

# A Concise Review on the Synthesis of Pyrazole Heterocycles

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## Abstract

**Study background:** Pyrazole moiety, being called as pharmacophore, plays an important role in many biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry. In addition pyrazoles are also used extensively as useful synthons in organic synthesis. These derivatives have wide spread biological activities such as anticancer, analgesic, anti-inflammatory, antimicrobial, antiviral, anticonvulsant, antihistaminic and anti-HIV. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry.

**Methodology:** The steps included condensation followed by cyclization or MCR, either in a step-wise manner or in one pot has been achieved successfully to obtain this class of heterocycles under different conditions. Phosphorus oxychloride (POCl<sub>3</sub>), dimethyl formamide, acetamide and hydrazine are the most common reagents used for the synthesis of pyrazole appended heterocyclic skeletons.

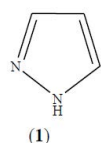
**Results:** The reaction schemes resulted in the synthesis of heterocyclic appended pyrazoles in potential yields under either simple reaction conditions or microwave irradiation.

**Conclusion:** These protocols provide convenient strategies to annelate different heterocyclic nuclei with widespread bioactive pyrazoles thereby extending the categories of heterocyclic systems. These strategies also provide valuable information for the further design of more active biological agents through various modifications and derivatizations.

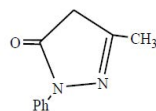
**Keywords:** Pyrazole; Dimethyl formamide; Phosphorus oxychloride; Hydrazine

## Introduction

Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process and analysis of drugs in late development or in the market shows that 68 % of them are heterocycles. Hence it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention in the recent years. The pyrazole system (1) consists of a doubly unsaturated five membered ring with two adjacent nitrogen atoms. Knorr [1,2] first synthesized compounds containing this system in 1883 by the reaction of ethyl acetoacetate with phenyl hydrazine, which yielded 1-phenyl-3-methyl-5-pyrazolone (2). Knorr [3] introduced the name pyrazole for these compounds to denote that the nucleus was derived from pyrrole by the replacement of a carbon by nitrogen. They synthesized many members of this class and systematically investigated their properties.

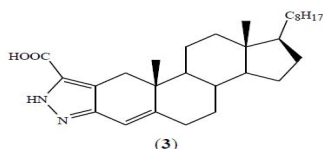


(1)



(2)

Literature survey has revealed that till 1930s very little had been done for the synthesis of steroidal pyrazole derivatives. Probably the first steroidal pyrazole was reported in 1938 by Ruzicka et al. [4] and only a single derivative; cholest-4-eno [3,2-c] pyrazole-5-carboxylic acid (3) was mentioned.

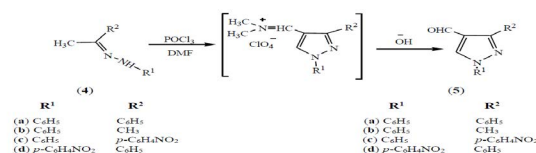


(3)

After a considerable span of time, much attention has been paid by a number of organic chemists towards the synthesis of several steroidal pyrazoles. The effect on different biological activities produced by the fusion of a pyrazole ring to the steroid nucleus has prompted us to investigate such type of compounds. The compounds containing pyrazole ring system can be synthesized by different routes and here we have summarized only important examples, as below.

## Reaction Protocols

Kira et al. [5] reported that treatment of acetophenone phenylhydrazone (4a-d) with two moles of DMF-POCl<sub>3</sub> in DMF at 70-80°C for 6 h gave immonium perchlorate. Alkaline hydrolysis of immonium perchlorate afforded 1,3-diarylpyrazole-4-carboxaldehyde (5a-d).



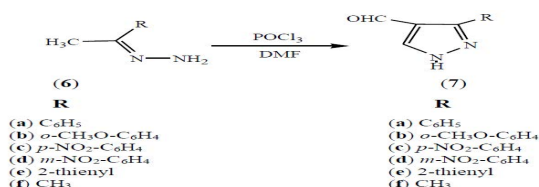
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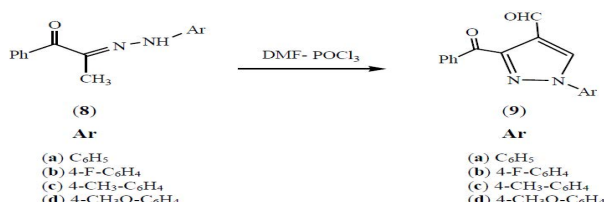
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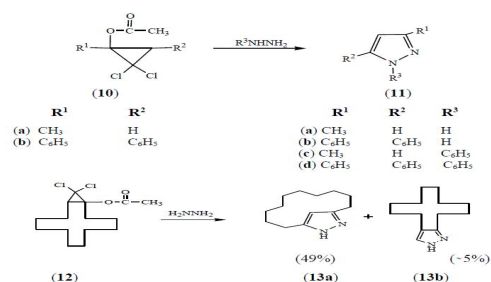
Kira et al. [6] synthesized 3-substituted pyrazole-4-carboxaldehyde (7a-f) by the reaction of semicarbazones (6a-f) with two moles of DMF-POCl<sub>3</sub> in DMF.



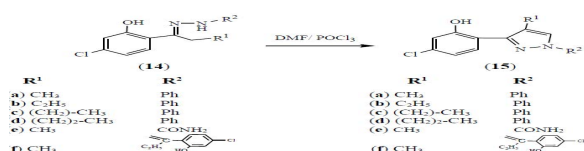
Bavatenko et al. [7] reported substituted pyrazoles (9a-d) by cyclizing aryl hydrazones (8a-d) under Vilsmeier conditions.



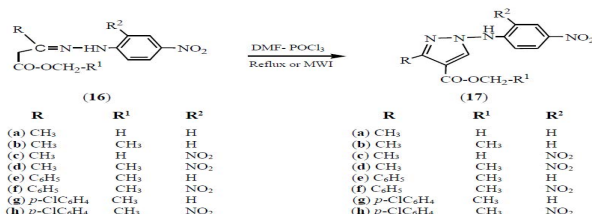
3,5-Disubstituted pyrazoles (11a-d) were obtained by the reaction of gem-dichlorocyclopropylacetates (10a,b) with 4 equivalents of hydrazine or phenyl hydrazine at room temperature while metacyclophane (13a) and its isomer (13b) were obtained from 1-acetoxycyclo[10.1.0]tridecane (12) with hydrazine under same condition [8].



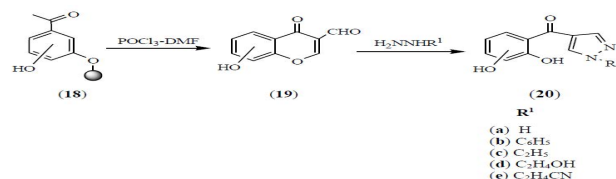
Pawar and Borse [9] reported 4-n-alkyl substituted pyrazoles (15a-f) from phenyl hydrazones (14a-d), semicarbazone (14e) and azine of 2-n-acyl-5-chlorophenol (14f) by monoformylation and cyclization by using one mole of the Vilsmeier-Haack reagent (DMF-POCl<sub>3</sub>).



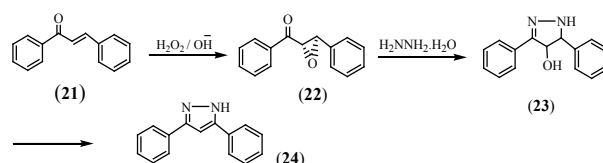
Sridhar [10] reported pyrazole-4-carboxaldehyde (17a-h) by the reaction of hydrazones of aliphatic and aromatic methylketones (16a-h) with Vilsmeier reagent. They also studied the reactivity of hydrazones of β-ketoesters towards Vilsmeier reagent, both by conventional and microwave methods.



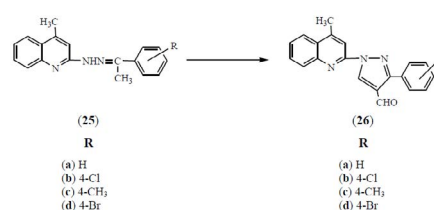
Borrell et al. [11] synthesized pyrazole library by using Merrifield resin as a solid-phase support to a hydroxyacetophenone (18), Vilsmeier-Haack formylation on methyl group and cyclization with substituted hydrazine to afford 4-hydroxybenzoyl-1-substituted pyrazoles (20a-e).



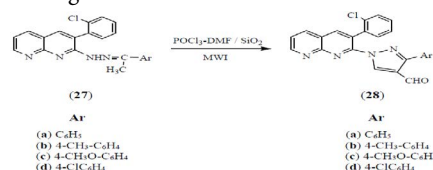
Dhar and Bhat [12] reported the synthesis of 3,5-diphenyl-1H-pyrazole (24) from chalcone (21) by the action of hydrazine hydrate on chalcone-epoxide (22) followed by simultaneous dehydration in presence of catalytic amount of concentrated sulphuric acid in acetic acid.



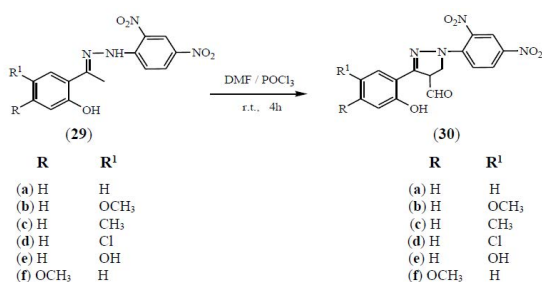
Kidwai et al. [13] used microwave irradiation and synthesized 4-methyl-2-[3'-substituted-phenyl-4'-formylpyrazolyl] quinoline (26a-d) by the reaction of hydrazones of methylquinoline (25a-d) with DMF and POCl<sub>3</sub> under microwave irradiation of 3-4 min.



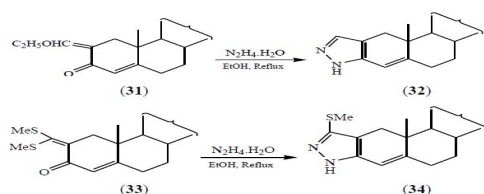
3-Aryl-4-formyl-1-[3(2-chlorophenyl)-1,8-naphthyridin-2-yl] pyrazoles (28a-d) were obtained when hydrazones (27a-d) were subjected to microwave irradiation [14] in the presence of Vilsmeier-Haack reagent.



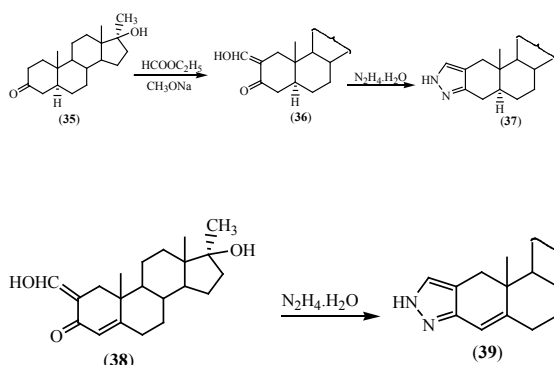
Selvi and Perumul [15] synthesized 4-ethoxy-4H-benzopyrano [4,3-c]pyrazoles (30a-f) from *o*-hydroxyacetophenone-2,4-dinitrophenylhydrazone (29a-f) under Vilsmeier conditions.



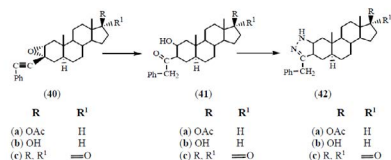
Singh et al. [16] reported the synthesis of pyrazolo [3,2-c]cholest-4-ene (32) and [1'H]-5'-(methylthio) pyrazolo [3,2-c]cholest-4-ene (34) from 2-ethoxymethylene-4-cholest-4-en-3-one (31) and bis (methylthio) methylene cholest-4-en-3-one (33), respectively by the action of hydrazine hydrate in ethanol under reflux.



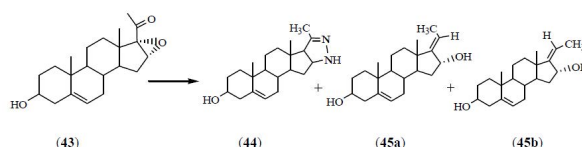
Clinton et al. [17] reported that the treatment of 17 $\alpha$ -methylandrostan-17 $\beta$ -ol-3-one (35) with ethylformate and sodium methoxide gave 2-hydroxymethylene derivative (36) which on condensation with hydrazine gave 17 $\beta$ -hydroxy-17 $\alpha$ -methylandrostan-3-one [3,2-c] pyrazole (37). Similar treatment of 2-hydroxymethylene-17 $\alpha$ -androstan-4-en-17 $\beta$ -ol-3-one (38) furnished 17 $\beta$ -hydroxy-17 $\alpha$ -methylandrostan-4-eno [3,2-c] pyrazole (39).



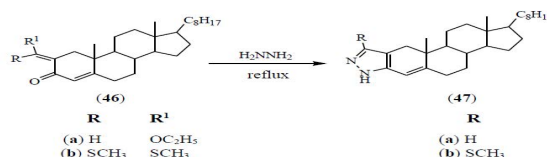
Berbalk et al. [18] reported that the epoxyandrostan-4-ene (40a-c) underwent formolysis to give phenyl acetylandrostan-4-ene (41a-c) which on further cyclocondensation with hydrazine afforded steroidal pyrazoles (42a-c).



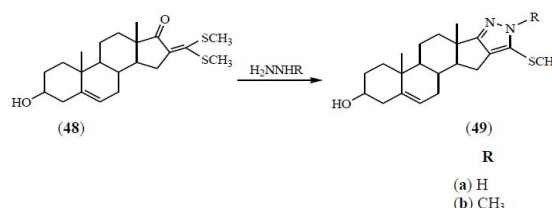
Bonn and Dodson [19] carried out the hydrazine reduction of 16 $\alpha$ , 17-epoxy-pregnenolone (43) to obtain 3 $\beta$ -hydroxyandrost-5-eno [16,17-c]-5-methylpyrazole (44) along with the two isomeric allylic alcohols, 5,17 [20]-(*cis*)-pregnadiene-3 $\beta$ , 16 $\alpha$ -diol (45a) and 5,17 [20]-(*trans*)-pregnadiene-3 $\beta$ , 16 $\alpha$ -diol (45b).



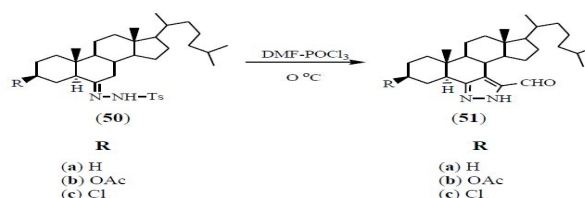
Laitonjan et al. [20] synthesized substituted steroidal [3,2-c] pyrazoles (47a,b) by the reaction of 2-ethoxymethylene-4-cholestan-3-one (46a) and 2-bis (methylthio) methylene cholest-4-en-3-one (46b) with hydrazine hydrate and refluxed for 3 h.



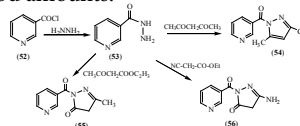
Peseke et al. [21] reported that the treatment of 3 $\beta$ -acetoxy-16-[bis (methylthio) methylene]-5-androst-5-en-17-one (48) with hydrazine hydrate and methylhydrazine afforded the 5-methylthio-pyrazolo [4',3':16,17] androst-5-en-3 $\beta$ -ols (49a,b).



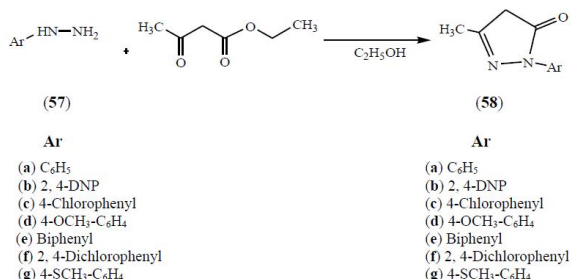
Shamsuzzaman et al. [22] reported that the treatment of 5 $\alpha$ -cholestan-6-one tosylhydrazones (50a-c) with Vilsmeier reagent gave 5'-formyl-5 $\alpha$ -cholestan [6,7-c] pyrazole derivatives (51a-c) in 60-65% yields.



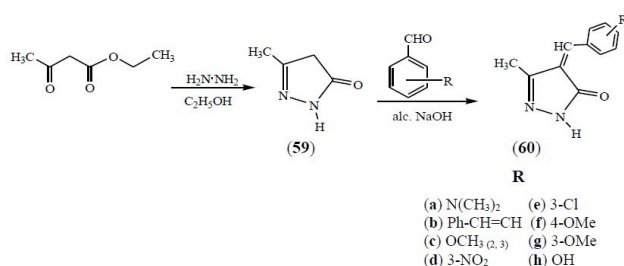
Sidhaye et al. [23] reported that nicotinoyl chloride (52) reacted with hydrazine and gave nicotinohydrazide (53). The compound (53) on reaction with acid derivatives yielded (3,5-dimethyl-1H-pyrazol-1-yl)(pyridine-3-yl) methanone (54), 3-methyl-1-nicotinoyl-1H-pyrazol-5(4H)-one (55), 3-amino-1-nicotinoyl-1H-pyrazol-5(4H)-one (56) in good amounts.



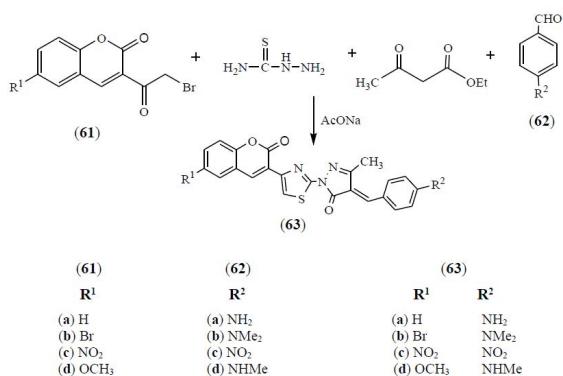
Isloor et al. [24] reported the reaction of substituted hydrazines (57a-g) with ethyl acetoacetate in absolute alcohol which provided the corresponding substituted pyrazolones (58a-g) in good yields.



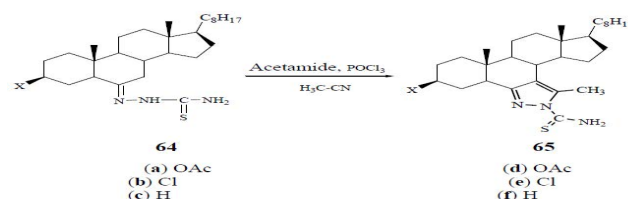
Mariappan et al. [25] reported that the reaction of ethyl acetoacetate with hydrazine hydrate in absolute alcohol yielded pyrazolone (59). The pyrazolone (59) upon reaction with different substituted aromatic aldehydes in presence of alcoholic sodium hydroxide yielded corresponding substituted pyrazolones (60 a-h).



Rao and Chunduru [26] reported the one pot synthesis of 4-arylidene-3-methyl-1-[4-(2-oxo-2H-chromen-3-yl)]-thiazol-2-yl]-1H-pyrazol-5(4H)-ones (63a-d) by reacting 3-(2-bromoacetyl) coumarin derivatives (61a-d), thiosemicarbazide, ethyl acetoacetate and substituted aryl aldehydes (62a-d) in presence of sodium acetate in acetic acid.



Ayaz M Dar and Shamsuzzaman [27] also reported the expeditious and convenient synthesis of new 5 $\alpha$ -cholestano [6,7-c]-5'-methyl-1'-carbothioic acid amide pyrazoles (65d-f) based on the reaction of 5 $\alpha$ -cholestan-6-one thiosemicarbazones (64a-c) with modified Vilsmeier-Haack reagent (H<sub>3</sub>C-CO-NH<sub>2</sub>/POCl<sub>3</sub>).



## Conclusion

In this article we have mentioned the different routes for the synthesis of pyrazole derivatives. The steps included condensation followed by cyclization or multi-component reaction (MCR), either in a step-wise manner or in one pot; either simple refluxing/stirring or microwave irradiation, has been achieved successfully to obtain the aforementioned class of heterocycles under different conditions. Most of the preparative methods included phosphorus oxychloride (POCl<sub>3</sub>), dimethyl formamide, acetamide and hydrazine as common reagents for the synthesis of pyrazole appended heterocyclic skeletons. Also many series of substituted pyrazole fused six membered heterocycles possessing N-, S and O- have been constructed in potential yields. Hence these protocols provide convenient strategies to annelate different heterocyclic nuclei with widespread bioactive pyrazoles thereby extending the categories of heterocyclic systems.

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