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Synthesis of Pyrazoles and Bipyrazoles- a Review

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ABSTRACT

The various methods of synthesizing pyrazole and bipyrazole moieties have always been a subject of interest for medicinal chemists. Primarily, the pyrazoles have been synthesized from diketones, hydrazones, acetylenes and more recently from chalcones. The bipyrazoles in turn have been derived from pyrazoles. The important methods of synthesis including the recent techniques have been reported in this review.

Keywords: Pyrazole, Bipyrazole, heterocyclic, chalcones.

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INTRODUCTION

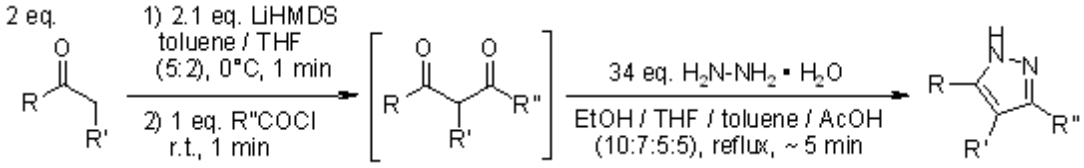
Pyrazole and Bipyrazole were synthesized for the first time in 1883 and 1893 respectively, since then many publications about their derivatives have been reported in the literature. Pyrazole and Bipyrazole are very interesting class of heterocycles that have remarkable common pharmacological activities. For example, they were reported to possess potential antimicrobial, anti-inflammatory, antifungal, antitumor, antihistaminic and inhibiting/deactivating activity of liver alcohol dehydrogenase and oxidoreductase enzymes.[1-8] Pyrazoles also used as anti-anxiety,[9,10] antipyretic,[11] anticonvulsant,[12] antidepressant,[13] antihyperglycemic[14] and insecticidal agent.[3] Bipyrazole shows cytotoxic, cardiovascular and diuretic activity. It also used in photographic, paint industry and in the synthesis of heat resistant polymers[8]. Synthesis and chemistry of the pyrazole nucleus has received much attention in recent years due to its outstanding biological activities. The important progression of microbial infections and the recrudescence of resistance towards the antibiotics used nowadays incite the researchers to make more efforts to discover and synthesize new molecules with systemic activity.[15] This review is intended to get the reader acquainted with this interesting group of synthetic organic compounds. It is the objective of this review to summarize the various new up to date methods of synthesis of pyrazole and bipyrazoles.

Synthesis

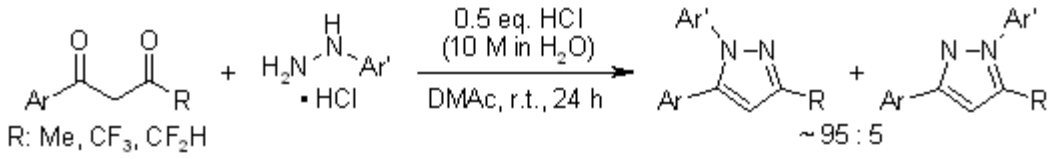
A. Synthesis of pyrazoles:

1. From Diketones:

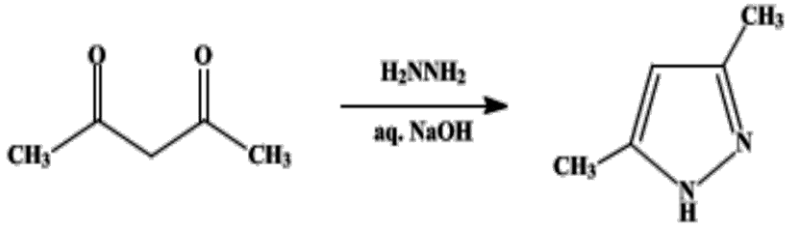
1,3-Diketones, which were synthesized in situ from ketones and acid chlorides, were converted into pyrazoles by the addition of hydrazine. This method allows a fast and general synthesis of previously inaccessible pyrazoles and synthetically demanding pyrazole-containing fused rings.[16]



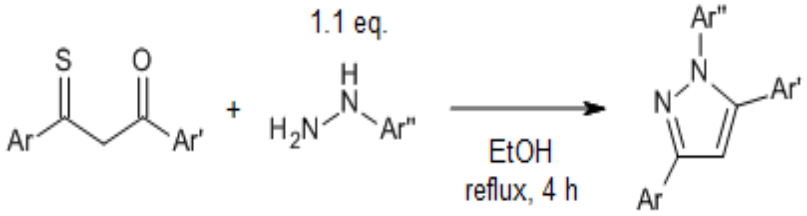
A highly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles based on the condensation of 1,3-diketones with arylhydrazines proceeds at room temperature in N,N-dimethylacetamide and furnishes pyrazoles in good yields.[17]



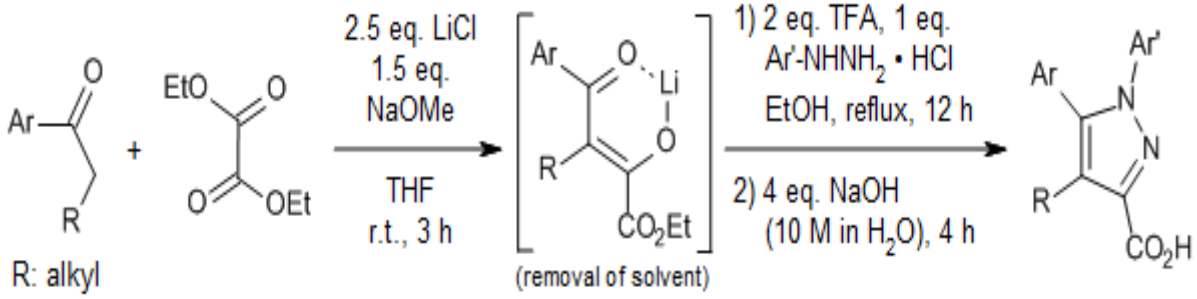
3, 5-Dimethylpyrazole has been prepared from acetylacetone and hydrazine hydrate in ethanol or hydrazine sulfate in aqueous alkali.4, 5, 6 The latter method is preferred, because the reaction with hydrazine hydrate is sometimes violent.3,4 3,5-Dimethylpyrazole also has been prepared by hydrolysis and decarboxylation of the 1-carbamido- or 1-carboxamidine derivatives, obtained by reaction of semicarbazide or aminoguanidine with acetylacetone, and from 1,2-pentadien-4-one and hydrazine hydrate.[18]



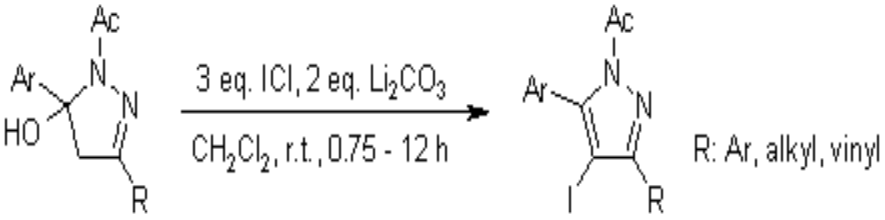
Two highly regioselective routes enable the synthesis of unsymmetrically substituted pyrazoles with complementary regioselectivity from active methylene ketones. The reaction of the easily accessible 1,3-bisaryl-monothio-1,3-diketone or 3-(methylthio)-1,3-bisaryl-2-propenones with arylhydrazines furnished 1-aryl-3,5-bisarylpyrazoles with complementary regioselectivity at position 3 and 5.[19]



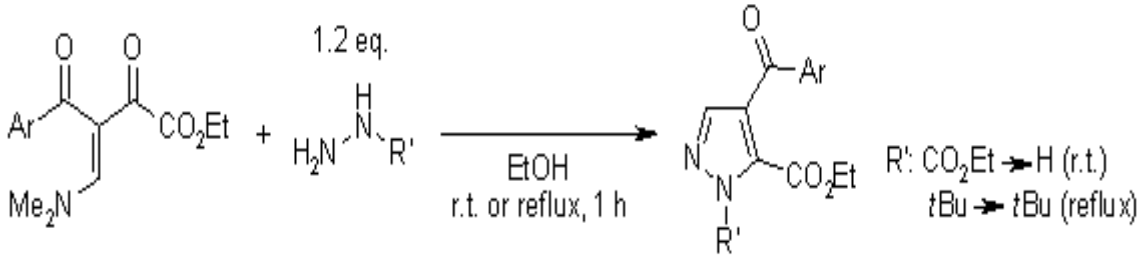
"One-Pot" Synthesis of 4-Substituted 1,5-Diaryl-1H-pyrazole-3-carboxylic Acids via a MeONa/LiCl-Mediated Sterically Hindered Claisen Condensation-Knorr Reaction-Hydrolysis Sequence.[20]



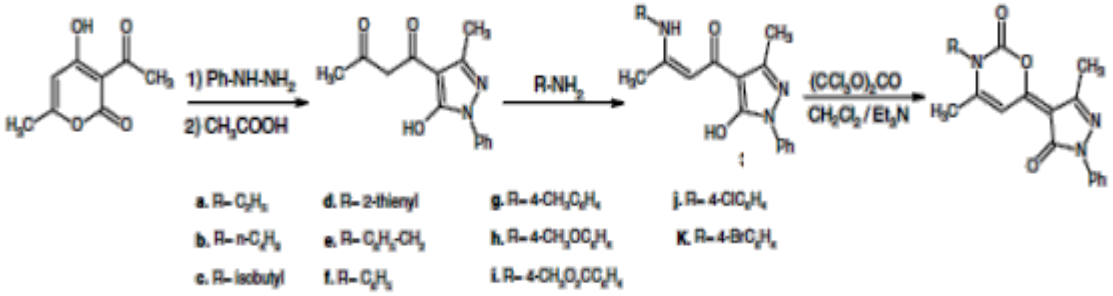
Various 1-acyl-5-hydroxy-4,5-dihydro-1H-pyrazoles have been prepared in good yields from the corresponding 2-alkyn-1-ones. The resulting dihydropyrazoles undergo dehydration and iodination in the presence of ICl and Li_2CO_3 at room temperature to provide 1-acyl-4-iodo-1H-pyrazoles.[21]



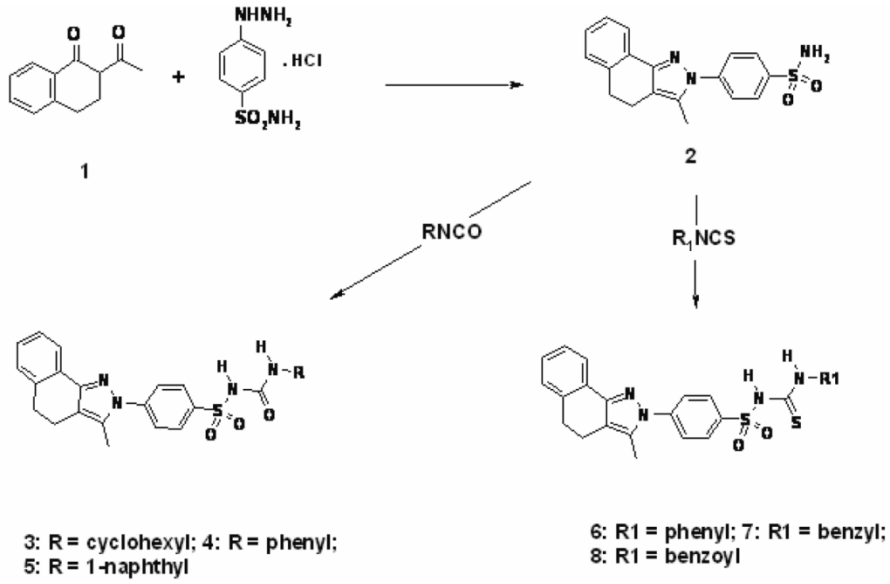
A series of 4-substituted 1H-pyrazole-5-carboxylates was prepared from the cyclocondensation reaction of unsymmetrical enaminodiketones with tert-butylhydrazine hydrochloride or carboxymethylhydrazine. The compounds were obtained regiospecifically and in very good yields.[22]



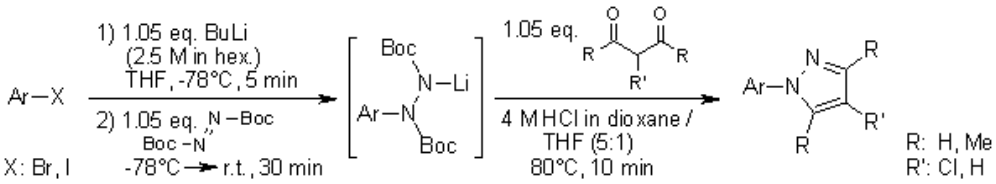
Cyclisation of pyrazolo-b-enaminones 3 readily obtained from 4-aceto acetyl pyrazol 2 with triphosgene led to the formation of N-substituted pyrazolo-1,3-oxazin-2-ones 4 in good yields. Estimation of pharmacotherapeutic potential, possible molecule mechanisms of action, toxic/side effects and interaction with drug-metabolizing enzymes were made for synthesised compounds on the basis of prediction of activity spectra for substances (PASS) prediction results and their analysis by PharmaExpert software. COX inhibition predicted by PASS was confirmed by experimental evaluation.[23]



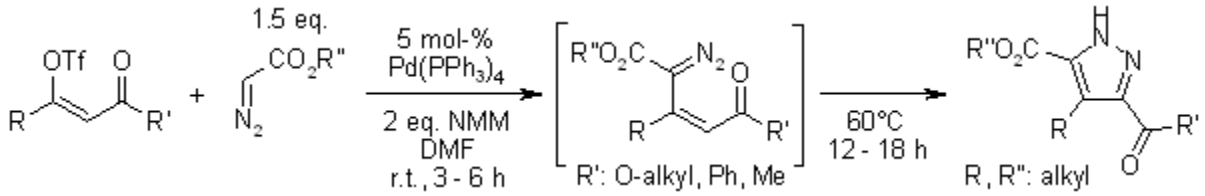
Synthesis and biological activity of 3-Methyl-2-(4-substituted phenyl)-4,5 dihydronaphtho[1,2-c]-pyrazoles was described by M. S. AlSaadi et al. The results revealed that some compounds displayed promising in-vitro antitumour activity. Sulfonylthioureido group emerged as the most favourable pharmacophore.[24]



A simple one-pot method allows the synthesis of diversely functionalized N-arylpyrazoles from aryl nucleophiles, di-tert-butylazodicarboxlate, and 1,3-dicarbonyl or equivalent compounds.[25]

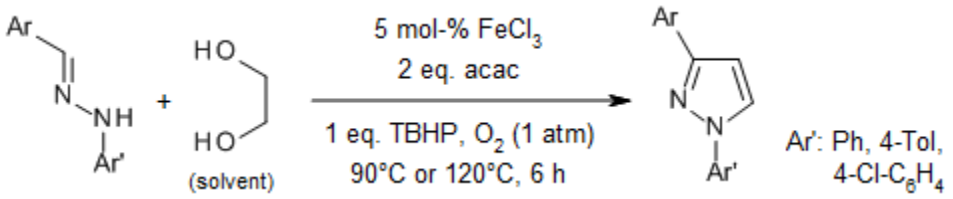


A tandem catalytic cross-coupling/electrocyclization allows the conversion of differentially substituted acyclic and cyclic enol triflates and an elaborated set of diazoacetates to provide the corresponding 3,4,5-trisubstituted pyrazoles with a high degree of structural complexity.[26]

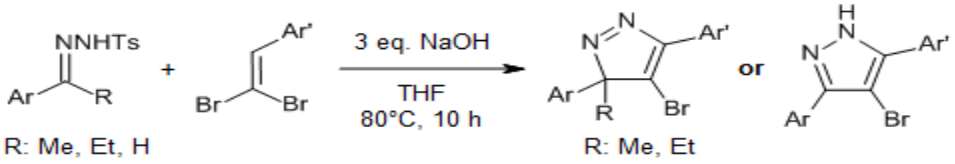


2. From Hydrazones

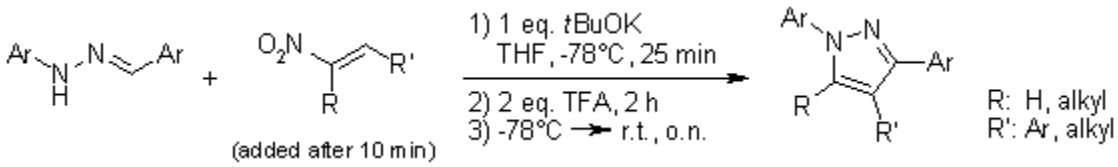
An iron-catalyzed route for the regioselective synthesis of 1,3- and 1,3,5-substituted pyrazoles from the reaction of diarylhydrazones and vicinal diols allows the conversions of a broad range of substrates.[27]



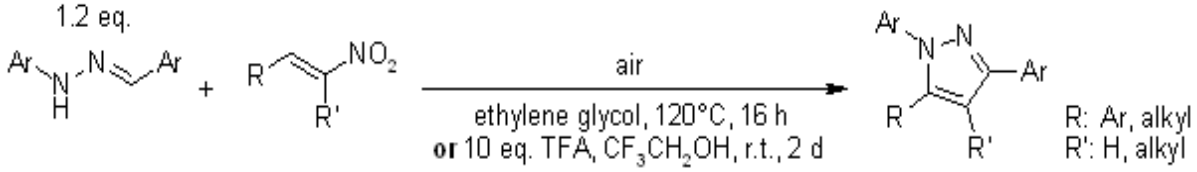
A simple, highly efficient, 1,3-dipolar cycloaddition of diazo compounds and alkynyl bromides gives 3,5-diaryl-4-bromo-3H-pyrazoles or the isomerization products 3,5-diaryl-4-bromo-1H-pyrazoles in good yields. The diazo compounds and alkynyl bromides were generated in situ from tosylhydrazones and gem-dibromoalkenes, respectively. The reaction system exhibited high regioselectivity and good functional group tolerance.[28]



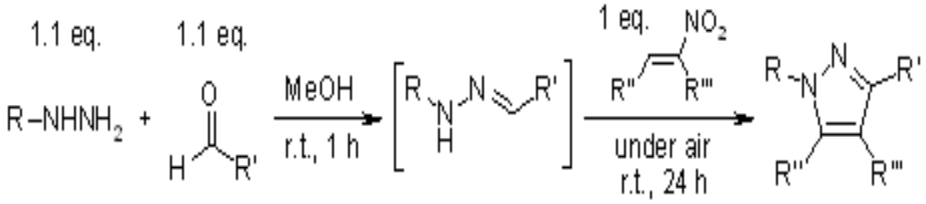
A regioselective synthesis of tri- or tetrasubstituted pyrazoles by the reaction of hydrazones with nitroolefins mediated with strong bases such as t-BuOK exhibits a reversed, exclusive 1,3,4-regioselectivity. Subsequent quenching with strong acids such as TFA is essential to achieve good yields. A stepwise cycloaddition reaction mechanism is proposed.[29]



Two general protocols for the reaction of electron-deficient N-arylhydrazones with nitroolefins allow a regioselective synthesis of 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles. Studies on the stereochemistry of the key pyrazolidine intermediate suggest a stepwise cycloaddition mechanism.[30]

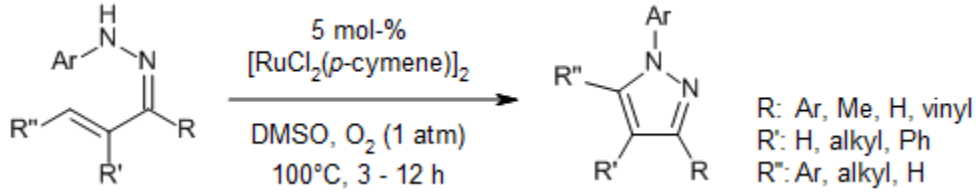


A regioselective one-pot synthesis of substituted pyrazoles from N-monosubstituted hydrazones and nitroolefins gives products in good yields. A key nitropyrazolidine intermediate is characterized and a plausible mechanism is proposed.[31]

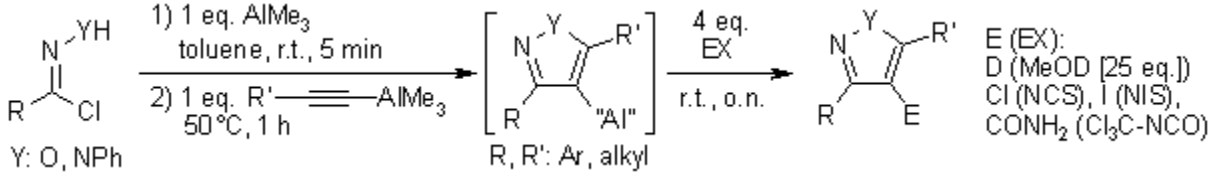


An unprecedented ruthenium (II)-catalyzed oxidative C-N coupling method enables a facile intramolecular synthesis of various synthetically challenging tri- and tetrasubstituted pyrazoles in

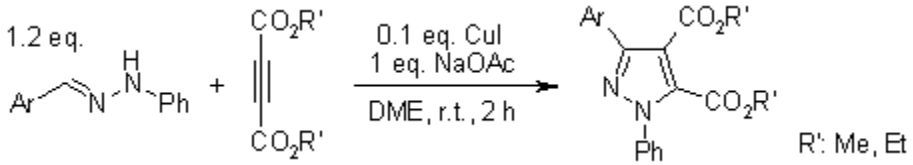
the presence of oxygen as oxidant. The reaction demonstrates excellent reactivity, functional group tolerance, and high yields.[32]



Alumino-heteroles are obtained from simple precursors in a fully chemo- and regioselective manner by a metalative cyclization. The carbon-aluminum bond is still able to react further with several electrophiles, without the need of transmetalation providing a straightforward access to 3,4,5-trisubstituted isoxazoles and 1,3,4,5-tetrasubstituted pyrazoles.[33]

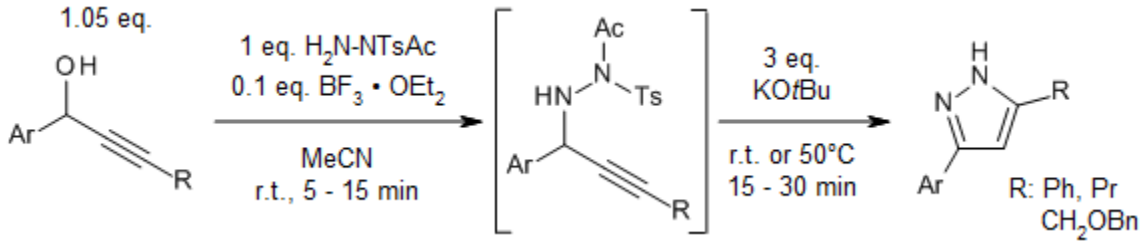


An easy and efficient copper-catalyzed reaction for the synthesis of polysubstituted pyrazoles from phenylhydrazones and dialkyl ethylenedicarboxylates tolerates a range of functionalities, and the corresponding adducts can be obtained in moderate to good yields.[34]

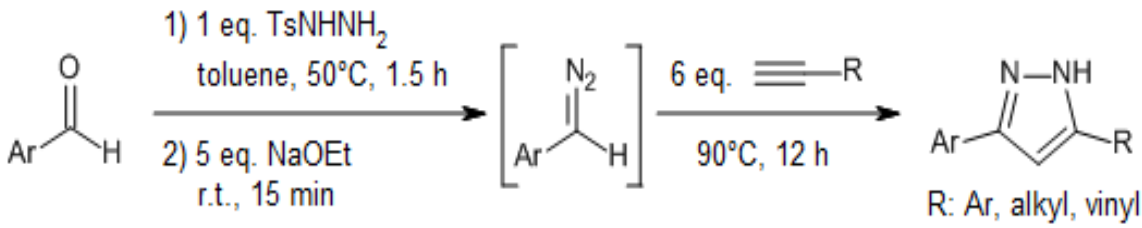


3. From Acetylenes

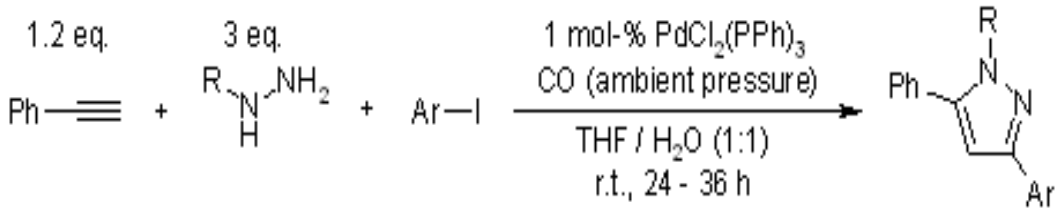
A new and efficient metal-free, two-component, one-pot approach to a variety of 3,5-disubstituted 1H-pyrazoles from propargylic alcohols in good overall yields proceeds via an acid-catalyzed propargylation of N,N-diprotected hydrazines followed by base-mediated 5-endo-dig cyclization.[35]



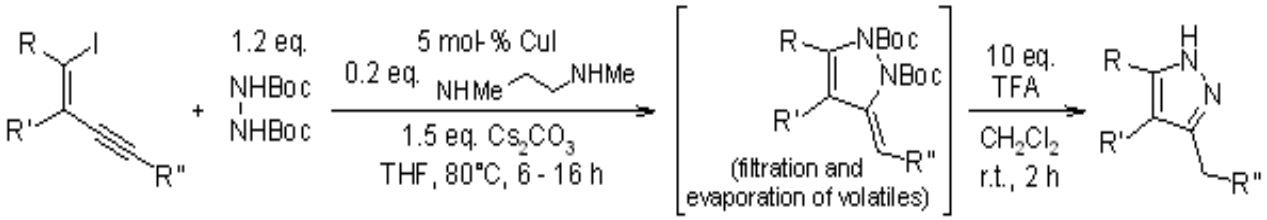
An efficient, general, one-pot, three-component procedure for the preparation of 3,5-disubstituted 1H-pyrazoles includes condensation of substituted aromatic aldehydes and tosylhydrazine followed by cycloaddition with terminal alkynes. The reaction tolerates various functional groups and sterically hindered substrates to afford the desired pyrazoles in good yields.[36]



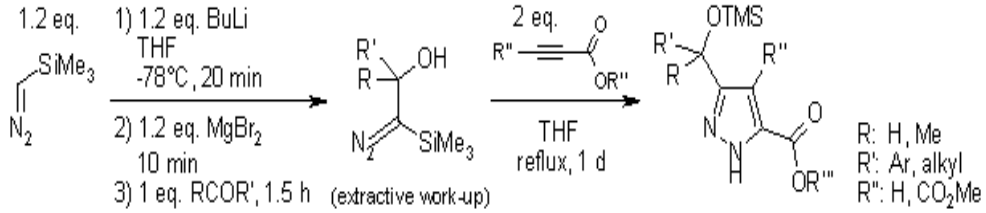
Pyrazole or isoxazole derivatives are prepared by a palladium-catalyzed four-component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide under ambient pressure, and an aryl iodide.[37]



A general, highly flexible Cu-catalyzed domino C-N coupling/hydroamination reaction constitutes a straightforward alternative to existing methodology for the preparation of pyrroles and pyrazoles.[38]

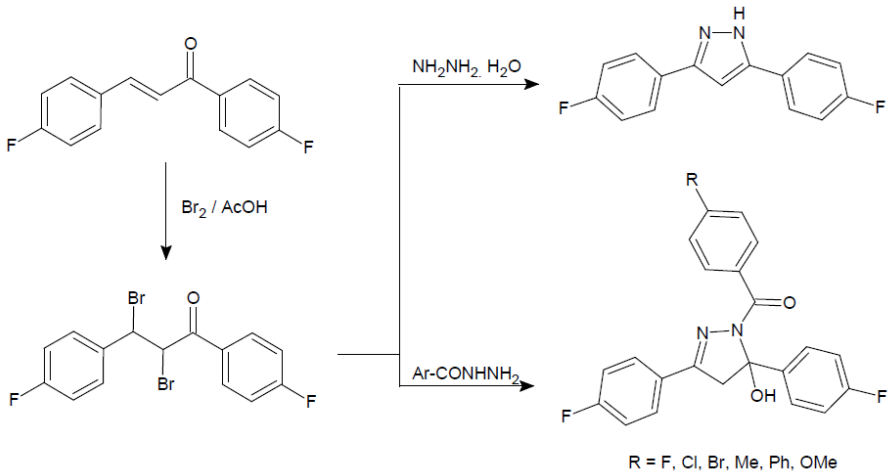


The reaction of diazo(trimethylsilyl)methylmagnesium bromide with aldehydes or ketones gave 2-diazo-2-(trimethylsilyl)ethanols, which were applied to the synthesis of di- and trisubstituted pyrazoles via [3+2] cycloaddition reaction with ethyl propiolate or dimethylacetylenedicarboxylate.[39]

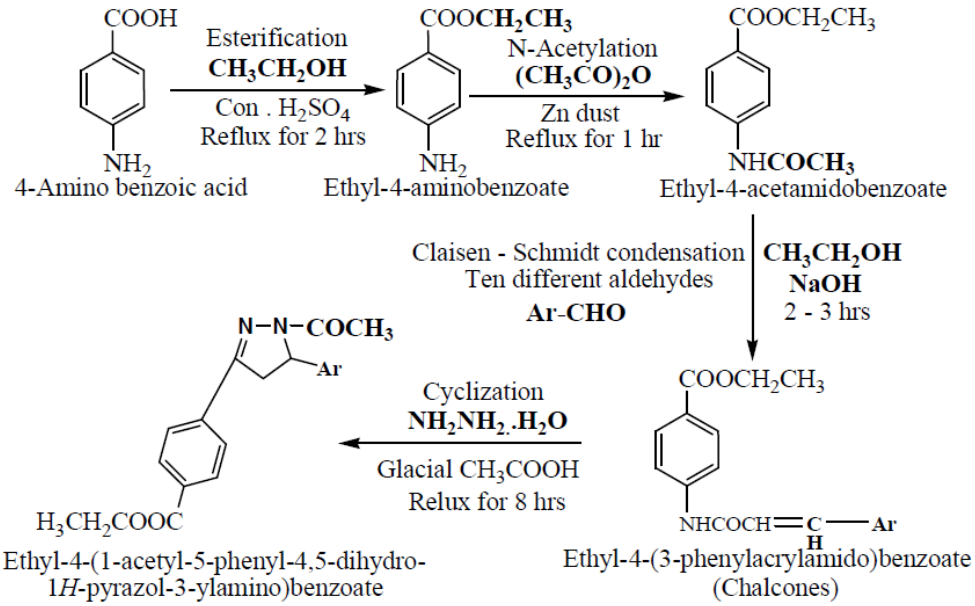


4. From Chalcones

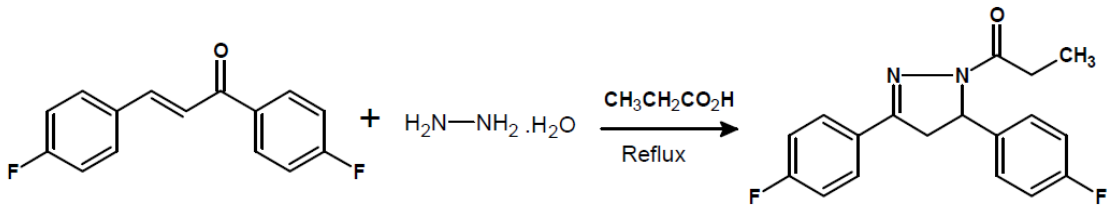
The synthesis of pyrazole derivatives were carried out by reacting the *α,β*-dibromo 4,4' difluoro chalcone with various hydrazine derivatives according to the reaction sequence depicted below.[40]



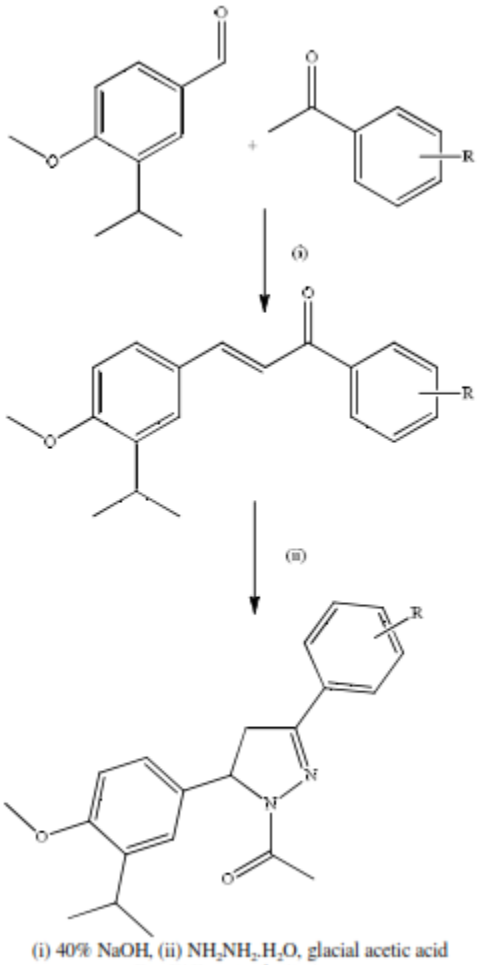
Pyrazole derivative is prepared from *p* – Amino benzoic acid and ethanol. Chalcone has been prepared by the condensation reaction of Ethyl-4-acetamido benzoate and different ten aldehydes. These chalcones are cyclized with hydrazine hydrate and glacial acetic acid under reflux condition give pyrazole derivatives.[41]



Another pyrazole derivative compound is synthesized by the reaction of 4,4'-difluoro chalcone with hydrazine hydrate in propionic acid under reflux condition.[42,43]



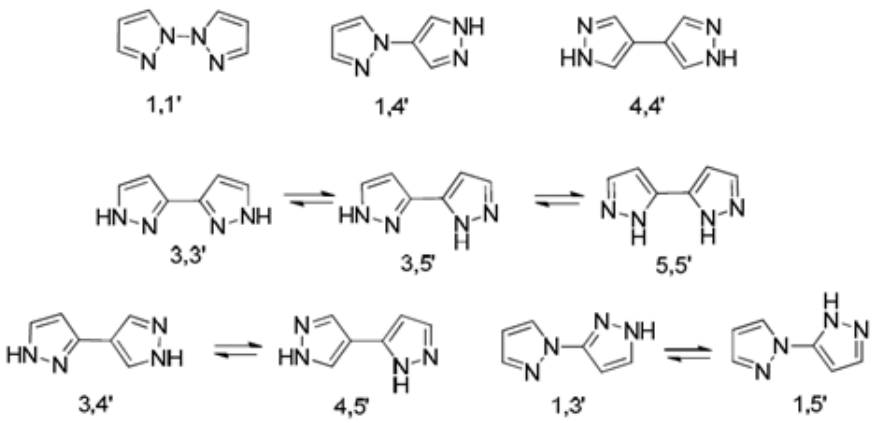
Substituted Chalcone and pyrazole derivatives have been prepared by reacting 3-isopropyl-4-methoxybenzaldehyde with various aromatic ketones by using alkali as catalyst to afford (E)-3-(isopropyl-4-methoxyphenyl)-1-aryl-prop-2-en-1-ones. These compounds on reaction with hydrazine in the presence of acetic acid give 1-acetyl-3-aryl-5-(3-isopropyl-4-methoxyphenyl)pyrazoles.[44]



(i) 40% NaOH, (ii) $NH_2NH_2.H_2O$, glacial acetic acid
R = Different substitutions

B. Synthesis of Bipyrazoles:

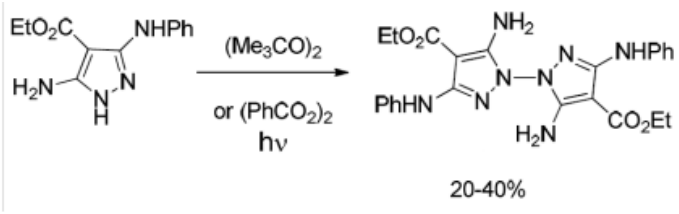
The synthetic methodologies towards ten main classes of bipyrazole systems (according to the type of connection between them): 1,1'-, 1,3'-, 1,4'-, 1,5'-, 3,3'-, 3,4'-, 3,5'-, 4,4'-, 4,5'- and 5,5'-junctions. According to numbering there are pertinent ten systems of bipyrazole which differ in the position of the bond between the two pyrazole rings as shown below.



Three main types of connections between two pyrazole moieties can be considered; N,N-, C,N-, and C,C-linked bipyrazoles.

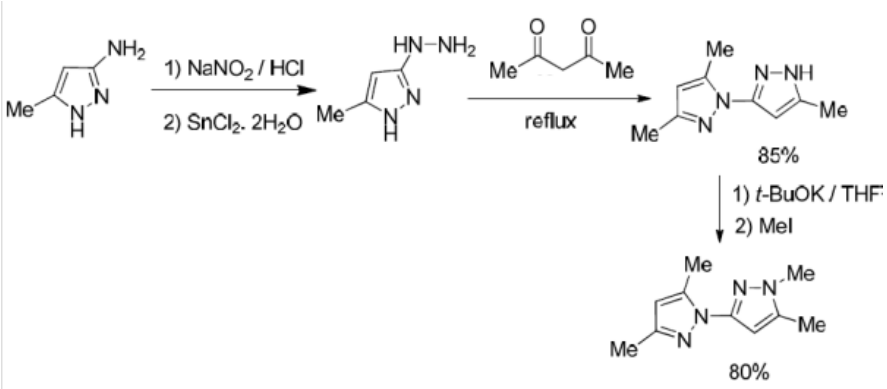
1. 1,1'-bipyrazoles

Photolysis of ethyl 5-amino-3-(phenylamino)pyrazole-4-carboxylate which is a very good antioxidant, with tert-butyl peroxide or with dibenzoyl peroxide under mild reaction conditions resulted in radical dimerization of the pyrazole and led to the formation of the 1,1'-bipyrazole derivative in 40 and 20% yields, respectively.[45]

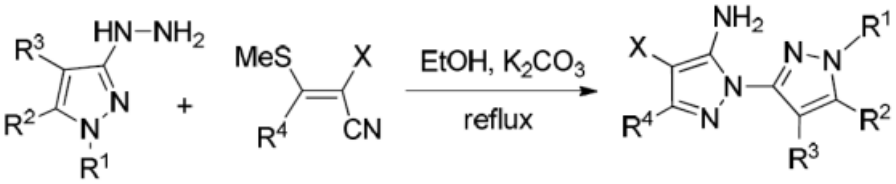


2. 1,3'-bipyrazoles

Diazotization of 3-amino-5-methylpyrazole in HCl followed by reduction with tin chloride gave 3-hydrazino-5-methyl-1H-pyrazole. Cyclocondensation reaction of it with acetylacetone afforded 3,5,5'-trimethyl-1'H-1,3'-bipyrazole in high yield. The methylation of this in the presence of t-BuOK led to the formation of 1',3,5,5'-tetramethyl-1'H- 1,3'-bipyrazole in high yield.[46-48]

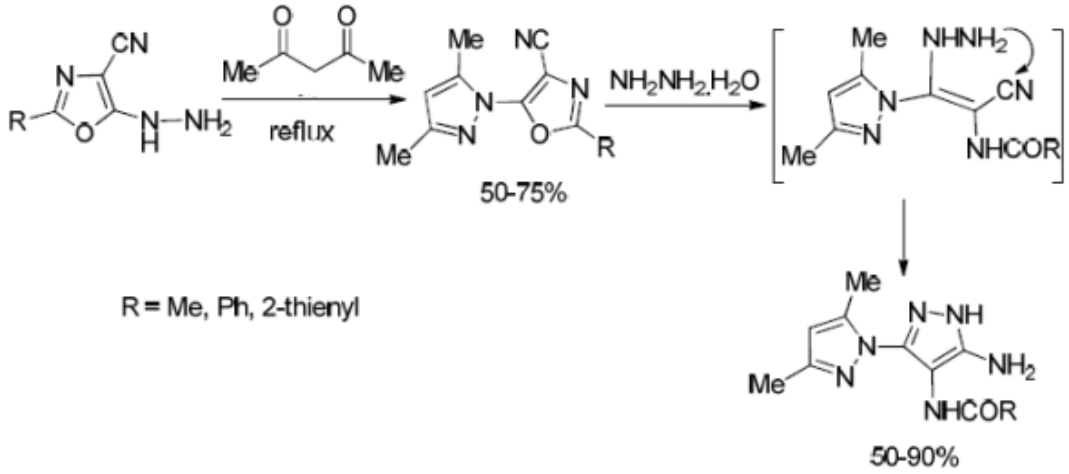


The 1,3'-bipyrazole derivatives were prepared in good yields by cyclocondensation of the acrylonitrile derivatives with 3-pyrazolylhydrazines in the presence of potassium carbonate in refluxing ethanol.[49,50]

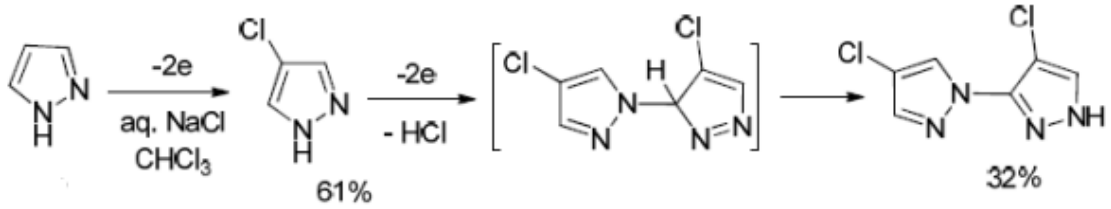


R^1 = H, Me, Et; R^2 = H, Me, OMe, SMe, CF_3; R^3 = H, Cl, Br, CN, CO_2Et
R^4 = H, Me, SMe, CF_3, Ph; X = H, CN, CO_2Et,

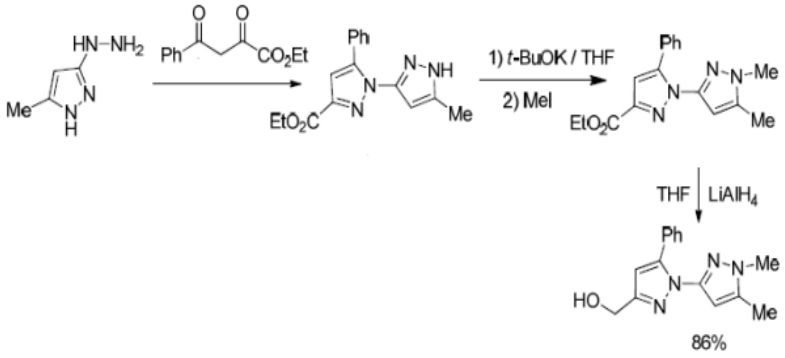
Transformation of the 5-hydrazino-1,3-oxazole-4-carbonitriles into 5-(pyrazol-1-yl)- 1,3-oxazole-4-carbonitriles**,** in good yields, was achieved upon its heating with acetylacetone. Further treatment of 5-(pyrazol-1-yl)-1,3-oxazole-4-carbonitriles with hydrazine hydrate in refluxing ethanol resulted in the opening of 1,3-oxazole ring and furnished the corresponding 1,3'-bipyrazoles in moderate to high yields via the intermediates as depicted below.[51,52]



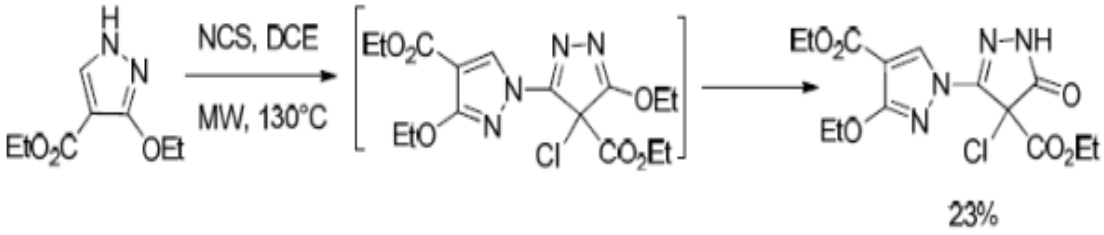
Electrochlorination of the unsubstituted pyrazole in aqueous NaCl solution in the presence of CHCl3 on Pt anode at a current of 3 A and 15 °C led to the formation of 4- chloropyrazole which underwent further dimerization under the reaction condition to give 4,4'-dichloro-1,3'-bipyrazole in reasonable yield, through the intermediate.[53]



Treatment of 3-hydrazinopyrazole with the benzoylpyruvate ester yielded the 1,3'- bipyrazole ester derivative in 36% yield. Methylation of this in the presence of t-BuOK gave the 1,3'-bipyrazole derivative in 29%. Finally, reduction of this using LiAlH4 in THF afforded 1,5'-dimethyl-3-hydroxymethyl-5-phenyl-1,3'-bipyrazole in 86% yield.[54]

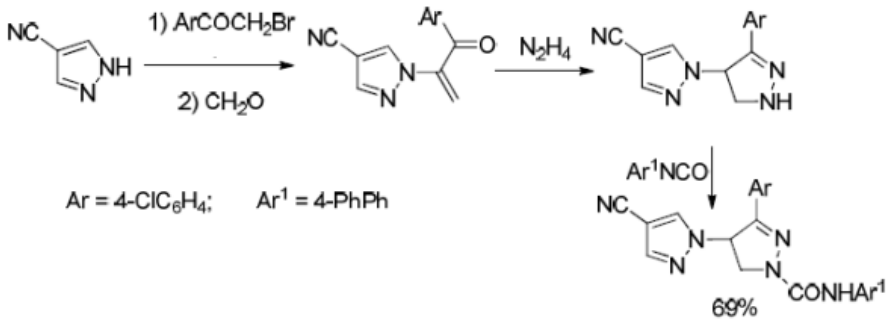


5-Chlorination of ethyl 3-ethoxypyrazole-4-carboxylate with N-chlorosuccinimide (NCS) under microwave irradiation at 130 °C in dichloroethane (DCE) led to the formation of the 1,3'-bipyrazole derivative in 23%. Mechanistically, occurrence of this compound was suggested via the hydrolysis of the 4-chlorinated ethoxypyrazole moiety of the intermediate upon working-up of the reaction.[55,56]

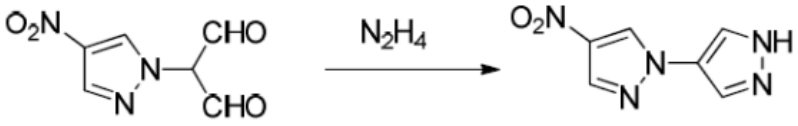


3. 1,4'-bipyrazoles

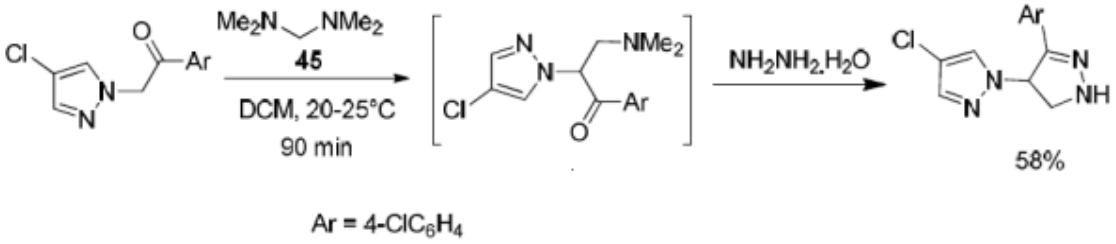
Reaction of 1H-pyrazole-4-carbonitrile with 4-chlorophenacyl bromide followed by condensation with formaldehyde resulted in the formation of the pyrazole derivative. When the latter compound was heated with hydrazine, the 1,4'-bipyrazole was obtained. Reaction of the 1,4'-bipyrazole 4-phenylphenylisocyanate afforded the 1,4'-bipyrazole derivative in 69% yield.[57,58]



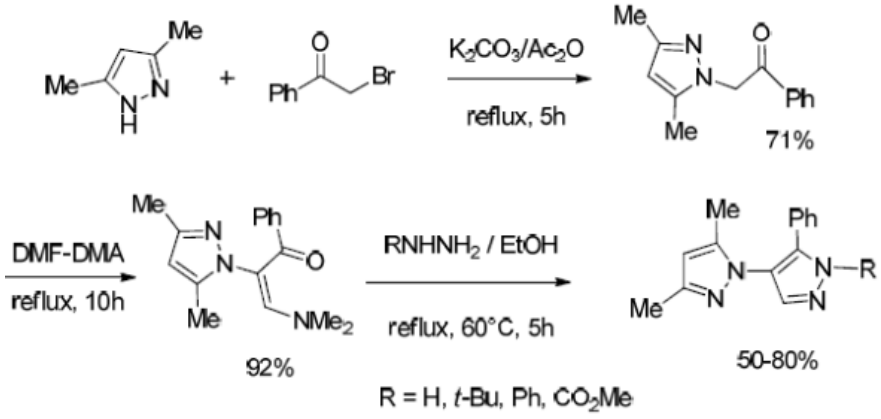
4-Nitro-1'H-1,4'-bipyrazole was obtained via condensation reaction of 2-(4-nitro 1Hpyrazol- 1-yl)malonaldehyde with hydrazine hydrate.[59]



Keeping a mixture of bis(dimethylamino)methane and (4-chloro-1-pyrazolyl)-4-chloroacetophenone in dichloromethane at 20-25 °C for 90 min gave the non-isolable intermediate which upon treatment with hydrazine hydrate gave the 1,4'-bipyrazole derivative in 58% yield.[60]

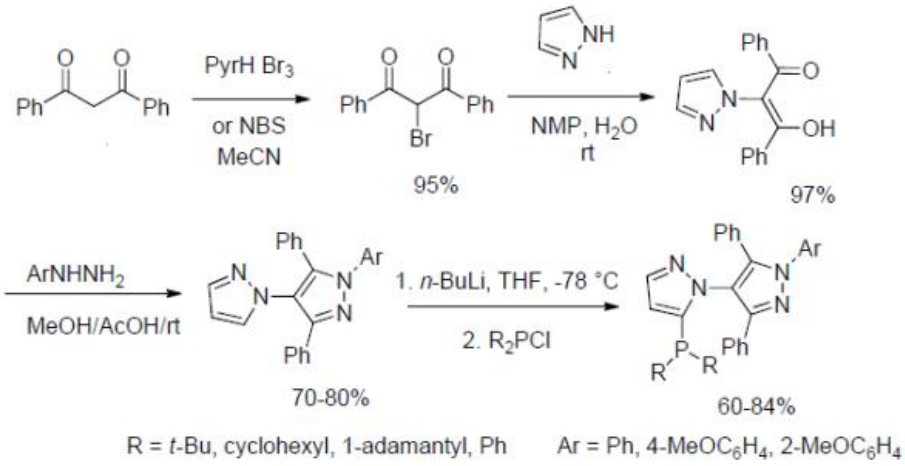


2-(3,5-Dimethyl-1H-1-pyrazolyl)acetophenone was prepared in 71% yield through the alkylation reaction of 3,5-dimethyl-1H-pyrazole with phenacyl bromide under reflux of anhydrous acetone containing potassium carbonate. Condensation of the latter compound with 1.2 equivalent of neat N,N-dimethylformamide-dimethylacetal (DMF-DMA) under reflux gave 3-dimethylamino-2-(3,5-dimethyl-1H-1-pyrazolyl)-1-phenyl-2-propen-1-one in 92% yield. The dimethylaminoenone was converted into 1,4'-bipyrazoles by its reaction with hydrazine derivatives.[61]

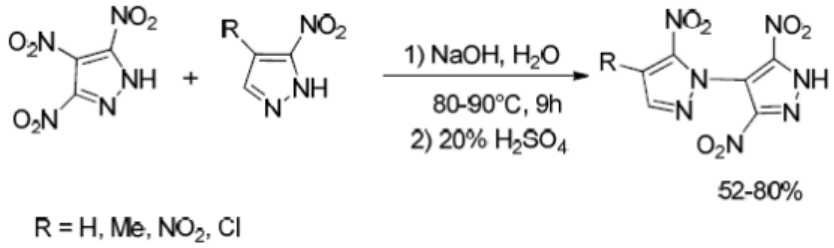


The synthesis 5-(di-tert-butylphosphino)-1-(1, 3, 5-triphenyl-1H-pyrazol-4-yl)-1Hpyrazole (Bippyphos) and its derivatives has been reported in four steps. The key precursor to Bippyphos was the preparation of the bipyrazole derivative via a one-pot bromination of 1,3-diphenylpropane-1,3-dione followed by alkylation with pyrazole in N-methyl-2-pyrrolidinone (NMP) followed by

condensation of the product 55 with phenylhydrazine. Lithiation of it followed by trapping with di-alkylchlorophosphine afforded the Bippyphos derivatives in good yields.[62, 63]

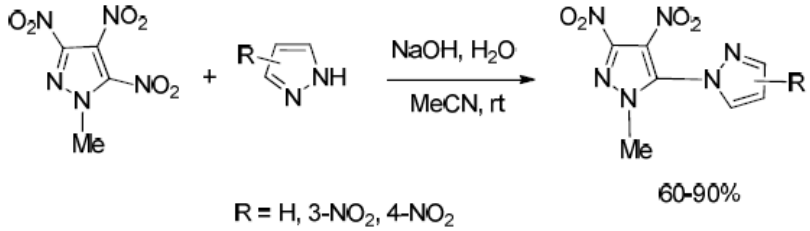


The reaction of 3,4,5-trinitro-1H-pyrazole (TNP) with 1H-pyrazoles in water in the presence of 2 equiv. NaOH at 80–90 °C followed by acidification gave the corresponding 1,4´-bipyrazoles in good yields, where the 1H-pyrazoles selectively substitute the 4- positioned nitro group in the TNP.[64]

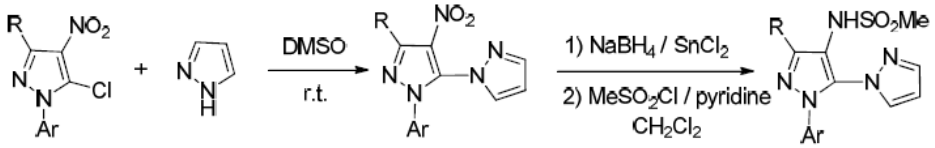


4. 1,5'-bipyrazoles

In contrast to the behavior of 3,4,5-trinitro-1*H*-pyrazole (TNP) towards 1*H*-pyrazoles where the substitution took place at the 4-positioned nitro group, the reactivity of 1-methyl- 3,4,5-trinitropyrazole (MTNP) behaved completely different compared to TNP and the nucleophilic substitution proceeded regiospecifically at the 5-position. Thus, reaction of MTNP with 1*H*-pyrazole or nitropyrazoles in the presence of NaOH at room temperature afforded the corresponding 1,5´-bipyrazole derivatives in high yields.[65]

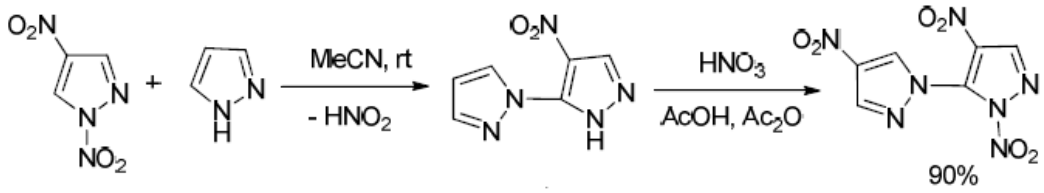


The activated 5-chloropyrazoles underwent nucleophilic substitution of its chlorine atom with pyrazole (as a nucleophile) in dimethylsulfoxide (DMSO) at room temperature led to the formation 1,5'-bipyrazole derivatives in good yields. Further reduction of the nitro group in compounds using NaBH4/SnCl2 followed by treatment with methanesulfonyl chloride and pyridine in dichloromethane afforded 4'- (methylsulfonylamino)-1,5'-bipyrazole.[66,67]



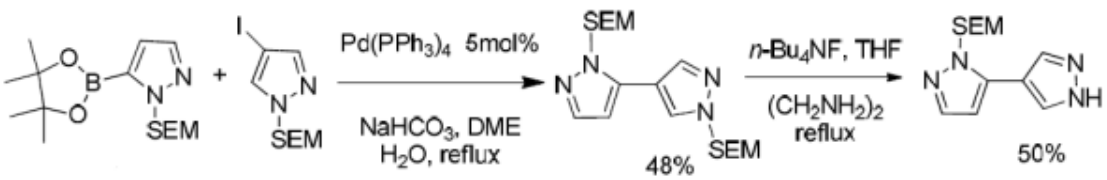
Ar = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$
R = H, Me

Reaction of pyrazole with 1,4-dinitropyrazole in acetonitrile at room temperature resulted in the formation of 4'-nitro-1,5'-bipyrazole in excellent yield through *cine*substitution reaction where the entering group (pyrazole) occupied position-2 adjacent to the leaving group (NO2). Further, nitration of with nitric acid in a mixture of acetic acid and acetic anhydride at reflux led to the formation of 1',4',4 trinitro-1,5'-bipyrazole in 90% yield.[68,69]



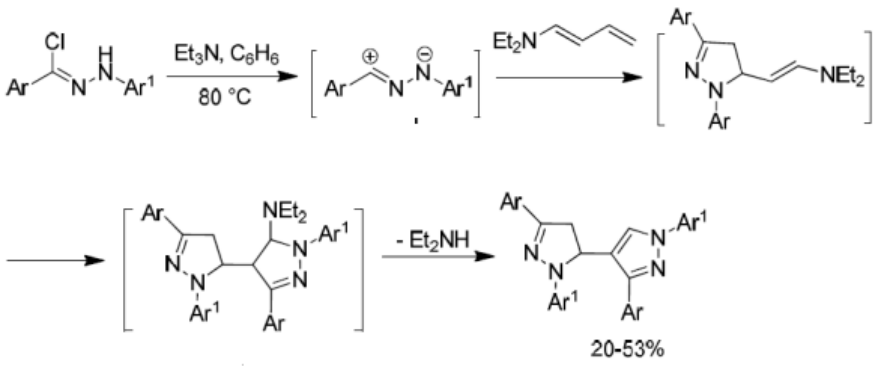
5. 4,5'-bipyrazoles

Reaction of 5-pyrazolylboronic ester with 4-iodo-1-[2- (trimethylsilyl)ethoxy]methyl pyrazole in the presence of Pd(PPh3)4 and NaHCO3 in refluxing dimethoxyethane (DME)/water gave the 1,1'-di(SEM)-4,5'-bipyrazole derivative in 48% yield; [2-(trimethylsilyl)ethoxy]methyl = SEM]. Deprotection of this using *n*- Bu4NF and ethylenediamine in refluxing THF resulted in removing only one SEM group of the 4,5'-bipyrazole to give the mono-protected 4,5'-bipyrazole in 50% yield.[70]



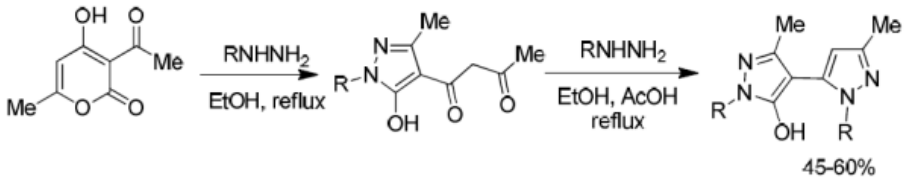
SEM = 2-(trimethylsilyl)ethoxy]methyl

The reaction of *N*,*N*-diethylbuta-1,3-dien-1-amine with two equivalents of diarylnitrilimines [derived from the hydrazonyl chloride under the effect of Et3N] in benzene at 80°C gave the corresponding 4,5'-bipyrazole derivatives in 20-53% yields. The reaction took place *via* the two intermediates.[71]



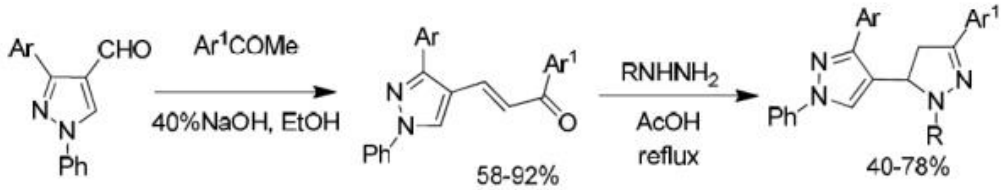
Ar/Ar^1 = Ph/Ph; Ph/4-ClC$_6$H$_4$; Ph/4-NO$_2$C$_6$H$_4$; 4-NO$_2$C$_6$H$_4$/Ph

3-Acetyl-2-pyranone was transformed into 4-(acetoacetyl)-5-hydroxy-3- methylpyrazoles up on its treatment with hydrazine or phenylhydrazine in refluxing ethanol. In addition, treatment of the latter pyrazoles with hydrazine derivatives resulted in the formation of the corresponding 4,5'-bipyrazoles.[72]



R = H, Ph

Reaction of pyrazole-4-carboxaldehyde with acetophenones in NaOH and ethanol at 50 °C afforded the 4-pyrazolylpropenones in high yields. Heating the latter propenones with hydrazines yielded the corresponding 4,5'-bipyrazole derivatives.[73-75]

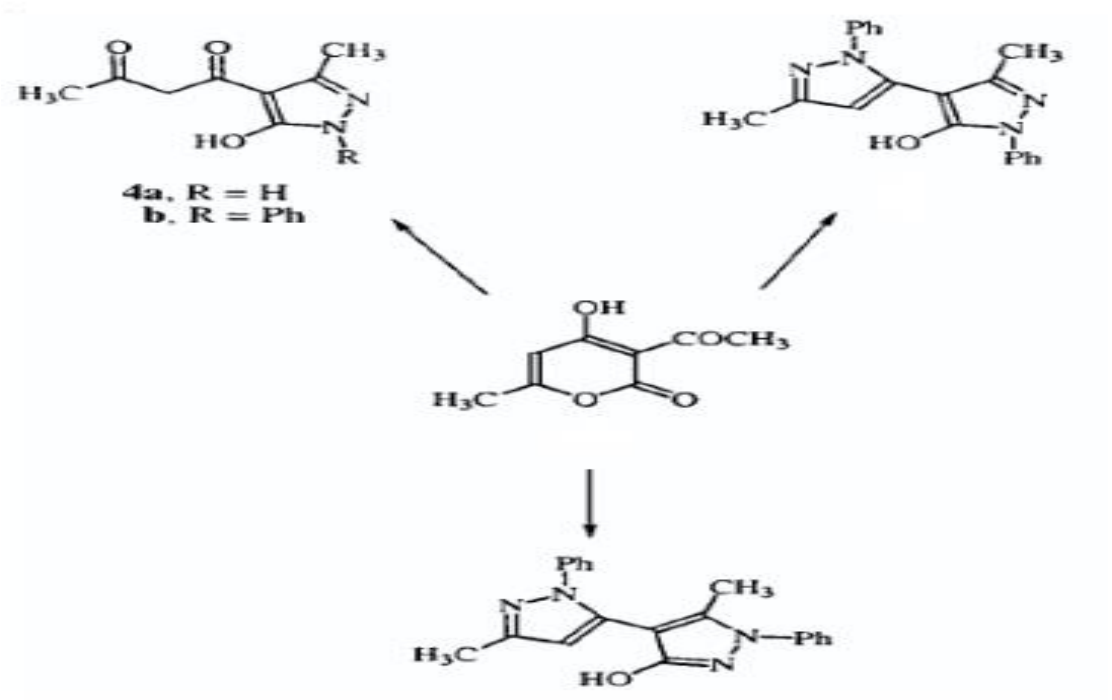


Ar = Ph, 4-MeSC$_6$H$_4$, 2-thienyl, 3-pyridyl

Ar^1 = Ph, 4-MeC$_6$H$_4$, 4-EtC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-MeSC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-OHC$_6$H$_4$

R = H, Ph

Synthesis of bipyrazoles and pyrazoloisoxazoles from Dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one) was carried out by Abderrahman Bendaas and Hamdi. They used Phenylhydrazine and other hydrazines to give bipyrazoles and pyrazoloisoxazoles.[76]



CONCLUSION

A lot of work has been done for the synthesis of pyrazole and bipyrazole derivatives in the recent past. Bipyrazoles can be derived from pyrazoles which are mostly synthesized by conventional methods. Synthesis of pyrazoles from methylene ketones, alkanyl bromides and propargylic alcohols are some novel approaches for this system. Also, appending a suitable pharmacophore to these compounds have resulted in development of efficient biologically active compounds.

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