

PİRAZOL TÜREVLERİNİN SENTEZ YÖNTEMLERİ
SYNTHESIS METHODS OF PYRAZOLE DERIVATES

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ÖZET

Bu derlemede pirazollerin sentez süreçlerini incelemek hedeflenmiştir. Heterosiklik bileşiklerin önemli bir sınıfını oluşturan pirazoller biyoaktif özelliklerinden dolayı geniş bir çalışma alanı olarak önemi artarak devam etmektedir. Pirazoller biyolojik aktif çeşitliliğine sahiptir. Bu bileşikler ilaç araştırmalarında ve tarım ürünleri geliştirmesinde kullanılmaktadır. Böylece pirazollerin sentezi için geliştirilmiş metotlar daha önemli hale gelmektedir.

Anahtar Kelimeler: Heterosiklik kimya, organik kimya, organik sentez, pirazol.

ABSTRACT

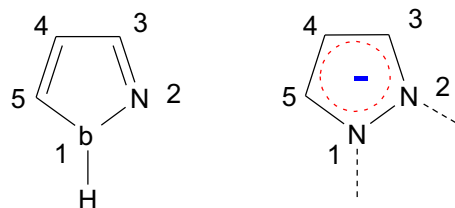
In this review was aimed to describe process synthesis of pyrazoles. Important classes of heterocyclic compounds forming pyrazoles have continued to grow important because of their wide-spread of study area by biological activity. The pyrazoles have biological activities diversity. These compounds are used in the development of agricultural products and in drug researches. Thus, the methods developed for the synthesis of pyrazoles are becoming more importance.

Key Words: Heterocyclic chemistry, organic chemistry, organic synthesis, pyrazole.

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1. INTRODUCTION

Chemistry of heterocyclic compounds is one of the most complicated of the organic chemistry. Chemistry of heterocyclic compounds is interesting for the diversity of its synthetic procedures and equally theoretical implications for physiological and industrial significance of heterocyclic compounds. In particular, heterocyclic compounds commonly investigate only in themselves but also many natural products, many drugs, medicines and dyes. It seems heterocyclic more than one-third of organic compounds. Many alkaloids, vitamins, antibiotics, many synthetic pesticides and dyes *i.e.*, and so many substances are closely connected with the life cycle (such as nucleic acids). The most important "heteroatom" is available nitrogen, oxygen and sulfur. Pyrazole is a simple aromatic ring an organic compound of the heterocyclic series by is characterized five-membered ring structure which comprises located adjacent two nitrogen atoms and three carbon atoms in scheme1. Pyrazoles have π -electrons in the heterocycle. N atom attracts ring electrons due to electro negativity so that the C (3) and C (5) becomes partially electropositive and becomes suitable to participate in nucleophilic. All of the 1,2-azoles, pyridine nitrogen and C (4) atoms have been focused on the π -electron and moves positive charge as well as other heteroatoms. C (3) and C (5) atom of the π -electron charge can be positive or negative depending on the heterocycle. The highest degree of bond C (3)-N and C (4) - C (5) was found between atoms. Bond order is the lowest of the heteroatoms. N atom of nucleophilic and the steric accessibility can be varied by appropriate ring substitution. Although attractive features and powerful advances in the chemistry of pyrazole, The interest show on pyrazole and pyrazole derivative compounds have been limited up to 70s [1].



Scheme1. Pyrazole

The pyrazole is one of heterocyclic compounds. Firstly pyrazole was obtained from decarboxylation pyrazol-3,4,5-tricarboxylic acid in figure1. Pyrazole was defined for the first time by Buchner in 1889 [2].

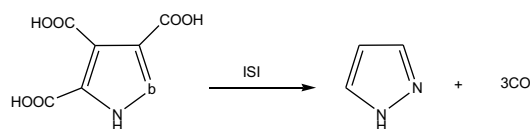
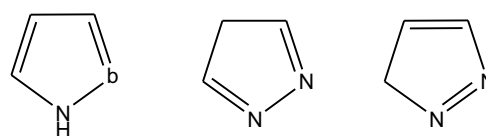


Figure1. Synthesis of pyrazole

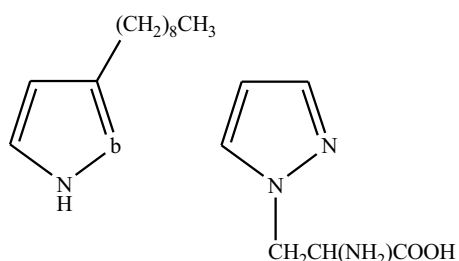
Basic information on their aromatic properties were obtained to compared with benzene derivatives about chemistry of organic substances bearing pyrazole group. Since try to pyrazole, it was based on a structural problem with the center present Tautomerism of the N-substituent and resulting from derivatives and isomers of the N-substituent. Pyrazole ring can be represented by different tautomeric structures in scheme2. Three tautomeric forms can be written for pyrazole non-substituents.



Scheme2. Tautomeric structures of pyrazole non-substituents

Until recently pyrazole was believed absent in nature. However the first natural pyrazole derivative was isolated by Japanese workers in 1954. Houltuynia cordata was isolated from 3-n-nonyl pyrazole which is a

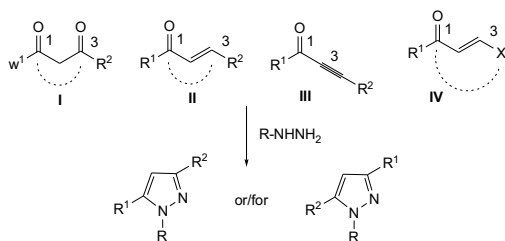
plant of the family "Piperaceae" Tropical Asia [3]. They observed the antimicrobial activity. Another natural pyrazole derivative is Levo-β-(1-pyrazolyl) alanine [4]. Pyrazolic amino acids were isolated from watermelon seed (*Citrullus Vulgaris*). They are currently the only known natural pyrazole derivatives in scheme3.



Scheme3. Examples of naturally occurring pyrazoles

2. SYNTHESIS OF PYRAZOLES

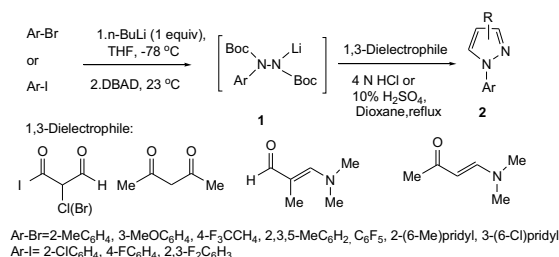
3 - and 5-positions in the various alkyl or aryl substituents including the 1,3-dicarbonyl (I), α, β-unsaturated carbonyl compounds (II, III) and β-enaminones or related compounds (IV) such as 1,3 positions two electrophilic carbon feature with a triple carbon units that act as a pair of nucleophile containing a suitable cyclocondensation with hydrazine for the preparation of pyrazole to functional C-3 and C-5 is used a very common method in scheme4 [5].



Scheme4. Synthesis of substitute pyrazole

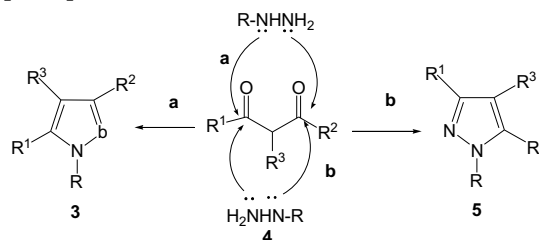
Recently a study of conducted, one-pot approach based on cyclocondensation of compounds 1,3-di electrophilic with aryl hydrazine Bis-Boc protected (1) was shown as

an alternative method suitable for the synthesis of some difficult available of N-aryl pyrazoles (2) in scheme5 [6].



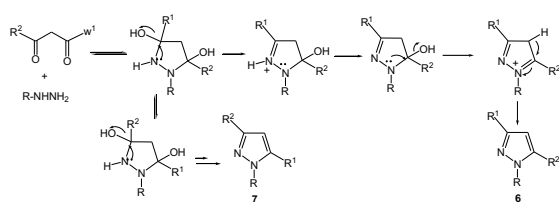
Scheme5. Synthesis of N-aryl pyrazoles

1,3-diketones, β-ketoesters and 2,4-diketoester condensation with hydrazines were widely used in the preparation N-substituent and non N-substituent -3,5- and 3,4,5-alkyl/(het)aryl pyrazoles, alkoxy pyrazoles and pyrazole of carboxylic esters, respectively. 3- and 5-positions in the various alkyl (4) and aryl (5) bearing the substituent simple pyrazoles could occur in that condensed effectively hydrazines with 1,3-diketones (3) in scheme6 [7-10].



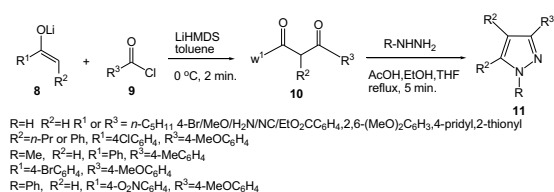
Scheme6. Synthesis of tetra substitute pyrazoles

Elguero et al. proposed the general mechanism following loss consecutively two molecules of water intermediate step which involved to form 3,5-dihydroxy pyrazolidine in the reaction of asymmetric 1,3-diketones with monosubstituted hydrazine. Formation two N-C bonds at carbonyl amine considered reversible whereas observed not reversible part of dehydration kinetically controlled step. Two 3,5-dihydroxy pyrazolidine were in balance and then these compounds showed that the product formed two different pyrazole (6,7) in scheme7



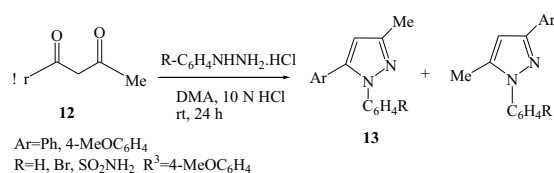
Scheme7. Synthesis of disubstitute pyrazoles

Enol ketone form (**10**) was synthesized mainly quickly effective in a single step by Heller and Natarajan. 1,3-diketones were not isolate but they were converted to 3,5-, 1,3,5-, 3,4,5-substituted pyrazoles (**11**) by adding to the medium suitable hydrazine in scheme8 [12].



Scheme8. Synthesis of trisubstitute pyrazoles

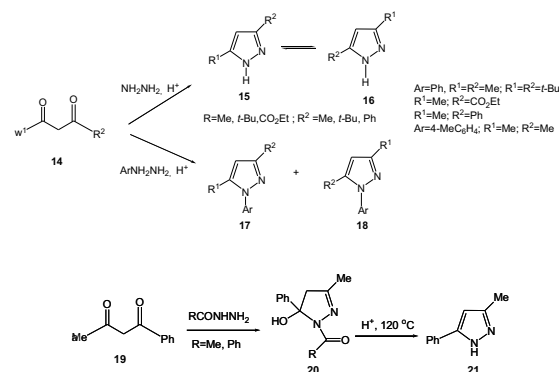
1,5-diaryl-3-methyl pyrazoles (**13**) were obtained by reaction of 1-aryl butane 1,3-diones (**12**) and aryl hydrazine chloride in reaction cyclocondensation of 1,3-diketones with hydrazines using alcohol or which is great acetic group an aprotic solvent N, N-dimethylacetamide (DMAc) in scheme9 [13]. The products were showed high stereoselectivity and productivity product,



Scheme9. Synthesis of 1,5-diaryl-3-methyl pyrazole

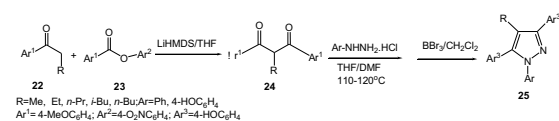
3,5-disubstituted pyrazoles (**15-18**) were synthesized in high yield as a direct result of activated 1,3-diketones (**14**) with hydrazine

without using any solvent with a catalytic amount of acid at room temperature. A single product (**21**) or a tautomeric mixture were obtained unsymmetrical with 1,3-diketones (**19**) in scheme10 [14].



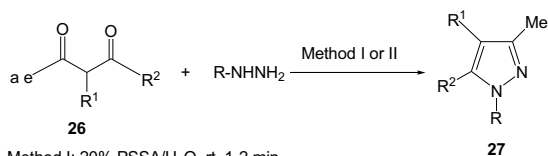
Scheme10. Synthesis of 3,5-disubstitute pyrazole

1,3-diketo structure of product (**24**) were obtained by interacting ketone derivatives (**22**) with the ester derivatives (**23**) when it placed with various reagents in the reaction. Especially 4-alkyl-1,3,5-triaryl (**25**) and 5-alkyl-1,3,4-triaryl pyrazoles were extensively investigated as ligands for the estrogen receptor [15-18]. Both in the solution and solid phase were developed methodologies for the consisting of synthesis of these compounds in scheme11 [19, 20].



Scheme11. Synthesis of tetrasubstitute pyrazole

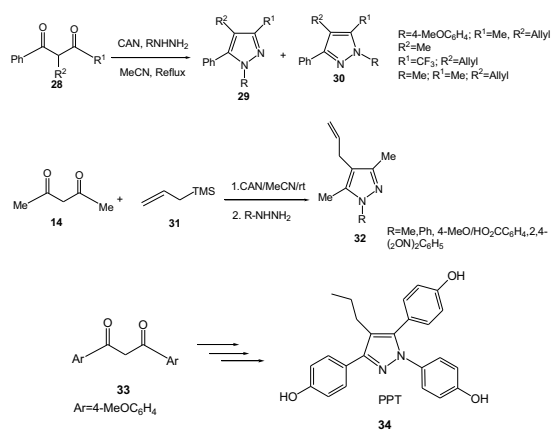
Symmetrical substituted pyrazole (**27**) was synthesized in high yield according to I or II the method catalyzed condensation polystyrene supported sulfonic acid (PSS) or 12-Tungston phosphoric acid (H3PW12O40) at room temperature between in aqueous medium hydrazines/hydrazide and 2,4-pentadione (**26**) derivatives in scheme12 [21, 22].



Method I: 20% PSSA/H₂O, rt, 1-2 min.
 R¹=H; R²=Me; R=Ph, 4-ClC₆H₄, MeCO, PhCO, 2-Furyl-CO, 2-thionyl-CO
 R¹=Cl; R²=Me; R=Ph, 4-ClC₆H₄, MeCO, 2-Furyl-CO, 2-thionyl-CO
 R¹=Et; R²=Me; R=Ph, 4-ClC₆H₄, 2-Furyl-CO, 2-thionyl-CO
 Method II: H₃PW₁₂O₄₀ (1% mole H₂O), rt, 6-60 min.
 R¹=H, Me; R²=Me; R=H, Ph, 4-MeC₆H₄, 4-ClC₆H₄, MeCO

Scheme12. Synthesis of tetrasubstituted pyrazole

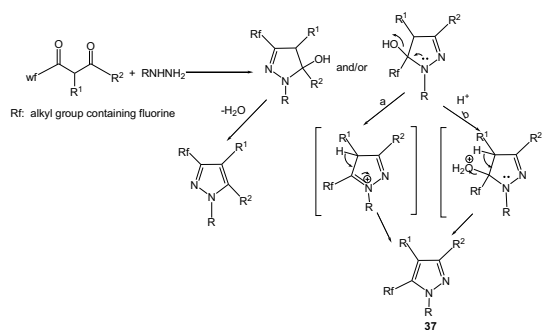
Devery et al. were reported in the literature a new method for synthesis of 1,3,4,5-alkyl/aryl substituted pyrazoles (**29**, **30**) [23]. That method includes synthesis of substituted pyrazole (**32**) with the addition of cerium-catalyzed substituted hydrazines after cerium ammonium nitrate (CAN), allyl trimethyl silane (**31**) and 1,3-diketones (**14**) interaction. The propantriol pyrazole (PPT) (**34**) was obtained in 30% yield over 4 steps in scheme 13. PPT was used as estrogen receptor agonist



Scheme13. Synthesis of 1,3,4,5- alkyl/aryl substitute pyrazole and PPT

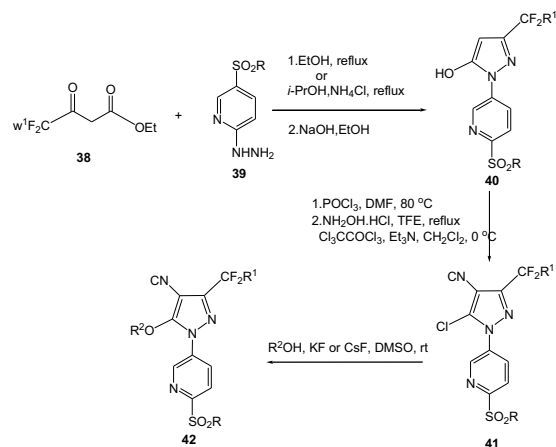
Most of fluorine or fluorocarbon-containing pyrazoles (**35**) were an area of active researches. These compounds were investigated in the field of agricultural chemistry and medicine. Because these compounds were in biological activity the most frequently cited in the

literature which have contain trifluoromethyl derivatives. Reagents and reaction conditions investigated widely effects in the condensation reaction between fluorine-containing 1,3-diketones and mono-substituted hydrazines in scheme14 [24-27].



Scheme14. Synthesis of fluorine-containing pyrazoles

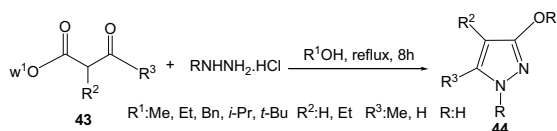
A single 3/5 - substituted pyrazole (**40**) product or 3/5-substituted mixture of pyrazoles (**41**) and 3/5-substituted alkoxy pyrazole (**42**) were formed depending on reaction conditions as a result of condensation reaction β-ketoesters (**38**) and the related hydrazines in scheme15 [28].



w=Me; R¹=H,F; R²=C₁PrCH₂,cyBuCH₂,cyHept,cyHex-3-enCH₂, (4-Methylene)-cyHexCH₂,(2-/3-Me)cyHex, (4-Ethyl)cyHex,1,2-(Me)₂Pr
 R=NH₂; R¹=F; R²=C₁Hept,(3-Me)cyHex,(4-Ethyl)cyHex,(4-4-F₃)cyHex,cyHeptCH₂, 2,2-(Me)₂Pr

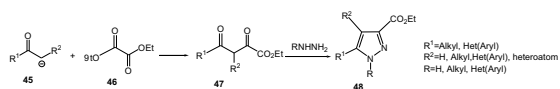
Scheme15. Synthesis of 3/5-substituted alkoxy pyrazoles

3-alkoxy-pyrazole (**44**) was conducted directly for the preparation with a simple method as a result of the condensation reaction between alkyl acetoacetate (**43**) with mono hydrazine chloride in scheme16 [29, 31].



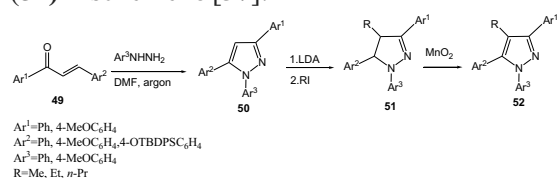
Scheme16. Synthesis of 3-alkoxy-pyrazole

[3 +2] ring closure reaction was frequently used for synthesizing pyrazole 3-(5) carboxylic acid ester between 1, 3-diketoester with hydrazines. The diethyl oxalates (**46**) with the enolate of ketone (**45**) were reported as Claisen condensation in the literature. The 3 (5)-carboxylic acid derivatives (**48**) were synthesized by reaction hydrazines with 1,3-diketoester (**47**). Some of these compounds demonstrated significant activity in pharmacology in scheme17 [32-36].



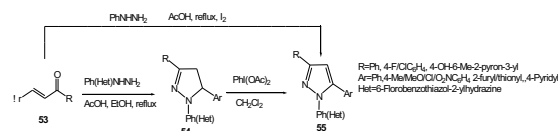
Scheme 17. Synthesis of pyrazol 3 (5)-carboxylic acid

3,5-diaryl pyrazoles (**50**) were easily obtained in high yield by Claisen-Schmidt condensation of chalcone with (1,3-diaryl-2-propen-1-one) (**49**). The pyrazoline (**51**) was synthesized using the appropriate reagents. A series of 4-alkyl-1,3,5-triaryl pyrazole (**52**) were synthesized with oxidation of compound (**51**) in scheme18 [37].



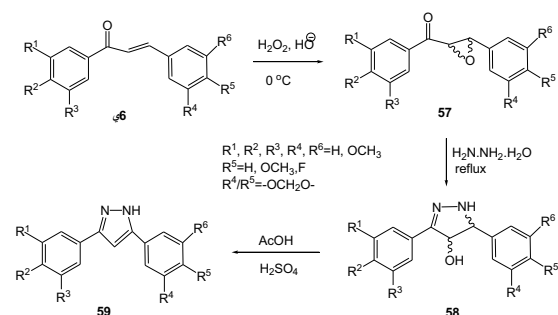
Scheme18. Synthesis of 4-alkyl-1,3,5-triaryl pyrazole

The substituted pyrazoles (**55**) were obtained by oxidation pyrazolines (**54**) which formed by the interaction various hydrazines with 1,3-diaryl-2-propen-1-one (**53**) derivatives in scheme19 [38-40].



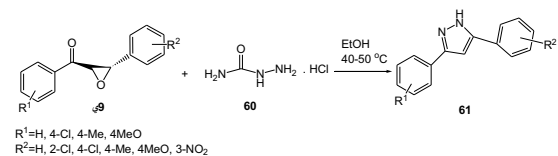
Scheme 19. Synthesis of trisubstitute pyrazoles

The most of pyrazoline (**58**) compounds were obtained to converting the epoxides (**57**) which occurred 1,3-diaryl-2-propen-1-one (**56**) by Bhat et al. 3,5-diaryl pyrazoles (**59**) were synthesized interaction of (**58**) the with appropriate hydrazine in scheme20 [41].



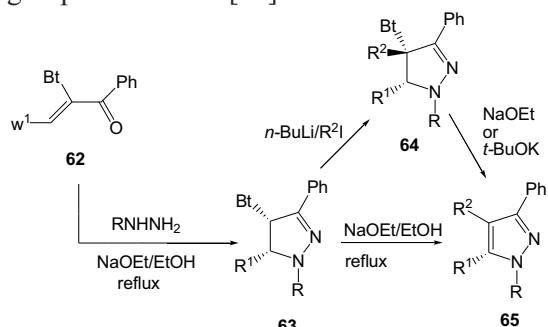
Scheme20. Synthesis of 3,5-diaryl pyrazoles

A series of 3,5-diaryl-1H-pyrazole (**61**) were synthesized to a way easier and safer rather than high toxic effects of hydrazine hydrate by the interaction with the α -epoxy ketones (**59**) using semicarbazide hydrochloride salt (**60**) in scheme21 [42].



Scheme 21. Synthesis of 3,5-diaryl-1H-pyrazoles

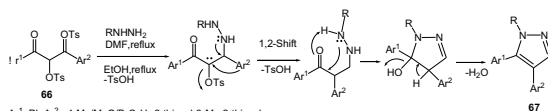
A series of 1,3,5-trisubstituted pyrazole (65) was synthesized with the interaction of a mild base which pyrazoline (63) intermediate of product by condensation the appropriate hydrazines and α -enone (62) including a leaving group in scheme22 [43].



Bt=Benzotriazolyl
 $R^2=H$, $R=Me$ or Ph; $R^1=i-Pr$, Ph, 4-MeC₆H₄, 3-Pyridyl
 $R^2=H$, $R=Me$ or Ph; $R^1=i-Pr$, Ph, 4-MeC₆H₄, $R=Me$; $R^1=4-MeC_6H_4$
 $R^2=n-Bu$ or Allyl or Bn; $R=Ph$; $R^1=4-MeC_6H_4$

Scheme22. Synthesis of 1,3,5-trisubstitute pyrazoles

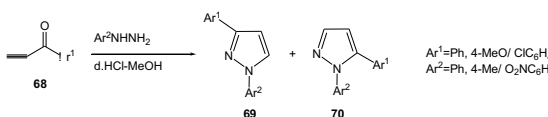
The yield of less trisubstituted pyrazoles (67) were prepared with reacting α,β -chalcone of ditosylate (66) and an appropriate hydrazine in scheme 23 [44].



$Ar^1=Ph$; $Ar^2=4-Me/MeO/Br/C_6H_4$, 2-thionyl-3-Me-2-thionyl
 $Ar^1=4-MeC_6H_4$; $Ar^2=4-MeC_6H_4$, 2-thionyl-3/5-Me-2-thionyl
 $Ar^1=4-MeC_6H_4$; $Ar^2=Ph$, 4-MeC₆H₄, 2-thionyl-3-Me-2-thionyl
 $Ar^1=4-ClC_6H_4$; $Ar^2=Ph$, 4-MeC₆H₄, 2-thionyl-3/5-Me-2-thionyl
 $R=Ph$, CO(S)NH₂

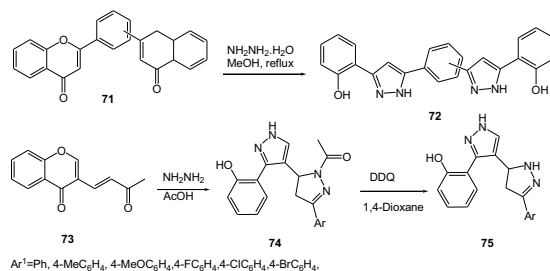
Scheme23. Synthesis of 1,4,5-trisubstitute pyrazoles

1,3- and 1,5-substituted pyrazoles (69,70) were synthesized as the result of condensation Yrones (68) and substituted hydrazines in scheme 21 [45-48].

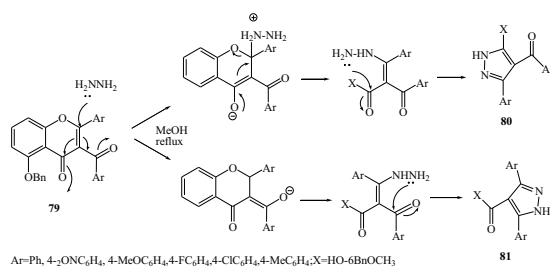


Scheme24. Synthesis of 1,3- and 1,5-disubstituted pyrazoles

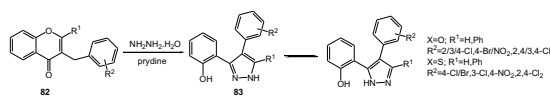
The required substituted pyrazoles were synthesized to interaction of with various hydrazines of chiral oxazolidines and tetrahydropiranyloxy yrones under the appropriate reaction conditions. Silva et al were worked a series of compounds based on including these structures at the synthesis various pyrazole derivatives (72, 74, 75, 77, 78) using equivalent formyl groups such as alkoxymethylene, aminomethyl and dimethylaminomethylene [49-52]. A series of 3,4-diaryl-5-methyl pyrazole (80, 81) was used for the synthesis that previously obtained method based on chromen-4-one (79). Some of the compounds were synthesized. These compounds were tried about inhibition of cell proliferation



$Ar^1=Ph$, 4-MeC₆H₄, 4-MeOC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄.



$Ar=Ph$, 4-ONC₆H₄, 4-MeOC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-MeC₆H₄; X=HO-6BnOCH₃

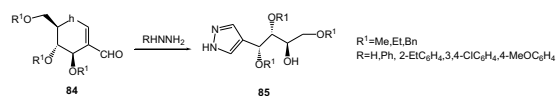


X=O; R¹=H, Ph
 $R^2=2/3/4-Cl$; 4-Br/NO₂; 2,4/3,4-Cl₂
 $X=S$; R¹=H, Ph
 $R^2=4-Cl/Br$; 3-Cl; 4-NO₂; 2,4-Cl₂

Scheme25. Synthesis of 3,4-diaryl-5-methyl pyrazoles

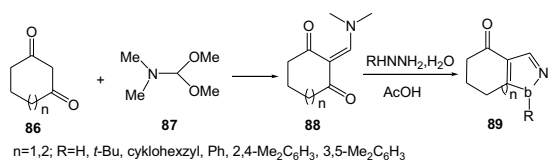
A series of 4-substituted pyrazole (85) were synthesized based on a aryl hydrazines of 2-formula glycol (84) any solvent. The yield of the reaction products were compared with done separately of the results obtained under thermal

conditions and microwave radiation in scheme26 [54].



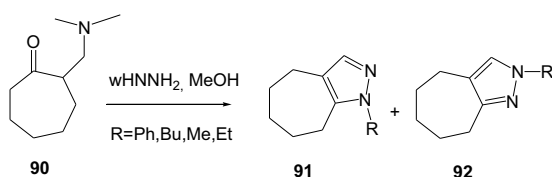
Scheme26. Synthesis of 4-substituted pyrazoles

Firstly 1,3-cyclo alkanedione (**88**) was obtained with react dimethyl formamide dimethyl acetal (DMFDMA) (**86**) and β -enamindione (**87**) in one step under microwave radiation. Then a series of 4,5-fused of cycloalkonoes that 1-substituted pyrazoles (**89**) was conducted hydrazine and the obtained product in scheme27 [55].



Scheme27. Synthesis of 4,5-fused of cycloalkonoes 1-substituted pyrazoles

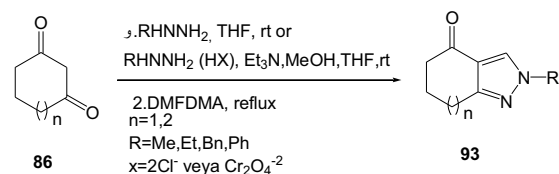
Fused of cyclopentanone 1-substituted pyrazoles (**91**, **92**) were synthesized to condensation reaction of the enamindione (**90**) with various hydrazines in solvent and appropriate conditions, changing the product formed itself and stereoisomer mentioned depending on the molecular size of hidrazine and the reaction temperature in scheme28 [56].



Scheme28. Synthesis of fused pyrazoles

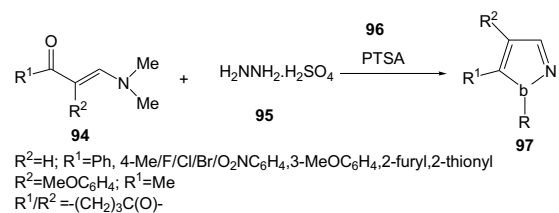
The pyrazole products (**93**) were synthesized in excellent yield with ring closure cycloalkyl 1,3-dione with various mono substituted of hydrazines in a single step

appropriate reaction conditions. The obtained pyrazoles were exhibited pharmacologic activity in scheme29 [57-59].



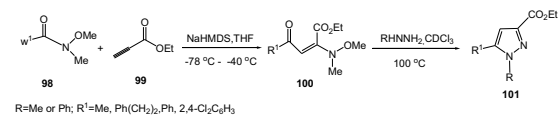
Scheme29. Synthesis of fused cyclohexanone pyrazoles

Longhi et al were synthesized a series of 5-(het)-aryl-NH pyrazoles (**97**) with reaction hydrazine sulfate (**95**) and β -dimethylaminovinyl ketone (**94**) using as catalyst p-toluene sulfonic acid (**96**) solid phase any solvent conditions in scheme30 [60].



Scheme30. Synthesis of 5-(het)-aryl-NH pyrazoles

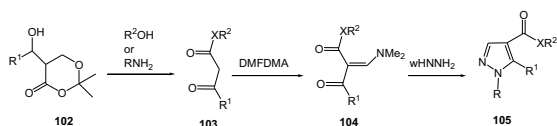
Persson and Nielsen were developed an effective method of interaction the hydrazines of compound (**100**) which obtained product from Weinreb amides (**98**) and ethyl propionate (**99**) in the appropriate solvent and temperature for the synthesis of pyrazole-3-carboxylate (**101**) in scheme31 [61].



Scheme31. Synthesis of pyrazole-3-carboxylate

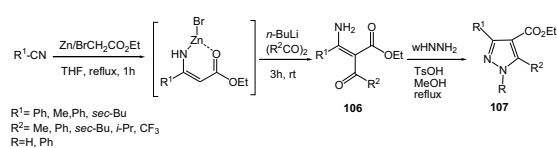
Giacomelli et al were synthesized by β -keto esters and the β -keto amide derivatives (**103**)

which obtained as a result of ring opening interaction of various alcohols and amines, acylation derivatives of acid chloride as known Meldrum's acid (**102**). A series of 1,5-substituted 4-pyrazole of ester and amide derivatives (**105**) were obtained by interaction hydrazines of compound (**104**) in scheme32 [62].



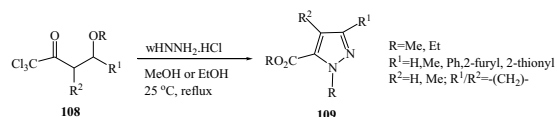
Scheme32. Synthesis of 1,5-substituted 4-pyrazole ester and amide

A series of 4-substituted pyrazole (**107**) were synthesized in high yield by condensation of the interaction various hydrazines and α -ethoxycarbonyl- β -Enaminones (**106**) with catalytic amount of p-TsOH in suitable solvent medium. The obtained pyrazole products were used as histamine analogs in scheme33 [63-65].



Scheme33. Synthesis of 4-substituted pyrazole

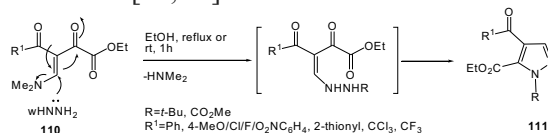
Flores et al were synthesized β -alkoxyvinyl trichloro methyl ketone (**108**) as starting products then alkoxy carbonyl pyrazole derivative (**109**) was synthesized in good yields to interaction with hydrazine hydrochloride or phenyl hydrazine in medium suitable solvent in scheme34 [66].



Scheme34. Synthesis of alkoxy carbonyl pyrazole

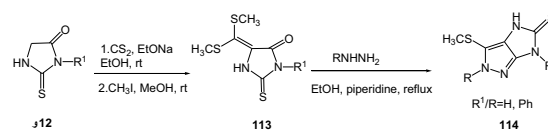
Martins et al proposed reaction mechanism about how the reaction occurs in synthesis.

They were synthesized directly a serial 4-acyl pyrazole-5-carboxylate (**111**) products from unsymmetrical of enaminodiketoester (**110**) in scheme35 [67, 68].



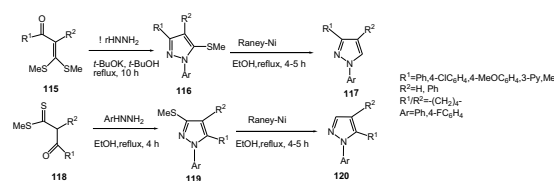
Scheme35. Synthesis of 4-acyl pyrazole-5-carboxylate pyrazole

Thio-, silyl- and halo pyrazoles were used as a building block in heterocyclic chemistry due to easy replacement by carbon or heteroatomic substitutions. The pyrazole was synthesized primary by reaction with hydrazines as synthon of α -oxoketen S-S-acetal [69]. According that method the pyrazole was obtained by condensation a hydrazine and 2-thiohydanto (imidazolidyne 2,4-dione) (**114**) in the suitable solvent for the synthesis of methylsulfanyl-imidazo [4,5-c] pyrazole (201) in scheme36 [70].



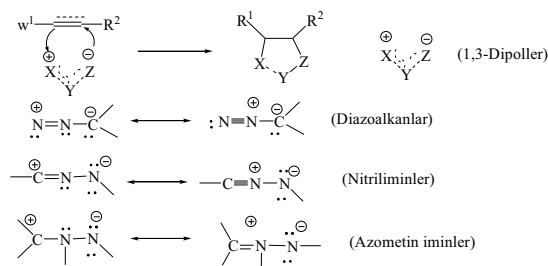
Scheme36. Synthesis of methylsulfanyl-imidazo [4,5-c] pyrazole

Peruncheralathan et al were synthesized 1-aryl-3-(methylthio)-4,5-substituted/cyclic pyrazoles (**117**) and 1-aryl-3,4-substituted/cyclic-5-(methylthio)-pyrazoles (**120**) as a result of condensation of aryl hydrazines with β -oxodithioesters (**115**) and α -oxoketen thioacetals (**118**) in scheme37 [71-73].



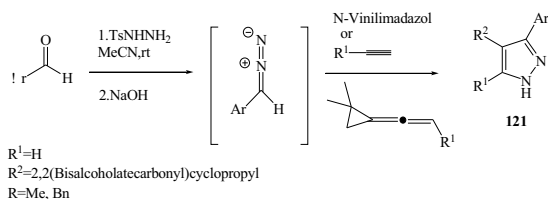
Scheme37. Synthesis of substituted pyrazoles

1,3-dipolar cycloaddition reaction is used one of the widely synthetic instruments for obtaining substituted pyrazoles [74]. The 1,3-dipolar are used three main classes as [CNN] synton including diazoalkanes, nitrile imines and azomethine imines in scheme38.



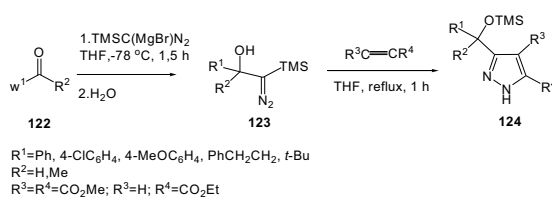
Scheme38. 1,3-dipolar classes

1,3-dipolar cyclo addition was carried out effectively with alkynes the electron-rich of diazo compounds under thermal conditions. But diazo compounds are potentially explosive and toxic due to natural processing and preparation is hazardous. These problems were overcome by used a method for multiplication of aryl diazomethane from suitable tosyl hydrazone derivatives. Thus, for preparation of 3,5-aryl pyrazoles from aromatic aldehydes (**121**) were used as a functional in one step in scheme39 [75, 76].



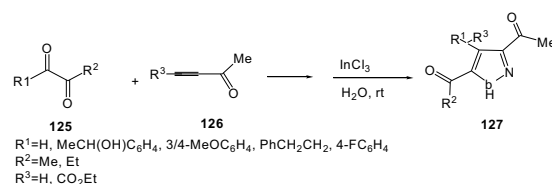
Scheme39. Synthesis of 3,5-aryl pyrazoles

Di- and tri-substituted pyrazoles (**124**) were synthesized with [3 + 2] cycloaddition between derivatives of dimethyl acetylene dicarboxylate or ethyl propylate (**122**) and 2-diazo-2-(trimethylsilyl) ethanol (**123**) in scheme40 [77].



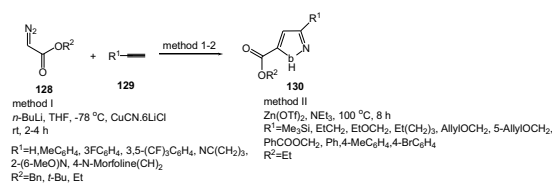
Scheme40. Synthesis of di- and tri-substituted pyrazoles

Jiang et al were synthesized carbonyl and ethoxy carbonyl pyrazoles (**127**) by 1,3-dipolar cyclo addition of molecules between alkinolate or alkinone (**125**) and cyclic or acyclic α -diazo carbonyl (**126**) compounds using catalysis InCl_3 in water at room temperature in scheme41 [78].



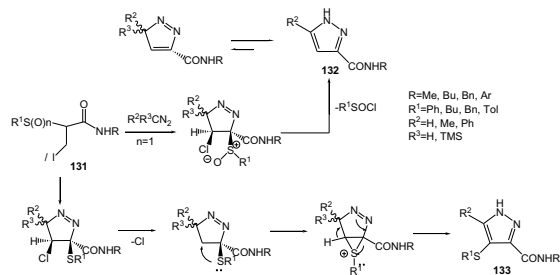
Scheme41. Synthesis of carbonyl and ethoxy carbonyl pyrazoles

Recently alkynes were begun a broad workspace for the synthesis of pyrazole. Qi et al synthesized a series of 3,5-disubstituted pyrazole (**130**) as a result of cyclo addition diazo carbonyl (**128**) of compounds a series of alkyne (**129**) in the reaction medium. They worked how affects yield alkyl and aryl alkynes and aryl alkynes by adding $\text{Zn}(\text{OTf})_2$ any solvent at a certain temperature. They were determined that alkyne gave better yields in scheme42 [79].



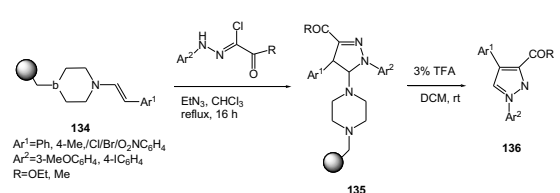
Scheme42. Synthesis of carbonyl and ethoxycarbonyl pyrazole

Recently β -chloro acryl amide were reported systematic work dipolarofilic on behavior oxidation levels of sulfide and sulfate against phenyl azomethane, trimethylsilyl azomethane, diazomethane and diazoethane in scheme43 [80].



Scheme43. Synthesis of the substituted pyrazole

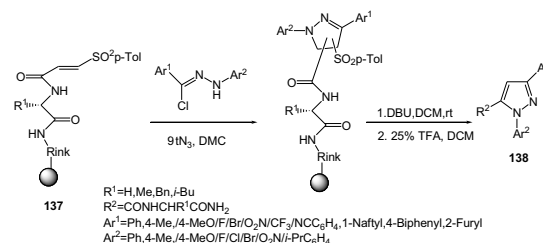
Nitrile imines were obtained by interacted a base and hydrazoneyl halide in the reaction medium. Last decade 1,3-cyclo alkenes participate of nitrile imines were used for the synthesis of substituted pyrazole [81]. This methods that rimonabant, the cannabinoid type-1 COX-2 of selective inhibitors were applied for the synthesis of stereo-selective in the solid phase [82, 83]. In addition reaction (135) was synthesized between nitrile imines and aryl acetaldehyde with gummy piperazine (134). Then 1,4-diaryl pyrazole-3-carboxylate (136) was synthesized directly separated from the resin acidic medium in scheme44 [84].



Scheme44. Synthesis of 1,4-diaryl pyrazole-3-carboxylate

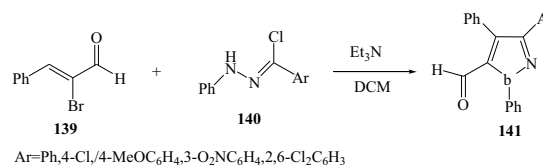
Vinyl sulphones polymer supported (137) were used stereo selective dipolarophile for derivatives a series of 1,3-diaryl pyrazole (138)

at 1,3-cyclo addition reaction with nitriles imines in scheme45 [85].



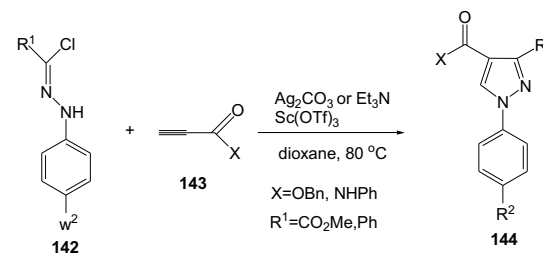
Scheme45. Synthesis of 1,3-diaryl pyrazole

The tetra substituted pyrazole (141) was obtained in high yield by 1,3-dipolar cycloaddition α -bromocinnamaldehyde (139) with C-aryl-N-phenyl nitrile imines (140) in scheme46 [86].



Scheme46. Synthesis of tetra substituted pyrazole

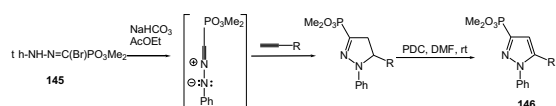
Synthesis of pyrazole (144) was reported both the catalyst and without the catalyst 1,3-cyclo addition reactions taking place between C-carboxymethyl-N-aryl (143) and C-aryl-N-aryl nitrile imines (142) in scheme47 [87].



Scheme47. Synthesis of 4 - and 5-substituted pyrazole

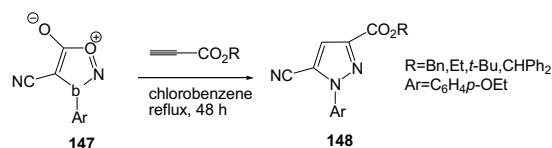
N-phenyl-5-substituted-3- dimethoxy phosphone pyrazoles (146) were obtained in

low yield with 1,3-dipolar cycloaddition of nitrile imines and monosubstituted alkynes using phosphonate groups (**145**) instead of carboxylate groups for preparation of compounds having pharmacological activity in scheme 48 [88].



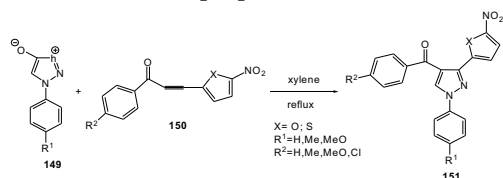
Scheme 48. Synthesis of N-phenyl-5-substituted-3-dimethoxy phosphone

Sydnone (**147**) was stable meso-ionic compounds relatively as dipolar type azomethine imine. These compounds were readily obtained by dehydrating cyclo of N-substituted-N-nitroso amino acids with reagents such as acetic anhydride. 3,5-disubstituted-pyrazole (**148**) was comprised due to extraction of carbon dioxide by 1,3-dipolar cycloaddition with acetylenes in scheme 49 [89, 90].



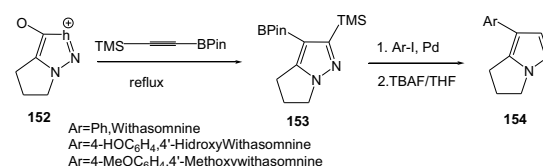
Scheme 49. Synthesis of 3,5-disubstituted-pyrazole

Hedge et al used unsymmetric α , β -acetylenic phenones (**150**) including 5-nitro furan as dipolarophiles at the 1,3-dipolar cycloaddition with N-aryl sydonone (**149**) for the synthesis of a series of 1-aryl-3-(5-nitro-2-furyl)-4-arylpyrazoles (**151**). The similar results were made using thiophene substituting furan in scheme 50 [91].



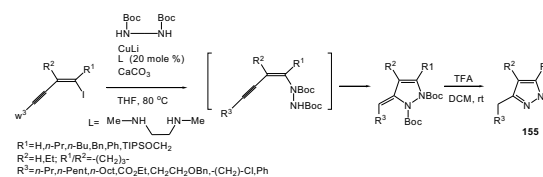
Scheme 50. Synthesis of 1-aryl-3-(5-nitro-2-furyl)-4-arylpyrazoles

Synthesis of novel pyrazoles (**154**) were conducted with reacting substituted furo-pyrazoles (**153**) and sydone (**142**) with three Withasomnine that occur naturally in scheme 51 [92].



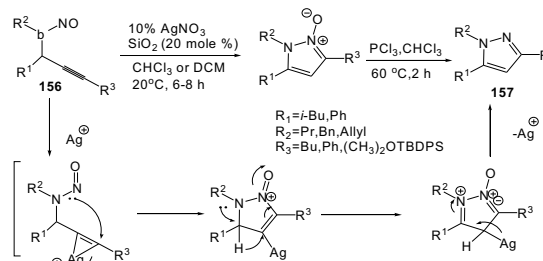
Scheme 51. Synthesis of substituted pyrazoles

Alkynes with metal of activity lead to formation of the pyrazoles result of cyclization 5-exo/endo-dig to participate nucleophilic nitrogen derivatives intramolecular. Synthesis of 3 (5)-3,5- and 3,4,5- substituted pyrazoles (**155**) were reported in the literature in scheme 52 [93].



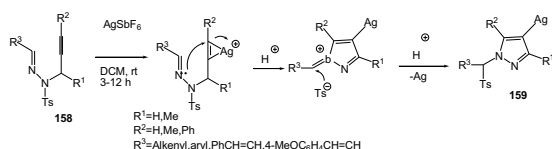
Scheme 52. Synthesis of 3 (5)-, 3,5- and 3,4,5- substituted pyrazoles

The 1,3,5-trisubstituted pyrazoles (**157**) were synthesized with 5-endo-dig ring closure from alkynyl nitroso amines (**156**) using a catalyst at room temperature [94]. The obtained yields were quite high and even two products were observed quantitatively in scheme 53.



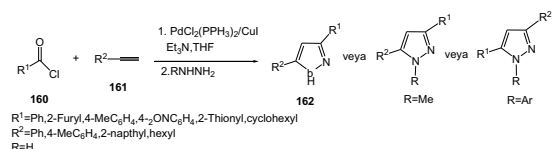
Scheme 53. Synthesis of 1,3,5-trisubstituted pyrazole

Propargyl N-sulfonyl hydrazones (**158**) were used for the synthesis 1,3- and 1,5-disubstituted pyrazoles (**159**) in the medium silver (II) catalyst and the reaction was carried out at high productivity to interaction with various hydrazones as catalyst together %5 mol AgSbF_6 with dry dichloromethane in the reaction medium in scheme54 [95].



Scheme54. Synthesis of 1,3- and 1,5-disubstituted pyrazoles

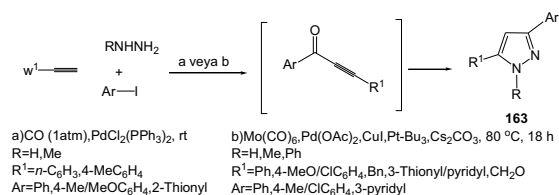
Multi-component reaction was reactions leading to the formation simultaneously of the desired a combinations of two or more building block. For example, 3,5-disubstituted pyrazole (**162**) were synthesized to react using catalyst at the appropriate temperature acid chloride (**160**), alkyne (**161**) and hydrazines which three components in a single step in scheme55 [96, 98].



Scheme55. Synthesis of 3,5-disubstituted pyrazole

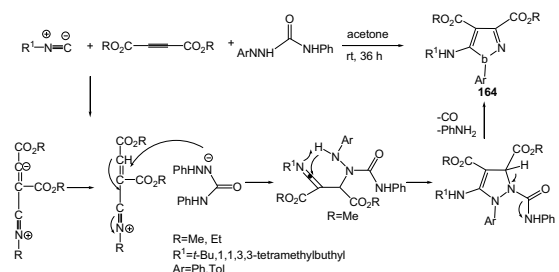
3,5-diaryl pyrazole (**163**) was synthesized by reacting using a catalyst four components in one step terminal coupling alkynes, methyl hydrazine, the aryl iodide and carbon monoxide *i.e.* in scheme 56 [98]. It was reported that the reaction takes place with use the hexane carbonyl molybdenum instead of carbon monoxide in the multi-component reaction [99]. Particularly it was the subject for multi-component reaction to isocyanate-based in the

heterocyclic chemistry [100].



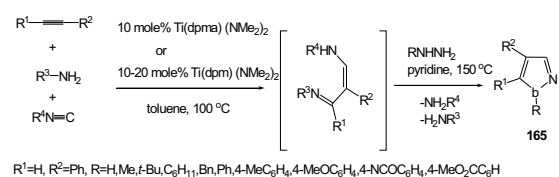
Scheme56. Synthesis of 3,5-diaryl pyrazole

Adib et al synthesized dialkyl 5-(alkylamino)-1-arylpyrazole-3,4-dicarboxylate (**164**) in good yield according to the multi-component reaction at room temperature in scheme 57 [101].



Scheme57. Synthesis of dialkyl 5-(alkylamino)-1-arylpyrazole-3,4-dicarboxylate

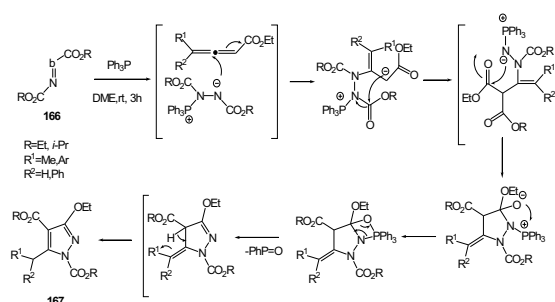
Recently a series of 1-aryl-4,5-disubstituted pyrazole (**165**) was obtained only one product using catalyst together 1,3-diimides and hydrazine or its derivatives in scheme 58 [102].



Scheme58. Synthesis of 1-aryl-4,5-disubstituted pyrazole

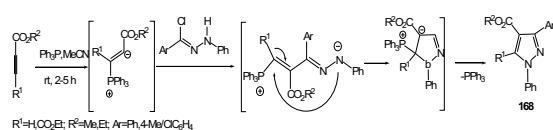
The strategies developed for pyrazole compounds which are considerable because of indicate the potential biological activity pyrazole carboxylic acid and derivatives.

For example, high-functional derivatives of pyrazole-4-carboxylic acid (**167**) were synthesized in good yields with the addition the Huisgen of isoelectronic of the product which obtained from the reaction of dialkyl azodicarboxylate, 4-substituted allenates (**166**) and triphenyl phosphine [103]. The reaction mechanism was proposed a cyclization containing a carbon-nitrogen migration of carbonyl group alkoxy, double bond isomerization and the elimination of triphenyl phosphide oxide in scheme 59.



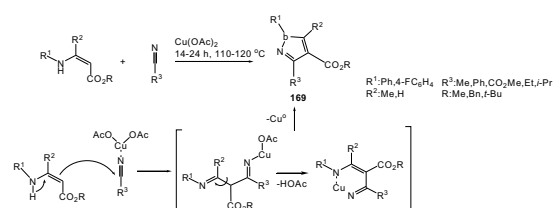
Scheme59. The mechanism proposed for the reaction of tetra substituted pyrazoles

Substituted pyrazol-4-carboxylates (**168**) were obtained to addition hydrazonoyl chloride isoelectronic to intermediate product including from acetylenic esters and triphenyl phosphine [104]. Then the expected pyrazole was occurred ring closure with release of the triphenyl phosphine in scheme60.



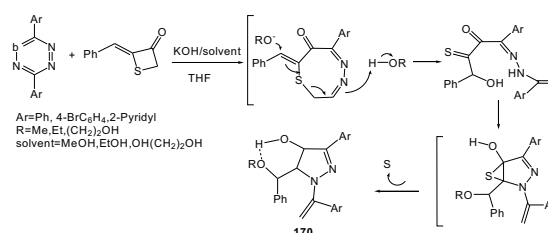
Scheme60. Synthesis of tetra substituted pyrazole

Recently important and effective a method was reported in the literature that contained an oxidative bond formation C-C/N-N from nitriles and the enamine for the synthesis of tetra substituted pyrazole-4-carboxylate (**169**) in scheme61 [105].



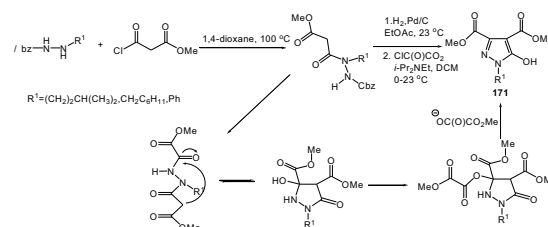
Scheme61. Synthesis of tetra substituted pyrazole-4-carboxylate

Tetra substituted pyrazole-4-ol (**170**) was obtained from the reaction 3,6-diaryl-1,2,4,5-tetrazine and thioethanone in THF at room temperature in scheme62 [106].



Scheme62. Synthesis of tetra substituted pyrazole-4-ol

Dragovich et al were proposed a new procedure for the preparation 1-substituted-5-hydroxypyrazole (**171**) which including ester groups at the 3,4-position. These compounds were prepared in three steps including coupling methyl malonyl chloride and monosubstituted benzyl carbazide. 5-hydroxy-3-pyrazole carboxylate was observed to occurring reaction that introduce intermolecular to the carbonyl carbon of an amide part of oxalyl and a methylene carbon part of malonyl in scheme63 [107].



Scheme63. Synthesis of 5-hydroxy-3-pyrazole carboxylate

3. CONCLUSION

In conclusion, this review has shown in the synthesis some of pyrazoles. The substituted pyrazoles have wide application both pharmaceuticals and in the agricultural industry. For this reason, the methods developed for the synthesis of these compounds are becoming more importance. Finally, plenty of examples were provided for synthesis of pyrazoles. This guidance document is used for most research studies and researches.

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