: Formation of IXa and b and XVI—

Suspension of II or III (2 g) in dry benzene (50 ml) was added to an ethereal solution of alkylmagnesium halide (prepared from 0.9 g magnesium; 7 g alkyl halide and 40 ml dry ether). The reaction mixture was refluxed (steam bath) for 2 hr, set aside at room temperature and then decomposed with a cold solution of hydrochloric acid (10 %). The yellow solid obtained was crystallized from suitable solvents to give IXa and b and XVI, respectively.

Action of hydroxylamine hydrochloride on IXb: Formation of XI—

A mixture of IXb (0.01 mol), hydroxylamine hydrochloride (0.012 mol) pyridine (20 ml) and a few drops of water was refluxed for 5 hr. The reaction mix-

Table 1. Physical Data of Various Compounds Prepared

Compound	M.p. ⁺ °C	Yield (%)	Compound	M.P. ⁺ °C	Yield (%)
II	249(a)	20	IXa	138(c)	53
III	254(b)	5	IXb	232(d)	57
IV	115(c)	15	X	146(b)	73
V	214(b)	8	XI	244(b)	70
Via	152(d)	87	XII	210(d)	80
VIb	144(d)	90	XIII	188(e)	40
VIc	170(d)	85	XIV	170(d)	88
VII	179(d)	70	XV	175(d)	68
VIIIa	254(b)	90	XVI	229(d)	48
VIIIb	245(b)	82	XVII	196(d)	45
VIIIc	235(b)	60	XVIII	248(b)	77

+All the compounds gave satisfactory elemental analyses. Solvents used for recrystallization were:

(a) Acetic acid, (b) benzene, (c) petroleum ether (60-80°), (d) ethanol, (e) methanol.

ture was poured into ice-cold HCl. The solid separated was crystallized from suitable solvents to give XI.

Action of thiourea on IXb: Formation of XII-

A cold solution of IXb (0.01 mol) and thiourea (0.01 mol) in abs. ethanol (20 ml) was treated with conc. H₂SO₄ (2 ml). The reaction mixture was set aside at room temperature for 24 hr neutralized with NaHCO₃ to give XII.

Hydrolysis of III and IV: Formation of XIII and XVII-

Compound III or IV (1 g) was heated with 10% alcoholic potassium hydroxide (20 ml) for 3 hr. After standing overnight, a crystalline compound separated. When it was dissolved in water and acidified with dilute hydrochloric acid, it rapidly gave a white precipitate, which was recrystallized from suitable solvents to give XIII and XVII, respectively.

Acetylation of IV: Formation of XVIII-

A solution of IV (0.01 mol) in pyridine (10 ml)

was treated with acetyl chloride (0.02 mol) and the reaction mixture heated on a water-bath for 2 hr, cooled and poured into dil. HCl. The solid thus obtained was crystallized from suitable solvent to give XVIII.

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