

4H-Pyrano[2,3-c]pyrazoles: a review

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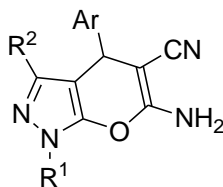
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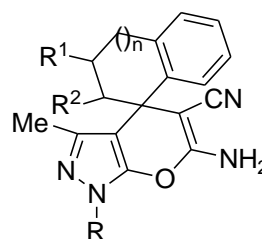
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Abstract

This review summarizes the synthetic pathways to pyrano[2,3-c]pyrazoles which either have a hydrogen atom, aryl substituent or condensed spiro group at the 4-position. Synthesis focuses on two component or MCR's including three, four and five components. Reaction conditions are variable including a green approach, nanoparticulate catalyst, microwave irradiation, ultrasonic irradiations and other catalysts. Most commonly used reagents are pyrazolones, benzylidenemalononitrile, hydrazines, β -ketoesters, malononitrile, aldehydes and ketones. Various substituted phenyl, naphthalene, anthracene, furan, thiophene, indole, tetrahydroquinoline have been incorporated at 4-position while amino and cyano groups at sixth and fifth position respectively and posses diverse biological properties.



6-aminopyranopyrazole-5-cabonitriles



Spiropyranopyrazoles

Keywords: Pyrazolones, 6-aminopyranopyrazole-5-cabonitriles, synthesis, mechanism, biological activities

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1. Introduction

Pyranopyrazoles are an important class of heterocyclic ring systems, which can be prepared by a diverse range of synthetic procedures,^{1,2} have important pharmacological properties,¹⁻³ been the topic of theoretical studies,⁴ and are of industrial significance.^{5,6} Out of four possible isomeric forms, pyrano[2,3-*c*]pyrazole (**1**), pyrano[4,3-*c*]pyrazole (**2**), pyrano[3,2-*c*]pyrazole (**3**) and pyrano[3,4-*c*]pyrazole (**4**), isomer **1** is the most widely studied.¹ The synthesis, derivatization and biological activities of a range of derivatives of **1** have been reported (Figure 1).^{1,2}



Figure 1. Structures of isomeric pyranopyrazoles.

The first synthesis of pyrano[2,3-*c*]pyrazoles (**1**) was reported by Stollé, who prepared it from hydrazine and ethyl acetoacetate.⁷ Wolff also reported its synthesis at about the same time.⁸ In 1973, Junek and Aigner synthesized some polynitrile derivatives of pyrano[2,3-*c*]pyrazoles which initiated developments in functionalized pyranopyrazoles synthesis such as pyrano[2,3-*c*]pyrazol-6-one (**5**), pyrano[2,3-*c*]pyrazol-4-one (**6**) and 4*H*-pyrano[2,3-*c*]pyrazole (**7**) (Figure 2).⁹ Khan and co-workers also synthesized various derivatives of **5** and **6**.^{10, 11}

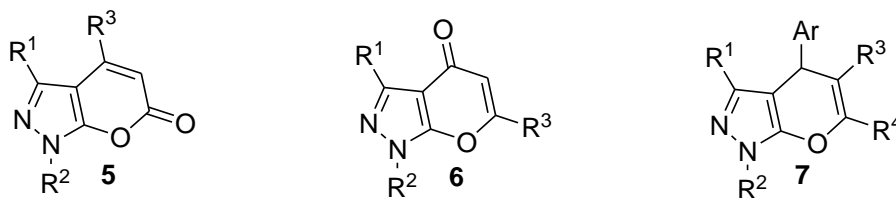


Figure 2. Derivatives of pyranopyrazoles.

This review focuses on the developments in the chemistry of derivatives of **7**, especially their synthesis and leaving the treatment of pyranopyrazolones outside the scope of the present review. Pyranopyrazole **7** shows various biological activities such as Chk1 inhibitors, acetylcholinesterase (AChE) inhibitors (Figure 3).^{1,3}

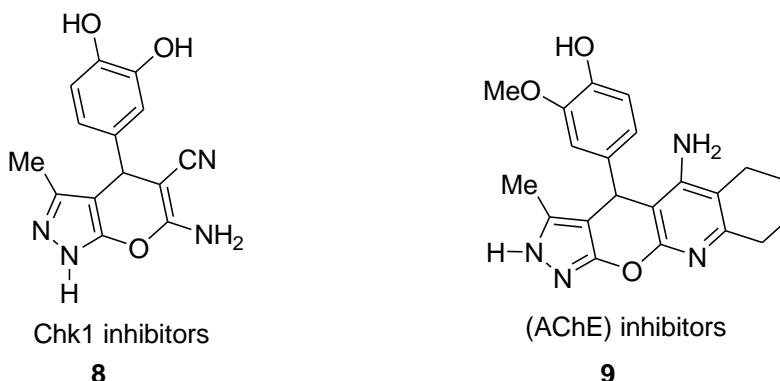


Figure 3

Emphasis has been given to the various methods published in the literature, to synthesize a number of 4-arylpyranopyrazoles or 4-spiropyranopyrazoles using different reactants with/without catalyst in solvents (organic/ionic/water) or without solvent at various temperatures under changing reaction conditions together with the reported mechanism. Methods are represented based on the number of components condensed together to generate the resultant compounds. This review does not include all publications in this area, but what we consider to represent seminal articles related to the topic. To the best of our knowledge, it is the first attempt to summarize the synthetic methods of 4-spiropyranopyrazoles, as the other reviews^{1,2} also includes derivatives **5** and **6** as well as their reactions.

2. Synthesis of Pyrano[2,3-*c*]pyrazoles (7)

2.1. Two component syntheses

Junek and Aigner treated tetracyanoethylene with pyrazol-5-one and 5-aminopyrazole to obtain pyrano[2,3-*c*]pyrazoles (**10**), pyrazolo[3,4-*b*]pyridines (**11**) and dipyrazolyl malonodinitriles (**12**) respectively depending on reaction condition (Figure 4).⁹ 6-Amino-1,3-disubstituted-4,4,5-tricyanopyrano[2,3-*c*]pyrazole (**10**) was obtained by refluxing the appropriate pyrazolone and tetracyanoethylene in ethanol.

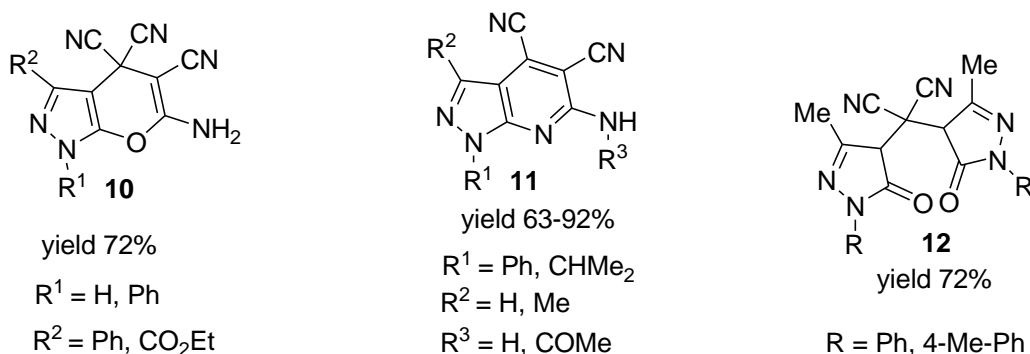
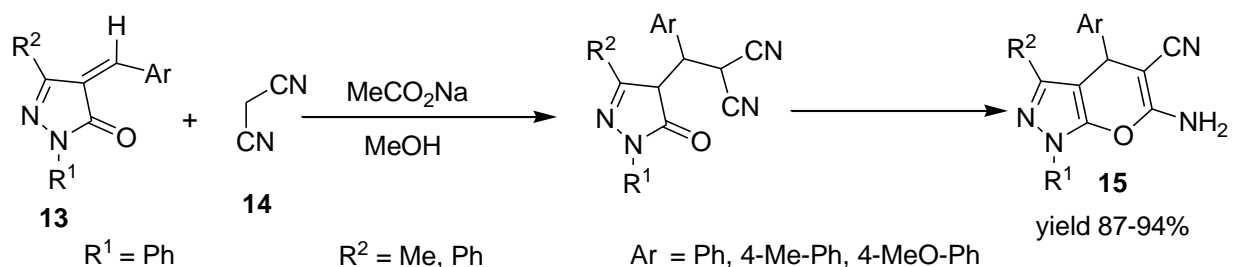


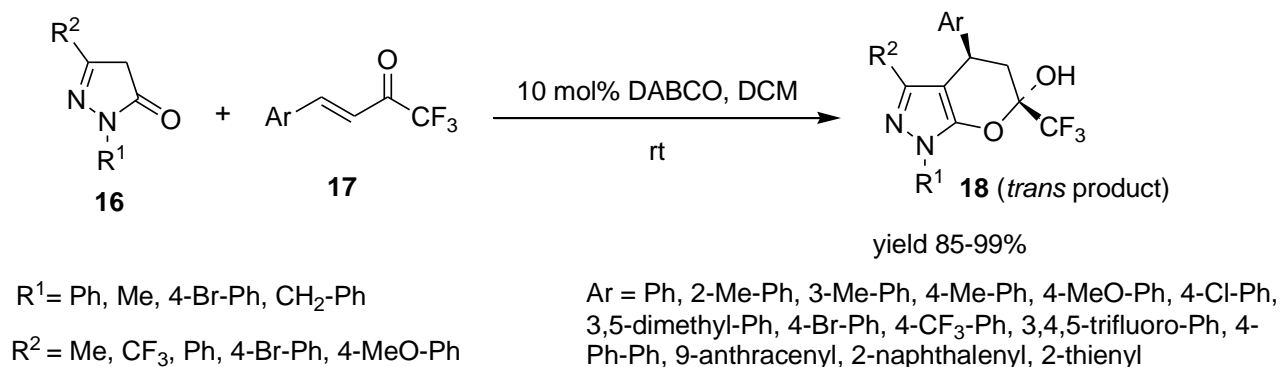
Figure 4

Otto refluxed 4-benzylidene-pyrazol-5-one (**13**) with malononitrile (**14**) in methanol in the presence of sodium acetate catalyst to obtain pyrano[2,3-*c*]pyrazole (**15**)¹² (Scheme 1).



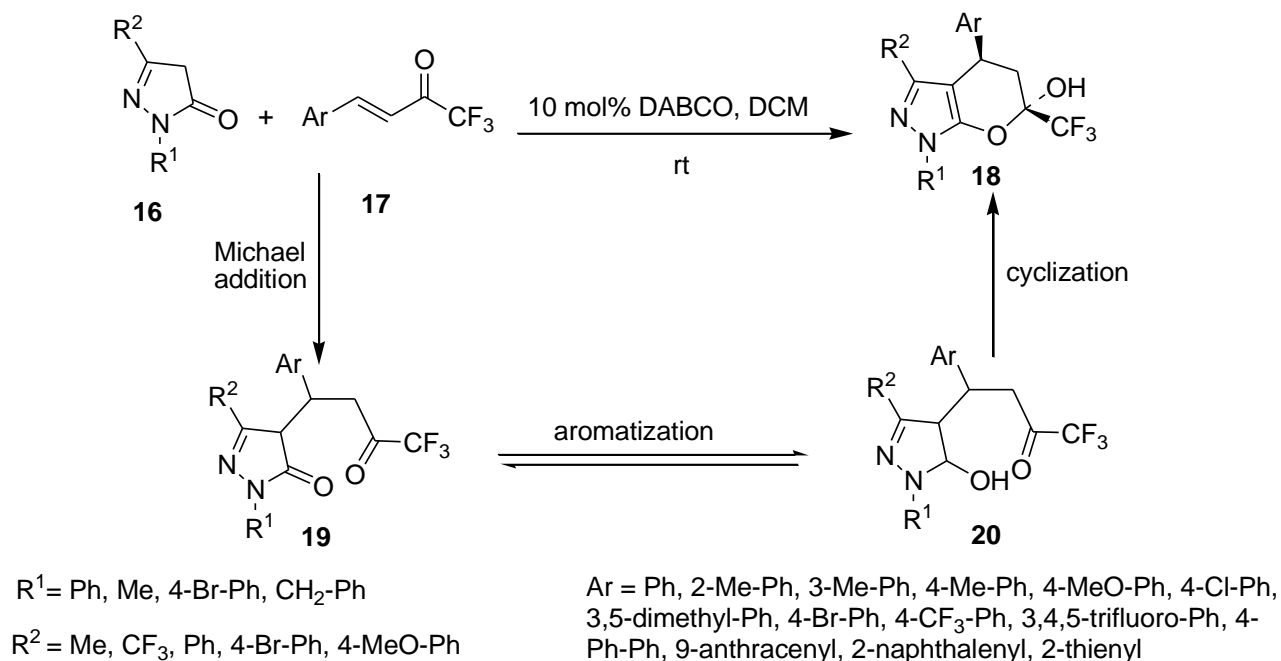
Scheme 1

Wang *et al.* developed an efficient synthesis of 6-hydroxy-6-trifluoromethyl-pyrano[2,3-*c*]pyrazoles (**18**) in excellent yields (85-99%) using 10 mol% of 1,4-diazobicyclo[2.2.2]octane (DABCO) as base in DCM solvent at room temperature.¹³ Other bases such as triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), *N,N*-dimethylaniline ($\text{C}_6\text{H}_5\text{NMe}_2$) were also tested in different solvents. All bases showed good results, but 20 mol% of DABCO was found to be an excellent catalyst to provide diastereoselective control in the formation of pyranopyrazoles (6:1-30:1). X-Ray crystallographic analysis of the major isomer indicated that the *trans*-products were predominantly formed (Scheme 2).



Scheme 2

The reaction route is believed to involve tandem Michael addition of pyrazolone **16** to the α,β -trifluoromethyl ketones (**17**), followed by aromatization and cyclization (Scheme 3).¹³



Scheme 3

Tetrahydroquinoline derivatives are well known for antibiotic, antitumor, anti-allergic, antidepressant, anti-ulcer, anticonvulsant, anti-fertility, antioxidant and herbicidal applications.¹⁴ Hence, Pandit and Lee synthesized tetrahydroquinolines bearing pyranopyrazoles **21-23** in acetonitrile containing 10 mol% of EDDA at 60 °C for 1–2 h (Figure 5).¹⁵ The *cis*-stereochemistry of the product was confirmed by X-ray crystallography and rationalized by the mechanism outlined in Scheme 4.

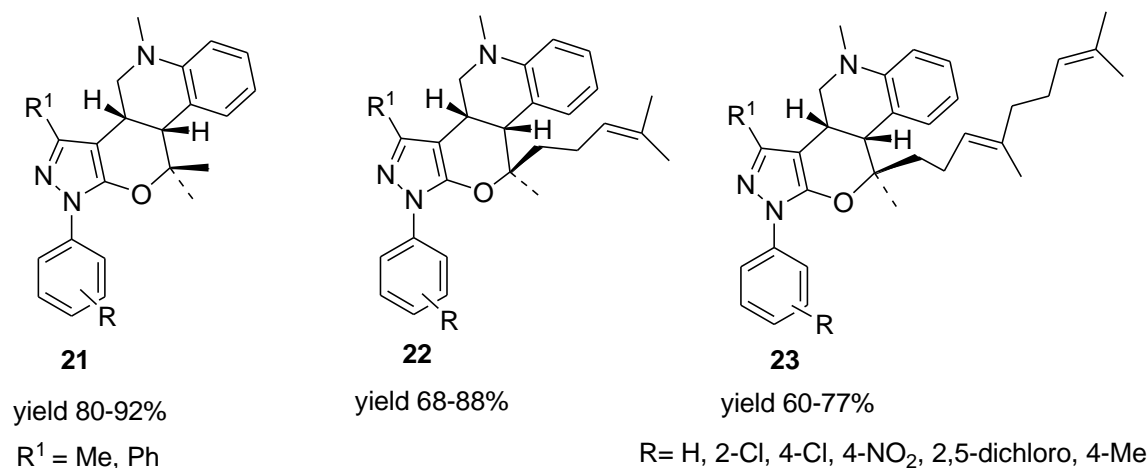
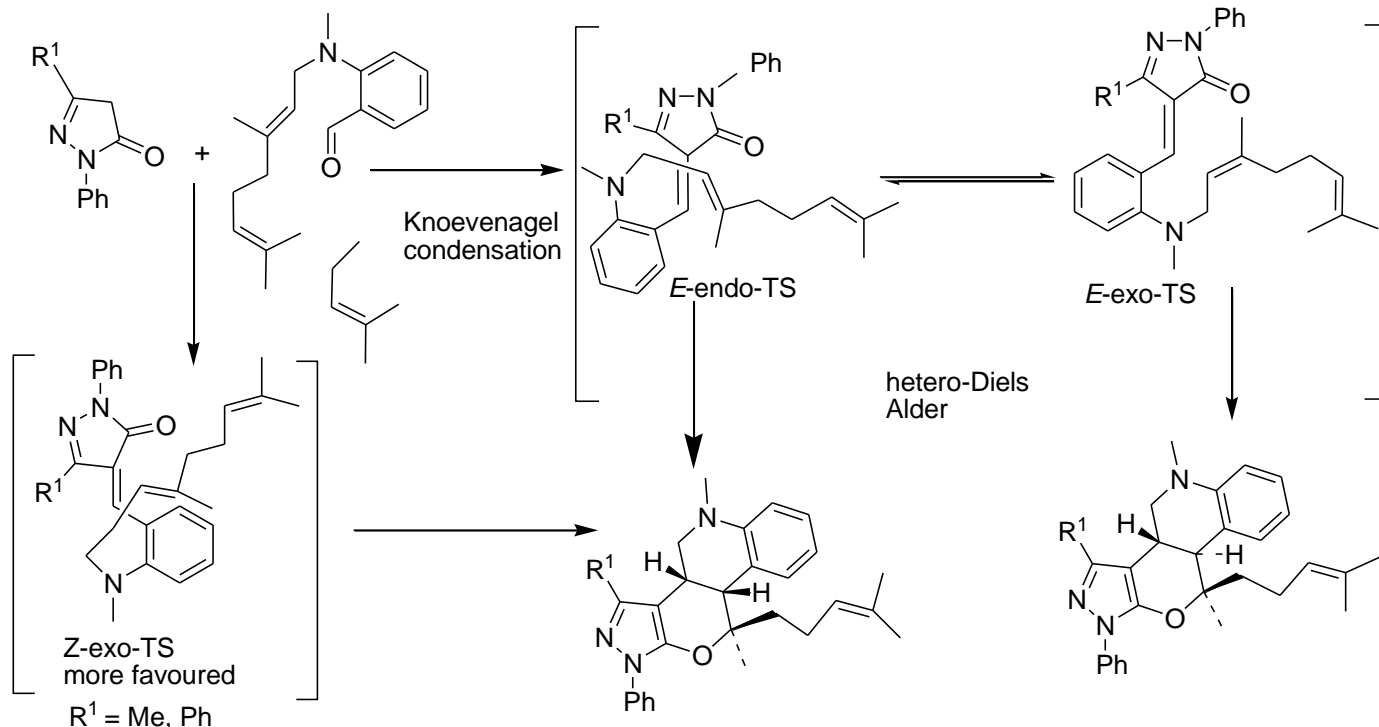
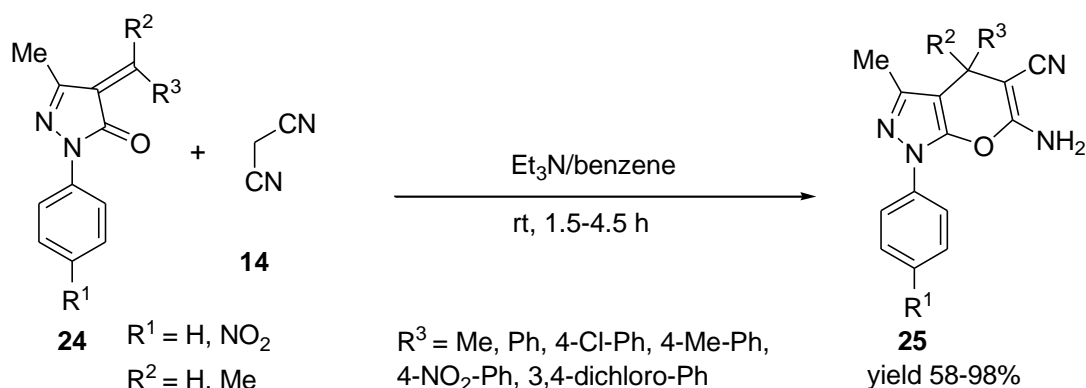


Figure 5



Scheme 4. Mechanism.

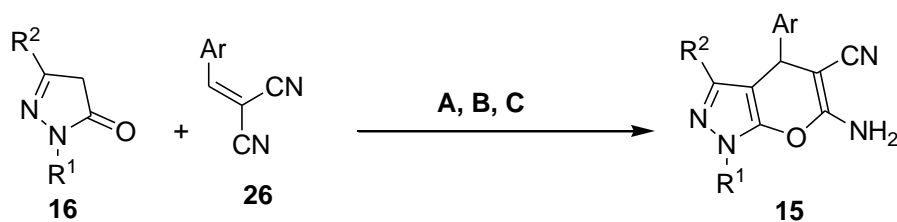
In the literature, various derivatives of **24** were reacted with malononitrile (**14**) in benzene as solvent containing triethylamine giving pyranopyrazoles **25**, which were screened for fungicidal, herbicidal and insecticidal activities.¹⁶ All compounds were inactive fungicidal and insecticidal agents however, one compound was active herbicidal agent (Scheme 5).



Scheme 5

Gogoi and Zhao carried out enantioselective synthesis by reacting pyrazol-5-one **16** and benzylidenemalononitrile (**26**) under catalytic action of different cinchona alkaloids including quinine, cupreine, 9-*epi*-cupreine and 9-*epi*-amino-9-deoxyquinine in various solvents (CH₂Cl₂, CHCl₃, THF, ether, benzene, MeCN).¹⁷ Cupreine gave excellent selectivities in dichloromethane and the enantioselectivity found to be highly dependent on the reaction conditions, structure of the catalysts and the substrates hence, enantioselectivity (*ee*^c) decreased with small changes in catalyst, solvent and with presence of substituent on

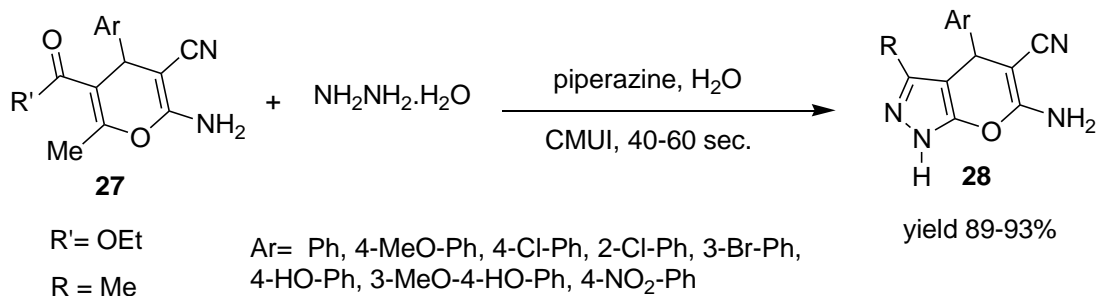
the phenyl ring of the benzylidenemalononitrile (Scheme 6 A). The structure was confirmed by X-ray studies. Ahmad and co-workers subjected an ethanolic solution of pyrazolone **16** and benzylidemalononitrile (**26**) containing piperidine to microwave irradiation for two min to get pyranopyrazoles, which were subjected to various derivatization reactions.⁵ The synthesized compounds were found to be effective anti-oxidants for lubricating oil (Scheme 6 B). Similarly, Elziaty and co-workers refluxed ethanolic solutions of both reactants in the presence of piperidine for 1 h to get pyranopyrazoles which treated with various reagents (formic acid, acetamide, acetic anhydride, aldehydes e.t.c) to form important condensed heterocyclic moieties¹⁸ (Scheme 6 C).



Scheme	R ¹	R ²	Ar	Conditions	Yield
A	H	Me, Et, Ph	Ph, 4-Me-Ph, 4-MeO-Ph, 4-Cl-Ph, 4-Br-Ph, 4-I-Ph, 4-F-Ph, 4-CN-Ph, 4-NO ₂ -Ph, 3-Br-Ph	CH ₂ Cl ₂ , rt, cupreine 5 mol%	79-96%
B	Ph	Me	4-HO-Ph	EtOH, piperidine, MW 160 W, 2 min	51-83%
C	H	Me	4-Cl-Ph	EtOH, piperidine, reflux 1 h	85%

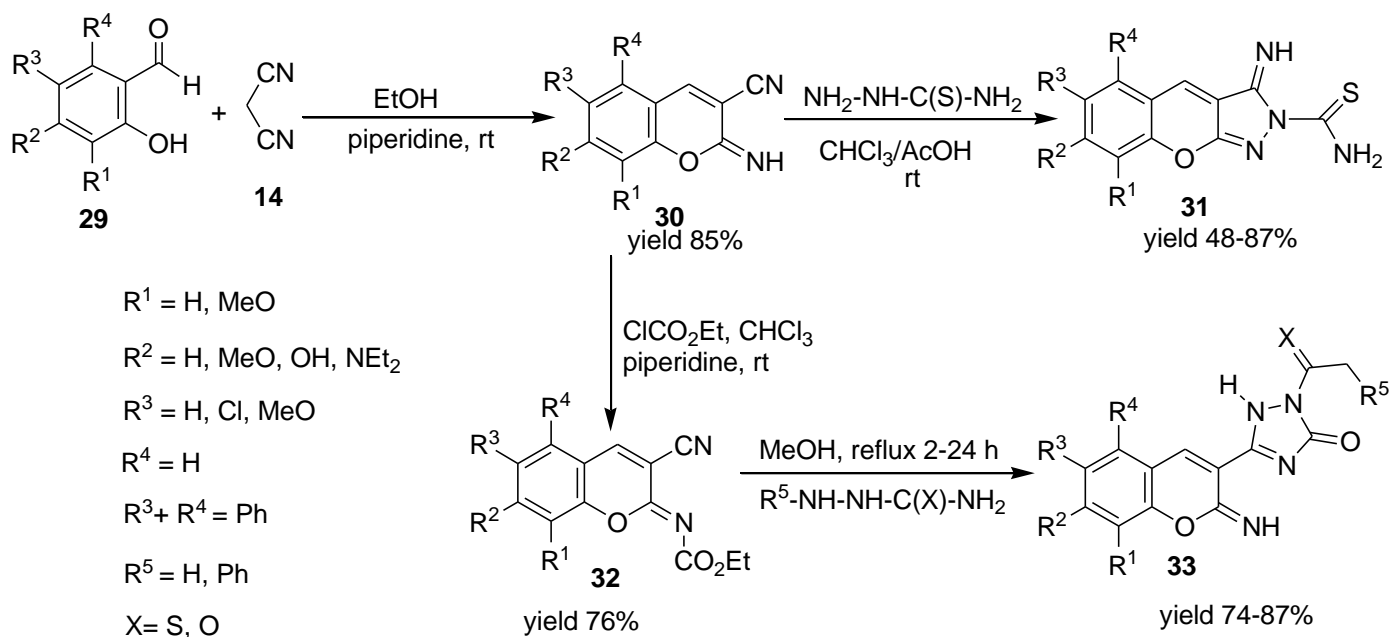
Scheme 6

Water as a green solvent, is the most environmentally friendly, safe and inexpensive choice to decrease pollution, toxicity and cost of a reaction.¹⁹ Peng and co-workers used pure aqueous media for reaction of 5-alkoxycarbonyl-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans (**27**) and hydrazine hydrate in the presence of a catalytic quantity of piperazine by three methods (i) heating (ii) exposing to microwave irradiation (iii) exposing to a combination of microwave and ultrasound irradiation where, the latter was found to be excellent in terms of yield within short time²⁰. It was assumed that powerful ultrasound irradiation causes cavitations and high-velocity interparticle collisions, which cleaned the surface, thus mass transfer between two phases increased and the reaction completed fast without need of any organic co-solvent (Scheme 7).

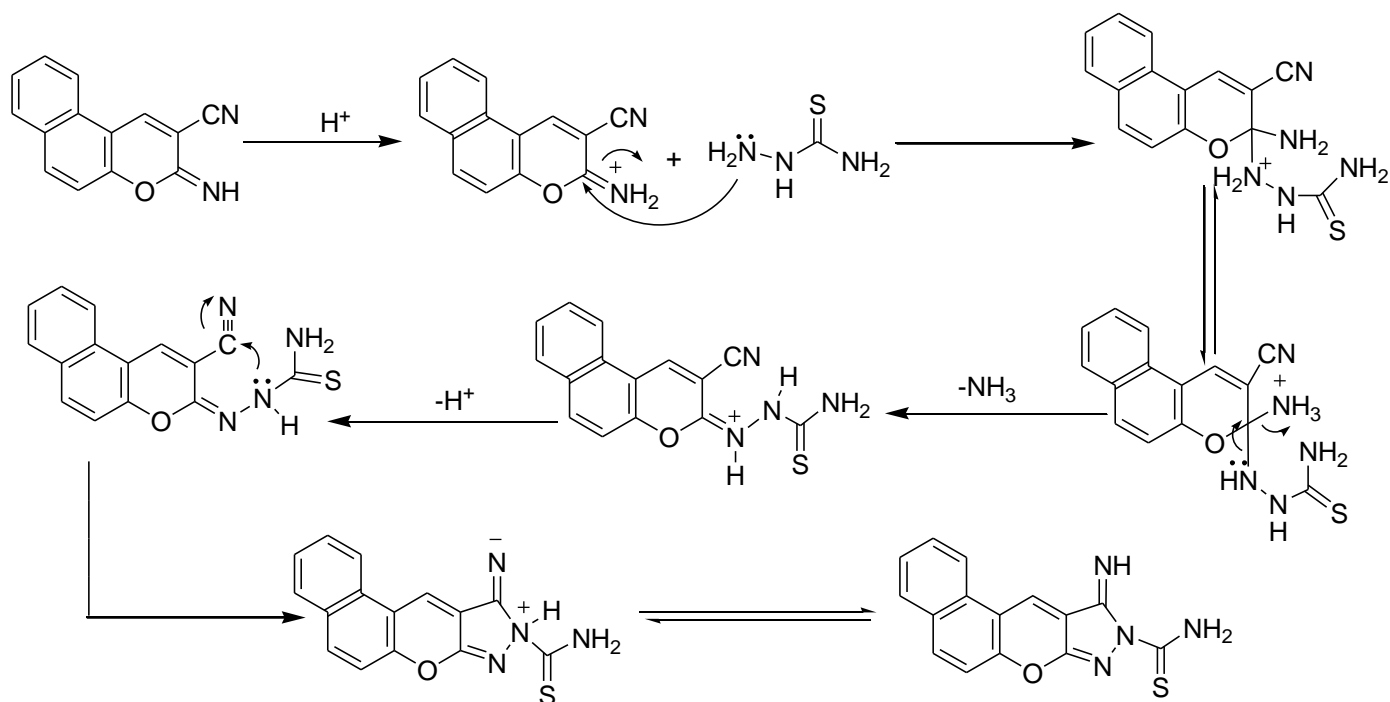


Scheme 7

Trichili and co-workers allowed a solution of substituted hydroxybenzaldehyde/naphthaldehyde **29** and malononitrile in ethanol containing piperidine to stir to get 3-cyanoiminocoumarins (**30**). These were reacted with thiosemicarbazide at room temperature in chloroform to form benzopyrano[2,3-c]pyrazoles (**31**), or derivatized to 3-cyano-*N*-ethoxycarbonyliminocoumarin (**32**) which was further refluxed with 4-phenylsemicarbazide or thiosemicarbazide to form 3-triazolonyliminocoumarins (**33**)²¹ (Scheme 8). The proposed mechanism of reaction is given (Scheme 9).

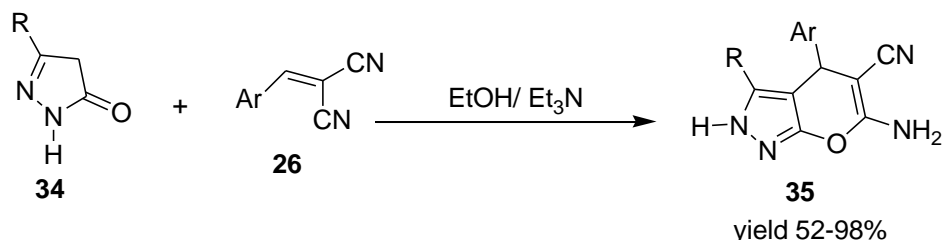


Scheme 8



Scheme 9. Mechanism.

Shestopalov and co-workers treated 3-(methyl, phenyl, *t*-butyl, methoxymethylene, trifluoromethyl)-substituted-5-pyrazolones **34** with heterocyclic or polyalkylated benzylidemalononitrile (**26**) to get 4-aryl-pyranopyrazoles **35** in good to excellent yields.²² Reaction was found to be successful for sterically hindered aldehydes as well as to electron-withdrawing and electron-donating substituents at the 3-position of the pyrazoles. X-Ray crystallography studies showed that these pyranopyrazoles exist in the 2-*H* tautomeric form rather than as 1-*H* (Scheme 10).

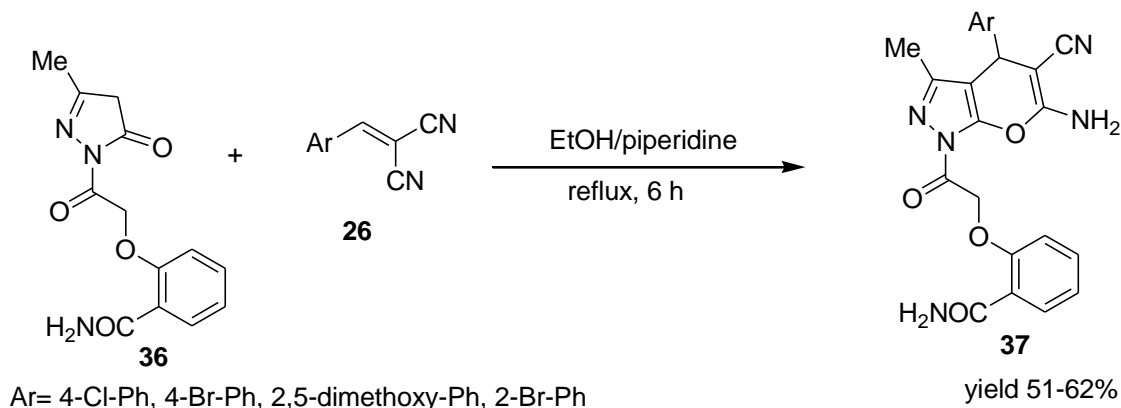


R= Me, Et, Pr, Bu^t, Ph, CF₃, MeO-CH₂, Me-CO₂CH₂, 4-Me-C₆H₄SCH₂

Ar= 2,4,6-trimethyl-Ph, 2,4,6-trimethyl-3-NO₂-Ph, 2,4,6-trimethyl-3,5-dinitro-Ph, 2-Me-Ph, 2,4,6-trimethyl-3-EtOCH₂-Ph, 2,4,6-triethyl-Ph, 2-thienyl, 2,5-dimethoxy-Ph, 2,3,4-trimethoxy-Ph, 2-methoxy-Ph, 2,4,5-trimethoxy-Ph, 3-pyridinyl, 2-furanyl, 2-CF₃Ph, 2-(OCH₂-(2'-Cl-Ph))Ph

Scheme 10

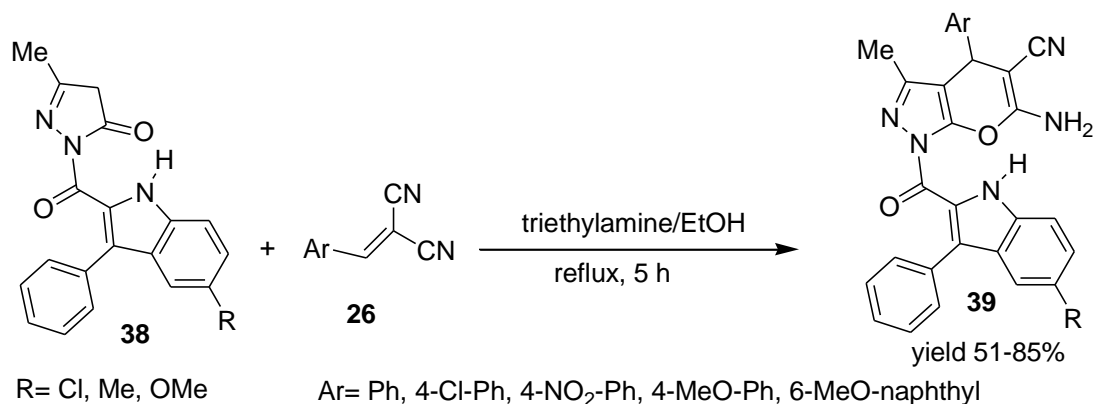
Ismail and co-workers refluxed 2-(2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)-2-oxoethoxy)benzamide (**36**) and benzylidemalononitrile (**26**) in absolute ethanol containing piperidine to produce benzamide based pyranopyrazoles **37** (Scheme 11), which were subjected to derivatization and subsequently screened for their anti-inflammatory and ulcerogenic activities.²³ All compounds were found to be active but, one bearing 2,5-dimethoxyphenyl group at the 4-position showed excellent results compare to the other analogues which suggested that the presence of electron-donating group is favorable for anti-inflammatory activity.



Ar= 4-Cl-Ph, 4-Br-Ph, 2,5-dimethoxy-Ph, 2-Br-Ph

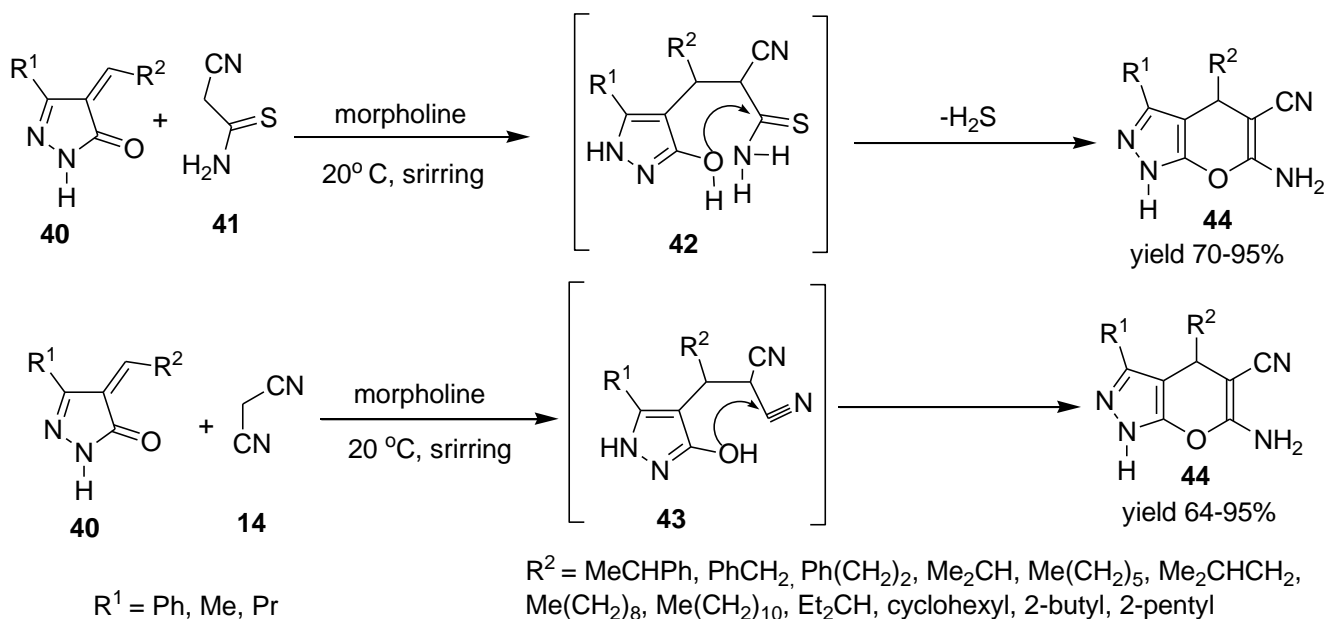
Scheme 11

Similarly, Saundane and co-workers refluxed 3-methyl-1-(5'-substituted-3'-phenyl-1*H*-indol-2'-carbonyl)-5-(4*H*)pyrazolones (**38**) with benzylidemalononitrile (**26**) in ethanol containing triethylamine to provide indole based pyranopyrazoles **39** (Scheme 12) and subjected these to further derivatization.²⁴ All compounds were tested for biological activities and found to be active antibacterial and antifungal agents and exhibited good scavenging activity.



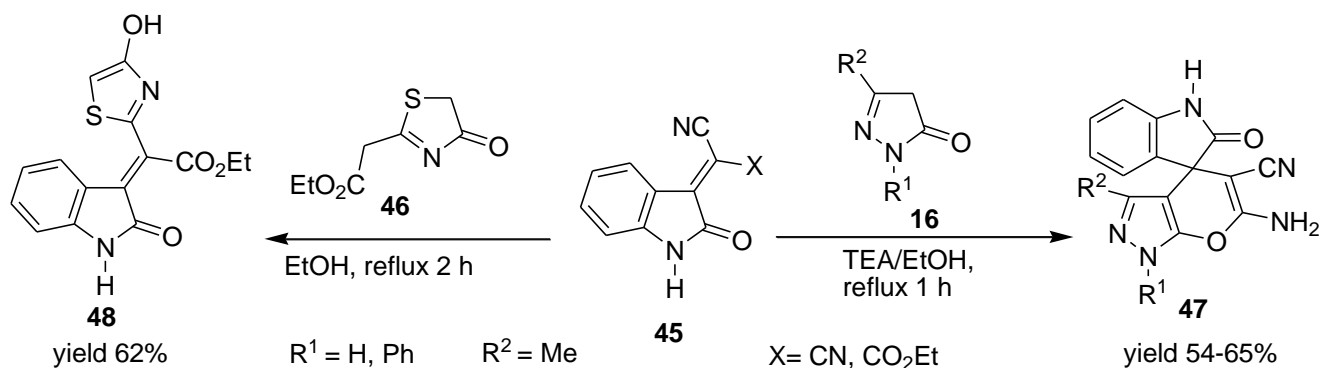
Scheme 12

Dyachenko and Rusanov allowed to stir benzylidene-pyrazolone (**40**) with cyanothioacetamide (**41**) or malononitrile (**14**) in an ethanolic solution containing morpholine to obtain various pyranopyrazoles **44**.²⁵ The reaction mechanism was proposed to involve the Michael adduct **42-43**, which cyclized with concomitant removal of hydrogen sulphide in case of cyanothioacetamide (Scheme 13). An X-ray study of 6-amino-5-cyano-4-isopropyl[hexyl]-3-phenyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazoles showed its 2*H*,4*H*-isomeric form rather than previously reported 1*H*,4*H*-isomeric form was adopted in the solid state.



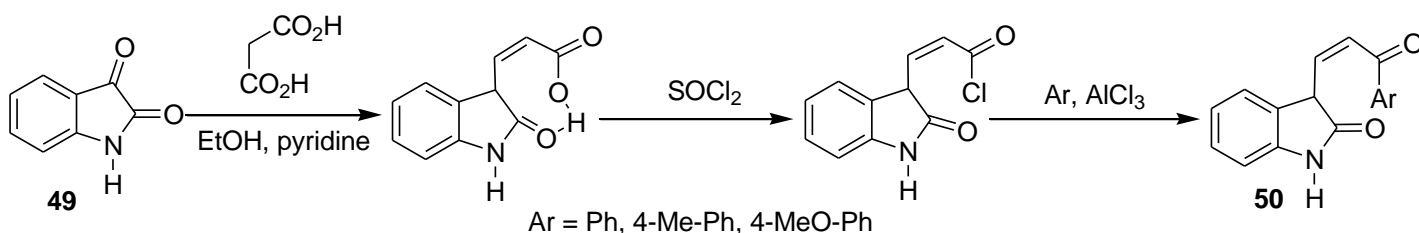
Scheme 13

Hafez and co-workers reacted 2-oxo-3-substituted indole (**45**) with pyrazolone **16** or 2-ethoxycarbonylmethyl-2-thiazolin-5-one (**46**) in boiling ethanol to prepare spiro-pyranylidolone (**47**) and ethyl-2-(4-hydroxythiazol-2-yl)-2-(2-oxoindolin-3-ylidene)acetate (**48**) derivatives respectively (Scheme 14).²⁶

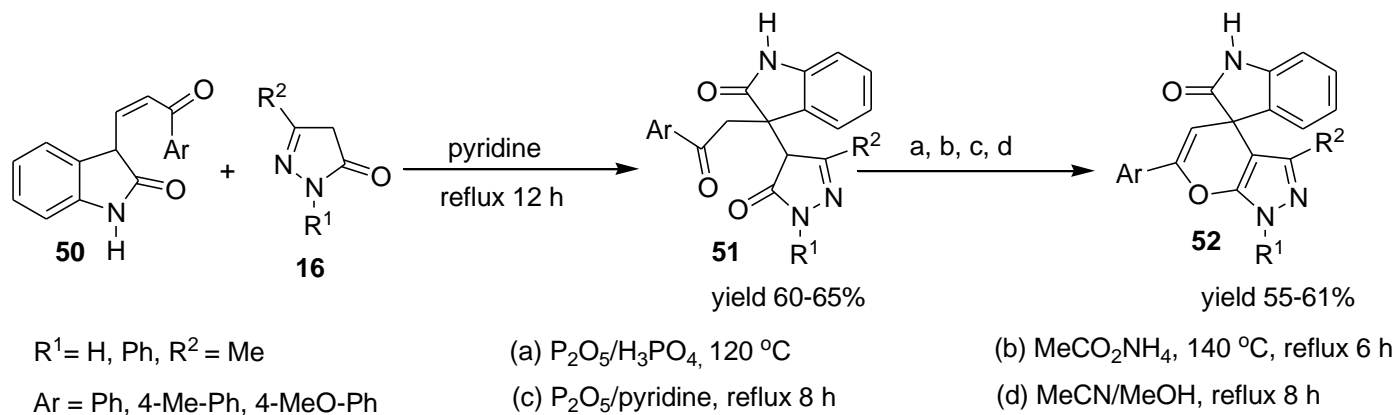


Scheme 14

In another scheme of reaction, indole-2,3-dione (**49**) was derivatized with malonic acid, thionyl chloride and various arenes to produce intermediate **50** (Scheme 15), which on refluxing with pyrazolone **16** in pyridine formed intermediate **51** which cyclized using different reagents such as phosphorus pentoxide, ammonium acetate and acetonitrile at reflux temperature to afford spiro[indoline-3,4'-(pyrazolo[4,5-b]pyran)]-2-ones (**52**) (Scheme 16).²⁷



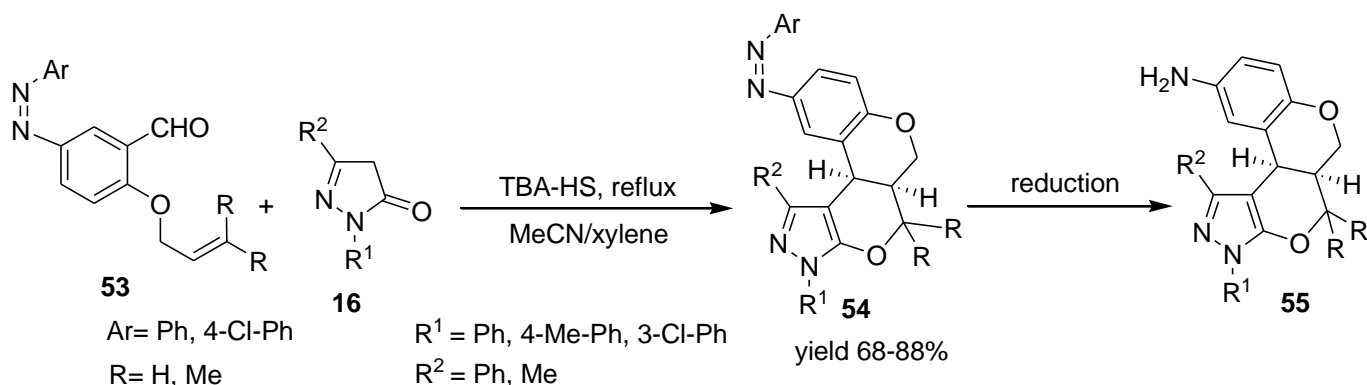
Scheme 15



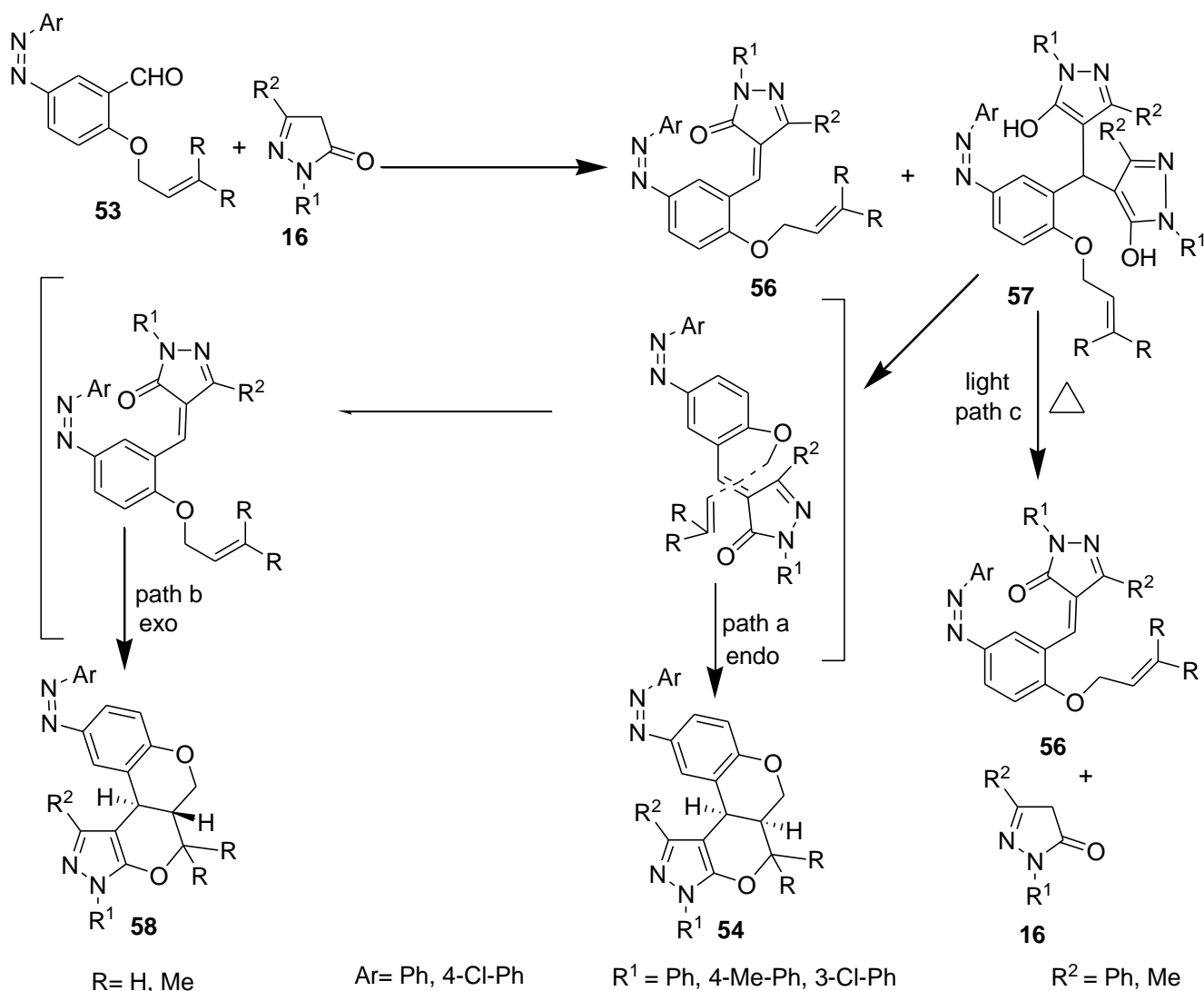
Scheme 16

Parmar and co-workers treated various aldehydes with allyl/prenyl bromide in DMF under catalytic effect of anhydrous K_2CO_3 to obtain substituted benzaldehydes **53**, which when refluxed with pyrazolone **16** in

xylene/acetonitrile containing tetrabutylammonium hydrogen sulphate (25 mol%) gave benzopyran-annulated pyrano[2,3-c]pyrazoles (**54**), which can also be reduced to aminopyranopyrazoles **55** (Scheme 17).²⁸



Scheme 17

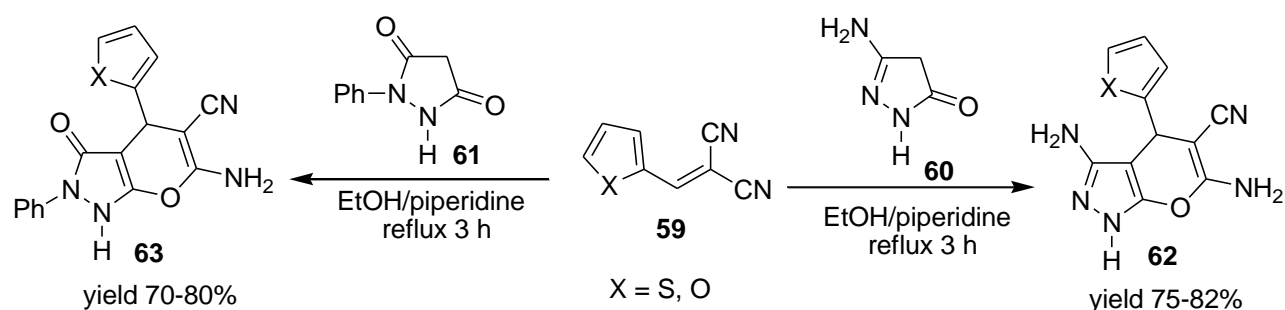


Scheme 18

The reaction mechanism is believed to involve a domino/Knoevenagel-hetero-Diels-Alder sequence including attack of TBA-HS on pyrazolone and generating a reactive tetrabutyl ammoniumpyrazolonate, which

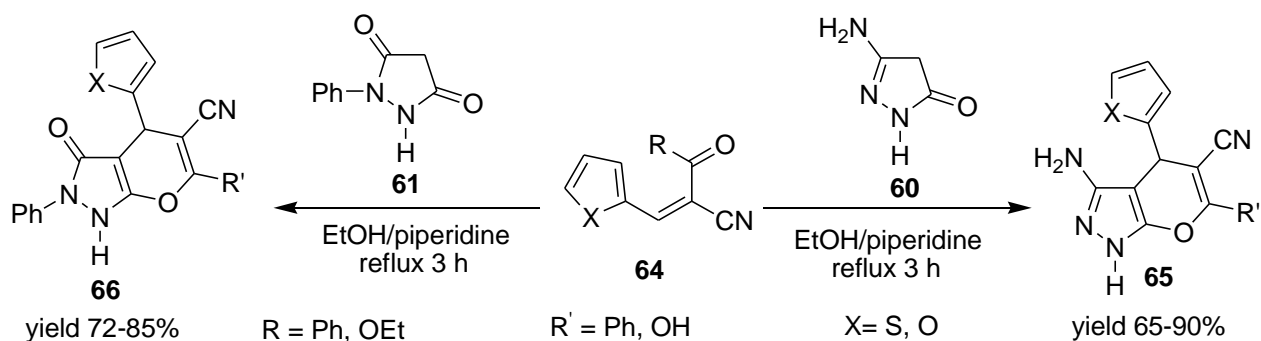
reacts with aldehydes to form the Knoevenagel adduct **56** and Knoevenagel-Michael adduct **57**.²⁸ The synthesis of the latter, was confirmed by spectroscopic data and its conversion to Knoevenagel adduct **56** and pyrazolone **16** under the influence of heat, light, or long time storage (**path c**). Similarly, intermediate **57** under reflux, afforded **54** and **58** which supported the assumption that the initially formed Michael adduct is converted into the Knoevenagel intermediate on subsequent reflux (Scheme 18). Stereochemistry of reaction was predicted as *endo*- (**path a**) and *exo*- (**path b**) of dienophile but, NMR data revealed the *cis*- form **54** as dominant.

α,β -Unsaturated nitriles being versatile synthons have been used by Elgemeie and co-workers.²⁹ In one scheme of reaction, (2-cyano-3-furan/thiophen-2-yl)acrylonitrile (**59**) was refluxed with 3-aminopyrazolin-5-one (**60**) and pyrazolidin-3,5-dione (**61**) in the presence of base which, catalyzed Michael addition of the pyrazole methylene to acrylonitrile, followed by carbonyl attack at the cyanocarbon to afford 3-amino pyrano[2,3-*c*]pyrazoles (**62**) and 3-oxo-pyrano[2,3-*c*]pyrazoles (**63**) respectively (Scheme 19).



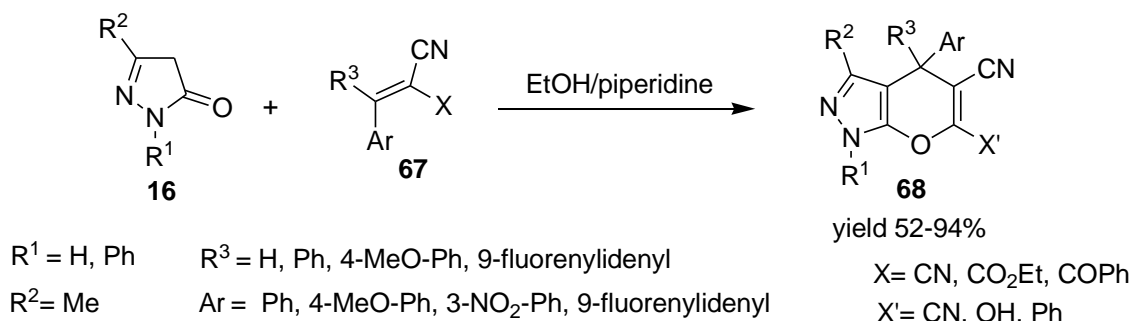
Scheme 19

Similarly, **64** reacted with 3-aminopyrazolin-5-one (**60**) and pyrazolidin-3,5-dione (**61**) and proceeded *via* elimination of water/ethanol to form 3-amino-6-phenyl/hydroxypyrano[2,3-*c*]pyrazoles (**65**) and 3-oxo-6-phenyl/hydroxypyrano[2,3-*c*]pyrazoles (**66**) respectively²⁹ (Scheme 20).



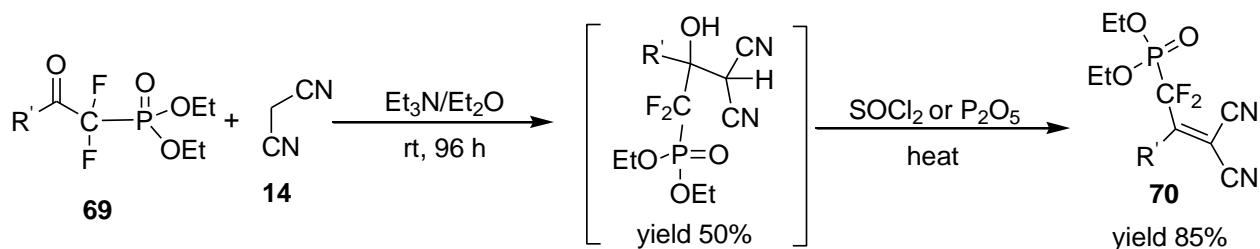
Scheme 20

Abdou and co-workers, in a simple procedure, refluxed various alkene derivatives **67** and pyrazolones in piperidine containing ethanolic solution to produce a variety of pyranopyrazoles bearing carbonitrile, hydroxyl or a phenyl group at the 6-position³⁰ (Scheme 21).



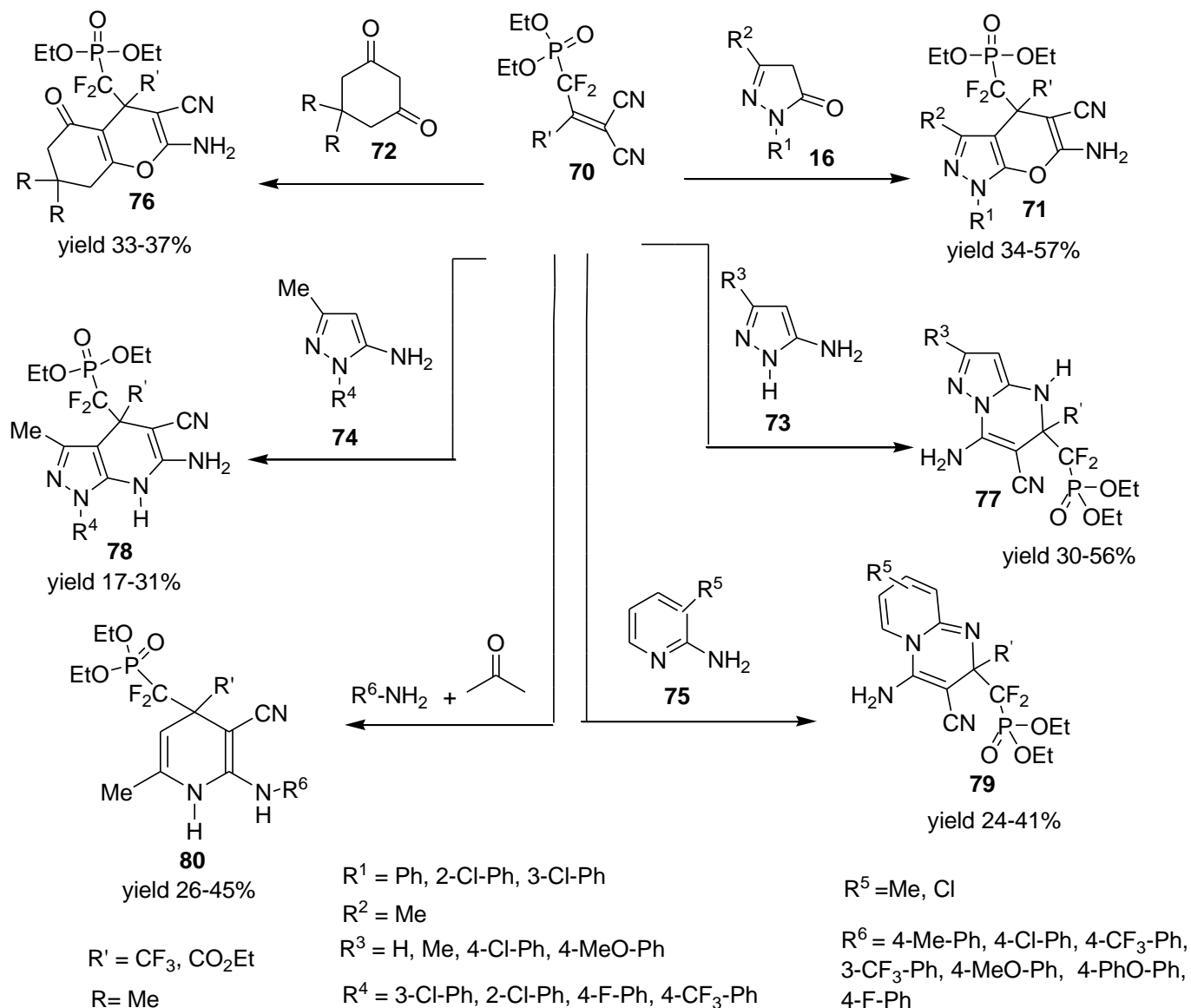
Scheme 21

Pasternak and co-workers prepared and condensed the fluoralkylphosphonate bearing ketone **69** with malononitrile followed by dehydration with thionyl chloride or phosphorus pentoxide to yield intermediate **70** (Scheme 22).³¹



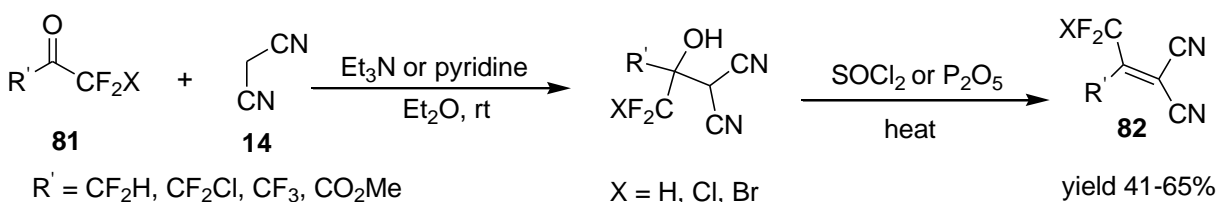
Scheme 22

The intermediate **70** condensed at C-4 of pyrazolone **16** followed by cyclization to form pyranopyrazoles **71**.³¹ Similarly, alkenes **70** reacted with dimedone **72**, 1-un/substituted aminopyrazoles **73**, **74**, aminopyridine **75** and mixture of aniline and acetone to form tetrahydrochromene **76**, pyrazolopyrimidines **77**, pyrazolopyridine **78**, benzopyrimidine **79** and pyridine derivatives **80**. It was observed that unsubstituted aminopyrazole cyclized at the *N*-1 position affording pyrazolopyrimidine while, substituted aminopyrazoles cyclized at the exocyclic -NH₂ group and gave pyrazolopyridines (Scheme 23). Structures were confirmed by X-ray studies.

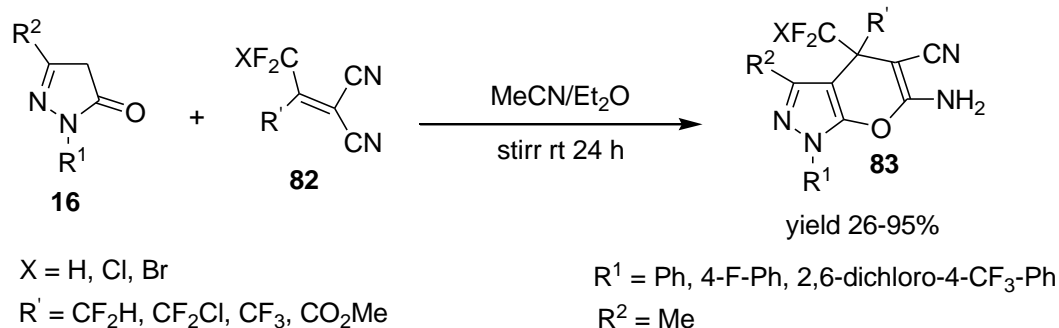


Scheme 23

Similarly, fluoroketone **81** and malononitrile were treated either by reported method or with little modification to obtain a slightly modified alkene 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene (**82**) (Scheme 24).³² The resultant alkenes **82** reacted with pyrazol-5-one to produce fluorinated pyranopyrazoles **83** (Scheme 25). Reaction of this alkene with acyclic amidine and aminopyrazole followed similar fashion as above. X-Ray studies of compounds confirm structures.

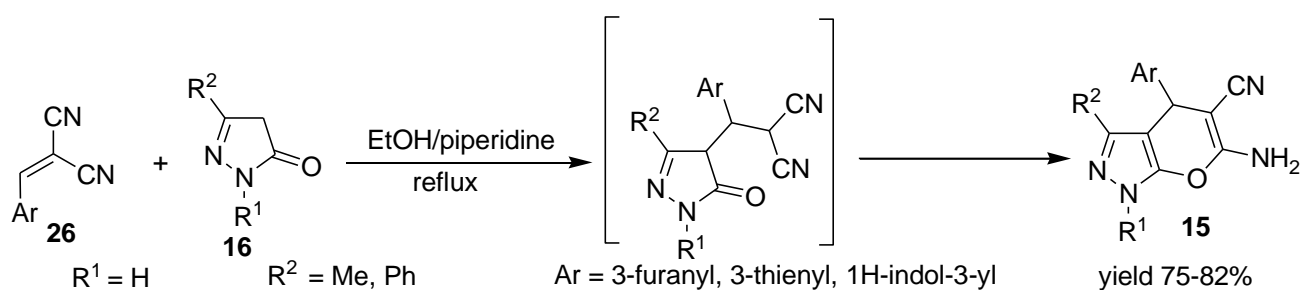


Scheme 24



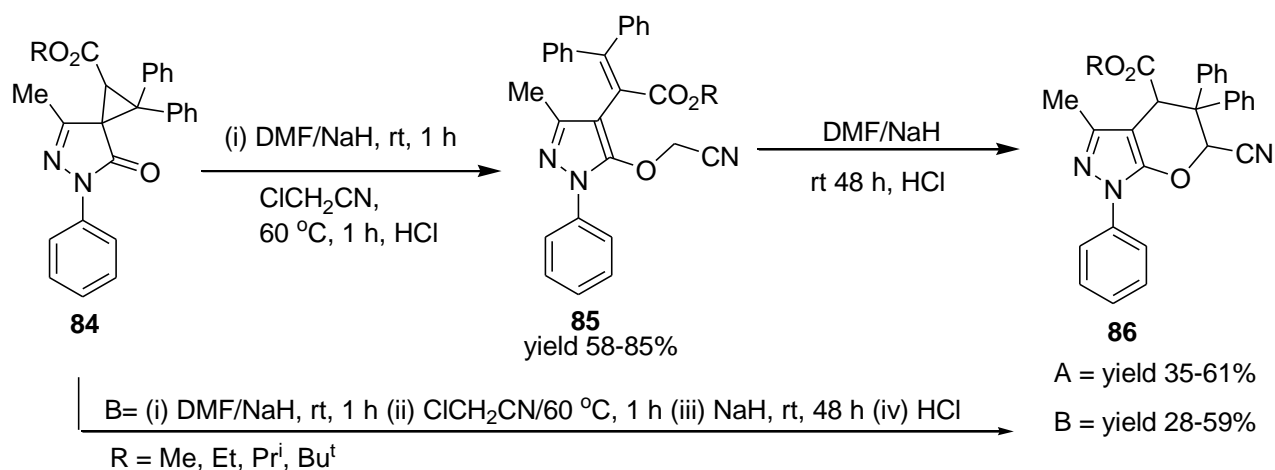
Scheme 25

Abdelrazek and co-workers prepared 4-heteroaryl pyranopyrazoles **15** by refluxing benzylidene derivatives with pyrazolones in ethanolic solvent containing piperidine catalyst (Scheme 26).^{33, 34} All compounds exhibited moderate molluscicidal activity against *Biomphalaria alexandrina* snails.



Scheme 26

In addition to these methods, Maruoka *et al.* adopted ring transformation and cyclization procedure by treating spirocyclopropanepyrzoles **84** and chloro acetonitrile in DMF solvent containing sodium hydride either *via* one pot or two steps involving synthesis of intermediate, cyanomethoxy pyrazole **85** which further cyclized to 6-cyano-5-disubstituted pyranopyrazoles (**86**) (Scheme 27).³⁵



Scheme 27

The reaction was also tried using potassium *t*-butoxide in *N,N*-dimethylformamide and potassium *t*-butoxide in *t*-butyl alcohol, but failed.³⁵ Spirocyclopropanepyrazoles were subjected to ring opening using either using NaH/DMF, or titanium (IV) chloride in chloroform and afforded pyrazol-3-one **87** and carboxylic acid **88** in case of butyl acetate (Figure 6).

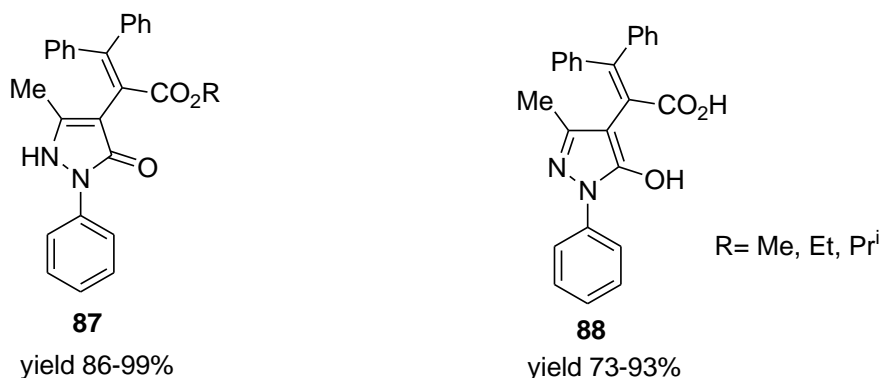


Figure 6

2.2 Three components synthesis (MCRs)

Most of these examples used pyrazolone, aldehydes and malononitrile and allowed to react together under different reaction conditions to form a variety of pyranopyrazoles. Jin and co-workers added *p*-dodecylbenzenesulfonic acid (DBSA), as phase transfer catalyst, for uniform dispersion of reactants to get a better yield (84-94%) (Scheme 28 A).³⁶ Initially, the reaction was tested in the absence of catalyst and yielded traces of product or no product as in case of 4-dimethylaminobenzaldehyde, which has strong electron donating dimethylamino group that has significant contributions of the quinoid resonance form, hence reactivity decreased **89-90** (Figure 7).

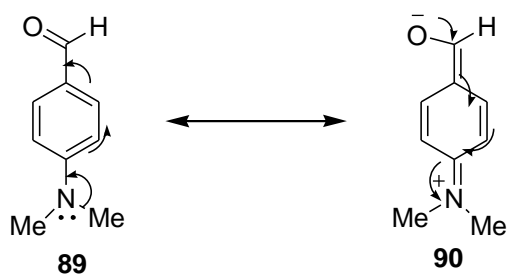
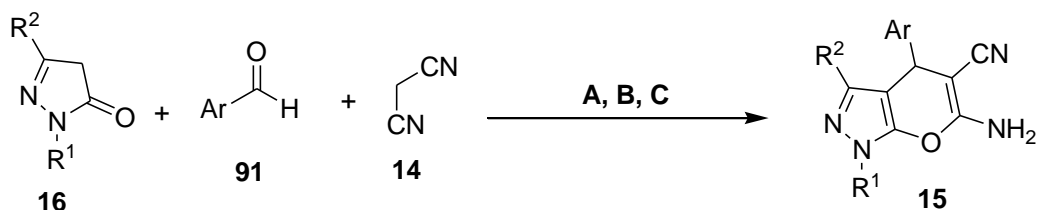


Figure 7

In another attempt, various PTC namely, TBAB, DBSA, sodium dodecyl sulphate (SDS) and HTMAB were tested for similar reactants where HTMAB was found best in term of yield³⁷ (Scheme 28 B). The reaction conditions worked equally for aromatic aldehydes with electron-withdrawing and donating substituents, but did not proceed for aliphatic aldehydes probably, due to their low reactivity. Prajapati and co workers refluxed substituted aldehydes, malononitrile and 1-(2,4-dinitrophenyl)-3-methylpyrazol-5-one in ethanol containing

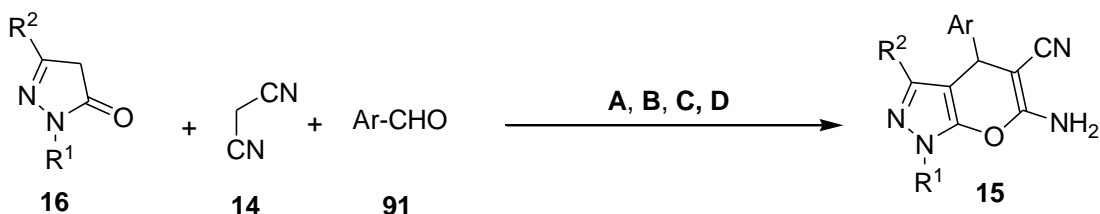
piperidine catalyst to give the respective pyranopyrazoles which were found to be good antibacterial agents (Scheme 28 C).³⁸



Scheme	R ¹	R ²	Ar	Condition	Yield
A	Ph	Me	Ph, 4-Me-Ph, 4-MeO-Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 3-NO ₂ -Ph, 4-NO ₂ -Ph, 4-HO-Ph, 2,4-dichloro-Ph, 3,4-dioxymethylene-Ph	H ₂ O, 10 mol% DBSA, 60 °C, 3 h	84-94%
B	Ph	Me	Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 4-Me-Ph, 4-MeO-Ph, 4-NO ₂ -Ph, 3-NO ₂ -Ph, 2,4-dichloro-Ph, 4-HO-Ph, 3,4-dioxymethylene-Ph	H ₂ O, 10 mol% HTMAB, 85-90 °C	79-92%
C	2,4-dinitro-Ph	Me	Ph, 4-Cl-Ph, 2-Cl-Ph, 4-MeO-Ph, 3-NO ₂ -Ph, 4-NMe ₂ -Ph, 2-HO-Ph, 4-HO-Ph, 3,4-dimethoxy-Ph, 3-MeO-4-HO-Ph	EtOH, piperidine, reflux 3 h	70-76%

Scheme 28

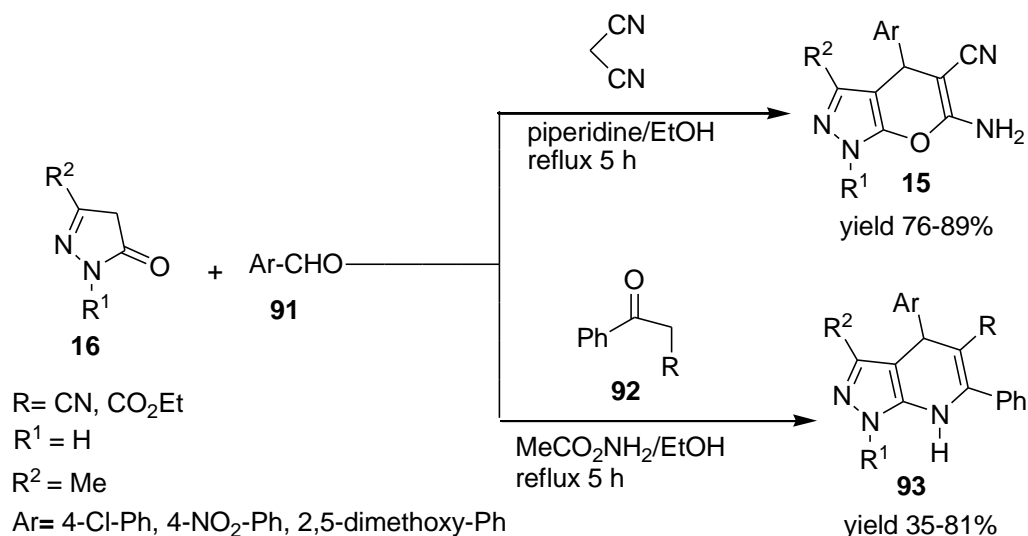
Pyranopyrazoles bearing a trifluoromethyl group at the 3-position were obtained by reaction of aldehydes, malononitrile and trifluoromethylpyrazol-5-one, in water as solvent without catalyst at 90 °C, in good yields in 3-5 h (Scheme 29 A).³⁹ The yield of the product is not affected by the electronic nature of the aryl substituents. Bhavanarushi and co-workers prepared fluopyranopyrazoles by grinding similar reactants in a pestle mortar using DBU as catalyst and established the molecular mechanism for DNA binding of resultant products (Scheme 29 B).⁴⁰ Microwave irradiation to eliminate the need of heat, enhances the rate of reaction, is a widely applicable technique and has been used for the synthesis of pyranopyrazoles within 2-8 min in dry ethanol containing piperidine catalyst (Scheme 29 C).⁴¹ Diaminopyrano[2,3-c]pyrazoles were prepared at room temperature in ethanolic solvent containing secondary amine/organic bases such as pyridine, piperidine and pyrrolidine.⁴² The resultant compounds were found to be potential antibacterial agent while, some of them also exhibited antifungal activity (Scheme 29 D).



Scheme	R ¹	R ²	Ar	Condition	Yield
A	Ph	CF ₃	Ph, 4-Cl-Ph, 4-Br-Ph, 4-F-Ph, 3-NO ₂ -Ph, 4-NO ₂ -Ph, 2-F-Ph, 3,4,5-trimethoxy-Ph, 4-CHO-Ph, 3-F-Ph, 4-HO-3-NO ₂ -Ph	H ₂ O, 90 °C, 3-5 h	78-90%
B	Ph, 3-Cl-Ph, 4-F-Ph	CF ₃	Ph, 4-NO ₂ -Ph, 3-MeO-Ph, 4-Me-Ph, 4-F-Ph, 4-MeO-Ph, 2-furanyl, 2-thienyl	DBU, grinding at rt	81-88%
C	Ph	Me	Ph, 4-Cl-Ph, 4-Br-Ph, 4-MeO-Ph, 4-NO ₂ -Ph, 3-NO ₂ -Ph	piperidine/EtOH, MW, 2-8 min	61-91%
D	Ph	NH ₂	Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 4-Me-Ph, 4-MeO-Ph, 2-Br-Ph, 3-Br-Ph, 4-Br-Ph, 2-NO ₂ -Ph, 3-NO ₂ -Ph, 4-NO ₂ -Ph, 2-HO-Ph, 4-HO-Ph, 4-F-Ph, 2,4-dichloro-Ph, 2,6-dichloro-Ph, 3,4-dimethoxy-Ph, 2,5-dimethoxy-Ph, 3,4,5-trimethoxy-Ph	sec. amine, EtOH, rt, 15-60 min	64-90%

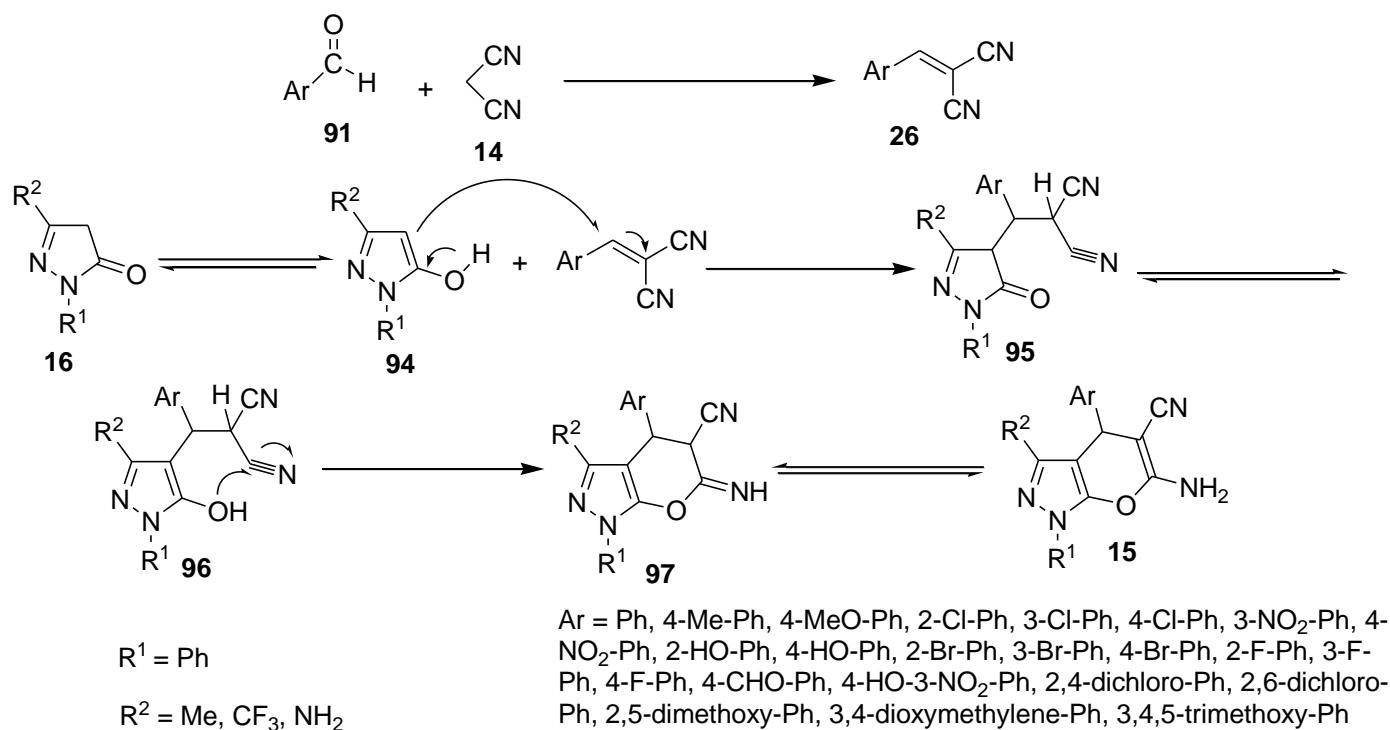
Scheme 29

Pyrazolone and aldehydes were refluxed together with malononitrile to give 6-aminopyrano[2,3-c]pyrazoles (**15**), or with 3-oxo-3-phenylpropanenitrile (**92**) to afford 6-phenylpyrazolo[3,4-*b*]pyridine-5-carboxylate (**93**).⁴³ These compounds showed remarkable anticancer activity on human tumor cell lines (Scheme 30).



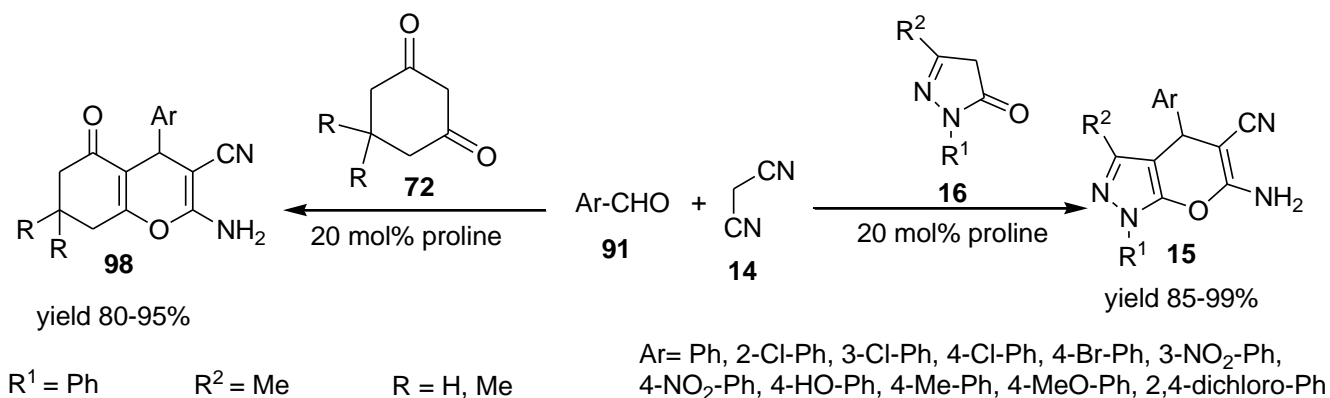
Scheme 30

In the literature,^{36, 37, 39, 42} the most reported mechanism involves fast Knoevenagel condensation of aldehyde and malononitrile to form α -cyanocinnamitrile derivatives, which are attacked by the active methylene of the pyrazolone **94** to give the intermediate **95**. Tautomerization of **95** possibly to **96** is followed by intramolecular nucleophilic attack of OH group on the cyano moiety to afford a cyclic intermediate **97** which, tautomerizes to give final pyranopyrazoles **15** (Scheme 31).



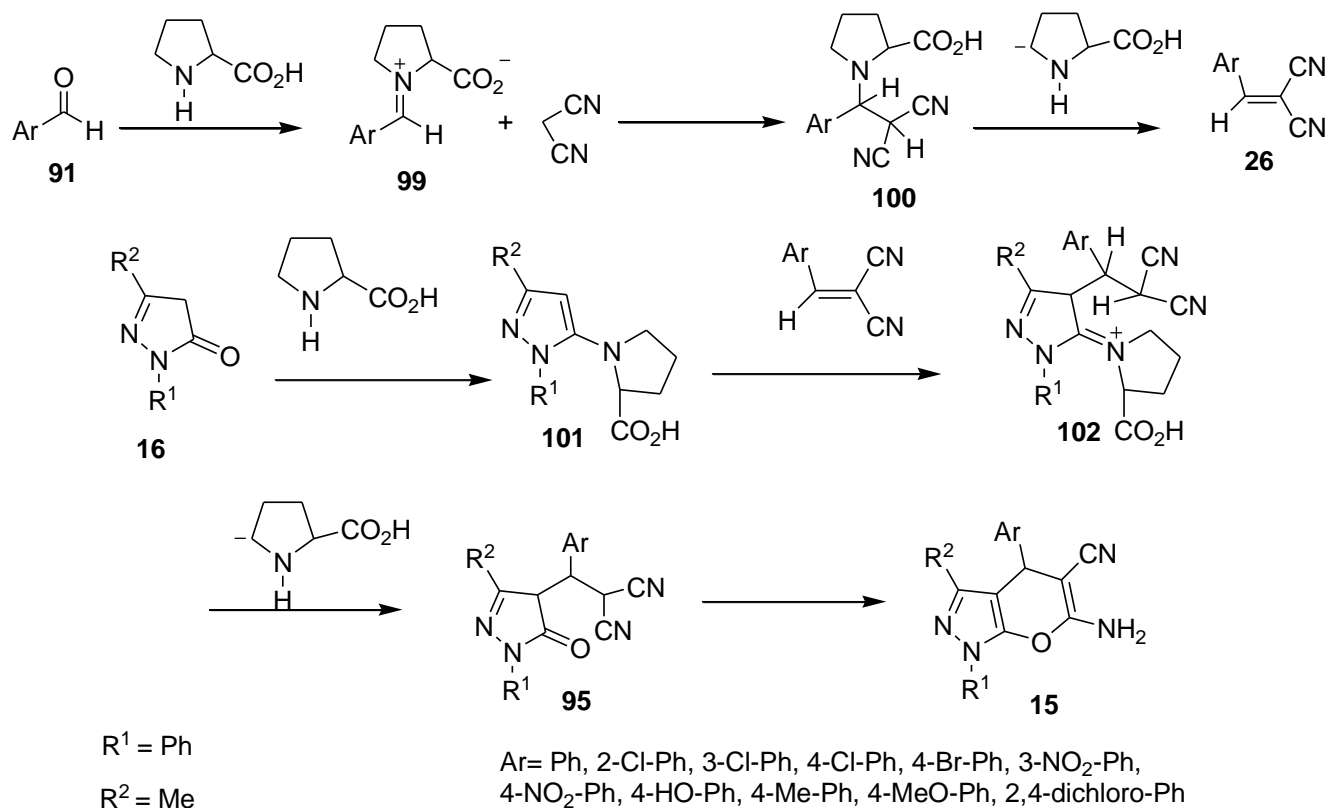
Scheme 31. Mechanism.

Heating, irradiation and solvent-free, environmentally friendly method was developed by grinding the aryl aldehydes and malononitrile with pyrazol-5-one or dimedone (**72**) in the presence of 5-25 mol% D,L-proline catalyst to get pyranopyrazoles **15** and benzo[*b*]pyrans (**98**) respectively (Scheme 32).⁴⁴



Scheme 32

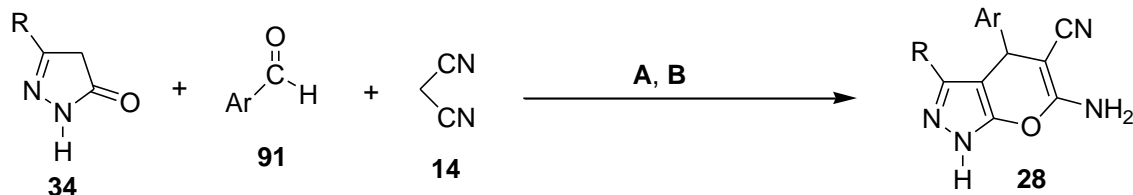
A possible mechanism under catalytic effect of D,L-proline is proposed which, follows same sequence of steps, but the intermediates are formed by direct interaction of the catalyst with reactants⁴⁴ (Scheme 33).



Scheme 33. Mechanism.

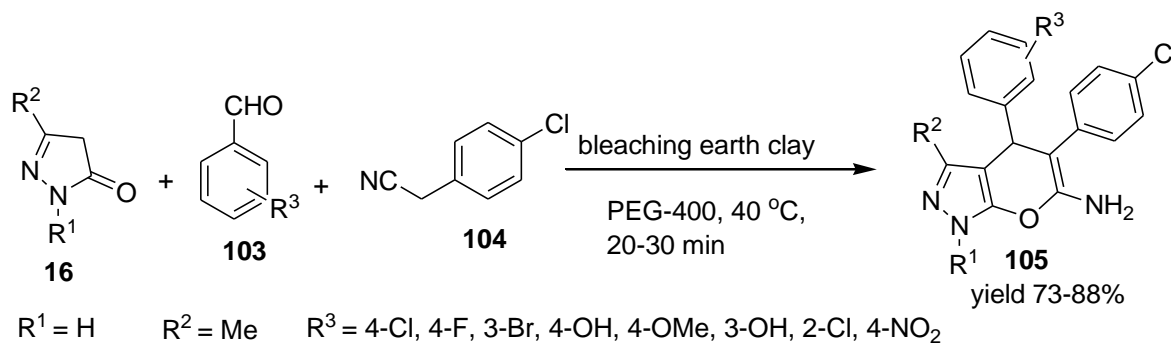
Some two component protocols have been also applied for three component syntheses. Thus aromatic aldehydes, malononitrile, pyrazolone and triethylamine were heated in ethanol to give *N*-unsubstituted pyrano[2,3-*c*]pyrazoles (**28**) (Scheme 34 A).²² Similarly, cinchona alkaloids were also used as catalysts at room temperature with/without drying agents (Na_2SO_4 , $\text{MS}(4 \text{ \AA})^e$), and gave better yield of enantioselectively (*ee*^c) products in some reactions, but poor yields in others¹⁷ (Scheme 34 B).

Kamble and co-workers replaced toxic, volatile solvents (MeOH, EtOH, MeCN) with thermally stable, non-volatile, easily available, miscible and recyclable polyethylene glycol (PEG-400), which increased the yield within short reaction times.⁴⁵ Bleaching earth clay, a heterogeneous base used as catalyst due to its selectivity, acidic/basic nature, thermal stability and easy separation by filtration. Substituted benzaldehyde **103** was reacted with pyrazolone and (4-chlorophenyl)acetonitrile (**104**) containing 10 wt% of catalyst to get 4,5-diarylpyrano[2,3-*c*]pyrazoles (**105**) in 73-88% yields within 20-30 min (Scheme 35).



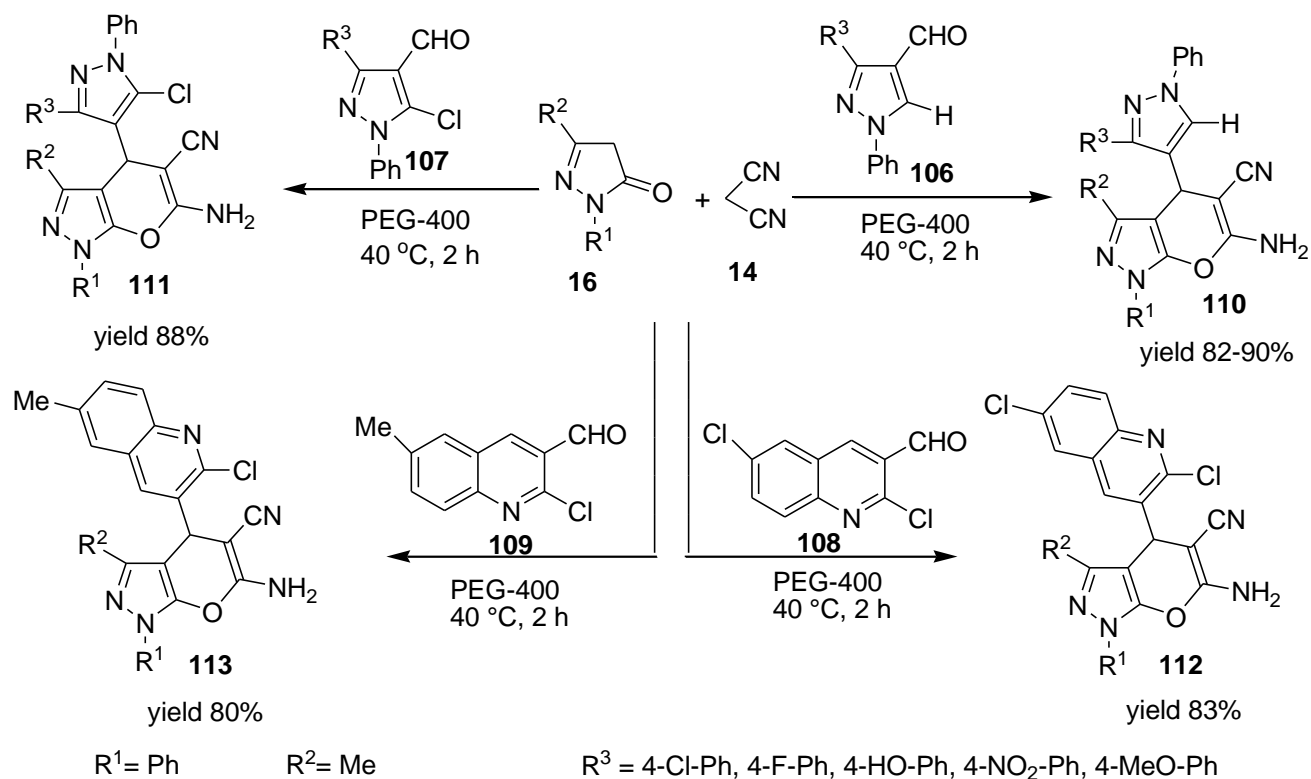
Scheme	R	Ar	Condition	Yield
A	Me, Et, Pr ⁿ , Bu ^t , Ph, CF ₃ , MeOCH ₂ , MeCO ₂ CH ₂ , 4-Me-Ph-S-CH ₂	2-CF ₃ -Ph, 2-Me-Ph, 2,4,6-trimethyl-Ph, 2,4,6-trimethyl-3-NO ₂ -Ph, 2,4,6-trimethyl-3,5-dinitro-Ph, 2,4,6-trimethyl-3-EtOCH ₂ -Ph, 2,4,6-triethyl-Ph, 2,5-dimethoxy-Ph, 2,3,4-trimethoxy-Ph, 2-methoxy-Ph, 2-furanyl, 2,4,5-trimethoxy-Ph, 2-thienyl, 3-pyridinyl, 2-(OCH ₂ -(2'-Cl-Ph))Ph	EtOH/Et ₃ N, heat	52-97%
B	Me, Et, Ph	Ph, 4-Me-Ph, 4-MeO-Ph, 4-Cl-Ph, 4-CN-Ph, 4-NO ₂ -Ph, 3-Br-Ph, 4-Br-Ph, 4-I-Ph, 4-F-Ph	CH ₂ Cl ₂ , rt, additive cuperine 5 mol%	79-96%

Scheme 34



Scheme 35

Dawane *et al.* also used polyethylene glycol (PEG-400) without catalyst for the reaction of pyrazol-5-one, malononitrile and substituted hetarylaldehydes at 40 °C.⁴⁶ The reaction condition was found successful for 3-substituted-1-phenyl-pyrazol-4-carbaldehyde (**106**), 5-chloropyrazol-4-carbaldehyde (**107**), 2,6-dichloroquinoline-3-carbaldehyde (**108**) and 2-chloro-6-methylquinoline-3-carbaldehyde (**109**) to get various pyranopyrazoles **110-113** (Scheme 36). Antibacterial and antifungal activities of the synthesized compounds were tested and, mostly the analogues were found to be active antibacterials. Moreover, results revealed the position of the halo group affects the biological activity and pyrazolone aldehydes having halogen the 2-position of substituent exhibited both activities.



Scheme 36

Novel heterogeneous, eco-friendly silica sodium carbonate (SSC) catalyzed synthesis of pyranopyrazoles **114** by treating pyrazolone, malononitrile, and substituted benzaldehydes/naphthaldehyde in water/ethanol mixture (1:2) (Figure 8) has been reported.⁴⁷ At first, the catalyst is prepared by drying silica gel 60 at 120 °C, adding thionyl chloride while cooling on ice, keeping cold for 30 min, then refluxing for 48 h followed by filtration to isolate the silica chloride. Silica chloride and sodium bicarbonate were allowed to react in *n*-hexane, and washed with water to remove remaining sodium bicarbonate. This novel catalyst was found to be effective in small quantity (1 mol%) and reusable without significant loss in activity. The reaction mechanism is represented as Scheme 37.

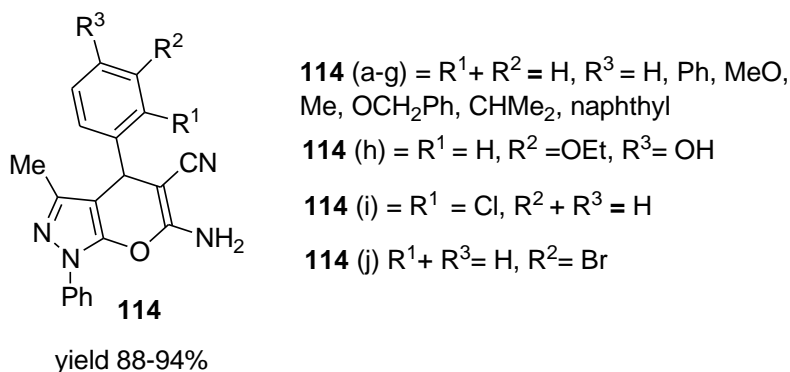
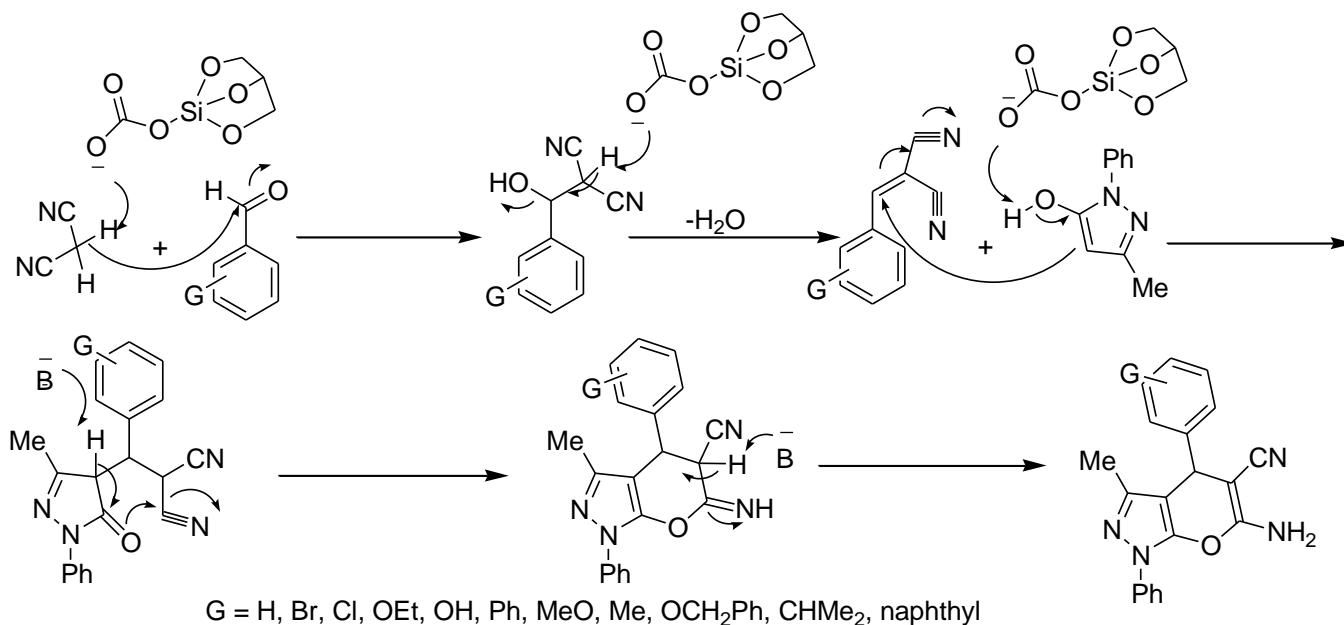
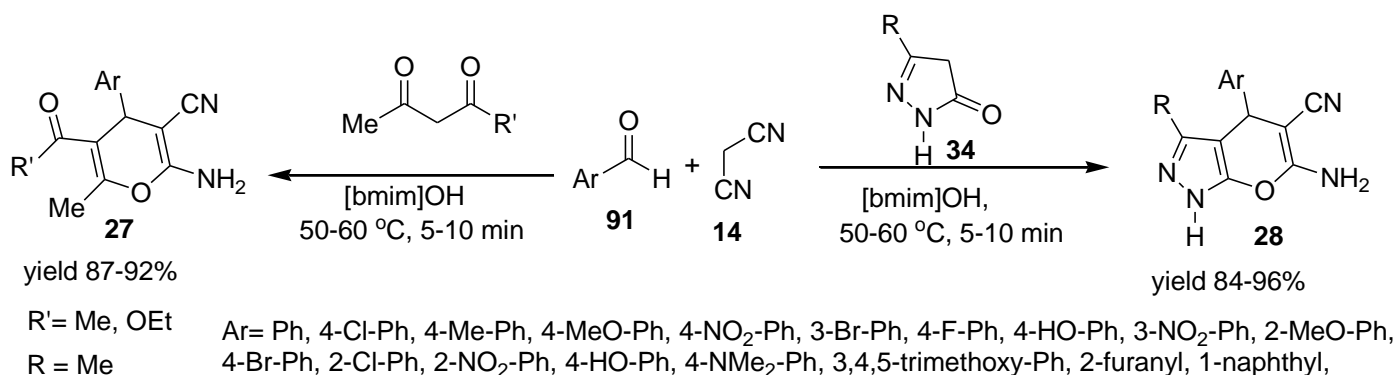


Figure 8



Scheme 37. Mechanism.

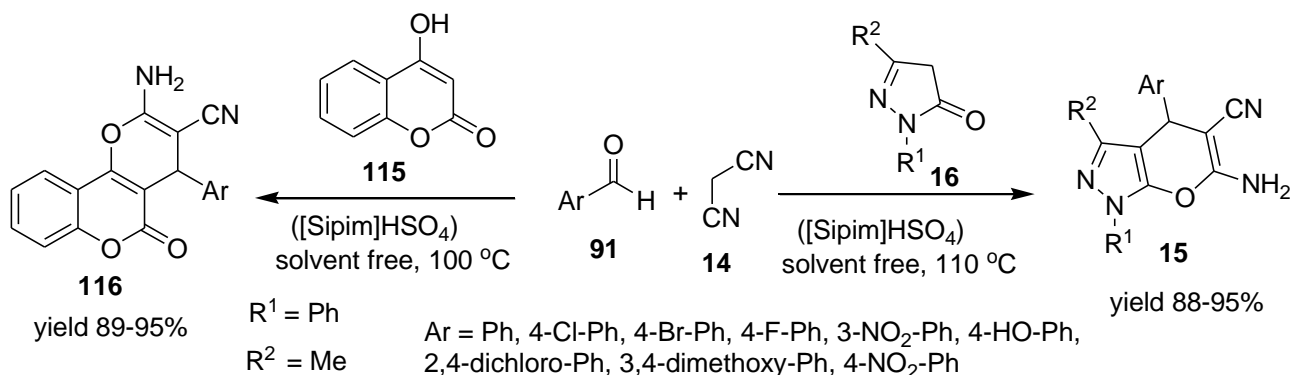
Brønsted acidic task-specific ionic liquids, being highly thermal stable, nonflammable, tunable polar, low vapor pressure, recyclable are used as solvent and catalyst.^{48, 49} Khurana and Chaudhary used 1-butyl-3-methylimidazolium hydroxide, for the synthesis of pyrano[2,3-*c*]pyrazoles and 4*H*-pyran derivatives.⁵⁰ When pyrazolone, arylaldehydes and malononitrile are mixed in 20 mol% of [bmim]OH, pyranopyrazoles are produced, while, pyran derivatives were obtained by replacing pyrazolone with ethyl acetoacetate or acetylacetone (Scheme 38). In the synthesis of pyranopyrazoles, the nature of substituent has very little effect on the reaction rate and yield of the products while, aryl aldehydes with electron withdrawing groups reacted faster than those with electron donating groups to form pyran derivatives. Furthermore, other ionic liquids such as [bmim]Br and [bmim]BF₄ were also applied to pyran synthesis, but failed.



Scheme 38

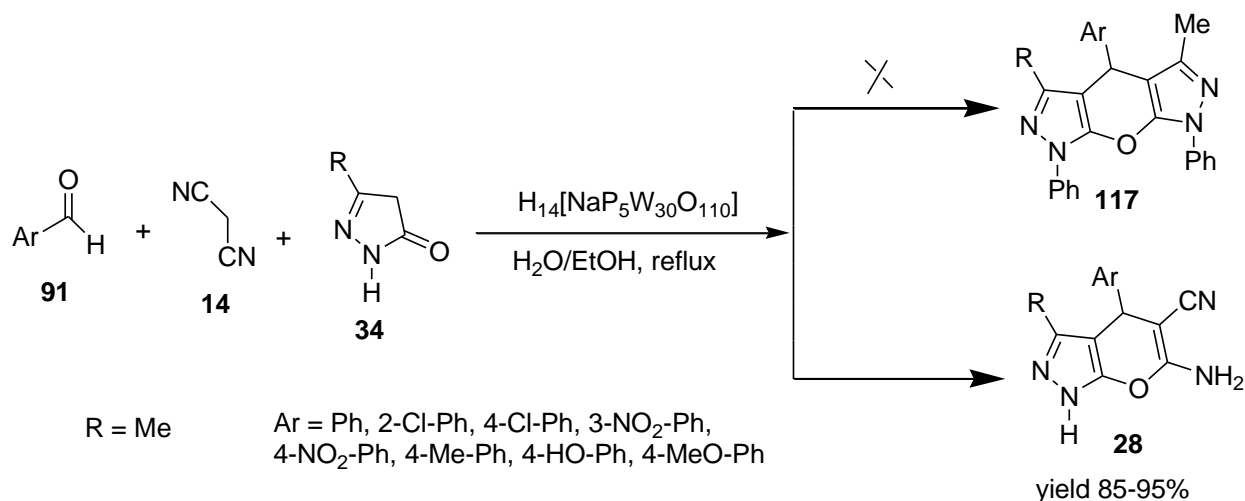
Niknam and Piran prepared recyclable silica-grafted *N*-propylimidazolium hydrogen sulphate ([Sipim]HSO₄) and heated it with reactants at 110 °C under solvent-free conditions to obtain pyranopyrazoles **15**.⁵¹ When pyrazolone was replaced with 4-hydroxycoumarin (**115**) and heated at 100 °C, 3,4-dihydropyrano[*c*]chromenes were produced **116** (Scheme 39). Thus reaction is applicable for variety of aldehydes as well lactones such as

coumarin. It was also observed that the catalyst is recyclable and could be used four times without any significant loss in activity.



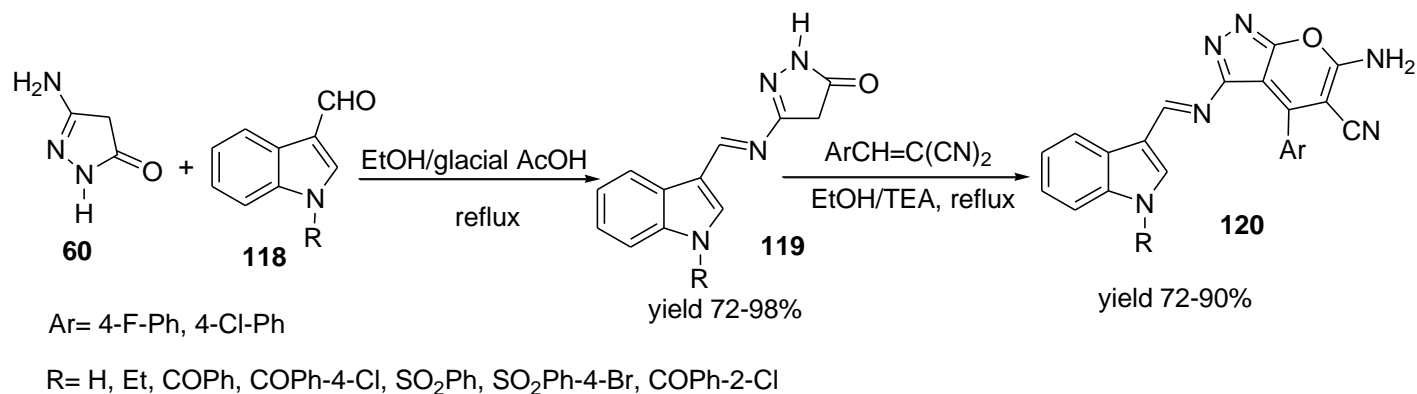
Scheme 39

Similarly, Heravi and co-workers used Preyssler type heteropolyacid $\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$ under solvent free conditions, but this failed to produce any products.⁵² However when used in water/ethanol mixture, excellent results were obtained, probably due to two reasons (a) the first stage of the reaction includes Knoevenagel condensation, which is faster in water, and (b) the PKa of HPA depends on the solvent. Reaction conditions found effective for pyrazolone, barbituric acid, aldehydes having electron-donating and electron withdrawing substituent but, did not work for ethyl cyanoacetate, diethyl malonate, ethyl benzoylacetate, ethyl acetoacetate and acetophenone (Scheme 40).



Scheme 40

Mandour and co-workers treated 3-amino-5-pyrazolone (**60**) with *N*-substituted indole-3-carboxaldehydes (**118**) under acidic conditions to form substituted pyrazol-5-ones **119**, which were refluxed with *p*-fluoro/chlorobenzylidenemalononitrile to form 3-[(*N*-substituted indol-3-yl)methyleneamino]-6-amino-4-aryl-pyrano[2,3-*c*]pyrazol-5-carbonitrile (**120**) (Scheme 41).⁵³

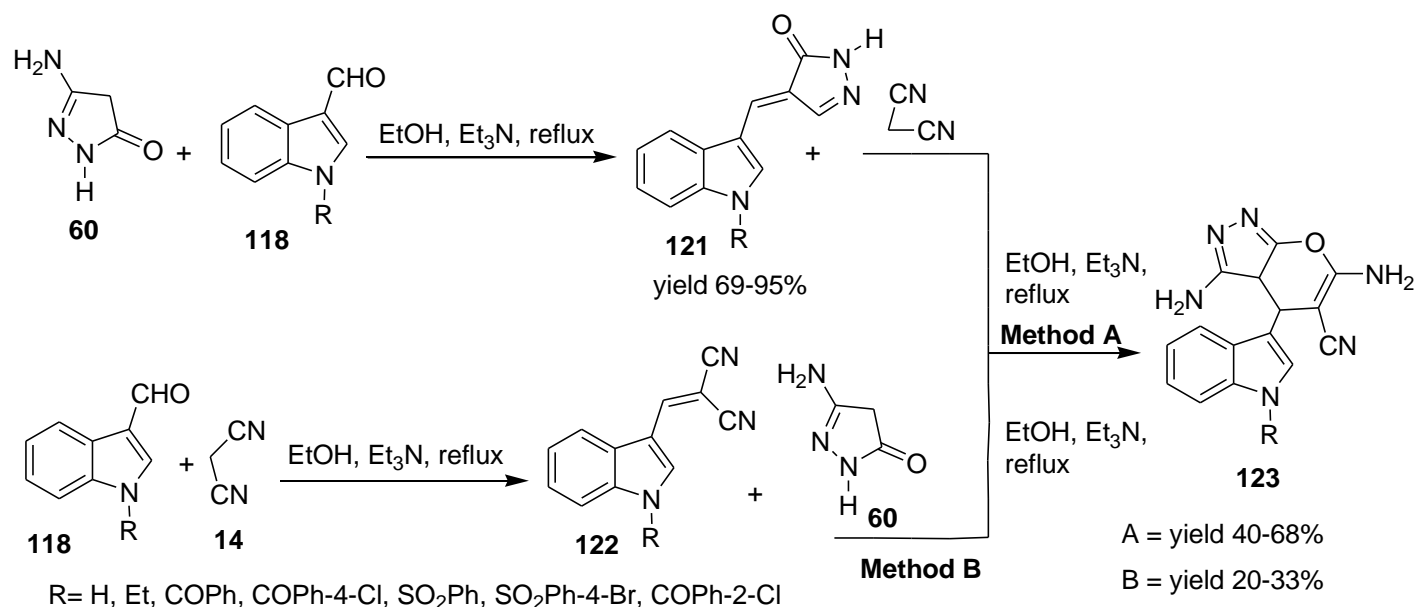


Scheme 41

In addition, indole-aldehydes (**118**) also reacted under basic conditions to form 4-indolepyrano[2,3-c]pyrazoles (**123**) by two sequence.⁵³

(a) Aminopyrazolones (**60**) and indolecarboxaldehydes (**118**) refluxed in ethanol containing triethylamine to form intermediate **121**, which further reacted with malononitrile to form pyrano[2,3-c]pyrazoles (**123**).

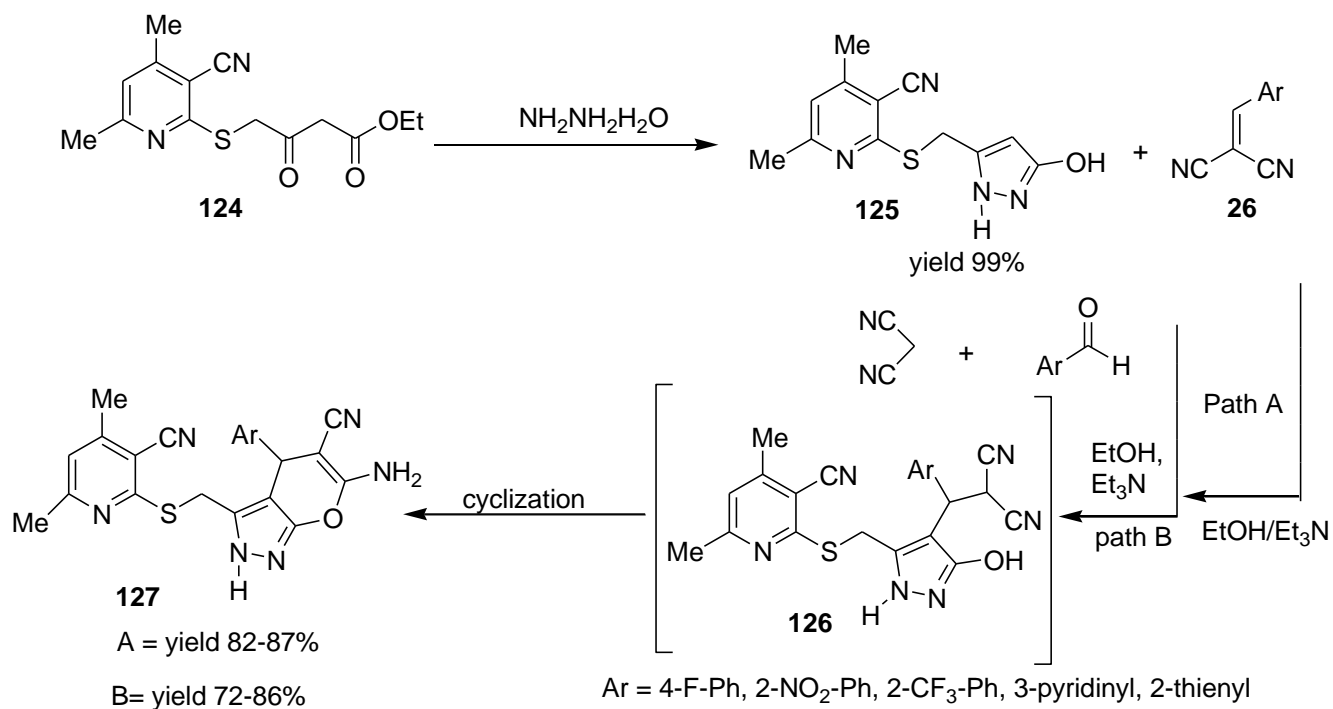
(b) Under the same reaction conditions, indolecarboxaldehydes (**118**) refluxed with malononitrile (**14**) to form intermediate **122**, which reacted with aminopyrazolone (**60**) to form pyranopyrazoles **123** (Scheme 42). The synthesized compounds were tested for biological activities where all exhibited remarkable anti-inflammatory, analgesic and anticonvulsant activities and most of the analogues found potential antimicrobial agent. Some compounds showed anticonvulsant potency more than both anti-inflammatory and analgesic activities. It was also observed that presence of halo atoms increased biological action.



Scheme 42

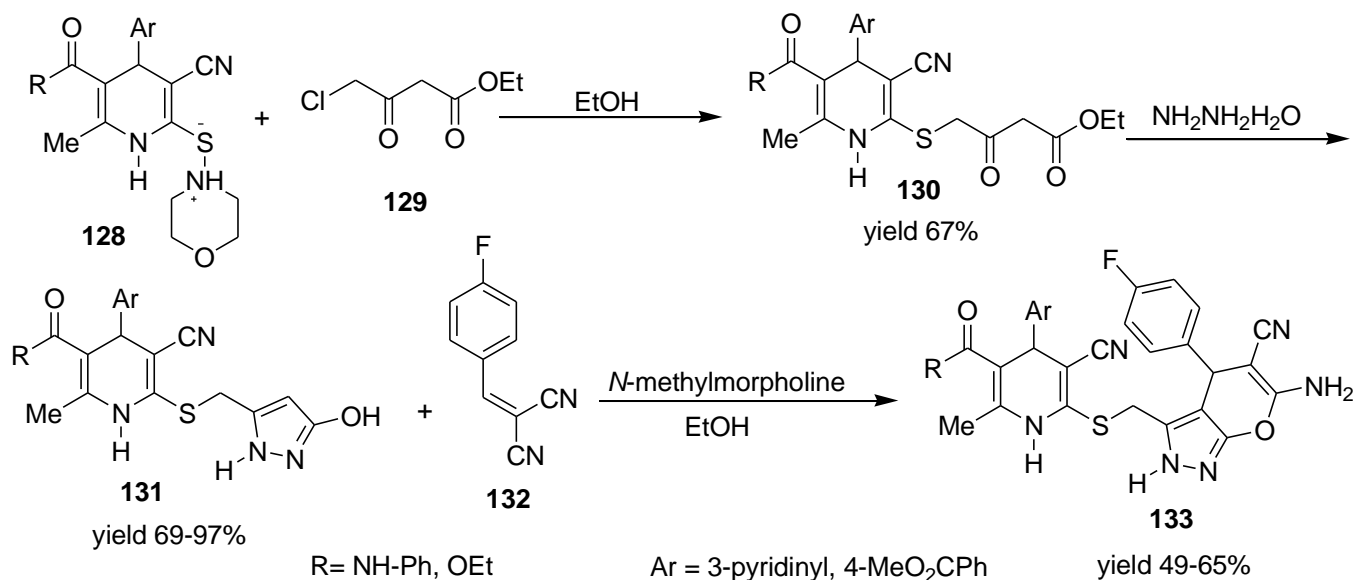
Rodinovskaya and co-workers used 4-(3-cyanopyridin-2-yl-thio)acetoacetic ester (**124**) to synthesize pyridine based pyrazolone **125** which further reacted with benzylidemalononitriles (**26**) (path A) or with aldehydes and malononitrile in ethanol containing triethylamine (path B) to form Michael adduct **126** as an

intermediate, which finally cyclized to afford pyranopyrazole **127** containing methylthiopyridine substituents at 2-position (Scheme 43).⁵⁴



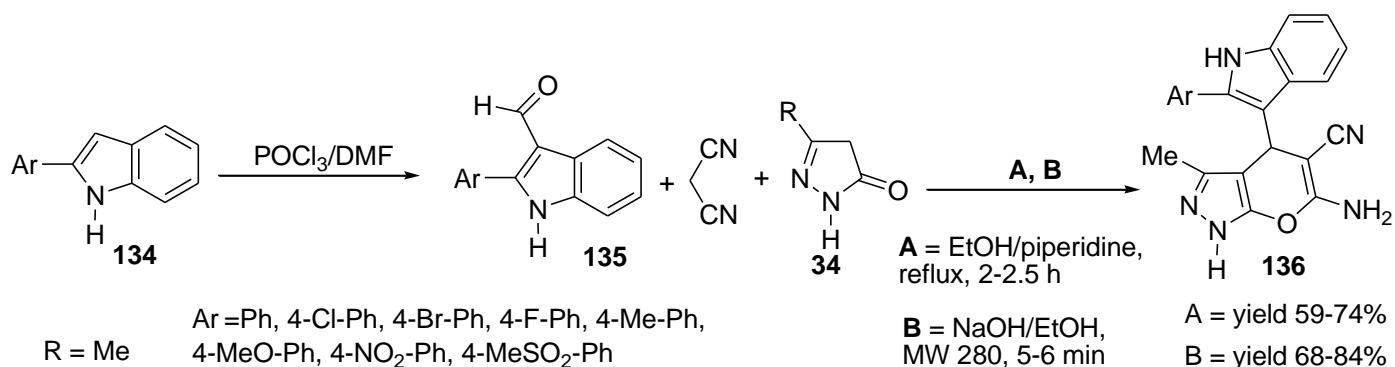
Scheme 43

Similarly, alkylated morpholinium 1,4-dihydropyridine-2-thiolate (**128**) with ethyl 4-chloroacetoacetate (**129**) yielded 2-(3-ethoxycarbonyl-2-oxopropylthio)-1,4-dihydropyridine (**130**) which was treated with hydrazine hydrate to form 2-(pyrazol-5-ylmethylthio)-1,4-dihydropyridine (**131**) that was further refluxed with 4-fluorobenzylidene malononitrile (**132**) to form highly substituted pyranopyrazoles **133**.⁵⁴ X-Ray crystallography revealed its tautomeric form with the hydrogen attached to second nitrogen of the pyrazole ring (Scheme 44).



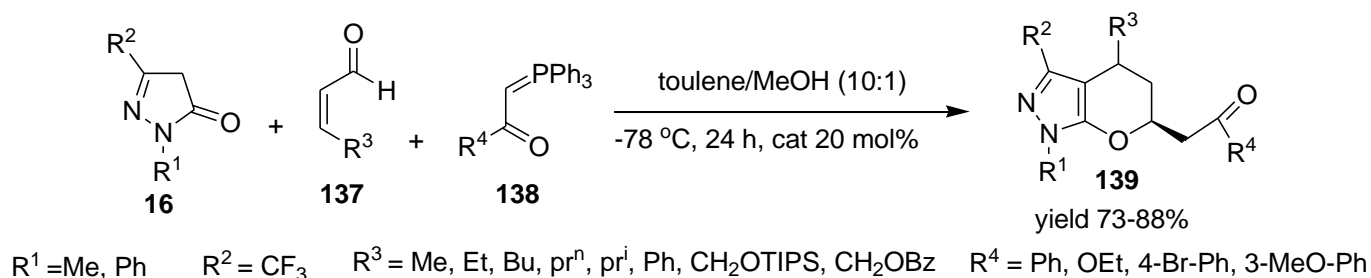
Scheme 44

Kathrotiya and co-workers carried out Vilsmeier-Haack reaction of indole **134** to form 2-(4-un/substitutedphenyl)-1*H*-indole-3-carboxaldehydes (**135**) which reacted with malononitrile and pyrazol-5-one to form indole 2-substituted pyranopyrazoles **136** (Scheme 45).⁵⁵ The reaction mechanism was proposed to involve Knoevenagel condensation between aldehydes and malononitrile with loss of water, followed by Michael addition and cyclization to form pyranopyrazoles as mentioned in Scheme 31. These were tested for antibacterial activity against eight human pathogens. Some analogues were found more active than standard drugs.



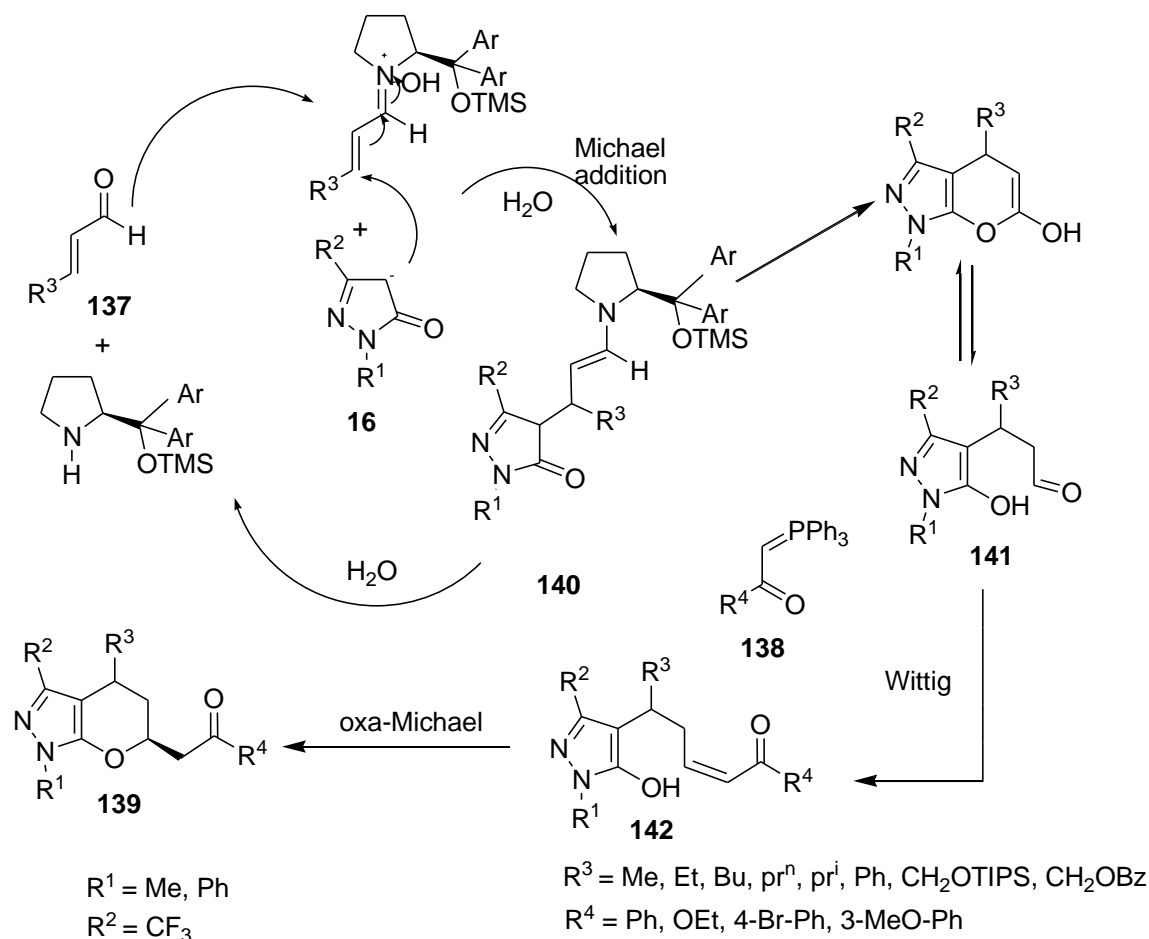
Scheme 45

Enders and co-workers tested different secondary amines as catalysts for reaction of α,β -unsaturated aldehydes **137** and Wittig reagent **138** to prepare enantioselective tetrahydropyranopyrazoles **139** where, MacMillan imidazolidinone showed excellent result in chloroform/toluene with a small amount of methanol (Scheme 46).⁵⁶ One pot reaction gave better yields and enantioselectivity than a two-step synthesis. Furthermore, NOESY experiments revealed that the major diastereomer shows *trans* configuration.



Scheme 46

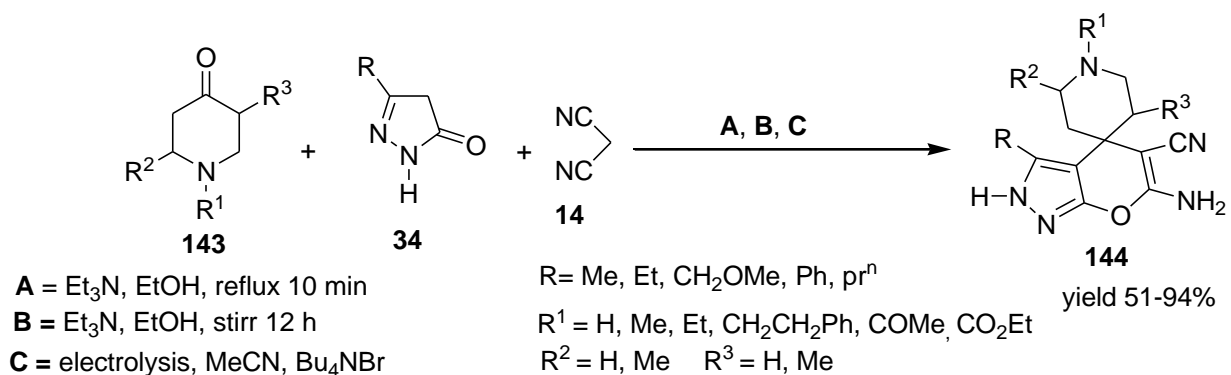
Reaction is believed to be catalyzed by secondary amine to form Michael intermediate **140** which cyclized to form 6-hydroxy pyranopyrazoles **141**, followed by Wittig reagent initiated ring-opening **142** and finally oxo-Michael domino reaction to give final product **139** (Scheme 47).⁵⁶ Wittig reaction with electron-rich or neutral substituents of phosphoranes showed greater enantioselectivity and yield as compare to slightly electron-deficient phosphoranes. Structure of compound was confirmed by X-ray studies.



Scheme 47. Mechanism.

Shestopalov *et al.* replaced aldehydes with substituted piperidin-4-ones (**143**) to prepare spiro-4-(piperidine-4')pyrano[2,3-*c*]pyrazole (**144**) by following methods

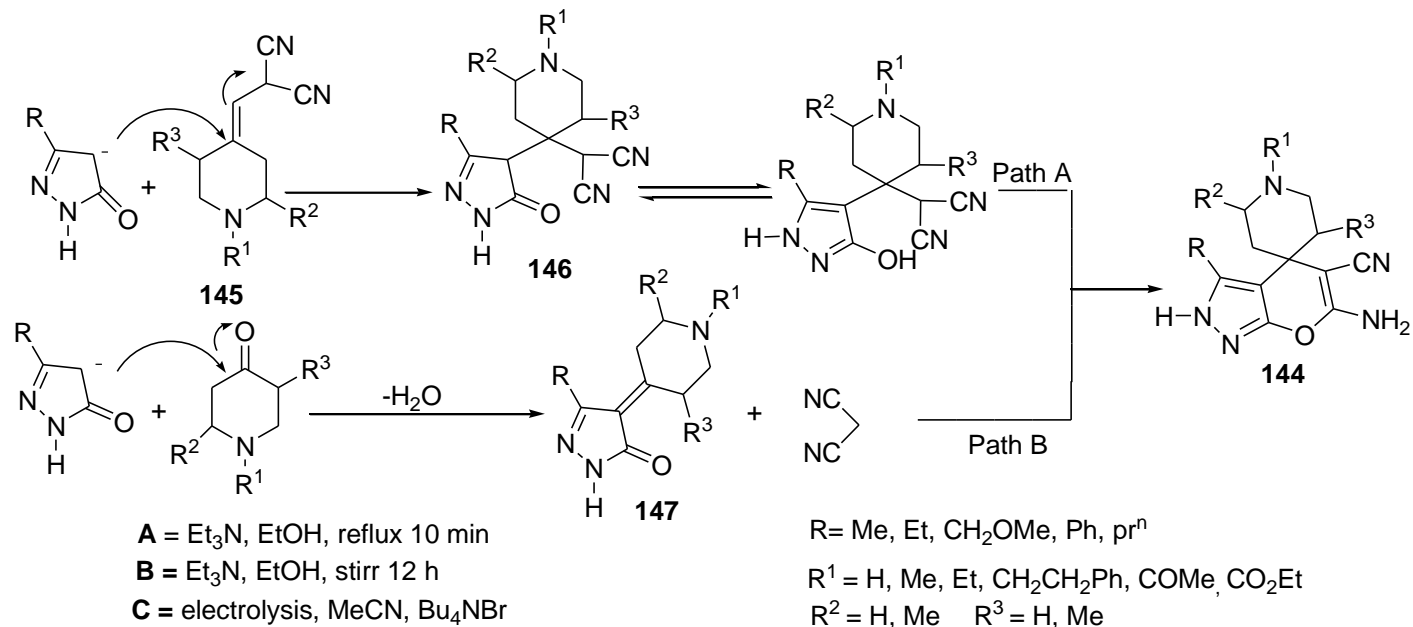
- Refluxing for 10 min in the presence of triethylamine
- Stirring at room temperature without base for 12 h
- Electrolysis in acetonitrile using 40 mL of 0.1 M Bu_4NBr as catholyte gives pyranopyrazoles **144** regioselectively (Scheme 48).⁵⁷



Scheme 48

It was proposed that the reaction proceeds by two plausible pathways.⁵⁷

- (a) Initial reaction of malononitrile and ketone yields alkene **145** which reacts further with pyrazolone to give Michael adduct **146**, which cyclises to form pyranopyrazole **144** (Path A)
- (b) Ketone and pyrazolone react to form intermediate **147** which reacts with malononitrile (Path B) (Scheme 49)



Scheme 49

Malononitrile and ketone were treated to obtain nitrile **145** which being reactive and unstable dimerized to **148**, which supported Pathway B.⁵⁷ Similarly, reaction with sterically hindered ketone named, adamantan-2-one, yielded a Michael adduct **149** which did not undergo further reaction (Figure 9).

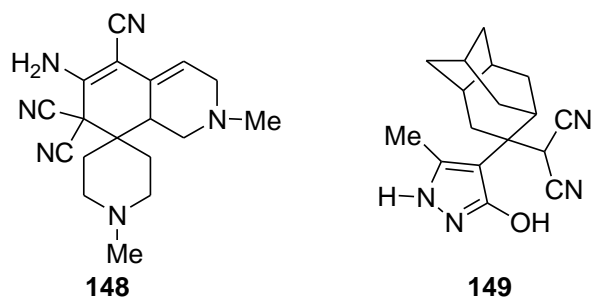
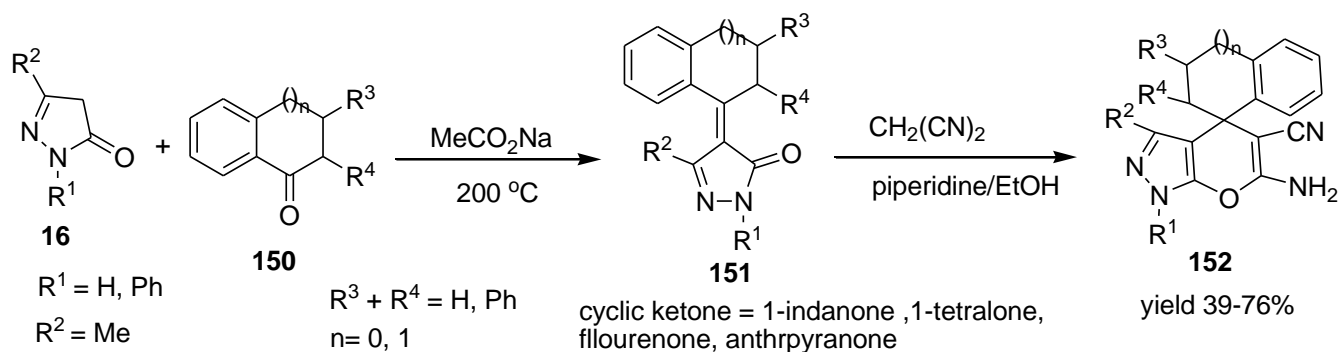


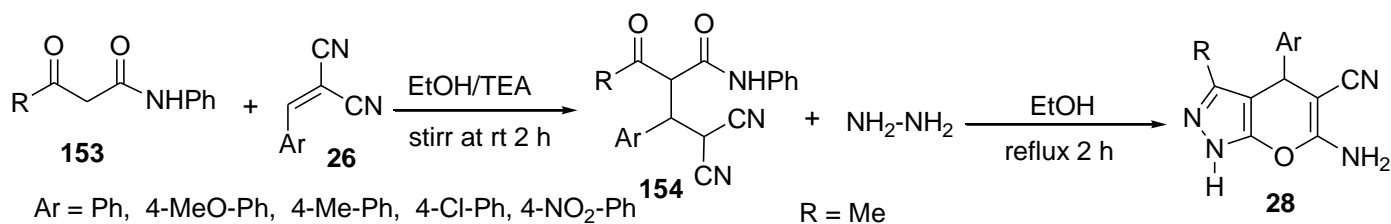
Figure 9

Al-Thebeiti carried out a solvent-free synthesis by fusing pyrazolone and cyclic ketone **150** in the presence of anhydrous sodium acetate at 200 °C to get intermediate **151** which were refluxed with malononitrile to obtain spiropyrano[2,3-c]pyrazoles (**152**) and derivatized further to oxo- and amino- pyrimidines using various reagents.⁵⁸ Some of the synthesized analogues exhibited moderate antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* (Scheme 50).



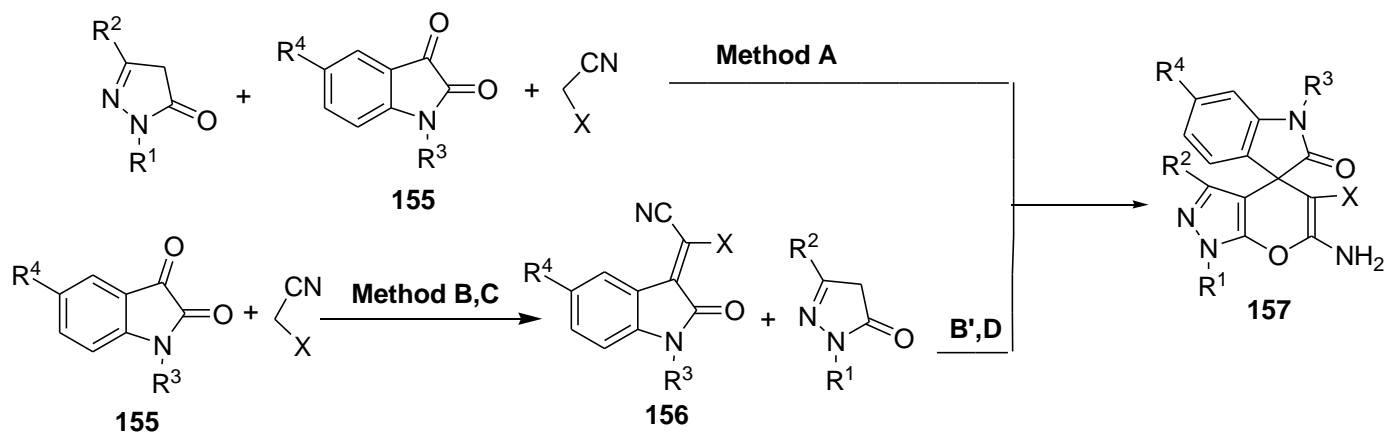
Scheme 50

Riad and co-workers reacted acetoacetanilide (**153**) and α -cyanocinnamionitrile derivatives to produce intermediate **154** which when either treated with hydrazine hydrate to form pyrano[2,3-*c*]pyrazole (**28**) (Scheme 51) or cyclized under acidic conditions gave pyran derivatives.⁵⁹ It was also observed that these pyranopyrazoles could be converted easily to pyrazolopyridines in acetic acid and ammonium acetate. These compounds showed moderate inhibition effect on bacteria.



Scheme 51

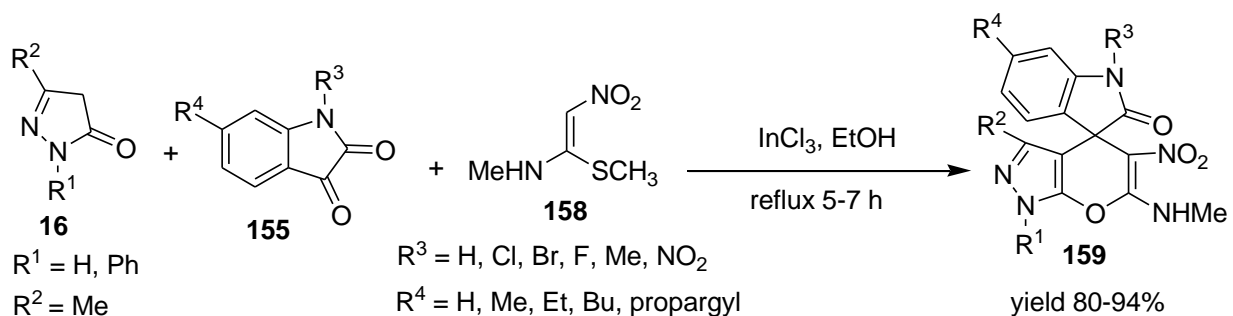
In addition to these ketones, un/substituted isatin (**155**) has been widely used for synthesis of spiro-2-oxindole-pyranopyrazoles. Redkin and co-workers treated isatin, with a suitable CH acid (malononitrile/cyanoacetic ester) and pyrazolones *via* one pot (Scheme 52 A) or two step method involving reaction of isatin and CH acid to form intermediate **156** which further reacts with pyrazolone to form pyranopyrazoles **157** (Scheme 52 B).⁶⁰ It was assumed that the formation of the Michael adduct is common in both methods which cyclized regioselectively to pyrano[2,3-*c*]pyrazol bearing spiro-2-oxindole derivatives. Similarly, Dandia and co-workers ground N-unsubstituted isatin **155** and malononitrile in agate mortar or subjected to microwave irradiation at 640 W to get intermediate **156** (Scheme 52 C) which adsorbed on neutral alumina using methanol and treated with pyrazolone to get pyranopyrazoles **157**⁶¹ (Scheme 52 D).



Method	R ¹	R ²	R ³	R ⁴	X	Condition	Yield
A	H	Me	H, Me, Bu	H, Me	CN, CO ₂ Et	EtOH, TEA, heat if X= CN, Reflux 2 h, if X= COOEt	55-74%
B	H	Me	H, Me, Bu	H, Me	CN, CO ₂ Et	EtOH, TEA, rt/ heat B'= EtOH, TEA, reflux 1-2 h	43-68%
C	Ph, 5-Cl-Ph, 5-NO ₂ -Ph, 5,7-dimethyl-Ph	Me	H	H	CN	solid satate ground or MW, 640 W, 30 sec.	60-98%
D	Ph, 5-Cl-Ph, 5-NO ₂ -Ph, 5,7-dimethyl-Ph	Me	H	H	CN	alumina/ MeOH, MW, 640 W	90-94%

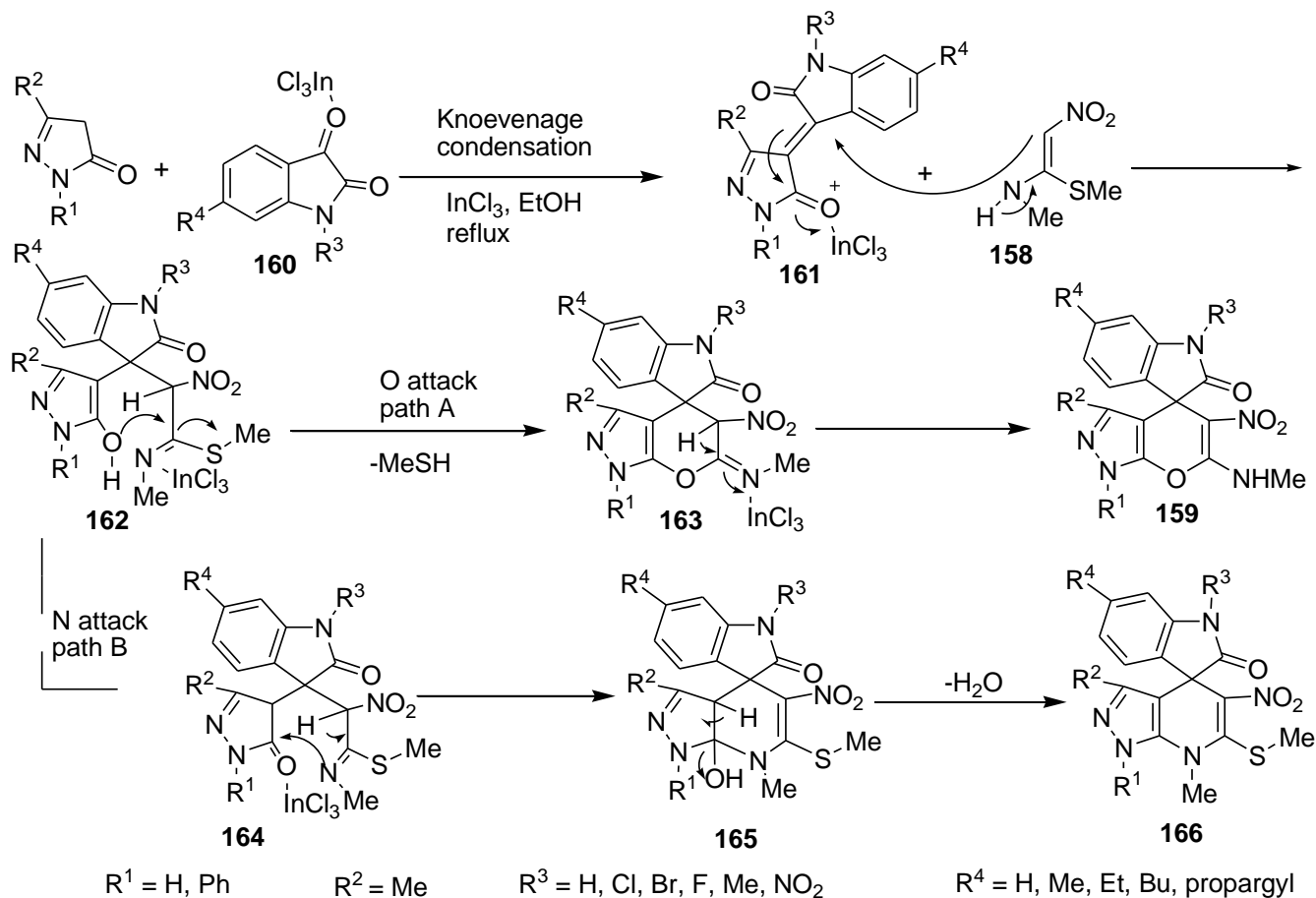
Scheme 52

Poomathi and co-workers developed one-pot regioselective synthesis of spirooxindoles using isatins (**155**), pyrazoles and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) (**158**) under the catalytic action of Lewis acid such as SnCl₂·2H₂O, PTSA·H₂O, FeCl₃, In(OTf)₃, AlCl₃, and BiCl₃ in MeOH, EtOH and MeCN using different mol% quantity where 20 mol% of InCl₃ in ethanol afforded highest yield without any need of column chromatographic purification (Scheme 53).⁶²



Scheme 53

The reaction mechanism was proposed to involve indium chloride initiated Knoevenagel condensation of pyrazolone and isatin producing an adduct **161**, which acts as Michael acceptor and readily underwent Michael-type addition with NMSM to form an open chain intermediate **162**.⁶² The intermediate has the possibility to follow path A (O-cyclization) or path B (N-cyclization) to give product **166**, but only pyranopyrazoles **159** were obtained *via* elimination of MeSH. X-Ray studies of 7-chloro-3-(3-methyl-6-(methylamino)-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)indolin-2-one additionally also favored O-cyclization (Scheme 54).



Scheme 54. Mechanism.

Shanthi and co-workers also used indium (III) chloride as catalyst either in acetonitrile at reflux temperature or under microwave irradiation adsorbed on silica gel.⁶³ Carbonyl compounds as pyrazolone, indenoquinoxaline, naphthol, 4-hydroxycoumarin or 3*H*-chromene-2,4-dione reacted with malononitrile/ethyl cyanoacetate and isatin under these reaction conditions to prepare spirooxindoles and spiroindenoquinoxaline **167-169** (Figure 10). Reaction conditions did not work for aniline replacing naphthol and enone.

Mandha *et al.* carried out a non-catalytic synthesis in water/ethanol mixture using various carbonyl compounds such as aldehydes **91**, isophthalaldehyde (**170**), indole-2,3-dione (**49**), and 9-fluorenone (**171**).⁶⁴ The reaction mechanism is believed to involve Knoevenagel condensation between the carbonyl compounds and malononitrile to form various benzylidemalononitrile as intermediates **26**, **172-174**, which underwent Michael addition with pyrazolin-5-one, followed by intramolecular cyclization to form polyfunctional

pyranopyrazoles **15**, **175-177**. These were tested for antibacterial, anti-inflammatory and cytotoxicity (Scheme 55). X-Ray studies confirmed the 2-*H* tautomeric form.

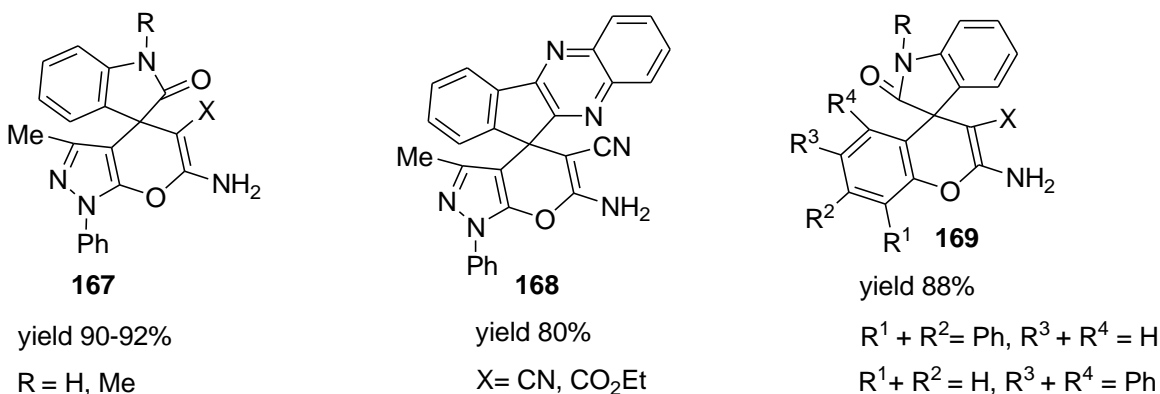
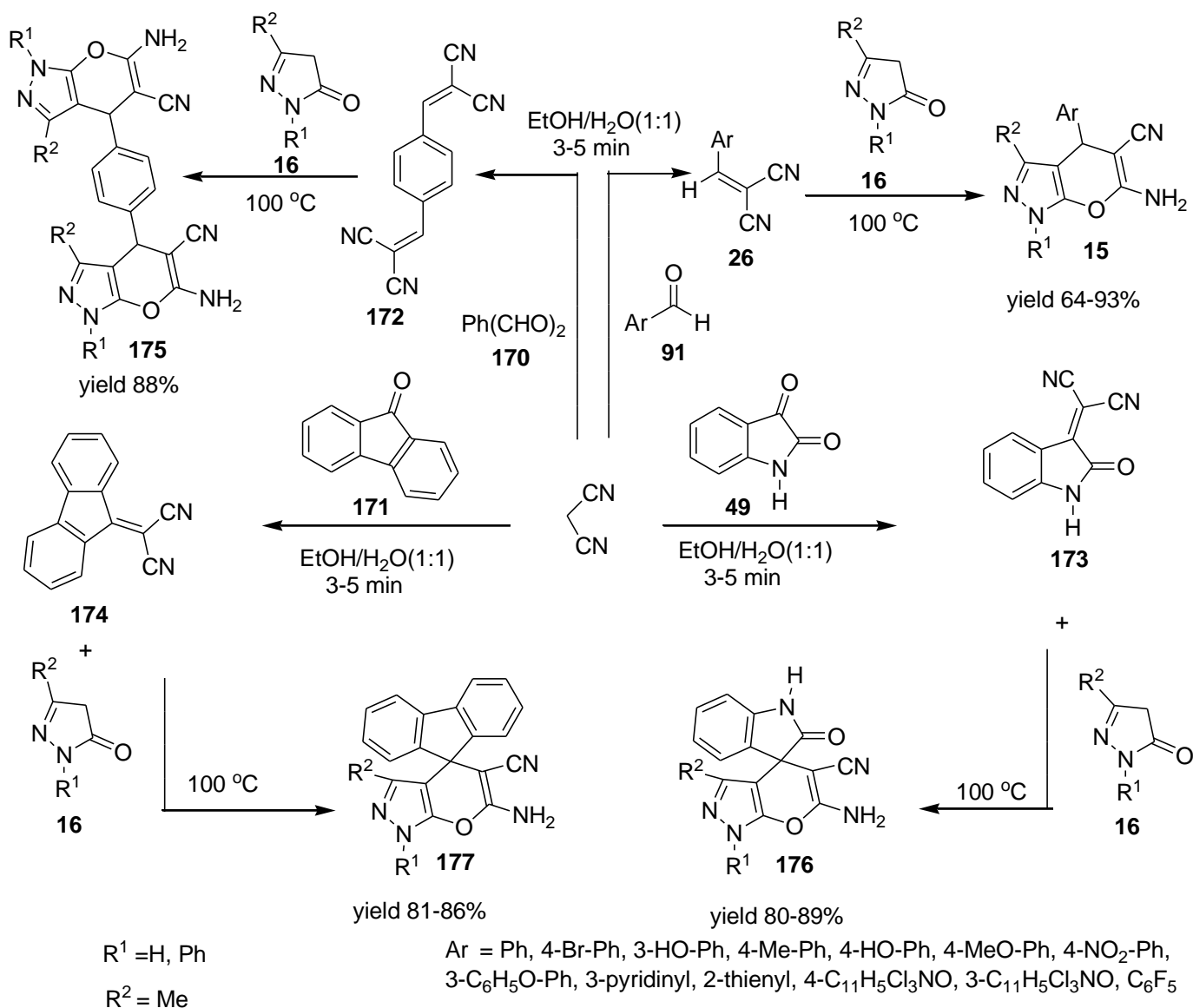
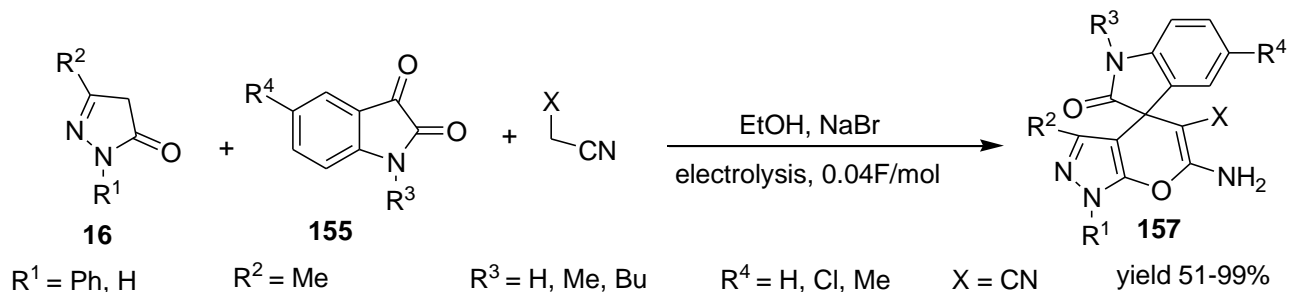


Figure 10



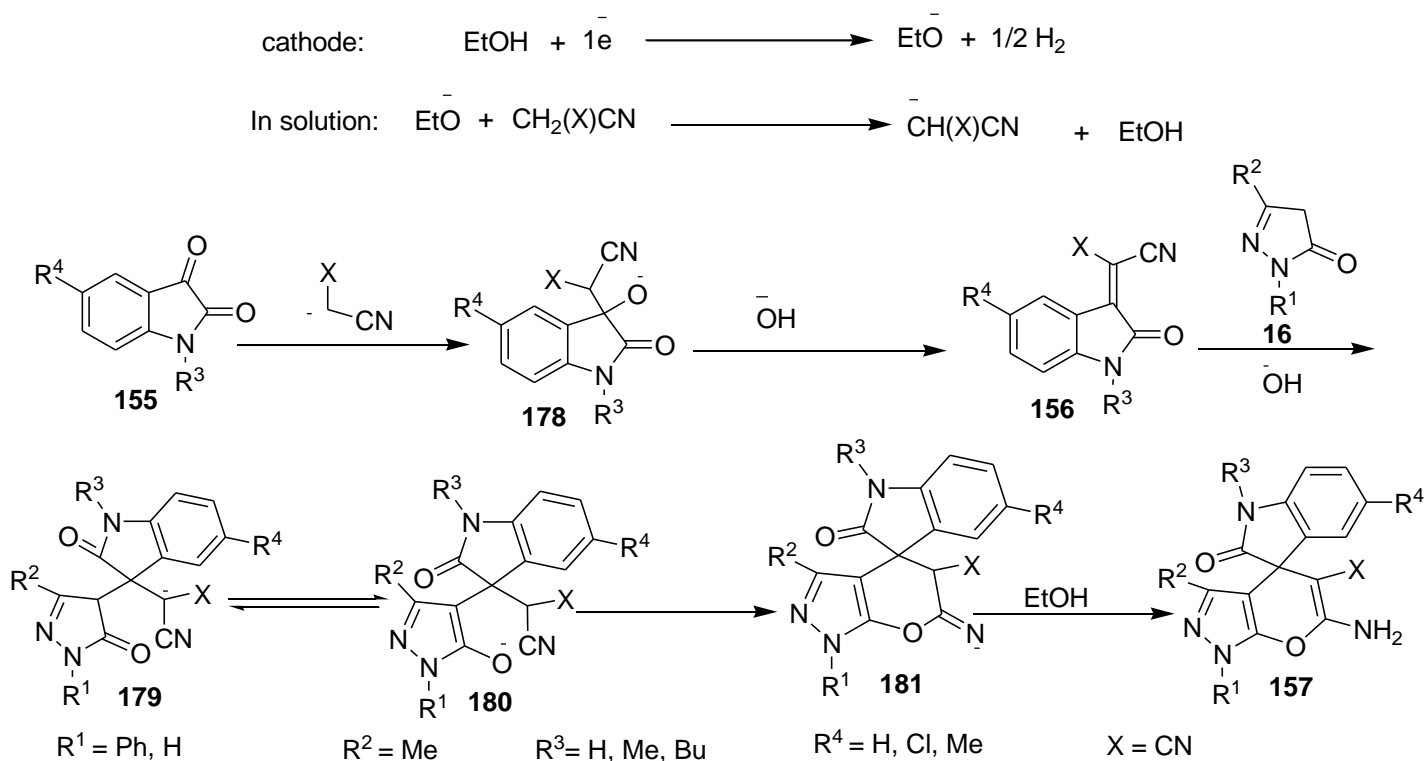
Scheme 55

Elinson and coworkers electrolyzed an ethanolic solution of isatin, malononitrile, pyrazolone and sodium bromide in an undivided cell having a magnetic stirrer.⁶⁵ Reaction was found to be successful after passing 0.04 F/mol quantity of electricity at different densities but, 2 mA/cm² was found optimal to obtain excellent yields of spiro[indole-3,4-pyrano[2,3-c]pyrazoles] (**157**) (Scheme 56).



Scheme 56

The reaction mechanism was proposed to involve ethoxide ion catalyzed Knoevenagel condensation of malononitrile and isatin with elimination of hydroxide ion to give electron-deficient Knoevenagel adduct **156**, followed by Michael addition of pyrazolone to form Michael adduct **179** and finally cyclization to form pyran ring system (Scheme 57).⁶⁵



Scheme 57

Litvinov and Shestopalov reacted aromatic aldehydes, malononitrile with the corresponding nucleophilic agents including pyrazolone to synthesize various condensed heterocyclic moieties and derivatized further to pyrimidine derivatives **182-183** (Figure 11).⁶⁶

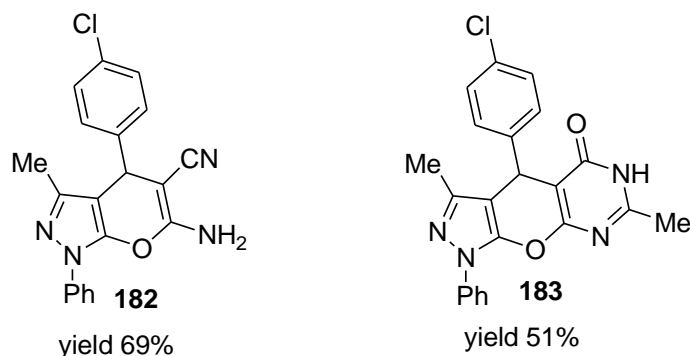
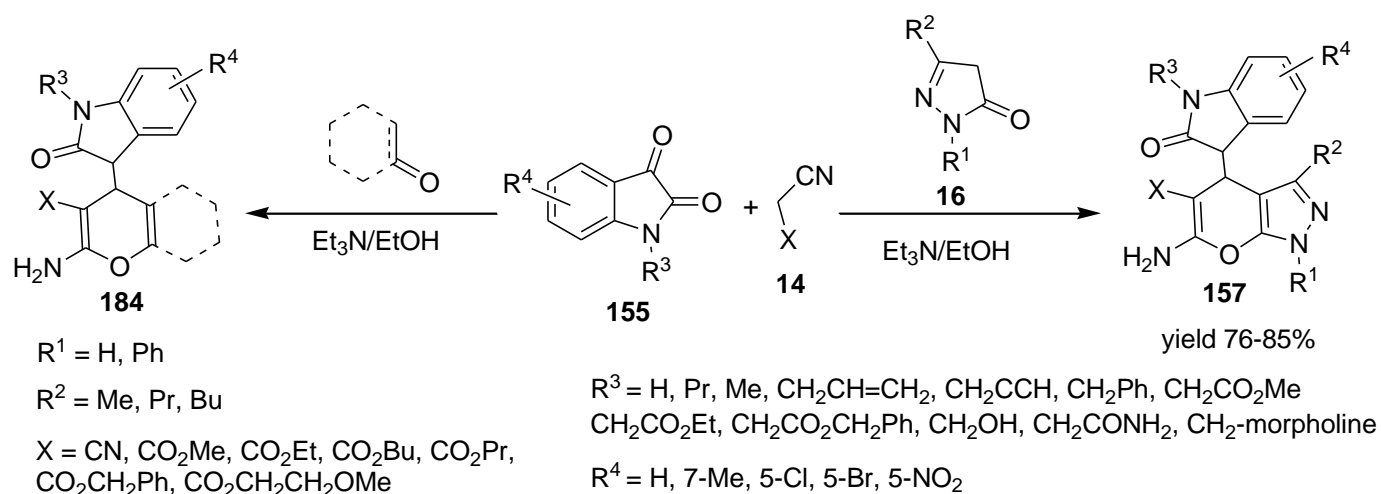


Figure 11

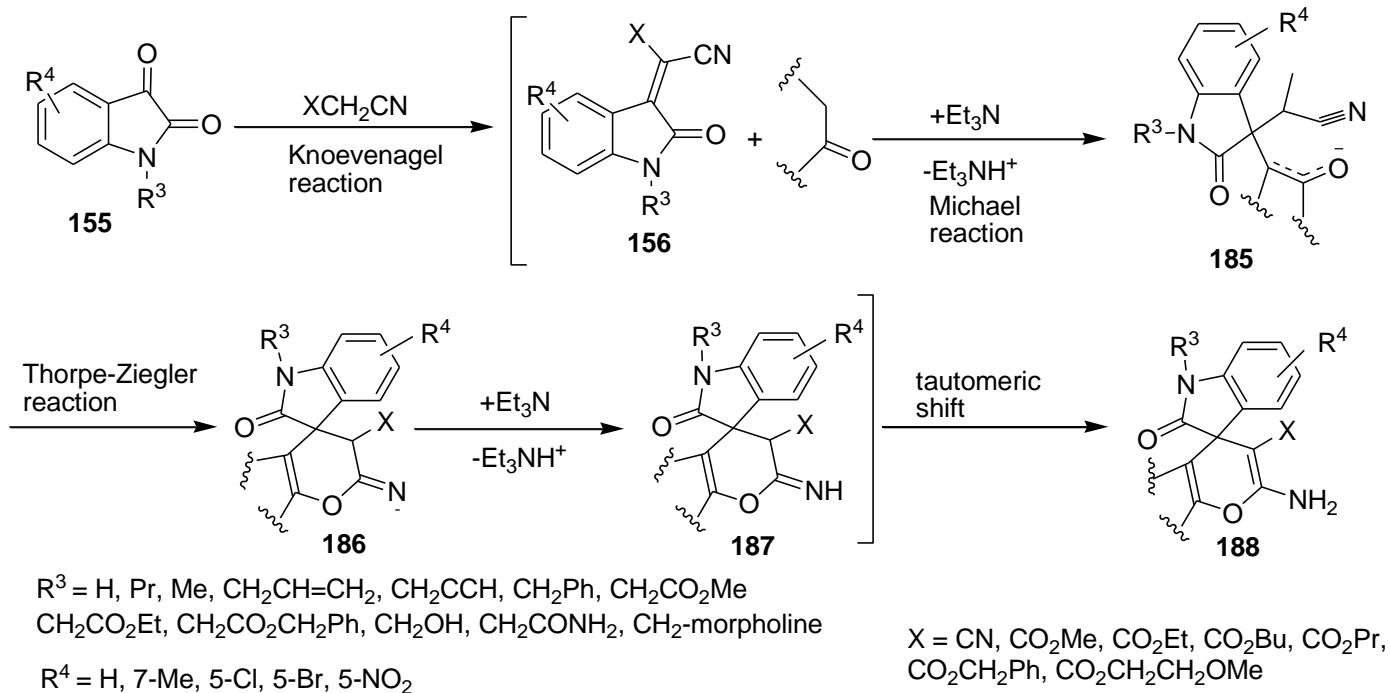
In another series of work, substituted and annulated pyran derivatives were prepared *via* one pot combinatorial synthesis starting with isatin, cyanoacetic acid derivatives, and various carbonyl compounds. Carbonyl compound (β -ketoesters) yielded non-annulated pyran while, annulated pyrans were obtained using β -diketones, *meta*-aminophenol, 4-hydroxycoumarin, and pyrazolones⁶⁷ (Scheme 58).



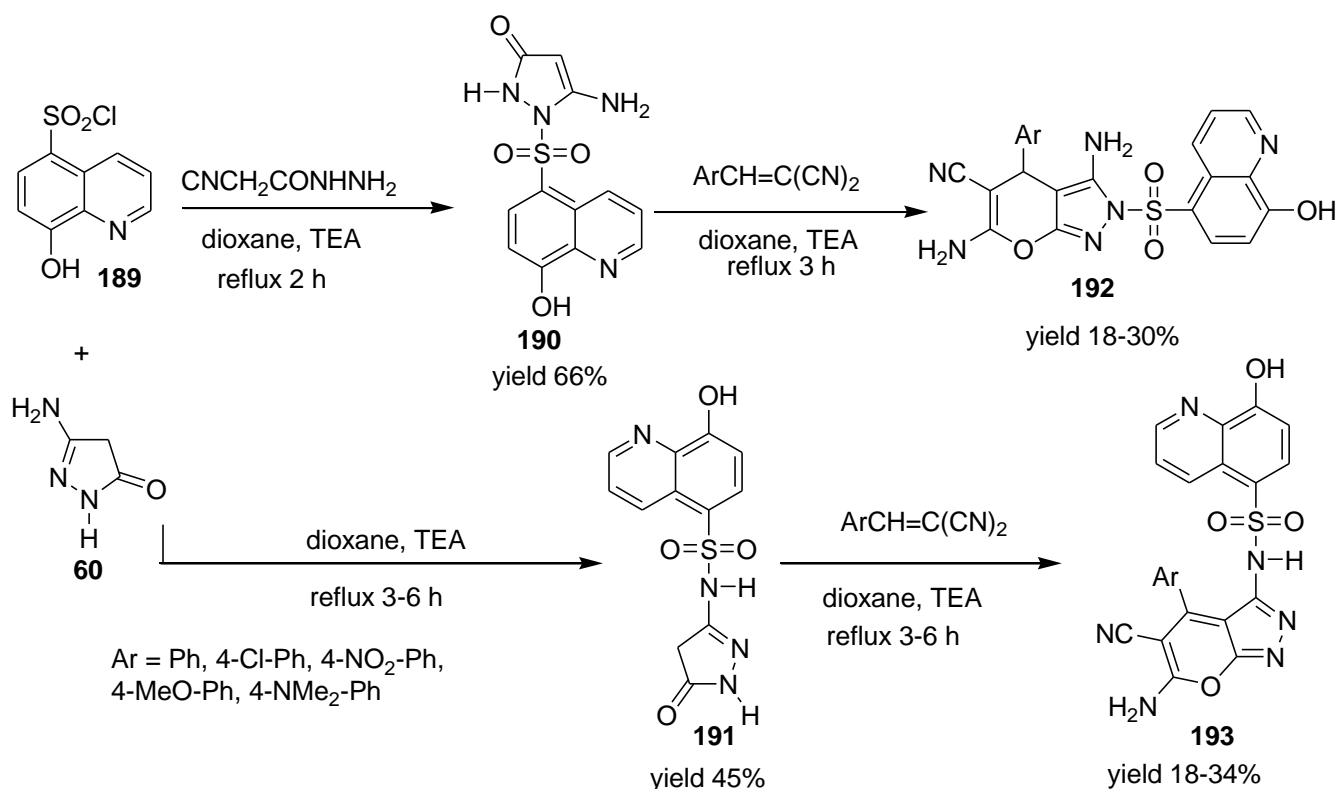
Scheme 58

It was proposed that the Knoevenagel condensation between isatin and CH-acidic derivative to form alkene **156** is the first step, alkene reacts with the carbonyl compound to give the Michael adduct **185**, followed by attack of enolate oxygen on the nitrile group (Thorpe-Ziegler type reaction) and finally tautomerizing to form the target compounds⁶⁷ (Scheme 59).

Kassem and co-workers refluxed 8-hydroxyquinoline-5-sulfonyl chloride (**189**) either with 2-cyanoacetic acid hydrazide or 3-amino-5-pyrazolone **60** to produce the sulfonyl based pyrazolones **190**, **191** which were further reacted with benzylidemalononitriles to provide 8-hydroxyquinoline bearing pyrano[2,3-*c*]pyrazoles (**192**, **193**) (Scheme 60).⁶⁸ The synthesized compounds were tested for antibacterial and antiviral activities, where pyrazolone **190**, **191** and pyranopyrazolones **192**, **193** showed antibacterial activity while only pyrazolones were found to be potent antiviral agents.



Scheme 59

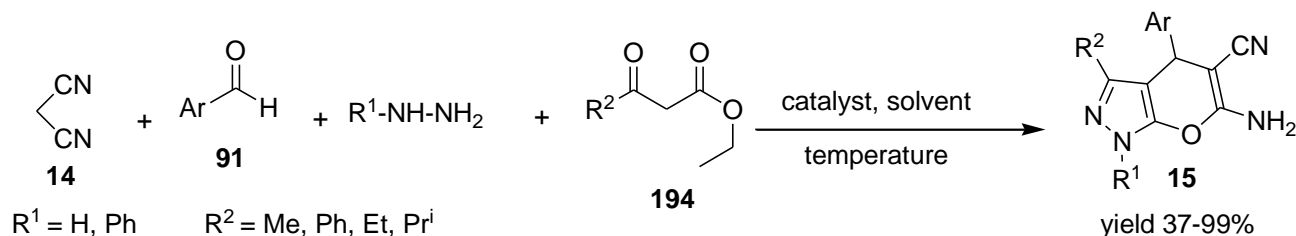


Scheme 60

2.3 Four components synthesis

Pyrano[2,3-c]pyrazoles are generally prepared by reacting aldehydes, malononitrile, β -ketoester and hydrazine with/without catalyst. Various catalyst, solvents, temperature and green techniques have been applied for

number of carbonyl compounds, β -keto- ester and un/substituted hydrazine. Most of the reactions were tried without catalyst in different organic solvents such as DMSO, DMF, THF, MeCN, CHCl_3 , CH_2Cl_2 , $\text{ClCH}_2\text{CH}_2\text{Cl}_2$, MeOH, MeC_6H_5 , EtOH as well as water (DD Water, ultra pure water) (Scheme 61).

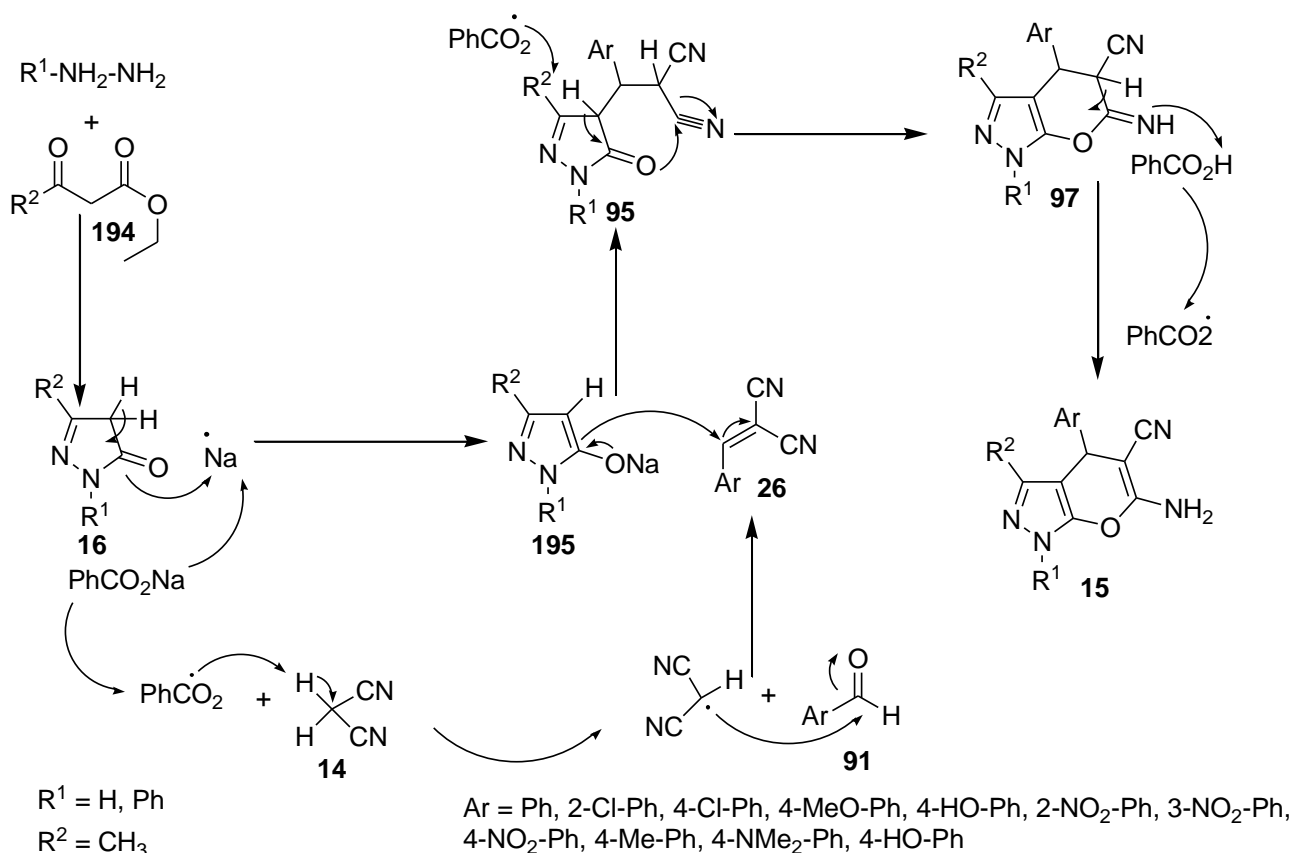


Ar = Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 2-MeO-Ph, 3-MeO-Ph, 4-MeO-Ph, 2-HO-Ph, 3-HO-Ph, 4-HO-Ph, 2-NO₂-Ph, 3-NO₂-Ph, 4-NO₂-Ph, 4-Me-Ph, 2-F-Ph, 4-F-Ph, 4-CN-Ph, 2-Br-Ph, 3-Br-Ph, 4-Br-Ph, 2-NH₂-Ph, 4-NH₂-Ph, 4-CF₃-Ph, 4-Br-3-Me-Ph, 4-F-3-Me-Ph, 4-Me₂N-Ph, 3-Me-4-F-Ph, 4-EtO-Ph, 3-EtO-4-HO-Ph, 2-HO-5-NO₂-Ph, 3-HO-4-MeO-Ph, 3-MeO-4-HO-Ph, 2-MeO-4-HO-Ph, 4-MeO-2-HO-Ph, 2-Me-4-MeO-Ph, 4-(OH)₂B-Ph, 2-MeO-3-(OH)₂B-Ph, 3,5-dichloro-Ph, 2,6-dichloro-Ph, 2,3-dichloro-Ph, 2,4-dichloro-Ph, 2,4-difluoro-Ph, 2,5-dimethyl-Ph, 3,5-dimethyl-Ph, 2,4,6-trimethyl-Ph, 2,5-dimethoxy-Ph, 3,4-dimethoxy-Ph, 3,5-dimethoxy-Ph, 3,4,5-trimethoxy-Ph, 2,3,4-trimethoxy-Ph, 5-bromothieryl, 5-chlorothieryl, 1-piperazinyl, 2-pyridinyl, 4-pyrrolyl, 1-naphthyl, 9-anthranlyl, N-methylindol-3-yl, 3-pyridinyl, 4-pyridinyl, 2-furanyl, 2-thienyl, butyl, propionyl, isopropyl

Scheme 61

- Zolfigol *et al.* catalyzed synthesis using the highly stable, readily available, metal free, less toxic and reusable organocatalysts such as isonicotinic acid and picolinic acid, where 10 mol% of isonicotinic acid at 80 °C showed better results than latter one.⁶⁹ Reaction conditions were suitable for aromatic aldehydes, aliphatic aldehydes, *N*-phenylhydrazine and hydrazine hydrate.
- Sidekha and co-workers used imidazole (0.5 mmol) in water at 80 °C for various aldehydes and did not observe any effect of substituents on yield and rate of reaction.⁷⁰ Geometric parameters and vibrational frequencies of 6-amino-4-(4'-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyranopyrazole were also calculated using B3LYP method. Computed values were multiplied with scale factor 0.9614, to offset anharmonicity in real system for both FTIR and FT-Raman.
- Kiyani and co-workers carried out synthesis in organic solvents (THF, CHCl_3 , CH_2Cl_2 , EtOH) or water and observed solvent effect on reaction time and yield of products.⁷¹ Water containing 15 mol% of sodium benzoate gave best yield. Aldehydes containing donor substituents increased reactivity and yield as compare to electron withdrawing substituents. Additionally, steric hindrance also played role as evidenced by the slower reaction of 2-nitrobenzaldehyde compare to 4-nitrobenzaldehyde. But in case of hydrazine, reactions of phenylhydrazine took longer time than hydrazine hydrate to give products in good yield. Reaction mechanism is represented as Scheme 62.
- Vasuki and Kumaravel tested potassium carbonate and the organic bases piperidine, triethylamine, diethylamine, pyrrolidine, morpholine, piperazine for synthesis.⁷² Benzaldehyde reacted well without any catalyst, while other aromatic aldehydes reacted in the presence of 5-10 mol% of piperidine in aqueous media at room temperature. Various mono, di and tri-substituted aromatic aldehydes, hetaryl aldehydes and aliphatic aldehydes used successfully. X-Ray crystallography study confirms the 2-*H* tautomeric form of pyranopyrazoles.
- Pawar and co-workers developed an inexpensive and environmental friendly method in water/ethanol mixture using 20 mol% of citric acid.⁷³ Various organocatalysts such as oxalic acid, picric acid, succinic acid, *p*-toluenesulfonic acid and sulfamic acid were also tested in different organic solvents at reflux temperature, but

the best yield was obtained in water/ethanol mixture at 80 °C. Mono and disubstituted benzaldehyde as well as 9-anthracenecarboxaldehydes and furan-2-carbaldehyde showed positive results.



Scheme 62

6. Madhusudana and Pasha used inexpensive, non-toxic, environmental friendly and easily available iodine catalyst in water solvent at 25 °C to get excellent yields.⁷⁴ Reaction was unsuccessful in absence of catalyst and solvent, non-polar solvent gave poor yield while increasing the polarity, increased the yield and shortened reaction time. The reaction was applied successfully for aromatic and hetaryl aldehydes.

7. Glycine replaced iodine and reaction was carried out in various organic solvent, obtained excellent yields in water solvent within 5-20 min.⁷⁵ Substituted aldehydes containing electron-donating and electron withdrawing groups worked equally well.

8. In water, reactants stirred in the presence of piperidine catalyst to give pyranopyrazoles, which showed inhibition to steel corrosion.⁶

9. Cetyltrimethylammonium chloride (CTACl) used as a phase transfer catalyst, which increased the hydrophobic surfaces and accelerate the reaction rates of heterogeneous multi-component reactions, to prepare pyranopyrazoles at 90 °C.⁷⁶ Aromatic aldehydes showed good results, but aliphatic aldehydes such as butanal or pentanal showed only small traces of product presumably due to competing of aldol condensation.

10. Kanagaraj and Pitchumani compared the catalytic action of methylamine, diethylamine, triethylamine, piperidine and per-6-amino- β -cyclodextrin for pyranopyrazoles synthesis where latter, gave excellent yield without solvent in 1 min.⁷⁷ It was proposed that per-6-ABCD have seven free primary amino groups, thus behaves as an efficient supramolecular host and base catalyst. In the first step, the carbonyl compounds bind within the CD cavity then reacts with malononitrile by Knoevenagel condensation to form

ylidenemalononitrile. These intermediates have enzyme-like binding, which ensure tight fitting in cavities and facilitates further Michael addition of the ylidene malononitrile to pyrazolone, followed by cyclization and tautomerization. To support this mechanism, an inclusion complex was formed by mixing equimolar amounts of adamantane and per-6-ABCD and used as catalyst, absence of any product confirms inclusion to per-6-ABCD cavities essential for pyranopyrazoles synthesis.

11. An easily available, cheap, and non-toxic catalyst sodium bisulphite was used under ultrasound irradiation without any solvent.⁷⁸ It was assumed that ultrasonic cavitations created microscopic internal high pressure and high temperature. Electron donating and/or withdrawing substituents of aromatic aldehydes showed no effect on yield of pyranopyrazoles.

12. Alumina and alumina supported reagents have well known surface properties and specific porous structures, hence the catalytic efficiency of α -alumina, basic alumina and KF-alumina examined using 30 mol% of each catalyst.⁷⁹ The order of reactivity is found to be alumina > KF-alumina > basic alumina. The higher activity of α -alumina was attributed to the amphoteric nature and the greater surface area allowing for greater adsorption of the reactants on its surface. Aromatic, poly functional and aliphatic aldehydes used under this condition.

13. Reddy and Garcia carried out eco friendly synthesis using montmorillonite K-10 as catalyst. The reaction has an advantage of catalyst recovery and reusability for several time.⁸⁰

14. Phenylboronic acid (5 mol%) in water at reflux temperature was used for aromatic and hetero-aromatic aldehydes.⁸¹ Electron donating or withdrawing groups, at any position (*p*, *m* or *o*) of aldehyde, gave good yield, but electron withdrawing substituted aldehydes reacted slowly while aliphatic aldehydes gave poor yields. The reaction mechanism proposed to involve initial binding of PhB(OH)₂ with carbonyl oxygen.

15. Kumar and co-workers used inexpensive, mild, water-tolerant and eco-friendly tetraethyl ammonium bromide (10 mol%) catalyst in boiling water for aromatic, hetero-aryl and aliphatic aldehydes.⁸²

16. Nagarajan and Reddy synthesized pyranopyrazoles without solvent and catalyst at room temperature within 3-11 min.⁸³ Aldehydes bearing electron-releasing groups at the *para* position gave better yield than electron-withdrawing groups at the same position. Similarly, disubstituted aldehyde with electron-donating groups at *para* and *meta* positions required shorter reaction time and gave higher yield. Reaction conditions worked equally for aliphatic aldehydes.

17. Moeinpour and Khojastehnezhad used Ni_{0.5}Zn_{0.5}Fe₂O₄ nanoparticles in water to get maximum yield at room temperature.⁸⁴ Catalyst was separated easily by an external magnet, reused six times, studied by XRD patterns which showed no change in structure, weight and reactivity. Initially, nanoparticles were prepared by mixing equimolar solutions of FeCl₃, NiCl₂, ZnCl₂ and NaOH, then coating silica and polyphosphoric acid on the nanoparticles. The nanoparticles were found to be spherical, average size less than 70 nm in diameter and narrowly distributed.

18. Babaie and Sheibani prepared MgO nanoparticles by treating aqueous magnesium hydroxide gels, magnesium nitrate and liquid ammonia and used these nanoparticles for pyranopyrazoles synthesis using malononitrile, aromatic aldehydes, phenyl hydrazine/hydrazine hydrate and different ethyl 3-alkyl-3-oxopropanoate in acetonitrile at room temperature in 5-45 min.⁸⁵

19. Various iron oxides such as Fe₃O₄, Fe₃O₄ nanoparticles and recovered Fe₃O₄ nanoparticles were compared for pyranopyrazoles synthesis where nanoparticles in fresh and recovered state showed excellent results.⁸⁶ Nanoparticles were prepared by treating FeCl₃.6H₂O, FeCl₂.4H₂O with NaOH. Out of different solvents, ultra pure water was found to be excellent.

20. Saha and co-workers used 10 mol% of ZrO_2 nanoparticles for MCR pyranopyrazoles synthesis at room temperature in water/ethanol mixture (6: 1).⁸⁷ The structure of ZrO_2 was confirmed as tetragonal and 17 nm in particle size.

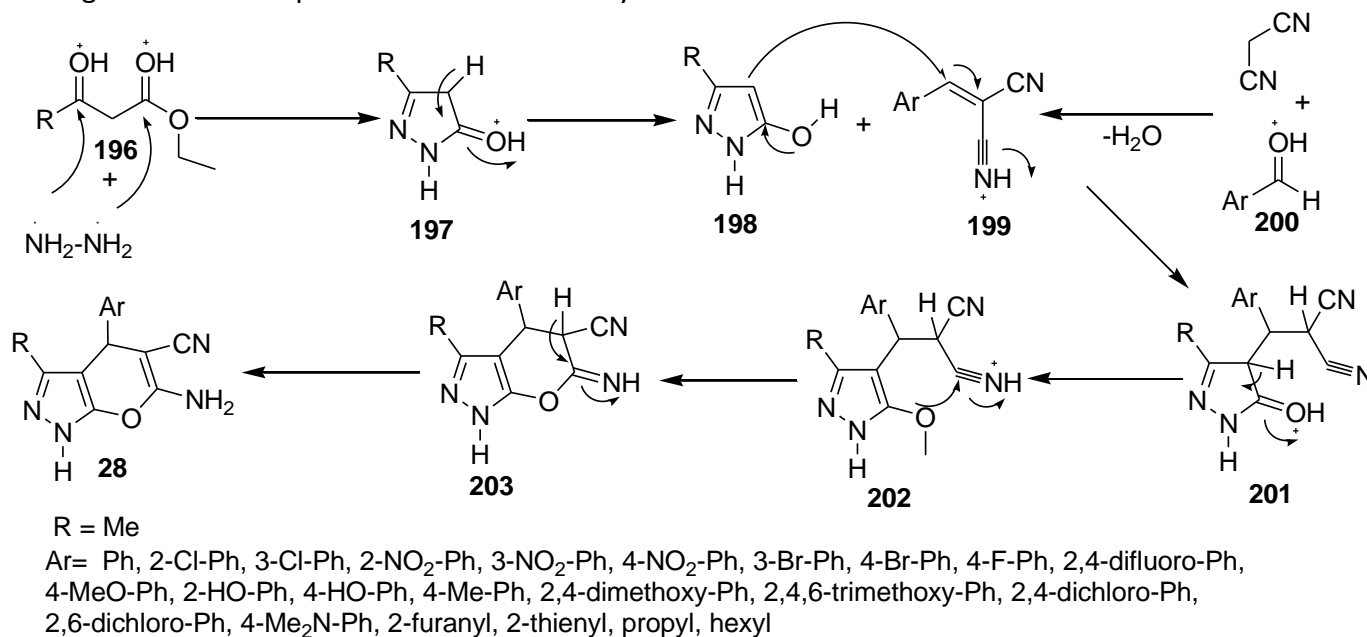
21. Borhade and Uphade prepared ZnS nanoparticles by mixing and stirring together a solution of zinc nitrate, sodium dodecyl sulphate and sodium sulphide and confirmed the elemental composition by EDAX spectrum and structure by XRD, SEM, TEM techniques.⁸⁸ These particles were found to be single-phase, hexagonal with average crystallite size of 20 nm and compared with $FeCl_3$, $SnCl_4$, P_2O_5 , $ZnCl_2$, bulk ZnS and ZnS nanoparticles. Nanoparticles technique was found most effective catalyst for synthesis of pyranopyrazoles at room temperature.

22. Ebrahimipour *et al.* Carried out condensation of 5-bromo-2-hydroxybenzaldehyde with 2-amino-4-methylphenol to form a ligand, which reacted with $Ni(OAc)_2 \cdot 4H_2O$ and 1-Methylimidazole to form mixed ligand complex $[Ni(L)(mimi)]$ either at reflux temperature to obtain bulk form or under ultrasonic irradiation to get nano-sized particles.⁸⁹ Both forms were tested for pyranopyrazoles synthesis and revealed that mixed ligand $[Ni(L)(mimi)]$ in either form, gave better yields, but nanoparticles are more efficient. The structure of the nanoparticles was found to be composed of finely dispersed nanorods with average diameter 45 nm.

23. Shinde and co-workers synthesized pyranopyrazoles in water at reflux, but obtained poor yield.⁹⁰ To increase efficiency silica gel 60 used as a catalyst, which increased the yield of product and decreased reaction time at room temperature. Reaction was found to be equally good for small scale, large scale, electron withdrawing and electron donating substituted aldehydes.

24. Nimbalkar and co workers initially synthesized triethylammonium hydrogen sulphate $[Et_3NH][HSO_4]$ and used it to carry out multicomponent synthesis of pyranopyrazole at room temperature.⁸⁸ The synthesized compounds were subjected to molecular docking and in vitro anticancer study where were found active against cancer cell lines.

25. The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate containing bases such as triethylamine, diethylamine, piperidine, L-proline and potassium carbonate used for synthesis.⁹² L-proline (10 mol%) showed excellent results at 50 °C within 5-10 min. Other ionic liquids including 1-butyl-3-methylimidazolium hexafluorophosphate $[Bmim]PF_6$ and 1-butyl-3-methylimidazolium bromide $[Bmim]Br$ were also used and showed good result except for 4-chlorobenzaldehyde.



Scheme 63

26. Chavan and co-workers compared the catalytic activity of silicotungstic acid with FeCl₃, ZnCl₂, SnCl₄, P₂O₅ and CAN, where the former showed excellent result at 60 °C.⁹³ Aromatic aldehydes produced high yield as compare to aliphatic aldehydes. NOE study of pyranopyrazoles confirmed its 2-*H* tautomeric form.

27. A mixture of anhydrous choline chloride and anhydrous urea in a 2:1 ratio heated at 50 °C to form a homogenous liquid that catalyses the formation of pyranopyrazoles (62-95%) under solvent free condition.⁹⁴ The reaction was found to be applicable for hydrazine hydrate, phenylhydrazine, various β-ketoesters such as ethyl isobutyroylacetoacetate, ethyl benzoylacetoacetate, aromatic and hetero aromatic aldehydes.

28. Ebrahimi and co-workers used a task specific ionic liquid named, 3-methyl-1-(4-sulphonic acid)butylimidazolium hydrogen sulphate [(CH₂)₄SO₃HMIM][HSO₄] to carry out synthesis at room temperature.⁹⁵

29. Devkate and co-workers also used same Bronsted acid ionic liquid in various aprotic and protic solvents, but obtained excellent results under solvent free condition.⁹⁶

30. Amin and co-workers replaced malononitrile with 2-cyanoacetamide and refluxed with other three reactants in methanol to obtain 5-carboxamide pyranopyrazoles (**204**) which was found antibacterial and antifungal agents⁹⁷ (Figure 12).

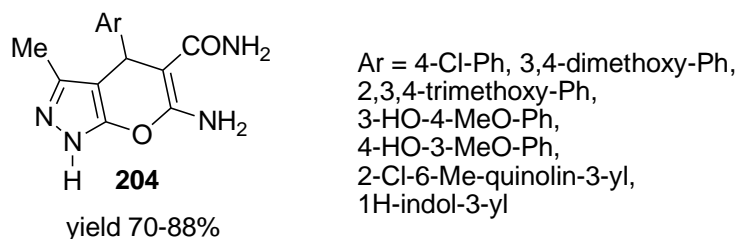
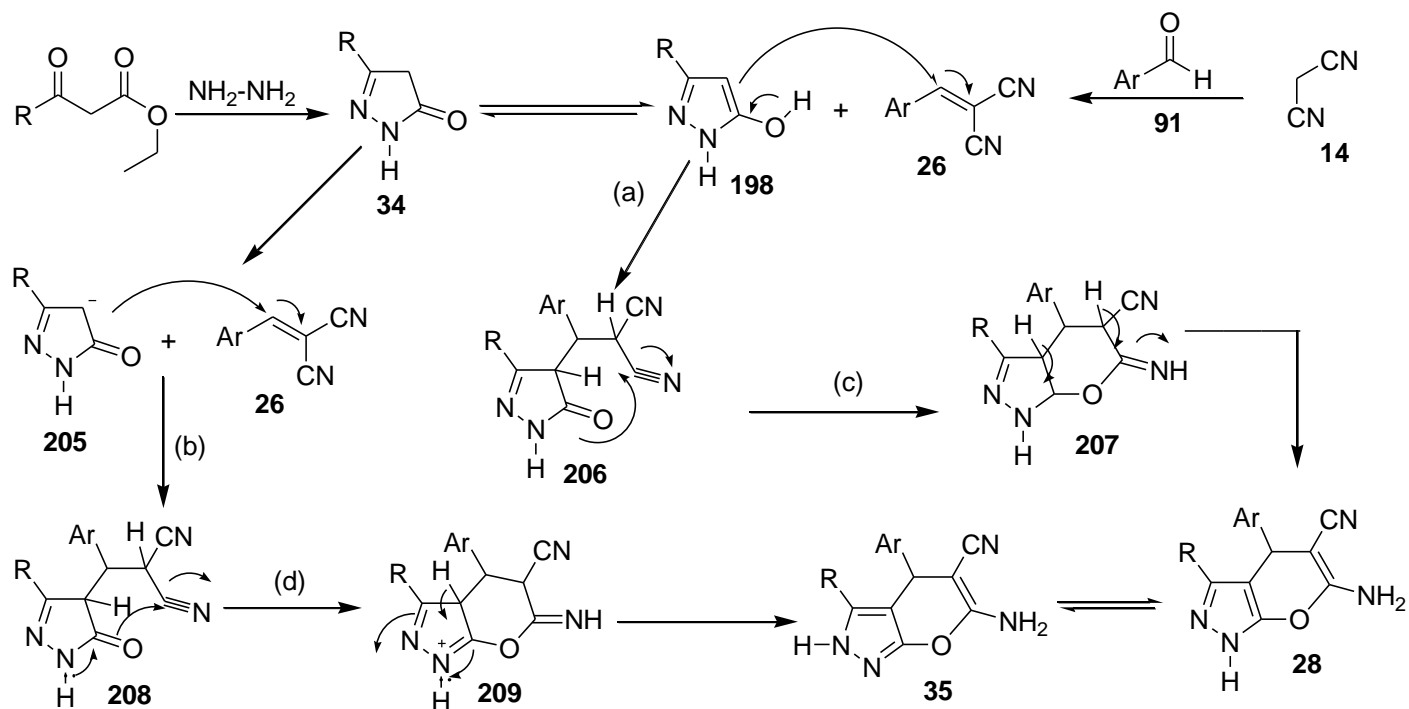


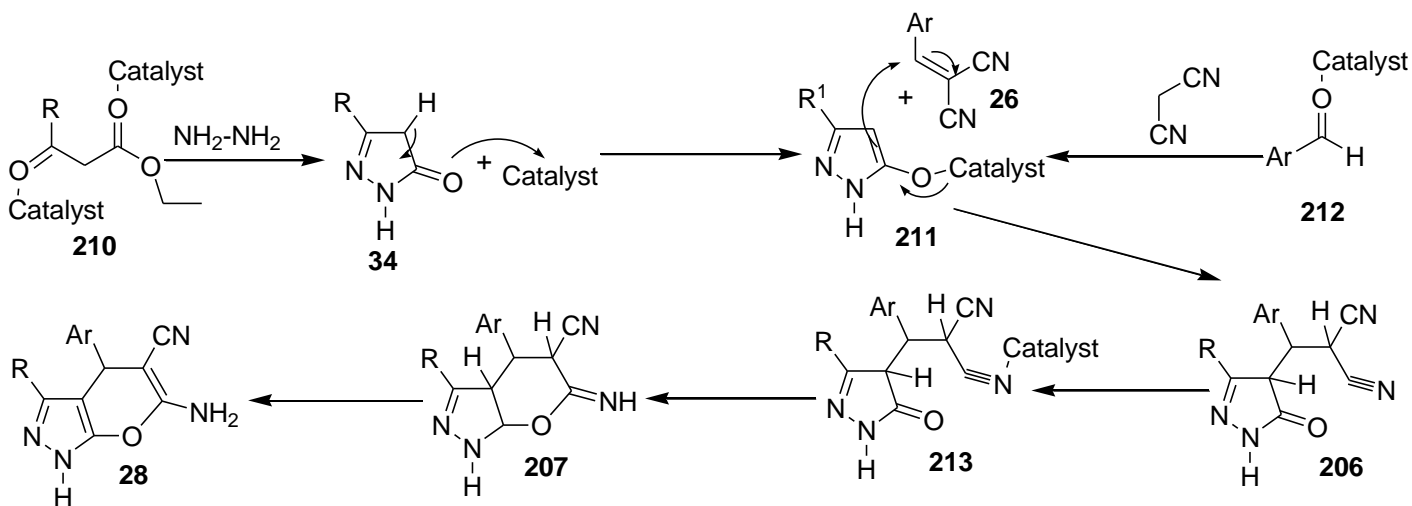
Figure 12

In four components synthesis, mostly reported mechanism involves the following steps (i) Reaction of hydrazine and the β-ketoester to form pyrazolone, which tautomerizes to the enol form **198**. For this purpose, various β-ketoesters such as ethyl acetoacetate, phenyl acetoacetate, ethyl 3-alkyl-3-oxopropanoate, ethyl isobutyroylacetoacetate and ethyl benzoylacetoacetate have been treated with hydrazine hydrate and phenylhydrazine (ii) Synthesis of ylidemalononitrile **26** by Knoevenagel condensation of aldehydes and malononitrile. Mono substituted aromatic aldehydes, disubstituted aromatic aldehydes, hetero-aromatic aldehydes, alicyclic aldehydes as well as ketones have been used (iii) Reaction of pyrazolone and ylidemalononitrile to form Michael adduct **206/208** either following path **a** or **b** (iv) Cyclization of Michael adduct involving attack of pyrazolone on nitrile group to form cyclic intermediate **207/209** by path **c** or **d** (v) Tautomerization of intermediate to form 4*H*-pyrano[2,3-*c*]pyrazoles **35/28**^{72, 74, 76, 80, 83, 84, 86, 92, 94, 95, 97} (Scheme 64).



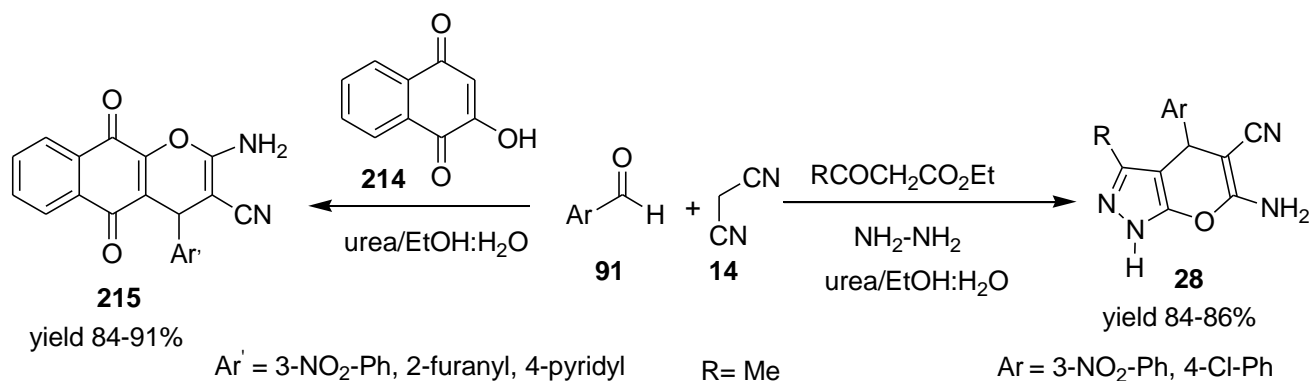
Scheme 64. Catalyst free synthesis of pyranopyrazole.

Another proposed mechanism involves binding of carbonyl oxygen with metals of catalyst such as PhB(OH)₂,⁸¹ MgO,⁸⁵ ZrO,⁸⁷ mixed ligand [Ni(L)(mimi)],⁹⁰ or with hydrogen of silica gel⁹¹ to promote the reaction. Afterwards reaction proceeded according to the first mechanism (Scheme 65).



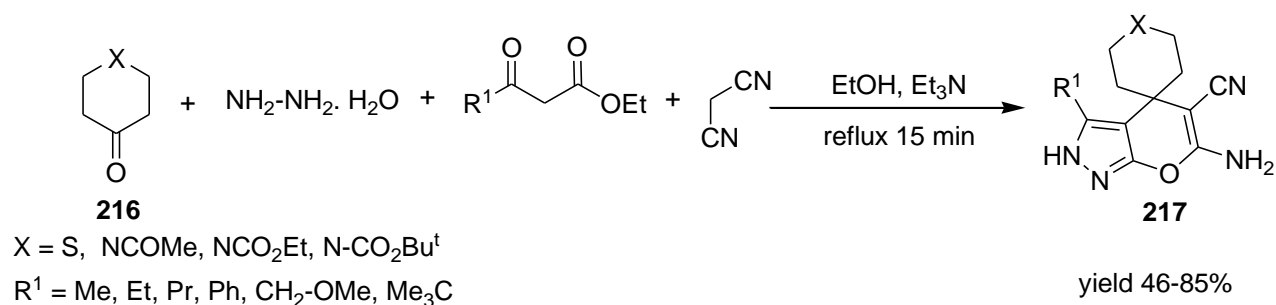
Scheme 65. Catalyst-initiated synthesis of pyranopyrazole.

Brahmachari and Banerjee prepared pyrano[2,3-c]pyrazoles (**28**) and various pyran-annulated heterocycles **215** using urea (10 mol%) in water/ethanol (1:1) mixture (Scheme 66).⁹⁸



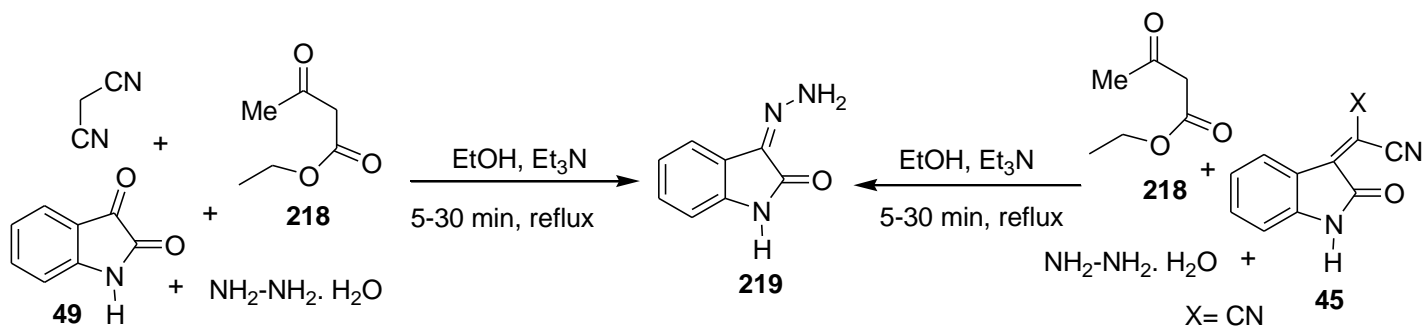
Scheme 66

Litvinov and co-workers successfully carried out regioselective synthesis in boiling ethanol containing triethylamine for electron withdrawing/donating substituted aldehydes, naphthaldehyde, hetero-aromatic aldehydes, *N*-substituted piperidin-4-one, tetrahydrothiopyran-4-one, isatins and other saturated cyclic ketones but, failed for pyvaloylacetic ester because of the steric constraints (Scheme 67).⁹⁹



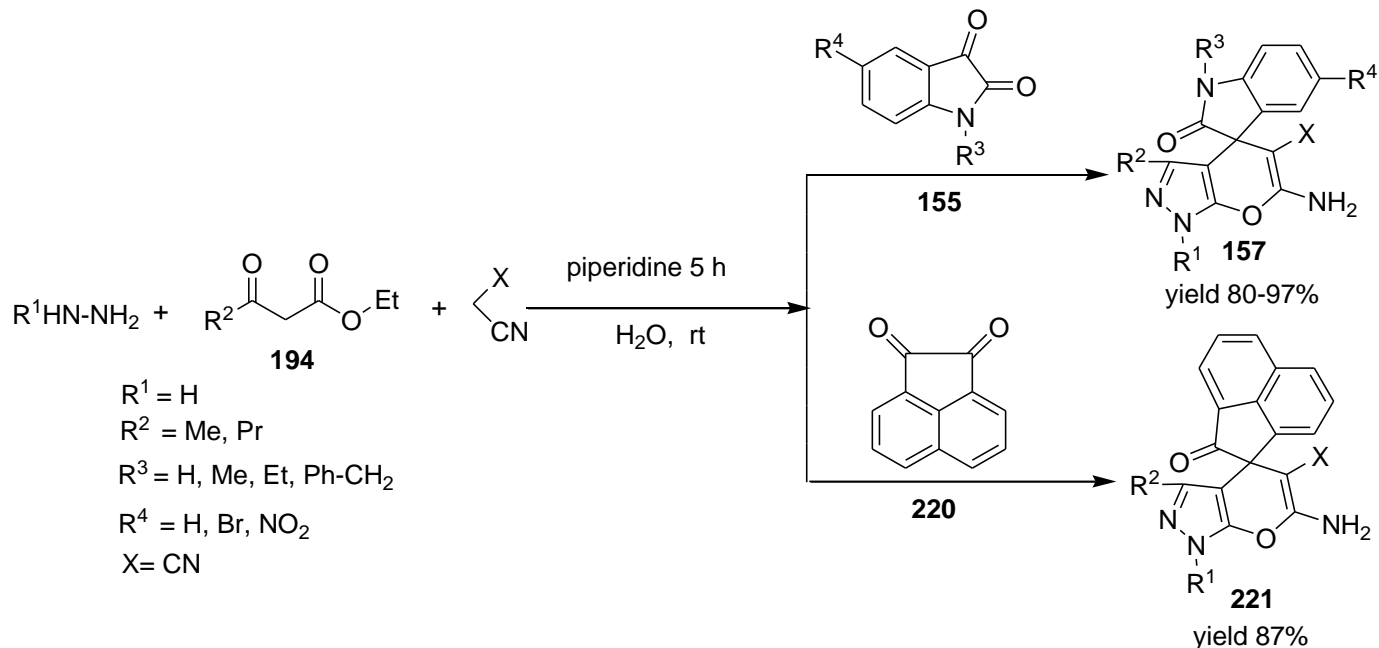
Scheme 67

Sequence of reactants was found important for pyranopyrazoles synthesis as isatin monohydrazone **219** is formed by adding all four reactants or three reactants (oxindole, hydrazine hydrate and β -ketoesters) simultaneously (Scheme 68).⁹⁹

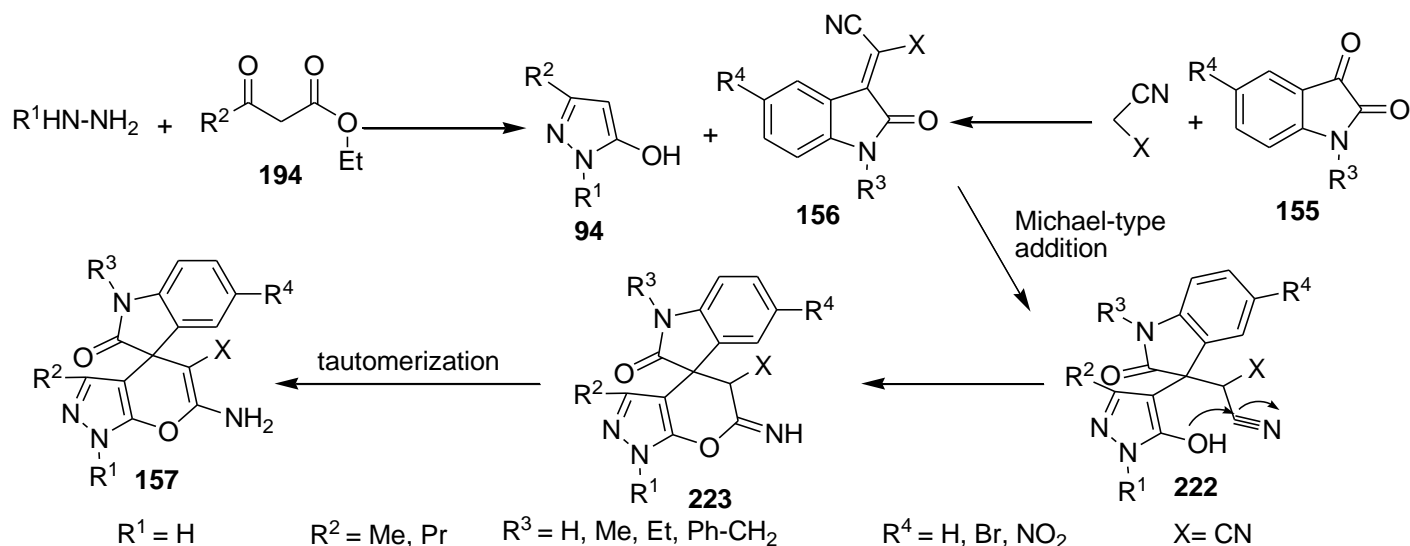


Scheme 68

Ahadi and co-workers allowed malononitrile, hydrazine hydrate, β -ketoesters to react with isatin and acenaphthylene-1,2-dione (**220**) in water containing piperidine to get spiroindoline and acenaphthylene pyranopyrazoles **157**, **221** (Scheme 69).¹⁰⁰ Reaction mechanism was assumed to involve initial synthesis of pyrazolone and alkene as intermediates followed by Michael addition to get **222** which tautomerize to final product (Scheme 70). Synthesized compounds showed good antibacterial activity.



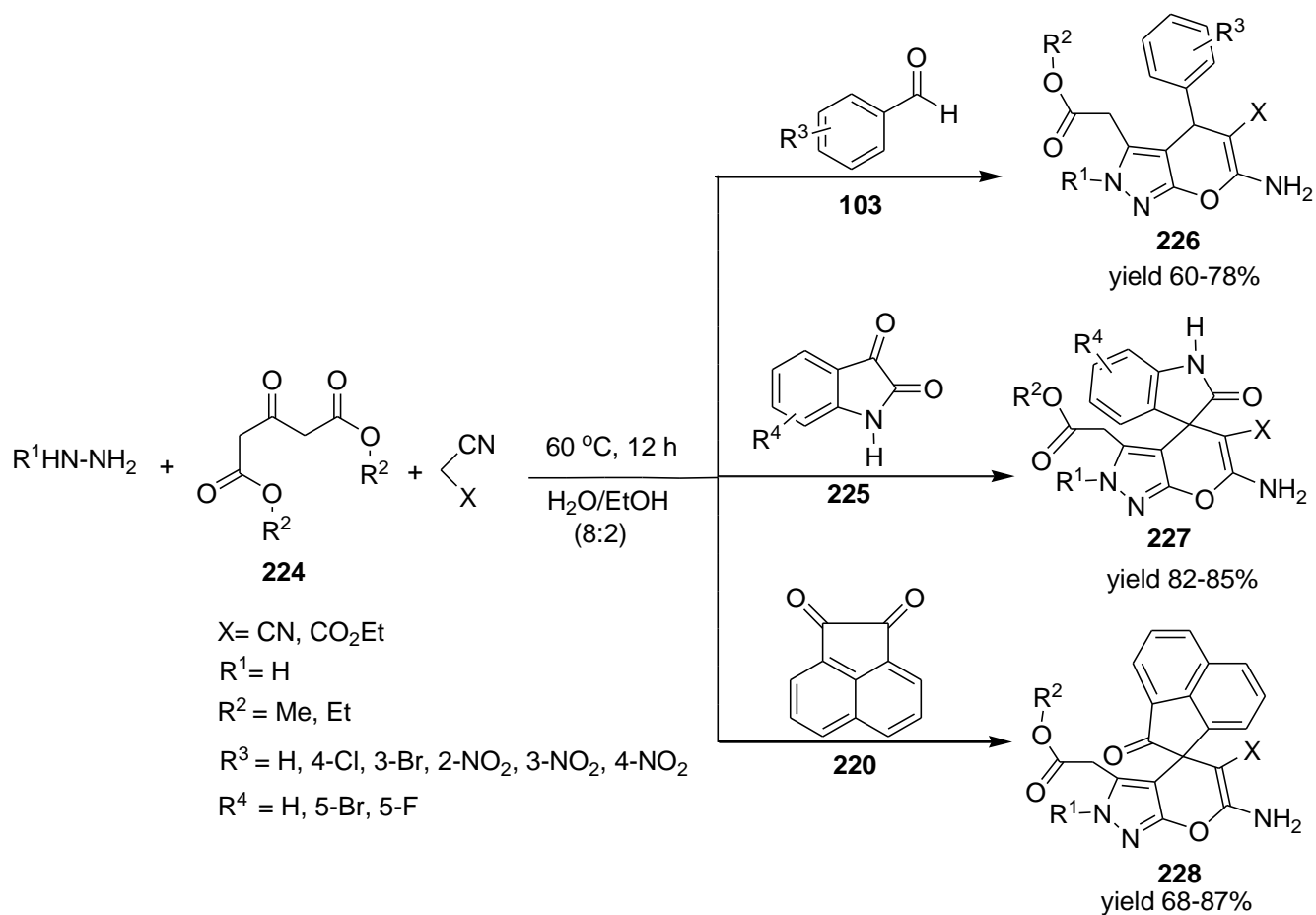
Scheme 69



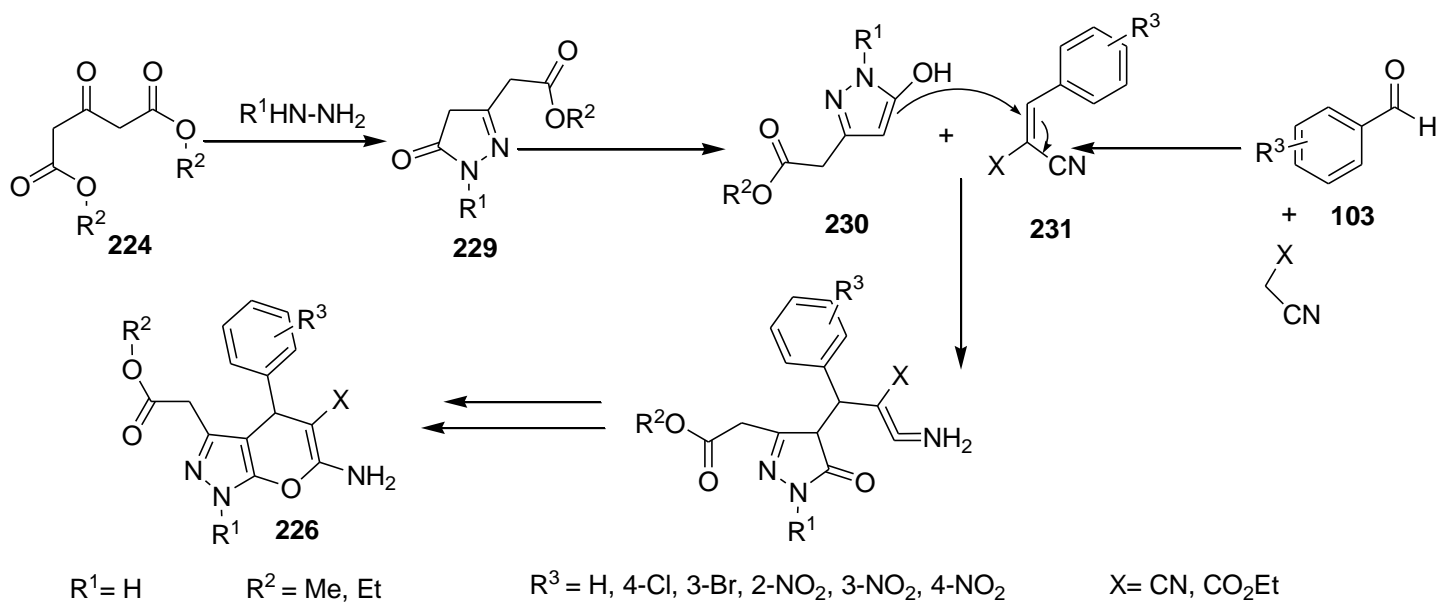
Scheme 70

Koohshari and co workers carried out regio- and chemio-selective synthesis of ethyl acetate bearing pyranopyrazoles in water/ethanol (8:2) without any catalyst at temperature range of 25-82 °C.¹⁰¹ Different dialkyl 3-oxopentanedioate (**224**) and carbonyl compound such as aldehydes, isatin and acenaphthenequinone have been applied to obtain a variety of pyranopyrazoles **226-228** (Scheme 71). The reaction mechanism for

synthesis of **226** was presented and assumed to involve formation of various intermediates **229-232** (Scheme 72).

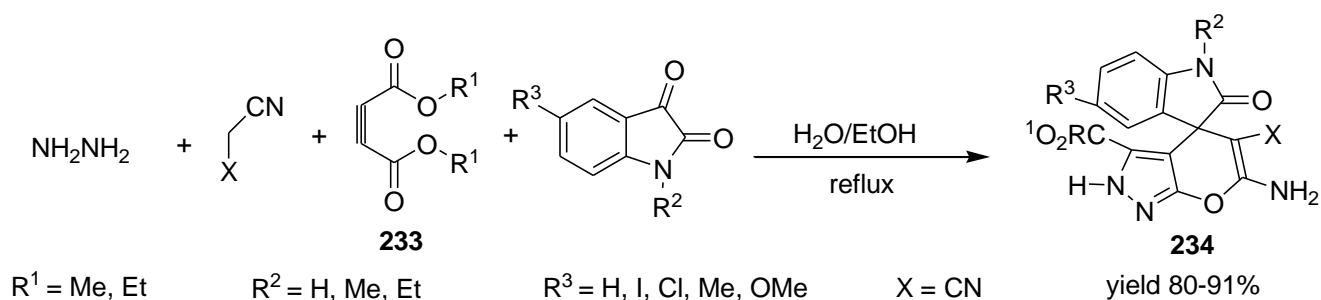


Scheme 71



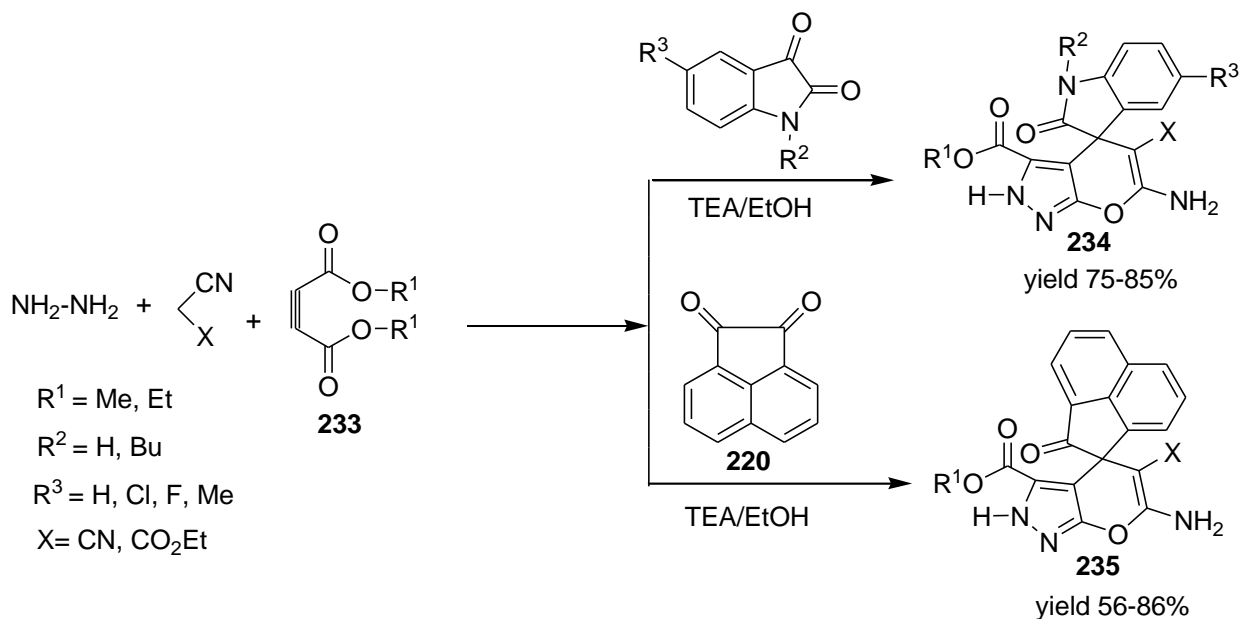
Scheme 72

Pore *et al.* used acetylenic esters **233** instead of β -ketoesters in water/ethanol mixture at reflux temperature to desire indolinepyranopyrazole **234**.¹⁰² The reaction protocol worked for isatin, 5-substituted isatin, *N*-substituted isatin, diethyl acetylenedicarboxylate (DEAD) and dimethyl acetylenedicarboxylate (DMAD) (Scheme 73). Reactivity of isatin possessing electron donating or withdrawing substituents did not show any significant difference, but product **234** obtained by only adding reactants in following sequence (i) hydrazine hydrate (ii) acetylenic ester (iii) solvent (iv) isatin (v) malononitrile. The reaction mechanism involves fast and exothermic reaction of DEAD/ DMAD with malononitrile to form ethoxy pyrazolone other reaction steps are similar.



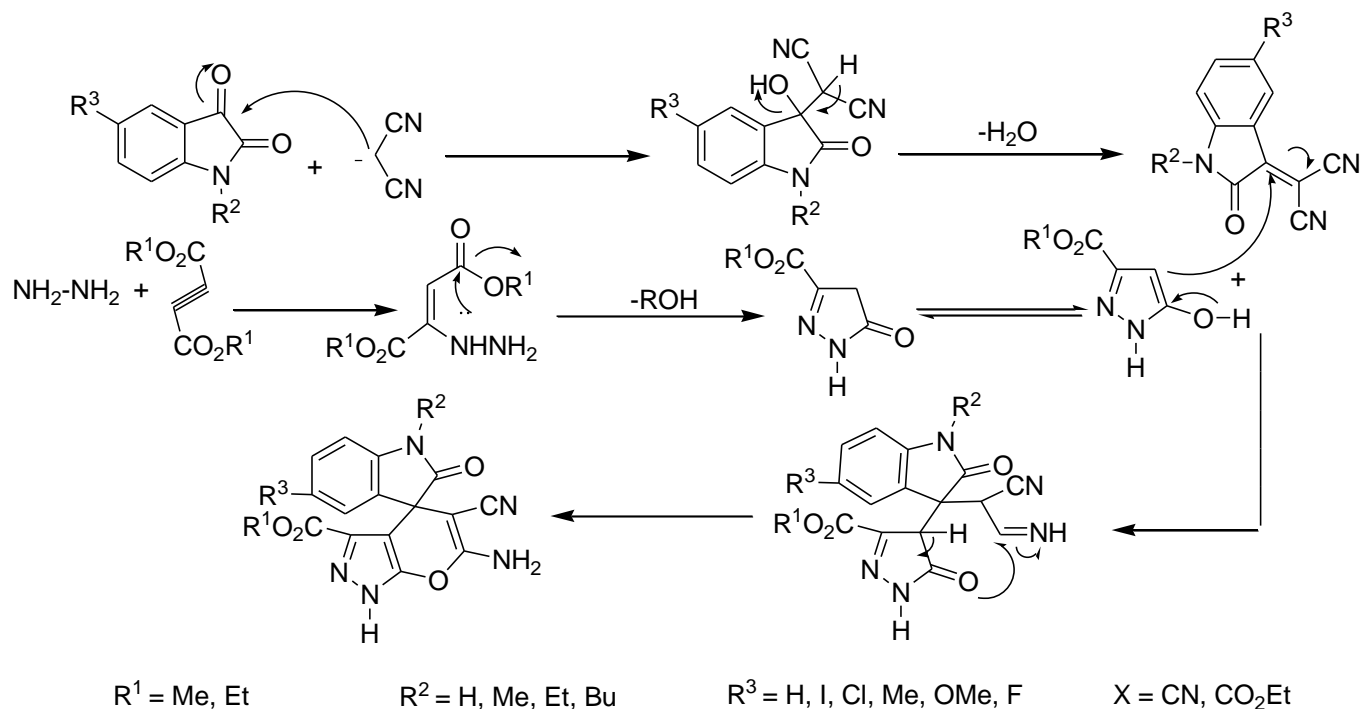
Scheme 73

Similarly, Wang and co-workers prepared spiroarylpyranopyrazoles in ethanol solvent containing triethylamine (Scheme 74).¹⁰³ Structures were confirmed by X-ray.



Scheme 74

The mechanism of both reactions is summarized and represented below^{102, 103} (Scheme 75).



Scheme 75

Meglumine (10 mol%) in ethanol/water mixture was used as catalyst for the reaction of carbonyl compounds such as aldehydes, ketone, isatin or acenaphthylene-1,2-dione, to get pyranopyrazoles **28**, **236-238** (Figure 13).¹⁰⁴

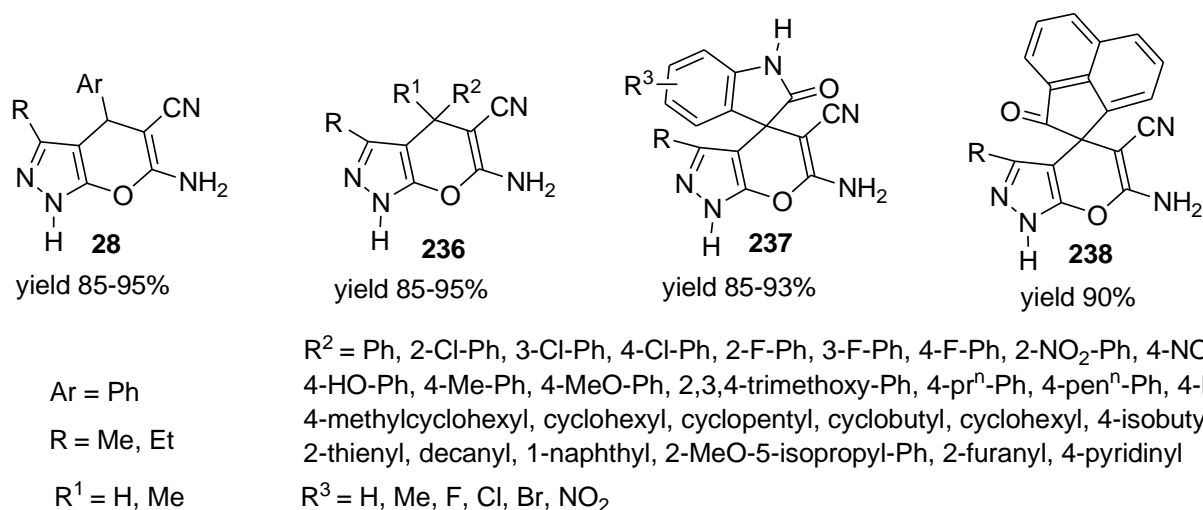
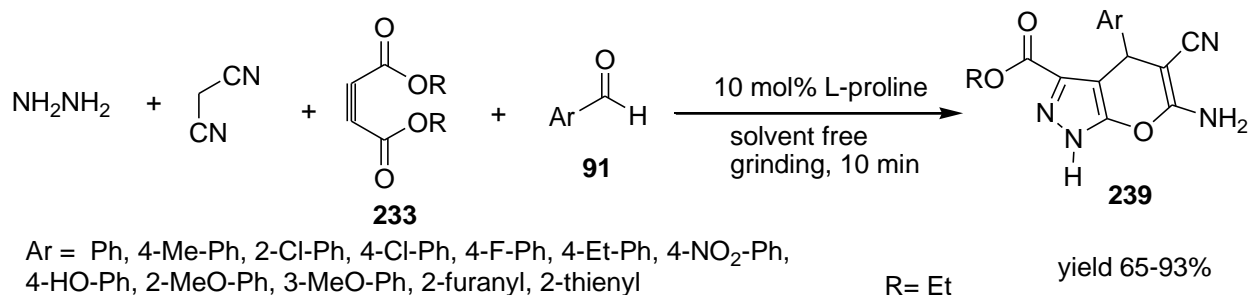


Figure 13

Ambethkar and co-workers ground reactants together in a pestle mortar using L-proline (10 mol%) as the catalyst, aryl aldehydes with the electron withdrawing groups gave better yields (Scheme 76).¹⁰⁵ Compounds **239** were tested for *in vitro* antioxidant and antimicrobial activities.



Scheme 76

Zonouz and co-workers prepared pyranopyrazoles **240** without catalyst in water at 50-60 °C in 66-88 % yield¹⁰⁶ (Figure 14).

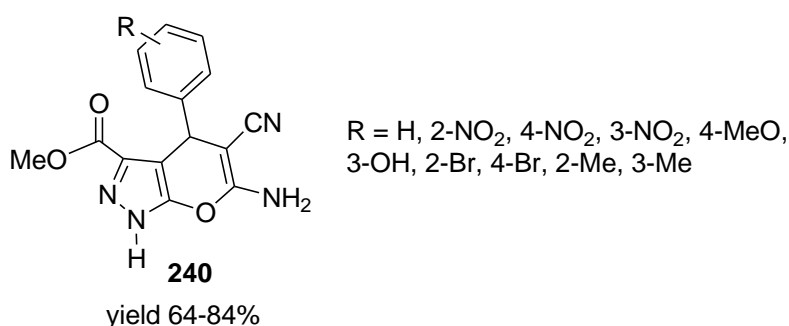


Figure 14

Triethylamine, piperidine or chitosan as catalysts were used to obtain pyranopyrazoles **241** at reflux temperature either by four components or reacting pyrazolone with benzylidemalononitrile.¹⁰⁷ NOE difference experiments confirmed the attachment of hydrogen to second nitrogen of pyrazole. An intermediate **242**, was obtained by replacing ethyl acetoacetate with ethyl cyanoacetate and pyrano[2,3-*c*]pyrazol-4-one (**243**) by refluxing pyrazolone with cyanoacetic acid and acetic anhydride (Figure 15).

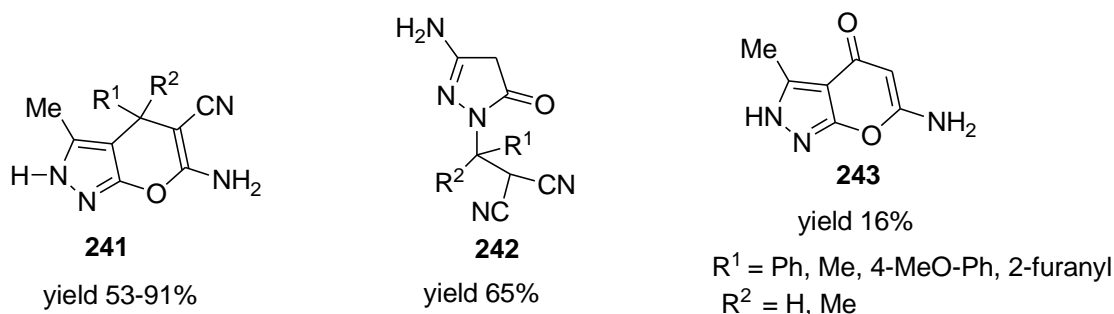
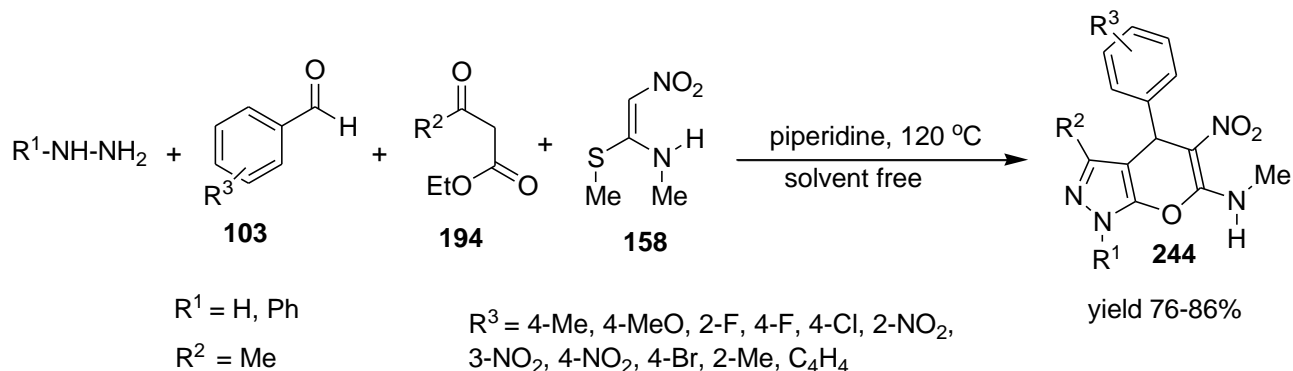


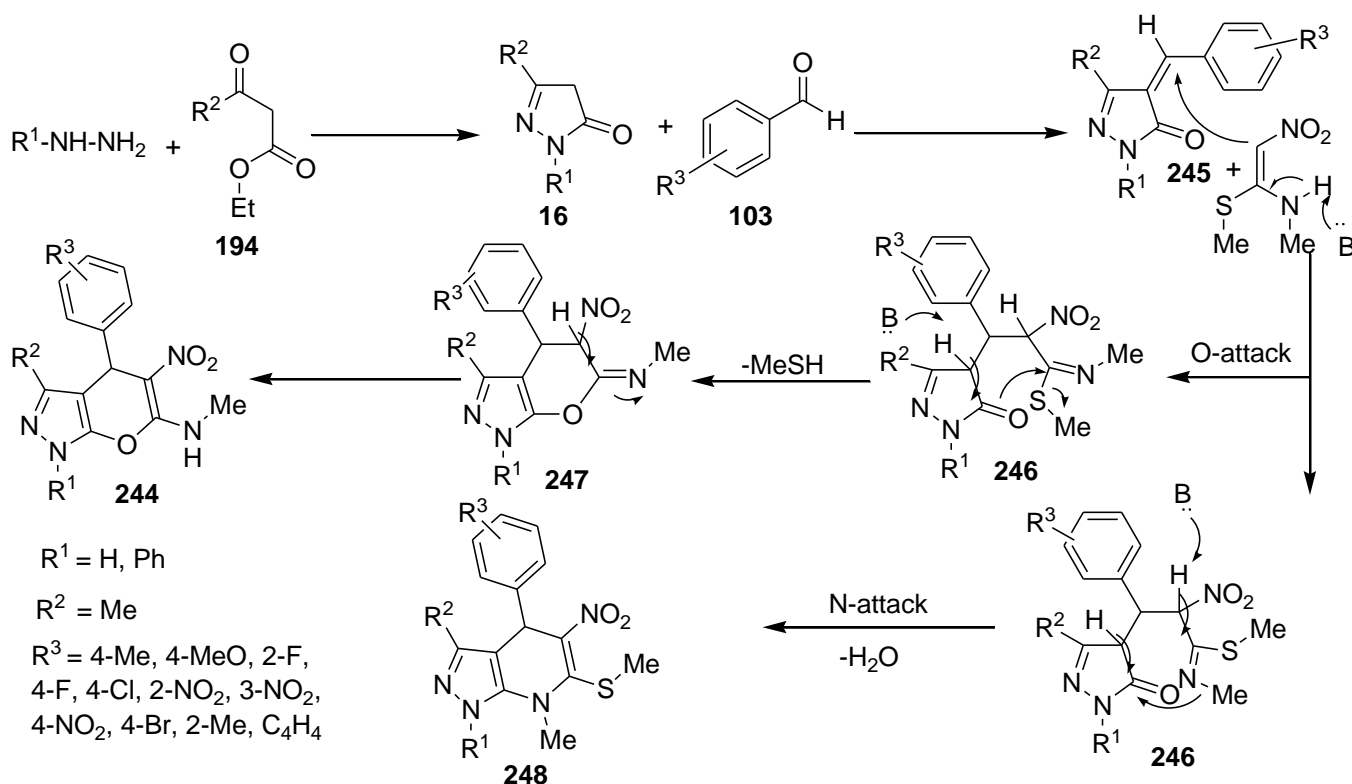
Figure 15

Jayabal and Paramasivan used a versatile synthon, *N*-methyl-1-(methylthio)-2-nitroethenamine (**158**) under solvent-free condition to get chemo- and regioselective 6-*N*-methylpyranopyrazoles **244** in 76-86% yields (Scheme 77).¹⁰⁸



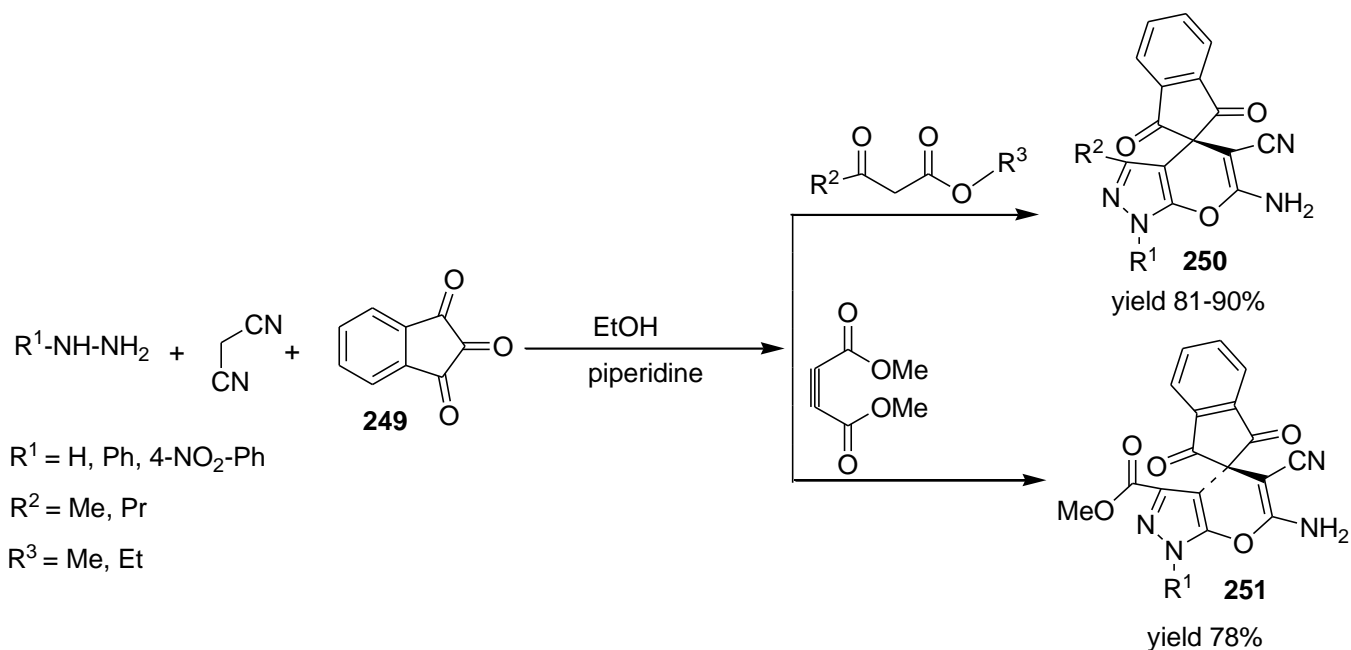
Scheme 77

The reaction mechanism is supposed to involve¹⁰⁸ (i) Synthesis of pyrazolone (ii) Knoevenagel condensation of pyrazolone with aldehydes to form the Michael acceptor **245** (iii) An immediate Michael-type addition of nitroketene-*N,S*-acetal to give intermediate **246** (iv) Cyclization by eliminating a molecule of methanethiol **247** (v) Tautomerization. It was also proposed that intermediate **246** may undergo *N*-attack and by eliminating a molecule of water to yield **248**, but this was not isolated (Scheme 78).



Scheme 78

Alizadeh and Bayat developed a concise and regioselective route for spiro[pyranopyrazoles] **250**, **251** by reaction of indane-1,2,3-trione (**249**), malononitrile, hydrazine derivatives with β -ketoesters and dimethyl acetylenedicarboxylate (Scheme 79).¹⁰⁹



Scheme 79

Reaction was found to be effective for a variety phenyl derivatives, however electron withdrawing groups at the 2-position, resulted in the formation of oxa-aza-[3.3.3]propellanes (**252**)¹⁰⁹ (Figure 16).

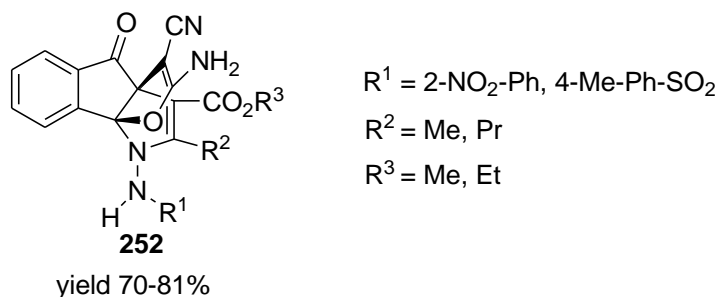
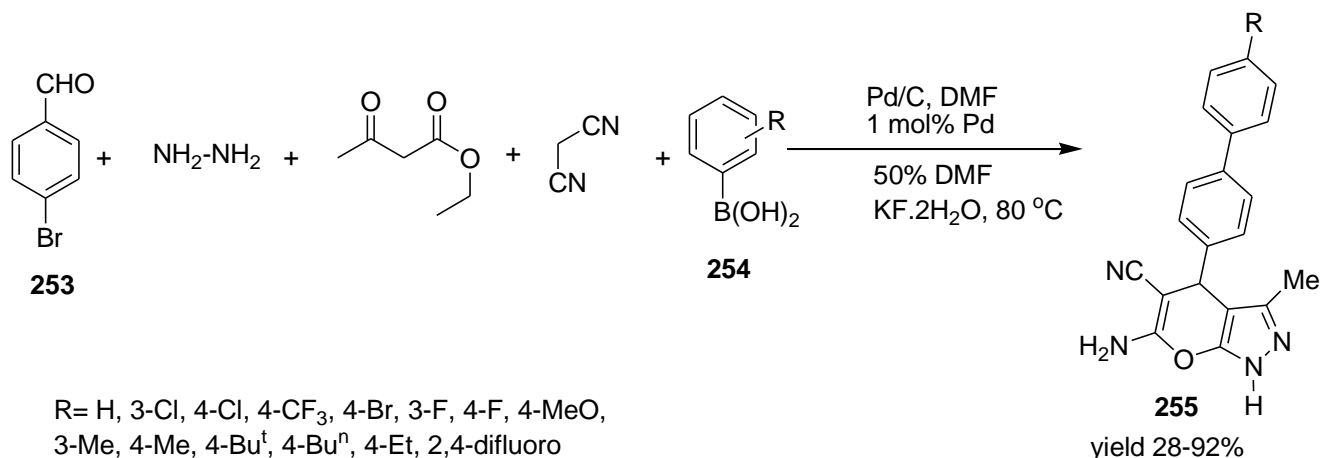


Figure 16

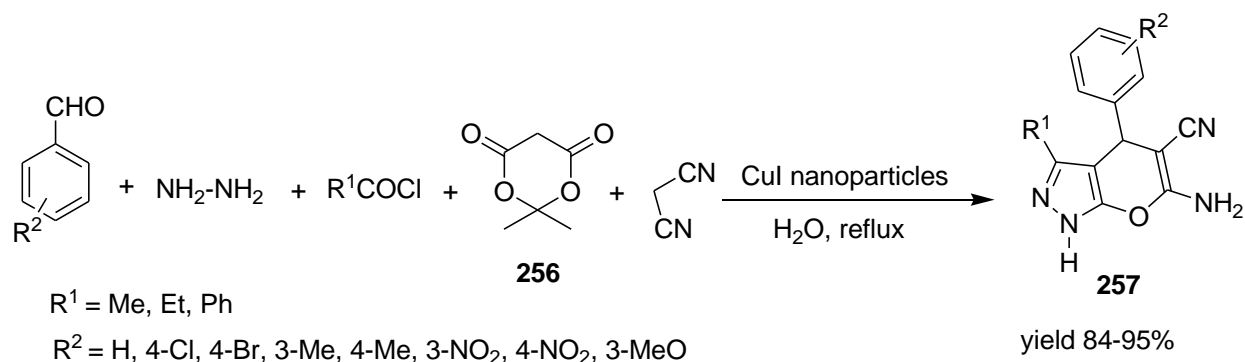
2.4 Five Component Synthesis

Lu and co-workers carried out one pot synthesis of pyranopyrazoles involving Suzuki coupling between 4-bromobenzaldehyde (**253**) and arylboronic acid (**254**) under dehalogenating effect of $\text{KF}\cdot 2\text{H}_2\text{O}$ in the presence of Pd/C at 80 °C.¹¹⁰ Firstly, 4-bromobenzaldehyde and arylboronic acid were added to form substituted biphenyl aldehydes later on, other reagents were added and allowed to react for 5-6 hr.



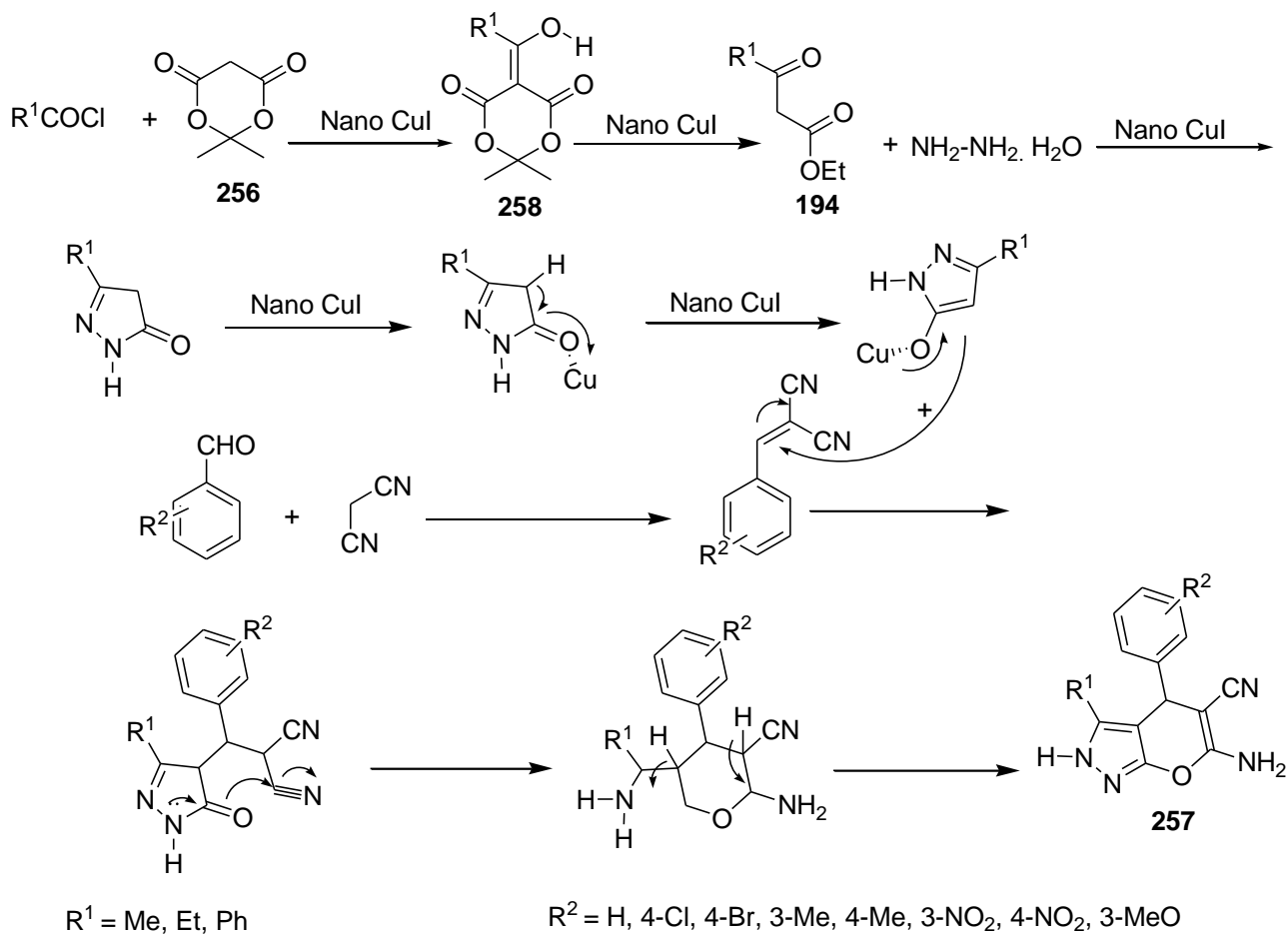
Scheme 80

Another five components synthesis involves a mixture of acid chlorides, Meldrum's acid (**256**), aromatic aldehydes, hydrazine hydrate and malononitrile in the presence of CuI nanoparticles.¹¹¹ Catalyst prepared by ultrasonic cleaning of CuSO₄ in HCl and characterized by SEM, XRD, EDAX analysis.



Scheme 81

The reaction mechanism was proposed to involve synthesis of β -ketoester in *situ* by nucleophilic substitution of Meldrum's acid to acetyl chloride.¹¹¹ Other steps include synthesis of pyrazolone, alkene and Michael adduct followed by cyclization and tautomerization (Scheme 82).



Scheme 82. Mechanism.

3. Biological Activities

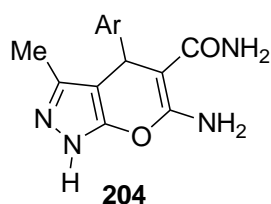
Pyranopyrazoles in general are biologically active and have remarkable antimicrobial^{53,58}, anticancer,⁴³ anti-inflammatory,^{23,53,112} analgesic, anticonvulsant, anti-platelet, vasodilator,³ antifungal,^{24,42,97} potential Chk1 inhibitors,^{113,114} herbicidal¹⁶ and molluscicidal properties.^{33,34} Moreover, pyranopyrazoles were found to be effective inhibitors to steel corrosion⁶ and as antioxidants for lubricant oil.⁵

Since these MCRs can lead to a variety of pyrano[2,3-*c*]pyrazoles by virtue of aryl and hetaryl aldehydes, hydrazines and malononitriles and other reactants, the researchers from time to time have subjected the novel synthesized compounds to diverse type of biological activities which may be summed up in the following:

Tetrahydroquinolines derivatives being biological active anti-HIV, antibacterial, antifungal, antimalarial, antitrypanosomal, antitumor, psychotropic, anti-allergic, anti-inflammatory, and estrogenic agents, were incorporated with pyranopyrazoles to obtain potential biologically active compounds **21-23**.¹⁵

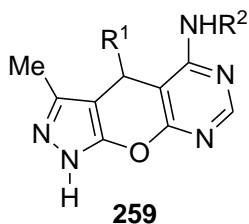
Taconi and co-workers prepared pyranopyrazoles **25** and screened for fungicidal, herbicidal and insecticidal activities.

Ismail and co-workers prepared benzamide based pyranopyrazoles **37** and screened for their anti-inflammatory and ulcerogenic activities. All compounds were found to be active but, compound **263** showed excellent anti-inflammatory and good prostaglandin inhibitory activity²³ (Figure 18).



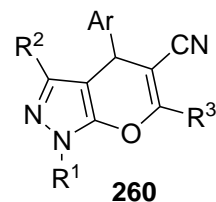
antibacterial and antifungal

Ar= 4-Cl-Ph, 3,4-dimethoxy-Ph,
2,3,4-trimethoxy-Ph, 3-HO-4-MeO-
Ph, 1H-indol-3-yl, 4-HO-3-MeO-Ph
2-Cl-6-Me-quinolin-3-yl



anti-inflammatory agent

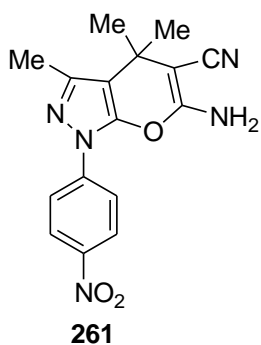
R¹ = 3,4-dichloro-Ph,
naphthyl, thienyl
R² = H, Me



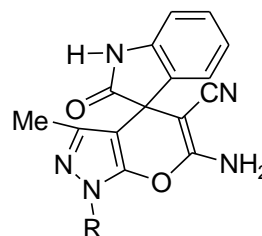
potential Chk1 inhibitors

R¹ = H, PhR² = Me, 1-methylimidazoleR³ = NH₂, ⁺NH₃

Ar = 4-MeO-Ph, 3,4-dihydroxy-Ph,
3,4-dimethoxy-Ph, 2-pyridinyl, C₅H₈N-Me



herbicidal agent



R = H, Ph

antibacterial

Figure 17

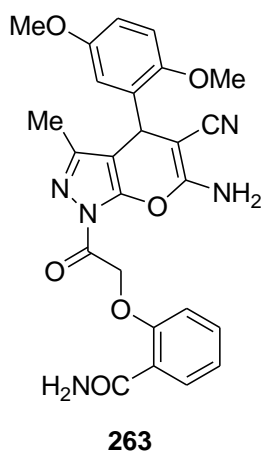


Figure 18

Some indole based pyranopyrazoles **39** were found to be active antibacterial, antifungal and anti-oxidant agents.²⁴

4-Hetaryl pyranopyrazoles **15** exhibited moderate molluscicidal activity against *Biomphalaria alexandrina* snails.^{33,34} while other derivatives of **15** showed antibacterial, antifungal, anti-inflammatory and anticancer activity against liver carcinoma cells.^{38,64,43}

Compounds **110-113** were found active antibacterial. Moreover, derivatives containing halo group at 2nd position of substituent exhibited both antibacterial and antifungal activities.⁴⁶

Pyranopyrazoles **123** showed biological, anti-inflammatory, analgesic, anticonvulsant activities and were found potential antimicrobial agent. It was observed that presence of halo atoms increased biological action.⁵³ Pyranopyrazoles **136** were tested for antibacterial activity against eight human pathogens and some were found active more than the standard drugs.⁵⁵

Spiropyrano[2,3-c]pyrazoles **152** exhibited moderate antimicrobial activity against *Escherichia coli* and *staphylococcus aureus*.⁵⁸

Derivatives of compounds **28** showed moderate inhibition effect on bacteria.⁵⁹

Various derivatives of pyranopyrazoles **175-177** showed antibacterial, anti-inflammatory and cytotoxicity.⁶⁴

Pyrano[2,3-c]pyrazoles **192, 193** exhibited moderate antibacterial activity.⁶⁸

Synthesized compounds **157, 221** showed good antibacterial activity.¹⁰⁰

Compounds **239** were tested for *in vitro* antioxidant and antimicrobial activities and found active agents.¹⁰⁵

4. Conclusions

This review summarizes the synthesis of pyrano[2,3-c]pyrazoles which, either have a hydrogen atom at 4-position or condensed spiro group. Synthesis focuses on two component or multi-component reactions including three, four and/or five reactants. Reactions conditions are variable including green approach, nanoparticulates, heteropolyacid, reflux temperature, room temperature, organic catalyst, microwave and ultrasonic irradiations. Most common reagents for synthesis are pyrazolone, benzylide, hydrazine, β -ketoesters, malononitrile, aldehydes and ketones. Various substituted phenyl, polynuclear naphthalene, anthracene as well as number of heterocyclic moiety such as furan, thiophene, indole, tetrahydroquinoline have been incorporated at 4-position. Most of the pyrano[2,3-c]pyrazoles have amino and cyano groups at sixth and fifth position respectively, but some shows variations and have hydrogen, aryl or other group. Compounds are reported as antibacterial, antifungal, anti-oxidant, anti-inflammatory, anti-ulcerogenic, anti-analgesic, anticonvulsant and insecticidal agents. X-Ray studies done to confirm the structure and position of hydrogen atom in the pyrazolone ring.

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