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DEHYDROACETIC ACID AND ITS DERIVATIVES AS STARTING SYNTHONS FOR SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Abstract – From the last few years, dehydroacetic acid (DHA) has been found to show its immense contribution to the synthesis of various heterocyclic moieties. The present review reveals the various synthetic methods, developed from 2000 to 2015, to heterocyclic scaffolds considering DHA as starter. The present literature ensures the versatility of DHA for the synthesis of heterocyclic compounds, hence considered as versatile synthon.

CONTENTS

1. INTRODUCTION

3-Acetyl-4-hydroxy-6-methylpyran-2-one, commonly known as dehydroacetic acid **1** (abbreviated as DHA) and the products derived from it, found wide application in food, pharmaceutical as well as cosmetic industry. It has been used in the manufacturing of jelly-like ice cream[1] and as preservative for food and vegetables.[2,3] Sodium dehydroacetate is used in the preparation of preservative for moon cake, antimicrobial emulsifier, high water content cake, cereal for mosaic handicraft, efficient broad spectrum food compound preservative and mould proofing agent for feedstuff.[4-9] DHA has also been used in the manufacturing of low pH fibres and the articles made from these fibres such as tampons or wipes which

provide health benefit to the user by hindering the growth of bacteria, reagent for detecting the activity of creatine kinase MB isoenzyme (CK-MB).[10,11]

2. BRIEF HISTORY, METHODS OF PREPARATION AND REACTIVITY OF DHA

Geuther in 1866 discovered DHA as one of the products of the pyrolysis of ethyl acetoacetate.[12] It has also been isolated from natural resources.[13,14] The name dehydroacetic acid is derived from the fact that it is made up of four molecules of acetic acid with the elimination of four molecules of water. Various methods employed for the synthesis of DHA are given in **Schemes 1-4**. Chalaca[15] studied the NMR of various tautomeric forms of DHA. Moreover, DHA has several reactive sites, therefore, the molecule is susceptible to attack by a variety of nucleophilic and electrophilic reagents. A nucleophile can attack the carbonyl of the acetyl side chain located at 3-position, the lactone carbonyl at 2-position, the carbonyl carbon at 4-position and the carbon atom terminating the conjugated carbon chain at 6-position of pyran-2-one nucleus. On the other hand, an electrophile can attack either at C(3) or C(5). Being highly reactive, DHA and its derivatives act as a versatile starting material for the synthesis of a wide variety of organic compounds (**Figure 1**).

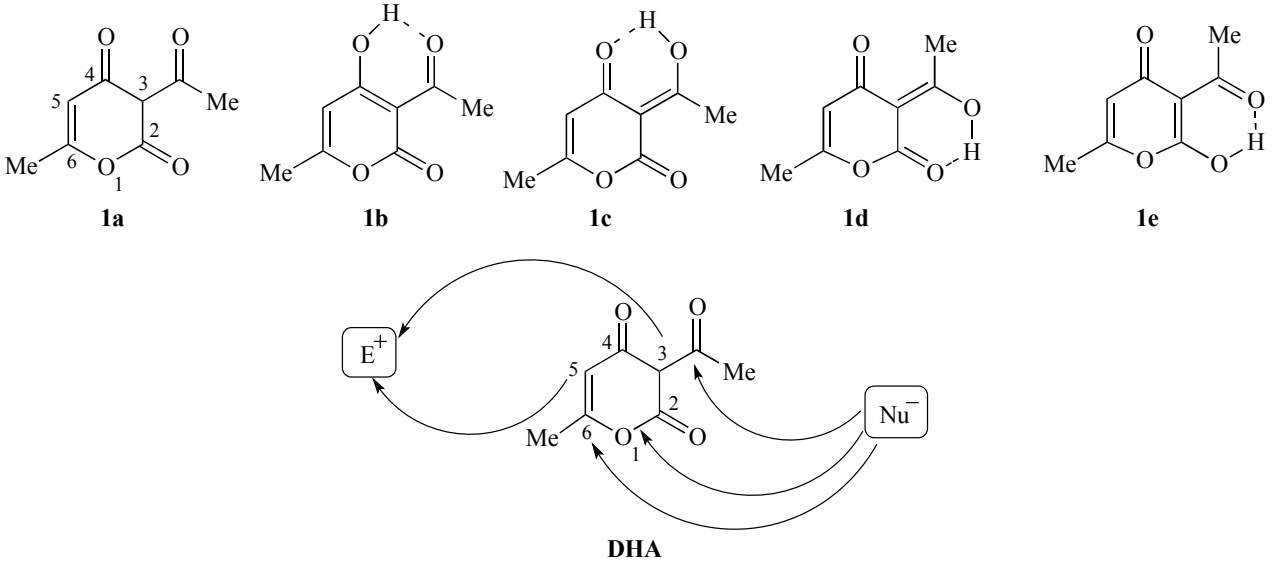
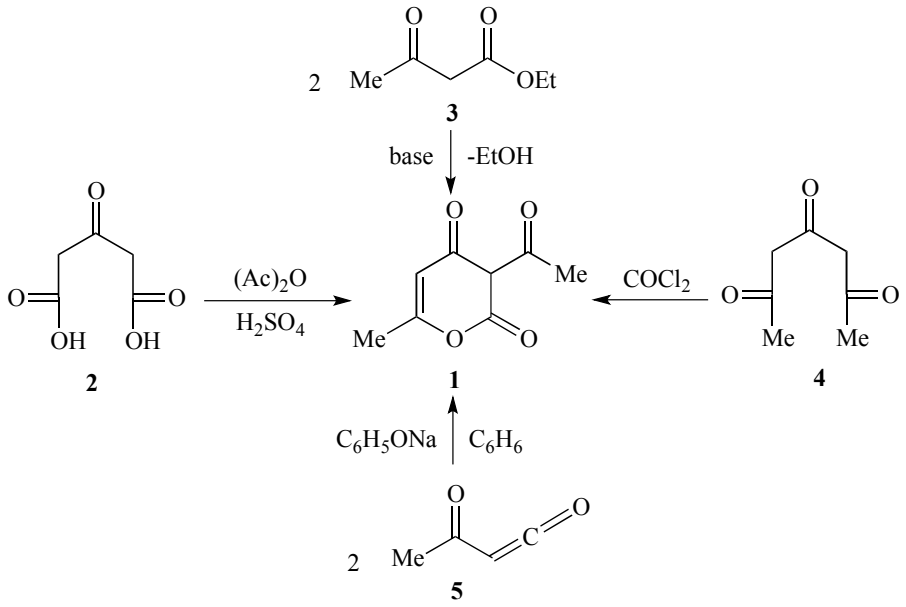


Figure 1

Pechmann's method reported in the literature for the synthesis of DHA *via* 3-oxopentanedioic acid, which condensed with acetic anhydride in the presence of sulphuric acid and 2,6-dimethyl-γ-pyrone-3-carboxylic acid was obtained which underwent rearrangement to DHA.[16] Arndt and Nachtwey reported a method for the synthesis of DHA, which proceeded by the elimination of one molecule of ethyl alcohol from two molecules of ethylacetoacetate in the presence of base.[17] Kaushal *et al.*

launched a synthetic method of DHA from self condensation of heptane-2,4,6-trione in the presence of phosgene.[18] Steele *et al*. developed a method for the synthesis of DHA *via* polymerization of but-1-ene-1,3-dione in boiling benzene solution with sodium phenoxide.[19] All these methods well depicted in **Scheme 1**.



Scheme 1

3. APPLICATIONS OF DHA IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

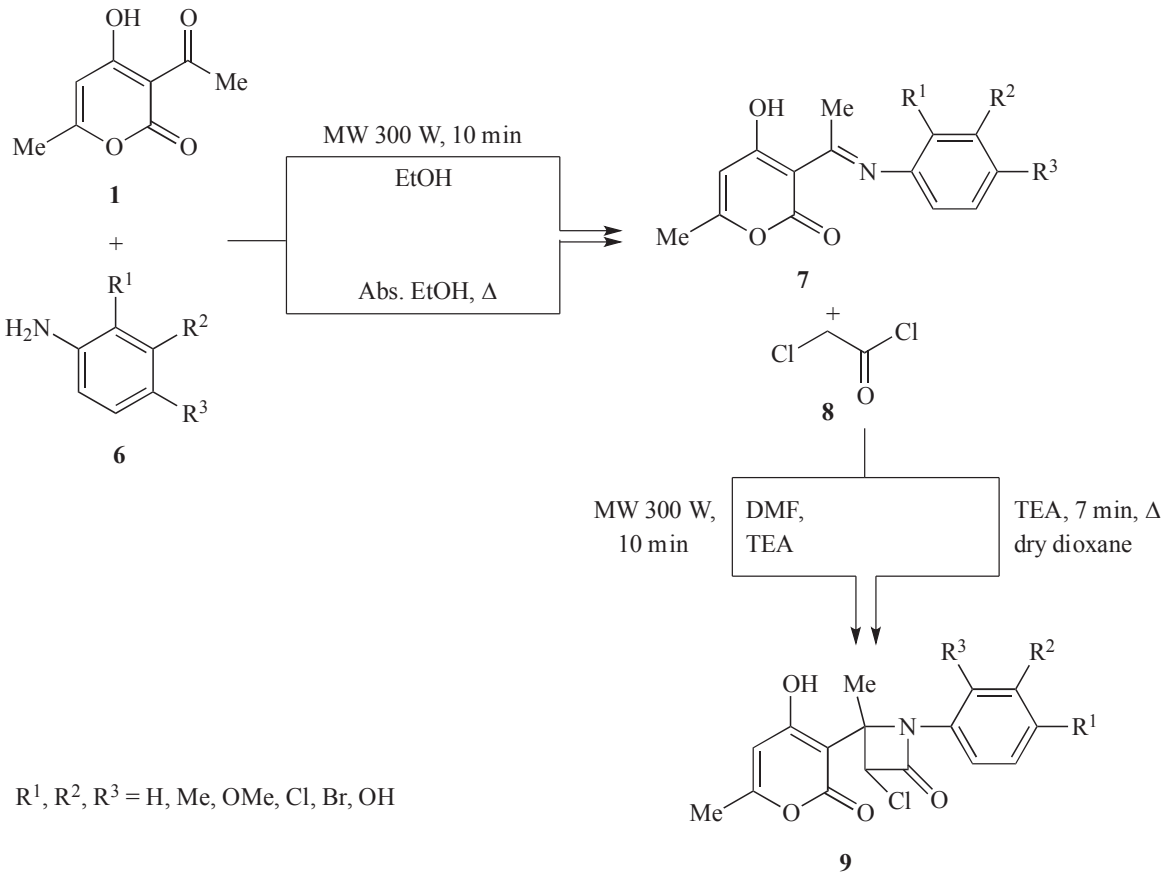
A couple of reviews have been found in literature which highlight the applications of DHA in the synthesis of heterocyclic compounds.[20,21] But hereby, some recent advances of DHA and its derivatives in the synthesis of heterocyclic compounds is being summarized in the form of a review.

A. SYNTHESIS OF HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN ATOM

A.1 SYNTHESIS OF FOUR MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING ONE NITROGEN ATOM

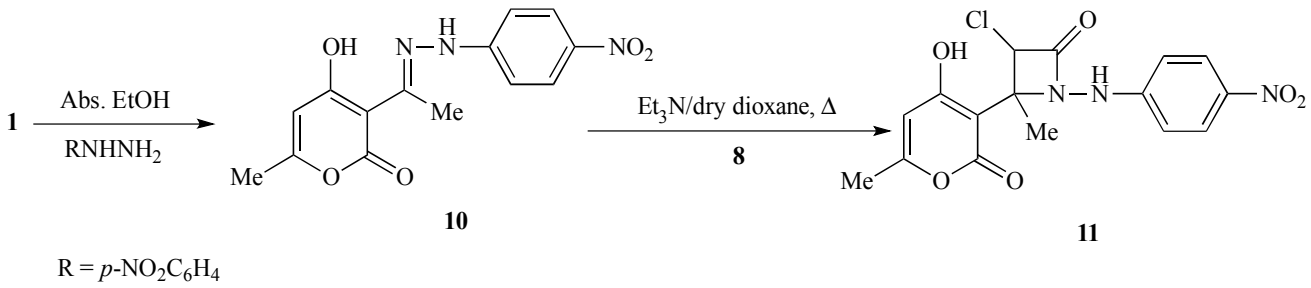
A.1.1 AZETIDINONES

Pulate *et al*. have synthesized novel azetidinones from dehydroacetic acid **1** *via* microwave-assisted method. This method involves the reaction of DHA **1** with primary aromatic amines **6** to yield Schiff's base **7** by using MW irradiations at 300 W for 10 min which on subsequent irradiation for 7 min with chloroacetyl chloride **8** in presence of triethylamine and dimethylformamide afforded azetidinones **9** in excellent yields. A conventional method for the synthesis of **9** involves condensation of DHA **1** and *p*-methylaniline in absolute ethanol, followed by refluxing of Schiff's base with **8** in dioxane in the presence of catalytic amount of triethylamine under anhydrous condition (**Scheme 2**).[22,23]



Scheme 2

Synthesis of *N*-aminoazetidinone **11** was accomplished *via* reaction of chloroacetyl chloride **8** with 4-nitrophenyl-1-[1-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)ethylidene]hydrazine **10**, which in turn was furnished by reaction of DHA **1** with *p*-nitrophenylhydrazine in dry dioxane with catalytic amount of Et_3N (**Scheme 3**).[23]

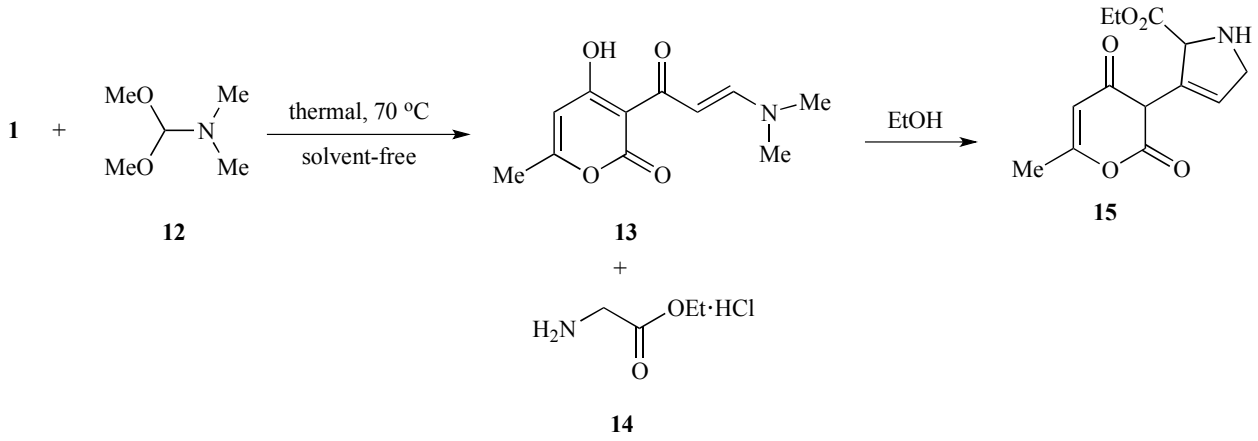


Scheme 3

A.2 SYNTHESIS OF FIVE MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING ONE NITROGEN ATOM

A.2.1 PYRROLES

β-Enaminone **13**, obtained by the reaction of DHA **1** and *N,N*-dimethylformamide dimethyl acetal **12** under thermal solvent-free conditions, on reaction with ethyl glycinate hydrochloride **14** in boiling ethanol afforded the formation of ethyl 3-(6-methyl-3,4-dihydro-2,4-dioxo-2*H*-pyran-3-yl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate **15** (**Scheme 4**).[24,25]



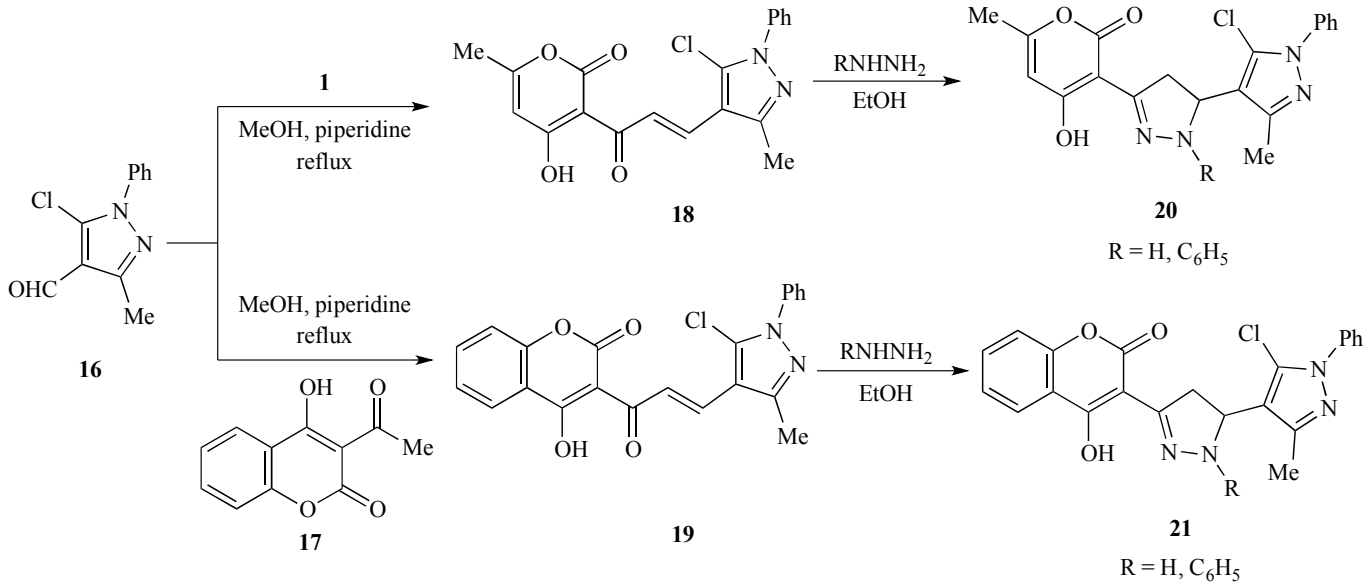
Scheme 4

A.3 SYNTHESIS OF FIVE MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING TWO NITROGEN ATOMS

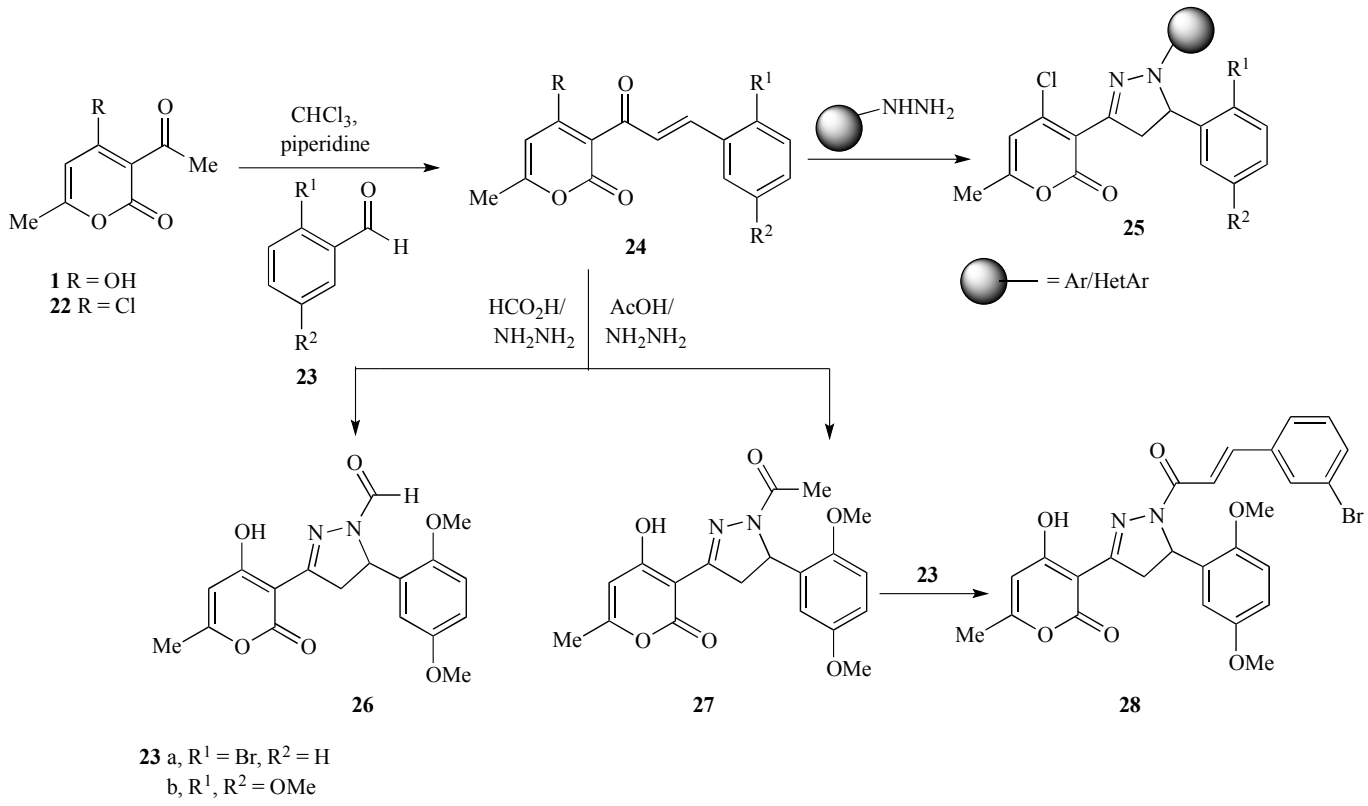
A.3.1 PYRAZOLINES AND PYRAZOLES

Siddiqui *et al*. reported the synthesis of 3,5-heteroaryl-4,5-dihydropyrazoles **20**, **21** by the reaction of hydrazines with heterochalcones **18**, **19** which in turn, were synthesized by Claisen-Schmidt condensation of 5-chloro-3-methyl-1-phenylpyrazole-4-carbaldehyde **16** with DHA **1** and 3-acetyl-4-hydroxycoumarin **17**, respectively (**Scheme 5**).[26]

Redha *et al*. reported the synthesis of pyrazolines **25** *via* reaction of DHA chalcones **24** with aryl/heteroarylhydrazines. Compound **19**, obtained by Claisen-Schmidt condensation of aldehydes **23** with DHA **1** and 3-acetyl-4-chloro-6-methyl-3,4-dihydropyran-2-one (Cl-DHA) **22**, accomplished by refluxing DHA **1** with $POCl_3$. Synthesis of *N*-formyl **26** and *N*-acetylpyrazolines **27** was accomplished by treating chalcone **24** with hydrazine hydrate in the presence of formic acid and glacial acetic acid respectively and pyrazolinechalcone **28** was obtained by reaction of **27** with *o*-bromobezaldehyde **23** (**Scheme 6**).[23,27]

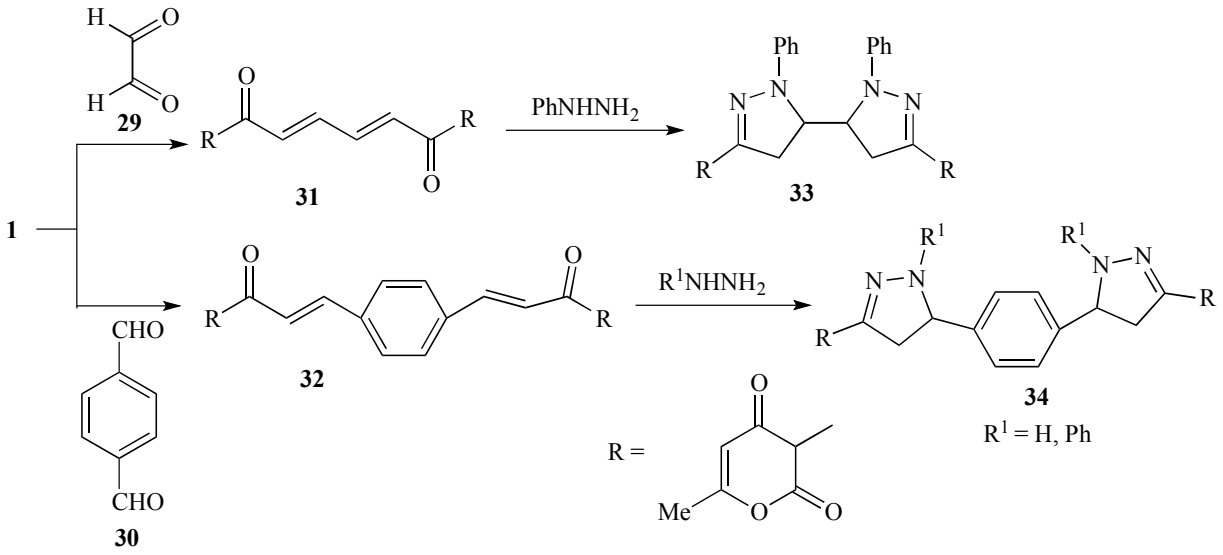


Scheme 5



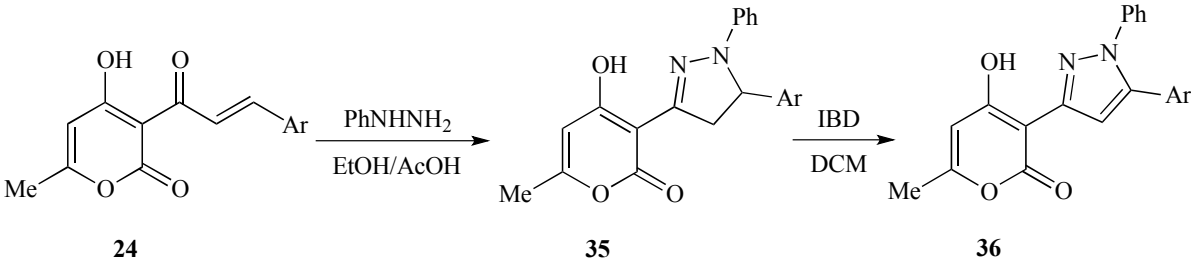
Scheme 6

A unique approach towards the synthesis of bispyrazolines **33**, **34** has been reported *via* reaction of hydrazines with *bis*-DHA chalcones **31** and **32**, obtained by reaction of dehydroacetic acid **1** with oxaldehyde **29** and terephthalaldehyde **30** respectively (**Scheme 7**).[27]



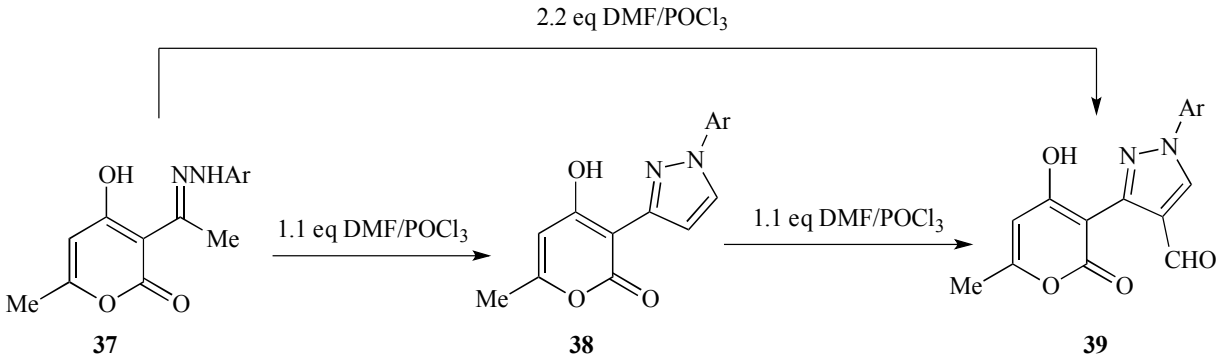
Scheme 7

Iodobenzene diacetate (IBD) mediated oxidation of 1,5-diphenyl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-pyrazolines **35**, furnished by 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans **24** on treatment with arylhydrazines, to respective pyranylpyrazoles **36** has been reported (**Scheme 8**).[28]



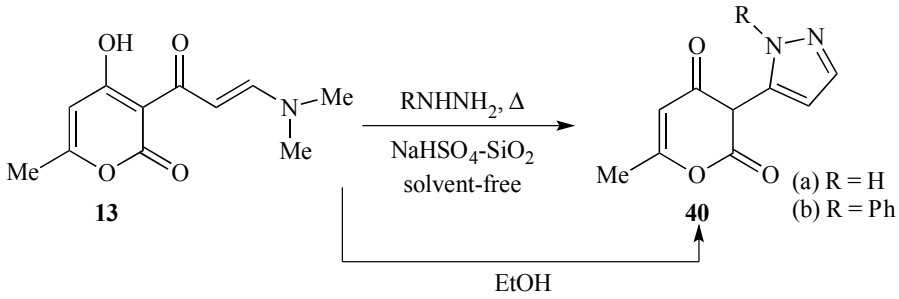
Scheme 8

It has been reported that DHA hydrazones **37** on double Vilsmeier-Haack reaction gave 4-formyl-3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-1-arylpyrazoles **39**. The intermediate, 3-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-1-arylpyrazoles **38** has also been isolated using 1.1 eq of DMF/$POCl_3$, which undergo further formylation to corresponding 4-formylpyrazoles **39** under Vilsmeier-Haack reaction conditions (**Scheme 9**).[29]



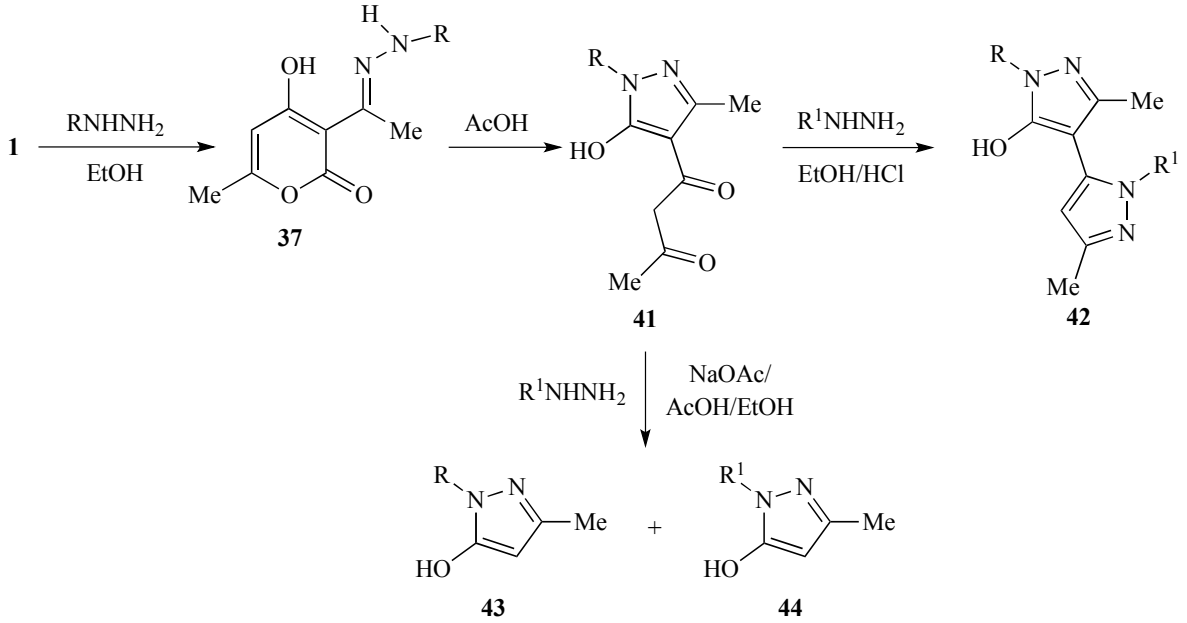
Scheme 9

A convenient and environment benign approach for the synthesis of novel pyranylpyrazoles **40** *via* *β*-enaminones **13** using $NaHSO_4$–SiO_2 as an efficient, non toxic, recyclable catalyst, has been reported by Siddiqui *et al*. Reaction of *β*-enaminone **13** with hydrazine hydrate or phenylhydrazine afforded pyranylpyrazoles **40** at lower temperature. Synthesis of pyranylpyrazole derivative **40a** was also reported by conventional heating of *β*-enaminone **13** with hydrazine hydrate in ethanol (**Scheme 10**).[24,25]



Scheme 10

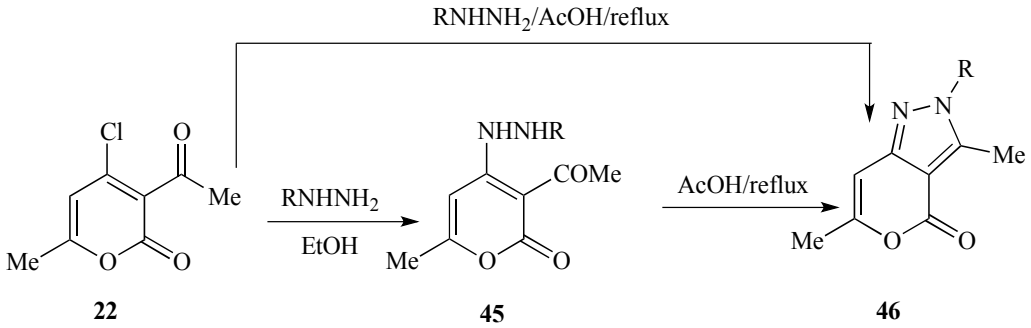
The divergent behaviour of aryl/heteroarylhydrazines towards 1-aryl/heteroaryl-5-hydroxy-3-methylpyrazol-4-yl-1,3-butanediones **41**, obtained from smooth skeletal rearrangement of *N*-substituted aryl/heteroarylhydrazones **37** of DHA **1** by refluxing in glacial acetic acid was exemplified by our research group, under two reaction conditions. Whereas formation of bipyrazoles **42** was reported in EtOH/HCl irrespective of the nature of hydrazine, in NaOAc/AcOH/EtOH, the product formed depended upon the nature of hydrazine. Phenylhydrazine, pyridylhydrazine, and *p*-nitrophenylhydrazine, 4,6-dimethylpyrimidin-2-ylhydrazine led to the exclusive formation of the bipyrazole **42** but in case of 2,4-dinitrophenylhydrazine, 2-benzothiazolylhydrazines, 2-quinolylhydrazines, 1-naphthylhydrazine, C-C bond cleavage occurred to give pyrazol-5-ols **43** and **44**. It was proposed that bulk and/or strong electron withdrawing nature of substituents on hydrazines in these cases played a key role in C-C bond fission (**Scheme 11**).[30,31]



R = C_6H_5, *p*-ClC_6H_4, 4-methyl-2-quinolyl, 4,6-dimethylpyrimidin-2-yl
R^1 = C_6H_5, *p*-$NO_2C_6H_4$, 2,4-DNP, naphthyl, 2-pyridyl, 4-methyl-2-quinolyl, 6-methylbenzothiazol-2-yl, 6-methoxybenzothiazol-2-yl, 6-fluorobenzothiazol-2-yl, 5-methoxybenzothiazol-2-yl, benzothiazol-2-yl, 4,6-dimethylpyrimidin-2-yl

Scheme 11

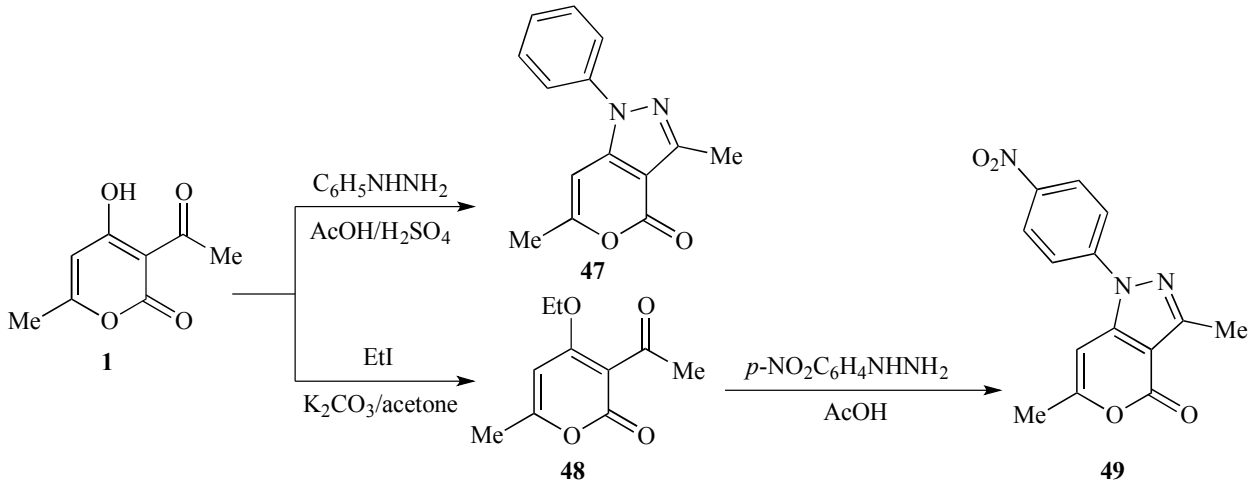
A useful approach for the synthesis of pyrano[4,3-*c*]pyrazoles **46** using new hydrazino derivatives of dehydroacetic acid **45**, prepared by the reaction of Cl-DHA with substituted hydrazines, has been developed. The six-membered lactone (pyran-2-one) ring has been identified as a suitable central ring template to design selective COX-2 inhibitors. *In vitro* and *in vivo* analysis of some of the compounds **45d**, **45g**, **46e** have been found to exhibit dual analgesic and anti-inflammatory profile and therefore serve as lead molecules for further synthetic and biological evaluation (**Scheme 12**).[32]



R = C_6H_5, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, 4-phenyl-2-thiazolyl, 4-methyl-2-quinolyl

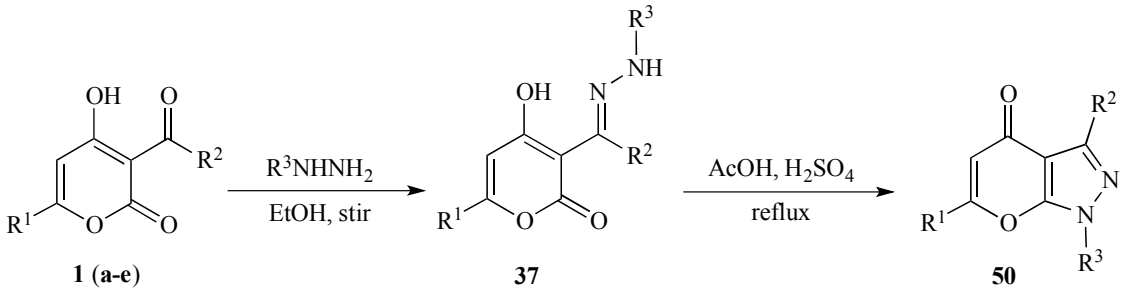
Scheme 12

Regioisomeric 3,6-dimethyl-1-phenylpyrano[4,3-*c*]pyrazol-4-one **47** was obtained by the reaction of phenylhydrazine with dehydroacetic acid **1** in acetic acid-H_2SO_4. Alternatively, DHA was converted to its analog **48** by treating with ethyl iodide, K_2CO_3 in dry acetone and **48** was condense with *p*-nitrophenylhydrazine to yield 3,6-dimethyl-1-(4-nitrophenyl)pyrano[4,3-*c*]pyrazol-4-one **49**. The conversion of OH group of DHA **1** to ethoxy group, makes it a better leaving group, reduces H-bond stabilization, increases reactivity and was easily attacked by less nucleophilic center of *p*-nitrophenylhydrazine (**Scheme 13**).[23]



Scheme 13

James *et al*. reported one pot synthesis of pyrano[2,3-*c*]pyrazoles **50** *via N*-substituted hydrazones **37** of DHA and its analogues **1a-e** when subjected to reflux in glacial acetic acid, H_2SO_4 for 1 h (**Scheme 14**).[33]

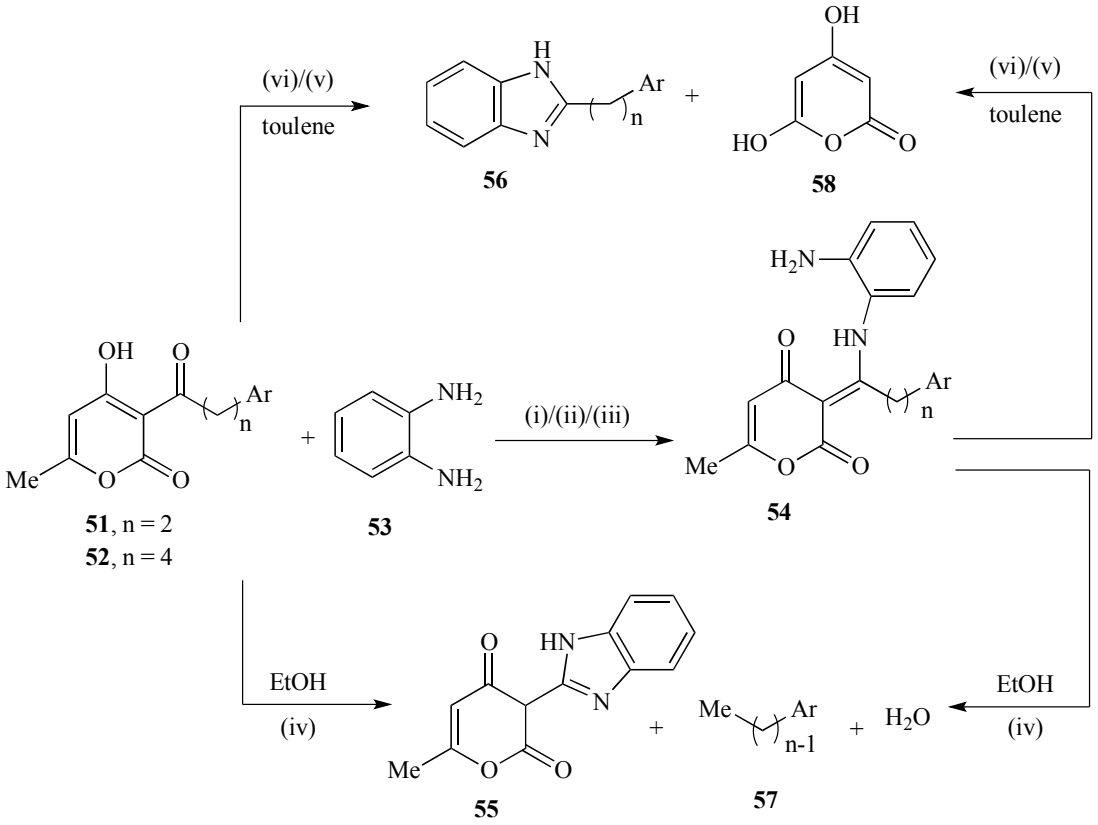


Scheme 14

A.3.2 BENZIMIDAZOLES

Nabila *et al*. explored the interesting chemistry of structural analogues of DHA **1**; 4-hydroxy-6-methyl-3-(3-arylpropanoyl)-2*H*-pyran-2-ones **51** and 4-hydroxy-6-methyl-3-(5-phenylpentanoyl)-2*H*-pyran-2-one **52** with *o*-phenylenediamine **53** which led to the formation of 2-substituted benzimidazoles **55**, **56** either

one pot or *via* ketimine intermediates **54** depending upon different reaction conditions. Reaction of **53** with **51** and **52** in ethanol under MW irradiations at 100W for 4 min yielded 2-benzimidazoles **55** along with the formation of water and alkylbenzene **57** whereas deacylation was observed in toluene under thermal and MW irradiations at 200 W for 4 min furnished 2-alkylbenzimidazoles **56** with the formation of triacetic acid lactone (TLA) **58**, a natural product of polyketide origin. Ketimine intermediate **54**, obtained by reaction of **51** and **52** with **53** in ethanol at room temperature in 6 h (i), refluxed 30 min (ii) and MW irradiations at 100W for 1 min (iii), yielded benzimidazoles **55**, **56** when subjected to reaction condition (iv, v, vi) (**Scheme 15**).[34]



(i) stir for 6 h at rt; (ii) thermal refluxing for 1 h; (iii) MW irradiation at 100 W for 1 min; (iv) MW irradiation at 100 W for 4 min; (v) thermal refluxing for 3 h; (vi) MW irradiation at 200 W for 4 min

51 Ar = C_6H_5, *p*-ClC_6H_4, 3,4-$Cl_2C_6H_3$ **52** Ar = C_6H_5

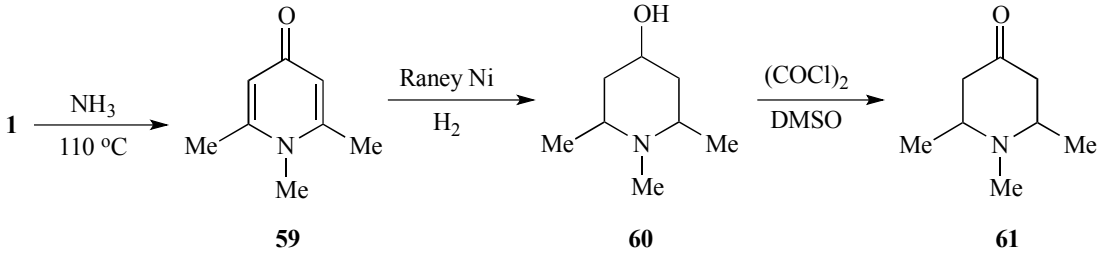
Scheme 15

A.4 SYNTHESIS OF SIX MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING ONE NITROGEN ATOM

A.4.1 PYRIDINES

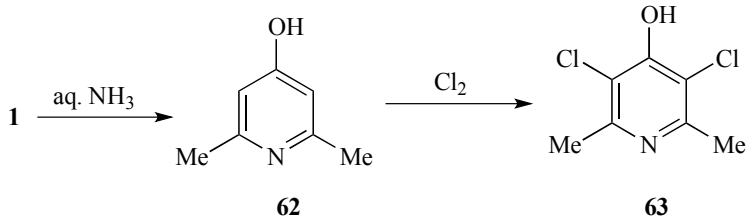
It has been reported that DHA **1** on reaction with ammonia rearranged to 1,2,6-trimethylpyridin-4(1*H*)-one **59** which upon reduction with Raney Ni gives

1,2,6-trimethylpiperidin-4-ol **60**. Further, Swern oxidation of **60** was carried out with DMSO-oxalyl chloride to yield 1,2,6-trimethylpiperidin-4-one **61** (**Scheme 16**).[35]



Scheme 16

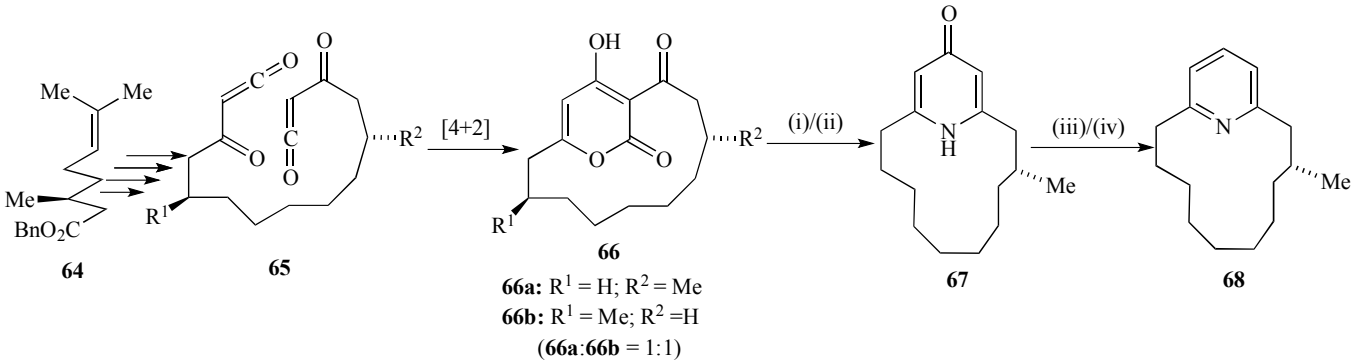
Treatment of DHA **1** with aq. ammonia, however, resulted into an aromatized 2,6-dimethyl-4-hydroxypyridine **62** following a similar rearrangement, which was further chlorinated with chlorine to yield 2,6-dimethyl-3,5-dichloro-4-hydroxypyridine **63** (**Scheme 17**).[36]



Scheme 17

It was implied efficiently to synthesize (R)-(+)-muscopyridine **68** from the readily available benzyl (R)-citronellate **64** in 12 steps with 40% overall yield. The key steps of synthesis involved the intramolecular [4+2] cycloaddition of bisketene **65** to afford a bridged pyrone **66** in 1:1 ratio. Both the isomers **66a** and **66b** of *para*-cyclophanes mixture were subjected to transform to (R)-(+)-muscopyridine **68**. This synthesis has found applications in the formation of 2,6-bridged pyridines (**Scheme 18**).[37]

Condensation of DHA **1** with 7-aminoindazole **69** in the presence of *p*-toluenesulfonic acid (PTSA) and *n*-butanol as a solvent has been reported to afford new *N*-(1*H*-7-indazolyl)pyridinones **70a** and **70b**. During this reaction, the initial attack of the amino group takes place on the C-6 of the DHA **1**, giving the intermediate 5-(1*H*-7-indazolylamino)-2-acetyl-3-oxohex-4-enoic acid. This intermediate after decarboxylation followed by subsequent intramolecular cyclization afforded *N*-(1*H*-7-indazolyl)-2,6-dimethylpyridin-4-one **70a**. However, esterification of intermediate carboxylic acid with *n*-butanol, followed by intramolecular cyclization, led to the formation of butyl 1,4-dihydro-1-(1*H*-7-indazolyl)-2,6-dimethyl-4-oxopyridine-3-carboxylate **70b** (**Scheme 19**).[38]

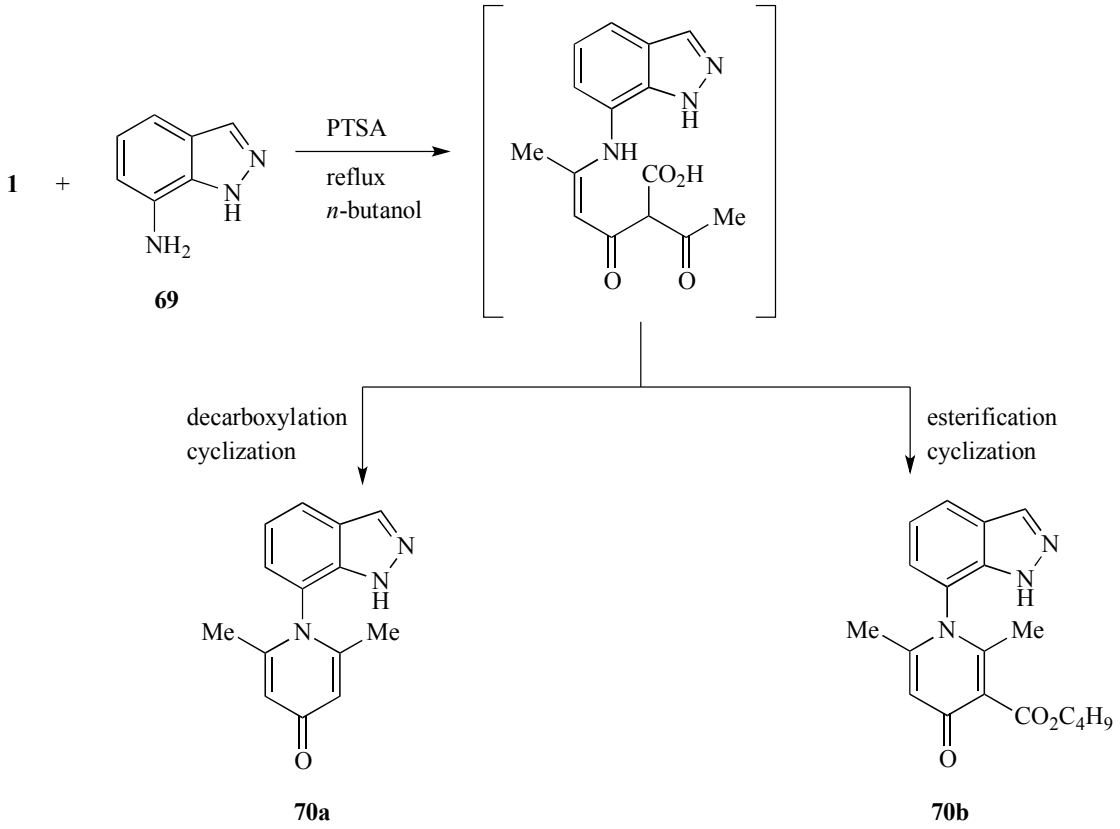


64 **65** **66** **67** **68**

66a: R^1 = H; R^2 = Me
66b: R^1 = Me; R^2 =H
(**66a**:**66b** = 1:1)

Reagents and conditions: (i) conc. HCl, reflux, 12 h, 89%; (ii) NH_3, EtOH, sealed tube, 140 °C, 3 d, 87%; (iii) $POCl_3$, reflux, 1 h, 93%; (iv) H_2/Pd–C, AcONa, rt, 12 h, 89%

Scheme 18

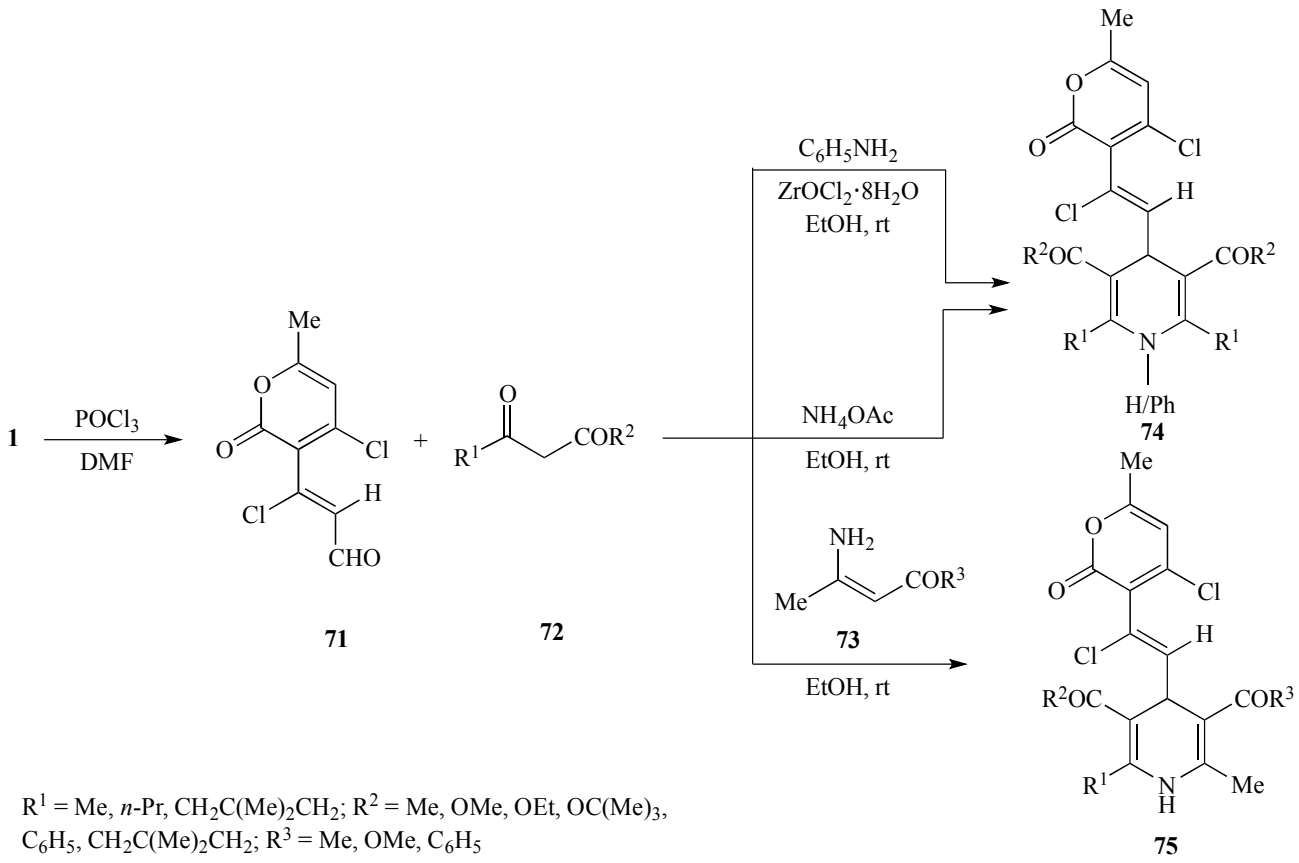


69 **70a** **70b**

Scheme 19

Shahrisa *et al*. reported the synthesis of new symmetrical 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)vinyl]-substituted 1,4-dihydropyridines **74** under two different reaction conditions: a) in the presence of ammonium acetate at room temperature in ethanol as solvent, b) aniline, $ZrOCl_2 \cdot 8H_2O$as a catalyst at room temperature *via* the modified Hantzsch reaction of *β*-dicarbonyl compounds **72** with (*Z*)-3-chloro-3-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)acrolein **71**,

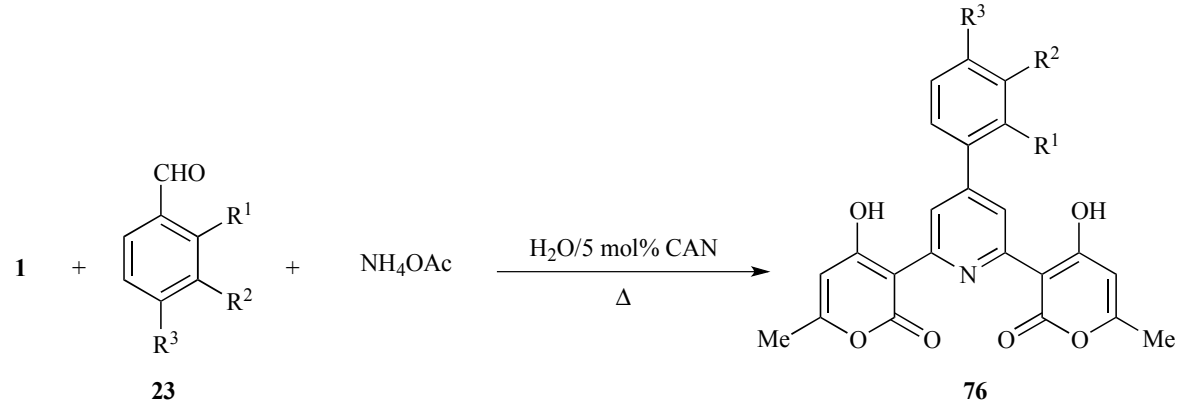
obtained by the Vielsmeier-Haack formylation of DHA **1**. In the presence of enamino esters and ketones **73**, unsymmetrical 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2*H*-pyran-3-yl)vinyl] substituted 1,4-dihydropyridines **75** were obtained by reaction of **71** and **72** in moderate to good yields at room temperature (**Scheme 20**).[39,40]



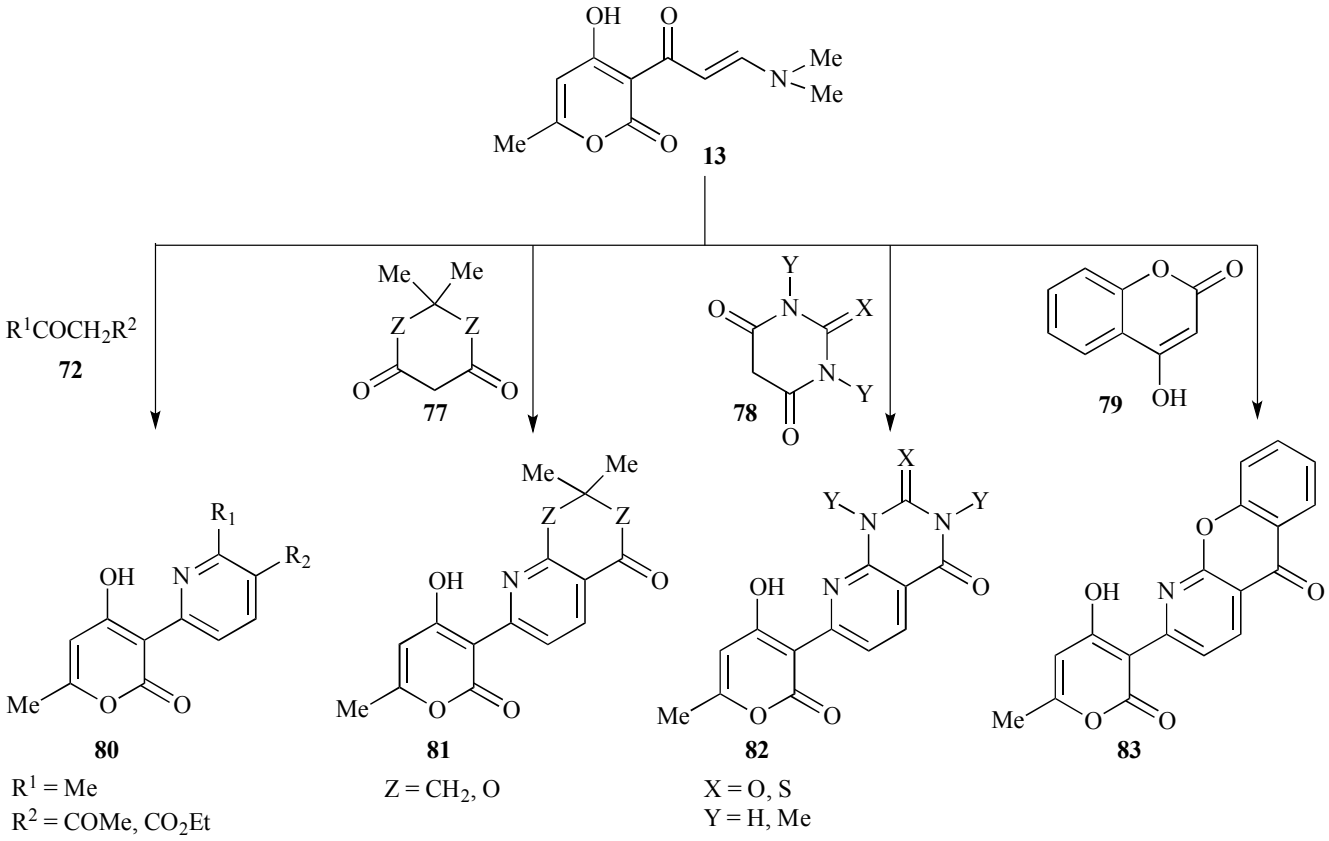
Scheme 20

A one pot multi-component simple, efficient, and green method for the synthesis of a variety of 2,4,6-trisubstituted pyridine derivatives **76** *via* an improved Hantzsch reaction of dehydroacetic acid **1** with aldehydes **23** and ammonium acetate catalyzed by small amount of ceric ammonium nitrate (CAN) in aqueous medium have been developed by Vedula *et al*. The reaction conditions are mild and gave excellent yields of products. This method does not involve the use of volatile organic solvents and thus, is an environment friendly process (**Scheme 21**).[41]

Siddiqui *et al*. also studied the reaction of *β*-enaminone **13** with active methylene compounds such as *β*-dicarbonyl compounds **72**, cyclic *β*-dicarbonyl compounds **77**, 2-substituted pyrimidinediones **78**, 4-hydroxy-2*H*-chromen-2-one **79** corresponding pyranylpyridine derivatives **80**, **81**, **82** and **83** were obtained in excellent yield (**Scheme 22**).[25]

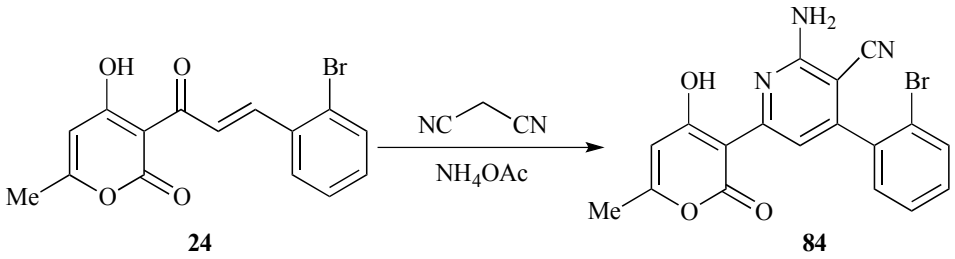


Scheme 21



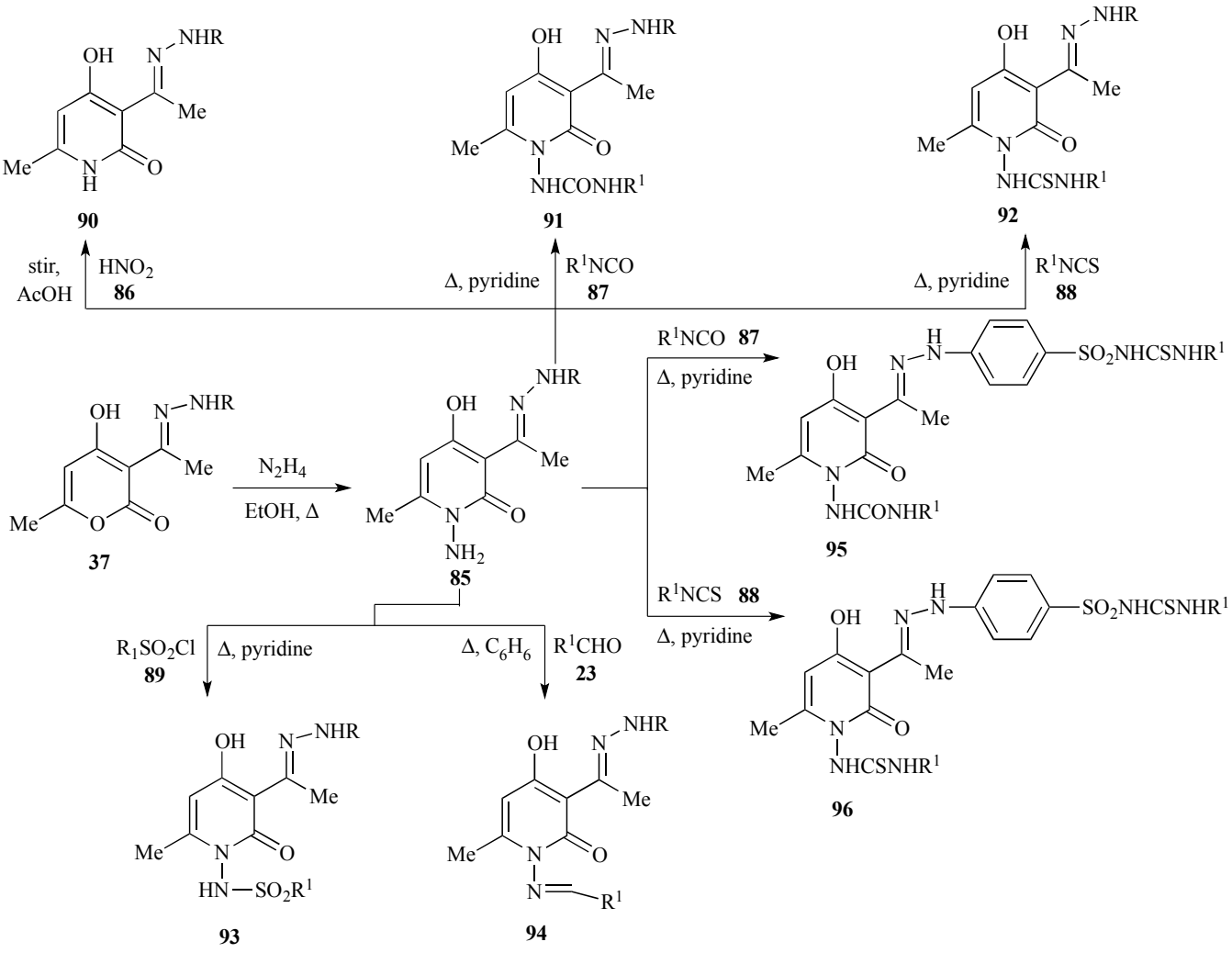
Scheme 22

A versatile synthetic route for the synthesis of 2-amino-4-(2-bromophenyl)-6-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)nicotinonitrile **84** was reported by the reaction of chalcone analogues of DHA **24** with malononitrile in the presence of ammonium acetate (**Scheme 23**).[23]



Scheme 23

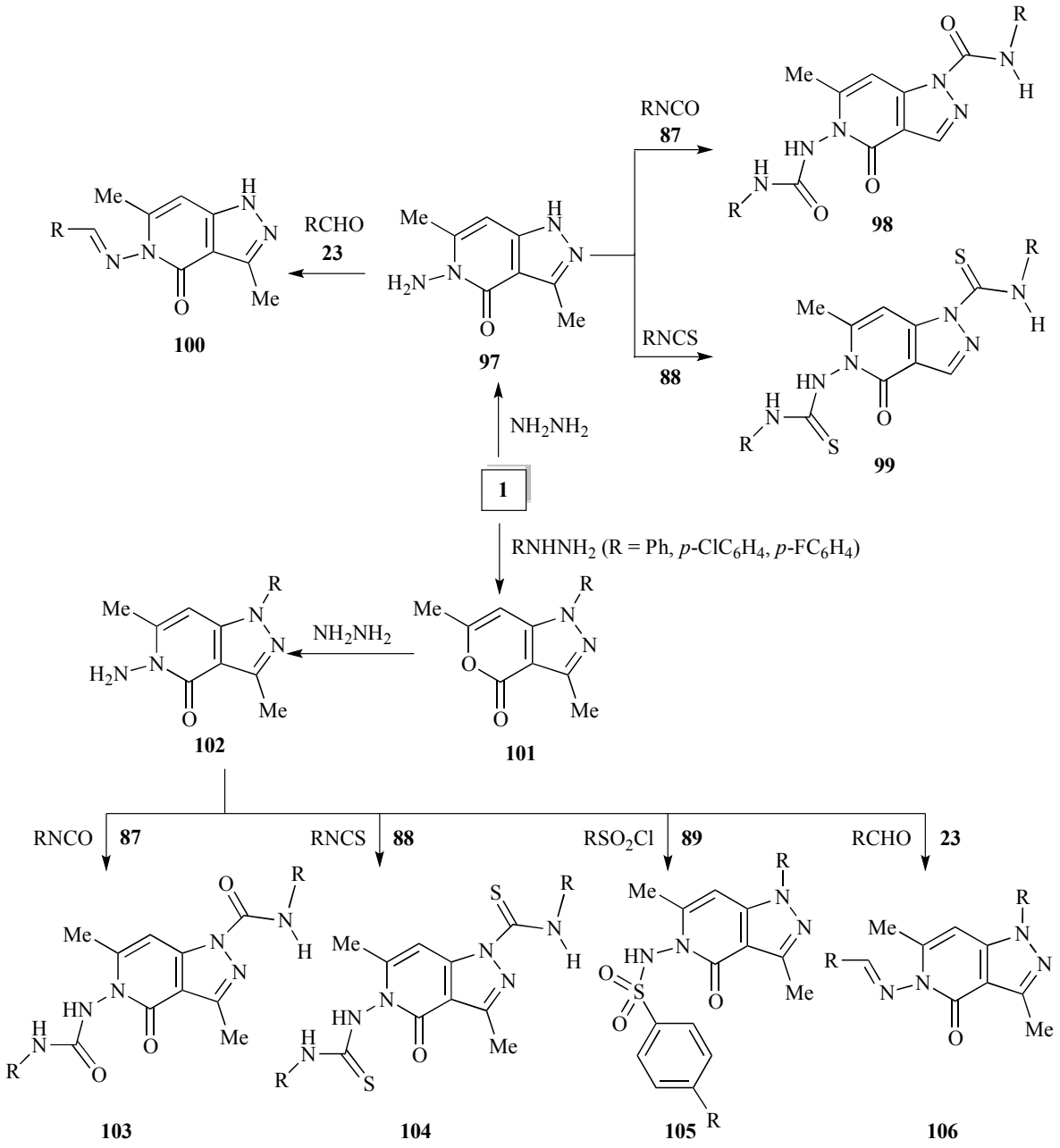
Faidallah *et al*. reported a novel series of 2-pyridone analogues **90**, **91**, **92**, **93**, **94**, **95** and **96** as antimycobacterial and antifungal agents. *N*-Aminopyridones **85**, the key precursor was synthesised by the reaction of *N*-substituted hydrazones of DHA **37** with hydrazine hydrate. Aminopyridone **85** on reaction with nitrous acid **86**, isocyanates **87**, isothiocyanates **88**, arylsulphonyl chlorides **89**, aromatic aldehydes **23** furnished corresponding 2-pyridinones **90**, 2-pyridoneureas **91**, 2-pyridonethioureas **92**,



Scheme 24

2-pyridonesulphonamides **93** and hydrazonopyridin-2-ones **94**. Interestingly, on prolonged heating, formation of diureas **95** and dithioureas **96** was observed *via* reaction of **85** with **87** and **88**, respectively (**Scheme 24**).[43]

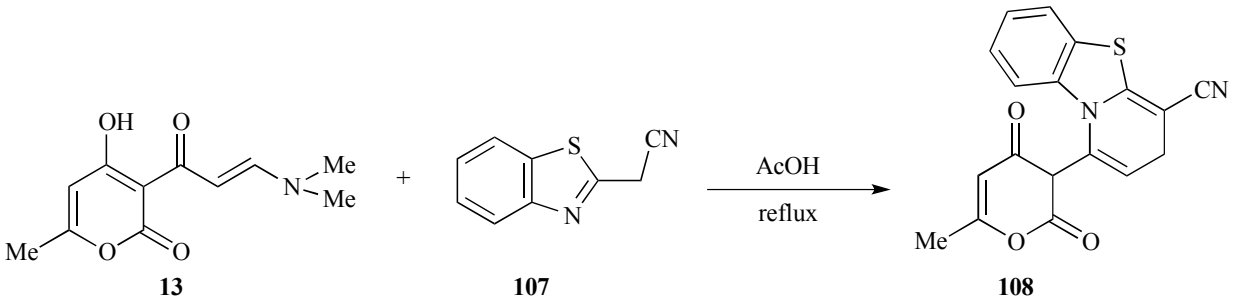
A novel series of polysubstituted fused pyrazolopyridones was synthesized to screen their synergistic effect on antimicrobial and anticancer activity. Reaction of DHA **1** with hydrazine hydrate in 1:2 ratio yielded *N*-aminopyrazolopyridone **97** which on treatment with isocynates **87**, isothiocyanates **88** and aldehydes **23** gave corresponding ureas **98**, thioureas **99**, arylidenes **100** whereas reaction of DHA **1** with



Scheme 25

aryl hydrazines in 1:1 ratio gave pyrazolopyrans **101** which furnished pyrazolopyridones **102** on treatment with hydrazine hydrate and the corresponding urea **103**, thiourea **104**, sulphonamide **105**, arylidene **106** derivatives were achieved *via* reaction of **102** with isocyanates **87**, isothiocyanates **88**, arylsulphonyl chlorides **89** and aldehydes **23** respectively (**Scheme 25**).[44]

A facile synthetic route to benzothiazolopyridinylpyrone **108** by exploring the reactivity of *β*-enaminone **13** derived from DHA towards 2-cyanomethylbenzothiazole **107** in refluxing glacial acetic acid was reported (**Scheme 26**).[24]

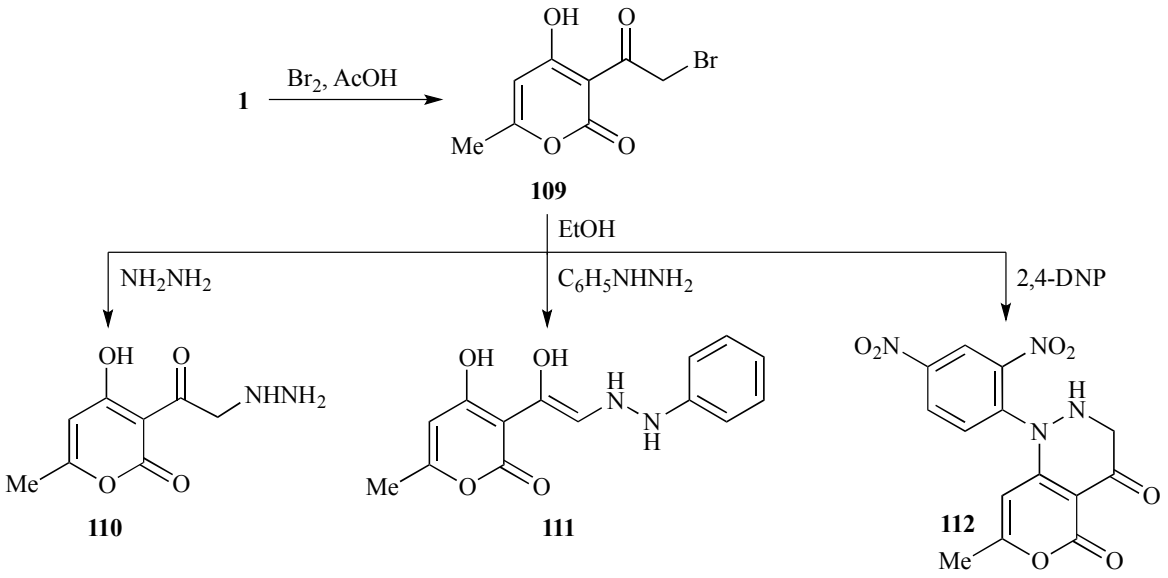


Scheme 26

A.5 SYNTHESIS OF SIX MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING TWO NITROGEN ATOMS

A.5.1 PYRIDAZINES

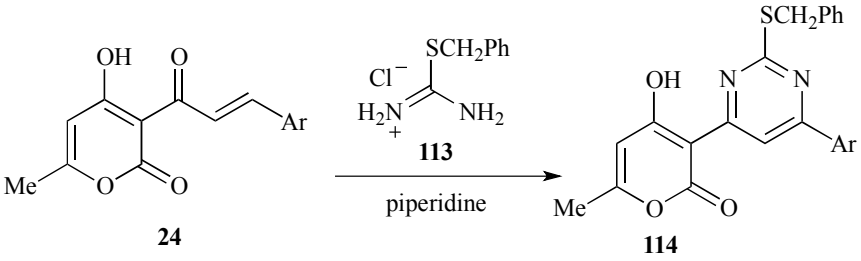
Under ethanol refluxing condition, reactivity of binucleophiles such as hydrazine hydrate, phenylhydrazine, 2,4-DNP was studied towards 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **109**, synthesized *via* bromination of DHA **1** in glacial acetic acid. Reaction of **109** with hydrazine hydrate and phenylhydrazine yielded 3-(2-hydrazinylacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **110** and 4-hydroxy-3-[1-hydroxy-2-(2-phenylhydrazinyl)vinyl]-6-methyl-2*H*-pyran-2-one **111** by elimination of one molecule of HBr, whereas reaction of **109** with 2,4-dinitrophenylhydrazine resulted into the formation of 1-(2,4-dinitrophenyl)-7-methyl-2,3-dihydro-1*H*-pyrano[4,3-*c*]pyridazine-4,5-dione **112**, through the generation of an unstable intermediate (analog of ketone form of **111**) which undergoes cyclocondensation to yield **112** (**Scheme 27**).[45]



Scheme 27

A.5.2 PYRIMIDINES

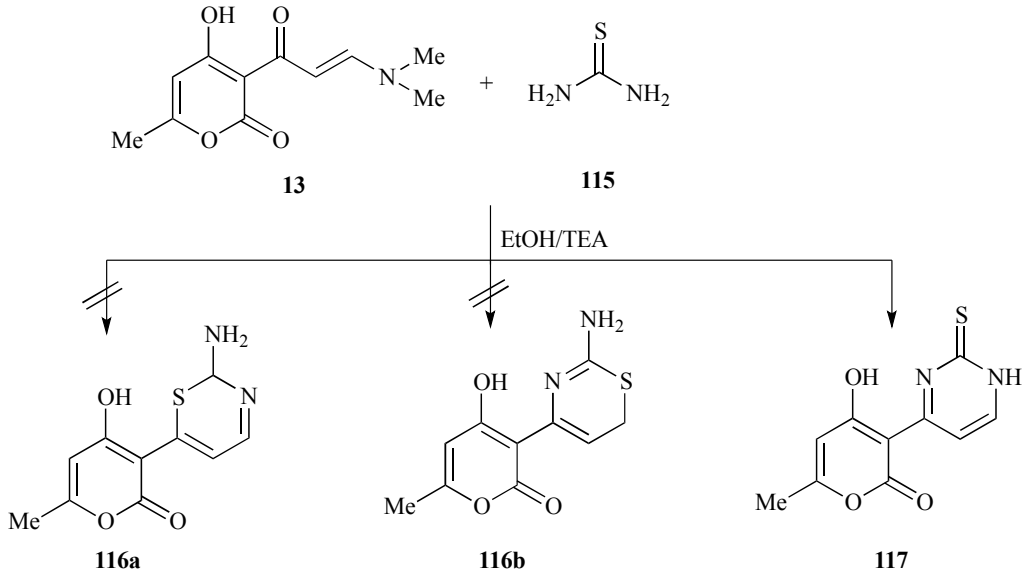
An easy access to a series of pyrimidines bearing a pyronyl side chain in the 4-position *i.e.* 6-substituted 4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-*S*-benzylthiopyrimidines **114** was achieved by the condensation of 3-cinnamyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyrans (chalcone analogues of DHA) **24** with *S*-benzylisothiouronium chloride (SBT) **113** in the presence of piperidine as a base and chloroform as solvent. Since the compound expected from the condensation of SBT with chalcones would be dihydropyrimidines, it was apparent that *in situ* oxidation of dihydropyrimidines had occurred (**Scheme 28**).[46]



Scheme 28

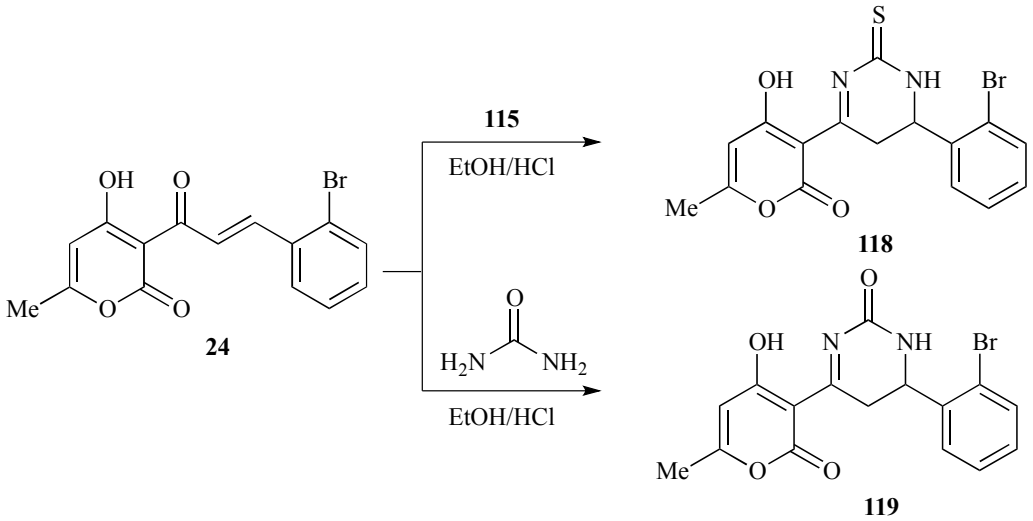
The site selectivity in cycloaddition was studied by the reaction of *β*-enaminone **13** with thiourea **115** with catalytic amount of triethylamine in refluxing ethanol. Out of the three possible isomeric cycloadducts **116a**, **116b** and **117**, pyrimidinethione **117** was obtained as an exclusive product. Confirmation of structure **117** was done on the basis of IR and ^{1}H NMR spectroscopy. The IR spectrum

showed absorption band at 1320 cm^{-1} corresponding to C=S and ^1H NMR exhibited two doublets at δ 5.30 and 6.30 ppm with coupling constant (J = 6.80 Hz) assignable to pyrimidine protons (**Scheme 29**).[24]



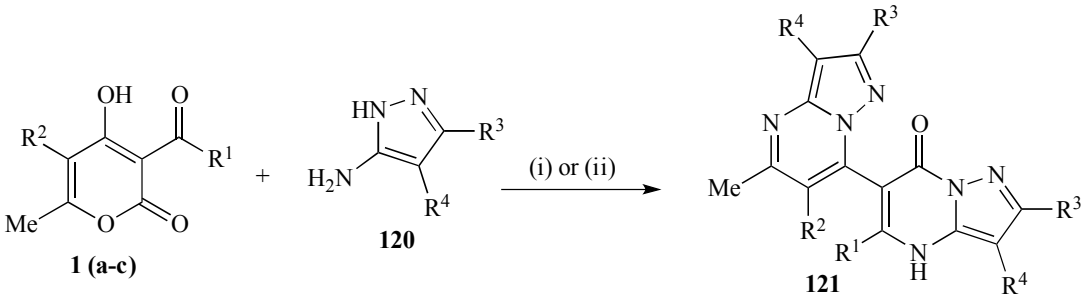
Scheme 29

DHA chalcone **24** was also choosen to confirm the selective nature of binucleophilic thiourea **115**. The reaction again resulted corresponding cycloadduct *i.e.* pyrimidinethione **118** and same results were obtained with urea as leading to the formation of **119** (**Scheme 30**).[23]



Scheme 30

In our laboratory, synthesis of novel bi(pyrazolo[1,5-*a*]pyrimidinyl)-7-ones **121** was reported by the reaction of 3- and/or 4-substituted 5-aminopyrazoles **120** with DHA analogues **1 (a-c)** in refluxing ethanol in 2:1 ratio as promising antibacterial agents (**Scheme 31**).[47]

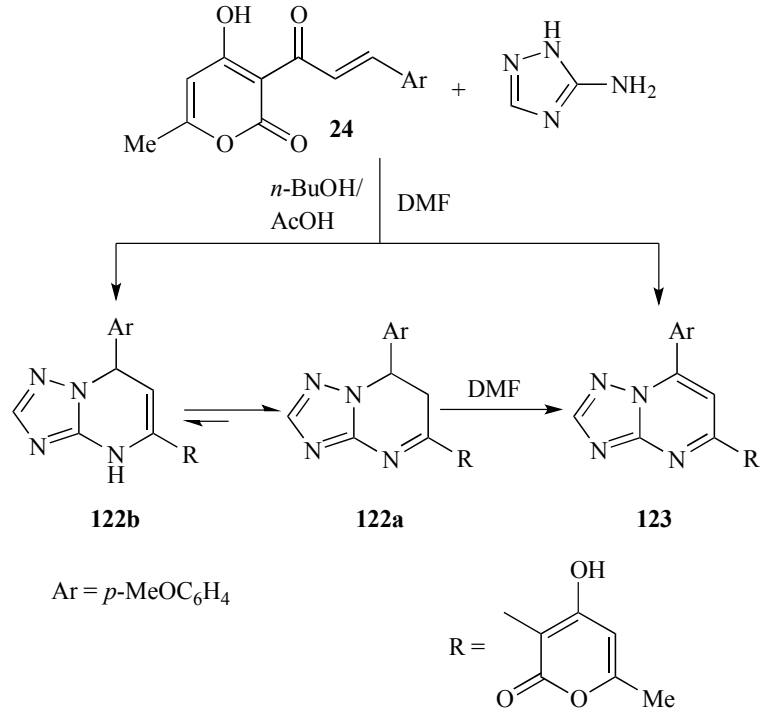


1 R^1, R^2 = (a) = Me, H; (b) = Me, Br; (c) = Et, H

(i) = EtOH, 6 h
(ii) = EtOH-AcOH, reflux, 5h

Scheme 31

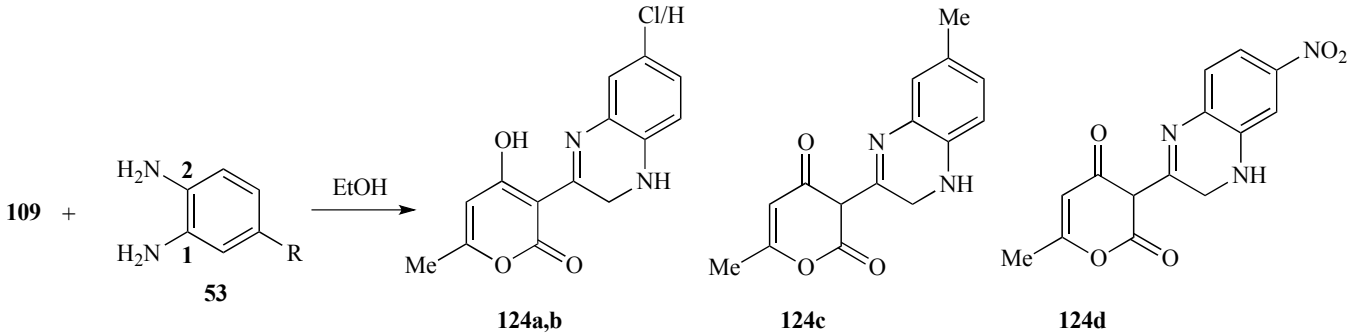
Roman *et al*. reported the synthesis of 5-(4-hydroxy-6-methylpyran-2-on-3-yl)-7-(4-methoxyphenyl)-6,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine **122** and 5-(4-hydroxy-6-methylpyran-2-on-3-yl)-7-(4-methoxyphenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine **123** *via* reaction of DHA chalcone **24** with aminoazole containing amidine fragment. They investigated the tautomeric equilibrium between **122a** and **122b**, spectroscopically which suggested the existence of **122** exclusively in **a** form (**Scheme 32**).[48]



Scheme 32

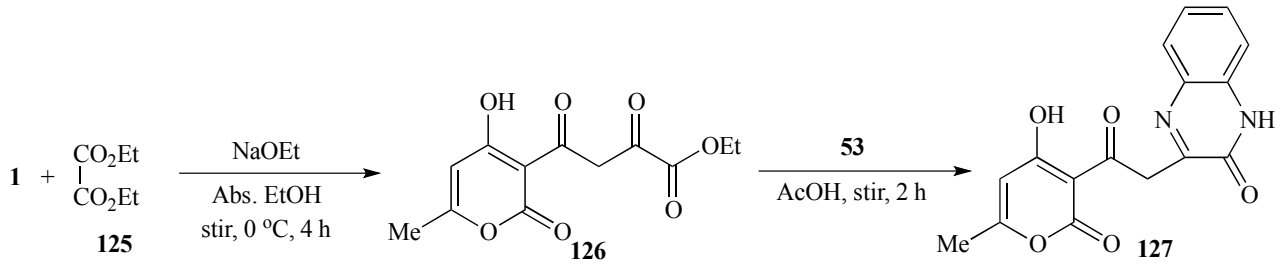
A.5.3 PYRAZINES

Djamila *et al*. reported the synthesis of benzopyrazines **124** (**a-d**) *via* reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **109** with *o*-phenylenediamines (*o*-PDAs) **53** bearing H, Cl, Me, SNO_2 as substituents, yielded in each case a single pure product. When an electron donating, *o*, *p*-directing, group (Cl, Me) is present, the 1-NH_2 reacts first whereas in case of electron withdrawing NO_2 group, a *m*-director, the 2-NH_2 group reacts first. Spectroscopic studies revealed the existence of pyranone ring in enolic form in compounds **124a**,**b** and keto form in compounds **124c**,**d** (**Scheme 33**).[45]



Scheme 33

A novel method for the synthesis of quinoxaline derivative **127** involves reaction of *o*-phenylenediamine (*o*-PDA) **53** with ethyl-4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2,4-dioxobutanoate **126** which in turn, was furnished *via* reaction of DHA **1** with diethyl oxalate **125** and sodium ethoxide at 0 °C in abs. ethanol (**Scheme 34**).[26]

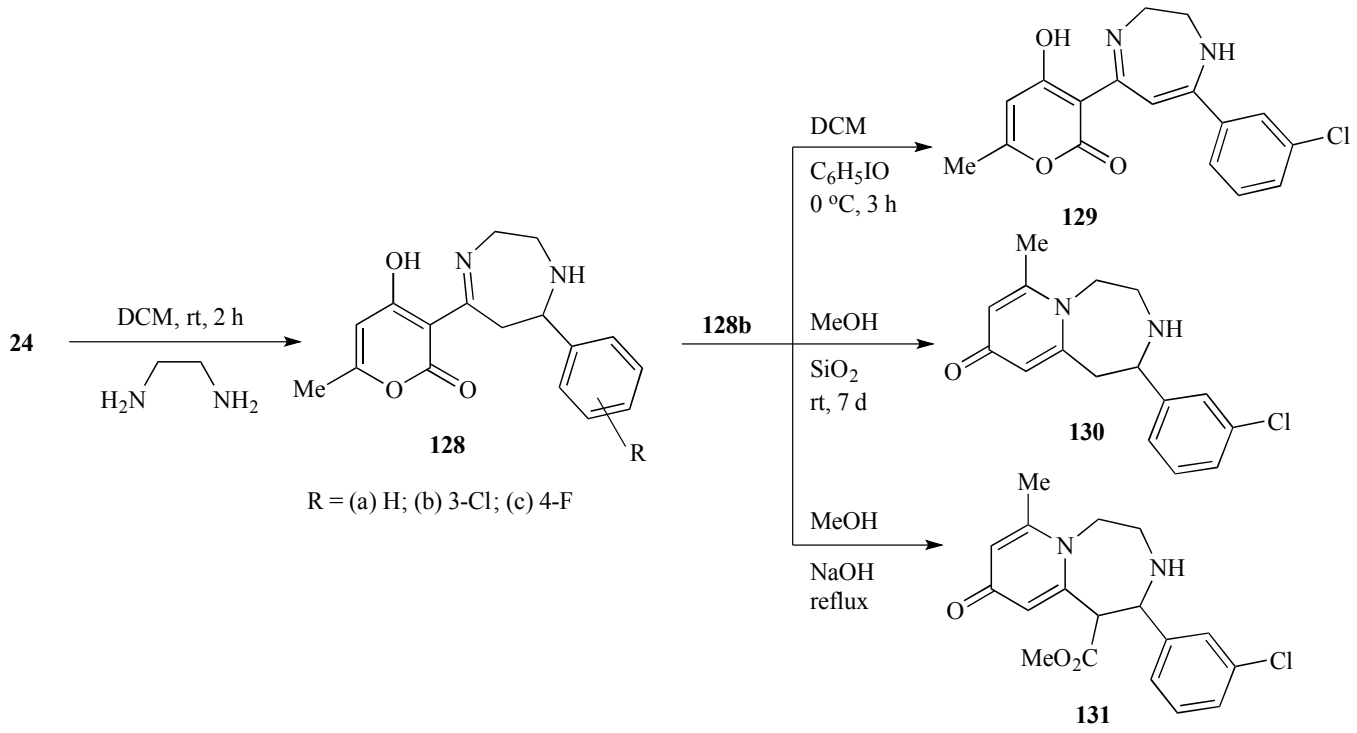


Scheme 34

A.6 SYNTHESIS OF SEVEN MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING TWO NITROGEN ATOMS

A.6.1 DIAZEPINES

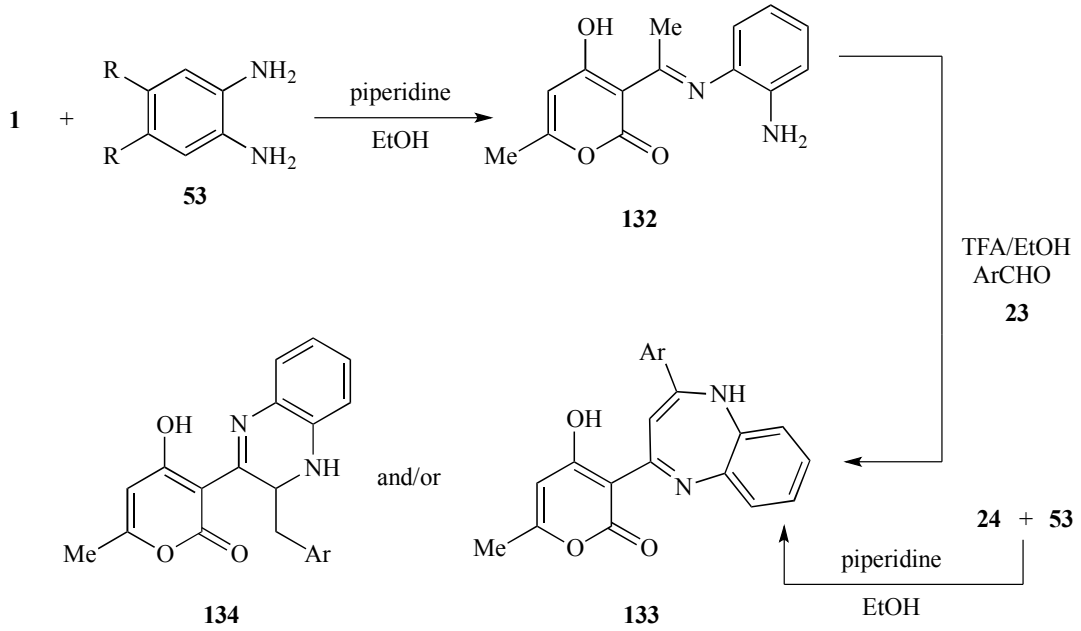
$GABA_A$ (γ-aminobutyric acid-A) receptor subunits α_1, α_2, α_3 and α_4 are unselectively affected by benzodiazepines. In this course, to test the selective affinity to $GABA_A$ receptor subtypes, 1,4-diazapine derivatives, were synthesized as potential agonist of benzodiazepine receptor by Briel *et al*. A series of tetrahydro-1*H*-1,4-diazepines **128a-c**, dihydro-1*H*-1,4-diazepine **129** and pyrido[1,2-*d*][1,4]diazepines **130** and **131** *via* a new synthetic approach was prepared with DHA chalcones **24** as substrate. Compound **128b** showed 34% and 45% inhibition, **129** showed similar and **130** showed little affinities to $GABA_A$ receptor subtypes $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\gamma_2$ respectively. On contrary, **130** displayed no affinity to $\alpha_1\beta_2\gamma_2$ and $\alpha_5\beta_3\gamma_2$ receptor subtypes (**Scheme 35**).[49]



Scheme 35

Tijou *et al*. reported that DHA **1**, on treatment with *o*-phenylenediamine **53** afforded the intermediate ketimine **132** which on reaction with various aromatic aldehydes **23** in ethanol in the presence of a catalytic amount of trifluoroacetic acid yielded the corresponding 1,5-benzodiazepines **133**. But in some cases, in addition to the expected 1,5-benzodiazepine **133**, a second compound of identical molecular formula, which sometimes is the major compound, 1,4-benzodiazines (3,4-dihydroquinoxalines) **134** has been obtained depending upon the structure of the aldehyde and to a lesser extent on the diamine.

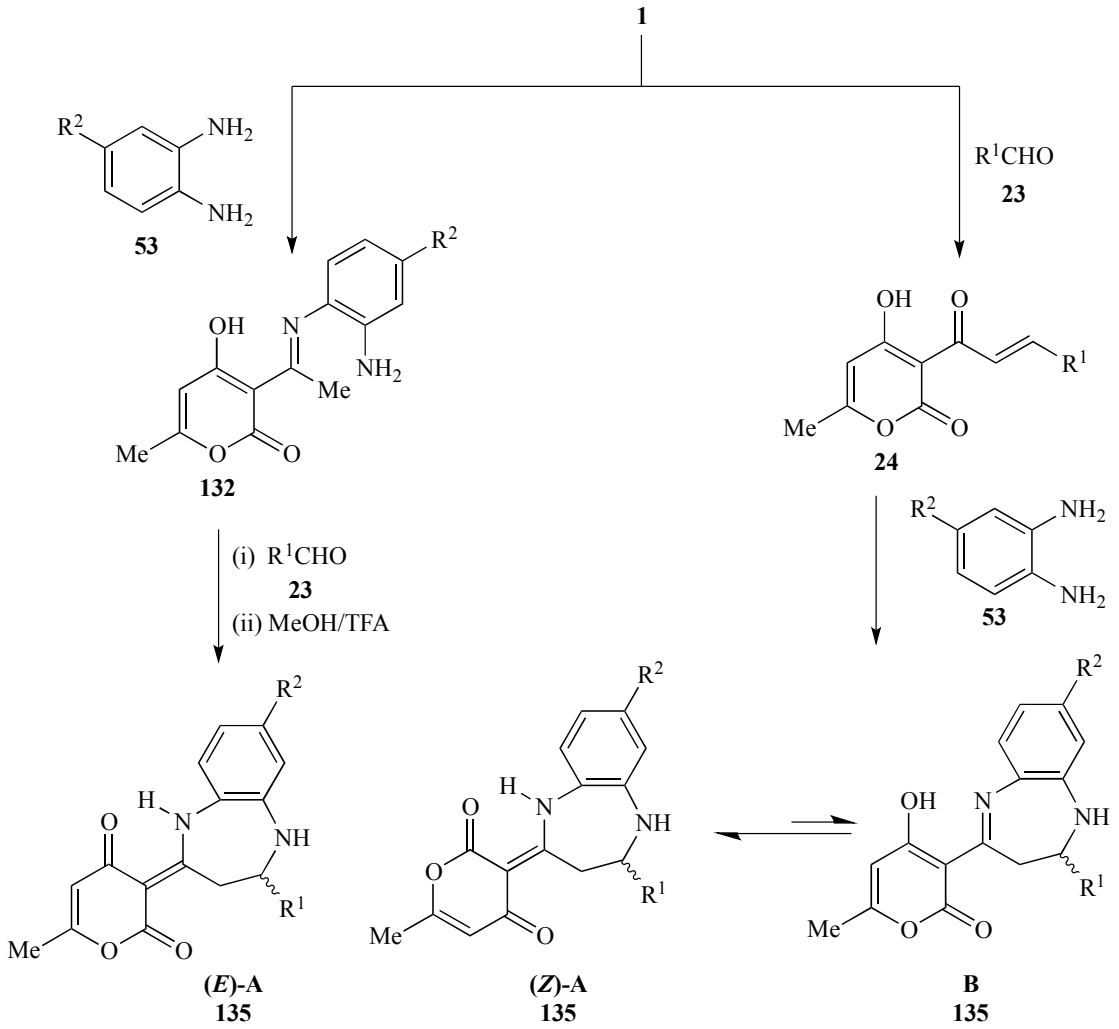
Synthesis of 3,4-dihydro-2-pyronyl-1,5-benzodiazepine derivatives **133** also, has been reported by the reaction of chalcone analogues of DHA **24** with *o*-phenylenediamine **53** (**Scheme 36**).[50,51,52]



R = H, Me, Cl; Ar = C_6H_5, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-$CF_3C_6H_4$, 2-pyridyl

Scheme 36

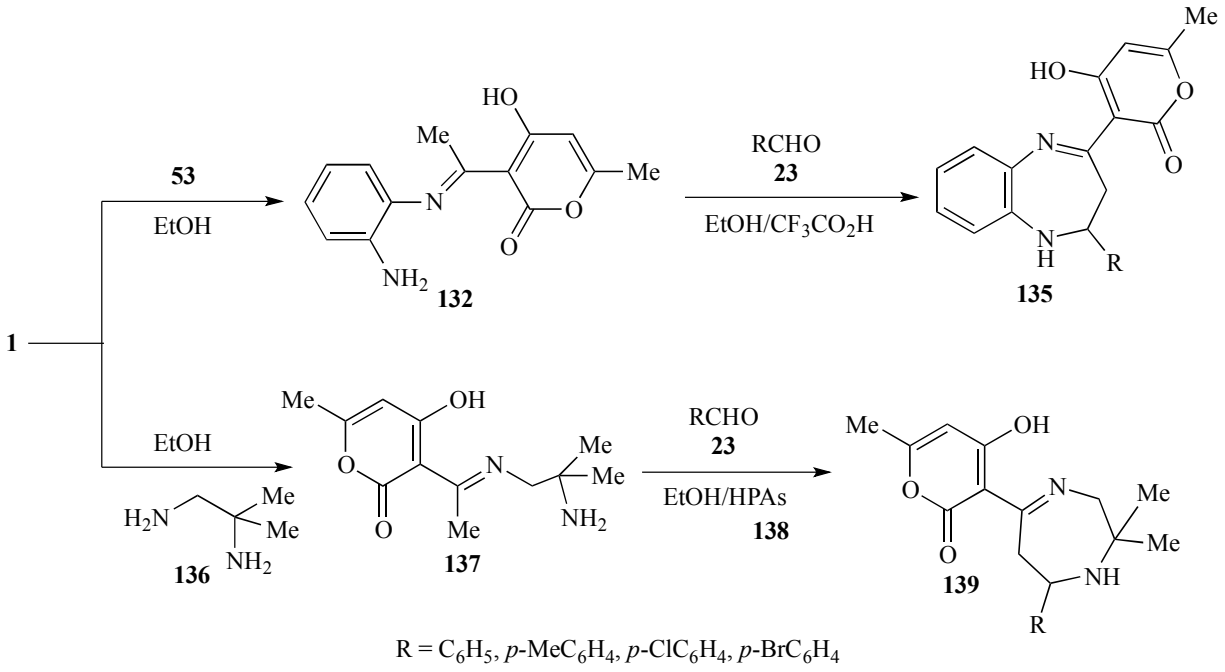
Synthesis of 1,5-benzodiazepines by the reaction of *o*-phenylenediamines (*o*-PDAs) **53** with dehydroacetic acid DHA **1** or conjugate analogues is largely reported in the literature, but still with uncontrolled stereochemistry. Rabahi *et al*. carried out a comprehensive mechanistic study on the formation of 1,5-benzodiazepine **135** following different organic routes and the structure was established based on liquid-state 2D NMR, single-crystal X-ray diffraction and theoretical calculations allowing the classification of two prototropic forms **135A** (enaminopyrane-2,4-dione) and **135B** (imino-4-hydroxypyran-2-one). Evidences were presented to show that most of the reported 1,5-benzodiazepine **135** structures arising from DHA and derivatives preferentially adopt the (*E*)-enaminopyrane-2,4-diones **135A** (**Scheme 37**).[53]



R^1 = styryl, *o*-hydroxyphenyl; R^2 = H, Me

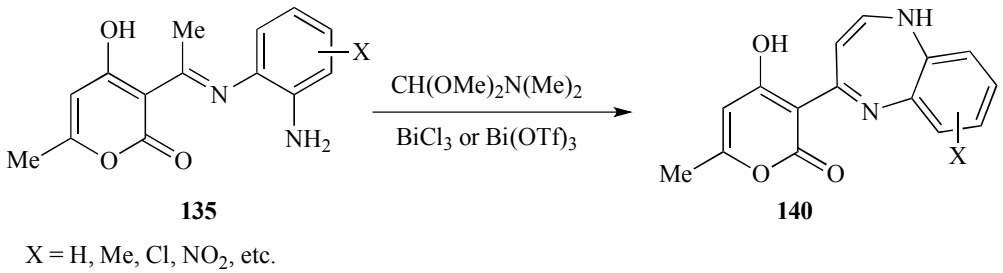
Scheme 37

A series of Keggin type heteropolyacids (HPAs) e.g. $H_3PW_{12}O_{14}$ and $H_{3+x}PMo_{12-x}V_xO_{40}$ with x = 0-3, in comparision to CF_3CO_2H, as catalyst was tested to develop an efficient and improved method with high yield and short reaction time for the synthesis of diazepines, because of the bifunctional character of HPAs *i.e.* strong bronsted acidity and high oxidative power. Synthesis of 1,5-benzodiazepine **135** and 1,4-diazepine **139** derivatives was undertaken by reaction of ketimine intermediates **132** and **137**, obtained by the reaction of DHA **1** with *o*-phenylenediamine (*o*-PDA) **53** and 1,3-aminomethylpropane **136**, with various aldehydes. The order of efficiency of catalyst followed the sequence: $H_5PMo_{10}V_2O_{40}$ > $H_6PMo_9V_3O_{40}$ > $H_4PMo_{11}VO_{40}$ > $H_3PMo_{12}O_{40}$ > $H_3PW_{12}O_{40}$. The best catalytic performance was attributed to $H_5PMo_{10}V_2O_{40}$ catalyst and selected for the synthesis of benzodiazepine and diazepine rings (**Scheme 38**).[54]



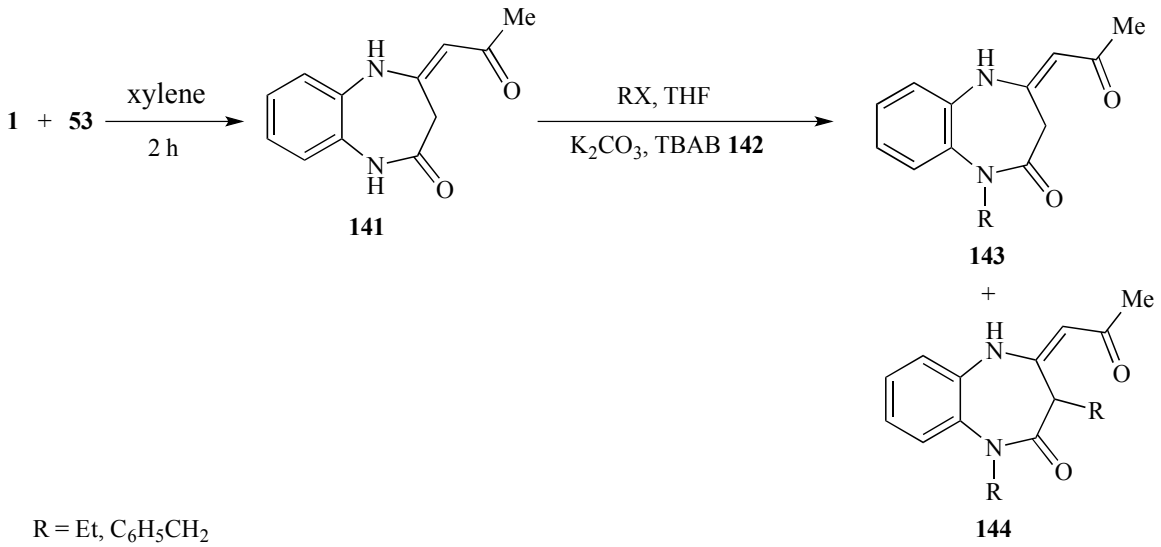
Scheme 38

A new heterocyclization method for the synthesis of benzodiazepine derivatives **140** have been developed by reaction of ketimine derivatives **135** with *N,N*-dimethylformamide dimethyl acetal in the presence of bismuth triflate or bismuth chloride (**Scheme 39**).[55]



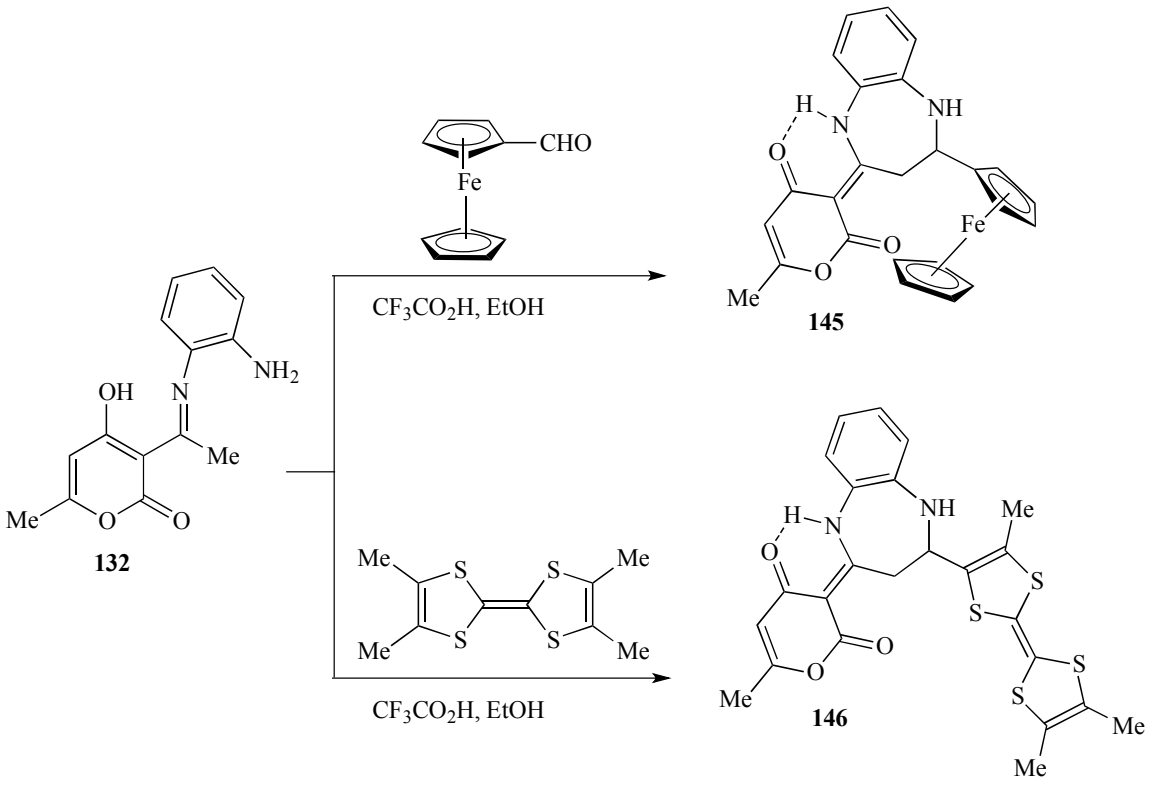
Scheme 39

Interestingly, refluxing DHA **1** with *o*-PDA **53** in xylene led to the formation of 4-(2-oxopropylidene)-1,5-benzodiazipin-2-one **141** rather than formation of ketimine intermediate as reported by Mohamed *et al*. Alkylation of **141** with an appropriate alkylating agent in the presence of phase-transfer catalyst (PTC), tetra-*n*-butylammonium bromide (TBAB) **142**, at room temperature led to the formation of isomeric alkylated products **143**, **144**. Psychotropic investigation of resulted compounds showed non-toxic and sedative effect on central nervous system (**Scheme 40**).[56]



Scheme 40

A simple and compatible approach for the synthesis of a series of electroactive 1,5-benzodiazepines **145** and **146** bearing the electroactive moiety, either a ferrocene or tetrathiafulvalene core, has been developed *via* reaction of ketimine intermediate **132** with ferrocene carboxaldehyde and trimethyltetrathiafulvalene carboxaldehyde respectively, with catalytic amount of trifluoroacetic acid. The electron donating ability of these redox active 1,5-benzodiazepines has also been studied together with their molecular structures



Scheme 41

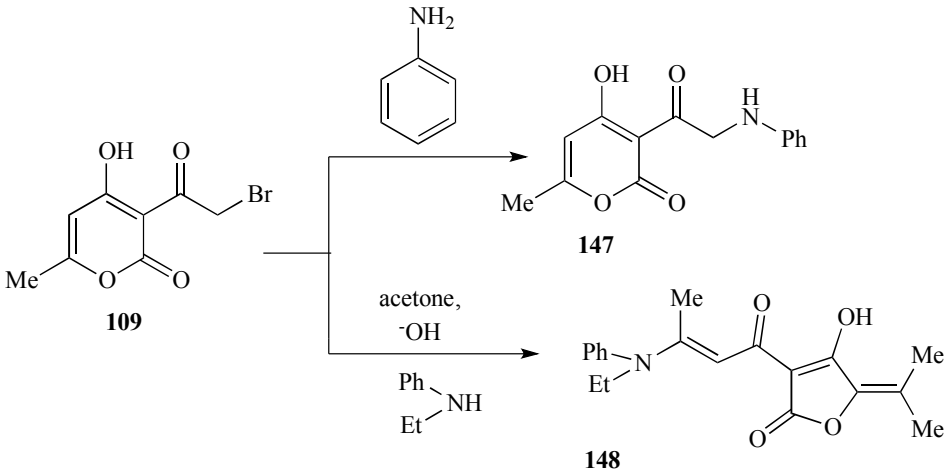
by X-ray diffraction. The results of latter revealed that the diazepine rings adopt the enamine form due to intramolecular hydrogen bonding between the N-H of the enamine and the carbonyl of DHA. All the synthesized benzodiazepines has been found to exhibit reversible oxidation processes at low oxidation potentials, due to the presence of the electrophore tetrathiafulvalene or ferrocene (**Scheme 41**).[57]

B. SYNTHESIS OF HETEROCYCLIC COMPOUNDS CONTAINING OXYGEN ATOM

B.1 SYNTHESIS OF FIVE MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING ONE OXYGEN ATOM

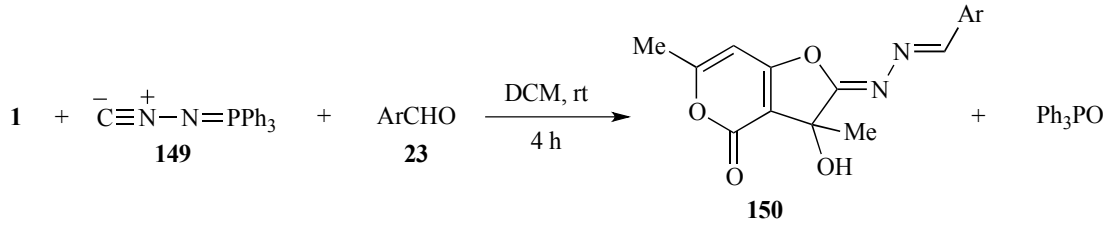
B.1.1 FURANS

Briel *et al*. reported the efficient conversion of 3-bromoacetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **109** to furan with amines and the reaction was highly influenced by the type of amine. In contrast to aniline, where a dehydroacetic acid derivative **147** was obtained, utilization of phenylethylamine in acetone gave a rearrangement-reaction and yielded substituted furan-2-one **148**, butenolides system, as an important nucleus present in natural products (**Scheme 42**).[58]



Scheme 42

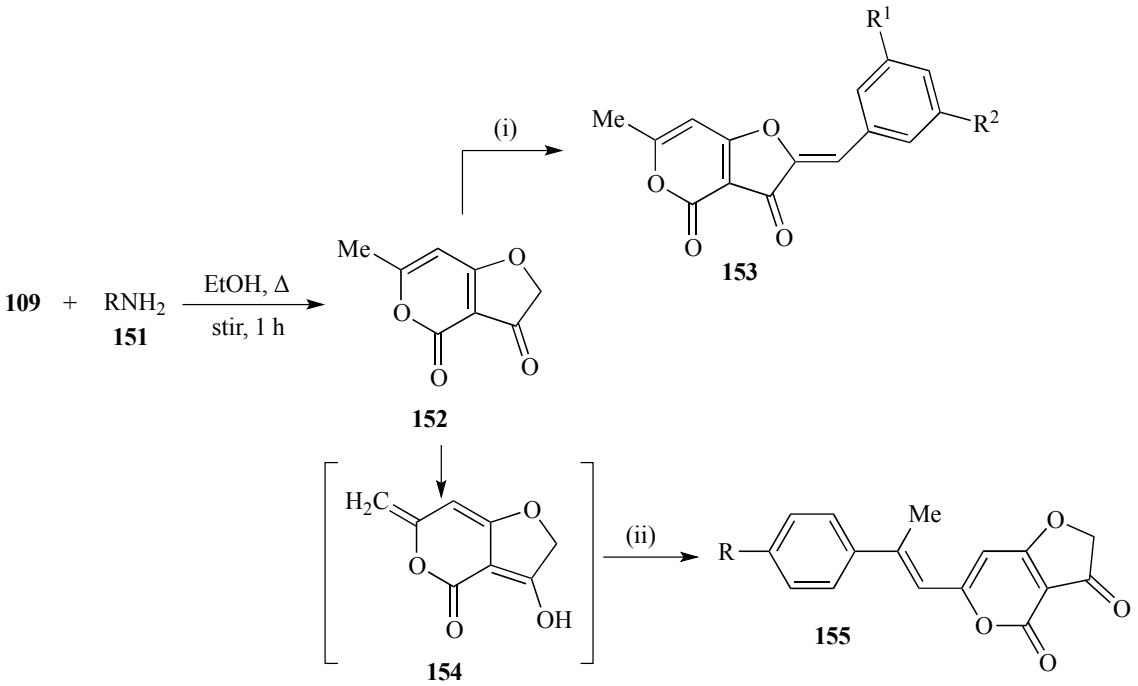
Adib *et al*. reported a simple synthesis of 2-hydrazinylidene-3-hydroxy-4*H*-furo[3,2-*c*]pyran-4-ones **150** by 1:1:1 addition reaction of dehydroacetic acid **1**, (isocyanoimino)(triphenyl)phosphorane **149** and an aromatic aldehyde **23** under mild conditions (**Scheme 43**).[59]



Ar = *p*-$NO_2C_6H_4$, *p*-FC_6H_4, *m*-ClC_6H_4, *m*-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_4$, furan-2-yl

Scheme 43

Djamila *et al*. have reported a facile condensation reaction of 6-methyl-4*H*-furo[3,2-*c*]pyrane-3,4-dione **152**, obtained from the intramolecular cyclocondensation of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **109** assisted by aliphatic amines **151**, with benzaldehydes and acetophenones leading to the formation of novel 2-arylidene-6-methyl-2*H*-furo[3,2-*c*]pyrane-3,4-diones **153** and 6-(2-arylprop-1-enyl)-2*H*-furo[3,2-*c*]pyrane-3,4-diones **155**. Route followed for the synthesis of **155** proceed *via* formation of an unstable intermediate **154** (**Scheme 44**).[60]



151 R = Me, Et, Bu, Hex
153 R^1, R^2 = (a) H, H; (b) OMe, H; (c) Cl, H; (d) Br, H; (e) NO_2, H; (f) H, NO_2
155 R = (a) H; (b) Br

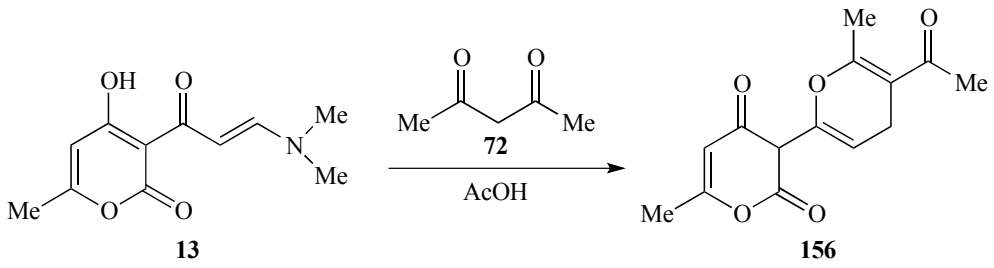
Reagents and conditions: (i) = aromatic aldehydes, HCl/AcOH, reflux 3 h
(i i) = acetophenones, HCl/AcOH, reflux 1 h

Scheme 44

B.2 SYNTHESIS OF SIX MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING ONE OXYGEN ATOM

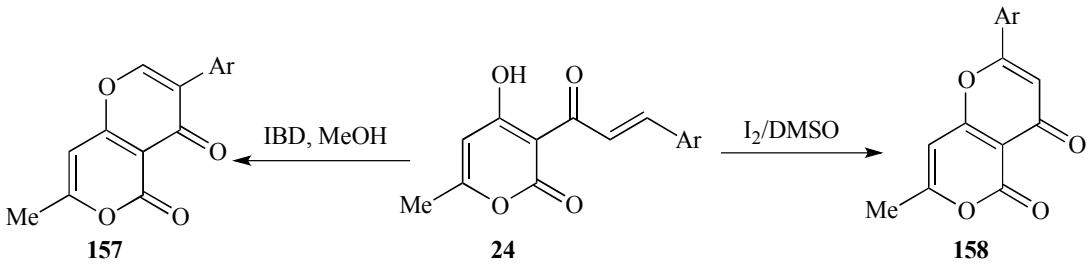
B.2.1 PYRANS

The reactivity of DHA *β*-enaminone **13** towards C-nucleophile, having an active methylene group was studied by Fadda *et al*. The reaction of **13** with acetylacetone **72**, as a C,O-binucleophile, in glacial acetic acid proceeded *via* addition of an active methylene group of acetylacetone to the activated double bond in the *β*-enaminone **13** to give a cyclic non-isolable intermediate which underwent intramolecular cyclization to form 3-(5-acetyl-6-methyl-4*H*-pyran-2-yl)-6-methyl-3*H*-pyrane-2,4-dione **156** (**Scheme 45**).[24]



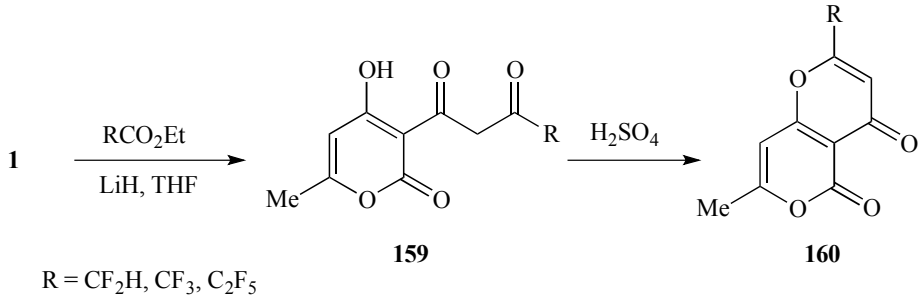
Scheme 45

A novel and convenient route to the synthesis of 3-aryl-7-methylpyrano[4,3-*b*]pyrane-4*H*,5*H*-diones (isoflavone analogues of DHA) **157** *via* the oxidative cyclization of chalcone analogues of DHA **24** has been reported using IBD as an oxidising agent. Interestingly, Prakash *et al* reported the reaction of **24** with I_2/DMSO instead of IBD, resulting into an efficient and facile one step synthesis of regioisomeric 2-aryl-7-methylpyrano[4,3-*b*]pyrane-4*H*,5*H*-diones (flavone analogues of DHA) **158** (**Scheme 46**).[61,62]



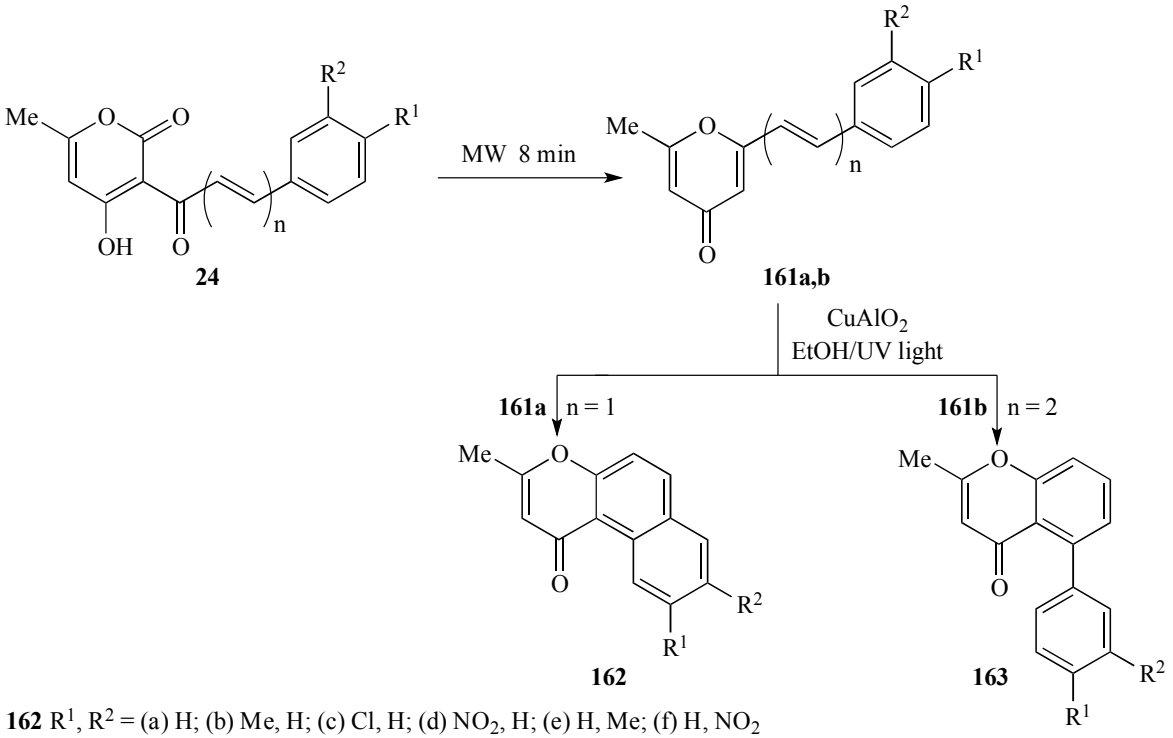
Scheme 46

Synthesis of fluorinated 7-methylpyrano[4,3-*b*]pyrane-4*H*,5*H*-diones **160** has been reported by the cyclization of 3-acetoacetyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyran **159** in the presence of conc. H_2SO_4. 3-Acetoacetyl-4-hydroxy-6-methyl-2-oxo-2*H*-pyran **159**, was obtained by the Claisen condensation of DHA with fluorinated esters in the presence of LiH in THF (**Scheme 47**).[63]



Scheme 47

Nabila *et al*. reported an efficient and novel synthetic method of benzo[*f*]chromen-1-ones **162** and phenyl-4*H*-chromen-4-ones **163** using delafossite catalyst ($CuAlO_2$) through photooxidative cyclization of 6-[2-arylvinyl]-4*H*-pyran-4-ones **161a** (n = 1) and 6-[4-phenylbuta-1,3-dien-1-yl]-4*H*-pyran-4-one **161b** (n = 2) which in turn, were furnished *via* microwave irradiation, hydrolysation and decarboxylation of chalcone analogues of DHA **24** (**Scheme 48**).[64]

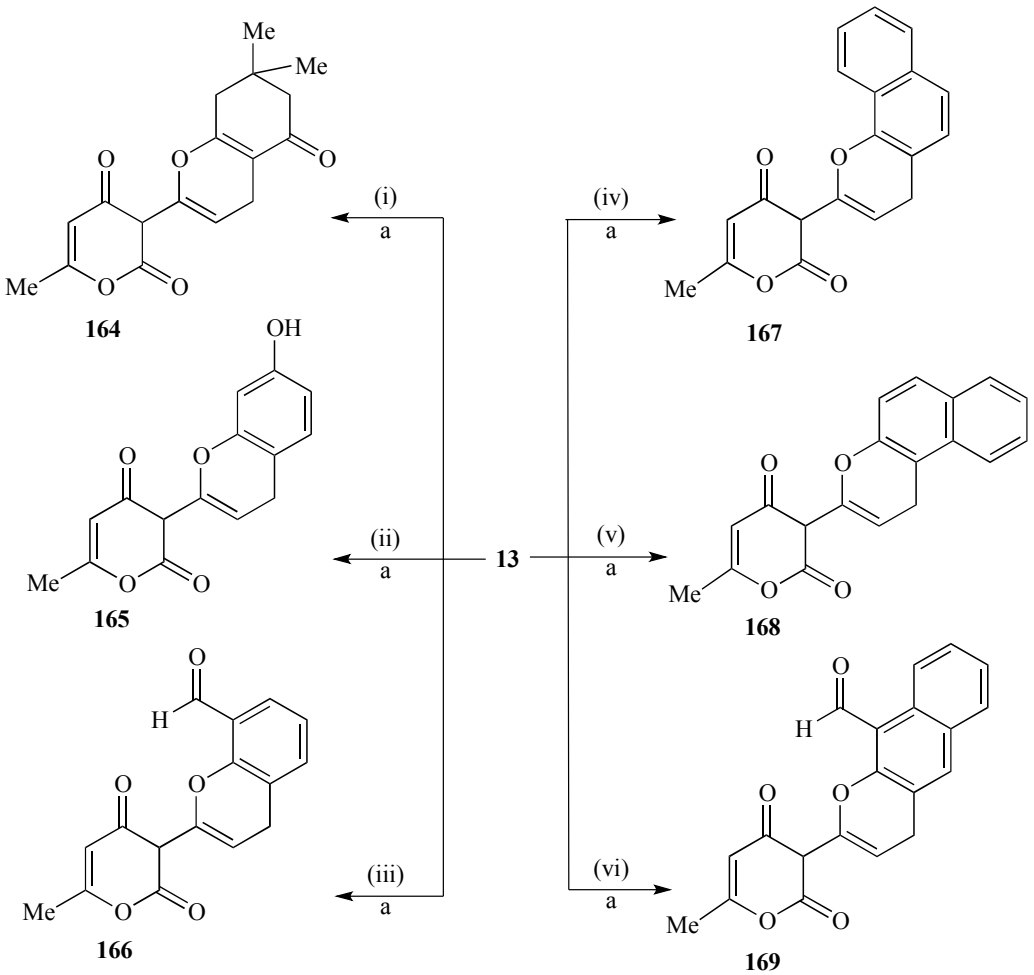


162 R^1, R^2 = (a) H; (b) Me, H; (c) Cl, H; (d) NO_2, H; (e) H, Me; (f) H, NO_2
163 R^1, R^2 = H

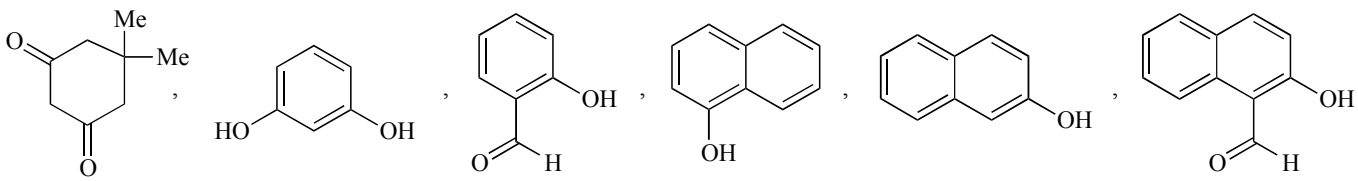
Scheme 48

Fadda *et al*. reported an efficient synthetic methodology allowing a simple introduction of a plethora of substituents into the structure of *β*-enaminone **13** and attracting attention due to its high reactivity as building blocks for the preparation of coumarin derivatives named chromen **164**, **165**, **166** and benzochromen **167**, **168**, **169** when subjected to react with N and C-nucleophiles such as dimedone (i),

resorcinol (ii), salicylaldehyde (iii) and α-naphthol (iv), β-naphthol (v), 2-hydroxy-1-naphthaldehyde (vi) respectively. All the synthesized compounds were screened for their antimicrobial activity. Incorporation of 2-pyrone ring to the chromen nucleus at position-3 showed good antimicrobial activity against Gram-positive bacteria in compound **166** and enhanced activity in compounds **167**, **168** due to the polynuclear heterocyclic system whereas **164** showed moderate antimicrobial activity because of the positive inductive effect of the two methyl groups attached to the tetrahydrochromen ring (**Scheme 49**).[24]



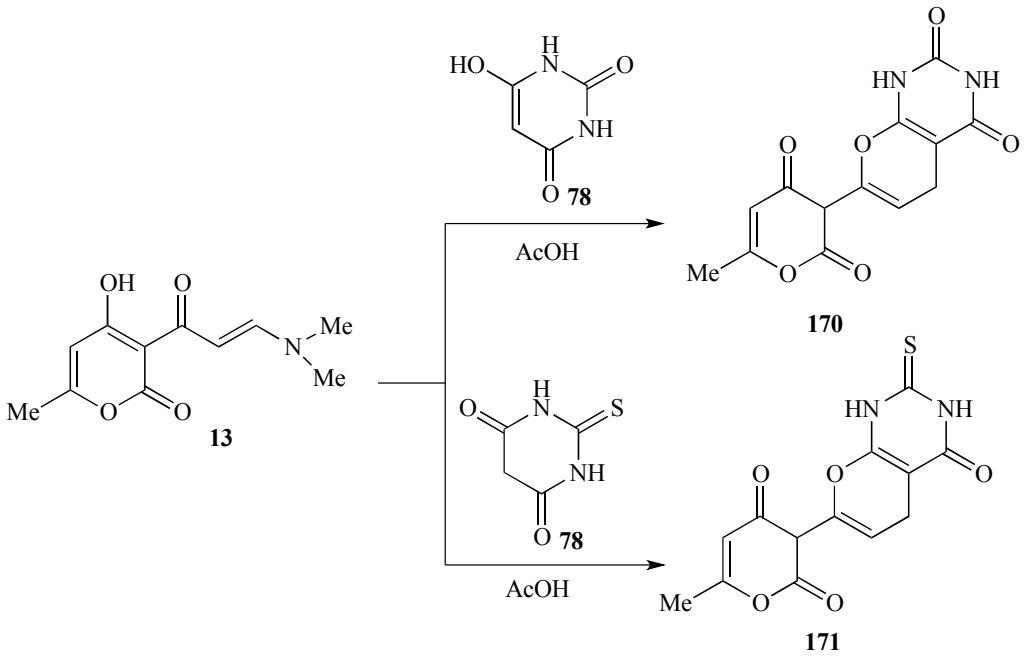
Reagents and reaction conditions: a = AcOH



(i) (ii) (iii) (iv) (v) (vi)

Scheme 49

Similar study was undertaken involving cyclocondensation of *β*-enaminone **13** towards an active active methylene group as a constituent of heterocyclic ring e.g. barbituric acid **78** and thiobarbituric acid **78** in glacial acetic acid which afforded the respective pyrano[2,3-*d*]pyrimidines *i.e.* 7-(6-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyran-3-yl)-1*H*-pyrano[2,3-*d*]pyrimidine **170** and 6-methyl-3-(4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidin-7-yl)-2*H*-pyrane-2,4(3*H*)-dione **171**. Compound **171** was found to be equipotent to chloramphenicol (reference drug) in inhibiting the growth of *Bacillus subtilis* and *Bacillus thuringinesis* (Gram-positive bacteria) (**Scheme 50**).[24]



Scheme 50

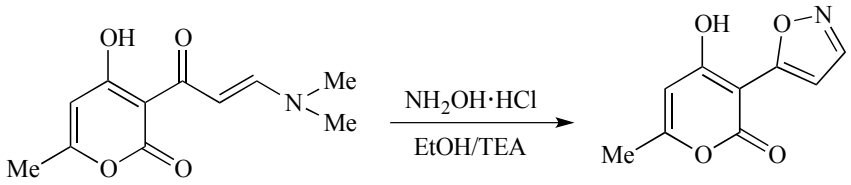
C. SYNTHESIS OF HETEROCYCLIC COMPOUNDS CONTAINING TWO HETEROATOMS

C.1 SYNTHESIS OF FIVE MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN AND OXYGEN ATOMS

C.1.1 ISOXAZOLES

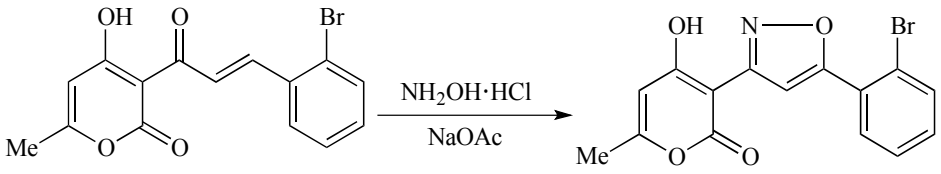
Synthesis of an orange colour compound identified as 3-(isoxazol-5-yl)-6-methyl-2*H*-pyrane-2,4-dione **172** was achieved by the treatment of *β*-enaminone **13** with hydroxylamine hydrochloride in refluxing ethanol with a catalytic amount of triethylamine (**Scheme 51**).[24]

DHA chalcone **24** was also used for the synthesis of 3-(5-(2-bromophenyl)isoxazol-3-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **173** by treating with hydroxylamine hydrochloride and sodium acetate under refluxing ethanol (**Scheme 52**).[23]



13 172

Scheme 51



24 173

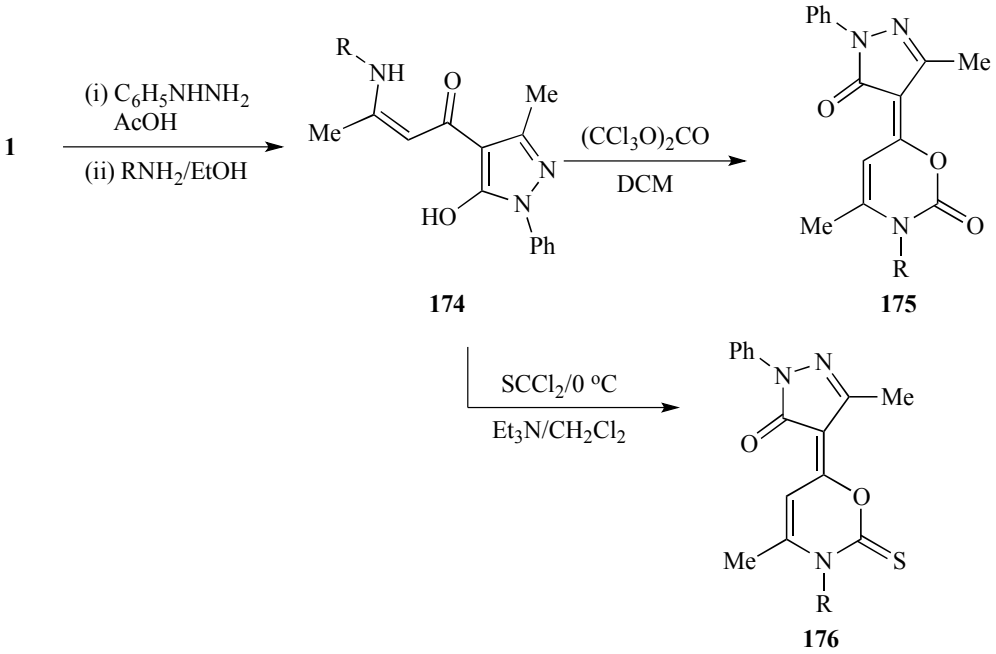
Scheme 52

C.2 SYNTHESIS OF SIX MEMBERED HETEROCYCLIC COMPOUNDS CONTAININGNITROGEN AND OXYGEN ATOMS

C.2.1 OXAZINES

Benaamane *et al*. reported the reaction of DHA with phenylhydrazine followed by reaction with amines to form pyrazolo-enaminones **174** which upon further cyclization with triphosgene in dichloromethane in the presence of triethylamine afforded *N*-substituted pyrazolooxazin-2-ones **175**. Further study was carried out by synthesizing a series of *N*-Substituted [phenylpyrazolo]oxazine-2-thiones **176** by the reaction of pyrazolylenaminone **174** with thiophosgene in presence of triethylamineas COX-LOX inhibitors and influence of the replacement of the oxo-group of *N*-substituted [pyrazolo]oxazin-2-ones **175** with thioxo-group on the COX inhibition activity has also been studied. The study revealed that the substitution of the oxygen of the oxo-group of the oxazin-2-one ring by sulphur resulted in a four to over ten-fold improvement of COX and LOX inhibitory action (**Scheme 53**).[65,66]

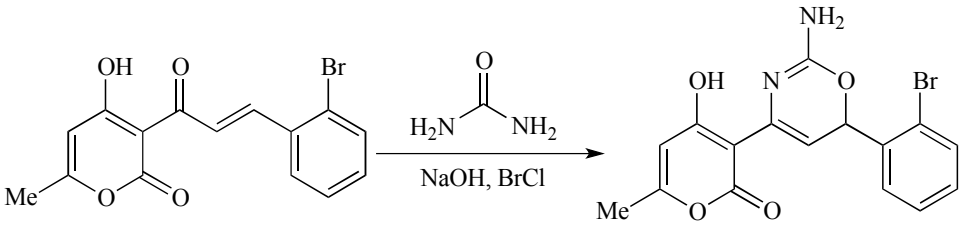
Synthesis of 3-(2-amino-6-(2-bromophenyl)-6*H*-1,3-oxazin-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **177** was achieved by investigating the reactivity of DHA chalcone **24** towards binucleophile, urea, in basic medium whereas in acidic medium, the reactivity of **24** towards urea changed leading to the formation of pyrimidine ring **119** instead of oxazine ring (**Scheme 54**).[23]



174 175 176

R = Et, *n*-C_4H_9, $(Me)_2CH_2CH$, $CH_2C_6H_5$, C_6H_5, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$MeO_2CC_6H_4$, 2-thienyl

Scheme 53



24 177

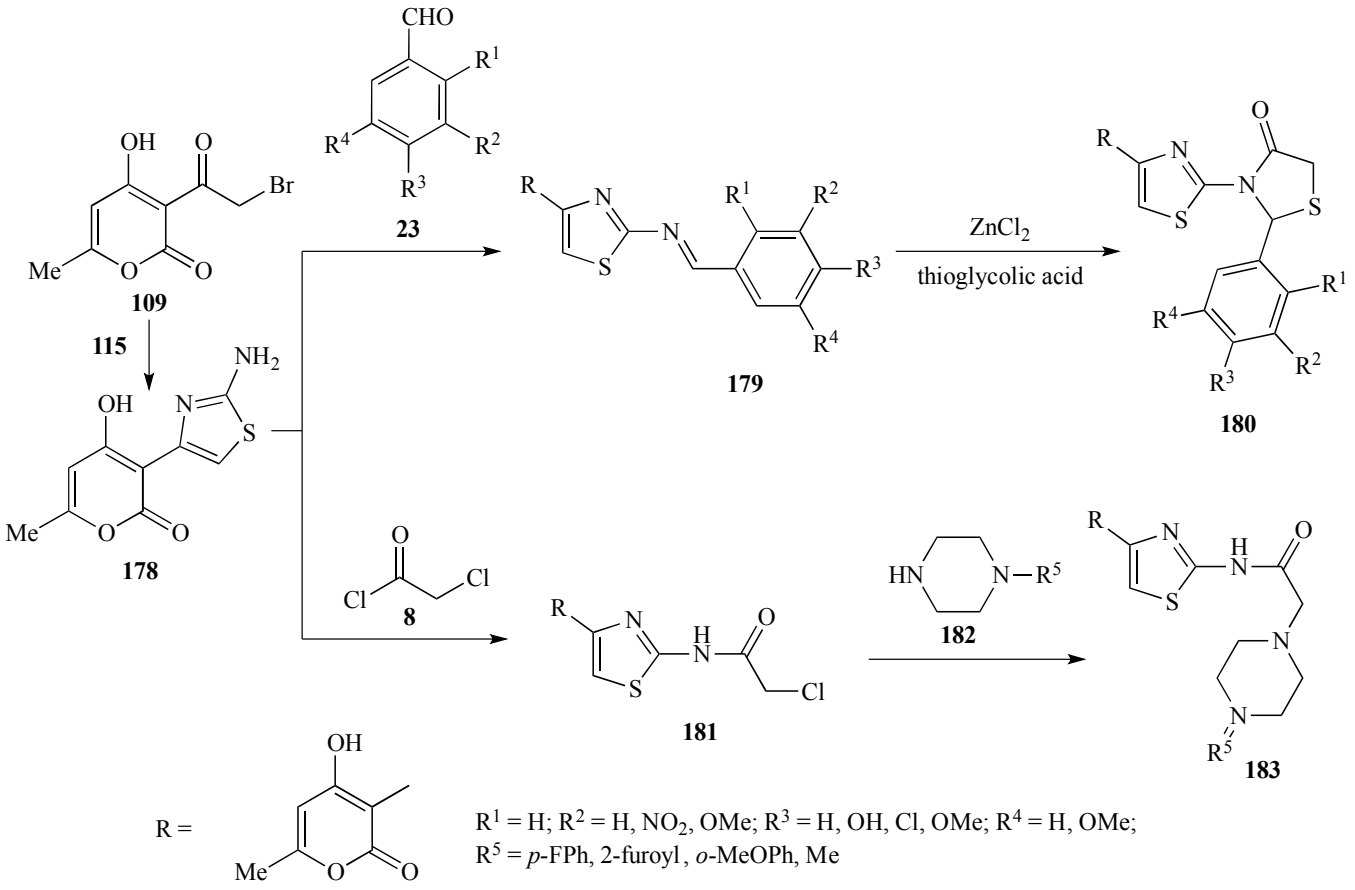
Scheme 54

C.3 SYNTHESIS OF FIVE MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN AND SULPHUR ATOMS

C.3.1 THIAZOLES

Synthesis of a series of novel pyran scaffolds of thiazolidin-4-one and piperazine as potent bi-heterocyclic molecules has been reported by Swamy *et al*. The intermediate, 2-amino-1,3-thiazol-4-yl-2*H*-pyran-2-one **178**, was synthesized by condensation of **109** with thiourea **115**. The reaction of **178** with different aromatic aldehydes **23** yielded substituted Schiff's base derivatives **179**. The cyclization of Schiff's base derivatives **179** in the presence of thioglycolic acid with a pinch of zinc chloride afforded 2,3-[4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-1,3-thiazol-2-yl]-1,3-thiazolidin-4-ones **180**. The

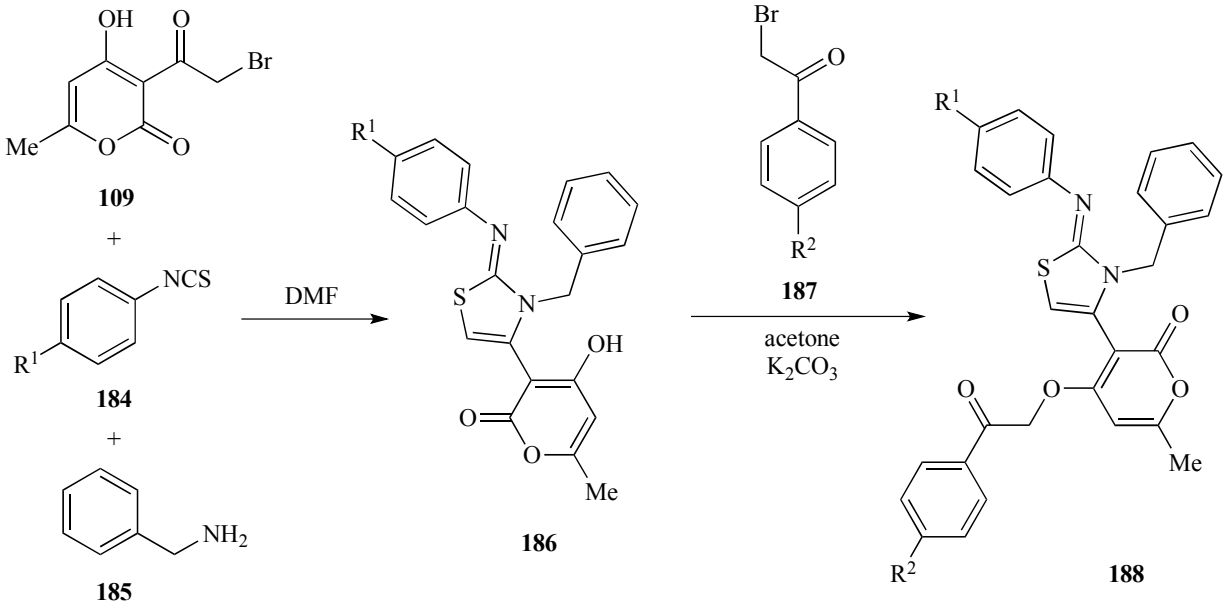
intermediate **178** was also treated with chloroacetyl chloride **8** to give **181** followed by reaction with substituted piperazine **182** to afford piperazine derivatives **183** (**Scheme 55**).[67]



Scheme 55

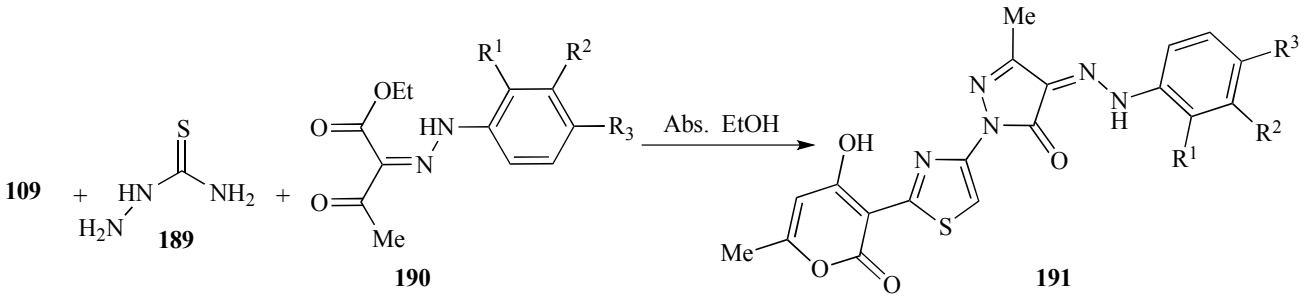
Vedula *et al*. reported an easy, highly efficient and convenient one pot, two-step approach for the synthesis of 3-(3-benzyl-2-(phenylimino)-2,3-dihydrothiazol-4-yl)-6-methyl-4-(2-oxo-2-phenylethoxy)-3,4-dihydro-2*H*-pyran-2-ones **188** from 3-(3-benzyl-2-(phenylimino)-2,3-dihydrothiazol-4-yl)-4-hydroxy-6-methyl-3,4-dihydro-2*H*-pyran-2-ones **186** and *α*-bromoketones **187**. The compounds **186** were synthesized by a multi-component reaction between **109**, substituted isothiocyanatobenzene **184** and benzylamine **185** in dimethylformamide (**Scheme 56**).[68]

A novel one pot synthesis of 4-(2-arylhydrazono)-1-(4-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)thiazol-2-yl)-3-methyl-1*H*-pyrazol-5(4*H*)-one **191** by the multi-component reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **109** with thiosemicarbazide **189** and ethyl 2-(2-arylhydrazono)-3-oxobutanoates **190** in absolute ethanol has been reported (**Scheme 57**).[69]



R^1 = H, Me; R^2 = H, OMe, Cl, Br, NO_2, C_6H_5

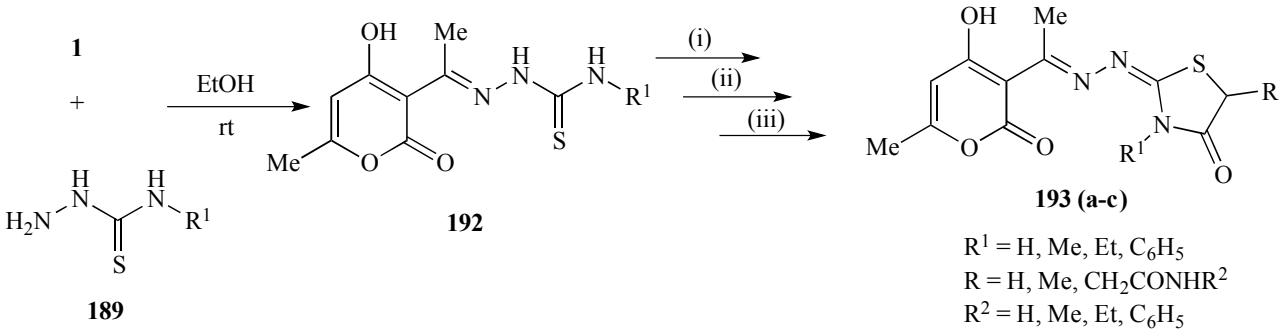
Scheme 56



R^1 = H, Me, NO_2, OMe, CO_2H; R^2 = H, NO_2, OMe; R^3 = H, Me, NO_2, OMe

Scheme 57

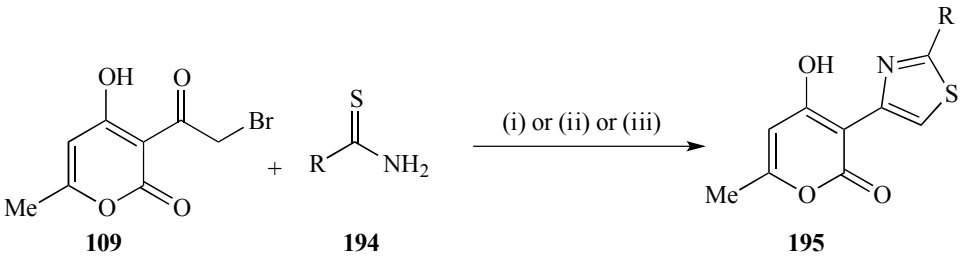
A series of thiosemicarbazones **192** and 4-thiazolidinones **193 (a-c)** were synthesized and evaluated for their *in vitro* antimicrobial activity. Condensation of dehydroacetic acid **1** with thiosemicarbazide **189** in ethanol at room temperature yielded the thiosemicarbazones **192**. These compounds were exploited to synthesize the 4-thiazolidinones **193a** *via* their reactions with ethyl 2-bromopropionate. Derivatives **193b** were prepared by reaction of the thiosemicarbazones with phenyl bromoacetate. The 4-thiazolidinones **193c** were obtained by treatment of compound **192** with maleimide derivatives in refluxing ethanol, under sulphuric acid catalysis (**Scheme 58**).[70]



Reagents and conditions:
(i) ethyl 2-bromopropionate, 3 eq. AcONa anhydrous, conc. H_2SO_4 or 0.12% of keggin heteropolyacid ($H_3PW_{12}O_{40}$, nH_2O), MeCN, reflux;
(ii) phenyl bromoacetate, 3 eq. AcONa anhydrous, conc. H_2SO_4, MeCN, reflux.;
(iii) MeCN, H_2SO_4, maleimide derivatives, reflux

Scheme 58

Novel 4-hydroxy-6-methyl-3-(2-substituted-thiazol-4-yl)-2*H*-pyran-2-ones **195** have been prepared from the reaction of **109** with thioamides, thiourea, and diphenylthiocarbazone **194** using three methods. The conventional Hantzsch reaction, microwave assisted and an alternative source of heating, the solvent free reaction conditions in the presence of neutral aluminium oxide. The three methods yielded the same solid compounds. The main advantage of microwave irradiation was the shortening of the reaction time, from 5 h in the case of conventional method to 5-10 minutes by microwave assisted (**Scheme 59**).[60]

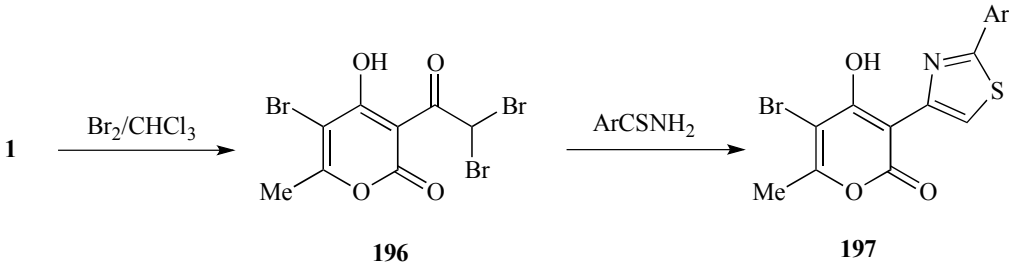


R = Me, NH_2, $NHNH_2$, $CSNH_2$, $N{=}NC_6H_5$

Reagents and conditions: (i) EtOH, reflux, 4-6 h; (ii) EtOH, microwave irradiation, 5-10 min; (iii) solvent free, solid support of neutral aluminium oxide, microwave irradiation, 5-10 min

Scheme 59

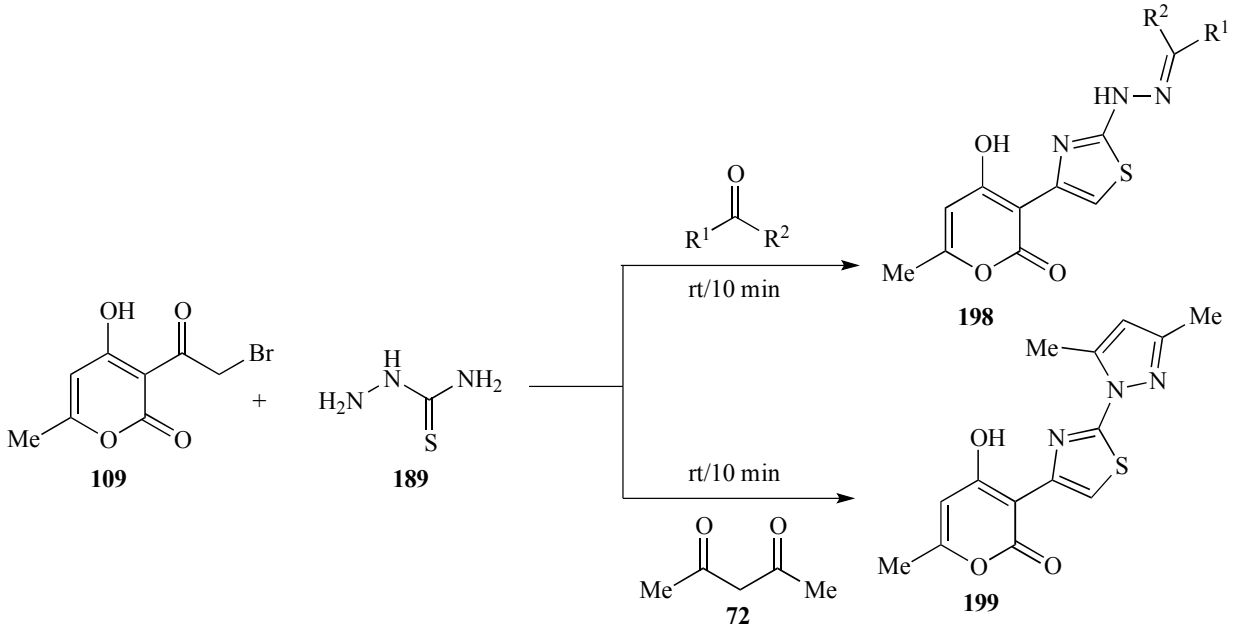
A novel synthesis of pyranylthiazoles **197** was reported from our laboratory involving the reaction of, non-lachrymatory 5-bromo-3-(2,2-dibromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **196**, furnished by the treatment of three equivalents of bromine with DHA **1** at 0 °C, with various thioamides and thioureas. The advantage of using 2,2-dibromo-DHA derivative **196** involves short reaction time, mild reaction condition, high yield and easy isolation of product (**Scheme 60**).[71-73]



Ar = C_6H_5, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4

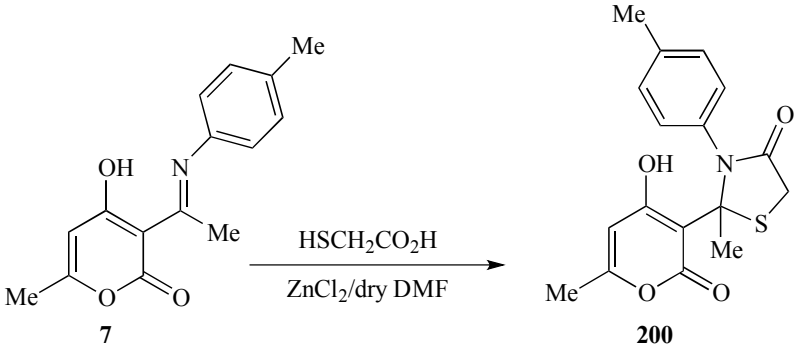
Scheme 60

Santhosh *et al*. reported a facile one pot method for the synthesis of 4-hydroxy-3-[2-(*N*'-substituted-hydrazino)thiazol-4-yl]-6-methylpyran-2-ones **198** and 4-hydroxy-6-methyl-3-[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)thiazol-4-yl]-2*H*-pyran-2-one **199** *via* multi-component reaction of **109**, with thiosemicarbazide **189** and *α*-ketones or acetylacetone **72** (**Scheme 61**).[74]



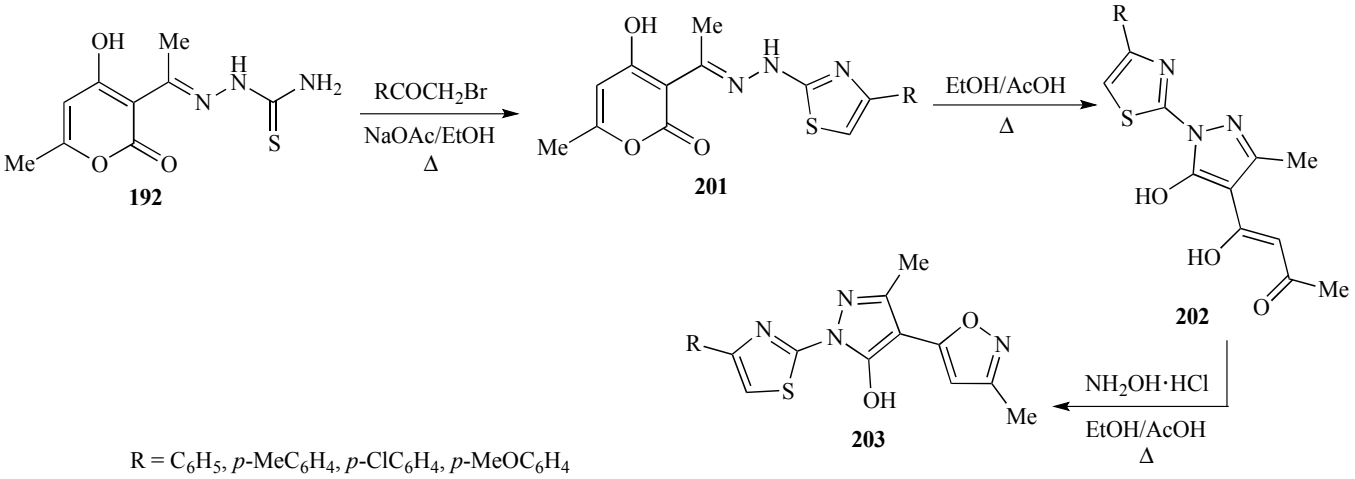
Scheme 61

It has been reported that azomethenes **7** provided an efficient route for the synthesis of 2-(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)-2-methyl-3-*p*-tolylthiazolidin-4-one **200** by the reaction of **7** with thioglycolic acid in the presence of Lewis acid catalyst (anhydrous $ZnCl_2$) and dry DMF (**Scheme 62**).[23]



Scheme 62

A series of 1-(4-(4-substituted-phenyl)thiazol-2-yl)-3-methyl-4-(3-methylisoxazol-5-yl)-1*H*-pyrazol-5-ols **203** was synthesized by multi-step process. Thiosemicarbazone **192** on reaction with *α*-bromoketones yielded thiazolyl hydrazones **201** which give rise to 1-(5-hydroxy-3-methyl-1-substituted-pyrazol-4-yl)-1,3-butanediones **202** in ethanol-acetic acid. Subsequent reaction of **202** with hydroxylamine yielded title compound **203** (**Scheme 63**).[75]

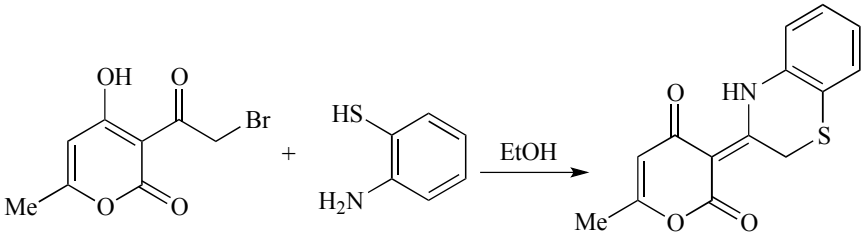


Scheme 63

C.4 SYNTHESIS OF SIX AND SEVEN MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN AND SULPHUR ATOMS

C.4.1 THIAZINES AND THIAZEPINES

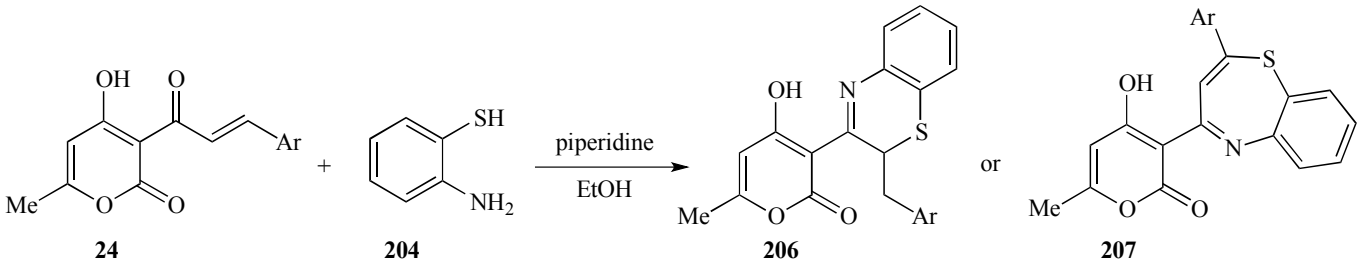
A facile condensation reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **109** with *o*-aminobenzenethiol **204** afforded six membered heterocyclic compound 3-(2*H*-benzo[*b*]thiazin-3(4*H*)-ylidene)-6-methyl-2*H*-pyrane-2,4(3*H*)-dione **205** (**Scheme 64**).[39]



109 **204** **205**

Scheme 64

Prakash *et al.* reported the reaction of 2-aminothiophenol **204** with the chalcone analogues of DHA **24**, which afforded 1,4-benzothiazines **206** and 1,5-benzothiazepines **207** depending upon the reaction conditions and structure of the aldehydes. When Ar = *o*-$NO_2C_6H_4$ and *p*-$NO_2C_6H_4$, a mixture of **206** and **207** were obtained whereas in case of Ar = 4-pyridyl, 1,4-benzothiazines **206** was obtained exclusively and in rest of the cases, 1,5-benzothiazepine **207** was formed as an exclusive product (**Scheme 65**).[80]



24 **204** **206** **207**

Ar = C_6H_5, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-HOC_6H_4, *o*-HOC_6H_4, *p*-$MeOC_6H_4$, *p*-$(Me)_2NC_6H_4$, *o*-$O_2NC_6H_4$, *p*-$O_2NC_6H_4$, *m*-$O_2NC_6H_4$, 2-thienyl, 2-pyridyl

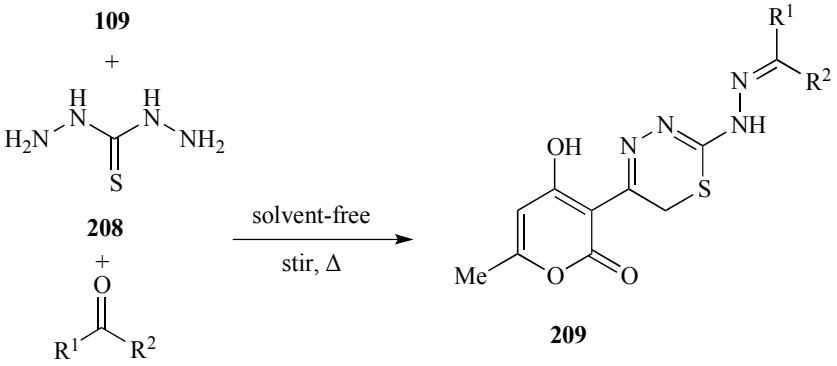
Scheme 65

D. SYNTHESIS OF HETEROCYCLIC COMPOUNDS CONTAINING THREE HETEROATOMS

D.1 SYNTHESIS OF SIX MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING TWO NITROGEN AND ONE SULPHUR ATOMS

D.1.1 THIADIAZINES

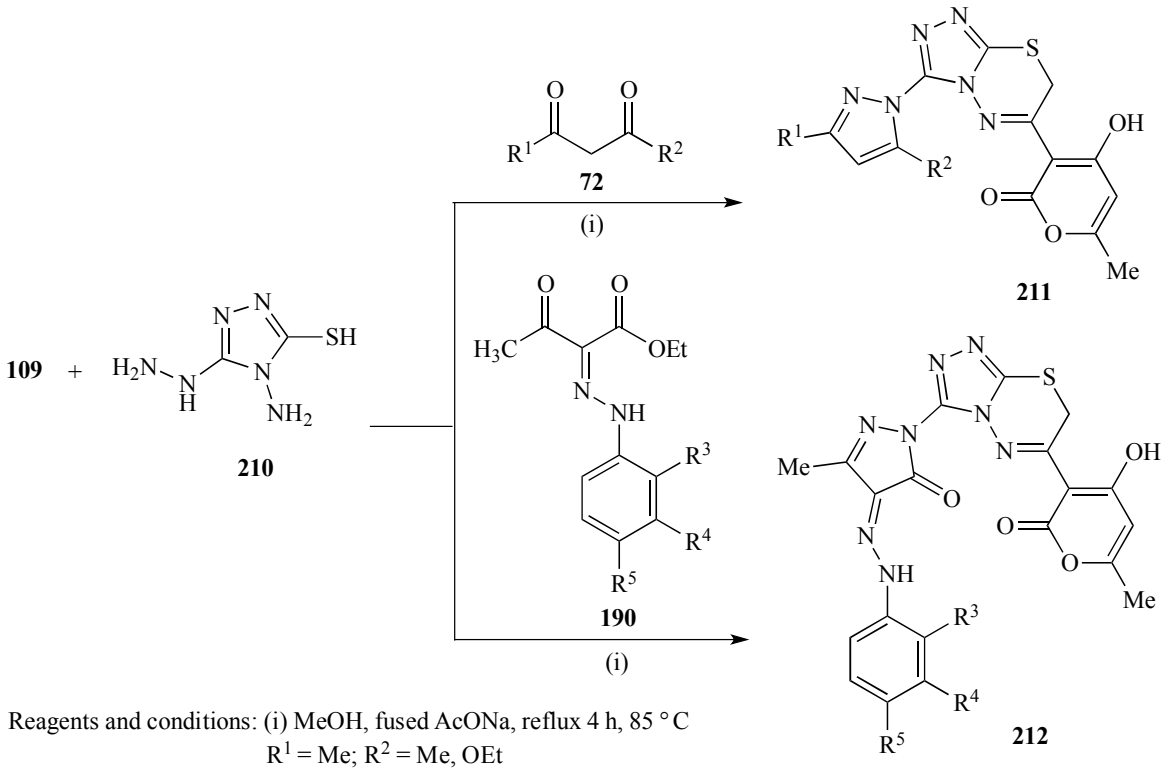
A facile synthesis of 1,3,4-thiadiazin-5-yl-pyran-2-one derivatives **209** is achieved *via* a three-component reaction involving 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **109**, thiocarbohydrazide **208** with various carbonyl compounds in one pot under stirring. The main advantage of this procedure is the short reaction time, high yields, simple workup, and purification of products by non-chromatographic methods, *i.e.* by simple recrystallization from ethanol (**Scheme 66**).[77]



R^1 = H, Me, cyclohexylidene; R^2 = Me, Et, C_6H_5, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-ClC_6H_4, cyclohexylidene, etc.

Scheme 66

A series of simple hydrazono pyrazolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-6-yl)-2*H*-pyran-2-ones **211** and **212** derivatives have been efficiently synthesized *via* one-pot, multi-component reaction of equimolar mixture of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **109** with 4-amino-5-hydrazino-4*H*-[1,2,4]triazole-3-thiol **210** and acetyl acetone/ethyl acetoacetate or ethyl-2-(2-phenylhydrazono)-3-oxobutanoate **72** in NaOAc/MeOH under reflux conditions. The striking feature of the synthesis is that different hetero atom bonds like C–S, N=C, N–C, N=C (compound **211**) and C–S, N=C, N–C=O, and



Reagents and conditions: (i) MeOH, fused AcONa, reflux 4 h, 85 °C
R^1 = Me; R^2 = Me, OEt

Scheme 67

N=C (compound **212**) are formed simultaneously in one pot leading to selective novel hetero cyclization without formation of any other products (**Scheme 67**).[78]

4. CONCLUSION

The present survey updates and highlights the synthesis of various heterocyclic moieties designed on DHA **1**. The motto of the study is to gather all the routes and ways to the synthesis of targeted and unexpected compounds from DHA. Hence the outcome of the review provides an easily accessible approach towards the synthesis of heterocyclic compounds by various synthetic methods taking DHA **1** as a starting nucleus.

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