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Review

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Synthesis of various pyrazole-fused heterocyclic systems using pyrazole-4-carbaldehydes as versatile precursors

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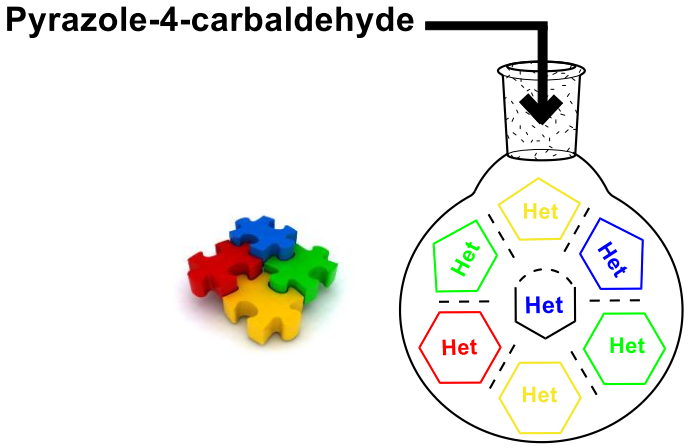
Abstract

The discovery of intriguing properties shown by a large number of pyrazole derivatives has sparked a surge in interest in pyrazole chemistry over the last decade. They exist in a variety of natural products, dyes, and as scaffolds in a variety of drugs and pharmaceutical active ingredients. This review demonstrated various methods for the construction of pyrazole-fused heterocycles using pyrazole-4-carbaldehydes as effective precursors. Heterocyclic compounds mentioned in this review are arranged into categories based on the size of the heterocyclic ring as well as the position and number of the heteroatoms.



Keywords: Pyrazole-4-carbaldehydes, synthesis, cyclization, cyclocondensation, pyrazole-substituted heterocycles

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1. Introduction

Heterocycles are an essential class of compounds that make up more than half of all known organic compounds. They can be found in a variety of natural products and biomolecules such as hormones, antibiotics, alkaloids, vitamins, and so on. Heterocyclic compounds are of great concern in our everyday life. They are used in a variety of industries, including agrochemicals, pharmaceuticals, and veterinary products. They are also used as starting materials for the production of sanitizers, developers, anti-ordinates, corrosion inhibitors, and other products.[1–12] Nitrogen-containing heterocycles constitute the core structures of a variety of biologically active compounds and have a wide range of applications in chemistry, biology, and other fields. Many naturally occurring *N*-heterocyclic compounds have physiological and pharmacological properties and are components of a wide range of biologically important molecules, including vitamins, nucleic acids, pharmaceuticals, antibiotics, dyes, and agrochemicals.[4,13–18] Furthermore, heterocycles containing nitrogen are essential in coordination chemistry.[19] Pyrazoles are aromatic heterocycles with two nitrogen atoms in their five-membered rings that are well-known. They are a significant heterocyclic family that includes a wide variety of chemical, biological, agrochemical, and pharmaceutical properties.[8,20–24] Several drugs have been produced from pyrazole derivatives.[25–30] The use of pyrazole derivatives in semiconductors, liquid crystals, and organic light-emitting diodes applications have been extensively investigated.[31–35]

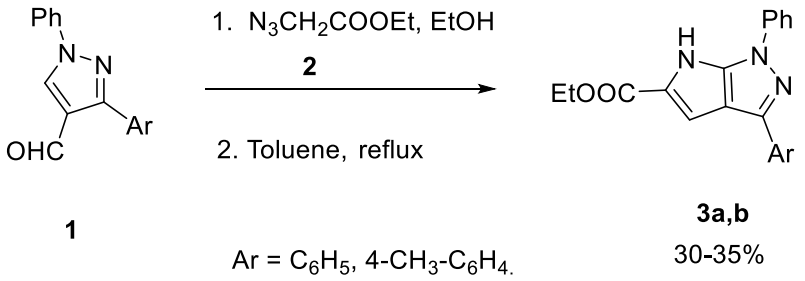
In continuation of our interest in reviewing various synthetic approaches to a variety of heterocycles[36–51], this review highlights the utility of pyrazole-4-carbaldehydes in the preparation of pyrazole-fused heterocyclic systems over the last two decades. Very recently, we reviewed the usefulness of pyrazole-4-carbaldehydes as versatile precursors for different pyrazole-substituted heterocyclic systems.[52] Heterocyclic compounds mentioned in this review are arranged based on the size of the heterocyclic ring as well as the position and number of the heteroatoms.

2. Synthesis of Fused Pyrazoles

2.1. Pyrazole fused within a bicyclic system

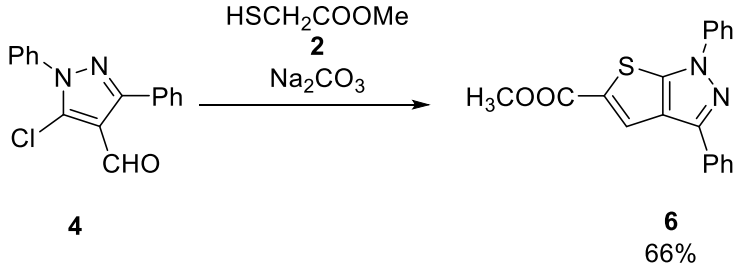
2.1.1. Fused [5-5] system with three heteroatoms. 2.1.1.1. Pyrrolo[2,3-*c*]pyrazole. Aly *et al*.[53] reported that heating of 3-aryl-1-phenyl-1*H*-pyrazol-4-carbaldehydes **1** with ethyl azidoacetate **2** in ethanol followed by

heating in toluene at reflux gave pyrrolo[2,3-*c*]pyrazole derivatives **3a** and **3b** in 30 and 35% yield, respectively (Scheme 1).



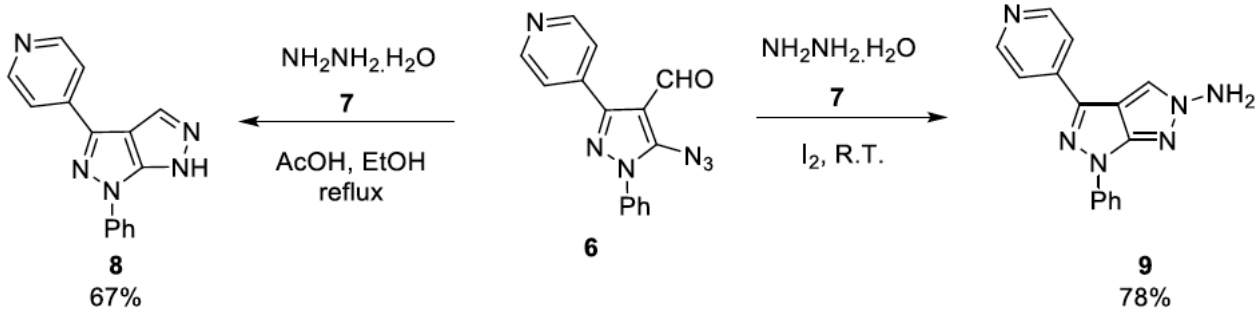
Scheme 1. Synthesis of pyrrolo[2,3-*c*]pyrazole derivatives **3a** and **3b.**

2.1.1.2. Thieno[2,3-*c*]pyrazole. Methyl 1,3-diphenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylate **5** was prepared by the reaction of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **4** with methyl thioglycolate **2** in ethanol in the presence of anhydrous sodium carbonate[54] (Scheme 2).



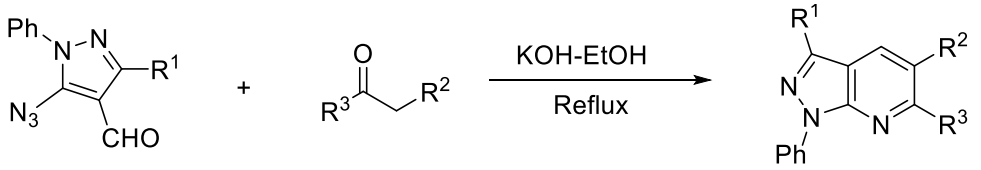
Scheme 2. Synthesis of methyl-1,3-diphenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylate **5.**

2.1.2. Fused [5-5] system with four heteroatoms. 2.1.2.1. Pyrazolo[3,4-*c*]pyrazole. Aly *et al*.[55]reported that treatment of 5-azido-1-phenyl-3-pyridin-4-yl-1*H*-pyrazole-4-carbaldehyde **6** with hydrazine hydrate **7** in the presence of acetic acid in ethanol at reflux yielded 1-phenyl-3-pyridin-4-yl-1,6-dihydropyrazolo[3,4-*c*]pyrazole **8**. On the other hand, treatment of **7** with hydrazine hydrate **7** at room temperature in the presence of iodine afforded 6-phenyl-4-pyridin-4-yl-6*H*-pyrazolo[3,4-*c*]pyrazol-2-ylamine **9** (Scheme 3).



Scheme 3. Synthesis of pyrazolo[3,4-*c*]pyrazoles **8** and **9.**

2.1.3. Fused [5-6] system with three heteroatoms. 2.1.3.1. Pyrazolo[3,4-*b*]pyridine. Zheng *et al.*[56] reported that one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes **6a** and **6b** with the appropriate arylethanone **2a–c**, acetone **2d**, acetylacetone **2e** or benzoylacetone **2f** in a solution of ethanolic KOH afforded the corresponding pyrazolo[3,4-*b*]pyridine derivatives **10a-j** (Scheme 4).

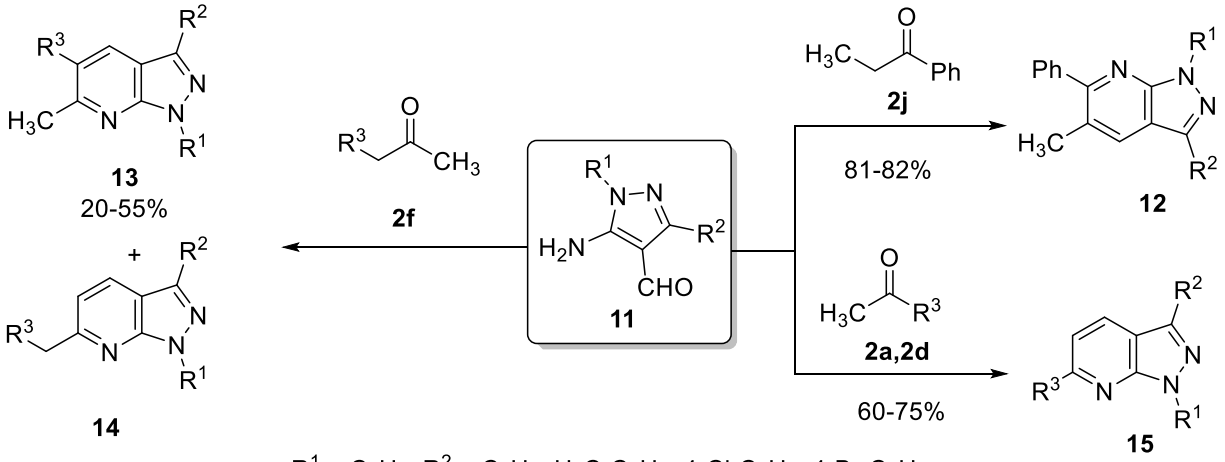


6a-b **2a-f** **10a-o**
60-88%

R^1 = CH_3, C_6H_5; R^2 = H, $COCH_3$; R^3 = C_6H_5, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, CH_3.

Scheme 4. Synthesis of pyrazolo[3,4-*b*]pyridine derivatives **10a-j.**

Condensation of 5-amino-1*H*-pyrazole-4-carbaldehyde **11** with propiophenone **2j** afforded 3-(4-aryl)-5-methyl-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine derivatives **12**[57]. On the other hand, condensation of 5-aminopyrazole-4-carbaldehydes **11** and unsymmetric dialkylketones **2f** yielded a mixture of isomeric pyrazolo[3,4-*b*]pyridine derivatives **13** and **14**[58]. A series of 1,3,6-trisubstituted and 1,3,5,6-tetrasubstituted pyrazolo[3,4-*b*]pyridines **15** has been synthesized by condensation of **11** with α-methylene ketones such as acetone **2d** or acetophenones **2a** with potassium hydroxide as a basic catalyst[58] (Scheme 5).



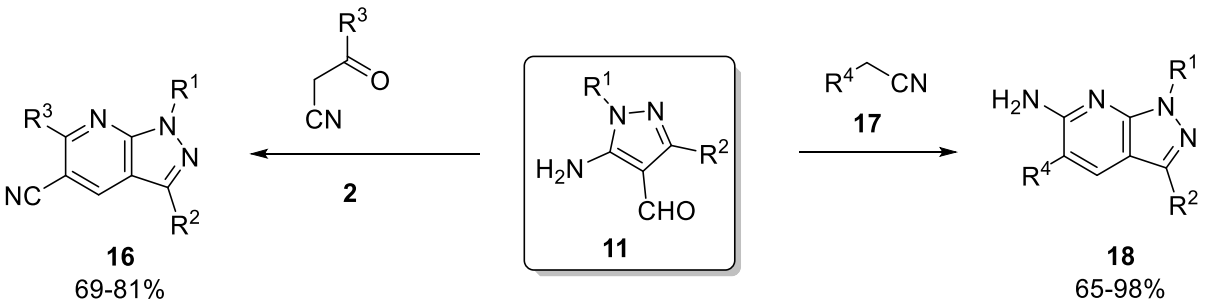
13 20-55% + **14**

11 **12** **15**

R^1 = C_6H_5; R^2 = C_6H_5, H_3C-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4;
R^3 = CH_3, C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, $H_5C_6CH_2$.

Scheme 5. Synthesis of pyrazolo[3,4-*b*]pyridine derivatives **12**,**13**,**14** and **15.**

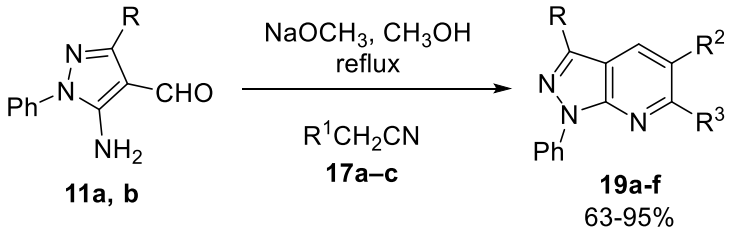
Friedländer condensation of 5-amino-1*H*-pyrazole-4-carbaldehyde **11** with acetonitrile derivatives **2** in ethanol in the presence of a catalytic amount of piperidine yielded the corresponding pyrazolo[3,4-*b*]pyridine-5-carbonitriles **16**[58,59]. 6-Aminopyrazolo[3,4-*b*]pyridines **18** were obtained by the condensation of **1** with the corresponding cyanomethyl derivatives **17**[57,59–61](Scheme 6).



R^1 = C_6H_5; R^2 = CH_3, C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4;
R^3 = Benzo[*d*]thiazole, C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-H_3C-C_6H_4; R^4 = 1H-Benzo[*d*]imidazoxle, Benzo[*d*]thiazole, 5-Chloro-benzo[*d*]oxazole, CN, C_6H_5, $CONH_2$.

Scheme 6. Synthesis of pyrazolo[3,4-*b*]pyridines **16** and **18.**

Panda *et al.*[62] reported that treatment of 5-amino-1*H*-pyrazole-4-carbaldehyde **11a** and **11b** with various active methylene compounds **17a-c** in the presence of an excess of sodium methoxide heated at reflux in methanol gave the corresponding pyrazolo[3,4-*b*]pyridines **7a-f** (Scheme 7).

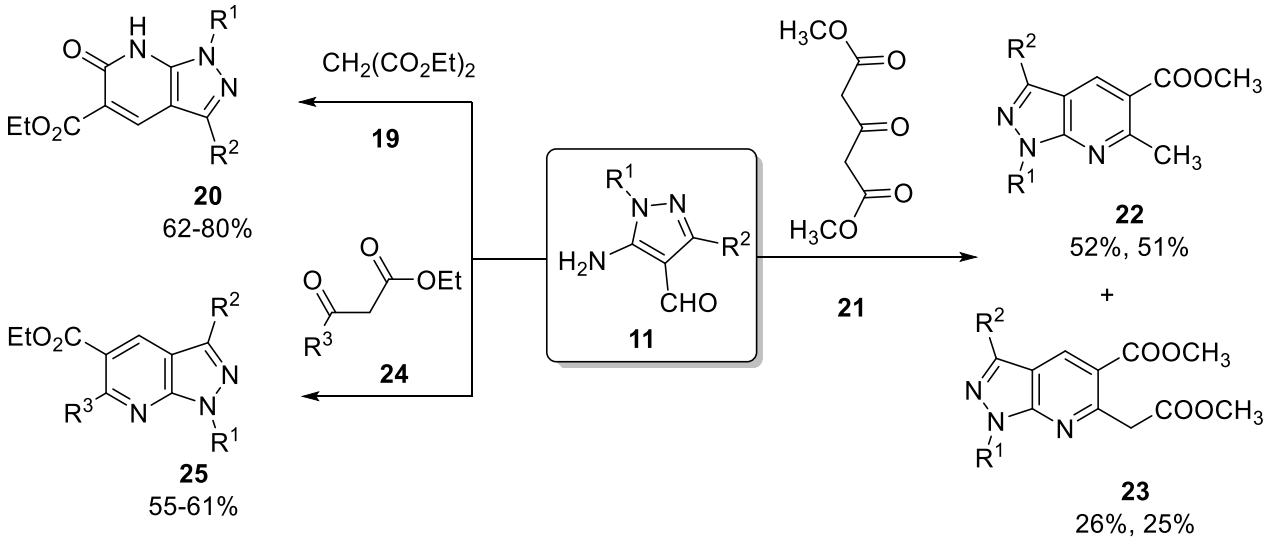


R = C_6H_5, CH_3; R^1 = $CONH_2$, CN, CO_2Et; R^2 = $CONH_2$, CN; R^3 = NH_2, OH.

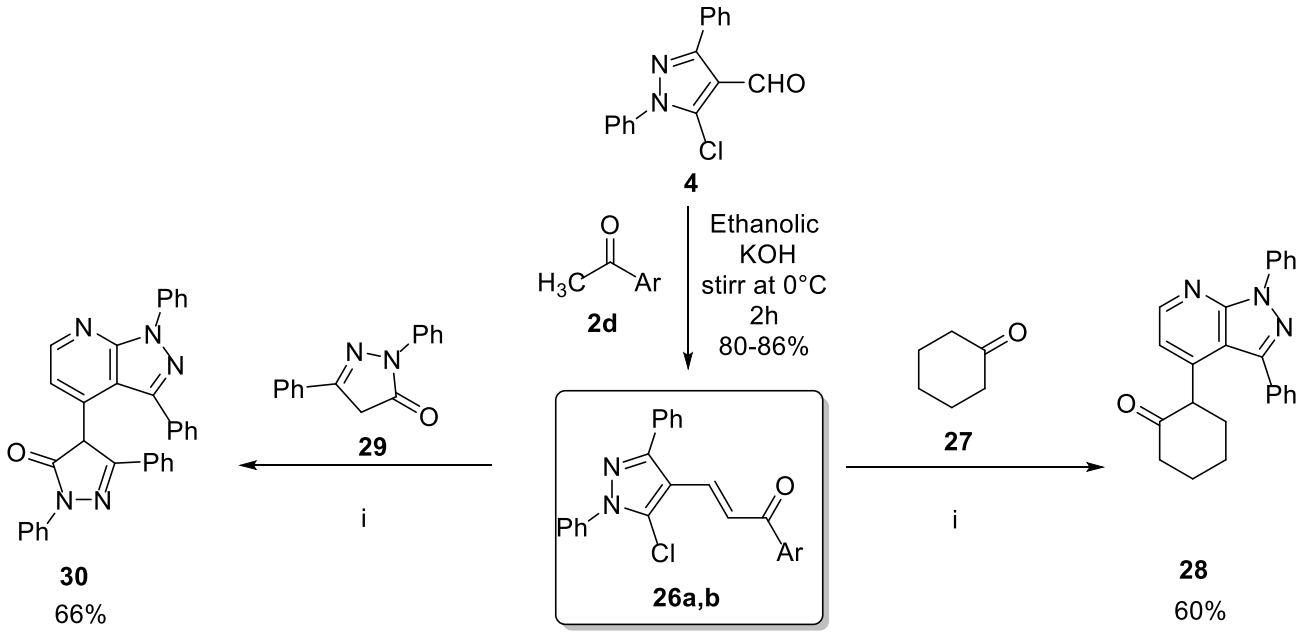
Scheme 7. Synthesis of pyrazolo[3,4-*b*]pyridines **19a-f.**

5-Amino-1*H*-pyrazole-4-carbaldehyde **11** reacted with diethyl malonate **19** to give the corresponding ethyl 6-oxo-6,7-dihydropyrazolo[3,4-*b*]pyridine-5-carboxylate derivatives **20**[58,60]. On the other hand, condensation of **11** with dimethyl-3-oxopentanedioate **21** yielded a mixture of methyl 6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylates **22** and methyl 6-(2-methoxy-2-oxoethyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylates **23**[57]. Condensation of **11** with *β*-ketoesters **24** in the presence of piperidine as a basic catalyst yielded pyrazolo[3,4-*b*]pyridine-5-carboxylates **25**[58](Scheme 8).

Babaqi *et al.*[63] reported that 1-aryl-3-(5-chloro-l,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-l-ones **26a** and **26b** were prepared by Knoevenagel condensation of 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **4** with acetophenone or *p*-methylacetophenone **2d**. Treatment of **26a** and **26b** with cyclohexanone **27** or 1,3-diphenyl-2-pyrazolin-5-one **29** afforded 2-(1,3-diphenyl-1H-pyrazolo[3,4-b]pyridin-4-yl)cyclohexan-1-one **28** or 4-(1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)-2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one **30**, respectively, *via* Michael addition followed by cyclization and subsequent diarylation (Scheme 9).

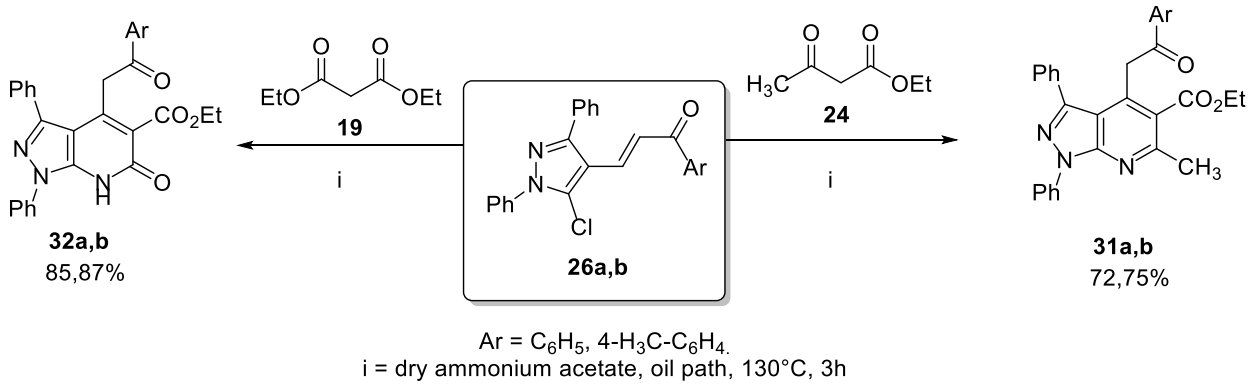


Scheme 8. Synthesis of pyrazolo[3,4-*b*]pyridines **20**, **22**, **23** and **25.**



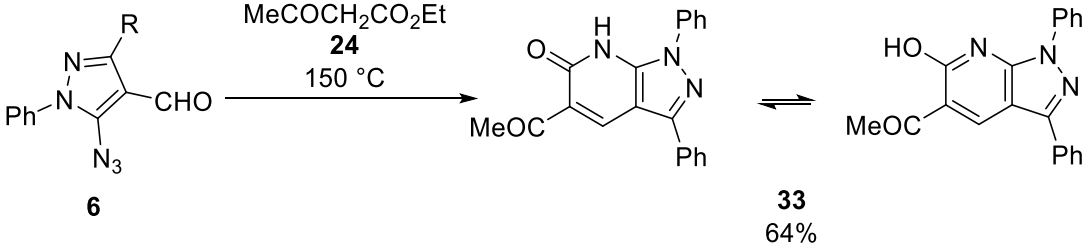
Scheme 9. Synthesis of pyrazolo[3,4-*b*]pyridine derivatives **28** and **30.**

The base-catalyzed Michael addition of **26a** and **26b** with ethyl acetoacetate **24** followed by cyclization under the same conditions yielded ethyl 4-(2-aryl-2-oxoethyl)-6-methyl-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate derivatives **31a** and **31b**. On the hand reaction of diethyl malonate **19** with **26a** and **b** under the same conditions gave ethyl 4-(2-aryl-2-oxoethyl)-6-oxo-1,3-diphenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylates **32a** and **b** (Scheme 10).[63]



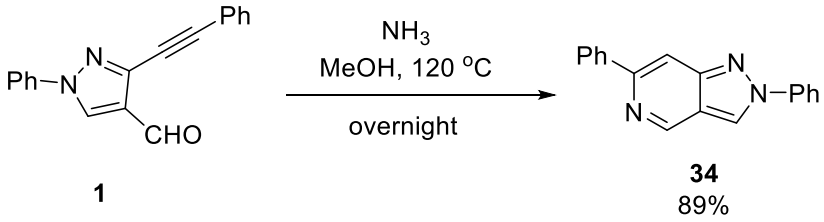
Scheme 10. Synthesis of pyrazolo[3,4-*b*]pyridine derivatives **31** and **32.**

El-Metwally and Khalil[64] reported that azidoformylpyrazole **6** was fused with ethyl acetoacetate **24** at 150 °C to give 5-acetyl-1,3-diphenyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one **33** which exists as a mixture of keto-enol forms (Scheme 11).



Scheme 11. Synthesis of 5-acetyl-1,3-diphenyl-1,7-dihydro-6*H*-pyrazolo[3,4-*b*]pyridin-6-one **33.**

2.1.3.2. Pyrazolo[3,4-*c*]pyridine. Arbačiauskienė[65] reported that treatment of 1-phenyl-3-(phenylethynyl)-1*H*-pyrazole-4-carbaldehyde **1** bearing the phenylethynyl moiety adjacent to the carbonyl group with dry ammonia under elevated temperature and pressure afforded 2,6-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridine **34** (Scheme 12).

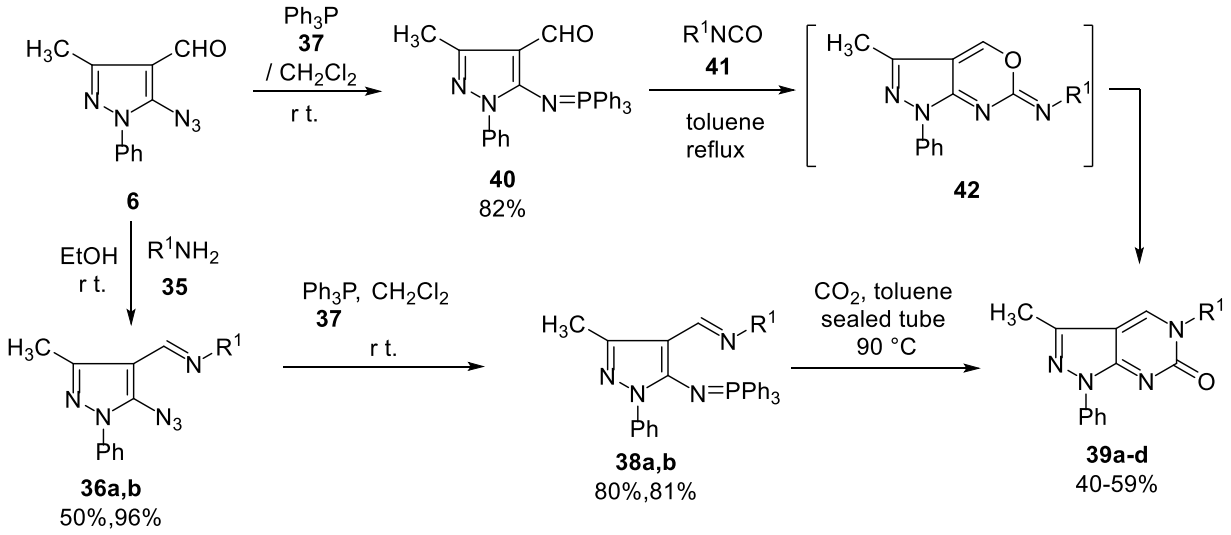


Scheme 12. Synthesis of 2,6-diphenyl-2*H*-pyrazolo[4,3-*c*]pyridine **34.**

2.1.4. Fused [5-6] system with four heteroatoms. 2.1.4.1. Pyrazolo[3,4-*d*]pyrimidine. Molina *et al.*[66] reported that treatment of 5-azido-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **6** with aromatic amines **35** in ethanol gave the corresponding 1-(5-azido-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*-arylmethanimines **36a** and **b**. The preparation of the desired iminophosphoranes **38** and **40** was accomplished through the classical Staudinger reaction of 5-azidopyrazoles **6** and **36** with triphenylphosphine **37,** respectively. The reaction of

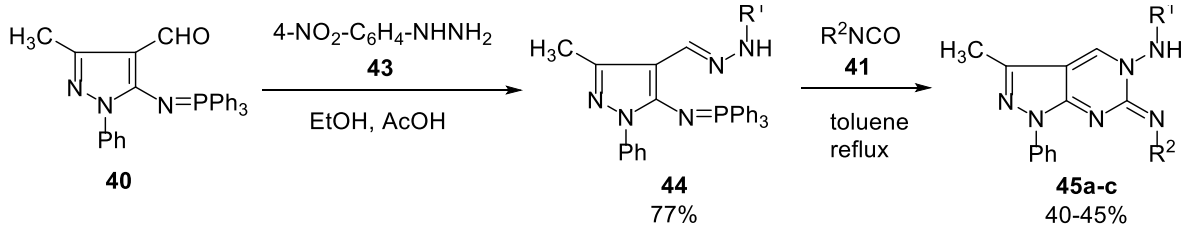
iminophosphorane **40** with isocyanates **41** resulted in the formation of the corresponding pyrazolo[3,4-*d*]pyrimidines **39**. The **40** → **19** conversion involves an initial aza-Wittig reaction between 5-((triphenylphosphaneylidene)amino)-1*H*-pyrazole-4-carbaldehyde **40** and isocyanate **41** to give a carbodiimide which undergoes electrocyclic ring closure to give an unstable 3-methyl-*N*,1-diphenylpyrazolo[3,4-*d*][1,3]oxazin-6-imine **42**. The latter compound by a typical Dimroth rearrangement undergoes ring-opening and closure to furnish **39** in a 15% yield. However, compounds **39** were also prepared in good yields from *N*-(3-methyl-1-phenyl-4-((phenylimino)methyl)-1*H*-pyrazol-5-yl)-1,1,1-triphenylphosphanimine **38** and carbon dioxide (Scheme 13).

Triphenylphosphanimine **44** was prepared by the reaction of **40** and (*p*-nitrophenyl)hydrazine **43**. The reaction of triphenylphosphanimine **44** with isocyanates **41** gave the pyrazolo[3,4-*d*]pyrimidines **45** (Scheme 14).[66]



R^1 = C_6H_5, 4-H_3C-C_6H_4; R^2 = C_2H_5, CH_2=CH-CH_2-, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4.

Scheme 13. Synthesis of 3-methyl-1-phenyl-5-aryl-1,5-dihydro-6*H*-pyrazolo[3,4-*d*]pyrimidin-6-one **39.**



R^1 =$_4$-O_2N-C_6H_4; R_2 = C_2H_5, CH_2=CH-CH_2-, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4.

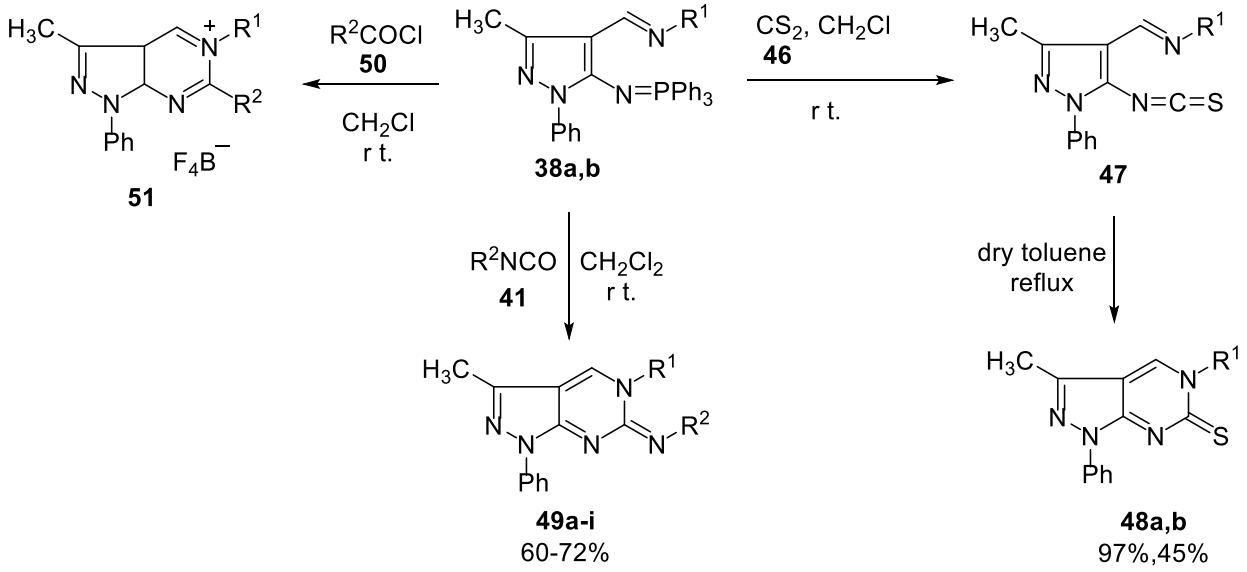
Scheme 14. Synthesis of pyrazolo[3,4-*d*]pyrimidines **45.**

When triphenylphosphanimine **38** were treated with carbon disulfide **46**, pyrazolopyrimidines **48** were formed. The mechanisms of the conversion of **38** into **48** are supported by the isolation in some cases of the isothiocyanate **47** which by heating in dry toluene at reflux temperature was converted into the corresponding

fused pyrimidine **48**. The reaction of triphenylphosphanimines **38** with isocyanates **41** gave the corresponding pyrazolo[3,4-*d*]pyrimidines **49**.

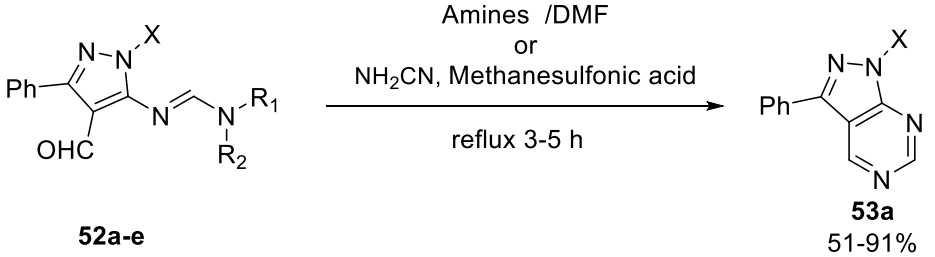
On the other hand, the reaction of triphenylphosphanimines **38** with acyl chlorides **50** gave the corresponding pyrazolo[3,4-*d*]pyrimidinium salts **51** (Scheme 15).[66]

The intermolecular heterocyclization from *N*'-(4-formylpyrazol-5-yl)formimidamide **52** with various amines[67] or cyanamide (NH_2CN) in acidic solution at reflux[68] afforded the corresponding 1-aryl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **53** (Scheme 16).



R^1 = C_6H_5, 4-H_3C-C_6H_4; R^2 = C_2H_5, CH_2=CH-CH_2-, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4.

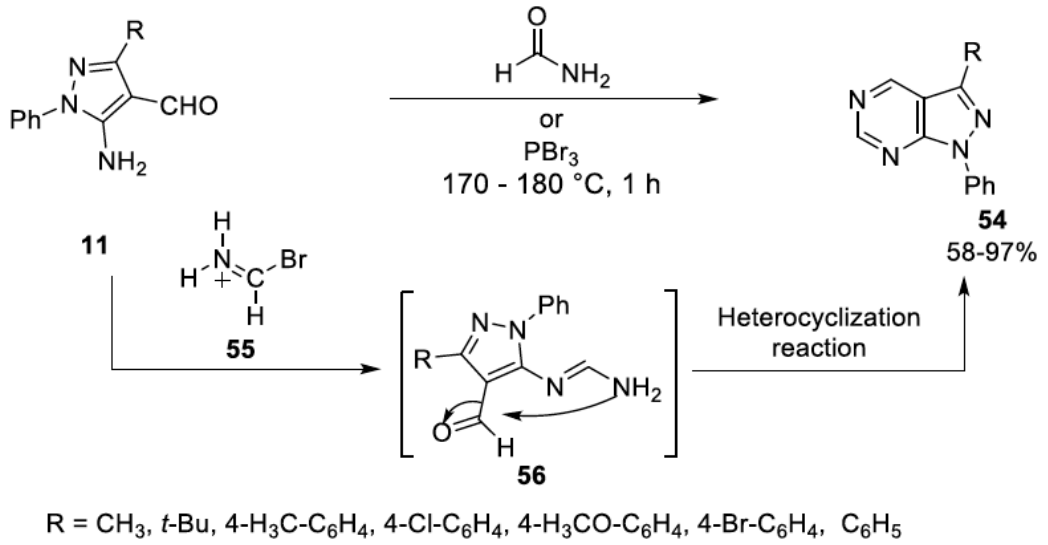
Scheme 15. Synthesis of pyrazolo[3,4-*d*]pyrimidines **48**, **49** and **51.**



X = C_6H_5, 2-H_3C-C_6H_4, 3-H_3C-C_6H_4, 4-H_3C-C_6H_4, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-H_3CO-C_6H_4, 4-O_2N-C_6H_4; NR^1R^2 = $N(CH_3)_2$, $N(C_2H_5)_2$, N(i-Pr)$_2$, N(n-Bu)$_2$, Piperidinyl; Amines[65] = Hexamethylenetetramine, $LiN(Si(CH_3)_3)_2$, $NaN(Si(CH_3)_3)_2$, $NH(Si(CH_3)_3)_2$.

Scheme 16. Synthesis of 1*H*-pyrazolo[3,4-*d*]pyrimidines **53.**

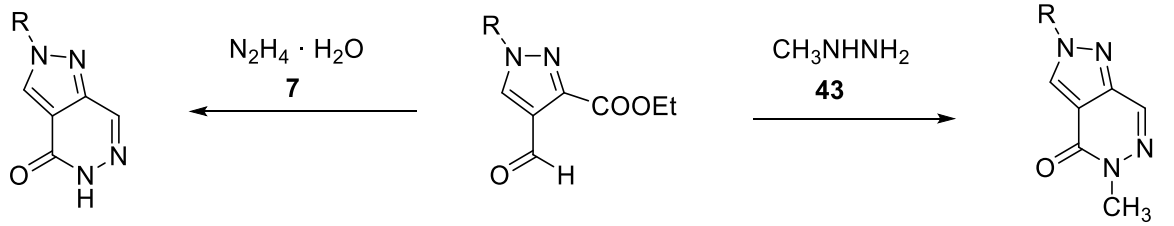
Cyclization of 5-aminopyrazole-4-carbaldehyde **11** with formamide[69,70] or benzamide[70] and phosphorus tribromide (PBr_3)[69] afforded pyrazolo[3,4-*d*]pyrimidines **54**. A series of **11** reacted with reactive species **55** generated from the reaction of HCHO and PBr_3. The reaction proceeds by an amidination reaction to give the intermediate **56** followed by heterocyclization to give **54**[69] (Scheme 17).



R = CH_3, *t*-Bu, 4-H_3C-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4, 4-Br-C_6H_4, C_6H_5

Scheme 17. Synthesis of pyrazolo[3,4-*d*]pyrimidines **54.**

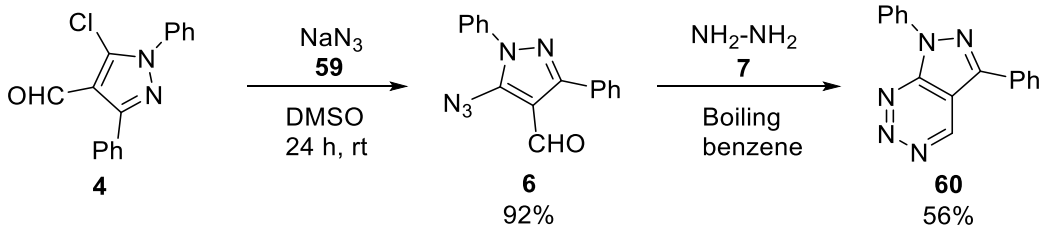
2.1.4.2. Pyrazolo[3,4-*d*]pyridazine. Matiichuk *et al.*[71] reported that reactions of ethyl 1-aryl-4-formyl-1*H*-pyrazole-3-carboxylates **1** with hydrazine **7** and methylhydrazine **43** led to the formation of the corresponding pyrazolo[3,4-*d*]pyridazin-4-ones **57** and **58**, respectively (Scheme 18).



R = C_6H_5, 4-Cl-C_6H_4.

Scheme 18. Synthesis of pyrazolo[3,4-*d*]pyridazin-4-ones **57** and **58**.

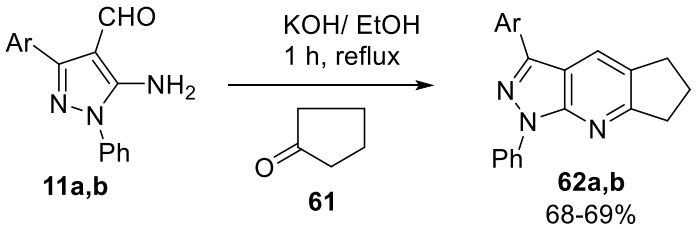
2.1.5. Fused [5-6] system with five heteroatoms. 2.1.5.1. Pyrazolo[3,4-*d*][1,2,3]triazine. El-Metwally and Khalil[64] reported that pyrazole-4-carbaldehyde **4** was treated with sodium azide **59** in DMSO to give 5-azido-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **6**[72] which reacted with hydrazine hydrate **7** to give pyrazolo[3,4-*d*][1,2,3]triazine **60**[64] (Scheme 19).



Scheme 19. Synthesis of pyrazolo[3,4-*d*][1,2,3]triazines **60.**

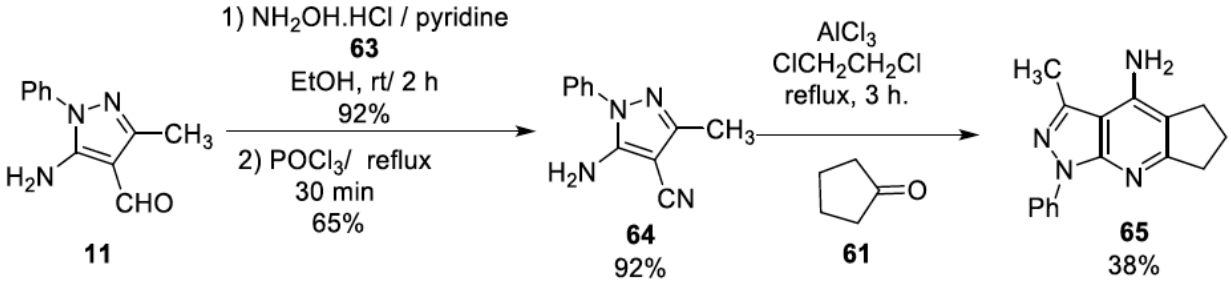
2.2. Pyrazole fused within a tricyclic system

2.2.1. Fused [5-5-6] system with three heteroatoms. 2.2.1.1. Clopenta[*b*]pyrazolo[4,3-*e*]pyridine. Jachak *et al.*[70] reported that the cyclocondensation of 5-amino-1*H*-pyrazole-4-carbaldehyde **11** with cyclopentanone **61** yielded cyclopenta[*b*]pyrazolo[4,3-*e*]pyridines **62** in ethanolic KOH at reflux (Scheme 20).



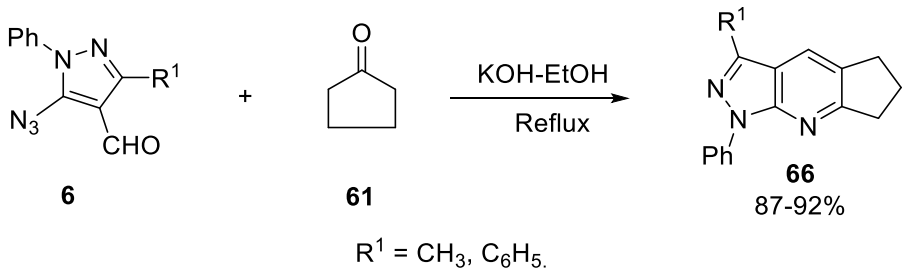
Scheme 20. Synthesis of cyclopenta[*b*]pyrazolo[4,3-*e*]pyridines **62.**

Barreiro *et al.*[61] reported that stirring of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **11** in ethanol with hydroxylamine hydrochloride **63** and pyridine followed by reaction with $POCl_3$ at reflux gave 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonitrile **64**. 3-Methyl-1-phenyl-1,5,6,7-tetrahydrocyclopenta-[*b*]pyrazolo[4,3-*e*]pyridin-4-amine **65** was then obtained from Friedländer condensation of **64** with cyclopentanone **61**(Scheme 21).



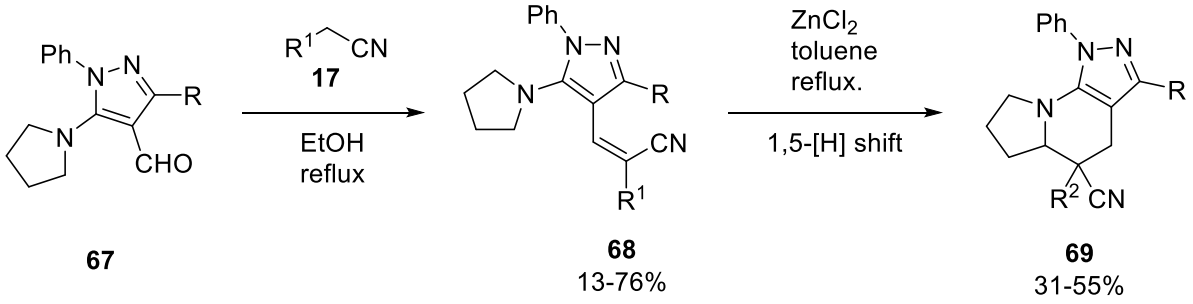
Scheme 21. Synthesis of tetrahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridin-4-amine **65.**

Zheng *et al.*[56] reported that a one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes **6** with cyclopentanone **61** in a solution of ethanolic KOH afforded the corresponding 1,5,6,7-tetrahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridines **66** (Scheme 22).



Scheme 22. Synthesis of tetrahydrocyclopenta[*b*]pyrazolo[4,3-*e*]pyridines **66.**

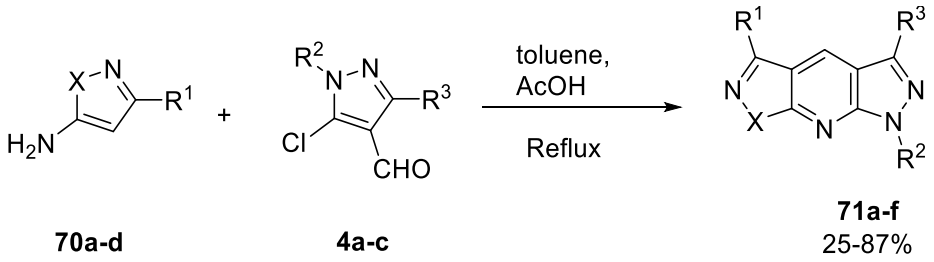
2.2.1.2. Pyrazolo[3,4-*e*]indolizine. The reaction of 5-(pyrrolidin-1-yl)-1*H*-pyrazole-4-carbaldehyde **67** with methylene active nitriles **17** afforded 2-((5-(pyrrolidin-1-yl)pyrazol-4-yl)methylene derivatives **68**. The latter compound was then cyclized intramolecularly in the presence of zinc chloride to produce the corresponding pyrazolo[3,4-*e*]indolizine **69**[73,74] (Scheme 23).



R = CH_3, C_2H_5, C_3H_7; R^1 = CN, $CONH_2$, $CSNH_2$; R^2 = $CONH_2$, $CSNH_2$.

Scheme 23. Synthesis of pyrazolo[3,4-*e*]indolizines **69.**

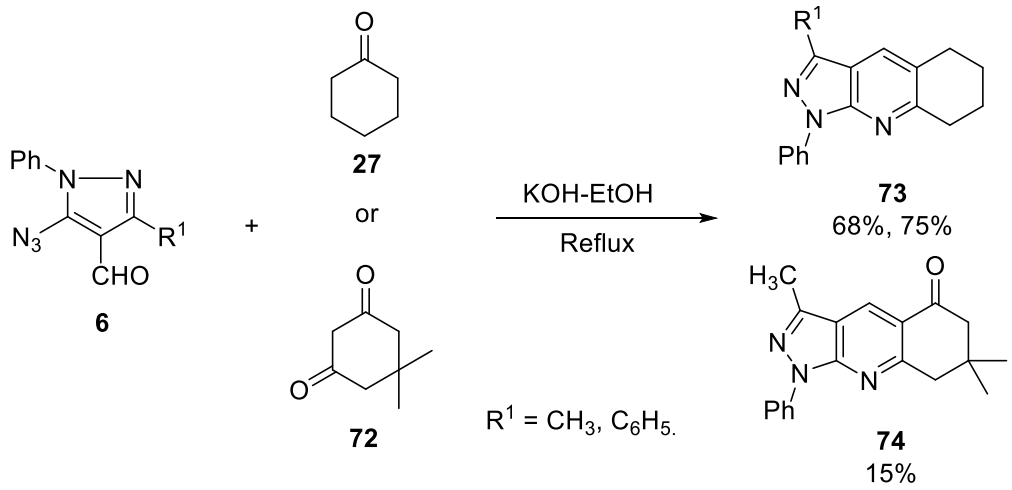
2.2.2. Fused [5-5-6] system with five heteroatoms. 2.2.2.1. Dipyrazolo[3,4-*b*:4',3'-*e*]pyridine. 2.2.2.2. Isoxazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridine. 2.2.2.3. Isothiazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridine. Abramov *et al.*[75] reported that [1+1] condensation reaction of 5-amino-1,2-azoles **70a-d** with 5-chloropyrazole-4-carbaldehydes **4a-c** at reflux in toluene afforded the corresponding dipyrazolo[3,4-b:4',3'-*e*]pyridines, isoxazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridine and isothiazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridine **71a-f** (Scheme 24).



R^1 = CH_3, C_6H_5; R^2 = C_6H_5, CH_3; R^3 = CH_3, C_6H_5; X = NC_6H_5, O, S, NCH_3.

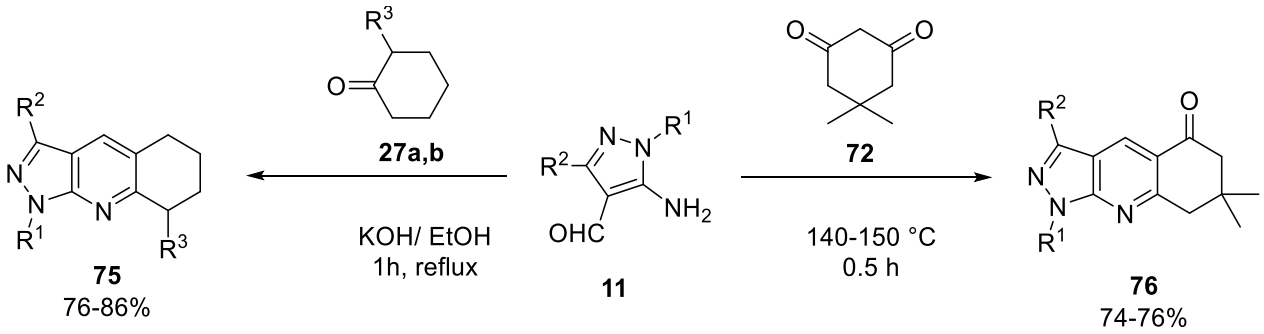
Scheme 24. Synthesis of dipyrazolo[3,4-*b*;4',3'-*e*]pyridines **71a, 71b,** and **71f**, isoxazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridines **71c** and **71d** and isothiazolo[5,4-*b*]pyrazolo[4,3-*e*]pyridines **71e.**

2.2.3. Fused [5-6-6] system with three heteroatoms. 2.2.3.1. Pyrazolo[3,4-*b*]quinoline. Zheng *et al.*[56] reported that one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes **6** with cyclohexanone **27** or dimedone **72** in a solution of ethanolic KOH afforded the corresponding 5,6,7,8-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinolines **73** and 3,7,7-trimethyl-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one **74**, respectively (Scheme 25).



Scheme 25. Synthesis of tetrahydro-1*H*-pyrazolo[3,4-*b*]quinolines **73** and **74.**

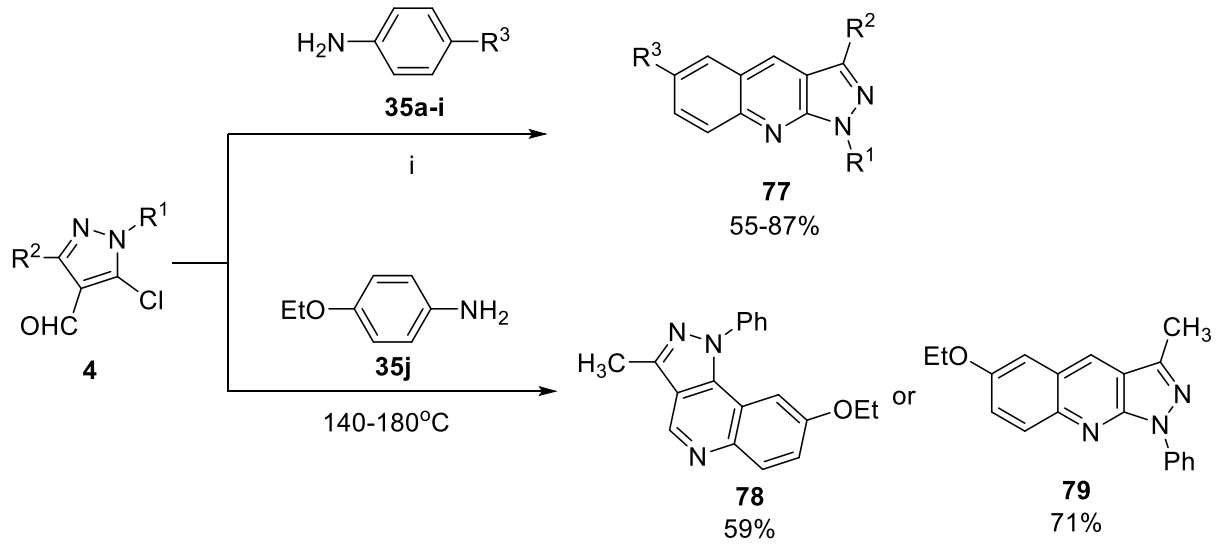
Condensation of cyclohexanone **27a**[62,70] or 2-methyl-1-cyclohexanone **27b**[70] with 5-amino-1*H*-pyrazole-4-carbaldehyde **11** afforded pyrazolo[3,4-*b*]quinoline derivatives **75**[62,70]. Heating **11** with dimedone **72** furnished pyrazolo[3,4-*b*]quinolinone derivatives **76**[70] (Scheme 26).



R^1 = C_6H_5; R^2 = 4-Cl-C_6H_4, 4-Br-C_6H_4, CH_3, C_6H_5; R^3 = H, CH_3.

Scheme 26. Synthesis of pyrazolo[3,4-*b*]quinolinone derivatives **75** and **76.**

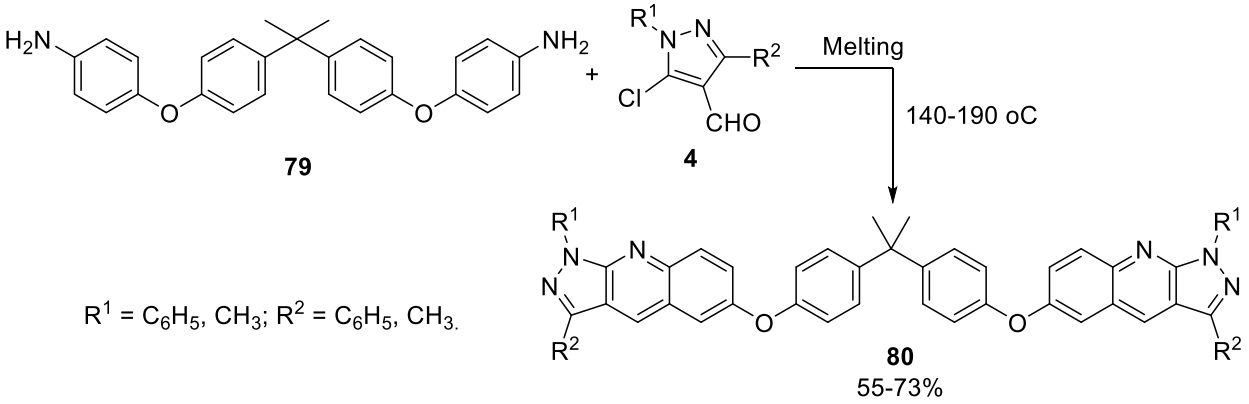
Reaction of 5-chloropyrazole-4-carbaldehydes **4** and 4-subistituted aniline **35a-i** under various conditions afforded the corresponding 1,3,6-trimethyl-1*H*-pyrazolo[3,4-*b*]quinoline **77**[76–81]. On the other hand, fusion of 4-ethoxyaniline **35j** with 1-phenyl-3-methyl-5-chloro-pyrazole-aldehyde **4** afforded 8-ethoxy-3-methyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline **78** or 6-ethoxy-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline **79**[82] (Scheme 27).



R^1 = 4-Br-C_6H_4, C_6H_5, 4-H_3CO-C_6H_4, CH_3; R^2 = C_6H_5, 4-Br-C_6H_4, 4-OCH_3-C_6H_4, CH_3; R^3 = $N(CH_3)_2$, Br, $N(C_6H_5)_2$, $N(C_6H_5)$(1-Naphthyl), 9-N-Carbazolyl, $C(C_6H_5)_3$, OCH_3, $COOC_2H_5$, H.
i = heating slowly for 20 min on an oil bath at 140-200 °C[74], melting 120-180°C[75], melting 140-200°C[75], melting 140 - 210°C. [76,77,78], melting 140 - 190°C [79].

Scheme 27. Synthesis of pyrazolo[3,4-*b*]quinolines **77** and **78** and 1*H*-pyrazolo[3,4-*c*]quinoline **79.**

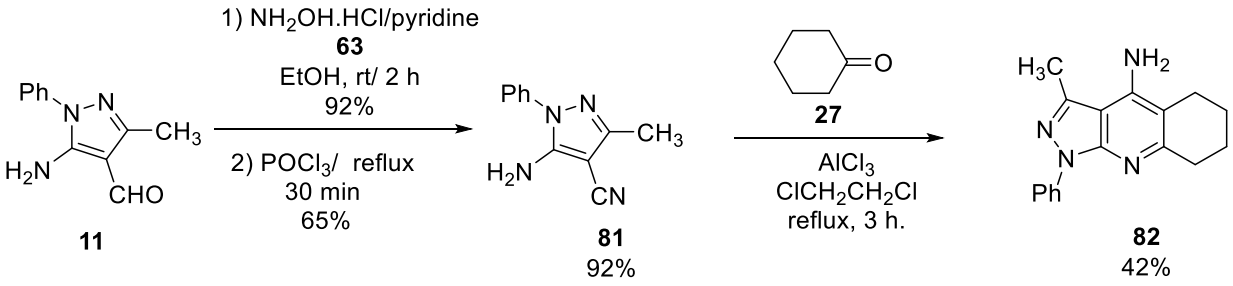
Gondek *et al.*[83] reported that aniline derivative **79** and 5-chloropyrazole-4-carbaldehydes **4** were heated together at 140–190 °C for 60 min to get pyrazolo[3,4-*b*]quinolines **80** (Scheme 28).



R^1 = C_6H_5, CH_3; R^2 = C_6H_5, CH_3.

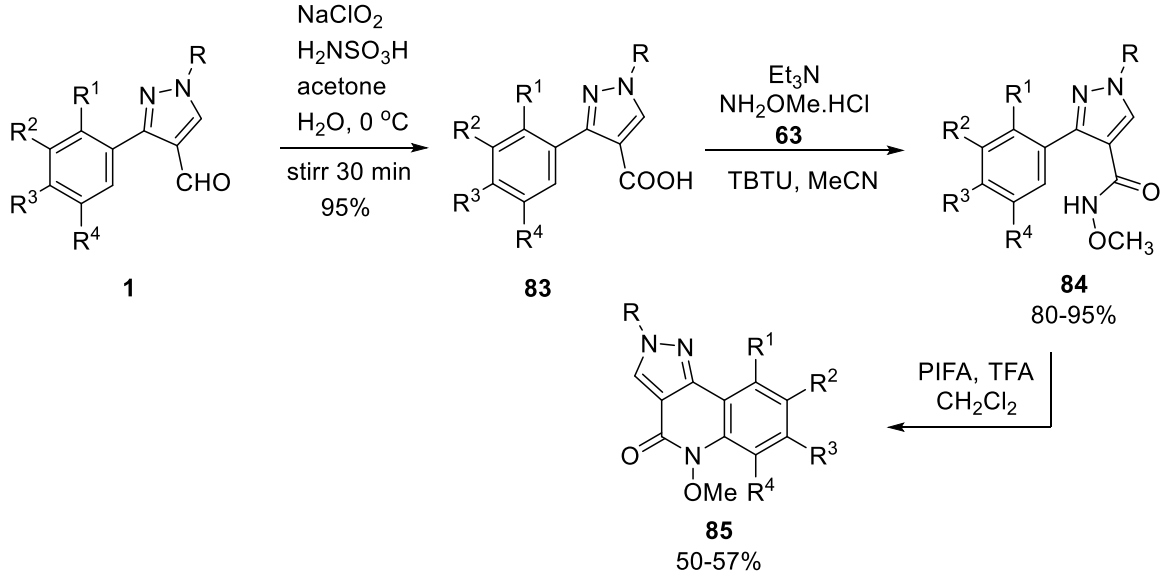
Scheme 28. Synthesis of pyrazolo[3,4-*b*]quinolines **80.**

Barreiro *et al.*[61] reported that stirring of 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **11** in ethanol at room temperature with hydroxylamine hydrochloride and pyridine to afforded the oxime intermediate. Next, 5-amino-3-methyl-1-phenyl-1*H*-5-pyrazole carbaldehyde oxime was reacted with phosphorus oxychloride at reflux to give 5-amino-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonitrile **81**. 3-Methyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-pyrazolo[3,4-*b*]quinolin-4-amine **82** was obtained from Friedländer condensation of **81** with cyclohexanone **27** (Scheme 29).



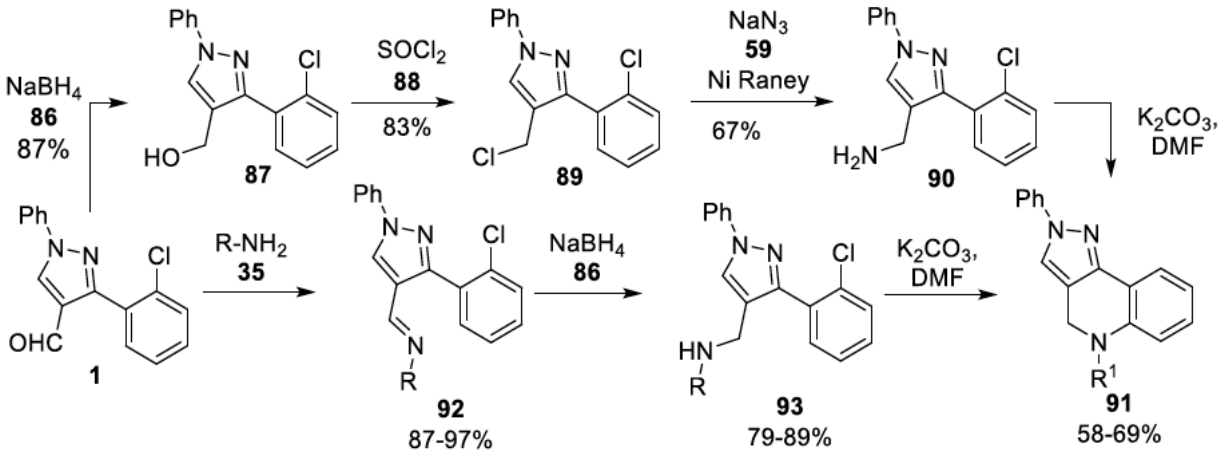
Scheme 29. Synthesis of tetrahydro-1*H*-pyrazolo[3,4-*b*]quinolin-4-amine **82.**

2.2.3.2. Pyrazolo[4,3-*c*]quinoline. Christodoulou *et al.*[84,85] reported that oxidation of the pyrazole-carbaldehydes **1** with $NaOCl_2$ in the presence of sulfamic acid as a scavenger, furnished the corresponding acids **83** which were treated with methoxylamine hydrochloride **63** in the presence of the uronium-coupling reagent *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) to provide amides **84**. The latter compounds were cyclized by phenyliodine bis(trifluoroacetate) PIFA and trifluoroacetic acid (TFA), to furnish the target 5-methoxy-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-ones **85** (Scheme 30).



Scheme 30. Synthesis of 5-methoxy-2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-ones **85.**

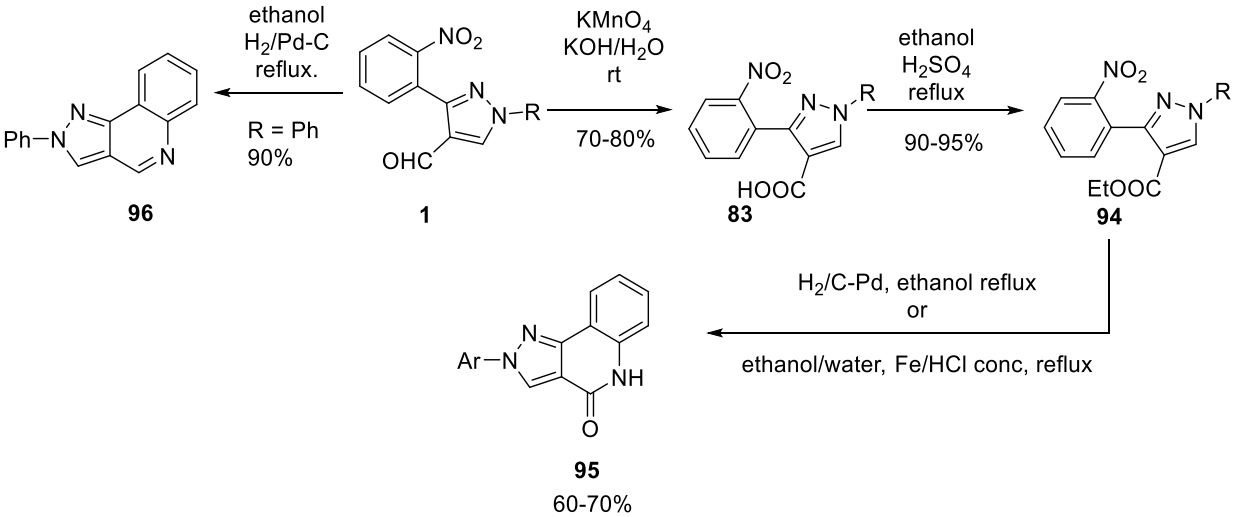
Bratenko *et al.*[86] reported that reduction of 3-(2-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** using $NaBH_4$ **86** afforded (3-(2-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methanol **87**. Compound **87** reacted with thionyl chloride **88** to afford 4-(chloromethyl)-3-(2-chlorophenyl)-1-phenyl-1*H*-pyrazole **89** which was converted into *N*-[3-(2-chlorophenyl)-pyrazol-4-yl]methylamine **90** upon treatment with sodium azide **59** and subsequent reduction with Raney Ni. The condensation of aldehyde **1** with alkylamines **35** provided azo-methines **92** which on reduction using $NaBH_4$ gave *N*-alkyl-*N*-pyrazolylmethylamines **93**. Heating of *N*-pyrazolylmethylamine **90** and *N*-alkyl-*N*-pyrazolylmethylamines **93** in boiling DMF in the presence of potassium carbonate led to the formation of the target 2-phenyl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolines **91** (Scheme 31).



R = Bu, C_6H_{11}, $HOCH_2CH_2$, $HOCH_2CH_2CH_2$, $CH_2C_6H_5$; R^1 = H, Bu, C_6H_{11}, $HOCH_2CH_2$, $HOCH_2CH_2CH_2$, $CH_2C_6H_5$.

Scheme 31. Synthesis of 2*H*-pyrazolo[4,3-*c*]-quinolines **91.**

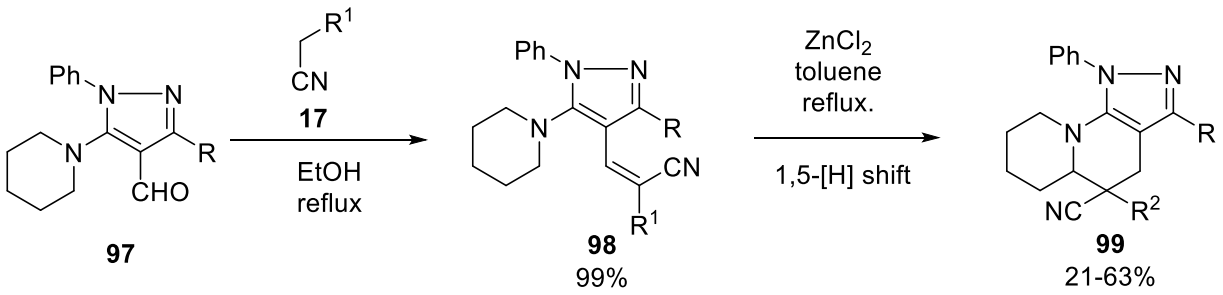
Baraldi *et al.*[87] reported that the oxidation of the pyrazole-4-carbaldehydes **1** with $KMnO_4$ yielded the pyrazole-4-carboxylic acids **83** that were transformed to the respective esters **94** in a mixture of ethanol and sulfuric acid. Hydrogenation of **1a** using hydrogen/Pd-C in ethanol afforded 2-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline **96**. Reduction of **94** with hydrogen/Pd-C or using iron powder and concentrated solution of HCl afforded 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolin-4-ones **95** (Scheme 32).



R = C_6H_5, 4-Cl-C_6H_4, 4-H_3C-C_6H_4, 4-H_3CO-C_6H_4, 3-Cl-C_6H_4, 3,4-di-Cl-C_6H_3, 4-F-C_6H_4, 2- Cl-C_6H_4, 4-($H_3CH_2CH_2CH_2C$)-C_6H_4, 4-(H_5C_2)-C_6H_4, 4-Isoprpyl-C_6H_4.

Scheme 32. Synthesis of 4*H*-pyrazolo[4,3-*c*]quinolin-4-ones **95.**

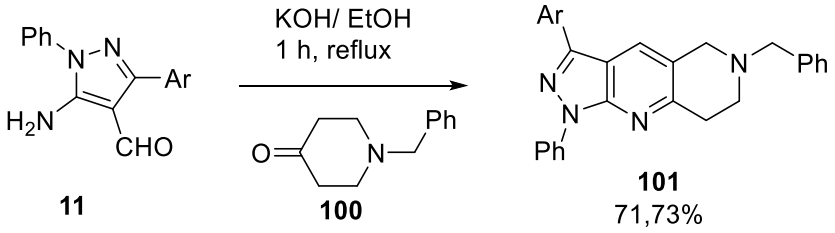
2.2.3.3. Pyrazolo[4,3-*c*]quinolizine. The reaction of 5-(piperidin-1-y)-1*H*-pyrazole-4-carbaldehyde **97** with active methylene nitriles **17** afforded arylidene **98** which then cyclized intramolecularly in the presence of zinc chloride to produce the corresponding 1,4,5,5a,6,7,8,9-octahydropyrazolo[4,3-*c*]quinolizines **99**[73,74] (Scheme 33).



$R = CH_3, C_2H_5$; $R^1 = CN, CONH_2$; $R^2 = CN, CONH_2$.

Scheme 33. Synthesis of octahydropyrazolo[4,3-*c*]quinolizines **99.**

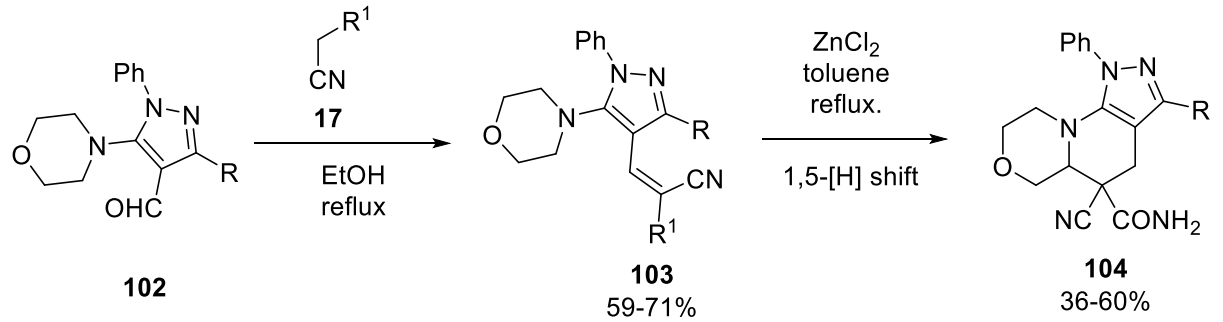
2.2.4. Fused [5-6-6] system with four heteroatoms. 4.2.4.1. Pyrazolo[3,4-*b*][1,6]naphthyridine. Jachak *et al.*[70] reported that the cyclocondensation of 5-amino-1*H*-pyrazole-4-carbaldehyde **11** with *N*-benzyl-4-piperidone **100** yielded pyrazolo[3,4-*b*][1,6]naphthyridines **101** in good yield (Scheme 34).



Ar = 4-Cl-C_6H_4, 4-Br-C_6H_4.

Scheme 34. Synthesis of pyrazolo[3,4-*b*][1,6]naphthyridines **101.**

2.2.4.2. Pyrazolo[4',3':5,6]pyrido[2,1-*c*][1,4]oxazine. Reaction of 5-morpholino-1*H*-pyrazole-4-carbaldehydes **102** with active methylene nitriles afforded arylidene derivatives **103** which then cyclized intramolecularly in the presence of zinc chloride to produce the corresponding 5-cyano-pyrazolo[4',3':5,6]pyrido[2,1-*c*][1,4]oxazine-5-carboxamides **104**[73,74] (Scheme 35).

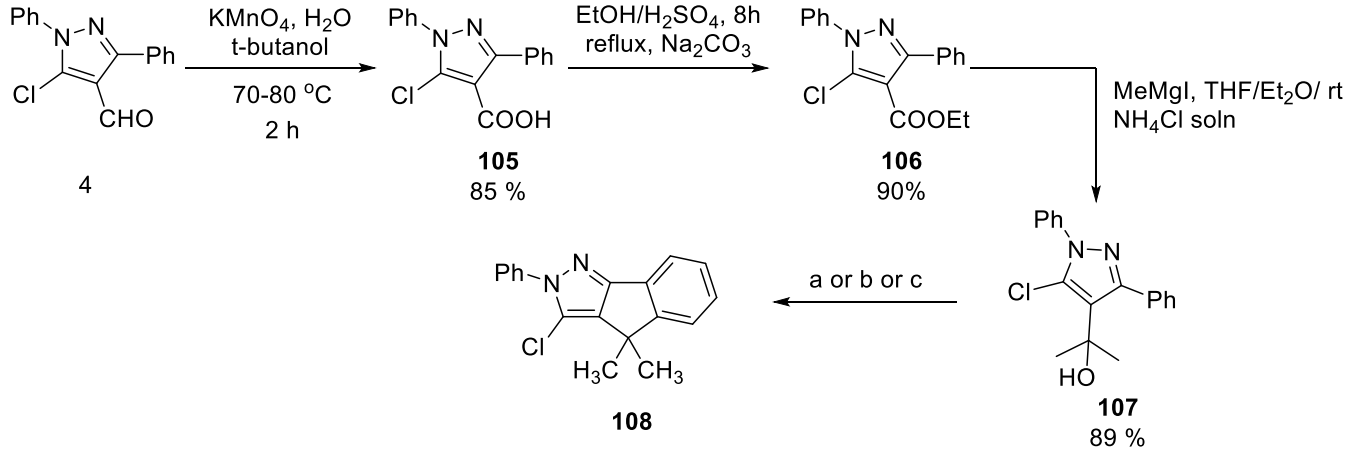


$R = CH_3, C_2H_5$; $R^1 = CN, CONH_2$.

Scheme 35. Synthesis of pyrazolo[4',3':5,6]pyrido[2,1-*c*][1,4]oxazine-5-carboxamides **104.**

2.2.5. Fused [6-5-5] system with two heteroatoms. 2.2.5.1. Indeno[1,2-*c*]pyrazole. El-Aal *et al.*[88] reported that 5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxylic acid **105** were obtained utilizing $KMnO_4$ oxidation of the

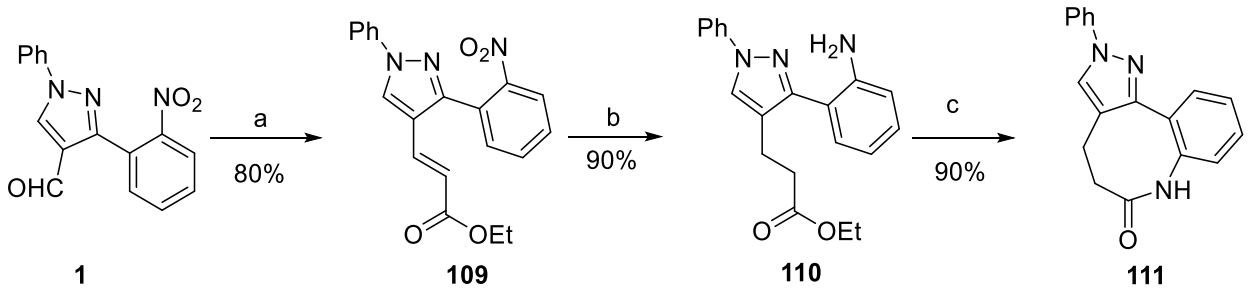
5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **4**. Heating **105** in absolute ethanol at reflux and concentrated sulfuric acid afforded ethyl-5-chloro-1,3-diphenyl-1*H*-pyrazole-4-carboxylate **106** which were smoothly reacted with the Grignard reagent to give alkanols **107**. Cyclization of the 2-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)propan-2-ol **107** by a Friedel–Crafts-type ring closure afforded the 3-chloro-2,4-dihydro-4,4-dimethyl-2-phenylindeno[1,2-*c*]pyrazole **108** (Scheme 36).



a: $AlCl_3$/ CH_3NO_2, DCM, 20 h, rt (86%); b: Phosphorus pentoxide (P_2O_5), Toluene, 8 h, reflux (75%);
c: Phenylpropanolamine (PPA), 4 h, 200-210 °C (72%).

Scheme 36. Synthesis of 3-chloro-2,4-dihydro-4,4-dimethyl-2-phenylindeno[1,2-*c*]pyrazole **108.**

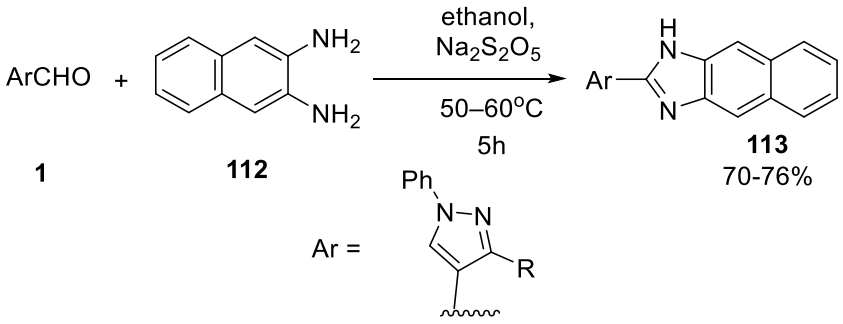
2.2.6. Fused [6-5-8] system with three heteroatoms. 2.2.6.1. Benzo[*b*]pyrazolo[3,4-*d*]azocine. Baraldi *et al.*[87] reported that reaction of 3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** with triphenyl-λ^5-phosphanylidene-acetic acid ethyl ester (Wittig reaction) afforded ethyl-3-(3-(2-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)acrylate **109** which was hydrogenated to give ethyl-3-(3-(2-aminophenyl)-1-phenyl-1*H*-pyrazol-4-yl)acrylate **110**. Subsequent treatment of **110** with NaH afforded 2-phenyl-2,4,5,7-tetrahydro-6*H*-benzo[*b*]pyrazolo[3,4-*d*]azocin-6-one **111** (Scheme 37).



a: Tripheny phosphanylidene-acetic acid ethyl ester, $CHCl_3$, 70 °C; b: Ethanol, C-Pd, H_2, c: NaH 60%, toluene, reflux.

Scheme 37. Synthesis of 6*H*-benzo[*b*]pyrazolo[3,4-*d*]azocin-6-one **111.**

2.2.7. Fused [6-6-5] system with two heteroatoms. 2.2.7.1. Naphtho[2,3-*d*]imidazole. Reddy *et al*.[89] reported that naphtho[2,3-*d*]imidazoles **113** were synthesized by the reaction of pyrazole-4-carbaldehyde **1** with naphthalene-2,3-diamine **112** in ethanol and sodium meta-bisulphite ($Na_2S_2O_5$) (Scheme 38).

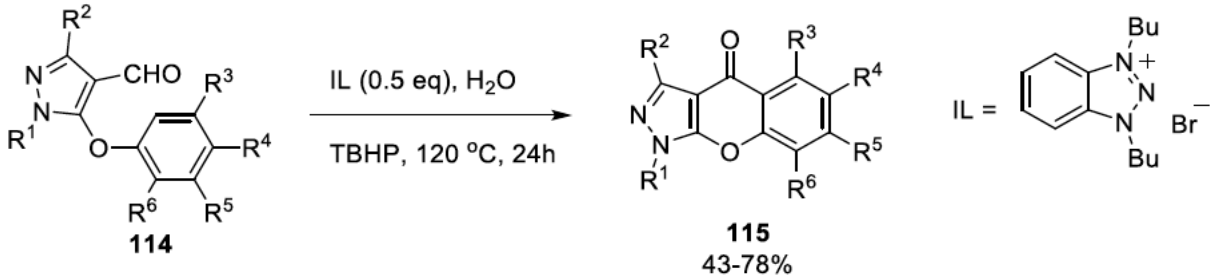


R = C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-H_3CO-C_6H_4.

Scheme 38. Synthesis of naphtho[2,3-*d*]imidazoles **113.**

2.2.8. Fused [6-6-5] system with three heteroatoms

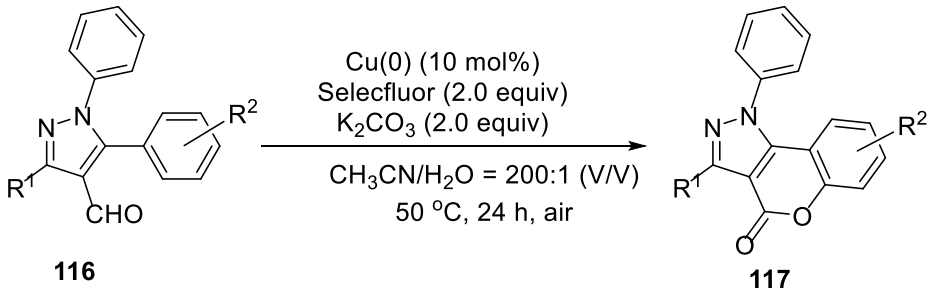
2.2.8.1. Chromeno[2,3-*c*]pyrazole. Heterocyclic ionic liquid (IL) promoted C−H bond oxidative cross-coupling reaction for the intramolecular annulation of 5-(aryloxy)-1*H*-pyrazole-4-carbaldehydes **114** to chromeno[2,3-*c*]pyrazol-4(1*H*)-ones **115**[90] (Scheme 39).



R^1 = C_6H_5, CH_3; R^2 = CH_3, C_6H_5; R^3 = H, CH_3; R^4 = H, Cl, Br, F, CN, NO_2, CH_3, C_6H_5, t-Bu, OCH_3;
R^3R^4 = -$(CH)_4$-; R^5 = H, OCH_3, CH_3; R^6 = H, CF_3, CH_3, OCH_3.
IL: 1,3-Dibutyl-1H-benzo[d]-[1,2,3]triazol-3-ium bromide ([Dbbta]Br)
TBHP = tert-Butyl hydroperoxide as oxidant free.

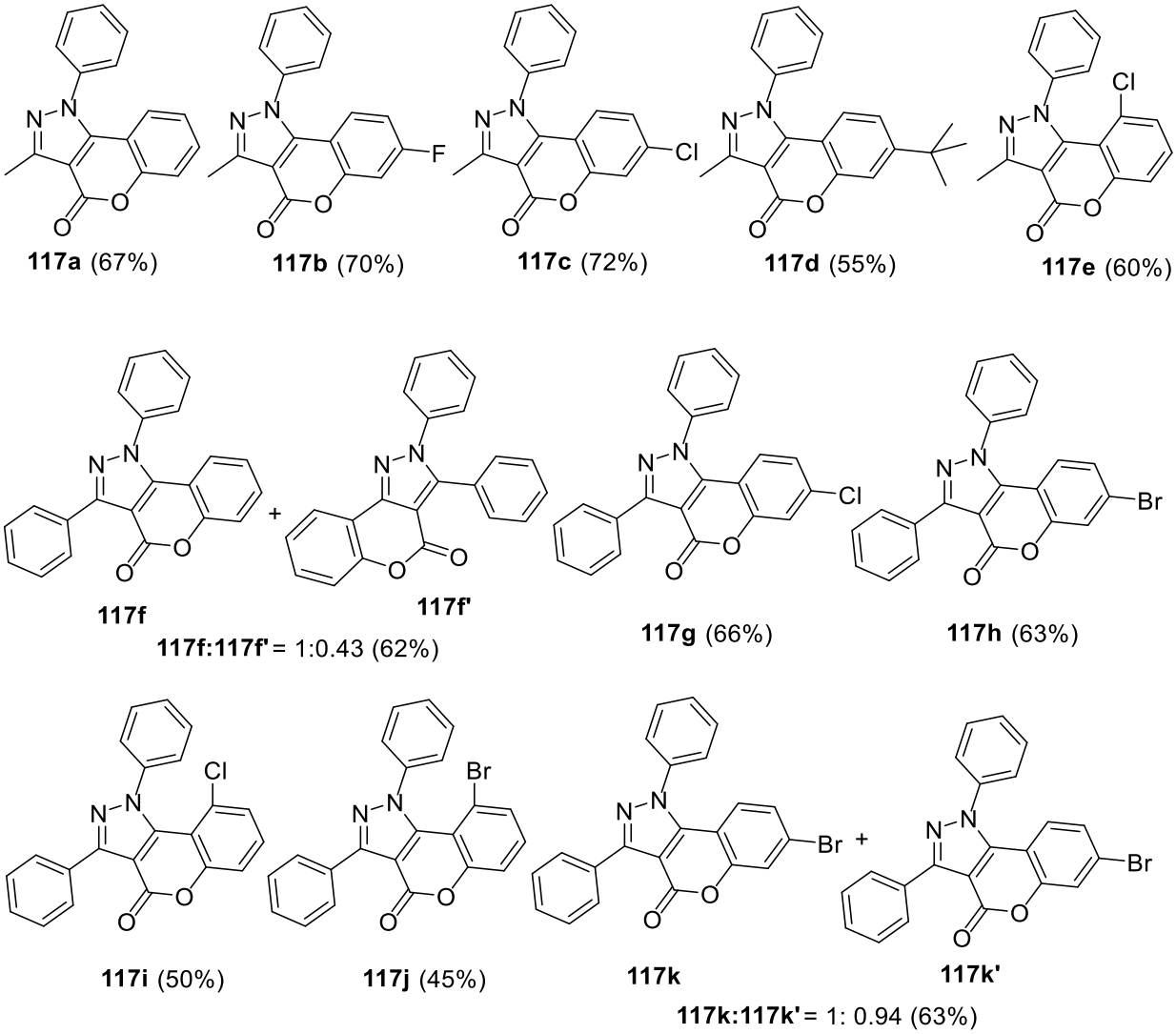
Scheme 39. Synthesis of chromeno[2,3-*c*]pyrazol-4(1*H*)-ones **115.**

2.2.8.2. Chromeno[4,3-*c*]pyrazole. Under a Cu(0)/Selectfluor catalyzed system, a range of 3-methyl-1,5-diphenyl-1*H*-pyrazole-4-carbaldehydes **116** could be intramolecularly lactonized to chromeno[4,3-*c*]pyrazoles **117** in moderate to good yields (55-72%, **117a**-**e**, Scheme 40, Table 1). For substrate **116** possessing two phenyl rings adjacent to the formyl group, the cross-dehydrogenative C-O coupling reaction predominantly took place in the phenyl ring substituted with stronger electron-withdrawing groups (**117g**-**117j**, Scheme 40, Table 1). When **116f** was used as the substrate, the reaction gave a regioisomeric mixture of **117f** and **117f'** in a total yield of 62% with a molar ratio of 1:0.41 determined by NMR analyses (**116f**, Scheme 40, Table 1). Similarly, the intramolecular lactonization of **116k** resulted in a regioisomeric mixture of **117k** and **117k'** in a total yield of 63% with a molar ratio of 1:0.94 (**116k**, Scheme 40, Table 1).[91]



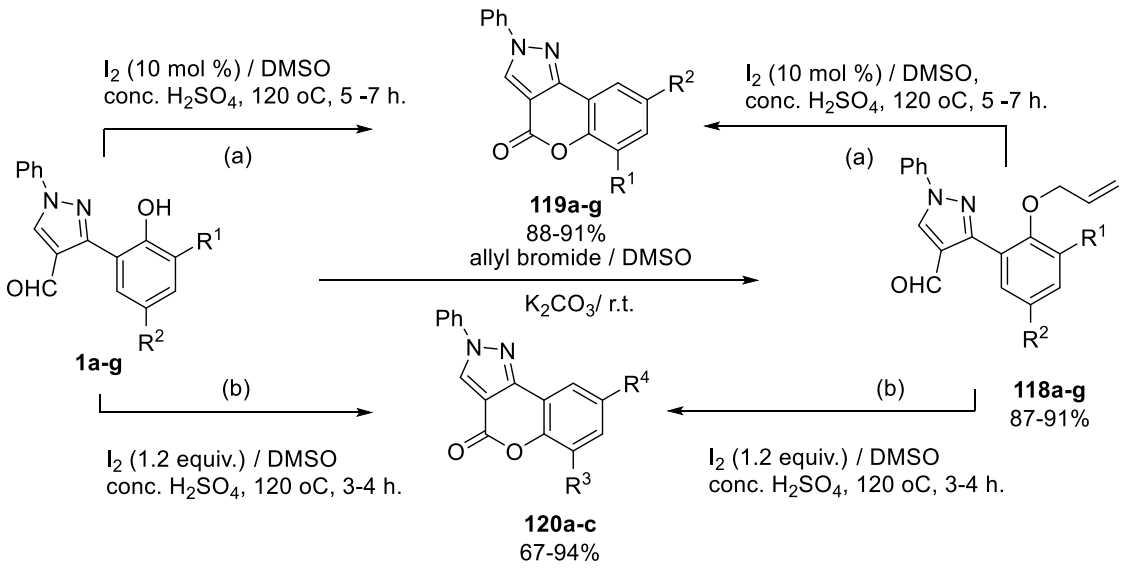
Scheme 40. Synthesis of chromeno[4,3-*c*]pyrazoles **117.**

Table 1. Cu(0)/Selecfluor system-catalyzed double C-H activation/oxygen insertion of 5-arylpyrazole-4-carbaldehydes **116a,b**



Lokhande *et al.*[92] reported the synthesis of 3-(2-(allyloxy aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes **118a-g** *via* stirring of pyrazole-4-carbaldehydes **1a-g** with allyl bromide in DMSO, K_2CO_3. When 3-(2-hydroxyaryl)pyrazole-4-carbaldehydes **1a-g** or 3-(2-(allyloxyaryl)pyrazole-4-carbaldehydes **118a-g** were heated at 120 ℃ in DMSO in the presence of iodine (10 mol %) and 4-5 drops of concentrated H_2SO_4, 2-arylpyrazolo[4,3-*c*]coumarin derivatives **119a-g** were obtained in good yields. On the other hand, when

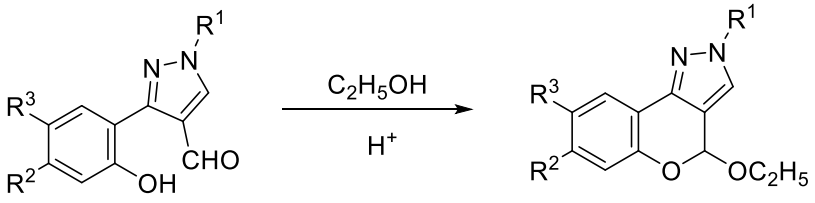
3-(2-hydroxyaryl)pyrazole-4-carbaldehydes **1a-c** or 3-(2-(allyloxyaryl)pyrazole-4-carbaldehydes **118a-c** were heated at 120 ℃ DMSO in the presence iodine (1.2 equiv.) and 4-5 drops of concentrated H_2SO_4 gave 2-phenylchromeno[4,3-*c*]pyrazol-4(2*H*)-one derivatives **120a-c** (Scheme 41).



	R^1	R^2		R^1	R^2			R^1	R^2		R^1	R^2
1a	H	Cl	**118a**	H	Cl	**119a**	1a	H	Cl	**120a**	I	Cl
1b	H	Br	**118b**	H	Br	**119b**	1b	H	Br	**120b**	I	Br
1c	Cl	H	**118c**	Cl	H	**119c**	1c	Cl	H	**120c**	Cl	I
1d	Cl	Cl	**118d**	Cl	Cl	**119d**	1d	Cl	Cl			
1e	Br	Br	**118e**	Br	Br	**119e**	1e	Br	Br			
1f	Br	Cl	**118f**	Br	Cl	**119f**	1f	Br	Cl			
1g	Br	Me	**118g**	Br	Me	**119g**	1g	Br	Me			

Scheme 41. Synthesis of 2-phenylchromeno[4,3-*c*]pyrazol-4(2*H*)-one derivatives **119** and **120.**

3-(2-Hydroxy-substitutedphenyl)-1-aryl-1*H*-pyrazole-4-carbaldehydes **1** were cyclized to 4-ethoxy-2,4-dihydrochromeno[4,3-*c*]pyrazoles **121** upon treatment with ethanol containing a catalytic amount of hydrochloric acid[93] or sulfuric acid[94] to 4-ethoxy-2,4-dihydrochromeno[4,3-*c*]pyrazoles **121**[93, 94] (Scheme 42).

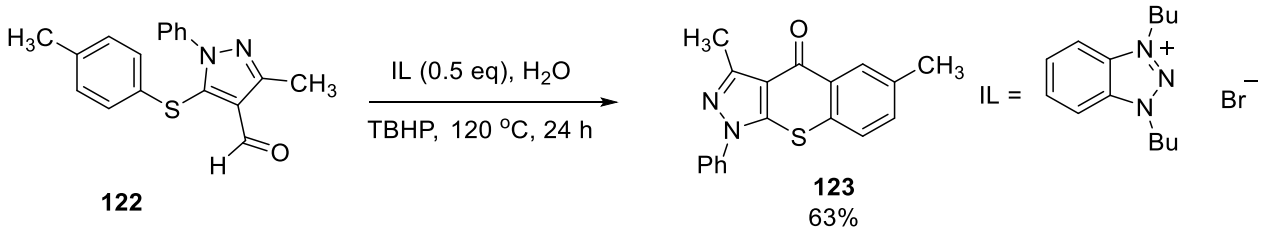


1 **121**
52-85%

R^1 = C_6H_5, 4-Cl-C_6H_4, 2-H_3C-C_6H_4, 2-H_3CO-C_6H_4, 2,4-di-(H_3C)-C_6H_3, 2,4-di-(O_2N)-C_6H_3;
R^2 = H, OCH_3; R^3 = H, CH_3, OCH_3, Cl.

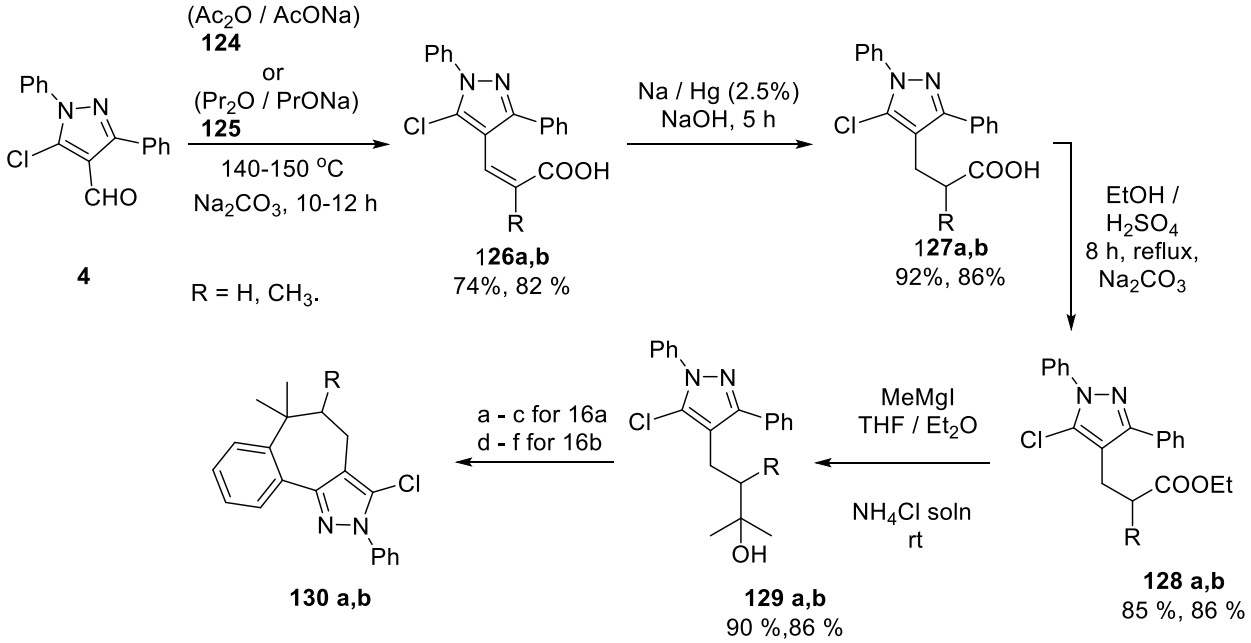
Scheme 42. Synthesis of 4-ethoxy-2,4-dihydrochromeno[4,3-*c*]pyrazoles **121.**

2.2.8.3. Thiochromeno[2,3-*c*]pyrazole. Li *et al.*[90] reported that intramolecular cross-coupling reaction of 3-methyl-1-phenyl-5-(*p*-tolylthio)-1*H*-pyrazole-4-carbaldehyde **122** using 1,3-dibutyl-1*H*-benzo[*d*][1,2,3]triazol-3-ium bromide IL and *tert*-butyl hydroperoxide (TBHP) as an oxidant afforded 3,6-dimethyl-1-phenylthiochromeno[2,3-*c*]pyrazol-4(1*H*)-one **123** (Scheme 43).



Scheme 43. Synthesis of phenylthiochromeno[2,3-*c*]pyrazol-4(1*H*)-one **123.**

2.2.9. Fused [6-7-5] system with two heteroatoms. 4.2.9.1. Benzo[6,7]cyclohepta[1,2-*c*]pyrazole. El-Aal *et al.*[88] reported that acrylic acids **126a** and **126b** were obtained by heating of pyrazole-4-carbaldehyde **4** with acid anhydride **124** and **125** and sodium salt of the corresponding acid, respectively. Subsequent reduction of **126a** and **126b** with sodium amalgam gave propanoic acid derivatives **127a** and **127b** which underwent esterification upon treatment with ethanol in the presence of sulfuric acid to give ethyl propanoate derivatives **128a** and **128b**. The reaction of Grignard reagent CH_3MgI in ether with esters **128a** and **128b** gave 4-(5-chloro-1,3-diphenyl-1*H*-pyrazol-4-yl)-2,3-dimethylbutan-2-ols **129a** and **129b**. Cyclization of compounds **129a** and **129b** by a Friedel–Crafts-type ring closure afforded benzo[6,7]cyclohepta[1,2-*c*]pyrazole derivatives **130a** and **130b**, respectively (Scheme 44).

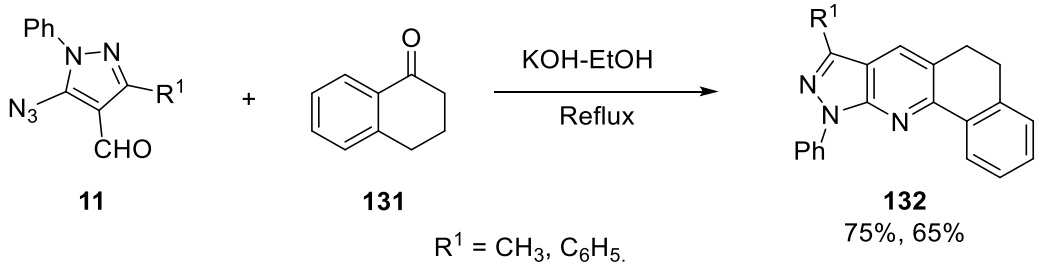


a: $AlCl_3$ / CH_3NO_2, DCM, 1 h, rt (83%); b: P_2O_5, PhH, 4 h, reflux (79%); c: PPA, 1 h, 200-210 °C (74%); d: $AlCl_3$ / CH_3NO_2, DCM, 1 h, rt (86%); e: P_2O_5, PhH, 4 h, reflux (80%); f: PPA, 1 h, 200-210 °C (77%).

Scheme 44. Synthesis of benzo[6,7]cyclohepta[1,2-*c*]pyrazole derivatives **130.**

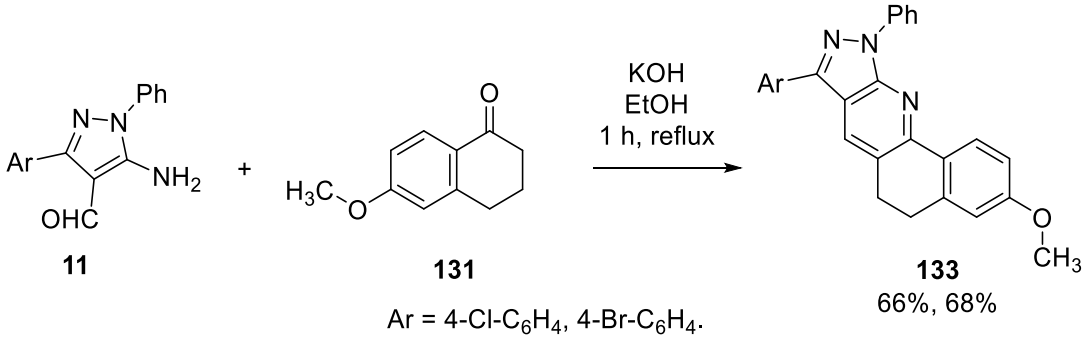
2.3. Pyrazole fused within a tricyclic system

2.3.1. Fused [6-5-6-6] system with three heteroatoms. 2.3.1.1. Benzo[*h*]pyrazolo[3,4-*b*]quinoline. Zheng *et al.*[56] reported that a one-pot reaction of 5-azido-1-phenylpyrazole-4-carbaldehydes **11** with 1-tetralone **131** in a solution of ethanolic KOH afforded the corresponding 10-phenyl-6,10-dihydro-5*H*-benzo[h]pyrazolo[3,4-*b*]quinolines **132** (Scheme 45)**.**



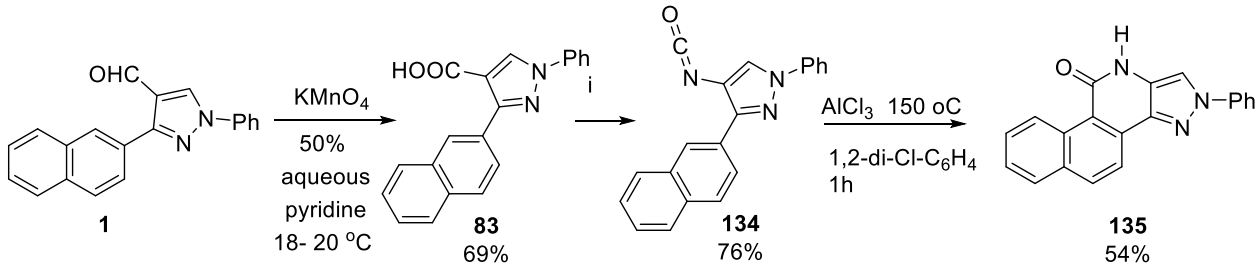
Scheme 45. Synthesis of 10-phenyl-6,10-dihydro-5*H*-benzo[*h*]pyrazolo[3,4-*b*]quinolines **132.**

Jachak *et al.*[70] reported that the cyclocondensation of **11** with 6-methoxy-1-tetralone **131** yielded benzo[*h*]pyrazolo[3,4-*b*]quinolines **133** in moderate yields (Scheme 46).



Scheme 46. Synthesis of benzo[*h*]pyrazolo[3,4-*b*]quinolines **133.**

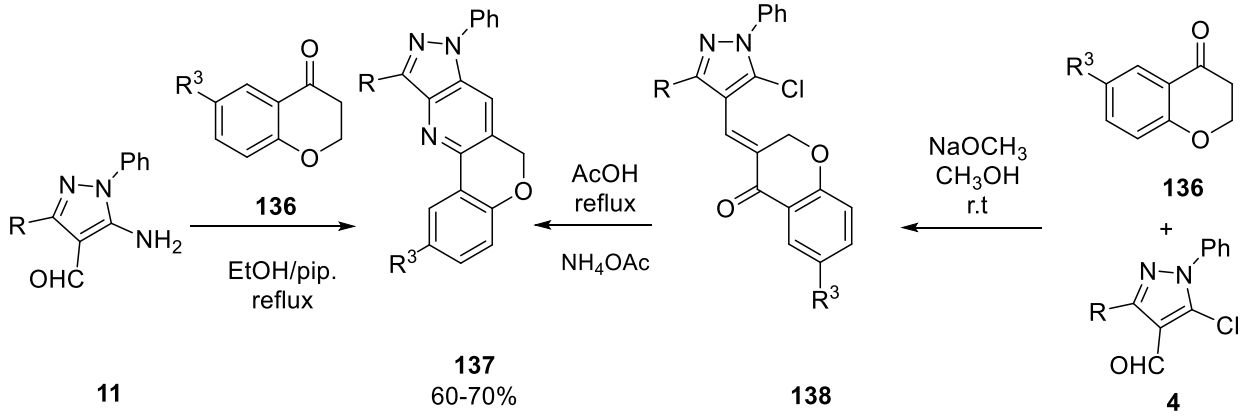
2.3.1.2. Benzo[*h*]pyrazolo[4,3-*c*]isoquinolin. Vovk *et al*.[95] reported that treatment of 4-formyl-3-(2-naphthyl)-3-(naphthalen-2-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1** with potassium permanganate afforded 3-(2-naphthyl)-1-phenylpyrazole-4-carboxylic acid **83**. Heating of compound **83** with thionyl chloride and drops of DMF followed by treatment of the acid chloride formed with trimethylsilyl azide in toluene afforded 4-isocyanato-3-(2-naphthyl)-1-phenylpyrazole **134**. When a solution of **134** in *o*-dichlorobenzene was added to a suspension of $AlCl_3$ in *o*-dichlorobenzene, 2-phenyl-2*H*-benzo[*h*]pyrazolo[4,3-*c*]isoquinolin-10(11*H*)-one **135** was obtained in good yield (Scheme 47).



i = 1) $SOCl_2$ / DMF anh. / toluene boiled for 2 h;
2) trimethylsilyl azide in toluene boiling mixture over 0.5 h; 3) heated for 4 h until evolution of N_2 ceased.

Scheme 47. Synthesis of 2*H*-benzo[*h*]pyrazolo[4,3-*c*]isoquinolin-10(11*H*)-one **135**

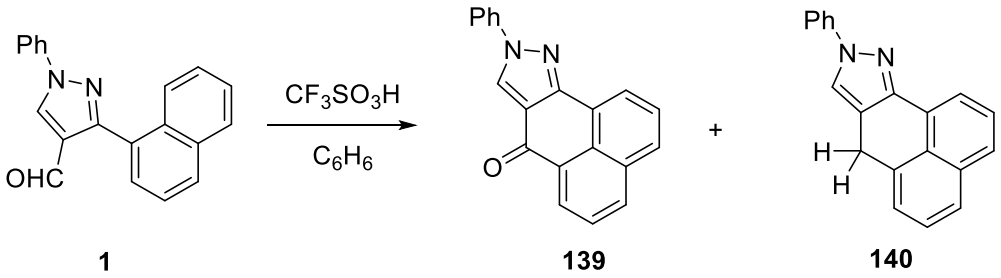
2.3.2. Fused [6-6-5-6] system with three heteroatoms. 2.3.2.1. Benzopyrano[4',3'-*e*] pyrazolo[3,4-*b*]pyridine. Sabitha *et al*.[59] reported that the condensation of 5-amino-1-phenyl-1*H*-pyrazole-4-carbaldehyde **11** with 4-chromanone **136** at reflux in ethanol in the presence of a catalytic amount of piperidine gave 8-phenyl-6,8-dihydrochromeno[4,3-*b*]pyrazolo[3,4-*e*]pyridines **137**. Also, when, 5-chloro-1-phenyl-1*H*-pyrazole-4-carbaldehyde **4** was treated with 4-chromanone **136** in NaOEt/EtOH at room temperature it gave the 8-phenyl-6,8-dihydrochromeno[4,3-b]pyrazolo[3,4-e]pyridines **137** *via* the intermediacy of **138** by heating in AcOH with NH_4OAc (Scheme 48).



R = CH_3, Ph; R^3 = H, CH_3, Cl.

Scheme 48. Synthesis of chromeno[4,3-*b*]pyrazolo[3,4-*e*]pyridines **137.**

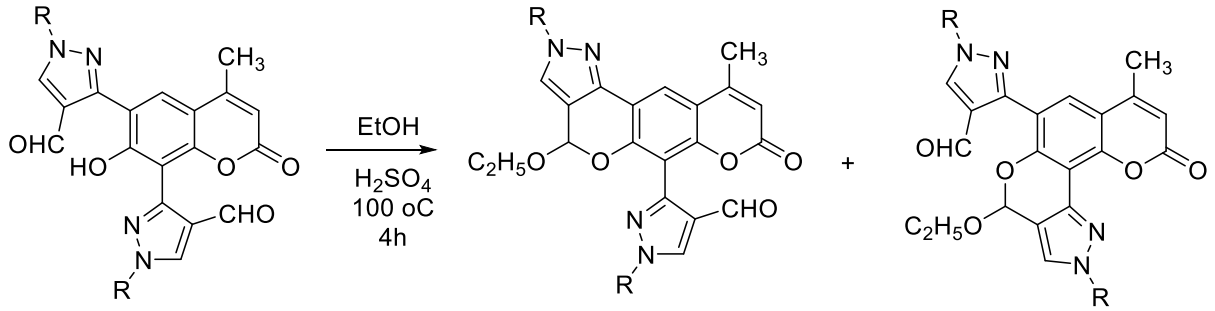
2.3.3. Fused [6-6-6-5] system with two heteroatoms. 2.3.3.1. Naphtho[1,8-*fg*]indazole. Naphthyl-substituted pyrazole **1** undergo intramolecular Friedel–Crafts-type reactions to afforded 9-phenylnaphtho[1,8-*fg*]indazol-7(9*H*)-one **139** and 9-phenyl-7,9-dihydronaphtho[1,8-*fg*]indazole **140** in roughly equimolar amounts *via* reaction with trifluoromethanesulfonic acid (CF_3SO_3H)[96] as Brønsted acid (Scheme 49).



1 **139** **140**

Scheme 49. Synthesis of naphtho[1,8-*fg*]indazolone **139** and 7,9-dihydronaphtho[1,8-*fg*]indazole **140.**

2.3.4. Fused [6-6-6-5] system with four heteroatoms. 2.3.4.1. Pyrano[3',2':6,7]chromeno[4,3-*c*]pyrazole. Ajay *et al.*[97] reported that pyrano[3',2':6,7]chromeno[4,3-*c*]pyrazoles **141** and pyrano[2',3':5,6]chromeno[4,3-*c*]pyrazoles **142** were synthesized by the cyclocondensation reaction of 3,3'-(7-hydroxy-4-methyl-2-oxo-2*H*-chromene-6,8-diyl)bis(1-aryl-1*H*-pyrazole-4-carbaldehydes) **1** in ethyl alcohol in the presence of conc. H_2SO_4 under reflux conditions (Scheme 50).



1

141
48-59%

142
36-38%

R = H, 4-H_3C-C_6H_4, 4-H_3OC-C_6H_4, 4-F-C_6H_4, $CONH_2$, $CSNH_2$.

Scheme 50. Synthesis of pyrano[3',2':6,7]chromeno[4,3-*c*]pyrazoles **141** and pyrano[2',3':5,6]chromeno[4,3-*c*]pyrazoles **142.**

Conclusions

Nitrogen-based heterocyclic chemistry is a special and significant branch of organic chemistry that has recently gotten a lot of attention. There has been a lot of emphasis on developing new structures for this class of molecules. *N*-heterocyclic compounds' pharmacological properties have been reported.

They are components of a wide range of biologically important naturally occurring compounds. Due to their broad range of applications, pyrazole derivatives are one of the most active groups of five-member heterocycles among the various nitrogen-containing heterocycles. The utility of pyrazole-4-carbaldehydes as precursors for the preparation of pyrazole-fused heterocyclic systems over the last two decades was highlighted in this study. Our group recently reviewed various synthetic methods for the preparation of pyrazole-4-carbaldehydes and their utility as versatile precursors for various pyrazole-substituted heterocyclic systems as hybrid molecules. The heterocyclic compounds discussed in this review are categorized according

to the size of the heterocyclic ring, as well as the position and number of heteroatoms. We hope that this study will be useful to researchers interested in medicinal chemistry as well as synthetic organic chemists.

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