Recent developments in aminopyrazole chemistry

Hany Fakhry Anwar\textsuperscript{a,b,*} and Mohamed Hilmy Elnagdi\textsuperscript{c}

\textsuperscript{a}School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, P.O. Box 1068 Blindern, N-0316, Oslo, Norway
\textsuperscript{b}Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt
\textsuperscript{c}Department of Chemistry, Faculty of Science, University of Kuwait, P.O. Box 5969, Safat 13060, Kuwait

E-mail: hany.anwar@farmasi.uio.no

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, \textsuperscript{1}H-\textsuperscript{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-\textit{a}]pyrimidines, pyrazolo[3,4-\textit{b}]pyridines, pyrazoldiazonium salts, structure elucidation

Table of Contents

1. Introduction
2. Synthesis of 3(5)-aminopyrazoles
2.1 Reactions of \(\alpha,\beta\)-unsaturated nitriles with hydrazines
2.2 Reactions of hydrazines with 3-oxo-alkanenitriles
2.3 Synthesis from substituted hydrazones
2.4 Miscellaneous syntheses
3. Synthesis of 4-aminopyrazoles
3.1 Reduction of 4-nitroso, nitro, and azopyrazoles
3.2 Reaction of arylhydrazononitrile with functionally substituted alkylhalides
3.3 Miscellaneous syntheses
4. Synthesis of 1-aminopyrazoles
5. Synthesis of diaminopyrazoles
5.1 Synthesis of 3,5-diaminopyrazole and its derivatives
5.2 Synthesis of 4,5-diaminopyrazoles
6. Chemical reactivity of aminopyrazoles
6.1 3(5)-Aminopyrazoles
6.1.1 Reactions with electrophilic reagents
6.1.2 Diazotizations
6.1.3 Halogenation
6.1.4 Acylation
6.1.5 Reactivity toward bidentate electrophiles
6.1.6 Reactions with aldehydes and ketones
6.1.7 Cycloaddition and dipolar cycloadditions
6.1.8 Intramolecular cyclization
6.1.9 Miscellaneous
6.2 4-Aminopyrazoles
6.3 1-Aminopyrazoles

1. Introduction

The chemistry of aminopyrazoles has been extensively investigated in the past. The considerable biological and medicinal activities of pyrazoles and azolopyrazoles, for which aminopyrazoles are preferred precursors, have stimulated these investigations. Interest in aminopyrazole synthesis and chemistry has recently been revived. The established activity of Zaleplon (1), Viagra (2) as well as Allopurinol (3) is surely behind this interest (Figure 1).

Chemistry of 3(5)-aminopyrazoles has been reviewed in 1983 by Elnagdi et al. and more recently in 2004 by El-Taweel and Abu Elmaati. 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.

![Chemical structures of Zaleplon (1), Viagra (2) and Allopurinol (3).](image)

**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 hydrazines17-20 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

\[ \text{CN} \xrightarrow{\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}} (98\%) \xrightarrow{\text{H}_2\text{SO}_4/\text{EtOH}} (98\%) \xrightarrow{\text{i) p-TsCl, NaHCO}_3 \text{ ii) NaO-i-Pr, i-PrOH}} \]

Scheme 1

Similar syntheses have been extensively employed. Thus, reacting 9 with hydrazine hydrate afforded 1023-26 (Scheme 2). Recently, Quiroga et al.26c have described the synthesis of 5-aminol-1-aroylpyrazoles which were prepared from β-aminocrotononitrile with compounds containing the hydrazine moiety (Z–NHNH₂, Z = C₆H₅C(O), aryl-C(O), H₂NC(S)) in the presence of sodium acetate in 80-97% yields.

\[ \text{Y} = \text{CCl}_3, \text{OEt, NMe}_2, \text{SMe, NH-aryl.} \]

\[ \text{X} = \text{H, Ph, aryl, Het., CN, CO}_2\text{Et, CONH-Het.} \]

\[ \text{R}^1 = \text{H, SMe, NHPh, NH-aryl} \]

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, while 13 produced 14 on reaction with hydrazine hydrate (Scheme 3).

**Scheme 3**

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

**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. When reacted with aminoguanidine nitrate, however, 19 (R = 4-fluorophenyl) afforded only 20 in 62% yield. The reaction of 22 with hydrazine hydrate afforded the aminopyrolopyrazole 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).\(^{36}\)

A new synthesis of 5-aminopyrazoles on a solid support \textit{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).\(^{37}\)
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, CO₂R) 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 °C.\(^{42}\)
Scheme 9

Recently, heptanenitrile (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

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

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

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).

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
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

Scheme 16

2.4 Miscellaneous syntheses
The rearrangement of N-aminopyrazole (58) in hydrobromic acid afforded 7 via intermediacy of 59 (Scheme 17).50

Scheme 17
It has been reported that 5-substituted aminopyrazoles 62 were formed via gently heating \( \beta \)-ketoamides 60 with aryl or alkylhydrazines and Lawesson’s reagents (LR). Intermediacy of 61 is postulated (Scheme 18).51

\[
\begin{align*}
R^1 &= \text{Et, Bn, Ph}; \\
R^2 &= \text{H, Me, Et, Bn}; \\
R^3 &= \text{H, Me, Ph}; \\
R^4 &= \text{Me, Ph}; \\
R^5 &= \text{Bn, Ph}
\end{align*}
\]

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

\[
\begin{align*}
R^1 &= \text{H, Ph}; \\
R^2 &= \text{Me, Ph}; \\
R^3 &= \text{Me}
\end{align*}
\]

Scheme 19

3-Methyl-4-nitro-5-phenyl-1H-pyrazole (65) has been reduced using Pd/C and H\(_2\) to yield corresponding aminopyrazole 66 (Scheme 20).53
Scheme 20

4-Aminoantipyrine 67 was readily obtained via reduction of 4-nitroantipyrine 68 with H₂-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

Scheme 21

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

Scheme 22

R = H, Me, CH₂CHOH, CH₂CH₂OAc, Ph; X = H, CO₂Et, Het.
3.2. Reaction of arylhydrazononitrile with functionally substituted alkylhalides

This synthesis has recently been developed initially by Goncalves et al. who reported that mesoxalalonitrile arylhydrazones $75a$ reacted with functionally substituted hydrazines in triethylamine solutions to yield 4-aminopyrazole-5-carbonitriles $77a$. Subsequently, Elnagdi et al. 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.

![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).

![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. On the other hand, the addition of nitrilimines 83 to the benzoxazine 84 afforded 85 that underwent ring chain tautomerism and finally gave 86 (Scheme 25).
The reaction of tetrazines 87 with cyanotrimethylsilane (TMSCN) gave the corresponding 4-aminopyrazole derivatives 88 and 89 (Scheme 26). The 4-aminopyrazoles were obtained via extension of Gabriel’s synthesis of amino acids. Thus, reacting 90 with α-bromoacetophenone gave 91 that condensed with dimethylformamide dimethyl acetyal (DMF-DMA) to yield 92. The latter reacted with hydrazine hydrate to yield 93 which was converted to 94 (Scheme 27).
4. Synthesis of 1-aminopyrazoles

These are obtained by \textit{N}-amination of pyrazoles. Unsubstituted pyrazole (95) gave only 58 while substituted pyrazole 96 gave mixtures of \textit{N}-1 and \textit{N}-2-aminated products 97\textit{a} and 97\textit{b} (Scheme 28).
5. Synthesis of diaminopyrazoles

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

It has been reported in old German literature\(^7\)\(^0\) that malononitrile (98) reacted with hydrazine hydrate to yield 3,5-diaminopyrazole 99. Subsequently Sato,\(^7\)\(^1\) Taylor, Hartke\(^7\)\(^2\) and Elnagdi and co-workers\(^7\)\(^3\) have established that the product was really \(^1\)\(^0\)\(^2\); formed via initial dimerisation of malononitrile to yield 101. 3,5-Diaminopyrazole was subsequently prepared via reacting 100 with hydrazines\(^7\)\(^4\)\(^a\) (Scheme 29).

\[
\begin{align*}
\text{CN} & \quad \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \\
\text{98} & \quad \text{R} = \text{H} \\
\text{H}_2\text{N} & \quad \text{NC} \\
\text{101} & \quad \text{EtOH (38\%)} \\
\text{PhNHNH}_2 & \quad \text{102}
\end{align*}
\]

Scheme 29

Coupling malononitrile with aromatic diazonium salts afforded corresponding arylhydrazones 103 that reacted with hydrazine hydrate to yield arylazo-3,5-diaminopyrazoles 104.\(^7\)\(^3\)\(^b\) These compounds have been found interesting as formulation for hair dyes, antimicrobial agents and antitumor agents (Scheme 30).\(^7\)\(^3\)\(^c\),\(^7\)\(^4\)\(^b\),\(^c\)

\[
\begin{align*}
\text{ArN} & \equiv \text{N} \\
\text{103} & \quad \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \\
\text{N} & \quad \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \\
\text{104} & \quad \text{H}_2\text{N}
\end{align*}
\]

Scheme 30

Recently, Elnagdi \textit{et al.}\(^7\)\(^5\) have successfully synthesized 4-benzylpyrazole-3,5-diamine (107) \textit{via} reducing benzylidemalononitrile (105) to 106 with sodium borohydride and reacting the latter with hydrazine hydrate to 107. Compound 107 has been previously obtained by Soto \textit{et al.}
al. via initially monoalkylating malononitrile (98) with 108 and subsequent reaction of 106 with hydrazine hydrate (Scheme 31).

\[ \text{Ph-CN} \rightarrow \text{Ph-CN} \rightarrow \text{Ph-CN} + \text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} \]

Scheme 31

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

\[ \text{NC} \rightarrow \text{NH}_2 \rightarrow \text{PhN=C=O} \]

Scheme 32

Phenacylmalononitrile (112) has been reported by Abdelrazek et al. to react with hydrazine hydrate to yield 4-phenacylpyrazole-3,5-diamine (113) as sole product. Abdelrazek claimed utility for synthesis of a variety of condensed aminopyrazoles. Elnagdi et al. have subsequently noted isolation of the pyridazine-6-one (114a) as well as 113 on reacting 112 with hydrazine. Recently, however, Abdelrazek 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 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. 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

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-aminopyrazoles 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
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 monoelctrophiles 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).

![Figure 2. Sites of electrophilic attack in the 3(5)-aminopyrazole.](image)

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. On the other hand, attempted coupling with benzoylacetonitrile (127), enaminonitriles 129, enaminones 131, 3-aminoacetonitrile (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.\textsuperscript{84,85} \(\beta\)-Naphthol reacted in the same way.\textsuperscript{84c,86} \(\alpha\)-Chloroacetylacetone 137 as well as ethyl \(\alpha\)-chloroacetoacetate afforded also heterocyclic hydrazidic halides 138 via a Japp-Klingemann acyl group cleavage (Scheme 36).\textsuperscript{87}

\begin{equation}
\begin{array}{c}
\text{Scheme 36} \\
3H\text{-pyrazolo}[5,1-c][1,2,4]\text{triazoles 139 were obtained from diazotized 122 and diphenyldiazomethane in 28-78\% yield (Scheme 37).}\textsuperscript{88}
\end{array}
\end{equation}
Reactivity of aminopyrazoles in diazotization and coupling was discussed in a recent report and the pattern demonstrated previously was confirmed.\textsuperscript{89}

Moyano \textit{et al.} have reported the isolation of pyrazolotriazines 141 and 145 on diazotization of 140 (Scheme 38).\textsuperscript{89}

Scheme 38

Diazotization of 146 afforded diazonium derivative 147 that readily cyclized into 148. Similarly, diazotization of 149 gave 150 (Scheme 39).\textsuperscript{90,91}

Scheme 39
Diazotization of 151 gave diazo-3(methylsulfonyl)-1H-pyrazole 152 that reacted with aryl isocyanates in dichloromethane to give 153 (Scheme 40).92

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

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

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).  

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.

Scheme 44

Treatment of 166 with bromine water gaveazo dyes resulting from dimerization through the amino groups, which was reduced to starting 167 by with zinc in acetic acid (Scheme 45).
6.1.4. Acylation. Acylation of 168 afforded a mixture of the 3(5)-acylamino-2-pyrazolylamine 169 as well as the acylpyrazoles 170 and 171 (Scheme 46).\textsuperscript{26c,99} Acylation using various reagents may be restricted to the 5-NH\textsubscript{2} group,\textsuperscript{100} especially when position 5 is blocked (Scheme 47).\textsuperscript{101,102}

\begin{align*}
\text{R}^1 &= \text{Me} \\
\text{Ar} &= 2,6-\text{Me}_2\text{C}_6\text{H}_3
\end{align*}

Scheme 46

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).\textsuperscript{103}
Isocyanates and isothiocyanates, respectively, reacted with aminopyrazoles 168 yielding the corresponding urea 182a and the thiourea 182b (Scheme 49).  

\[
\begin{align*}
\text{R}^1 = & \text{t-Bu, alkyl;} \\
\text{R}^2 = & \text{t-Bu, Ph}
\end{align*}
\]

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 \text{i-Pr}_2\text{NEt} 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\text{2} gave 187 in 71% yield. The latter could readily be cyclized into 188 in 65% yield (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-\( \beta \)-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 (Scheme 51).

Scheme 50

Scheme 51
The reaction of 122 with arylidenemalononitrile has been initially reported to yield 195. 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. Many examples of this reaction have been reported and in some cases the single crystal X-ray structure analysis was reported (Scheme 52).

![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).

![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 $\alpha,\beta$-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$_3$N, while, when the reaction was conducted in the presence of t-BuOK, 202 was formed (Scheme 54).\textsuperscript{111}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme54.png}
\end{center}
\end{scheme}

\textbf{Scheme 54}

Al-Mousawi et al.\textsuperscript{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.\textsuperscript{113} These products were obtained upon reacting 175 with the mixture of malononitrile and aromatic aldehydes in an ionic liquid (Scheme 55).\textsuperscript{114} Similarly, mixtures of aldehydes and ethyl cyanoacetate afforded 204.\textsuperscript{115} Also 203 was obtained from reacting 175 with aldehydes and 2-cyanoethanethioamide under microwave irradiation.\textsuperscript{116}

\begin{scheme}
\begin{center}
\includegraphics[width=\textwidth]{scheme55.png}
\end{center}
\end{scheme}

\textbf{Scheme 55}

Quite similar to this reaction is the reaction of 175 with mixtures of aldehydes and aroylacetonitrile 205 to yield 206 (Scheme 56).\textsuperscript{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. Enaminonitriles behaved similarly. Thus 122 gave 213. Pyrazol-5-amine 122 reacted with 214 to yield 215 (Scheme 59). Interestingly, Zaleplon derivatives were prepared in this way. It has been reported that 122 reacted with 216 to yield the dihydropyrazolo[1,5-α]pyrimidine 217. 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.

Scheme 59

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

Synthesis of the functionalized pyrazolo[1,5-a]pyrimidines were described from amniopyrazoles 222 and 3-hydroxy-2-arylacrylaldehydes 224 upon microwave irradiation or conventional heating to yield 225. Also pyrazolo[1,5-a]pyrimidines 227 were obtained from gem α-oxoketenedithioacetals 226 with aminopyrazoles 122 mainly at exocyclic amine moiety (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 (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 (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 (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\textsuperscript{134} (Scheme 65).

On the other hand, mixture of 238, 239 and 240 were obtained from the reaction of 168 with 235\textsuperscript{134} (Scheme 66).
Scheme 66

The reaction of 241 with the same reagent 235 afforded 242 as sole product in 68-72% yields\textsuperscript{134} (Scheme 67).

Scheme 67

A regioselective one-pot synthesis of pyrazolo[1,5-\(\alpha\)]pyrimidine derivatives 246 from aminopyrazole 7 and \(\alpha,\beta\)-unsaturated imines 245 which was generated in situ from methyl phosphonate, nitrile, and aldehyde\textsuperscript{135} (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).

\[
\begin{align*}
\text{Me} & \quad \text{N} & \quad \text{NH}_2 & \quad \text{Me} \\
\text{N} & \quad \text{H} & \quad \text{Ar} & \quad \text{OH} & \quad \text{N} \\
\text{Me} & \quad \text{Me} & \quad \text{N} & \quad \text{N} & \quad \text{N} \\
\end{align*}
\]

\( \text{Ar} = \text{Ph}, 4-\text{MeC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4 \)

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).

\[
\begin{align*}
\text{Me} & \quad \text{N} & \quad \text{NH}_2 & \quad \text{Me} \\
\text{N} & \quad \text{H} & \quad \text{ArCHO} & \quad \text{Ph} \\
\text{Me} & \quad \text{Ph} & \quad \text{Ar} & \quad \text{Ph} \\
\end{align*}
\]

\( \text{Ar} = \text{Ph}, 4-\text{FC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2-\text{FC}_6\text{H}_4, 4-\text{CF}_3\text{C}_6\text{H}_4, 2-\text{CF}_3\text{C}_6\text{H}_4, 2-\text{O}_2\text{NC}_6\text{H}_4, 3-\text{O}_2\text{NC}_6\text{H}_4, 4-\text{O}_2\text{NC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4, \text{Het.} \)

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 \( \alpha \)-methyl 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).

\[
\begin{align*}
\text{Ar} & \quad \text{R}^2 & \quad \text{R}^1 \\
\text{N} & \quad \text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

(20-25%)

(51-55%)

\[
\begin{align*}
\text{Ar} & \quad \text{CHO} & \quad \text{Me} & \quad \text{R}^2 \\
\text{N} & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{Ar} & \quad \text{NH}_2 & \quad \text{Me} & \quad \text{R}^2 \\
\end{align*}
\]

(61-75%)

\[
\begin{align*}
\text{Ar} & \quad \text{R}^1 & \quad \text{R}^2 \\
\text{N} & \quad \text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\( \text{Ar} = 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4 \\
\text{R}^1 = \text{Me}, \text{Ph}, \text{aryl} \\
\text{R}^2 = \text{Me}, \text{CH}_2\text{CN}, \text{CH}_2\text{Ph}, \text{aryl}, \text{CO}_2\text{Et} \)

Scheme 71
Similarly, 253 condensed with cyclohexanedione 257 and with cyclopentanone (258) to yield 259 and 260, respectively \(^{139}\) (Scheme 72).

![Scheme 72](image)

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).

![Scheme 73](image)

Sodium naphthoquinone-4-sulfonate 264 reacted with 5-aminopyrazole (7) to yield pyrazolyl-naphthoquinone 265 \(^{141}\) (Scheme 74).

![Scheme 74](image)
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](image)

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](image)

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.\textsuperscript{143} Thus, treating \textit{277} with 10\% NaOH solution afforded \textit{278}\textsuperscript{147} (Scheme 78).

Scheme 78

6.1.9 Miscellaneous. The 2,4-dichloropyrimidines \textit{279} reacted with aminopyrazoles \textit{280} in the presence of triethylamine to give 4-substituted 2-chloropyrimidines \textit{281}. For inactivated pyrimidines (e.g. 5-Me/H) the reaction mixture was heated to 70 °C. Nucleophilic aromatic substitution of \textit{281} with amines to yield \textit{282} was affected by heating under basic conditions\textsuperscript{148} (Scheme 79).
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 (Scheme 80).

Scheme 80

Treatment of 5-amino-1H-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 (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\(_2\)Et 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.\textsuperscript{154}

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

Scheme 84

The reaction of 300 with 2,6-bis(trifluoromethyl)-4H-pyran-4-one (304) in methanol gave a mixture of 303, 305, and 306.\textsuperscript{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 (Scheme 85).
Scheme 85

Cyclization of 309 with POCl₃ 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-1H-pyrazolo[3,4-b]quinolines which were potent inducers of apoptosis¹⁵⁷ (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 313⁶⁷ (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]

**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]

**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]

**Scheme 93**


References

2006, 43, 931.
70. von Rothenburg, R. Chem. Ber. 1894, 27, 685.


134. (a) Guerrini, G.; Ciciani, G.; Cambi, G.; Bruni, F.; Selleri, S.; Besnard, F.; Montali, M.; Martini, C.;


Author’s biography

**Hany Fakhry Anwar** was born in Cairo, Egypt, in 1979. He received his B.Sc. in chemistry (2001) and his M.Sc. in organic chemistry (2005) from Cairo University. Recently, he received his Ph.D. from the School of Pharmacy, Department of Pharmaceutical Chemistry, Oslo University. Hany F. Anwar has published ten research papers in organic chemistry. His research interests focus on the synthesis of heterocyclic compounds and natural products, and synthesis of molecules with biological activity.

**Mohamed Hilmy Elnagdi** was born in Egypt in September 1941. He graduated from the Faculty of Science at Cairo University in 1962; since that date, Prof. Elnagdi has worked at Cairo University, Faculty of Science, in the Chemistry Department. Prof. Elnagdi obtained his M.Sc. in 1966, Ph.D. in 1969, and D.Sc. in 1982. He has also been awarded a Diploma in Applied Chemistry from Tokyo Institute of Technology in 1973. Prof. Elnagdi has been professor of organic chemistry at Cairo University since 1980. He worked as professor of organic chemistry
at Kuwait University from 1993 to 1999, then as visiting professor at the same university in 2003. Prof. Elnagdi has received fellowships from several institutions, including NTNF Norway taken at University of Oslo (1977); Visiting Associate Professor at the University of Utah in 1976 with Prof. L. B. Townsend; Alexander von Humboldt Fellowship at the University of Bonn with Profs. H. Wamhoff and R. Regitz. The Alexander von Humboldt Foundation has continually supported his activities in Germany, enabling him to cooperate with many German colleagues including Profs. K. Hafner, K. S. Hartki, M. Hoffmann, and H. H. Otto. Prof. Elnagdi has specialized in the synthesis of polyfunctional heterocycles and has published around 350 papers in this area as well as 15 review articles. In addition, he got several national and regional research awards and published several books.