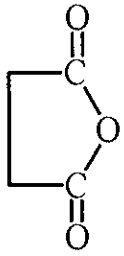
CHEMISTRY OF β-AROYLACRYLIC ACIDS

A) Synthesis of β-Aroylacrylic Acids

I) From aroyl-β-bromopropionic acids

β-Benzoylacrylic acid (I) was prepared from benzoyl-β-bromopropionic acid[1-4](II) when treated with anhydrous sodium acetate in hot acetic acid[5].

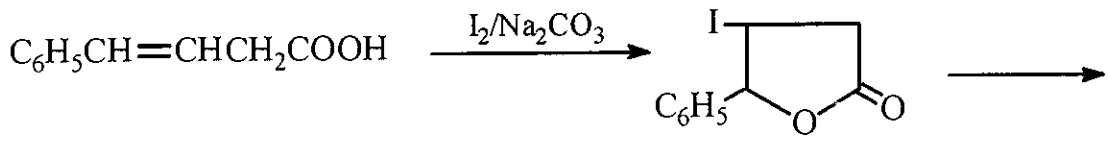


$$+ \quad C_6H_6 \xrightarrow{AlCl_3} C_6H_5COCH_2CH_2COOH$$

$$\xrightarrow{Br_2} C_6H_5COCHCH_2COOH \quad (II) \xrightarrow[AcONa]{AcOH} C_6H_5COCH{=}CHCOOH \quad (I)$$

II) From β,γ-unsaturated acids

β,γ-unsaturated acids reacts with iodine in the presence of a large excess of sodium carbonate giving iodolactone (III) which gave the corresponding β-aroylacrylic acids[6, 7] (I)



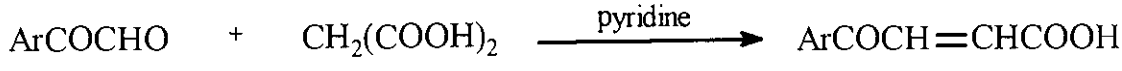
(III)

$C_6H_5COCH{=}CHCOOH$

(I)

III) By condensation of glyoxals with malonic acids

β-Aroylacrylic acid (I) was obtained by condensation of phenylglyoxal and/or β-naphthylglyoxal with malonic acid in pyridine [8].

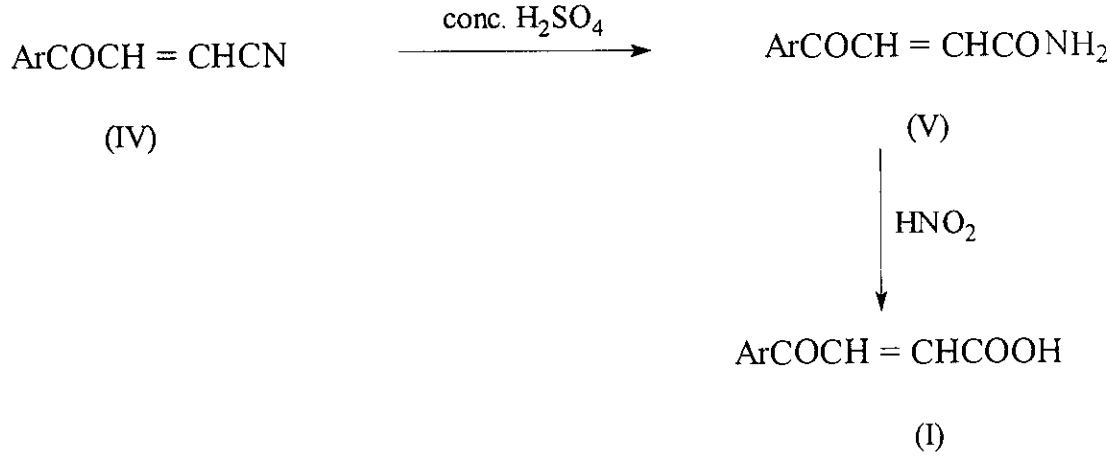


(I)

Ar = phenyl, β-naphthyl

IV) Hydrolysis of nitriles

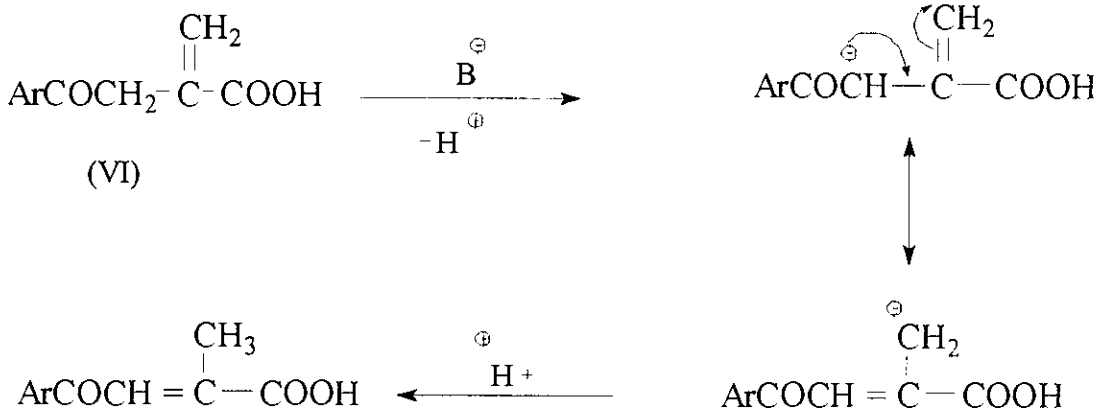
Keeping β-aroylacrylonitriles (IV) in concentrated sulphuric acid gave the corresponding amides (V) which on treatment with nitrous acid yielded the corresponding β-aroylacrylic acids (I)[9].



(I)

V) From keto acids

When keto acids (VI) were treated with trimethylamine, it were isomerised to β-aroyl-α-methylacrylic acid (VII) according the following mechanism [10].

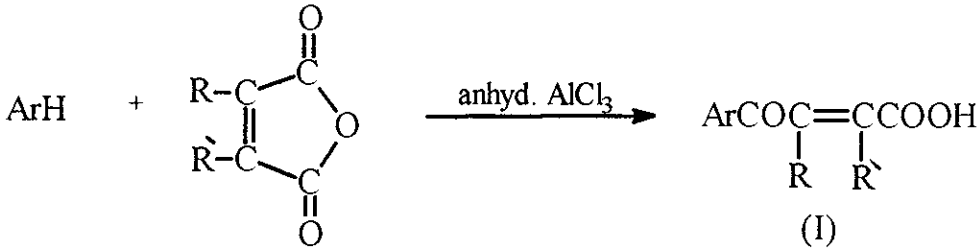


(VI)

(VII)

VI) Friedel-Crafts reaction

The Friedel-Crafts reaction between an aliphatic dibasic anhydride (or it's substituted) and aromatic compound results in the formation of an aroyl acid (I)[11-14].



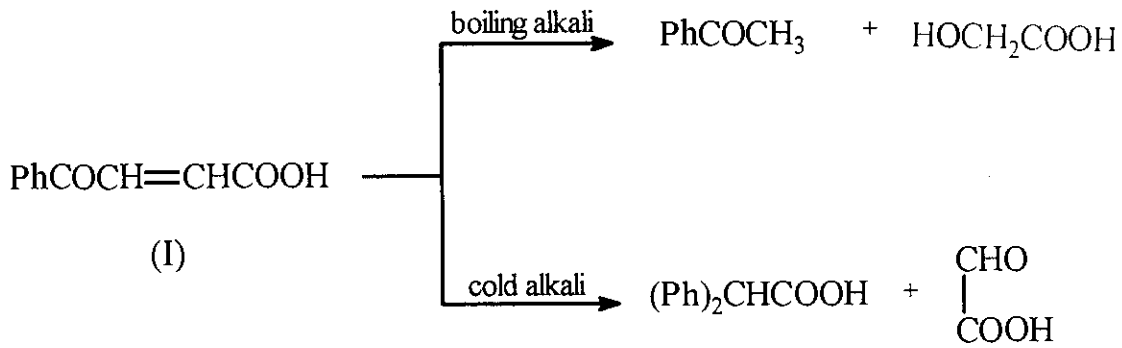
(I)

Ar-H =	R =	R` =
a; benzene	H	H
b; anisol	H	H
c; benzene	H	CH_3
d; biphenyl	CH_3	CH_3

B) Reactions of β-Aroylacrylic Acids

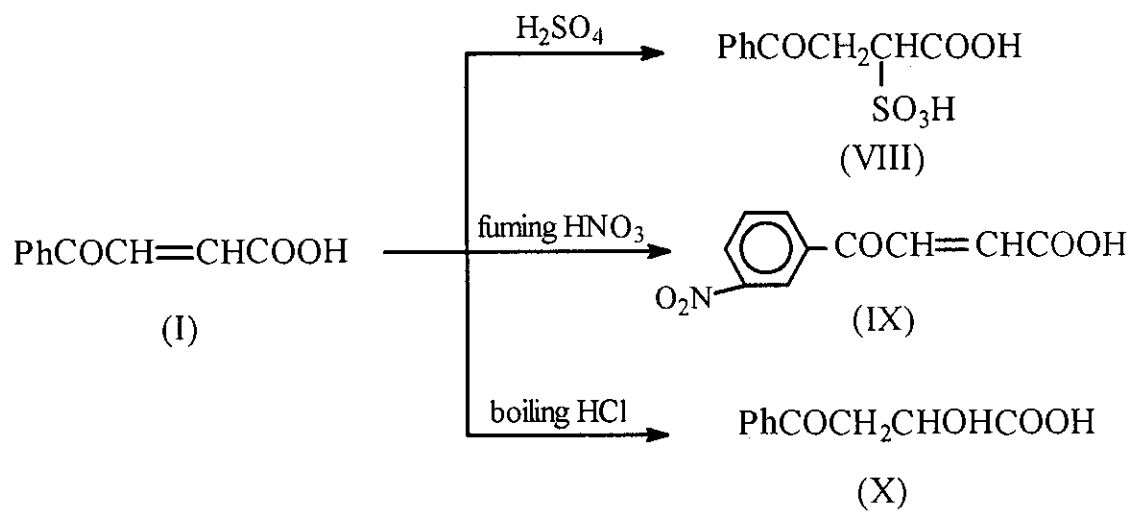
I) Action of alkali

Benzoylacrylic acid decomposed by boiling alkali to acetophenone and glycollic acid while cold alkali decomposed it to diphenyl acetic acid[15].



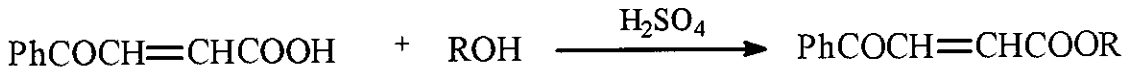
II) Action of acids

Treatment of β-benzoylacrylic acid with sulphuric acid produced α-sulpho-β-benzoylpropionic acid (VIII)[13] while with fuming nitric acid gave the m-nitro derivative (IX)[13]. Treatment of (I) with diluted hydrochloric acid gave β-benzoyllactic acid (X)[16].



III) Esterification

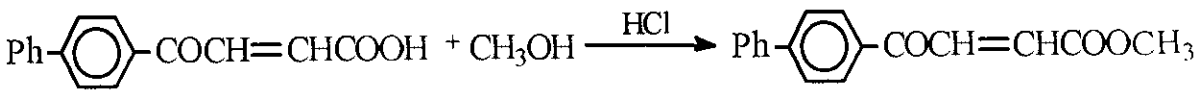
Usual esterification of (I) produces benzoylacrylic esters[17] (XI).



(I) (XI)

R = isopropyl, butyl, isobutyl, isoamyl, benzyl

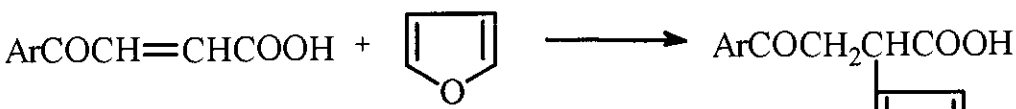
Also hydrogen chloride gas may be used as catalyst in the preparation of methyl-β-(4-phenylbenzoyl)acrylate (XII)[11].



(I) (XII)

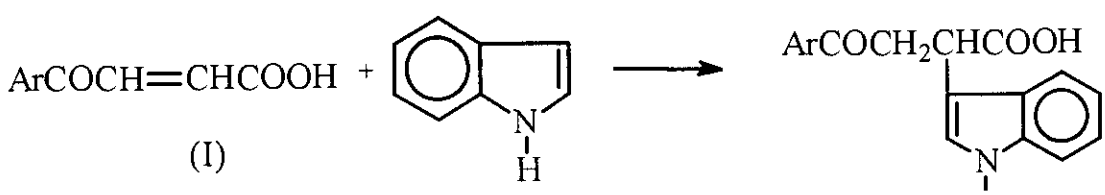
IV) Alkylation

Alkylation of furan with β-aroylacrylic acids gave α-(3-furyl)- β-aroylpropionic acids (XIII)[18].



(I) (XIII)

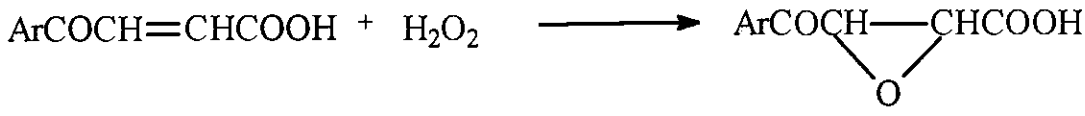
Treatment of β-aroylacrylic acids in benzene solution with indole was used as preparative method for α-(3-indoyl)-β-aroylpropionic acids (XIV)[19].



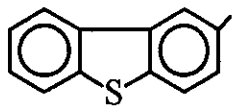
(I) (XIV)

V) Epoxidation

The epoxidation of β-aroylacrylic acids (XV) with hydrogen peroxide in alkaline medium gave α,β-epoxyacrylic acids (XVI)[20, 21].

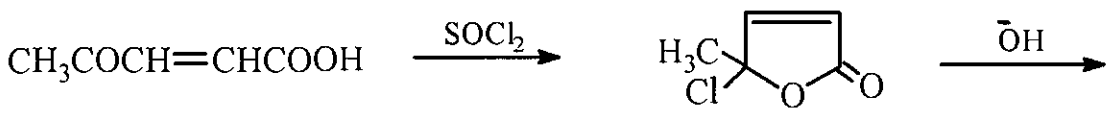


(XV) (XVI)

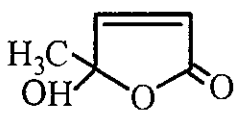
Ar = 2,4-$Cl_2.C_6H_3$; 

VI) Reaction with thionyl chloride

It has been reported that acetylacrylic acid (XVII) was isomerised by thionyl chloride to 5-chloro-2,5-dihydro-2-oxofuran (XVIII) which converted to (XIX) with aqueous alkali [22].



(XVII) (XVIII)

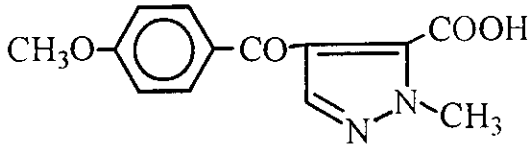


(XIX)

VII) Action of diazomethane

Addition of diazomethane to 4-methoxybenzoylacrylic acid (XX) gave 1-methyl-4-(4'-methoxylbenzoyl)-5-pyrazolo-carboxylic acid (XXI)[23].

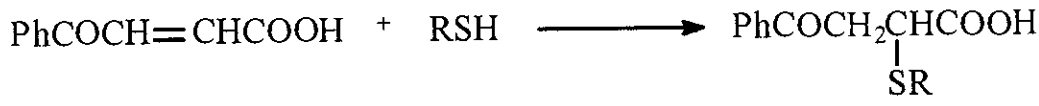
(XX)



(XXI)

VIII) Addition of mercaptans

Mercaptans were added to the olefinic double bond in benzoylacrylic acid (I) to give the adduct (XXII)[24, 25].



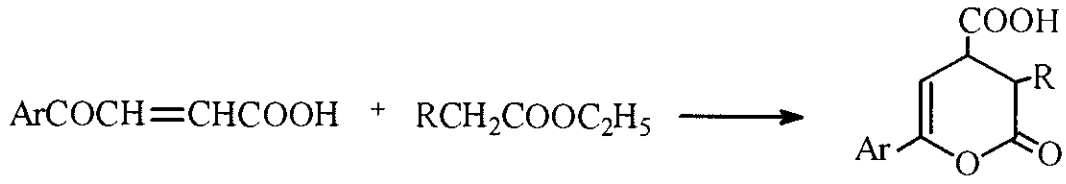
(I) (XXII)

R = H, Ph

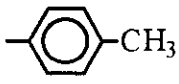
IX) Michael reaction

The unsaturated keto acids reacted under Michael conditions where the double bond is activated by both a keto and carboxyl group[26-30].

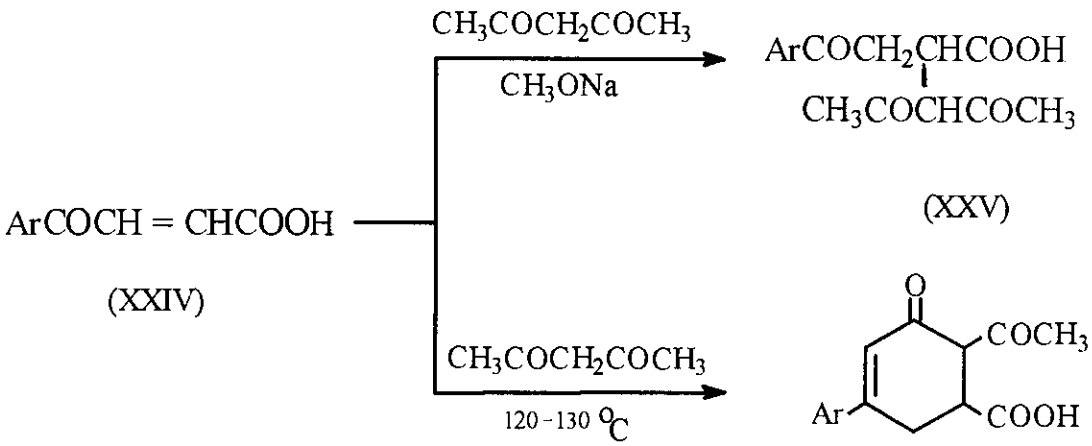
β-(p-toluoyl- or p-chlorobenzoyl)acrylic acids reacts with diethyl-malonate and ethylacetoacetate under Michael conditions[31] to give cyclic product (XXIII) or normal Michael addition products depending on the reaction condition.



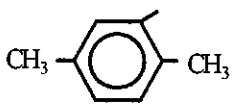
(I) (XXIII)

Ar =  ; R = $COOC_2H_5$, $COCH_3$

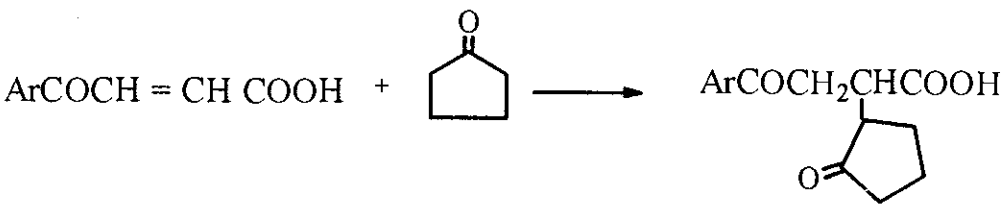
Acetylacetone readily added to β-(2,5-dimethylbenzoyl)acrylic acid (XXIV) under Michael conditions to give the normal adduct (XXV) or cyclic adduct (XXVI)[27, 28].



(XXIV) (XXV) (XXVI)

Ar = 

Also the addition of cyclopentanone to β-aroylacrylic acid (XXVII) in alcholic sodium hydroxide gives Michael adduct (XXVIII)[32].

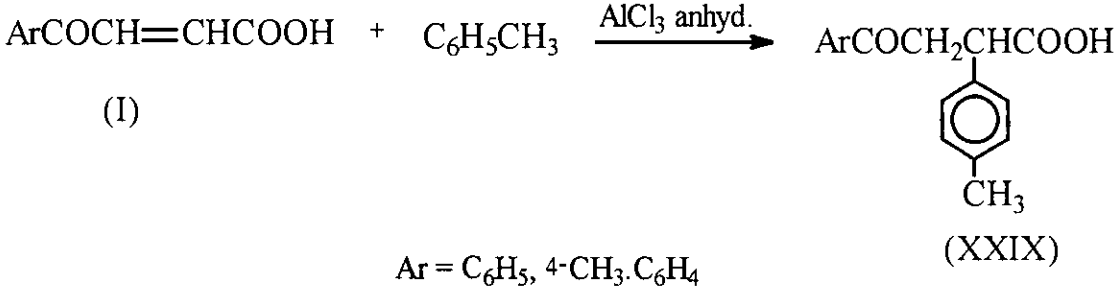


(XXVII) (XXVIII)

Ar = C_6H_5., 4-$CH_3.C_6H_4$., 4-$C_6H_5.C_6H_4$

X) Friedel-Crafts reaction

The Friedel-Crafts catalysed reaction of β-aroylacrylic acids with aromatic compounds involves addition to the olefinic double bond. Thus (β-benzoyl or β-toluyl)acrylic acids (I) were treated with toluene in presence of anhydrous aluminum chloride, addition occurred alpha to the carbonyl group with formation of 2-tolyl-3-benzoylpropionic acid (XXIX)[33, 34].



It is interesting to note that[35] in β-aroylacrylic acids the polarization of the olefinic double bond by the ketone outweighs that caused by carbonyl group i.e., α-carbon accept the nucleophiles more readily than β-carbon atom. So β-aroylacrylic acid behave as α,β-unsaturated ketone rather than α,β-unsaturated acids in their mode of addition.

The reaction of the olefinic double bond in β-aroylacrylic acid (XXX) with aromatic hydrocarbons under Friedel-Crafts conditions extended to benzene, ethylbenzene, m-xylene, p-xylene, o-xylene and/or p-cymene to give the corresponding α-aryl-β- aroylpropionic acid (XXXI)[36].

$$ArCOCH{=}CHCOOH + \grave{A}r\,H \xrightarrow{AlCl_3\ anhyd.} ArCOCH_2\underset{\displaystyle Ar'}{\underset{|}{C}}HCOOH$$

(XXX) (XXXI)

Ar =	Ar' =
a; 2, 4-$(CH_3)_2C_6H_3$	2, 4-$(CH_3)_2C_6H_3$
b; 2, 4-$Br(CH_3)C_6H_3$	2, 5-$(CH_3)_2C_6H_3$
c; 2, 4-$Br(CH_3)C_6H_3$	3, 4-$(CH_3)_2C_6H_3$
d; 3, 4-$(CH_3)_2C_6H_3$	2, 5-$CH_3[CH(CH_3)_2]C_6H_3$

XI) Action of ammonia

The reaction of benzoylacrylic acid (I) with ammonium hydroxide afforded the formation of α-amino-β-benzoylpropionic acid (XXXII)[37, 38].

$$PhCOCH{=}CHCOOH + NH_4OH \longrightarrow PhCOCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

(I) (XXXII)

XII) Addition of amines

Several investigations were reported on the reaction of β-aroylacrylic acid with amines, where the addition of amines occurs at the more reactive α-carbon atom to give α-amino-γ-keto acids[39, 40].

The reaction of β-benzoylacrylic acid (I) with different amines afforded α-amino-β-benzoylpropionic acid (XXXIII).

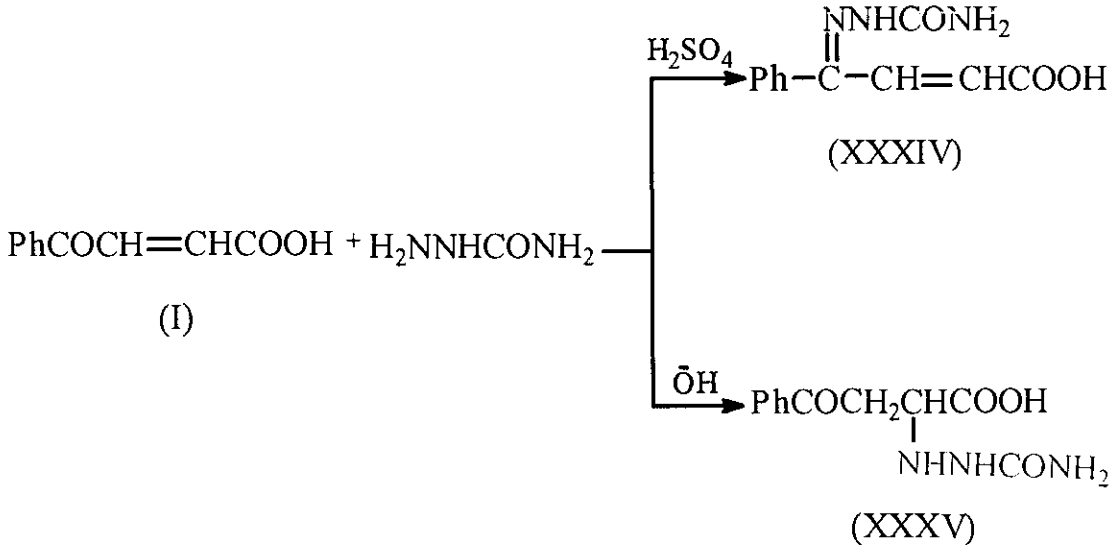
$$PhCOCH{=}CHCOOH + RNH_2 \longrightarrow PhCOCH_2\underset{\displaystyle NHR}{\underset{|}{C}}HCOOH$$

(I) (XXXIII)

R = $OH\text{-}CH_2CH_2$, $C_6H_5CH_2$, 4-$CH_3O\text{-}C_6H_4$

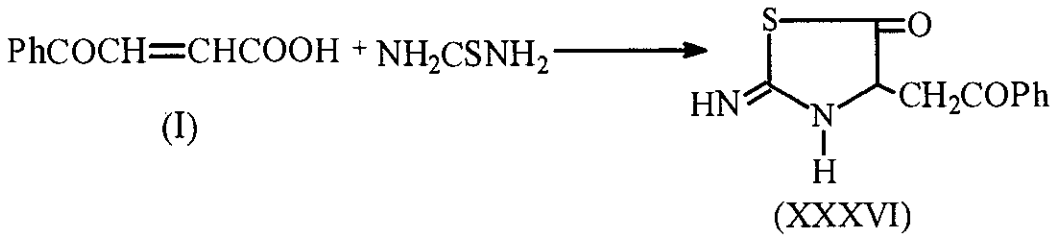
XIV) Action of semicarbazide

Benzoylacrylic acid (I) reacts with semicarbazide in presence of sulphuric acid and give the semicarbazone (XXXIV), on the other hand in presence of alkaline medium, the addition product (XXXV) was obtained[41].

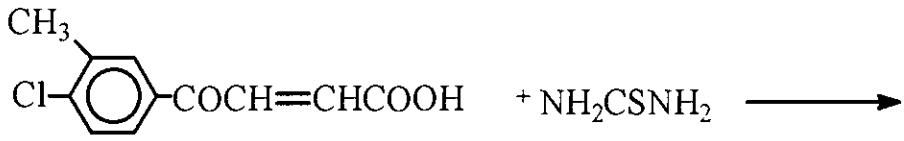


XIV) Action of thiourea

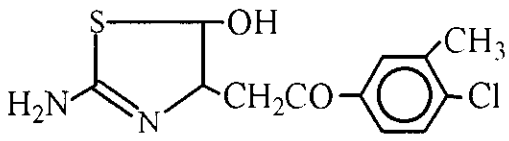
β-Benzoylacrylic acids (I) reacted with thiourea in presence of dilute acetic acid and slight excess of sodium carbonate to give 2-imino-4-oxo-5-phenacylthiozolidine (XXXVI)[42, 43].



It was reported that[44, 45] thiourea reacts with ethyl-β-benzoylacrylate to give 2-amino-4-ethoxy-5-benzoylmethylthiazole. Also It reacts with β-(4-chloro-3-methyl)benzoylacrylic acid (XXXVII) to give 2-amino-4-hydroxy-5-(4′-chloro-3′-methylbenzoyl)methylthiazole (XXXVIII).

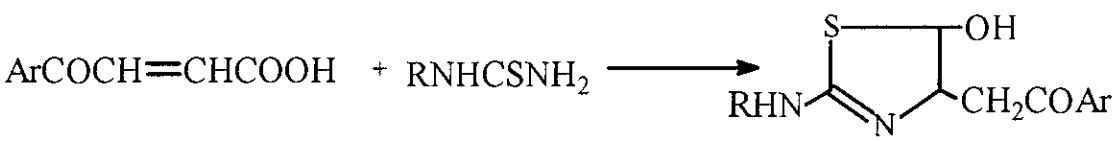


(XXXVII)



(XXXVIII)

Reactions of β-aroylacrylic acid (I) with thiourea, benzylthiourea and phenylthiourea are useful as synthetic route for preparation of 2-amino-4-hydroxy-5-aroylmethylthiazole (XXXIX)[47].



(I)

(XXXIX)

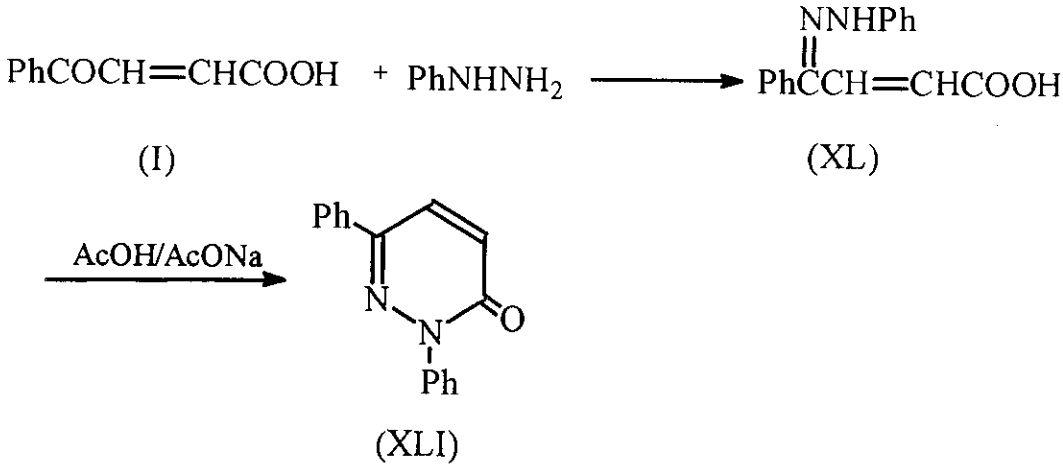
R =	Ar =
a; H	4-OCH_3.C_6H_4
b; $CH_2C_6H_5$	4-OCH_3.C_6H_4.
c; $CH_2C_6H_5$	4-C_6H_5.C_6H_4.

XV) Action of hydrazines

β-Aroylacrylic acid and its ester react with hydrazine hydrate or methylhydrazine to give pyridazin-3-ones however, with phenylhydrazine or substituted phenylhydrazine an intermediate hydrazone is obtained which could be cyclised to 3-pyridazinones[48-53].

β-Benzoylacrylic acid or its methyl ester reacts with phenylhydrazine to give the corresponding phenylhydrazone (XL) which on refluxing with

acetic acid and sodium acetate gives 2,3-dihydro-2,6-diphenyl-3-oxopyridazine (XLI)[54].



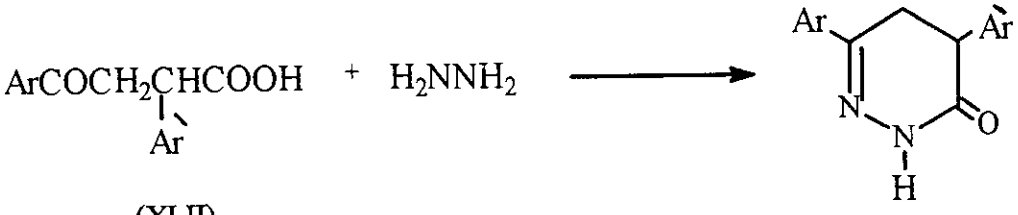
(XLI)

CHEMISTRY OF PYRIDAZIN-3(2H)-ONES

A) Synthesis of Pyridazin-3(2H)-ones

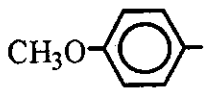
1) By action of hydrazine on β-aroylpropionic acids

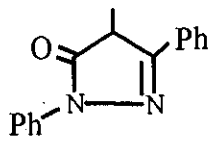
It was reported that[55-64] the condensation of β-aroylpropionic acid derivatives (XLII) with hydrazine hydrate yielded the corresponding pyridazinone derivatives (XLIII).

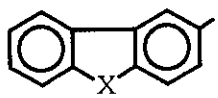


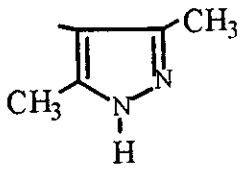
(XLII) (XLIII)

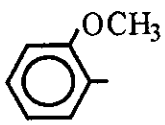
Ar = Ar` =

a) 



b) 



c) 

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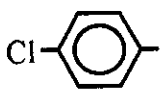
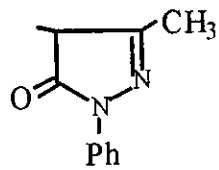
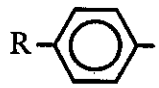
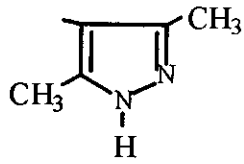
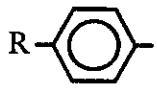
d) 



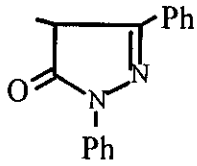
e) 

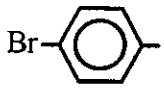
R = Cl, CH_3O



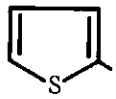
f) 

R = Cl, CH_3

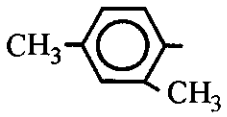


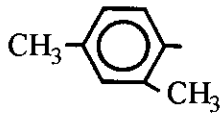
g) 

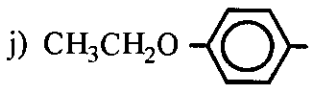
H

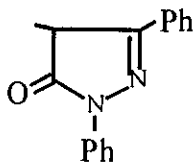
h) 

Ph

i) 

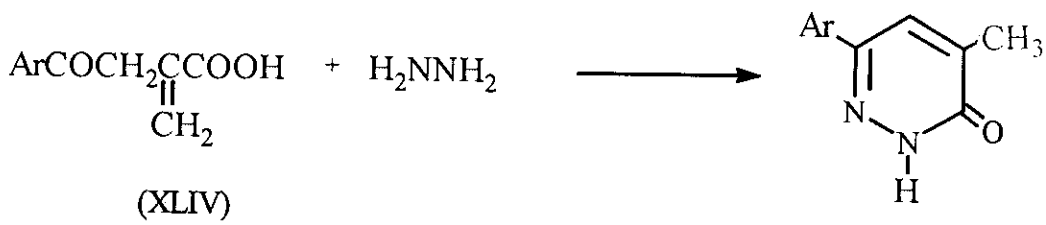


j) 



2) By action of hydrazine hydrate on β-aroyl-α-methylene-propionic acids

The condensation of hydrazine hydrate with β-aroyl-α-methylene-propionic acid (XLIV) furnished mainly 6-aryl-4-methylpyridazin-3(2H)-ones (XLV)[65].



(XLIV) (XLV)

3) By action of hydrazine hydrate on a mixture of α-dicarbonyl compounds and carboxylic acid derivatives

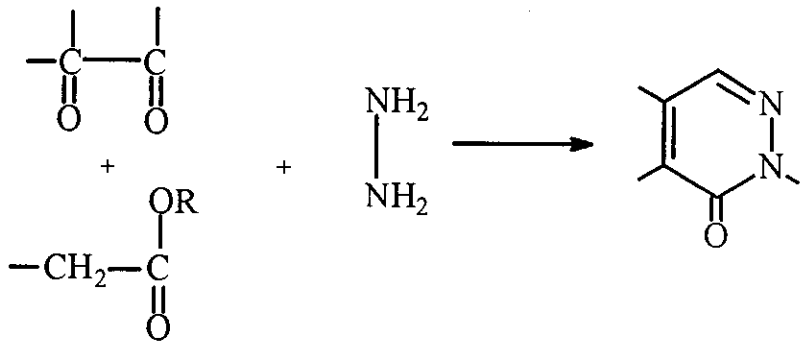
In this methods a mixture of three available starting materials are usually empolyed[66]:

a) An α-dicarbonyl compound.

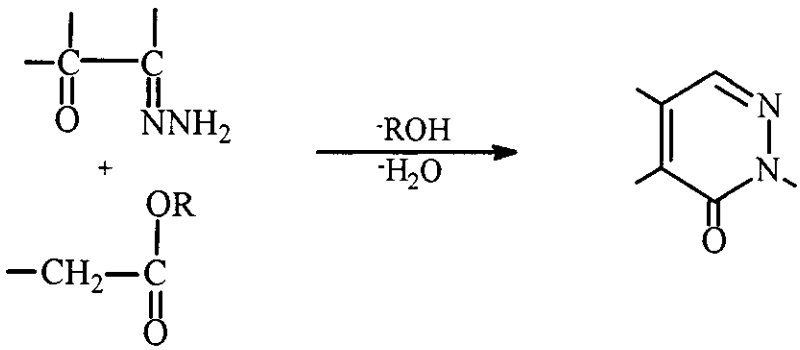
b) A carboxylic acid derivative containing a reactive methylene group.

c) Hydrazine or mono substituted hydrazine.

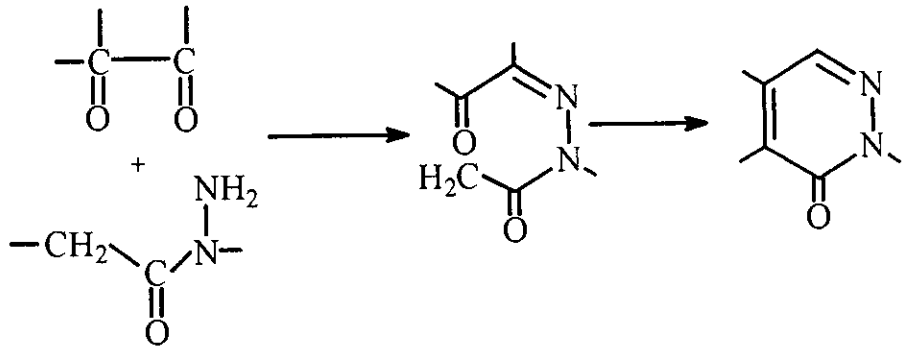
The synthesis could be represented according to the following Scheme:



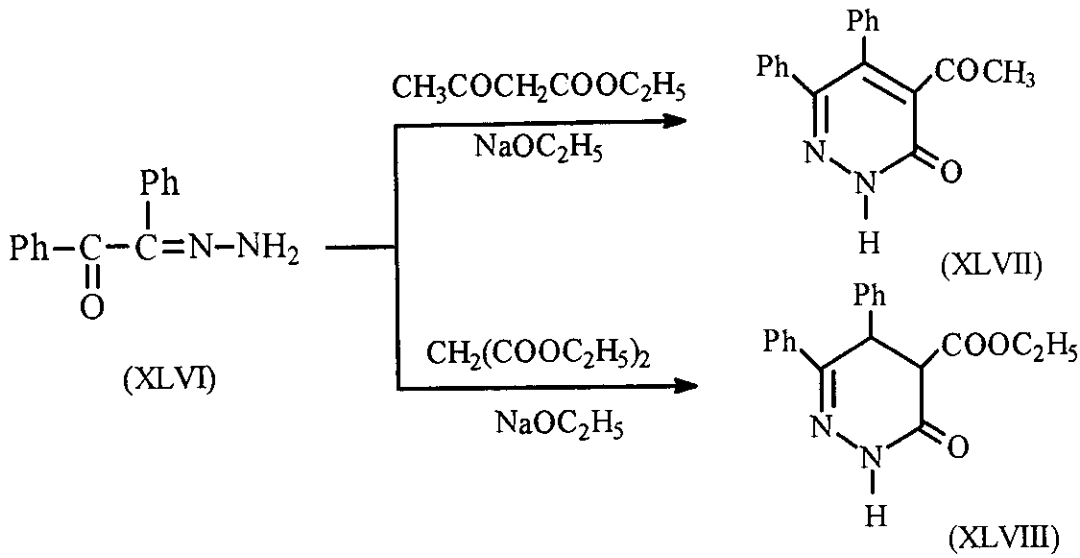
The reaction may be takes place by condensation of the mono-hydrazone of α-dicarbonyl compound with the ester of the carboxylic acid containing an active methylene group. This method is recommended when using aromatic diketones and could be represented by a general equation as follows:



Alternatively, the hydrazide of the acids is allowed to condense with an α-diketone followed by ring closure as follows:

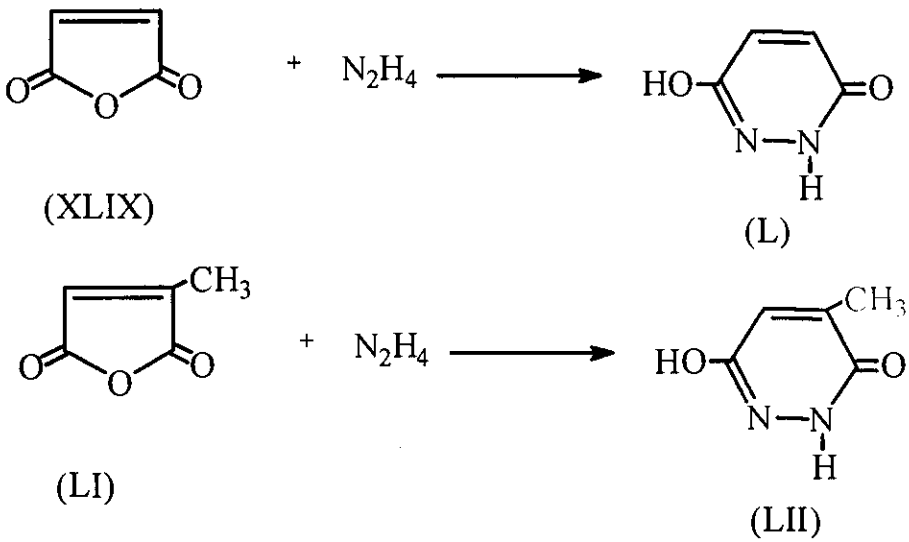


Among the dicarbonyl compounds used in this synthesis are diacetyl, benzoylacetyl, benzil, cyclohexanedione, methylglycoxal and phenanthraquinone. The acid derivatives participating in the synthesis are diethylmalonate, ethylcyanoacetate, ethylaectoacetate, ethylphenylacetate, ethylhippurate and ethylacetoacetate. For example the condensation of benzil monohydrazone (XLVI) with ethylacetoacetoacetate or diethylmalonate in the presence of sodium ethoxide gave 4-acetyl (XLVII) or 4-carboethoxy-5,6-diphenylpyridazin-3(2H)-ones (XLVIII)[67] respectively.



4) From unsaturated dibasic acid anhydrides

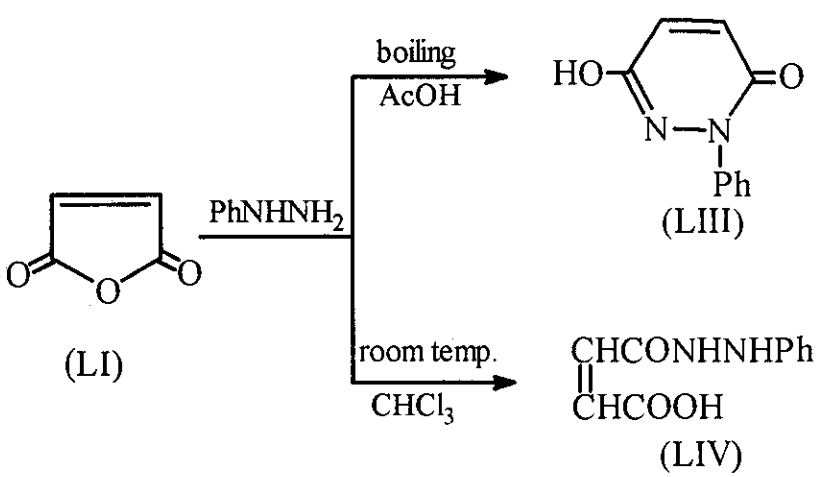
Maleic (XLIX) and citraconic (L) anhydrides react with hydrazine hydrate to give 6-hydroxy (LI) and 6-hydroxy-4-methyl (LII) pyridazin-3(2H)-ones respectively[68].



(XLIX) (L)

(LI) (LII)

Phenylhydrazine reacts with maleic anhydride in boiling acetic acid to give 6-hydroxy-2-phenylpyridazin-3(2H)-one (LIII)[69]. The intermediate monophenylhydrazide (LIV) could be isolated when the reaction was carried out at room temperature in chloroform. However, the monophenylhydrazide was cyclised to pyridazinone (LIII) on heating.

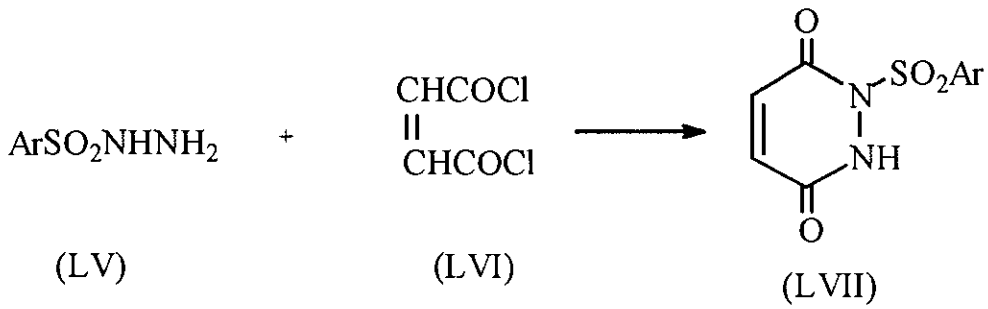


(LI) (LIII)

(LIV)

5) By condensation of arylhydrazide and maleoyl chloride

Addition of arylsulphonyl hydrazide (LV) to maleoyl chloride (LVI) in presence of pyridine gave the corresponding pyridazinone (LVII)[70].

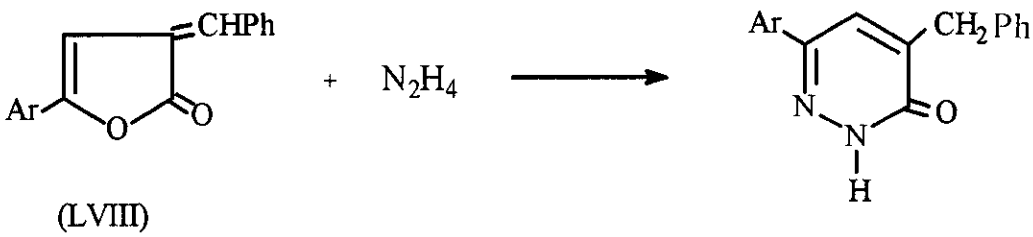


(LV) (LVI) (LVII)

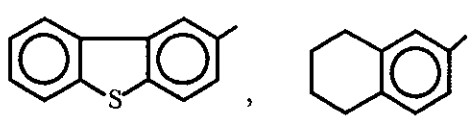
Ar = C_6H_5, 3-COOH.C_6H_4, 4-Cl.C_6H_4, 4-Br.C_6H_4.

6) By action of hydrazine hydrate on lactones

The reaction of 3-benzylidene-5-aryl-2(3H)-furanones (LVIII) with hydrazine hydrate affect the fission of the heterocyclic ring and yielded the corresponding pyridazinone derivatives (LIX)[71, 72].

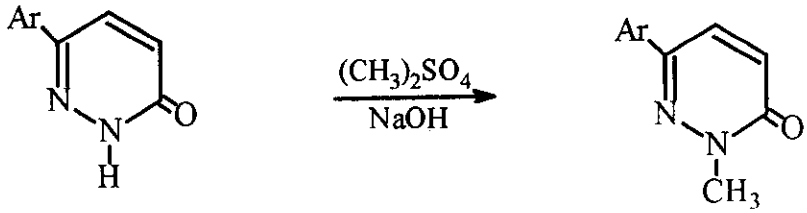


(LVIII) (LIX)

Ar = 

7) By action of substituted hydrazine on chalcone

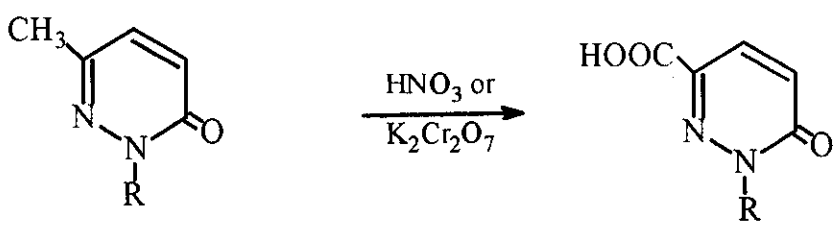
The reaction of chalcones (LX) and acetone cyanohydrine gave the corresponding γ-ketonitrile (LXI) which on hydrolysis gave the acid (LXII) which condensed with substituted hydrazines and yielded the pyridazinone derivatives (LXIII)[73].



(LXVIII) (LXIX)

2) Action of oxidizing agents

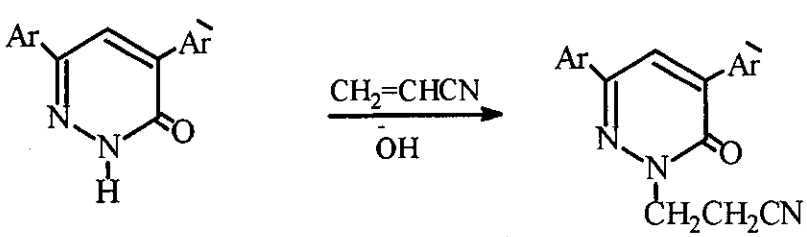
The stability of the hetero-ring in pyridazin-3(2H)-ones towards oxidizing agents is illustrated by the oxidation of pyridazinone derivatives (LXX) with nitric acid or potassium dichromate and sulphuric acid to 6-carboxypyridazin-3(2H)-one (LXXI) and its methyl derivatives[79].



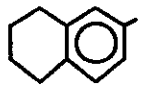
(LXX) (LXXI)

3) Reaction with acrylonitrile

4,6-Diarylpyridazin-3(2H)-ones (LXXII) react with acrylonitrile in ethanol containing catalytic amount of aqueous sodium hydroxide to yield corresponding 2-(2\`-cynoethyl)pyridazinone derivatives (LXXIII) [72, 80-81].

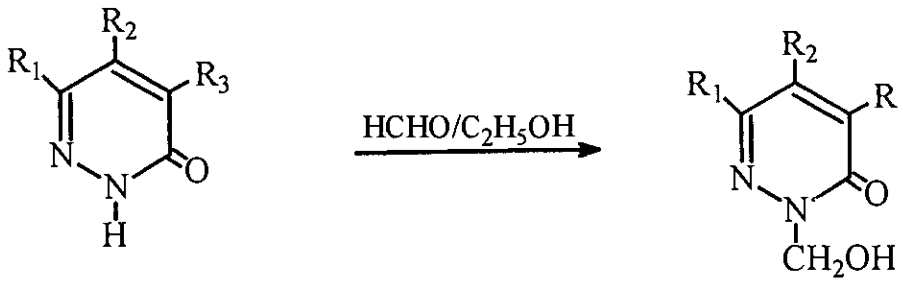


(LXXII) (LXXIII)

	Ar =	$\overset{\frown}{Ar}$ =
a;	Ph	H
b;	Ph	Ph
c;		$PhCH_2$

4) Reaction with aldehyde (Mannich reaction)

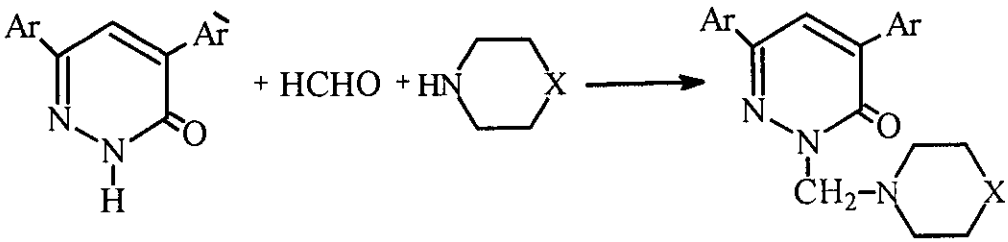
When pyridazinone derivatives (LXXIV) were allowed to react with formaldehyde in ethanolic solution give 2-hydroxymethylpyridazinone derivatives (LXXV)[82, 83].



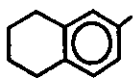
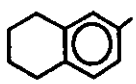
(LXXIV) (LXXV)

	R_1 =	R_2 =	R_3 =
a;	H	Cl	Cl
b;	Ph	Ph	$COCH_3$

On the other hand when 4,6-diarylpyridazinones (LXXVI) react with formaldhyde in the presence of secondary amines namely piperidine or morpholine in ethanol proceeded normally to give the Mannich bases (XXVII)[72, 81, 84,85].



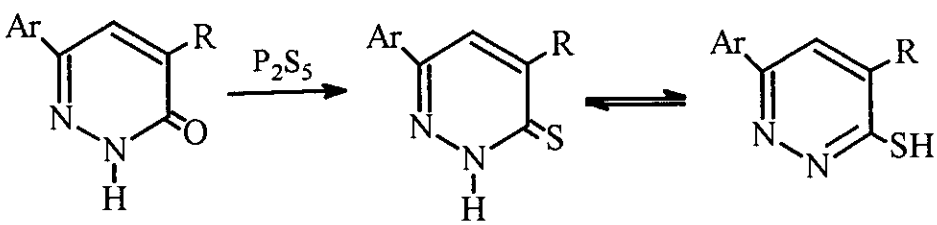
(LXXVI) (LXXVII)

	Ar	Ar`	X
a)	Ph	COPh	CH_2
b)	Ph	COPh	O
c)		CH_2Ph	CH_2
d)		CH_2Ph	O
e)	$4\text{-}OCH_3.C_6H_4$	Ph	CH_2
f)	COPh	$4\text{-}CH_3.C_6H_4$	CH_2

II) Action of nucleophiles

1) Reaction with phosphorous pentasulphide

It was reported that[86-90] when the pyridazinone derivatives (LXXVIII) were submitted to react with phosphorous pentasulphide in boiling xylene yielded the corresponding pyridazinethione derivatives (LXXIX).

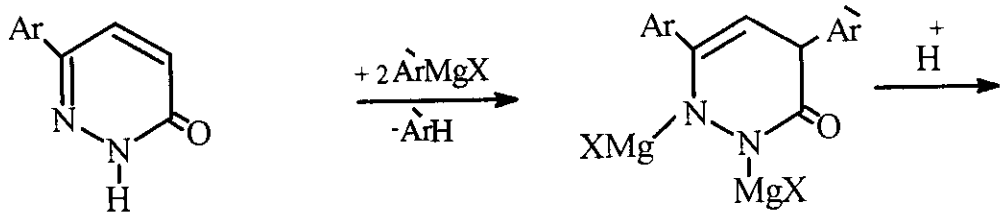


(LXXVIII) (LXXIX)

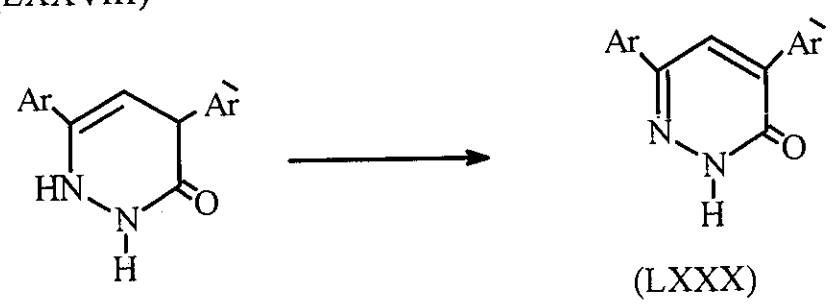
Ar =	R =
a) 4-$CH_3.C_6H_4$	H
b) C_6H_5	CH_3
c) 4-$CH_3.C_6H_4$	CH_3
d) 2-$C_6H_5.C_6H_4$	H

2) Action of Grignard reagents

When 6-arylpyridazin-3(2H)-one (LXXVIII)[91-93] were treated with different arylmagnesium bromide, the corresponding 4,6-diarylpyridazin-3(2H)-ones (LXXX) were obtained (the reaction take place by 1,4-addition to the -C=C–C=N-).



(LXXVIII)

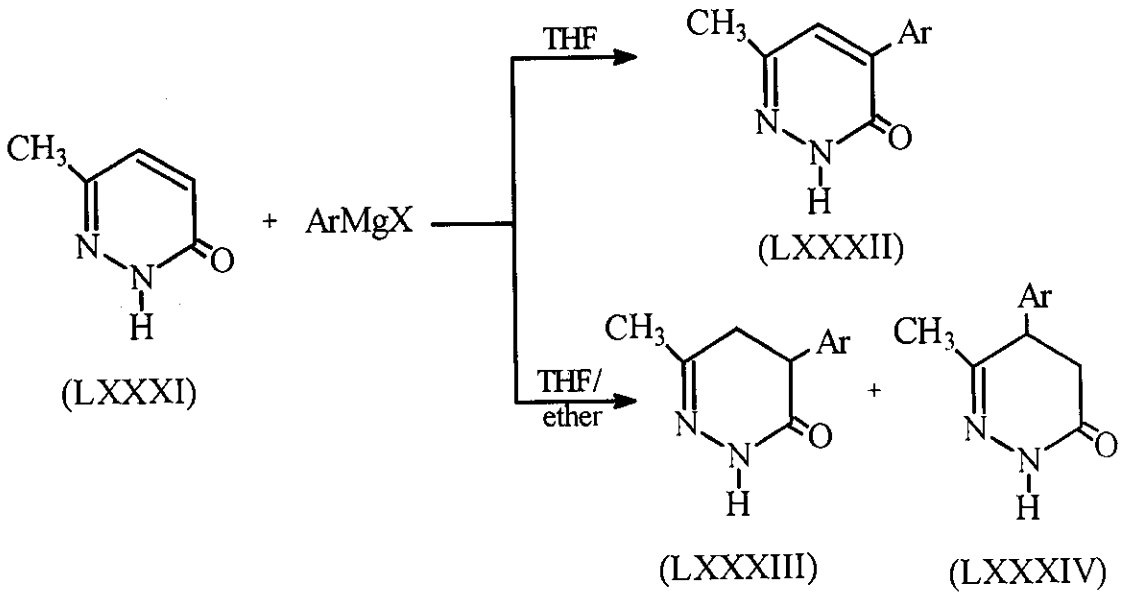


(LXXX)

Further investigation[94] on the reaction of Grignard reagent with 6-methylpyridazin-3(2H)-ones (LXXXI) indicated that the addition was depended mainly on the solvent used, thus when tetrahydrofuran was used the reaction take place via 1,4-addition to -C=C–C=N- system followed by dehydrogenation to give the corresponding 4-aryl-6-methylpyridazin-3(2H)-ones (LXXXII). But when the reaction was carried out in a mixture of ether-tetrahydrofuran as solvent a mixture of two compounds were obtained, the predominant product was found to be 4-aryl-4,5-dihydro-6-

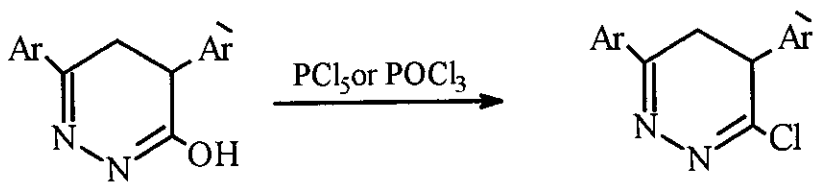
methylpyridazin-3(2H)-ones (LXXXIII) which formed by 1,4-addition to C=C–C=N- system with dehydrogenation.

The second product was 5-aryl-4,5-dihydro-6-methylpyridazin-3(2H)-ones (LXXXIV) which resulted from 1,4-addition to -C=C–C=O system.



3) Reaction with phosphorous pentachloride

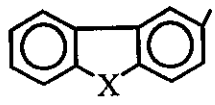
It was reported that[56, 95-97] when pyridazinone derivatives (LXXXV) were submitted to react with phosphorous pentachloride or phosphorous oxychloride, it gave the corresponding chloropyridazine derivatives (LXXXVI).



(LXXXV) (LXXXVI)

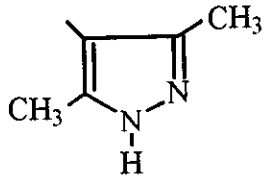
	Ar =	Ar' =
a)	$C_6H_4.Br(4)$	$2,5\text{-}CH_3[CH(CH_3)_2]C_6H_3$
b)	$2,4\text{-}(CH_3)_2C_6H_3$	$2,4\text{-}(CH_3)_2C_6H_3$

c) 

d) 

X = S, NH

-CH_3

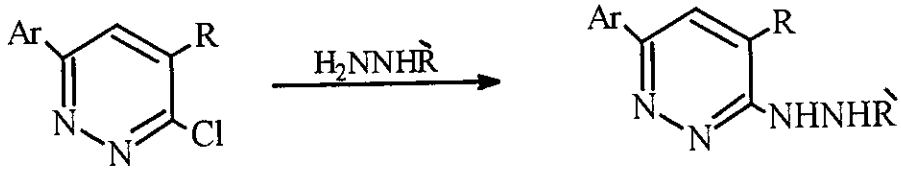


REACTIONS OF HALOPYRIDAZINES

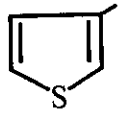
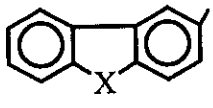
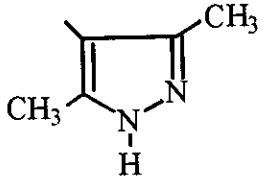
Halopyridazines represent a good precursors for synthesis many condensed and non-condensed heterocycles. This is because nucleophilic displacement of halogen atom takes place very easy by different reagent (as hydrazine, thiourea, sodium azide and other nucleophiles).

1) Replacement of halogen atom by hydrazino group

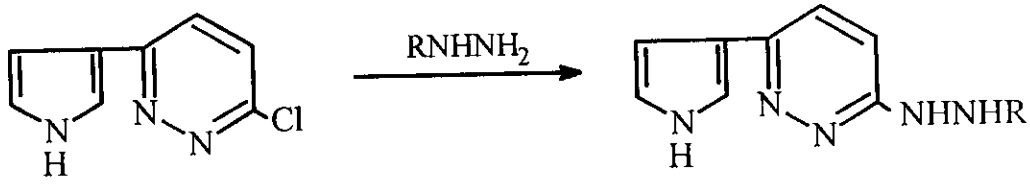
Treatment of chloropyridazine with hydrazine hydrate or substituted hydrazines gave the hydrazino derivatives (LXXXVII)[56, 97-100].



(LXXXVII)

Ar =	R =	$\tilde{R}$ =
a) 	CH_3	H
b)  X = S, NH		Ph

Also the reaction of 3-chloro-6-(2-pyrrolyl)pyridazine (LXXXVIII) with hydrazine hydrate gave the corresponding hydrazinopyridazine (LXXXIX)[101].

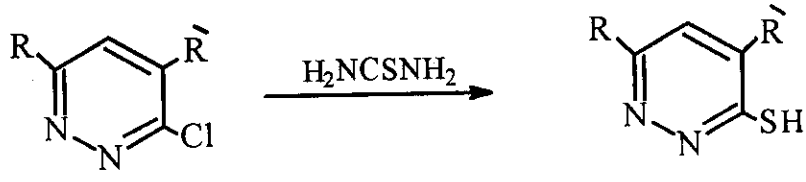


(LXXXVIII) (LXXXIX)

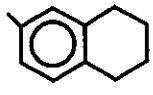
R = H, Ph

2) Replacement of halogen atom by thiol group

Pyridazinethione derivatives (XCI) has been prepared by addition of thiourea to alcoholic solution of chloropyridazine derivatives (XC)[72,102,103].

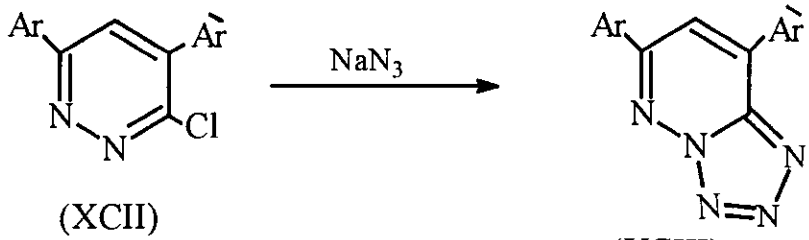


(XC) (XCI)

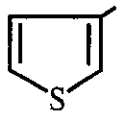
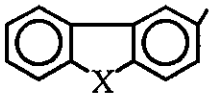
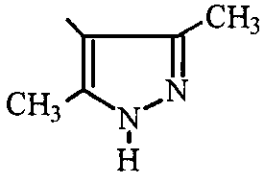
	R =	R' =
a)		CH_2Ph
b)	Cl	H
c)	CH_3	CH_2Ar
d)	Ph	$COCH_3$

3) Replacement of halogen atom by azido group

The reaction of chloropyridazine derivatives (XCII) with sodium azide gave the corresponding tetrazolopyridazines (XCIII)[36,56,97,104].



(XCII) (XCIII)

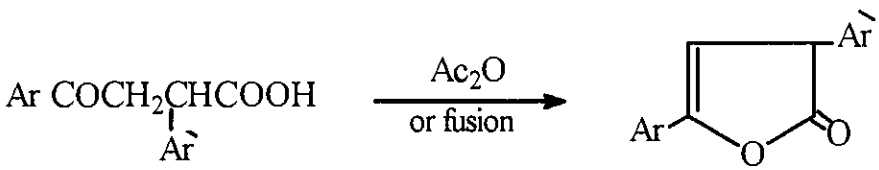
Ar =	Ar\ =
a) 2,4$(CH_3)_2C_6H_3$-	2,4$(CH_3)_2C_6H_3$-
b) 2,4-Br$(CH_3)C_6H_3$-	2,5-$(CH_3)_2C_6H_3$-
c) 	-CH_3
d)  X = S, NH	

Chemistry of Furanones

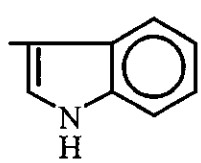
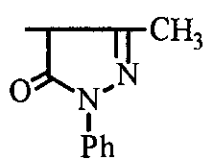
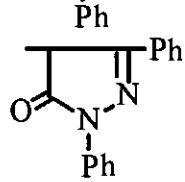
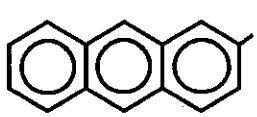
A) Synthesis of 2(3H)- Furanones

1) From α-aryl-β-aroylpropionic acids

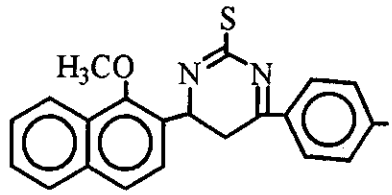
The dehydration of α-aryl-β-aroylpropionic acids (XCIV) with acetic anhydride or by fusion at their melting points gave furanone derivatives (XCV)[19,71,105-112].



(XCIV) (XCV)

Ar =	Ar =
a; 4-C_6H_5-C_6H_4	
b; 4-Br-C_6H_4	2, 3, 5-$(CH_3)_3C_6H_2$
c; 4-Br.C_6H_4	
d; 4-Cl.C_6H_4	
e; 4-C_6H_5-C_6H_4	2, 5-$(CH_3)_2$-C_6H_3
f; 	Ph
g; 4-C_2H_5-C_6H_4	CH_2Ph
h; 3, 4-$(Cl)_2C_6H_3$	CH_2Ph

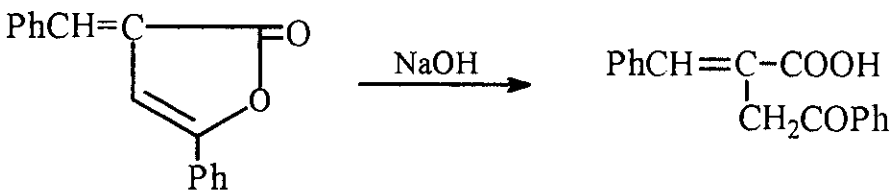
i; 4-C_6H_5-C_6H_4



B) Reactions of 2(3H)-Furanones

1) Action of acids and bases

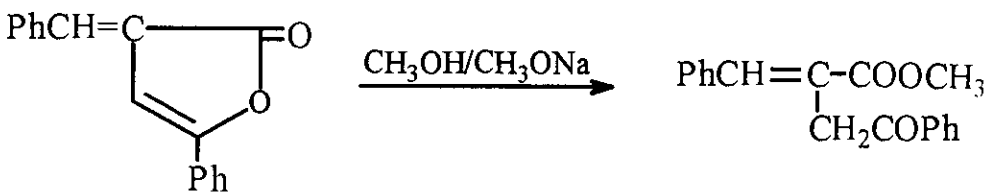
Acids and/or bases hydrolysis furanones to give γ-keto acids. Hydrolysis of 3-benzylidene-5-phenyl-2(3H)-furanone (XCVI) with dilute sodium hydroxide gave α-phenacylcinnamic acid (XCVII) which was reconverted into lactone on treatment with acetic anhydride.[113]



(XCVI) (XCVII)

2) Reaction with alcohols

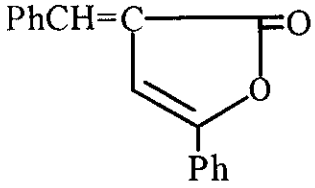
It was stated that[113] the furanone (XCVI) reacted with methanol in presence of methoxide to yield methyl ester of the corresponding acid (XCVIII).



(XCVI) (XCVIII)

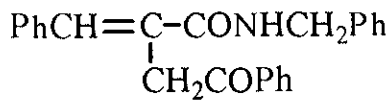
3) Reaction with amines, hydrazines and ammonia

It was reported that[113] the reaction of 3-benzylidene-5-phenyl-2(3H)-furanone (XCVI) with benzylamine afforded the γ-ketobenzylamine (IC)



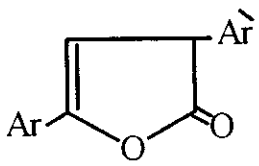
(XCVI)

$PhCH_2NH_2$



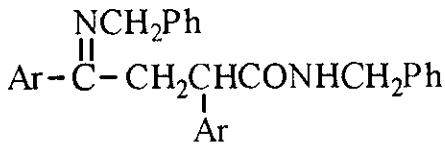
(IC)

when γ-biphenyl-α-(3-indolyl)-$\Delta^{\beta,\gamma}$-butenolide (XCVa) reacts with benzylamine in refluxing butanol gave schiff base product (C) [19].



(XCVa)

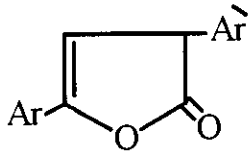
$PhCH_2NH_2$, butanol



(C)

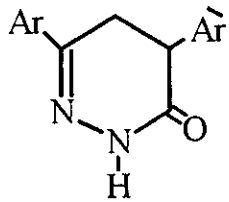
Ar = 4-C_6H_5-C_6H_4, Ar` = 3-indolyl.

On the other hand[19,71,106,107,110] when 3,5-diaryl-2(3H)-furanone (XCV) reacts with hydrazine hydrate in boiling ethanol gave the corresponding 4,6-diarylpyridazin-3(2H)-one (CI).



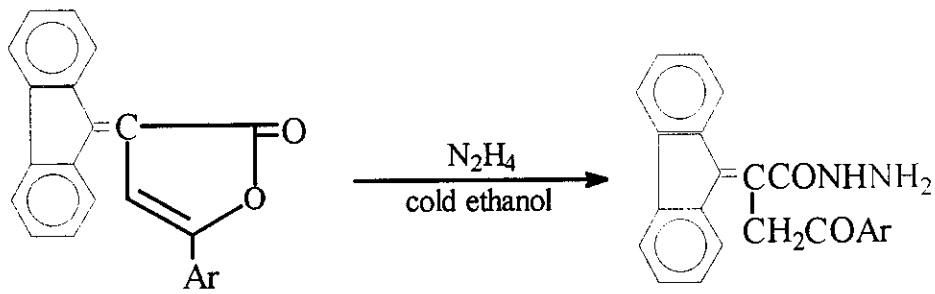
(XCV)

N_2H_4



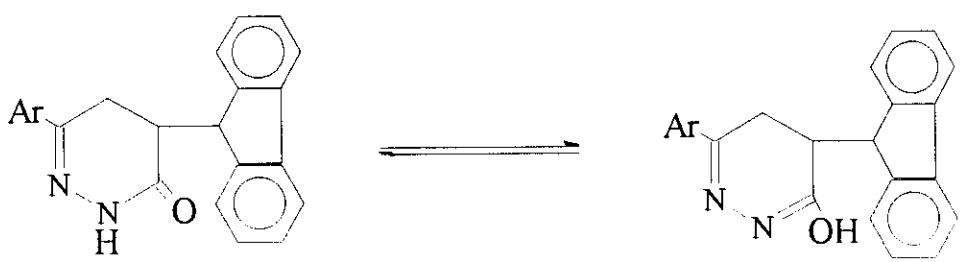
(CI)

Also it was reported that[114] the reaction of furanone derivative (CII) with hydrazine hydrate in cold ethanol gave the hydrazide derivative (CIII).



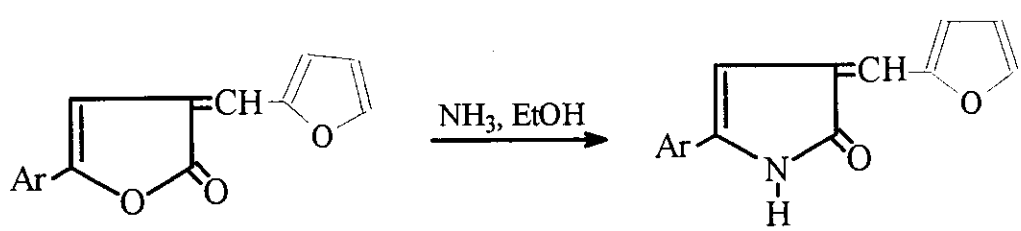
(CII) (CIII)

But when (CII) reacted with hydrazine hydrate in boiling ethanol it gave the pyridazinone (CIV) or its tautomers (CV).



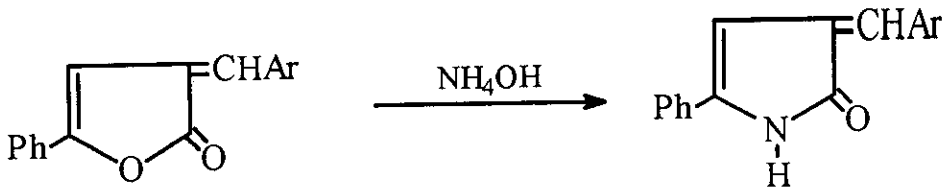
(CIV) (CV)

The aminolysis of furanone[115] (CVI) with ammonia gas in ethanol gave the corresponding pyrrolinone (CVII).



(CVI) (CVII)

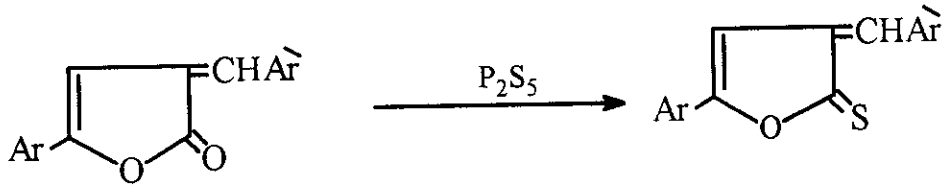
Also reaction of furanone[116] (CVIII) with aqueous ammonia in presence of potassium carbonate or ethanol gave the corresponding pyrrolinones (CIX).



(CVIII) (CIX)

4) Action of phosphorous pentasulphide

Replacement of the carbonyl-oxygen in 2(3H)-furanones by sulphur was affected by phosphorous pentasulphide, thus 3-arylidene-5-aryl-2(3H)-furanones (CX) reacts with phosphorous pentasulphide in dry xylene with the formation of 3-arylidene-5-aryl-2,3-dihydrofuran-2-thione (CXI)[118].

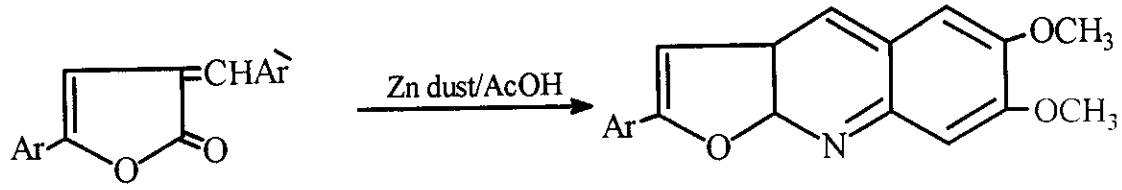


(CX) (CXI)

Ar =	Ar' =
a) C_6H_5	C_6H_5
ii(C_6H_5	4-CH_3.C_6H_4
iii(C_6H_5	4-OCH_3.C_6H_4
iv(C_6H_5	4-Cl.C_6H_4

5) Conversion to other heterocycles

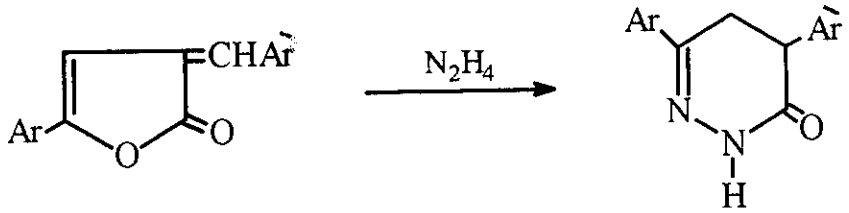
Furoquinolines (CXIII) had been prepared from the reduction of furanone (CXII) by using zinc dust in acetic acid[119].



(CXII) (CXIII)

Ar = 3,4-$(OCH_3)_2$-C_6H_3, Ar' = 2-NO_2- 4,5$(OCH_3)_2$-C_6H_2

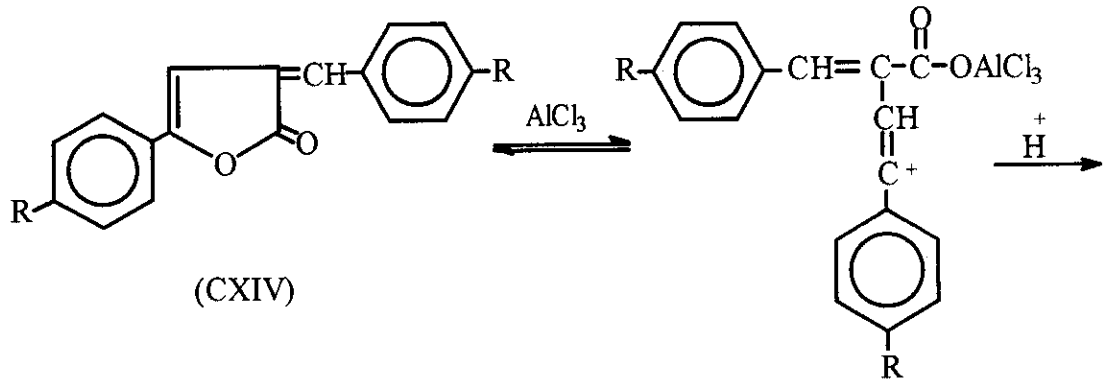
Also the pyridazinones (CVII) were prepared from the reaction of furanones (XCV) with hydrazine hydrate in boiling ethanol [19,71,106,107,110].



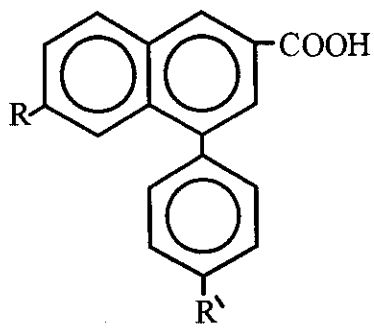
(XCV) (CVII)

6) Friedel-Crafts reaction

The reaction of 3-arylidene-5-aryl-2(3H)-furanones (CXIV) with benzene and anhydrous aluminum chloride gave 4-aryl-2-naphthoic acid (CXVI)[108,120] which formed via an intramolecular alkylation reaction. The butenolide (CXIV) is firstly converted to a resonance stabilized carbonium ion (CXV) which by electrophilic attack at ortho-position gave (CXVI).



(CXIV) (CXV)

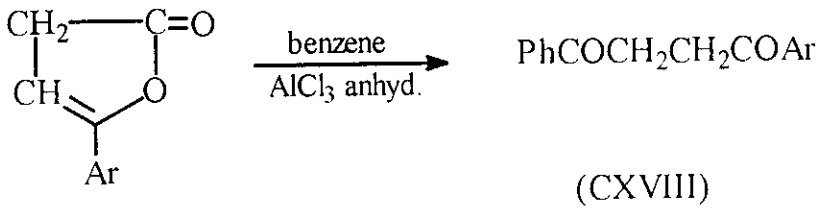


(CXVI)

R = H, OCH_3

R` = H, C_2H_5

The reaction of furanone (CXVII) having no exocyclic double bond under Friedel-Crafts conditions [121] give 1-aroyl-2-benzoylethane (CXVIII).



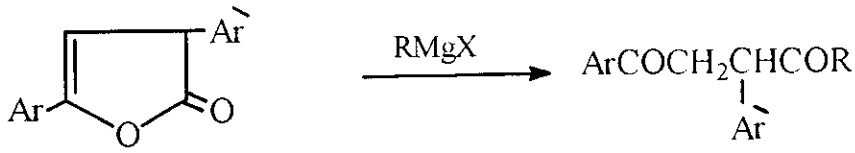
(CXVII) (CXVIII)

The formation of (CXVIII) was explained as the formation of acylium ion intermediate which by electrophilic attack on benzene nucleus the diketones were formed.

7) Reaction with organometallic compounds

3-Arylidene-2(3H)-furanones possess the features of α, β-unsaturated carbonyl systems due to the arylidene group which exocyclic to the lactone ring.

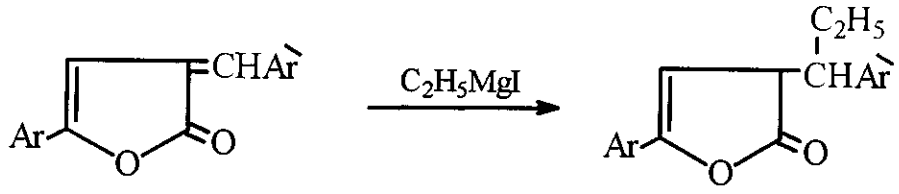
It was reported[122-125] that the reactions of series of 2(3H)-furanones (XCV) with ethylmagnesium iodide or benzylmagnesium chloride yielded 1,4-butandione (CXIX) via ring opening reaction of furanone ring.



(XCV) (CXIX)

Ar =	Ar\ =	R =
a; C_6H_5	C_6H_5	CH_3
b; 4-CH_3.C_6H_4	C_6H_5	CH_2Ph
c; 4-C_6H_5.C_6H_4	CH_2Ph	CH_3

Also it was reported that[126] 3-arylidene-2(3H)-furanones (CXX) reacted with ethylmagnesium iodide and gave the furanone derivatives (CXXI) via 1,2-addition to exocyclic double bound.

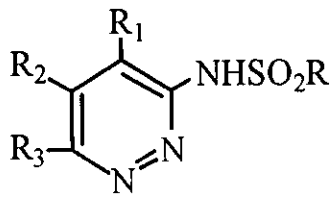


(CXX) (CXXI)

Ar = Ar` = 4-Br.C_6H_4

6)Pyridazines as antihypertensive

Pyridazine sulfonamide derivatives (CXXVII) useful as antihypertensive and antagonists [136].



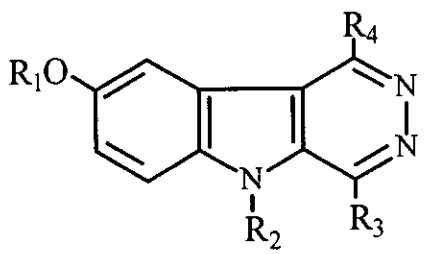
(CXXVII)

R = Ph, naphthyl, biphenyl.

R_1, R_2, R_3 = H, alkoxy, aryl, aryloxy, aralky, halo, CN, NO_2, CHO, COOH.

7) Pyridazines as vasodilator activity

Pyridazinoindole derivatives (CXXVIII) have antihypertensive and showed vasodilator activity[137].

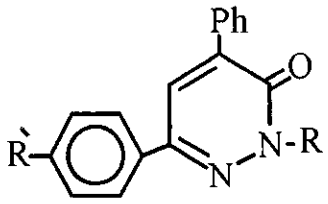


(CXXVIII)

R_1 = alky$_1$, R_2 = cycloalkyl, R_3, R_4 = $NHNH_2$

8) Pyridazinones as anticonvulsant

4,6-Diaryl-3-pyridazinones (CXXIX) showed anticonvulsant activity as well as weak sedative or ataxic effect[138].

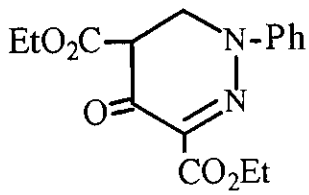


(CXXIX)

R =H, R^{1} = H, F, Cl

9) Pyridazinones have antimicrobial activity

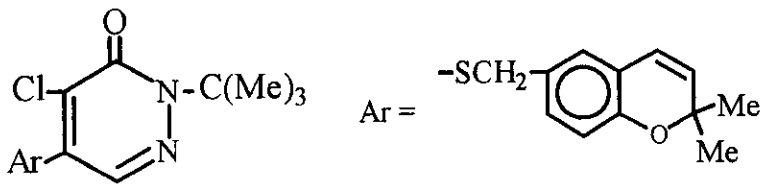
Pyridazinedicarboxylate (CXXX) have antimicrobial activity[96,139].



(CXXX)

10) Pyridazinones as pesticides

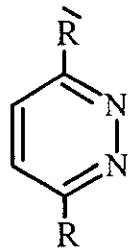
2-Tetrabutyl-4-chloro-5-arylpyridazinone derivative (CXXXI) useful as pesticides [140,141].



(CXXXI)

11) Pyridazines as herbicides

3,6-Disubstituted pyridazines[142,143] (CXXXII) are useful as herbicides.

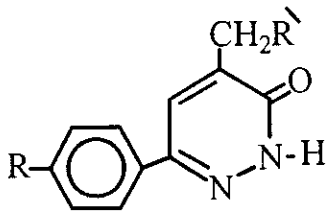


(CXXXII)

R = CH_3, C_2H_5, R` = NHC_6H_4, halogen

12) Pyridazinones as bactericidal

4,6-Disubstituted pyridazinones (CXXXIII) have bactericidal and fungicidal activities [144].



(CXXXIII)

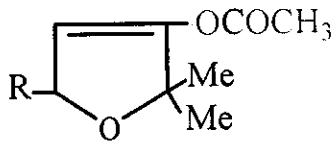
R = H, Me, OMe, Cl, R` = 2-MeO.C_6H_4, 2,4,6- $(MeO)_3C_6H_2$

Pharmacological Activities of Furanones Derivatives

The furanone ring system is a common feature in a wide variety of natural products and has attracted the attention of organic chemists because of their biological activities and versatile utilization in organic synthesis.

1) Furane derivatives have antitumor, hypolipidemic and antibiotic activities

Dihydrofurane derivatives (CXXXIV) have an antitumor protective, hypolipidemic and antibiotic activity[145].

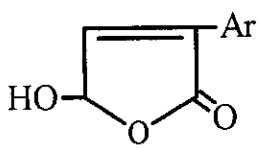


(CXXXIV)

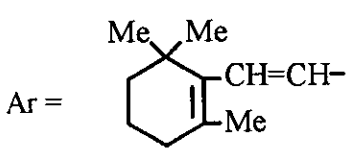
R = CH_3, n-pentyl, phenyl

2) Furanone have antiulcer effect

5-Hydroxybutenolides (CXXXV) exhibited potent inhibitory activity as antiulcer effect[146].

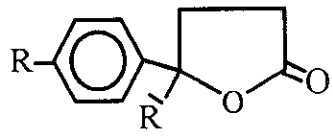


(CXXXV)



3) Furanone derivatives have antimicrobial activity

Furanone derivatives (CXXXVI) have antimicrobial activity [147].

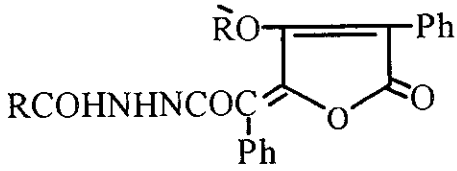


(CXXXVI)

R = Br, Cl, R' = 4-OHC_6H_4, 2,4$(OH)_2C_6H_3$, 2,5$(OH)_2C_6H_3$

4) Furanones have bactericidal activity

3,4,5-Trisubstituted furanone derivatives (CXXXVII) have bactericidal activities against both gram-positive and gram-negative bactria[148].

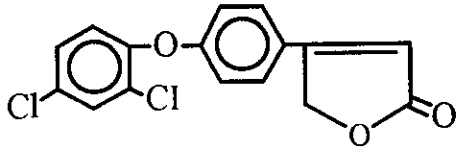


(CXXXVII)

R = Ph, substituted Ph, pyridyl, R' = H, butyl-

5) Furanones have herbicidal activity

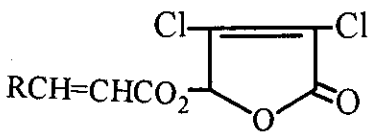
4-[4'-(2',4'-Dichlorophenoxy)phenyl]-2-furanone (CXXXVIII) has herbicidal activity against broad-leaf weeds[149].



(CXXXVIII)

6) Furanones as agrochemical fungicides

3,4-Dichloro-5-aryl-2(5H)-furanone (CXXXIX) used as agrochemical fungicides which effective against Botrytis Cinerea and Alternaria infestans[150,151].



(CXXXIX)

R =