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
2. Brief history, methods of preparation and reactivity of DHA
3. Applications of DHA in the synthesis of heterocyclic compounds
   A. Synthesis of heterocyclic compounds containing nitrogen atom
      A.1 Synthesis of four membered heterocyclic compounds containing one nitrogen atom
         A.1.1 Azetidinones
      A.2 Synthesis of five membered heterocyclic compounds containing one nitrogen atom
         A.2.1 Pyrroles
      A.3 Synthesis of five membered heterocyclic compounds containing two nitrogen atoms
         A.3.1 Pyrazolines and pyrazoles
         A.3.2 Imidazoles
      A.4 Synthesis of six membered heterocyclic compounds containing one nitrogen atom
         A.4.1 Pyridines
      A.5 Synthesis of six membered heterocyclic compounds containing two nitrogen atoms
         A.5.1 Pyridazines
A.5.2 Pyrimidines
A.5.3 Pyrazines
A.6 Synthesis of seven membered heterocyclic compounds containing two nitrogen atoms
A.6.1 Diazepines

B. Synthesis of heterocyclic compounds containing oxygen atom
B.1 Synthesis of five membered heterocyclic compounds containing one oxygen atom
B.1.1 Furans
B.2 Synthesis of six membered heterocyclic compounds containing one oxygen atom
B.2.1 Pyrans

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
C.2 Synthesis of six membered heterocyclic compounds containing nitrogen and oxygen atoms
C.2.1 Oxazines
C.3 Synthesis of five membered heterocyclic compounds containing nitrogen and sulphur atoms
C.3.1 Thiazoles
C.4 Synthesis of six and seven membered heterocyclic compounds containing nitrogen and sulphur atoms
C.4.1 Thiazines and thiazepines

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

4. Conclusion

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 and as preservative for food and vegetables. 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. 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).\textsuperscript{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.\textsuperscript{12} It has also been isolated from natural resources.\textsuperscript{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\textsuperscript{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](image_url)

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.\textsuperscript{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.\textsuperscript{17} Kaushal et al.
launched a synthetic method of DHA from self condensation of heptane-2,4,6-trione in the presence of phosgene.\textsuperscript{18} Steele \textit{et al.} developed a method for the synthesis of DHA \textit{via} polymerization of but-1-ene-1,3-dione in boiling benzene solution with sodium phenoxide.\textsuperscript{19} All these methods well depicted in Scheme 1.

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Synthesis of \(N\)-aminoazetidinone 11 was accomplished via reaction of chloroacetyl chloride 8 with 4-nitrophenyl-1-[1-(4-hydroxy-6-methyl-2-oxo-2H-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\(_3\)N (Scheme 3).\(^{23}\)
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-2H-pyran-3-yl)-2,5-dihydro-1H-pyrrole-2-carboxylate 15 (Scheme 4).24,25

\[
\begin{align*}
1 & \quad 12 \\
\text{thermal, 70°C} & \quad \text{solvent-free} \\
\rightarrow & \\
13 & \\
+ & 14 \\
\text{EtOH} & \\
\rightarrow & \\
15 & \\
\end{align*}
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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 POCl₃. 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
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).
Iodobenzene diacetate (IBD) mediated oxidation of 1,5-diphenyl-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-2-pyrazolines 35, furnished by 3-cinnamoyl-4-hydroxy-6-methyl-2-oxo-2H-pyran-35, on treatment with arylhydrazines, to respective pyranylpyrazoles 36 has been reported (Scheme 8).28

It has been reported that DHA hydrazones 37 on double Vilsmeier-Haack reaction gave 4-formyl-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1-arylpyrazoles 39. The intermediate, 3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-1-arylpyrazoles 38 has also been isolated using 1.1 eq of DMF/POCl3, which undergo further formylation to corresponding 4-formylpyrazoles 39 under Vilsmeier-Haack reaction conditions (Scheme 9).29
A convenient and environment benign approach for the synthesis of novel pyranlypyrazoles 40 via β-enaminones 13 using NaHSO₄–SiO₂ 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 pyranlypyrazoles 40 at lower temperature. Synthesis of pyranlypyrazole derivative 40a was also reported by conventional heating of β-enaminone 13 with hydrazine hydrate in ethanol (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-quinolylyhydrazines, 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).
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
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$_2$SO$_4$. Alternatively, DHA was converted to its analog 48 by treating with ethyl iodide, K$_2$CO$_3$ 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](image1)

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$_2$SO$_4$ for 1 h (Scheme 14).$^{33}$

![Scheme 14](image2)

A.3.2 BENZIMIDAZOLES

Nabila et al. explored the interesting chemistry of structural analogues of DHA 1; 4-hydroxy-6-methyl-3-(3-arylpropanoyl)-2H-pyran-2-ones 51 and 4-hydroxy-6-methyl-3-(5-phenylpentanoyl)-2H-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).  

(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 \( \text{Ar} = \text{C}_6\text{H}_5, p-\text{ClC}_6\text{H}_4, 3,4-\text{Cl}_2\text{C}_6\text{H}_3 \)  
52 \( \text{Ar} = \text{C}_6\text{H}_5 \)  

Scheme 15

A.4 SYNTHESIS OF SIX MEMBERED HETEROCCYLIC 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(1H)-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](image)

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](image)

It was implied efficiently to synthesize (R)-(+-)muscyporidine 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)-(+-)muscyporidine 68. This synthesis has found applications in the formation of 2,6-bridged pyridines (Scheme 18).\(^{37}\)

Condensation of DHA 1 with 7-aminindazole 69 in the presence of p-toluenesulfonic acid (PTSA) and n-butanol as a solvent has been reported to afford new N-(1H-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-(1H-7-indazolylamino)-2-acetyl-3-oxohex-4-enoic acid. This intermediate after decarboxylation followed by subsequent intramolecular cyclization afforded N-(1H-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-(1H-7-indazolyl)-2,6-dimethyl-4-oxopyridine-3-carboxylate 70b (Scheme 19).\(^{38}\)
Scheme 18

Reagents and conditions: (i) conc. HCl, reflux, 12 h, 89%; (ii) NH₃, EtOH, sealed tube, 140 °C, 3 d, 87%; (iii) POCl₃, reflux, 1 h, 93%; (iv) H₂/Pd–C, AcONa, rt, 12 h, 89%

Scheme 19

Shahrisa et al. reported the synthesis of new symmetrical 4-[2-chloro-2-(4-chloro-6-methyl-2-oxo-2H-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, ZrOCl₂·8H₂O 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-2H-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-2H-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

\[
\begin{align*}
\text{R}^1 &= \text{Me}, \text{n-Pr}, \text{CH}_2\text{C(Me)}_2\text{CH}_2; \text{R}^2 = \text{Me}, \text{OMe}, \text{OEt}, \text{OC(Me)}_3, \\
&\quad \text{C}_6\text{H}_5, \text{CH}_2\text{C(Me)}_2\text{CH}_2; \text{R}^3 = \text{Me}, \text{OMe}, \text{C}_6\text{H}_5
\end{align*}
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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 \(\beta\)-enaminone 13 with active methylene compounds such as \(\beta\)-dicarbonyl compounds 72, cyclic \(\beta\)-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
A versatile synthetic route for the synthesis of 2-amino-4-(2-bromophenyl)-6-(4-hydroxy-6-methyl-2-oxo-2H-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).
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,
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
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](image)

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-2H-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-2H-pyran-2-one 110 and 4-hydroxy-3-[1-hydroxy-2-(2-phenylhydrazinyl)vinyl]-6-methyl-2H-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-1H-pyran[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
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-2H-pyran-3-yl)-2-S-benzylthiopyrimidines \( \text{114} \) was achieved by the condensation of 3-cinnamyl-4-hydroxy-6-methyl-2-oxo-2H-pyrans (chalcone analogues of DHA) \( \text{24} \) with S-benzylisothiouronium chloride (SBT) \( \text{113} \) 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 \textit{in situ} oxidation of dihydropyrimidines had occurred (Scheme 28).^{46}

The site selectivity in cycloaddition was studied by the reaction of \( \beta \)-enaminone \( \text{13} \) with thiourea \( \text{115} \) with catalytic amount of triethylamine in refluxing ethanol. Out of the three possible isomeric cycloadducts \( \text{116a, 116b} \) and \( \text{117} \), pyrimidinethione \( \text{117} \) was obtained as an exclusive product. Confirmation of structure \( \text{117} \) was done on the basis of IR and \(^1\text{H} \) NMR spectroscopy. The IR spectrum
showed absorption band at 1320 cm\(^{-1}\) corresponding to C=S and \(^1\)H NMR exhibited two doublets at \(\delta\) 5.30 and 6.30 ppm with coupling constant \((J = 6.80\ \text{Hz})\) assignable to pyrimidine protons (Scheme 29).\(^{24}\)

\[
\text{Scheme 29}
\]

DHA chalcone 24 was also chosen 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).\(^{23}\)

\[
\text{Scheme 30}
\]

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).\(^{47}\)
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 31](image)

1 R¹, R² = (a) = Me, H; (b) = Me, Br; (c) = Et, H

(i) or (ii)

120

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

Scheme 31

![Scheme 32](image)

Ar = p-MeOC₆H₄

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-2H-pyran-2-one 109 with o-phenylenediamines (o-PDAs) 53
bearing H, Cl, Me, SNO₂ as substituents, yielded in each case a single pure product. When an electron
donating, o, p-directing, group (Cl, Me) is present, the 1-NH₂ reacts first whereas in case of electron
withdrawing NO₂ group, a m-director, the 2-NH₂ 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

\[
\begin{array}{c}
\text{109} + \text{R} \quad \text{EtOH} \\
\begin{array}{c}
\begin{array}{c}
\text{H₂N} \\
\text{H₂N}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{NH} \\
\text{NH}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{Cl/H} \\
\text{NO₂}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\end{array}
\end{array}
\end{array}
\end{array}
\end{array}
\begin{array}{c}
\text{124a,b} \\
\text{124c} \\
\text{124d}
\end{array}
\end{array}
\end{array}
\]

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-2H-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).⁵⁶

\[
\begin{array}{c}
\text{1} + \text{CO₂Et} \\
\begin{array}{c}
\text{CO₂Et} \quad \text{NaOEt} \\
\text{Abs. EtOH} \quad \text{stir, } 0 °C, 4 \text{ h}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{OH} \\
\text{CO}_2\text{O}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{OH} \\
\text{CO}_2\text{O}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{Et} \\
\text{Et}
\end{array}
\end{array}
\end{array}
\end{array}
\begin{array}{c}
\text{126} \\
\text{127}
\end{array}
\end{array}
\end{array}
\]

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 \( \alpha_{1}, \alpha_{2}, \alpha_{3} \) and \( \alpha_{4} \) 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

\[
\text{Scheme 35}
\]

Tijou et al. reported that DHA 1, on treatment with \( \sigma \)-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).\textsuperscript{50,51,52}

\begin{equation*}
\begin{aligned}
\text{1} & + \text{53} \xrightarrow{\text{piperidine, EtOH}} \text{132} \\
\text{132} & \xrightarrow{TFA/EtOH, ArCHO} \text{23} \\
\end{aligned}
\end{equation*}

\begin{equation*}
\begin{aligned}
\text{R} = \text{H, Me, Cl; } \text{Ar} = \text{C}_6\text{H}_5 , p-\text{MeC}_6\text{H}_4 , p-\text{MeOC}_6\text{H}_4 , p-\text{FC}_6\text{H}_4 , p-\text{CF}_3\text{C}_6\text{H}_4 , \text{2-pyridyl}
\end{aligned}
\end{equation*}

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 \textit{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 (\textit{E})-enaminopyrane-2,4-diones 135A (Scheme 37).\textsuperscript{53}
A series of Keggin type heteropolyacids (HPAs) e.g. H₃PW₁₂O₄₀ and H₃₋ₓPMo₁₂₋ₓ VₓO₄₀ with x = 0-3, in comparison to CF₃CO₂H, 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: H₅PMo₁₀V₂O₄₀ > H₆PMo₁₀V₃O₄₀ > H₄PMo₁₁VO₄₀ > H₃PMo₁₂O₄₀ > H₃PW₁₂O₄₀. The best catalytic performance was attributed to H₅PMo₁₀V₂O₄₀ catalyst and selected for the synthesis of benzodiazepine and diazepine rings (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).\(^{55}\)

Interestingly, refluxing DHA 1 with $o$-PDA 53 in xylene led to the formation of 4-(2-oxopropylidene)-1,5-benzodiazepin-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).\(^{56}\)
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 trimethyltetrahydrofulvalene 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.
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-2H-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

\[
\text{Scheme 42}
\]

Adib et al. reported a simple synthesis of 2-hydrazinylidene-3-hydroxy-4H-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
Djamila et al. have reported a facile condensation reaction of 6-methyl-4H-furo[3,2-c]pyrane-3,4-dione 152, obtained from the intramolecular cyclocondensation of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one 109 assisted by aliphatic amines 151, with benzaldehydes and acetophenones leading to the formation of novel 2-arylidene-6-methyl-2H-furo[3,2-c]pyrane-3,4-diones 153 and 6-(2-arylprop-1-eny)-2H-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).\(^6\)

![Scheme 43](image)

![Scheme 44](image)

151 \(R = \text{Me, Et, Bu, Hex}\)

153 \(R^1, R^2 = (a) \text{H, H}; (b) \text{OMe, H}; (c) \text{Cl, H}; (d) \text{Br, H}; (e) \text{NO}_2, \text{H}; (f) \text{H, NO}_2\)

155 \(R = (a) \text{H}; (b) \text{Br}\)

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

(ii) = acetophenones, HCl/AcOH, reflux 1 h
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-4H-pyran-2-yl)-6-methyl-3H-pyrane-2,4-dione 156 (Scheme 45).24

![Scheme 45](image)

A novel and convenient route to the synthesis of 3-aryl-7-methylpyrano[4,3-b]pyrane-4H,5H-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 I2/DMSO instead of IBD, resulting into an efficient and facile one step synthesis of regioisomeric 2-aryl-7-methylpyrano[4,3-b]pyrane-4H,5H-diones (flavone analogues of DHA) 158 (Scheme 46).61,62

![Scheme 46](image)

Synthesis of fluorinated 7-methylpyrano[4,3-b]pyrane-4H,5H-diones 160 has been reported by the cyclization of 3-acetoacetyl-4-hydroxy-6-methyl-2-oxo-2H-pyran 159 in the presence of conc. H2SO4. 3-Acetoacetyl-4-hydroxy-6-methyl-2-oxo-2H-pyran 159, was obtained by the Claisen condensation of DHA with fluorinated esters in the presence of LiH in THF (Scheme 47).63
Nabila et al. reported an efficient and novel synthetic method of benzo[f]chromen-1-ones 162 and phenyl-4H-chromen-4-ones 163 using delafossite catalyst (CuAlO$_2$) through photooxidative cyclization of 6-[2-arylvinyl]-4H-pyran-4-ones 161a ($n = 1$) and 6-[4-phenylbuta-1,3-dien-1-yl]-4H-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).$^{64}$

Fadda et al. reported an efficient synthetic methodology allowing a simple introduction of a plethora of substituents into the structure of $\beta$-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

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-2H-pyran-3-yl)-1H-pyrano[2,3-d]pyrimidine 170 and 6-methyl-3-(4-oxo-2-thioxo-1,3,4,5-tetrahydro-2H-pyran[2,3-d]pyrimidin-7-yl)-2H-pyran-2,4(3H)-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-2H-pyran-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-2H-pyran-2-one 173 by treating with hydroxylamine hydrochloride and sodium acetate under refluxing ethanol (Scheme 52).23
C.2 SYNTHESIS OF SIX MEMBERED HETEROCYCLIC COMPOUNDS CONTAINING NITROGEN 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 triethylamine as 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^
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-2H-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-2H-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](image)

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-2H-pyran-2-ones 188 from 3-(3-benzyl-2-(phenylimino)-2,3-dihydrothiazol-4-yl)-4-hydroxy-6-methyl-3,4-dihydro-2H-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-aryldrazono)-1-(4-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)thiazol-2-yl)-3-methyl-1H-pyrazol-5(4H)-one 191 by the multi-component reaction of 3-(2-bromoacetyl)-4-hydroxy-6-methyl-2H-pyran-2-one 109 with thiosemicarbazide 189 and ethyl 2-(2-aryldrazono)-3-oxobutanoates 190 in absolute ethanol has been reported (Scheme 57).69
A series of thiosemicarbazones 192 and 4-thiazolidinones 193 (a-c) were synthesized and evaluated for their \textit{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 \textit{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).\textsuperscript{70}
Novel 4-hydroxy-6-methyl-3-(2-substituted-thiazol-4-yl)-2H-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).  

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-2H-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).
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-1H-pyrazol-1-yl)thiazol-4-yl]-2H-pyran-2-one \( 199 \) via multicomponent reaction of \( 109 \), with thiosemicarbazide \( 189 \) and \( \alpha \)-ketones or acetylacetone \( 72 \) (Scheme 61).\(^{74}\)

It has been reported that azomethenes \( 7 \) provided an efficient route for the synthesis of 2-(4-hydroxy-6-methyl-2-oxo-2H-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 60**

**Scheme 61**
A series of 1-(4-(4-substituted-phenyl)thiazol-2-yl)-3-methyl-4-(3-methylisoxazol-5-yl)-1H-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-2H-pyran-2-one 109 with o-aminobenzenethiol 204 afforded six membered heterocyclic compound 3-(2H-benzo[b]thiazin-3(4H)-ylidene)-6-methyl-2H-pyrane-2,4(3H)-dione 205 (Scheme 64).39
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-NO2C6H4 and p-NO2C6H4, 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.

D. SYNTHESIS OF HETERO CYCLIC COMPOUNDS CONTAINING THREE HETEROATOMS

D.1 SYNTHESIS OF SIX MEMBERED HETERO CYCLIC 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-2H-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
A series of simple hydrazono pyrazolyl-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-2H-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-2H-pyran-2-one 109 with 4-amino-5-hydrazino-4H-[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

**Scheme 66**

Reagents and conditions: (i) MeOH, fused AcONa, reflux 4 h, 85 °C
R$^1$ = Me; R$^2$ = Me, OEt
N=C (compound 212) are formed simultaneously in one pot leading to selective novel heterocyclization without formation of any other products (Scheme 67).  

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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