Pyrazole-3(4)-carbaldehyde: synthesis, reactions and biological activity

Bakr F. Abdel-Wahab,[a] Rizk E. Khidre,[b,c]* and Abdelbasset A. Farahat[d]

[a]Chemistry Department, Faculty of Science and Arts, King Abdulaziz University, Khulais branch, Kingdom of Saudi Arabia
[b]Chemistry Department, Faculty of Science, Gazan University, Kingdom of Saudi Arabia;[c]Chemical Industries Division, National Research Centre, Dokki, 12622, Giza, Egypt;[d]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt
E-mail: rizkarein@yahoo.com

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Abstract

This review deals with synthesis and reactions of pyrazole-3(4)-carbaldehydes as well as their biological activity. The data on the methods of synthesis, chemical reactions, and biological activity of these heterocycles published over the last years are reviewed here for the first time.

Keywords: Vilsmeier-Haack reaction, phenylhydrazone, pyrazolecarbaldehyde, chalcone, hydroxyalkylation

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1. Introduction

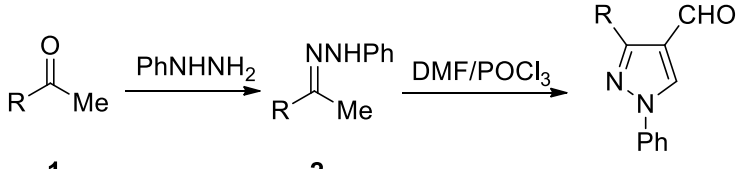
A literature survey revealed that a number of biologically active compounds have been synthesized using pyrazole-3(4)-carbaldehydes. These compounds show antimicrobial,[1-3] anti-inflammatory (COX-2 inhibitor and ulcerogenic activity),[3] antitubercular,[4] antitumor,[5,6] antiangiogenesis,[6] anti-parasitic,[7] and antiviral activity.[8] Despite this versatile importance, pyrazole-3(4)-carbaldehydes have not been previously reviewed. This review is not exhaustive; it is intended to get the reader acquainted with interesting group of synthetic organic compounds. It is the objective of this review to summarize the synthesis, the chemical reactions, and biological activity of pyrazole-3(4)-carbaldehydes till the end of 2010 and provide useful and up-to-date data for organic chemists.

2. Synthetic Methods

There have been a number of practically important routes to synthesise of pyrazole-3(4)-carbaldehydes, e.g. (*i*) Vilsmeier-Haack reaction of hydrazones, (*ii*) oxidation of the corresponding alcohols, and (*iii*) miscellaneous methods.

2.1. Vilsmeier-Haack reaction

3-Aryl(alkyl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** were obtained *via* the Vilsmeier-Haack reaction of the appropriate phenylhydrazones **2**, derived from the reaction of aryl methyl ketone **1** with phenylhydrazine (Scheme 1). [7, 9-16]



1 **2** **3**

R = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$,3-$NO_2C_6H_4$,
4-HOC_6H_4, 3-HOC_6H_4,2-HOC_6H_4, 3-$MeOC_6H_4$, 4-$CH_3C_6H_4$,
2,4-ClC_6H_3, $(CH_3)_2CH$-CH_2,phenyl, C_2H_5, n-C_3H_7,
n-C_4H_9, $CH_2CH(CH_3)_2$,$CH(CH_3)_2$, cyclohexyl

Scheme 1

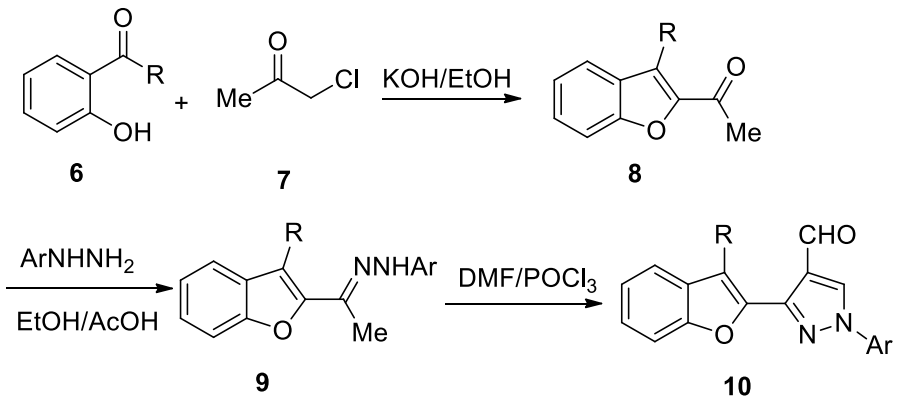
3-Substituted pyrazole-4-carbaldehyde **5** was prepared by formylation of semicarbazones **4**, derived from alkyl, phenyl, and cycloalkyl methyl ketones, with the complex of $POCl_3$ with dimethylformamide (Scheme 2).[16]

4 **5**

R = Ph, C_2H_5, n-C_3H_7, n-C_4H_9, $CH_2CH(CH_3)_2$, $CH(CH_3)_2$, cyclohexyl

Scheme 2

Salicylaldehyde (**6**, R = H) and 2-hydroxyacetophenone (**6,** R = Me) on reaction with chloroacetone **7** afforded the corresponding 2-acetylbenzofuran (**8**, R = H) and 2-acetyl-3-methylbenzofuran (**8**, R = Me) respectively. Compounds **8** on treatment with arylhydrazine in ethanol gave phenylhydrazones **9** which underwent cyclization with DMF/$POCl_3$ to produce substituted pyrazoles **10** (Scheme 3).[17]



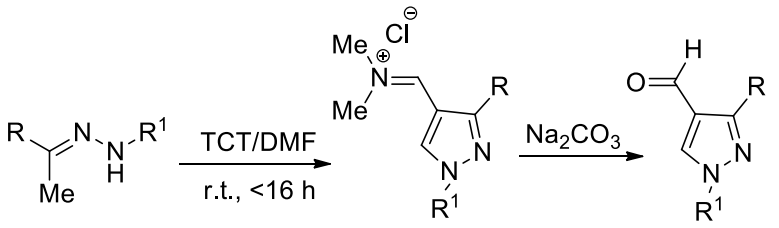
6 **7** **8**

9 **10**

R = H, CH_3; Ar = Ph, 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$

Scheme 3

A variety of 3-Aryl(alkyl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** can be prepared in good yields from the corresponding methyl ketone hydrazones **2**, upon treatment with 2,4,6-trichloro[1,3,5]triazine in *N*,*N*-dimethyl formamide at room temperature (Scheme 4).[18]



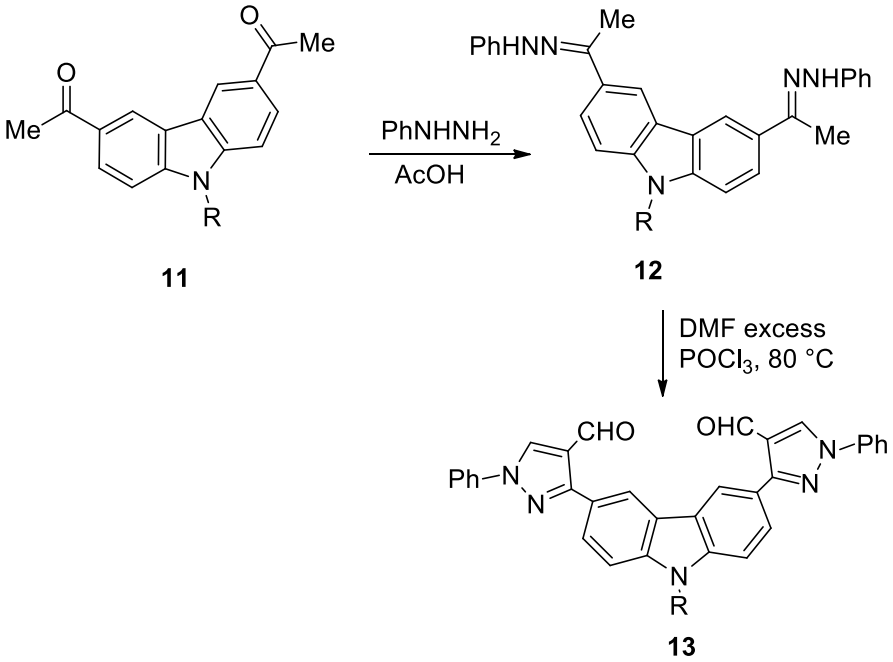
2 **3**

TCT = 2,4,6-trichloro[1,3,5]triazine

R = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-HOC_6H_4, 4-HOC_6H_4, 3,4,4-$(MeO)_3C_6H_2$, 4-ClC_6H_4, $(CH_3)_3C$-; R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4

Scheme 4

Ramu, and Rajagopal have been reported the synthesis of 3,6-di(pyrazol-4-yl)carbazoles **13**. The reaction of the Vilsmeier reagent with hydrazones of diacetylcarbazoles **12** yielded the corresponding pyrazole dicarbaldehydes **13** in good yields (Scheme 5).[19]



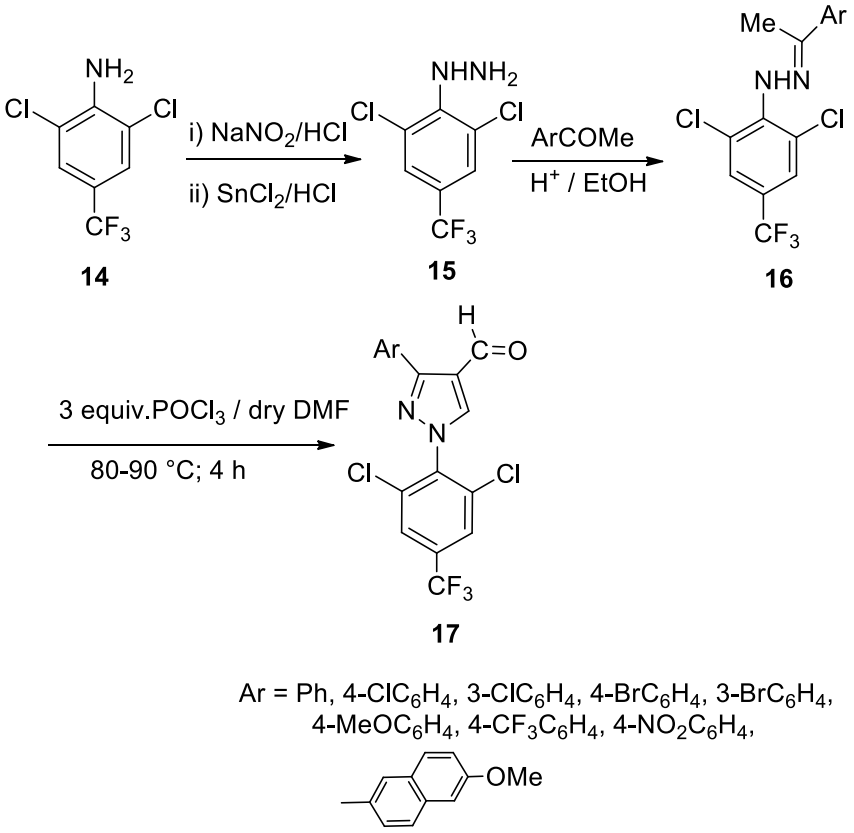
11 **12** **13**

R = Me, Et, n-Bu, CH_2Ph

Scheme 5

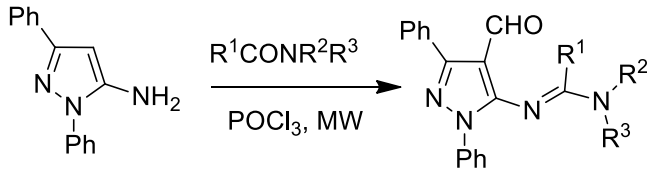
2,6-Dichloro-4-trifluoromethylphenylhydrazine **15** was synthesized from amine **14** through diazotization, followed by reduction using $SnCl_2$/HCl. Phenylhydrazones **16** were next

synthesized in almost quantitative yields by the reaction between the phenylhydrazine **15** and aryl methyl ketones. When hydrazones **16** reacted with three equivalents of Vilsmeier reagent at 80-90 °C for 4 h gave 1-[(2,6-dichloro-4-trifluoromethyl)phenyl]-3-aryl-1*H*-pyrazole-4-carbaldehydes **17** in good yields (Scheme 6).[20]



Scheme 6

N-*N*-Disubstituted-*N*`-[1,3-diphenyl-4-formyl-1*H*-pyrazol-5-yl]formimidamides **19** were synthesized by microwave irradiation of 5-amino-1,3-diphenyl-1*H*-pyrazole **18** with various amide solvents in the presence of $POCl_3$. The obtained formimidamides **19**, showed anticancer activity (Scheme 7).[21]

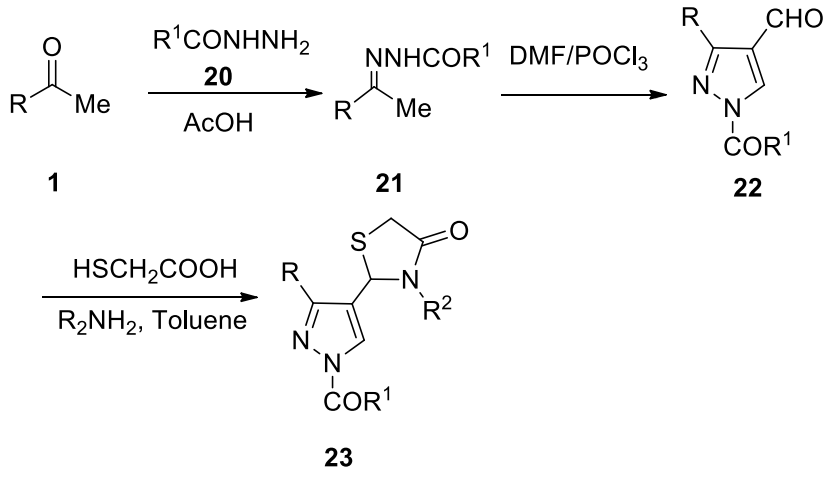


18 19

No	R^1	R^2	R^3
19a	H	Et	Et
19b	H	Pyrrolidinyl	
19c	H	Piperidinyl	
19d	H	H	Me
19e	Me	H	Me
19f	Et	H	Me
19g	Me	Me	Me
19h	Ph	Me	Me
19i	Et	Me	Me

Scheme 7

It was reported the synthesis of 3-(4-nitrophenyl)-1-(pyridin-4-ylcarbonyl)-1*H*-pyrazole-4-carbaldehyde **22**, using Vilsmeier Haack complex from *N*'-[1-(4-nitrophenyl)ethylidene]benzohydrazide **21**, which was prepared from reaction of 4-nitroacetophenone **1** and hydrazide **20**, in the presence of acetic acid. Pyrazolylthiazolidin-4-one **23**, has been synthesized by the reaction of pyrazole-4-carbaldehyde **22**, with 2-mercaptoacetic acid and different substituted aromatic amines in toluene (Scheme 8).[22]

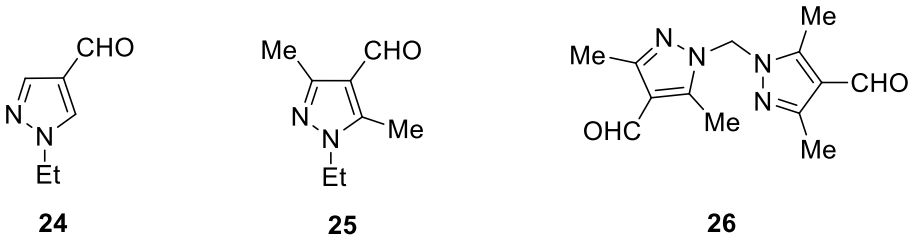


1 21 22 23

R = 4-$NO_2C_6H_4$; R^1 = 4-Pyridyl; R^2 = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-FC_6H_4, 4-BrC_6H_4

Scheme 8

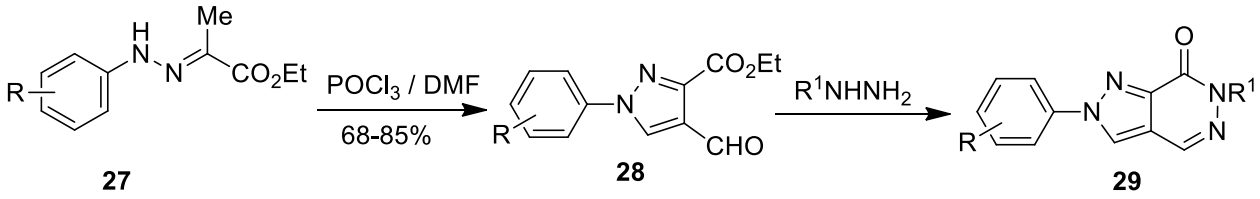
1-Ethylpyrazole-4-carbaldehyde **24**, 1-ethyl-3,5-dimethylpyrazole-4-carbaldehyde **25**, and 1,1'-methylenebis(3,5-dimethylpyrazole-4-carbaldehyde) **26**, were synthesized from the corresponding *N*-alkylpyrazoles by the Vilsmeier-Haack reaction (Figure 1).[23]



24 **25** **26**

Figure 1

Ethyl 2-(arylhydrazono)propanoates **27**, were reacted with the Vilsmeier-Haack reagent to give ethyl 1-aryl-4-formyl-1*H*-pyrazole-3-carboxylates **28**. Reactions of pyrazole derivatives with hydrazine and methylhydrazine led to the formation of the corresponding 2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-ones **29** (Scheme 9).[24,25]

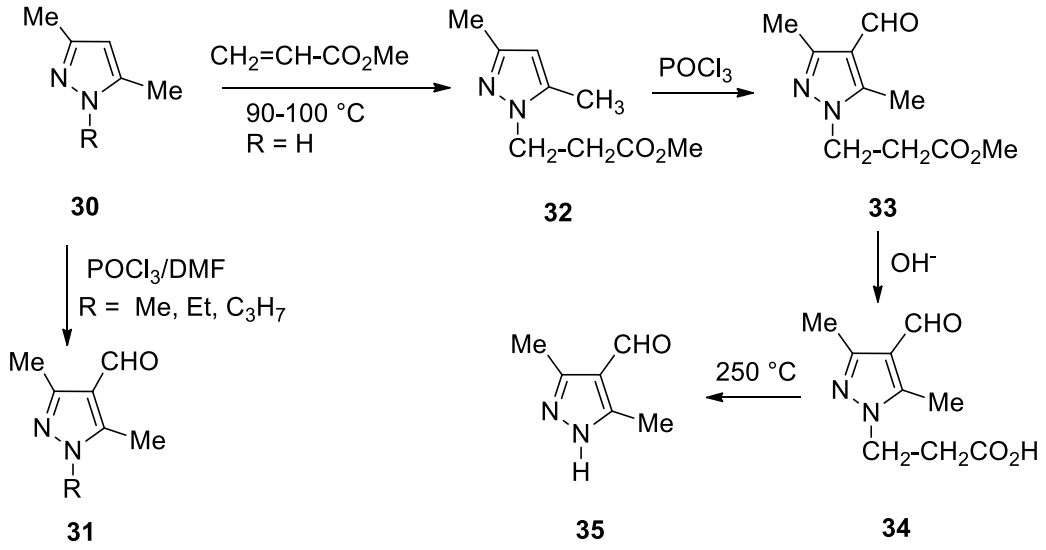


27 **28** **29**

R = H, 4-F, 2-Cl, 3-Cl, 4-Cl,3,4-Me_2, 4-MeO,3-F_3C, 2-MeOCO; R^1 = H, Me

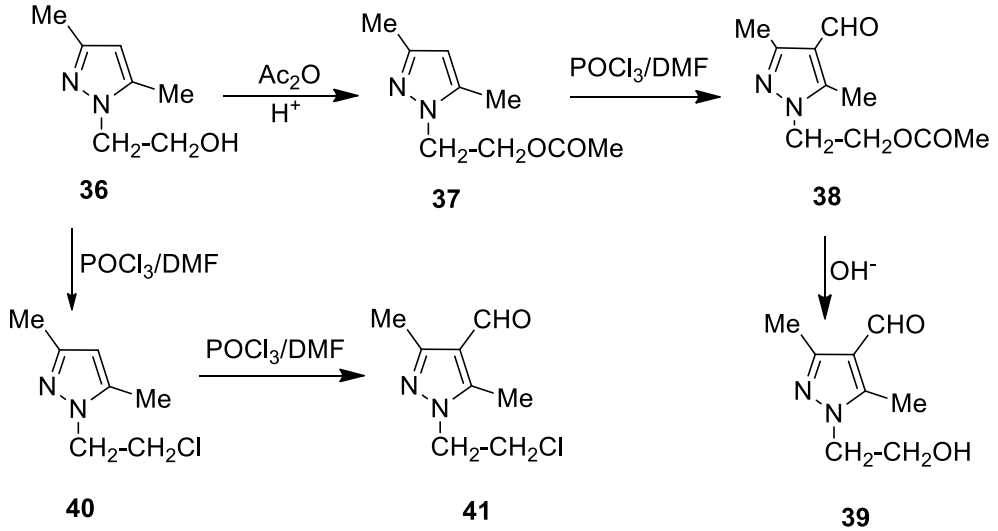
Scheme 9

Formylation of 3,5-dimethyl-1*H*-pyrazoles (**30**, R = alkyl) according to Vilsmeier-Haack, by using phosphoryl chloride in DMF at 90-120 ^oC, led to the formation of the corresponding 4-formyl derivatives **31**. In contrast, 3,5-dimethyl-1*H*-pyrazole (**30**, R = H) failed to undergo formylation at the position 4 under analogous conditions. It is presumed that electrophilic substitution in the molecule (**30**, R = H) occurs at the nitrogen atom to give ammonium ion, which hampers formylation at the 4 position. The formyl group in 3,5-dimethyl-1*H*-pyrazole-1-carbaldehyde is extremely labile and is readily eliminated by the action of basic reagents (NaOH). 3,5-Dimethyl-1*H*-pyrazole-4-carbaldehyde **35** was synthesized by reaction of (**30**, R = H) with methyl acrylate followed by reaction with $POCl_3$/DMF followed by alkaline hydrolysis of methyl *β*-(4-formyl-3,5-dimethyl-1*H*-pyrazol-1-yl)propionate **33** and subsequent heating of the acid **34** formed (Scheme 10).[26]



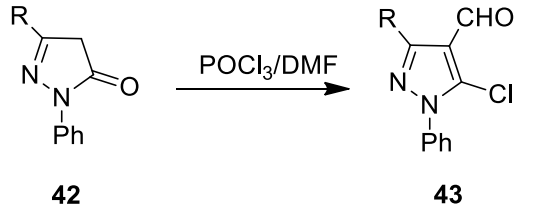
Scheme 10

1-(2-Hydroxyethyl)-3,5-dimethyl-1*H*-pyrazole **36** does not undergo Vilsmeier–Haack formylation and substitution of the hydroxyl group in the 2-hydroxyethyl moiety by chlorine atom to form compound **40**. The reaction of *N*-chloroethylpyrazole **40** with Vilsmeier reagent afforeded *N*-chloroethylpyrazole-4-carbaldehyde **41**. Synthesis of 1-(2-hydroxyethyl)-3,5-dimethyl-1*H*-pyrazole-4-carbaldehyde **39** took place by acylation of **36** with acetic anhydride to give acylated product **37**, which readily underwent Vilsmeier-Haack formylation to give **38** followed by hydrolysis as described in Scheme 11.[27]



Scheme 11

5-Chloro-1-phenyl-3-pyridin-4-yl-1*H*-pyrazole-4-carbaldehyde **43** was obtained by the reaction of 2-phenyl-5-pyridin-4-yl-2,4-dihydropyrazol-3-one **42** with dimethylformamide and phosphorus oxychloride under Vilsmeier-Haack reaction conditions (Scheme 12).[28]

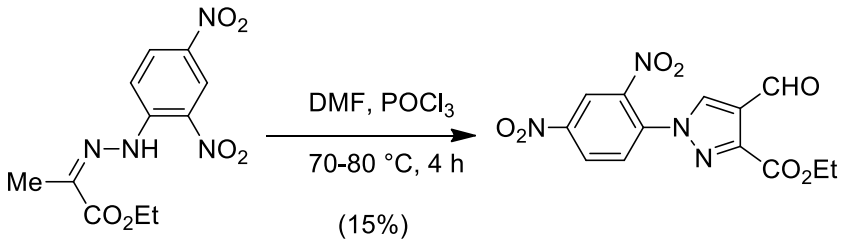


42 **43**

R = 4-Pyridyl; Ar = Ph, 4-$CH_3C_6H_4$

Scheme 12

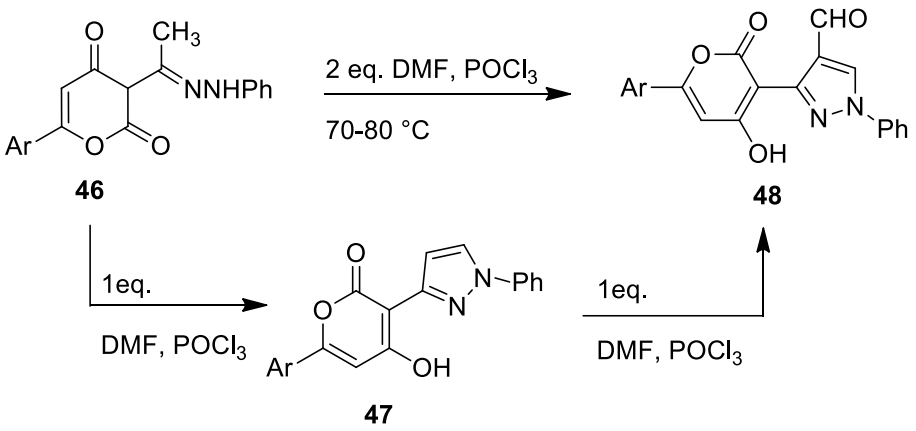
Ethyl 1-(2,4-dinitrophenyl)-4-formyl-1*H*-pyrazole-3-carboxylate **45** was prepared in 15% yield from 2,4-dinitrophenylhydrazone **44** by treatment with 8 equivalents of $POCl_3$ (Scheme 13), which has antibacterial activity against *E. coli*, *S. aureus*, *En. Faecalis and P. aeruginosa*.[29]



44 **45**

Scheme 13

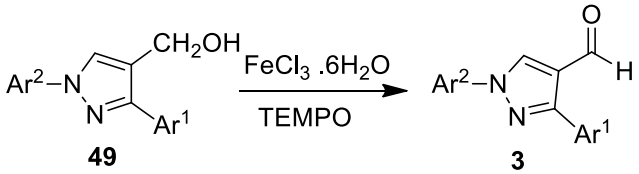
Arylhydrazones of dehydroacetic acid (DHA) **46** underwent Vilsmeier-Haack reaction to generate the corresponding 3-(4-hydroxy-2-oxo-6-aryl-2*H*-pyran-3-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **48**. However, when the reaction was performed using one equivalent of Vilsmeier reagent, 3-(pyran-2-on-3-yl)pyrazoles **47** were obtained, which underwent smooth conversion to **48** on further treatment with another equivalent of the Vilsmeier-Haack reagent (Scheme 14).[30]



Scheme 14

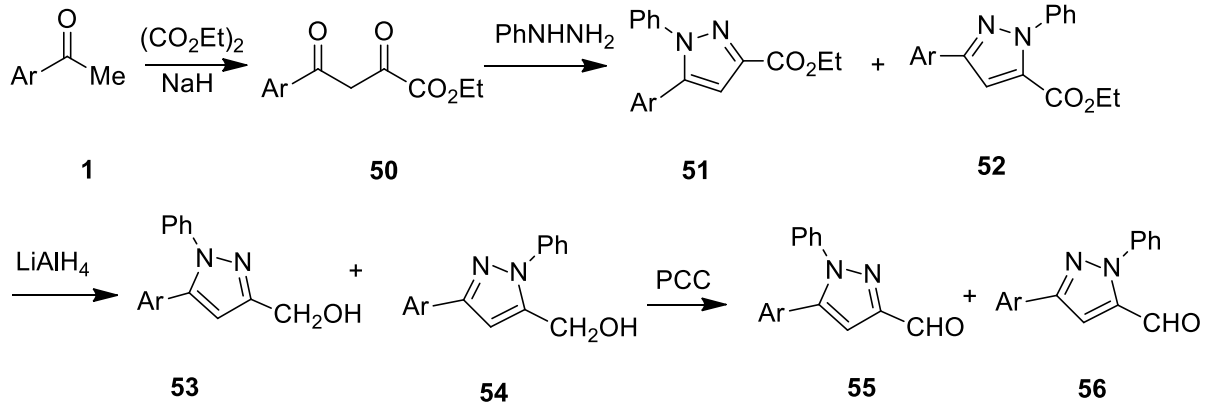
2.2. Oxidation of the corresponding alcohols

1,3-Diaryl-1*H*-pyrazole-4-carbaldehydes **3** were prepared by oxidation of the corresponding (1,3-diaryl-1*H*-pyrazol-4-yl)methanol **49** in 50-85% yields by $FeCl_3.6H_2O$ catalyzed by a free radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). This reaction gave high yield of the corresponding aldehydes with no over oxidation to carboxylic acids (Scheme 15).[31]



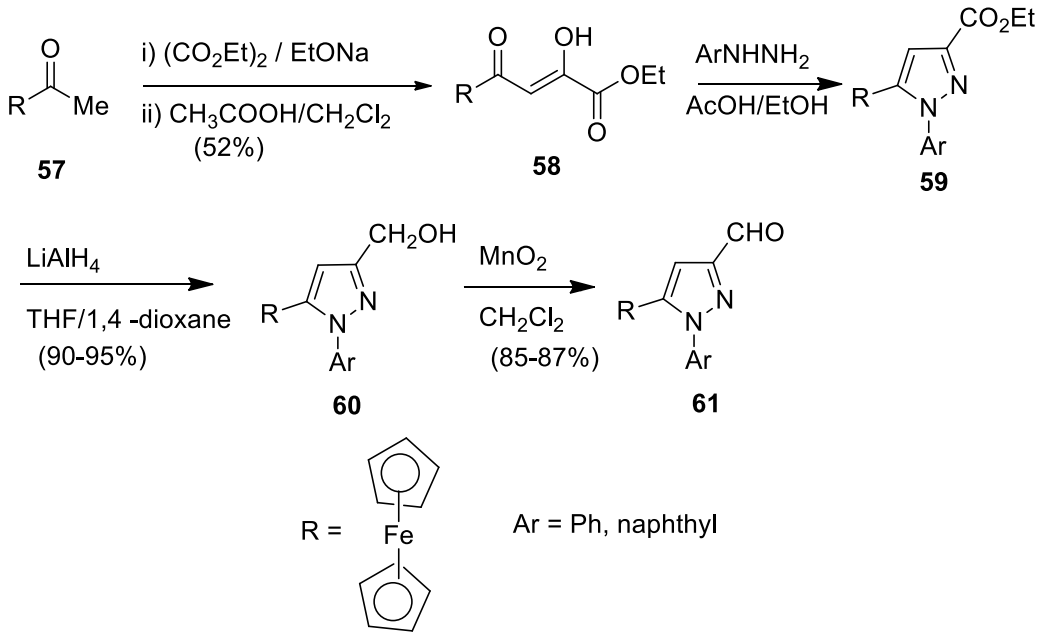
Scheme 15

Treatment of acetophenones **1** with diethyl oxalate in the presence of NaH furnished the diketoesters **50**. Reaction of **50** with phenylhydrazine in the presence of catalytic amount of TFA yielded a mixture of pyrazole esters **51** and **52**. The mixture containing both regioisomers was treated with $LiAlH_4$ in dry diethyl ether to afford the product as a mixture of **53** and **54**. Due to significant difference in the polarity of these alcohols, they were easily separated via column chromatography over silica gel. Compounds **53** were obtained as the major isomer while **54** were separated as the minor product. Subsequently, these alcohols **53** and **54** were subjected to oxidation in the presence of PCC, affording 1,5-disubstituted-1*H*-pyrazole-3-carbaldehyde **55** and 1,3-disubstituted-2*H*-pyrazole-5-carbaldehyde in 55-57% and 75-80% yields, respectively (Scheme 16).[9]



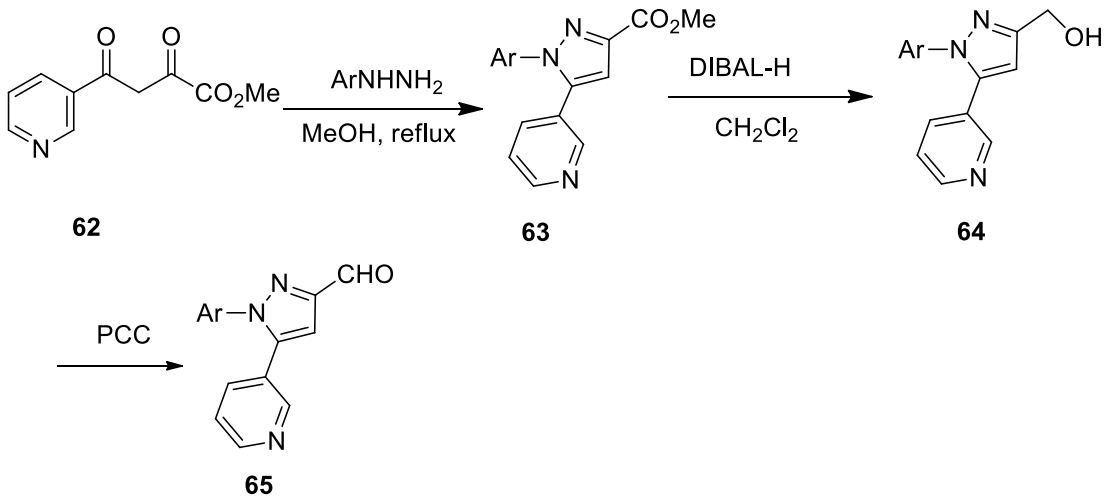
Scheme 16

Claisen condensation of acetyl ferrocene **57** and diethyl oxalate in the presence of NaOEt was reported to furnish ethyl 2,4-dioxo-4-ferrocenylbutanoate **58** in 52% yield. Esters of 1-aryl-5-ferrocenyl-1*H*-pyrazole-3-carboxylic acids **59** were synthesized in high yields by the condensation between ethyl 2,4-dioxo-4-ferrocenylbutanoate **58** (enol form) and arylhydrazines in boiling ethanol in the presence of a catalytic amount of acetic acid. The corresponding alcohols **60** were obtained by reduction of esters **59** with $LiAlH_4$ in a mixture of THF and 1,4-dioxane. Oxidation with MnO_2 in CH_2Cl_2 at room temperature led to the formation of aldehyde **61** (Scheme 17).[32]



Scheme 17

Pyridyl-2,4-dioxo-butanoate **62** was reacted with 4-(methylsulfonyl)phenylhydrazine in methanol at reflux temperature to afford **63**. The ester group in **63** was reduced with DIBAL-H to give the corresponding hydroxymethyl-(3-pyridyl)pyrazole derivative **64**. The oxidation of **64** with pyridinium chlorochromate afforded (3-pyridyl)pyrazole-4-carbaldehyde **65** (Scheme 18).[33]

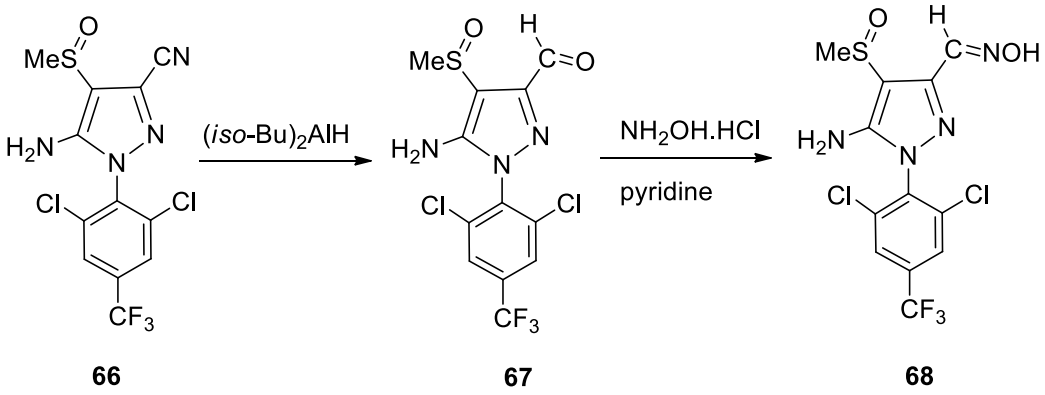


62 **63** **64** **65**

Scheme 18

2.3. Miscellaneous Methods

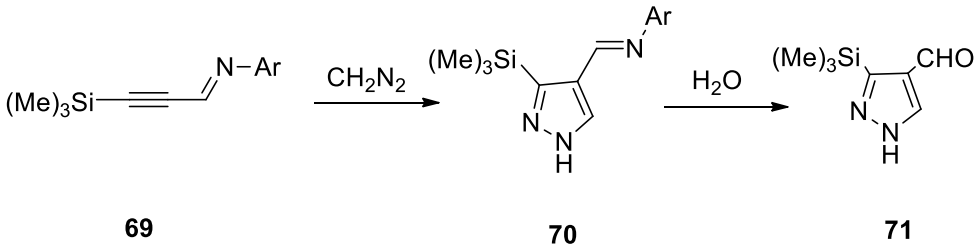
5-Amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-(methylsulfinyl)-1*H*-pyrazole-3-carbonitrile **66** was reduced to the corresponding aldehyde **67** using (*iso*-Bu)$_2$AlH. Pyrazole-3-carbaldehyde **67** was converted to oxime **68** with hydroxylamine.HCl in pyridine (Scheme 19).[34]



66 **67** **68**

Scheme 19

Hydrolysis of 4-arylaminomethyl-3-trimethylsilylpyrazoles **70**, obtained by the reaction of *α,β*-acetylenic aldimines **69** with diazomethane, afforded 3-trimethylsilyl-1,2-pyrazole-4-carbaldehyde **71** in a good yield (Scheme 20).[35]



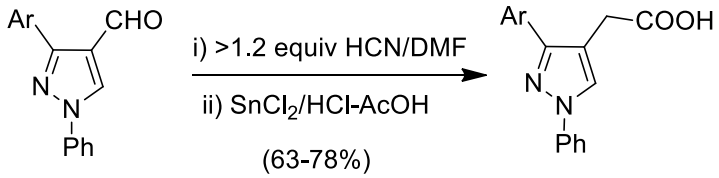
69 **70** **71**

Scheme 20

3. Chemical Reactions

3.1. Addition and reduction

1,3-Diarylpyrazol-4-ylacetic acids **72**, which are known antiinflammatories and thrombocyte aggregation inhibitors, are prepared by reaction of 1,3-diaryl-1*H*-pyrazole-4-carbaldehydes **3** with ≥ 1.2 equiv of HCN (prepared *in situ* from NaCN or KCN and an organic or inorganic acid) in a polar solvent (DMF, 2-PrOH, 2-BuOH) at 5-40 °C, to give aldehyde cyanohydrin and then reduction with 1 equiv of $SnCl_2$ in HCl-AcOH (Scheme 21).[36]

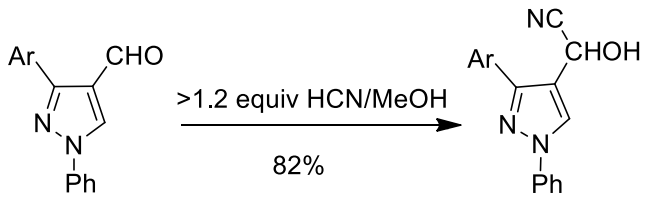


3 **72**

Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4

Scheme 21

Cyanohydrins of pyrazolecarbaldehydes **73** were prepared as intermediates for inflammation inhibitors by a safer method comprising reaction of the parent 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** with ≥ 1.2 equiv of HCN (Scheme 22).[3]

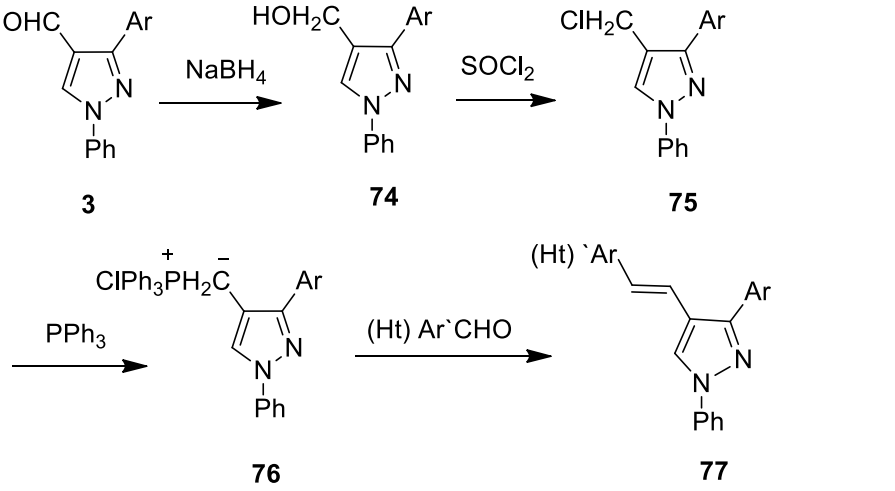


3 **73**

Ar = Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4

Scheme 22

3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** were reduced with sodium borohydride under mild conditions to give hydroxymethylpyrazoles **74** which were converted into the corresponding 4-chloromethyl derivatives **75** by treatment with thionyl chloride. The subsequent reaction with triphenylphosphine led to the formation of triphenyl(4-pyrazolylmethyl)phosphonium chlorides **76**, and Wittig reaction of the latter with aromatic or heteroaromatic aldehydes yielded 4-[2-arylethenyl]pyrazoles **77** (Scheme 23).[38]



3 **74** **75**

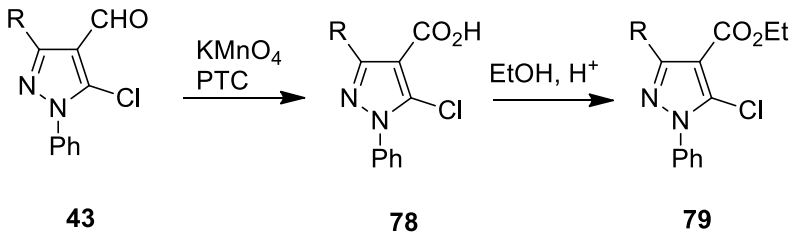
76 **77**

Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 4-PhC_6H_4, 2-thienyl; Ar` = 4-$NO_2C_6H_4$, 5-NO_2-2-furyl

Scheme 23

3.2. Oxidation

5-Chloro-1-phenyl-3-(pyridin-4-yl)-1*H*-pyrazole-4-carbaldehyde **43** was subjected to oxidation with potassium permanganate to afford pyrazole-4-carboxylic acid **78**, which converted to the corresponding ethyl ester **79** by reaction with ethanol in acidic medium (Scheme 24).[28]

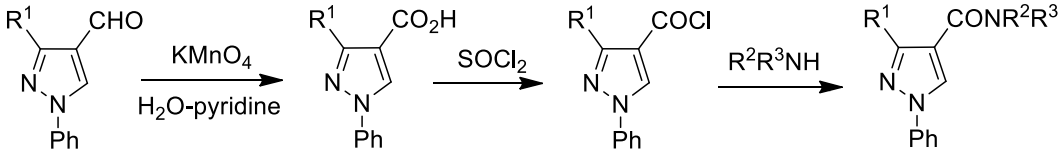


43 **78** **79**

R = 4-pyridyl

Scheme 24

3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** were cleanly oxidized by potassium permanganate in water-pyridine medium to afford the corresponding acids **80** in high yield, these were further converted into the corresponding chlorides **81** and amides **82** as depicted in Scheme 25.[39]

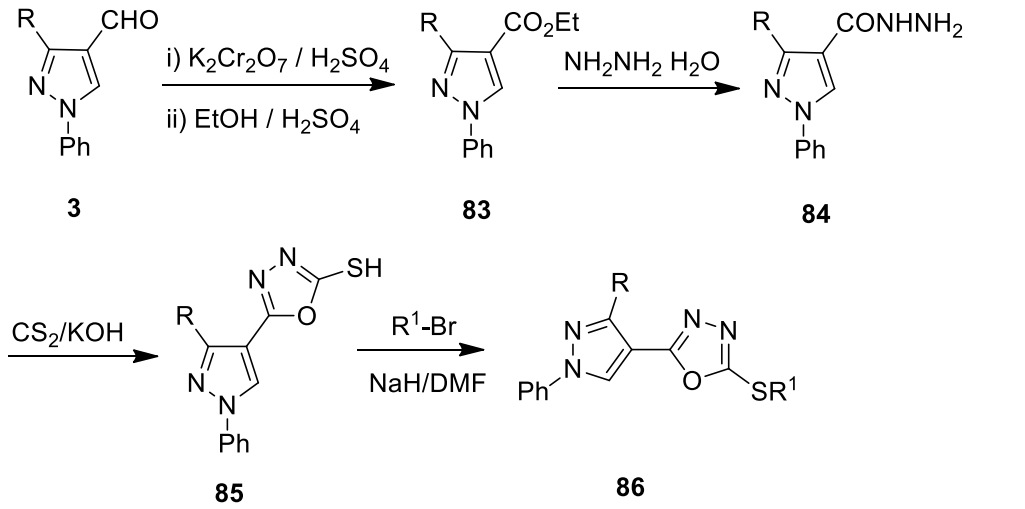


3 **80** **81** **82**

R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-EtC_6H_4, 4-PhC_6H_4, 3-pyridyl, 2-thienyl; R^2 = H, R^3 = 3-$Et_2NSO_2C_6H_4$; R^2,R^3 = 1-CH_2-2-$C_2H_4C_6H_4$; R^2 = H, R^3 = 3,5-$Cl_2C_6H_3$; R^2,R^3 = 2,2`- $C_6H_4CH_2CH_2C_6H_4$; $R^2$ = H, $R^3$ =2-tetrahydrofurylmethyl; $R^2$,$R^3$ = $(CH_2CH_2)_2NPh$; $R^2$ = H, $R^3$ = 3-morpholinosulfonylphenyl; $R^2$,$R^3$ = 2,2`-$C_6H_4CH_2CH_2C_6H_4$

Scheme 25

Abu-Zaied et al., reported the synthesis of pyrazolyloxadiazoles **86**. Thus, 3-substituted-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** were converted to 1,3,4-oxadiazole derivatives **84** by oxidation using acidic $K_2Cr_2O_7$ followed by esterification to pyrazole esters **83**, which reacted with hydrazine to give hydrazides **84**. Finally, compounds **84** were converted to pyrazolyloxadiazole **85** when reacted with carbon disulphide in KOH solution. Pyrazolyloxadiazoles **85** reacted with alkyl bromides or halosugars in the presence of basic medium to produce alkylated adducts **86** (Scheme 26).[13]

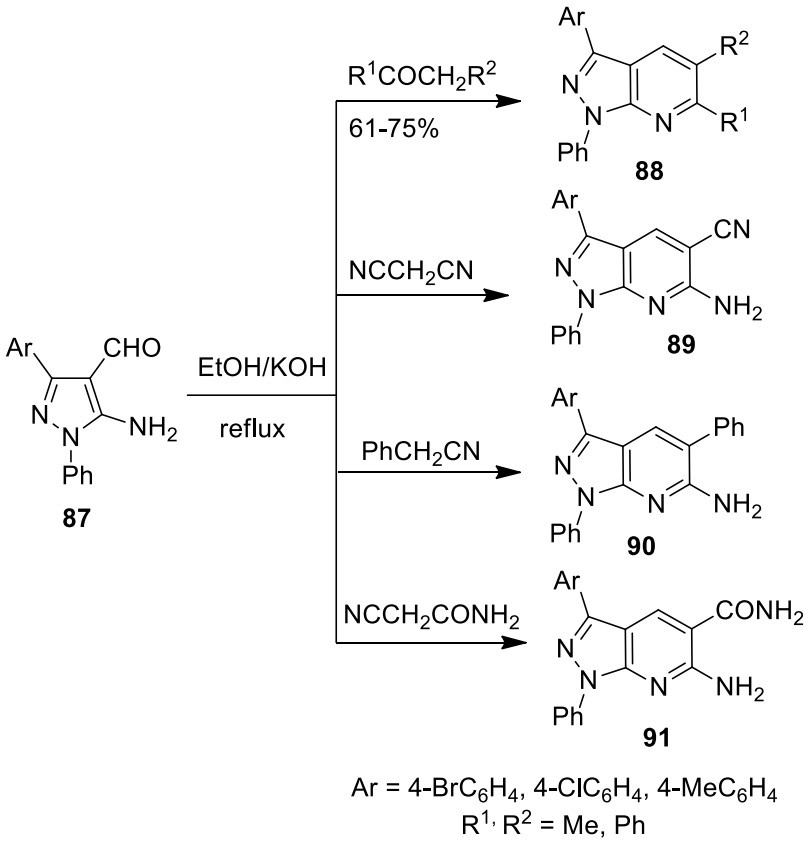


R = $(CH_3)_2CH$-CH_2; R^1 = $CH_3SCH_2CH_2$, $CH_3CH_2OCH_2CH_2$, (2,3,4,6-tetra-*O*-acetyl-α-D-gluco (or galacto)) pyranosyl

Scheme 26

3.3. Condensation reactions

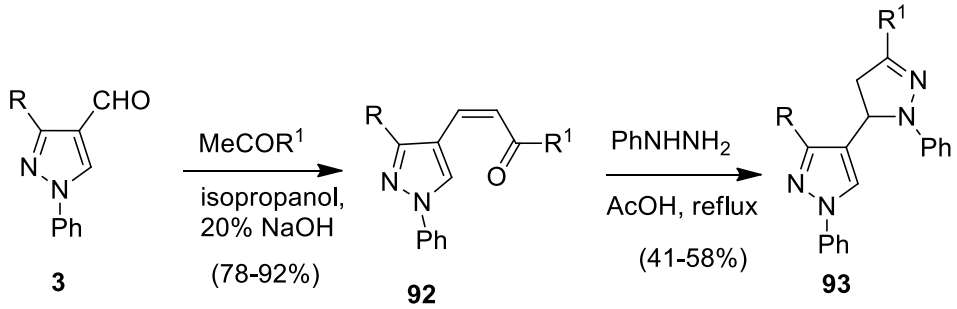
3.3.1. Reactions with active methylene compounds.1,3,5,6-Tetrasubstituted pyrazolo[3,4-*b*]pyridines **88**-**91** have been synthesized by Friedländer condensation of 5-aminopyrazole-4-carbaldehydes **87**, with active methylene compounds such as ketones, malononitrile, phenyl acetonitrile, and cyanoacetamide, respectively, in alcoholic potassium hydroxide as a basic catalyst (Scheme 27).[40-42]



Ar = 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4
R^1, R^2 = Me, Ph

Scheme 27

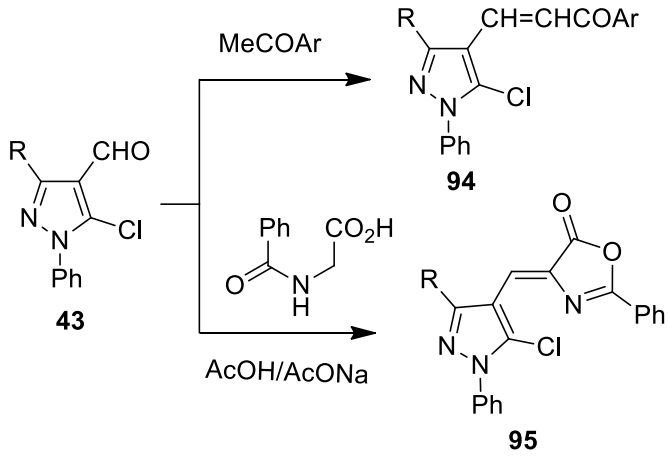
3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** underwent aldol condensation reactions with methyl ketones to give diaryl pyrazolylpropenones **92**. Chalcones **92** underwent cyclocondensation with phenylhydrazine to give pyrazolyl pyrazoline derivatives **93** useful as potential components of luminescent composite dyes (Scheme 28).[43]



R = Ph, 2-thienyl, 5-Me-2-furyl, 3-pyridyl; R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$, 2-furyl, 2-thienyl

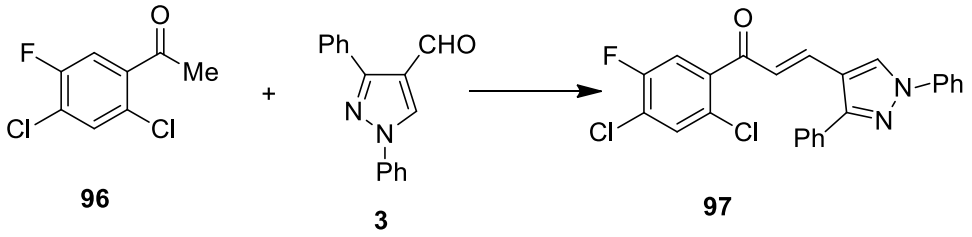
Scheme 28

5-Chloro-1-phenyl-3-(pyridin-4-yl)-1*H*-pyrazole-4-carbaldehyde **43** was allowed to react with different reagents such as aromatic ketones and hippuric acid to afford *α,β*-unsaturated ketones **94**, and 5-oxazolones **95**, respectively (Scheme 29).[28]



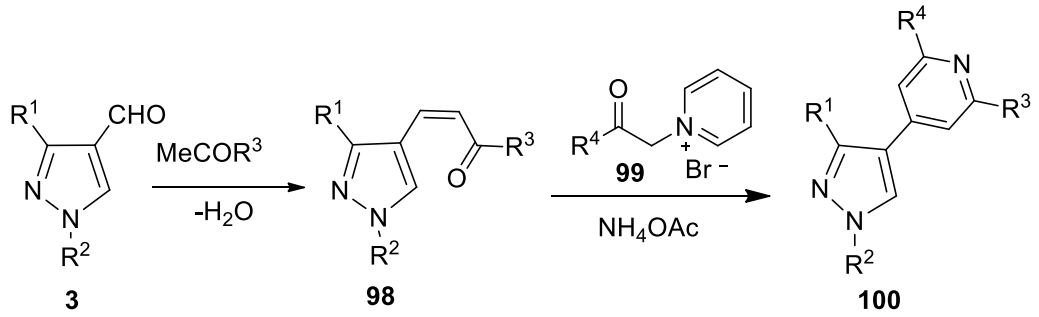
Scheme 29

2,4-Dichloro-5-fluoroacetophenone **96** was reacted with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** to give 1-(2,4-dichloro-5-fluorophenyl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one **97** (Scheme 30).[44]



Scheme 30

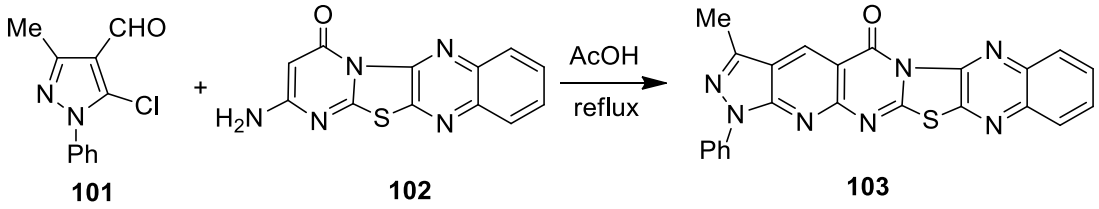
The reaction of 1,3-diaryl-1*H*-pyrazole-4-carbaldehydes **3** with various substituted acetophenones in methanol in the presence of EtONa gave the corresponding *α,β*-unsaturated ketones **98** in good yields. Refluxing **98** with different phenacyl pyridium bromides in acetic acid in the presence of ammonium acetate under Krohnke's conditions gave pyridinylpyrazoles **100** in good yields (Scheme 31).[45]



R^1 = 2,4-FC_6H_3; R^2 = 4-BrC_6H_4; R^3 = 4-ClC_6H_4 , 4-BrC_6H_4 , 4-MeC_6H_4, 4-FC_6H_4; R^4 = Ph, 4-ClC_6H_4

Scheme 31

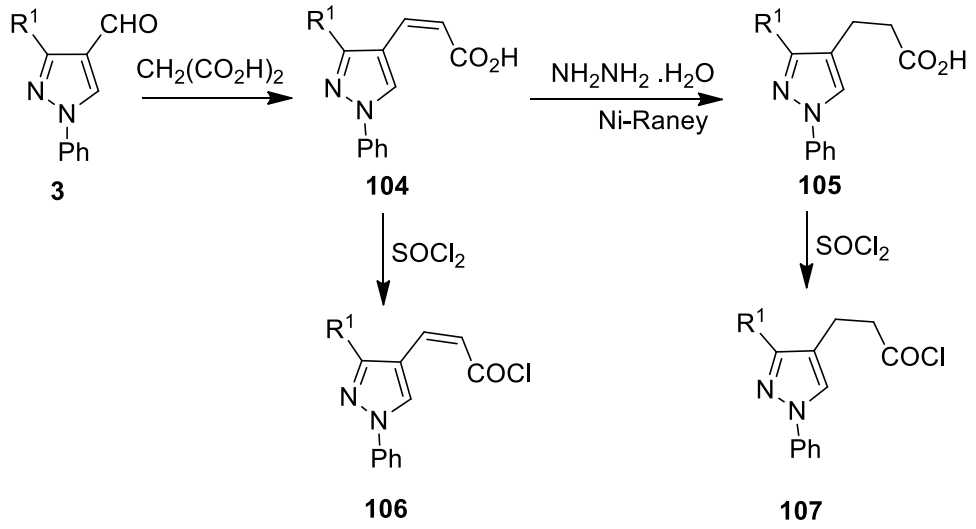
2-Aminopyrimidothiazolo[4,5-*b*]quinoxalin-4-one **102** was utilized as a key intermediate for the synthesis of pyrimidothiazolo[4,5-*b*]quinoxaline derivatives **103** *via* reaction with 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **101** in acetic acid at reflux temperature (Scheme 32).[46]



Scheme 32

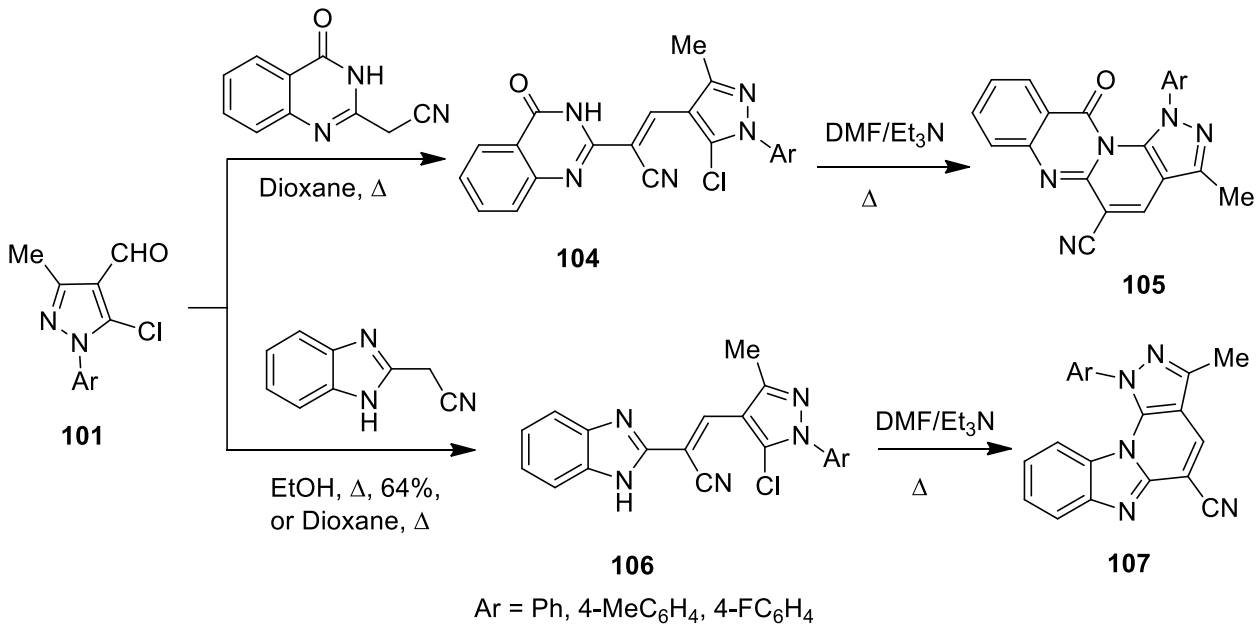
Condensation of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** with malonic acid furnished 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)propenoic acids **104,** which in the presence of *Raney* nickel reduced to the corresponding propanoic acids **105**. The successive conversion of both type acids into the corresponding acyl chlorides, was performed by reaction with thionylchloride (Scheme 33).[47]

The reaction of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)acetonitrile and 2-(1*H*-benzo[d]imidazol-2-yl)acetonitrile with 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehydes **101** in ethanol or dioxane gave the corresponding quinazolyl-2-propenenitrile **104** and benzimidazolyl-2-propenenitrile **106**, respectively. Intramolecular cyclization of the latter compounds in DMF in the presence of Et_3N afforded pyrazolo[3,4-*b*]pyrido[2,1-*b*]quinazoline-5-carbonitrile **105**, and benzo[4,5]imidazo[1,2-*a*]pyrazolo[4,3-*e*]pyridine-5-carbonitrile **107**, respectively (Scheme 34).[48]



R^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 3-pyridyl, 3-coumaryl

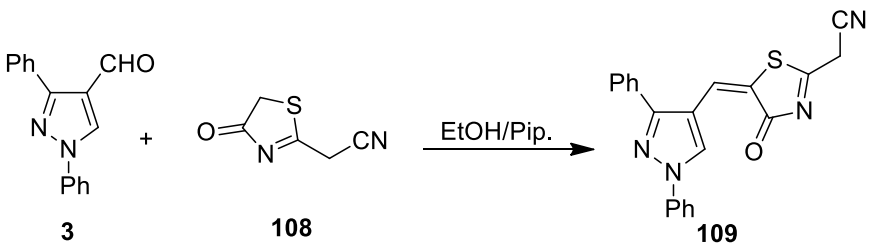
Scheme 33



Ar = Ph, 4-MeC_6H_4, 4-FC_6H_4

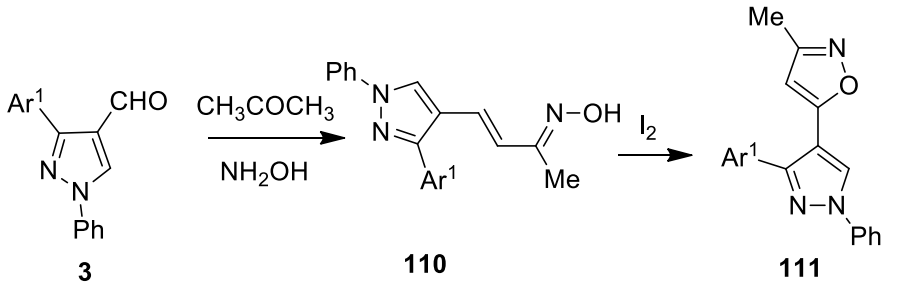
Scheme 34

Condensation of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** with 2-cyanomethyl-4-thiazolinone **108** in ethanol containing a few drops of piperidine yielded methylene derivative **109** (Scheme 35).[49]



Scheme 35

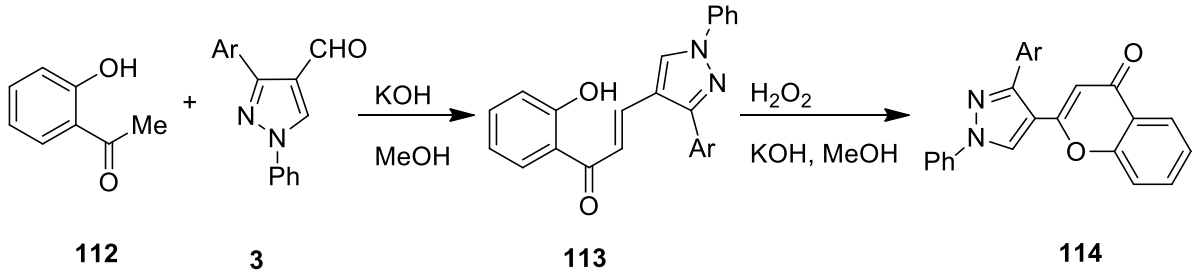
Oximes of 4-(4-pyrazolyl)-3-buten-2-ones **110**, obtained by successive reaction of **3** with acetone and hydroxylamine, upon treatment with iodine suffered an oxidative cyclization, yielding 4-(5-isoxazolyl)pyrazoles **111** (Scheme 36).[50]



Ar^1 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-EtC_6H_4, 4-$MeOC_6H_4$

Scheme 36

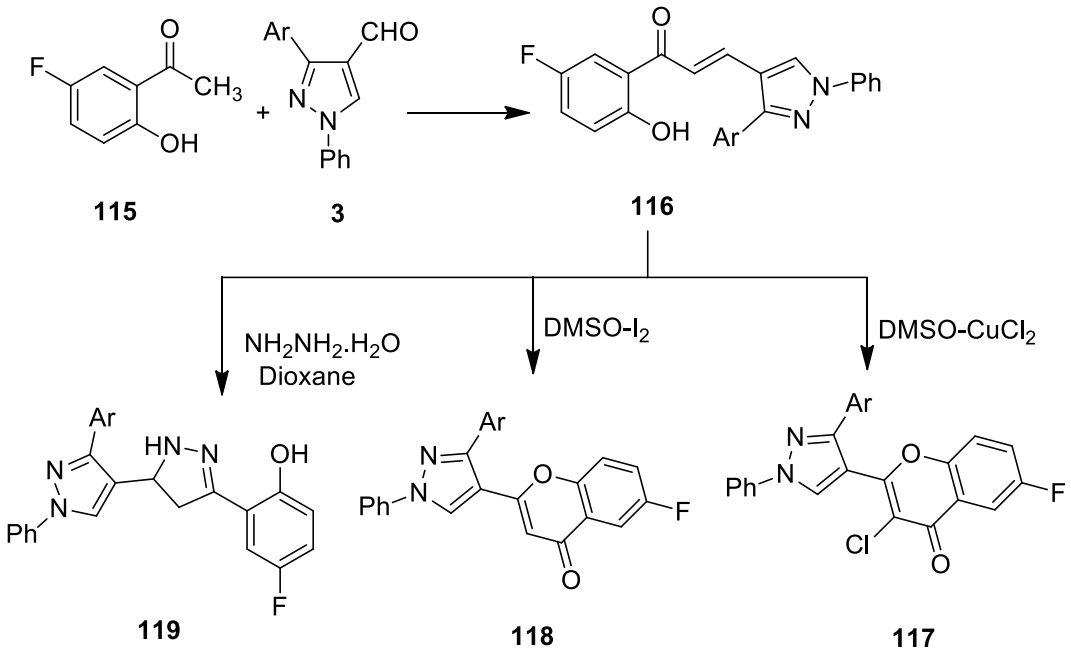
Pyrazole-4-carbaldehyde **3** was reacted with 2-hydroxyacetophenone **112** in methanol in the presence of KOH to give chalcone **113**. Oxidation of **113** with hydrogen peroxide (H_2O_2) in KOH/MeOH afforded 2-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-chromen-4-ones **114** in high yields, these compounds showed antifungal activity (Scheme 37).[51,52]



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$

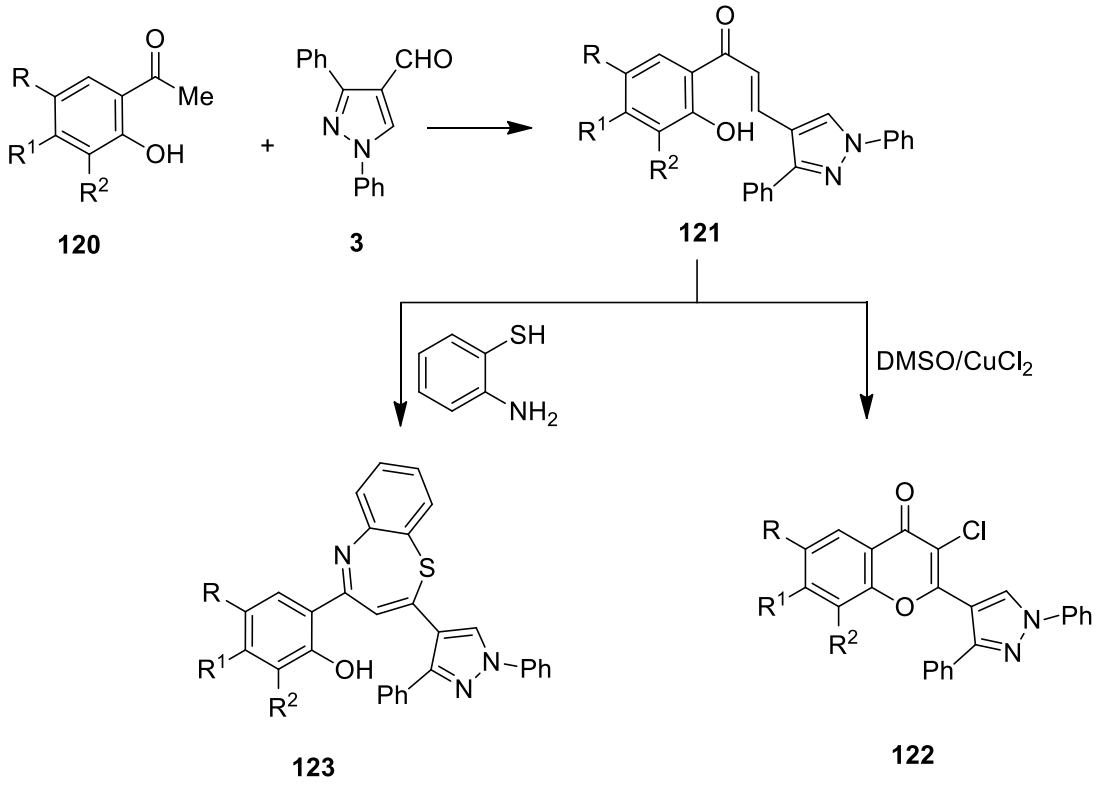
Scheme 37

Base-catalyzed condensation of 5-fluoro-2-hydroxyacetophenone **115** with 3-aryl-1-phenyl-1*H*-pyrazol-4-carbaldehyde **3**, gave 1-(5-fluoro-2-hydroxyphenyl)-3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-2-propen-1-ones **116**. On oxidative cyclization with DMSO-$CuCl_2$, **116** gave 2-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-3-chloro-6-fluorochromones **117**. On cyclization with DMSO-I_2, **116** gave 2-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-6-fluorochromones **118**. When **116** was heated with N_2H_4 in dioxane, 5-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-3-(5-fluoro-2-hydroxyphenyl)-4,5-dihydropyrazolines **119** was formed. These compounds exhibited moderate antibacterial and moderate to high antifungal activities (Scheme 38).[53]



Scheme 38

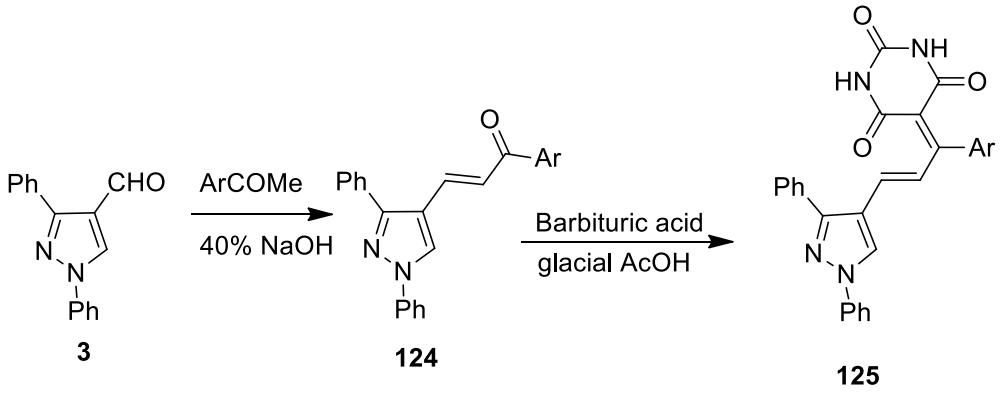
Condensation of substituted 2-hydroxyacetophenones **120** with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** produced the pyrazolylpropenones **121**, which on oxidative cyclization with DMSO/$CuCl_2$ gave the (diphenyl-1*H*-pyrazol-4-yl)chlorochromone **122**. Condensation of **121** with 2-aminothiophenol gave the benzothiazepines **123** (Scheme 39).[54]



R, R^1 = H, Me; R^2 = Me, Cl, Br

Scheme 39

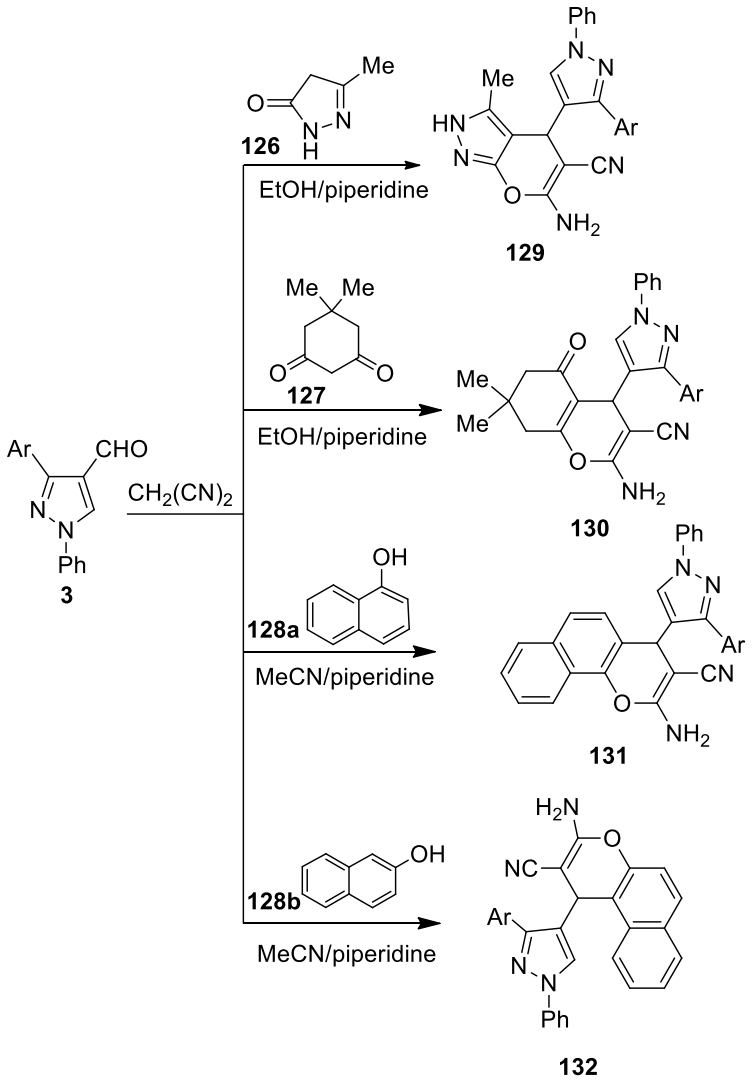
Chalcones **124** were synthesized by reaction of **3** with derivatives of aryl methyl ketone. Condesation of **124** with barbituric acid in the presence of acetic acid afford Barbitones **125** (Scheme 40).[55]



Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-HOC_6H_4, 4-HOC_6H 4-$NH_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-C_4H_3O, 2-C_4H_3S

Scheme 40

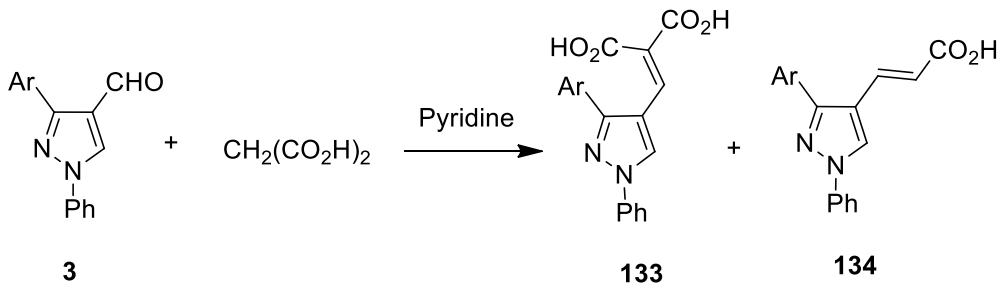
4-Pyrazolyl-4*H*-pyrazolopyran **129**, 4-pyrazolyltetrahydrochromene-3-carbonitrile **130**, and 4-pyrazolylnaphthopyrans **131** and **132** were synthesized by one-pot base-catalyzed cyclocondensation reactions of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3**, malononitrile, with substituted pyrazolin-5-ones **126**, dimedone **127**, or naphthols **128a,b**, respectively (Scheme 41). Some of these compounds tested as antimicrobial.[56]



Ar = Ph, 4-BrC_6H_4, 4-CC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 2-thienyl

Scheme 41

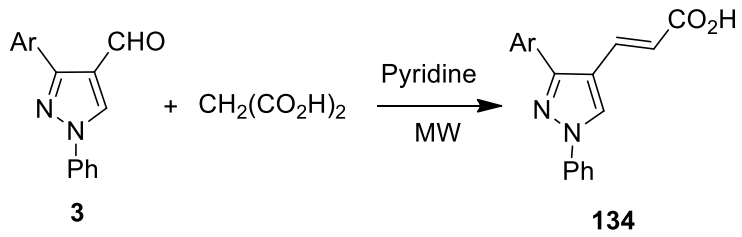
Pyrazolylacrylic acids **134** and pyrazolylmethylenemalonic acids **133** were prepared by the Knoevenagel condensation of 1,3-diaryl-1*H*-pyrazole-4-carbaldehydes **3** with malonic acid or ester (Scheme 42). Some of these compounds showed anti-inflammatory activity and were less active, but less toxic than phenylbutazone.[57]



Ar = Ph, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, biphenyl

Scheme 42

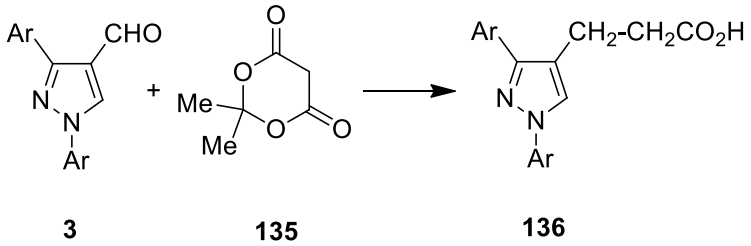
Under microwave activation, 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** reacted with malonic acid in the presence of a small amount of pyridine to give 3-(4-pyrazolyl)propenoic acids **134** in high yields (Scheme 43).[58]



Ar = Ph, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-thienyl, 3-pyridyl, 3-coumaryl, 3-NO$_2$C$_6$H$_4$, 4-PhC$_6$H$_4$, 3-NO$_2$-4-MeOC$_6$H$_3$, 2-benzofuryl, 6-benzodioxanyl

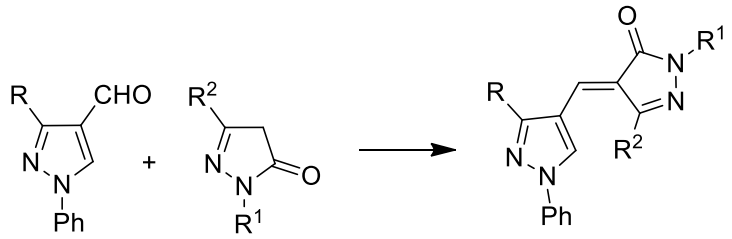
Scheme 43

A simple and rapid synthesis of 3-(1,3-diaryl-1*H*-pyrazol-4-yl)propanoic acids **136** using Meldrum's acid **135** from the corresponding aldehydes **3** was reported (Scheme 44).[59]



Scheme 44

Knoevenagel condensation of 1,3-diphenyl-1*H*-pyrazol-4-carbaldehyde **3** has been carried out with 3-methyl-1-phenylpyrazolin-5-(4*H*)-one **137** as condensing agent was carried out to give 4-pyrazolylmethylenepyrazol-5-one **138**, using Borate Zirconia (B_2O_3/ZrO_2) solid acid catalyst in aqueous medium[60] or an ionic liquid (ethylammonium nitrate) at room temperature (Scheme 45).[61] In each conversion, the catalyst was successfully recovered and recycled without significant loss in yield and selectivity. On the other hand these compounds were synthesized by traditional, microwave, and ultrasonic irradiations.[62-67]

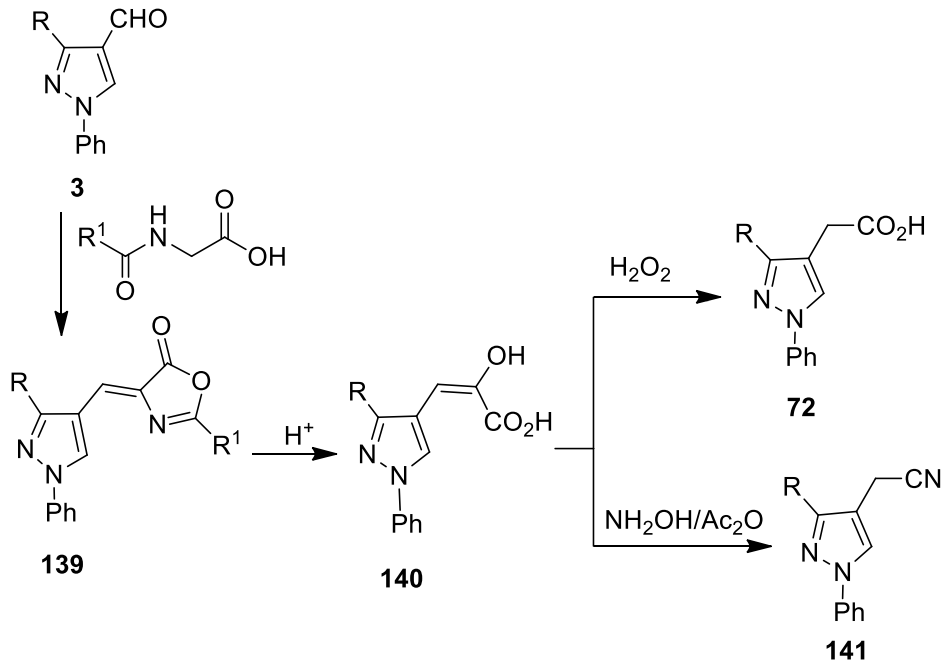


3 **137** **138**

R = C_3H_7, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4
4-BrC_6H_4; R^1 = Ph, 4-$NO_2C_6H_4$; R^2 = Me, CF_3

Scheme 45

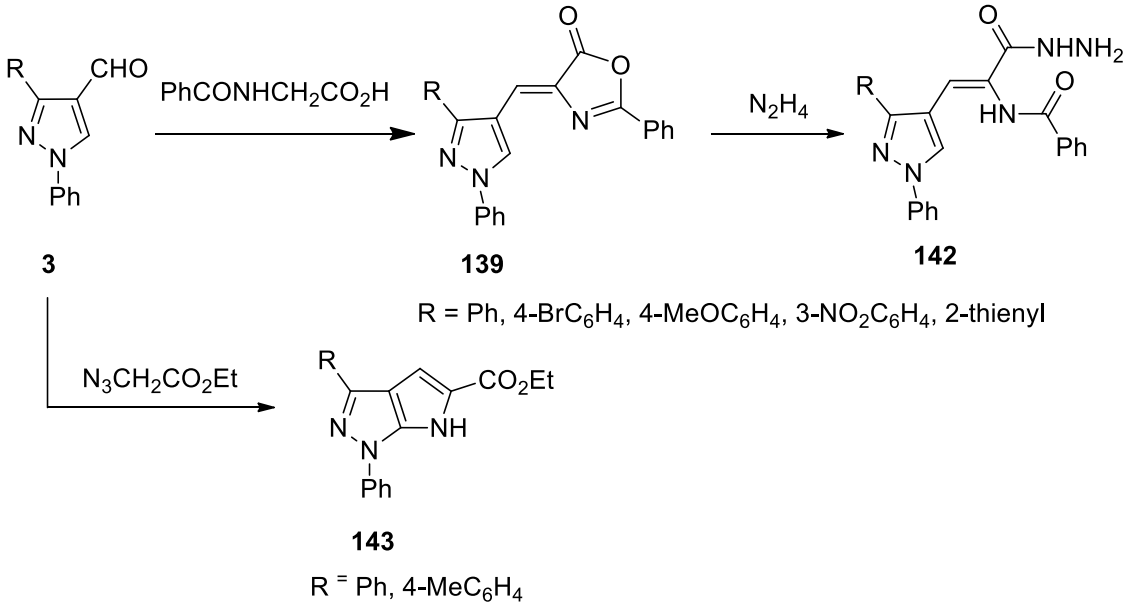
Pyrazolylmethyleneoxazolones **139** were prepared by condensation of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** with acylglycine and hydrolysed to give 3-aryl-1-phenyl-4-pyrazolylpyruvic acids **140**. These were converted to pyrazole-4-acetic acids **72** and pyrazole-4-acetonitriles **141** by oxidative decarboxylation using H_2O_2 and reaction with a mixture of hydroxylamine and acetic anhydride, respectively (Scheme 46).[68,69]



R = Ph, 4-ClC$_6$H$_4$, 2-thienyl; R^1 = Me, Ph

Scheme 46

Reactions of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** with various reagents, such as benzoylglycine, and ethyl azidoacetate, gave 4-(4-pyrazolidene)-1,3-oxazol-5-ones **139**, and pyrrolopyrazoles **143**, respectively. Treatment of **139** with hydrazine afford the corresponding hydrazides **142** (Scheme 47).[70,71]

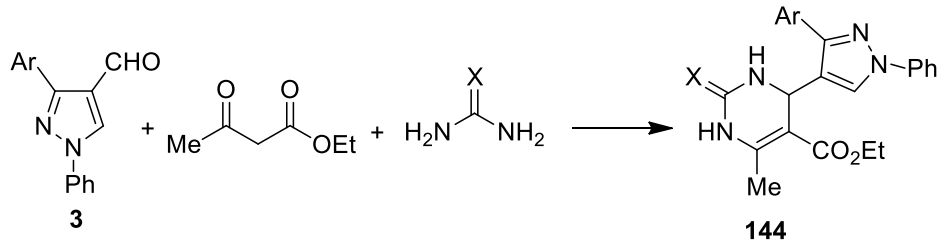


R = Ph, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 2-thienyl

R = Ph, 4-MeC$_6$H$_4$

Scheme 47

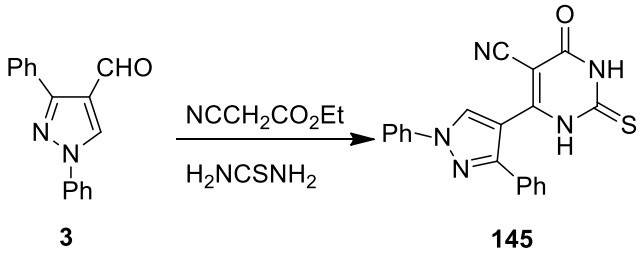
Biginelli coupling reaction of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** with ethyl acetoacetate and urea (thiourea) in the presence of $FeCl_3.6H_2O$,[72] phosphotungstic acid or a Keggin's type heteropoly acid,[73,74] afforded 4-(3-aryl-4-pyrazolyl)-1,2,3,4-tetrahydropyrimidin-2-ones (thiones) **144** (Scheme 48).



Ar = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-thienyl
X = O,S

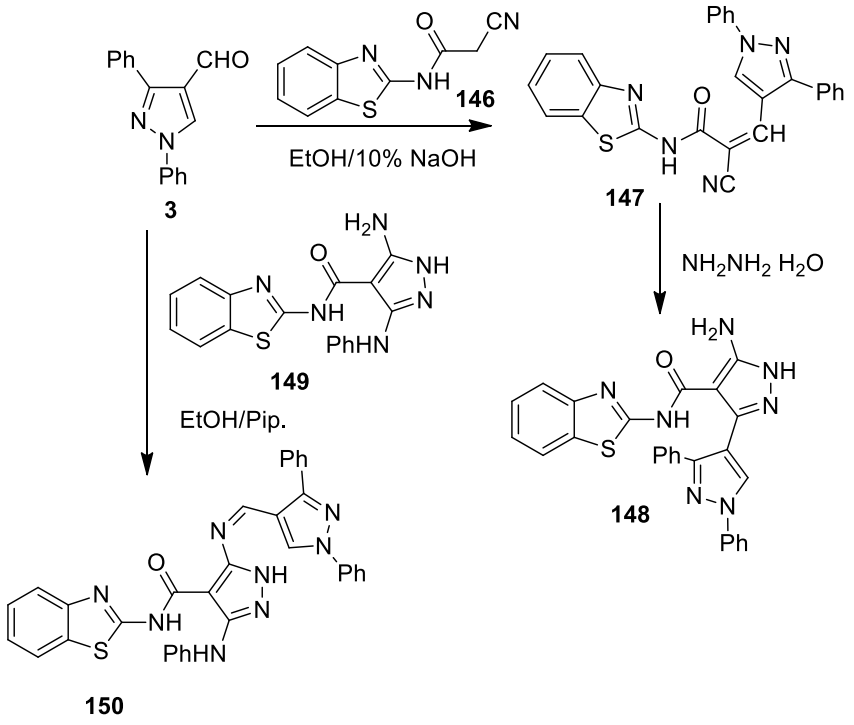
Scheme 48

1,3-Diphenyl-1*H*-pyrazole-4-carbaldehyde **3** was reacted with ethyl cyanoacetate and thiourea to give the pyrimidinethione **145** (Scheme **49**).[75]



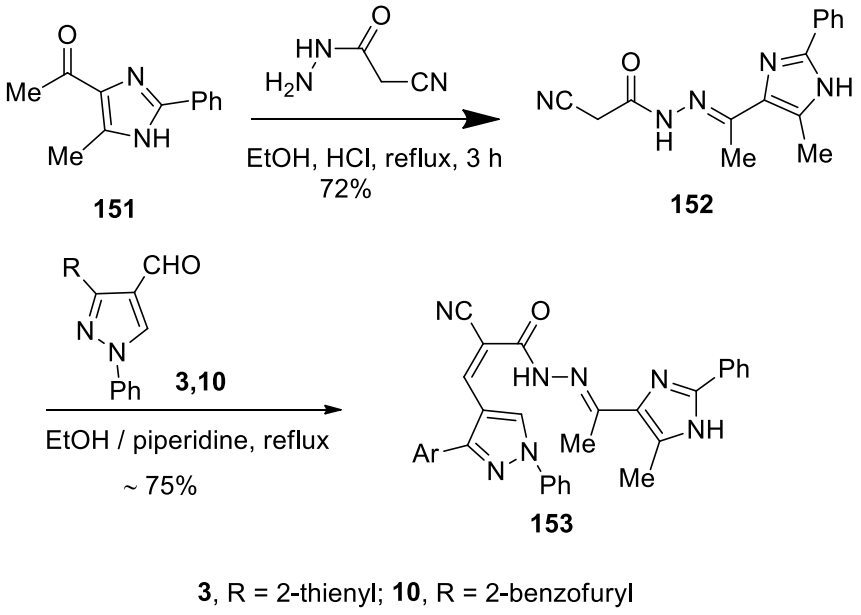
Scheme 49

The Knoevenagel condensation of *N*-(benzothiazol-2-yl)-2-cyanoacetamide **146** with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** in ethanolic sodium hydroxide (10%) afforded *N*-(benzothiazol-2-yl)-2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acrylamide **147**, and then addition of hydrazine hydrate to the activated double bond of the compound **147** in boiling ethanol afforded 5-amino-*N*-(benzothiazol-2-yl)-1`,3`-diphenyl-1*H*,1`*H*-3,4`-bipyrazole-4-carboxamide **148**. In addition, the condensation of 5-amino-*N*-(benzo[*d*]thiazol-2-yl)-3-(phenylamino)-1*H*-pyrazole-4-carboxamide **149** with **3** in boiling ethanol in the presence of a catalytic amount of piperidine furnished the corresponding Schiff's base **150** in an excellent yield (Scheme 50).[76]



Scheme 50

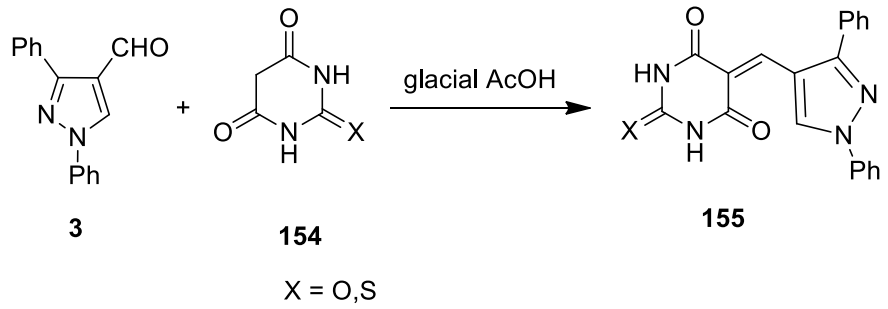
Cyanoacetylhydrazine was reacted with 4-acetyl-5-methyl-2-phenylimidazole **151** to give the hydrazide-hydrazone derivative **152**. The reaction of **152** with 3-heteroyl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** and **10** gave the knoevenagel adducts **153** in high yields (Scheme 51).[77]



3, R = 2-thienyl; **10**, R = 2-benzofuryl

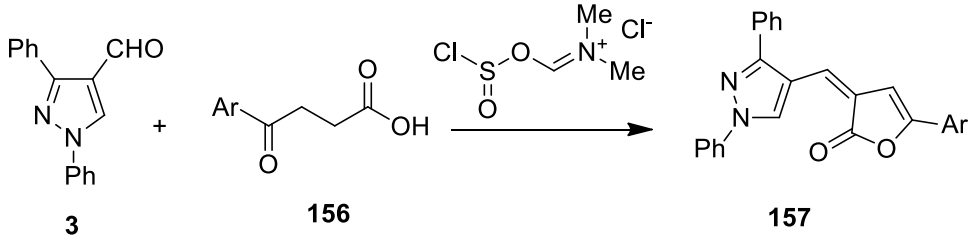
Scheme 51

Knoevenagel condensation of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehydes **3** with barbituric acid (**154**, X = O), thiobarbituric acid (**154**, X = S) in glacial AcOH gave the condensation products **155**. The synthesized barbitones (**155**, X = O) and thiobarbitones (**155**, X = S) showed antibacterial and antifungal activities (Scheme 52).[78]



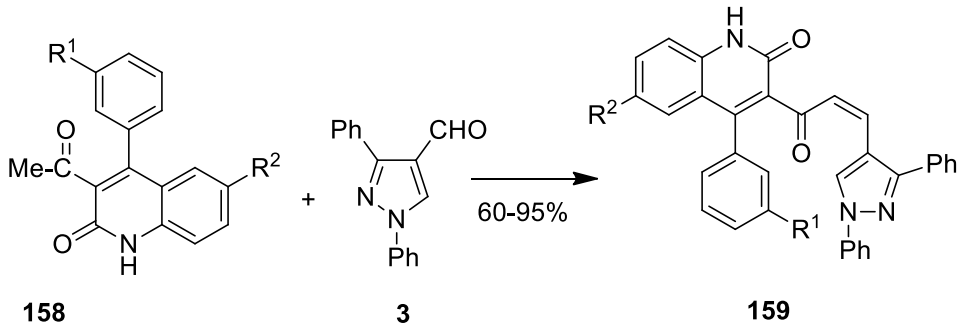
Scheme 52

5-Aryl-3-(1,3-diphenylpyrazol-4-ylmethylene)-2(3*H*)-furanones **157** were prepared by condensing 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** with 3-aroylpropionic acids **156** in the presence of *N*,*N*-dimethyl(chlorosulfinyloxy)methaniminium chloride as a cyclodehydrating agent (Scheme 53).[79]



Scheme 53

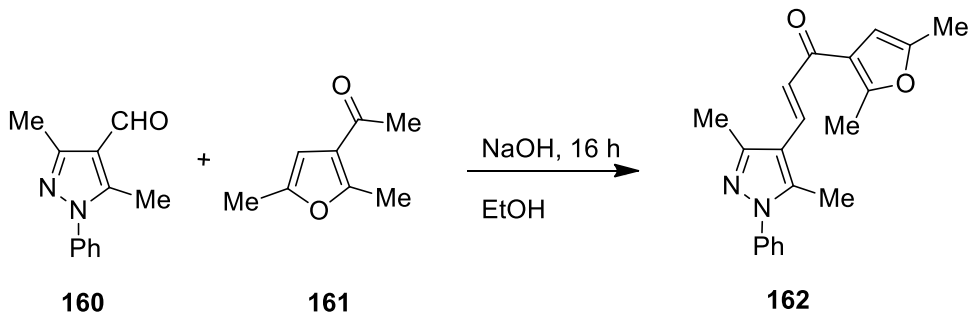
The crotonic condensation of 3-acetylquinolones **158** with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **3** gave *α,β*-unsaturated ketones **159** (Scheme 54).[80]



R^1 = H, Cl; R^2 = Br, Cl

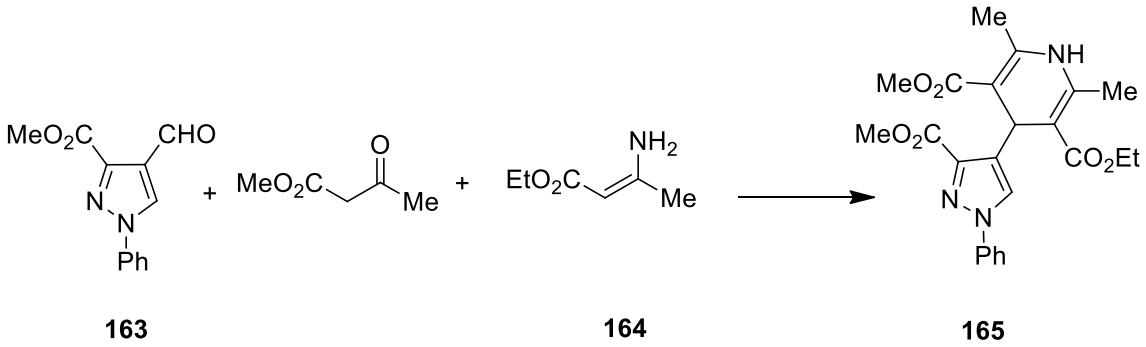
Scheme 54

3-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-1-(2,5-dimethyl-3-furanyl)prop-2-en-1-one **162** was synthesized in a high yield by an aldol condensation between 3-acetyl-2,5-dimethylfuran **161** and 3,5-dimethyl-1-phenylpyrazole-4-carbaldehyde **160** in ethanolic NaOH at room temperature (Scheme 55).[81]



Scheme 55

Cyclocondensation reaction of methyl 4-formyl-1-phenyl-1*H*-pyrazole-3-carboxylate **163** with methyl acetoacetate, and ethyl 3-aminocrotonate **164** in the presence of 3,4,5-trifluorobenzeneboronic acid, gave 3-ethyl 5-methyl 4-(3-methoxycarbonyl-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxilate **165** in 92% yield (Scheme 56).[82]

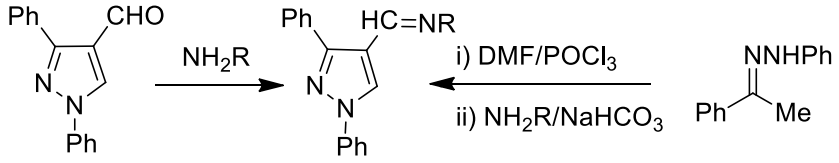


163 **164** **165**

Scheme 56

3.3.2. Reactions with semicarbazide, thiosemicarbazide, and hydroxylamine

1,3-Diphenyl-1*H*-pyrazole-4-carbaldehyde **3** was reacted with hydrazine, semicarbazide, thiosemicarbazide, or hydroxylamine affording the corresponding azomethines **166**, **167**, **168**, and **169** respectively which have antibacterial and antifungal activities.[78] On the other hand, the one-pot synthesis of hydrazone, semicarbazone, thiosemicarbazone, and oxime, derivatives of pyrazole-4-carbaldehydes **166-169** was accomplished by the Vilsmeier-Haack reaction of acetophenone phenylhydrazones **2** under a new workup procedure (i.e. treatment with hydrazine, semicarbazide, thiosemicarbazide, or hydroxylamine, followed by $NaHCO_3$) (Scheme 57).[15,83]

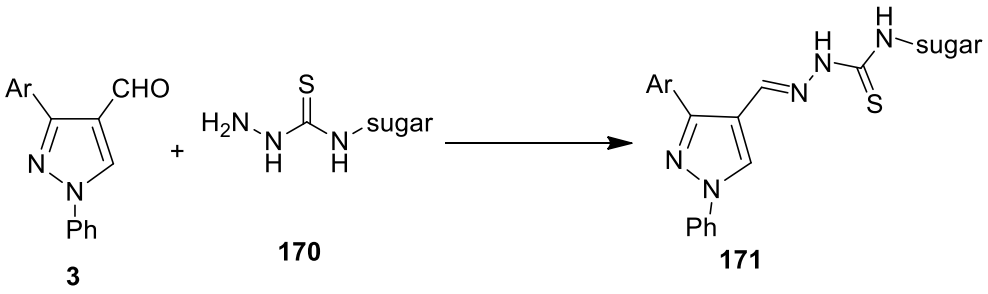


3 **166-169** **2**

166, R = NH_2; **167**, R = NH_2CONH-;
168, R = NH_2CSNH-; **169**, R = OH

Scheme 57

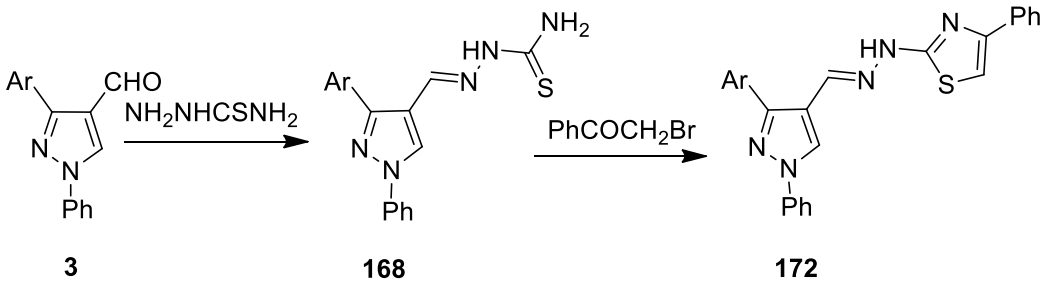
A series of *N*-glycosyl-*N'*-pyrazolylmethyleneaminothioureas **171** was synthesized *via* condensation of *N*-glycosyl-*N'*-aminothioureas **170** with 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** (Scheme 58).[84]



Ar = 4-$MeOC_6H_4$; sugar = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl, 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl

Scheme 58

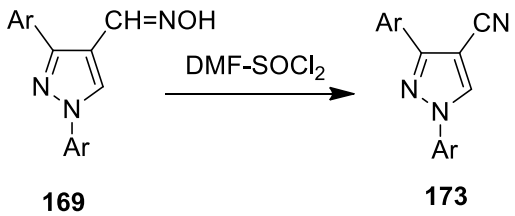
2,4-Disubstituted thiazole derivatives were synthesized by the reaction of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** with thiosemicarbazide to give thiosemicarbazone **168**. The latter compound underwent reaction with phenacyl bromide to give 2-(2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)-4-phenylthiazole **172** which have antibacterial activity (Scheme 59).[85]



Ar = Ph, 2-thienyl

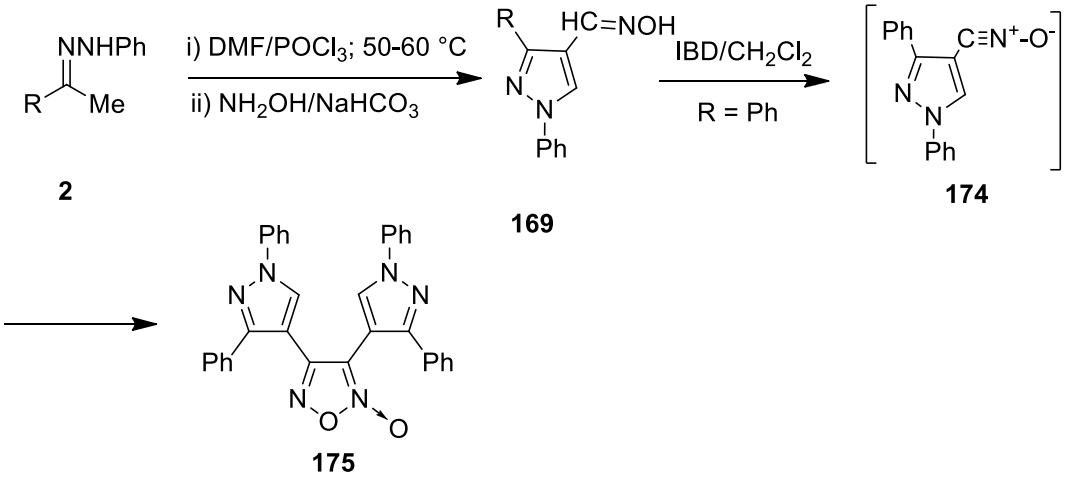
Scheme 59

Synthesis of 1,3-diaryl-4-cyanopyrazole **173** from the corresponding aldoxime **169** using dimethylformamide-thionyl chloride complex was reported (Scheme 60).[86]



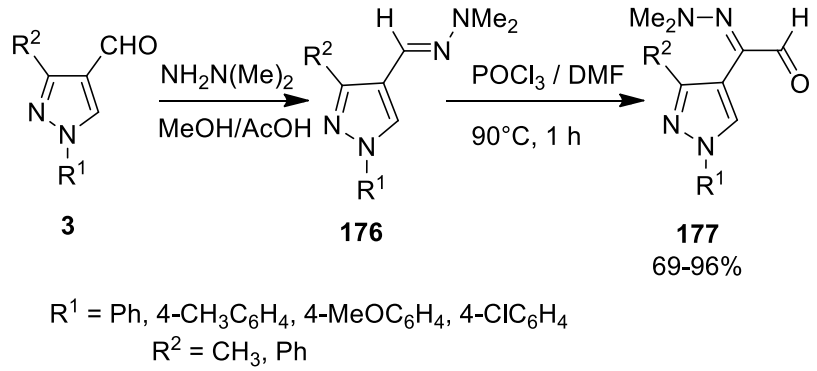
Scheme 60

The pyrazole-4-carbaldehyde oximes **169** were prepared by one-pot procedure involving Vilsmeier-Haack reaction of acetophenonephenylhydrazones **2**. Pyrazole-4-carbaldehyde oxime **169** was treated with iodobenzene diacetate (IBD, 1.1 equivalents) in dichloromethane at room temperature. A rapid reaction occurred and 3,4-bis(1,3-diphenylpyrazolyl)-1,2,5-oxadiazole-*N*-oxide **175** was obtained (Scheme 61).[87]



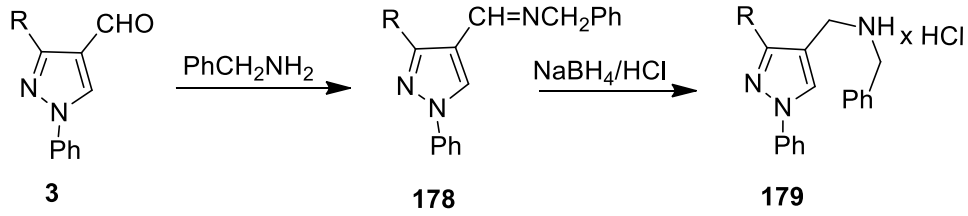
Scheme 61

Pyrazole-4-carbaldehyde-*N*,*N*-dimethylhydrazones **176**, prepared by condensation of **3** with *N*,*N*-dimethylhydrazine, were reacted with the Vilsmeier-Haack reagent, followed by hydrolysis, and electrophilic substitution reaction took place at the azomethine C-atom, giving 2-hydrazono-2-(1*H*-pyrazole-4-yl)ethanals **177**. Therefore, the electrophilic attack did not take place at the vinylogous position 5 of the pyrazoles (Scheme 62).[88]



Scheme 62

3.3.3. Reactions with amines. Reduction of Schiff's bases **178,** derived from reaction of 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** with benzylamine, using sodium tetrahydroborate gave *N*-benzyl-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanamine **179** (Scheme 63).[89]



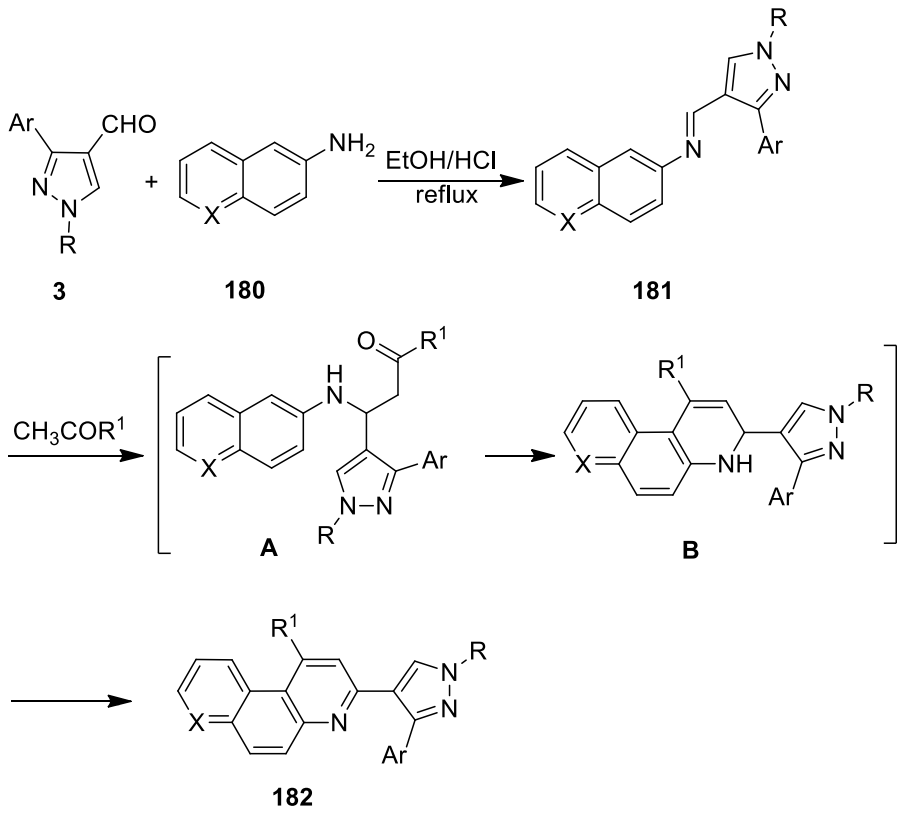
3 **178** **179**

R = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 4-pyridyl

Scheme 63

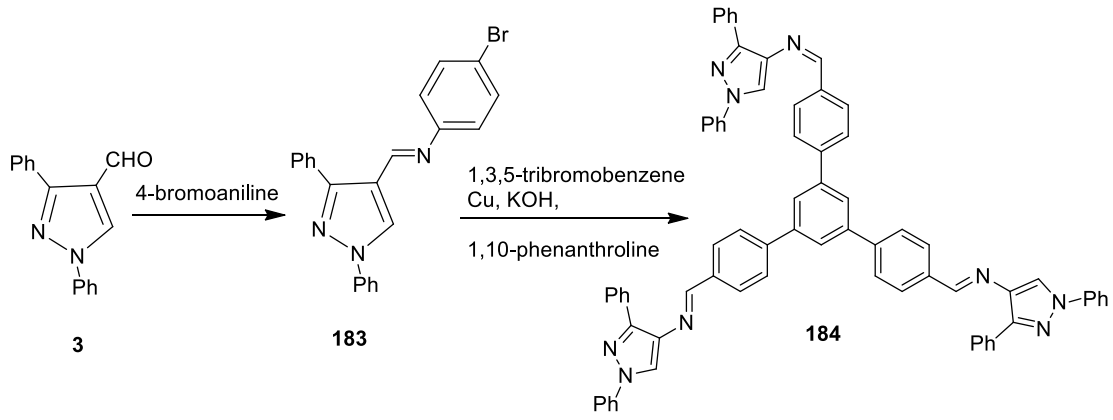
One pot synthesis of 3-(pyrazol-4-yl)-benzo[*f*]quinolines (**182**, X = CH) and pyrazolyl-4,7-phenanthroline (**182**, X = N) in 39-55% yields was reported.[90] Condensation of 3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde **3** with either 2-naphthylamine (**180**, X = CH) or 6-quinolylamine (**180**, X = N) and methyl ketones was performed in boiling ethanol in the presence of a catalytic quantity of hydrochloric acid. The aldehyde **3** was reacted with arylamine to give azomethine **181,** after that, addition of the which added methyl ketones to the C=N bond of the azomethine, cyclocondensation of the arising amino-ketones **A** gave into a dihydro derivatives of the azaphenanthrene **B**, and dehydrogenation of the latter into a completely aromatic **182** (Scheme 64).

The aldimine derivative, *N*-(4-bromophenyl)-*N*-[(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene] amine, **183** was obtained in 60% yield from reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde **3** with 4-bromoaniline. The aldimine derivative **183** and 1,3,5-tribromobenzene were dissolved in a mixture of DMF, electrolytic copper, KOH and 1,10-phenanthroline and the reaction mixture was heated for 15 h at 140 °C to give the 1,3,5-tris{[*N*-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene]-4-aminophenyl}benzene **184** (Scheme 65).[14]



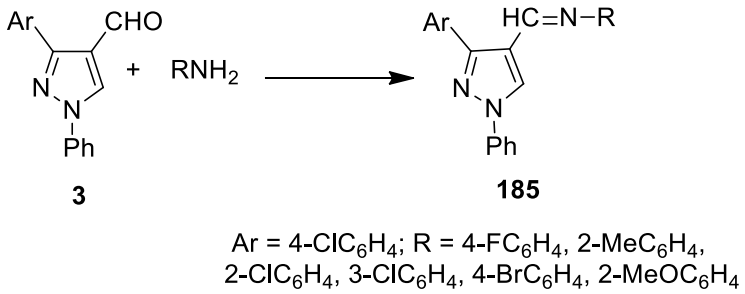
R = H; Ar = 4-FC_6H_4; R^1 = Me, Ph; X = CH, N

Scheme 64



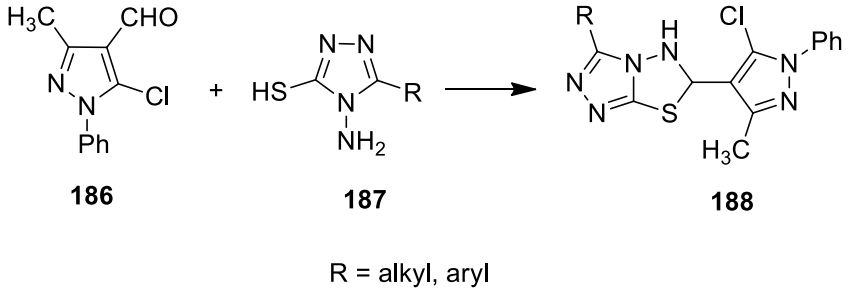
Scheme 65

3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** were functionalized at the 4-position by various substituted anilines, giving aldimines **185**. The latter compounds have antibacterial, analgesic, and antianxiety activities (Scheme 66).[7,10,91]



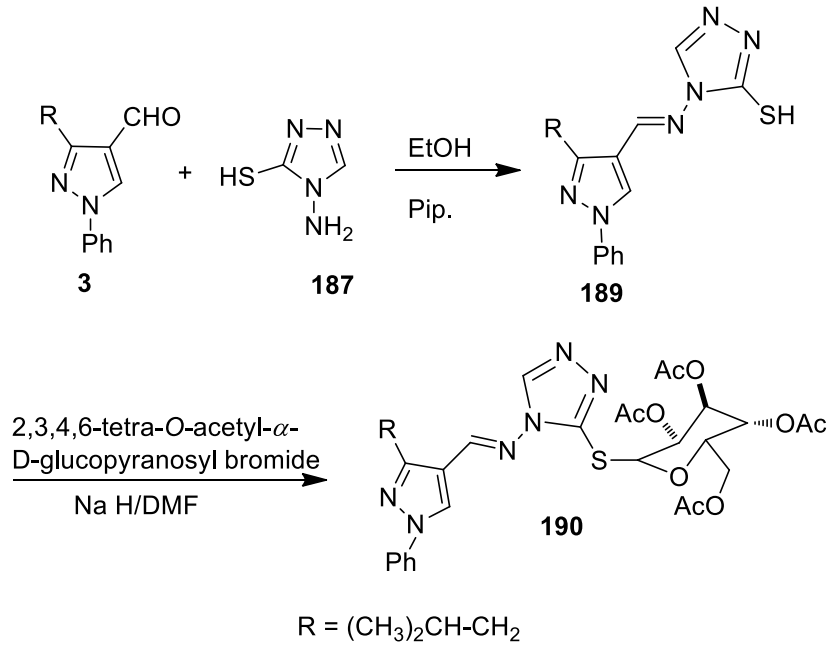
Scheme 66

1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazoles **188** have been given a great importance because of their special biological activities. Compounds **188** have been prepared through the intramolecular Mannich reaction of 4-amino-5-mercapto-1,2,4-triazoles **187** with 1-phenyl-3-methyl-5-chloropyrazole-4-carbaldehyde **186** as described in Scheme 67.[92]



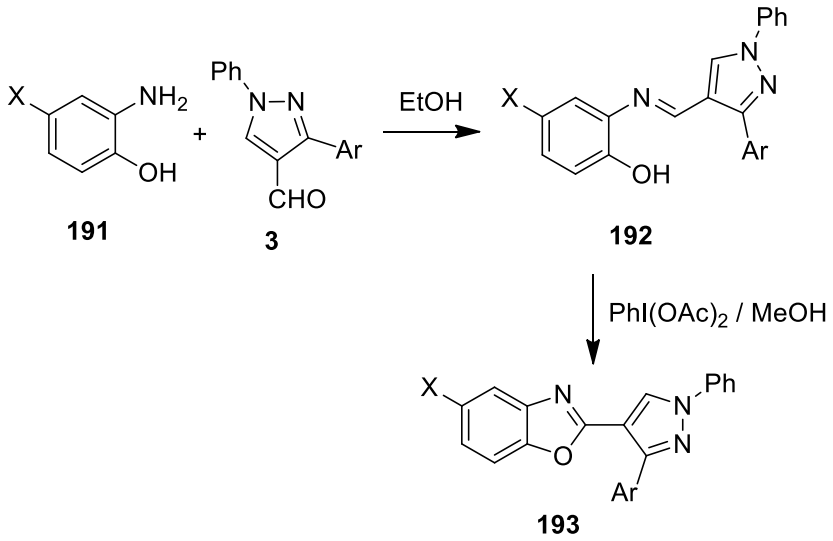
Scheme 67

When 3-isobutyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **3** was condensed with 4-amino-5-mercapto-1,2,4-triazoles **187** in ethanol in the presence of piperidine, the Schiff's base adducts **189** were obtained in high yields. *S*-Glycosides **190** were obtained in fairly good yields, on treatment of compounds **189** with 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide in the presence of NaH/DMF (Scheme 68).[13]



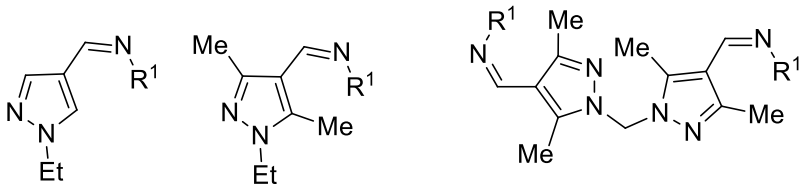
Scheme 68

Pyrazolylbenzoxazoles **193** were synthesized by oxidative intramolecular cyclization of the corresponding Schiff's bases **192**, which was synthesized by reaction of 2-aminophenol **191** with 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** in ethanol, by using iodobenzene diacetate in methanol (Scheme 69).[93]



Scheme 69

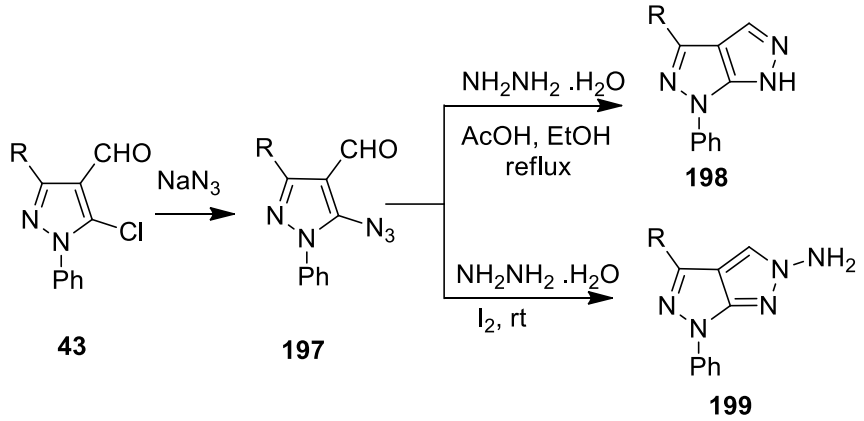
The reaction of 1-ethylpyrazole-4-carbaldehyde, 1-ethyl-3,5-dimethylpyrazole-4-carbaldehyde, and 1,1'-methylenebis(3,5-dimethylpyrazole-4-carbaldehyde) with primary amines (aniline, hydrazine, ethylenediamine, 1,4-phenylenediamine, and benzidine) gave the corresponding Schiff's bases **194-196**, respectively (Figure 2).[23]



R^1 = Ph, NH_2, CH_2-CH_2-NH_2, 4-$NH_2C_6H_4$, C_6H_4-$C_6H_4NH_2$

Figure 2

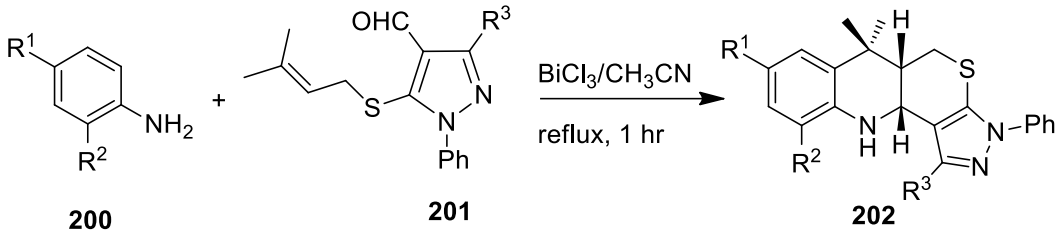
5-Chloro-1-phenyl-3-(pyridin-4-yl)-1*H*-pyrazole-4-carbaldehyde **43** was allowed to react with sodium azide to afford 5-azidopyrazole-4-carbaldehyde **197**, which was converted to pyrazolo[3,4-*c*]pyrazole **198** and pyrazolo[3,4-c]pyrazol-2(6*H*)-amine **199** by reaction with hydrazine in a mixture of ethanol and acetic acid at reflux temperature and in the presence of iodine at room temperature, respectively (Scheme 70).[28]



R = 4-pyridyl

Scheme 70

Ntramolecular [4+2] cycloaddition reactions of *N*-aryl imines generated *in situ* from substituted aniline **200** and the *S*-allyl derivatives of pyrazole-4-carbaldehydes **201** was carried out in the presence of a catalytic amount of $BiCl_3$ in acetonitrile to provide the corresponding hexahydropyrazolo[4`,3`:5,6]thiopyrano[4,3-*b*]quinolines **202** in excellent yields. The reactions are highly diastereoselective and the *cis* products are exclusively isolated (Scheme 71).[94]

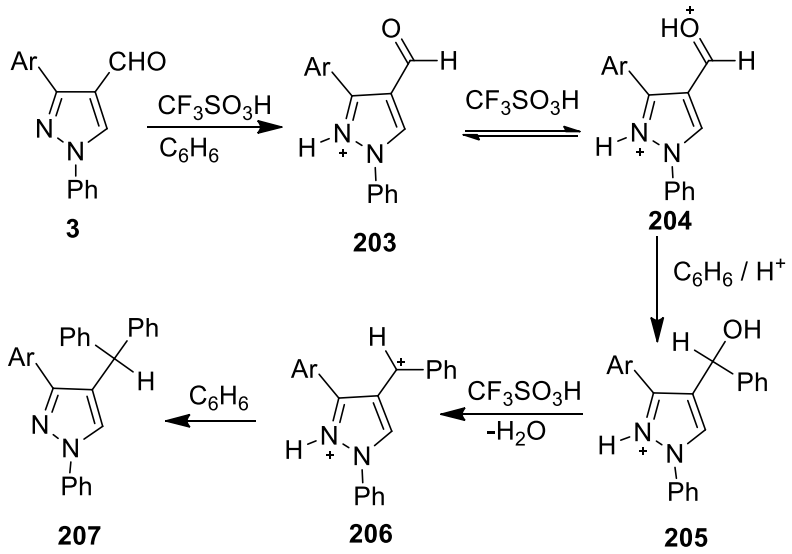


R^1 = H, Me, Cl, F; R^2 = H, Br; R^3 = Me, Ph

Scheme 71

3.4. Friedel–Crafts-type reaction (Hydroxyalkylation)

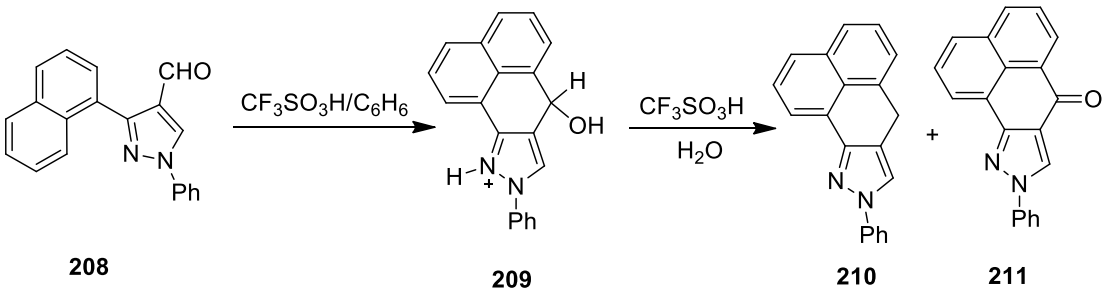
Aldehydes were reacted in the Brønsted superacid, triflic acid (CF_3SO_3H, TfOH), to generate electrophilic intermediates capable of reacting with an arene in condensation reactions. This reaction is called Friedel-Crafts-type conversion or known as hydroxyalkylation. Hydroxyalkylations are used in a variety of industrial synthetic methods, including the synthesis of bisphenol resins and Bakelite polymers, in the preparation of malachite green and related colorants, and in the preparation of pharmaceuticals, like bisacodyl and diarylhydantoins. When 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes **3** were reacted with the Brønsted superacid, CF_3SO_3H (triflic acid), in benzene, the condensation product **207** was obtained in good yield (70%-99%). The mechanism of hydroxyalkylation is thought to involve protonation of an aldehyde and subsequent attack of an arene by the carboxonium ion **204** as described in Scheme 72.[9]



Ar = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, Me, 3,4-$(OCH_2\text{-}CH_2O)\text{-}C_6H_3$, $C_6H_5\text{-}C_6H_4$

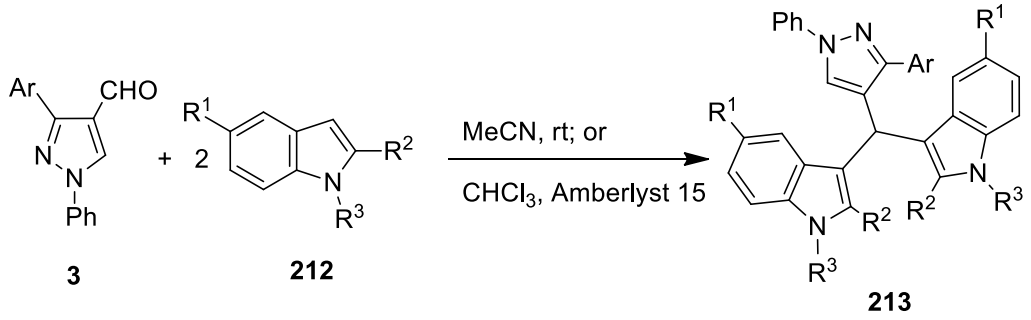
Scheme 72

Appropriately substituted pyrazoles can also undergo intramolecular Friedel–Crafts-type reactions. For example, the naphthyl-substituted pyrazole **208** gave two products **210** and **211** in roughly equimolar amounts. These products were consistent with a cyclization reaction to form the alcohol **209**, which disproportionate to the ketone **211** and methylene-bridged product **210**. Even in the presence of benzene, the intramolecular reaction occurred exclusively, and consequently, no hydroxyalkylation product was observed (Scheme 73).[95]



Scheme 73

Treatment of 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes **3** with substituted indoles **212** in acetonitrile at room temperature in the presence of phosphotungstic acid, [96] or in chloroform in the presence of Amberlyst 15,[97] resulted in the formation of pyrazolyl bisindoles **213** in 80-90% yields. The synthesized pyrazolyl bisindoles **213** have antimicrobial and antifungal activity (Scheme 74).



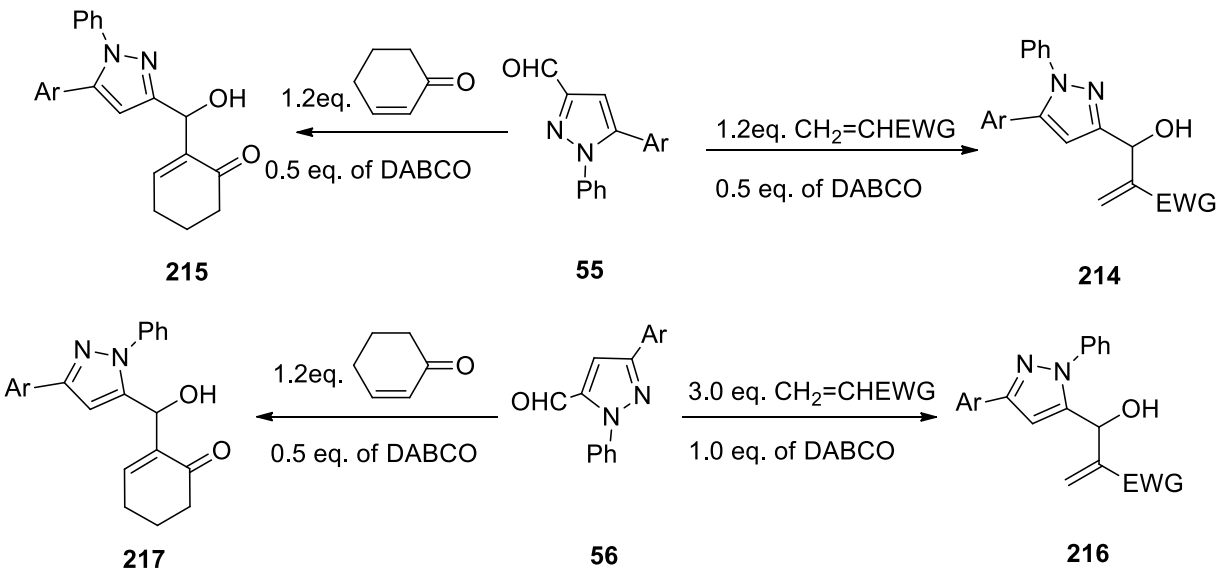
Ar = Ph, 4-ClC$_6$H$_4$,4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 2-thienyl
R^1 = H, Br, NO$_2$; R^2 = H, Ph; R^3 = H, Et

Scheme 74

3.5. Miscellaneous reactions

The Baylis-Hillman reaction of substituted pyrazole-3-carbaldehyde **55** and pyrazole-5-carbaldehyde **56** with activated alkene in the presence of DABCO (1,4-

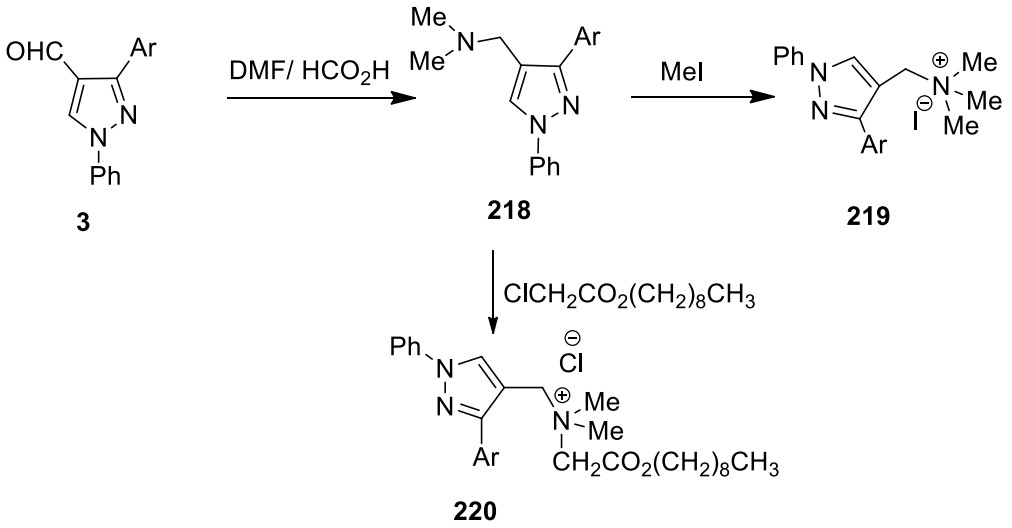
diazabicyclo[2.2.2]octane) as a catalyst, gave allylic alcohols **214-217** in 56-88% yields (Scheme 75).[9]



Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4; EWG = CN, CO_2Me,CO_2Et, CO_2Bu-t, COMe

Scheme75

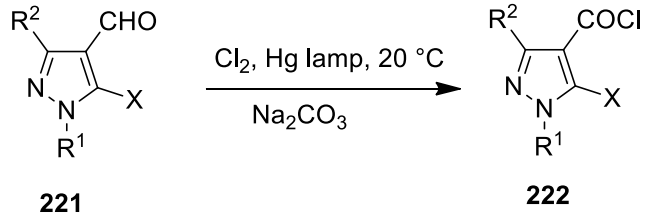
N,*N*-Dimethyl-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanamine **218** were prepared by reductive amination of the corresponding 3-aryl-1-phenyl-1H-pyrazole-4-carbaldehydes **3** with DMF and HCO_2H. Quaternization of the tertiary amines **218** using MeI gave the corresponding iodomethylates **219**, and alkylation by nonyl chloroacetate gave *N*,*N*-dimethyl-*N*-nonyloxycarbonilmethyl-4-pyrazolemethanammonium chloride **220**. Pyrazolemethylamines and its ammonium salts exhibit membrane-stabilizing, hemolytic and antibacterial activity against *S. aureus*, *E. coli*, and *C. albicans* (Scheme 76).[98]



Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4,4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, 4-pyridiny

Scheme 76

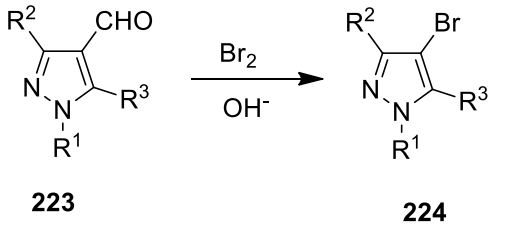
Pyrazolecarboxylic acid chlorides **222** were prepared in 95% yield by treatment of the corresponding aldehydes **221** with Cl_2 over 4 h irradiation using Hg lamp at 20 °C in chlorobenzene in the presence of Na_2CO_3 (Scheme 77).[99,100]



R^1 = R^2 = H, alkyl, alkoxyalkyl, aryl, heteroaryl, haloalkyl; X = F, Cl, Br

Scheme 77

Bromination of 1,3-dimethyl- **223a** and 1,5-dimethyl-1*H*-pyrazole-4-carbaldehyde **223b** in aqueous alkali afforded 4-bromo-1,3-dimethyl- **224a** and 4-bromo-1,5-dimethyl-pyrazoles **224b**, respectively (Scheme 78).[101]

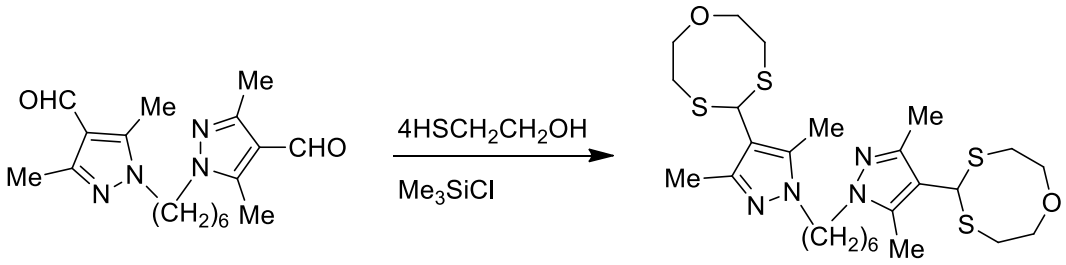


223 **224**

223,224a, $R^1 = R^2 = Me$; $R^3 = H$
223,224b, $R^1 = R^3 = Me$; $R^2 = H$

Scheme 78

Bispyrazole-4-carbaldehyde **225** was reacted with 2-sulfanylethanol in the presence of 10-fold amounts of chloro(trimethyl)silane to give 1,6-bis[3,5-dimethyl-4-(1,4,6-oxadithioctan-5-yl)-1*H*-pyrazol-1-yl]hexane **226** with high selectivity (Scheme 79).[102]



225 **226**

Scheme 79

4. Conclusions

This review has attempted to summarize the synthetic methods and reactions of pyrazole-4(3)-carbaldehydes. Many biologically active heterocyclic compounds have been synthesized from that heterocycle. These reactions greatly extended synthetic possibilities in organic chemistry.

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Authors' Biographies

Bakr F. Abdel-Wahab was born in 1978 in Mansoura, Egypt. He is a researcher of organic chemistry at National Research Centre, Giza, Egypt. He has got his B.Sc. in 1999 from Chemistry Department, Faculty of Science, Mansoura University, Egypt. He received his M.Sc. in 2003 from Mansoura University under the supervision of Professor Fathy A. Amer. He has awarded his Ph.D. degree in 2007 from Ain-Shams University, Cairo under the supervision of Professor Maher A. El-Hashash (D.Sc). His current research interests cover the development and mechanistic aspects of organic reactions and their applications in medicinal chemistry. Currently, he is an assistant professor of organic chemistry at the Department of Chemistry, Faculty of Science and Arts, King Abdulaziz University, Khulais Branch, Saudi Arabia.
http://sak.njb.kau.edu.sa

Rizk E. Khidre is a researcher of organic chemistry at National Research Centre, Giza, Egypt. He was born in 1974 in Mansoura, Egypt and received both B.S. degree (1996) and M.S. degree (2002) from Mansoura University (Professor A. H. Abdel-Rahman), and his Ph.D. degree from Ain-Shams University, Cairo under supervision of Professor Mounir A. I. Salem and Professor Wafaa M. Abdou (D.Sc). He received his PhD in 2009 in "Synthesis of Pharmaceutically Active Nitrogen-Heterocycles and Their Relevant Phosphonates." Dr. Rizk has specialized in the synthesis of heterocyclic and organophosphours compounds of expected biological activity.

Currently, he is an associated professor of organic chemistry, Faulty of Science, Gazan university, kingdom of Saudi Arabia.

Abdelbasset A. Farahat was born in 1980 in Mansoura, Egypt. He is a post doc. Researcher of Medicinal Chemistry at Georgia State University, Atlanta, Georgia, USA. He has got his B.Sc. in 2002 from Faculty of Pharmacy, Mansoura University, Egypt. He received his M.Sc. in 2006 from Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Mansoura University, under the supervision of Professor Hassan M. Eissa. He has awarded his Ph.D. degree in 2010 after a joint program between Mansoura University and Georgia State University, Atlant, Georgia, USA, under the supervision of Professor David W. Boykin. He is working now in A GATES funded project titled" Drug discovery for parasitic diseases".

