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UTILITY OF 2,4-DIOXOESTERS IN THE SYNTHESIS OF NEW HETEROCYCLES

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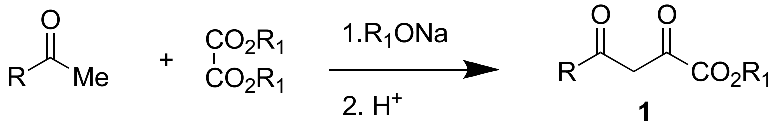
Abstract – This review deals with synthesis and reactions of 2,4-dioxoesters. Some of these reactions have been applied successfully to the synthesis of biologically important compounds. The data published over the last years on the methods of synthesis and chemical properties of 2,4-dioxoesters are reviewed here for the first time.

INTRODUCTION

2,4-Dioxoesters, the acylation products of methyl ketones with dialkyl oxalate, are valuable multi-purpose intermediates in organic synthesis and their preparation is well documented. 2,4-Dioxoesters are used in production e.g. pyrazole-3(5)-ethyl esters and their derivatives which are known to be important intermediates in the preparation of agrochemicals, microbicides, herbicides,[1] plant growth regulators and protectants,[2] and also production of 3(2*H*)-furanone ring system which is the key skeletal element of many natural product antitumor agents.[3] Recently a review on utility of regio- and chemoselective features of benzoylpyuravtes in heterocyclic synthesis has been appeared.[4] The main purpose of this review is to present a survey of the literature on the synthesis of 2,4-dioxoesters and its reactions and provides useful and up-to-date data for medicinal chemists.

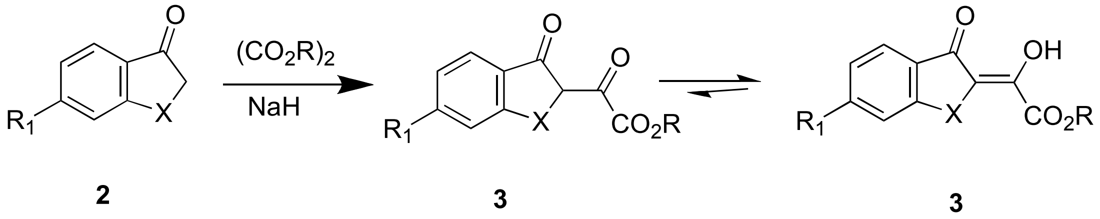
METHODS OF SYNTHESIS

2,4-Dioxoesters **1** were prepared by Claisen condensation of the appropriate methylketone with oxalic acid dialkyl esters in the presence of sodium alkoxides (Scheme 1) then acidified with dilute acid to give an excellent yields of the precursors **1**.[5-21]



Scheme 1 R= alkyl, aryl, heterocycle ; R_1 = Et, Me

Cyclic ketones **2** were condensed with dimethyl or diethyl oxalate to give the diketoester **3** which present in two tautomeric structures (Scheme 2).[22-26]



Scheme 2 X = $(CH_2)_{1-3}$, O ; R_1=R= Me, Et

CHEMICAL PROPERTIES OF 2,4-DIOXOESTERS

2,4-Diketoalkanoates have both the structural features of α-keto esters and β-diketones (Figure 1). In the case of α-keto esters **4**, the adjacent carboxyl moiety imparts the ketone with an enhanced electrophilic character due to its inductive withdrawal. However, this may be moderated by the presence of active protons due to keto/enol tautomerisation between **5** and **6**. In the case of β-diketones **4**, sharing an active methylene group enables both carbonyl functionalities to undergo keto/enol tautomery forming a Michael acceptor.[4]

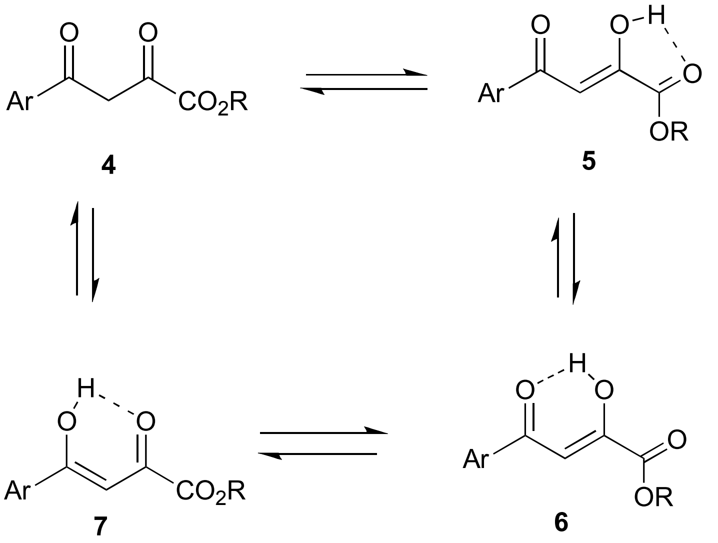
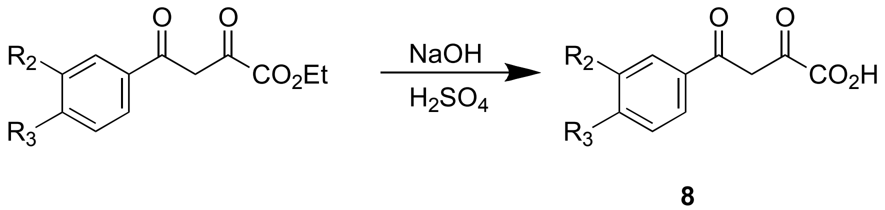


Figure 1: Expected tautomeric contributions in aroylpyruvates.

1. HYDROLYSIS

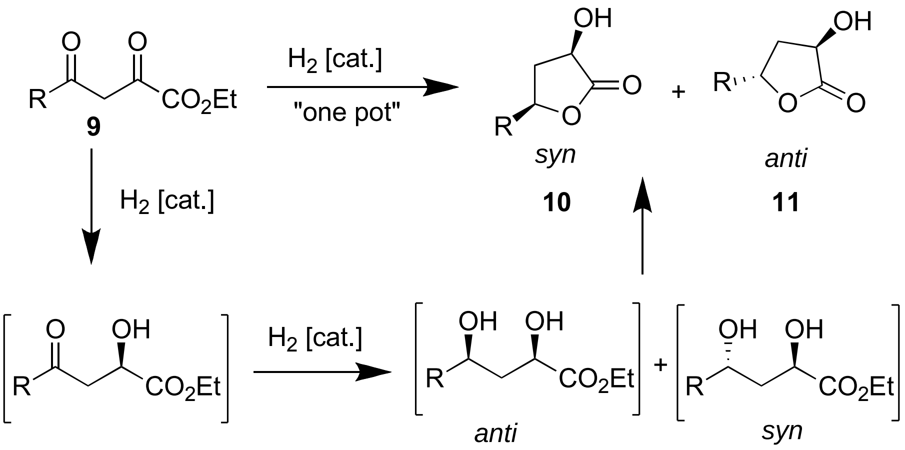
The β-diketo esters are converted to the corresponding pyruvic acids **8** (Scheme 3).[8, 27]



Scheme 3 R_2, R_3 = H, OMe, CF_3

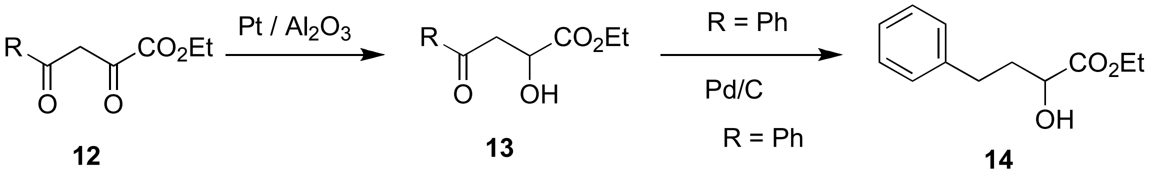
2. REDUCTION

The hydrogenation of 2,4-dioxovalerates **9**, in the presence of chiral rhodium or ruthenium catalysts provides direct access to 3-hydroxy-5-subs.tetrahydrofuran-2-one with syn:anti ratios of up to 84:16 and with up to 98% and 94% ee in the *syn* and *anti* form **10** and **11** respectively (Scheme 4).[28, 29]



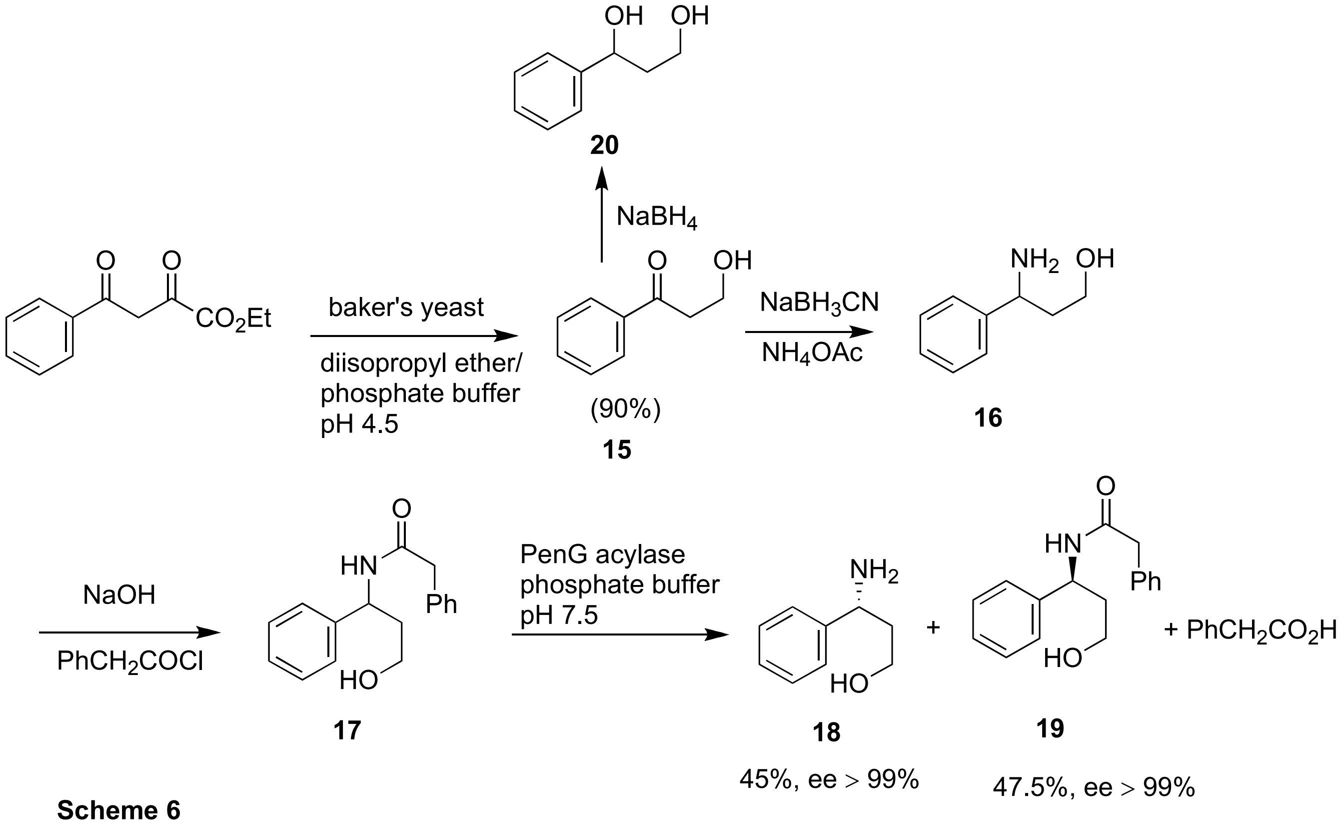
Scheme 4 R= Me, *i*-Bu, 2-thienyl

The derivatives of 4-substituted 2-hydroxybutyric acids are valuable synthons for the production of antihypertensive substances, homoamino acids, hydroxamic acids, and other compounds.[30,31] Thus hydrogenation of ethyl 4-substituted 2,4-dioxobutyrate **12** at palladium black and Pt/Al_2O_3 were studied. During the hydrogenation of compounds **12** at palladium black at room temperature with a hydrogen pressure of 1 atm in ethanol solution, the first reaction products are ethyl 2-hydroxy-4-oxo-4-subs.-butyrate **13**, which then reduced with Pd/C to give ethyl 2-hydroxy-4-phenylbutanoate **14** (Scheme 5).[32]



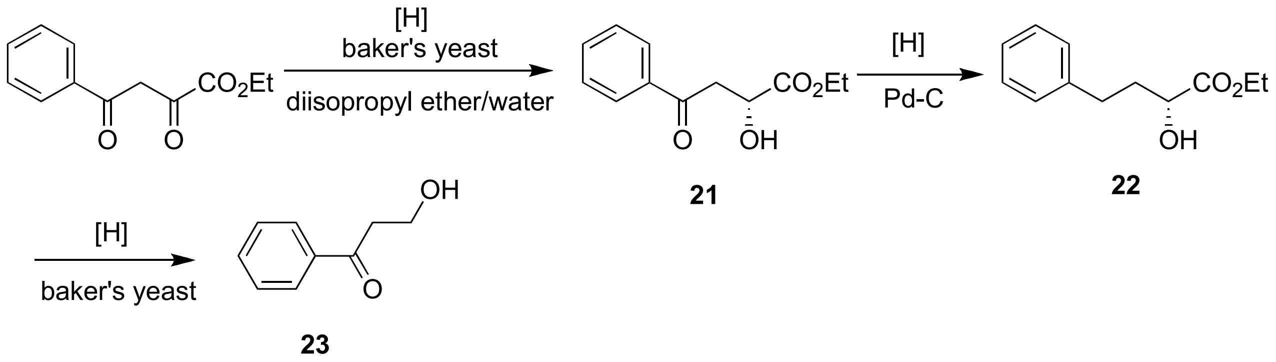
Scheme 5 R= Ph, 2-furyl

Ethyl 2,4-dioxo-4-phenylbutyrate was converted to 3-oxo-3-phenyl-1-propanol **15** in 90% yield by reaction with baker's yeast. Reductive amination with sodium cyanoborohydride in the presence of ammonium acetate gave the racemic 3-amino-3-phenyl-1-propanol **16** in 65% yield. Enzymic resolution of the corresponding *N*-phenylacetyl derivative with penicillin G acylase, immobilized on an epoxy resin gave (*S*)-amide **18** and (*R*)-amino **19** alcohols in high enantiomeric purity (ee >99%) and >45% yields for each enantiomer in addition to phenylacetic acid as side product, while reduction of **15** with sodium borohydride gave 1,3-diols **20** (Scheme 6).[33]



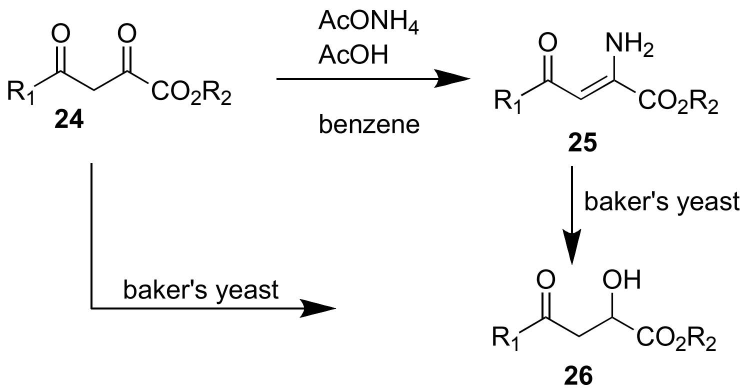
Scheme 6

Ethyl 2,4-dioxo-4-phenylbutyrate, was reduced enantio- and regiospecifically by baker's yeast in a diisopropyl ether/water two-phase system to give (-)-ethyl (*R*)-2-hydroxy-4-oxo-4-phenylbutyrate **21** with an 98% ee in 80% isolated yield. This (hydroxy)keto ester **21** was hydrogenated over Pd-C to obtain (-)-ethyl (*R*)-2-hydroxy-4-phenylbutyrate (HPB ester) **22,** an important intermediate for the synthesis of ACE inhibitors. Prolonged contact of the reduction product with baker's yeast produced 3-phenyl-3-oxopropanol **23** in 90% yield (Scheme 7).[8]



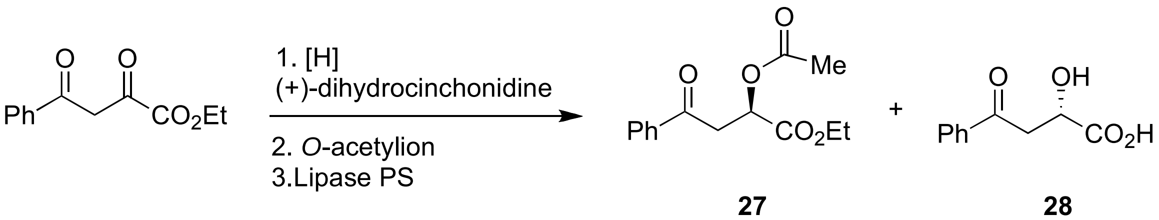
Scheme 7

2,4-Dioxoalkanoates **24** and the parent compound γ-keto-α-enamino esters **25** are regioselectively reduced by baker's yeast to *α*-hydroxy-γ-keto esters **26**, in moderate to good yields (Scheme 8).[34]



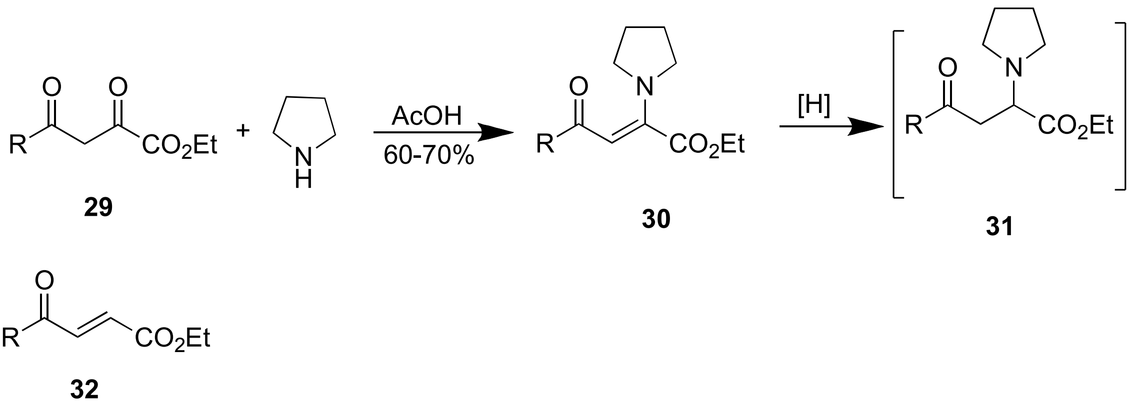
Scheme 8 R_1 =Et, Me; R_2 = Et, Me

Ethyl 2,4-dioxo-4-phenylbutanoate was hydrogenated in the presence of (+)-dihydrocinchonidine and the *O*-acetylated product underwent hydrolysis in the presence of lipase PS to give (*R*)-ethyl 2-acetoxy-4-oxo-4-phenylbutanoate of 99.6% ee **27** and (*S*)-2-hydroxy-4-oxo-4-phenylbutanoic acid of 99.4% ee **28** (Scheme 9).[35]



Scheme 9

Ethyl 2,4-dioxoalkanoates **29** react chemoselectively with pyrrolidine acetate at the more electrophilic C-2 carbonyl, producing enaminone esters **31**. Reduction of **31** with sodium cyanoborohydride followed by pyrrolidine elimination gave β-oxo-acrylates **32**[36] (Scheme 10).

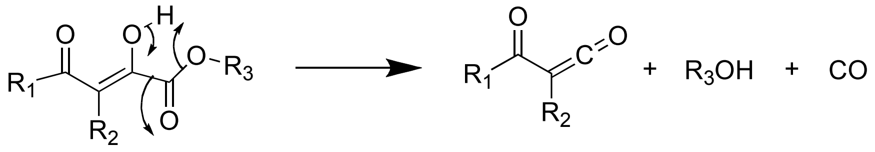


29 **30** **31** **32**

Scheme 10 R = Ph, furyl, Me, Et, H_2C:$CHCH_2CH_2$, Me_2CHCH_2, pentyl, hexyl

3. DECARBONYLATION

The α,γ-diketoesters **33** are subjected to decarbonylation conditions with excess methanol in a sealed reactor at a lower temperature (105-120 °C) to give carbon monoxide and ketenes **34** (Scheme 11).[37]

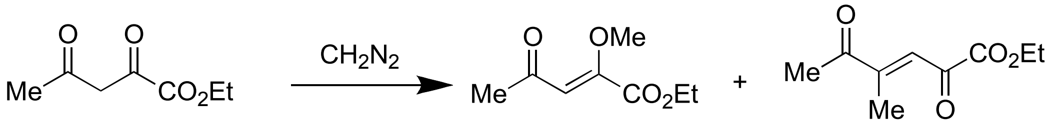


33 **34**

Scheme 11

4. ALKYLATION

Methylation of ethyl acetylpyruvate with diazomethane gave a mixture of two enol ethers, ethyl 2-methoxy-4-oxopent-2-enoate **35** and ethyl 4-methyl-2,5-dioxohex-3-enoate **36** in 68:77 to 23:32 ratios depending on the temperature (Scheme 12).[38,39]



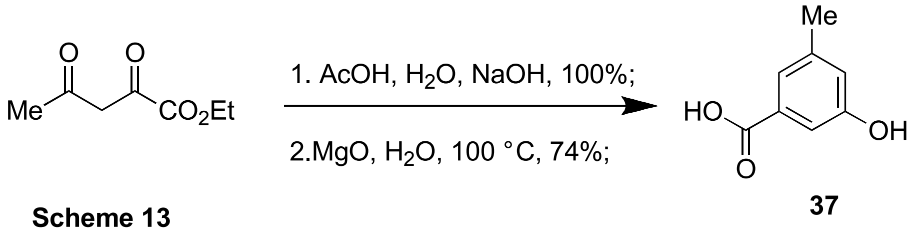
35 **36**

Scheme 12

REACTIONS OF 2,4-DIOXO-ESTERS

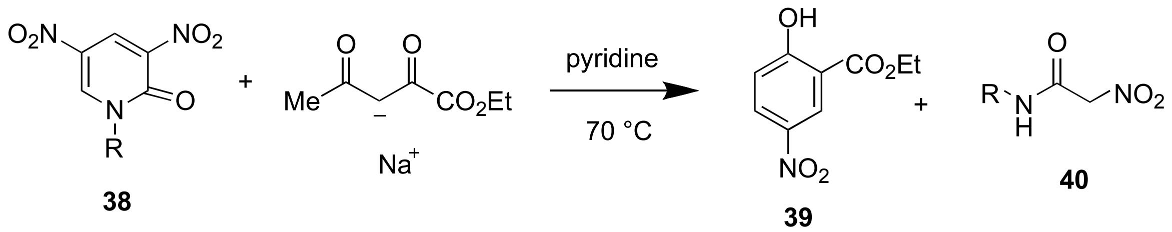
1. FORMATION OF BENZENE DERIVATIVES

3-Hydroxy-5-methylbenzoic acid **37**, which used in the synthesis of thrombin inhibitor, was prepared in high yield from ethyl 2,4-dioxopentanoate in two reaction steps by the reaction with acetic acid followed by treatment with magnesium oxide (Scheme 13).[40]



Scheme 13

The pyridones **38** reacted with sodium salt of ethyl acetopyruvate in pyridine at 70 °C to give 45.0-98.1% phenols **39** and 10.9-84.2% nitroacetamide **40**[41] (Scheme 14).



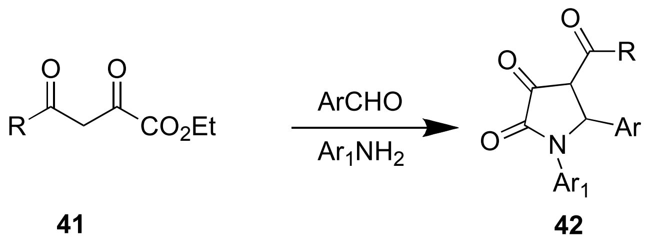
Scheme 14 R = Me, 3-$O_2NC_6H_4CH_2$, 2-pyridylmethyl, 2-pyridyl, 2,4-$(O_2N)_2C_6H_3$, MeO, 4-$O_2NC_6H_4CH_2O$

2. FORMATION OF HETEROCYCLES

2.1. FIVE MEMBERED SYSTEMS

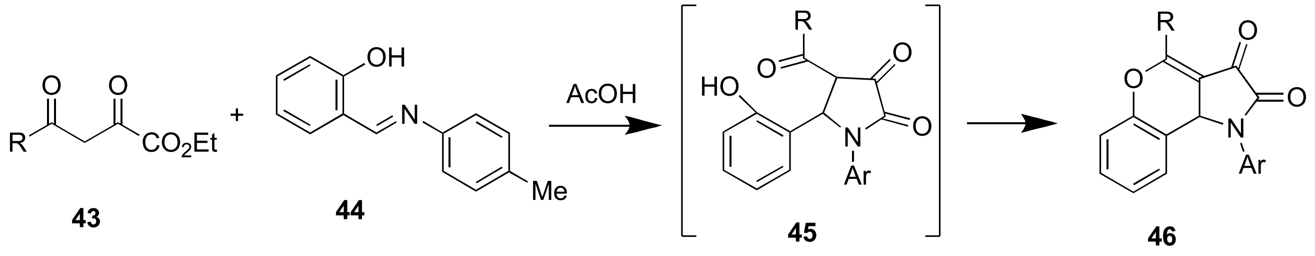
2.1.1. 2,4-PYRROLIDINEDIONES

The condensation of α,γ-diketoesters **41** with aromatic amine and aromatic aldehydes was a convenient method for the synthesis of 4-acyl-2,3-pyrrolidinediones **42** (Scheme 15).[14,42-47]



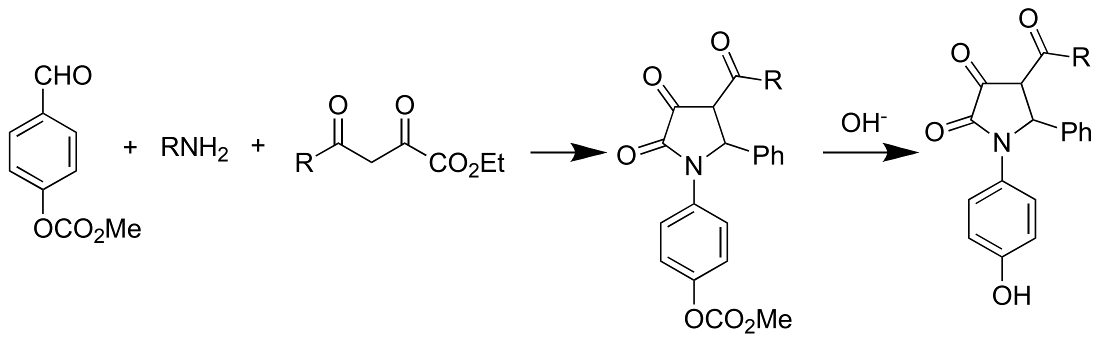
Scheme 15 R= alkyl, Aryl, heterocyles

The condensation of α,γ-diketoesters **43** with aldimines **44** derived from *o*-hydroxybenzaldehydes provides a route to the pyrrolo[3,2-*c*]benzopyran ring system **46**, via cyclization of the intermediate pyrrolidinedione **45** which was not isolated (Scheme 16).[45]



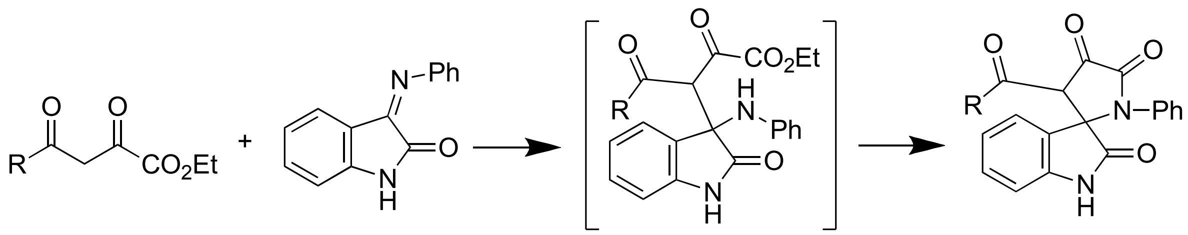
Scheme 16 R= Et, Ph, 4-tolyl

Some substitution products of 2,3-pyrrolidinones **47** and **48** are obtained by condensing an easily saponifiable derivative of a hydroxybenzaldehyde or a hydroxybenzaldehyde alkylcarbonic ester with primary amines and α,γ-diketoesters.[48] The products **47** may be treated then to remove the saponifiable group (Scheme 17). It has been found that these products are useful as drugs or intermediates for drugs.



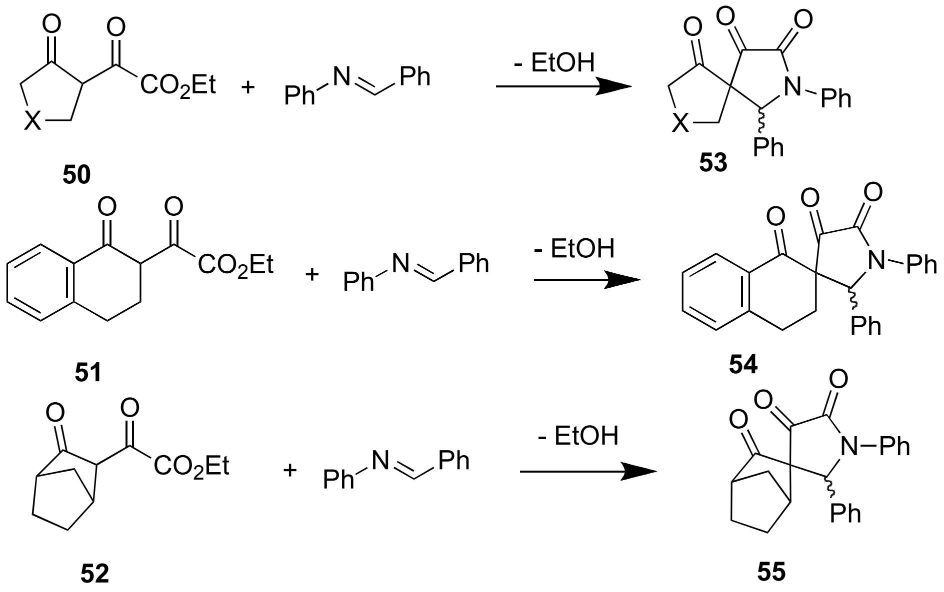
Scheme 17 R= Me, Ph

The condensation of α,γ-diketoesters with Schiff bases, was further extended to the use of ketimines, in such case, the spirocyclic system **49** was obtained via the formation of **50** (Scheme 18).[45]



Scheme 18 R= Me, Ph

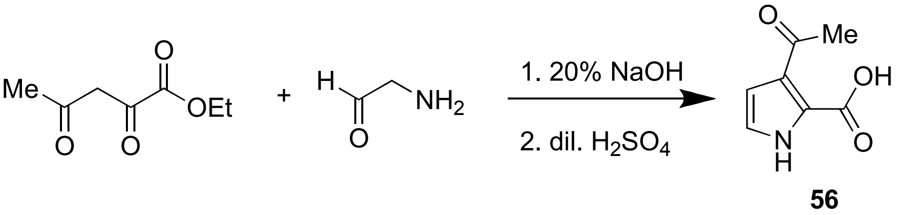
Reaction of 2-oxocycloalkylglyoxylate esters **50-52** with *N*-phenylmethyleneaniline yields 2-aza-3,4,6-trioxo-1,2-diphenylspiroalkanes **53-55** (Scheme 19).[49]



Scheme 19 X= CH_2, CH_2CH_2

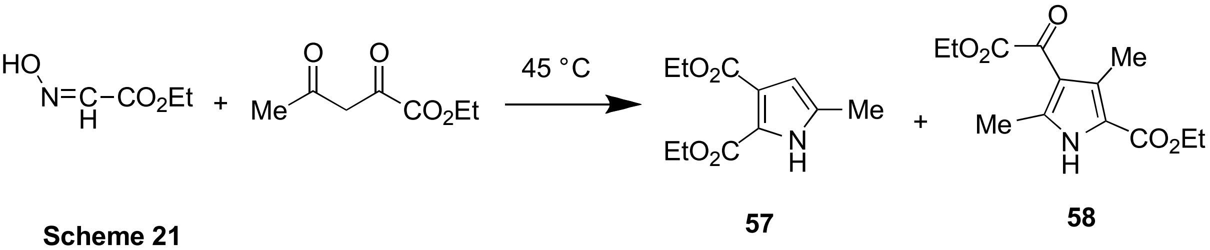
2.1.2. PYRROLES

3-Acetylpyrrole-2-carboxylic acid **56** was prepared by treatment of ethyl 2,4-dioxovalerate with aminoacetaldehyde in presence of 20% aqueous sodium hydroxide, followed by acidification (Scheme 20).[50]



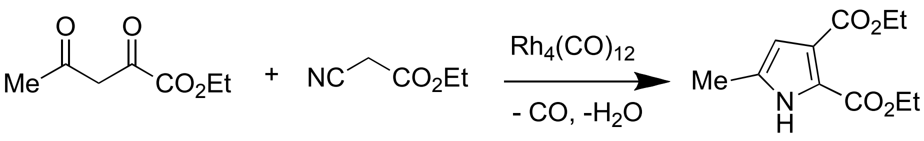
Scheme 20

Ethyl 2-(hydroxyimino)acetate and ethyl 2,4-dioxopentanoate were reacted with at 45 °C diethyl 5-methyl-2,3-pyrroledicarboxylate **57** and ethyl 5-ethoxycarbonyl-2,4-dimethyl-3-pyrroleglyoxylate **58** (Scheme 21).[51]



Scheme 21

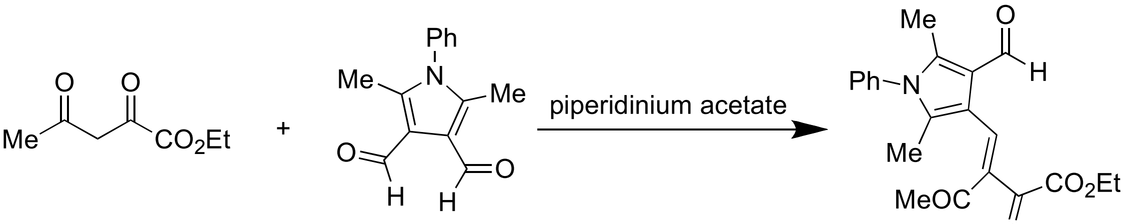
Low-valent rhodium complexes are efficient catalysts for the activation of α-C-H bond of isonitriles. Catalytic synthesis of pyrrole **59**, in 76% yield, can be performed by cyclocondensation of ethyl 2-cyanoacetate with ethyl 2,4-dioxopentanoate (Scheme 22).[52]



Scheme 22

59

Pyrrole chalcone **61** was prepared in by piperidineacetate-catalyzed condensation of 2,5-dimethyl-1-phenyl-1*H*-pyrrole-3,4-dicarbaldehyde **60** with ethyl acetylpyruvate (Scheme 23).[53]



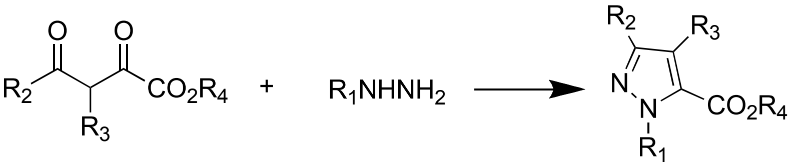
Scheme 23

60

61

2.1.3. PYRAZOLES

Hydrazine and its monosubstituted derivatives react smoothly with 2,4-dioxoesters in a highly chemoselective manner to afford 3,5-difunctionalized pyrazoles as only one product.[54–59] Thus, 1-alkyl-5-pyrazolecarboxylic acid esters **64**, which are intermediates for pyrazolecarboxamide derivatives useful as drugs and agrochemicals, are in high yields prepared by mixing alkylhydrazine **63** with acylpyruvic acid **62** (Scheme 24).[60-65]



62

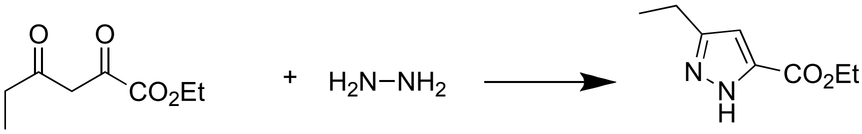
63

64

Scheme 24

R_1, R_2 = alkyl, cycloalkyl; heteocycles, R_3 = H, alkyl, cycloalkyl;
R_4 = alkyl

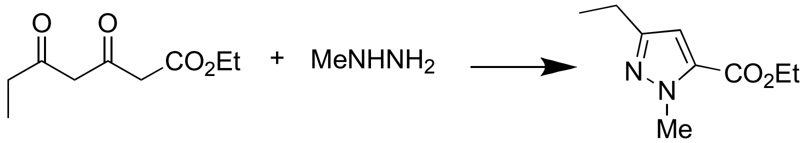
Ethyl 3-ethyl-5-pyrazolecarboxylate **65**, which is an intermediate for the acaricide tebufenpyrad, was synthesized at a yield of more than 87% with ethyl propionylpyruvate and hydrazine hydrate or dihydrazine sulfate (Scheme 25).[66-69]



Scheme 25

65

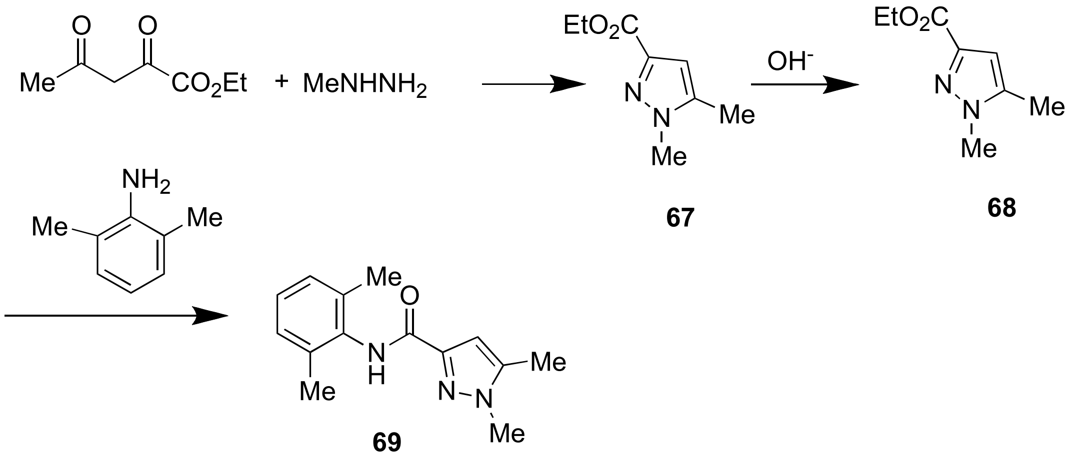
Ethyl propionylpyruvate was reacted with methylhydrazine with the molar ratio above 1: 1.2 to give 95% of ethyl 3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylate **66** (Scheme 26).[70-72]



Scheme 26

66

Ethyl 2,4-dioxopentanoate was cyclocondensed with methylhydrazine and the product **67** was saponified to give 1,5-dimethylpyrazole-3-carboxylic acid **68** which were amidated by 2,6-dimethylbenzenamine to give title compound **69** (Scheme 27). The latter compound gave complete protection against electroshock-induced convulsions to mice at 15 mg/kg i.v.[73,74]



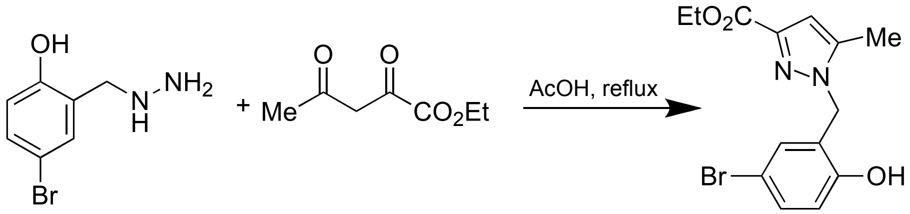
67

68

69

Scheme 27

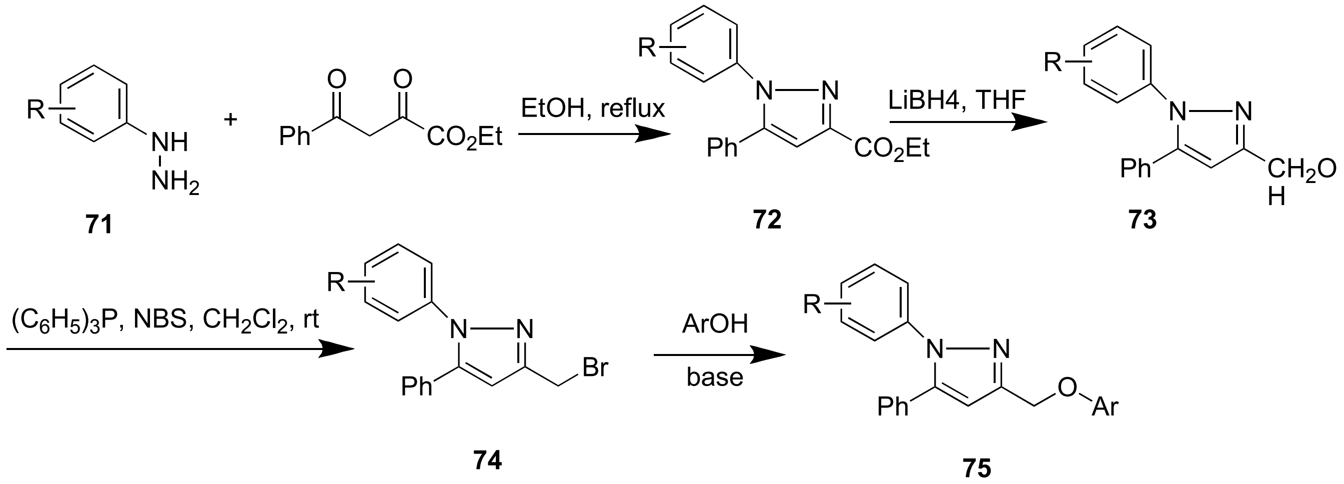
4-Bromo-2-(hydrazinylmethyl)phenol treated with ethyl 2,4-dioxopentanoate to yield predominantly the desired regioisomer **70** which was conveniently purified by preferential crystallization from the reaction mixture upon cooling (Scheme 28).[75]



70

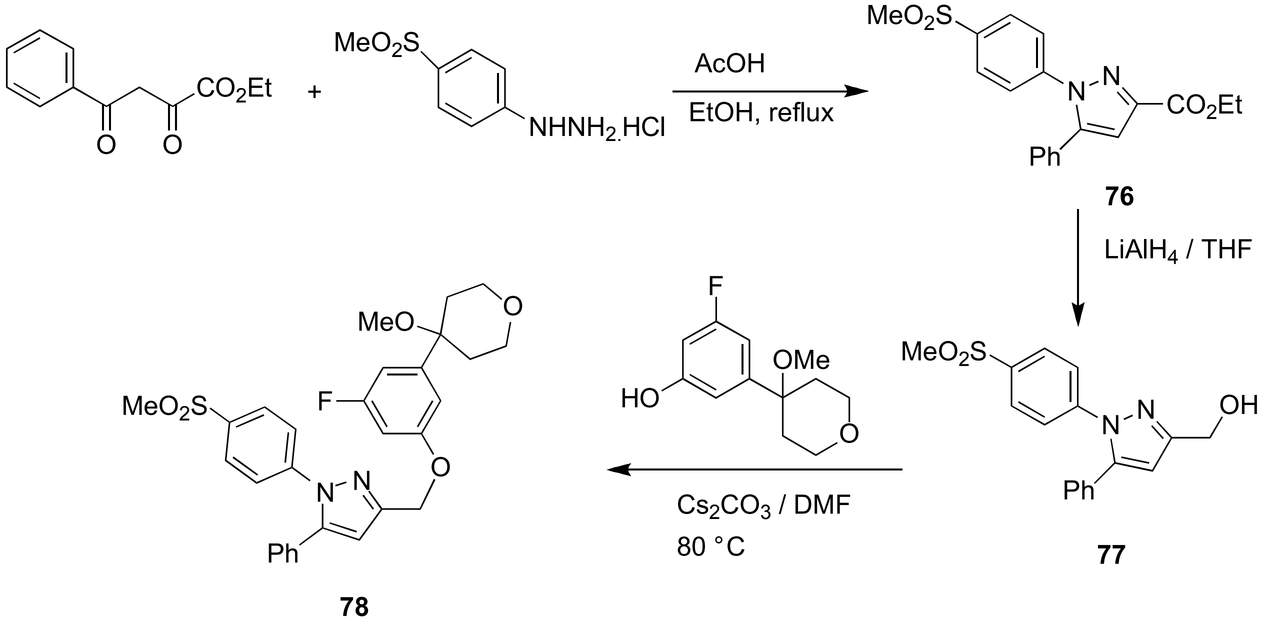
Scheme 28

The synthesis of 1,5-diarylpyrazoles **72** was done (Scheme 29) by regioselective cyclization of arylhydrazines **71** with ethyl 2,4-dioxo-4-phenylbutanoate in refluxing ethanol. Esters **72** were reduced with $LiBH_4$ (anhydrous THF, argon), yielding the primary alcohols **73**. Bromination of the crude products with $(C_6H_5)_3P$-NBS gave the pyrazoles **74**. The alkyl bromides **74** were reacted with diverse phenols in basic medium to give 3-Phenoxymethylpyrazoles **75** which are useful in prostate cancer chemotherapy.[76]



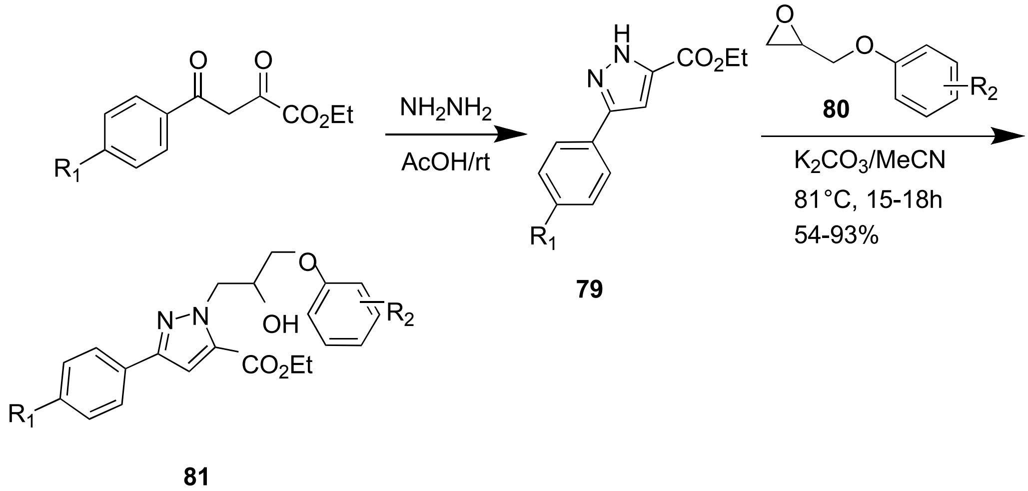
Scheme 29 R= 4-CH_3SO_2, H, 4-F, 4-Cl, 4-Me, 4-OMe, 4-NH_2SO_2, 4-CF_3O, 3,4-Cl_2, 3,4-$(Me)_2$

The diarylpyrazole backbone **76** was prepared from ethyl 2,4-dioxo-4-phenylbutanoate and the corresponding 4-methylsulfonylphenylhydrazine and acetic acid in refluxing ethanol. Compound **76** was reduced in the presence of $LiAlH_4$ in anhydrous THF yielding the 1-(4-methylsulfonylphenyl)-5-phenyl-1*H*-pyrazole-3-methanol **77**. The alcohol **77** was then mesylated in the presence of triethylamine in dichloromethane and reacted with 3-fluoro-5-(4-methoxytetrahydro-2*H*-pyran-4-yl)phenol and Cs_2CO_3 in DMF at 80 °C to yield 3-{[(3-fluoro-5-(4-methoxytetrahydro-2*H*-pyran-4-yl)phenoxy)methoxy]methyl}-1-(4-(methylsulfonyl)phenyl)-5-phenyl-1*H*-pyrazole **78** (Scheme 30) which used as dual cyclooxygenase-2/5-lipoxygenase inhibitor.[77]



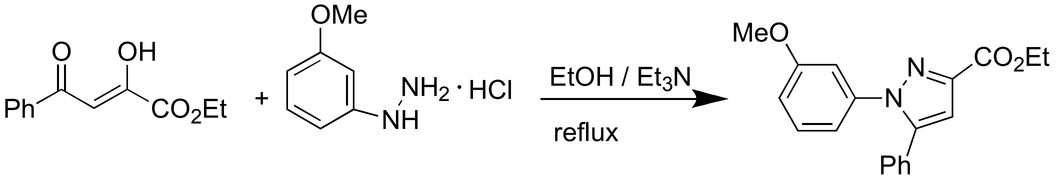
Scheme 30

Synthesis of ethyl 1-(2`-hydroxy-3`-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate **81** is outlined in Scheme 31. Starting compounds, ethyl 3-aryl-1*H*-pyrazole-5-carboxylate and hydrazine. The reaction of ethyl 3-aryl-1*H*-pyrazole-5-carboxylate **79** with 2-aryloxymethylepoxide **80** in the presence of potassium carbonate at refluxing in acetonitrile afforded ethyl 1-(2`-hydroxy-3`-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate **81** in moderate yields and completely regioselectivity.[7]



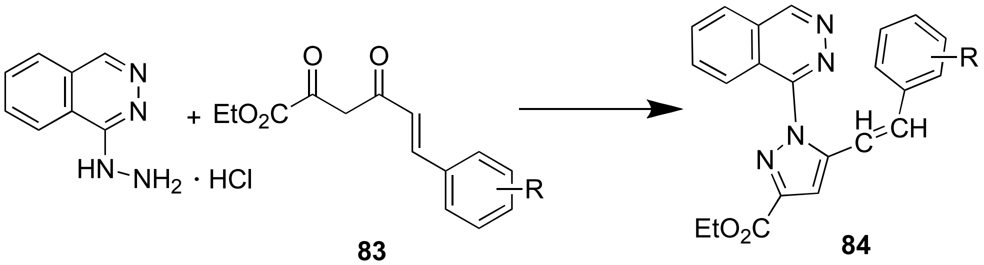
Scheme 31 R_1= H, Me, OMe; R_2= H, 2-OMe, 2-NO_2, 4-NO_2, 4-Cl

1-(3-Methoxyphenyl)-5-phenyl-1*H*-pyrazole-3-carboxylic acid ethyl ester **82** was prepared in 36% yield by the reaction of ethyl 4-phenyl-2,4-dioxobutanoate with 3-methoxyphenylhydrazine hydrochloride in dry ethanol under a nitrogen atmosphere and in the presence of equivalent of triethylamine at refluxing temperature (Scheme 32).[78]



Scheme 32 **82**

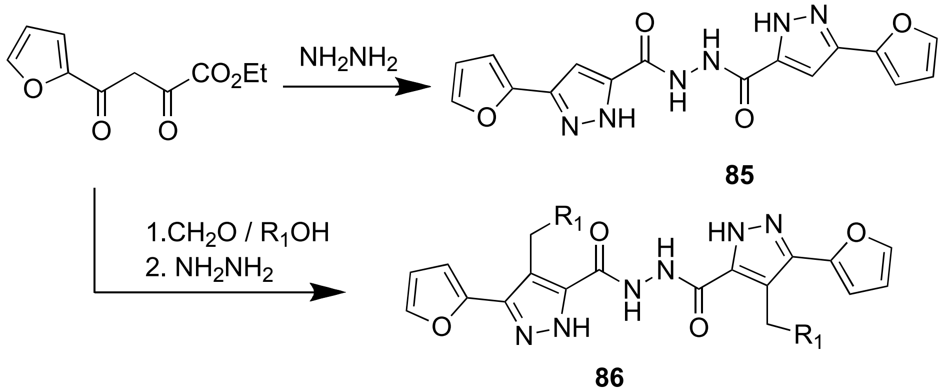
Cyclocondensation of 1-(phthalazin-1-yl)hydrazine-HCl and substituted ethyl cinnamoylpyruvates **83** gave 1-(1-phthalazinyl)-3-carbethoxy-5-(3- or 4-substituted styryl)pyrazoles **84**[79] (Scheme 33).



83 **84**

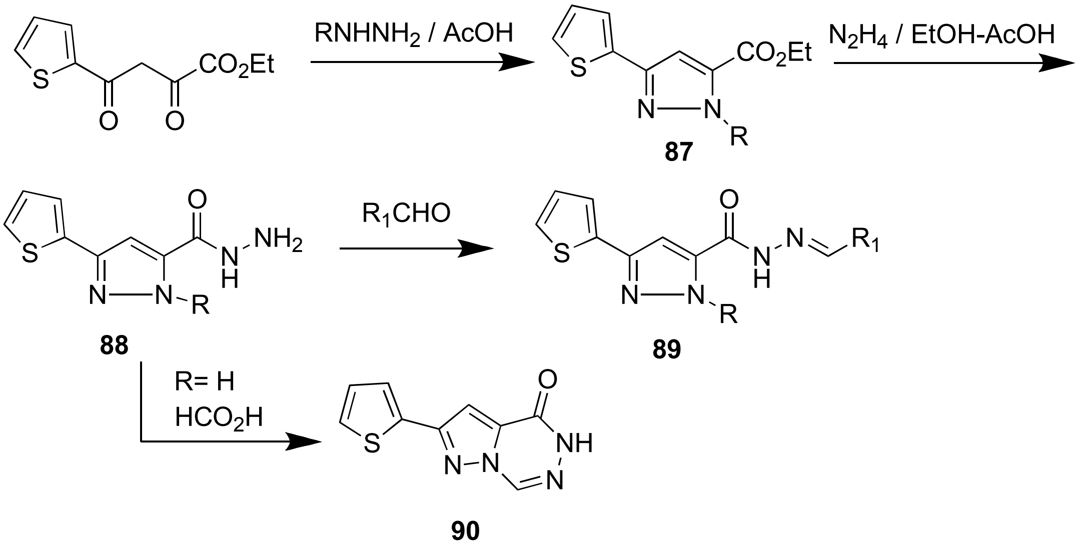
Scheme 33 R_2 = H, 4-MeO, 4-Cl, 3-MeO, 4-NO_2

Ethyl (2-furoyl)pyruvate condensed with hydrazine to give bis(furylpyrazole)hydrazide **85**. While condensing with formaldehyde and phenols and hydrazine gave **86** (R = CH_2R_1)[80] (Scheme 34).



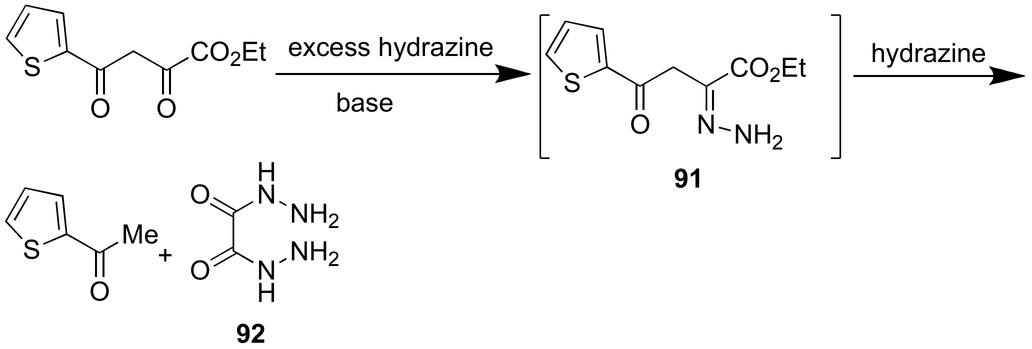
Scheme 34 R_1 = 2-naphthyl, 2,4-$(HO)_2MeC_6H_3$

Cyclization of ethyl 2-thenoylpyruvate with hydrazines in acetic acid gave pyrazole derivative **87** which reacted with hydrazine in refluxing EtOH/AcOH to give hydrazides **88** in high yields. Reaction of **88** with aldehydes and formic acid gave **89** and pyrazolotriazinone **90**, respectively in good yields (Scheme 35).[17,81]



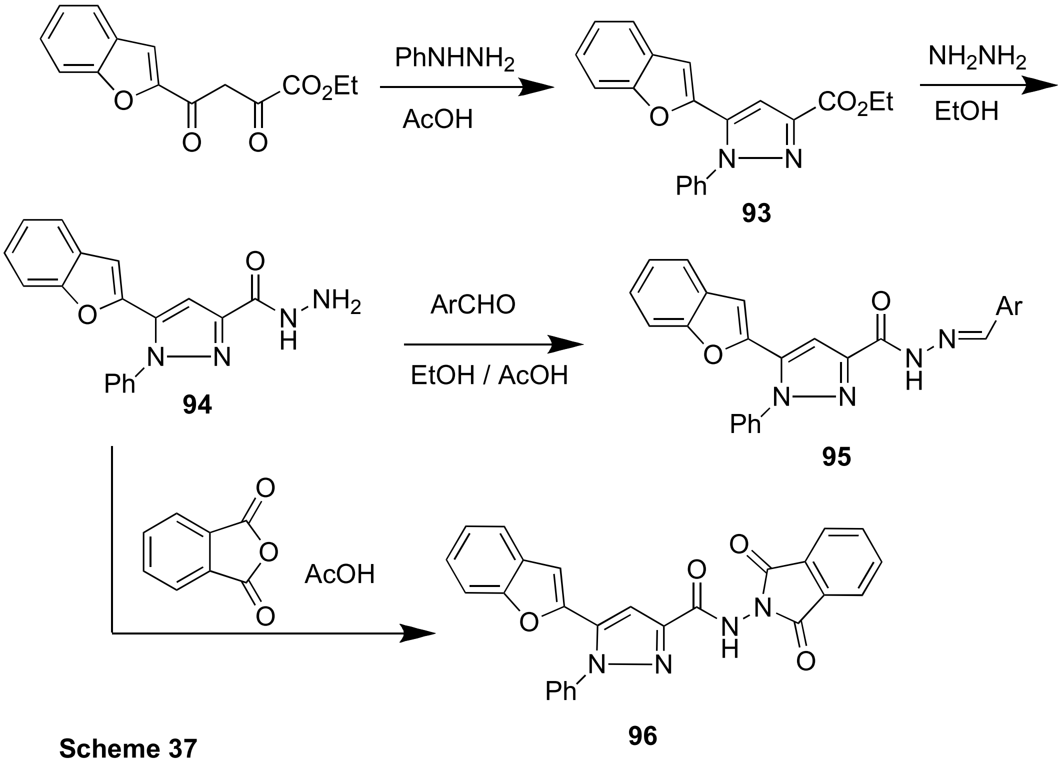
Scheme 35 R= H, Ph; R_1 = Ar

While reaction of ethyl 2-thienoylpyruvate with hydrazine hydrate in neutral or basic medium led to the decomposition to 2-acetylthiophene and oxalohydrazide **92** (Scheme 36).[17]



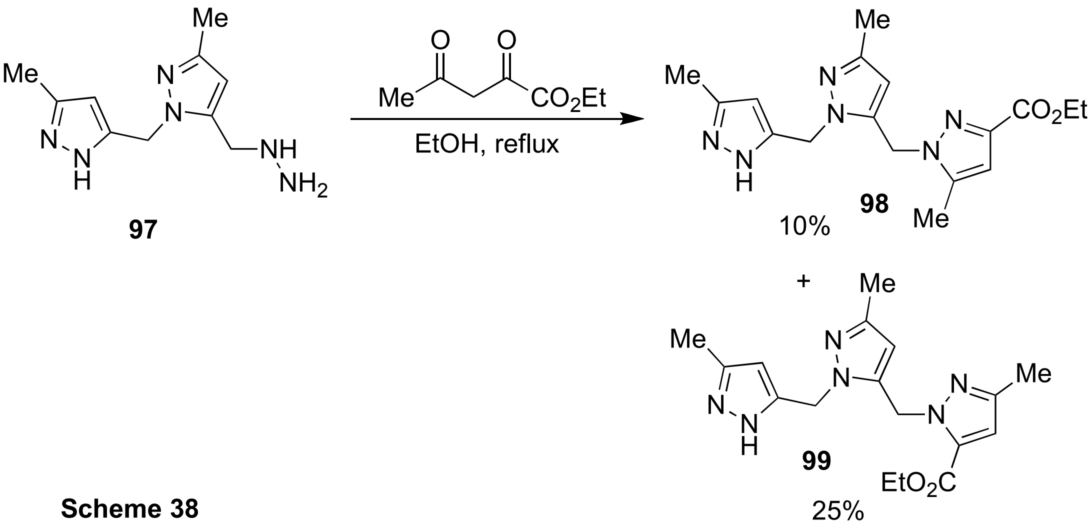
Scheme 36

Recently, Abdel-Wahab et al. reported the reaction of ethyl 2-benzofuroylpyruvate with phenylhydrazine in glacial acetic acid to give the pyrazole-3-carboxylate **93** which then reacted with hydrazine hydrate to give the corresponding carbohydrazide **94**, Reactivity of the latter hydrazide towards aromatic aldehydes and phathalic anhydride were studied to give the corresponding hydrazones **95** and imides **96** (Scheme 37).[15,82,83]



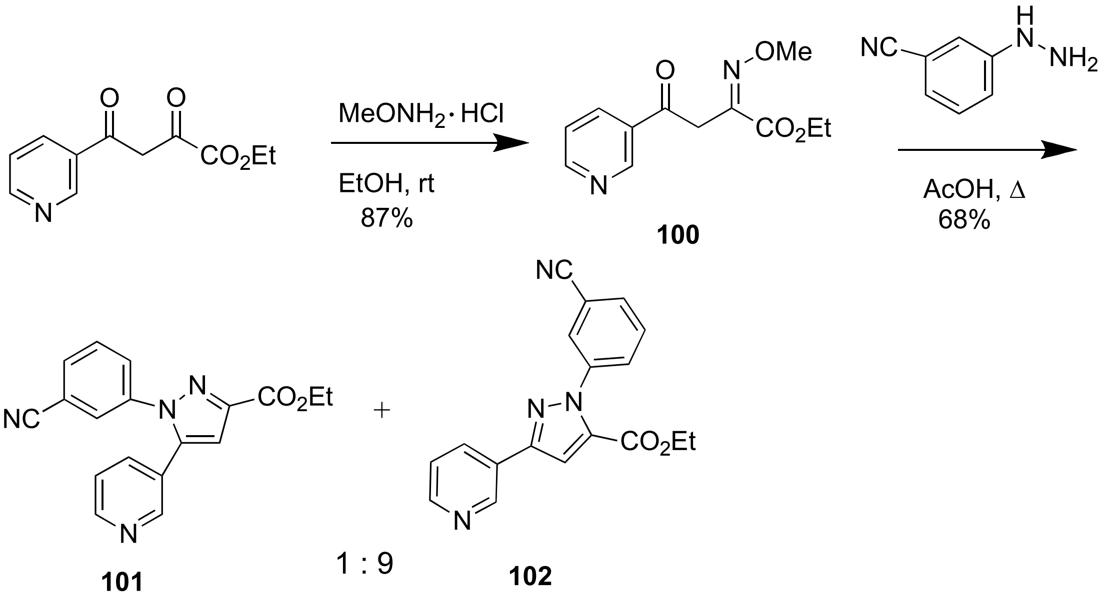
Scheme 37

When 5-hydrazinylmethyl-3-methyl-1-(3-methyl-1*H*-pyrazol-5-yl)methyl)-1*H*-pyrazole **97** was treated with ethyl 2,4-dioxopentanoate in ethanol gave a mixture of two *tris*-pyrazoles **98** and **99** in 10% and 25% yields respectively (Scheme 38).[84]



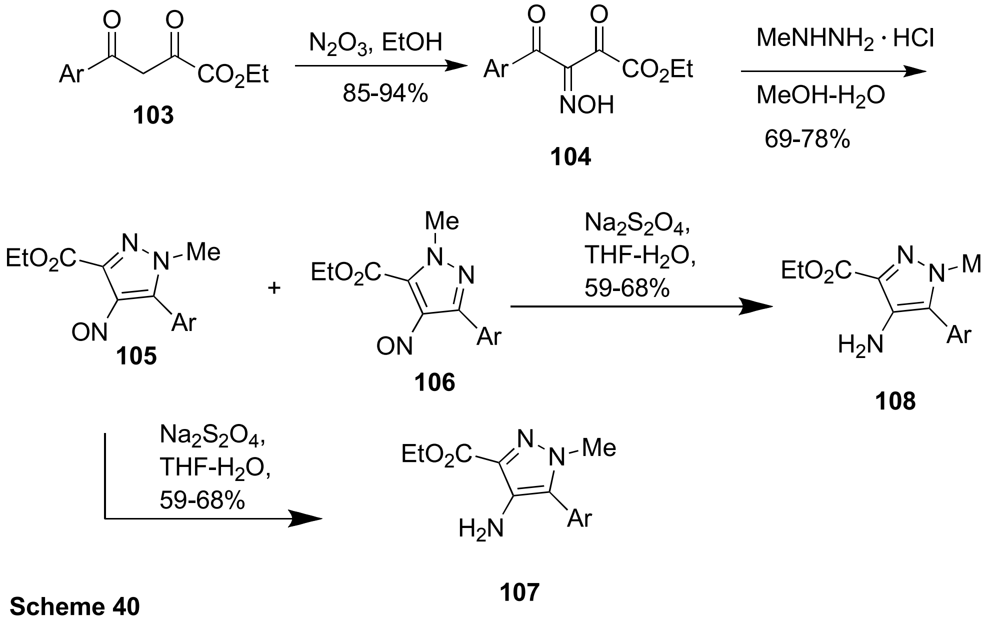
Scheme 38

When ethyl 2,4-dioxo-4-(pyridin-3-yl)butanoate was treated with methoxyamine hydrochloride gave ethyl 2-methoxyimino-4-oxo-4-(pyridin-3-yl)butanoate **100**, which then reacted with 3-hydrazinylbenzonitrile to give a mixture of two isomers **101** and **102** in a percentage 1:9 respectively (Scheme 39).[65]



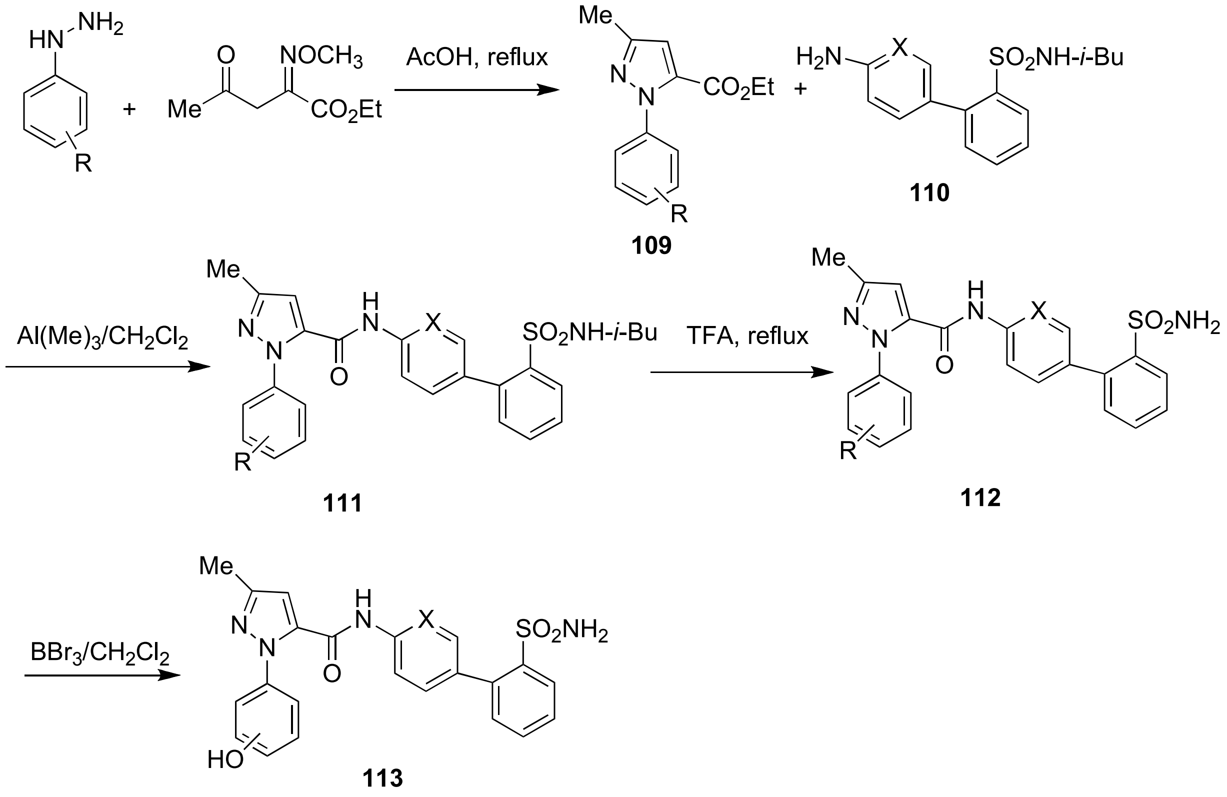
Scheme 39

Treatment of pyruvate **103** with dinitrogen trioxide (generated from sodium nitrite and HCl) in ethanol gave the oxime **104**. Cyclization of **104** with methyl hydrazine gave a mixture of the nitroso pyrazoles **105** and **106**, which were separated by flash chromatography. Reduction of the nitroso group with sodium dithionite in aqueous THF gave the respective aminopyrazoles **107** and **108** (Scheme 40).[85]



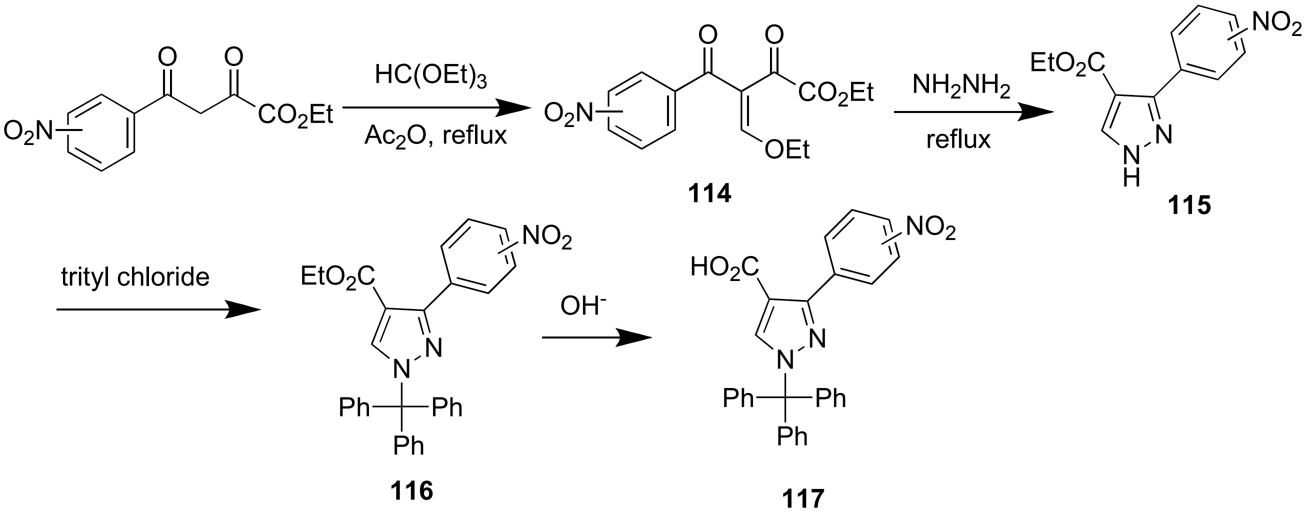
Scheme 40

Ethyl 3-methyl-1-phenyl-1*H*-5-carboxypyrazoles **109** were prepared regioselectively from a condensation of the appropriate phenylhydrazine and ethyl 2-(*N*-methoxyimino)-4-oxopentanoate.[86,87] Coupling of ester **109** with the known amines **110** gave good yields of the amides **111.** Deprotection of the *tert*-butylsulfonamide moiety, by treatment with trifluoroacetic acid, afforded compounds **112.** Treatment of the methoxy-substituted precursor compounds **112** with excess boron tribromide afforded the phenolic analogues **113** (Scheme 41), which is useful as non-amidine factor Xa inhibitors.[88,89]



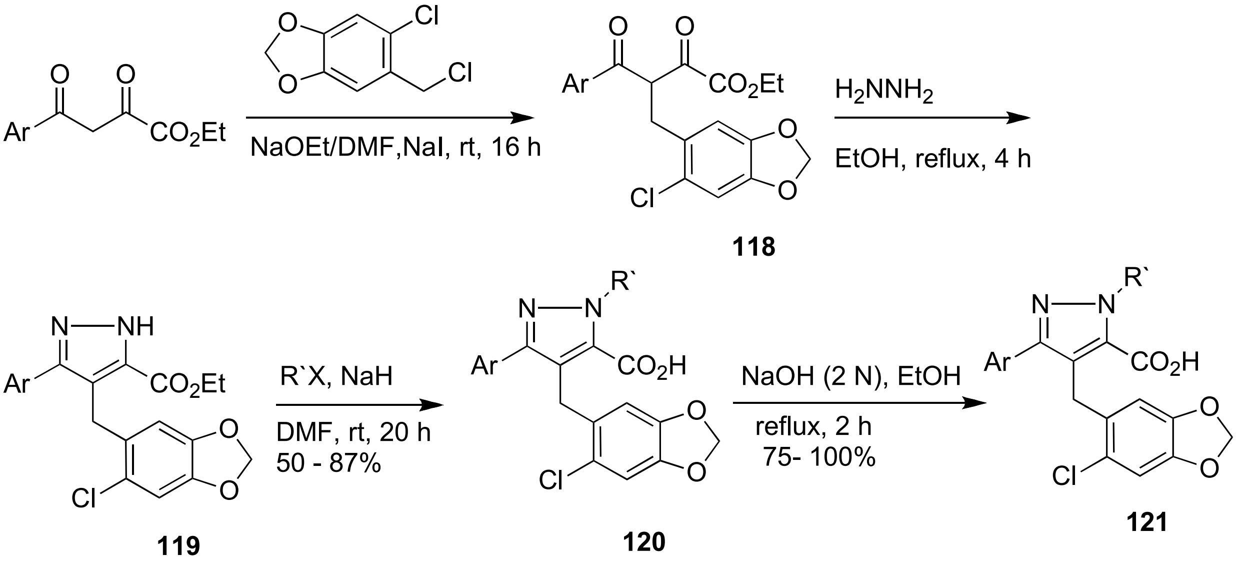
Scheme 41 R = H, 2-OMe, 3-OMe, 4-OMe; X = CH, N, C-F

The pyrazole derivatives were synthesized from para or meta nitrobenzaldehydes which was refluxed with triethyl orthoformate to give the enol ether **114**. Cyclization of **114** with hydrazine afforded **115** that were then linked to trityl resin through one of the pyrazole nitrogens. The hydrolysis of the ester **116** to **117** by alkali (Scheme 42).[90]



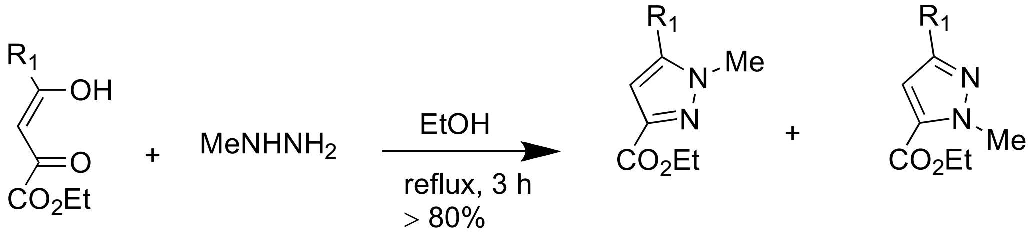
Scheme 42

C-Alkylation of α,γ,-diketoesters with 6-chloropiperonyl chloride were performed in the presence of EtONa and NaI in DMF. The crude compounds **118** were allowed to react directly with hydrazine monohydrate in ethanol to afford the desired pyrazole esters **119**. Regioselective alkylation of **119** with the requisite alkyl halide or alkyl tosylate in the presence of NaH in DMF at room temperature gave compounds **120**. Finally, the pyrazole acids **121** (Scheme 43) were obtained after saponification in good yields which useful as potent nonpeptide endothelin antagonists.[6]



Scheme 43

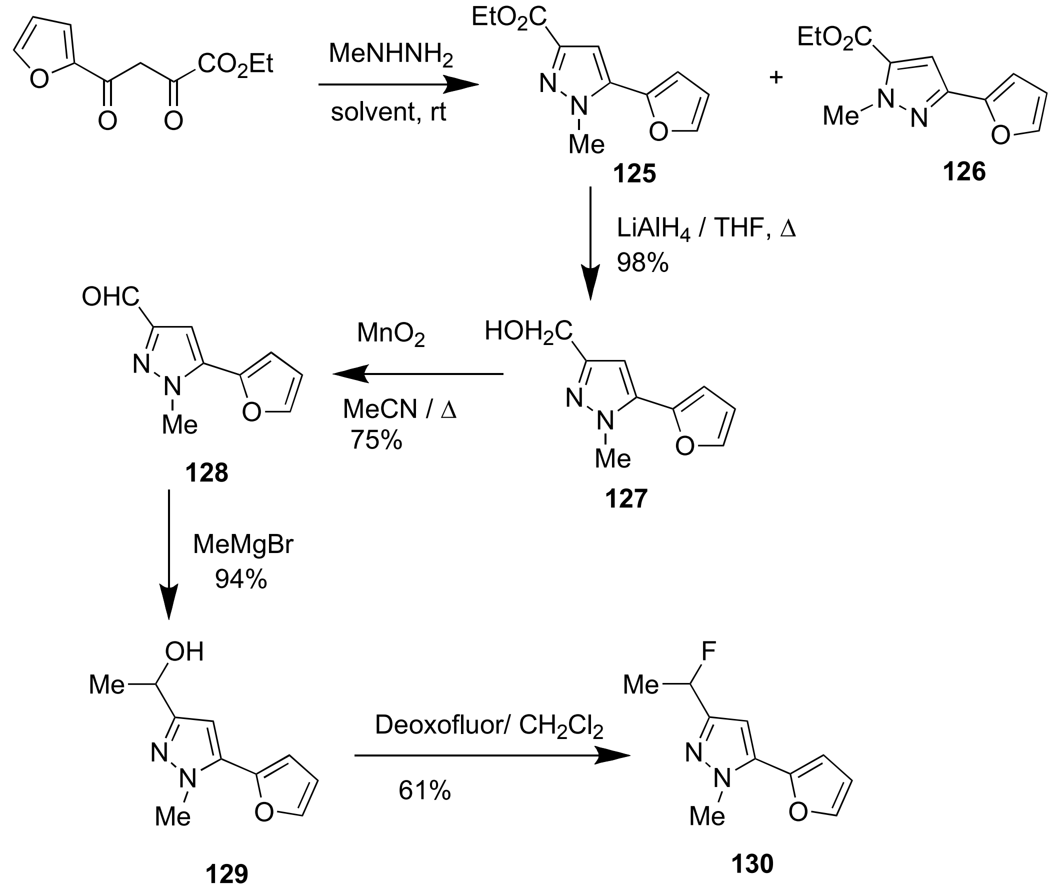
The target compounds **123**, **124** starts from 2,4-dioxopentanoic acid ethyl ester **122** (R_1 = Me) or the 2,4-dioxo-4-phenyl-butyric acid ethyl ester **122** (R_1 = Ph). These *β*-diketo compounds undergo reactions with methyl and phenyl hydrazine, yielding a 2:1 to 1:2 mixture of the two isomeric disubstituted pyrazole-3-carboxylic acid ethyl esters **123** and **124**, respectively (Scheme 44).[91,92]



122 **123** **124**

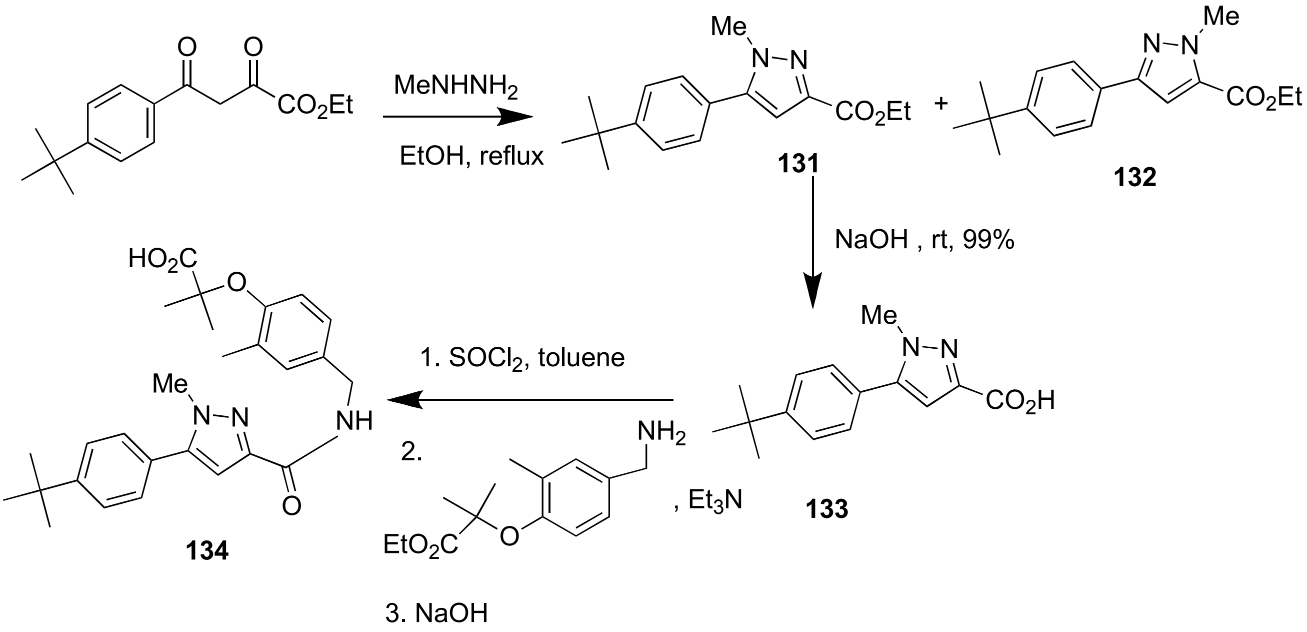
Scheme 44 R_1 = Me, Ph

The reaction of the ethyl 4-(furan-2-yl)-2,4-dioxobutanoate with methylhydrazine in ethanol at room temperature afforded an almost 1:1 mixture of the two 5-furyl **125** and 3-furyl **126** regioisomers in high yield; these were then easily separated with the aid of flash chromatography. In contrast to the lack of regioselectivity observed in EtOH, when the condensation reaction was carried out with the fluorinated solvents TFE and HFPI, the ratio increased to 93:7 in favor of the desired regioisomer **125**, which was obtained in almost quantitative yield. 3-(Ethoxycarbonyl)-5-(2-furyl)-*N*-methylpyrazole **125** was then converted into the aldehyde **128**, obtained in 75% combined yield through a two-step sequence involving $LiAlH_4$ reduction to the corresponding alcohol **128** and subsequent oxidization with MnO_2, Compound **127** was then used as the key intermediate for the preparation of the rest of the fluorinated analogs of tebufenpyrad (Scheme 45). Reaction of **128** with MeMgBr afforded the 1-hydroxyethyl derivative **129** in 94% yield. Subsequent treatment of **129** with deoxofluor provided the monofluorinated derivative **130** in 61% yield.[93,94]



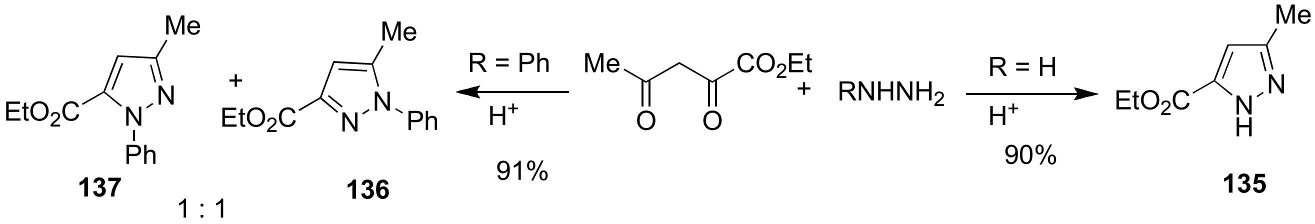
Scheme 45

GSK183390A **134** has recently emerged as a potent dual agonist of PPARα/γ and a candidate for treatment of dyslipidemia, the synthesis of 2-{4-[(5-(4-tert-butylphenyl)-1-methyl-1*H*-pyrazole-3-carboxamido]methyl]-2-methylphenoxy}-2-methylpropanoic acid **134** is depicted in Scheme 46 via coupling of benzylamine and pyrazole. The condensation between methylhydrazine and diketoester produced a mixture of 1,3,5-trisubstituted pyrazole **131** and its isomer **132**. Coupling of **131** with benzylamine derivatives in the presence gave the target drug **134** in 73% yield.[16]



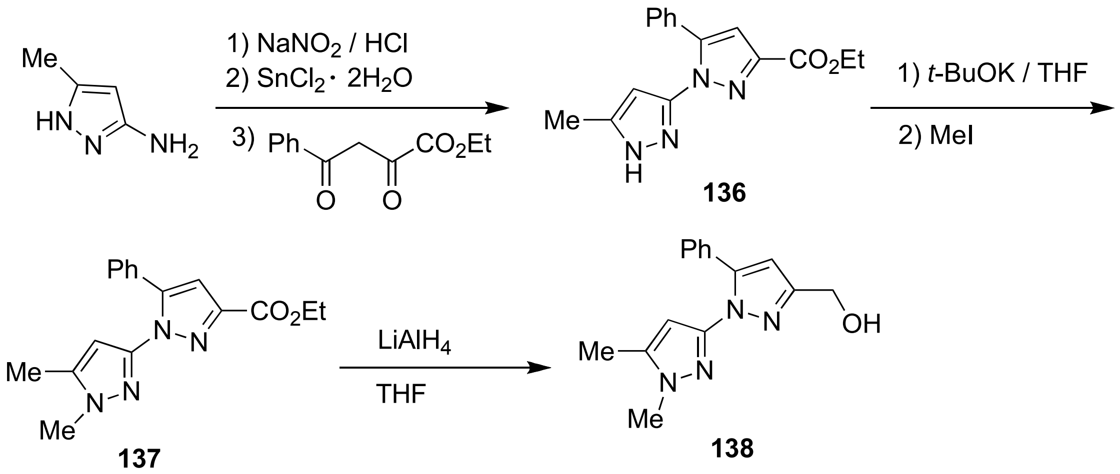
Scheme 46

Solventless condensation of ethyl 2,4-dioxopentanoate and a hydrazine in the presence of a catalytic amount of sulfuric acid at room temperature afforded pyrazole derivatives **135** in high yield, while its reaction with phenylhydrazine under the same conditions gave the equal percentage of two pyrazole isomers **136** and **137** (Scheme 47).[95]



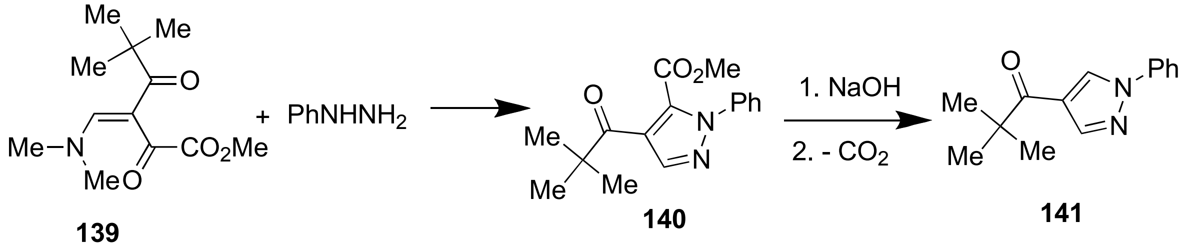
Scheme 47

Compound **136** was prepared from commercially available 5-methyl-1*H*-pyrazol-3-amine by diazotation in HCl followed by reduction with tin chloride and the intermidiate diamine is not isolated but has immediately undergone a condensation with the β-diketones to give the ester **136** in a 36% yield. The methylation of this product in the presence of *t*-BuOK as base led to one isolated α-isomer **137** in a 29%, Finally, the compound **137** was convert to the target product **138** using $LiAlH_4$ as agent of reduction (Scheme 48).[96]



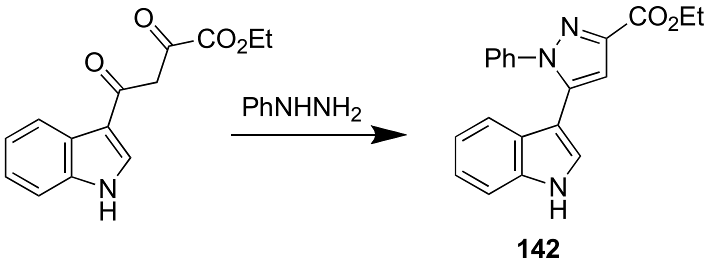
Scheme 48

Reaction of methyl 5,5-dimethyl-3-dimethylaminomethylene-2,4-dioxohexanoate **139** with phenylhydrazine afforded methyl 1-phenyl-4-pivaloyl-1*H*-pyrazole-5-carboxylate **140** which was converted to 1-phenyl-4-pivaloyl-1*H*-pyrazole **141** by basic hydrolysis followed by loss of carbon dioxide (Scheme 49).[97]



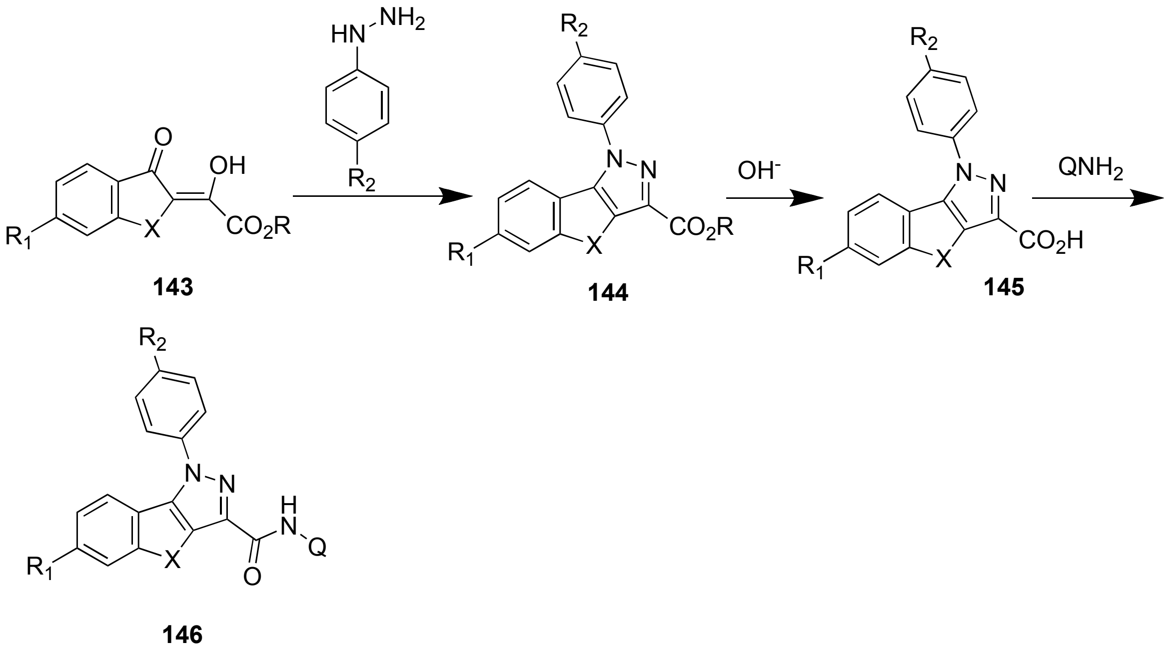
Scheme 49

Reaction of ethyl 4-(1*H*-indol-3-yl)-2,4-dioxobutanoate[98,99] with phenylhydrazine in refluxing acetic acid gave the pyrazole **142** (Scheme 50).[99]



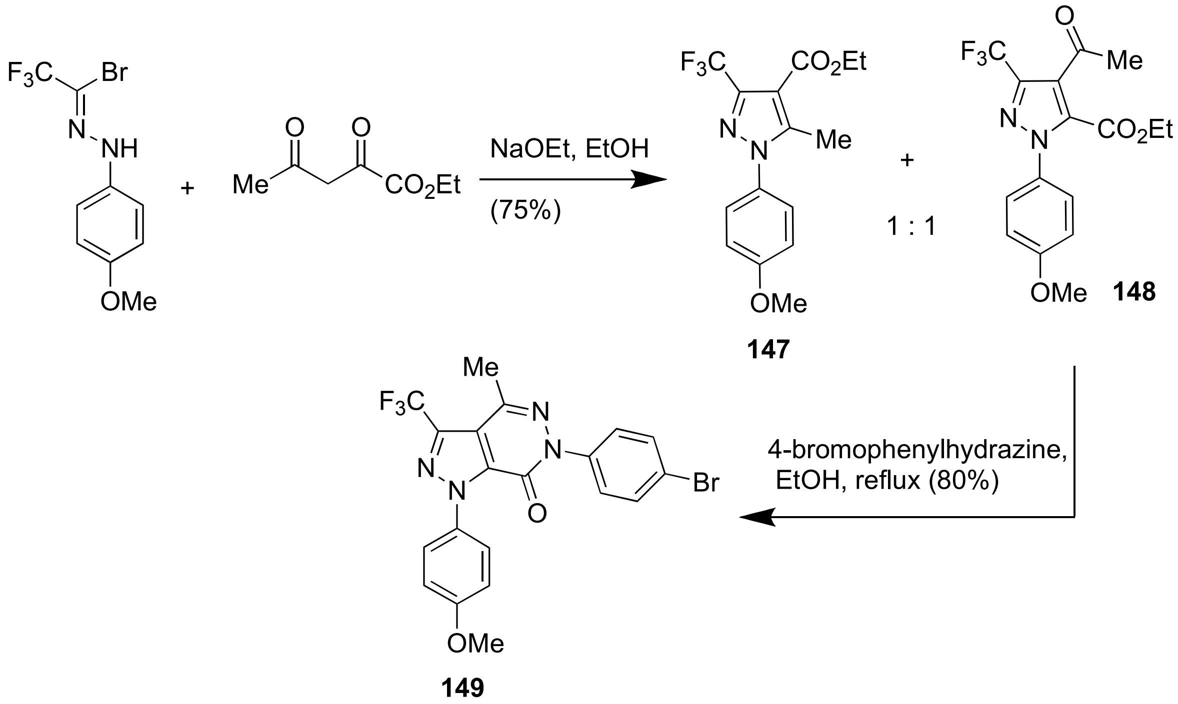
Scheme 50

Condensed pyrazoles **146** which exhibit antiproliferative activity were prepared by treating **143** with arylhydrazines, followed by ester hydrolysis and amination of **145** to give the target molecules (Scheme 51).[21-25]



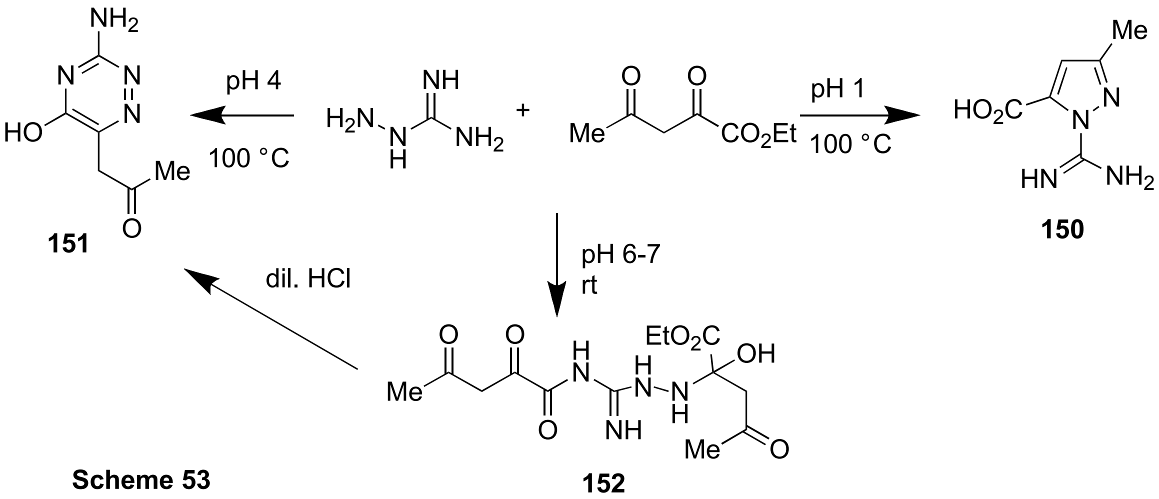
Scheme 51 X = $(CH_2)_{1-3}$, CH:CH, O; R = CO_2Me, CO_2Et, R_1 = H, Cl, OMe, NMe_2, OH; R_2 = H, 4-Cl, 4-F, 2-Cl, 3-Me, 4-CO_2H, 2-Me, 4-OMe, 2-CO_2H

The 1*H*-pyrazolo-[3,4-*d*]-pyridazin-7(6*H*)-one core analog **149** was prepared. Therefore, 1-(1-bromo-2,2,2-trifluoroethylidene)-2-(4-methoxyphenyl)hydrazine was treated with ethyl 2,4-dioxovalerate in the presence of ethanolic sodium ethoxide to afford a good yield of a separable 1:1 mixture of pyrazole regioisomers **147** and **148**. The desired **148** was smoothly condensed with 4-bromophenylhydrazine in refluxing ethanol to give the 1*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one core **149** (Scheme 52), which crystallized out of solution upon cooling.[100]



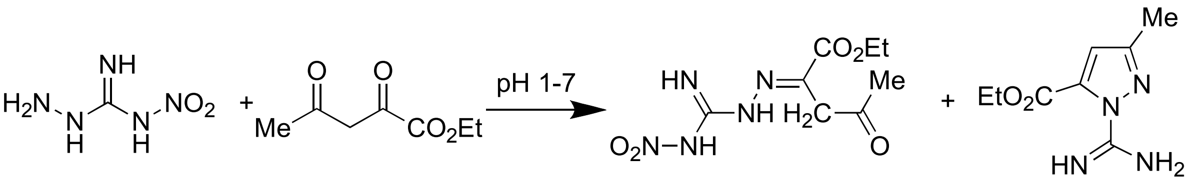
Scheme 52

Aminoguanidine was treated with ethyl acetopyruvate at 100 °C and pH 1 to give pyrazole **150**, whereas the reaction at pH 4 gave triazine **151**. While at room temperature and at pH 6-7 gave the dimer **152** that was hydrolyzed by dil. HCl to give **151** (Scheme 53).[101]



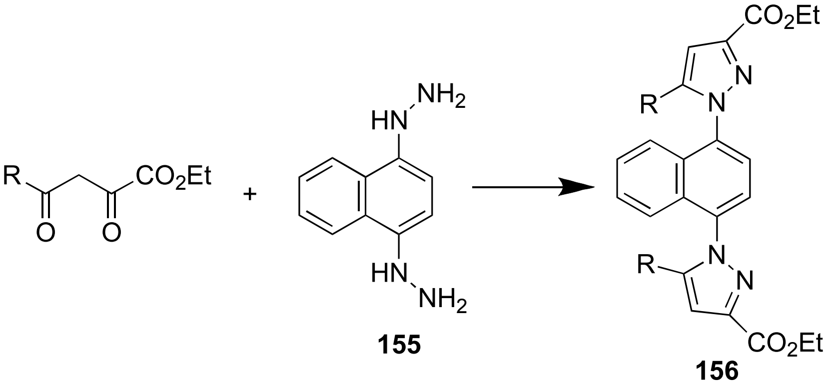
Scheme 53

Nitroaminoguanidine was treated with ethyl acetopyruvate at pH 1-7 to give **153** and pyrazole-5-ester **154** (Scheme 54).[101]



Scheme 54

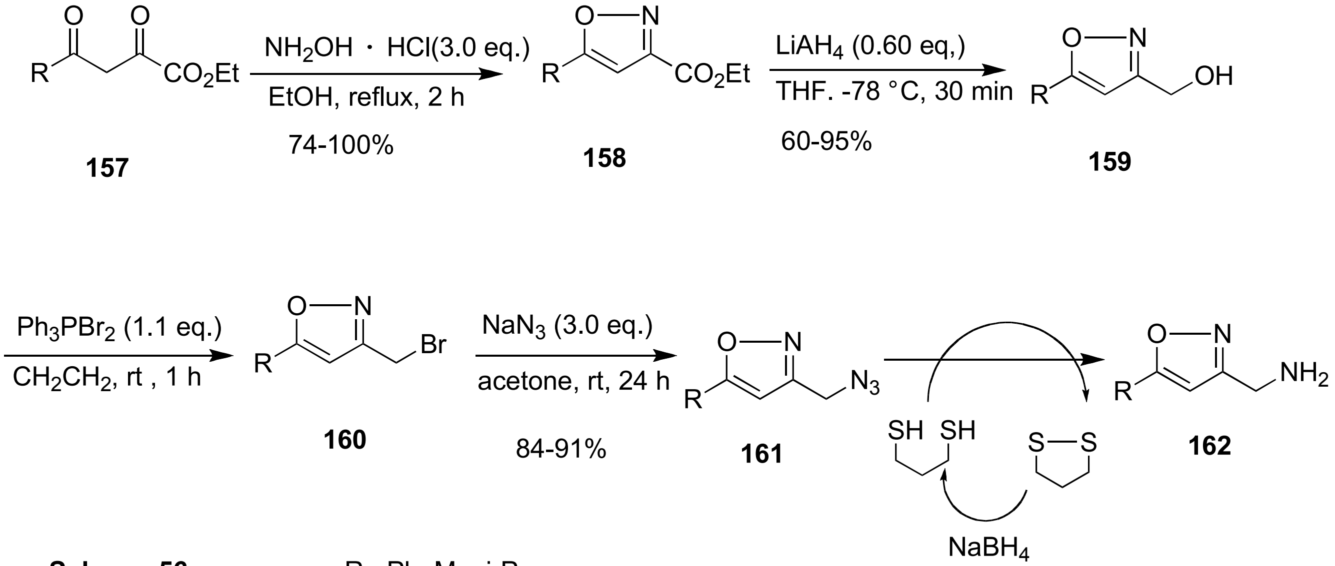
Dihydralazine **155** reacted with ethyl 2,4-dioxoalkanoates to give dipyrazolylphthalazines **156** (Scheme 55).[102]



Scheme 55 R = Ph, anisyl, tolyl

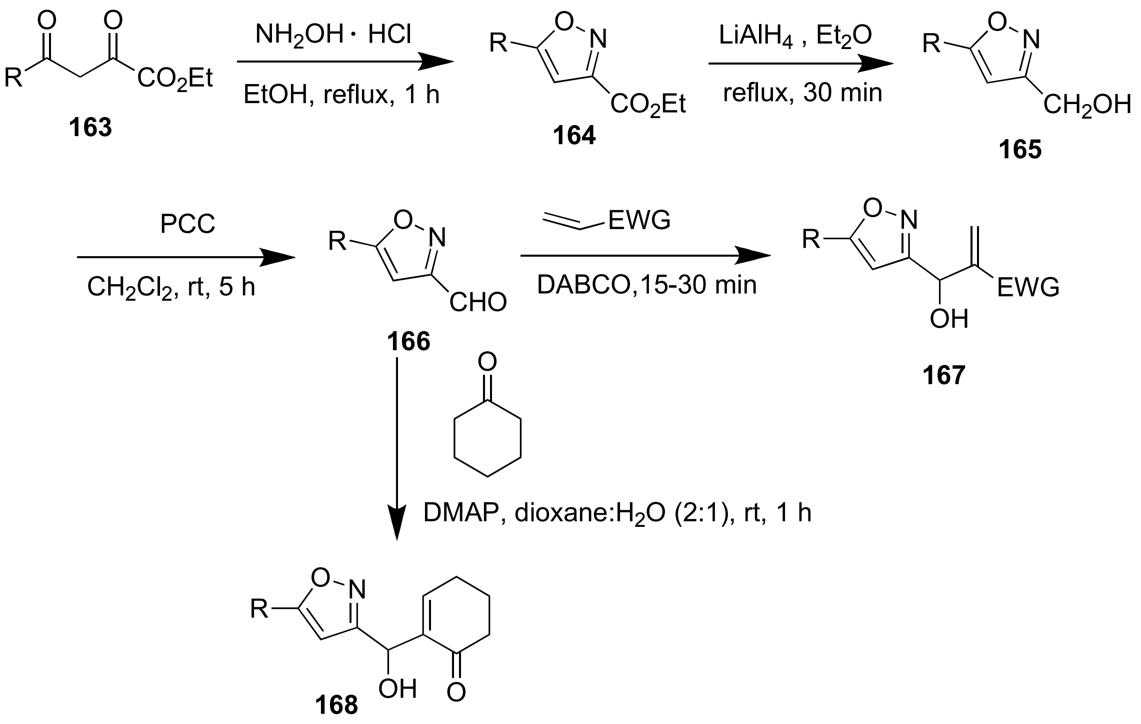
2.1.4. ISOXAZOLES

Diketoester **157** was converted to isoxazole ester **158** upon reaction with hydroxylamine hydrochloride in refluxing ethanol. Isoxazole ester **158** was reduced to the corresponding alcohol **159** using lithium aluminum hydride in THF at -78 °C. Alcohol **159** was treated with triphenylphosphine dibromide to furnish bromide **160**, which was converted to isoxazole azide **161** by reaction with sodium azide in acetone, azide **161** can be converted to the corresponding amine **162** by using 1,3-propanedithiol reduced organic azides selectively to amines, itself being oxidized to the cyclic disulfide (Scheme 56).[10]



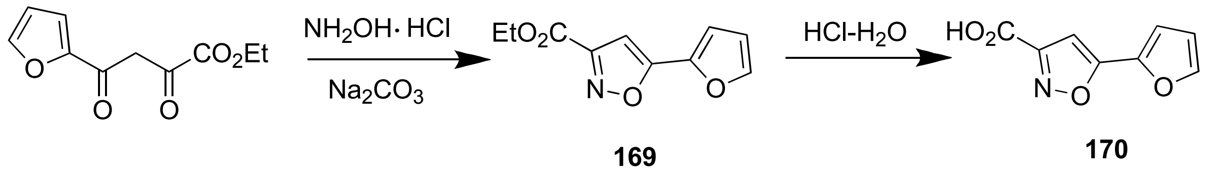
Scheme 56 R= Ph, Me, i-Pr

The reaction of 2,4-diketo esters **163** with hydroxylamine hydrochloride gave 3-isoxazole esters **164**, in excellent yield, these ester were reduced with lithium aluminum hydride and the resulting alcohols **165** were oxidized with pyridinium chlorochromate (PPC) to yield substituted 3-isoxazolecarbaldehydes **166**. These aldehydes were then treated with various activated alkenes in the presence of DABCO in the absence of any solvent to furnish the Baylis-Hillman adducts **167** in excellent yields, also, the isoxazolecarboaldehydes undergo fast reaction with cyclohexenone in the presence of DMAP to give **168** (Scheme 57).[103]



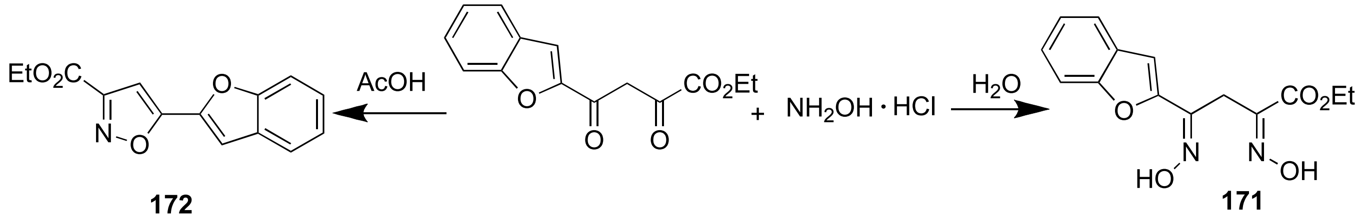
Scheme 57 R= Ph, 4-MeC_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4; EWG = CN, $CONH_2$, CO_2R

Ethyl 2-furoylpyruvate was reacted with hydroxylamine hydrochloride in the presence of sodium carbonate to afford ethyl 5-(2-furyl)-3-isoxazolecarboxylate **169** which then hydrolyzed with HCl-H_2O to give 5-(2-furyl)-3-isoxazolecarboxylic acid **170** (Scheme 58).[14]



Scheme 58

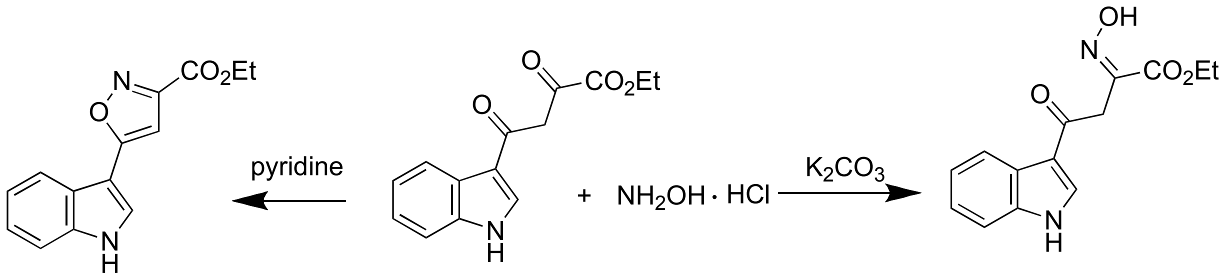
Ethyl 2-benzofuroylpyruvate on treatment with hydroxylamine hydrochloride in water give the dioxime **171**, while in acetic acid afforded ethyl 5-(2-benzofuryl)-3-isoxazolecarboxylate **172** (Scheme 59).[15]



Scheme 59

Reaction of with hydroxylamine hydrochloride in the presence of anhydrous potassium carbonate to give the corresponding oxime **173** while in pyridine gave ethyl isoxazole-3-carboxylate **174** in good yields

(Scheme 60).[18]

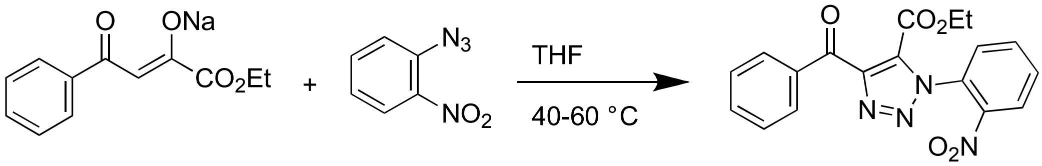


174 **173**

Scheme 60

2.1.5. TRIAZOLES

The reactivity of benzolpyruvates as β-diketo moiety towards 1,3-dipoles was studied. Thus, when treated with an organic azide **175**, benzoylpyruvates may react to form cycloadducts, like 1,2,3-triazole **176** (Scheme 61).[104]

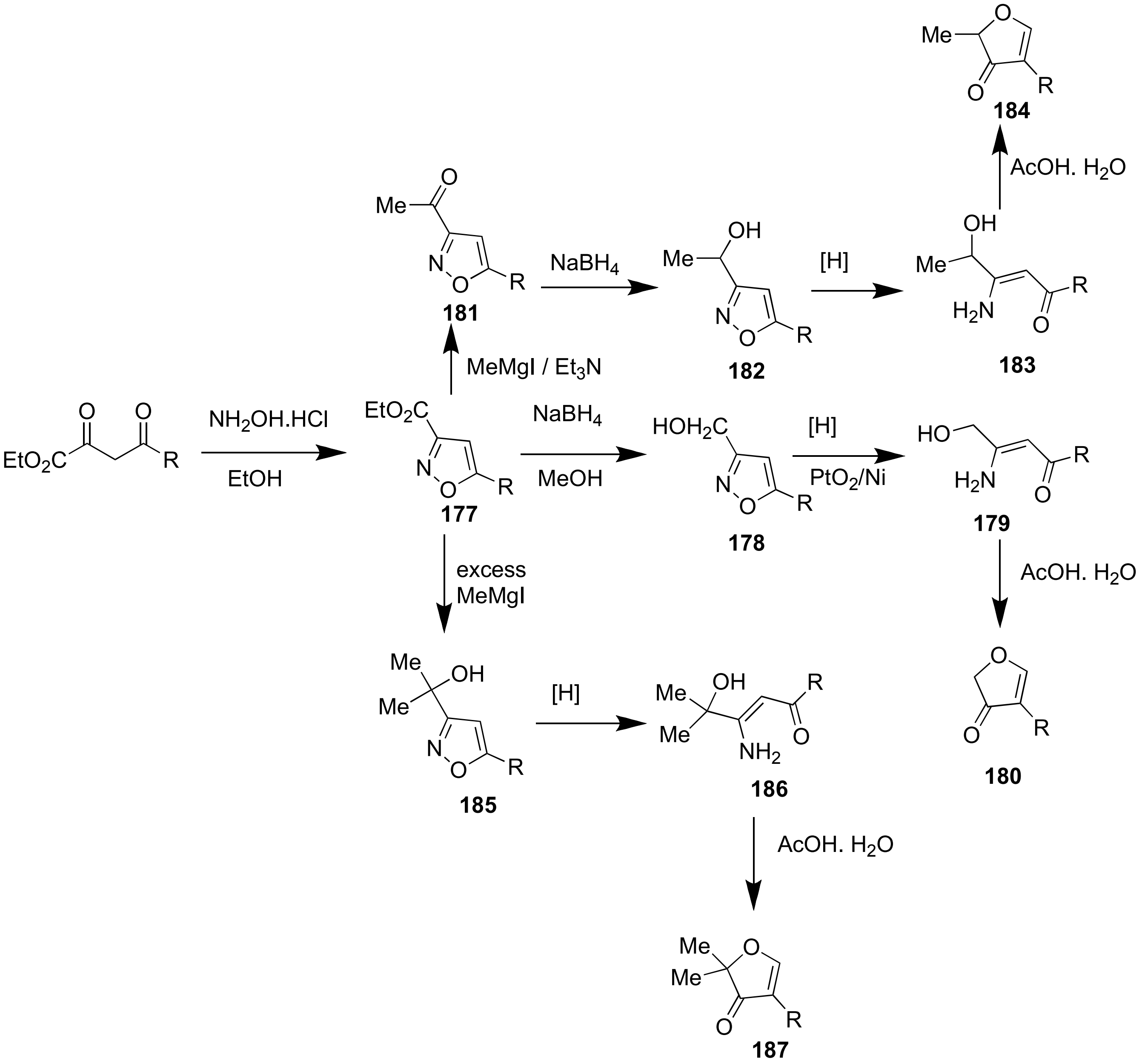


175 **176**

Scheme 61

2.1.6. FURANONES

Ethyl 2,4-dioxoalkanoates, are used in the synthesis of 3(2*H*)-furanone ring system, the key skeletal element of many natural product antitumor agents. The first method consisted in the reaction of the 2,4-dioxoalkanoates with hydroxylamine hydrochloride in ethanol to form in good yield the corresponding 3,5-disubstituted isoxazoles **177**.[105] Isoxazoles have long been regarded as a protected form of 1,3-diketones, from which are commonly prepared, by virtue of its catalytic or chemical reduction to β-enamino-ketones.[106] Primary alcohols **178** were obtained in essentially quantitative yield by action of sodium borohydride on **177** in methanol, while secondary alcohols **182** were derived in a two-step sequence, namely reaction with methyl magnesium iodide in the presence of triethylamine to give the ketone **181** followed by reduction with sodium borohydride. Tertiary alcohols **185** were directly obtained by treatment of **177** with an excess of Grignard reagent in more than 80% yield. On exposure of all the isoxazole alcohols to hydrogen and PtO_2/Ni-Raney mixture of catalysts in methanol a rapid reaction ensued to give the corresponding β-enaminoketones having a primary **179**, **183** or tertiary **186** γ-hydroxy group. All these vinylogous amides were cleanly transformed to 3(2*H*)-furanones **180**, **184** and **187** respectively by treatment at room temperature in AcOH:H_2O 2:1 mixture in good yields (Scheme 62).[3]



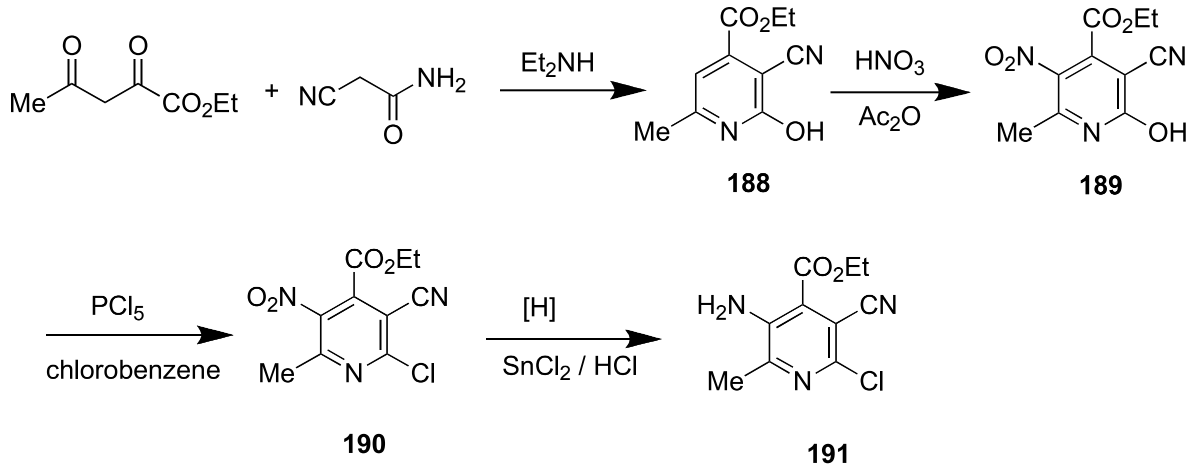
Scheme 62 R = Et, pentyl, Me_2CHCH_2, Ph, 2-$MeOC_6H_4$

2.2. SIX-MEMBERED SYSTEMS

2.2.1. PYRIDINE DERIVATIVES

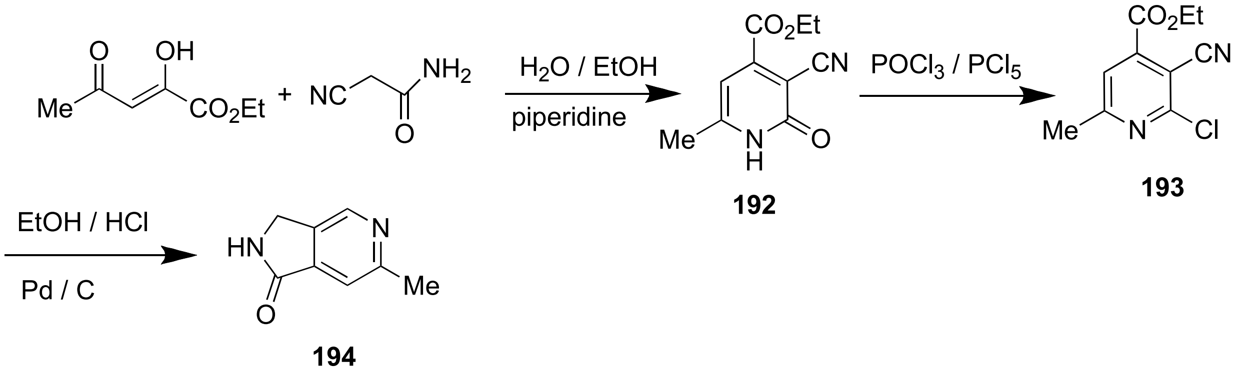
Ethyl 2,4-dioxopentanoate was condensed with 2-cyanoacetamide in the presence of diethyl amine to give ethyl 3-cyano-2-hydroxy-6-methylpyridine-4-carboxylate **188** which on nitration with nitric acid in acetic anhydride give the corresponding 5-nitro derivatives **189**, halogenation followed with reduction of the latter compound gave ethyl 3-amino-6-chloro-5-cyano-2-methylpyridine-4-carboxylate **191** (Scheme

63).[107]



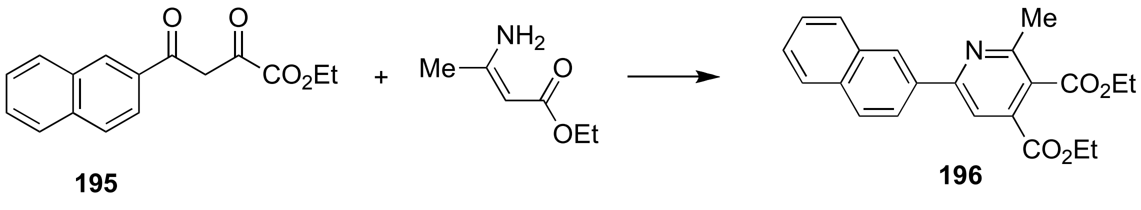
Scheme 63

Ethyl 2-hydroxy-4-oxopent-2-enoate was condensed with 2-cyanoacetamide in H_2O/ EtOH in piperdine to give ethyl 2-methyl-5-cyano-6(1*H*)-pyridone-4-carboxylate the tautomeric form of **192** which then treated with a mixture of PCl_5 and $POCl_3$ to give ethyl 2-methyl-5-cyano-6-chloro-4-pyridinecarboxylate **193**, Reduction of the latter compound followed by cyclization afforded 2-methyl-5-aminomethyl-4-pyridinecarboxylic acid lactam **194** in 41.7% (Scheme 64).[108]



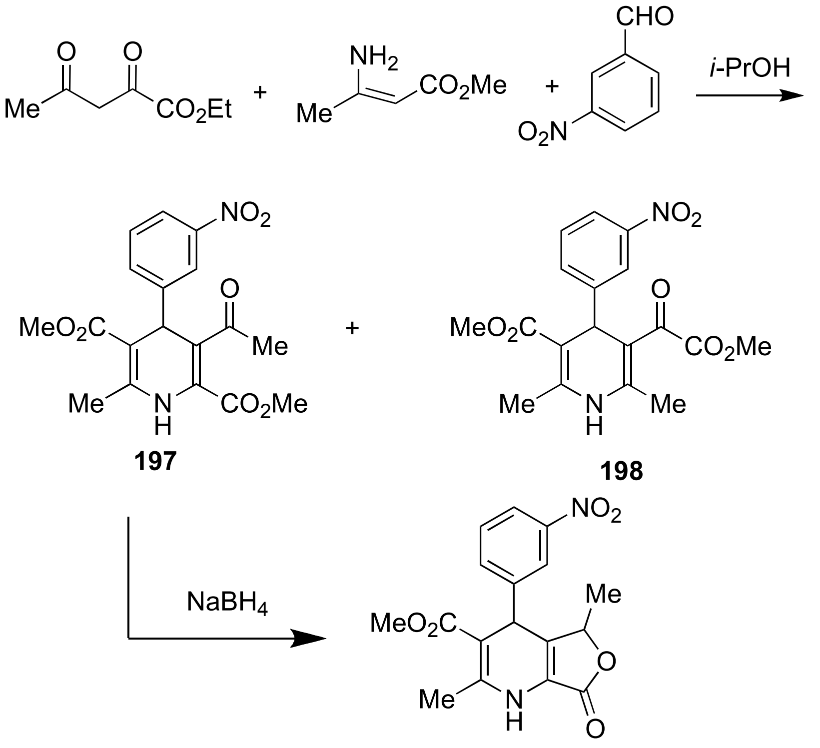
Scheme 64

Oka *et al.* reported the synthesis of diethyl 2-methyl-6-(naphthalen-2-yl)pyridine-3,4-dicarboxylate **196** by reaction of ethyl 4-(naphthalen-2-yl)-2,4-dioxobutanoate **195** with ethyl 3-aminobut-2-enoate (Scheme 65).[109]



Scheme 65

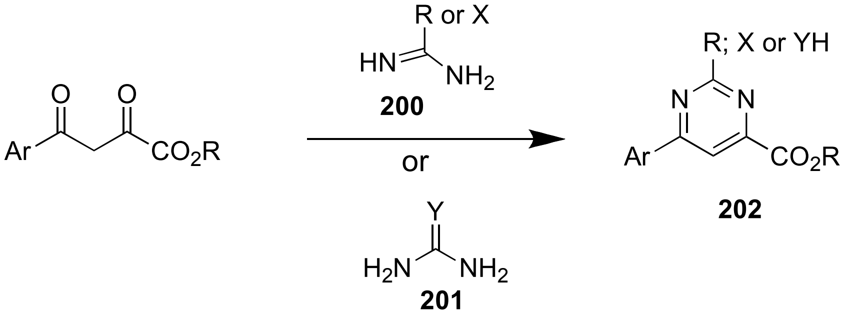
For the Hantzsch pyridine synthesis, methyl acetopyruvate was reacted with methyl 3-aminocrotonate and 3-nitrobenzaldehyde in isopropanol to give a mixture of two isomers **197** and **198** in 26.7 % and 9.2% yields, which separeted by column chromatogrphy. Reduction of **197** with sodium borohydride in alcohol led to lactone **199** (Scheme 66).[110]



Scheme 66 **199**

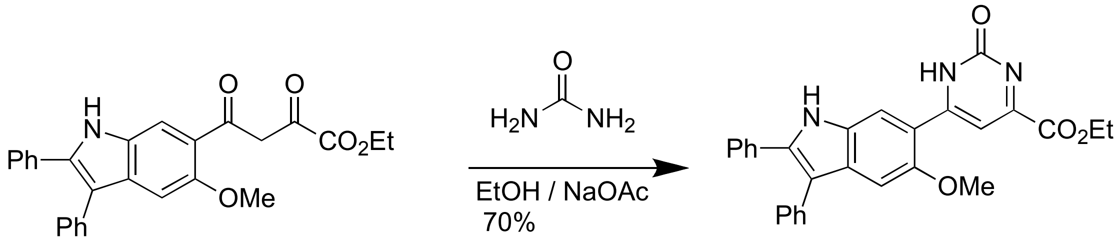
2.2.2. PYRIMIDIMES

Benzoylpyruvates can be reacted as β-diketones[111–114] with *N*,*N*`-dinucleophiles such as amidines **200a**, isoureas **200b**, guanidines **200c** (R =NH$_2$, NH-alkyl, NH-aryl etc.) and ureas **201** (R = O or S), Resulting in the formation of an aromatic or latent aromatic system, the reaction should accordingly be highly favored, yielding 2,4,6-trifunctionalized pyrimidines **202** or derivatives thereof (Scheme 67).



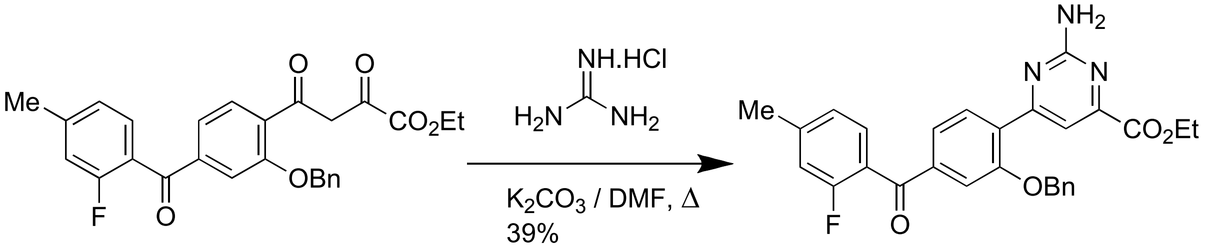
Scheme 67

The synthesis of pyrimidin-2-ones like **204** has been reported. Thus, the presence of base has been used to promote condensation between a benzoylpyruvate **203** and urea (Scheme 68).[115]



Scheme 68

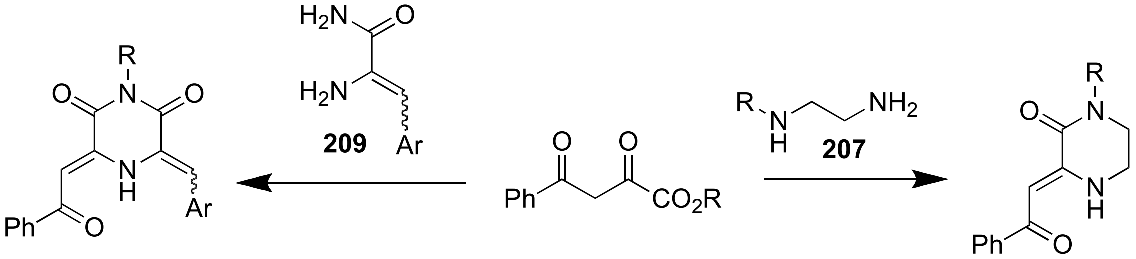
In a similar fashion, condensation between a benzoylpyruvate **205** and guanidine gives an entry to the imprinted 2-aminopyrimidine **206** (Scheme 69).[116]



Scheme 69

2.2.3. PIPERAZINES

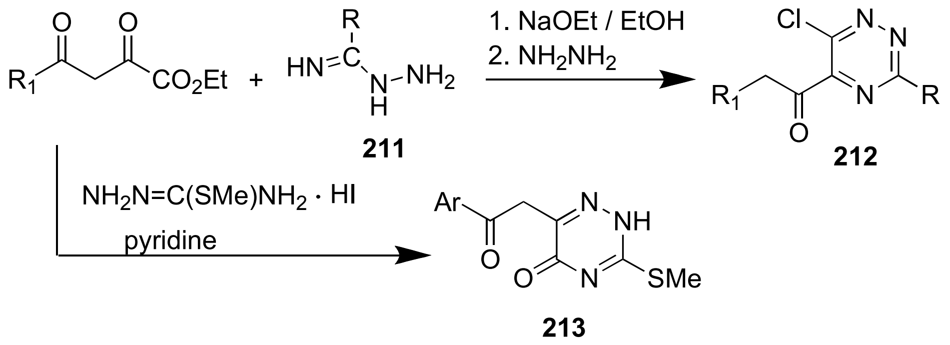
Benzoylpyruvate can react across α-keto ester moiety with *N*,*N*`-dinucleophiles. Reactions involving ethylene diamines **207** or α-amino acrylamides **209** lead to piperazine-2-one derivatives like **208** and **210** (Scheme 70).[117–120]



Scheme 70

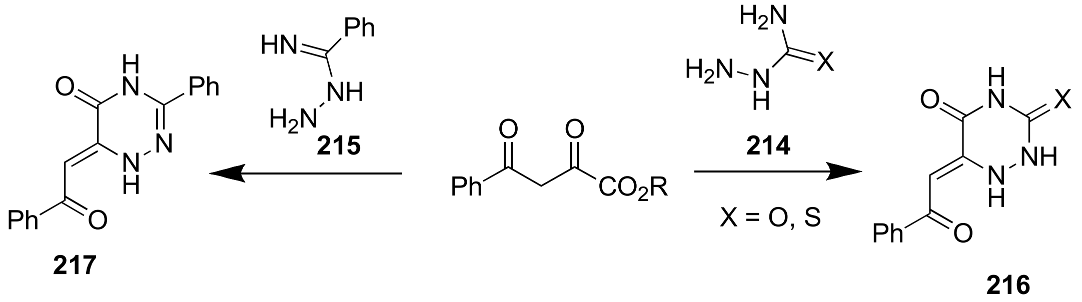
2.2.4. 1,2,4-TRIAZINES

Condensation of ethyl 2,4-dioxobutyrates with imidio-hydrazides **211** or *S*-methylisothiosemicarbazide hydroiodide in pyridine gave the corresponding 1,2,4-triazin-5(2H)-ones **212** and **213** in 50-80% (Scheme 71).[20,120-122]



Scheme 71 R = Me, Ph, $R_1 = CH_2COR_2$; R_2 = Ph, $4\text{-}MeC_6H_4$, $4\text{-}MeOC_6H_4$, $4\text{-}ClC_6H_4$

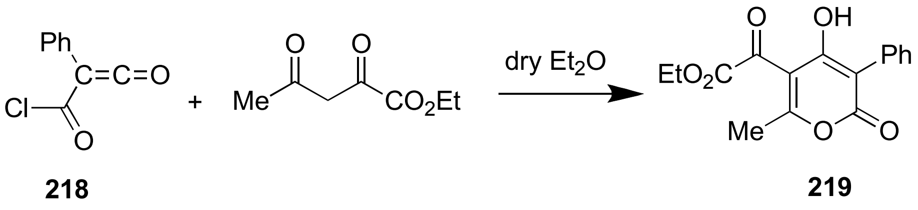
Similarly, reaction with semicarbazides **214** and aminoamidine **215** lead to 1,2,4-triazine-5-one derivatives like **216** and **217** (Scheme 72).[117-120]



Scheme 72

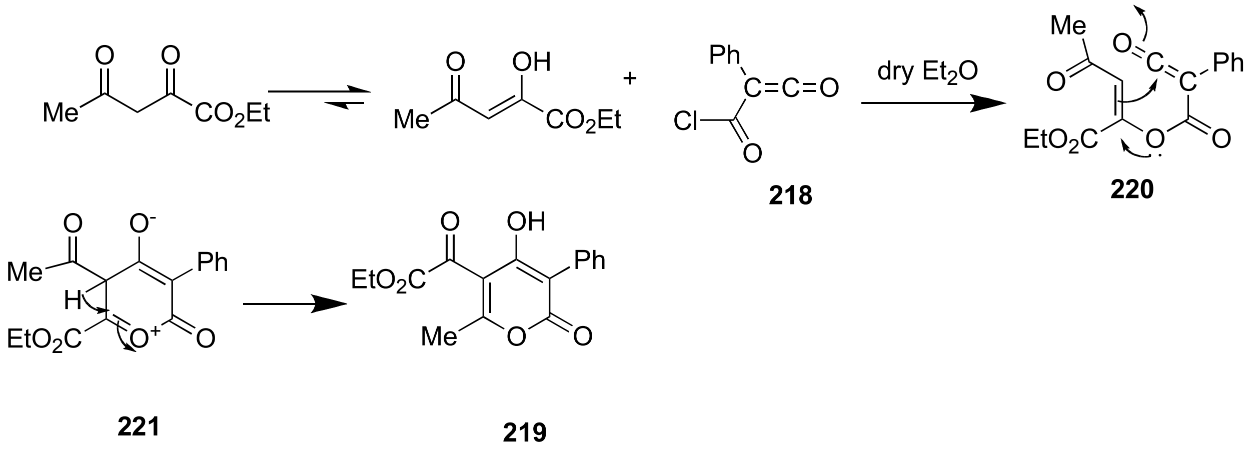
2.2.5. PYRONE DERIVATIVES

2-Pyrone derivatives **219** were prepared in a one step procedure from (chlorocarbonyl)phenylketene **218** and ethyl 2,4-dioxopentanoate (Scheme 73).[123]



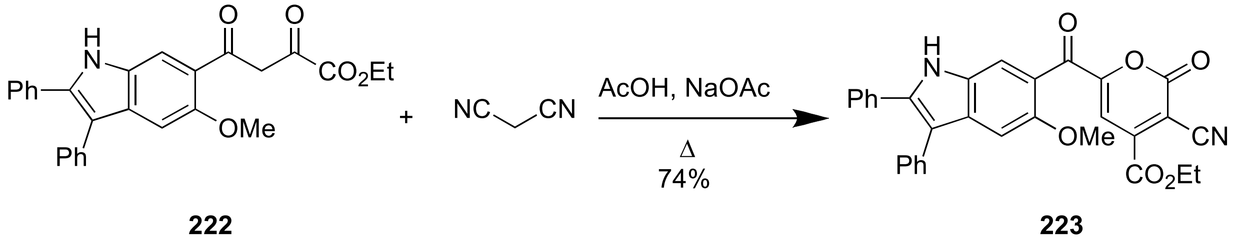
Scheme 73

Thus the cycloaddition mechanism represented in Scheme 74 accomplished by mixing the equimolar quantities of (chlorocarbonyl)phenyl ketene **218** and 1,3-diketones at ambient temperature in dry ether. 1,3-Diketones exist mainly in the enol forms, therefore, the OH group of the enol form will attack the acyl chloride of the ketene followed by ring closure of **220** to produce the product **219**.[123]



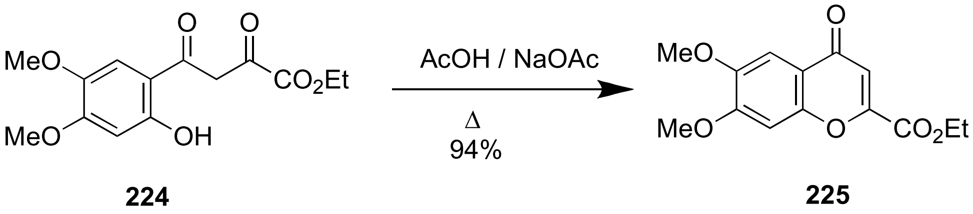
Scheme 74

The reaction between malononitrile and benzoylpyruvate **222** gave 3,4,6-functionalized pyran-2-one **223** (Scheme 75).[115] The incipient enolate, formed by initial conjugate addition, attacks in turn one of the electrophilic nitriles to render a 3,4,6-functionalized pyran-2-one **223**.



Scheme 75

Benzoylpyruvates may themselves serve as cyclic precursors in the absence of external nucleophiles. With heteroatoms located at the 2-position of the aryl moiety, as in the case of **224**, it is possible to obtain fusion by intramolecular cyclodehydration across the a-keto group. This approach has been used to prepare chromone esters like **225** (Scheme 76).[4]

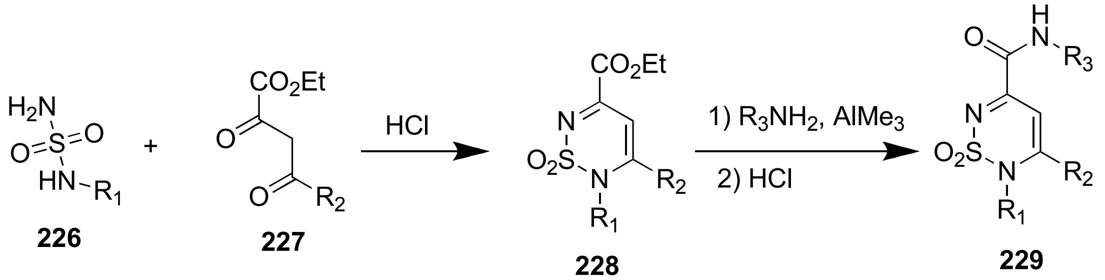


Scheme 76

2.2.6. THIADIAZINE DERIVATIVES

The synthesis of 2-substituted 1,2,6-thiadiazine-5-carboxylates were carried out with ethyl 2,4-

dioxovalerate **228**. Thus, the reaction of **227** with sulfamides **226** in ethanol or diglyme afforded the corresponding 3-methyl-1,2,6-thiadiazine-3-carboxylates **228**.The preparation of the amides **229** was carried by reaction of **228** with amines[124] (Scheme 77).

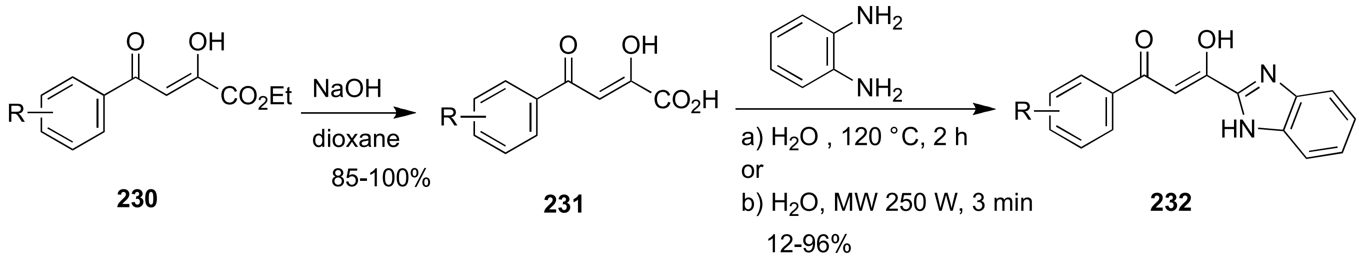


Scheme 77 R_1= Ph, 4-ClPh, benzyl, 2,4-diClBn, cyclohexyl, hexyl;
R_2= phenyl, 4-chlorophenyl, benzyl, cyclohexyl, hexyl;
R_3 = cyclohexyl, morpholinyl, piperidinyl, Ph

2.3. FUSED HETEROCYCLIC SYSTEMS

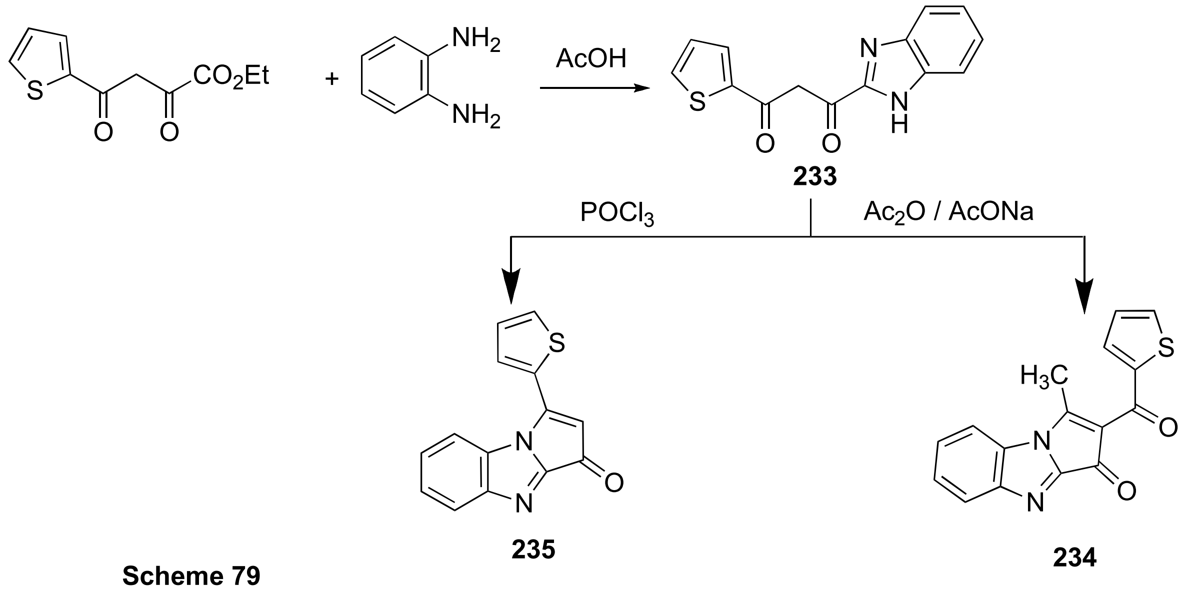
2.3.1. BENZIMIDAZOLE DERIVATIVES

The synthetic pathway to 1-aryl-3-(1*H*-benzimidazol-2-yl)-3-hydroxypropenone **232** are depicted in Scheme 1. The pyruvates **230** were converted by basic hydrolysis into the corresponding acids **231** which were subsequently condensed with 1,2-phenylenediamine hydrochloride to give the target compounds in microwave oven and conventional heating (Scheme 78).[19]



Scheme 78 R=H, 2-OH, 3-OH

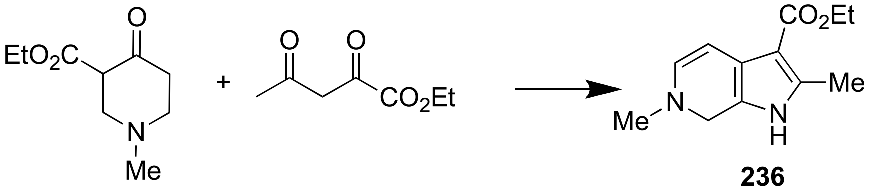
Condensation of ethyl 2-thionyl pyruvate with *o*-phenylenediamine in glacial acetic acid under reflux, gave the corresponding 1-(1*H*-benzimidazole-2-yl)-3-thiophen-2-yl)-propane-1,3-dione **233**. Pyrrolo[1,2-*a*]benzimidazole derivatives **234** and **235** were prepared via cyclocondensation of compound **233** with acetic anhydride in presence of sodium acetate and phosphorus oxychloride respectively (Scheme 79).[125]



Scheme 79

2.3.2. PYRROLO[2,3-*c*]PYRIDINE

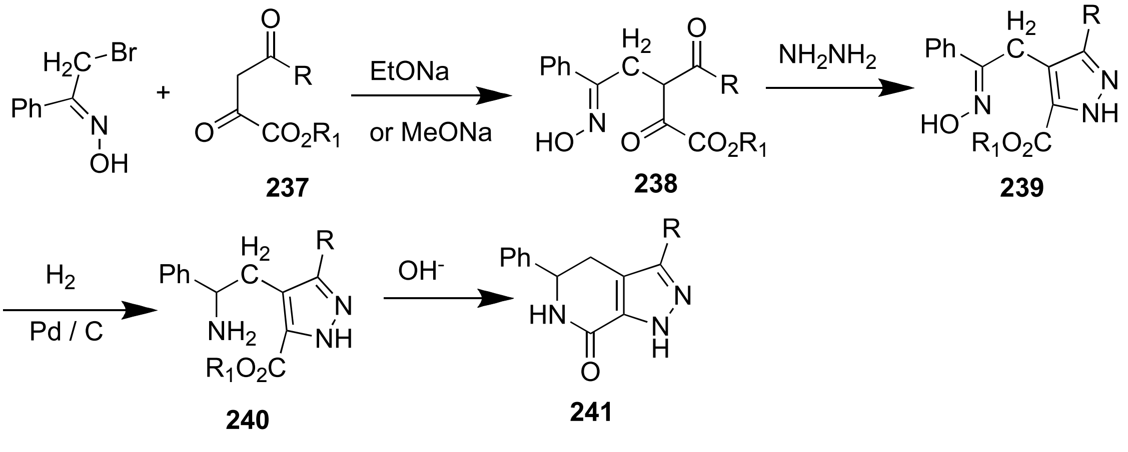
Ethyl 6,7-dihydro-2,6-dimethyl-1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylate **236** was obtained similarly by treatment of ethyl 2,4-dioxopentanoate with 3-ethoxycarbonyl-1-methyl-4-piperidone (Scheme 80).[51]



Scheme 80

2.3.3. PYRAZOLO[3,4-*c*]PYRIDINES

Pyrazolo[3,4-*c*]pyridines **241** were prepared by catalytic hydrogenation of **240** followed by cyclization. **240** were obtained (Scheme 81) by treating ω-bromoacetophenone oxime with sodium salt of acylpyruvate **237** and then hydrazine (yield 70-75%).[126]

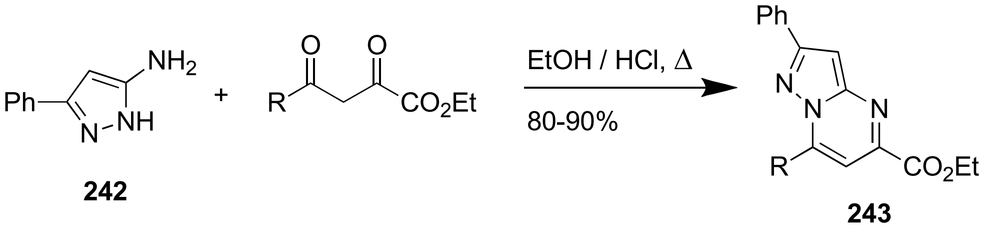


Scheme 81

R= Me, Ph; R_1 = Me, Et

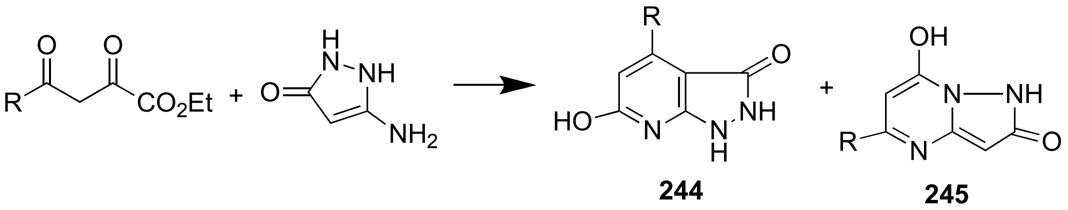
2.3.4. PYRAZOLOPYRIMIDINES

Reaction between benzoylpyruvates and five-membered aza-heterocyclic amines may offer an entry to a variety of [*a*]-fused pyrimidines, in consonance with the regiochemical supposition. An illustration of this strategy is cyclodehydration involving 3-aminopyrazole **242**, which affords only pyrazolo[1,5-*a*]pyrimidine **243** (Scheme 82).[127,128]



Scheme 82 R= Me, Ph

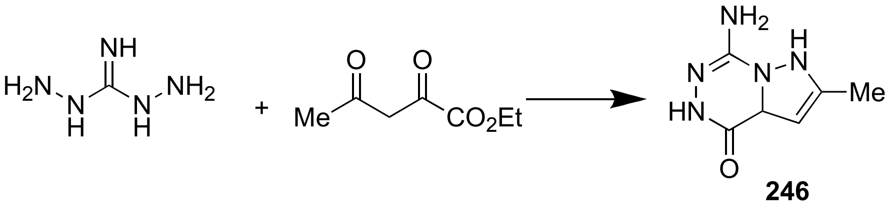
Cyclocondensation of 3-amino-3-pyrazolin-5-one with ethyl acylpyruvate gave chiefly pyrazolo[3,4-*b*]pyridinones **244** (Scheme 83) and smaller amount of pyrazolo[2,3-*a*]pyrimidin-2-(1*H*)-one **245** up to 30%.[129]



Scheme 83 R = Me, pyridyl, Ar

2.3.5. PYRAZOLO[1,5-*d*]TRIAZINES

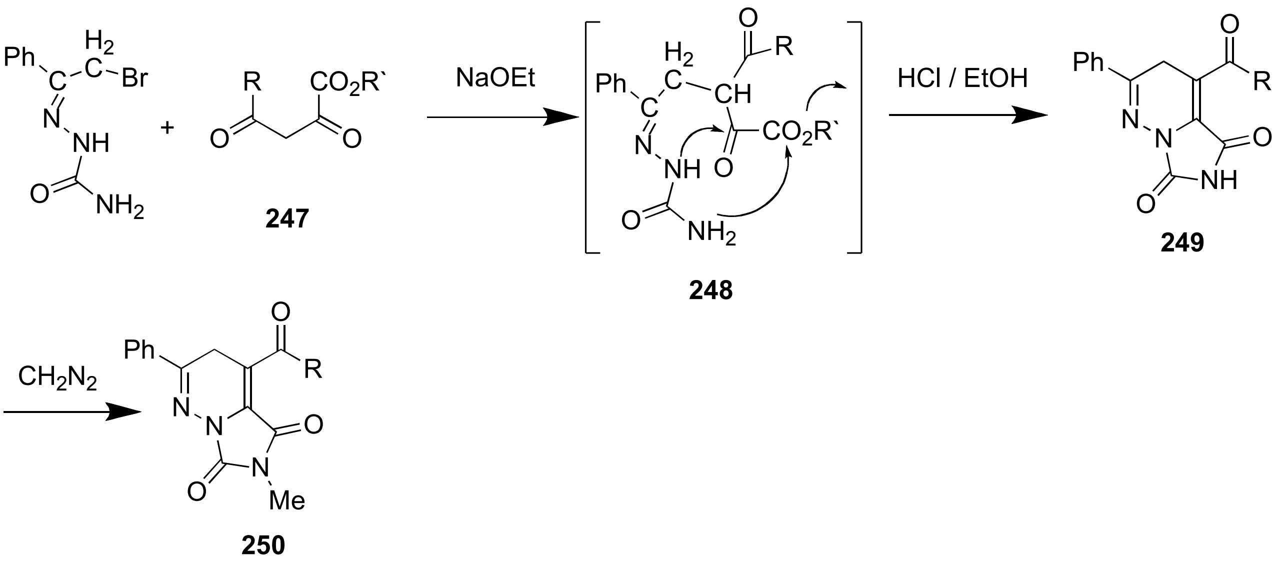
Diaminoguanidine was treated with ethyl 2,4-dioxopentanoate in either acid of neutral aqueous solution to give pyrazolo[1,5-*d*]triazine **246** (Scheme 84).[101]



Scheme 84

2.3.6. IMIDAZO[1,5-b]PYRIDAZINES

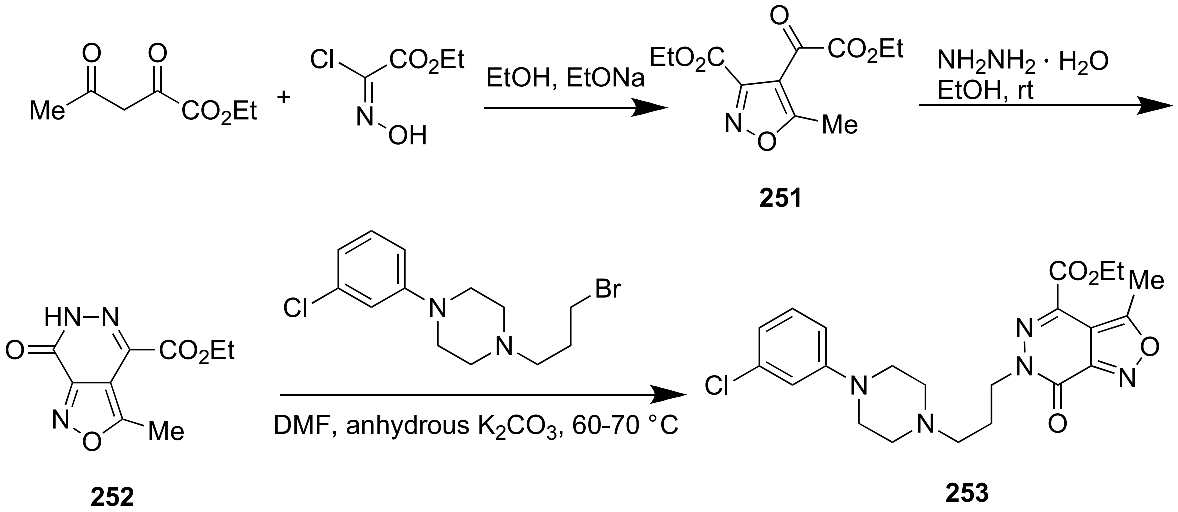
Ethyl or methyl acylpyruvates **247** were condensed with ω-bromo-acetophenonesemicarbazone in sodium ethoxide to give semicarbazone derivatives **248**, which underwent acid catalyzed intramolecular cyclization to afford the corresponding imidazo[1,5-*b*]pyridazinediones **249**, methylation of the latter with diazomethane afforded the *N*-methyl derivatives **250** (Scheme 85).[130]



Scheme 85 R= Me, Ph; R`= Me, Et

2.3.7. ISOXAZOLO[3,4-*d*]PYRIDAZINE DERIVATIVES

Ethyl 4-ethyloxoacetate-5-methylisoxazole-3-carboxylate **251**, was prepared by reaction of ethyl 2,4-dioxopentanoate with ethyl chloro(hydroximino)acetate in ethoxide solution. Reaction of **251** with hydrazine hydrate in ethanol gave ethyl {(6,7-dihydro-3-methyl-7-oxoisoxazole[3,4-*d*]pyridazinyl}-4-carboxylate **252**. Treatment of the latter with 1-(3-bromopropyl)-4-(3-chlorophenyl)piperazine in anhydrous DMF containing anhydrous K_2CO_3 give Ethyl 6-{[4-(3-chlorophenyl)piperazin-1-yl]propyl}-3-methylisoxazolo[3,4-*d*]pyridazin-7-(6*H*)-one-4-carboxylate **253** which is useful as potent antinociceptive agent.[131]

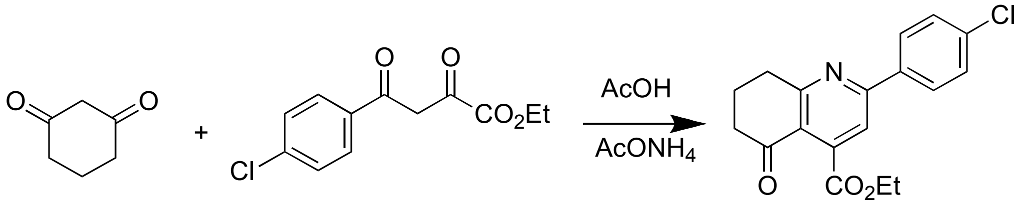


Scheme 86

2.3.8. QUINOLINE

Treatment of cyclohexane-1,3-dione with ethyl 4-(4-chlorophenyl)-2,4-dioxobutanoate led to 5,6,7,8-

tetrahydro-5-oxoquinoline-4-carboxylate derivative **254** (Scheme 87).[132]

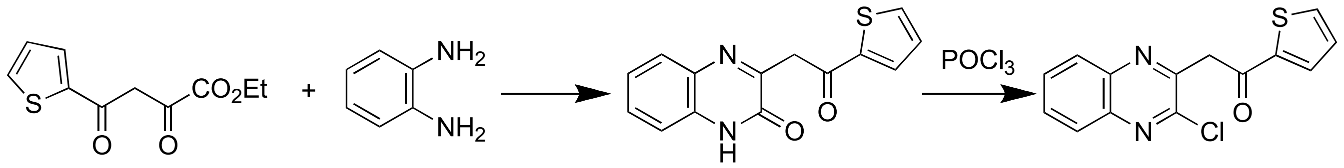


Scheme 87

254

2.3.9. QUINOXALINE DERIVATIVES

2-Chloro-3-(2'-thenoylmethyl)quinoxaline **256** was prepared by the reaction of 1,2-benzenediamine and 2-thienoyl pyruvate, followed by treatment with phosphorus oxychloride (Scheme 88).[133]

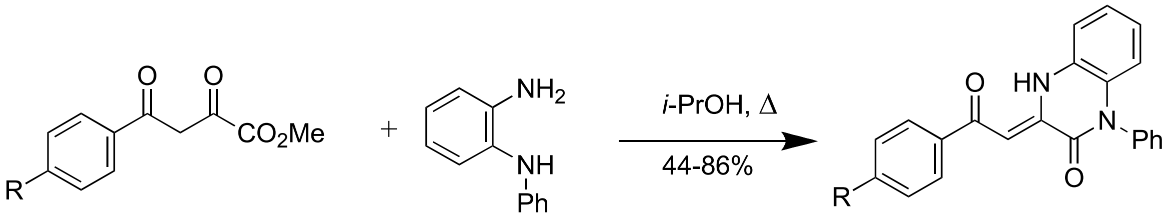


255

256

Scheme 88

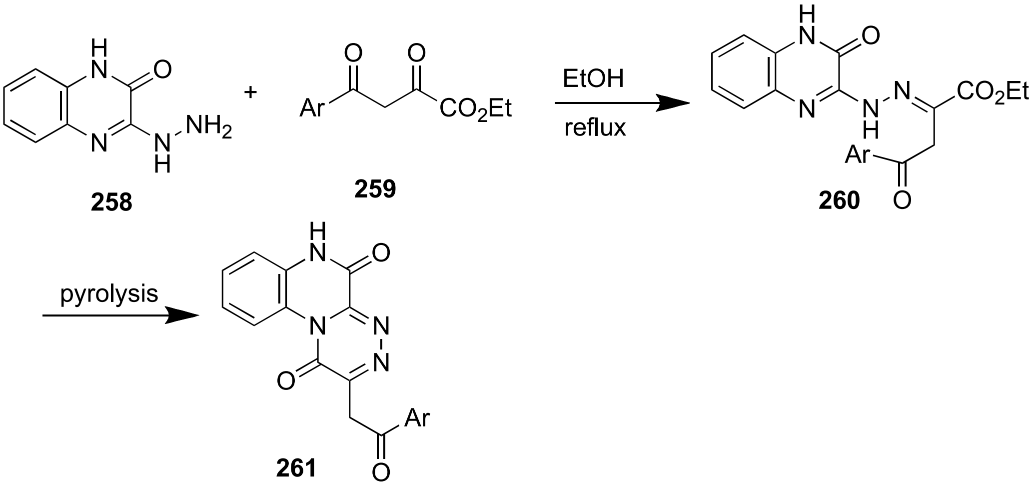
3-Functionalized 1*H*-quinoxaline-2-ones **257** can be made by reacting benzoylpyruvates with *N*-phenylbenzene-1,2-diamine (Scheme 89).[79,134–137]



257

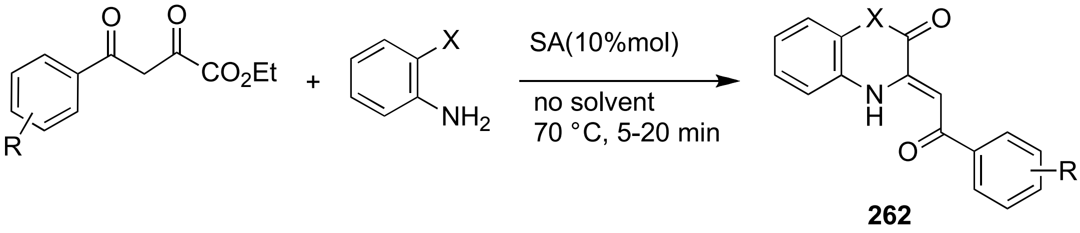
Scheme 89 R= Me, OMe, OEt, Br, Cl, F, NO_2

Reaction of 3-hydrazino-2(1*H*)-quinoxalinone **258** with ethyl aroyl pyruvates **259** afforded the corresponding hydrazones **260** which upon thermolysis at 230 °C eliminated a molecule of ethanol to give triazinoquinoxaline **261** (Scheme 90).[138]



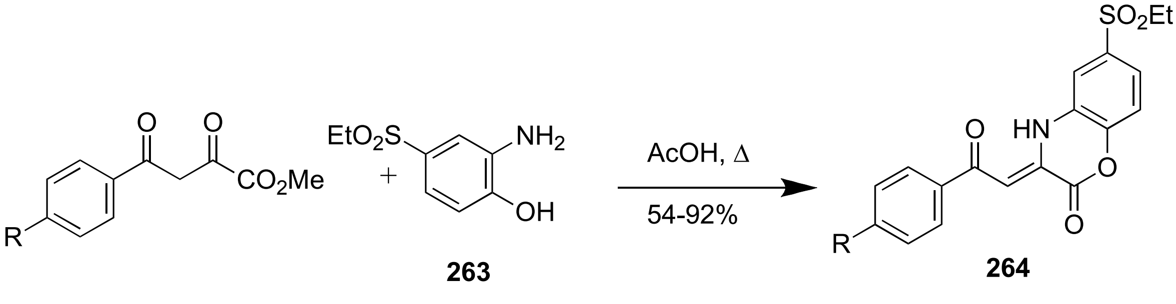
Scheme 90 Ar = Ph, 4-MeOC$_6$H$_4$

3-(2-Oxo-2-phenylethylidene)-3,4-dihydro-1*H*-quinoxalin-2-one **262** was prepared in 38% yield by solid state synthesis. Thus, when ethyl benzoylpyruvate and o-phenylenediamine were mixed and stirred at room temperature gave the title compound **262**. In the case of the condensation of ethyl benzoylpyruvate with o-aminophenol at room temperature, the solution-phase reaction afforded just product 3-(2-oxo-2-arylethylidene)-3,4-dihydro-benzo[1,4]oxazin-2-ones **262** in 31% yield. When sulfamic acid (SA) was used as catalyst in concentration 10% the yield of **262** raised 81% while **262** to 73% without using any solvent Also, the yield of other derivatives increased (Scheme 91).[139]



Scheme 91 R = H,4-Cl, 4-OH, 4-OMe, 4-NH$_2$, 4-NO$_2$; X=NH, O

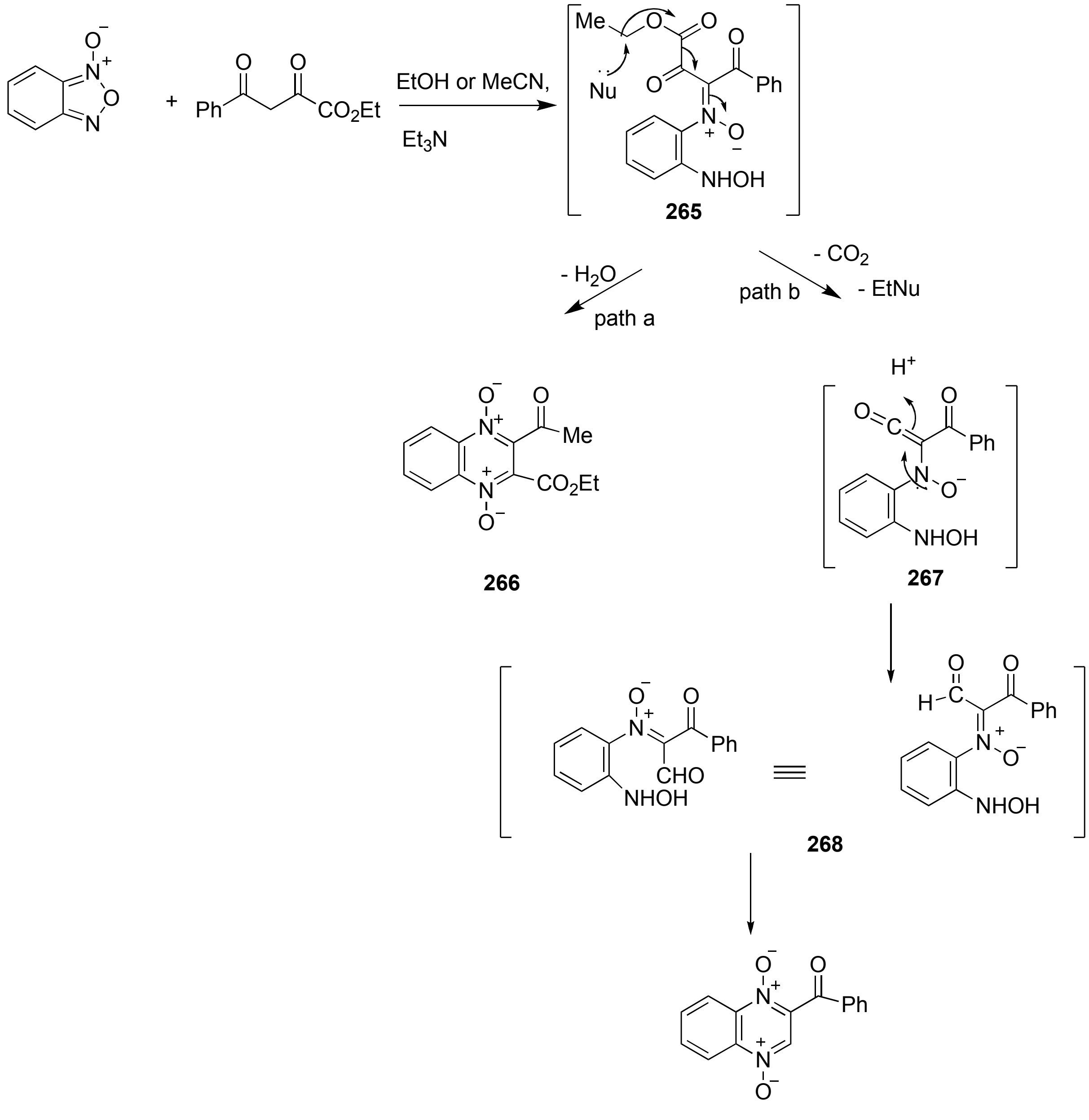
Cyclic *N*,*O*-dinucleophiles appended by a two-unit linker are restricted to 2-aminophenols. Thus, when a benzoylpyruvate reacts with 2-aminophenol **263** itself, the result is formation of the corresponding 1,4-benzoxazine-2-one **264** (Scheme 92).[140-142]



Scheme 92 R= H, Me, vinyl, OMe, OEt, Cl, Br, NO$_2$

The Beirut reaction of benzoyl pyruvate with 1,3-benzoxadiazole 1-oxide and ethyl 2,4-dioxo-4-phenylbutyrate in ethanol or acetonitrile, catalyzed by triethylamine, gave first ethyl 3-benzoylquinoxaline-2-carboxylate 1,4-dioxide **266** and then, in a slower reaction, 2-benzoylquinoxaline 1,4-dioxide **269**.[143]

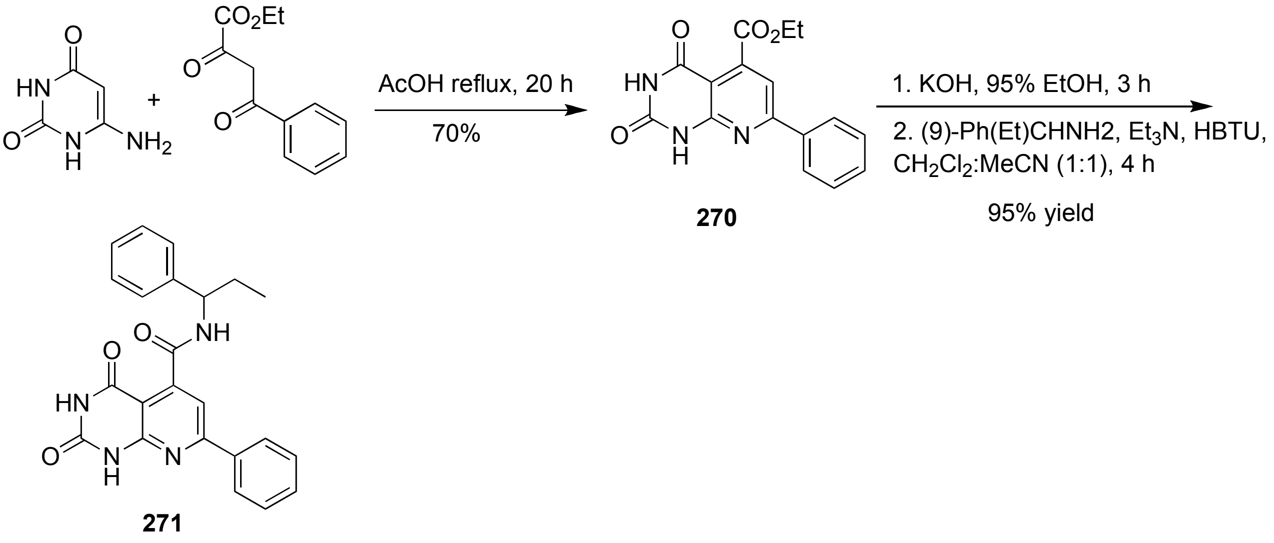
Pathways for the formation of the dioxides **266** and **269** are suggested in Scheme 93. The intermediate **265** is of the type proposed previously for the Beirut reaction of 1,3-benzoxadiazole 1-oxide with carbonyl compound cyclization and dehydration, path a, leads to the ester dioxide **266.** Nucleophilic attack on compound **265** with concomitant loss of carbon dioxide, path **b,** yields, after protonation of intermediate **267** the aldehyde **268**, Subsequent cyclodehydration produces the dioxide **269**.[143]



Scheme 93

2.3.10. PYRIDO[2,3-*d*]PYRIMIDINE

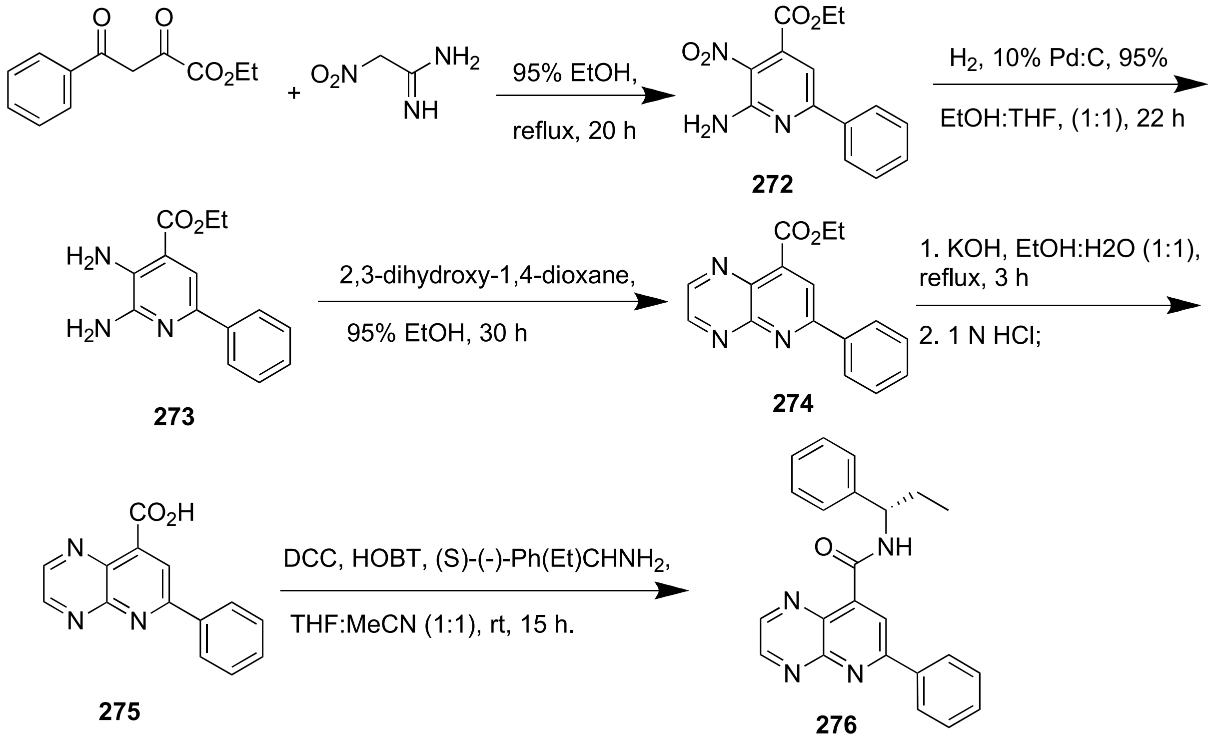
Condensation of ethyl benzoylpyurvate and 4-aminouracil in refluxing acetic acid afforded ethyl 2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylate **270** as shown in Scheme 94. Basic hydrolysis and coupling with (*R*,*S*)-1-phenylpropylamine provided compound **271**.[144]



Scheme 94

2.3.11. PYRIDO[2,3-*b*]PYRAZINES

Compound **276** was prepared as shown in Scheme 95. Thus, Guareschi condensation of nitroacetamidine with ethyl 2,4-dioxo-4-phenylbutanoate in refluxing ethanol resulted in high yields of ethyl 2-amino-3-

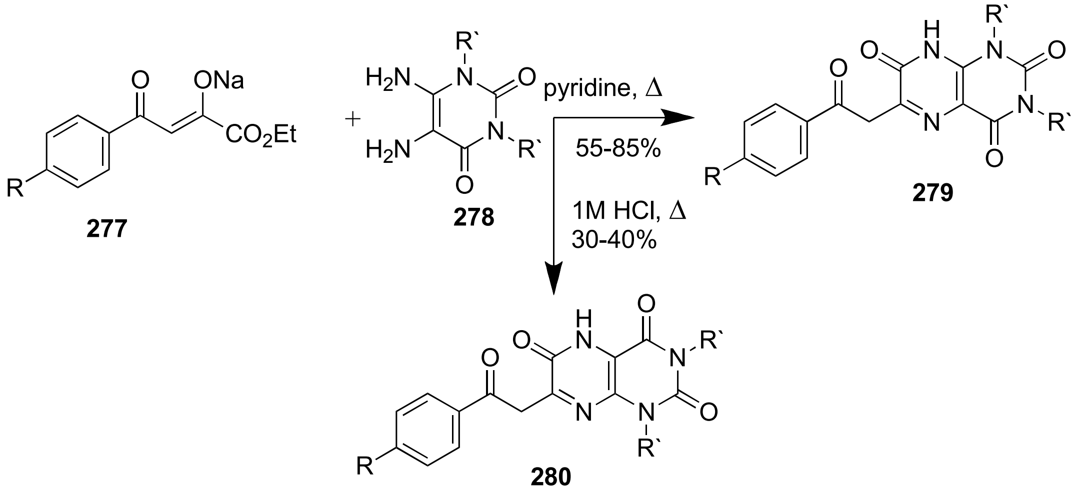


Scheme 95

nitro-6-phenylpyridine-4-carboxylate **272**, which was transformed into the diamine **273** by catalytic hydrogenation of the nitro function. The six-membered fused pyrazine ring was incorporated by condensation of **274** with a masked dialdehyde, the 2,3-dihydroxy-1,4-dioxane, producing ethyl 6-phenylpyrido[2,3-*b*]pyrazine-8-carboxylate **275**.[145] Subsequent hydrolysis of the ester functions under basic conditions and coupling reaction with (*S*)-(-)-1-phenylpropylamine afforded the desired secondary amide **276**.[144]

2.3.12. PTERIDINE

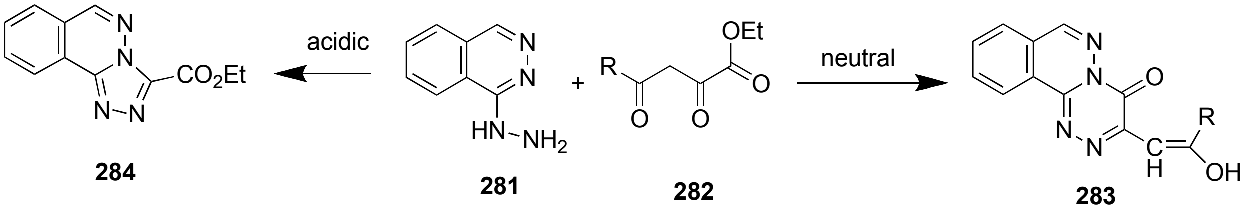
In some cases, the ethene bridged diamines need not an aromatic framework as support. For instance, benzoylpyruvates **277** react with 5,6-diaminopyrimidine-2,4-dione derivatives **278** yielding dihydropteridine-2,4,6-trione **279** and **280** (Scheme 96).[146] It has been demonstrated that, depending on whether the reaction media is basic or acidic, it is possible to influence the regioselectivity residing on the non-symmetrical nature of the *N*,*N*`-dinucleophile.



Scheme 96 R= H, Me, OMe, Cl; R`= H, Me

2.3.13. TRIAZOLO[3,4-*a*]PHTHALAZINES

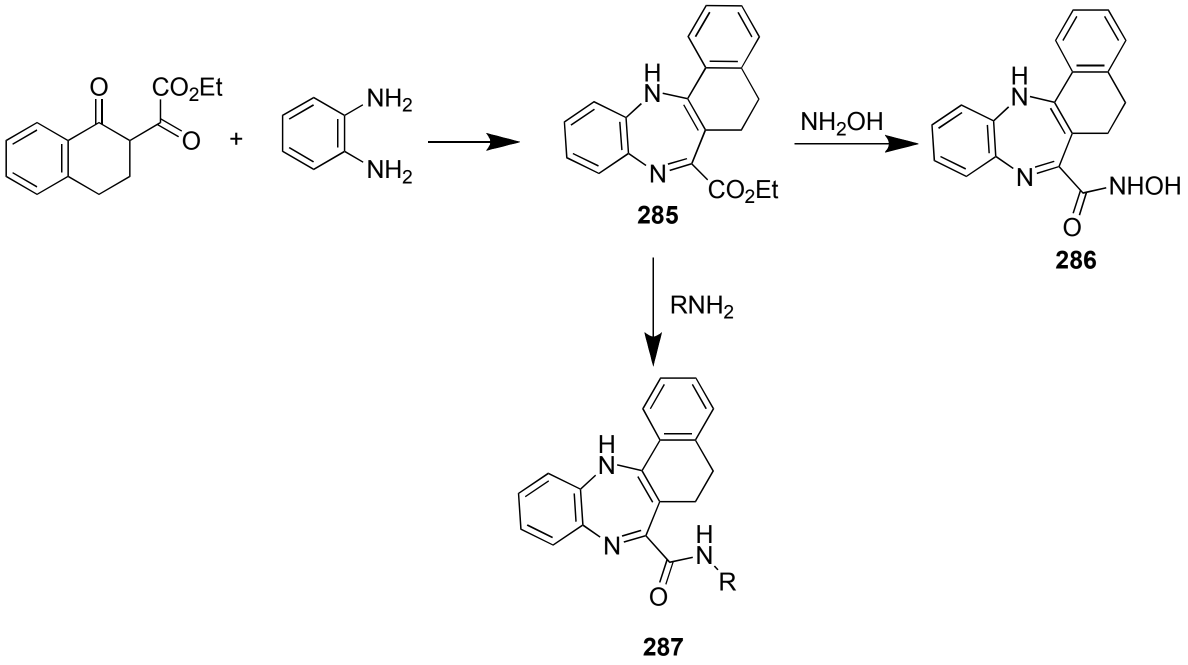
Cyclocondensation of 1-hydrazinophthalazine **281** with substituted ethyl benzoylpyruvates **282** gave under neutral reaction conditions, 3-[2-oxo-2-(substituted phenyl)ethyl]-4*H*-as-triazino[3,4-*a*]phthalazin-4-ones **283**. Under acidic but otherwise identical conditions, depending on the substituent, cyclocondensation gave 3-carbethoxy-s-triazolo[3,4-*a*]phthalazine **284**[79] (Scheme 97).



Scheme 97 R = $C_6H_4R_1$; R_1 = 4-Me, 4-MeO, 3-MeO, 4-Cl

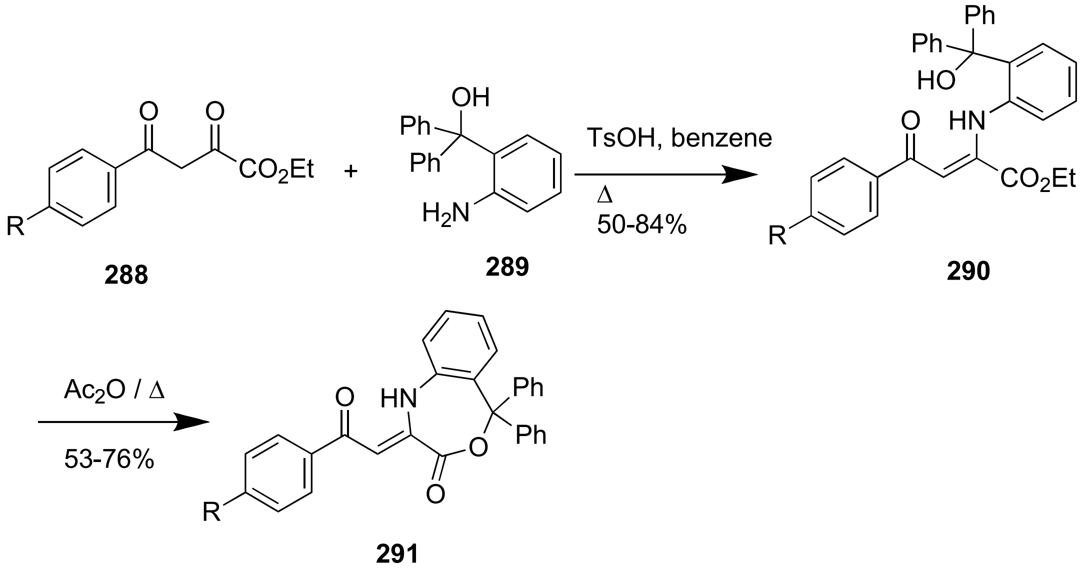
2.4. SEVEN MEMBERED RING

Cyclocondensation of ethyl 1,2,3,4-tetrahydro-1-oxo-2-naphthaleneglyoxylate with *o*-phenylenediamine gave 78% **285** which was treated with hydroxylamine hydrochloride to give 82% **286**. Amination of **285** by various amines and sulfa compounds gave 63-74% benzonaphtho-1,4-diazepines **287** (Scheme 98) which were useful as bactericides.[147]



Scheme 98 R = $NHCH_2CH_2NEt_2$, $N(CH_2CH_2OH)_2$, $N(CH_2CH_2CH_2OH)_2$, sulfanilamido-, sulfacetamido, 4-amino-N-2-pyrimidinyl-, 4-amino-N-2-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamido]-

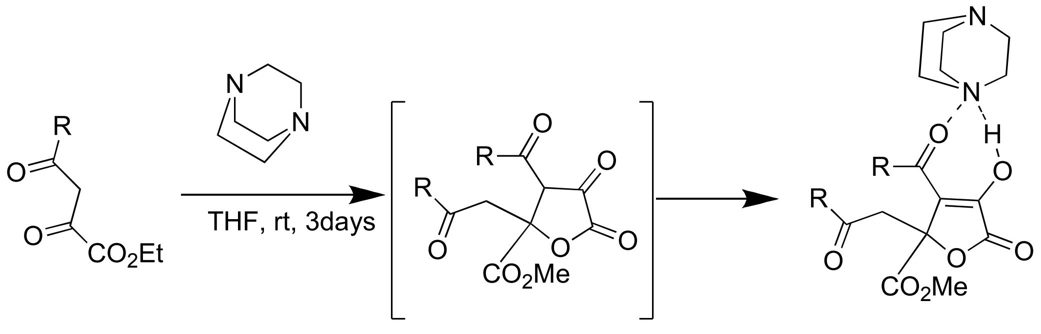
Benzoylpyruvates **288**, act as α-keto-ester on cyclodehydration with **289** led to intermediate β-enaminone **290** and then to 1,2-dihydrobenzo[*e*][1,4]oxazepin-3(5*H*)-one **291** by refluxing in acetic anhydride (Scheme 99).[148]



Scheme 99 R= H, Me, Cl

DIFFERENT REACTIONS

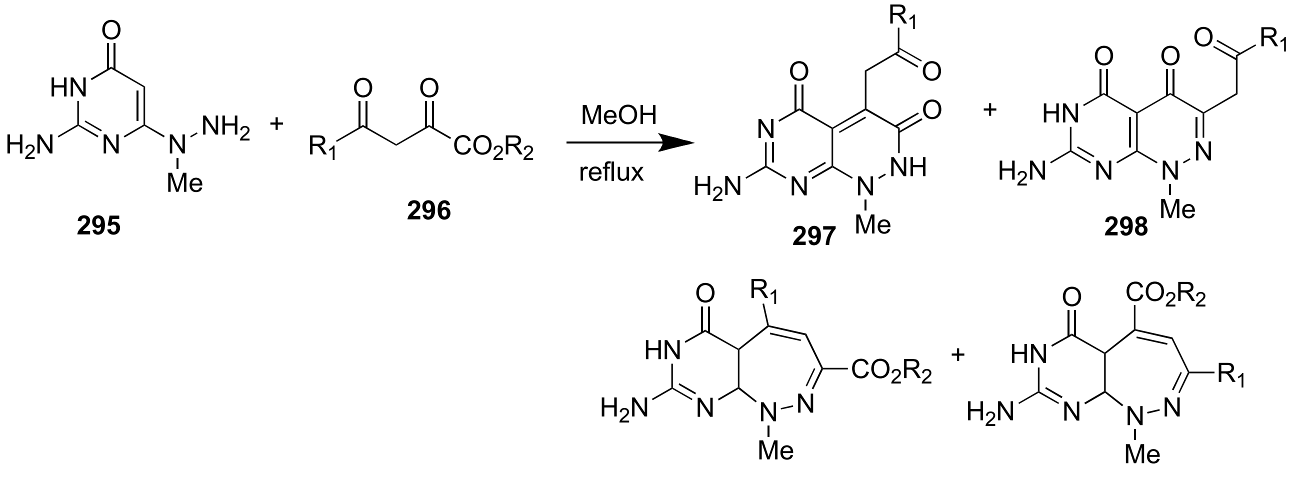
The self-condensation reaction of β-acylpyruvates **292** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded 4,5,5-trisubstituted tetrahydrofuran-2,3-diones derivatives **294** (Scheme 100).[149,150]



292 **293** **294**

Scheme 100 R = Me, Ph, 4-ClC_6H_4

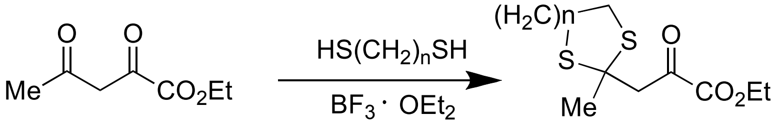
6-(1-Methylhydrazino)isocytosine **295** cyclizes with α,γ-dioxo esters **296** to give pyrimido[4,5-*c*]pyridazines **297**, **298** and 1*H*-pyrimido[4,5-*c*]-1,2-diazepines **299** and **300**, the latter being predominant in each case (Scheme 101).[151]



295 **296** **297** **298** **299** **300**

Scheme 101 R_1 = Ph, 3-pyridyl; R_2 = Me, Et

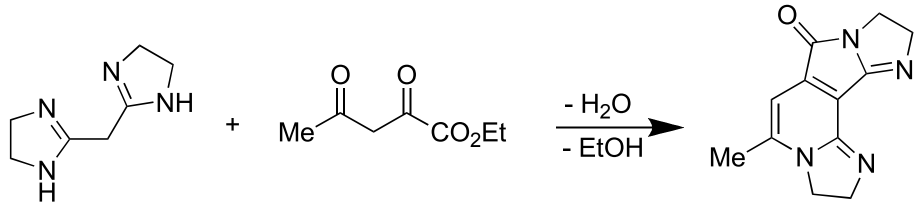
Cyclic monodithioacetals **301** of ethyl acetylpyruvate was prepared in 80% yield using boron trifluoride etherate as the acid catalyst (Scheme 102).[152]



301

Scheme 102 n=2,3

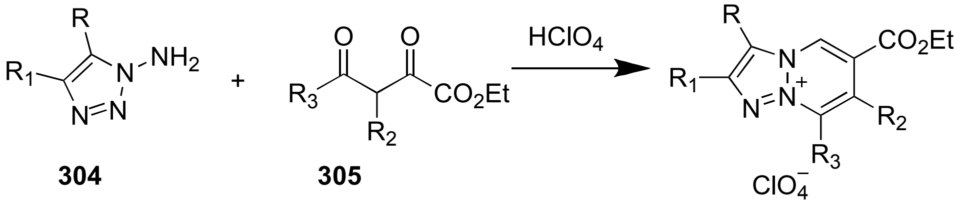
Tetracyclen **303** was prepared in 60% yield by reaction of bis(4,5-dihydro-1*H*-imidazol-2-yl)methane **302** with ethyl 2,4-dioxopentanoate (Scheme 103).[153]



302 **303**

Scheme 103

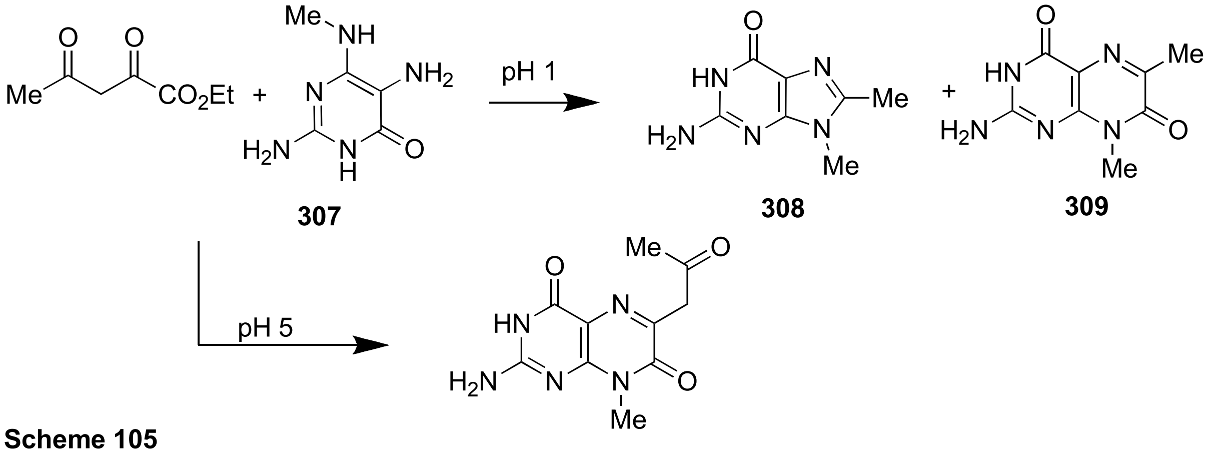
1,2,3-Triazolo-1,2,3-triazine salts **306** were prepared in 27-94% yields by cyclocondensation of the corresponding 1-aminotriazole **304** with ethyl acylpyruvates **305** (Scheme 104).[154]



304 **305** **306**

Scheme 104 R = H, Ph; R_1 = Ph; RR_1 = CH:CHCH:CH; R_2= H, Et; R_3 = Me, Ph

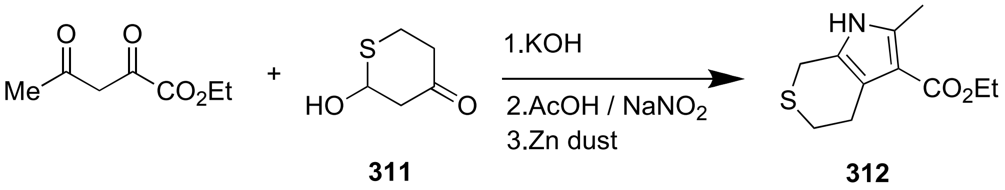
The condensation of 2,5-diamino-4-methylamino-6-oxo-1,6-dihydropyrimidine **307** with ethyl acetopyruvate gave 8,9-dimethylguanine **308** and isoxanthopterin **309** at pH 1, and 8-methyl-6-acetonylisoxanthopterin **310** at pH 5 (Scheme 105).[155]



307 **308** **309** **310**

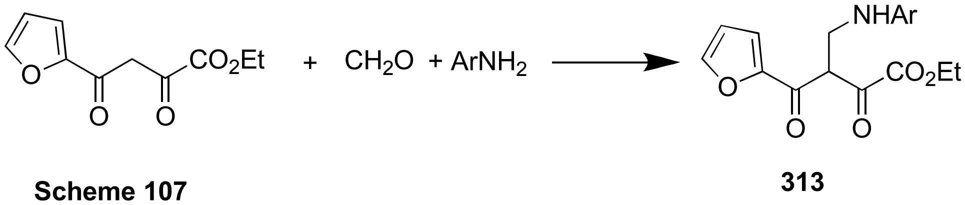
Scheme 105

Ethyl 2,4-dioxopentanoate was added to 3-hydroxy-4-thiacyclohexanone **311** in potassium hydroxide several weeks followed by acidification with acetic acid and then treatment with sodium nitrite and finally with Zn dust, to give ethyl 4,5,6,7-tetrahydro-2-methyl-1-aza-6-thiaindene-3-carboxylate **312** (Scheme 106).[51]



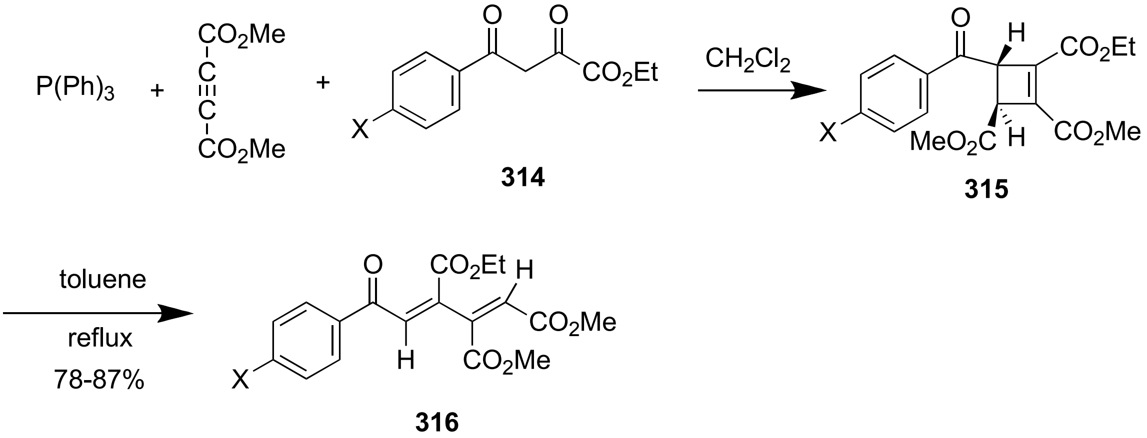
Scheme 106

Ethyl (2-furoyl)pyruvate underwent Mannich alkylation to give the β-furoyl-β-(arylmethyl)pyruvate **313** (Scheme 107).[62]



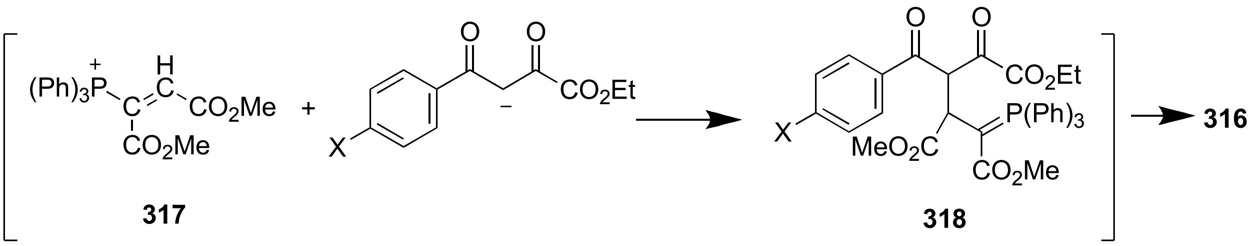
Scheme 107

Ethyl 4-aryl-2,4-dioxobutanoates **314** undergo intramolecular Wittig reaction with a vinyltriphenylphosphonium salt to yield cyclobutene derivative **315** which undergo electrocyclic ring-opening reactions in boiling toluene to produced highly electron-deficient 1,3-dienes **316** in quantitative yields (Scheme **108**).[156]



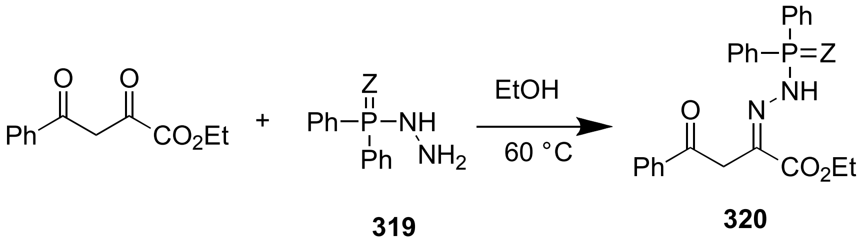
Scheme 108 X = H, Br, NO2

The mechanism involves addition-cyclization products apparently result from initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the 1:1 adduct **317**, followed by attack of the anion of **314** to vinyltriphenylphosphonium cation to form a phosphorane **318**, which is converted to strained carbocyclic ring system **316** (Scheme 109).[156]



Scheme 109

Reaction of hydrazines **319**, with ethyl 2,4-dioxo-4-phenylbutanoate in absolute ethanol at 60 °C gave 91% hydrazones **320** (Scheme 110).[157]



Scheme 110 Z = O, S

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