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SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM THE REACTIONS OF DEHYDROACETIC ACID (DHA) AND ITS DERIVATIVES

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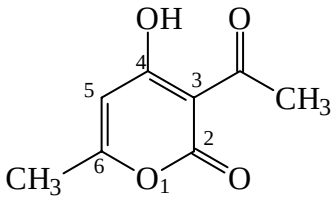
Abstract-3-Acetyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyran (Dehydroacetic acid, DHA) and its simple derivatives such as 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans (Chalcone analogues of DHA) find interesting applications in the synthesis of various heterocyclic compounds. The review highlighting this aspect covers literature up to 2003.

3-Acetyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyran (Dehydroacetic acid abbreviated as DHA) has been isolated from natural sources[1,2] and is also industrially utilizing a number of synthetic procedures. [3-6] The reactions of DHA and its derivatives have been shown to have a wide utility in organic synthesis. These developments along with the studies on related pyrone derivatives have been reviewed.[7]



DHA

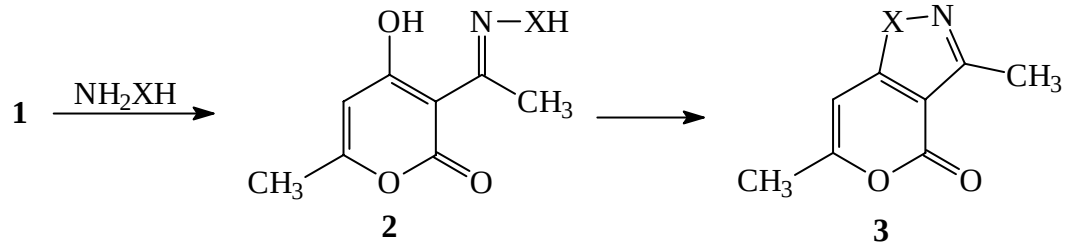
Since DHA has several reactive sites, the molecule is susceptible to attack by the nucleophilic and electrophilic reagents. A nucleophile can, in principle, attack the carbonyl of the acetyl side chain located at 3-position, the carbon atom terminating the conjugated carbon chain at 6-position, the lactone carbonyl at 2-position and the carbonyl carbon at 4-position of the molecule. On the other hand, an electrophile can attack either at C(3) or C(5).

As part of our investigations dealing with the synthesis and mechanistic studies of heterocyclic compounds, we have reported some useful transformations of DHA and its derivatives.[8-10] A literature

survey reveals that the reactions of DHA and its derivatives with different reagents can provide a versatile route to the synthesis of a wide variety of heterocyclic compounds. The present review aims at outlining the important reactions, which lead to the formation of 5-, 6- and 7-membered heterocyclic compounds involving DHA and its derivatives. The subject matter has been divided into three major Sections I, II and III. The first Section deals with the reactions that do not involve pyrone ring of DHA, whereas the second Section describes the reactions involving the pyrone moiety leading to the formation of heterocyclic compounds. In the third Section, two important miscellaneous examples of synthesis of heterocyclic compounds are summarized. Further divisions of these Sections are based on the size/types of the heterocyclic compounds whose synthesis has been achieved with these substrates.

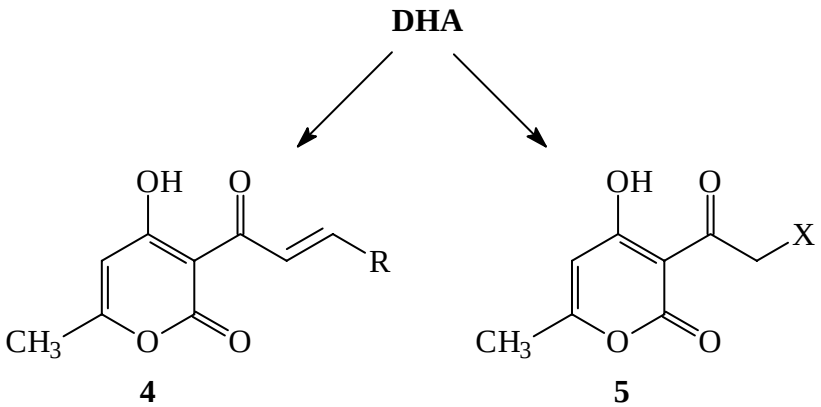
SECTION I: REACTIONS THAT DO NOT INVOLVE PYRONE MOIETY

Synthesis of heterocyclic compounds while retaining the pyrone moiety of DHA has been accomplished either from DHA itself or its derivatives. A general case of transformation of DHA into a heterocyclic compound is outlined in equation **I**. The first step involves formation of intermediates by the nucleophilic attack of NH_2XH on the carbonyl of $–COCH_3$ giving the product (**2**). The ring closure subsequently occurs with the formation of C(4)—X bond, the type (**3**).



(Eq. I)

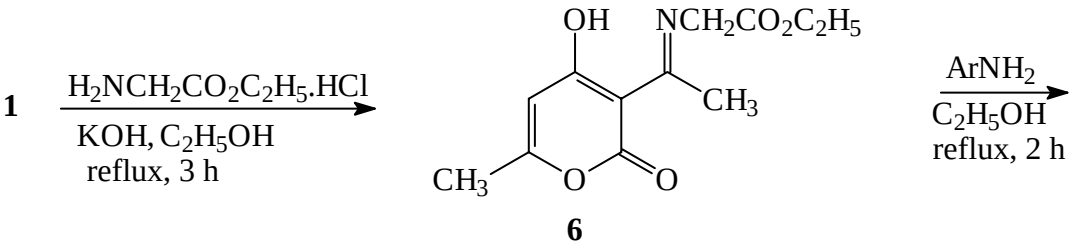
In the second category, $COCH_3$ group is modified into groups such as COCH:CHR (**4**) or $–COCH_2X$ (**5**) and then further reactions take place *via* these new functionalities present at C(3).



A) FIVE-MEMBERED HETEROCYCLIC COMPOUNDS

i) Pyranopyrroles

Treatment of DHA (**1**) and its derivatives (prepared by the action of phosphorus pentachloride on DHA) with ethyl glycinate in boiling ethanol gives ethyl *N*-α-ethylidine-α-(4-hydroxy-6-methyl-2-oxo-3-pyranyl)glycinate (**6**) which undergoes condensation with aromatic amines to give 1-(*N*-arylcarbamoyl)-1,4-dihydro-3,6-dimethyl-4-oxopyrano[3,4-*c*]pyrroles (**7**).[11]



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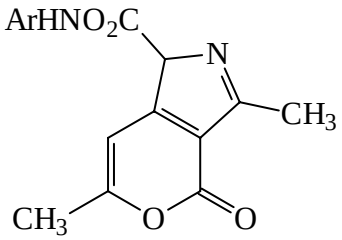
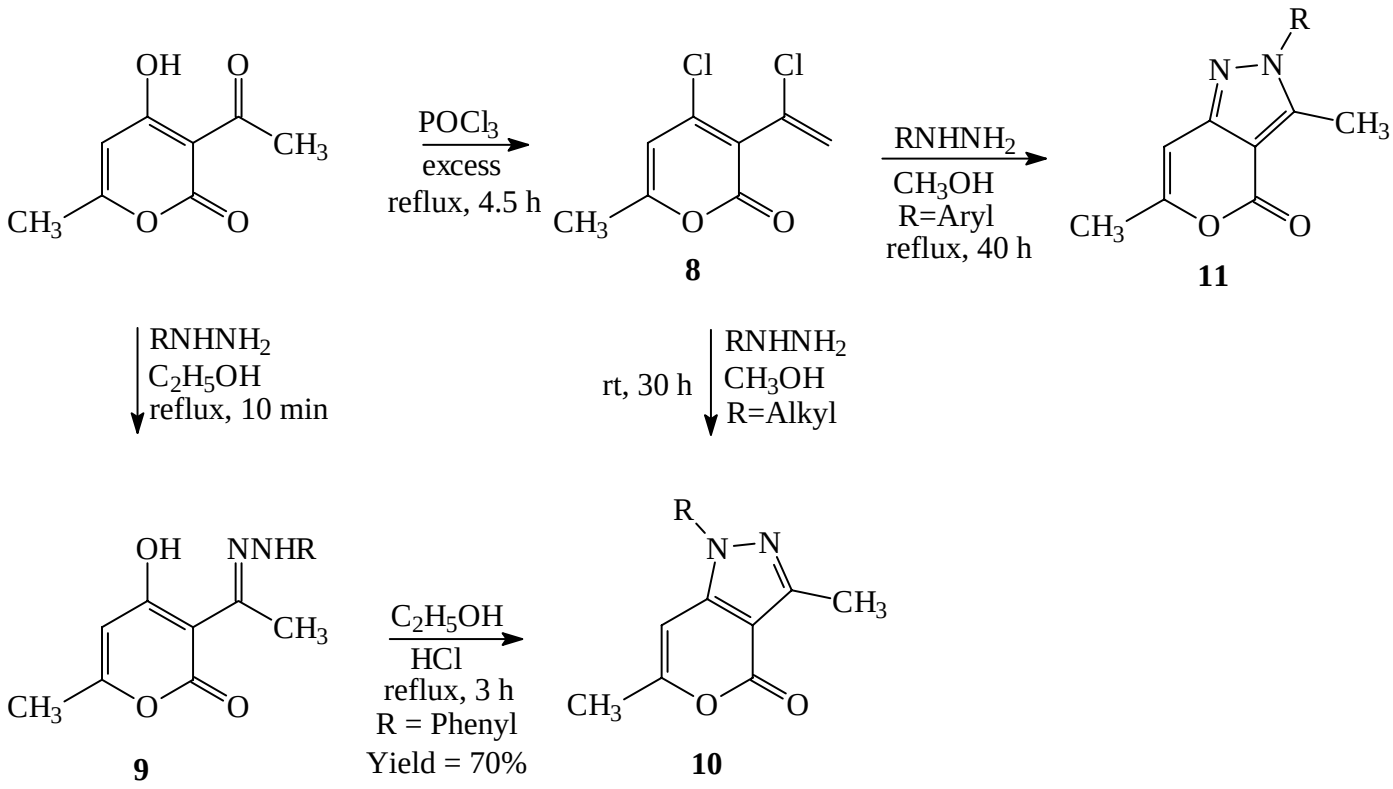


7

Ar	**Yield**
4-$CH_3C_6H_4$	62
4-$OCH_3C_6H_4$	68
NH_2	43
NHC_6H_5	52

ii) Pyranopyrazoles

Cyclization of DHA *N*-substituted hydrazones (**9**) is known to furnish 1-substituted 3,6-dimethylpyrano[4,3-*c*]pyrazol-4(1*H*)-ones (**10**).[11,12] However, the reaction is not straight forward as varying amounts of side products such as *N*,*N*′-disubstituted 5-hydroxy-3-methyl-4-(3-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrazoles are also formed. Cantos *et al.*[13,14] reported that the same pyranopyrazoles (**10**) can also be obtained regioselectively without any side reactions from *N*-alkylhydrazines and 4-chloro-3-(1-chlorovinyl)-6-methyl-2-oxo-2*H*-pyran (**8**), while *N*-arylhydrazines give the corresponding 2-aryl-3,6-dimethylpyrano[4,3-*c*]pyrazol-4(2*H*)-ones (**11**). NMR (NOE) methods including long-range selective heteronuclear ^{13}C $\{^1H\}$ NOE enhancement measurements, allowed unambiguous distinction between –4(1*H*)-ones and –4(2*H*)-ones.



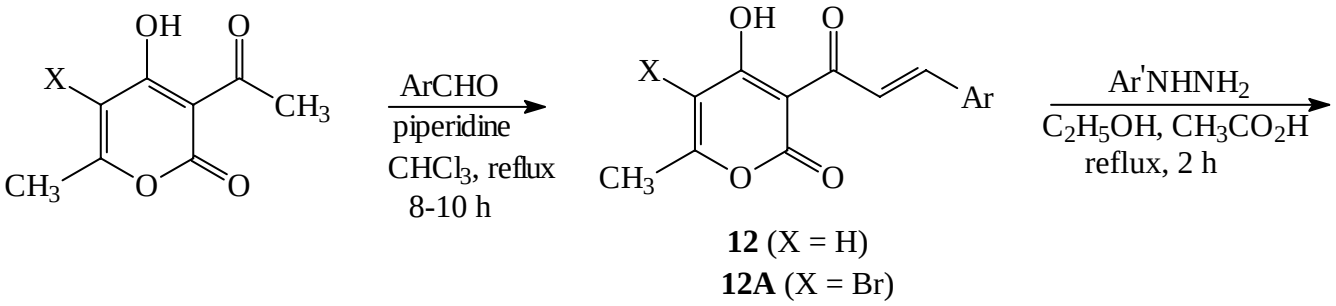
9a, R=Alkyl
9b, R=Aryl and Heteroaryl

10, R	**Yield**	**11, R**	**Yield**
CH_3	40	C_6H_5	53
CH_2CH_2OH	81	4-ClC_6H_4	83
H	21	4-$CH_3C_6H_4$	58
		2-Pyridyl	33
		3-$CF_3C_6H_4$	76

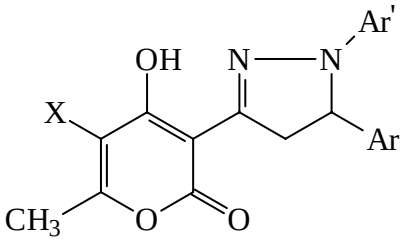
iii) Pyranylpyrazolines

Reaction of DHA with aromatic aldehydes yields 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans[15-17] (**12**) which on treatment with arylhydrazines ($Ar'NHNH_2$) in C_2H_5OH-CH_3CO_2H give the 1,5-diphenyl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-pyrazolines (**13**).[18-20] Some of these compounds have shown significant antifungal activity against the blast fungus of the rice plant *Pyricularia oryzae*.[21] The

same approach is effective for the synthesis of 1,5-diphenyl-3-(5-bromo-4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-pyrazolines (**14**, X = Br).[22]



12 (X = H)
12A (X = Br)

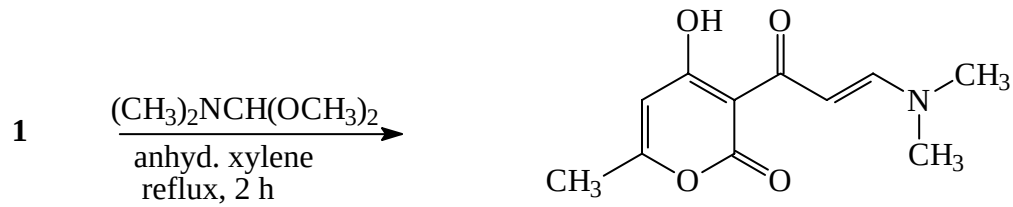


13 (X = H)
14 (X = Br)

X	**Ar**	**Ar'**	**Yield**
Br	C_6H_5, 4-OH-3-$OCH_3C_6H_3$, 2-OHC_6H_4	C_6H_5	25-30
Br	C_6H_5, 4-OH-3-$OCH_3C_6H_3$, 2-OHC_6H_4	4-$NO_2C_6H_4$	25-30
Br	C_6H_5, 4-OH-3-$OCH_3C_6H_3$, 2-OHC_6H_4	2,4-$(NO_2)_2C_6H_3$	30-35
H	C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4	C_6H_5	75-80
H	2-thienyl, 2-furyl, 4-pyridyl	C_6H_5	75-80

iv) Pyranylpyrazoles

DHA on condensation with *N*,*N*-dimethylformamide dimethylacetal generates 4-hydroxy-6-methyl-2-oxo-3-[3-dimethylaminoacryloyl]-2*H*-pyran (**15**), which on treatment with $NH_2NH_2.2H_2O$ leads to the cyclization, thereby producing 3-[4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl]pyrazole (**16**).[23]



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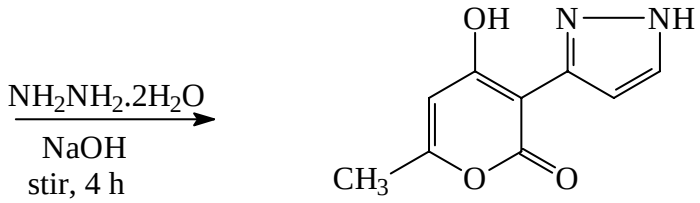

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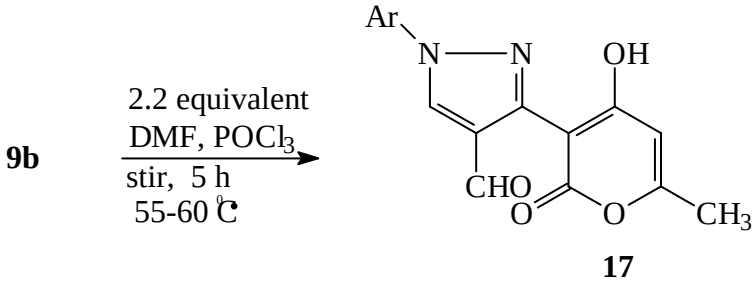
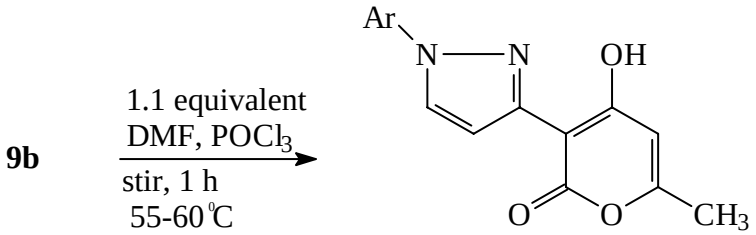
4-Formyl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-1-arylpyrazoles (**17**) have been synthesized from **9b** using Vilsmeier-Haack reagent.[24]



17

Ar	Yield
C_6H_5	58
4-$CH_3C_6H_4$	55
4-ClC_6H_4	52
4-$NO_2C_6H_4$	60
2,4-$(NO_2)_2$ C_6H_3	50

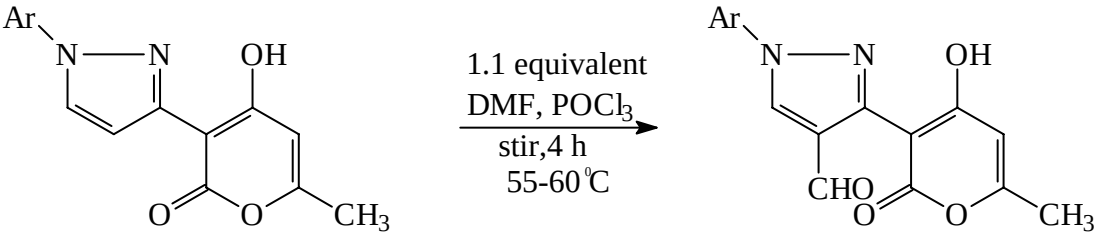
In a most recent development from our laboratory, it has been found that it is possible to synthesize the intermediates (**18**) by using 1.1 equivalent of $POCl_3$/DMF.[24]



18

Ar	Yield
C_6H_5	65
4-$CH_3C_6H_4$	63
4-ClC_6H_4	62
4-$NO_2C_6H_4$	70
2,4-$(NO_2)_2$ C_6H_3	60

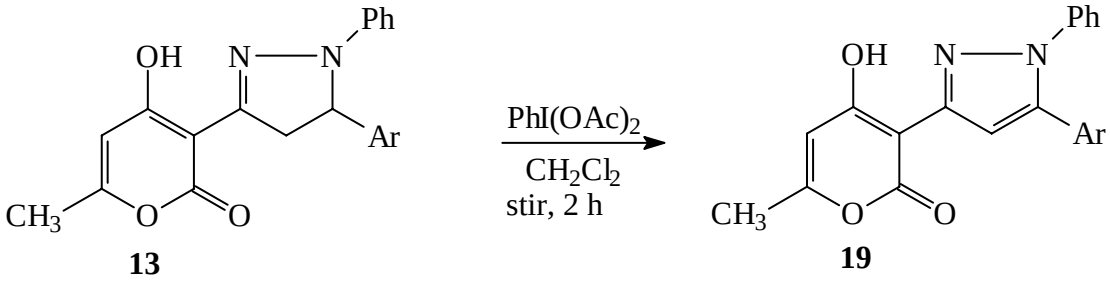
When cyclization of the hydrazones is carried out under the normal conditions of Vilsmeier-Haack reaction i.e. by stirring the mixture (2.2 equivalent of $POCl_3$/DMF) at 55-60°C for 4-5 h, the reaction gives the expected 4-formyl analogue (**17**). Alternatively, the products (**17**) have been obtained by the formylation of **18** with 1.1 equivalent of Vilsmeier-Haack reagent.



18 **17**

Ar	Yield	Ar	Yield
C_6H_5	58	4-$CH_3C_6H_4$	55
4-ClC_6H_4	52	4-$NO_2C_6H_4$	60
2,4-$(NO_2)_2$ C_6H_3	50		

Oxidation of pyranylpyrazolines (**13**) as described in subsection iii, using the oxidizing agent iodobenzene diacetate (IBD) in dichloromethane affords 1,5-diaryl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-pyrazoles (**19**).[24]



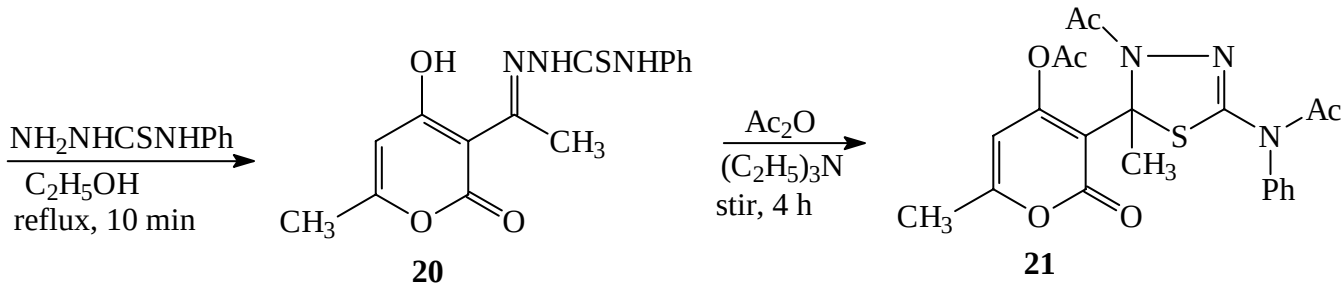
13 **19**

Ar	**Yield**
C_6H_5	82
4-$CH_3C_6H_4$	80
4-ClC_6H_4	81

Ar	**Yield**
2-thienyl	79
2-furyl	76
4-pyridyl	75

v) Pyranylthiadiazolines

Thiosemicarbazone of DHA (**20**) can be transformed into 2-(*N*-acylphenyl)-4-(*N*-acyl)-5-methyl-5-(4-acetoxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiadiazolines (**21**) on treatment with acetic anhydride and triethylamine.[25]



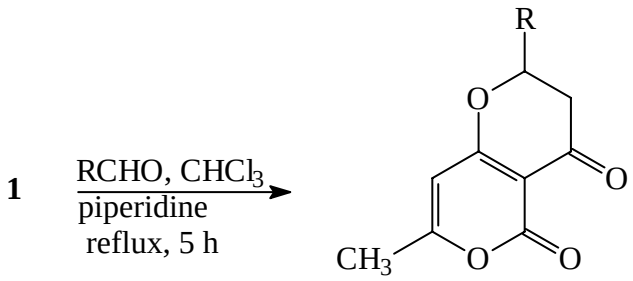
20 **21**

B) SIX-MEMBERED HETEROCYCLIC COMPOUNDS

i) Pyranopyrans

The preparation of pyranopyrans is significant both from synthetic as well as biological point of view. Several methods are available for the synthesis of 2-alkyl-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-

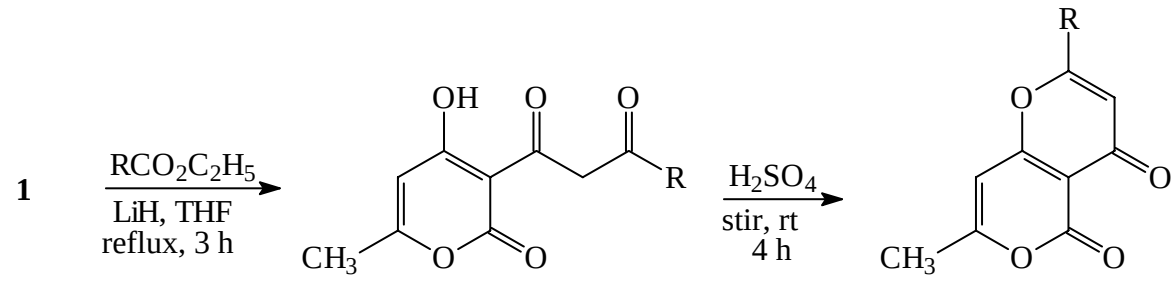
diones of the type (**22**).[26] These methods are based on two different approaches. The first approach involves dehydrogenation of 2,3-dihydro-2-alkyl-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-diones (**22**, flavanone analogues of DHA) by using oxidizing agents such as lead tetraacetate. The flavanones analogues (**22**) are prepared by the condensation of aliphatic aldehydes with DHA in the presence of piperidine. Interestingly the method is also applicable to the synthesis of 2-fluorinated alkyl analogues.



22

R	**Yield**
CH_2CH_2Ph	56
$CH(CH_3)_2$	60
$CH_2CH_2CH_3$	61

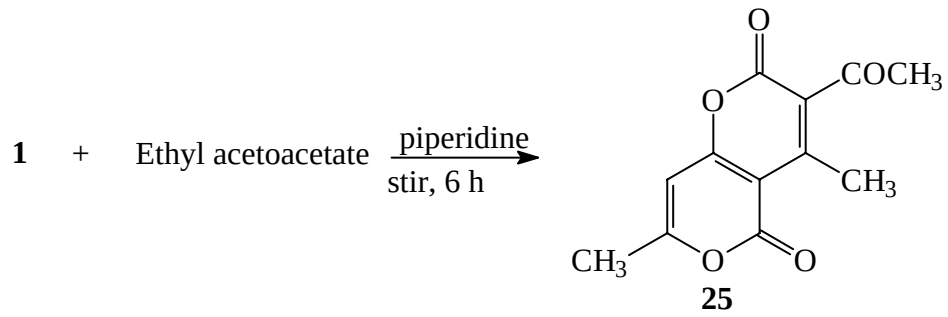
In the second approach, treatment of DHA (**1**) with esters $RCO_2C_2H_5$ in the presence of LiH in THF, affords β-diketones of the type 3-acetoacetyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyran (**23**).[27] Subsequent cyclization of **23** in the presence of conc. H_2SO_4 results in the formation of 2-substituted 7-methylpyrano[4,3-*b*]-4*H*,5*H*-diones (**24**). Due to the difficulties encountered in the preparation of 2-aryl analogues of **22**, the synthetic strategy for the synthesis of corresponding **24** follows different approach.



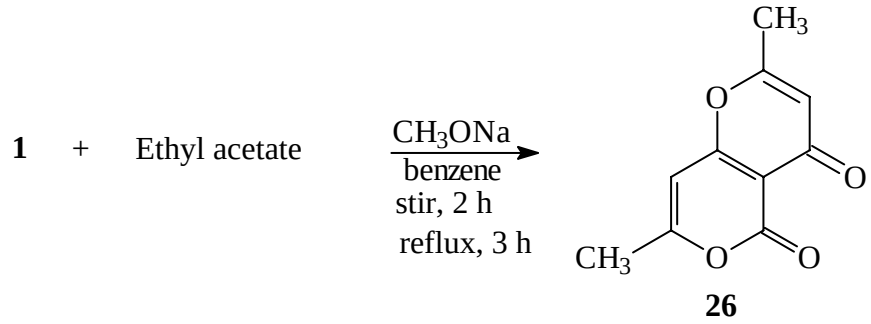
23 **24**

R	**Yield**
CF_2H	57
CF_3	55
CF_3 CF_2H	51

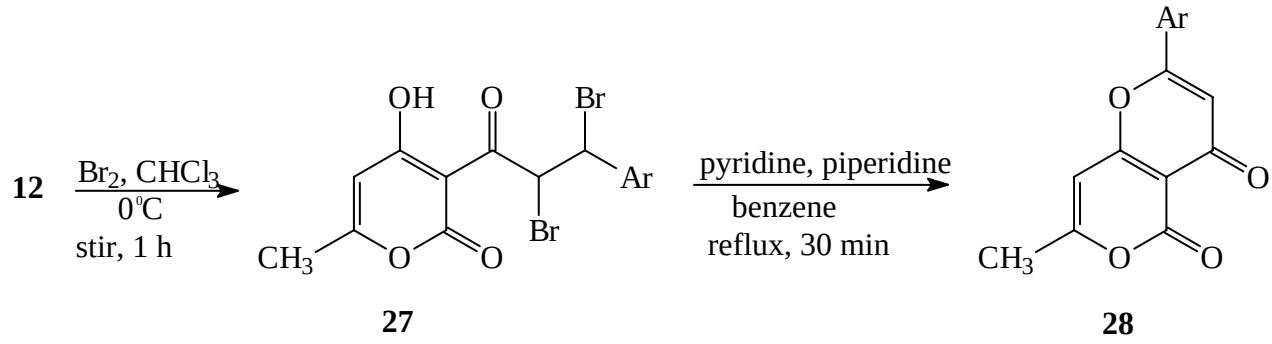
Condensation of DHA with ethyl acetoacetate in the presence of piperidine gives 3-acetyl-4,7-dimethylpyrano[4,3-*b*]pyran-2*H*,5*H*-dione (**25**).[11]



Treatment of DHA with ethyl acetate and sodium methoxide in benzene affords γ-pyrone derivative i.e., 2,7-dimethylpyrano[4,3-*b*]pyran-4*H*,5*H*-dione (**26**).[28]

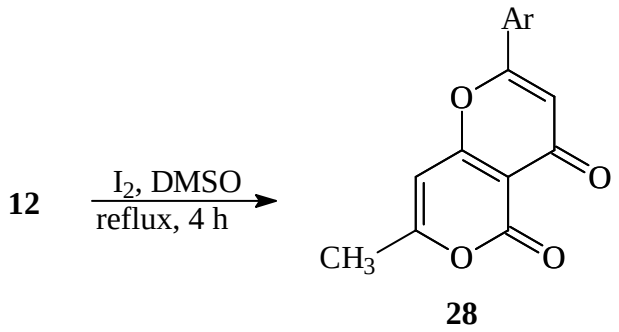


As compared to 2-alkyl substituted derivatives of the type (**24**), methods for the synthesis of 2-aryl analogues are limited. The main reason for this appears to be the failure of several attempts for the cyclization of 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans (**12**) to furnish 2-aryl analogues of **24** *via* Michael-type addition. This problem has been overcome by converting **12** into the corresponding dibromo derivatives (**27**) in excellent yields. These bromo derivatives (**27**) on heating with pyridine containing a few drops of piperidine give 2-aryl-7-methylpyrano[4,3-*b*]pyran-4*H*,5*H*-diones (**28**) in 60-70% yields.[29] This method has been found to have general applicability.



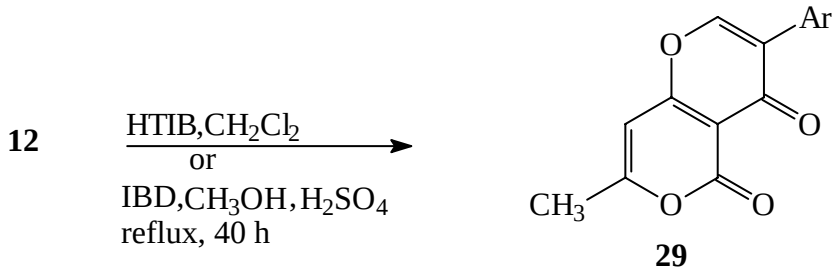
Ar	27, Yield	28, Yield	Ar	27, Yield	28, Yield
C_6H_5	95	60	2-ClC_6H_4	95	60
4-$NO_2C_6H_4$	100	75	4-$OCH_3C_6H_4$	95	65
4-$CH_3CH_2C_6H_4$	100	60			

The reaction of substituted 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans (**12**) in I_2/DMSO provides a facile method for the synthesis of 2-aryl-7-methylpyrano[4,3-*b*]pyran-4*H*,5*H*-diones (**28**).[30] This methodology constitutes a facile, one-step synthesis of **28** as compared to the previously reported procedure.



Ar	Yield	Ar	Yield
C_6H_5	55	2-ClC_6H_4	58
4-$NO_2C_6H_4$	50	4-$OCH_3C_6H_4$	56
4-$CH_3C_6H_4$	53	4-ClC_6H_4	58
4-FC_6H_4	56	2-$OCH_3C_6H_4$	55

Oxidative rearrangements are often encountered in the reactions involving I(III) reagents such as $(PhIOAc)_2$, and HTIB, particularly in the synthesis of heterocyclic compounds. Reaction of **12** and [hydroxy(tosyloxy)iodo]benzene, HTIB (1.1 equivalent) in dichloromethane gives 3-aryl-7-methylpyrano[4,3-*b*]pyran-4*H*,5*H*-dione (**29**, isoflavone analogues of DHA). This is the first report on the direct conversion of o-hydroxychalcone type compounds into isoflavone analogues.[24]

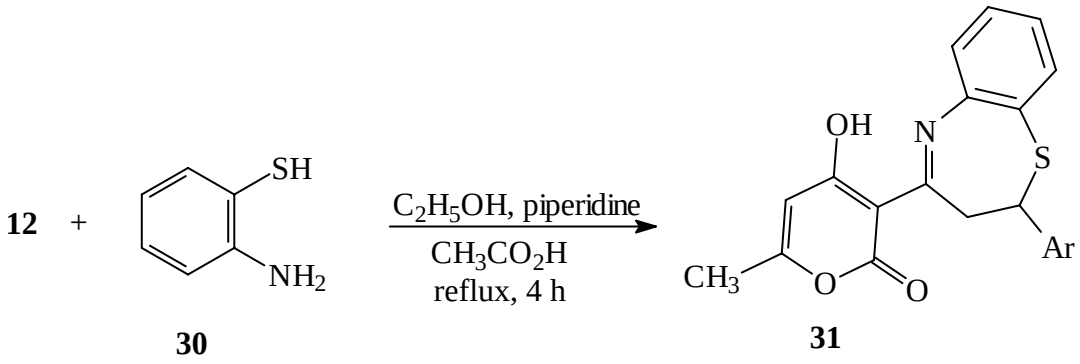


Ar	Yield
C_6H_5	50
4-$CH_3C_6H_4$	55
4-$OCH_3C_6H_4$	58
4-ClC_6H_4	50
2-$CH_3C_6H_4$	54
4-$(CH_3)_2CHC_6H_4$	52

C) SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS

i) Benzothiazepines

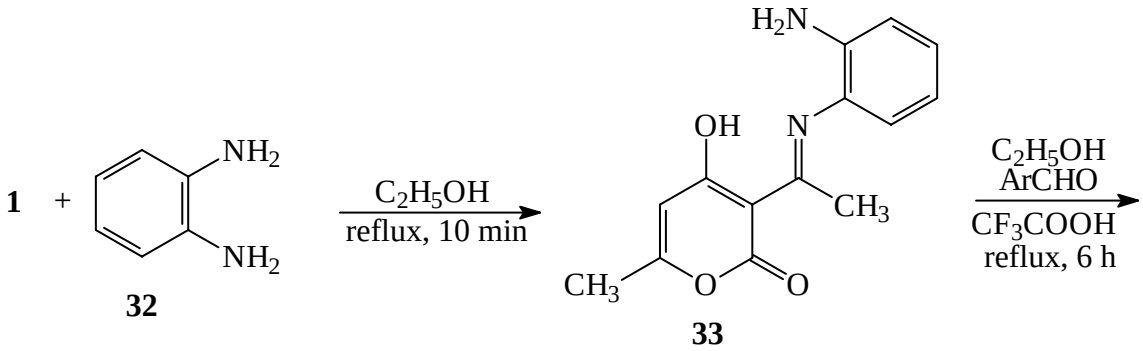
1,5-Benzothiazepines have attained much significance due to various biological properties associated with them. 3,4-Dihydro-2-aryl-4-pyronyl-1,5-benzothiazepines (**31**) have been synthesized by the reaction of 2-aminothiophenol (**30**) with the chalcone analogues of DHA (**12**).[31]

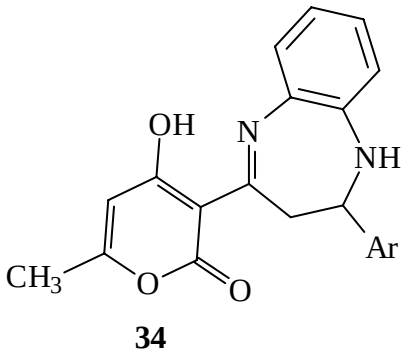


Ar	Yield	Ar	Yield
2-ClC_6H_4	65	2-$NO_2C_6H_4$	60
2-OHC_6H_4	68	4-$NO_2C_6H_4$	61
2,6-$(Cl)_2C_6H_3$	60	4-OHC_6H_4	67

ii) Benzodiazepines

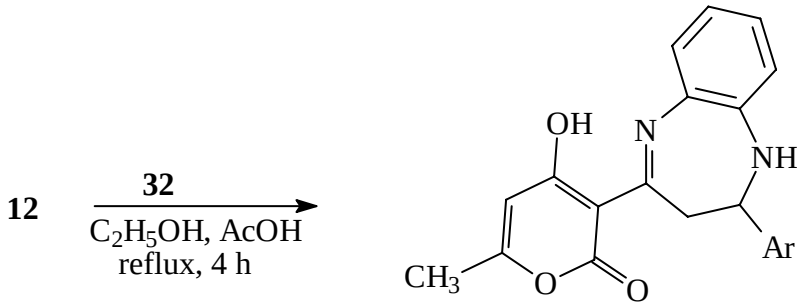
1,5-Benzodiazepines have found wide applications in medicines and may be considered as one of the most important classes of therapeutic agents associated with diverse biological properties. The ketimine compounds (**33**) have been prepared by treating DHA with *o*-phenylenediamine (**32**) followed by the treatment of the products (**33**) with aromatic aldehydes in ethanol in the presence of a catalytic amount of trifluoroacetic acid. This methodology affords the corresponding 3,4-dihydro-2-pyronyl-1,5-benzodiazepines (**34**).[32]





Ar	Yield	Ar	Yield
C_6H_5	79	4-ClC_6H_4	74
4-BrC_6H_4	73	4-$CH_3C_6H_4$	83
4-CNC_6H_4	75	4-OHC_6H_4	85
2-OHC_6H_4	83	4-$OCH_3C_6H_4$	88
4-$CO_2HC_6H_4$	65	4-biphenyl	84

An alternative and facile method for the synthesis of **34** has also been developed in our laboratory.[10] In this method, the reaction of **32** with 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans (**12**) in ethanol-acetic acid leads to the formation of 3,4- dihydro-2-pyronyl-1,5-benzodiazepines (**34**) in good yields.



34

Ar	**Yield**	**Ar**	**Yield**
C_6H_5	78	4-ClC_6H_4	75
4-$CH_3C_6H_4$	76	4-OHC_6H_4	69
2-OHC_6H_4	82	4-$OCH_3C_6H_4$	85
4-$(CH_3)_2NC_6H_4$	86	4-$NO_2C_6H_4$	76
2-thienyl	80	2-$NO_2C_6H_4$	83

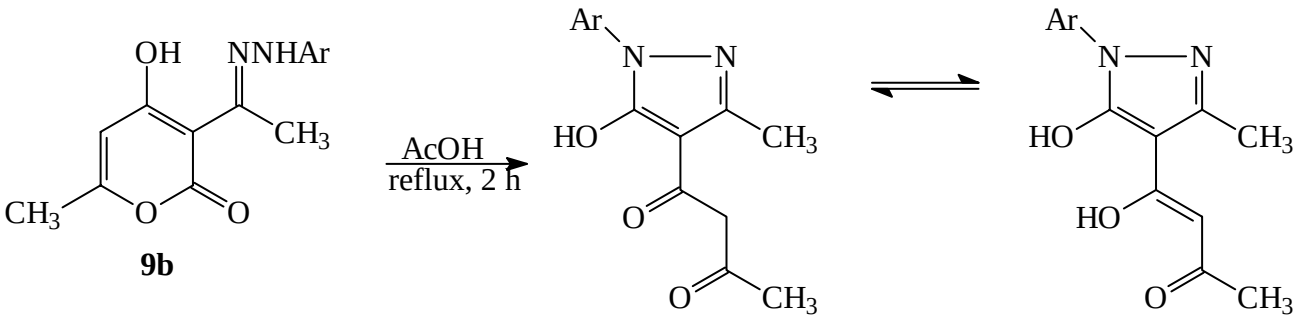
SECTION II: REACTIONS THAT INVOLVE PYRONE MOIETY

The reactions included in this Section proceed through the involvment of pyrone moiety of DHA with nucleophiles at C2 and C6 positions resulting in the initial opening of the ring, which in general, is followed by a different mode of cyclization leading to the formation of a new heterocyclic system.

A) FIVE-MEMBERED HETEROCYCLIC COMPOUNDS

i) Pyrazoles and Bipyrazoles

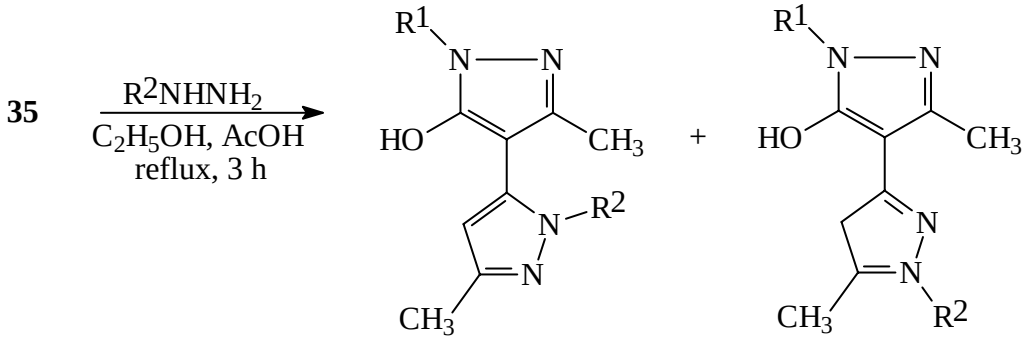
The reactions of DHA with hydrazines have been well investigated, and the intermediates have been isolated and identified. The initial step is the formation of the hydrazones (**9b**), which can be isolated and rearranged to 1-(5-hydroxy-3-methyl-1-substituted pyrazol-4-yl)-1,3-butanediones (**35**).[33] The tautomeric composition of compounds (**35**) has been investigated by a rigorous analysis of NMR spectroscopy and X-Ray crystallography.[8,34] The fragmentation pattern of **35** has been studied under electron-impact and the major processes described.[35]



9b **35A** **35B**

Ar	Yield	Ar	Yield
C_6H_5	58	2,4-$(NO_2)_2$ C_6H_3	57
4-ClC_6H_4	55	4-methylquinolin-2-yl	52
4-$NO_2C_6H_4$	60	2-benzothiazolyl	50

Condensation of **35** with hydrazines offer a single product which has been identified as the bipyrazolyl (**36A**) and not a mixture of isomers. Out of these two isomers, the correct structure is established with the help of X-Ray crystallography, NMR (^{1}H and ^{13}C) spectroscopy and the solid state (CPMAS) spectrum of the compound.[14,36-40]

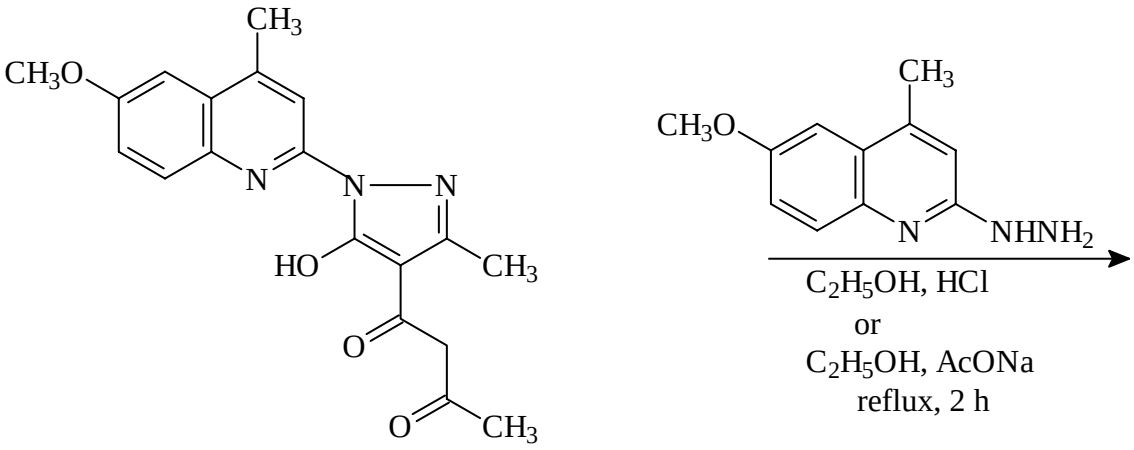


36A **36B**

R^1	R^2	Yield	R^1	R^2	Yield
C_6H_5	4-$NO_2C_6H_4$	58	C_6H_5	1-naphthyl	58
C_6H_5	2,4-(NO_2) C_6H_3	54	C_6H_5	4-methylquinolin-2-yl	69
C_6H_5	2-pyridyl	60	C_6H_5	2-benzothiazolyl	66

In addition to the cyclization reaction leading to the formation of bipyrazoles, and unprecedented reaction of **35** was observed while treating these compounds with hydrazines in ethanol/sodium acetate. In many cases, the reaction led to the cleavage of C—C bond resulting in the formation of two moles of

5-oxo-2-pyrazolines (**39**). The controlling factor for the C—C bond cleavage is the nature of the hydrazine employed in the second step of the reaction and the steric factor also appears to be playing an important role in the bond cleavage.[9,39-42] However, when the reaction is performed in ethanolic HCl, there was exclusive formation of bipyrazolyls. This divergent behavior of compounds (**35**) can be illustrated by treating a typical compound (**37**) (R^1 = 4-methyl-6-methoxyquinolin-2-yl), obtained by the rearrangement of **35**, which either undergoes cyclization to the corresponding bipyrazolyl (**38**) on treatment with ethanolic HCl or undergoes C—C bond fission to generates 2 moles of **39**.



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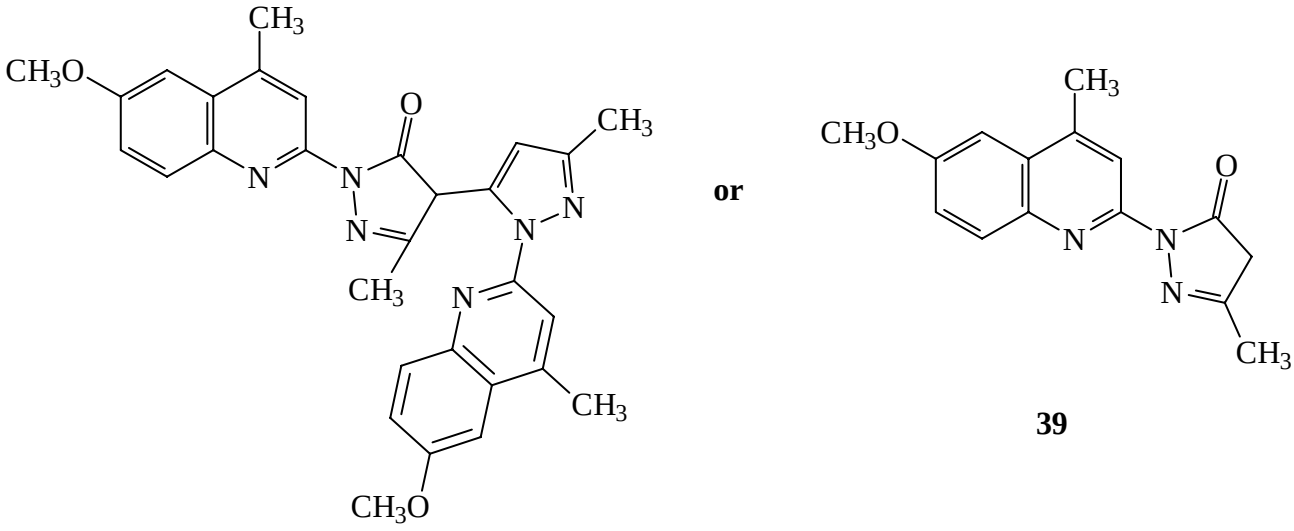
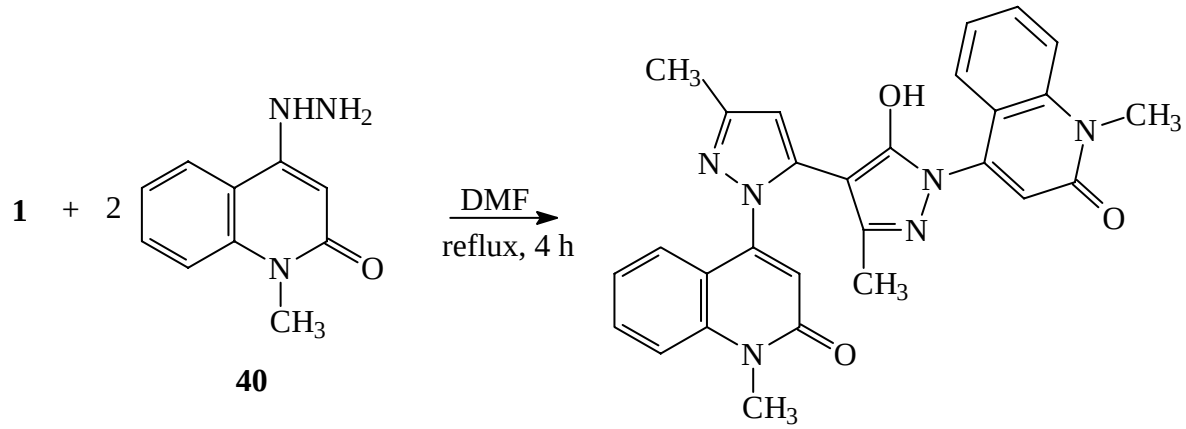


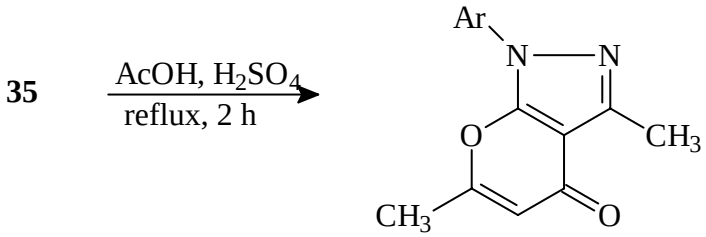
38 **39**

When DHA is treated with 4-hydrazino-1-methyl-2(1*H*)-quinolone (**40**) in DMF at the molar ratio of 1:2, an interesting bipyrazolylquinolone (**41**) is obtained.[43]



40 **41**

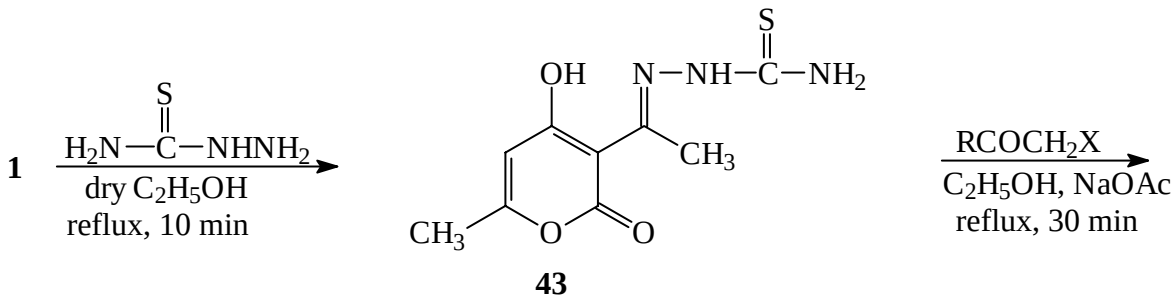
Refluxing 1-(5-hydroxy-3-methyl-1-substitutedpyrazol-4-yl)-1,3-butanedione (**35**) in acetic acid in the presence of sulfuric acid leads to the formation of pyranopyrazole (**42**).[44] It is interesting that compounds (**42**) are isomeric to compounds (**10**) and (**11**) described previously. Distinction between these isomeric pyranopyrazoles has been made by NMR (^{1}H and ^{13}C) spectroscopy.[44] Complete analyses have achieved utilizing homonuclear $^{1}H\{^{1}H\}$ and two-bond heteronuclear $^{13}C\{^{1}H\}$ nuclear Overhauser effects and selective decoupling experiments.



42

Ar	**Yield**
C_6H_5	62
2-pyridyl	77

Thiosemicarbazone (**43**) of DHA reacts smoothly with α-halo ketones to yield the corresponding thiazolylhydrazones (**44**) of DHA, which on refluxing in C_2H_5OH-AcOH rearrange to 1-[5-hydroxy-3-methyl-1-(2-thiazolyl)-4-pyrazolyl]-1,3-butanediones (**45**).[45]



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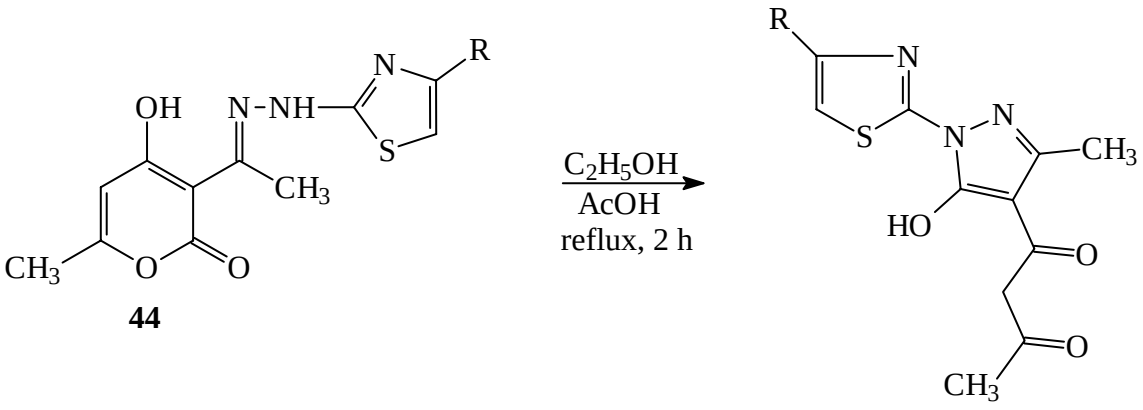


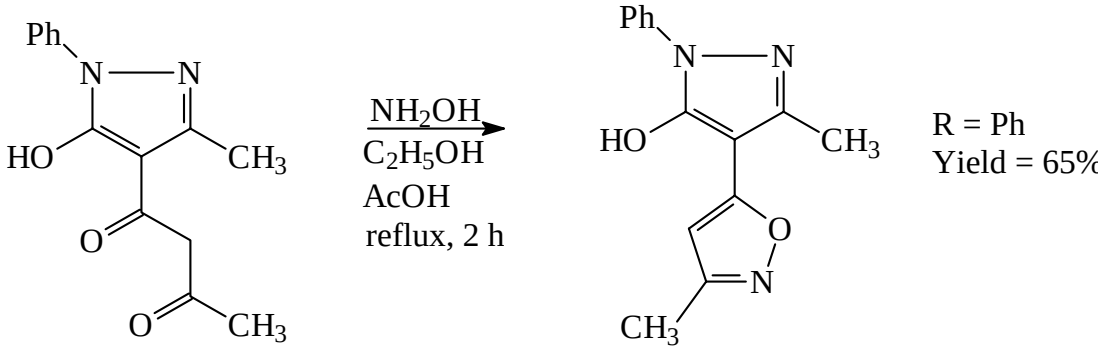
44 **45**

R	**Yield (44)**	**Yield (45)**
C_6H_5	73	59
2-thienyl	63	61
CH_3	72	65

The pyrazolylbutane-1,3-diones of the type (**35**) and (**45**) are important precursors for the synthesis of various heterocyclic compounds containing pyrazole moiety. Some of the important examples are presented in the following subsections (**ii**, Pyrazolylisoxazoles and **iii**, Pyrazolylpyrimidines).

ii) Pyrazolylisoxazoles

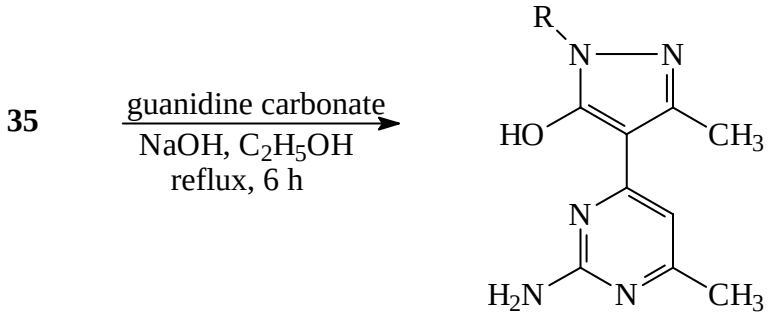
Hydrazine hydrate or arylhydrazines react with DHA to give 4-acetoacetyl-3-methylpyrazolin-5-ones (**35**). The conversion of **35** into pyrazoloisoxazoles (**46**) has been achieved on treatment with hydroxylamine.[40]



35 **46**

iii) Pyrazolylpyrimidines

2-Amino-6-methyl-4-(5-hydroxy-3-methyl-1-substituted pyrazol-4-yl)pyrimidines (**47**) can be synthesized by the condensation of 4-acetoacetyl-5-hydroxy-3-methyl-1*H*-substituted pyrazoles (**35**) and guanidine carbonate in ethanolic NaOH (40%).[46] Some of these compounds were found to show moderate level of antifungal activity.

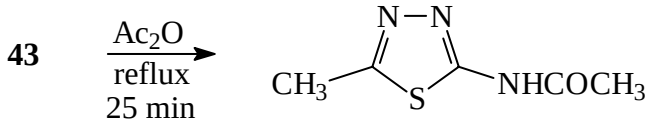


47

R	**Yield**	**R**	**Yield**
C_6H_5	72	4-ClC_6H_4	68
2-pyridyl	60	2-benzothiazolyl	78
4-methylquinolin-2-yl	69	4-methylthiazol-2-yl	61

iv) Thiadiazole

Under acylating conditions, DHA thiosemicarbazone (**43**) is transformed into 2-acylamino-5-methyl-1,3,4-thiadiazole (**48**) involving a C—C bond cleavage.[25] The reaction of phenyl thiosemicarbazone (**49**) of DHA with RCO_2H/C_2H_5OH affords 2-anilino-5-methyl-1,3,4-thiadiazole (**50**).



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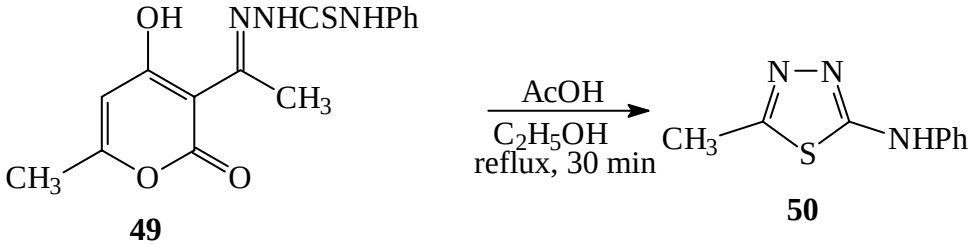
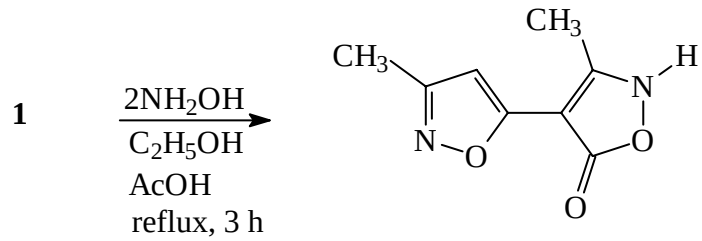


49 **50**

v) Bis-isoxazole

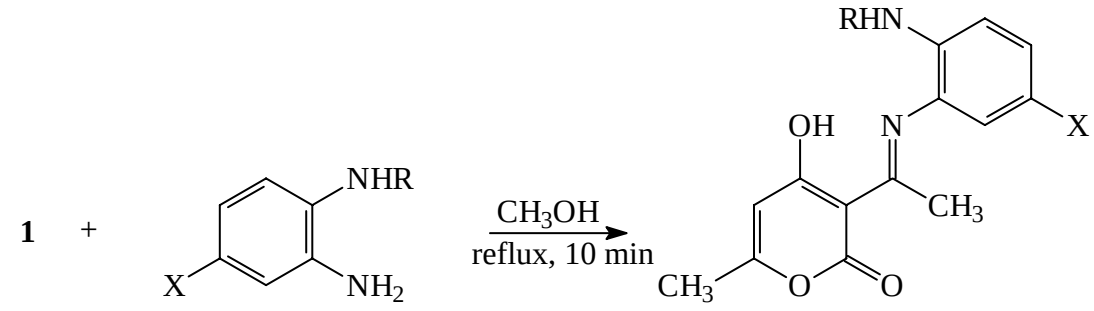
DHA on reaction with two molecules of hydroxylamine leads to the formation of bis-isoxazole (**51**).[47] All of the four electrophilic centers: C2, C4, C6 and the carbonyl of the acetyl chain react in the formation of **51**.



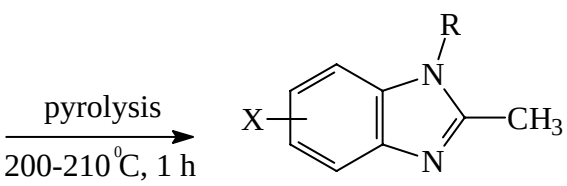
51

vi) Benzimidazoles

Condensation of substituted *o*-phenylenediamines (**52**) with DHA (**1**) leads to the formation of 3-[*N*-(substituted *o*-aminophenylphenyl)acetimidoyl]-4-hydroxy-6-methyl-2*H*-pyrones (**53**), which on pyrolysis give the corresponding 2-methyl-5-substituted benzimidazoles (**54**).[48,49]



52 **53**

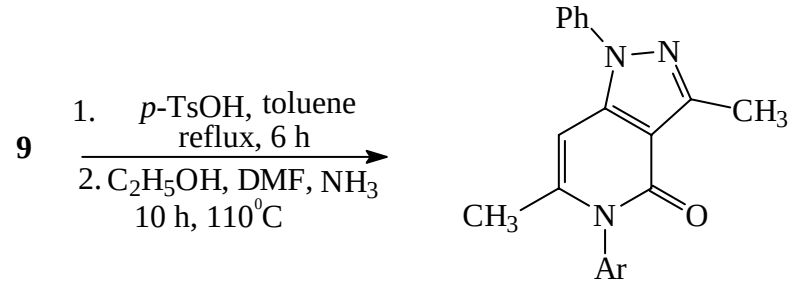


54

X	**R**	**Yield**
H	H, CH_3, CH_2Ph	45-65
6-Cl	CH_3	58
5-Cl	H, CH_3, CH_2Ph	45-60
5- CH_3	H, CH_2Ph	50-58

vii) Pyrazolopyridones

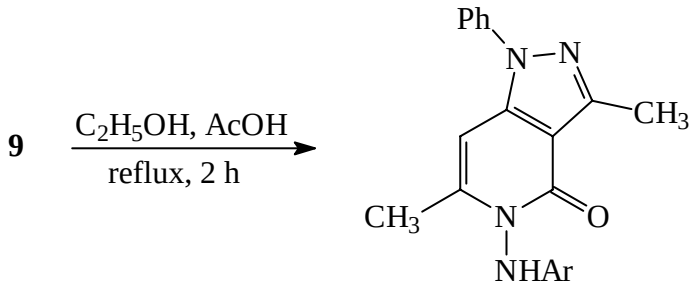
Two series of 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]pyridin-4-ones (**55**) and 3,6-dimethyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine-4-thiones have been prepared from DHA as starting material and evaluated for activity *in vitro*.[50] The activity of the synthesized compounds was compared with that of mirlinone as a reference. Several of the compounds have shown *inotropic* activity more potent than that of mirlinone.



55

Ar	**Yield**
C_6H_5	75
4-$OCH_3C_6H_4$	80
4-$CH_3C_6H_4$	83
2-$CH_3C_6H_4$	50
4-ClC_6H_4	75
4-FC_6H_4	34

It is relevant to mention that hydrazones (**9**) are reported to give 1-aminophenyl-3,6-dimethyl-4-oxo-1*H*-phenylpyrazolo[4,3-*c*]pyridines (**56**) by heating their solution in a mixture of ethanol and acetic acid, are obtained.[51] However reinvestigation of this study by Gelin *et al.* showed the products obtained from this reaction are5-hydroxy-3-methyl-1-phenyl-4-(3-methyl-1-phenylpyrazol-5-yl)pyrazole (bipyrazole, **36A**, $R^1 = R^2 = Ph$) rather than **56**.[33]



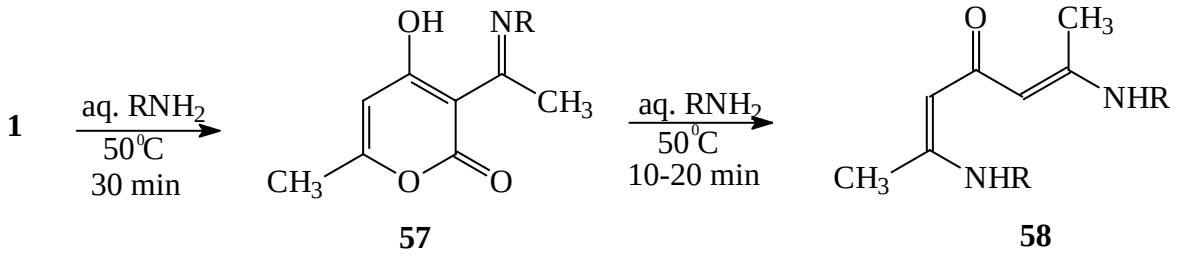
56

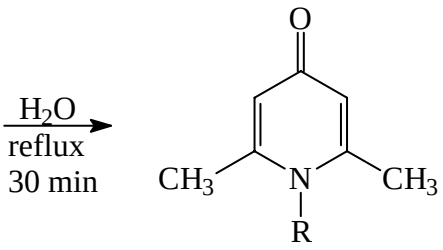
Ar	**Yield**
C_6H_5	60
4-$NO_2C_6H_4$	50
$CONH_2$	35

B) SIX-MEMBERED HETEROCYCLIC COMPOUNDS

i) Pyridines

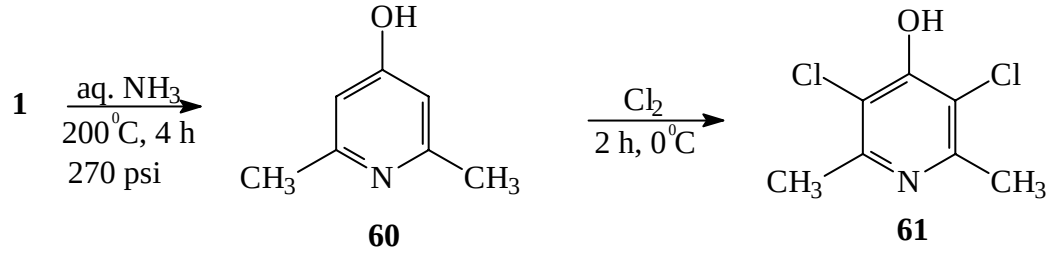
There are many examples of the transformations of DHA (**1**) into pyridones (**59**) by treatment with ammonia and primary amines.[52-55] This reaction has been extensively studied and the intermediates (**57**, **58**) have been isolated and identified.[56,57]



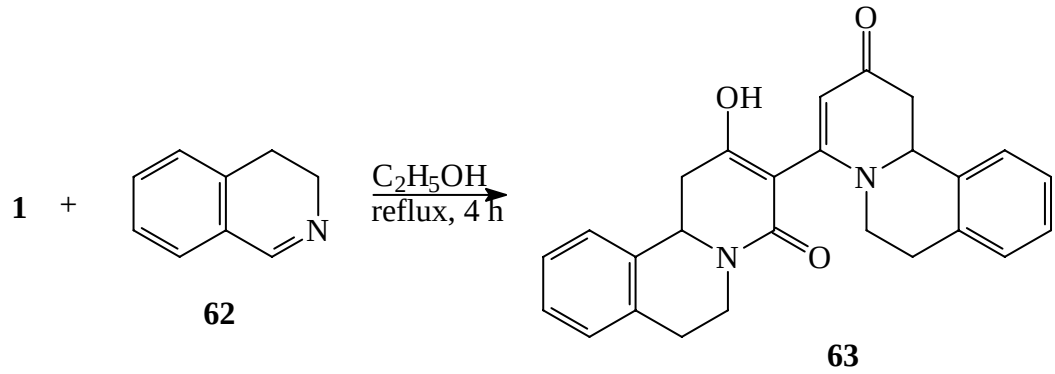


R	Yield (57)	Yield (58)	Yield (59)
CH_3	90	88	80
CH_2CH_3	90	87	82
NH_3	91	88	85

2,6-Dimethyl-3,5-dichloro-4-hydroxypyridine (**61**) has been synthesized by a two step reaction.[58] The reaction consists of treating DHA with aq. ammonia thus generating an intermediate product 2,6-dimethyl-4-hydroxypyridine (**60**) which is then chlorinated to give **61**.

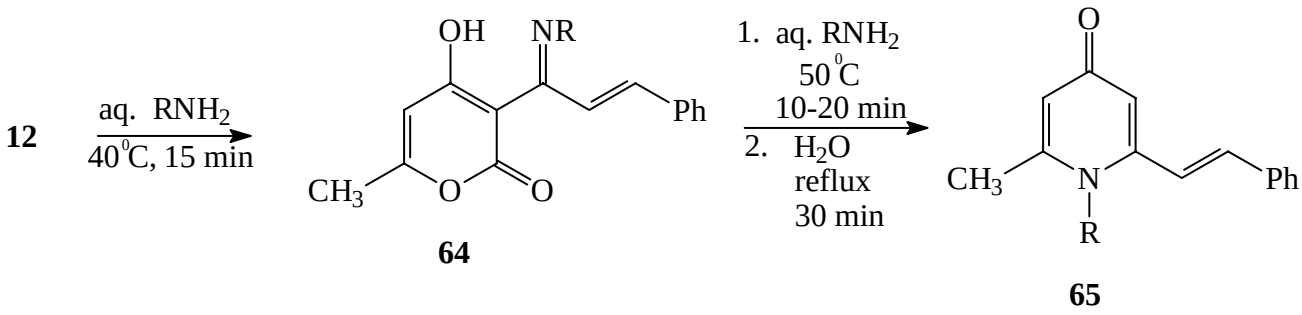


The reaction of DHA (**1**) with 3,4-dihydroisoquinoline (**62**) offers an illustrative example of the complexities encountered in opening-cyclization sequence.[59,60]



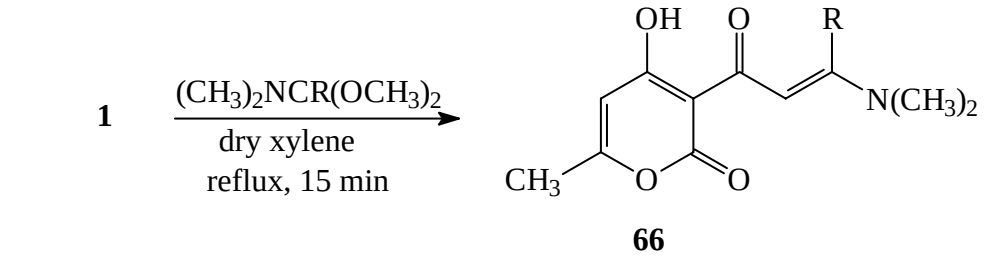
ii) Pyridones

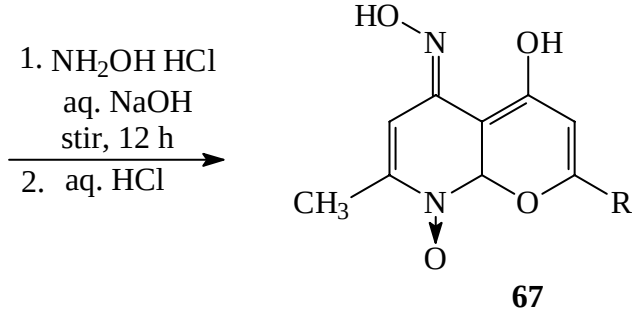
The reaction between 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans (**12**) and primary amines results in the formation of substituted 4-pyridones (**65**, R = H, CH_3). A plausible mechanism for this reaction involves the formation of Schiff's base (**64**) as the intermediate.[61]



iii) Pyranopyridine *N*-oxides

The reaction between the DHA with *N*,*N*-dimethylformamide dimethylacetal gives 4-hydroxy-6-methyl-2-oxo-3-[3-dimethylaminoacryloyl]-2*H*-pyran (**66**). Treatment of **66** with an excess of aq. $NH_2OH.HCl$ leads to the formation of 4-oxo-5-hydroxylamino-7-methyl-4*H*-pyrano[2,3-*b*]pyridine *N*-oxide (**67**).[23,62,63]

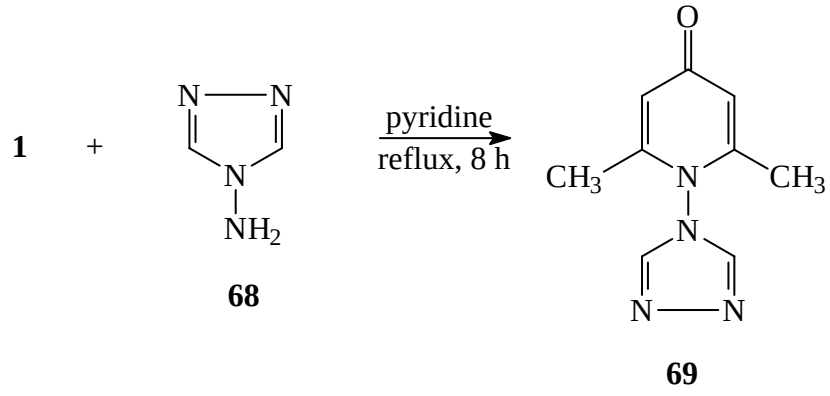


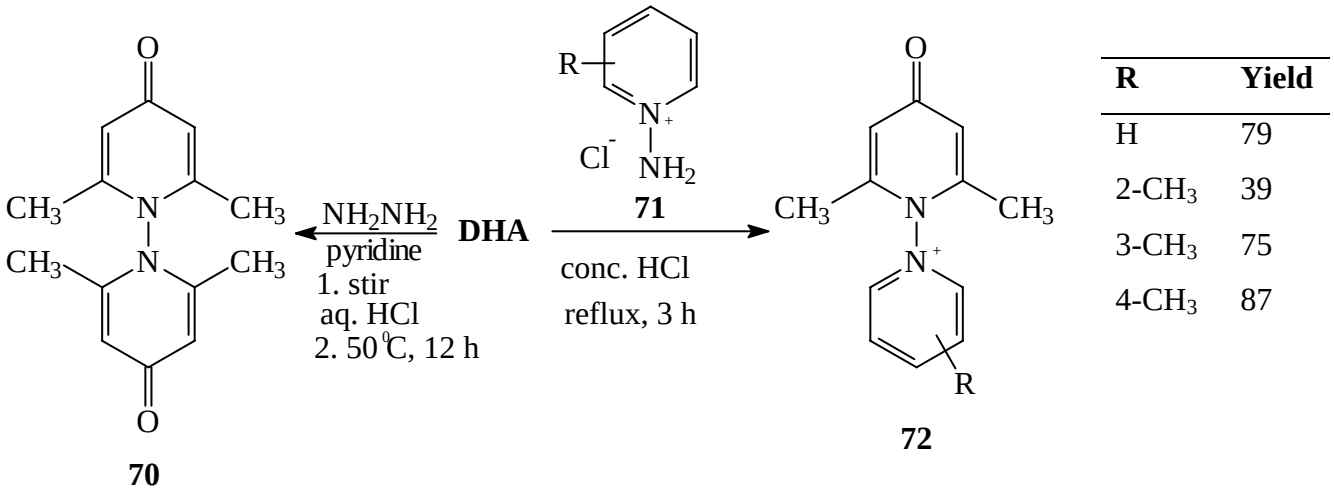


R	**Yield (66)**	**Yield (67)**
H	90	87
CH_3	72	83

iv) N,N′-linked Bi(heteroaryls)

Many interesting versions are encountered in the reaction of hydrazine with *N*-amino heterocycles. Thus, reactions of DHA with *N*-amino-1,2,4-triazole (**68**), hydrazine and *N*-aminopyridinium salts (**71**) produce *N*,*N*′-linked bi(heteroaryls) compounds (**69**, **70**, **72**), respectively.[64-66]

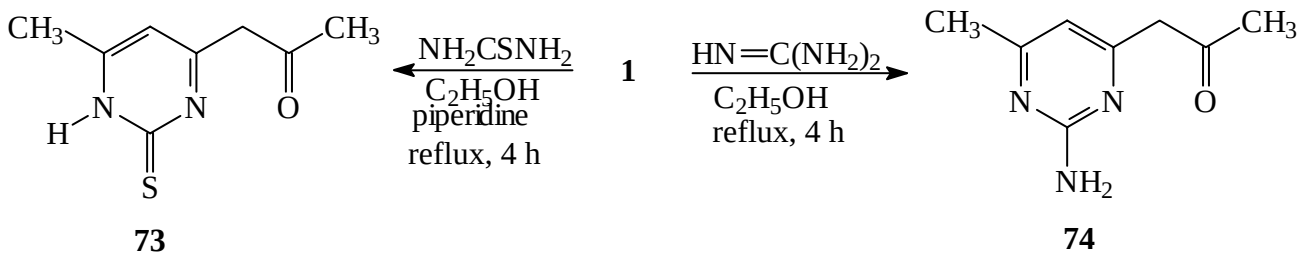




R	Yield
H	79
2-CH_3	39
3-CH_3	75
4-CH_3	87

v) Pyrimidines

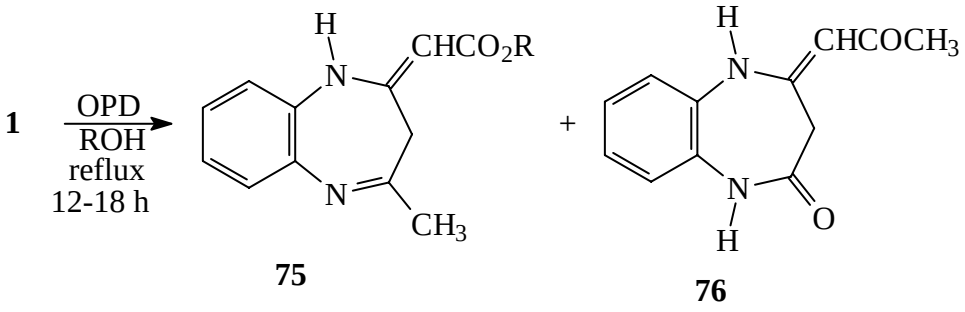
DHA is transformed into pyrimidine derivatives (**73**, **74**) by treatment with thiourea and guanidine.[67] Both these reactions probably proceed through the condensation of initial formed heptane-2,4,6-trione with thiourea and guanidine.



C) SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS

i) Benzodiazepines

The reaction of *o*-phenylenediamine (OPD) with DHA in different alcohols leads to the formation of 2-alkoxycarbonylmethylenebenzodiazepines (**75**) and 4-acetylmethylenebenzodiazepinones (**76**).[49] The alcohols used in this transformation include methyl alcohol, ethyl alcohol, *n*-propyl alcohol, isopropyl alcohol and sterically hindered *t*-butyl alcohol.

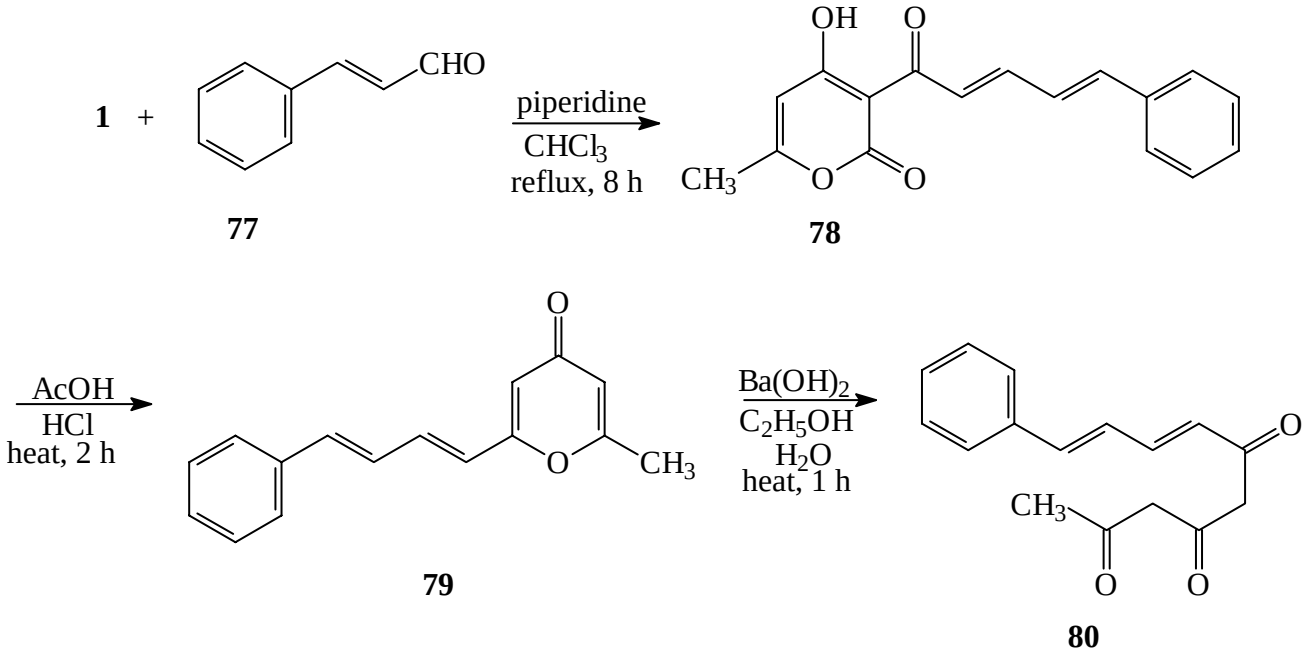


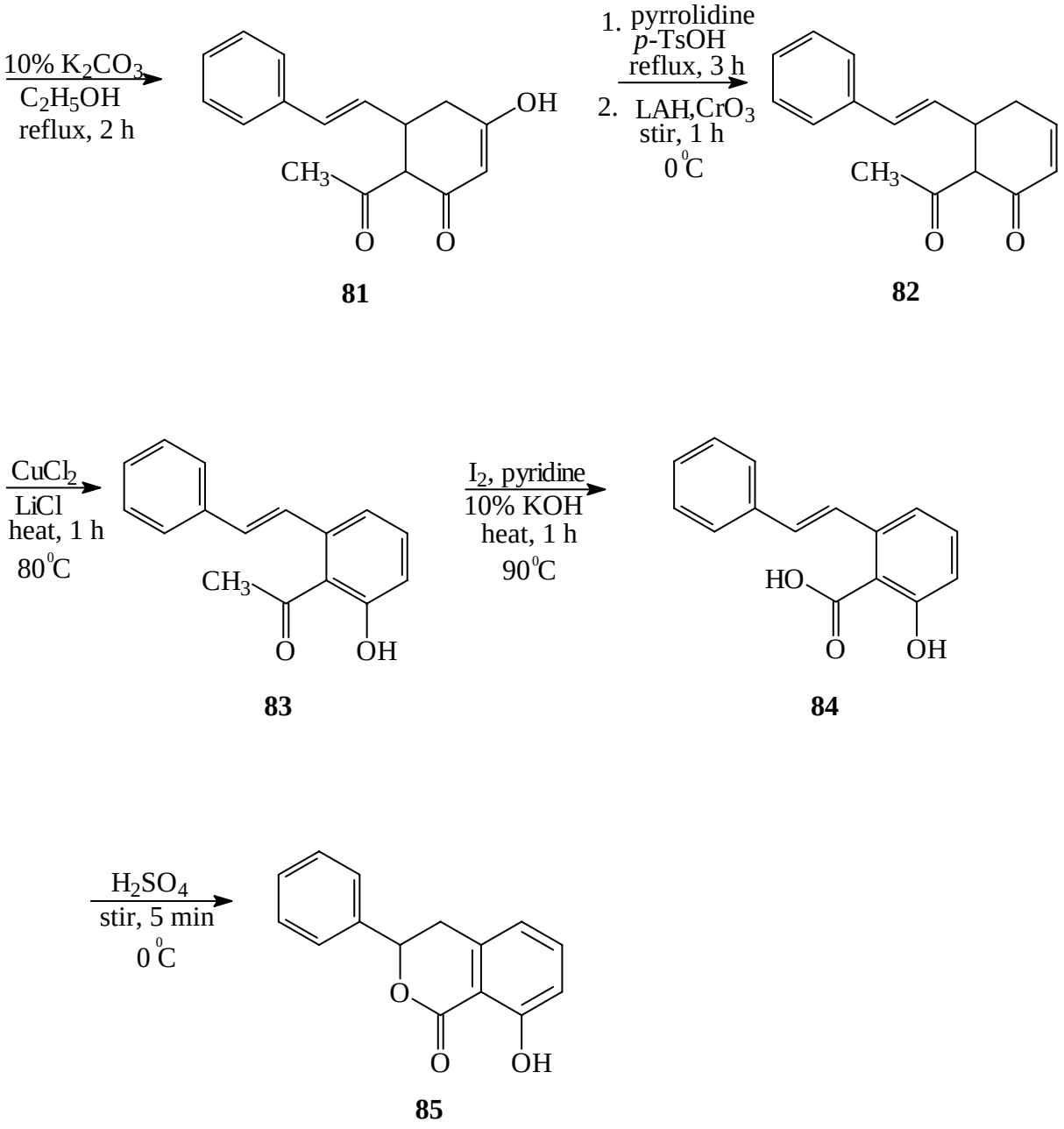
R	Yield
CH_3	65
CH_2CH_3	61
$CH_2CH_2CH_3$	58
$CH(CH_3)_2$	56
$C(CH_3)_3$	50

SECTION III: MISCELLANEOUS REACTIONS

A) Biogenetic synthesis of phenylisocoumarin

A biogenetic-type synthesis of a dihydroisocoumarin, 3,4-dihydro-8-hydroxy-3-phenylisocoumarin (**85**) from DHA and *trans*-cinnamaldehyde (**77**) modeled on the polyketide mode of biosynthesis has been reported by Takeuchi *et al.*[68,69] This is a multistep synthesis and reaction sequence is outlined in **Scheme 1**.

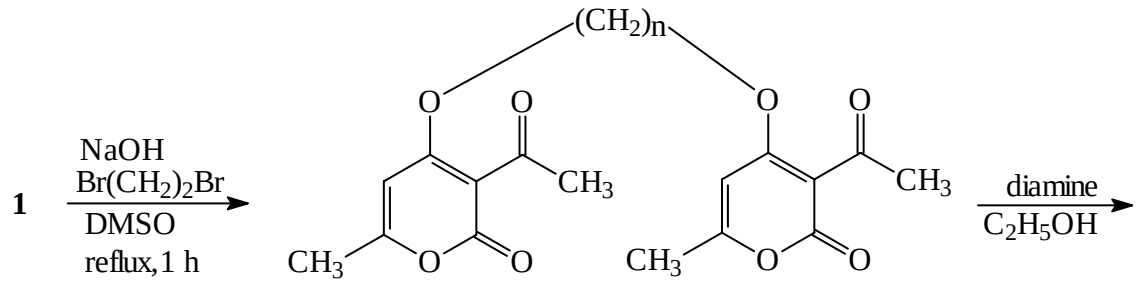




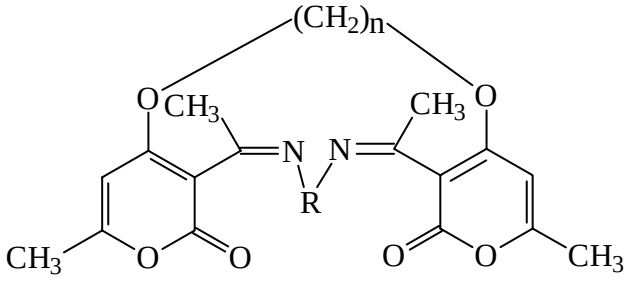
Scheme 1

B) Formation of macrocyclic imine ligands

A new series of macrocyclic ligands with different ring sizes (14-, 15- and 16-membered) are synthesized from DHA in a two-step reaction process involving Williamson's condensation (**86**) and Schiff base cyclization (**87**) reactions with various diamines such as 1,2- or 1,3-diaminoalkane, carbohydrazide and thiocarbohydrazide.[70] The structures of these macrocycles have been unequivocally established.



86 n = 2 or 3



87

R	**Yield**
$(CH_2)_2$	68
$(CH_2)_3$	65
NHCONH	64
NHCSNH	63

CONCLUSIONS

The above-mentioned examples of the application of DHA and its derivatives for the synthesis of a wide variety of heterocyclic compounds illustrate the versatility of this compound. It may further be mentioned that this inexpensive, crystalline, non-toxic and stable material has lot of unexplored potential for the synthesis of heterocyclic compounds, particularly due to the presence of so many reactive sites in the molecule.

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