Recent developments in aminopyrazole chemistry

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Abstract
Recently reported syntheses of 3(5)-aminopyrazoles, 4-aminopyrazoles, and 1-aminopyrazoles as well as of diaminopyrazoles and their general pattern of reactivity towards mono- and bidentate electrophiles have been surveyed. Emphasis has also been laid on techniques for ascertaining the site selectivity in reactions with electrophiles, including single crystal X-ray structure analysis, ^{1}H-^{15}N HMBC, and NOE intensity difference experiments as well as other modern 2D NMR techniques. Some thermally induced cycloadditions have also been treated.

Keywords: 3(5)-Aminopyrazoles, diaminopyrazoles, pyrazolo[1,5-*a*]pyrimidines, pyrazolo[3,4-*b*]pyridines, pyrazoldiazonium salts, structure elucidation

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1. Introduction

The chemistry of aminopyrazoles has been extensively investigated in the past.[1] The considerable biological and medicinal activities of pyrazoles[2] and azolopyrazoles,[3] for which aminopyrazoles are preferred precursors, have stimulated these investigations. Interest in aminopyrazole synthesis and chemistry has recently been revived.[4-8] The established activity of Zaleplon (**1**),[9] Viagra (**2**)[10] as well as Allopurinol (**3**)[11] is surely behind this interest (Figure 1).
Chemistry of 3(5)-aminopyrazoles has been reviewed in 1983 by Elnagdi *et al*.[12] and more recently in 2004 by El-Taweel and Abu Elmaati.[13] Significant progress occurred since the publication of these articles. We surveyed these developments and also chemistry of 4-aminopyrazoles, and 1-aminopyrazoles as well as chemistry of diaminopyrazoles. These topics to our knowledge have not been surveyed.

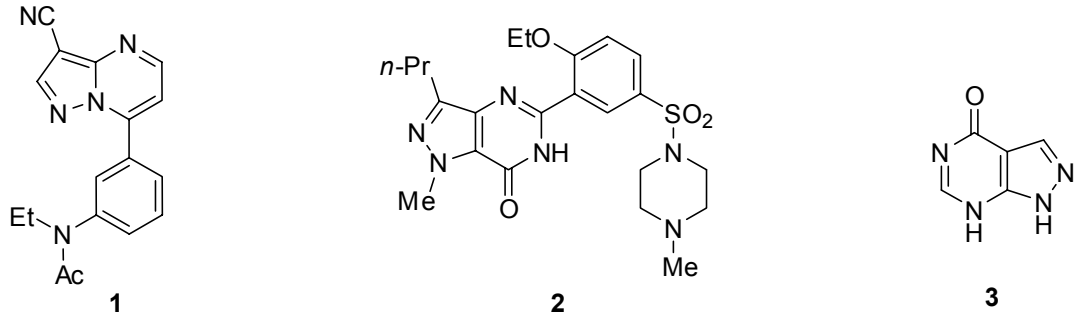


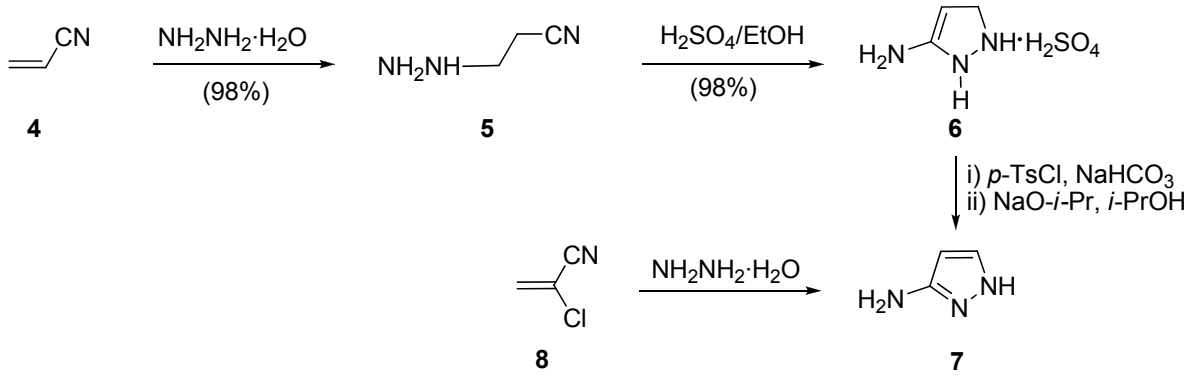
Figure 1. Structure of Zaleplon (**1**), Viagra (**2**) and Allopurinol (**3**).

2. Synthesis of 3(5)-aminopyrazoles

These are generally obtained from either reaction of hydrazines with α,*β*-unsaturated nitriles,[14-16] 3-oxoalkenonitriles and hydrazines[17-20] or reaction of hydrazonoyl halides with active methylenenitriles.[21] In addition, several other novel routes have been recently reported.

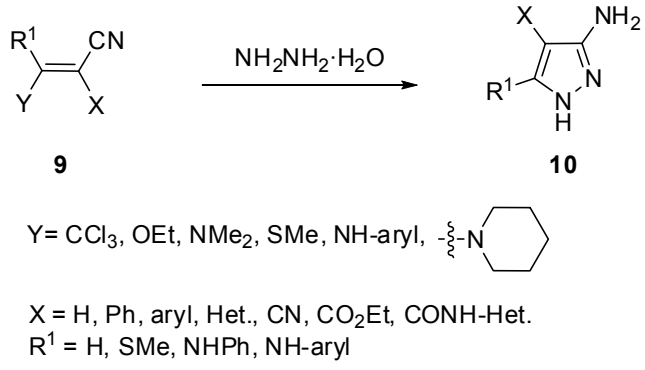
2.1 Reactions of α,*β*-unsaturated nitriles with hydrazines

This is the most extensively utilized route to 3(5)-aminopyrazoles. Thus aminopyrazole itself was prepared *via* reacting acrylonitrile (**4**) with hydrazine hydrate and subsequent cyclization of **5** to yield **6** and dehydrogenation of the latter affording **7**.[22] Compound **7** was directly obtained from reaction **8** and hydrazine (Scheme 1).[23]



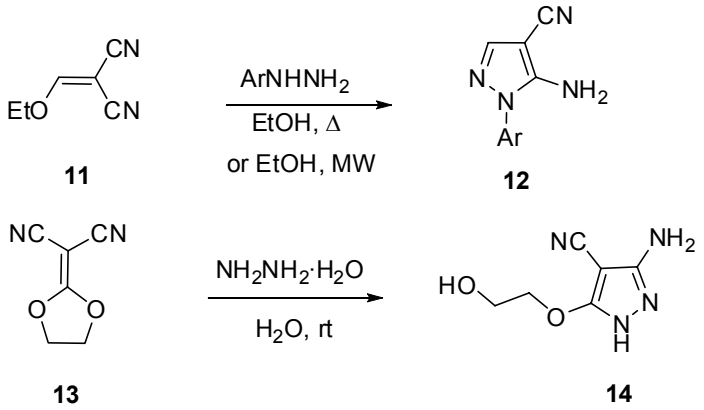
Scheme 1

Similar syntheses have been extensively employed. Thus, reacting **9** with hydrazine hydrate afforded **10**[23-26] (Scheme 2). Recently, Quiroga *et al.*[26c] have described the synthesis of 5-amino-1-aroylpyrazoles which were prepared from *β*-aminocrotononitrile with compounds containing the hydrazine moiety (Z–NHNH$_2$, Z = $C_6H_5C(O)$, aryl-C(O), $H_2NC(S)$) in the presence of sodium acetate in 80-97% yields.



Scheme 2

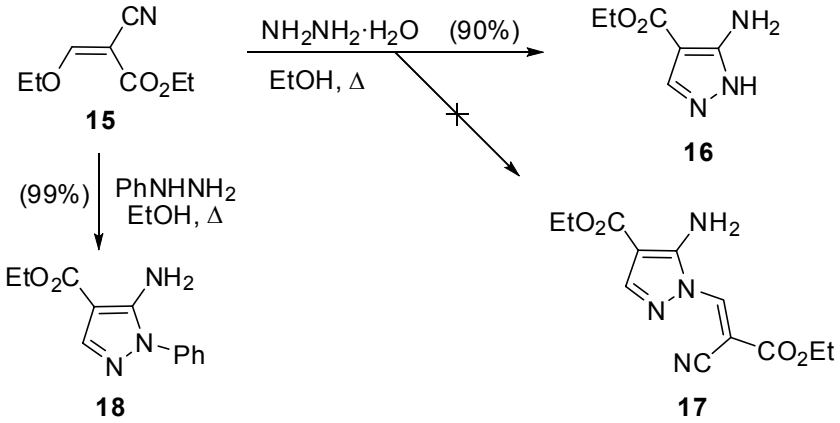
Recently, the reaction of arylhydrazines with **11** has been reported to afford **12** in 40-70% yields under thermal conditions and in 42-77% yields under microwave irradiation,[27] while **13** produced **14** on reaction with hydrazine hydrate (Scheme 3).[28]



Ar = Ph, 4-FC_6H_4, 2-ClC_6H_4, 2,4-$F_2C_6H_3$, 4-MeOC_6H_4, 2,4-$Me_2C_6H_3$, 3,5-$Me_2C_6H_3$, 2,6-Cl_2-4-$CF_3C_6H_2$

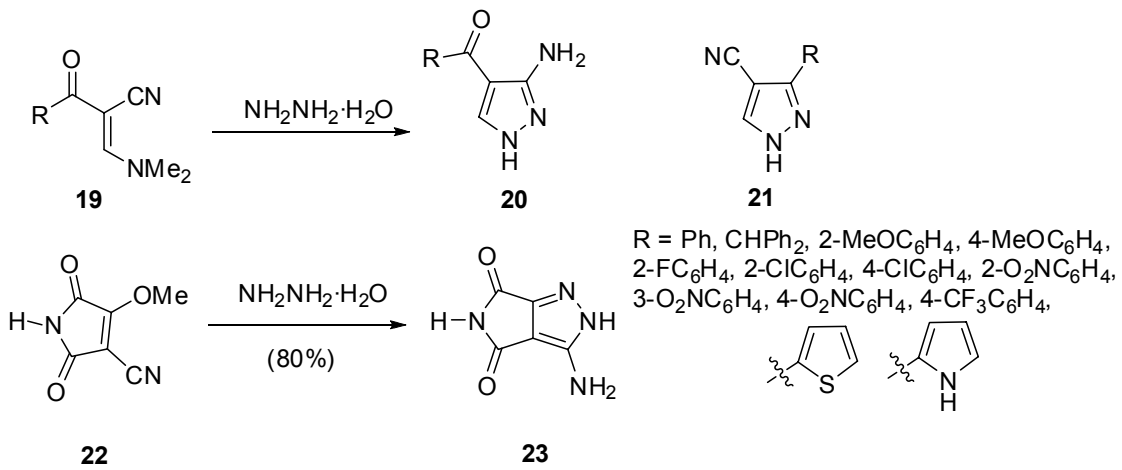
Scheme 3

Reacting **15** with hydrazine hydrate at 75 °C for 2 h afforded **16**.[29a] In old literature,[29b] **17** was the only isolated product. Also **15** reacted with phenylhydrazine to yield **18** (Scheme 4).[30]



Scheme 4

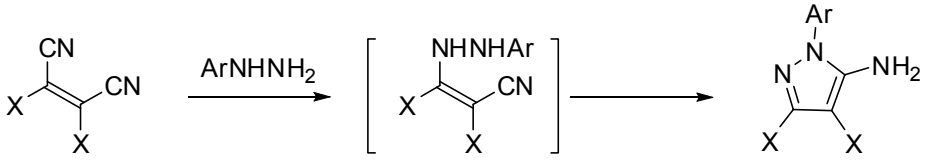
2-Aroyl-3-(dimethylamino)acrylonitrile **19** has been reported to react with hydrazine hydrate to yield either **20** or **21** or a mixture of both depending on substitution pattern.[31-33] When reacted with aminoguanidine nitrate, however, **19** (R = 4-fluorophenyl) afforded only **20** in 62% yield.[9] The reaction of **22** with hydrazine hydrate afforded the aminopyrolopyrazole **23** (Scheme 5).[34]



19 **20** **21** **22** **23**

Scheme 5

Treatment of diethyl 2,3-dicyanomaleate (**24a**) with arylhydrazines afforded **26a** *via* cyclization of initially formed arylhydrazone derivative **25a**.[35] This was further extended to 5-aminopyrazole-3,4-dicarbonitriles **26b** from **24b** and arylhydrazines (Scheme 6).[36]



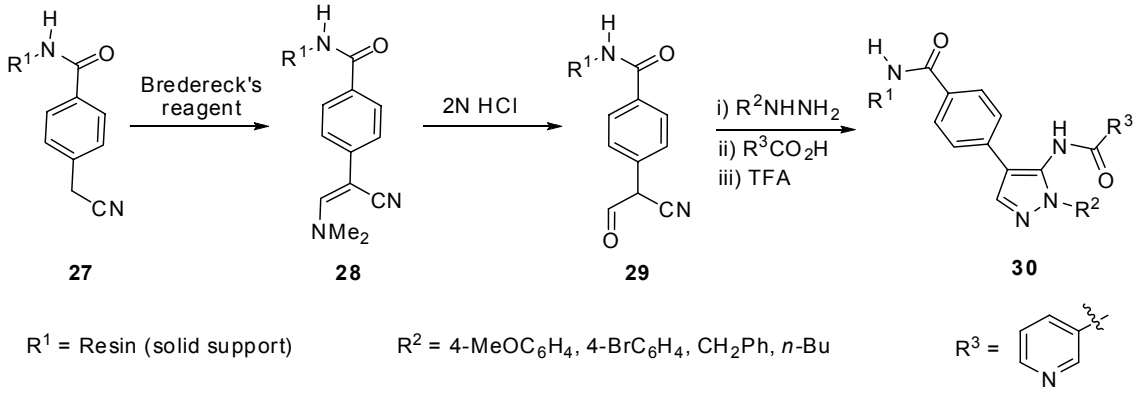
24a, X = CO_2Et
b, X = CN

25a,**b** **26a**,**b**

Ar = 4-FC_6H_4, 4-BrC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4,6-$Cl_3C_6H_2$

Scheme 6

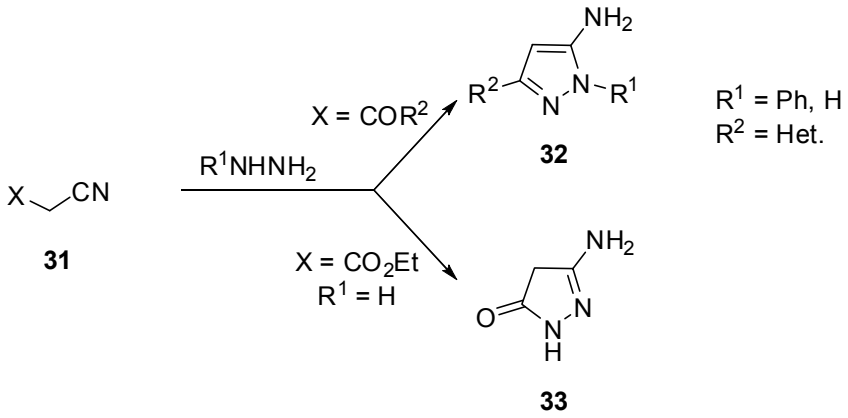
A new synthesis of 5-aminopyrazoles on a solid support *via in situ* generation of resin bound aldehyde nitriles has been described. Thus, treatment of **27** with Bredereck's reagent afforded **28** that was hydrolysed in 2N HCl to yield **29**. The latter reacted with hydrazines in the presence of organic acids in THF to yield **30** (Scheme 7).[37]



Scheme 7

2.2 Reactions of hydrazines with 3-oxo-alkanenitriles

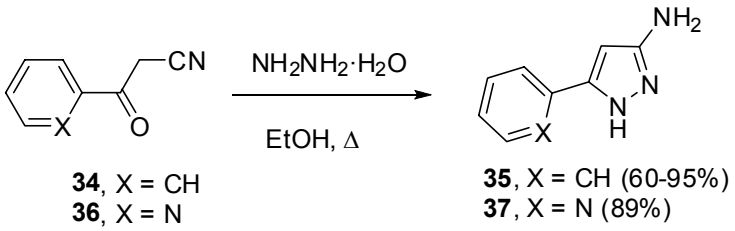
This is another general and efficient route to 3(5)-aminopyrazoles. Thus the reaction of **31** (X = COR, CO_2R) led to the formation of aminopyrazoles **32** and aminopyrazolone (**33**) (Scheme 8).[38,39]



Scheme 8

Recently, compounds **35** and **37** were synthesized by the reaction of **34** and **36** with hydrazine hydrate (Scheme 9).[40,41]

The reaction of 3-oxoalkanenitriles with tosylhydrazines also gave 1-tosyl-3-substituted pyrazole amines that were deprotected by brief treatment with NaOEt in EtOH/DMSO at 45 ^oC.[42]

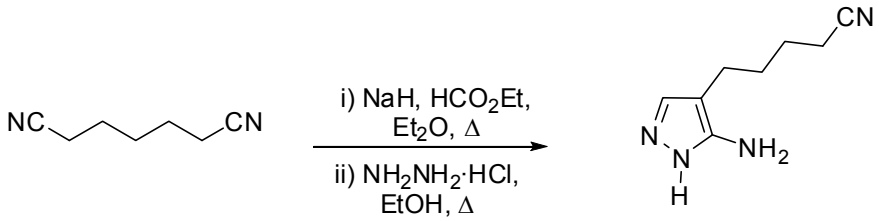


34, X = CH
36, X = N

35, X = CH (60-95%)
37, X = N (89%)

Scheme 9

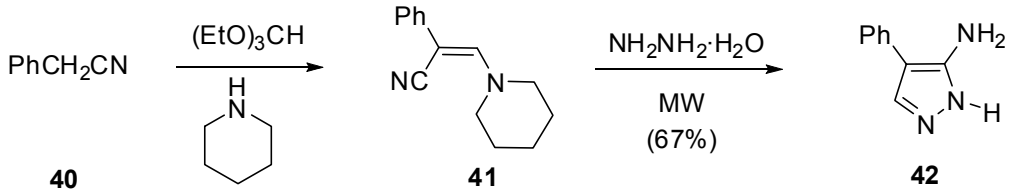
Recently, heptanedinitrile (**38**) was condensed with ethyl formate in presence of sodium hydride and the soformed formyl derivative was then reacted with hydrazine hydrate to yield **39** (Scheme 10).[43]



38 **39**

Scheme 10

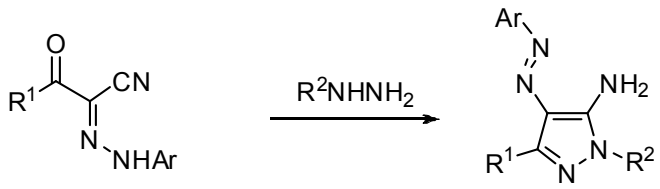
The reaction of benzylcyanide (**40**) with triethylorthoformate and piperidine has been reported to yield **41** which reacted with hydrazine hydrate in a microwave oven to yield **42** (Scheme 11).[44]



40 **41** **42**

Scheme 11

4-Arylazopyrazol-5-amines **44** were generally prepared from the reaction of corresponding arylhydrazone **43** and hydrazines. These were extensively investigated as dyes and a variety of derivatives were thus prepared (Scheme 12).[18,44,45]

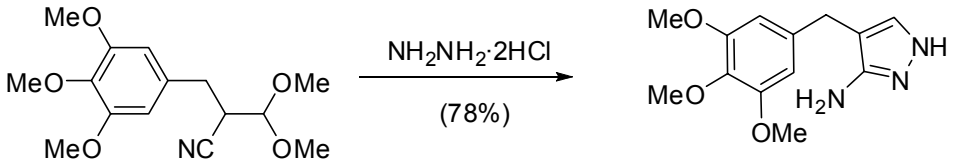


43 **44**

R^1 = H, Et, Ph; R^2 = H, aryl; Ar = Ph, aryl

Scheme 12

Reacting **45** with hydrazine hydrochloride afforded **46** which was used as a drug intermediate (Scheme 13).[46]

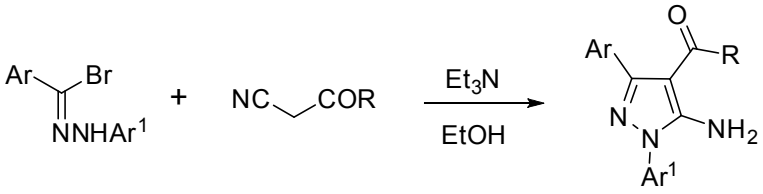


45 **46**

Scheme 13

2.3 Synthesis from substituted hydrazones

The reaction of hydrazonoyl halides **47** with active methylene nitriles is an established route to 3(5)-aminopyrazole.[21] A recent example was reported in reaction of **47** with benzoylacetonitrile **48** to yield **49** (Scheme 14).[47]

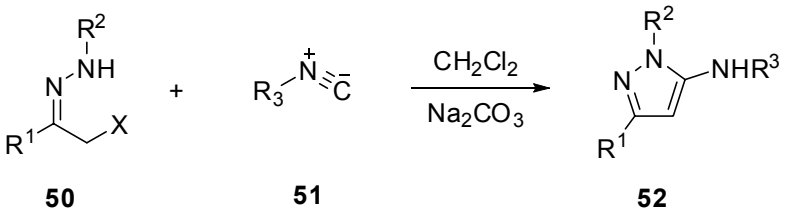


47 **48** **49**

Ar = 4-FC_6H_4, 2,4-$Cl_2C_6H_3$
Ar^1 = 4-$O_2NC_6H_4$

Scheme 14

An interesting synthesis of 3(5)-aminopyrazole derivatives **52** by a reaction of α-haloketone hydrazones **50** and isocyanides **51** has been reported (Scheme 15).[48]

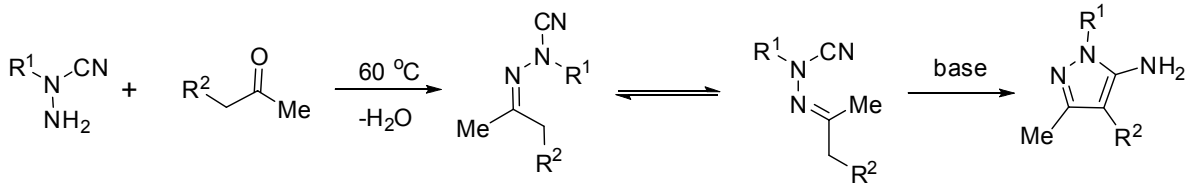


50 **51** **52**

R^1 = CO_2Et, Ph; R^2 = CO_2-*t*-Bu, 2,4-$(O_2N)_2C_6H_3$; R^3 = *t*-Bu, CH_2CO_2Et, $CH_2CH(OMe)_2$, 2-MeC_6H_4, 2-$CO_2MeC_6H_4$

Scheme 15

An alternative to this approach was the cyclization of **55** which was believed to exist in equilibrium with **56** to yield **57**. Compound **55** was produced by condensing **54** with *N*-cyanohydrazine **53** (Scheme 16).[49]



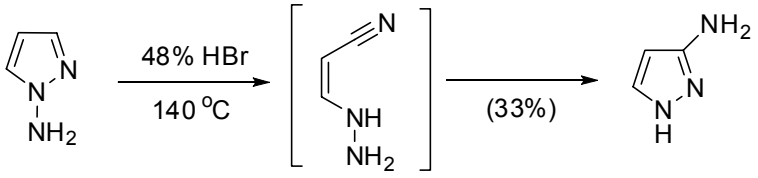
53 **54** **55** **56** **57**

R^1 = Me
R^2 = COMe

Scheme 16

2.4 Miscellaneous syntheses

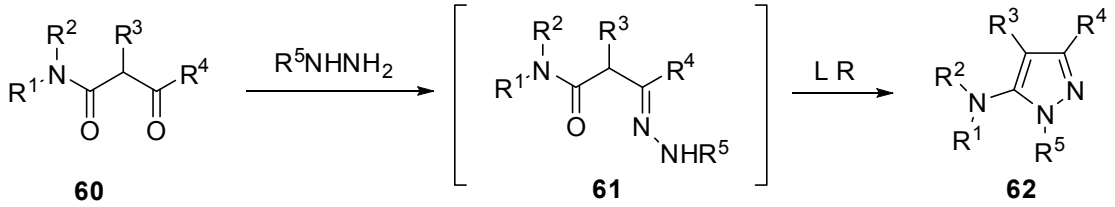
The rearrangement of *N*-aminopyrazole (**58**) in hydrobromic acid afforded **7** *via* intermediacy of **59** (Scheme 17).[50]



58 **59** **7**

Scheme 17

It has been reported that 5-substituted aminopyrazoles **62** were formed *via* gently heating *β*-ketoamides **60** with aryl or alkylhydrazines and Lawesson's reagents (LR). Intermediacy of **61** is postulated (Scheme 18).[51]



60 **61** **62**

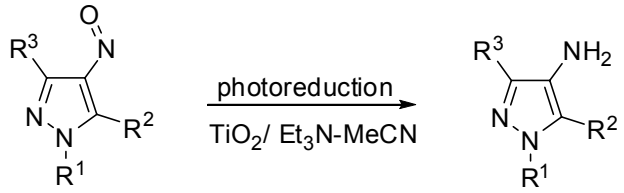
R^1 = Et, Bn, Ph; R^2 = H, Me, Et, Bn; R^3 = H, Me, Ph; R^4 = Me, Ph; R^5 = Bn, Ph

Scheme 18

3. Synthesis of 4-Aminopyrazoles

3.1. Reduction of 4-nitroso, nitro and azopyrazoles

The photosensitized reduction of 4-nitrosopyrazoles **63** using titanium dioxide as photocatalyst in the presence of triethylamine and acetonitrile afforded the corresponding 4-aminopyrazoles **64** (Scheme 19).[52]

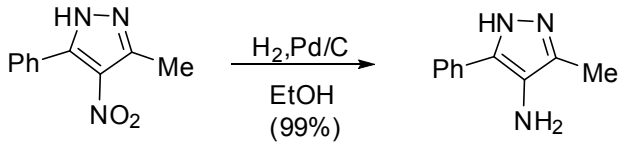


63 **64**

R^1 = H, Ph; R^2 = Me, Ph; R^3 = Me

Scheme 19

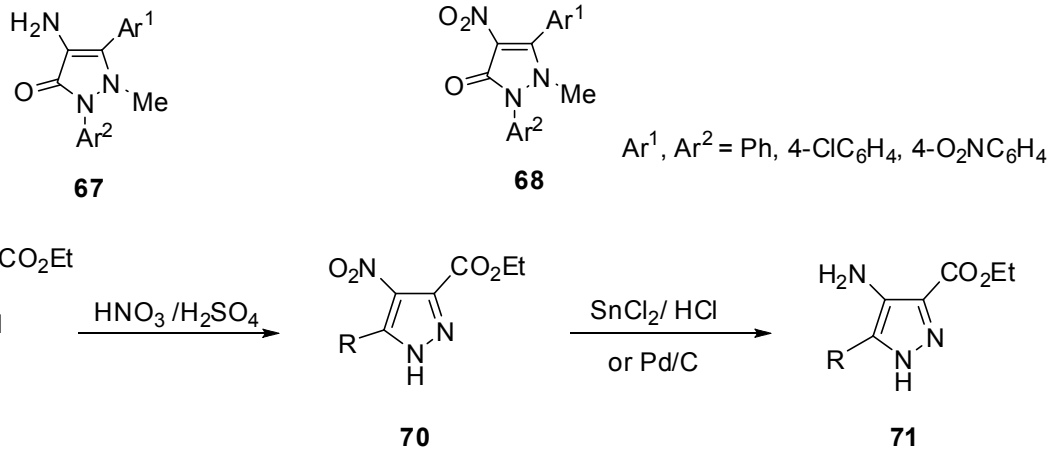
3-Methyl-4-nitro-5-phenyl-1*H*-pyrazole (**65**) has been reduced using Pd/C and H_2 to yield corresponding aminopyrazole **66** (Scheme 20).[53]



65 **66**

Scheme 20

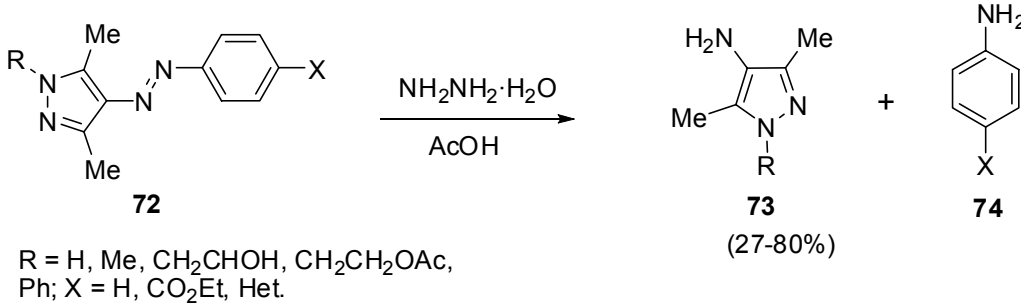
4-Aminoantipyrine **67** was readily obtained *via* reduction of 4-nitroantipyrine **68** with H_2-Pd/C.[54] 4-Aminopyrazole carboxylic esters **71** were generally obtained *via* nitration of pyrazoles **69** and subsequent reduction of the nitro group to form **70** which were precursors of Viagra (Sildenafil) and its derivatives (Scheme 21).[55,56]



67 **68** **69** **70** **71**

Scheme 21

Reductive cleavage of 4-arylazopyrazoles **72** with hydrazine hydrate has been claimed to afford **73** and **74** (Scheme 22).[57]



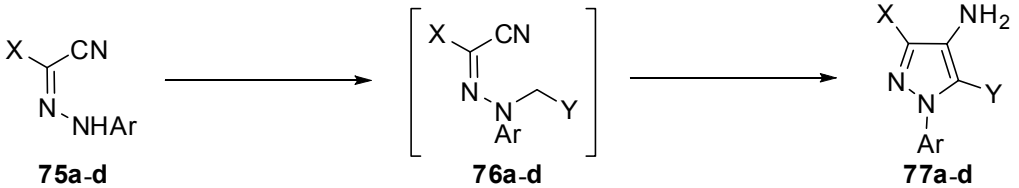
72 **73** (27-80%) **74**

R = H, Me, CH_2CHOH, CH_2CH_2OAc, Ph; X = H, CO_2Et, Het.

Scheme 22

3.2. Reaction of arylhydrazononitrile with functionally substituted alkylhalides

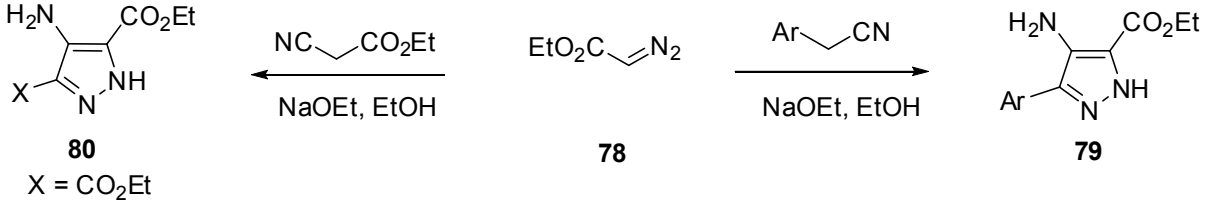
This synthesis has recently been developed initially by Goncalves *et al.*[58] who reported that mesoxalonitrile arylhydrazones **75a** reacted with functionally substituted hydrazines in triethylamine solutions to yield 4-aminopyrazole-5-carbonitriles **77a**. Subsequently, Elnagdi *et al.*[59-61] have extended this approach and could show that it is a general one of application for a variety of 2-arylhydrazononitriles **75b-d** (Scheme 23). Elnagdi *et al.* have recently reviewed achievements in this direction.[62]



Scheme 23

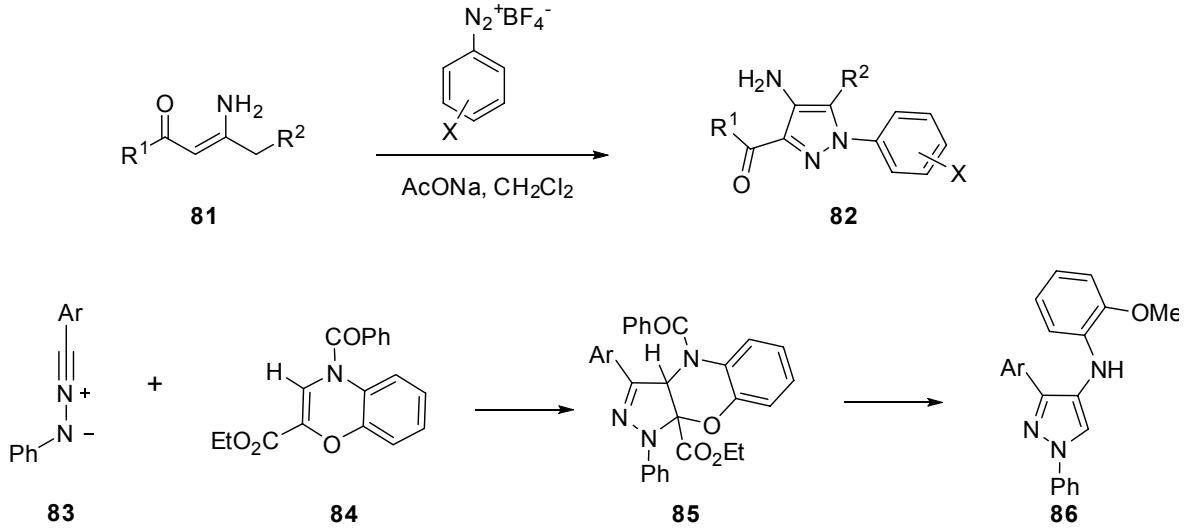
3.3. Miscellaneous syntheses

The reaction of ethyl diazoacetate (**78**) with arylacetonitriles afforded 4-aminopyrazole carboxylic esters **79**. Similarly, the reaction of **78** with ethyl cyanoacetate gave **80** (Scheme 24).[63]



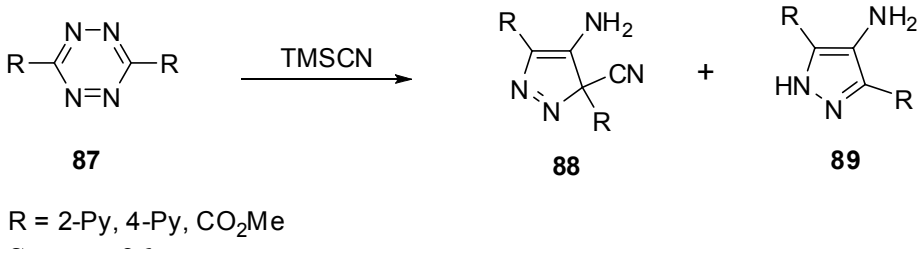
Scheme 24

A new method for the synthesis of substituted 4-amino-1-arylpyrazoles was described, starting from *β*-enaminones **81** and variously substituted benzenediazonium tetrafluoroborates to yield **82** under mild conditions.[64a] On the other hand, the addition of nitrilimines **83** to the benzoxazine **84** afforded **85** that underwent ring chain tautomerism and finally gave **86**[64b] (Scheme 25).



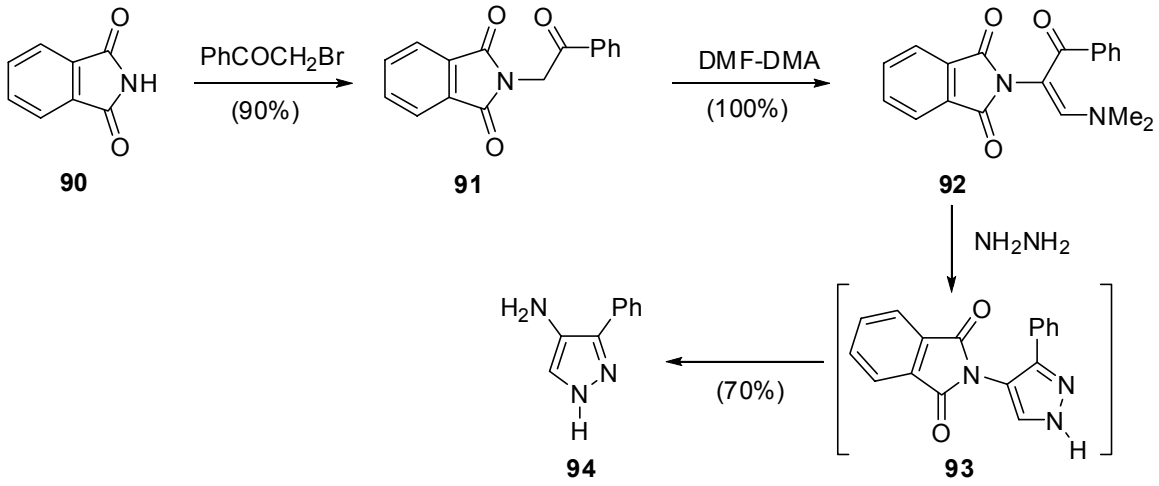
Scheme 25

The reaction of tetrazines **87** with cyanotrimethylsilane (TMSCN) gave the corresponding 4-aminopyrazole derivatives **88** and **89** (Scheme 26).[65]



Scheme 26

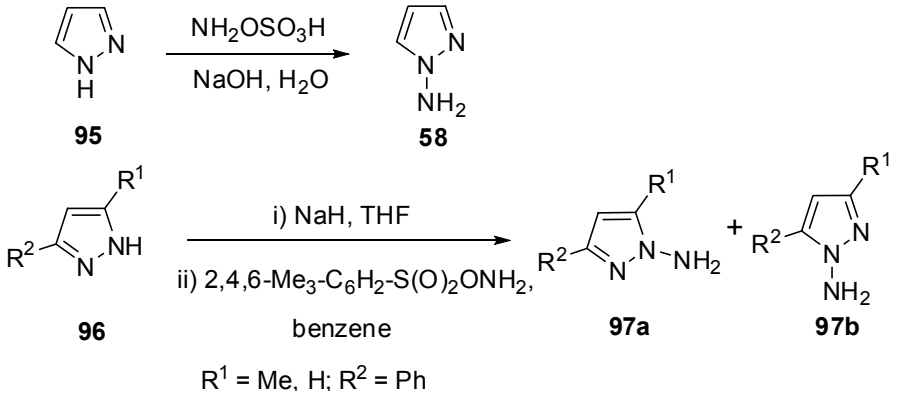
4-Aminopyrazoles were obtained *via* extention of Gabriel's synthesis of amino acids. Thus, reacting **90** with α-bromoacetophenone gave **91** that condensed with dimethylforamide dimethyl acetyal (DMF-DMA) to yield **92**. The latter reacted with hydrazine hydrate to yield **93** which was converted to **94** (Scheme 27).[66,67]



Scheme 27

4. Synthesis of 1-aminopyrazoles

These are obtained by *N*-amination of pyrazoles. Unsubstituted pyrazole (**95**) gave only **58** while substituted pyrazole **96** gave mixtures of *N*-1 and *N*-2-aminated products **97a** and **97b** (Scheme 28).[68,69]

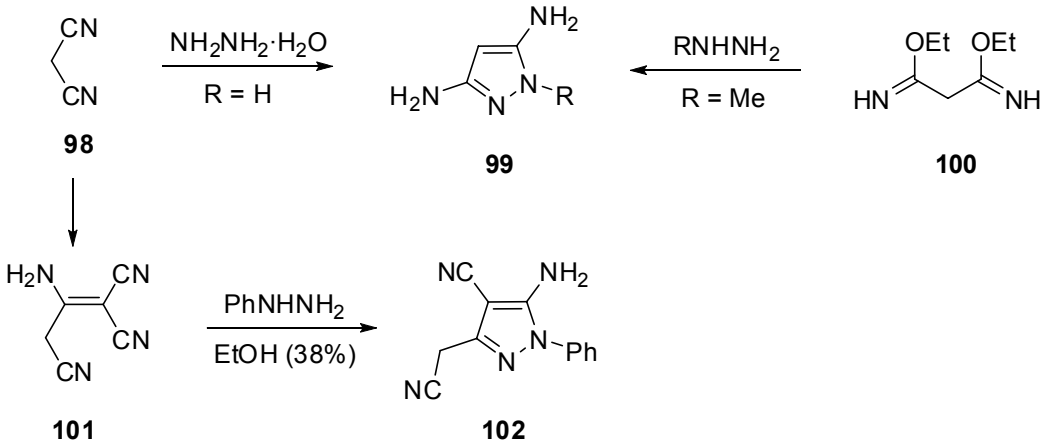


Scheme 28

5. Synthesis of diaminopyrazoles

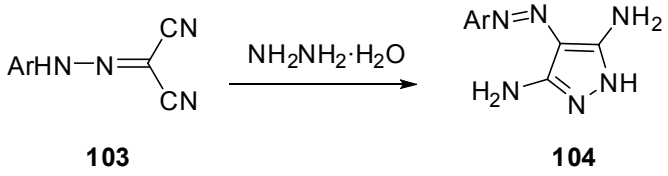
5.1. Synthesis of 3,5-diaminopyrazole and its derivatives

It has been reported in old German literature[70] that malononitrile (**98**) reacted with hydrazine hydrate to yield 3,5-diaminopyrazole **99**. Subsequently Sato,[71] Taylor, Hartke[72] and Elnagdi and co-workers[73] have established that the product was really **102**; formed *via* initial dimerisation of malononitrile to yield **101**. 3,5-Diaminopyrazole was subsequently prepared *via* reacting **100** with hydrazines[74a] (Scheme 29).



Scheme 29

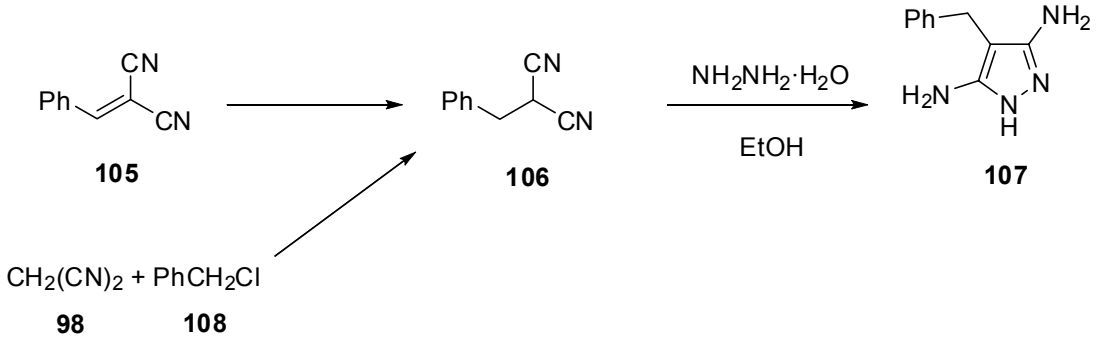
Coupling malononitrile with aromatic diazonium salts afforded corresponding arylhydrazones **103** that reacted with hydrazine hydrate to yield arylazo-3,5-diaminopyrazoles **104**.[73b] These compounds have been found interesting as formulation for hair dyes, antimicrobial agents and antitumor agents (Scheme 30).[73c,74b,c]



Scheme 30

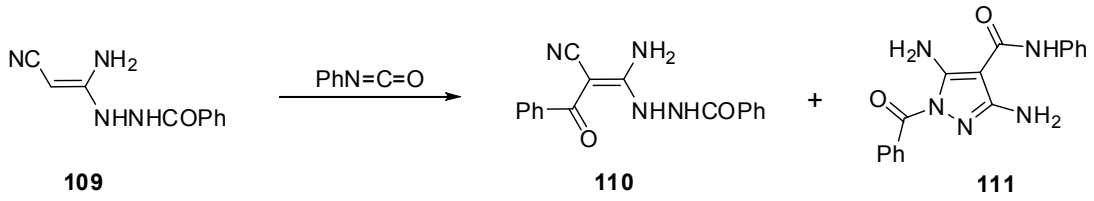
Recently, Elnagdi *et al*.[75] have successfully synthesized 4-benzylpyrazole-3,5-diamine (**107**) *via* reducing benzylidenemalononitrile (**105**) to **106** with sodium borohydride and reacting the latter with hydrazine hydrate to **107**. Compound **107** has been previously obtained by Soto *et*

al.[76] *via* initially monoalkylating malononitrile (**98**) with **108** and subsequent reaction of **106** with hydrazine hydrate (Scheme 31).



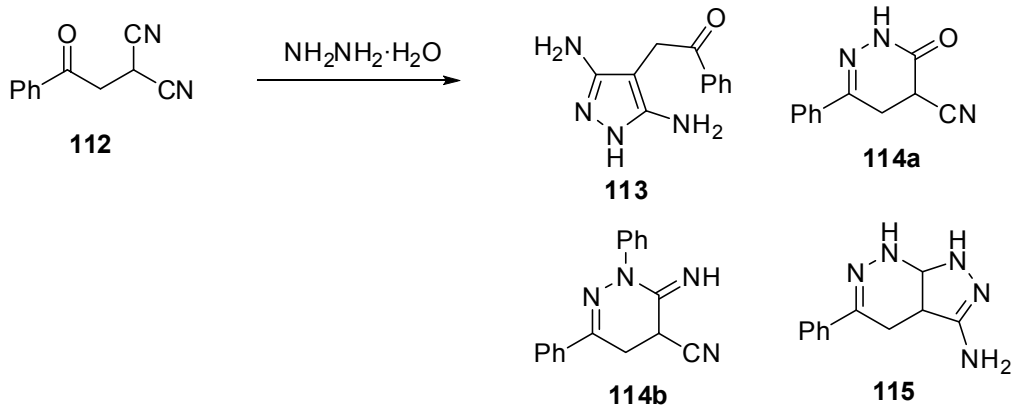
Scheme 31

The reaction of 3-(2-acylhydrazino)-3-aminopropenenitrile **109** with phenylisocyanate afforded a mixture of **110** and **111** (Scheme 32).[77]



Scheme 32

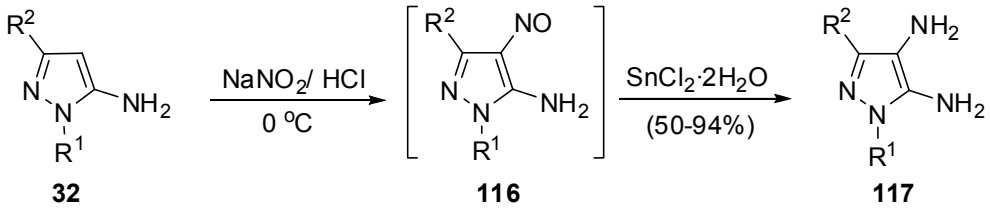
Phenacylmalononitrile (**112**) has been reported by Abdelrazek *et al.*[78a] to react with hydrazinehydrate to yield 4-phenacylpyrazole-3,5-diamine (**113**) as sole product. Abdelrazek[78b] claimed utility for synthesis of a variety of condensed aminopyrazoles. Elnagdi *et al.*[79] have subsequently noted isolation of the pyridazine-6-one (**114a**) as well as **113** on reacting **112** with hydrazine. Recently, however, Abdelrazek[80] claimed that in ethanol solution pyridazine-6-imine (**114b**) as well as the pyrazolo[3,4-*c*]pyridazine are formed in this same reaction. Recently, Al-Mousawi, Meier, Elnagdi and others[81] have looked into these conflicting findings and have concluded that in ethanol at room temperature **114a** is the sole isolable product in 90% yield. They could not detect any presence of **114b** and it is believed that if it was formed it should hydrolyze directly to **114a**. Upon refluxing **114a** with excess hydrazine or when **112** was refluxed with excess hydrazine **115** was produced. Al-Mousawi *et al.*[81] conclusions were supported by spectroscopic data (Scheme 33).



Scheme 33

5.2. Synthesis of 4,5-diaminopyrazoles

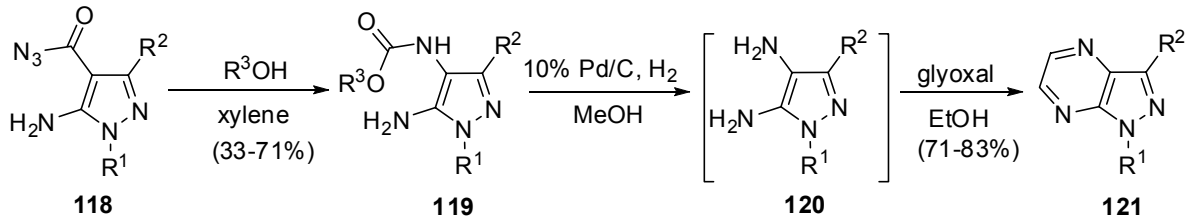
4,5-Diaminopyrazole derivatives **117** were obtained *via* nitrosation and reduction of 5-aminopyrazole derivatives **32** under mild conditions (Scheme 34).[82]



R^1 = Me, Ph, *p*-Tolyl; R^2 = Me, *t*-Bu, Ph

Scheme 34

1-Substituted 5-aminopyrazole-4-carbonylazines **118** were prepared from appropriate 5-aminopyrazole-4-carboxylates. The acyl azides undergo a Curtius rearrangement followed by quenching with alcohols to form the corresponding carbamates **119**. The 1-substituted 5-amino-4-benzyloxycarbonylaminopyrazoles **119** were unblocked by catalytic hydrogenolysis to give 4,5-diaminopyrazolones **120**. These 4,5-diaminopyrazoles were directly condensed with glyoxal to afford 1-substituted pyrazolo[3,4-*b*]pyrazines **121** (Scheme 35).[83]



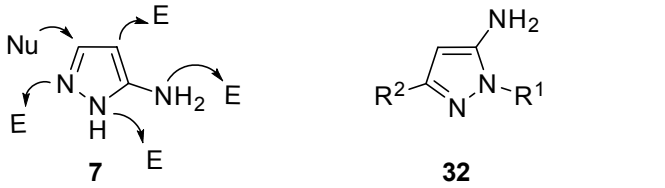
R^1 = Ph, Bn; R^2 = H, Me; R^3 = Et, Bn

Scheme 35

6. Chemical reactivity of aminopyrazoles

6.1. 3(5)-Aminopyrazoles

6.1.1. Reactions with electrophilic reagents. Over the years, numerous investigations on reactivity of monoelectrophiles and polydentate electrophiles toward pyrazol-5-amines have been reported. In fact, there are four sites for electrophile attack in **7** whereas three such sites are available for their reaction with **32** (Figure 2).



R^1, R^2 = alkyl, aryl, halogen, etc.

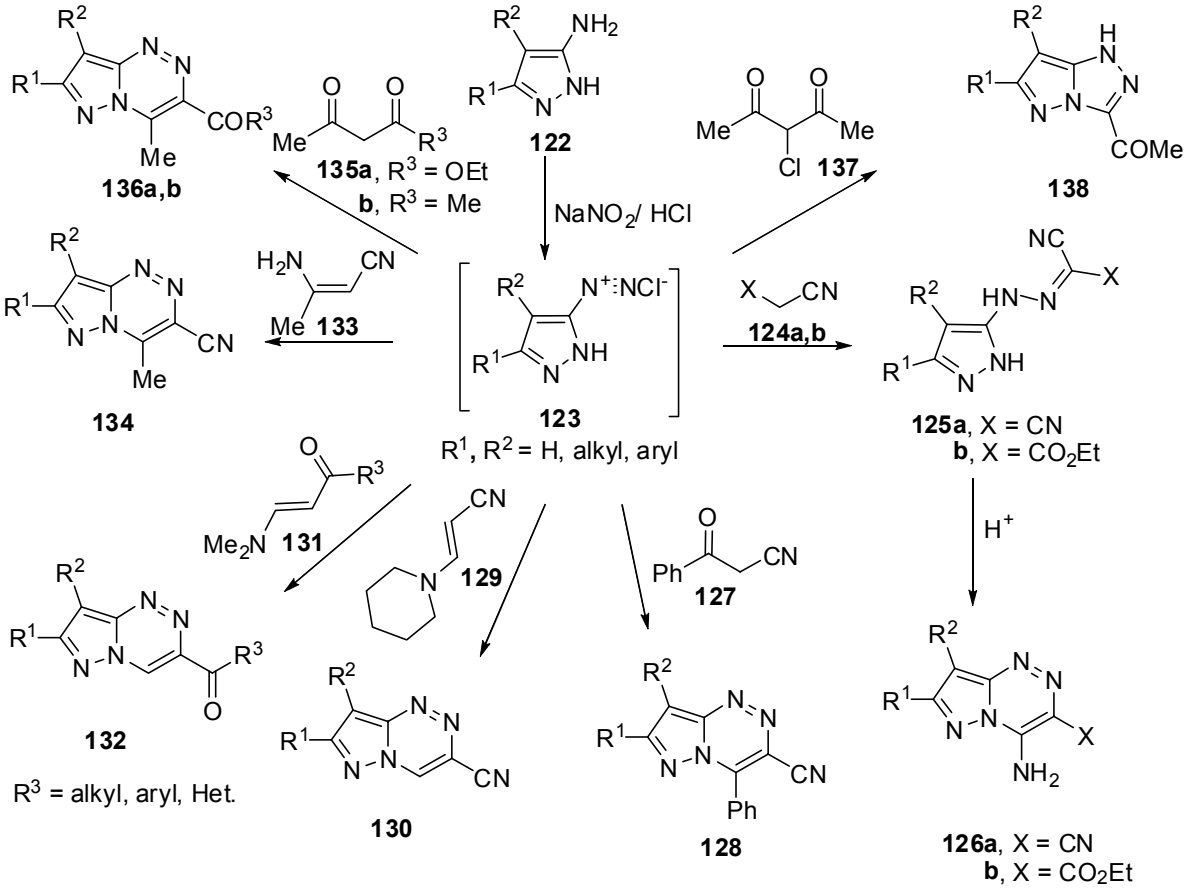
Figure 2. Sites of electrophilic attack in the 3(5)-aminopyrazole.

The nature of the end products in electrophilic substitution reactions seems to depend on the type of the reagent and reaction conditions.

6.1.2. Diazotizations. These reactions occur either at exocyclic amine or at C-4 because under these conditions the ring nitrogen, which is the most nucleophilic moiety, is protonated.

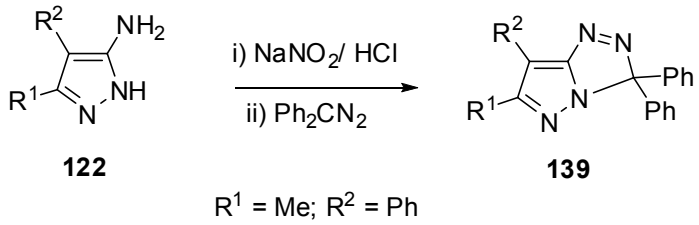
Thus, 3(5)-aminopyrazole **122** has been diazotized in acetic acid with HCl and sodium nitrite to yield pyrazoldiazonium salts **123**. These have been coupled with a variety of active methylene reagents like malononitrile and ethyl cyanoacetate (**124a**,**b**) to yield pyrazol-5-ylhydrazones **125a**,**b** that were readily cyclized into pyrazolo[5,1-*c*]-1,2,4-triazines **126a**,**b**.[19] On the other hand, attempted coupling with benzoylacetonitrile (**127**), enaminonitriles **129**, enaminones **131**, 3-aminocrotononitrile (**133**), ethyl acetoacetate and acetylacetone (**135a**,**b**) resulted in direct formation of pyrazolo[5,1-*c*]1,2,4-triazines **128**, **130**, **132**, **134**, and **136a**,**b**, respectively *via*

cyclocondensation reaction which took place under coupling reaction conditions.[84,85] *β*-Naphthol reacted in the same way.[84c,86] α-Chloroacetylacetone **137** as well as ethyl α-chloroacetoacetate afforded also heterocyclic hydrazidic halides **138** *via* a Japp-Klingemann acyl group cleavage (Scheme 36).[87]



Scheme 36

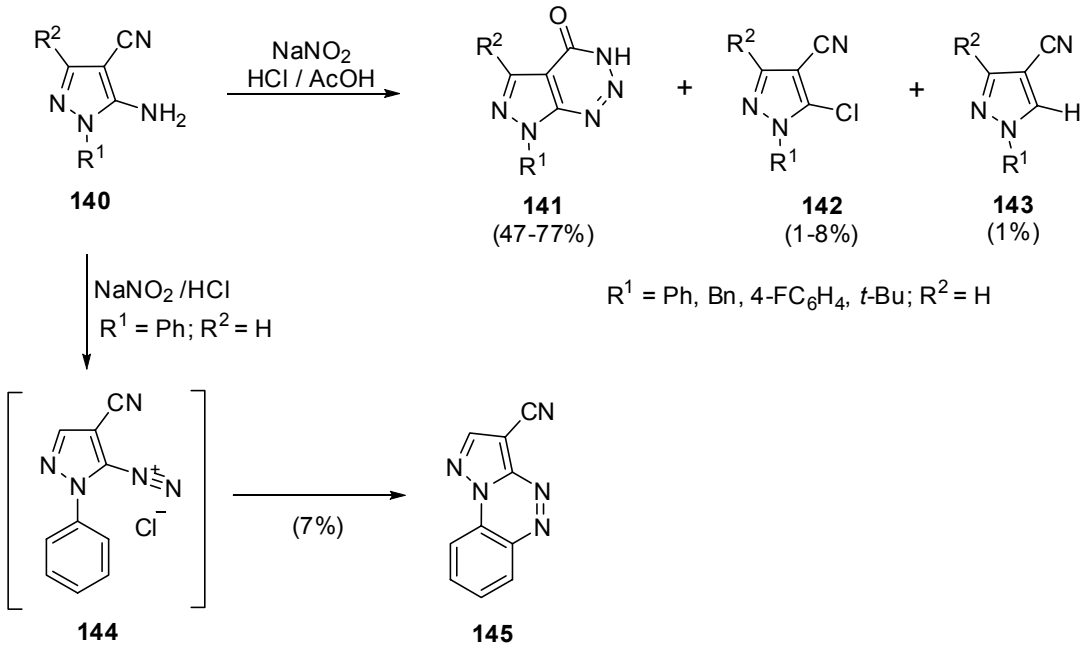
3*H*-pyrazolo[5,1-*c*][1,2,4]triazoles **139** were obtained from diazotized **122** and diphenyldiazomethane in 28-78% yield (Scheme 37).[88]



Scheme 37

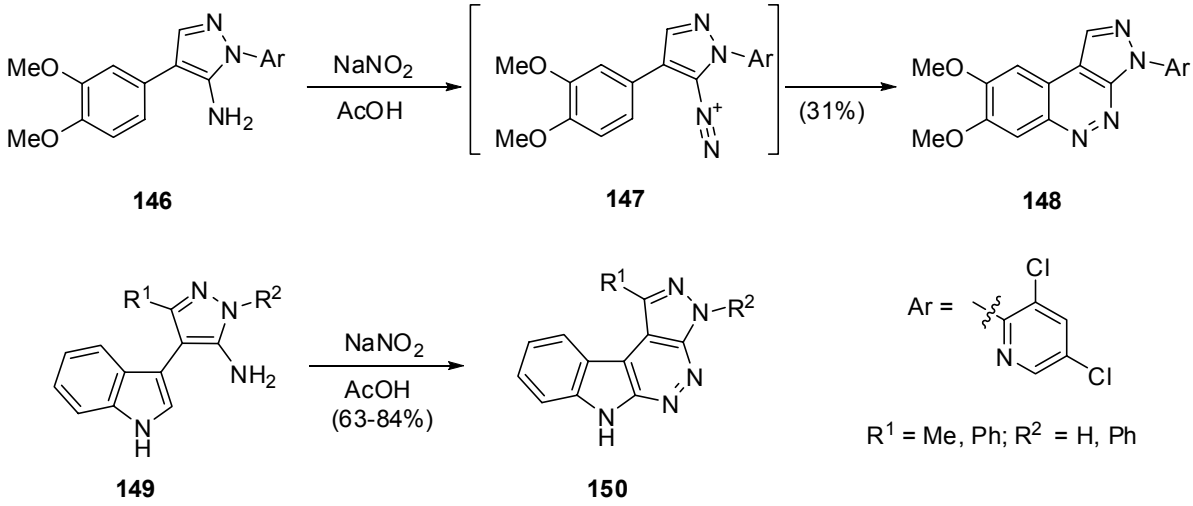
Reactivity of aminopyrazoles in diazotization and coupling was discussed in a recent report and the pattern demonstrated previously was confirmed.[89]

Moyano *et al.* have reported the isolation of pyrazolotriazines **141** and **145** on diazotization of **140** (Scheme 38).[89]



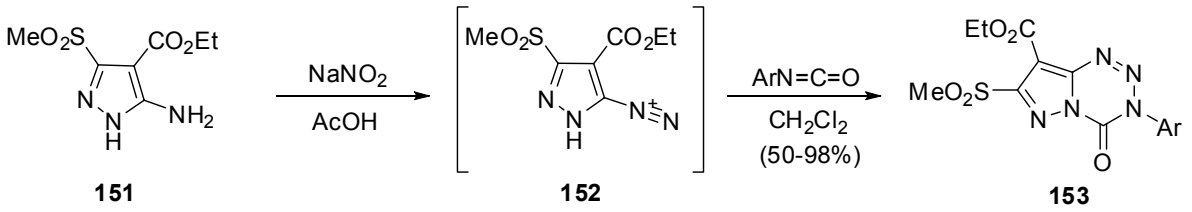
Scheme 38

Diazotization of **146** afforded diazonium derivative **147** that readily cyclized into **148**. Similarly, diazotization of **149** gave **150** (Scheme 39).[90,91]



Scheme 39

Diazotization of **151** gave diazo-3(methylsulfonyl)-1*H*-pyrazole **152** that reacted with aryl isocyanates in dichloromethane to give **153** (Scheme 40).[92]



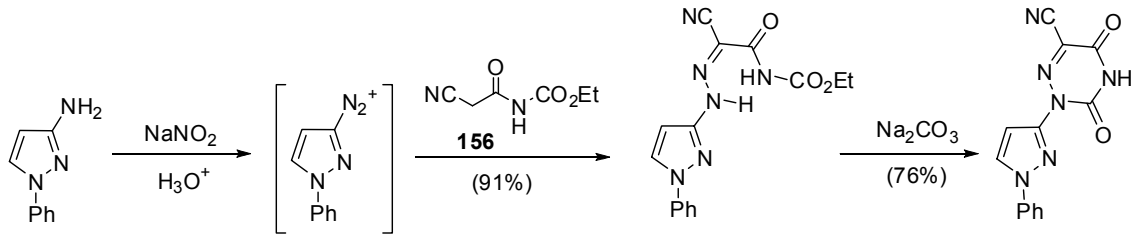
151 **152** **153**

Ar = Ph, 4-FC_6H_4, 2-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-CNC_6H_4, 4-$O_2NC_6H_4$, 2-$O_2NC_6H_4$, 2-$CF_3C_6H_4$, 4-$EtO_2CC_6H_4$

Scheme 40

Neutralization of diazotized pyrazolamines afforded diazonium betain that has been reported to add vinyl ethers, acetylenes and isocyanates.[93]

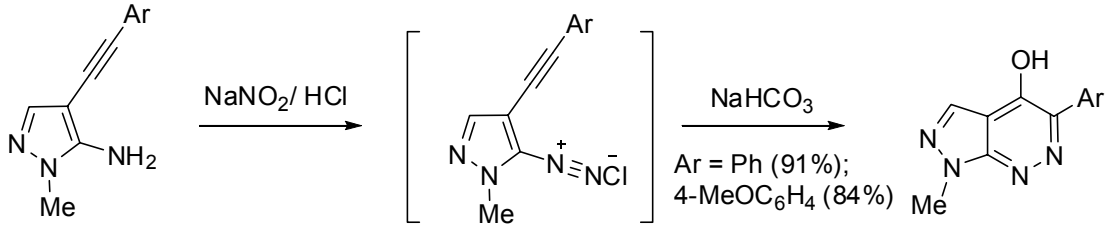
Diazotization of 3-amino-1-phenylpyrazole (**154**) gave the corresponding diazonium salt **155** that reacted with **156** to yield **157** that was readily cyclized into **158** (Scheme 41).[94]



154 **155** **157** **158**

Scheme 41

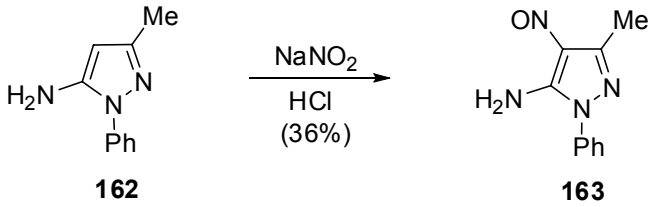
Diazotization of **159** afforded the corresponding diazonium chloride **160** that underwent 6π electrocyclization yielding pyrazolo[3,4-*c*]pyridazine **161** (Scheme 42).[95]



159 **160** **161**

Scheme 42

Attempted diazotization of **162** led to the formation of 4-nitroso derivative **163** (Scheme 43).[96]

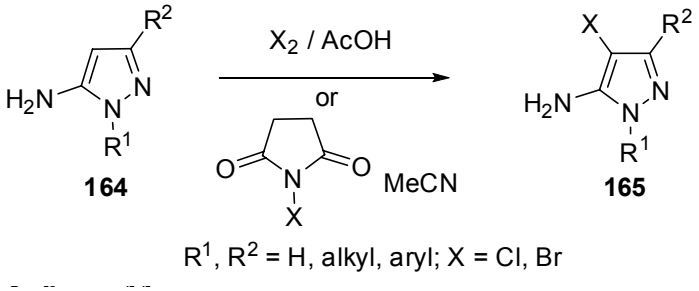


162 **163**

Scheme 43

6.1.3. Halogenation. Direct halogenation of 1,3-disubstituted 5-amino-pyrazoles **164** by halogen in acetic acid or *N*-chlorosuccinimide in acetonitrile afforded 4-halo-pyrazol-5-amines **165** (Scheme 44).[97a-c]

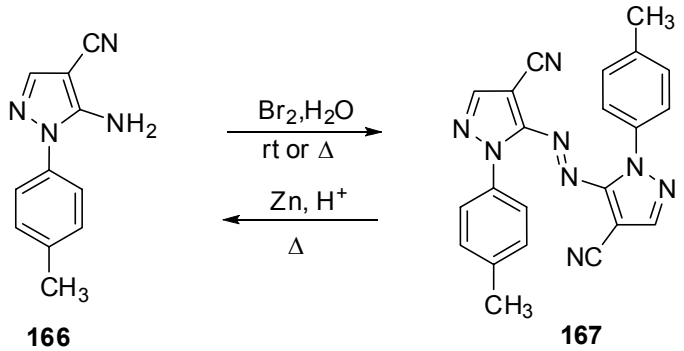
A novel green iodination of 3-aminopyrazole was described with iodine and hydrogen peroxide in water to give 4-iodo-3-aminopyrazole in 82% yield.[97d]



164 **165**

Scheme 44

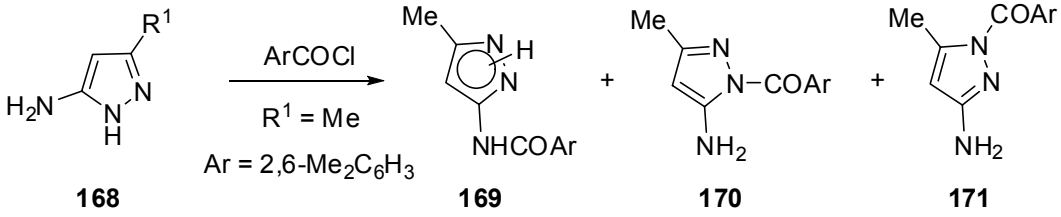
Treatment of **166** with bromine water gave azo dyes resulting from dimerization through the amino groups, which was reduced to starting **167** by with zinc in acetic acid (Scheme 45).[98]



166 **167**

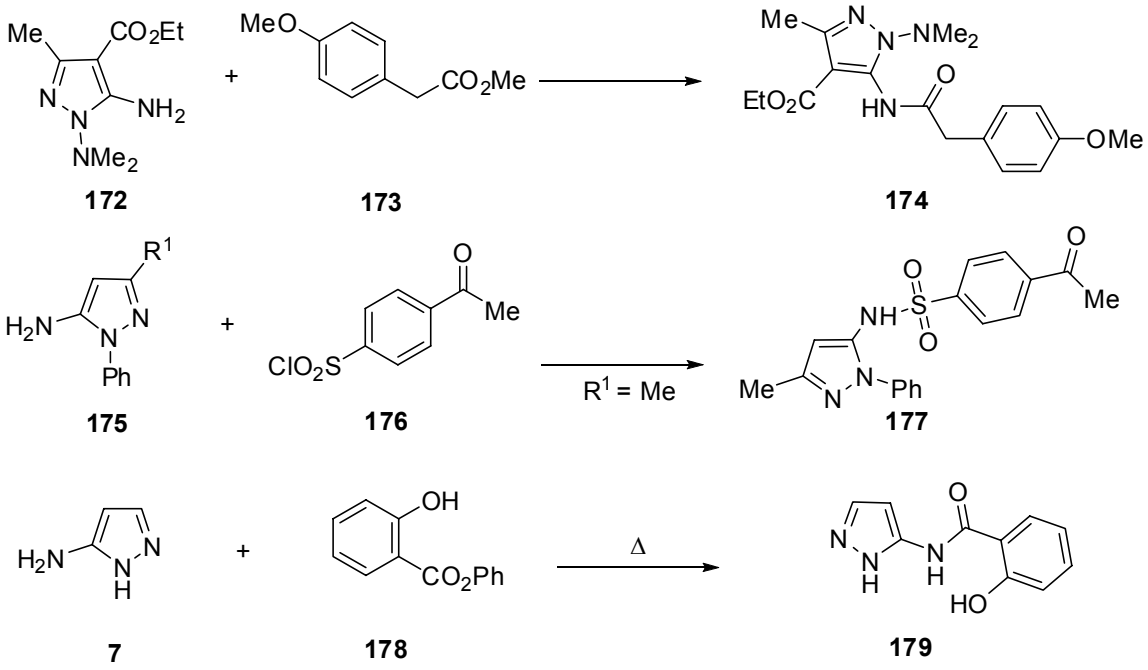
Scheme 45

6.1.4. Acylation. Acylation of **168** afforded a mixture of the 3(5)-acylaminopyrazole **169** as well as the acylpyrazoles **170** and **171** (Scheme 46).[26c,99] Acylation using various reagents may be restricted to the 5-NH_2 group,[100] especially when position 5 is blocked (Scheme 47).[101,102]



168 **169** **170** **171**

Scheme 46



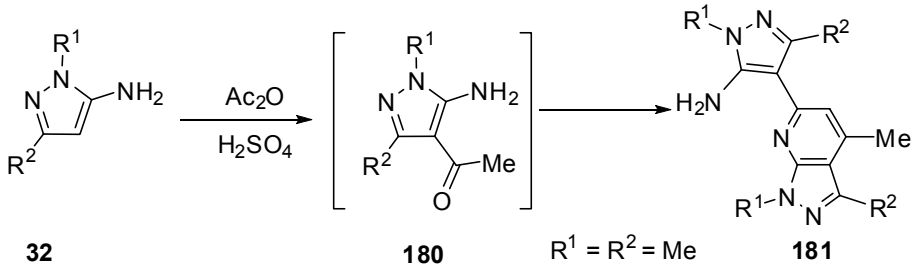
172 **173** **174**

175 **176** **177**

7 **178** **179**

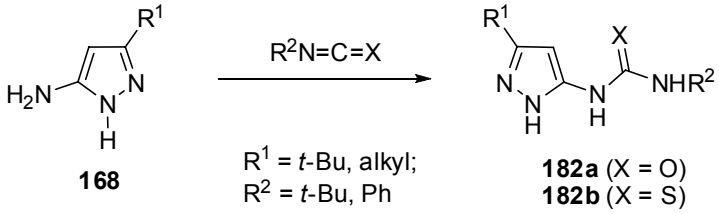
Scheme 47

Attempted acylation of 1,3-disubstituted-5-pyrazolamines (**32**) by acetic anhydride in the presence of sulfuric acid afforded **181**, most likely *via* intermediacy of **180** (Scheme 48).[103]



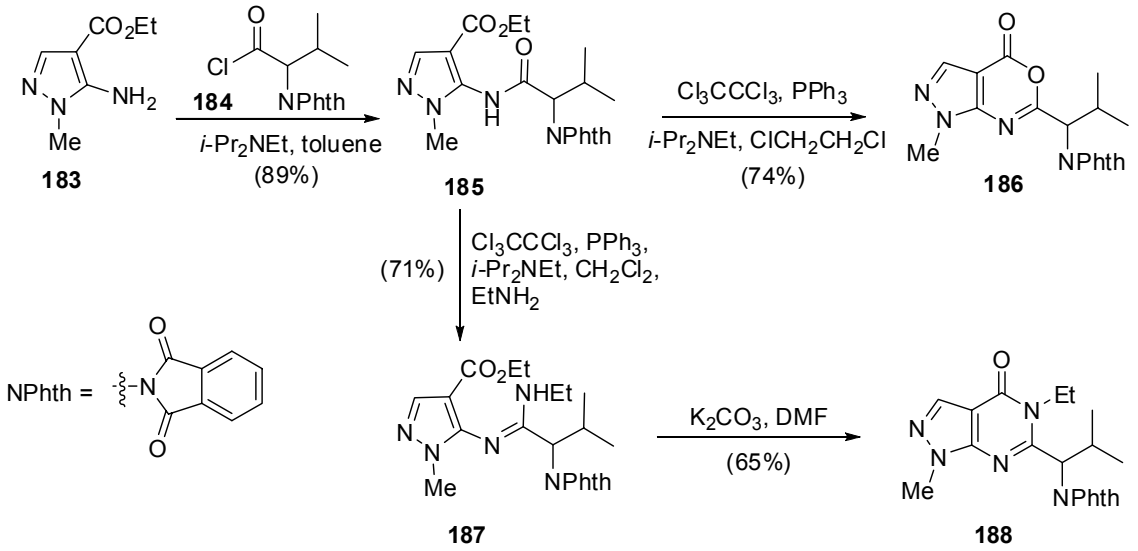
Scheme 48

Isocyanates and isothiocyanates, respectively, reacted with aminopyrazoles **168** yielding the corresponding urea **182a** and the thiourea **182b** (Scheme 49).[104,105]



Scheme 49

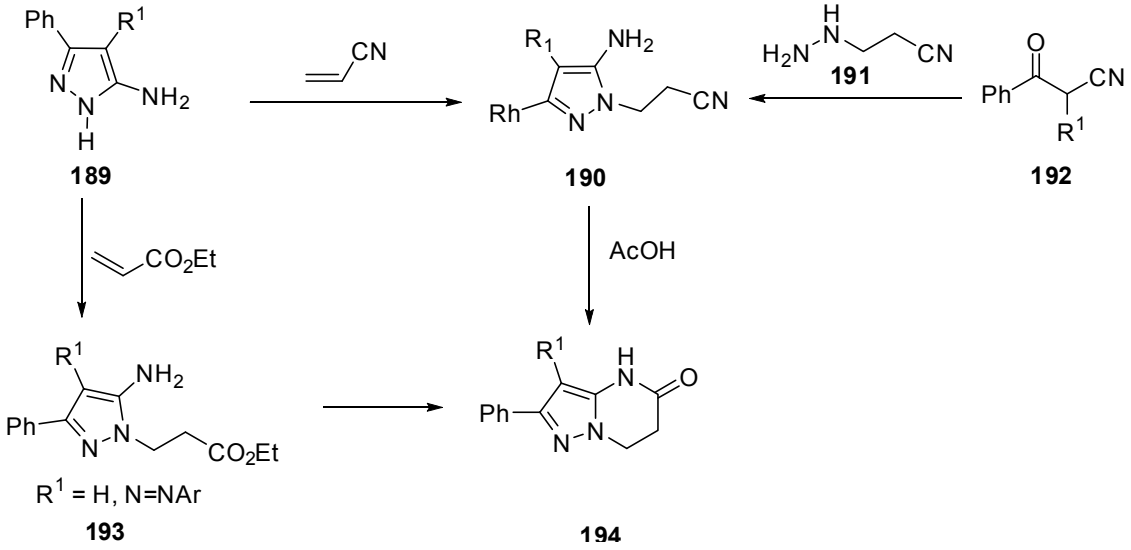
Treatment of commercially available ethyl 5-amino-1-methylpyrazole-4-carboxylate (**183**) by *rac*-2-(phthalylamino)isovaleryl chloride (**184**) under thermal conditions in toluene in the presence of *i*-Pr_2NEt afforded **185** in high yield (89%). The latter could be cyclized into **186** upon treatment with hexachloroethane and triphenylphosphine in dichloromethane. Treatment of **185** with the same reagents in the presence of $EtNH_2$ gave **187**in 71% yield. The latter could readily be cyclized into **188** in 65% yield (Scheme 50).[106]



Scheme 50

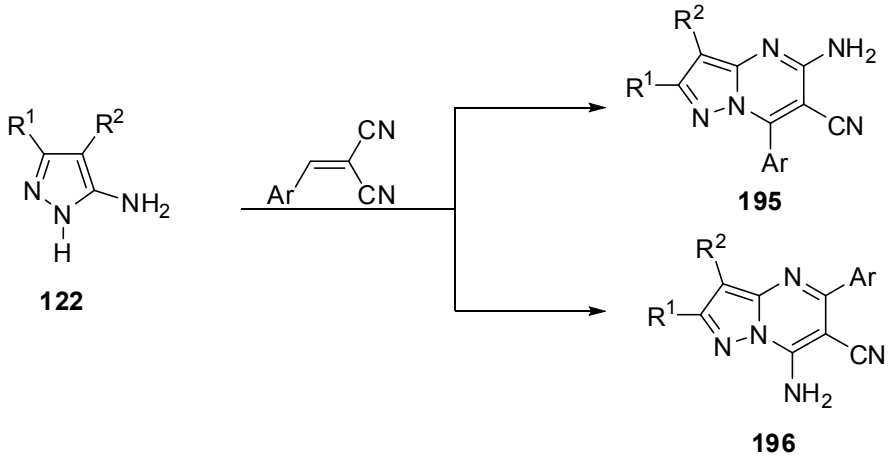
6.1.5. Reactivity toward bidentate electrophiles. Reactions of this type have been extensively utilized as a route to the synthesis of biologically interesting pyrazolo[1,5-*a*]pyrimidines as well as pyrazolo[3,4-*b*]pyridines. Unraveling site selectivity in these additions is not an easy task unless an acyclic intermediate can be isolated or the same reaction products can be synthesized by alternate routes. In several cases, modern NMR techniques studies were used to corroborate the structures of reaction products.

Elnagdi *et al.* have established that cyanoethylation of **189** occurred at *N*-1 and the reaction products **190** could be also prepared *via* reacting **192** with 1-*β*-cyanoethylhydrazine **191**. This cyanoethylation product could be subsequently cyclized into **194**. Compound **194** was obtained by reacting **189** with ethyl acrylate and subsequent cyclization of the formed **193**[18] (Scheme 51).



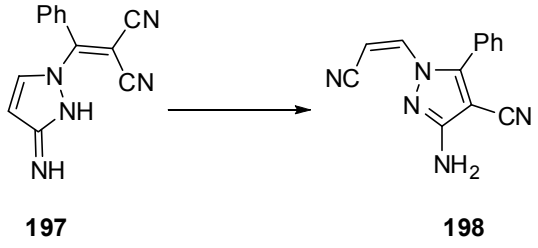
Scheme 51

The reaction of **122** with arylidenemalononitrile has been initially reported to yield **195**.[8g,107] However, recently it was shown that reactions of this type yielded **196**. Single crystal X-ray structure analysis and HMBC-^{15}N were successfully utilized to establish the structure.[44] Many examples of this reaction have been reported and in some cases the single crystal X-ray structure analysis was reported (Scheme 52).[61,108-110]



Scheme 52

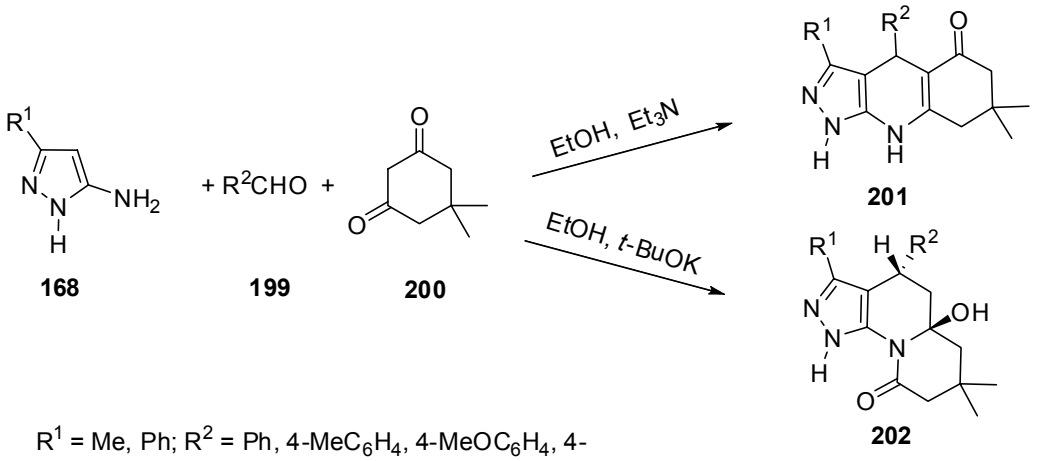
Wendt *et al*. have recently reported on the reactivity of aminopyrazole toward benzylidene malononitrile and firmly established the structure of the product by an X-ray crystal structure determination. Thus, they noted that, in addition to 7-amino-pyrazolo[1,5-*a*]pyrimidine (**196**, Ar = Ph; $R^1 = R^2 = H$) formed in ethanolic sodium ethoxide in 80% yield, a 7% yield of **198** was obtained. When the reaction was conducted in ethanolic triethylamine, a 68% yield of **196** together with a 21% yield of **198** as side product was formed. However, in refluxing pyridine only **196** could be isolated. It is believed that **198** is formed as a result of initial formation of **197** (Scheme 53).[110d]



Scheme 53

The reaction of an aldehyde, an active methylene reagent and aminopyrazoles has been extensively investigated recently. It is believed that the active methylene reagent initially condenses with the aldehyde to yield an α,*β*-unsaturated functional reagent that is then added to

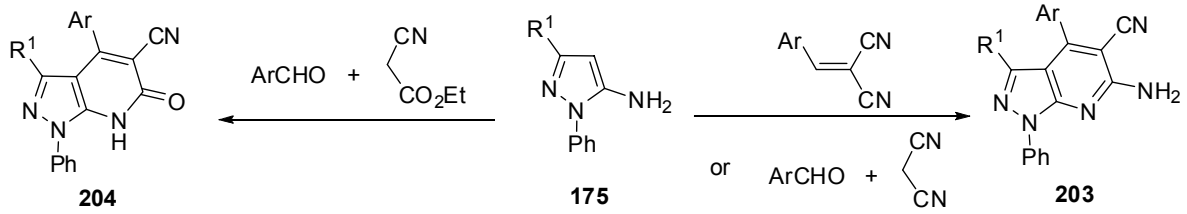
C-4 yielding an adduct that then subsequently cyclized yielding pyrazolo[3,4-*b*]pyridine moieties. For example, a mixture of **168** and **199** reacting with **200** gave **201** with refluxing ethanol in the presence of Et_3N, while, when the reaction was conducted in the presence of *t*-BuOK, **202** was formed (Scheme 54).[111]



R^1 = Me, Ph; R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-BrC_6H_4, 4-FC_6H_4

Scheme 54

Al-Mousawi *et al.*[112] have reported that 1-phenyl-5-pyrazolamine **175** reacted with arylidenemalononitrile to yield pyrazolo[3,4-*b*]pyridine **203**, the structures of which were established by NOE.[113] These products were obtained upon reacting **175** with the mixture of malononitrile and aromatic aldehydes in an ionic liquid (Scheme 55).[114] Similarly, mixtures of aldehydes and ethyl cyanoacetate afforded **204**.[115] Also **203** was obtained from reacting **175** with aldehydes and 2-cyanoethanethioamide under microwave irradiation.[116]

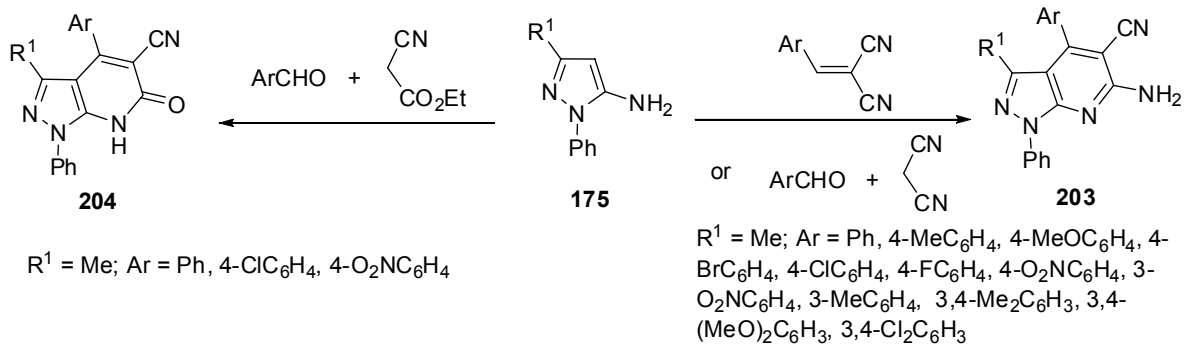


R^1 = Me; Ar = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$

R^1 = Me; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 3-MeC_6H_4, 3,4-$Me_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3,4-$Cl_2C_6H_3$

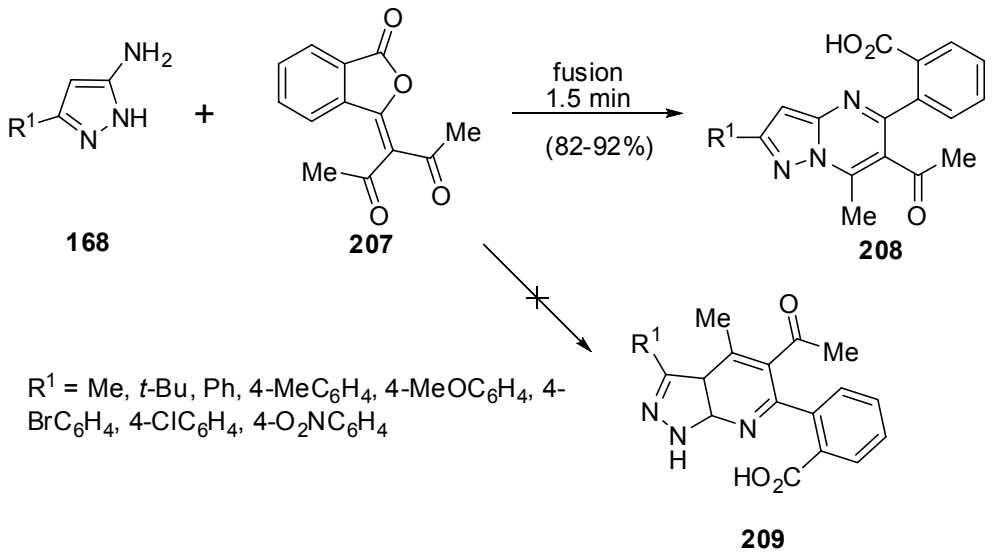
Scheme 55

Quite similar to this reaction is the reaction of **175** with mixtures of aldehydes and aroylacetonitrile **205** to yield **206** (Scheme 56).[117]



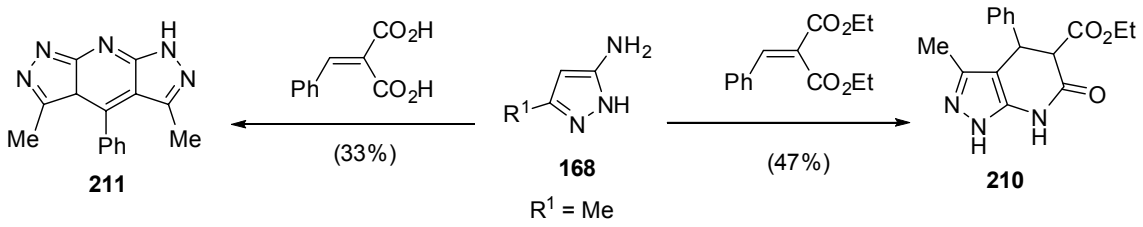
Scheme 56

This approach has been extensively utilized in recent years for the synthesis of 2-(pyrazolo[1,5-*a*]pyrimidin-5-yl)benzoic acids (**208**)[110a,b] (Scheme 57).



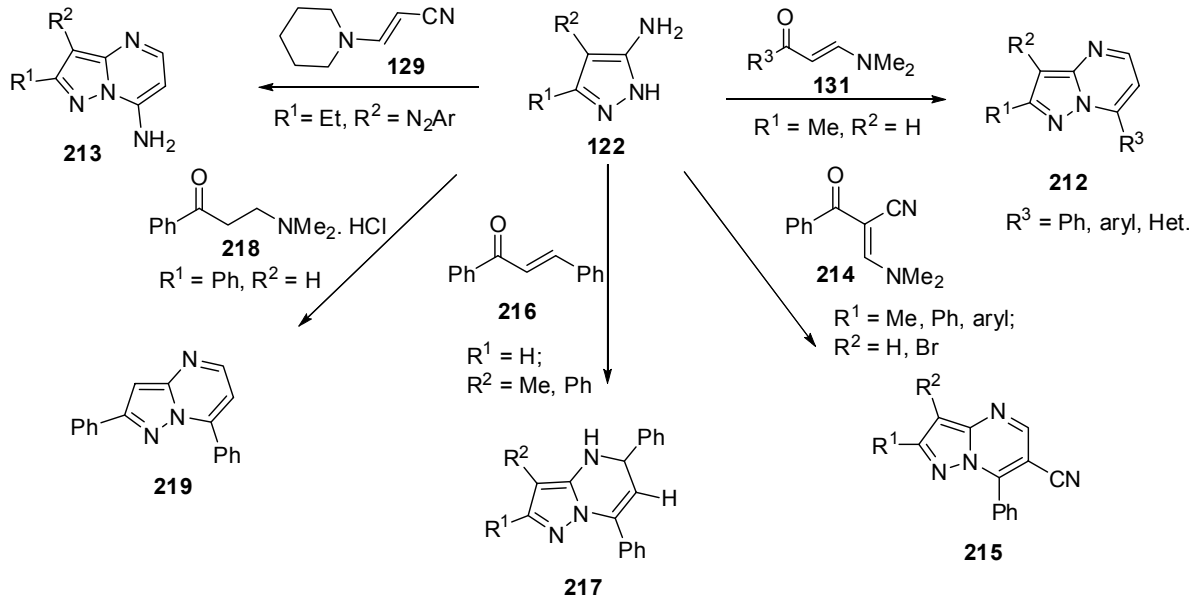
Scheme 57

Recently, cyclocondensation of **168** with diethyl benzylidenemalonate afforded 6,7-dihydropyrazolo-[1,5-*a*]pyrimidin-5-one (**210**). Also, cyclocondensation of **168** with 2-benzylidenemalonic acid in nitrobenzene gave dipyrazolo[3,4-*b*:4',3'-*e*]pyridine **211**[118] (Scheme 58).



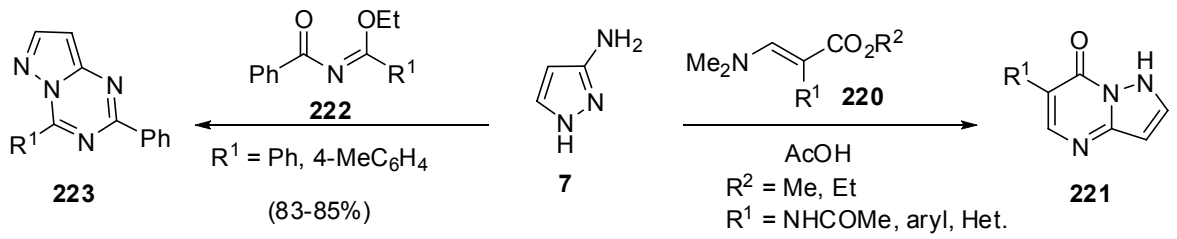
Scheme 58

The reaction of enaminones **131** with **122** afforded product **212** of initial attack at the exocyclic amino function as established by single crystal X-ray structure analysis.[45a,119,120] Enaminonitriles behaved similarly. Thus **122** gave **213**.[44] Pyrazol-5-amine **122** reacted with **214** to yield **215** (Scheme 59).[121-124] Interestingly, Zaleplon derivatives were prepared in this way.[125] It has been reported that **122** reacted with **216** to yield the dihydropyrazolo[1,5-*a*]pyrimidine **217**.[126,127] Similarly, heating **122** with **218** gave **219**. It is assumed that phenylvinylketone was initially formed on heating **218** and this then reacted with **122** to yield the final product.[128]



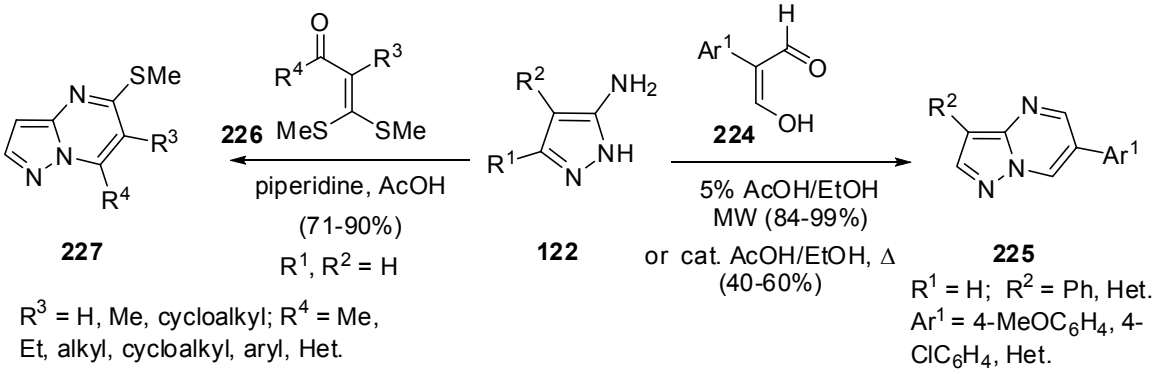
Scheme 59

Based on the enaminone methodology, the **220** reacted with aminopyrazole **7** to yield pyrazolo[1,5-*a*]pyrimidin-7-one **221**.[129] On the other hand, *N*-acyl-imidates **222** reacted with **7** to yield pyrazolo[1,5-*a*][1,3,5]triazine **223**[130] (Scheme 60).



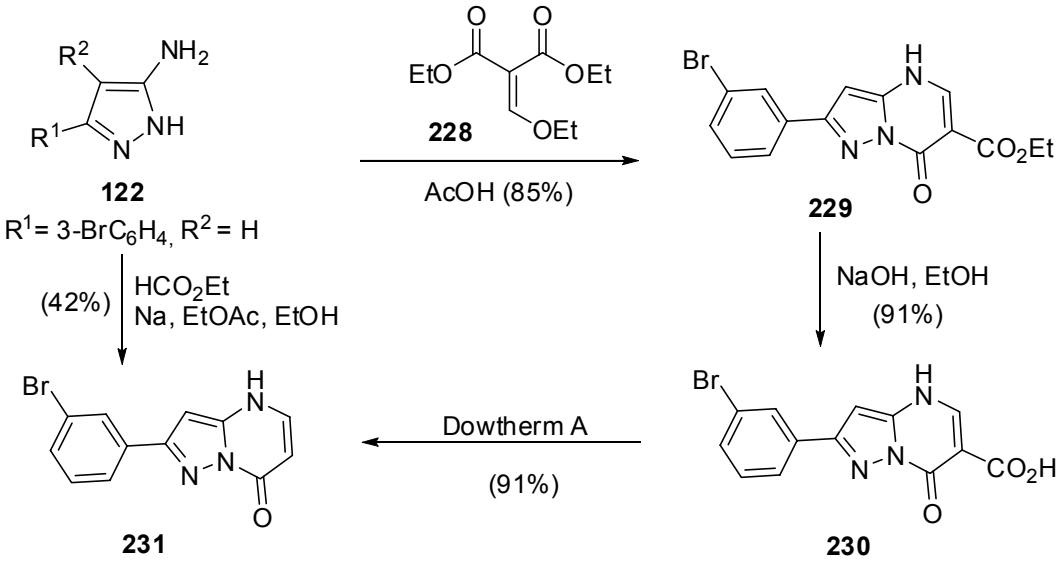
Scheme 60

Synthesis of the functionalized pyrazolo[1,5-*a*]pyrimidines were described from amniopyrazoles **122** and 3-hydroxy-2-arylacrylaldehydes **224** upon microwave irradiation or conventional heating to yield **225**.[27c] Also pyrazolo[1,5-*a*]pyrimidines **227** were obtained from gem α-oxoketenedithioacetals **226** with aminopyrazoles **122** mainly at exocyclic amine moiety [131] (Scheme 61).



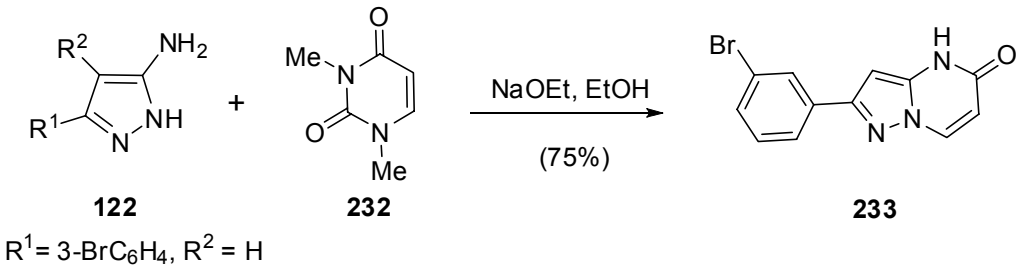
Scheme 61

Diethyl ethoxymethylenemalonate (**228**) reacted with aminopyrazoles **122** to yield **229**. This was saponified to yield **230** which could be decarboxylated yielding pyrazolo[1,5-*a*]pyrimidin-7-one **231**. Compound **231** could be directly obtained *via* reacting **122** with ethyl formylacetate generated in situ from reaction of ethyl formate and ethyl acetate[132] (Scheme 62).



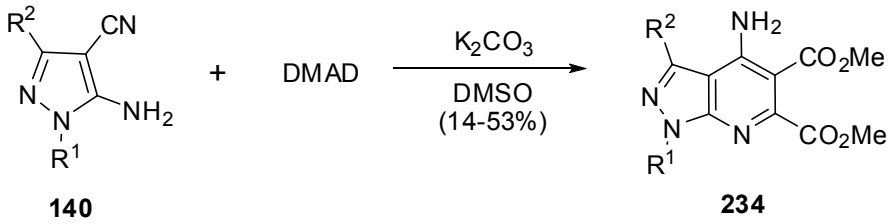
Scheme 62

It has been found that the isomer of **231**, pyrazolo[1,5-*a*]pyrimidin-5-one **233** was readily formed upon the treatment of **122** with 1,3-dimethyluracil (**232**) in ethanol. Structure of reaction products could be elucidated *via* NOE difference experiments with *N*-methylated **231** and **233**[132] (Scheme 63).



Scheme 63

The reaction of 5-aminopyrazole-4-carbonitriles **140** with dimethyl acetylenedicarboxylate (DMAD) in DMSO in the presence of potassium carbonate gave pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates **234** in 14-53% yields[133] (Scheme 64).

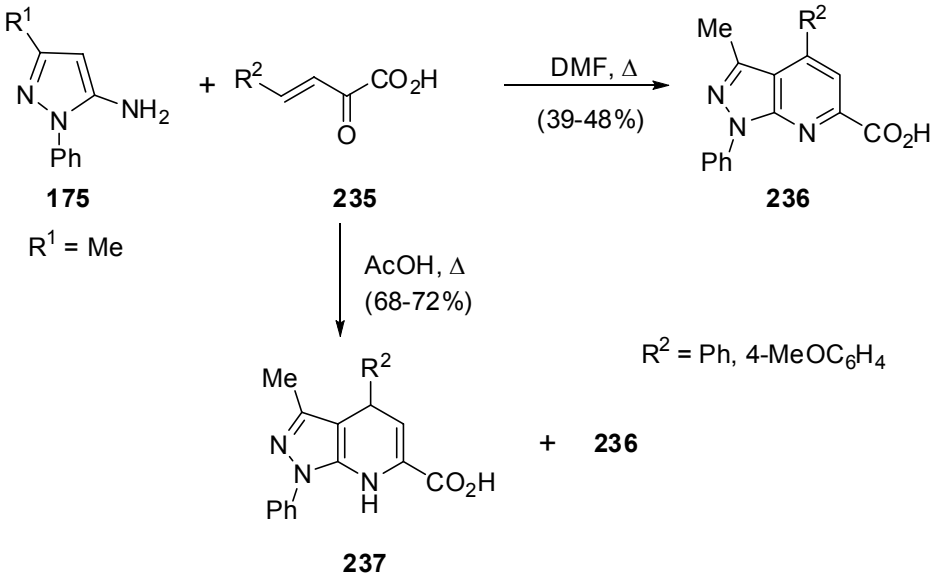


140 **234**

R^1 = Ph, 4-$O_2NC_6H_4$, SO_2-C_6H_4-4-Me, Het.
R^2 = H, Me, Ph, 4-$Me_2NC_6H_4$, SMe, S-aryl, Het.

Scheme 64

The reaction of **175** with **235** in refluxing DMF gave pyrazolo[3,4-*b*]pyridine-6-carboxylic acid **236** in 39-48% yields. The dihydro derivatives **237** were obtained in 68-72% yields when the reactions were conducted in AcOH. This product was contaminated with **236**[134] (Scheme 65).



175 **235** **236**

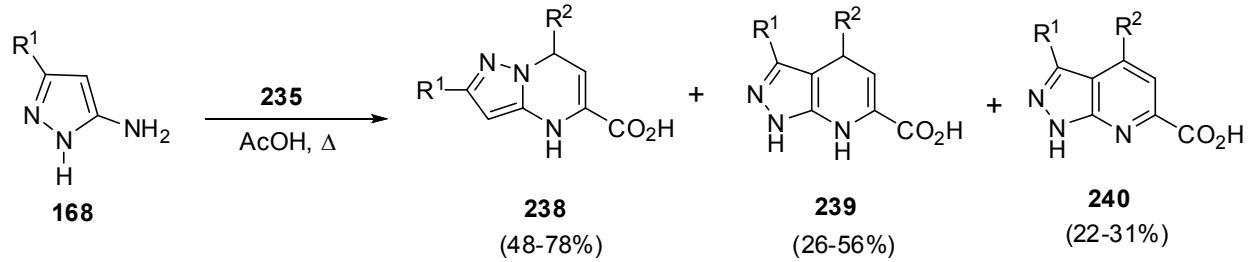
R^1 = Me

R^2 = Ph, 4-$MeOC_6H_4$

237

Scheme 65

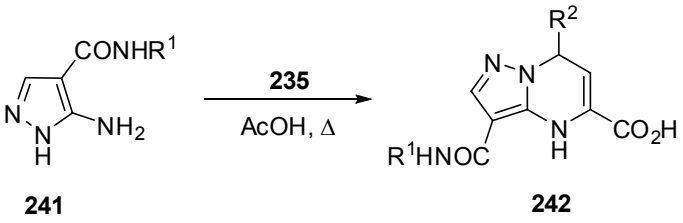
On the other hand, mixture of **238**, **239** and **240** were obtained from the reaction of **168** with **235**[134] (Scheme 66).



R^1 = Ph, 4-BrC_6H_4; R^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 66

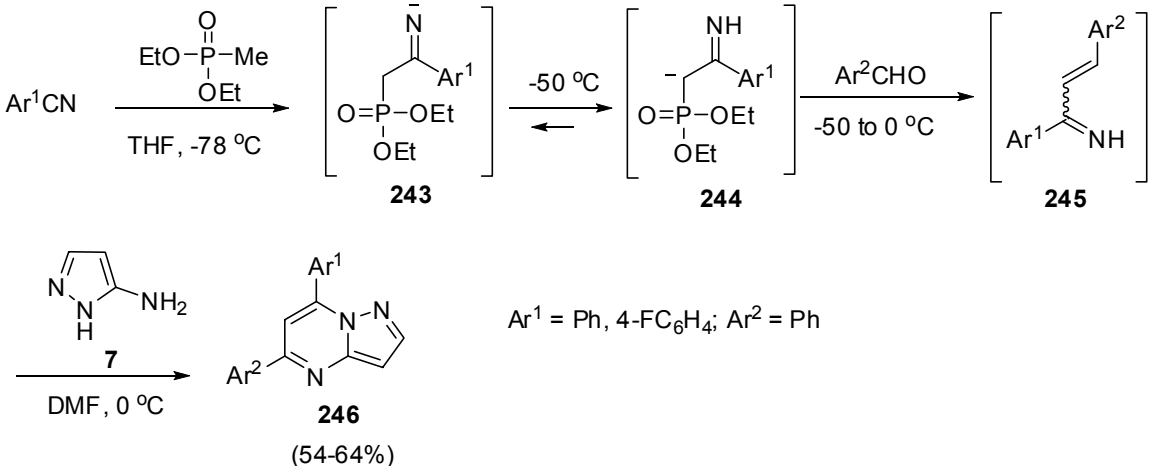
The reaction of **241** with the same reagent **235** afforded **242** as sole product in 68-72% yields[134] (Scheme 67).



R^1 = Ph, 4-$EtOC_6H_4$; R^2 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 67

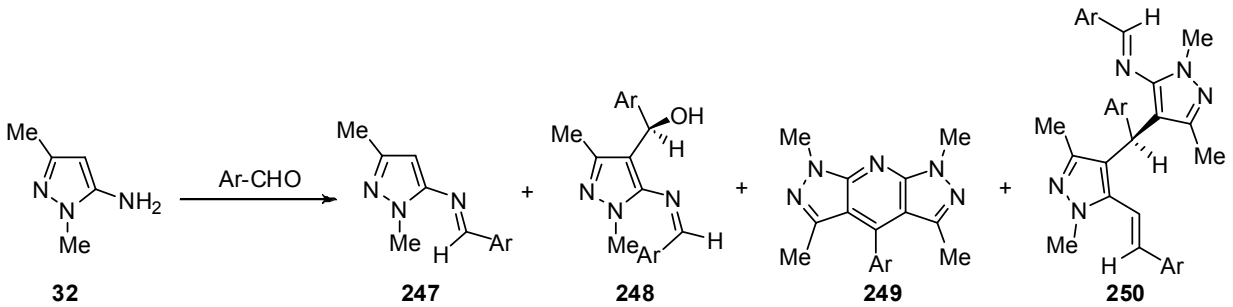
A regioselective one-pot synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives **246** from aminopyrazole **7** and α,β-unsaturated imines **245** which was generated in situ from methyl phosphonate, nitrile, and aldehyde[135] (Scheme 68).



Ar^1 = Ph, 4-FC_6H_4; Ar^2 = Ph

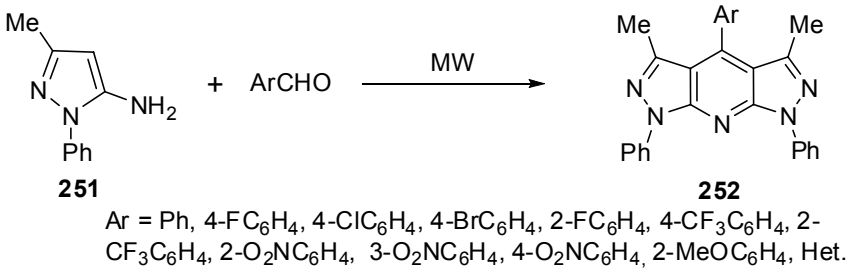
Scheme 68

6.1.6. Reactions with aldehydes and ketones. The reaction of 1,3-dimethyl-5-pyrazolamine **32** and *p*-substituted benzaldehydes yielded four different compounds **247-250**[136] (Scheme 69).



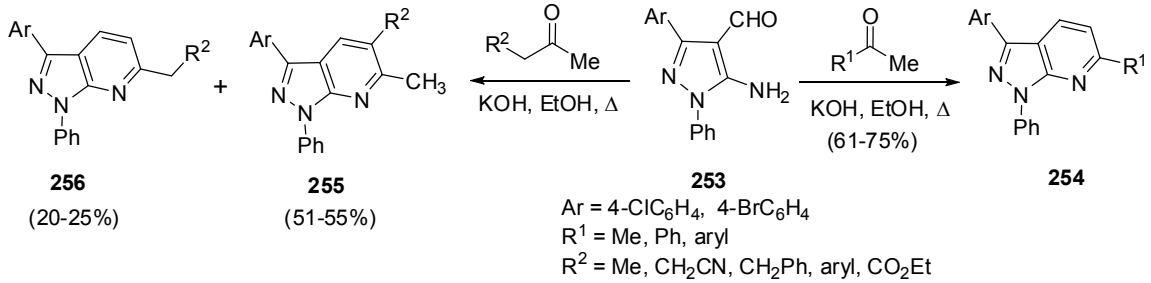
Scheme 69

Under microwave irradiation in absence of solvent, 1-aryl-3-methyl-5-aminopyrazoles (**251)** reacted with aldehydes to yield dipyrazolo[3,4-*b*:4',3'-*e*]pyridine derivatives **252**[137] (Scheme 70).



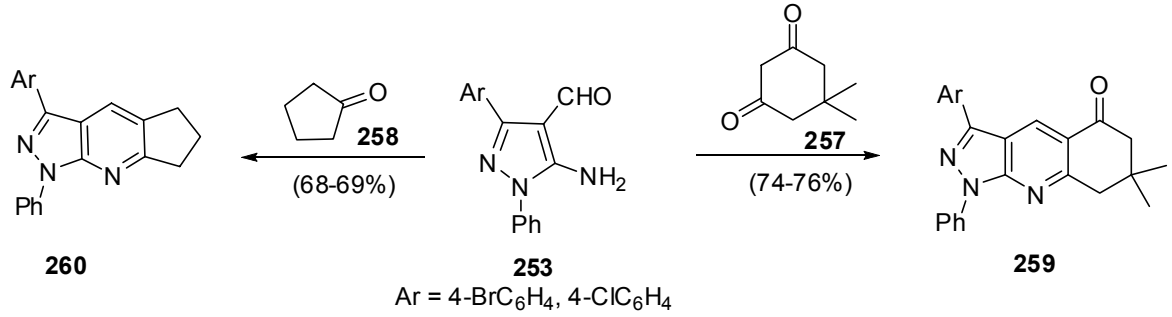
Scheme 70

A series of 1,3,6-trisubstituted and 1,3,5,6-tetrasubstituted pyrazolo[3,4-*b*]pyridines **254** has been synthesized by Friedländer condensation of 5-aminopyrazole-4-carbaldehydes **253** with α-methyle ketones such as acetone or acetophenones with KOH as a basic catalyst. Condensation with unsymmetrical ketones gave the mixture of isomeric products **255** and **256**[138] (Scheme 71).



Scheme 71

Similarly, **253** condensed with cyclohexanedione **257** and with cyclopentanone (**258)** to yield **259** and **260**, respectively[139] (Scheme 72).

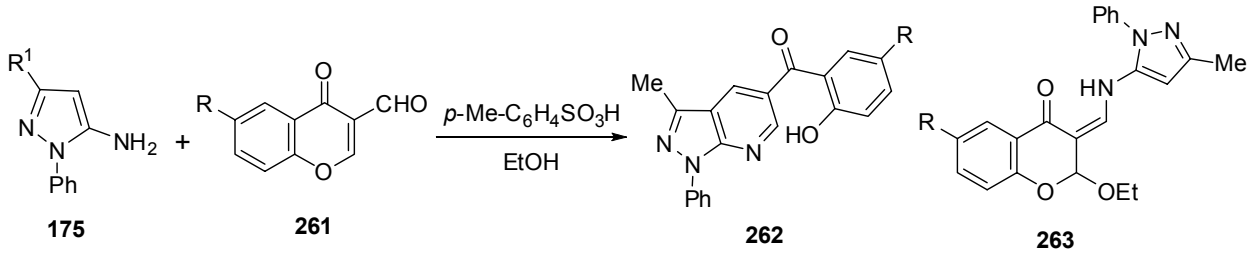


260 **253** **259**

Ar = 4-BrC_6H_4, 4-ClC_6H_4

Scheme 72

The reaction of 1-phenyl-3-methyl-5-aminopyrazole (**175**) with **261** in ethanol in the presence of *p*-toluenesulfonic acid afforded **262** or **263** depending on the reaction conditions[140] (Scheme 73).

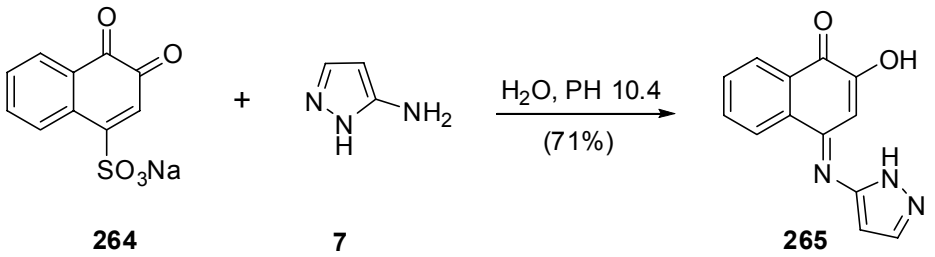


175 **261** **262** **263**

R^1 = Me R = H, Me, F, Cl, Br

Scheme 73

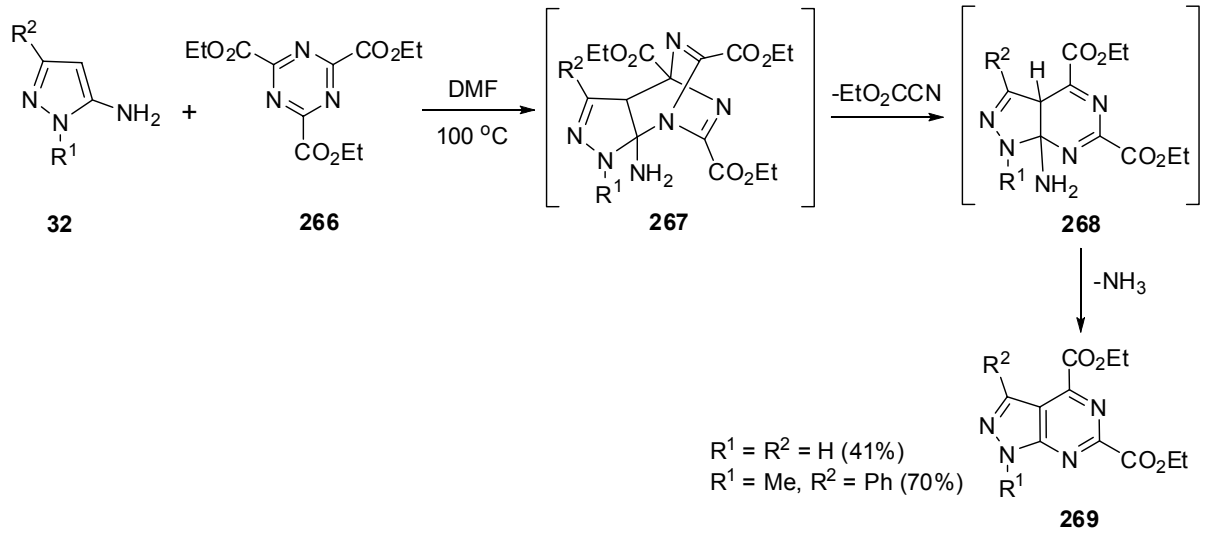
Sodium naphthoquinone-4-sulfonate **264** reacted with 5-aminopyrazole (**7**) to yield pyrazolyl-naphthoquinone **265**[141] (Scheme 74).



264 **7** **265**

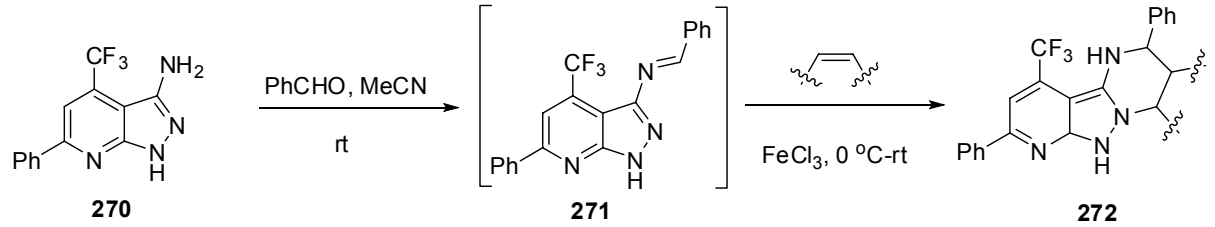
Scheme 74

6.1.7. Cycloaddition and dipolar cycloadditions. The [4+2] cycloaddition of various 5-aminopyrazoles **32** with 1,3,5-triazine-2,4,6-tricarboxylic acid triethyl ester (**266**) have been reported to yield **269** *via* intermediacy of **267** and **268**[142] (Scheme 75).



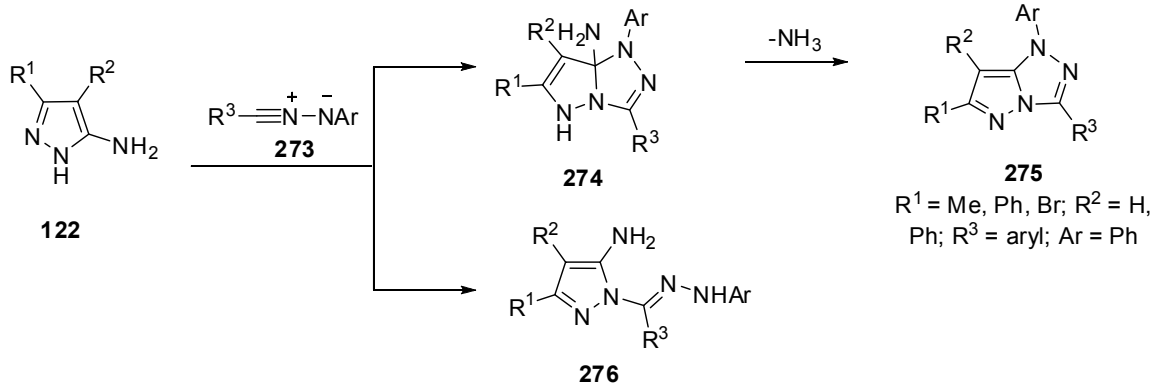
Scheme 75

Treatment of **270** and benzaldehyde in acetonitrile at room temperature in the presence of $FeCl_3$ with alkenes gave cycloadducts **272**. It was assumed that **271** was initially formed[143] (Scheme 76).



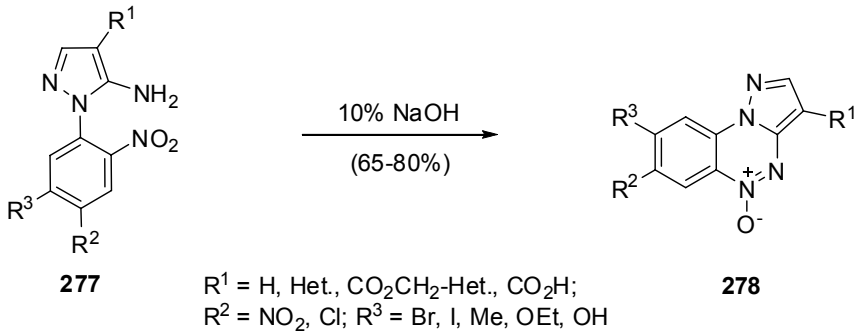
Scheme 76

3-Aminopyrazole derivatives **122** reacted with nitrile imines **273** (generated in situ) to yield pyrazolo[5,1-*c*]-1,2,4-triazoles **275** *via* intermediacy of **274**.[144] Some researchers isolated also **276**.[144a,145] This reaction has been extensively investigated and it was found that the nature of the end product depends on the nature of substituents on **122** and **273**[146] (Scheme 77).



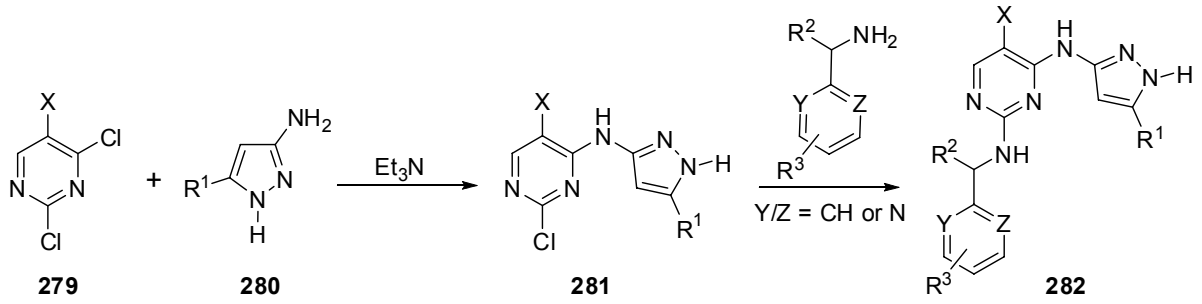
Scheme 77

6.1.8. Intramolecular cyclization. The pyrazolo[5,1-*c*]benzo-1,2,4-triazine 5-oxide system is obtained *via* intramolecular cyclization between the nitro and amino groups under basic conditions of suitable 5-amino-2′-nitrophenyl-pyrazoles.[143] Thus, treating **277** with 10% NaOH solution afforded **278**[147](Scheme 78).



Scheme 78

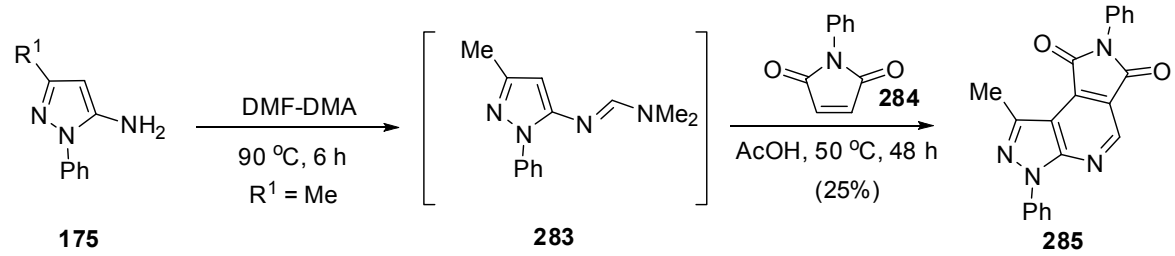
6.1.9 Miscellaneous. The 2,4-dichloropyrimidines **279** reacted with aminopyrazoles **280** in the presence of triethylamine to give 4-substituted 2-chloropyrimidines **281**. For inactivated pyrimidines (e.g. 5-Me/H) the reaction mixture was heated to 70 ^{o}C. Nucleophilic aromatic substitution of **281** with amines to yield **282** was affected by heating under basic conditions[148] (Scheme 79).



R^1 = cyclopropyl, H; R^2 = H, (*R*)-Me, (*S*)-Me, (*R*)-CH_2OH, (*R*)-CH_2OH;
R^3 = H, 3-OMe, 2-Cl, 4-F, 4-Cl; X = Br, Cl

Scheme 79

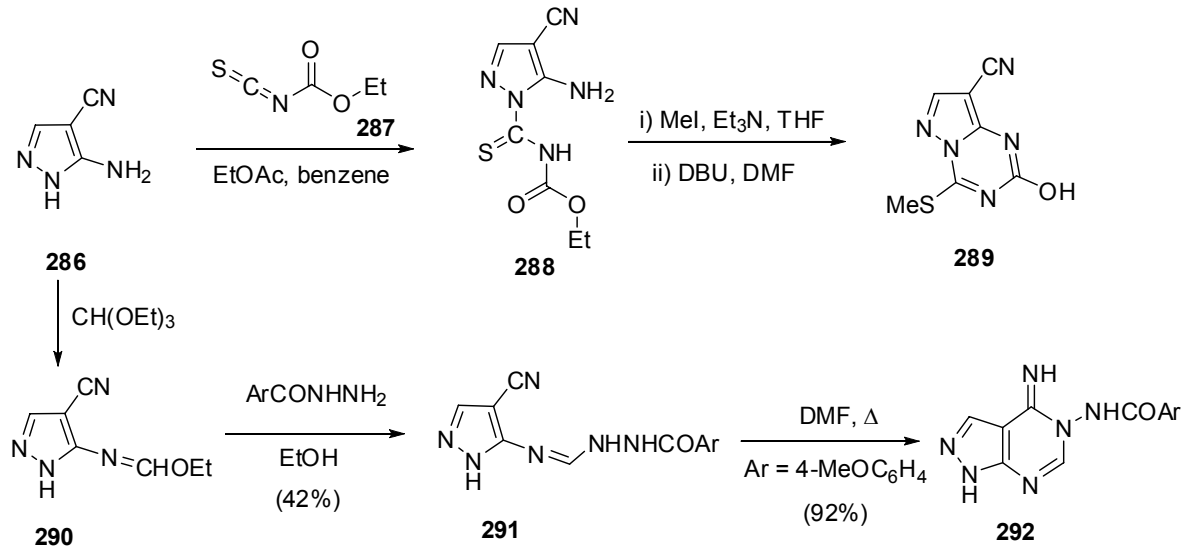
The condensation of 5-amino-1-phenyl-3-methylpyrazole (**175**) with dimethylformamide dimethyl acetal and *N*-phenylmaleimide (**284**) gave **285**. Compound **283** was proposed as an intermediate[149] (Scheme 80).



Scheme 80

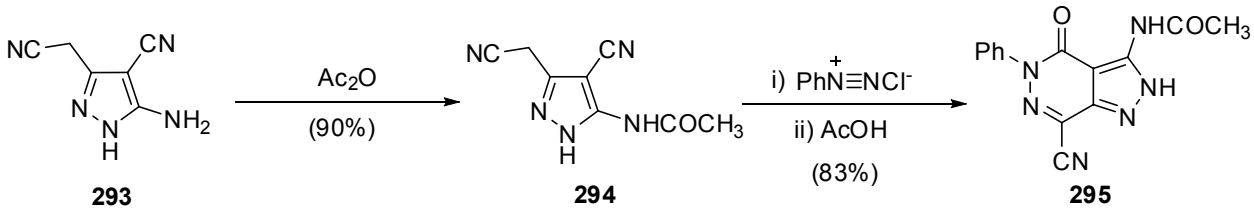
Treatment of 5-amino-1*H*-pyrazole-4-carbonitrile (**286**) with ethoxycarbonyl-isothiocyanate (**287**) gave corresponding pyrazolothiourea **288** that was alkylated and cyclized to yield the pyrazolotriazine **289**.[150]

Condensation of **286** with triethyl orthoformate afforded **290** which reacted with acylhydrazines to afford **291** that could be cyclized into **292**[151] (Scheme 81).



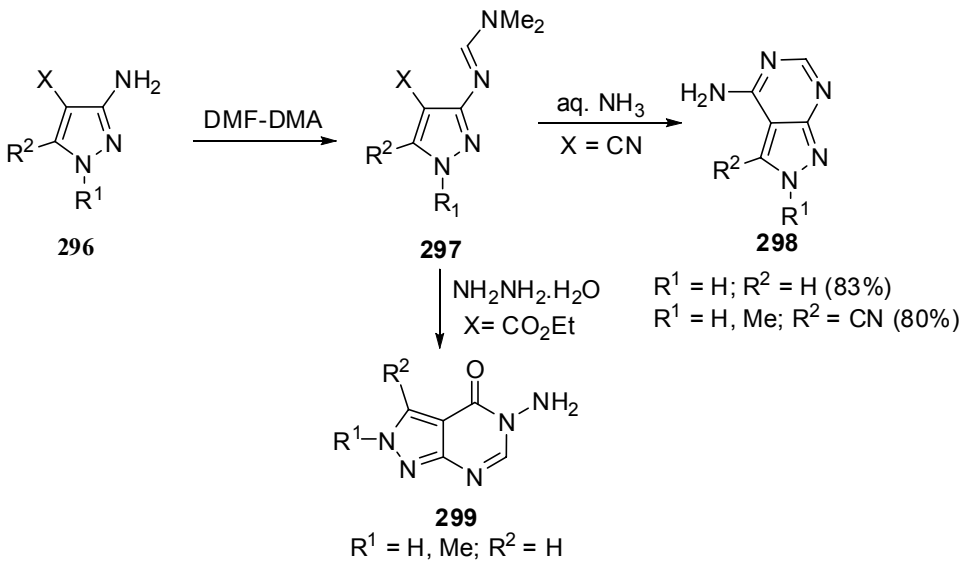
Scheme 81

Acylation of compound **293** with acetic anhydride afforded **294**, which coupled with benzenediazonium chloride and subsequently cyclized into **295**[108] (Scheme 82).



Scheme 82

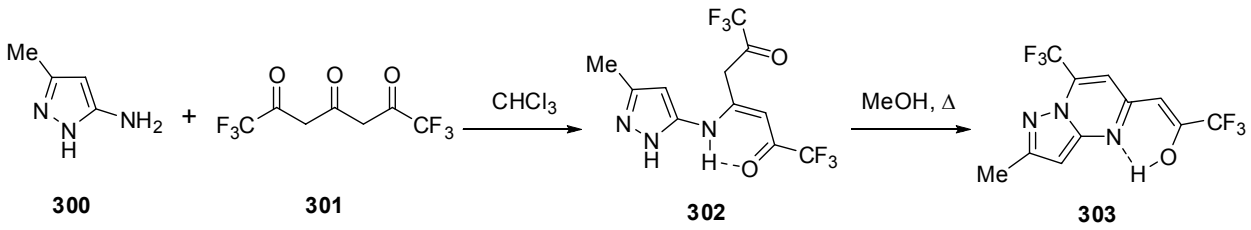
The reaction of **296** with DMF-DMA gave **297** that reacted with amines (X = CN) to yield **298**. Reaction of **297** with hydrazines; X = CO_2Et gave **299**[152,153] (Scheme 83).



Scheme 83

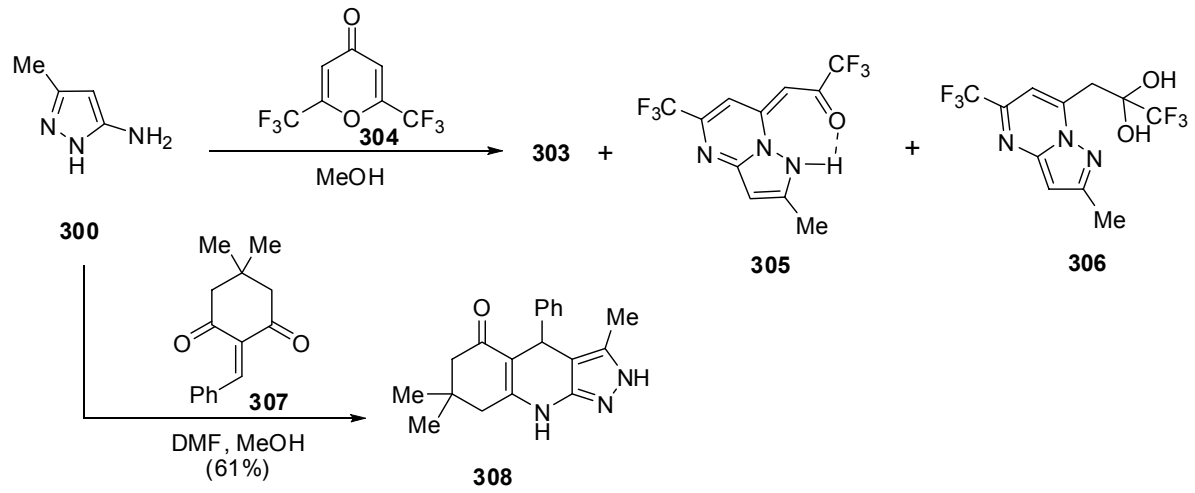
The parallel solution-phase synthesis of more than 2200 7-trifluoromethyl-substituted pyrazolo[1,5-*a*]pyridines and 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine carboxamides on a 50-100 mg scale has been accomplished *via* condensing 5-aminopyrazole derivatives with the corresponding trifluoromethyl-*β*-diketones.[154]

The condensation of 1,3,5-triketone **301** with 5-amino-3-methylpyrazole (**300**) afforded **302**. Refluxing the latter in methanol afforded **303**[155] (Scheme 84).



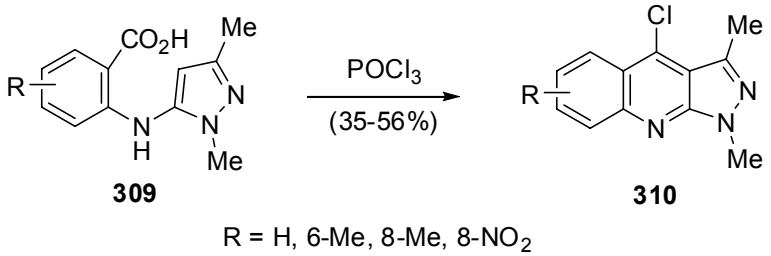
Scheme 84

The reaction of **300** with 2,6-bis(trifluoromethyl)-4*H*-pyran-4-one (**304**) in methanol gave a mixture of **303**, **305**, and **306**.[155] On the other hand, 2-benzylidene-5,5-dimethylcyclohexane-1,3-dione (**307**) reacted with **300** to yield pyrazolo[3,4-*b*]quinolinone **308** in 61% yield [156] (Scheme 85).



Scheme 85

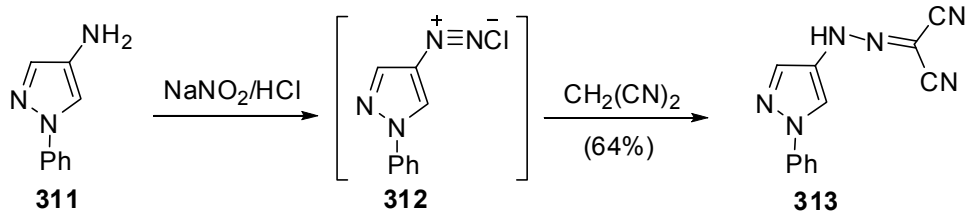
Cyclization of **309** with $POCl_3$ gave 4-chloro-1,3-dimethyl-pyrazolo[3,4-*b*]quinoline **310**, that was used recently as an intermediate for synthesis of a series of 4-amino-*N*-phenyl-1*H*-pyrazolo[3,4-*b*]quinolines which were potent inducers of apoptosis[157] (Scheme 86).



Scheme 86

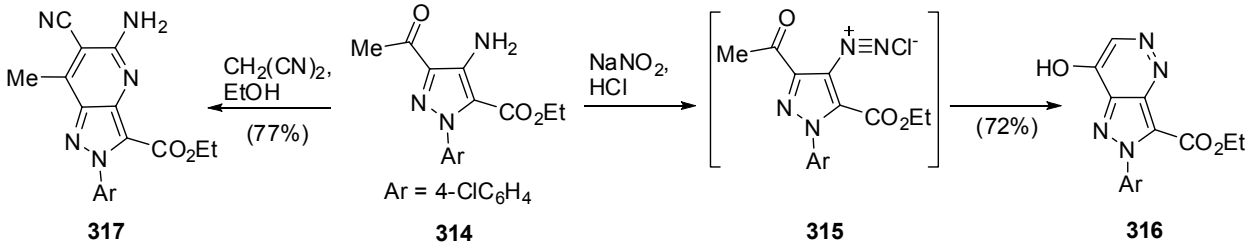
6.2 4-Aminopyrazoles

As expected for an aromatic amine, the 4-aminopyrazole **311** was diazotizable. The diazonium salt **312** was coupled with malononitrile to yield **313**[67] (Scheme 87).



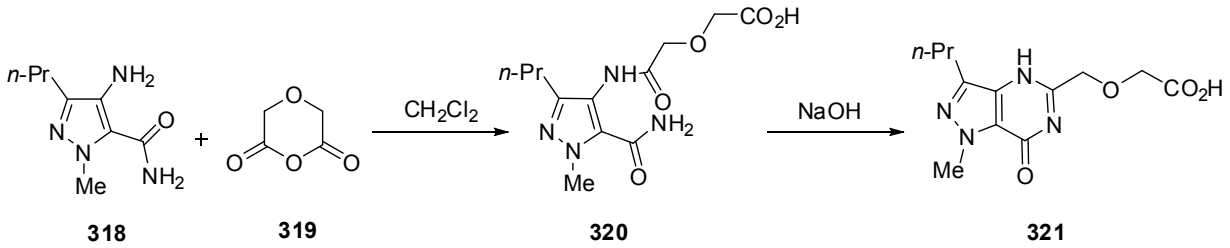
Scheme 87

Diazotization of 3-acetyl-4-aminopyrazole **314** gave pyrazolo[4,3-*c*]pyridazine derivatives **315** which smoothly cyclized into **316**. And condensing of **314** with malononitrile in refluxing ethanol gave pyrazolo[4,3-*b*]pyridine derivatives **317**[158] (Scheme 88).



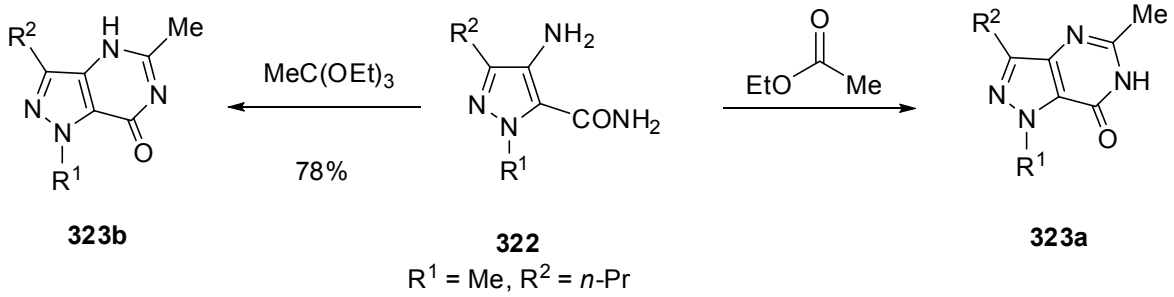
Scheme 88

The utility of 4-aminopyrazole-5-carboxamide derivatives as precursors to pyrazolo[4,3-*d*]pyrimidines has recently been surveyed by Elnagdi *et al*.[3] In addition to this, the reaction of **318** with 1,4-dioxane-2,6-dione (**319)** afforded **320** that readily cyclized into **321**[159] (Scheme 89).



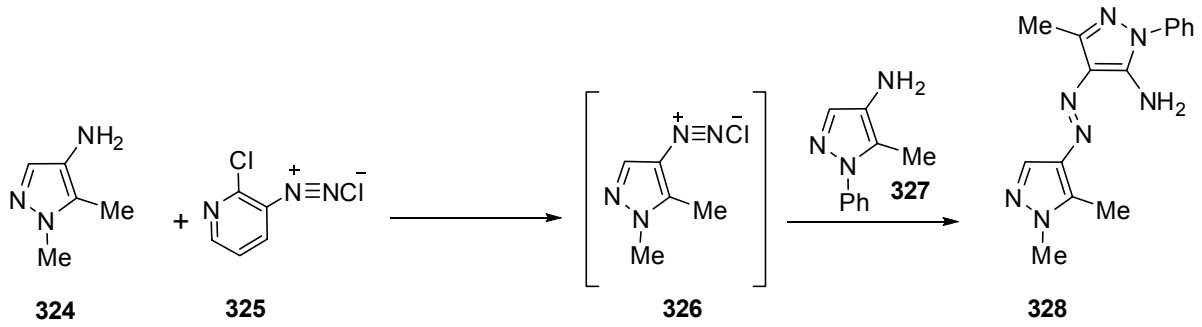
Scheme 89

The reaction of **322** with ethyl acetate gave pyrazolo[4,3-*d*]pyrimidin-7-ones **323a**.[160] Similarly, **322** reacted with triethyl orthoacetate to yield **323b**[161] (Scheme 90).



Scheme 90

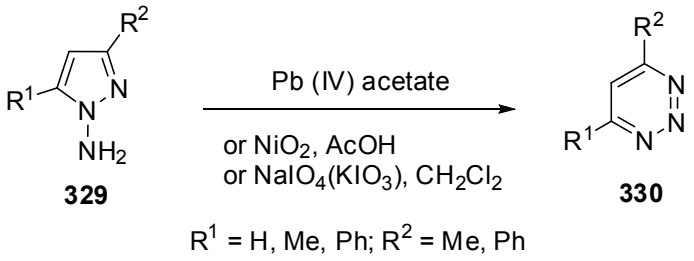
Unexpectedly, it was reported that 1,5-dimethyl-4-aminopyrazole **324** reacted with **325** to give intermediate **326** that reacted with **327** to afford **328**[162] (Scheme 91).



Scheme 91

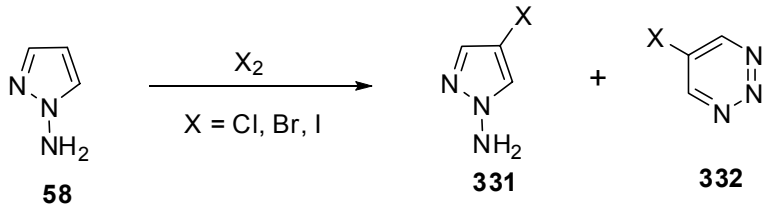
6.4 1-Aminopyrazole

Little has been reported. Oxidative rearrangement of *N*-aminopyrazole **329** to the 1,2,3-triazine **330** by lead tetraacetate,[68a,69] nickel peroxide-AcOH,[69] or $NaIO_4$ (KIO_3) have been reported[163] (Scheme 92).



Scheme 92

Treatment of **58** with 48% HBr gave **7**.[50] On the other hand, halogenation gave **331** and **332**[164] (Scheme 93).



Scheme 93

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