

HETEROCYCLES, Vol. 81, No. 1, 2010, pp. 1 - 55. © The Japan Institute of Heterocyclic Chemistry  
Received, 10th September, 2009, Accepted, 23rd October, 2009, Published online, 5th November, 2009  
DOI: 10.3987/REV-09-659

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

**Kamal M. Dawood,<sup>1</sup> Hassan Abdel-Gawad,<sup>2</sup> Hanan A. Mohamed,<sup>2</sup> and Bakr F. Abdel-Wahab<sup>2,\*</sup>**

<sup>1</sup> Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt

<sup>2</sup> Applied Organic Chemistry Department, National Research Centre, Dokki, Giza, Egypt

\*Corresponding author. Tel: 202 3371635; Fax: 202 7601877.

E-mail: Bakrfatehy@yahoo.com

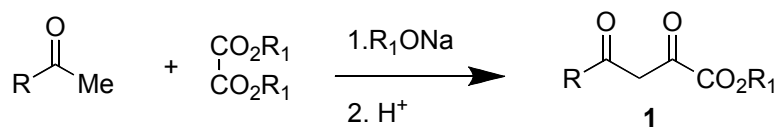
**Abstract** – This review deals with synthesis and reactions of 2,4-dioxoesters. Some of these reactions have been applied successfully to the synthesis of biologically important compounds. The data published over the last years on the methods of synthesis and chemical properties of 2,4-dioxoesters 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,<sup>1</sup> plant growth regulators and protectants,<sup>2</sup> and also production of 3(2*H*)-furanone ring system which is the key skeletal element of many natural product antitumor agents.<sup>3</sup> Recently a review on utility of regio- and chemoselective features of benzoylpyruvates in heterocyclic synthesis has been appeared.<sup>4</sup> 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.

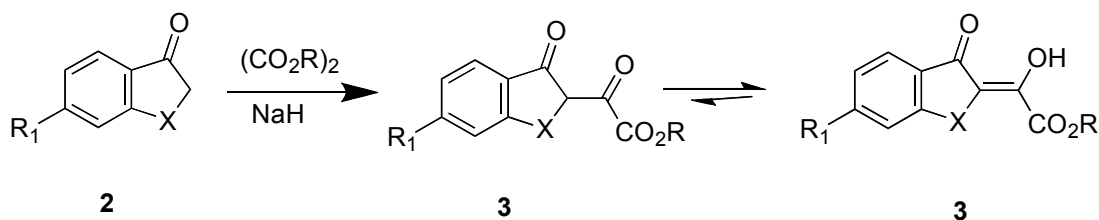
### METHODS OF SYNTHESIS

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**.<sup>5-21</sup>



**Scheme 1** R= alkyl, aryl, heterocycle ; R<sub>1</sub> = Et, Me

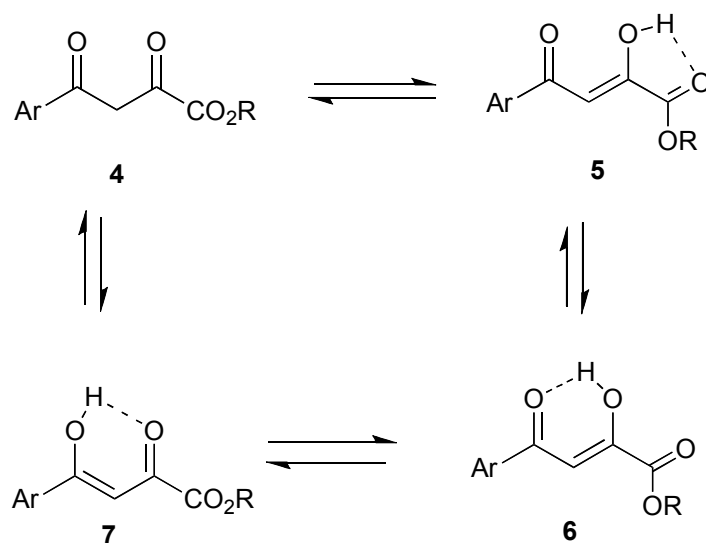
Cyclic ketones **2** were condensed with dimethyl or diethyl oxalate to give the diketoester **3** which present in two tautomeric structures (Scheme 2).<sup>22-26</sup>



**Scheme 2** X = (CH<sub>2</sub>)<sub>1-3</sub>, O ; R<sub>1</sub>=R= Me, Et

## CHEMICAL PROPERTIES OF 2,4-DIOXOESTERS

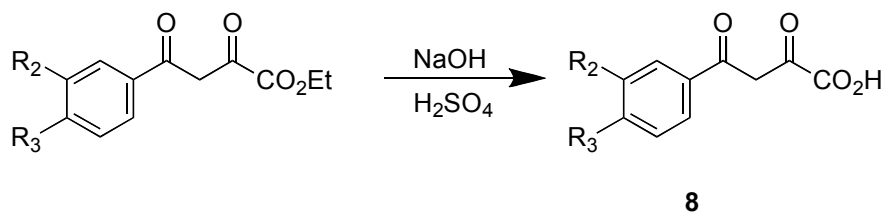
2,4-Diketoalkanoates have both the structural features of  $\alpha$ -keto esters and  $\beta$ -diketones (Figure 1). In the case of  $\alpha$ -keto esters **4**, the adjacent carboxyl moiety imparts the ketone with an enhanced electrophilic character due to its inductive withdrawal. However, this may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



**Figure 1:** Expected tautomeric contributions in aroylpyruvates.

## 1. HYDROLYSIS

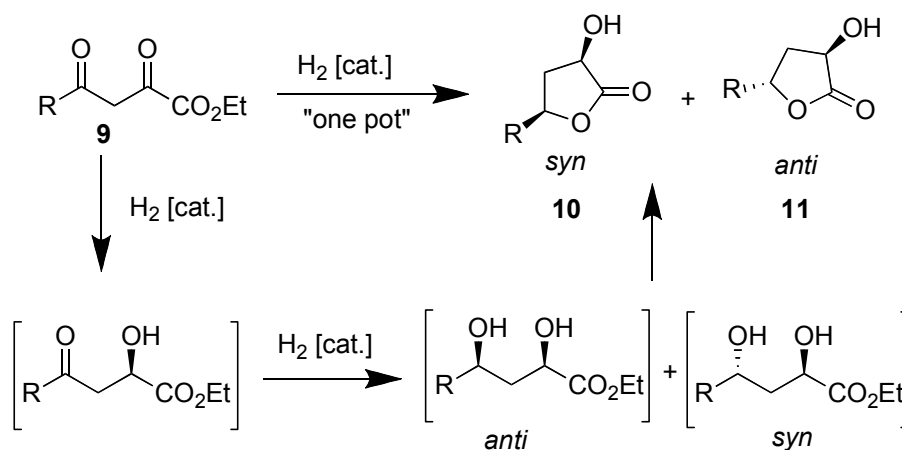
The  $\beta$ -diketo esters are converted to the corresponding pyruvic acids **8** (Scheme 3).<sup>8, 27</sup>



**Scheme 3**  $\text{R}_2, \text{R}_3 = \text{H, OMe, CF}_3$

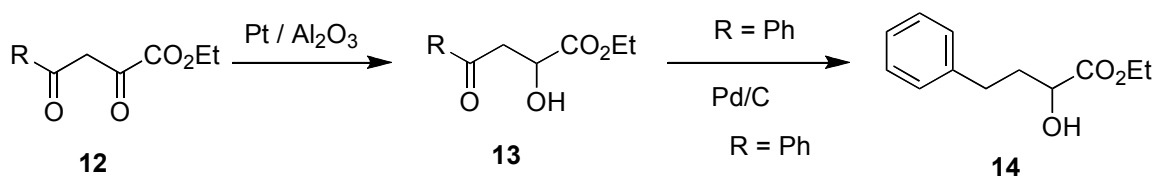
## 2. REDUCTION

The hydrogenation of 2,4-dioxovalerates **9**, in the presence of chiral rhodium or ruthenium catalysts provides direct access to 3-hydroxy-5-subst.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).<sup>28,29</sup>



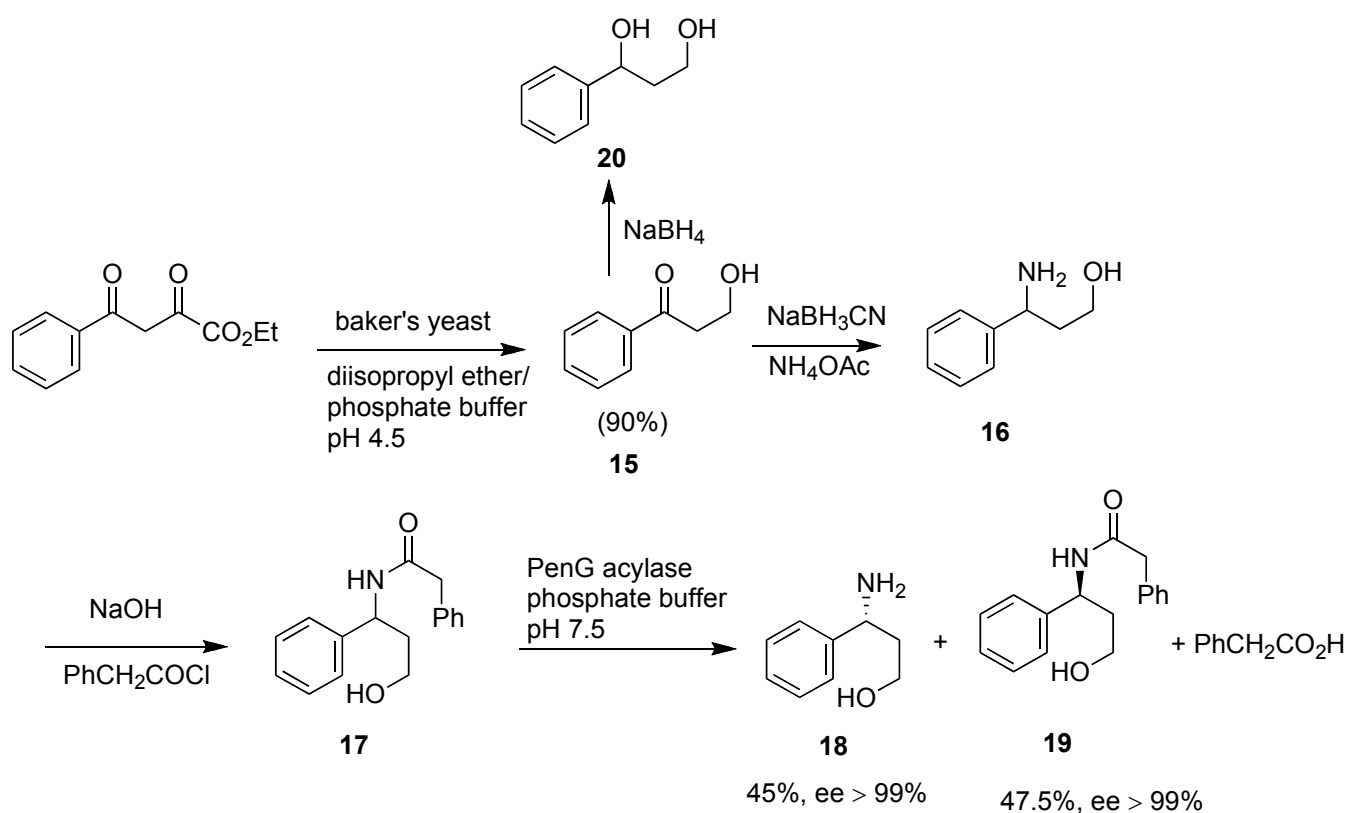
**Scheme 4**  $\text{R} = \text{Me, } i\text{-Bu, 2-thienyl}$

The derivatives of 4-substituted 2-hydroxybutyric acids are valuable synthons for the production of antihypertensive substances, homoamino acids, hydroxamic acids, and other compounds.<sup>30,31</sup> Thus hydrogenation of ethyl 4-substituted 2,4-dioxobutyrates **12** at palladium black and Pt/Al<sub>2</sub>O<sub>3</sub> 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-subst.-butyrate **13**, which then reduced with Pd/C to give ethyl 2-hydroxy-4-phenylbutanoate **14** (Scheme 5).<sup>32</sup>



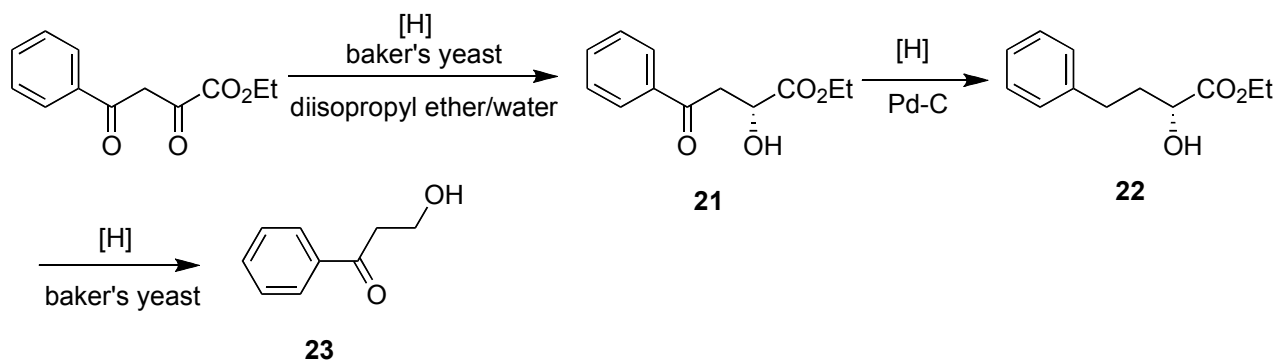
**Scheme 5**  $\text{R} = \text{Ph, 2-furyl}$

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).<sup>33</sup>



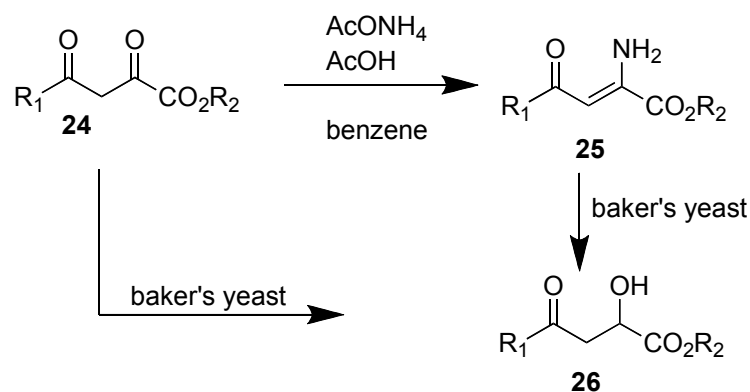
Scheme 6

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).<sup>8</sup>



Scheme 7

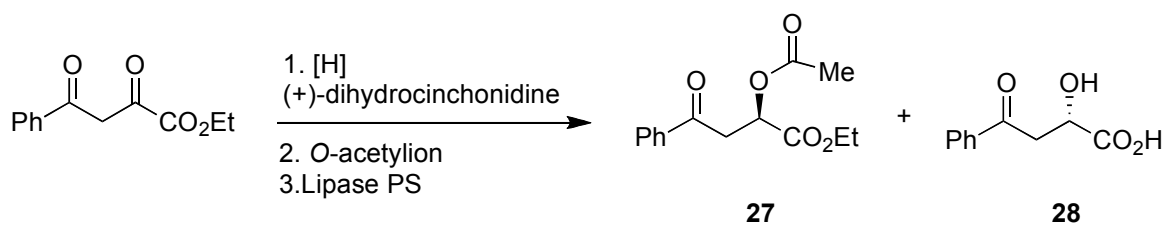
2,4-Dioxoalkanoates **24** and the parent compound  $\gamma$ -keto- $\alpha$ -enamino esters **25** are regioselectively reduced by baker's yeast to  $\alpha$ -hydroxy- $\gamma$ -keto esters **26**, in moderate to good yields (Scheme 8).<sup>34</sup>



Scheme 8

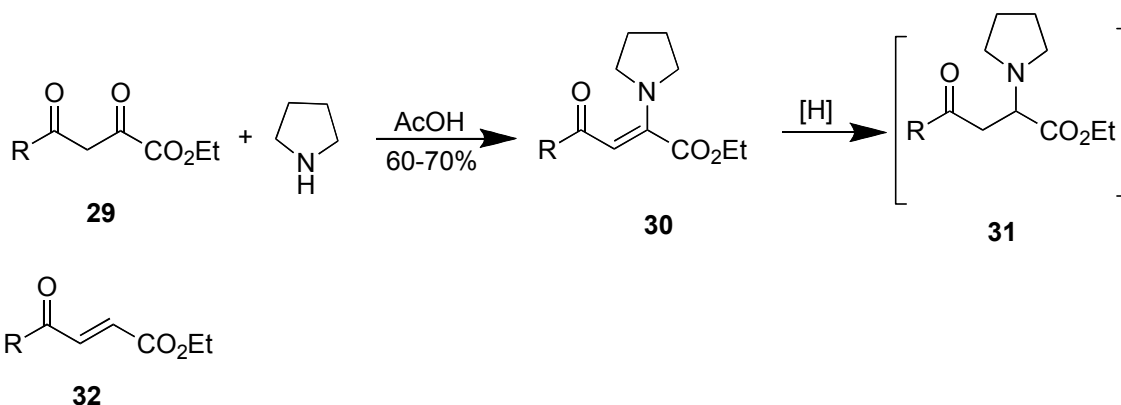
$R_1 = \text{Et, Me}; R_2 = \text{Et, Me}$

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).<sup>35</sup>



Scheme 9

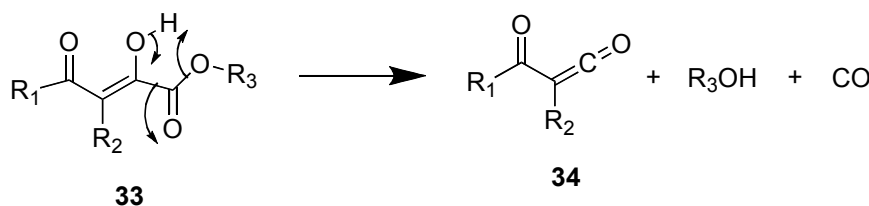
Ethyl 2,4-dioxoalkanoates **29** react chemoselectively with pyrrolidine acetate at the more electrophilic C-2 carbonyl, producing enaminone esters **31**. Reduction of **31** with sodium cyanoborohydride followed by pyrrolidine elimination gave  $\beta$ -oxo-acrylates **32**<sup>36</sup> (Scheme 10).



**Scheme 10** R = Ph, furyl, Me, Et, H<sub>2</sub>C:CHCH<sub>2</sub>CH<sub>2</sub>, Me<sub>2</sub>CHCH<sub>2</sub>, pentyl, hexyl

### 3. DECARBONYLATION

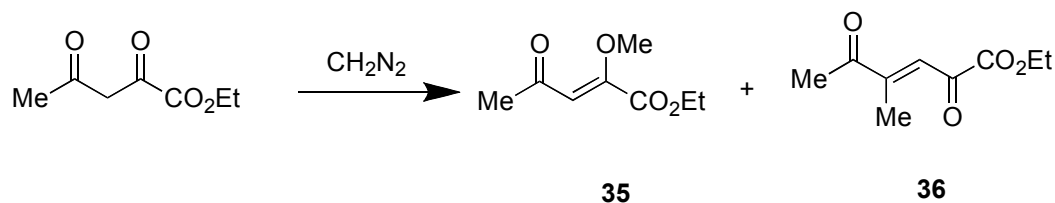
The  $\alpha,\gamma$ -diketoesters **33** are subjected to decarbonylation conditions with excess methanol in a sealed reactor at a lower temperature (105-120 °C) to give carbon monoxide and ketenes **34** (Scheme 11).<sup>37</sup>



**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).<sup>38,39</sup>

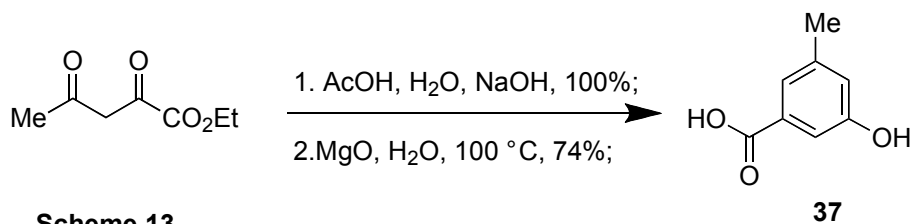


**Scheme 12**

## REACTIONS OF 2,4-DIOXO-ESTERS

### 1. FORMATION OF BENZENE DERIVATIVES

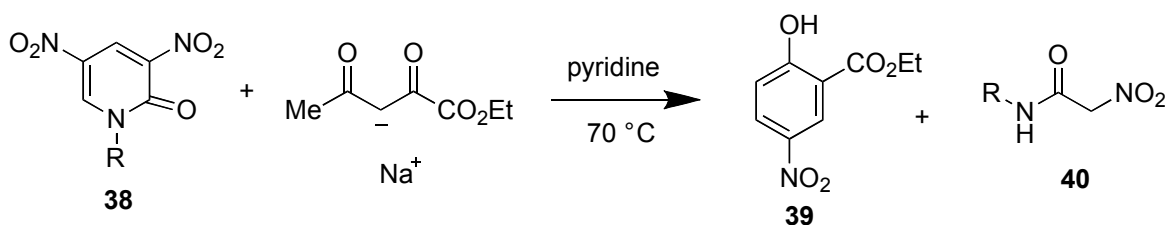
3-Hydroxy-5-methylbenzoic acid **37**, which used in the synthesis of thrombin inhibitor, was prepared in high yield from ethyl 2,4-dioxopentanoate in two reaction steps by the reaction with acetic acid followed by treatment with magnesium oxide (Scheme 13).<sup>40</sup>



Scheme 13

37

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**<sup>41</sup> (Scheme 14).



Scheme 14

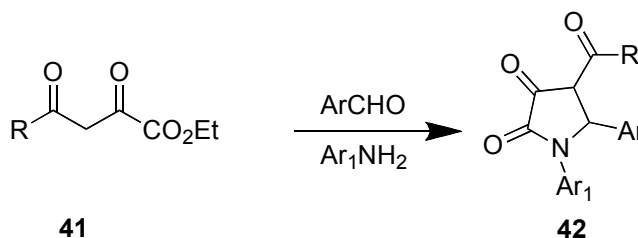
R = Me, 3-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>, 2-pyridylmethyl, 2-pyridyl, 2,4-(O<sub>2</sub>N)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, MeO, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>O

## 2. FORMATION OF HETEROCYCLES

### 2.1. FIVE MEMBERED SYSTEMS

#### 2.1.1. 2,4-PYRROLIDINEDIONES

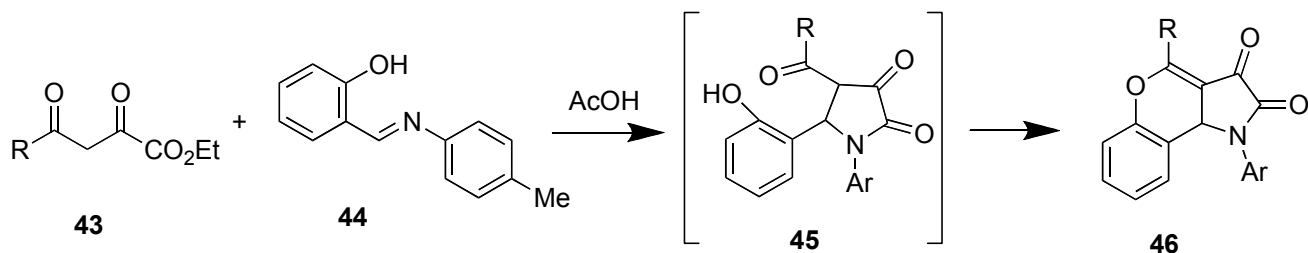
The condensation of  $\alpha,\gamma$ -diketoesters **41** with aromatic amine and aromatic aldehydes was a convenient method for the synthesis of 4-acyl-2,3-pyrrolidinediones **42** (Scheme 15).<sup>14,42-47</sup>



Scheme 15

R= alkyl, Aryl, heterocycles

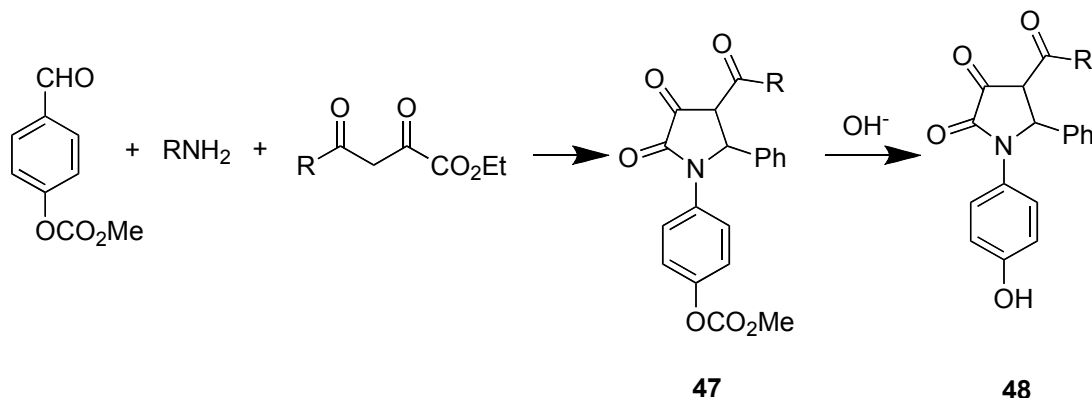
The condensation of  $\alpha,\gamma$ -diketoesters **43** with aldimines **44** derived from *o*-hydroxybenzaldehydes provides a route to the pyrrolo[3,2-*c*]benzopyran ring system **46**, via cyclization of the intermediate pyrrolidinedione **45** which was not isolated (Scheme 16).<sup>45</sup>



Scheme 16

R= Et, Ph, 4-tolyl

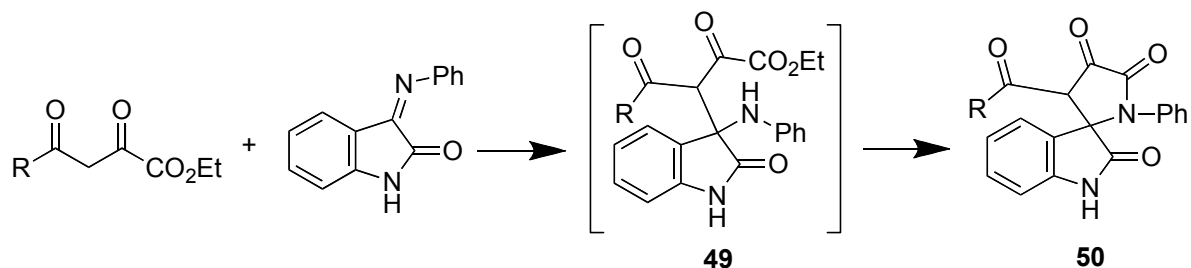
Some substitution products of 2,3-pyrrolidinones **47** and **48** are obtained by condensing an easily saponifiable derivative of a hydroxybenzaldehyde or a hydroxybenzaldehyde alkylcarbonic ester with primary amines and  $\alpha,\gamma$ -diketoesters.<sup>48</sup> The products **47** may be treated 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

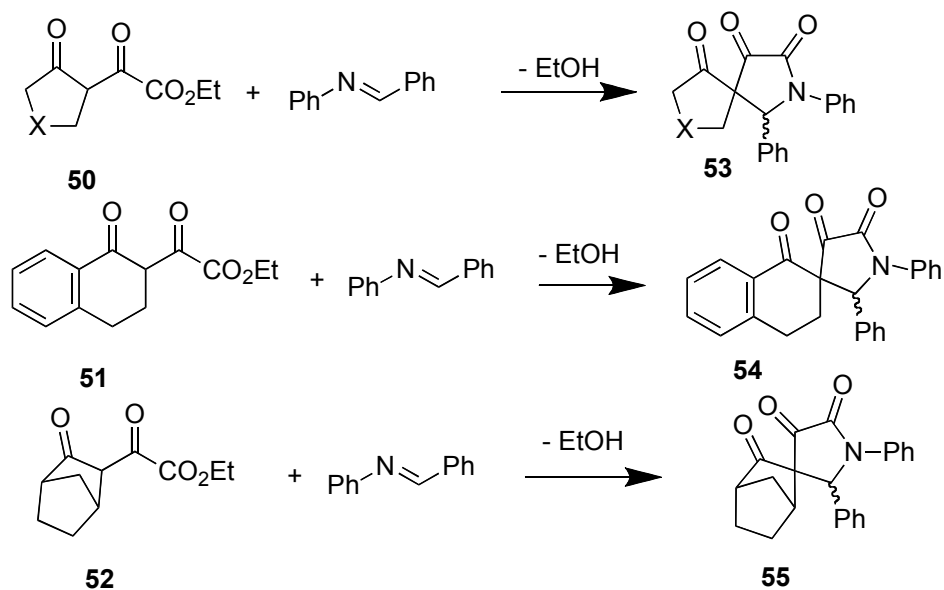
The condensation of  $\alpha,\gamma$ -diketoesters with Schiff bases, was further extended to the use of ketimines, in such case, the spirocyclic system **49** was obtained via the formation of **50** (Scheme 18).<sup>45</sup>



Scheme 18

R= Me, Ph

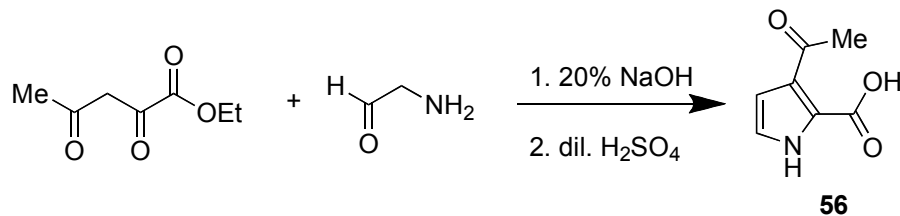
Reaction of 2-oxocycloalkylglyoxylate esters **50-52** with *N*-phenylmethylethaniline yields 2-aza-3,4,6-trioxo-1,2-diphenylspiroalkanes **53-55** (Scheme 19).<sup>49</sup>



Scheme 19 X = CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>

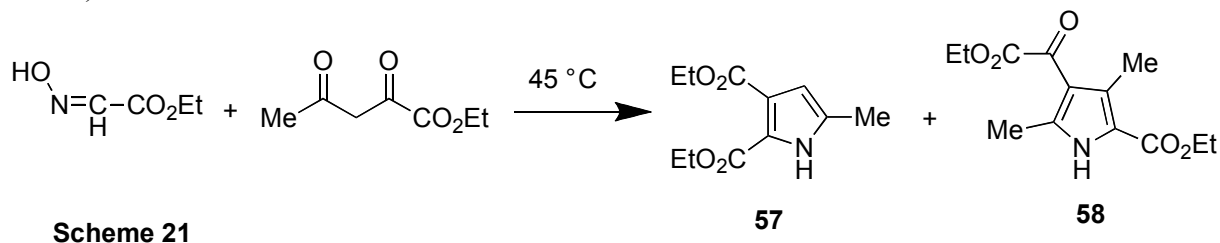
### 2.1.2. PYRROLES

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).<sup>50</sup>



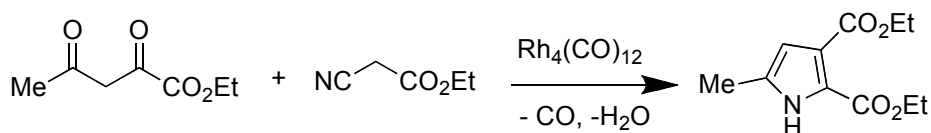
Scheme 20

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).<sup>51</sup>



Scheme 21

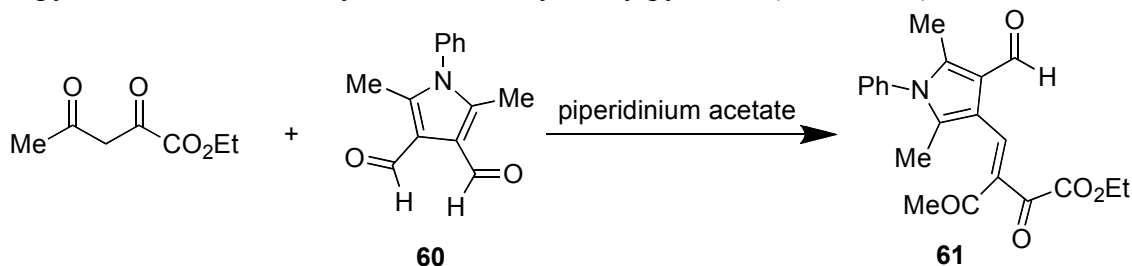
Low-valent rhodium complexes are efficient catalysts for the activation of  $\alpha$ -C-H bond of isonitriles. Catalytic synthesis of pyrrole **59**, in 76% yield, can be performed by cyclocondensation of ethyl 2-cyanoacetate with ethyl 2,4-dioxopentanoate (Scheme 22).<sup>52</sup>



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).<sup>53</sup>



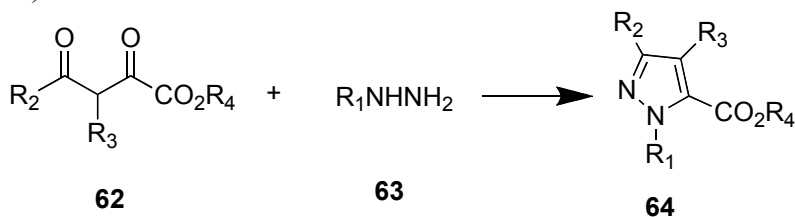
Scheme 23

60

61

### 2.1.3. PYRAZOLES

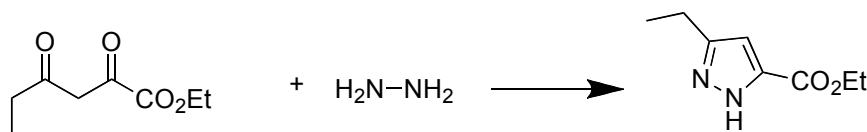
Hydrazine and its monosubstituted derivatives react smoothly with 2,4-dioxoesters in a highly chemoselective manner to afford 3,5-difunctionalized pyrazoles as only one product.<sup>54-59</sup> Thus, 1-alkyl-5-pyrazolecarboxylic acid esters **64**, which are intermediates for pyrazolecarboxamide derivatives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



Scheme 24

$\text{R}_1, \text{R}_2 = \text{alkyl, cycloalkyl; heteocycles, R}_3 = \text{H, alkyl, cycloalkyl; R}_4 = \text{alkyl}$

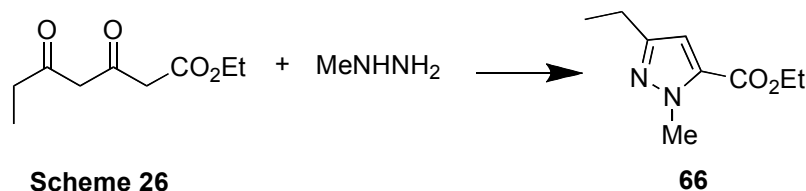
Ethyl 3-ethyl-5-pyrazolecarboxylate **65**, which is an intermediate for the acaricide tebufenpyrad, was synthesized at a yield of more than 87% with ethyl propionylpyruvate and hydrazine hydrate or dihydrazine sulfate (Scheme 25).<sup>66-69</sup>



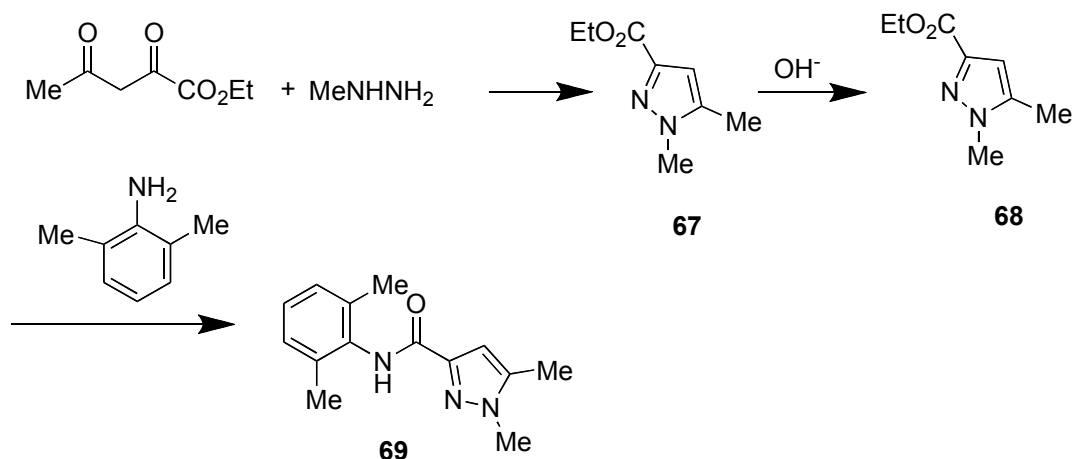
Scheme 25

65

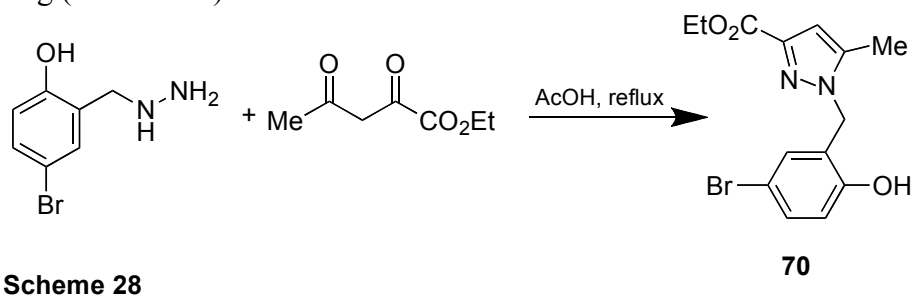
Ethyl propionylpyruvate was reacted with methylhydrazine with the molar ratio above 1: 1.2 to give 95% of ethyl 3-ethyl-1-methyl-1*H*-pyrazole-5-carboxylate **66** (Scheme 26).<sup>70-72</sup>



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.<sup>73,74</sup>

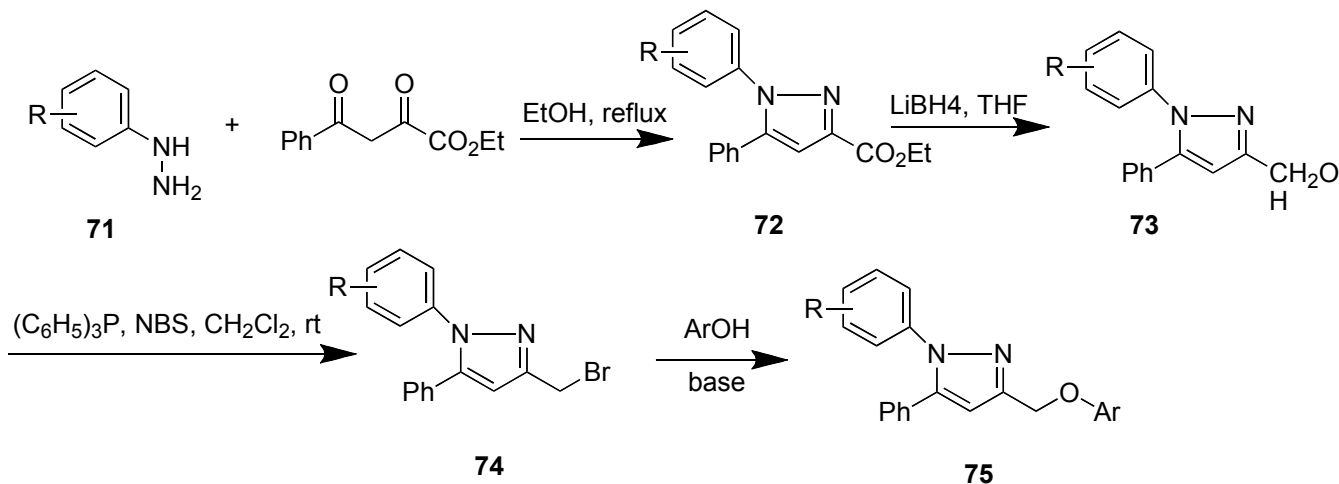


4-Bromo-2-(hydrazinylmethyl)phenol treated with ethyl 2,4-dioxopentanoate to yield predominantly the desired regioisomer **70** which was conveniently purified by preferential crystallization from the reaction mixture upon cooling (Scheme 28).<sup>75</sup>



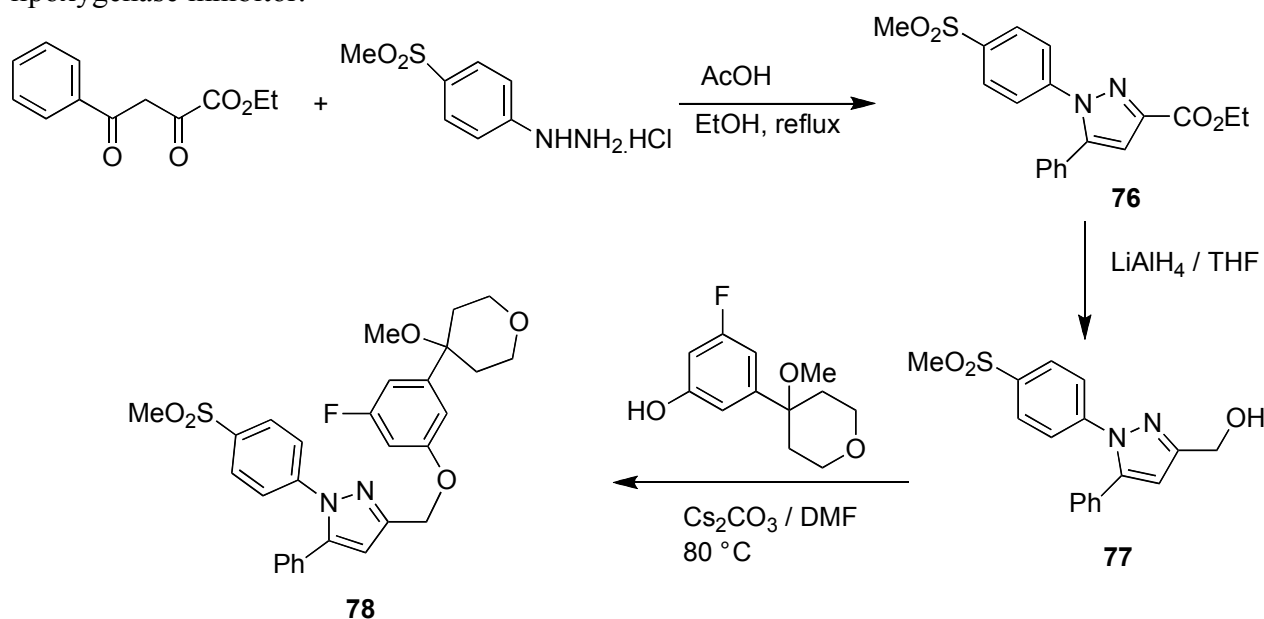
The synthesis of 1,5-diarylpyrazoles **72** was done (Scheme 29) by regioselective cyclization of arylhydrazines **71** with ethyl 2,4-dioxo-4-phenylbutanoate in refluxing ethanol. Esters **72** were reduced

with  $\text{LiBH}_4$  (anhydrous THF, argon), yielding the primary alcohols **73**. Bromination of the crude products with  $(\text{C}_6\text{H}_5)_3\text{P-NBS}$  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.<sup>76</sup>



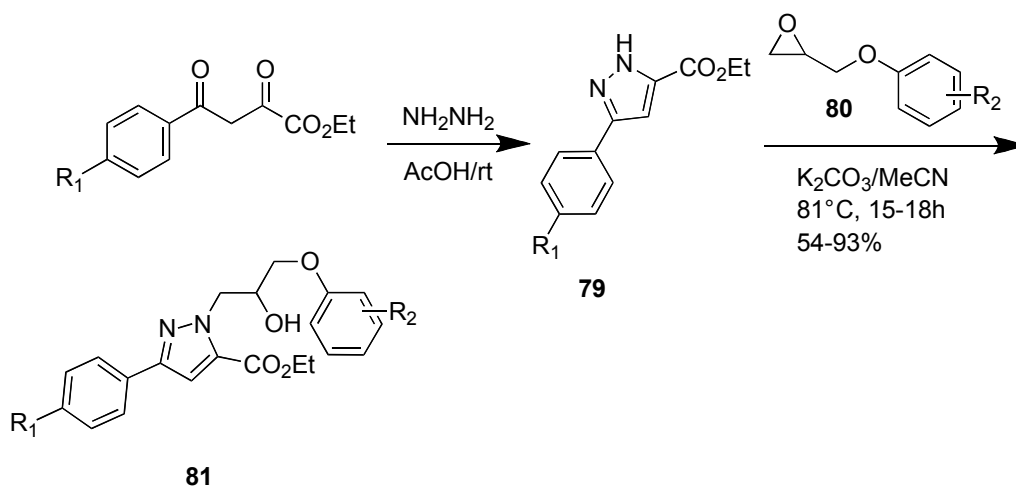
**Scheme 29** R = 4- $\text{CH}_3\text{SO}_2$ , H, 4-F, 4-Cl, 4-Me, 4-OMe, 4- $\text{NH}_2\text{SO}_2$ , 4- $\text{CF}_3\text{O}$ , 3,4- $\text{Cl}_2$ , 3,4-(Me)<sub>2</sub>

The diarylpiperazine 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  $\text{LiAlH}_4$  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  $\text{Cs}_2\text{CO}_3$  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.<sup>77</sup>



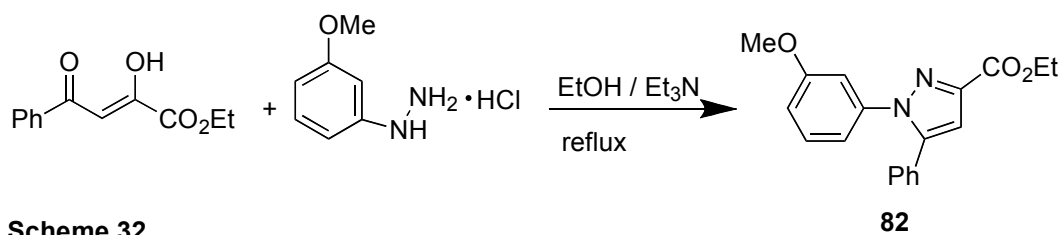
**Scheme 30**

Synthesis of ethyl 1-(2'-hydroxy-3'-aroxypopyl)-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-aryloxymethylepoxyde **80** in the presence of potassium carbonate at refluxing in acetonitrile afforded ethyl 1-(2'-hydroxy-3'-aroxypopyl)-3-aryl-1*H*-pyrazole-5-carboxylate **81** in moderate yields and completely regioselectivity.<sup>7</sup>



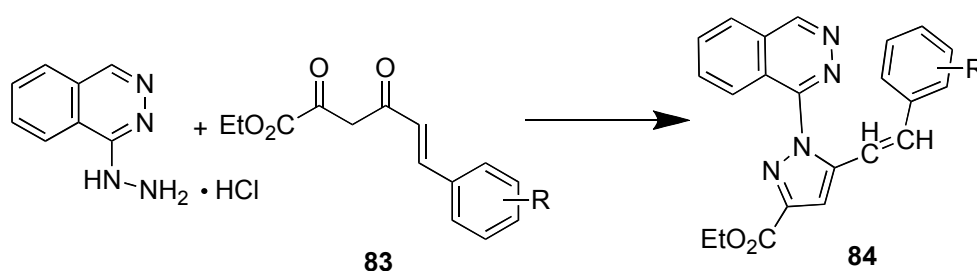
**Scheme 31**  $R_1 = \text{H, Me, OMe}; R_2 = \text{H, 2-OMe, 2-NO}_2, 4\text{-NO}_2, 4\text{-Cl}$

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).<sup>78</sup>



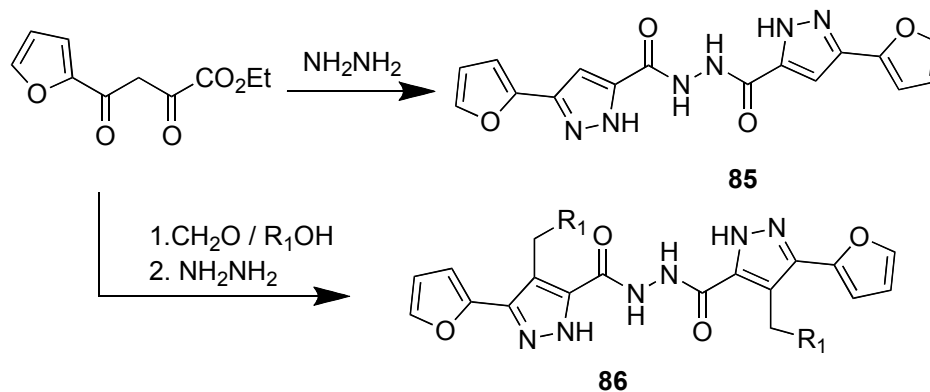
**Scheme 32**

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**<sup>79</sup> (Scheme 33).



**Scheme 33**  $R_2 = \text{H, 4-MeO, 4-Cl, 3-MeO, 4-NO}_2$

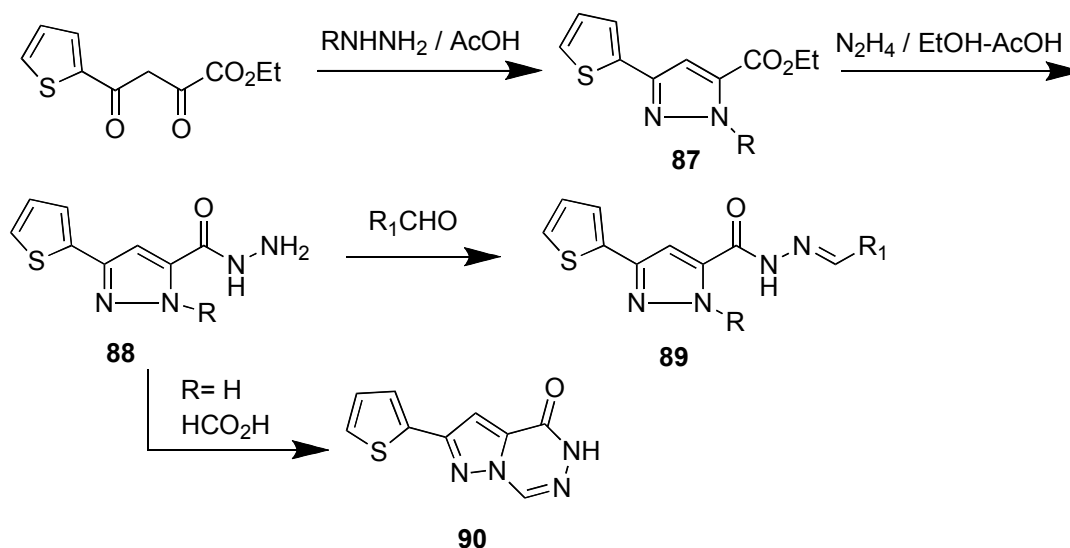
Ethyl (2-furoyl)pyruvate condensed with hydrazine to give bis(furylpyrazole)hydrazide **85**. While condensing with formaldehyde and phenols and hydrazine gave **86** ( $R = \text{CH}_2\text{R}_1$ )<sup>80</sup> (Scheme 34).



Scheme 34

$R_1 = 2\text{-naphthyl, } 2,4\text{-(HO)}_2\text{MeC}_6\text{H}_3$

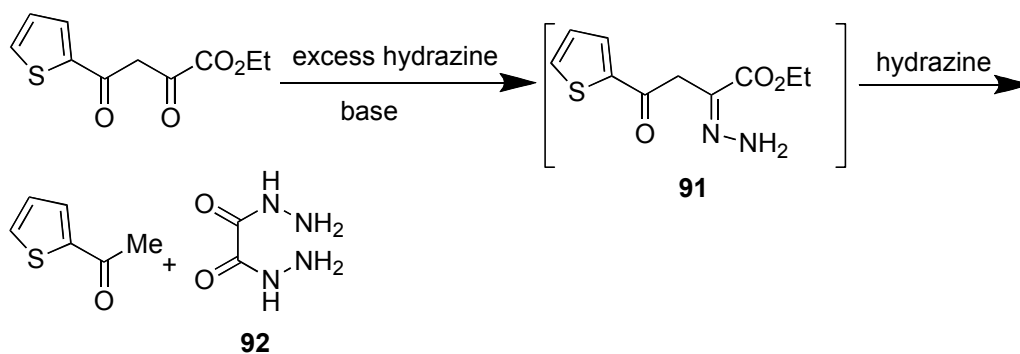
Cyclization of ethyl 2-thienoylpyruvate with hydrazines in acetic acid gave pyrazole derivative **87** which reacted with hydrazine in refluxing EtOH/AcOH to give hydrazides **88** in high yields. Reaction of **88** with aldehydes and formic acid gave **89** and pyrazolotriazinone **90**, respectively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



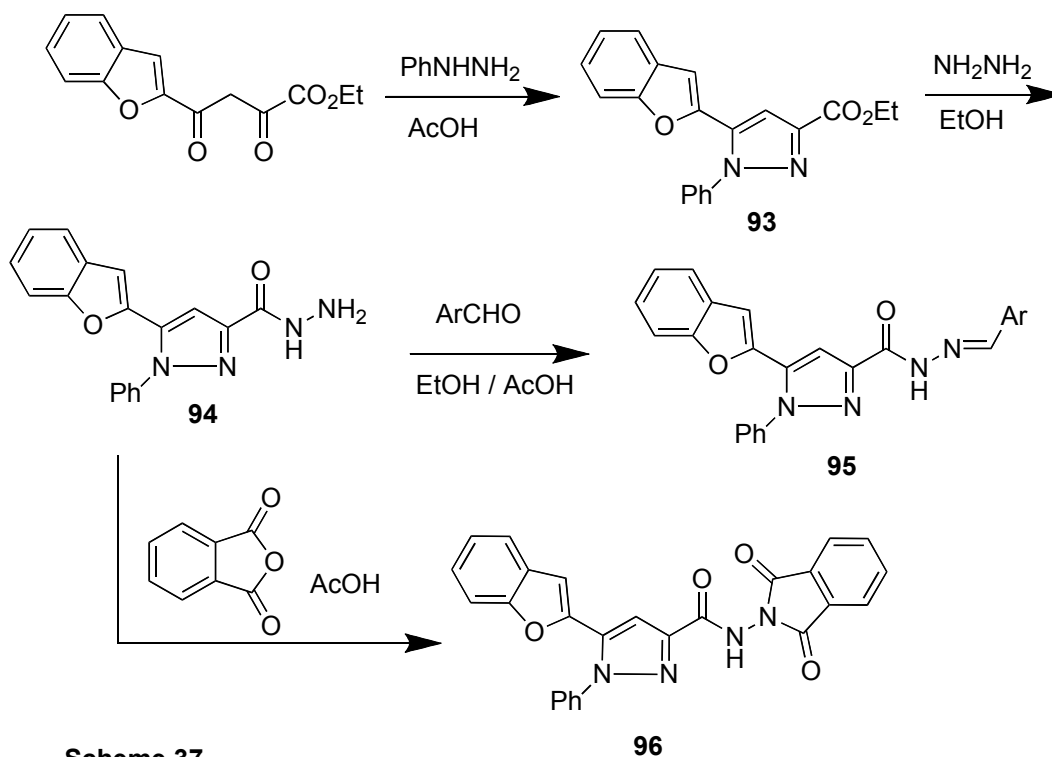
Scheme 35

$R = \text{H, Ph}; R_1 = \text{Ar}$

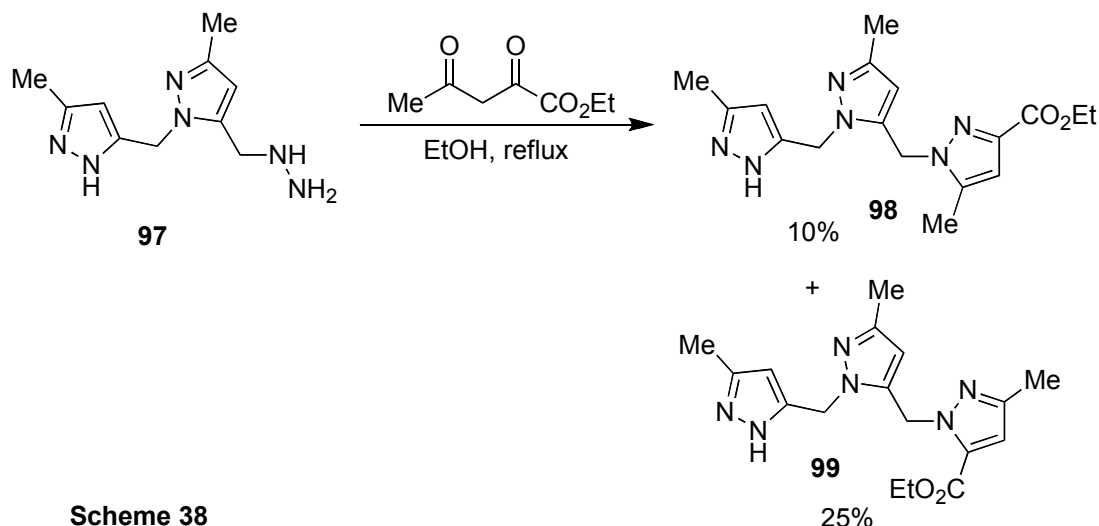
While reaction of ethyl 2-thienoylpyruvate with hydrazine hydrate in neutral or basic medium led to the decomposition to 2-acetylthiophene and oxalohydrazide **92** (Scheme 36).<sup>17</sup>

**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 phthalic anhydride were studied to give the corresponding hydrazones **95** and imides **96** (Scheme 37).<sup>15,82,83</sup>

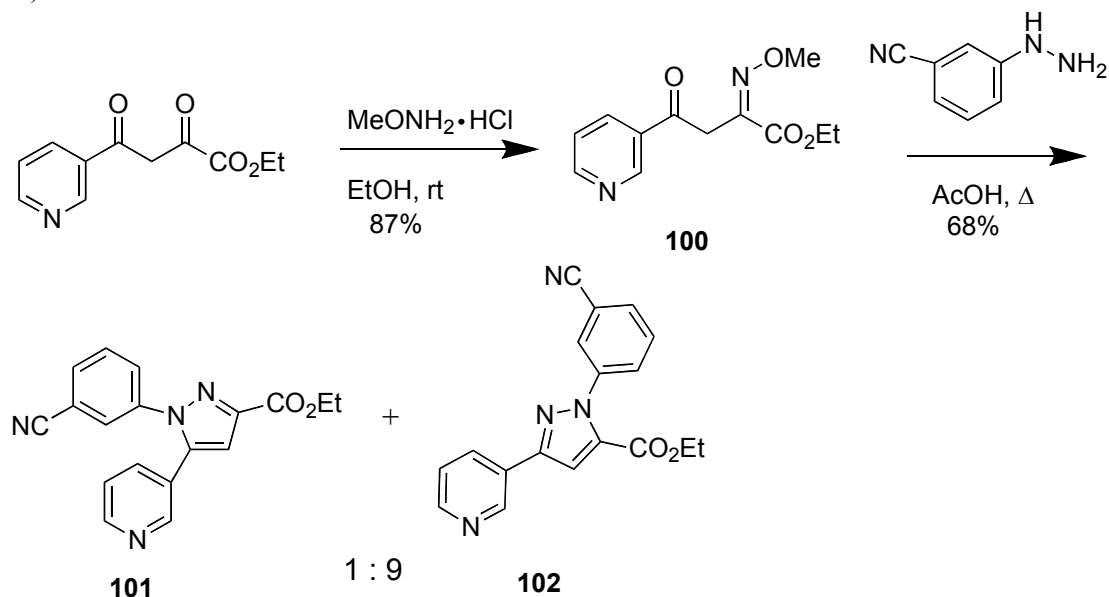
**Scheme 37**

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).<sup>84</sup>



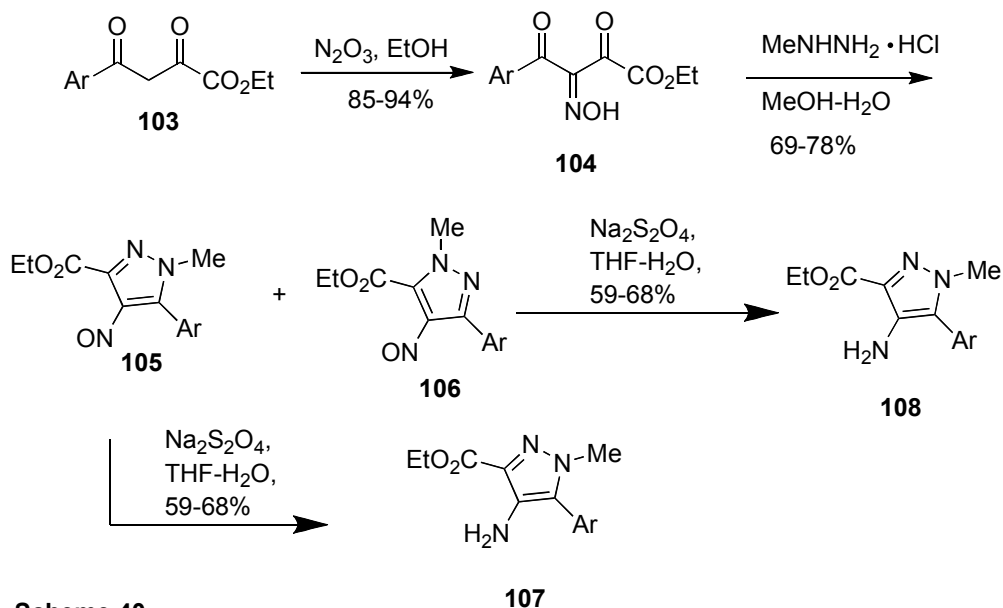
Scheme 38

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).<sup>65</sup>



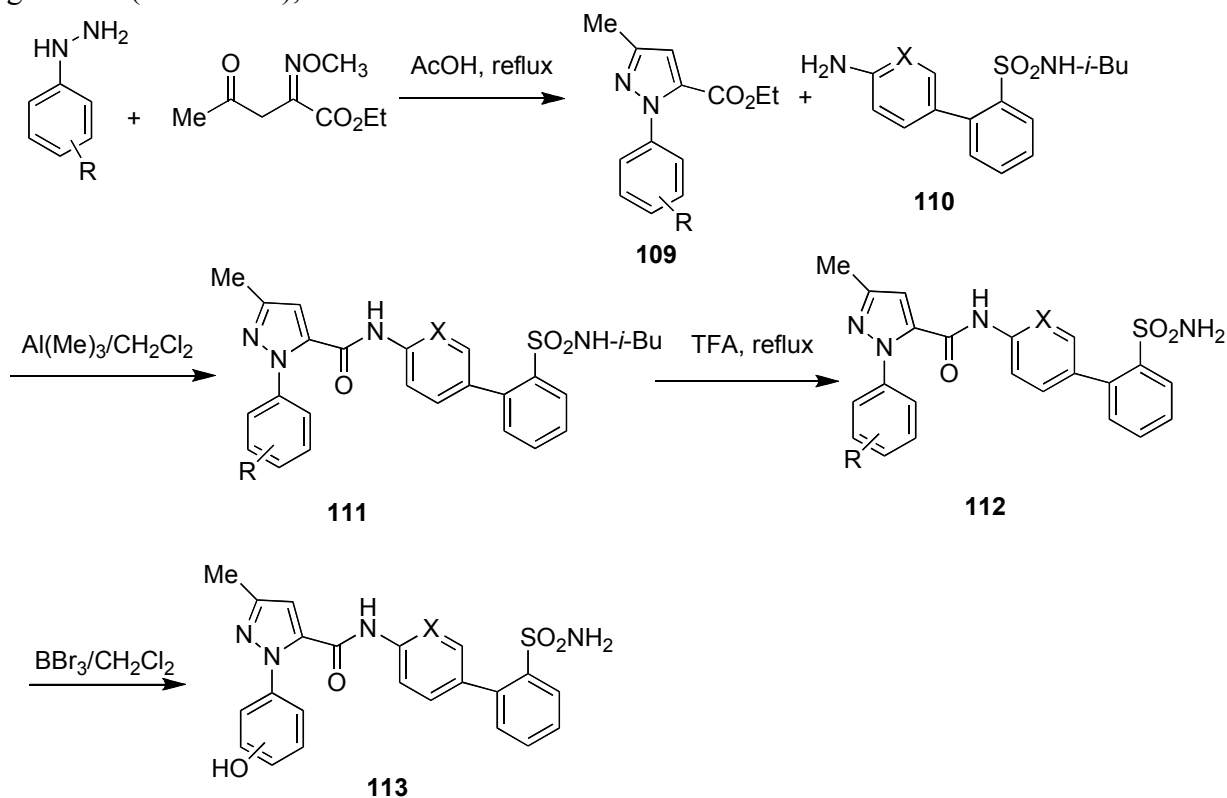
Scheme 39

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).<sup>85</sup>



Scheme 40

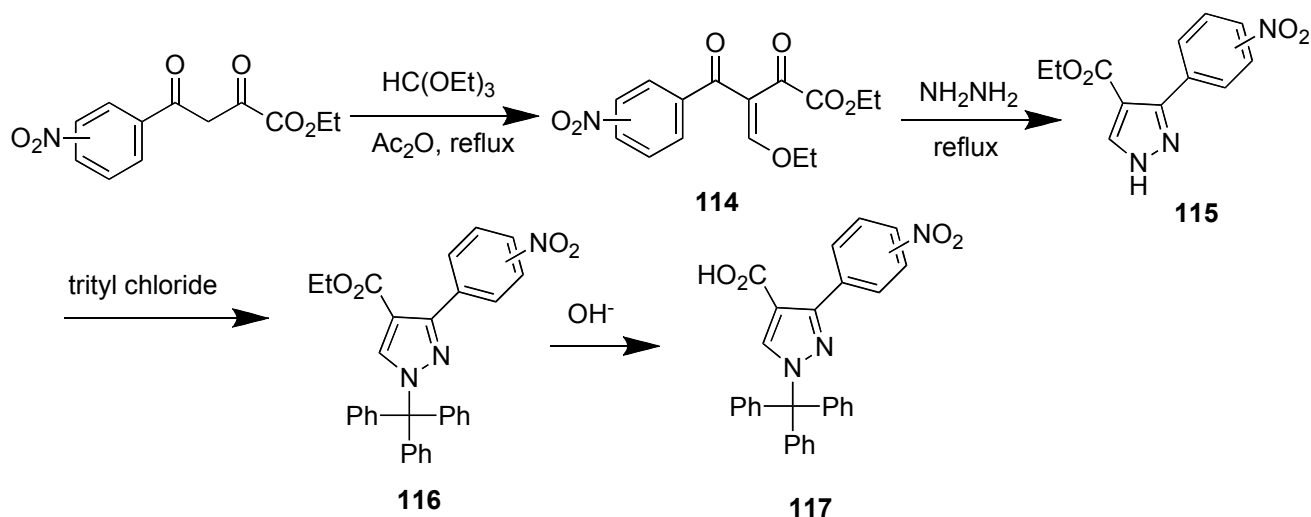
Ethyl 3-methyl-1-phenyl-1*H*-5-carboxypyrazoles **109** were prepared regioselectively from a condensation of the appropriate phenylhydrazine and ethyl 2-(*N*-methoxyimino)-4-oxopentanoate.<sup>86,87</sup> Coupling of ester **109** with the known amines **110** gave good yields of the amides **111**. 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-amidase factor Xa inhibitors.<sup>88,89</sup>



Scheme 41

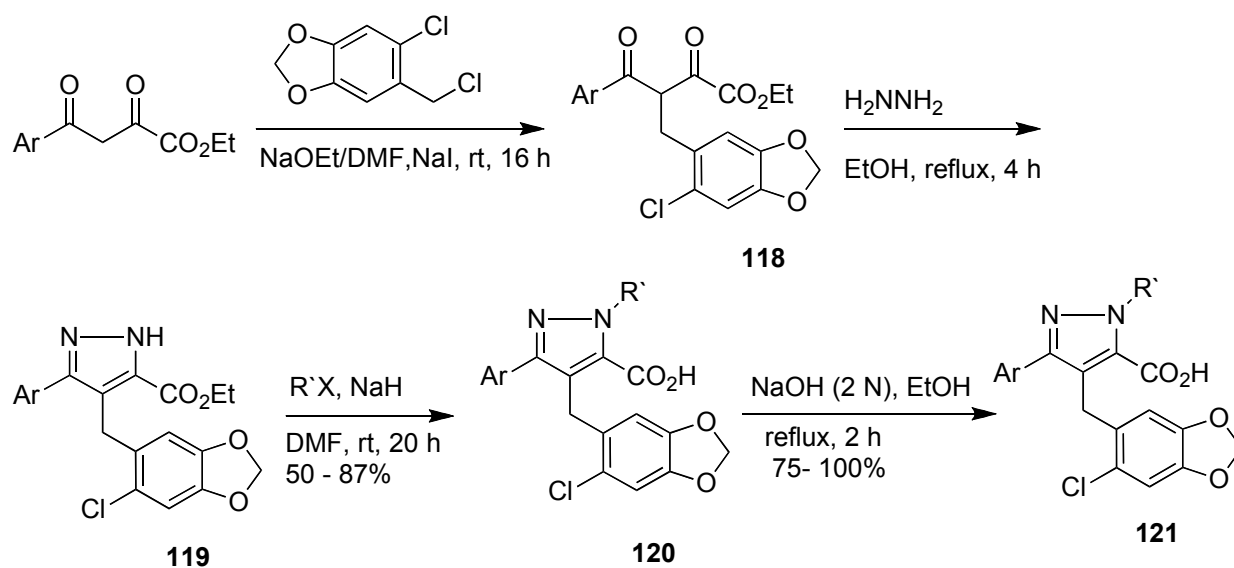
$\text{R} = \text{H}, 2\text{-OMe}, 3\text{-OMe}, 4\text{-OMe}; \text{X} = \text{CH}, \text{N}, \text{C-F}$

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).<sup>90</sup>



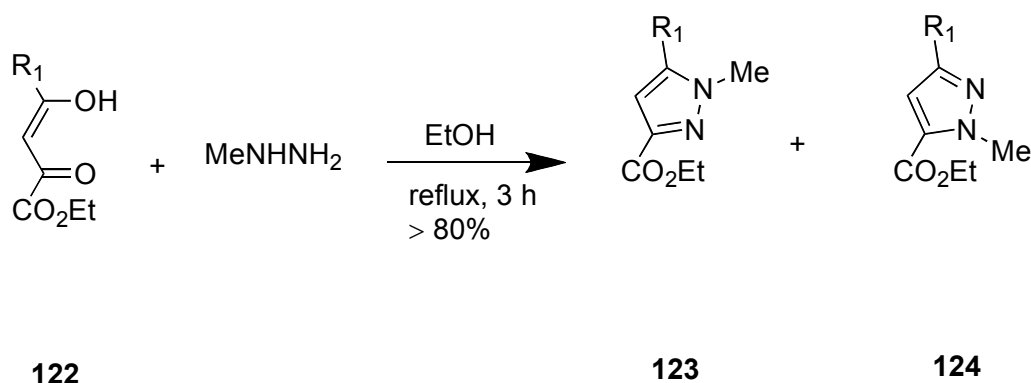
**Scheme 42**

C-Alkylation of  $\alpha,\gamma$ -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.<sup>6</sup>



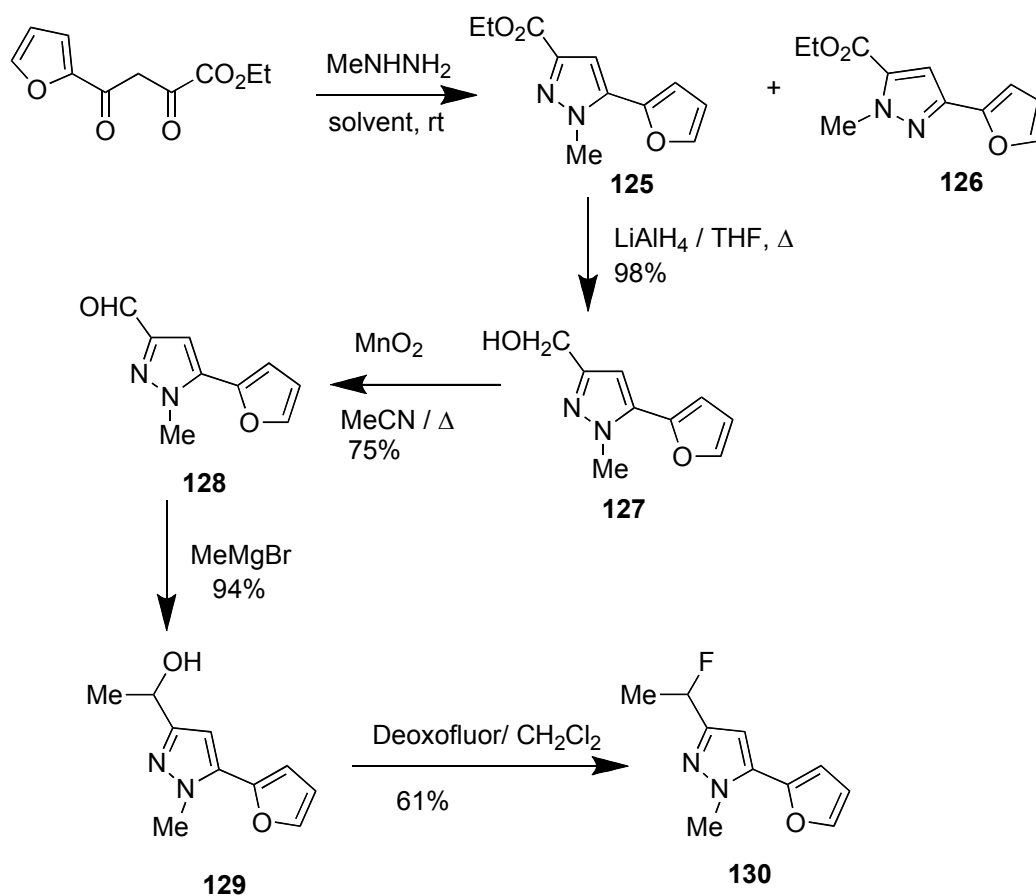
**Scheme 43**

The target compounds **123**, **124** starts from 2,4-dioxopentanoic acid ethyl ester **122** ( $R_1 = \text{Me}$ ) or the 2,4-dioxo-4-phenyl-butyric acid ethyl ester **122** ( $R_1 = \text{Ph}$ ). These  $\beta$ -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).<sup>91,92</sup>



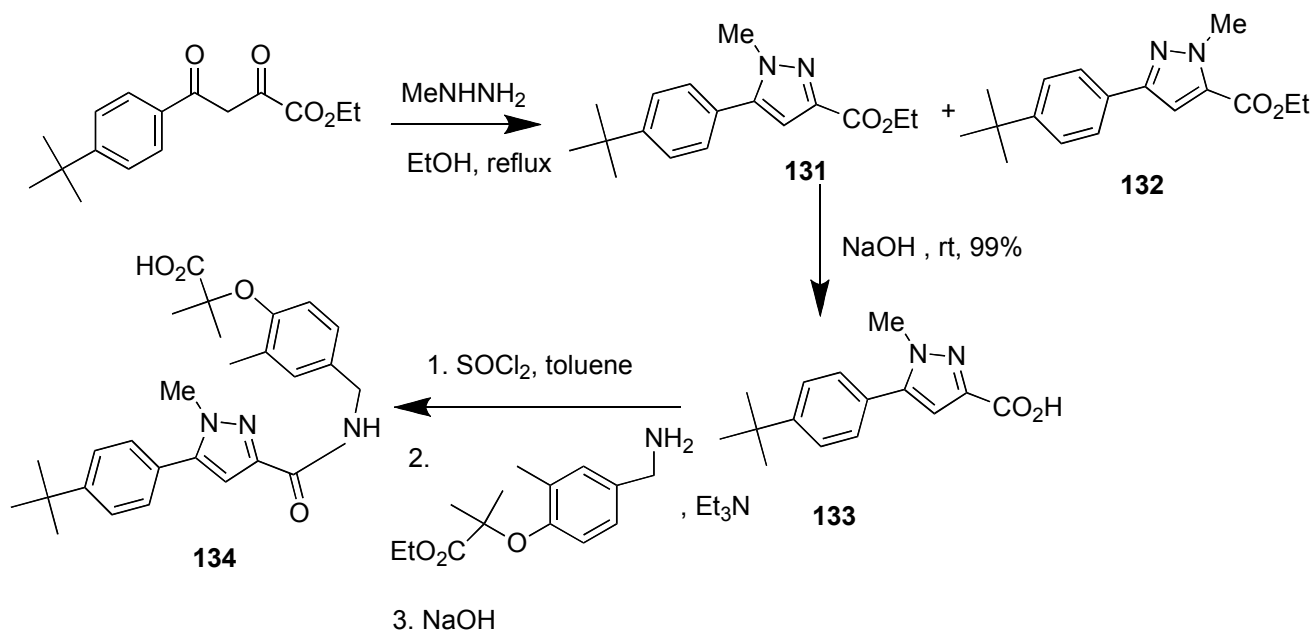
**Scheme 44**  $R_1 = \text{Me, Ph}$

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  $\text{EtOH}$ , 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  $\text{LiAlH}_4$  reduction to the corresponding alcohol **128** and subsequent oxidization with  $\text{MnO}_2$ . 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  $\text{MeMgBr}$  afforded the 1-hydroxyethyl derivative **129** in 94% yield. Subsequent treatment of **129** with deoxofluor provided the monofluorinated derivative **130** in 61% yield.<sup>93,94</sup>



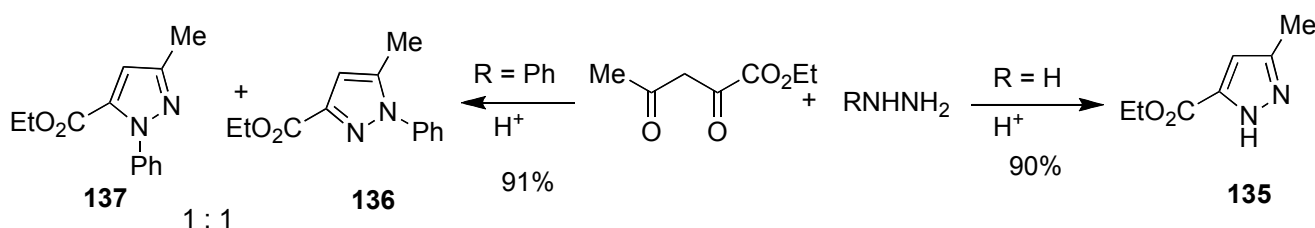
Scheme 45

GSK183390A **134** has recently emerged as a potent dual agonist of PPAR $\alpha/\gamma$  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.<sup>16</sup>



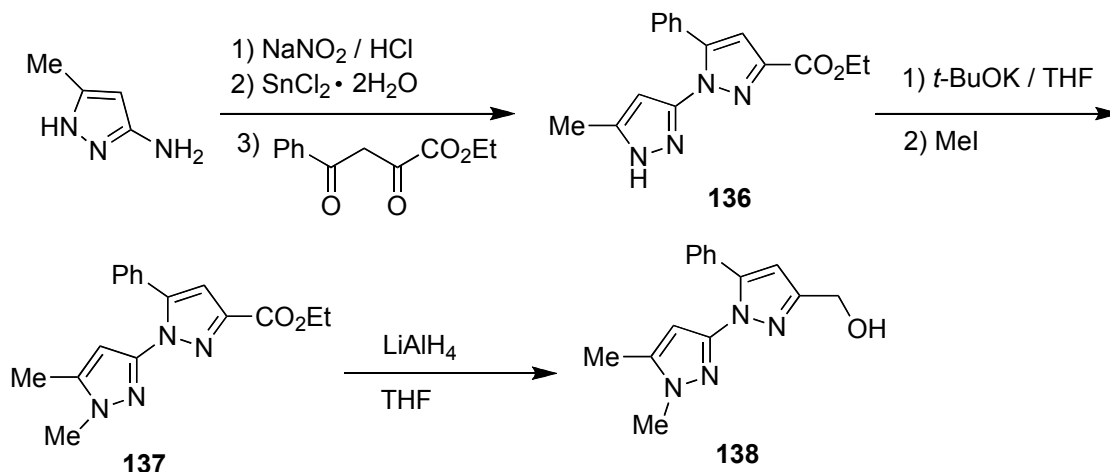
Scheme 46

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).<sup>95</sup>



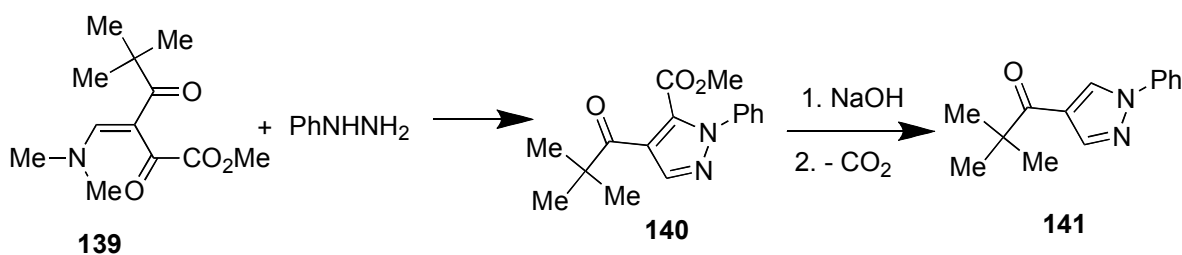
Scheme 47

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 intermediate diamine is not isolated but has immediately undergone a condensation with the  $\beta$ -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  $\alpha$ -isomer **137** in a 29%. Finally, the compound **137** was converted to the target product **138** using  $\text{LiAlH}_4$  as agent of reduction (Scheme 48).<sup>96</sup>



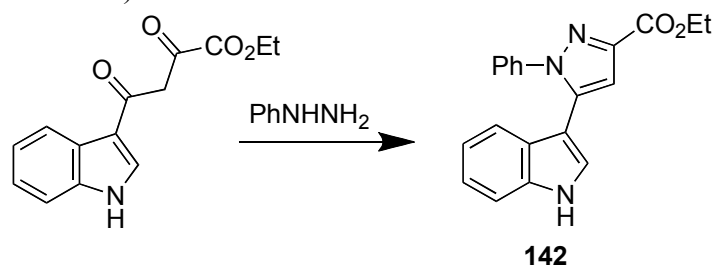
Scheme 48

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).<sup>97</sup>



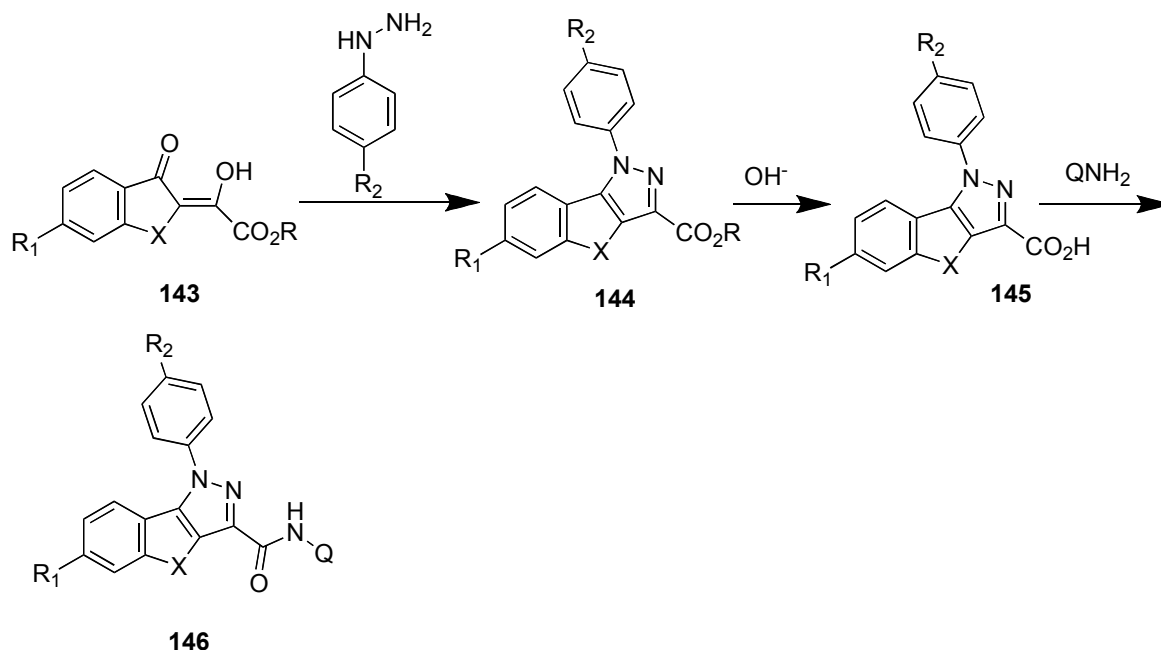
Scheme 49

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



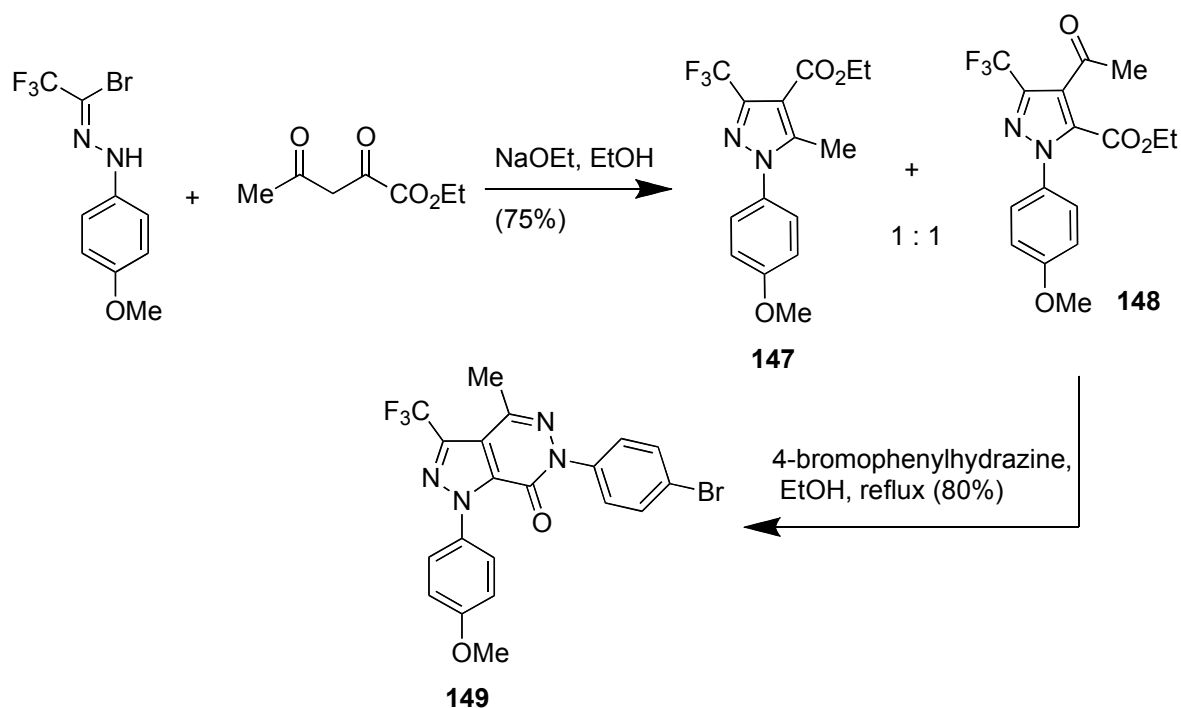
Scheme 50

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).<sup>21-25</sup>



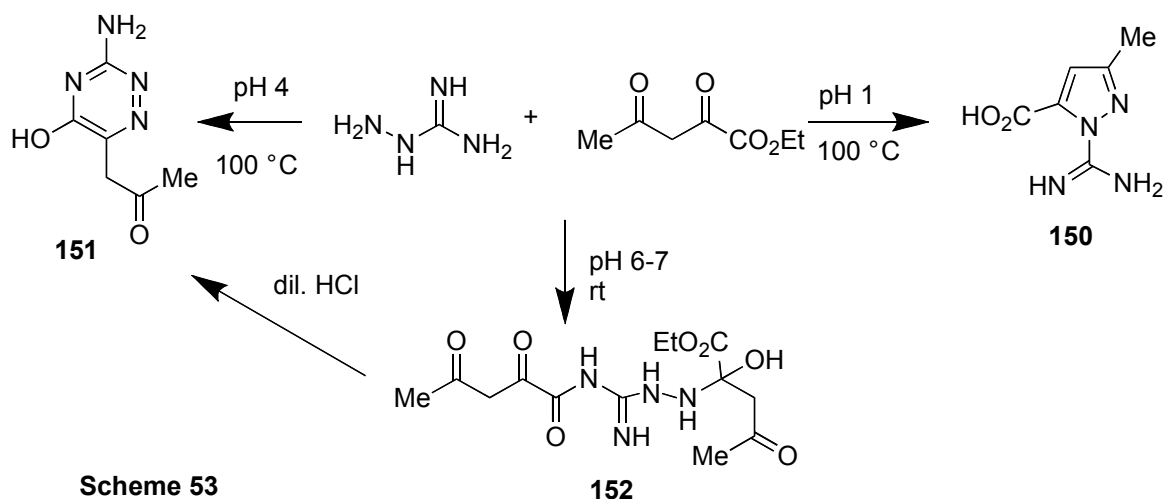
**Scheme 51** X = (CH<sub>2</sub>)<sub>1-3</sub>, CH:CH, O; R = CO<sub>2</sub>Me, CO<sub>2</sub>Et, R<sub>1</sub> = H, Cl, OMe, NMe<sub>2</sub>, OH;  
R<sub>2</sub> = H, 4-Cl, 4-F, 2-Cl, 3-Me, 4-CO<sub>2</sub>H, 2-Me, 4-OMe, 2-CO<sub>2</sub>H

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.<sup>100</sup>

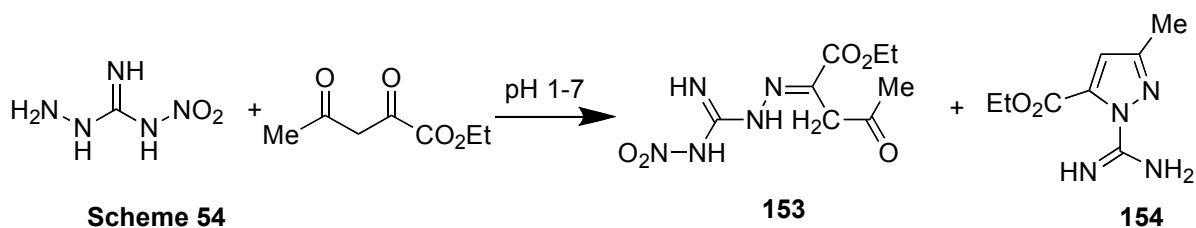


**Scheme 52**

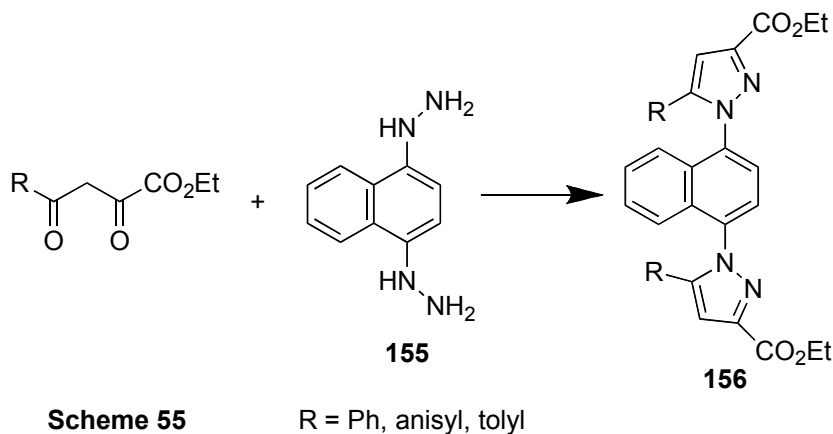
Aminoguanidine was treated with ethyl acetopyruvate at 100 °C and pH 1 to give pyrazole **150**, whereas the reaction at pH 4 gave triazine **151**. While at room temperature and at pH 6-7 gave the dimer **152** that was hydrolyzed by dil. HCl to give **151** (Scheme 53).<sup>101</sup>



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

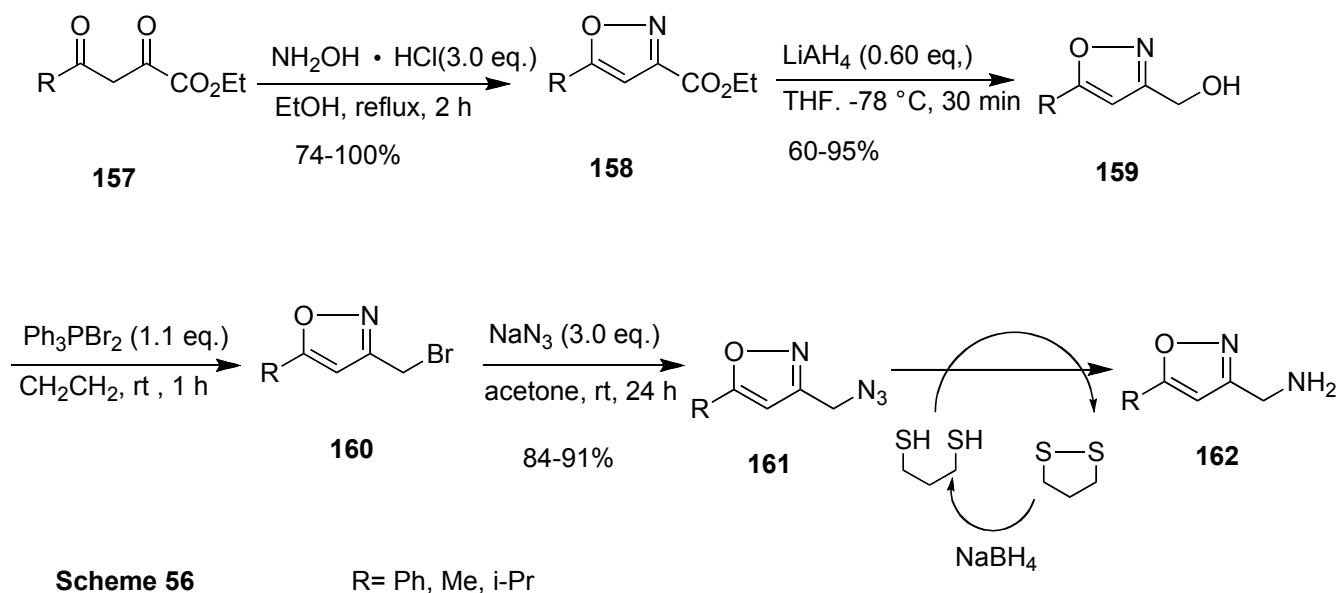


Dihydralazine **155** reacted with ethyl 2,4-dioxoalkanoates to give dipyrazolyolphthalazines **156** (Scheme 55).<sup>102</sup>

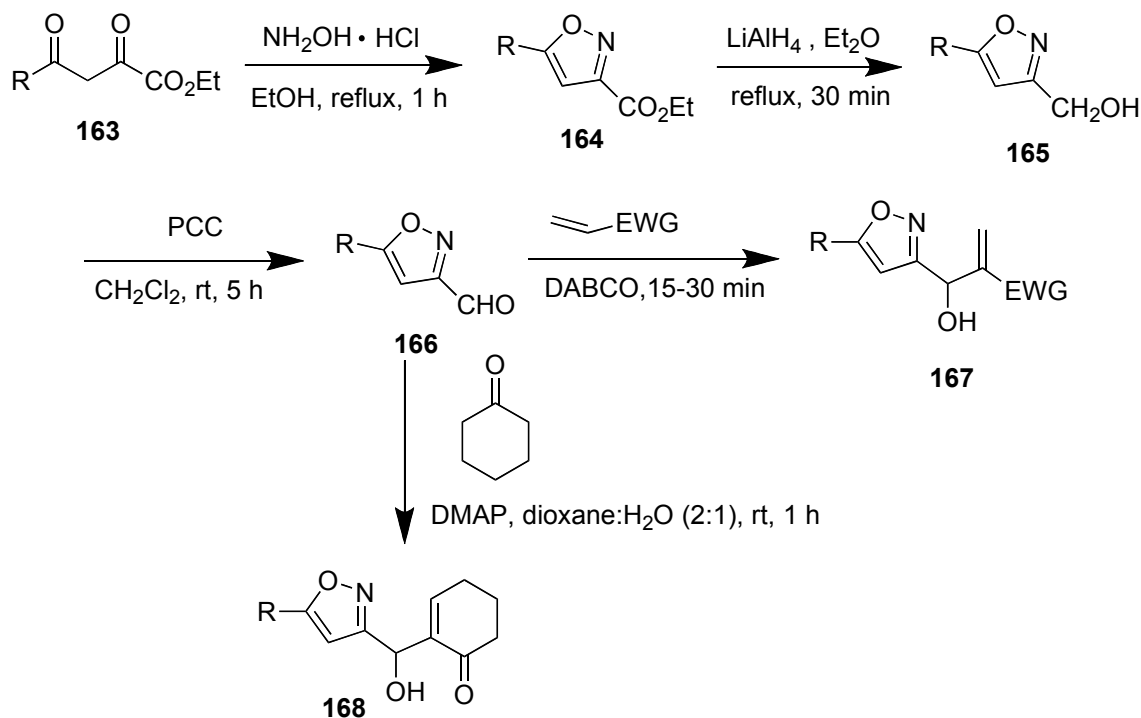


### 2.1.4. ISOXAZOLES

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  $-78\text{ }^{\circ}\text{C}$ . 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).<sup>10</sup>

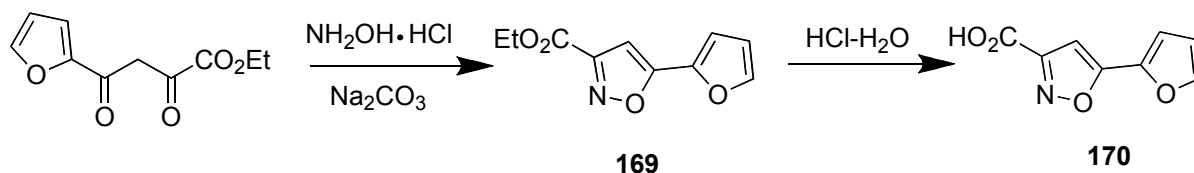


The reaction of 2,4-diketo esters **163** with hydroxylamine hydrochloride gave 3-isoxazole esters **164**, in excellent yield, these ester were reduced with lithium aluminum hydride and the resulting alcohols **165** were oxidized with pyridinium chlorochromate (PCC) to yield substituted 3-isoxazolecarbaldehydes **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 isoxazolecarbaldehydes undergo fast reaction with cyclohexenone in the presence of DMAP to give **168** (Scheme 57).<sup>103</sup>



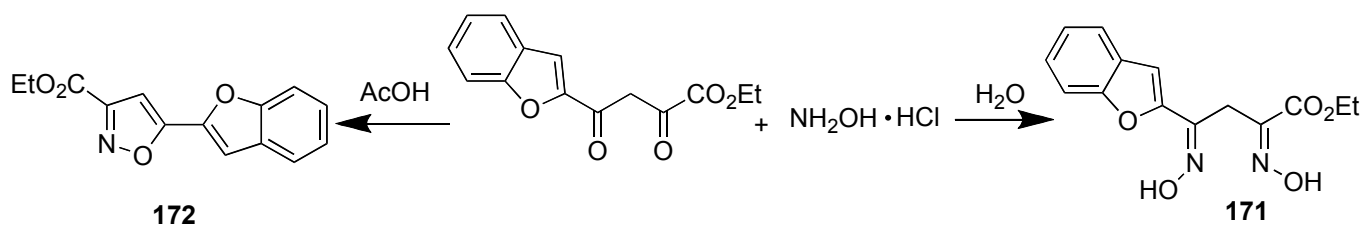
**Scheme 57** R= Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-Br-C<sub>6</sub>H<sub>4</sub>, 4-F-C<sub>6</sub>H<sub>4</sub>; EWG = CN, CONH<sub>2</sub>, CO<sub>2</sub>R

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<sub>2</sub>O to give 5-(2-furyl)-3-isoxazolecarboxylic acid **170** (Scheme 58).<sup>14</sup>



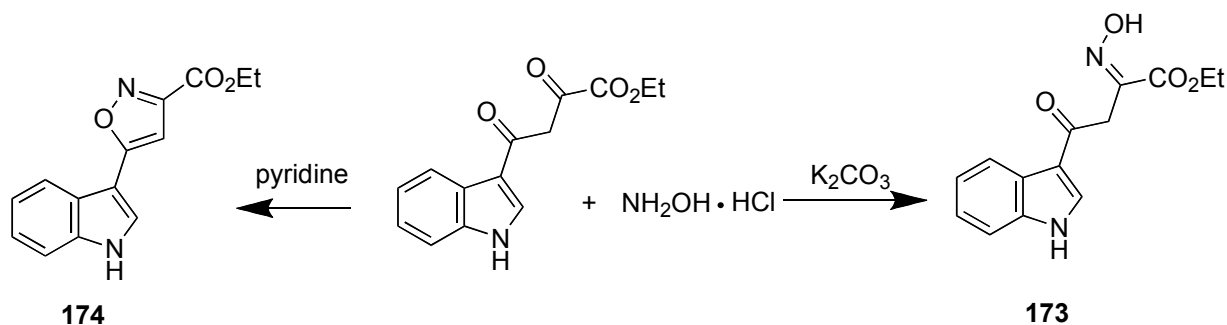
**Scheme 58**

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).<sup>15</sup>



**Scheme 59**

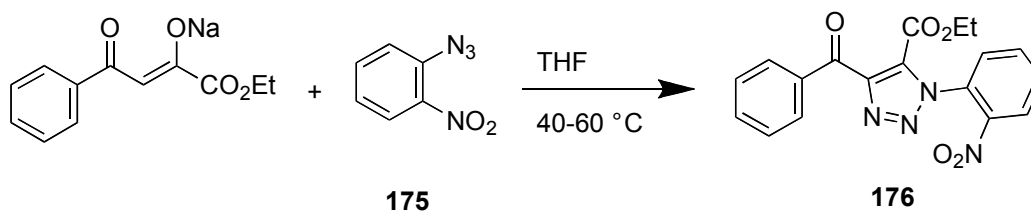
Reaction of with hydroxylamine hydrochloride in the presence of anhydrous potassium carbonate to give the corresponding oxime **173** while in pyridine gave ethyl isoxazole-3-carboxylate **174** in good yields

(Scheme 60).<sup>18</sup>

Scheme 60

### 2.1.5. TRIAZOLES

The reactivity of benzoylpyruvates as  $\beta$ -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).<sup>104</sup>

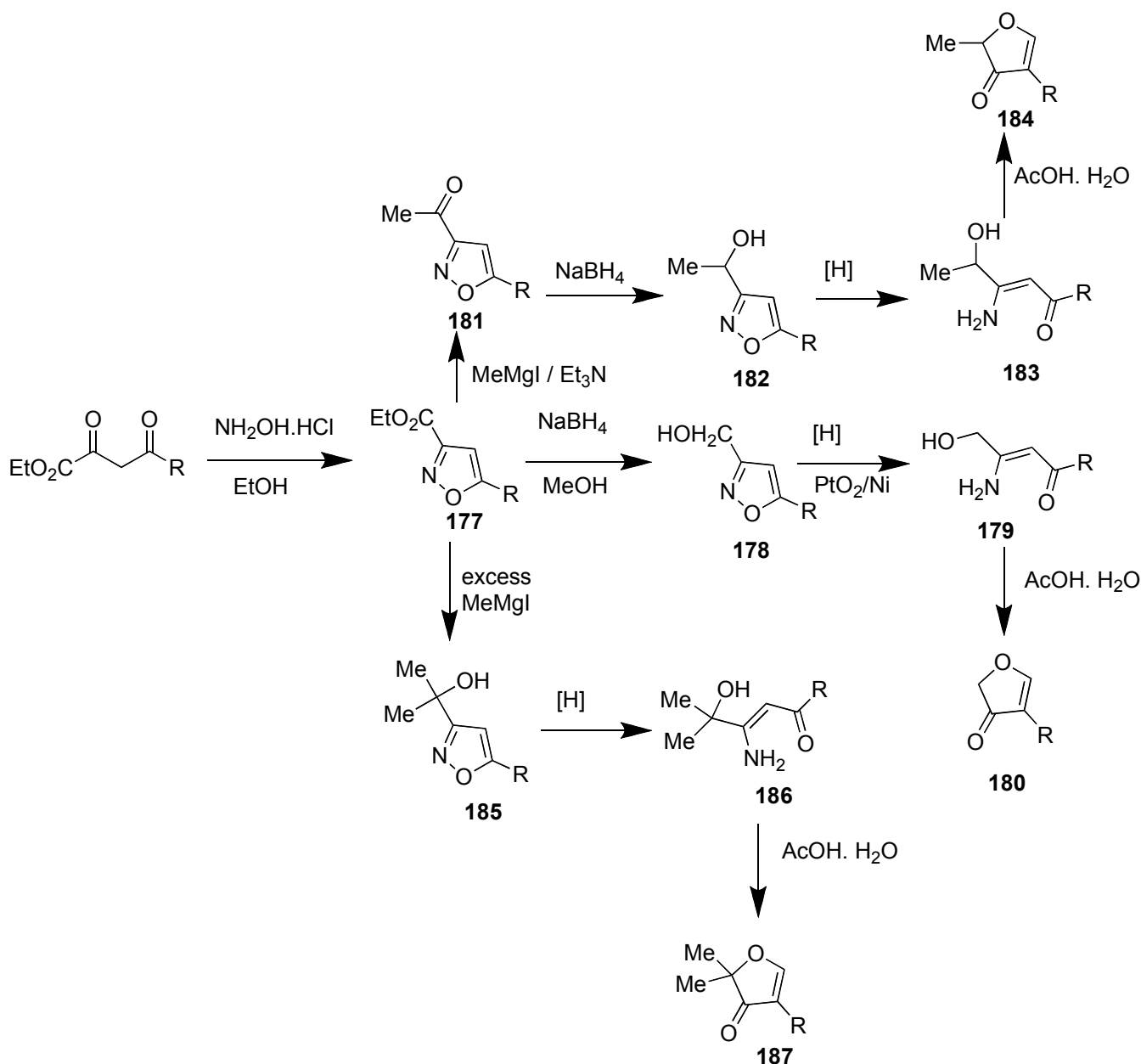


Scheme 61

### 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**.<sup>105</sup> 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  $\beta$ -enamino-ketones.<sup>106</sup> 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<sub>2</sub>/Ni-Raney mixture of catalysts in methanol a rapid reaction ensued to give the corresponding  $\beta$ -enamino-ketones having a primary **179**, **183** or tertiary **186**  $\gamma$ -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<sub>2</sub>O 2:1 mixture in good yields (Scheme 62).<sup>3</sup>



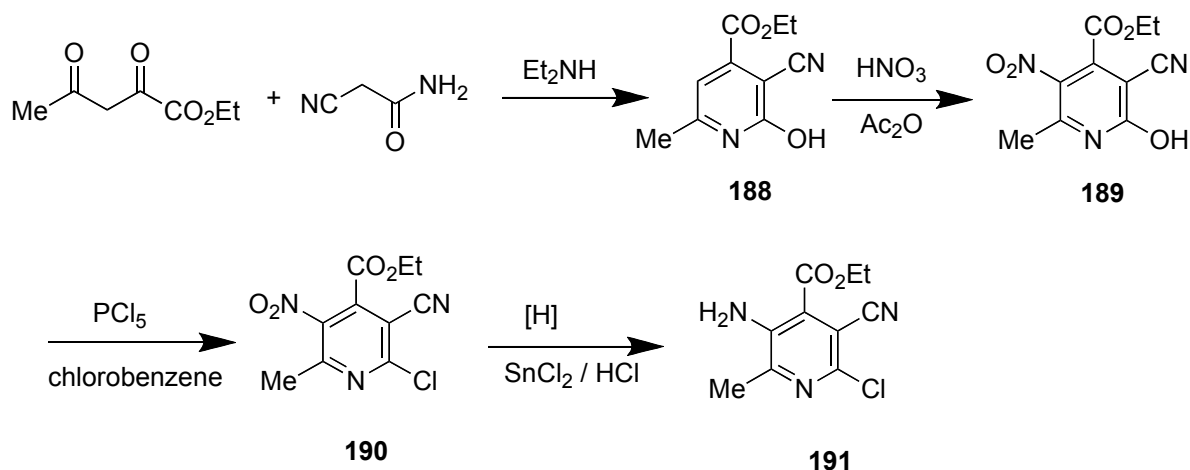
**Scheme 62**

R = Et, pentyl,  $\text{Me}_2\text{CHCH}_2$ , Ph, 2-MeOC<sub>6</sub>H<sub>4</sub>

## 2.2. SIX-MEMBERED SYSTEMS

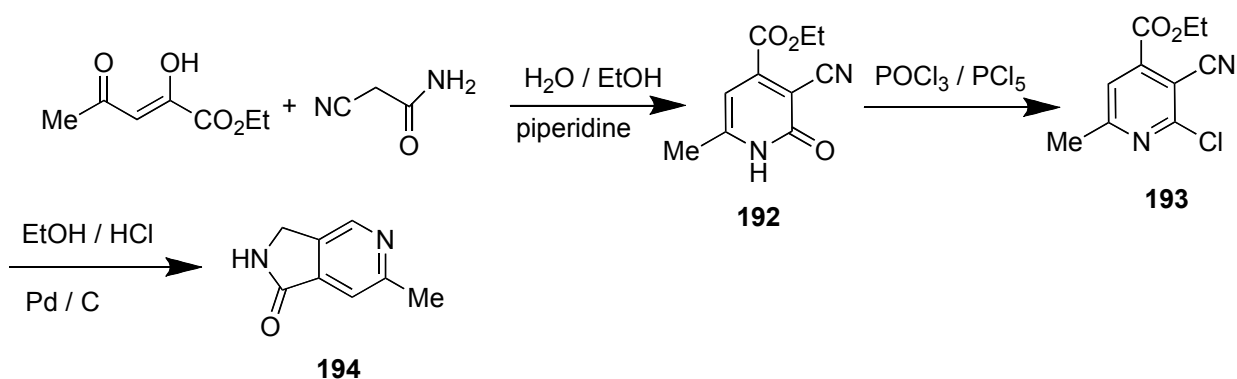
### 2.2.1. PYRIDINE DERIVATIVES

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).<sup>107</sup>

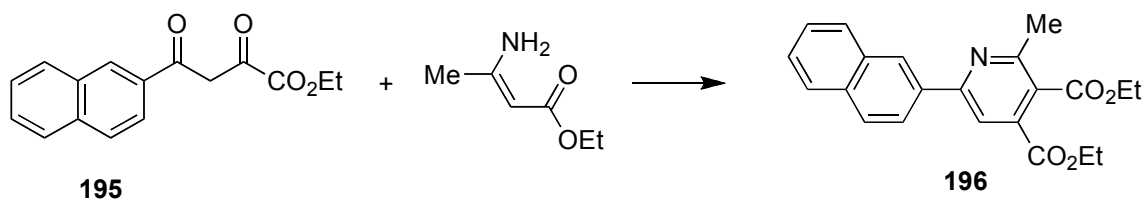
Scheme 63

Ethyl 2-hydroxy-4-oxopent-2-enoate was condensed with 2-cyanoacetamide in H<sub>2</sub>O/ EtOH in piperidine 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<sub>5</sub> and POCl<sub>3</sub> 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).<sup>108</sup>



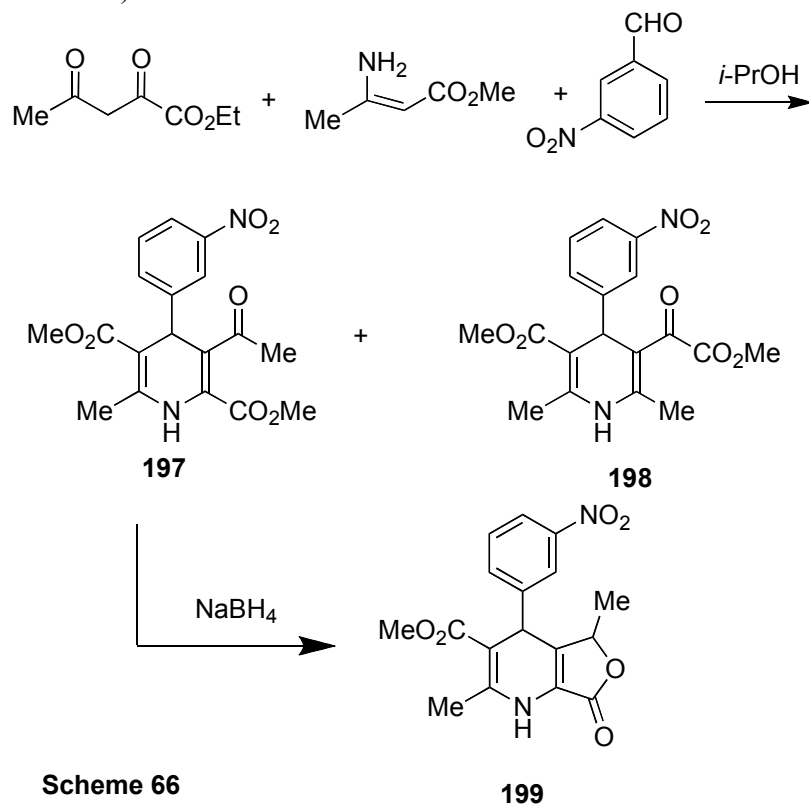
Scheme 64

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).<sup>109</sup>



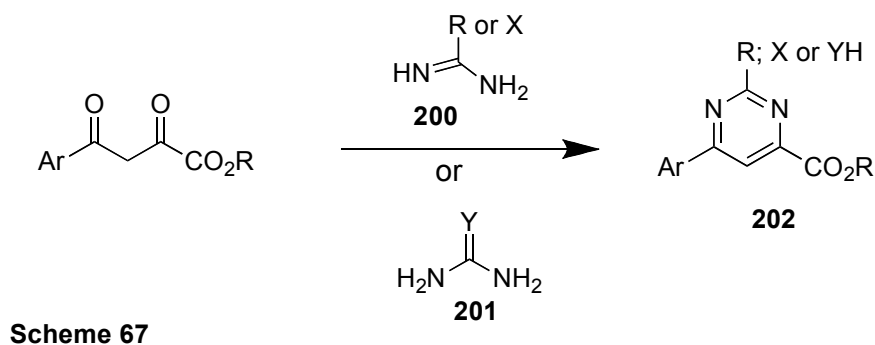
Scheme 65

For the Hantzsch pyridine synthesis, methyl acetoacrylate 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 separated by column chromatography. Reduction of **197** with sodium borohydride in alcohol led to lactone **199** (Scheme 66).<sup>110</sup>

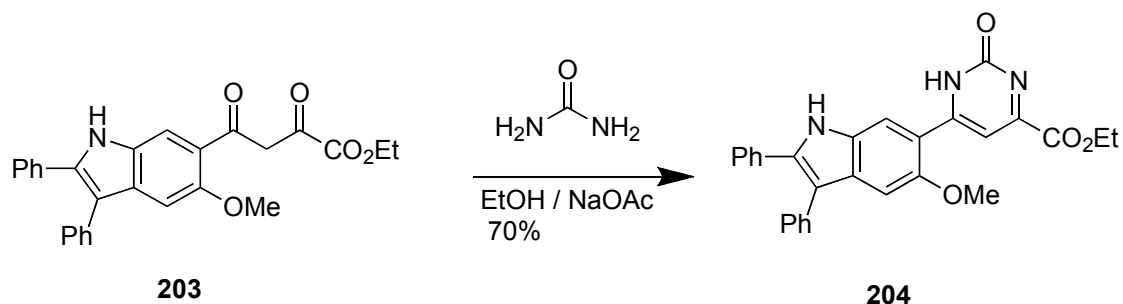


### 2.2.2. PYRIMIDINES

Benzoylpyruvates can be reacted as  $\beta$ -diketones<sup>111–114</sup> with *N,N*-dinucleophiles such as amidines **200a**, isoureas **200b**, guanidines **200c** ( $R = \text{NH}_2$ ,  $\text{NH-alkyl}$ ,  $\text{NH-aryl}$  etc.) and ureas **201** ( $R = \text{O}$  or  $\text{S}$ ), 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).

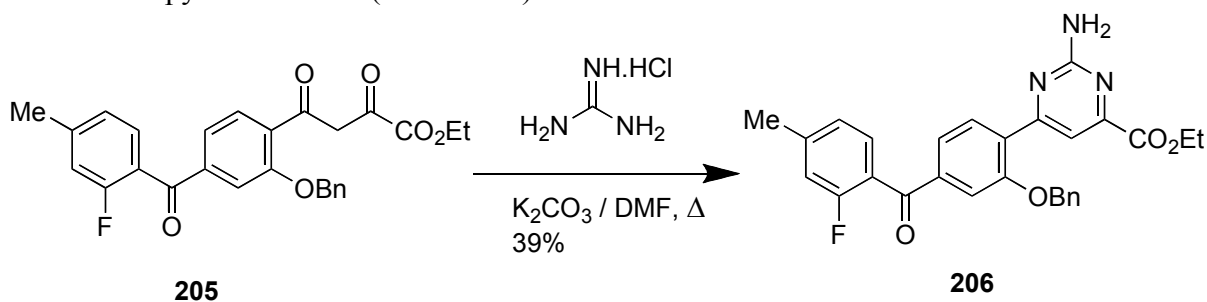


The synthesis of pyrimidin-2-ones like **204** has been reported. Thus, the presence of base has been used to promote condensation between a benzoylpyruvate **203** and urea (Scheme 68).<sup>115</sup>



Scheme 68

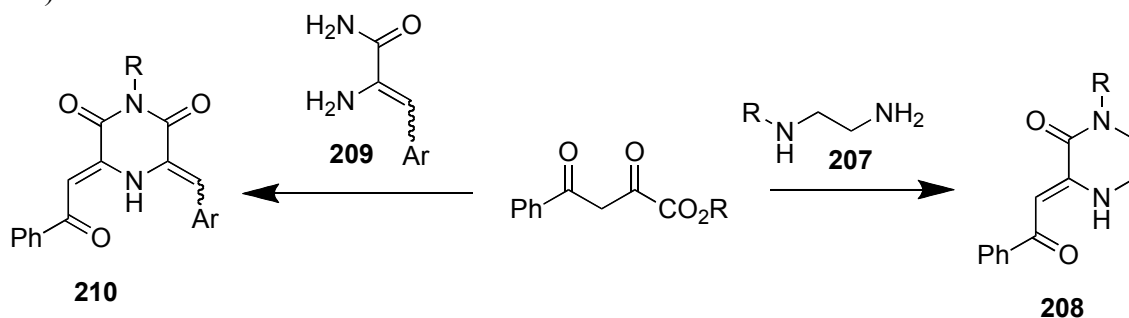
In a similar fashion, condensation between a benzoylpyruvate **205** and guanidine gives an entry to the imprinted 2-aminopyrimidine **206** (Scheme 69).<sup>116</sup>



Scheme 69

### 2.2.3. PIPERAZINES

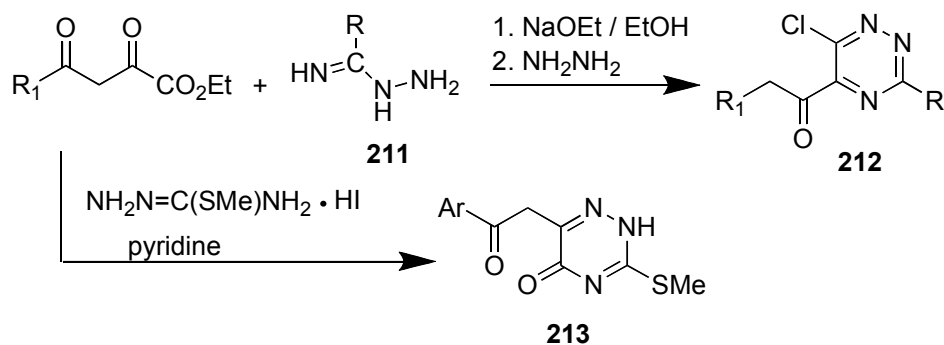
Benzoylpyruvate can react across  $\alpha$ -keto ester moiety with  $N,N$ -dinucleophiles. Reactions involving ethylene diamines **207** or  $\alpha$ -amino acrylamides **209** lead to piperazine-2-one derivatives like **208** and **210** (Scheme 70).<sup>117-120</sup>



Scheme 70

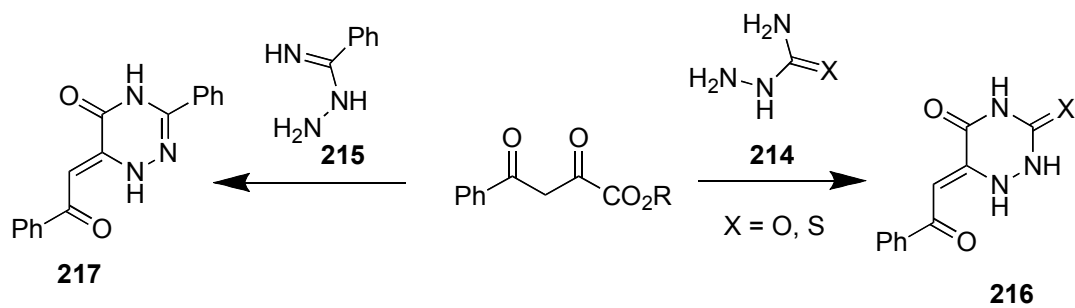
### 2.2.4. 1,2,4-TRIAZINES

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).<sup>20,120-122</sup>



**Scheme 71** R = Me, Ph, R<sub>1</sub> = CH<sub>2</sub>COR<sub>2</sub>; R<sub>2</sub> = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>

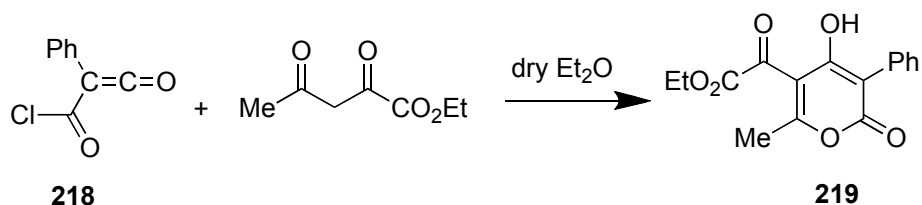
Similarly, reaction with semicarbazides **214** and aminoamidines **215** lead to 1,2,4-triazine-5-one derivatives like **216** and **217** (Scheme 72).<sup>117-120</sup>



**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).<sup>123</sup>

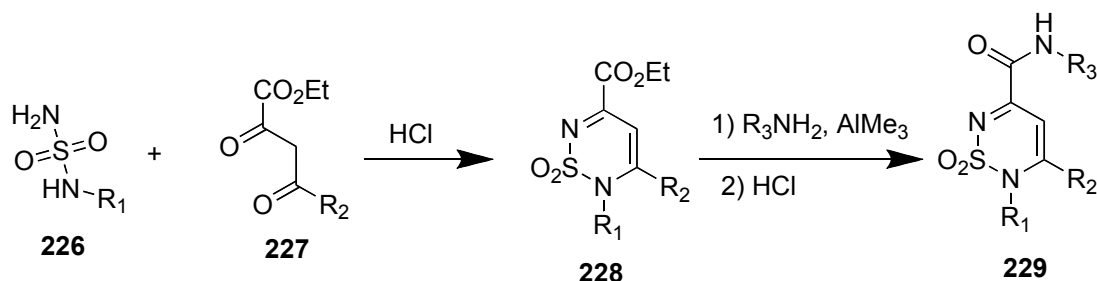


**Scheme 73**

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**.<sup>123</sup>



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<sup>124</sup> (Scheme 77).

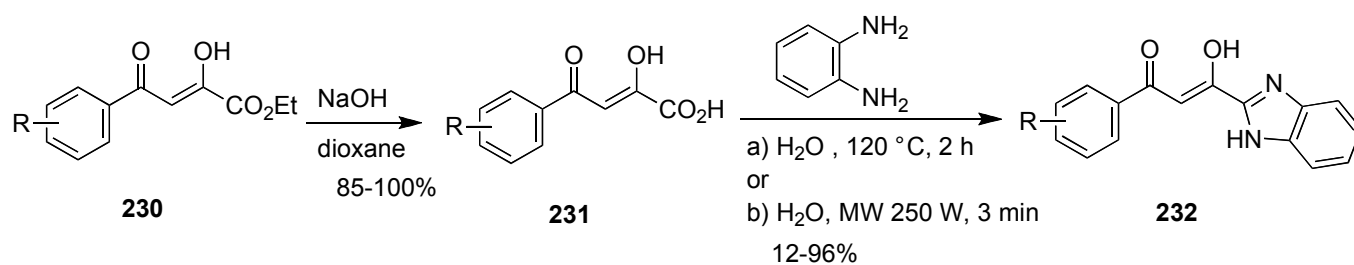


**Scheme 77** R<sub>1</sub>= Ph, 4-ClPh, benzyl, 2,4-diClBn, cyclohexyl, hexyl;  
R<sub>2</sub>= phenyl, 4-chlorophenyl, benzyl, cyclohexyl, hexyl;  
R<sub>3</sub> = cyclohexyl, morpholinyl, piperidinyl, Ph

## 2.3. FUSED HETEROCYCLIC SYSTEMS

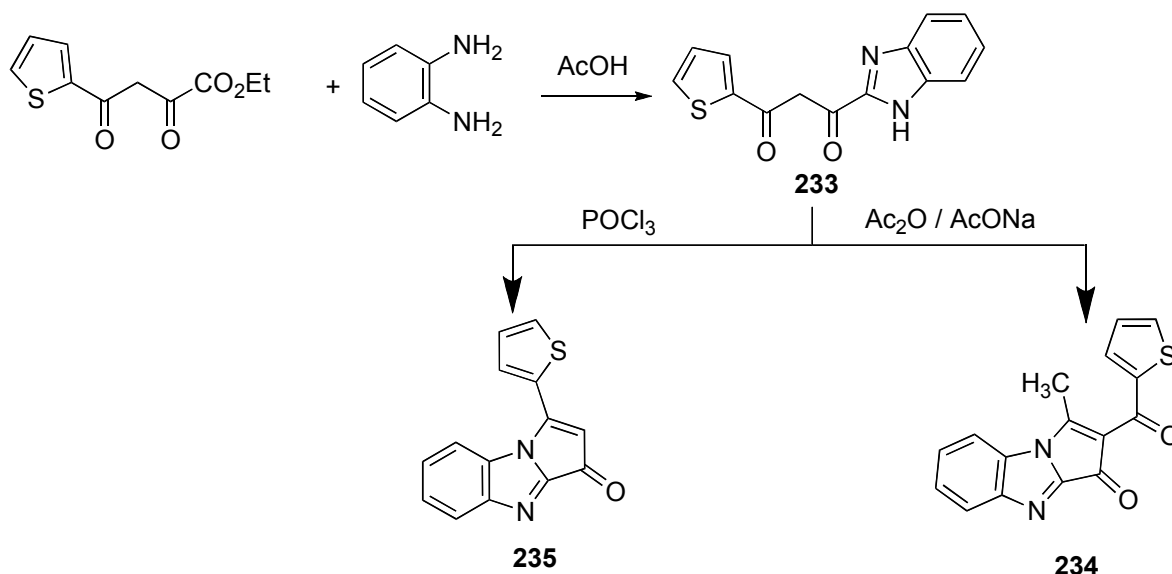
### 2.3.1. BENZIMIDAZOLE DERIVATIVES

The synthetic pathway to 1-aryl-3-(1*H*-benzimidazol-2-yl)-3-hydroxypropanone **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).<sup>19</sup>



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

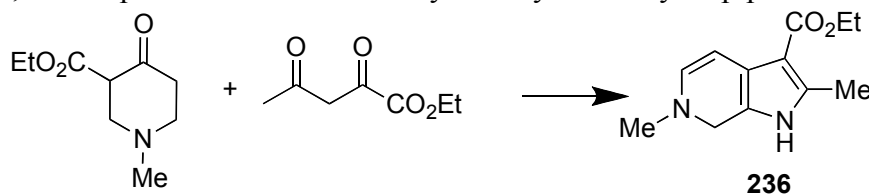
Condensation of ethyl 2-thionyl pyruvate with *o*-phenylenediamine in glacial acetic acid under reflux, gave the corresponding 1-(1*H*-benzimidazole-2-yl)-3-thiophen-2-yl)-propane-1,3-dione **233**. Pyrrolo[1,2-*a*]benzimidazole derivatives **234** and **235** were prepared via cyclocondensation of compound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



Scheme 79

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

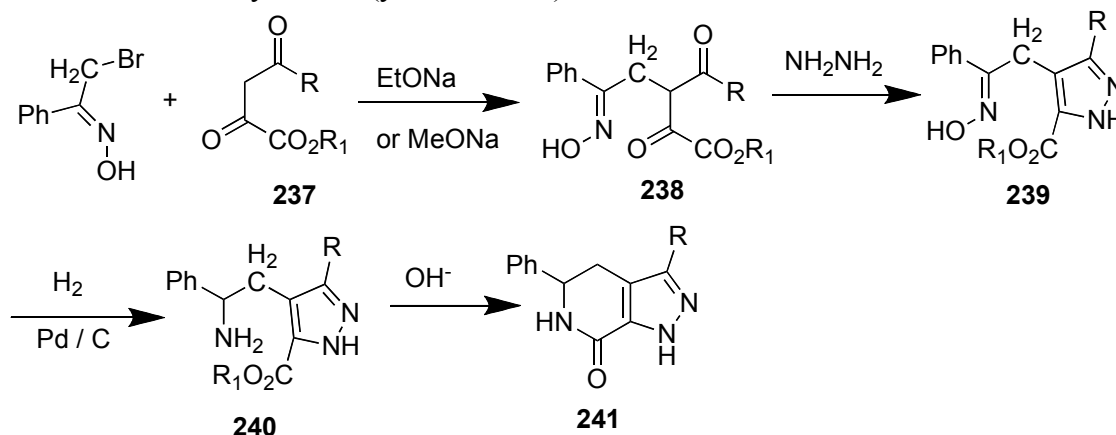
Ethyl 6,7-dihydro-2,6-dimethyl-1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylate **236** was obtained similarly by treatment of ethyl 2,4-dioxopentanoate with 3-ethoxycarbonyl-1-methyl-4-piperidone (Scheme 80).<sup>51</sup>



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%).<sup>126</sup>

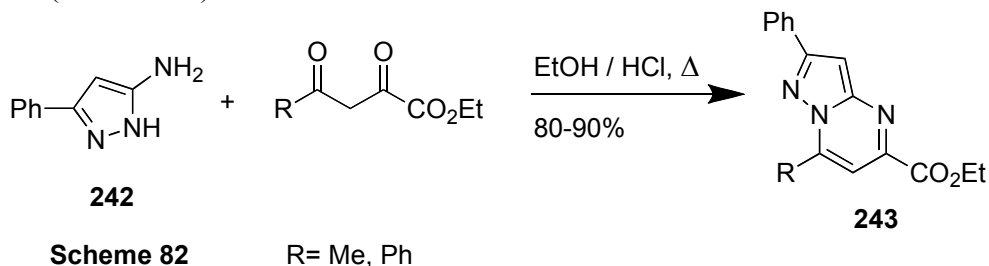


Scheme 81

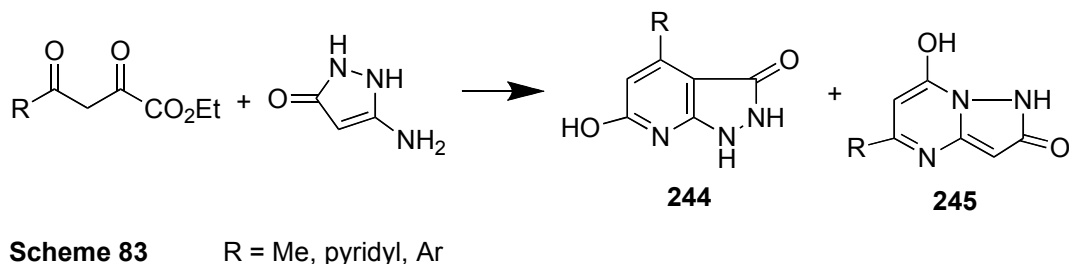
R = Me, Ph; R<sub>1</sub> = Me, Et

### 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).<sup>127,128</sup>

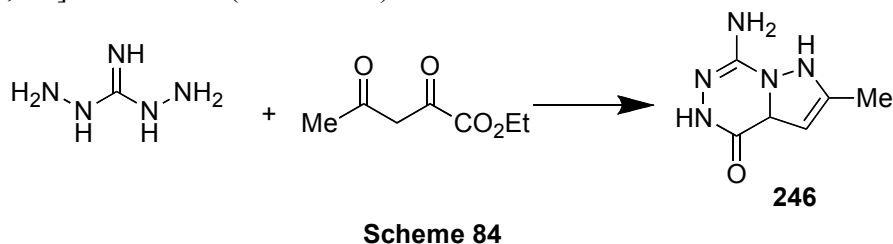


Cyclocondensation of 3-amino-3-pyrazolin-5-one with ethyl acylpyruvate gave chiefly pyrazolo[3,4-*b*]pyridinones **244** (Scheme 83) and smaller amount of pyrazolo[2,3-*a*]pyrimidin-2-(1*H*)-one **245** up to 30%.<sup>129</sup>



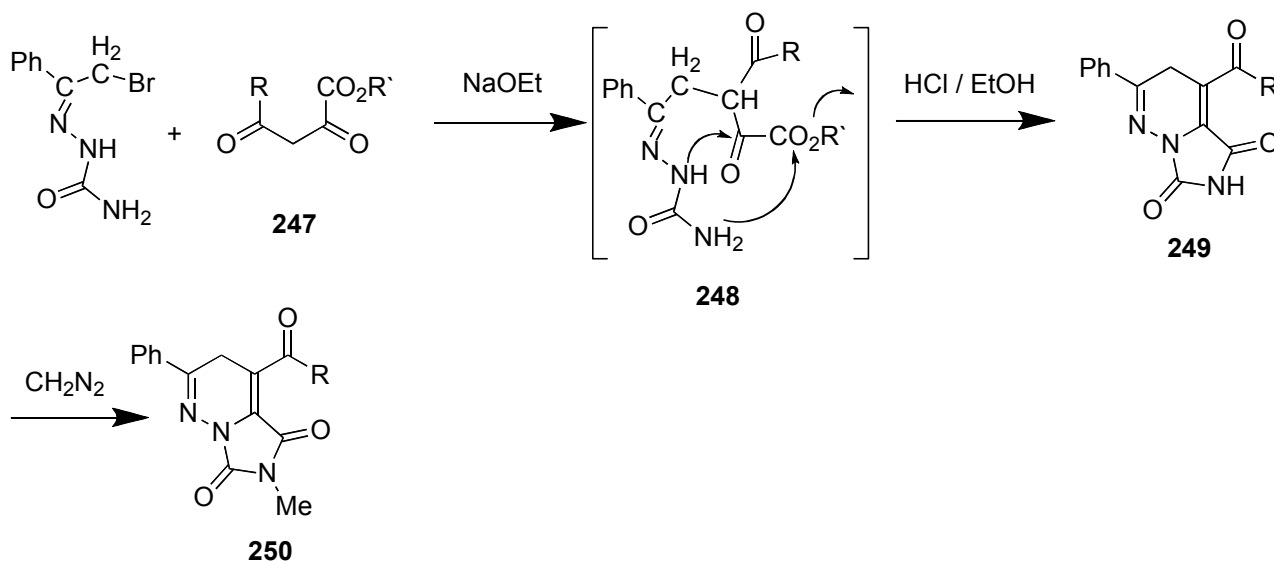
### 2.3.5. PYRAZOLO[1,5-*d*]TRIAZINES

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



### 2.3.6. IMIDAZO[1,5-*b*]PYRIDAZINES

Ethyl or methyl acylpyruvates **247** were condensed with  $\omega$ -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).<sup>130</sup>

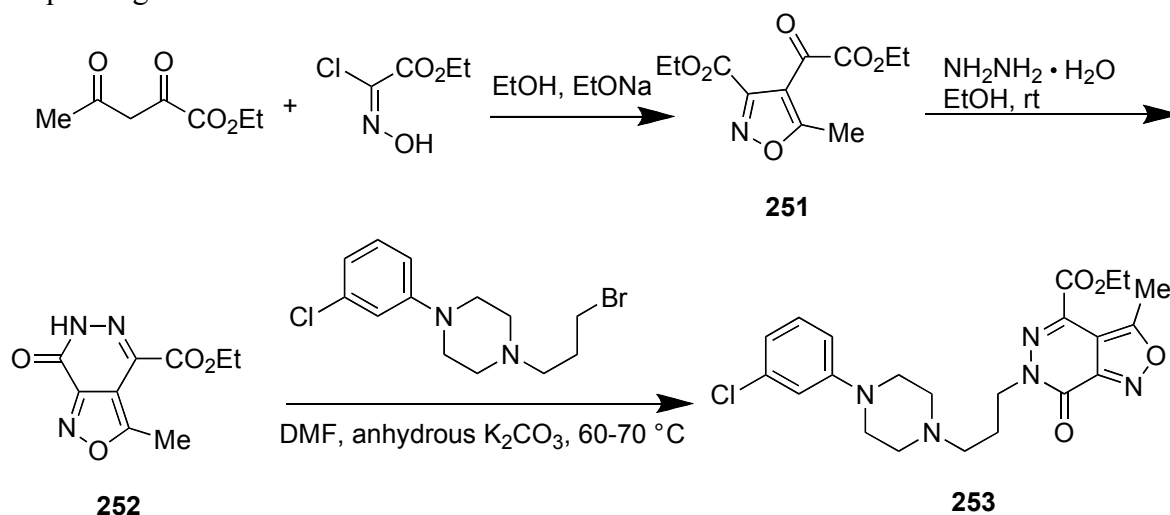


Scheme 85

R= Me, Ph; R'= Me, Et

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

Ethyl 4-ethoxyacetate-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<sub>2</sub>CO<sub>3</sub> 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.<sup>131</sup>

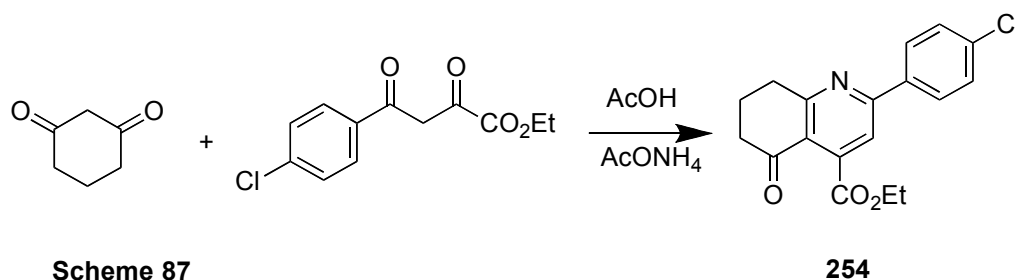


Scheme 86

### 2.3.8. QUINOLINE

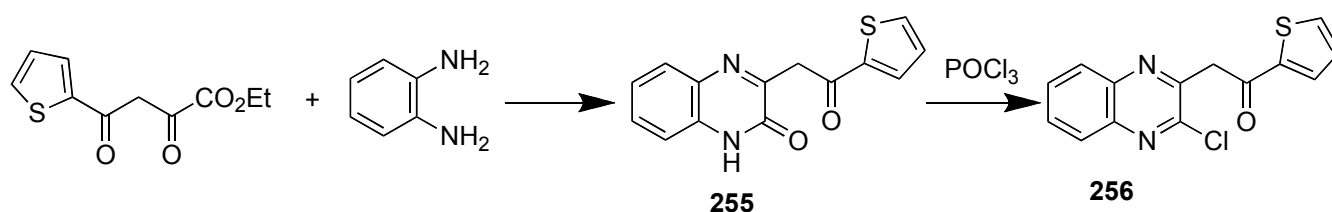
Treatment of cyclohexane-1,3-dione with ethyl 4-(4-chlorophenyl)-2,4-dioxobutanoate led to 5,6,7,8-

tetrahydro-5-oxoquinoline-4-carboxylate derivative **254** (Scheme 87).<sup>132</sup>

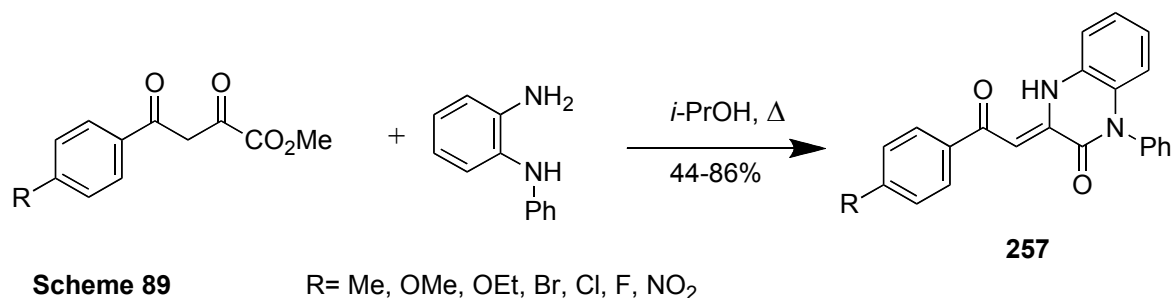


### 2.3.9. QUINOXALINE DERIVATIVES

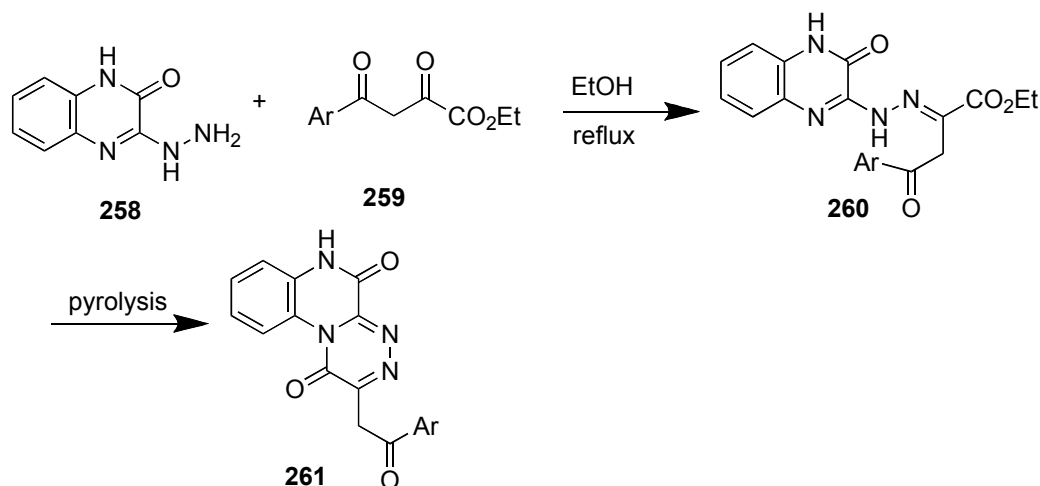
2-Chloro-3-(2'-thenoylmethyl)quinoxaline **256** was prepared by the reaction of 1,2-benzenediamine and 2-thienoyl pyruvate, followed by treatment with phosphorus oxychloride (Scheme 88).<sup>133</sup>



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



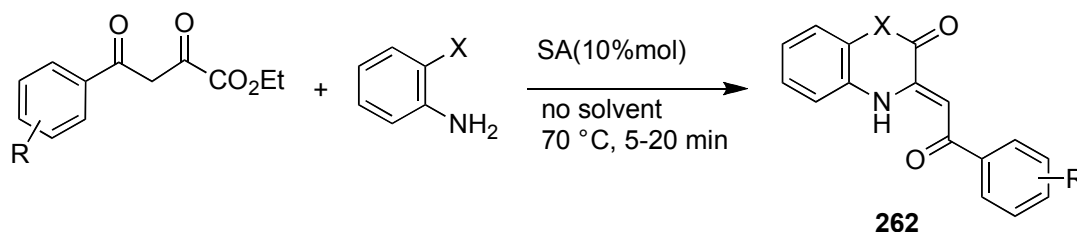
Reaction of 3-hydrazino-2(1*H*)-quinoxalinone **258** with ethyl aroyl pyruvates **259** afforded the corresponding hydrazones **260** which upon thermolysis at 230 °C eliminated a molecule of ethanol to give triazinoquinoxaline **261** (Scheme 90).<sup>138</sup>



Scheme 90

Ar = Ph, 4-MeOC<sub>6</sub>H<sub>4</sub>

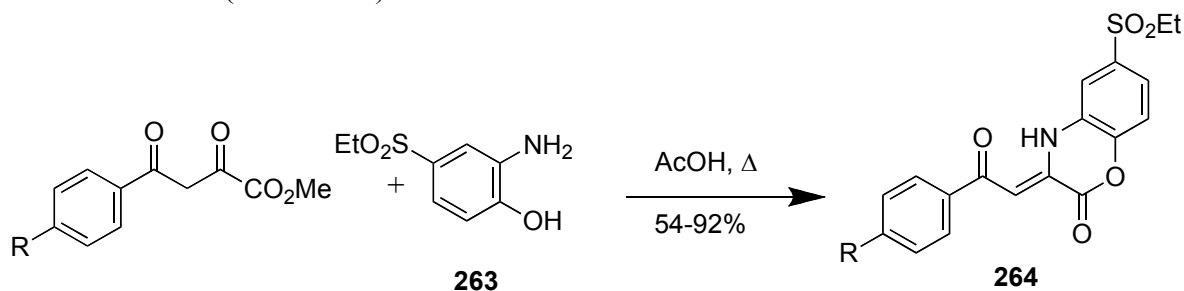
3-(2-Oxo-2-phenylethylidene)-3,4-dihydro-1*H*-quinoxalin-2-one **262** was prepared in 38% yield by solid state synthesis. Thus, when ethyl benzoylpyruvate and *o*-phenylenediamine were mixed and stirred at room temperature gave the title compound **262**. In the case of the condensation of ethyl benzoylpyruvate 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).<sup>139</sup>



Scheme 91

R = H, 4-Cl, 4-OH, 4-OMe, 4-NH<sub>2</sub>, 4-NO<sub>2</sub>; 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).<sup>140-142</sup>

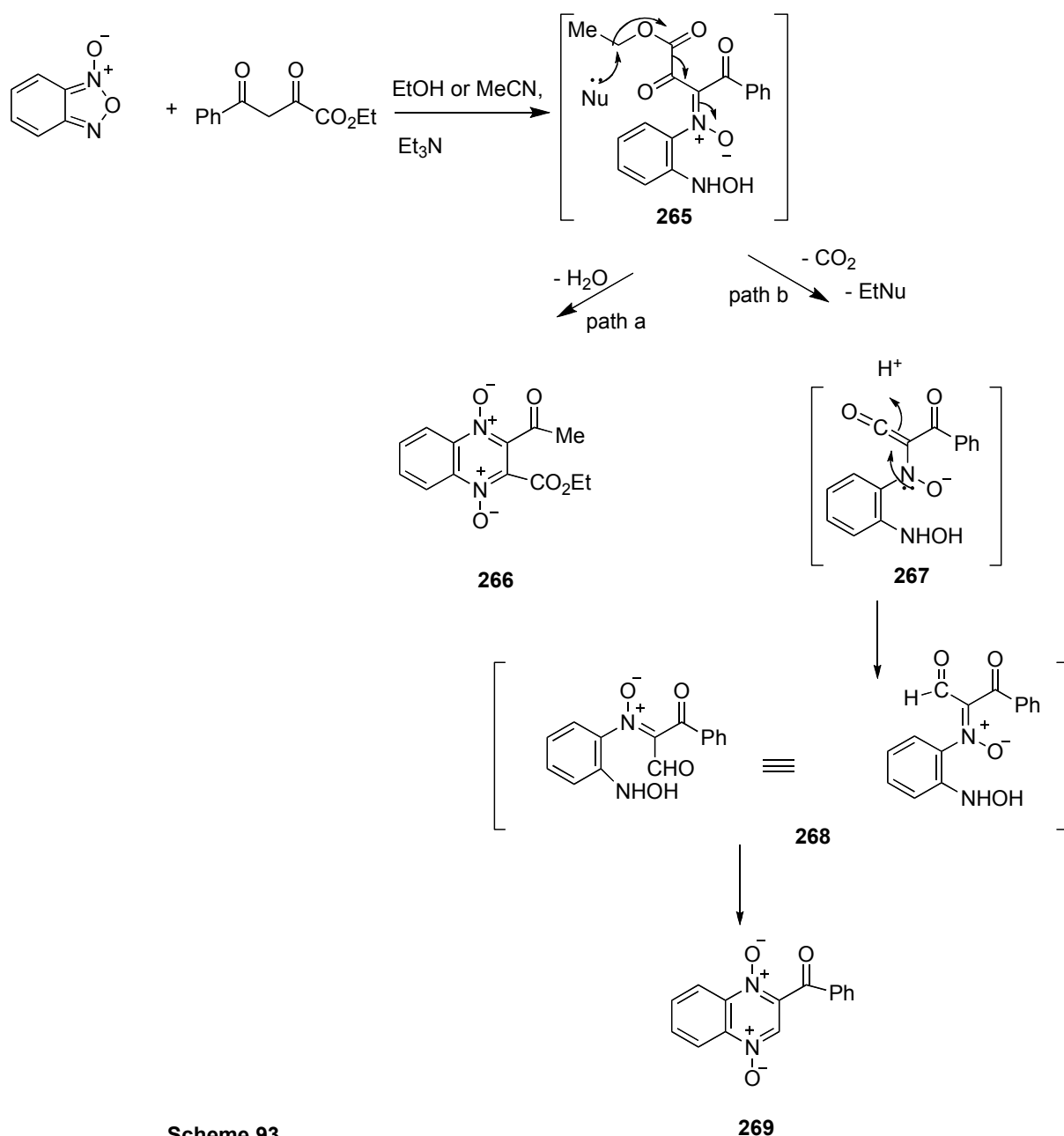


Scheme 92

R = H, Me, vinyl, OMe, OEt, Cl, Br, NO<sub>2</sub>

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**.<sup>143</sup>

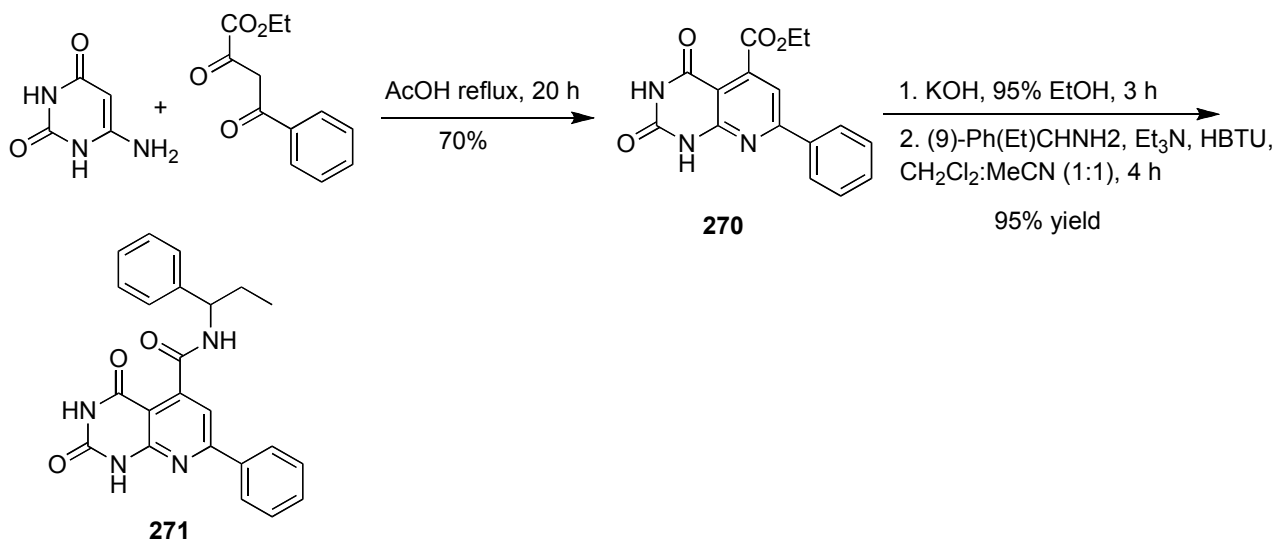
Pathways for the formation of the dioxides **266** and **269** are suggested in Scheme 93. The intermediate **265** is of the type proposed previously for the Beirut reaction of 1,3-benzoxadiazole 1-oxide with carbonyl compound cyclization and dehydration, path a, leads to the ester dioxide **266**. 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**.<sup>143</sup>



Scheme 93

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

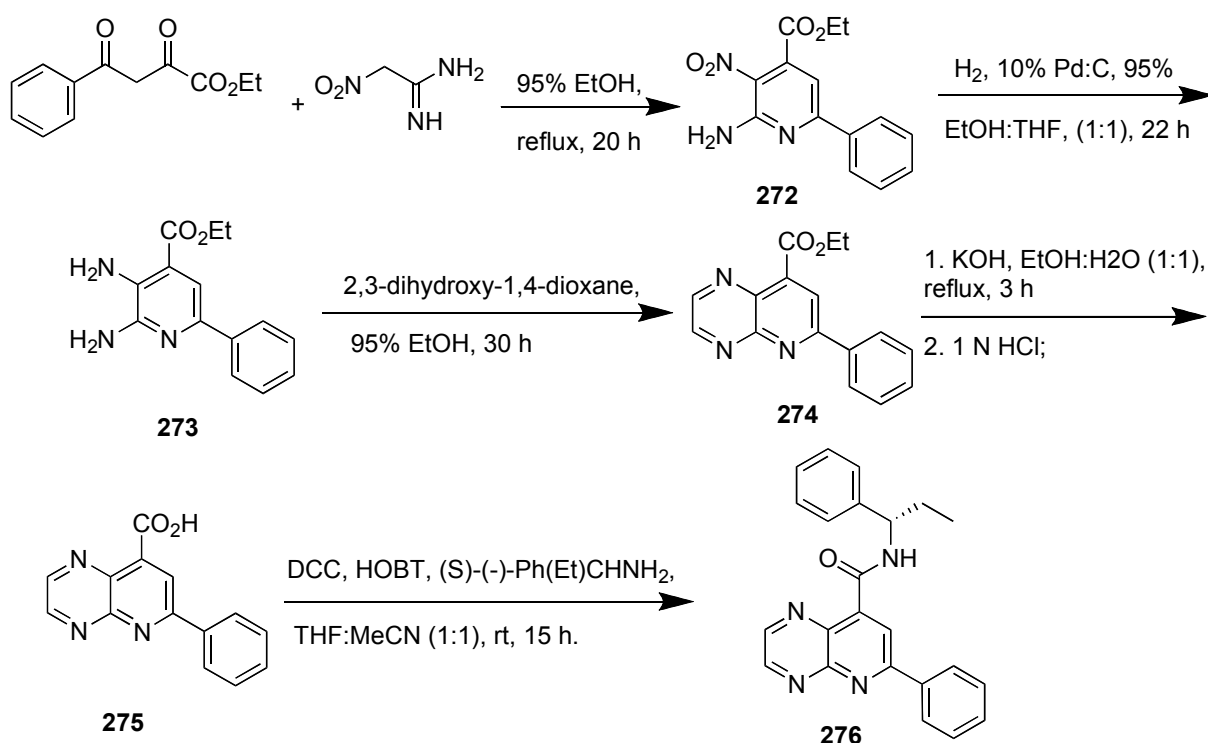
Condensation of ethyl benzoylpyruvate and 4-aminouracil in refluxing acetic acid afforded ethyl 2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylate **270** as shown in Scheme 94. Basic hydrolysis and coupling with (*R,S*)-1-phenylpropylamine provided compound **271**.<sup>144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



Scheme 94

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

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

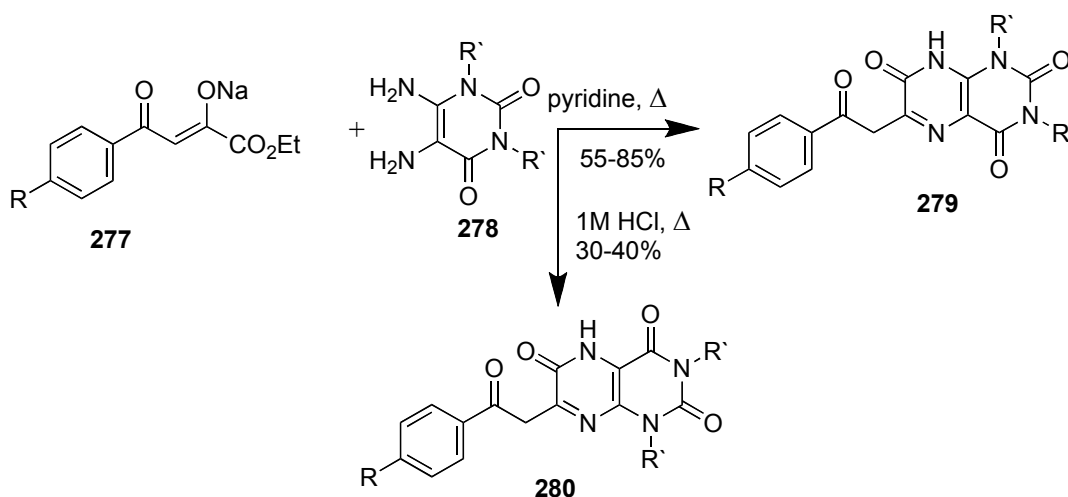


Scheme 95

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**.<sup>145</sup> Subsequent hydrolysis of the ester functions under basic conditions and coupling reaction with (*S*)-(-)-1-phenylpropylamine afforded the desired secondary amide **276**.<sup>144</sup>

### 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).<sup>146</sup> 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.

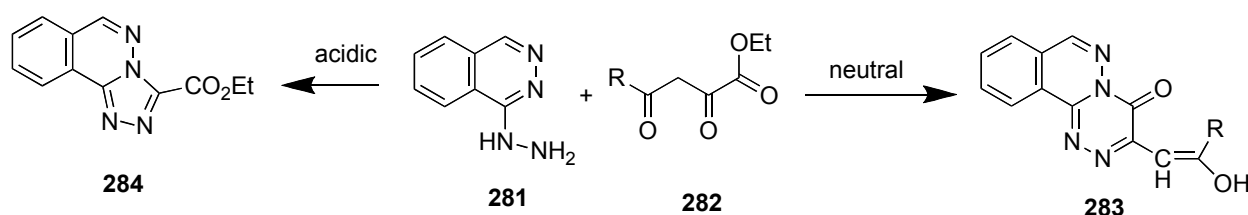


Scheme 96

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**<sup>79</sup> (Scheme 97).

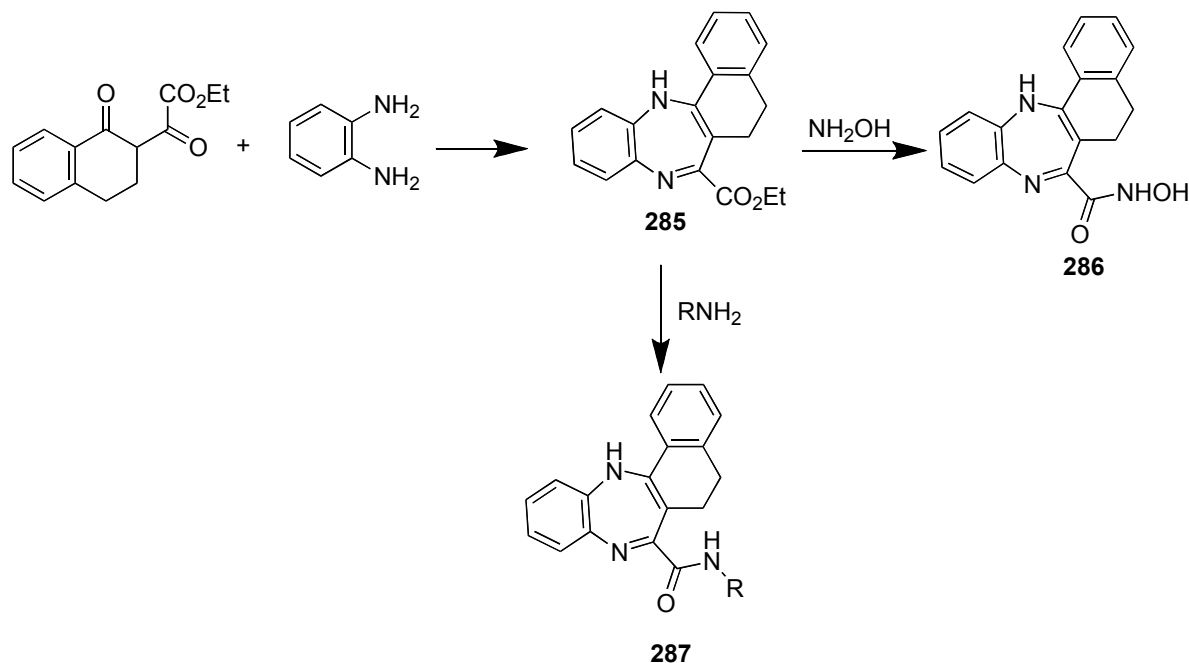


Scheme 97

R = C<sub>6</sub>H<sub>4</sub>R<sub>1</sub>; R<sub>1</sub> = 4-Me, 4-MeO, 3-MeO, 4-Cl

## 2.4. SEVEN MEMBERED RING

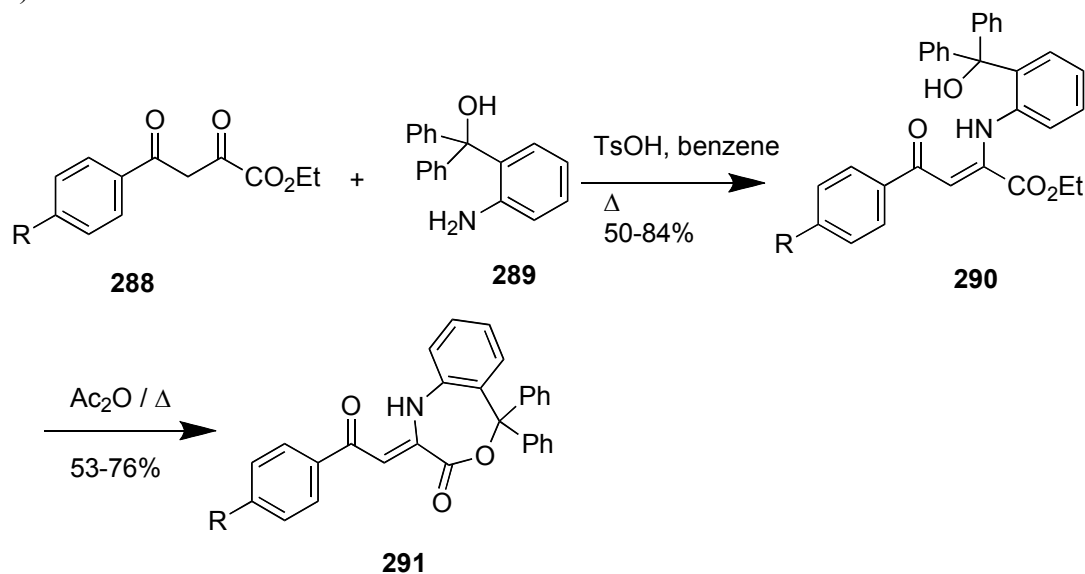
Cyclocondensation of ethyl 1,2,3,4-tetrahydro-1-oxo-2-naphthaleneglyoxylate with *o*-phenylenediamine gave 78% **285** which was treated with hydroxylamine hydrochloride to give 82% **286**. Amination of **285** by various amines and sulfa compounds gave 63-74% benzonaphtho-1,4-diazepines **287** (Scheme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



**Scheme 98**

R = NHCH<sub>2</sub>CH<sub>2</sub>NEt<sub>2</sub>, N(CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>OH)<sub>2</sub>, sulfanilamido-, sulfacetamido, 4-amino-N-2-pyrimidinyl-, 4-amino-N-2-(4,6-dimethyl-2-pyrimidinyl)benzenesulfonamido]-

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

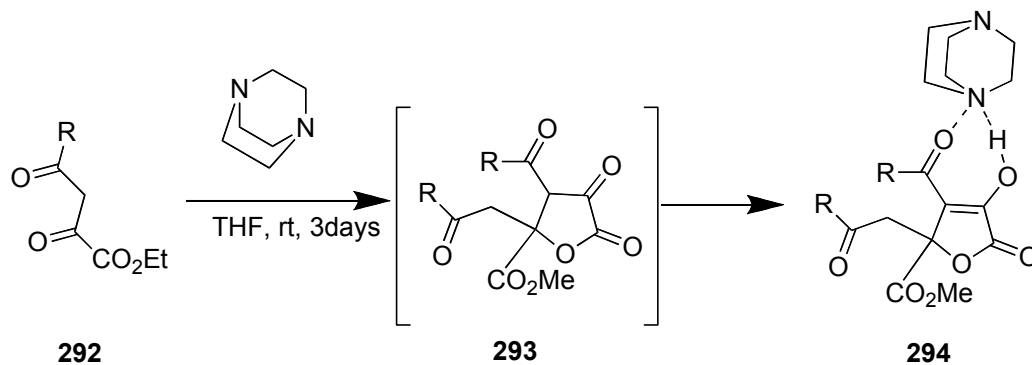


**Scheme 99**

R = H, Me, Cl

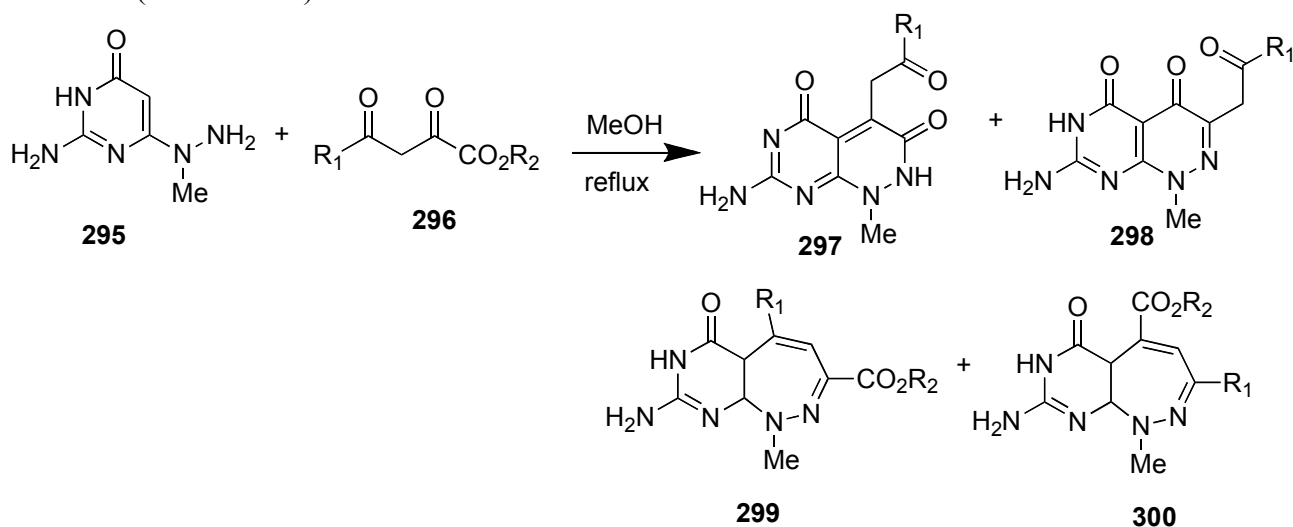
## DIFFERENT REACTIONS

The self-condensation reaction of  $\beta$ -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).<sup>149,150</sup>



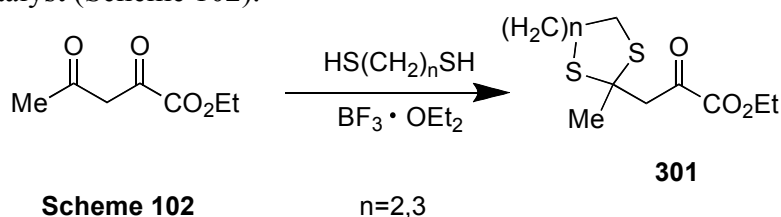
Scheme 100 R = Me, Ph, 4-ClC<sub>6</sub>H<sub>4</sub>

6-(1-Methylhydrazino)isocytosine **295** cyclizes with  $\alpha,\gamma$ -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).<sup>151</sup>



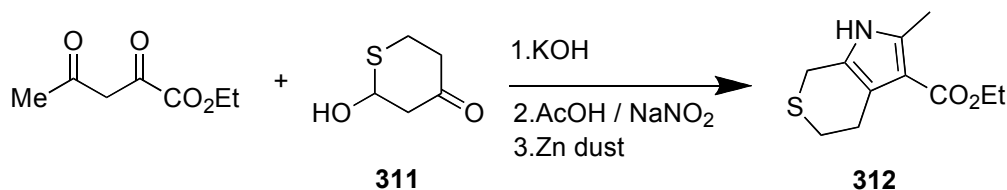
Scheme 101 R<sub>1</sub> = Ph, 3-pyridyl; R<sub>2</sub> = Me, Et

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



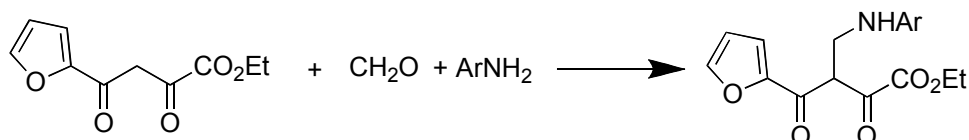
Scheme 102





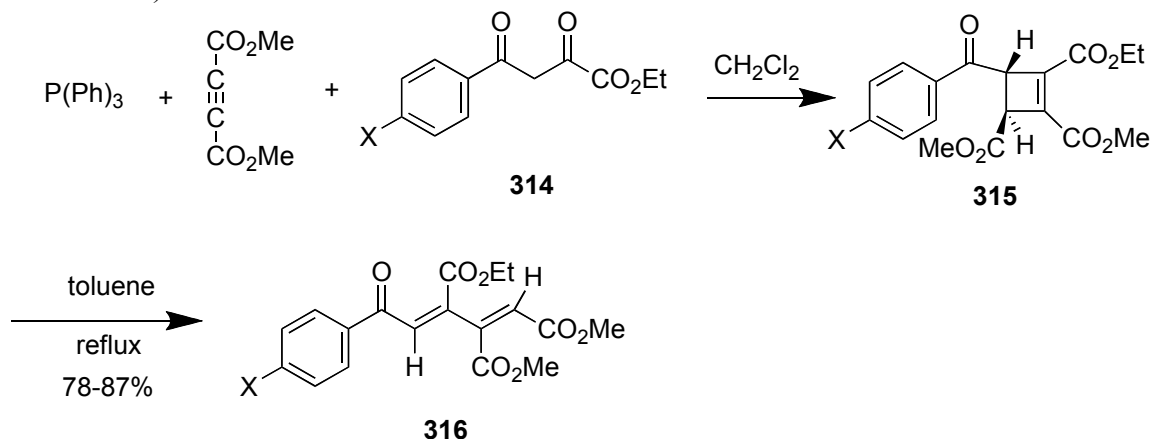
Scheme 106

Ethyl (2-furoyl)pyruvate underwent Mannich alkylation to give the  $\beta$ -furoyl- $\beta$ -(arylmethyl)pyruvate **313** (Scheme 107).<sup>62</sup>



Scheme 107

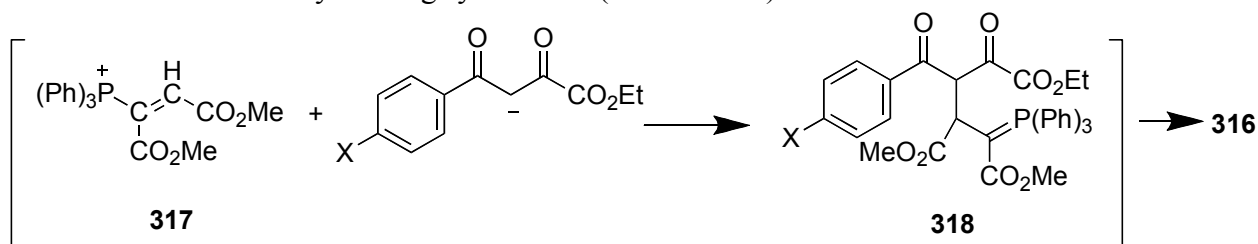
Ethyl 4-aryl-2,4-dioxobutanoates **314** undergo intramolecular Wittig reaction with a vinyltriphenylphosphonium salt to yield cyclobutene derivative **315** which undergo electrocyclic ring-opening reactions in boiling toluene to produced highly electron-deficient 1,3-dienes **316** in quantitative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



Scheme 108

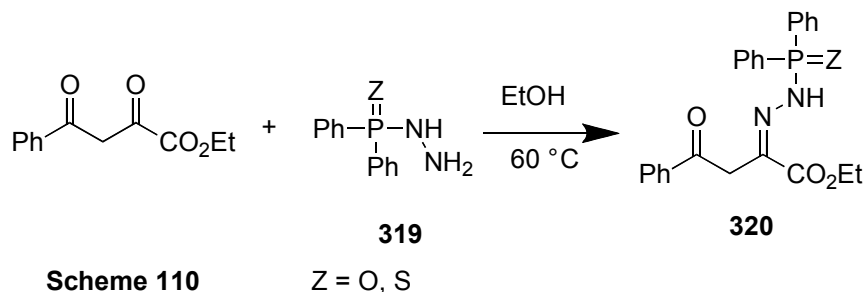
X = H, Br, NO<sub>2</sub>

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).<sup>156</sup>



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).<sup>157</sup>



## ACKNOWLEDGEMENTS

The authors would like to thank Abdelbasset A. Farahat, chemistry department, Georgia State University, Atlanta, Georgia, USA for helping in data collection and refining.

## REFERENCES

- H. Moser, B. Boehner, and W. Foery, EP 268, 554 (*Chem. Abstr.*, 1988, **110**, 23879); T. Ishii, H. Shimortori, Y. Tanaka, and K. Ishikawa, JP 01, 168, 675 (*Chem. Abstr.*, 1989, **112**, 35854); I. Okada, K. Yoshida, and M. Sekine, JP 02, 292, 263 (*Chem. Abstr.*, 1990, **114**, 185497).
- E. Sohn, R. Handle, H. Mildenerger, H. Buerstell, K. Bauer, and H. Bieringer, Ger. Patent 3, 633, 840 (*Chem. Abstr.*, 1988, **110**, 8202).
- P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, G. P. Pollini, and D. Simoni, *Tetrahedron*, 1987, **43**, 235.
- J. M. J. Nolsoe and D. Weigelt, *J. Heterocycl. Chem.*, 2009, **46**, 1.
- A. Cox, In *Comprehensive Organic Chemistry*; ed. by D. H. R. Barton, W. D. Ollis, I. O. Sutherland, Pergamon Press, New York, 1969; Vol. 2, p. 702.
- J. Zhang, S. Didierlaurent, M. Fortin, D. Lefrancois, E. Uridat, and J. P. Vevert, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2575.
- F. Wei, B.-X. Zhao, B. Huang, L. Zhang, C.-H. Sun, W.-L. Dong, D.-S. Shin, and J.-Y. Miao, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6342.
- N. W. Fadnavis and K. R. Radhika, *Tetrahedron: Asymmetry*, 2004, **15**, 3443.
- R. Braga, L. Hecquet, and C. Blonski, *Bioorg. Med. Chem.*, 2004, **12**, 2965.
- Y. Pei and B. O. S. Wickham, *Tetrahedron Lett.*, 1993, **34**, 7509.
- Y. Wakabayashi, A. Miyata, and H. Sato, JP 04149154(1992) (*Chem. Abstr.*, 1992, **117**, 170989).
- S. Imaki, J. Takuma, and K. Endo, *Jpn. Kokai Tokkyo Koho JP04069361* (1992) (*Chem. Abstr.*, 1992, **117**, 7522).

13. S. Matsutani, K. Hirai, M. Tsutsumiuchi, and T. Mizui, JP 61134346 (1986) (*Chem. Abstr.*, 1986, **105**, 225805).
14. C. Musante and S. Fatutta, *Gazz. Chim. Ital.*, 1958, **88**, 879.
15. S. Fatutta, *Gazz. Chim. Ital.*, 1959, **89**, 964.
16. L. M. Oh, H. Wang, S. C. Shilcrat, R. E. Herrmann, D. B. Patience, P. G. Spoons, and J. Sisko, *Org. Proc. Res. Develop.*, 2007, **11**, 1032.
17. K. M. Ghoneim, M. M. Badran, M. A. Shaaban, and S. El-Meligie, *Egypt. J. Pharm. Sci.*, 1988, **29**, 571 (*Chem. Abstr.*, 1989, **111**, 23436).
18. V. P. Gorbunova and N. N. Suvorov, *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, 1977, **14**, 754.
19. S. Ferro, A. Rao, M. Zappala, A. Chimirri, M. L. Barreca, M. Witriam, Z. Debyser, and P. Monforte, *Heterocycles*, 2004, **63**, 2727.
20. Y. A. Ibrahim, B. Al-Saleh, and A.-A. A. Mahmoud, *Tetrahedron*, 2003, **59**, 8489.
21. F. Kipnis, I. Levy, and J. Ornfelt, *J. Am. Chem. Soc.*, 1948, **70**, 4265, Figure 1.
22. R. W. Hamilton, *J. Heterocycl. Chem.*, 1976, **13**, 545.
23. H. M. Faidallah, S. A. Basaif, E. M. Sharshira, and A.A-Ba-Oum, *Egypt. J. Chem.*, 2002, **45**, 905 (*Chem. Abstr.*, 2004, **141**, 410854).
24. G. A. Pinna, M. A. Pirisi, J.-M. Mussinu, G. Murineddu, G. Loriga, A. Pau, and G. E. Grella, *Farmaco*, 2003, **58**, 749.
25. F. Campagna, F. Palluotto, A. Carotti, and E. Maciocco, *Farmaco*, 2004, **59**, 849.
26. J.-M. Mussinu, S. Ruiu, A. C. Mule, A. Pau, M. A. M. Carai, G. Loriga, G. Murineddu, and G. A. Pinna, *Bioorg. Med. Chem.*, 2003, **11**, 251.
27. S. Patil, S. Kamath, T. Sanchez, N. Neamati, R. F. Schinazi, and J. K. Buolamwini, *Bioorg. Med. Chem.*, 2007, **15**, 1212.
28. V. Blandin, J.-F. Carpentier, and A. Mortreux, *Tetrahedron: Asymmetry*, 1998, **9**, 2765.
29. V. Blandin, J.-F. Carpentier, and A. Mortreux, *Eur. J. Org. Chem.*, 1999, **8**, 1787.
30. G. I. Chipens, V. A. Slavinskaya, A. K. Strautinya, D. R. Kreile, D. E. Sile, E. Kh. Korchagova, and O. M. Galkin, Structure and Action of Inhibitors of Zinc-Containing Enzymes – Kinase II and Enkephalinase [in Russian], Zinatne, Riga (1990), p. 238.
31. V. Slavinska, D. Sile, E. Korchagova, and M. Katkevich, *Synth. Commun.*, 1996, **26**, 2229.
32. V. Slavinska, D. Sile, G. Rozenhal, G. Maurops, J. Popelis, M. Katkevich, V. Stonkus, and E. Lukevics, *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, 2006, **42**, 570.
33. N. W. Fadnavis, K. R. Radhika, and D. A. Vedamayee, *Tetrahedron: Asymmetry*, 2006, **17**, 240.
34. P. G. Baraldi, S. Manfredini, G. P. Pollini, R. Romagnoli, and V. Z. Simoni, *Tetrahedron Lett.*, 1992, **33**, 2871.
35. R. Oehrlein and G. Baisch, PCT Int. Appl. WO 2002040438 (2002) (*Chem. Abstr.*, 2002, **136**,

- 385942).
36. S. Manfredini, D. Simoni, V. Zanirato, and A. Casolari, *Tetrahedron Lett.*, 1988, **29**, 3997.
  37. D. W. Emerson, R. L. Titus, and R. M. Gonzaez, *J. Org. Chem.*, 1991, **56**, 5301.
  38. A. Haider and H. Wyler, *Helv. Chim. Acta*, 1983, **66**, 606.
  39. F. Chen and L. Zhao, CN 1995006 (2007) (*Chem. Abstr.*, 2007, **147**, 18943).
  40. T. Lu, T. Markotan, F. Coppo, B. Tomczuk, C. Crysler, S. Eisennagel, J. Spurlino, L. Gremminger, R. M. Soll, E. C. Giardino, and R. Bone, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3727.
  41. E. Matsumura, M. Ariga, and Y. Tohda, *Tetrahedron Lett.*, 1979, **16**, 1393.
  42. A. N. Maslivets, O. P. Krasnykh, and Yu. S. Andreichikov, *Zh. Organ. Kh.*, 1988, **24**, 2233.
  43. M. Dohrn and A. Thiele, *Ber.*, 1931, **64B**, 2863 (*Chem. Abstr.*, 1932, **26**, 1928).
  44. Y. Chigira, M. Masaki, and M. Ohta, *Chem. Pharm. Bull.*, 1969, **42**, 228.
  45. E. M. Afsah, H. A. Etman, W. S. Hamama, and A. F. Sayed, *Boll. Chim. Farmaceutico*, 1995, **134**, 547 (*Chem. Abstr.*, 1996, **124**, 260756).
  46. Yu. S. Andreichikov, V. L. Gein, and I. N. Anikina, *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, 1985, **21**, 1178 (*Chem. Abstr.*, 1987, **107**, 39766).
  47. N. M. S. Hasanien, Studies on Claisen condensation and its products. *M. Sc. Thesis*, Faculty of Science, Mansoura University, 1996.
  48. A. G. Schering, M. Dohrn, and H. Nahme, *Ger.* 678, 152, 1939 (*Chem. Abstr.*, 1939, **33**, 7963).
  49. D. W. Emerson, R. L. Titus, and M. D. Jones, *J. Heterocycl. Chem.*, 1998, **35**, 611.
  50. M. K. A. Khan, K. J. Morgan, and D. P. Morrey, *Tetrahedron*, 1966, **22**, 2095.
  51. G. H. Cookson, *J. Chem. Soc.*, 1953, 2789.
  52. H. Takaya, S. Kojima, and S.-I. Murahashi, *Org. Lett.*, 2001, **3**, 421.
  53. J. Vorkapic-Furac and M. Suprina, *Z. Chemie*, 1989, **29**, 176 (*Chem. Abstr.*, 1990, **112**, 76847).
  54. J. Büchi, H. R. Meyer, R. Hirt, F. Hunziker, E. Eichenberger, and R. Lieberherr, *Helv. Chim. Acta*, 1955, **79**, 670.
  55. L. M. Subramanian and G. S. Misra, *Synthesis*, 1984, 1063.
  56. F. Arano, D. Catarzi, V. Colotta, G. Filacchioni, A. Galli, C. Costagli, and V. Carlá, *J. Med. Chem.*, 2002, **45**, 1035.
  57. T. Herk, J. Brussee, A. M. C. H. Nieuwendijk, P. A. M. Klein, A. P. Ijzerman, C. Stannek, A. Burmeister, and A. Lorenzen, *J. Med. Chem.*, 2003, **46**, 3945.
  58. T. Majid, C. R. Hopkins, B. Pedgrift, and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 2137.
  59. G. Szabo, J. Fischer, and A. Kis-Varga, *Pharmazie*, 2006, **61**, 522.
  60. H. Yoshida, K. Oomori, M. Yokoi, and K. Fuse, *Jpn. Kokai Tokkyo Koho JP 07118238* (1995) (*Chem. Abstr.*, 1995, **123**, 169615).
  61. K. Harada, S. Nishino, and T. Harada, *Jpn. Kokai Tokkyo Koho JP 2001335564* (2001) (*Chem.*

- Abstr.*, 2001, **136**, 5989).
62. R. M. Saleh and I. M. El-Deen, *Rev. Roumain. de Chim.*, 1993, **38**, 1333 (*Chem. Abstr.*, 1994, **121**, 108560).
63. G. J. Reddy, D. Latha, and K. S. Rao, *Org. Prep. Proc. Int.*, 2004, **36**, 494.
64. E. Sohn, H. Mildenerger, K. Bauer, and H. Bieringer, EP 333131 (1989) (*Chem. Abstr.*, 1990, **112**, 153721).
65. J. M. Smallheer, R. S. Alexander, J. Wang, S. Wang, S. Nakajima, K. A. Rossi, A. Smallwood, F. Barbera, D. Burdick, J. M. Luetzgen, R. M. Knabb, R. R. Wexler, and P. K. Jadhav, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5263.
66. C. Tan, D. Shen, J. Weng, and D. Fan, *Zhejiang Daxue Xuebao, Lixueban*, 2005, **32**, 204 (*Chem. Abstr.*, 2005, **144**, 369957).
67. J. Yang and Y. Tian, *Xiandai Nongyao*, 2002, **1**, 11 (*Chem. Abstr.*, 2002, **138**, 221511).
68. J. Yang and Y. Tian, CN 1305996 (2001) (*Chem. Abstr.*, 2002, **137**, 140519).
69. M. J. S. Dewar and F. E. King, *J. Chem. Soc.*, 1945, 114.
70. C. Tan, D. Shen, J. Weng, and N. Sun, *Zhejiang Gongye Daxue Xuebao*, 2005, **33**, 331 (*Chem. Abstr.*, 2005, **144**, 294684).
71. B. Gu, W. Zhu, and W. Fan, *Xiandai Nongyao*, 2002, **1**, 9 (*Chem. Abstr.*, 2003, **139**, 52927).
72. M. Nakagawa, S. Hara, and M. Sogawa, JP 04224565 (1992) (*Chem. Abstr.*, 1992, **117**, 251349).
73. F. Lepage and B. Hublot, EP 459887 (1991) (*Chem. Abstr.*, 1992, **116**, 128914).
74. J. L. Huppertz, *Aust. J. Chem.*, 1983, **36**, 135 (*Chem. Abstr.*, 1983, **98**, 160637).
75. S. C. McKeown, A. Hall, G. M. P. Giblin, O. Lorthioir, R. Blunt, X. Q. Lewell, R. J. Wilson, S. H. Brown, A. Chowdhury, T. Coleman, S. P. Watson, I. P. Chessell, A. Pipe, N. Claytonb, and P. Goldsmith, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4767.
76. N. Pommery, T. Taverne, A. Telliez, L. Goossens, C. Charlier, J. Pommery, J.-F. Goossens, R. Houssin, F. Durant, and J.-P. Henichart, *J. Med. Chem.*, 2004, **47**, 6195.
77. S. Barbey, L. Goossens, T. Taverne, J. Cornet, V. Choessel, C. Rouaud, G. Gimeno, S. Yannic-Arnoult, C. Michaux, C. Charlier, R. Houssin, and J.-P. Henichart, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 779.
78. A. C. Donohue, S. Pallich, and T. D. McCarthy, *J. Chem. Soc., Perkin Trans. 1*, 2001, **21**, 2817.
79. A. Amer, K. Weisz, and H. Zimmer, *Heterocycles*, 1987, **26**, 1853.
80. R. M. Saleh and I. M. El-Deen, *J. Serbian Chem. Soc.*, 1991, **56**, 595 (*Chem. Abstr.*, 1992, **116**, 106163).
81. B. F. Abdel-Wahab and A.-A. S. El-Ahl, *Phosphorus, Sulfur Silicon Relat. Elem.*, (2009), in press.
82. B. F. Abdel-Wahab, H. A. Abdel-Aziz, and E. M. Ahmed, *Arch. Pharm. (Weinheim, Ger)*, 2008, **341**, 734.

83. B. F. Abdel-Wahab, H. A. Abdel-Aziz, and E. M. Ahmed, *Monatsh. Chem.*, 2009, **140**, 601.
84. A. Fruchier, B. Lupo, and G. Tarrago, *Can. J. Chem.*, 1985, **63**, 375.
85. J. Yuan, M. Gulianello, S. De Lombaert, R. Brodbeck, A. Kieltyka, and K. J. Hodgetts, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2133.
86. D. J. P. Pinto, M. J. Orwat, S. Wang, J. M. Fevig, M. L. Quan, E. Amparo, J. Cacciola, K. A. Rossi, R. S. Alexander, A. M. Smallwood, J. M. Luetngen, L. Liang, B. J. Aungst, M. R. Wright, R. M. Knabb, P. C. Wong, R. R. Wexler, and P. Y. S. Lam, *J. Med. Chem.*, 2001, **44**, 566.
87. W. T. Ashton and G. A. A. Doss, *J. Heterocycl. Chem.*, 1993, **30**, 307.
88. J. R. Pruitt, D. J. P. Pinto, R. A. Galemno, R. S. Alexander, K. A. Rossi, B. L. Wells, S. Drummond, L. L. Bostrom, D. Burdick, R. Bruckner, H. Chen, A. Smallwood, P. C. Wong, M. R. Wright, S. Bai, J. M. Luetngen, R. M. Knabb, P. Y. S. Lam, and R. R. Wexler, *J. Med. Chem.*, 2003, **46**, 5298.
89. Z. J. Jia, Y. Wu, W. Huang, E. Goldman, P. Zhang, J. Woolfrey, P. Wong, B. Huang, U. Sinha, G. Park, A. Reed, R. M. Scarborough, and B.-Y. Zhu, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1651.
90. D. Berta, M. Villa, A. Vulpeti, and E. Felder, *Tetrahedron*, 2005, **61**, 10801.
91. P. Herold, A. F. Indolese, M. Studer, H. P. Jalett, U. Siegrist, and H. U. Blaser, *Tetrahedron*, 2000, **56**, 6497.
92. A. Schmidt, T. Habeck, M. K. Kindermann, and M. Nieger, *J. Org. Chem.*, 2003, **68**, 5977.
93. S. Fustero, R. Roman, J. F. Sanz-Cervera, A. Simon-Fuentes, J. Bueno, and S. Villanova, *J. Org. Chem.*, 2008, **73**, 8545.
94. S. Fustero, R. Román, J. F. Sanz-Cervera, A. Simon-Fuentes, A. C. Cunat, S. Villanova, and M. Murgui, *J. Org. Chem.*, 2008, **73**, 3523.
95. Z.-X. Wang and H.-L. Qin, *Green Chem.*, 2004, **6**, 90.
96. A. Attayibat, S. Radi, A. Ramdani, Y. Lekchiri, B. Hacht, M. Bacquet, S. Willai, and M. Morcellet, *Bull. Korean Chem. Soc.*, 2006, **27**, 1648.
97. G. Menozzi, L. Mosti, P. Schenone, D. Donnoli, F. Schiariti, and E. Marmo, *Farmaco*, 1990, **45**, 167.
98. C. B. Barrett, R. J. S. Beer, G. M. Dodd, and A. Robertson, *J. Chem. Soc.*, 1957, 4810.
99. V. P. Gorbunova and N. N. Suvorov, *Chem. Heterocycl. Compd. (N. Y., NY, U. S.)*, 1972, **9**, 1374.
100. J. M. Fevig, J. Cacciola, J. Buriak, K. A. Rossi, R. M. Knabb, J. M. Luetngen, P. C. Wong, S. A. Bai, R. R. Wexler, and P. Y. S. Lam, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3755.
101. D. Bierowska-Charytonowicz and M. Konieczny, *Arch. Immun. Therap. Exp.*, 1976, **24**, 871 (*Chem. Abstr.*, 1977, **87**, 53221).
102. A. Amer, N. Rashed, M. M. Abdel Rahman, and H. Zimmer, *Heterocycles*, 1987, **26**, 1277.
103. A. K. Roy and S. Batra, *Synthesis*, 2003, 2325.

104. G. Biagi, I. Giorgi, O. Livi, V. Scartoni, L. Betti, G. Giannaccini, and M. L. Trincavelli, *Eur. J. Med. Chem.*, 2002, **37**, 565.
105. P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, G. P. Pollini, and D. Simoni *Tetrahedron Lett.*, 1984, **25**, 4313.
106. N. K. Kochetkov and S. D. Sokolov, "Advances in Heterocyclic Chemistry", ed. by A. R. Katritzky, Academic Press, New York, 1963.
107. P. A. Pieper, D. Yang, H. Zhou, and H. Liu, *J. Am. Chem. Soc.*, 1997, **119**, 1809.
108. H. Henecka, *Chem. Ber.*, 1949, **82**, 36.
109. Y. Oka, K. Omura, A. Miyake, K. Itoh, M. Tomimoto, N. Tada, and S. Yuruga, *Chem. Pharm. Bull.*, 1975, **23**, 2239.
110. J. Suh and Y. Hong, *Arch. Pharm. Res.*, 1990, **13**, 257.
111. A. Palani, S. Shapiro, J. W. Clader, W. J. Greenlee, S. Vice, S. McCombie, K. Cox, J. Strizki, and B. M. Baroudy, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 709.
112. L. Valgimigli, G. Brigati, G. F. Pedulli, G. A. DiLabio, M. Mastragostino, C. Arbizzani, and D. A. Pratt, *Chem. Eur. J.*, 2003, **9**, 4997.
113. D. V. Sevenard, O. G. Khomutov, O. V. Koryakova, V. V. Sattarova, M. I. Kodess J. Stelten, I. Loop, E. Lork, K. I. Pashkevich, and G.-V. Roschenthaler, *Synthesis*, 2000, 1738.
114. C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, 1953, **18**, 588.
115. A. H. Abd-El-Rahman, F. A. Amer, E. M. Kandeel, and S. I. El-Desoky, *Egypt. J. Chem.*, 1990, **31**, 59.
116. J. Lee, H. J. Kim, S. Choi, H. G. Choi, S. Yoon, J.-H. Kim, K. Jo, S. Kim, S.-Y. Koo, M.-H. Kim, J. I. Kim, S.-Y. Hong, M. S. Kim, S. Ahn, H.-S. Yoon, and H.-S. Cho, PCT Int Appl WO 2004/080979 (2004) (*Chem. Abstr.*, 2004, **141**, 277637).
117. M. M. Eid, M. A. Badawy, M. A. H. Ghazala, and Y. A. Ibrahim, *J. Heterocycl. Chem.*, 1983, **20**, 1709.
118. V. L. Gein, N. N. Kasimova, M. A. Panina, and E. V. Voronina, *Pharm. Chem. J.*, 2006, **40**, 410.
119. V. L. Gein, L. F. Gein, and I. A. Shevchenko, *Russ. J. Gen. Chem.*, 2003, **73**, 661.
120. S. A. Abdel-Hady, M. A. Badawy, A. M. Kadry, and Y. A. Ibrahim, *Sulfur Lett.*, 1988, **8**, 153.
121. Y. A. Ibrahim, S. A. L. Abdel-Hady, M. A. Badawy, and M. A. H. Ghazala, *J. Heterocycl. Chem.*, 1982, **19**, 913.
122. Y. S. Andreichikov, S. V. Kol'tsova, I. A. Zhikina, and D. D. Nekrasov, *Russ. J. Org. Chem.*, 1999, **35**, 1538.
123. H. Sheibani, M. R. Islami, H. Khabazzadeh, and K. Saidi, *Tetrahedron*, 2004, **60**, 5931.
124. C. Cano, P. Goya, J. A. Paez, R. Giron, and E. Sanchez, *Bioorg. Med. Chem.*, 2007, **15**, 7480.
125. H. K. Ibrahim, S. H. El-Tamany, R. F. El-Shaarawy, and I. M. El-Deen, *Macedonian J. Chem. Eng.*, 2008, **27**, 65.

126. O. Migliara, S. Petruso, and V. Sprio, *J. Heterocycl. Chem.*, 1979, **16**, 577.
127. G. Auzzi, L. Cecchi, A. Costanzo, and L. Pecori Vettori, *Farmaco*, 1979, **34**, 898.
128. G. Auzzi, L. Cecchi, A. Costanzo, L. Pecori Vettori, F. Bruni, R. Pirisino, and G. B. Ciottoli, *Farmaco*, 1979, **34**, 478.
129. R. Balicki, *Polish J. Chem.*, 1983, **57**, 1251 (*Chem. Abstr.*, 1985, **103**, 87802).
130. O. Migliara, S. Petruso, and V. Sprio, *J. Heterocycl. Chem.*, 1979, **16**, 1105.
131. M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini, and V. Dal Piaz, *J. Med. Chem.*, 2003, **46**, 1055.
132. T. Mulamba, R. El Boukili-Garre, D. Seraphin, E. Noe, C. Charlet-Fagnere, J. Henin, J. Laronze, J. Sapi, and R. Barret, *Heterocycles*, 1995, **41**, 29.
133. I. M. El-Deen and F. F. Mahmoud, *Phosphorus, Sulfur and Silicon Relat. Elem.*, 2000, **165**, 205.
134. D. G. Markees, *J. Heterocycl. Chem.*, 1989, **26**, 29.
135. R. B. Palkar and H. E. Master, *Indian J. Heterocycl. Chem.*, 2000, **10**, 37.
136. I. V. Mashevskaya, R. R. Makhmudov, G. A. Aleksandrova, O. V. Golovkina, A. V. Duvalov, and A. N. Maslivets, *Pharm. Chem. J.*, 2001, **35**, 196.
137. K. S. Bozdyreva, I. V. Smirnova, and A. N. Maslivets, *Russ. J. Org. Chem.*, 2005, **41**, 1081.
138. N. Rashed, A. M. El-Massry, E. H. El-Ashry, and A. Amer, *J. Heterocycl. Chem.*, 1990, **27**, 691.
139. M. Xia, B. Wu, and G.-F. Xiang, *Synth. Commun.*, 2008, **38**, 1268.
140. D. G. Orphanos and A. Taurins, *Can. J. Chem.*, 1966, **44**, 1795.
141. Z. G. Aliev, O. P. Krasnykh, A. N. Maslivets, and L. O. Atovmyan, *Russ. Chem. Bull.*, 2000, **49**, 2045.
142. V. L. Gein, N. A. Rassudikhina, and E. V. Voronina, *Pharm. Chem. J.*, 2006, **40**, 554.
143. A. Atfah and J. Hill, *J. Chem. Soc., Perkin Trans. 1*, 1989, 221.
144. G. A. M. Giardina, M. Artico, S. Cavagnera, A. Cerri, E. Consolandi, S. Gagliardi, D. Graziani, M. Grugni, D. W. P. Hay, M. A. Luttmann, R. Mena, L. F. Raveglia, R. Rigolio, H. M. Sarau, D. B. Schmidt, G. Zanoni, and C. Farina, *Farmaco*, 1999, **54**, 364.
145. M. C. Venuti, *Synthesis*, 1982, 61.
146. S. A. L. Abdel-Hady, M. A. Badawy, M. A. N. Mosselhi, and Y. A. Ibrahim, *J. Heterocycl. Chem.*, 1985, **22**, 801.
147. A. Zayed and J. Metri, *Egypt. J. Chem.*, 1981, **24**, 481 (*Chem. Abstr.*, 1983, **99**, 70679).
148. N. V. Kolotova, V. O. Kozminykh, E. V. Dolbilkina, and E. N. Kozminykh, *Russ. Chem. Bull.*, 1998, **47**, 2246.
149. H. J. Lee, T. Y. Kim, and J. N. Kim, *Synth. Commun.*, 1999, **29**, 4375.
150. J. N. Kim, H. J. Lee, K. Y. Lee, H. R. Kim, and E. K. Ryu, *Bull. Korean Chem. Soc.*, 1999, **20**, 1375 (*Chem. Abstr.*, 2000, **133**, 73900).

151. W. R. Mallory, R. W. Morrison, and V. L. Styles, *J. Org. Chem.*, 1982, **47**, 667.
  152. M. T. Barros, C. F. G. C. Geraldés, C. D. Maycock, and M. I. Silva, *Tetrahedron*, 1988, **44**, 2283.
  153. H. Meyer and J. Kurz, *Liebigs Ann. Chem.*, 1978, 1491.
  154. V. A. Chuiguk, G. N. Poshtaruk, and V. A. Goroshko, *Ukrainskii Khim. Zh. (Russ. Ed.)*, 1981, **47**, 76 (*Chem. Abstr.*, 1981, **94**, 175002).
  155. G. B. Barlin and W. Pfeleiderer, *Chem. Ber.*, 1969, **102**, 4032 (*Chem. Abstr.*, 1970, **72**, 43613).
  156. I. Yavary and A. R. Samzadeh-Kermani, *Tetrahedron Lett.*, 1998, **39**, 6343.
  157. F. V. Bagrov, T. V. Vasil'eva, and D. F. Bagrov, *Zh. Obshh. Khim.*, 1994, **64**, 1475 (*Chem. Abstr.*, 1995, **123**, 9523).
- 



**Kamal M. Dawood** was born in 1965 in Kafr-Elsheikh, Egypt. He graduated from Cairo University, Egypt in 1987 then he carried out his MSc and PhD studies under the supervision of Professor Ahmad Farag, Cairo University. He received his PhD in 1995 in the applications of hydrazonoyl halides in heterocyclic chemistry. In 1997 he was awarded the UNESCO Fellowship for one year at Tokyo Institute of Technology (TIT) and collaborated with Prof. T. Fuchigami in the field of 'Electrochemical Partial Fluorination of Heterocyclic Compounds'. In 1999, he was awarded the JSPS (Japan Society for Promotion of Science) Fellowship for two years and worked again with Professor Fuchigami at TIT in the same field.. He was awarded the Alexander von Humboldt Fellowship at Hanover University in 2004-2005 with Prof. A. Kirschning in the field of polymer supported palladium catalysed cross coupling reactions and in 2007 and 2008 with Prof. Peter Metz at TU-Dresden, Germany, and in the field of total synthesis of natural products. In 2002 he promoted to Associate Professor and in May 2007 he was appointed as Professor of Organic chemistry, Faculty of Science, Cairo University. In 2002 he received the Cairo University Award in Chemistry and in 2007 he received the State-Award in Chemistry.



**Hassan Abdel-Gawad** is an associate professor of organic chemistry at National Research Centre. He was born in 1968 in Giza, Egypt and received B.S. degree (1990) M.S. degree (1996) and Ph.D. degree (2001) from Cairo University under the supervision of Professors Issa M. I. Fakhr and N. A. Kassab. His current research interests covers the synthesis of the insecticides either radiolabelled or nonlabelled, extraction, isolation, and identification of their metabolites. In addition to, the synthesis of heterocycles.



**Hanan A. Mohamed** is a 2<sup>nd</sup> year Ph.D. candidate and a research associate of organic chemistry at National Research Centre. She obtained both B.S. degree (2001) and M.S (2006) from Cairo University under the direction of Prof. Kamal M. Dawood. Her current research interests lie in the area of the synthesis of biologically active new heterocycles.



**Bakr F. Abdel-Wahab** is a researcher of organic chemistry at National Research Centre. He was born in 1978 in Mansoura, Egypt and received both B.S. degree (1999) and M.S. degree (2003) from Mansoura University (Professor Fathy A. Amer), and his Ph.D. degree (2007) from Ain-Shams University under the direction of Professor Mahr A. El-Hashash (D.Sc), his current research interests covers the development and mechanistic understanding of organic reactions and their applications in medicinal chemistry. He is the author of over 17 international scientific papers and 6 reviews in heterocyclic chemistry.