Studies on the Condensation of 1,3-Diaryl-propen-1-one with Ethyl Cyanoacetate

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Summary: Michael condensation of 1[p-bromophenyl]-3-[p-chlorophenyl]-propen-1-one [I] with ethyl cyanoacetate in the presence of ammonium acetate leads to the formation of (II) 6-[p-bromophenyl]-2-hydroxy-4-[p-chlorophenyl] nicotinonitrile, and nicotinamide (III) as a major product. The reaction of (II) with phosphorous oxychloride, Grignard reagents and ethyl bromoacetate gives, 2-chloro-(IV), 3-acyl-(X) and 2-alkoxy (VII) pyridine derivatives. Reactions of (IV) with amines, hydrazine hydrate, sodamide and alkoxides are also investigated. (X) reacted with hydrazine hydrate and hydroxylamine hydrochloride to give substituted 1H-pyrazolopyridine (XI) and isoxazolopyridine (XII). Also, reaction of (VI) with hydrazine hydrate and (I) with urea, thiourea, hydrazine hydrate, phenylhydrazine and oxidation with hydrogen peroxide are described.

Introduction

Recently [2-5], it has been reported that chalcones react with ethyl cyanoacetate under Michael conditions in the presence of ammonium

acetate at high temperature to give the corresponding pyridones.

In the present work, the authors reinvestigated the same procedure using chalcone (I), and it was found that (I) condensed with ethyl cyanoacetate in the presence of ammonium acetate at high temperature affording a mixture of (II) and (III) respectively. The structure of (II) and (III) was confirmed by microanalysis (Table 1), and its I.R. spectrum which displayed νC=N at 2225 cm^{-1}, νCO of amides at 1670 - 1650 cm^{-1} alongwith a broad absorption band in the 3μ region, correlated for νNH, OH and $-CONH_2$ frequency. As a point of interest, the presence of (II) in lactam $\rightleftharpoons$lactim tautomeric equilibrium has been investigated, since, on its treatment with $POCl_3$, the 2-chloro-4,6-diarylnicotinonitrile [6] (IV) was obtained, whose I.R. spectrum lack the carbonyl absorption, while displayed νC$\equiv$N at 2220 cm^{-1} and νC=N at 1595 cm^{-1}.

Alkylation [7-9] of 2-chloropyridine derivative (IV) was investigated, thus treatment of (IV) with sodium methoxide and ethoxide, yielded 2-alkoxy pyridine derivative (Va,b) whose structure was supported by micro-analysis (Table I) as well as its I.R. spectrum which showed a strong absorption band characteristic of νC=N (2230 - 2220 cm^{-1}), νC=N at (1592 - 1590 cm^{-1}) and absence of -OH, -NH and -CO group.

The well known reactivity [10] of 2-halogen substituents in the pyridine nucleus promoted a study of the replacement of chlorine atom with amines. Therefore 2-chloropyridine derivative (IV) reacted with benzylamine, hydrazine as well as with phenylhydrazine in absolute ethanol producing the 2-benzyl-amino-, 2-hydrazino-, and 2-phenylhydrazino--3-cyano,4,6-diaryl pyridine (VIa-c). The I.R. spectrum of (VI) showed well defined absorptions for νNH at 3542, 3280 and 3320 cm^{-1}, νC=N at 1615, 1610 and 1616 cm^{-1}, νC$\equiv$N at 2228, 2224 and 2228 cm^{-1}.

Furthermore, treatment of (IV) with sodamide in dry xylene produced 2-aminoicotinonitrile (VId), whose I.R. spectrum showed a characteristic bands at 2223 cm^{-1} for C$\equiv$N, 1618 cm^{-1} for C=N and 3280 cm^{-1} for NH. Moreover, the 3-cyanopyridone derivative (II) was treated with ethyl bromoacetate afforded the O-alkylation product (VII), the structure of (VII) was confirmed by its I.R. spectrum which displayed νCO at 1748 cm^{-1}, characteristic for ester group, and νC$\equiv$N at 2226 cm^{-1}. Reaction of (VII) with hydrazine hydrate in boiling ethanol gave the hydrazide derivative (VIII). The I.R. spectrum showed bands at 1655, 2224 and (3290 - 3330) cm^{-1} attributable to νCO, νC$\equiv$N and νNH respectively. Another chemical proof for the existance of (II) in such lactam$\rightleftharpoons$lactim tautomeric equilibrium is, its acid hydrolysis to the corresponding 3-carboxy pyridone derivative (IX) which showed νCO of carboxylic group at 1680 cm^{-1}. Alkaline hydrolysis of (III) was found to give the same product (IX).

The behaviour of pyridone (II) was also investigated towards Grignard reagent, thus treatment of (II) with methyl magnesium iodide yielded the 3-acetyl-1H-pyrid-2-one (X). The I.R. spectrum of (X) revealed a strong absorption band at 1680 cm^{-1} characteristic for ,CO and absence of C$\equiv$N group. Compound (X) underwent condensation with hydrazine hydrate in boiling ethanol and with hydroxyl-

Table-1: Characterization data of compounds prepared.

Compd.	M.p.(°C)	Solvent yield %	Mol.Formula	Analysis %, Calcd./Found C	H	N
I	168	E, 93	$C_{15}H_{10}ClBrO$	55.98 55.61	3.10 3.31	--
II	> 280	B, 28	$C_{18}H_{10}ClBrN_2O$	56.03 56.42	2.59 2.73	7.26 7.42
III	139-40	L.p, 70	$C_{18}H_{12}ClBrN_2O_2$	53.53 53.14	2.97 3.15	6.93 7.21
IV	225	A, 70	$C_{18}H_9Cl_2BrN_2$	53.46 53.21	2.22 2.41	6.93 7.23
Va	268	B, 60	$C_{19}H_{12}ClBrN_2O$	57.07 56.83	3.00 3.20	7.00 7.11
Vb	219-20	B, 55	$C_{20}H_{14}ClBrN_2O$	58.04 57.89	3.38 3.25	6.77 6.58
VIa	190	B, 71	$C_{24}H_{15}ClBrN_3$	62.54 62.41	3.25 3.15	9.12 9.31
VIb	216-7	B, 66	$C_{18}H_{12}ClBrN_4$	54.06 54.23	3.00 3.14	14.02 14.21
VIc	249-50	B, 67	$C_{24}H_{16}ClBrN_4$	60.56 60.23	3.36 3.15	11.77 11.54
VId	> 270	E, 71	$C_{18}H_{11}ClBrN_3$	56.17 56.24	2.86 2.87	10.92 10.73
VII	153-4	E, 80	$C_{22}H_{16}ClBrN_2O_3$	55.99 55.67	3.39 3.26	5.93 6.17
VIII	> 280	E, 68	$C_{20}H_{14}ClBrN_4O_2$	52.45 52.32	3.06 3.32	12.24 12.14
IX	158	A, 45	$C_{18}H_{11}ClBrNO_3$	53.39 53.12	2.71 2.56	3.46 3.21
X	238-9	E, 73	$C_{19}H_{13}ClBrNO_2$	56.64 56.81	3.22 3.45	3.47 3.61
XI	280	E, 80	$C_{19}H_{13}ClBrN_3$	57.21 57.42	3.26 3.14	10.54 10.32
XII	247	B, 75	$C_{19}H_{12}ClBrN_2O$	57.70 57.38	3.00 3.21	7.00 6.82
XIIIa	> 280	B, 60	$C_{16}H_{11}ClBrN_2O$	52.96 52.74	3.03 3.21	7.72 7.59
XIIIb	245	B, 78	$C_{16}H_{11}ClBrN_2S$	50.72 50.43	2.90 3.11	7.39 7.15

Table-1:(cont'd...)

Compd.	M.p.(°C)	Solvent yield %	Mol.Formula	Analysis %, Calcd./Found C	H	N
XIV	124	L.p, 65	$C_{15}H_{10}ClBrO_2$	53.33 53.49	2.96 3.11	--
XV	247-8	B, 68	$C_{15}H_{12}ClBrO_3$	50.63 50.91	3.37 3.48	--
XVIa	62-3	E, 85	$C_{15}H_{12}ClBrN_2$	53.65 53.82	3.57 3.74	8.34 8.49
XVIb	148-9	E, 82	$C_{21}H_{16}ClBrN_2$	61.24 61.06	3.88 3.69	6.80 6.58

E = Ethanol, B = Benzene, L.p = Light petroleum (b.p. 60-80°C),
A = Acetic acid.

amine hydrochloride in boiling pyridine to give the substituted 1H-pyrazolo-, and isoxazolo-pyridine derivatives (XI) and (XII) respectively. The I.R. spectrum of (XI) showed characteristic bands around 1620, 1605 and 3410 cm^{-1} attributable to C=N, and NH respectively, and that of (XII) showed band at 1614 cm^{-1} characteristic for νC=N. On treatment of chalcone (I) with urea in acid medium (conc. H_2SO_4) and thiourea in alkaline medium gave 2-hydroxy-6-[p-bromophenyl]-4-[p-chlorophenyl]-dihydropyrimidine (XIIIa) and 2-mercapto-6-[p-bromophenyl]-4-[p-chlorophenyl]-dihydropyrimidine (XIIIb), respectively.

It is known that hydrogen peroxide reacts with α,β-unsaturated carbonyl compounds to give α,β-epoxy ketone [11]. This reaction has now been applied to the chalcone (I) for the synthesis of the α,β-epoxy ketone (XIV). The I.R. spectrum showed strong bands characteristic of CO at 1680 cm^{-1}, and epoxy linkage at 1250 cm^{-1}.

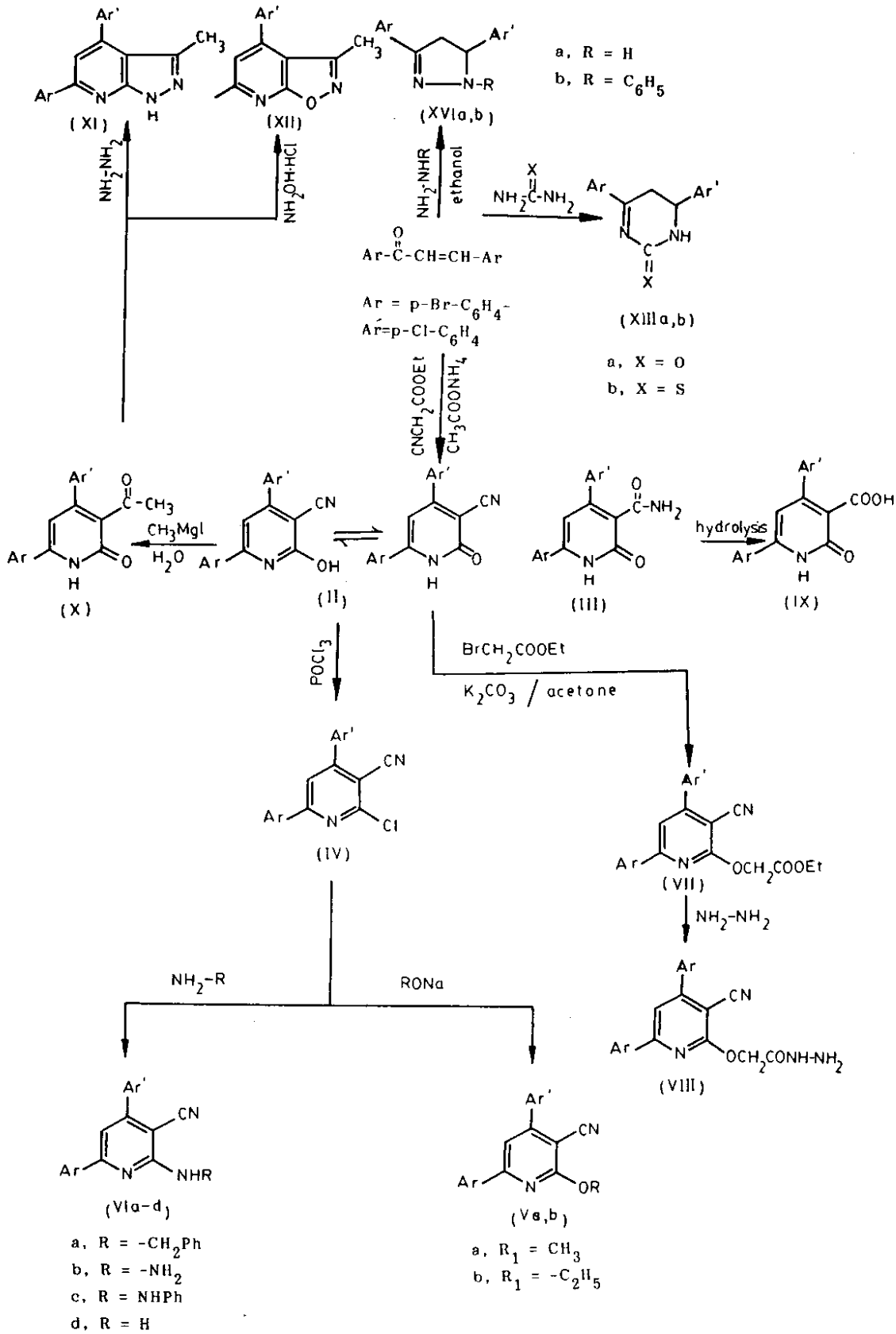
In general the oxirane ring of 1,2-epoxy ketones is opened by nucleophilic agents [12,13]. Thus the reaction of 1,2-epoxy ketone (XIV) with aqueous sodium hydroxide (as oxygen nucleophile) gave the atrolactic acid derivative (XV), via the intermediate α-diketone. The I.R. spectrum of (XV) showed bands at 1685 and 3380 cm^{-1} attributable to νCO and νOH. Moreover, the chalcone (I) was reacted with hydrazine hydrate and phenylhydrazine in boiling ethanol affording the pyrazolines [14] (XVa,b). Whose structures were confirmed by microanalysis (Table I), and the I.R. spectra which showed bands at 1600 - 1610 cm^{-1} for νC=N and 3300 - 3400 for νNH [15].

Experimental

The infrared spectra were determined with PYE UNICAM and PERKEN ELMAR 683 spectrophotometers using KBr wafer technique. Melting points are uncorrected. Characterization data of all compounds prepared are given in Table I.

Formation of 6-[p-bromophenyl]-2-hydroxy-4-[p-chlorophenyl]-nicotinonitrile (II) and nicotinamide (III):

A mixture of ethyl cyanoacetate (0.03 mol.), I(0.03 mol.) and ammonium acetate (0.24 mol.) was heated at 150


(XI)
(XII)
(XVIa,b)
a, R = H
b, R = C6H5
NH2-NH2
NH2OH·HCl
NH2-NHR
ethanol
NH2C(=X)-NH2
Ar-C(=O)-CH=CH-Ar
Ar = p-Br-C6H4-
Ar=p-Cl-C6H4
(XIIIa,b)
a, X = O
b, X = S
CNCH2COOEt
CH3COONH4
(X)
CH3Mgl
H2O
(II)
(III)
hydrolysis
(IX)
POCl3
BrCH2COOEt
K2CO3 / acetone
(IV)
(VII)
NH2-NH2
(VIII)
NH2-R
RONa
(VIa-d)
a, R = -CH2Ph
b, R = -NH2
c, R = NHPh
d, R = H
(Va,b)
a, R1 = CH3
b, R1 = -C2H5

- 160°C in an oil bath for 4 hr. The reaction mixture was cooled and the yellow oil obtained was washed several times with water. Then by fractional crystallization using light petroleum (b.p. 60-80°) and benzene, compounds II and III were separated.

Action of phosphorous oxychloride on II (Formation of IV):

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

Reaction of 2-chloro-4,6-diaryl nicotinonitrile (IV) with sodium methoxide and ethoxide: (Formation of Va,b):

A solution of (IV) (1 g) in methanol or ethanol (20 ml) was treated with sodium-methoxide or ethoxide (prepared by dissolving 0.23 g sodium in 10 ml methanol or ethanol respectively) and refluxed for 5 hrs, then allowed to cool. The solid obtained upon dilution of the reaction mixture with water was filtered off and crystallized from the suitable solvent to give (Va,b).

Formation of 2-benzylamino-4,6-diaryl-pyrid-2-one (VIa):

A suspension of (II) 0.5 g and benzylamine (4 ml) was refluxed for 2 hrs and allowed to cool. The reaction mixture was triturated with cold ethanol and the solid obtained was crystallized from the proper solvent to give (VIa).

Action of hydrazine hydrate on (I, IV, VII, X), and phenylhydrazine on (I, IV): Formation of XVIa, VIb, VIII, XI, XVIb and VIc):

A solution of I, IV, VII and X (0.01 mol.) and hydrazine hydrate or phenylhydrazine (0.01 mol.) in absolute ethanol (30 ml) was refluxed for 5 hrs. The products obtained after concentration and cooling were crystallized from a suitable solvent to give XVIa, VIb, VIII, XI, XVIb and VIc respectively.

Formation of 2-amino-3-cyano-3,6-diaryl pyridine VId:

A mixture of IV (0.01 mol.), sodamide (0.012 mol.) and dry xylene was refluxed for 12 hrs. The reaction mixture was diluted with water, then extracted with ether. The solid separated was crystallized from a suitable solvent to give VId.

Reaction of II with ethyl bromoacetate: Formation of (VII):

A mixture of II (0.01 mol.) ethyl bromoacetate (0.02 mol.), 2 g. of anhydrous potassium carbonate and dry acetone (30 ml) was refluxed on water bath for 30 hrs. The excess acetone was evaporated and then poured on water. The solid separated was filtered off and crystallized from a suitable solvent to give VII.

Hydrolysis of II to the corresponding acid: Formation of (IX):

A mixture of II (0.01 mol.), acetic acid (20 ml) and hydrochloric acid (20 ml) was refluxed for 5 hrs., cooled, then poured onto water, and filtered. The solid product was crystallized from the proper solvent to give IX.

Action of Grignard reagent on II: Formation of (X):

A suspension of II (2 g) in dry benzene (50 ml) was added to an ethereal solution of methyl magnesium iodide (prepared from 0.9 g magnesium, 7 g methyl iodide and 40 ml dry ether). The reaction mixture was refluxed (on steam bath) for 10 hrs,

set aside at room temperature and then decomposed with a cold solution of hydrochloric acid (10 %). The yellow solid obtained was crystallized from a suitable solvent to give X.

Reaction of X with hydroxylamine hydrochloride: Formation of (XII):

A mixture of X (0.01 mol.), hydroxylamine hydrochloride (0.012 mol.), pyridine (20 ml) and a few drops of water was refluxed for 5 hrs. The reaction mixture was poured into ice-cold HCl. The solid separated was crystallized from suitable solvent to give XII.

Action of urea on chalcone I: Formation of (XIIIa):

A mixture of I (0.01 mol.), urea (0.015 mol.), ethanol (20 ml) and conc. sulphuric acid (5 ml) was refluxed for 5 hrs. The mixture was concentrated, cooled, then neutralized by ammonium hydroxide. The solid obtained was filtered off, washed with water, and crystallized from a suitable solvent to give XIIIa.

Action of thiourea on I: Formation of (XIIIb):

A mixture of I (0.01 mol.), thiourea (0.01 mol.), sodium hydroxide (30 ml, 2 %) and ethanol (30 ml) was refluxed for 5 hrs. The solid product obtained after concentration and cooling was filtered off and crystallized from a suitable solvent to give XIIIb.

Epoxidation of chalcone I: Formation of (XIV):

A solution of I (0.01 mol.) in acetone (50 ml) and methyl alcohol (20 ml) was mixed with 5 % aqueous sodium hydroxide (10 ml) followed by the addition of hydrogen peroxide (30 %, 5 ml). The solution was shaken for one hour, and then allowed to stand overnight at room temperature, water was then added. The solid that separated was crystallized from a suitable solvent to give XIV.

Action of sodium hydroxide on the epoxide XIV: Formation of (XV):

The epoxide XIV (0.01 mol.) was refluxed with 10 % aqueous sodium hydroxide (10 ml for each gm. of epoxide) for 2 hrs. The alkaline solution was treated with charcoal, and extracted with ether. The aqueous layer on acidification by dilute HCl-ice, gave the product XV, which was filtered off and crystallized from a suitable solvent.

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