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Utilities of Pyrazolone and Its Derivative in Heterocyclic Synthesis and Their Biological Applications

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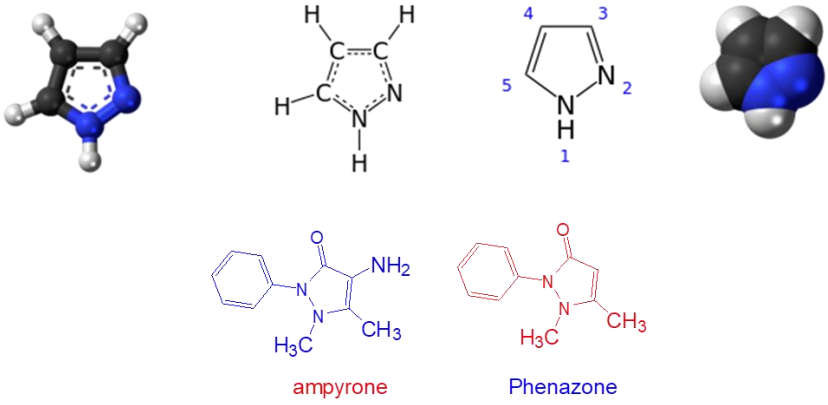
Abstract

Several pyrazoles with various substitutions at various positions were prepared starting from pyrazole and its derivatives. The biological activities of newly synthesized compounds were tested and evaluated in vivo and vitro for different types of diseases and showed good results, in addition to some examples of some pyrazoles containing heterocycles were established as drugs such as Celecoxib Lesopitron Sulfaphenazole Rimonabant Tebufenpyrad Betazole Tepoxalin Pyriprole Deracoxib Mavacoxib. Pyrazole (1,2-Diazole). It is a heterocyclic aromatic organic compound with a 5-membered ring of three carbon atoms and two adjacent nitrogen centers with the molecular formula C3H4N2 ; molar mass, 68.08 g mol−1; melting point, 66–70 °C, boiling point, 186–188 °C ; basicity (pKb), 2.5

***Keywords*:** Pyrazole, Celecoxib, Lesopitron, Pyriprole, Yellow 2G, Fipronil RS, Properties of pyrazole.

I-Properties of pyrazolone

The unique structure and functionality-enriched heterocyclic systems are of great significance in chemically and biologically related research areas. Especially, pyrazolone and their derivatives are an important classes of compounds and has been widely found in biologically active molecules and drug candidates. Furthermorer, diversely functionalized pyrazolone have also been identified as versatile synthetic building units for the construction of complex molecules and natural products. Therefore, great efforts were done to their preparations and chemical application.



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II.1. **Introduction**

1-Phenyl-2,3-dimethyl-3-pyrazolin-5-one (**1**) (antipyrine or phenazone) has a great deal of interest due to its design of nonsteroidal anti-inflammatory drugs (NSAIDs) with high safety profile is still a basic for the pharmaceutical industry and utilised in short- term treatment for common pain and in the long- term management of chronic inflammatory diseases, such as osteoarthritis and rheumatoid arthritis.[1] Although the great safety of known NSAIDs over the steroidal derivatives, they still have side effects, including development of peptic and duodenal ulcers, renal failure,[2] liver malfunctions[3] and strokes[4] Cyclooxygenase- 2 (COX- 2) inhibitors were introduced to overcome NSAID-related GI toxicity; however, they enhance cardiovascular risk, due to a reduction in endothelial prostaglandin I2 (PGI2) and enhanced levels of platelet collector thromboxane A2 (TXA2)[5] Traditional NSAIDs and coxibs are coupled but with much more risk of cardiovascular problems and stroke[6] Prostaglandins (PGs) from the cyclooxygenase pathway and leukotrienes (LTs) from the lipoxygenase pathway are both mediators of the inflammatory process generated from the same arachidonic acid (AA) cascade[7] Severe side effects of coxibs indicate that the biosynthetic pathway may switch the metabolism to other, which has fatal side effects[8, 9] Therefore, compounds that may inhibit COX- 2/5- LOX together will consequently shut off the production of mediators of inflammation from the AA pathway; thus, dual inhibition of COX- 2/5- LOX enzymes establishes a rational method for the development of new anti-inflammatory (AI) agents with a good safety profile.[10] Compounds inhibiting both COX- 2 and 5- LOX pathways may have higher AI efficacy accompanied by lower gastric toxicity compared with traditional COX inhibitors.[11] Dual COX- 2/5- LOX inhibitors containing pyrazole moiety include celecoxib and FPL 62064 (*N* - (4- methoxyphenyl)- 1- phenyl- 1*H* - pyrazol- 3- amine), which is a dual- acting pyrazole contained in AI drugs.[12] A potent dual COX- 2/5- LOX inhibitor, tepoxalin, demonstrates potent AI activity and is free of ulcerogenicity[13-15] (Figure 1).Inspired by celecoxib, FPL 62064, and tepoxalin, new pyrazolone derivatives 3a –p were synthesized by replacing the pyrazole moiety with a dihydropyrazolone nucleus, linked in C3 with 4-aminobenzoic acid or 4-aminobenzenesulfonamide. Moreover, position 4 of pyrazolone ring was substituted for a variety of chalcone derivatives, as it was reported that they have a promising effect in potentiating AI activity.[16, 17] In addition, N1, either substituted or unsubstituted for the phenyl ring, seemed to be important in interaction with the active site pocket of the COX-2 enzyme. In addition to, its wide applications in the field of pharmaceuticals [18-27] and as an analytical reagent.[28] The synthesis of antipyrine derivatives have also attracted a great deal of attention in view of their chemical, biological and pharmacological activities

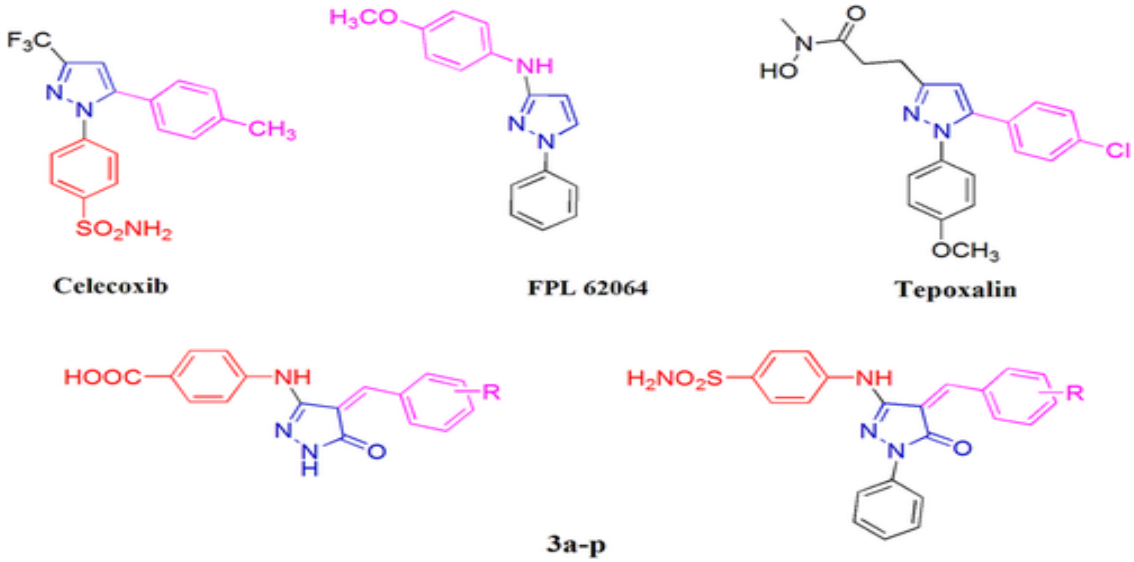


Fig.1a some selected drugs containing pyrazolone ring

This review shows the synthesis and reactions of some 4-substituted pyrazolone derivatives which incorporate materials appearing in *Chemical Abstracts* up to the of 07 February 2020

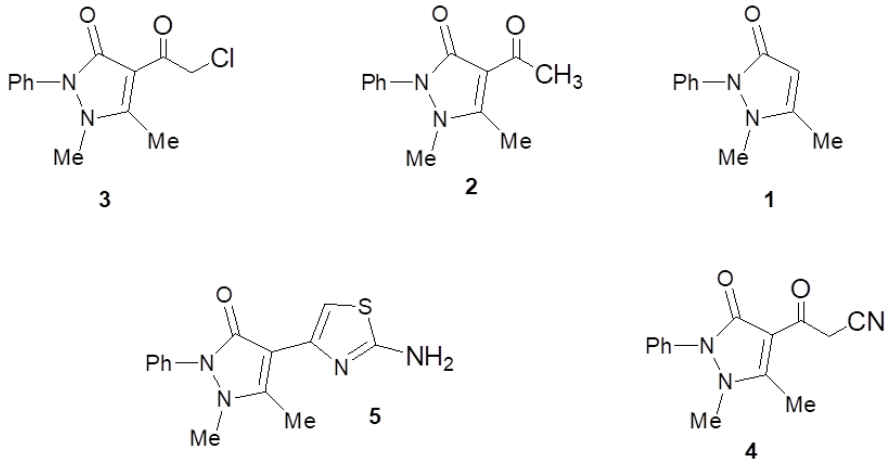
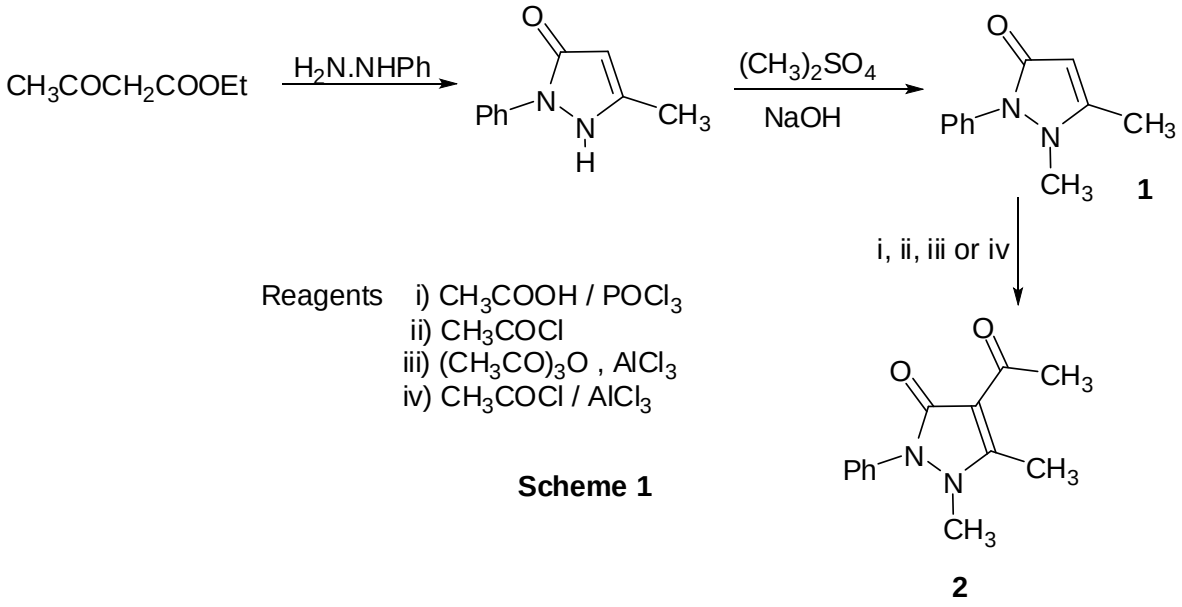


Figure 1b. Structures of 4-substituted pyrazolone derivatives

II.1. 1,2-Dihydro-1,5-dimethyl-2-phenyl-4-acetyl-3H-pyrazol-3-one (2)

II.1.1 Methods of preparation

Reaction of 1-phenyl-2,3-dimethyl-3-pyrazolin-5-one (**1**) with different reagents, for example, phosphorus oxychloride and acetic acid,[29] acetyl chloride,[30-32] or acetic anhydride in the presence of aluminum chloride and phosphorus oxychloride,[33] or acetyl chloride in the presence of aluminum chloride[34] is shown in scheme 1.



Scheme 1

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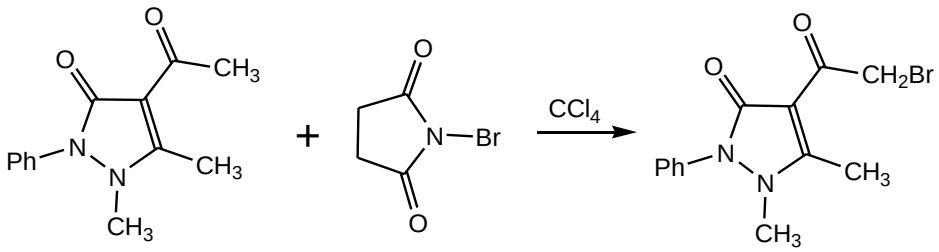
II.1.2 Reactions

II.1.2.1 Halogenation

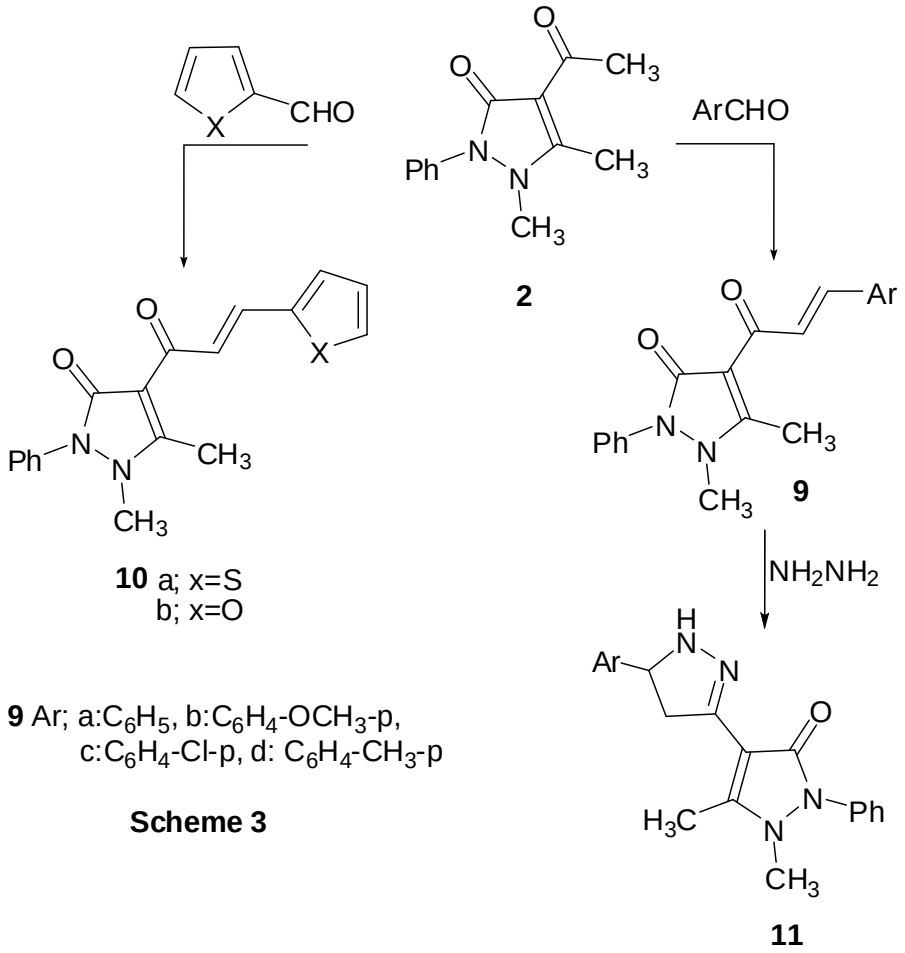
4-Acetylpyrazolone **2** reacts with N-bromosuccinamide (**7**) in carbon tetrachloride to give 4-bromoacetylpyrazolone **8**[30,35] (Scheme 2).



Scheme 2

II.1.2.2 Reaction with aromatic and heterocyclic aldehydes

Reaction of 4-acetylpyrazolone **2** with aromatic aldehydes afforded the corresponding arylidine derivatives **9a-d**. In a similar manner, heterocyclic aldehydes react with copound **2** to afford the hetarylidine derivatives **10a,b**. The 4-(pyrazolin-3-yl)pyrazolone derivatives **11**[36] were obtained via the reaction of the arylidine derivatives **9** with hydrazine hydrate (Scheme 3**).**

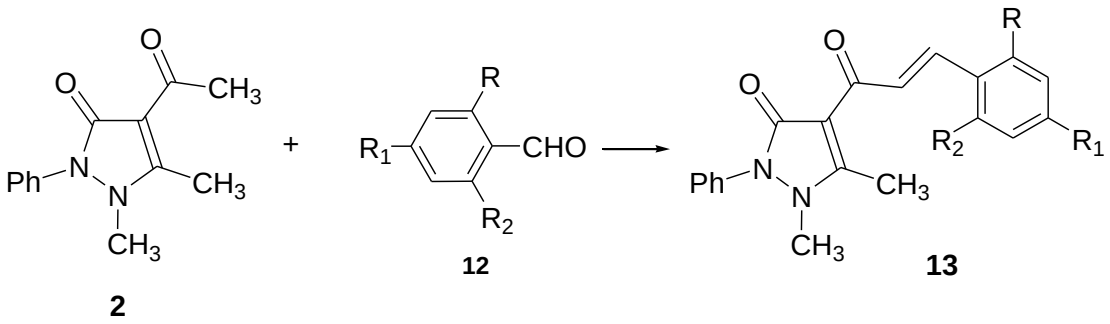


9 Ar; a:C_6H_5, b:C_6H_4-OCH_3-p, c:C_6H_4-Cl-p, d: C_6H_4-CH_3-p

Scheme 3

II.1.2.3 Reaction with 2,4,6-trisubstituted aromatic aldehydes

4-Acetylpyrazolone **2** reacted with 2,4,6-trisubstituted aromatic aldehydes **12** afforded arylidine derivative **13** [36] (scheme 4).



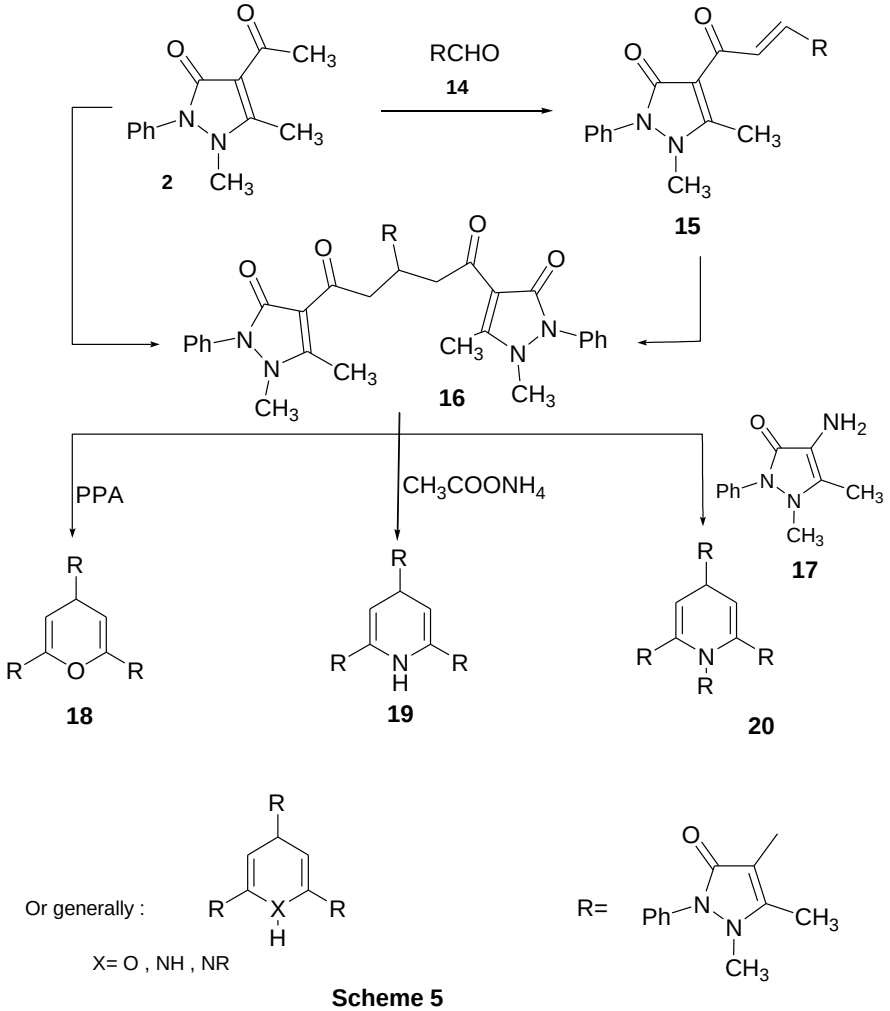
2 **12** **13**

R=OH, H, Cl ; R_1=H, $(CH_3)_2N$, Br, NO_2 ; R_2=H, Cl

Scheme 4

II.1.2.4 Reaction with 1,5-dimethyl-2-phenyl-2,3-dihydro-3-oxo-1H-pyrazol-4-carboxyldahyde 14

Condensation of 4-acetylpyrazolone **2** with 4-formylpyrazolone **14** afforded the corresponding condensation product **15**, which undwent further condensation with another molecule of aldehyde **14** to afford compound **16**. The latter compound could be obtained also by the reaction of aldehyde **14** with 4-acetylpyrazolone **2** in a molar ratio of 2:1. Cyclization reaction of **16** in the presence of polyphosphoric acid (PPA), ammonium acetate or 4-aminopyrazolone **17** in the presence of glacial acetic acid gave the pyran **18** , pyridine derivatives **19** or **20**, respectively, as shown in Scheme 5.[38]



Or generally :

X= O , NH , NR

R=

Scheme 5

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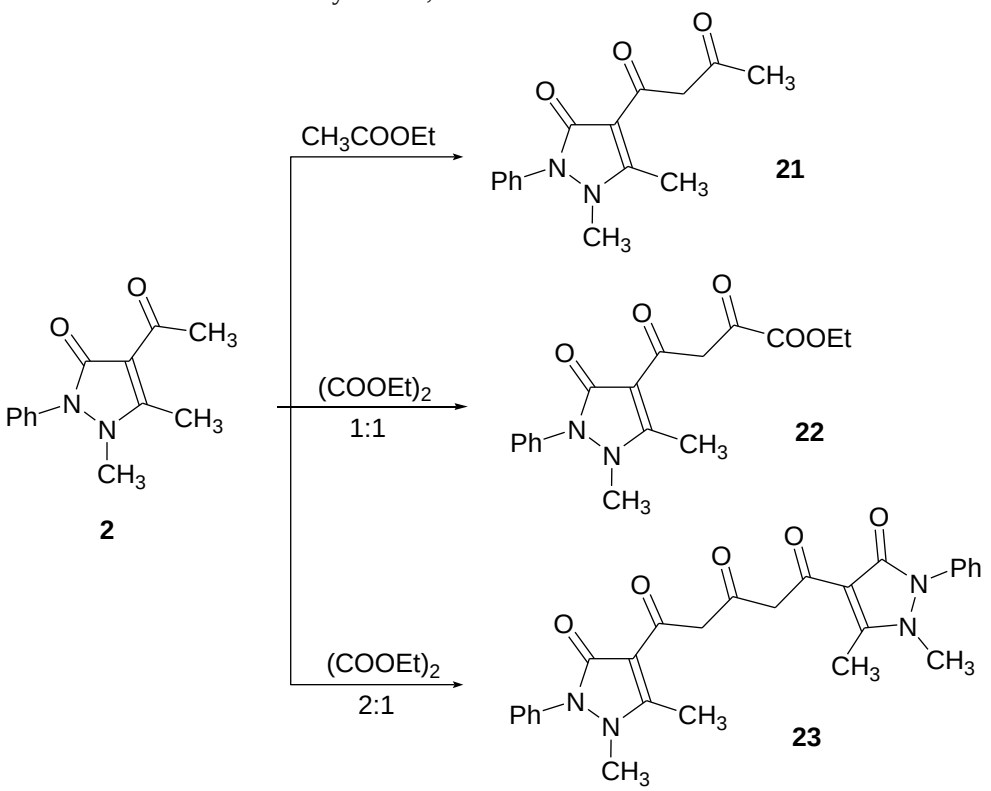
II.1.2.5 Claisen Condensation reaction

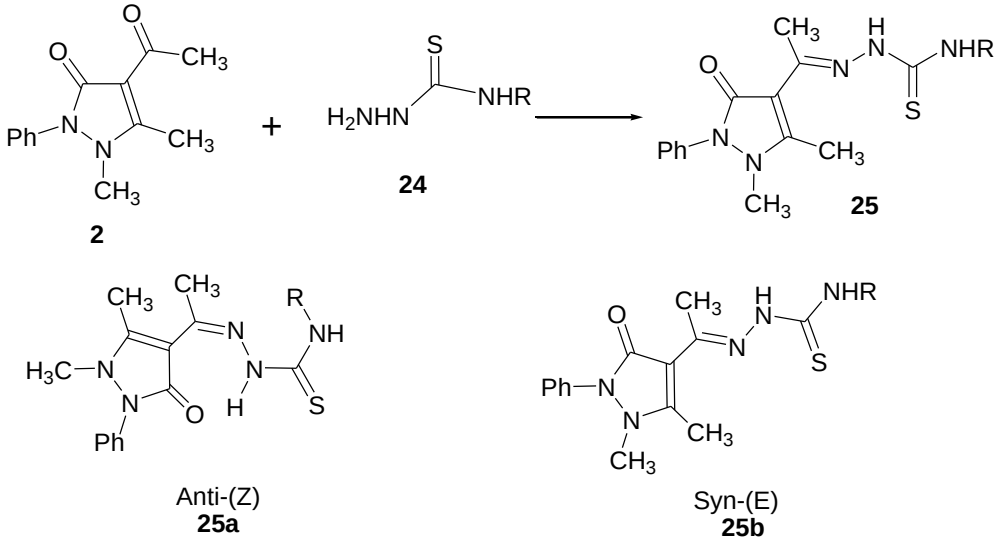
4-Acetylpyrazolone **2** undergoes Claisen Condensation with ethylacetate, and diethyloxalate in a molar ratio 1:1 and 2:1 to give the corresponding condensation products **21-23**, respectively, as reaveled in Scheme 6.[38]



Scheme 6

II.1.2.6 Condensation with Thiosemicarbazides

4-Substituted thiosemicarbazides **24** undwent condensation with 4-acetyl- pyrazolone **2** to give the corresponding thiosemicarbazone derivatives **25** which can exist in two isomeric forms **25a** and **25b** (Scheme 7).[39,40]

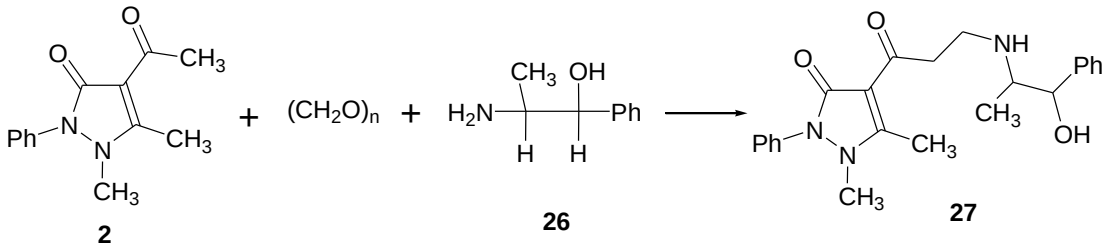


R= (Me, Et, allyl, Bu, cyclohexyl, Ph, 4-MeC$_6$H$_4$,4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$)

Scheme 7

II.1.2.7 Reaction with L-norephedrine

Condensation product **27**[41] was obtained via reaction of 4-acetylpyrazolone **2** with L-norephedrine **26** in the presence of paraformaldehyde in isopropyl alcohol (Scheme 8).

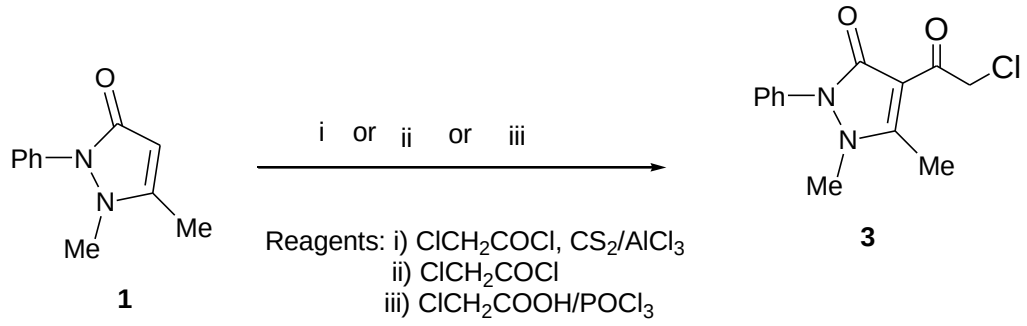


Scheme 8

II.2 1,2-dihydro-1,5-dimethyl-2-phenyl-4-(chloroacetyl)-3H-pyrazol-3-one (3)

II.2.1 Methods of Preparation

4-Chloroacetylpyrazolone **3** can be prepared from the reaction of 1-phenyl-2,3-dimethyl-3-pyrazolin-5-one **1** with different reagents, for example, chloroacetyl chloride in carbon disulphide in the presence of anhydrous aluminum chloride, [42-44] or chloroacetyl chloride, [31, 43, 45] or α-chloroacetic acid in the presence of phosphorus oxychloride[29] (Scheme 9).



scheme 9

II.2.2 Reactions of 1,2-dihydro-1,5-dimethyl-2-phenyl-4-(chloroacetyl)-3H-pyrazol-3-one (3)

II.2.2.1 Condensation Reactions

II.2.2.1.1 With aldehydes

4-Chloroacetylpyrazolone **3** reacts with p-chlorobenzaldehyde, p-nitro- benzaldehyde and thiophene-2-carboxyaldahyde to give products for which structure **29** was assigned. In contrast to this, p-methoxy and p-methylbenzaldehyde afforded the hydroxyfuranylbipyrazole derivatives **30** under the same conditions. The formation of **30** in this reaction was interpreted in terms of tautomerisation of intermediate **29** into **30A-B** which then loses water to yield the final isolable product **31**[36] (Scheme 10).

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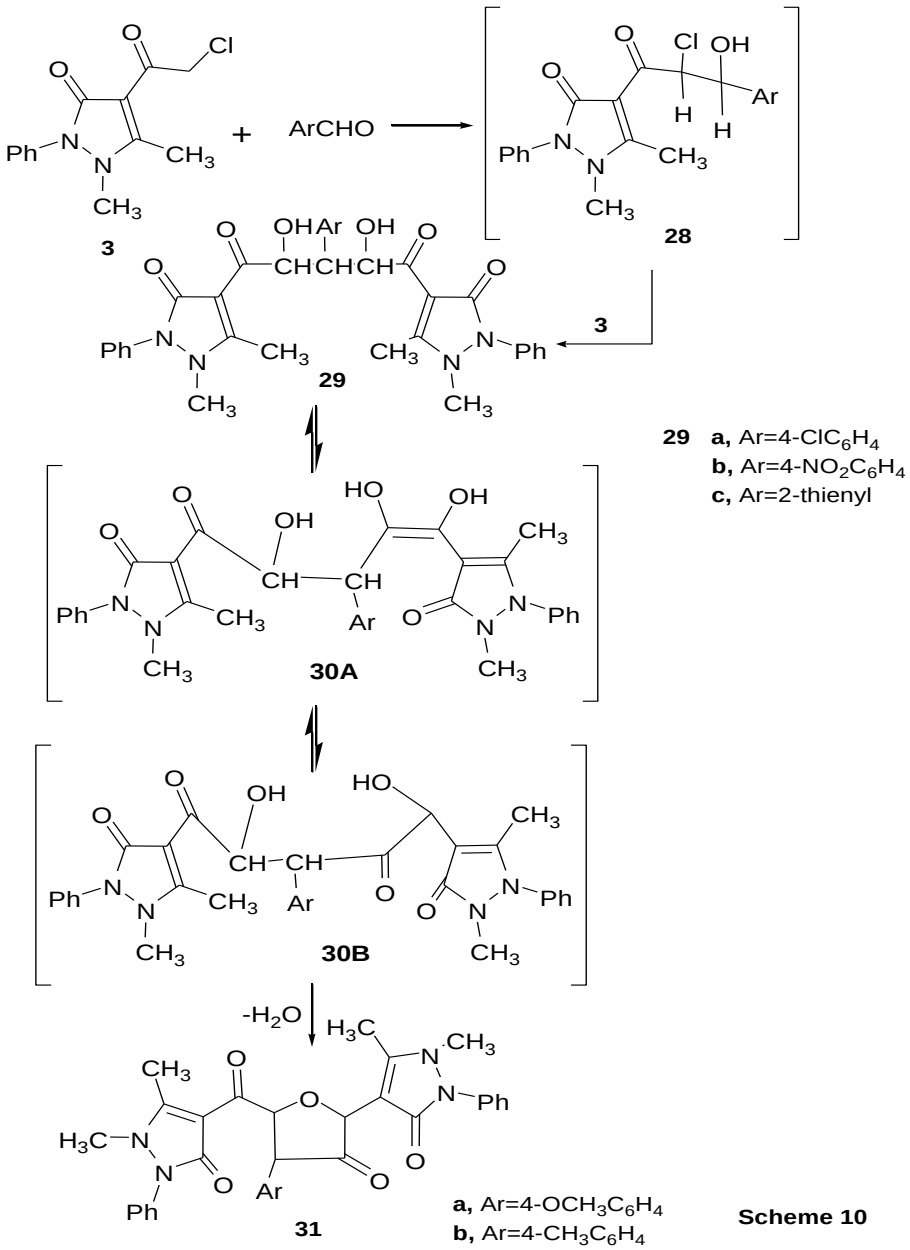
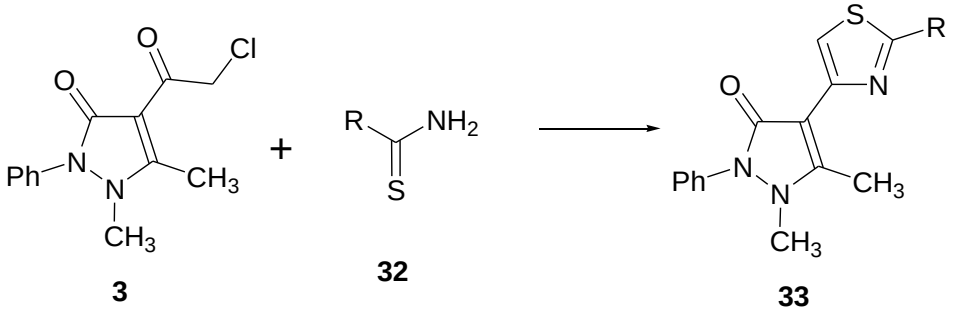


Scheme 10

II.2.2.1.2 With thioamides

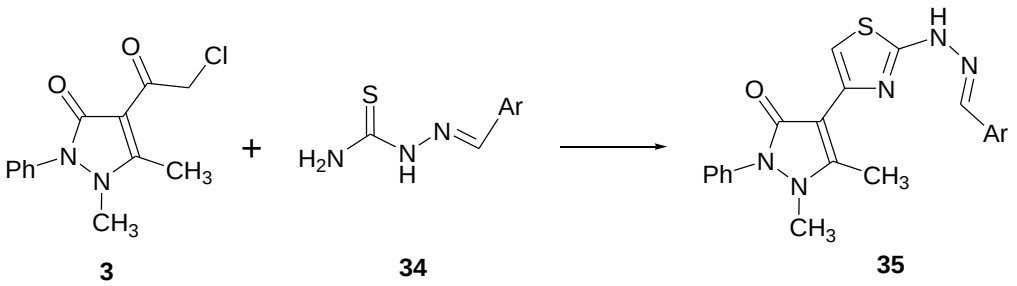
4-(4-Thiazolyl)pyrazolone derivatives **33**[46,47] was prepared via reaction of 4-chloroacetyl pyrazolone **3** with thioamide derivatives **32** as exhibited in scheme 11.



Scheme 11

II.3.2.1.3 With thiosemicarbazones

Condensation **of** compound **3** wih thiosemicarbazone derivatives **34** afforded the corresponding condensation product **35**[48-50] (scheme 12) .



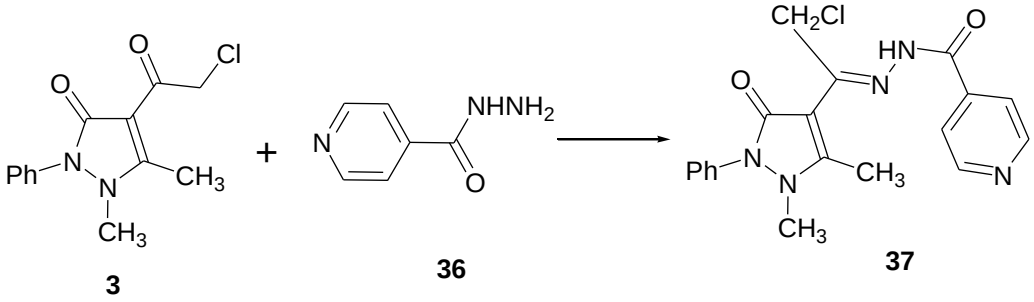
3 **34** **35**

Ar= 4-$OCH_3C_6H_4$, 2-OHC_6H_4, 2-ClC_6H_4, $Me_2NC_6H_4CH{=}CH^-$, cyclohexylidene, 4-$NO_2C_6H_4$, 3-$MeOC_6H_4$, 4-OHC_6H_4, 2-$NO_2C_6H_4$

Scheme 12

II.2.2.1.4 With hydrazides

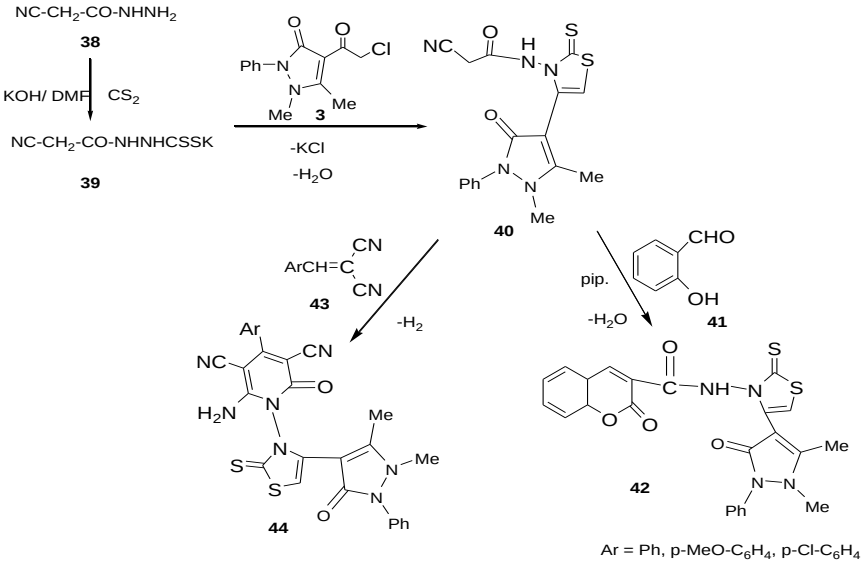
4-Chloroacetylpyrazolone **3** reacts with isonicotinic acid hydrazide **36** to afford the corresponding condensation product **37** [51] (scheme 13).



3 **36** **37**

Scheme 13

Also, it was be found that 2-cyanoethanoic acid hydrazide **38** when treated with carbon disulfide in DMF under basic conditions (KOH/DMF solution), gave the non-isolable intermediate **39** . The reaction of **39** with **3** afforded the thiazole derivative **40** . Compound **40** reacted with each of 2-hydroxybenzaldehyde **41** gave the benzo(b)pyran **42** that reacted with arylidenemalonitriles **43** to afford pyridine derivative **44**[52] (scheme 14).



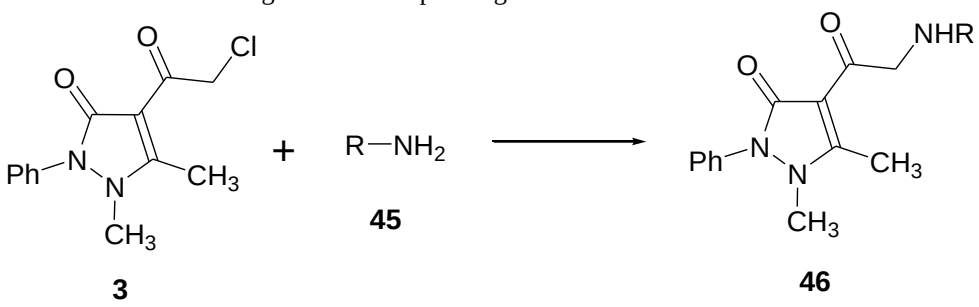
Ar = Ph, p-MeO-C_6H_4, p-Cl-C_6H_4

Scheme 14

*Corresponding author e-mail: taha_eldebss@yahoo.com.

II.2.2.2 Reaction with amines

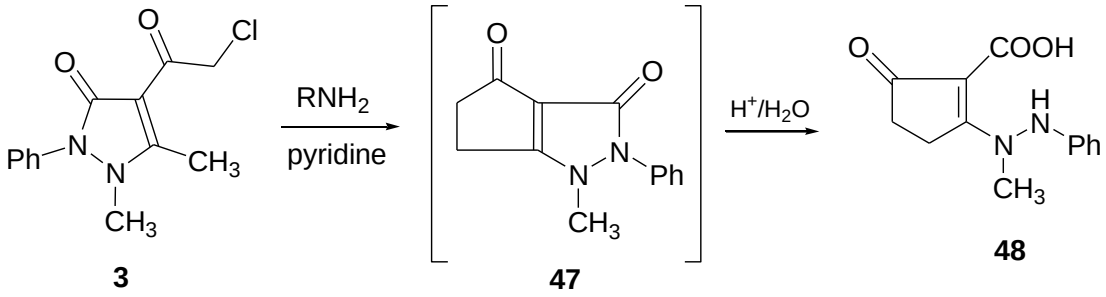
Treatmemt of chloroacetylpyrazolone **3** with amine derivatives **45** gave the corresponding 4-aminoacetylpyrazolone derivatives **46**[53] (scheme 15).



R= 4-Me-2-thiazole, 1-adamentyl, 4-$H_2NSO_2C_6H_4$, 4-$H_2N^-(C{=}NH)NHSO_2C_6H_4$, 4-(3,4-dimethyl-5-isoxazolylaminosulphonyl)phenyl

Scheme 15

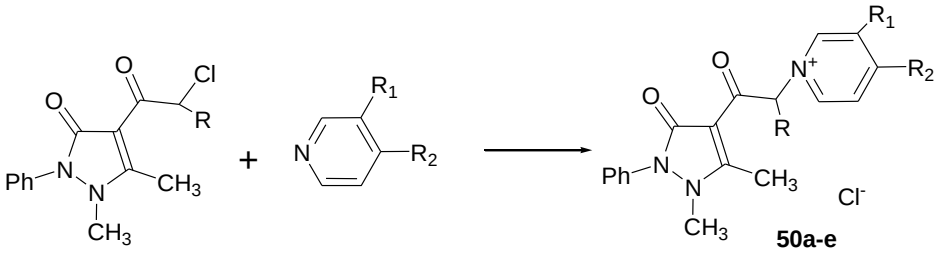
On the other hand, when the reaction of 4-chloroacetylpyrazolone **3** with different amines was carried out in pyridine solution, unexpectedly one and the same product **48** was obtained via the hydrolysable intermediate **47**. The same product was readily obtained on boiling **3** in pyridine solution[36] (Scheme 16).



Scheme 16

II.3.2.3 Reaction with pyridine derivatives

Compound **3** reacts with pyridine derivatives **49** to give 4-pyrazolonecarbonylalkylpyridinium chlorides **50a-e**[54] (scheme 17).

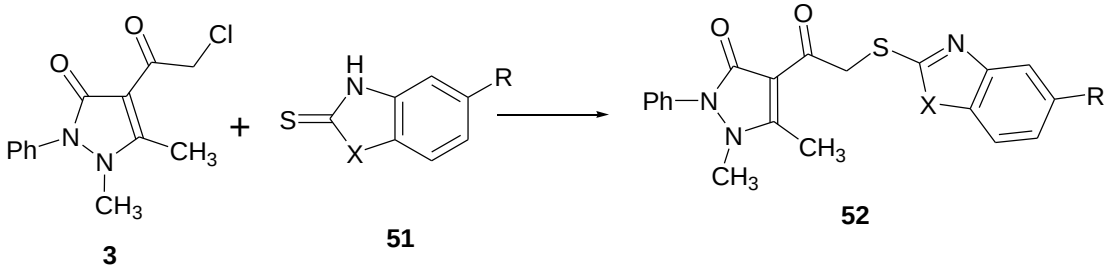


50	R	R1	R2
a	H	H	H
b	Me	CONH2	H
c	H	H	Me
d	Me	H	Me
e	H	CO2H	H

Scheme 17

II.3.2.4 Reaction with heterocyclic thiones

Reaction of 4-chloroacetylpyrazolone **3** with benzimidazole and benzthiazole-2-thione derivatives **51** afforded the corresponding 4-(benzazol-2-yl)thioacetylpyrazolone derivatives **52**[55] as seen in scheme 18.

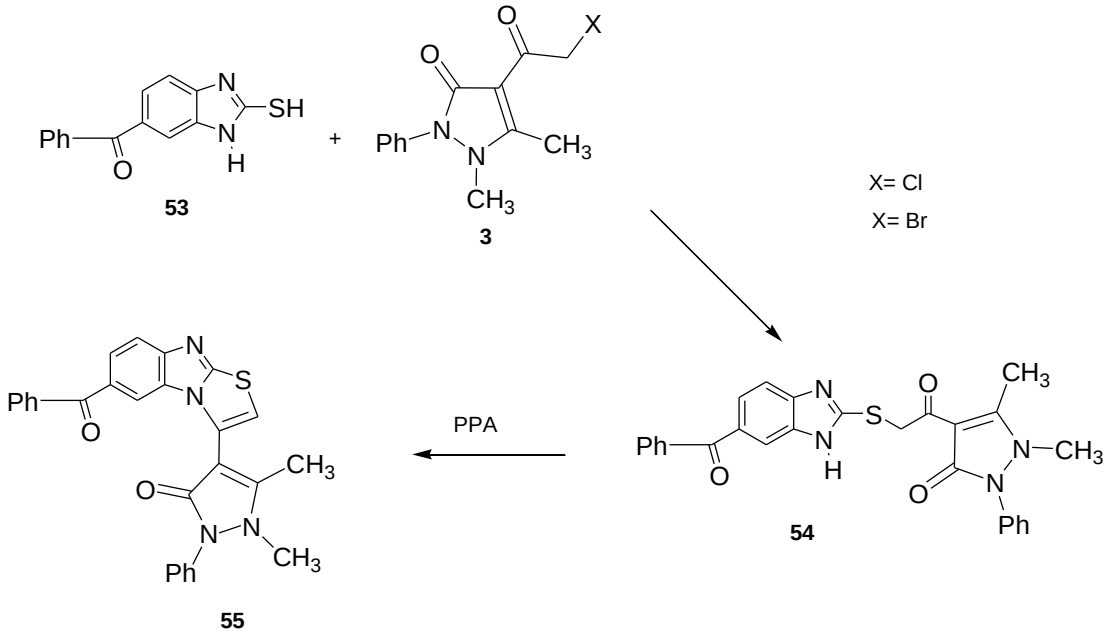


3 **51** **52**

X= NH; R=H, Cl, Me, NO_2
X= O, S; R=H

Scheme 18

6-Benzoyl-2-thiolobenzimidazole **53** reacts with **3** to give **54** which on treatment with PPA undergoes cyclodehydration and afforded 7-benzoyl -1,3-thiazolo[3,2-a]benzimidazole derivative **55**[56] (Scheme 19).

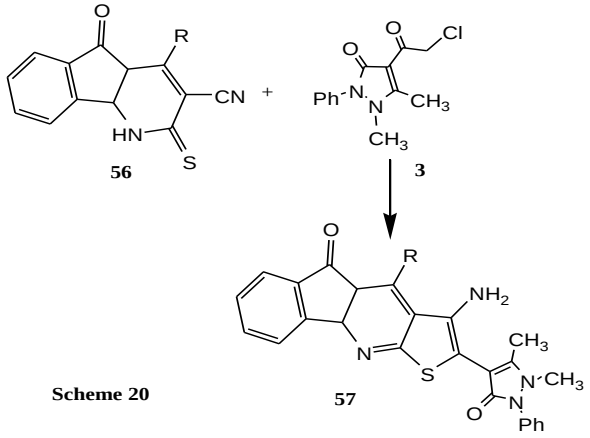


53 **3** **54** **55**

X= Cl
X= Br

scheme 19

Also, compound **3** reacted with indenopyridine -2-thione (**56**) to afford thieno[2,3-b]indeno[2,1-e]pyridine **57**[59] as seen in Scheme 20.



56 **3** **57**

Scheme 20

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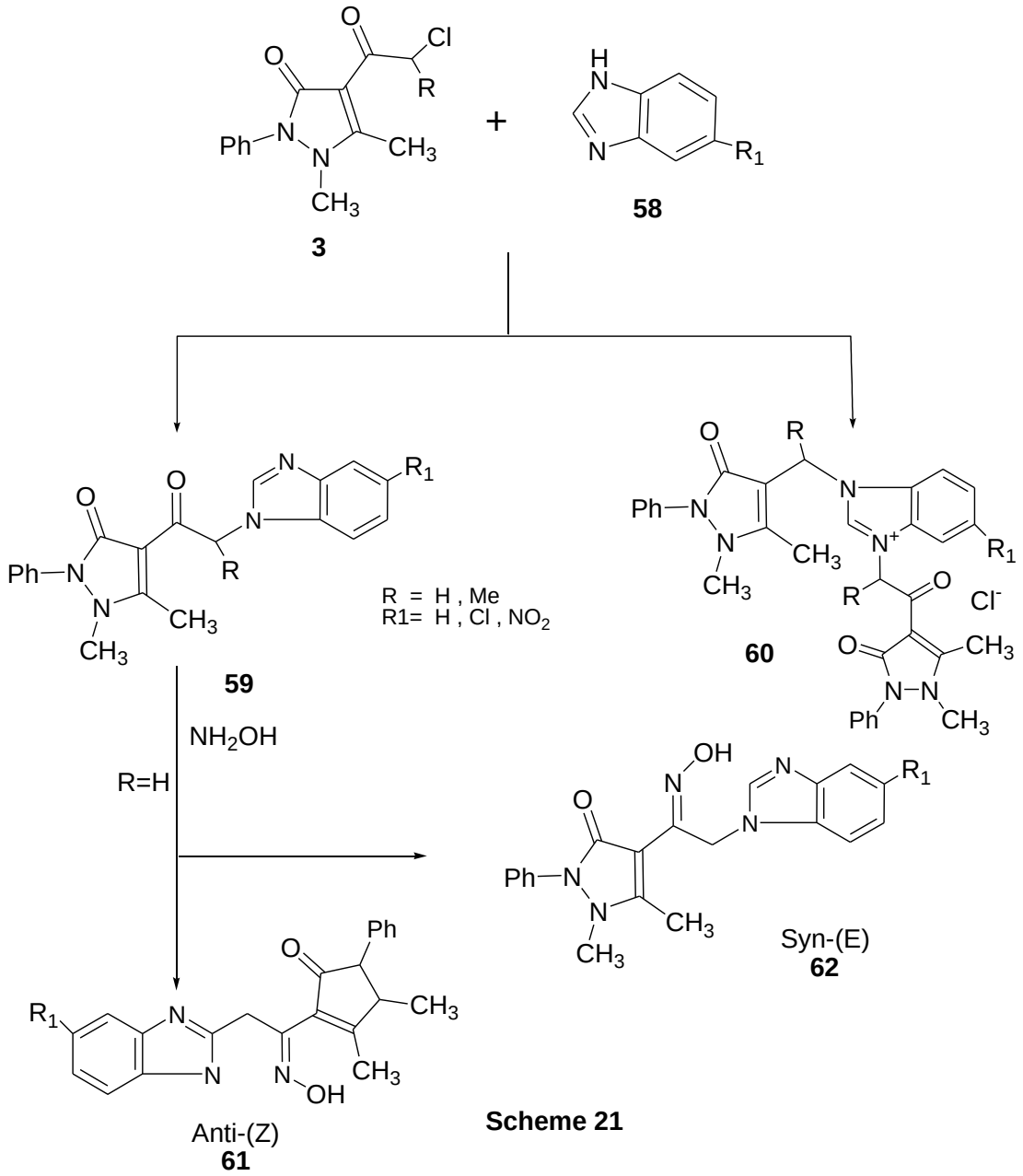
II.2.2.5 Reaction with benzimidazole derivatives

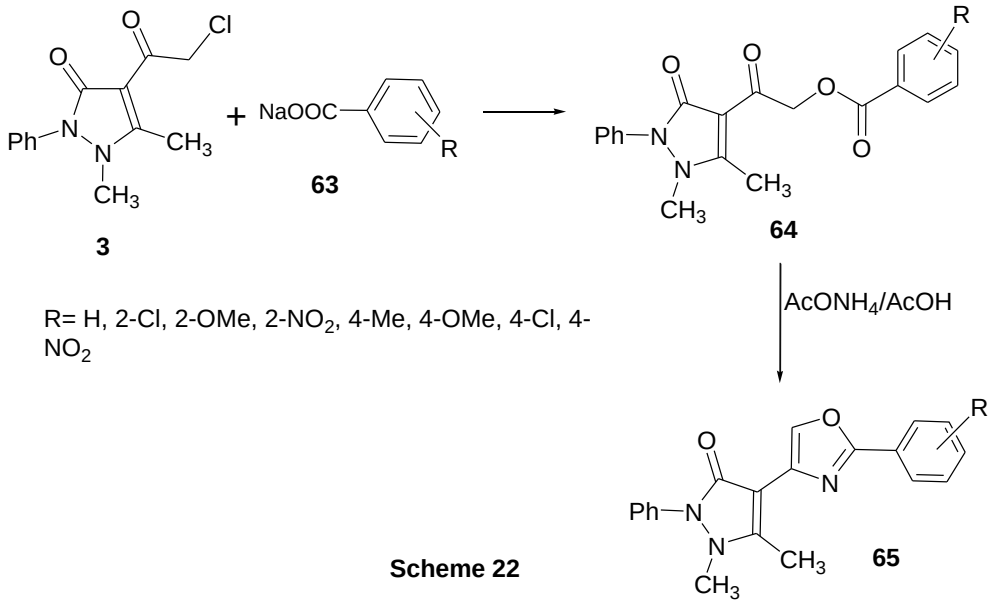
Compound **3** reacts with benzimidazoles **58** to give a mixture of two products,N1-(antipyroylalkyl)benzimidazole **59** and 1,3-bis(antipyroyl-alkyl)benzimidazolium chloride **60**. Condensation reaction of **59** with hydroxyl amine gives a mixture of ketoximes, *anti*- **61** and *syn*- **62**, geometrical isomers,[60] as exhibited in scheme 21.



Scheme 21

II.2.2.6 Reaction with sodium salt of aromatic acid derivatives

4-Chloroacetylpyrazolone **3** reacts with sodium salt of acids **63** to give (benzoyloxy)acetylantipyrines **64**. Treatment of compound **64** with ammonium acetate in acetic acid to afforded 4-(2-aryloxazol-4-yl)pyrazolone derivatives **65**[61] (Scheme 22).

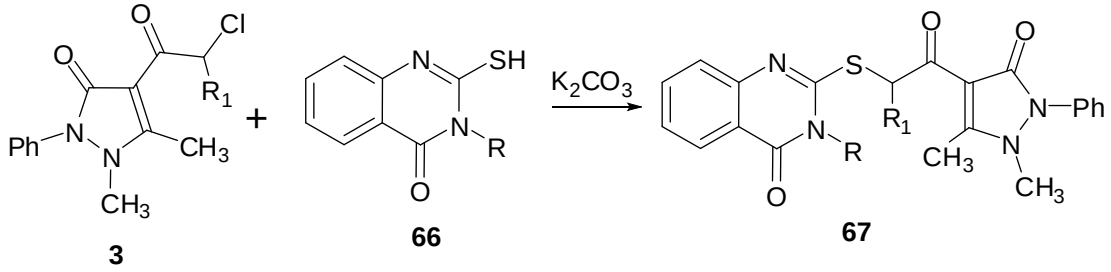


R= H, 2-Cl, 2-OMe, 2-NO_2, 4-Me, 4-OMe, 4-Cl, 4-NO_2

Scheme 22

II.2.2.7 Reaction with 2-mercapto-3-substituted-4-(3H)-quinazolinones

Reaction of 4-chloroacetylpyrazolone **3** with 2-mercapto-3-substituted-4-(3H)-quinazolinones **66** in the presence of potassium carbonate gave the corresponding product **67**[62] as seen in Scheme 23.



R = H, Et, Ph; R_1 = H , Me , Et

Scheme 23

II.2.2.8 Reaction with active-methylene niriles

Active-methylene nitriles **68** , in KOH/DMF solution , reacts with phenyl isothiocyanate to afford the non-isolable intermediate **69** .The latter compound **69** reacts with **3** to give the enaminonitrile derivative **70** . Compound **70** is a precursor to many compounds. It can undergo cyclization in the presence of piperidine to give 3-amino-thiophene derivative **71**, it can cyclize by conc. sulfuric acid to give thiazole derivative **72** which on treatment with hydrazine hydrate gives the thiazolyl-pyrazole derivative **73** . Compound **73** was also obtained by the reaction of **70** with hydrazine hydrate to afford the pyrazole derivative **74**, followed by treatment of **74** with conc. sulfuric acid[63] (Scheme 24).

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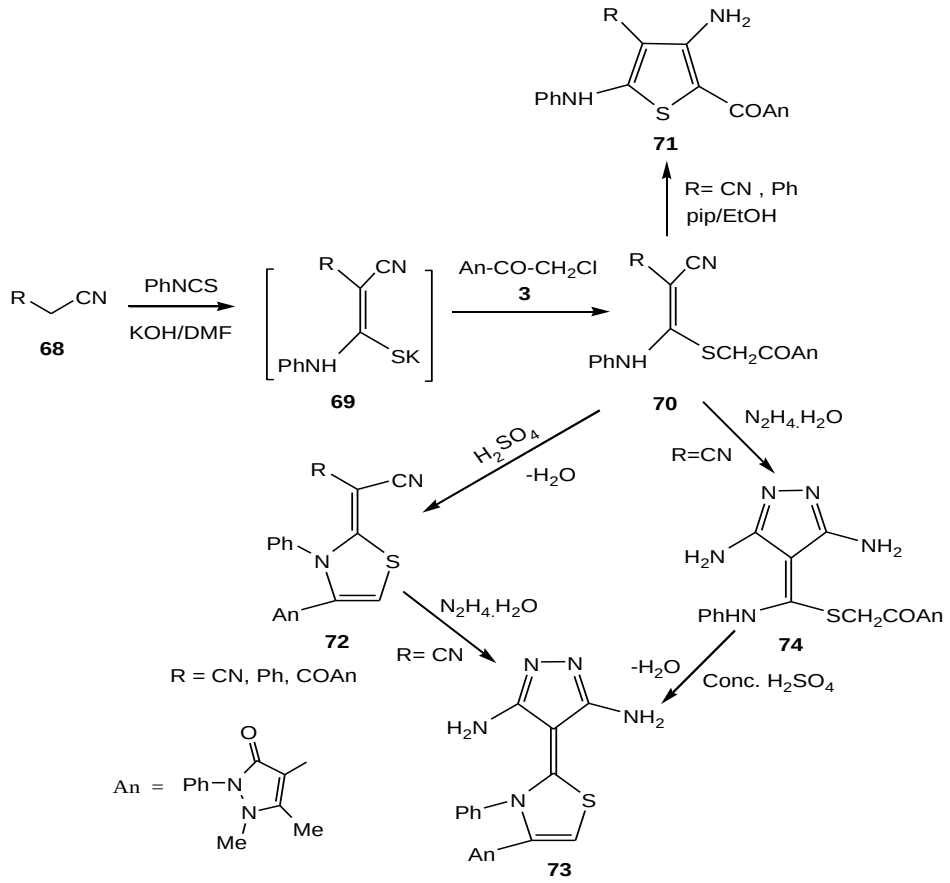
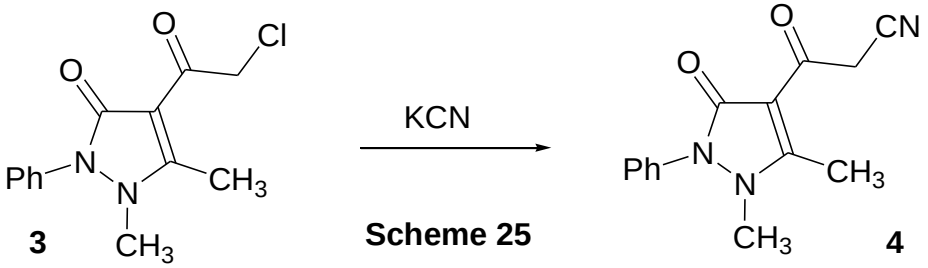


scheme 24

II.3. 1,5-Dimethyl-2-phenyl-2,3-dihydro-4-propanenitrile-3-dioxo-1H-pyrazole (4)

II.3.1 Preparation

Compound **4** was firstly prepared by Kaufman and Hyang *via* the action of potassium cyanide on 4-chloroacetylpyrazolone **3**[64] as shown in scheme 21.

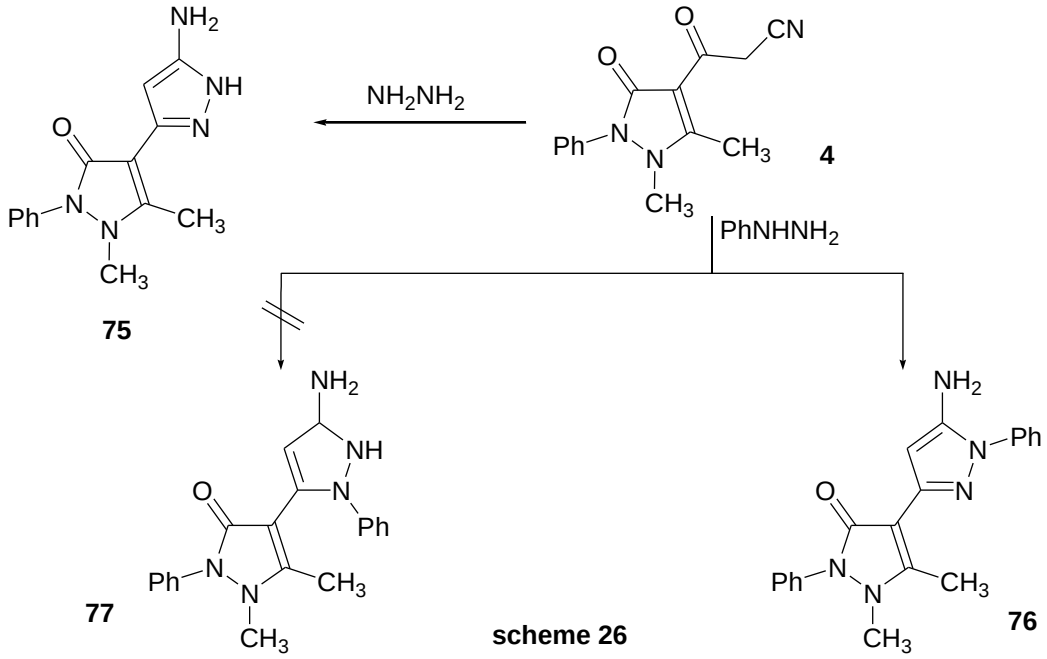


Scheme 25

II.3.2 Reactions

II.3.2.1 Reaction with hydrazines

Reaction of 4-cyanoacetylpyrazolone **4** with hydrazine hydrate yielded the aminopyrazole derivative **75**. It reacts also with phenyl hydrazine to yield the aminopyrazole derivative **76** not its isomer **77**[65] as shown in scheme 26.



scheme 26

5-Aminopyrazole derivative **75** reacts with acrylonitrile, in pyridine to yield 1:1 adduct for which structure **78** was suggested. Structure **78** was established by its synthesis from β-cyanoethylhydrazine **79** and pyrazolone **4**. Compound **78** readily cyclized into tetrahydropyrazolo[1,5-a] pyrimidine derivative **80** via treatment with acetic/hydrochloric acid mixture. The same product **80** could be directly obtained by the reaction of compound **75** with methylacrylate . Also the product **80** can be obtained by reaction of **75** with ethyl acrylate in dry pyridine via ethanol elimination .Compound **75** reacts with ethyl-β-bromopropionate to give **81.** Treatment of compound **75** with acetic acid[66,67] affords the 5 acetylaminopyrazole derivative **82** as shown in scheme 27.

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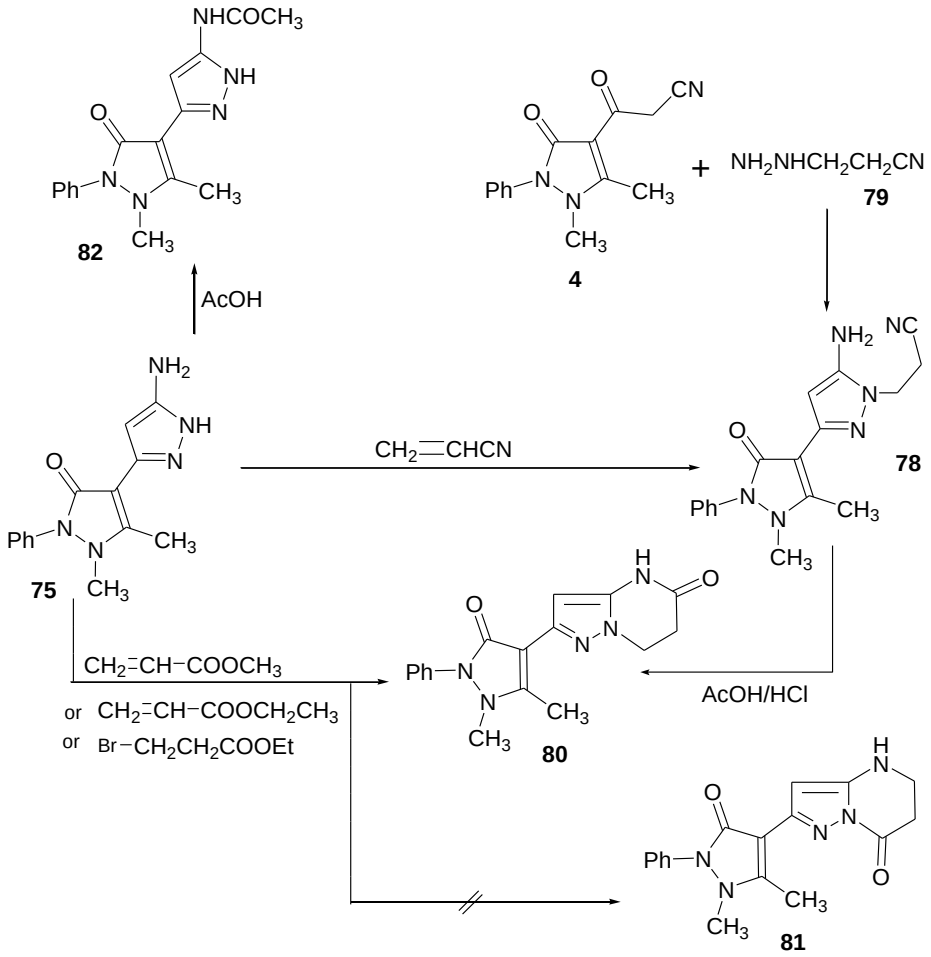
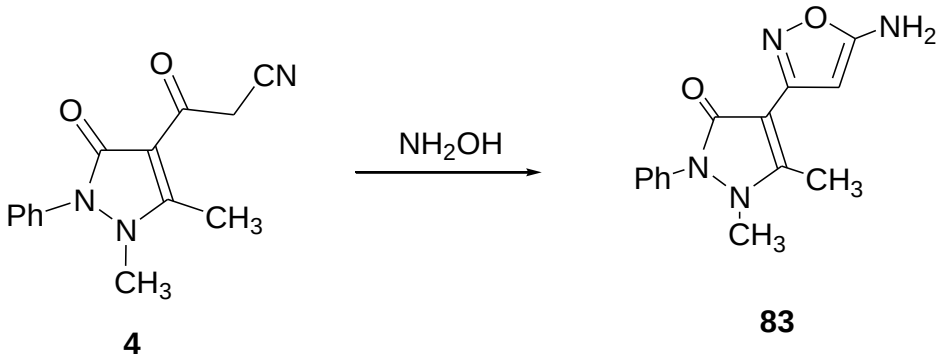


Scheme 27

II.3.2.2 Reaction of 4 with Hydroxyl amine

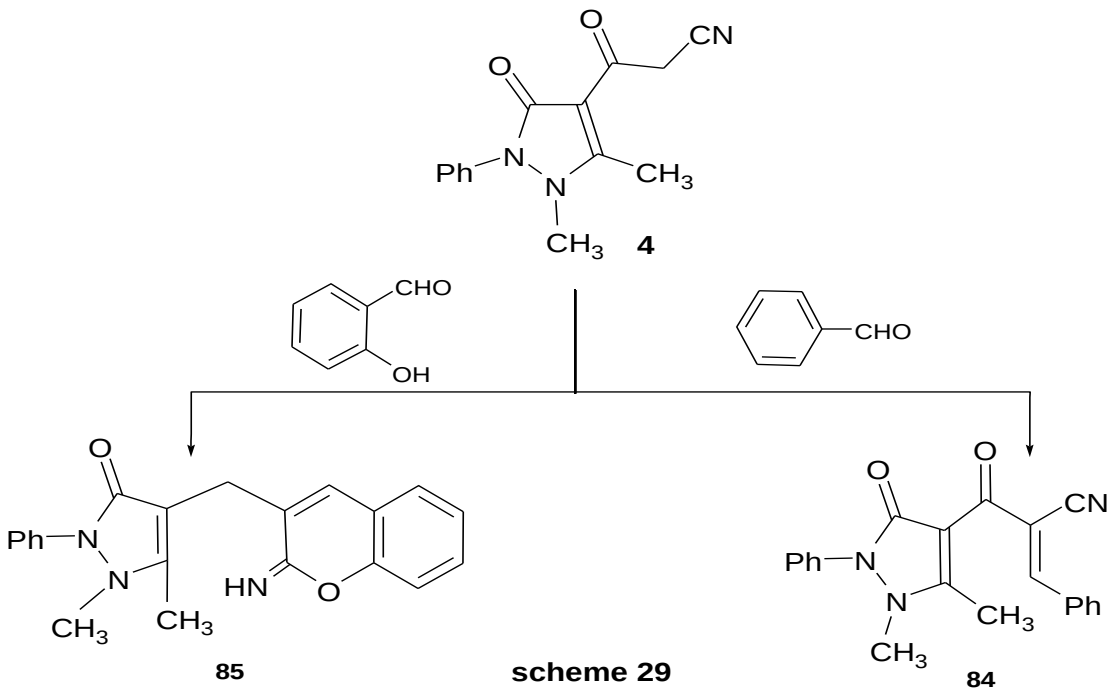
Treatment of compound **4** with hydroxyl amine afforded the aminoxazole derivative **83**[68] as shown in Scheme 28.



Scheme 28

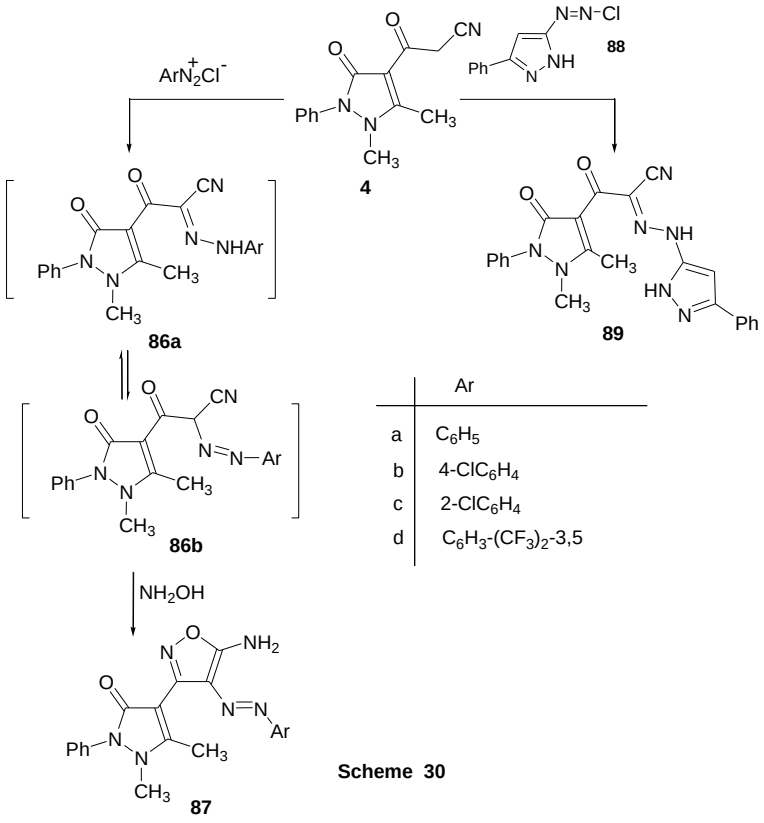
II.3.2.3 Condensation Reactions

4-Cyanoacetylpyrazolone **4** underwent condensation reaction with benzaldehyde to yield the corresponding bezylidine derivative **84**. On the other hand, treatment of **4** with salicyldehyde gave the coumarin derivative **85**[68] (scheme 29).



II.3.2.4 Reaction with aromatic and heterocyclic diazonium salts

Treatment of 4-cyanoacetylpyrazolone **4** with aromatic diazonium salts yielded the hydrazone **86**. The latter product reacts with hydroxylamine to yield aminoisoxazole derivative **87**. On the other hand, coupling of compound **4** with 3-phenylpyrazole-5-diazonium chloride **88** yielded the hydrazone **89** which could not undergo cyclization under a variety of conditions[68] as shown in scheme 30.



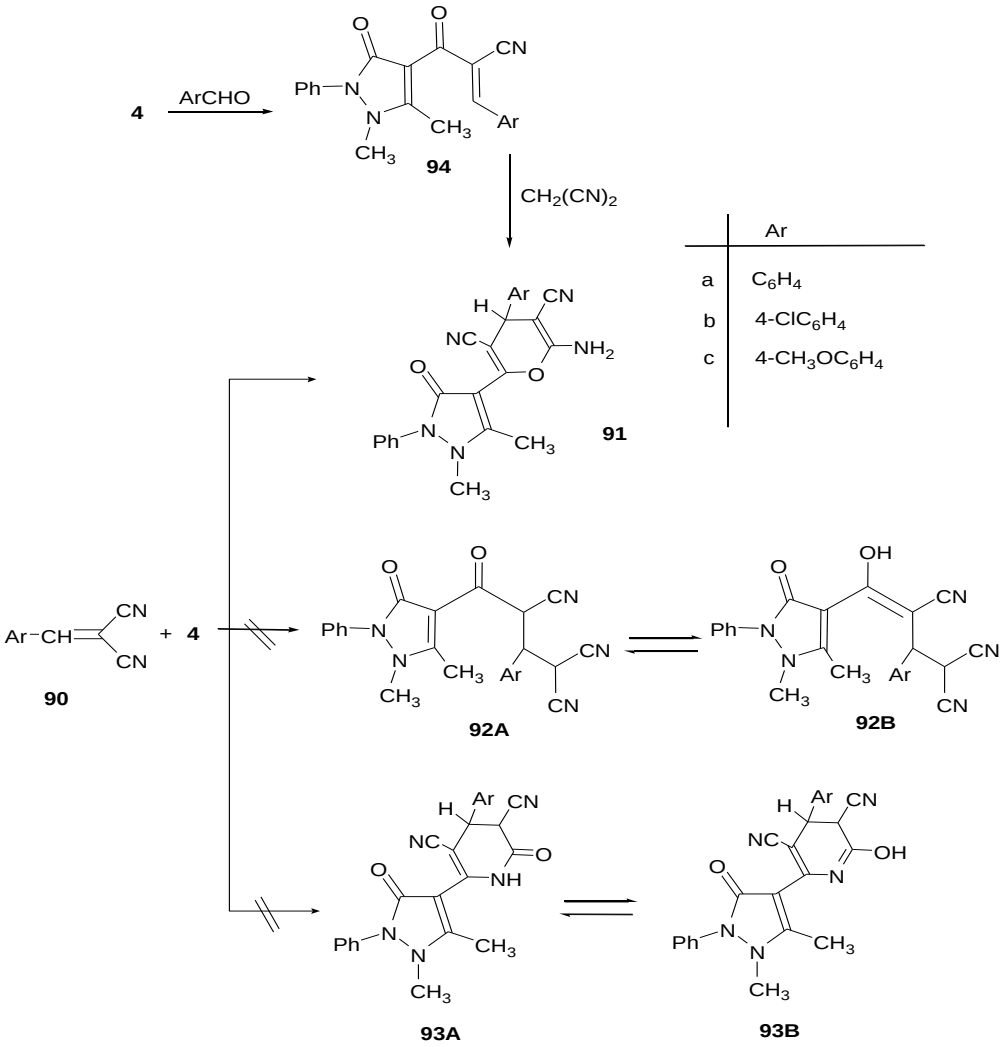
	Ar
a	C_6H_5
b	4-ClC_6H_4
c	2-ClC_6H_4
d	C_6H_3-$(CF_3)_2$-3,5

Scheme 30

*Corresponding author e-mail: taha_eldebss@yahoo.com.

II.3.2.5 Reaction with cinnamonitriles

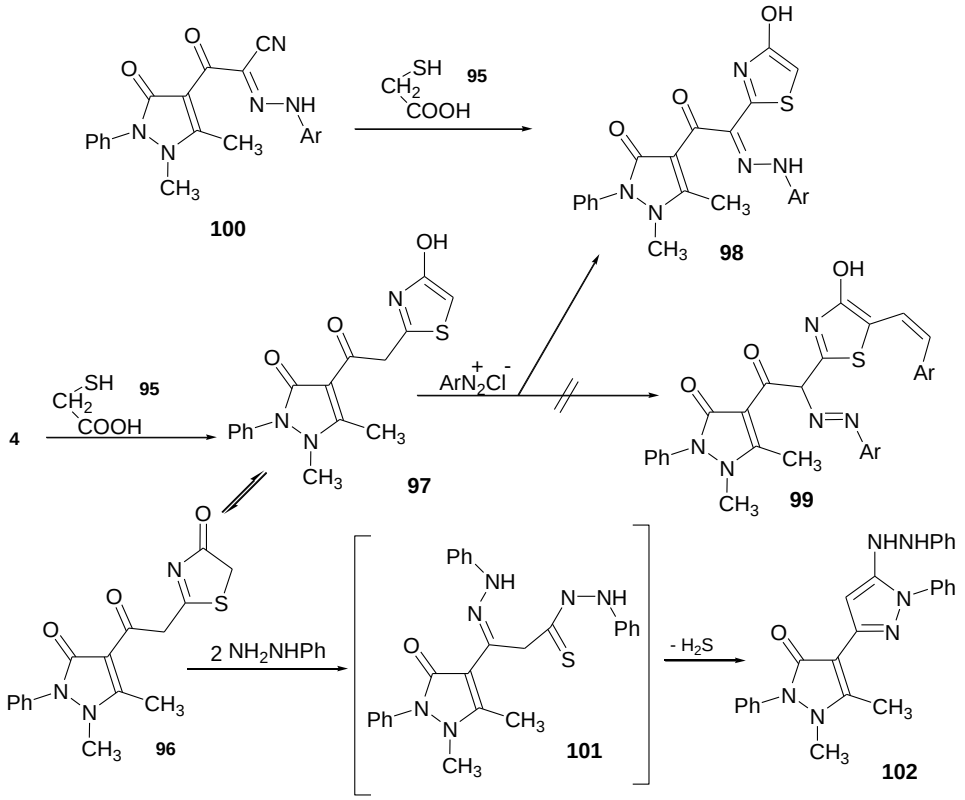
Reaction of 4-cyanoacetylpyrazolone **4** with the yilidene malononitriles **90** yielded 1:1 adducts[69] **91a-c**. The same products were prepared from the reaction of yilidine derivatives **94a-c** with malononitrile[70] (Scheme 31).



Scheme 31

II.3.2.6 Reaction with mercaptoacetic acid

Reaction of compound **4** with mercaptoacetic acid **95** in dry pyridine yielded two tautomeric structures **96** and **97**. Compound **97** afforded the monosubstituted arylazo derivative **98** even if coupled with two moles of aromatic diazonium chloride. The same product **(98**) can be prepared by coupling of **97** with one mole of arene diazonium salts or from the reaction of arylhydrazone **100** with mercaptoacetic **95** acid in dry pyridine. When compound **96** was heated with phenylhydrazine without solvent the phenylhydrazonopyrazole derivative **102** was formed. Compound **102** is assumed to be formed *via* intermediate **101** which readily cyclizes into the final isolable product **102**[71] as seen in (Scheme 32).

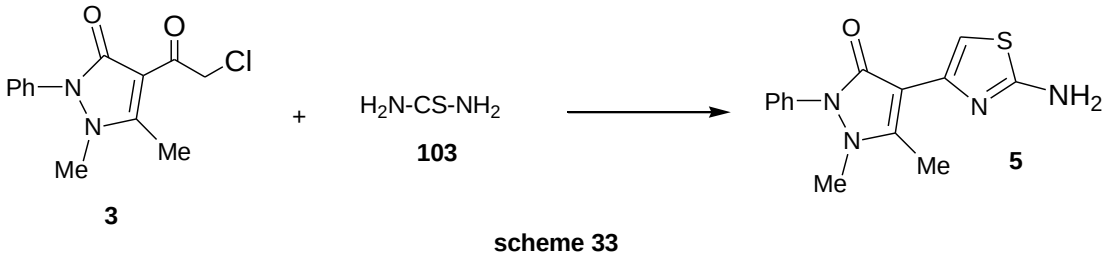


Scheme 32

II.4. 2-Amino-4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)thiazole (5)

II.4.1. Preparation of 5

Reaction of the chloroacetyl antipyrine **3** with thiourea afforded the 2-amino-4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)thiazole (**5**)[72] (scheme 33).

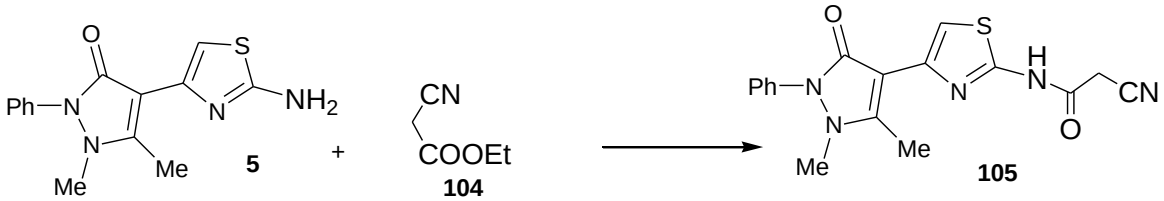


scheme 33

II.4.2. Reactions of 5

II.4.2.1 Reaction with ethyl cyanoacetate

Treatment of 5 with ethyl cyanoacetate 104, yielded 2-cyano-*N*-4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)thiazol-2-ylacetamide **105**[72] (Scheme 34).



Scheme 34

Compound **105** was reported as a precursor of many important heterocyclic compounds. For example, it reacts with acetophenone **106** to give **107** which when treated with sulfur yielded **108**[73] (Scheme 35).

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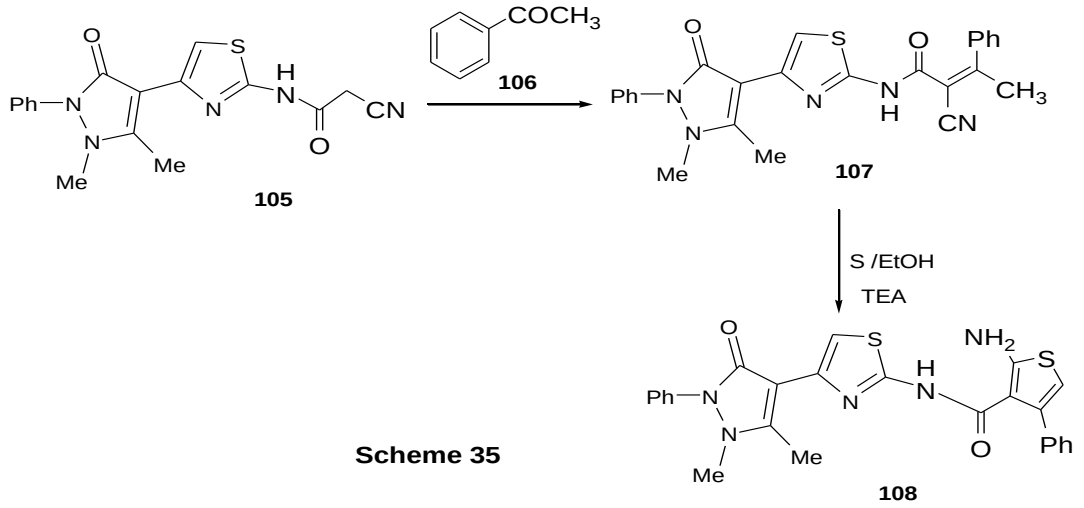
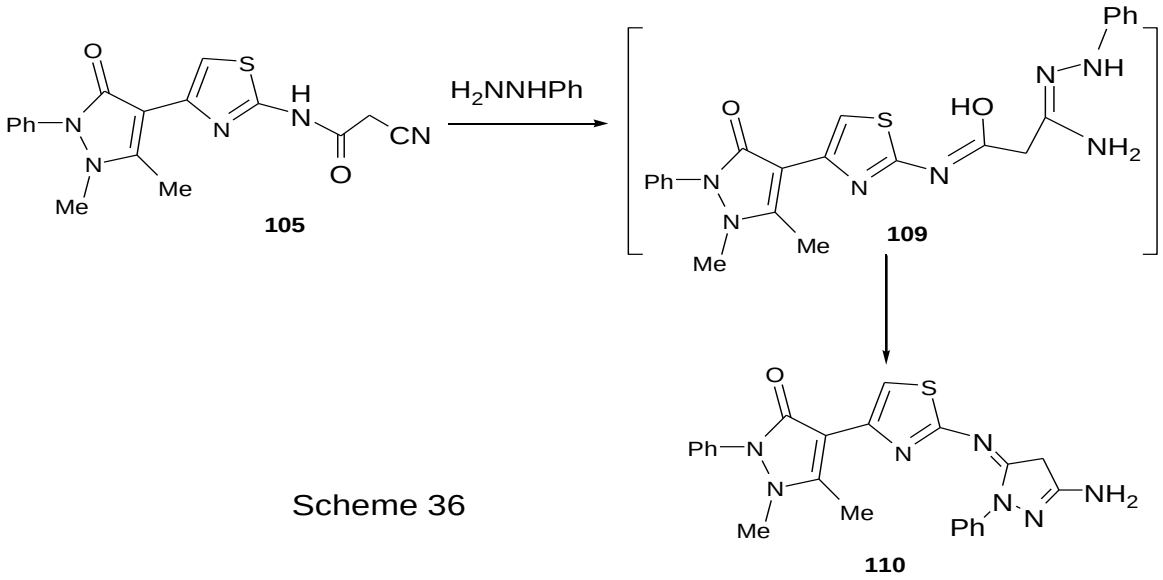


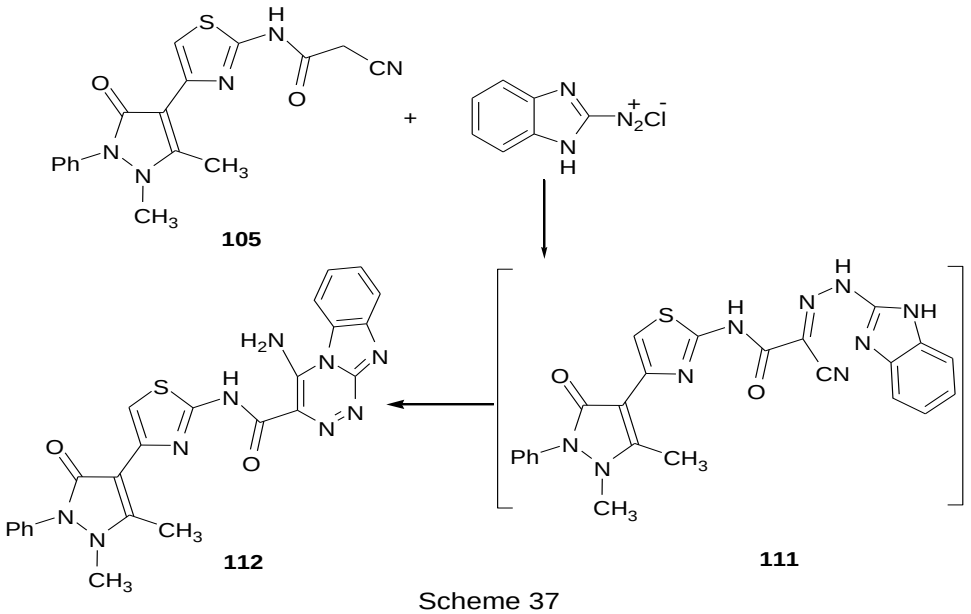
Scheme 35

On treatment of compound **105** with phenyl hydrazine, compound **110** is obtaind via the non-isolable intermediate **109**[73] (Scheme 36).



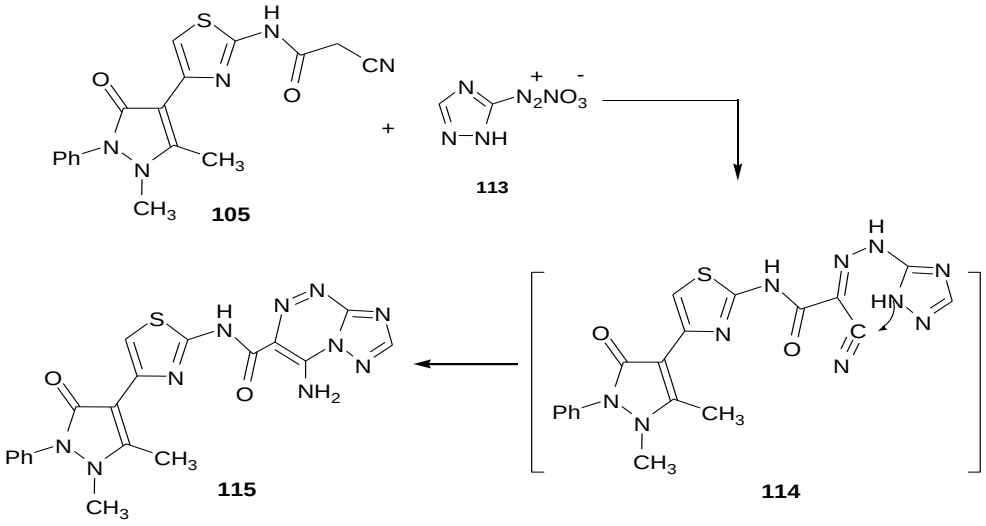
Scheme 36

Compound **105** underwent coupling raection in ethanolic sodium acetate trihydrate to afford **112** via the intermediate **111**[72] (Scheme 37).



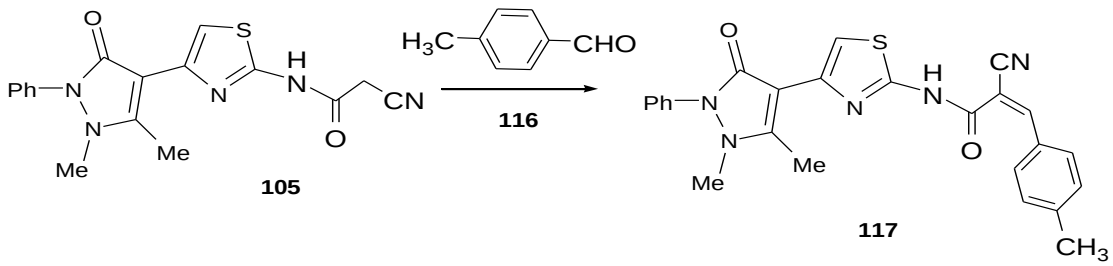
Scheme 37

Compound **105** couples smoothly with diazonium salt of aminotriazole **113** to yielded the 1,2,4-triazolo[5,1-c]1,2,4-triazine derivative **115** via the intermediate **114**[72] (Scheme 38).



Scheme 38

The reactivity of **105** toward Knoevenagel condensation was tested with 4-methyl benzaldehyde **116** yielded **117**[73] (scheme 39).



Scheme 39

II.4.2.2 Reaction with acetic anhydride

Compound **5** reacted also with acetic anhydride yielded the corresponding acetyl derivative **118**[73] (Scheme 40).

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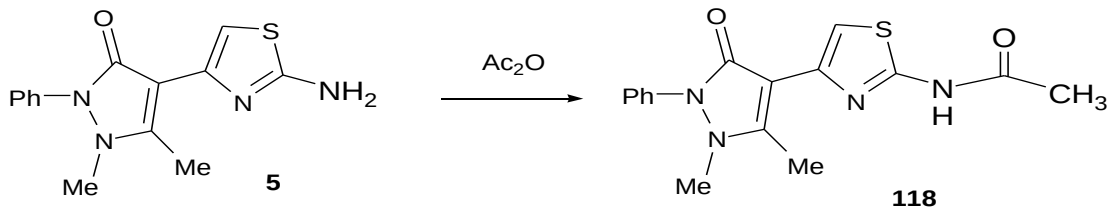
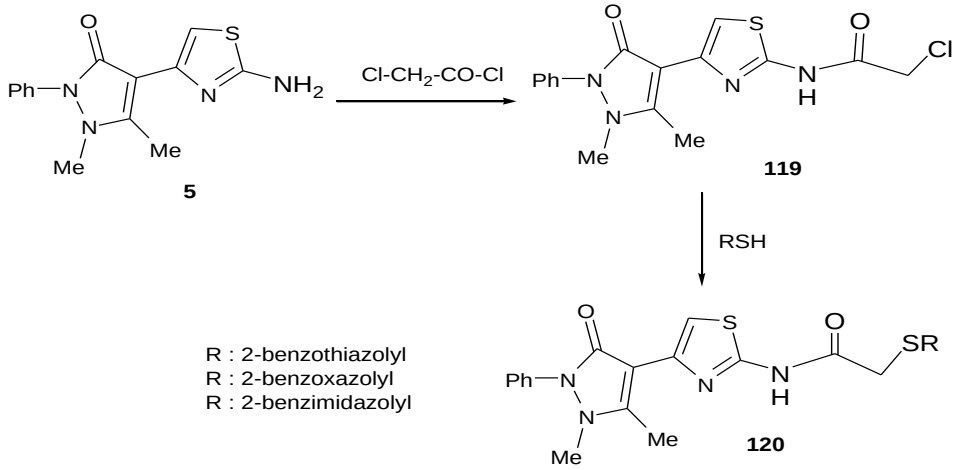


Scheme 40

II.4.2.3 Reaction with chloroacetyl chloride

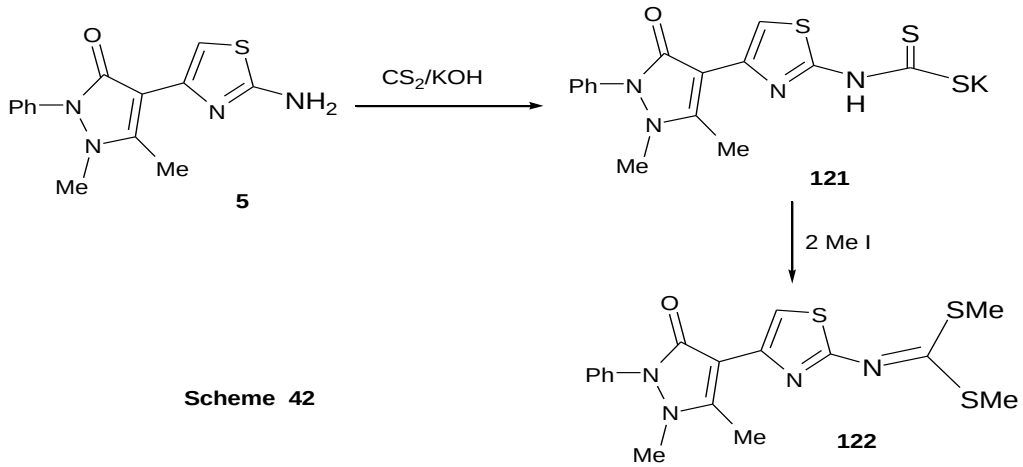
Treatment of compound **5** with chloroacetyl chloride yielded the chloro- acetyl derivative **119** which on treatment with mercapto derivatives affords the thioethers **120**[73] (Scheme 41).



Scheme 41

II.4.2.4 Reaction with carbon disulphide in alkaline medium

Compound **5** when treated with carbon disulphide in alkaline medium gave the salt **121** which on treatment with methyl iodide yields dimethyl dithiocarbonimidates **122**[73] (Scheme 42).

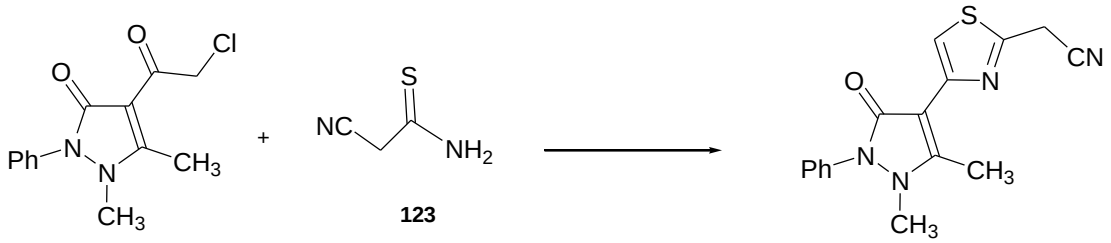


Scheme 42

II.5 [4-(1,2-Dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)-thiazol-2-yl]acetonitrile (124)

II.5.1 Preparation

Reaction of 4-chloroacetylpyrazolone **3** with 2-cyanoethanothioamide **123** in ethanol in presence of TEA afforded [4-(1,2-dihydro-1,5-dimethyl-2-phenyl-3-oxo-3H-pyrazol-4-yl)thiazol-2-yl]acetonitrile **124**[72] (Scheme 43).



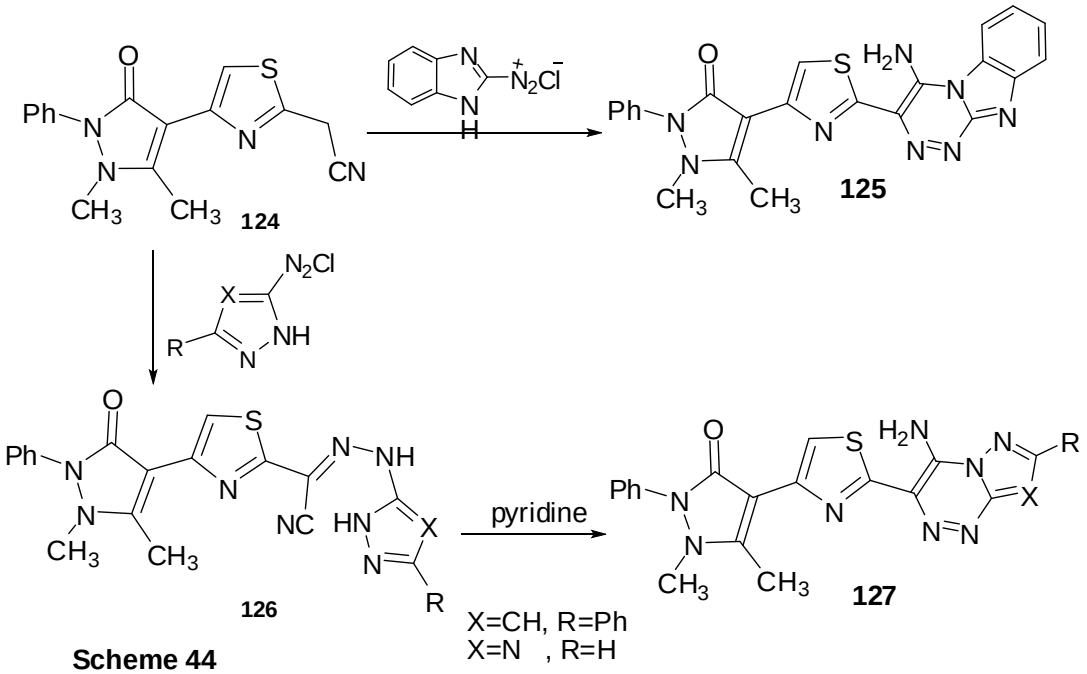
3 **123** **124**

scheme 43

II.5.2 Reactions of compounds 124

II.5.2.1 Coupling reactions

Compound **124** couples readily with the diazonium salts of aminobenzimidazole, aminotriazole and aminopyrazole and their derivatives in pyridine to give the corresponding 1,2,4-triazino[4,3-a]benzimidazole **125**, and 1,2,4-triazolo[5,1-c]1,2,4-triazine **127**, via the isolable intermediate **126**[72] (Scheme 44).



124 **125** **126** **127**

X=CH, R=Ph
X=N , R=H

Scheme 44

II.5.2.2 Reaction with aldehydes

Compound **124** reacts with benzaldehyde to afford the corresponding arylidine **128**. But **124** reacts with salicylaldehyde to afford 2-imino-chromen derivative **129** which converts to chromen-2-one **130** by hydrolysis with HCl[74,75] (Scheme 45).

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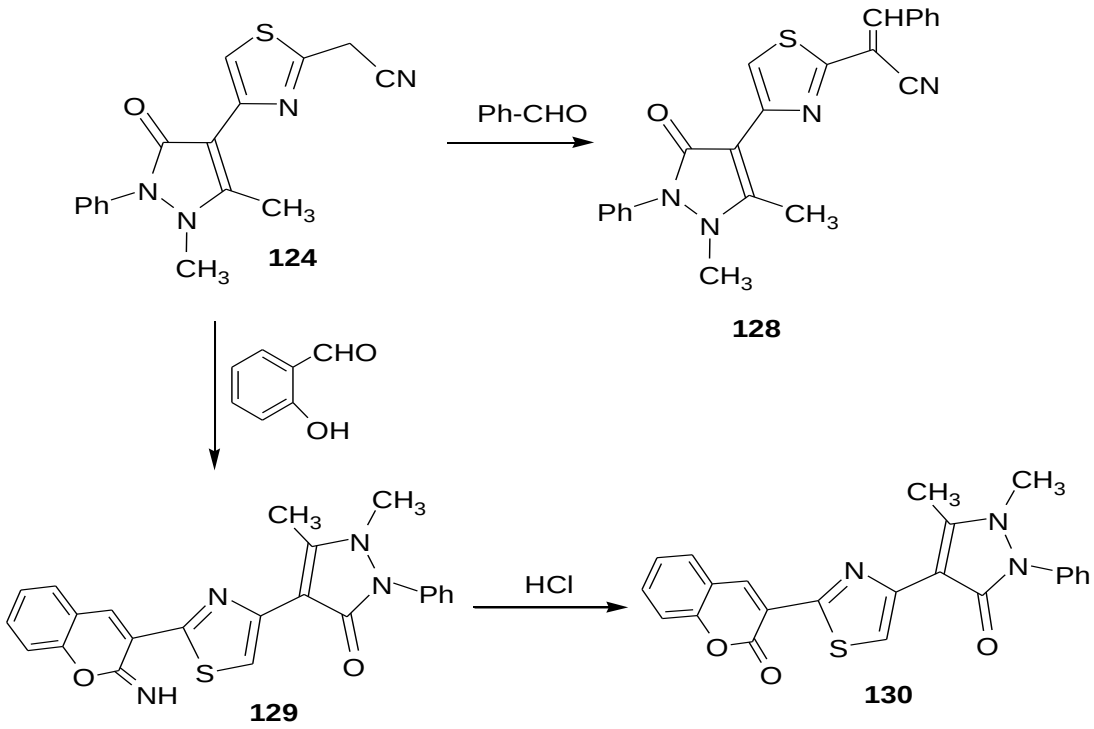

Scheme 45

Structures of dual COX- 2/5- LOX inhibitors containing pyrazole moiety (celecoxib, FBL 62064, and tepoxalin) is an important application of pyrazol derivatives [76]

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