Chapter 6

# Synthesis of Nitriles – Synthesis of 4-Cyano Pyrazole, 5-Aminopyrazole Derivatives and the Deamination of 5-Aminopyrazole Derivatives

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Additional information is available at the end of the chapter

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**Abstract**

Chemoselective reaction on 3-dimethylamino-2-aroyl-propenenitrile and hydrazine in acidic medium yields 4-cyano pyrazole, where as in basic medium yields 5-amino pyrazoles as major product.

**Keywords:** 4-Cyanopyrazole, 5-aminopyrazole, Deamination, Isopentyl nitrite, Chemoselective reactions

## 1. Introduction

Pyrazole is an organic compound having a molecular formula $C_3H_4N_2$, pentatomic heterocycle with a nitrogen heteroatom, having a five member ring structure with three carbon and adjacent two nitrogen atoms. Pyrazoles rarely occur in nature; in 1959, β-(1-pyrazolyl) alanine was isolated from the seeds of water melons (*Citurllus lanatus*) (L. Fowden). Pyrazoles exhibit wild range of biological activities such as anti-diabetic, antiviral, anti-cancer, anti-inflammatory, antibacterial, and antifungal activities).

**History:** Ludwig Knorr (1883) has given the name pyrazole to this class of compounds. The reduced forms of pyrazoles are pyrazoline and pyrazolidine. The substituted derivatives of pyrazole has been used in medicines and in other technical applications.

### 1.1. Physical properties

Pyrazole is a colorless solid, boiling points (b.p), 186-188°C, melting point (m.p.), 67-70 °C, a weak base $Pk_b$ = 11.5 ($pK_a$ of the conjugated acid 2.49 at 25 °C, Mol. Wt. 68.0776 g/mol, and soluble in water

### 1.2. Chemistry of pyrazole

The high m.p. and b.p. of pyrazole compared with 1-alkyl or aryl substituted pyrazoles are due to intermolecular hydrogen bonding which results in the dimmer. It is a tautomeric substance. Pyrazole is a weak basic and forms salts with inorganic acids; the imino hydrogen may be replaced by an acyl group.

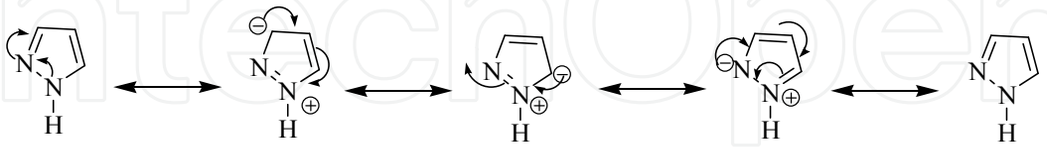

**Figure 1.** Resonating structures for pyrazole

Pyrazole resistant to oxidation and reduction reaction due to loss of aromaticity, but may be hydrogenated catalytically, first to pyrazoline, and then to pyrazolidine. Both of these compounds are stronger bases than pyrazole.

**Oxidation**: Pyrazole ring system is resistant to oxidizing agents but the side chain may be oxidized to carboxylic acid group in the presence of potassium permanganate.

**Reduction**: Pyrazole ring system can be reduced with molecular hydrogen and metal catalyst to pyrazole and pyrazolidine both are stronger bases than pyrazole.

### 1.3. Alkylation and acylation

The free N-H group in pyrazole can be alkylated with alkylating agents such as alkyl halides, diazomethane, and dimethyl sulfate or acylated using acid chloride and acetic anhydride.

**Electrophilic aromatic substitutions**: Pyrazole is an aromatic compound that exhibits all the properties of aromatic compounds such as electrophilic substitution reactions e.g. halogenation, nitration, sulfonation, etc., in neutral or in basic medium, but not in acidic medium. The substitution occurs at $C_4$-position through the formation of arenium ion intermediate.

**Reactions of pyrazoles with nucleophilies**: The presence of a strong electron-withdrawing group on pyazole assists nucleophilic substitution.

General synthesis:-

1. Pyrazoles and their derivatives were synthesized from hydrazine or its derivatives and a 1,3-dicarbonyl compound using an acid catalyst, the reaction is also known as Knorr pyrazole synthesis.
2. Sucrow reported the synthesis of pyrazole using monomethyl hydrazones of dialkyloxalacetates.
3. Hart and Brew Baker have described the cyclization of 1,3- bis(diazopropane) to pyrazole by a concerted intermolecular 1,3-dipolar cycloaddition reaction.

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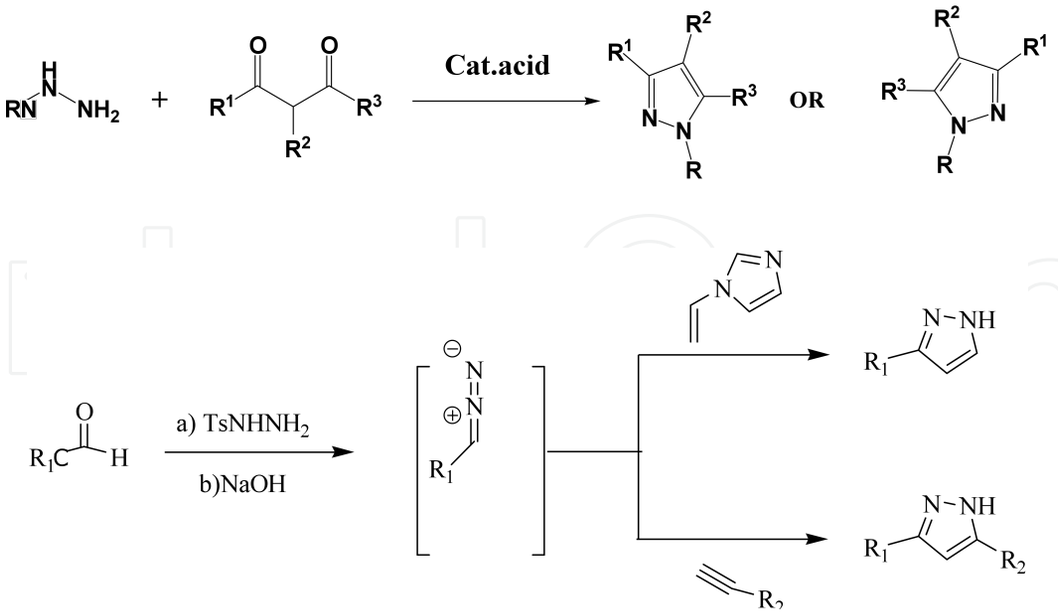


4. Pyrazoles are prepared by the action of hydrazine on 1,3-di-functional derivatives, such as carbonyl group, which can be replaced by a three-member ring, usually oxirane-aziridine-β-substituted-pyrrole-indole derivatives.

5. The addition of diazo compound to acetylenes gives pyrazole derivatives.

The same reaction as applied to olefin leads to dihydropyrazoles which are termed pyrazolines.

6. Reaction of hydrazine and their derivatives with $\alpha$, β-unsaturated aldehyde / ketones yields pyrazolines.

### 1.4. Pharmacological interest

Pyrazole nucleus constitutes a number of sub-structures of natural products and biologically active compounds. Several derivatives of these systems find use in medicine described as follows:

*Derivatives of pirolidine as drugs:* Piracetam (Nootropilum) polyvinylpyrrolidone used for dementia and cognitive problems such as a chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning.

*Derivatives of pyrazolone-5 as drugs:* Phenazone (antipyrine) *Antipyrine* and benzocaine otic are *used* to relieve ear pain and swelling caused by middle ear infections. The dipyrone (metamizole sodium) is an organic *sodium* salt of antipyrine substituted at C-4 by a methyl(sulfonatomethyl)amino group, commonly *used* as a powerful analgesic and antipyretic. The budirol (propiphenazonum) is an analgesic efficacy.

Derivatives of pyrazolidine-3, 5-dione as drugs: Phenylbutazone, tribuzonum, kebuzone. Derivatives of pirolidine as drugs: Piracetam (Nootropilum), polyvinylpyrrolidone used for

dementia cognitive problems such as a chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning.

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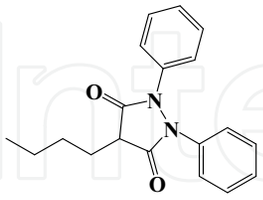
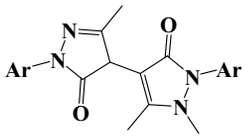
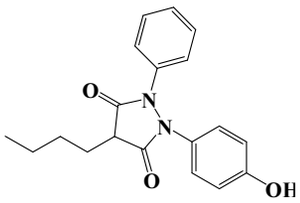
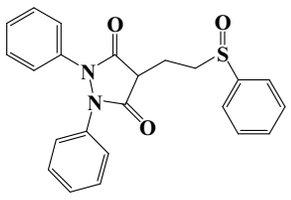
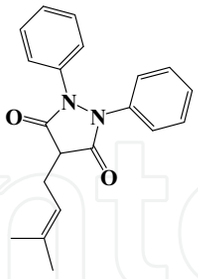
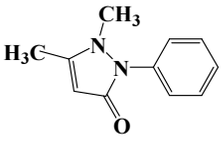
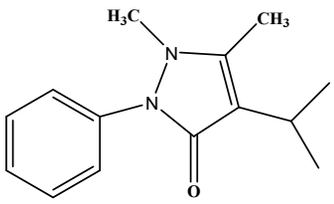
|  | **Phenylbutazone** is 4-butyl-1, 2-diphenyl pyrazolidine 3,5-dione used as analgesic, antiinflammatory, and antipyretic drugs, and also used for the treatment of rheumatic disorder. |
|  | **Forbisen** is 2, 2', 3, 3'-tetramethyl-1, 1'-diphenyl-4, 4'-bi-3, 3'-pyrazoline-5, 5'-dione a by-product obtained in the manufacture of antipyrine, and has been used in bovine anaplasmosis. |
|  | **Oxyphenbutazone** is used for the treatment of inflammation of the eyes and also is one of the active metabolite of phenylbutazone. |
|  | **Sulphinpyrazone** is an analogue of phenylbutazone having 2-phenylsulphinylethyl group in the place of *n*-butyl group at $C_4$-position; promotes excretion of uric acid and urate by inhibiting their tubular reabsorption. |
|  | **Feprazone**: Structurally, it is similar to phenylbutazone except that the former is having a 3 methylbutenyl substituent at $C_4$-position of pyrazoline-2,5-dione skeleton in place of a butyl substituent. Feprazone also finds use in the treatment of rheumatic disorders. |
|  | **Phenazone** is a pyrazoline derivative, chemically 2,3-dimethyl-1-phenyl 3-pyrazolin-5-one, available in white crystals or white crystalline powder soluble in water. Phenazone is well known for its analgesic and antipyretic actions. |
|  | **Propylphenazone** (4-isopropyl 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) is phenazone derivative with $C_4$-isopropyl side chain having analgesic properties. |

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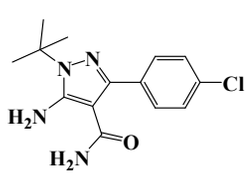
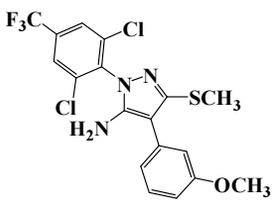
5-Pyrazolone derivatives are also used as cotton azo dye to improve quality such as brightness and light fastness property.

The 5-aminopyrazole system represents an important hetero-cyclic compound having considerable interest due their long history of applications in the pharmaceutical and agro-chemical industries [1-4].

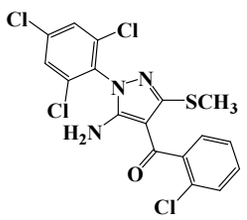
Literature reports over the past hundred years and their chemistry have been reviewed in 1964 [5] and in 1967 [6] and proved their importance in medicinal and technical applications. Structurally, simple 5-amino-1-tertbutylpyrazole-4-carboxamide **I** was found to inhibit p56 Lck [7]. The simple N-phenyl amide of 5-amino-1,3-dimethylpyrazole-4-carboxylic acid **II** has been shown to exhibit antifungal activity [8]. The 5-amino-1-(2,6-dichloro-4-trifluoromethyl) phenyl)-4-(3-ethoxyphenyl)-3-methyl thiopyrazole has been described as a potent GABA (γ-aminobutyric acid) inhibitor with selectivity toward insect versus mammalian receptors [9]. 5-Amino-4-benzoyl-3-methylthio-1-(2,4,6-trichlorophenyl)pyrazole **III** has been reported as a potent corti-cotrophin-releasing factor-1 (CRF-1) receptor antagonist [10]. The 5-amino-1-(4-methylphenyl) pyrazole **IV** has been tested as an NPY5 antagonist [11].



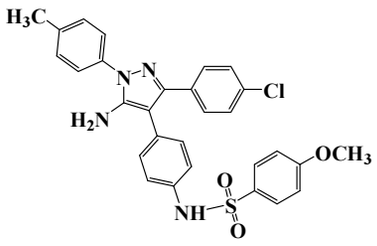

I




II




III




IV

The 5-amino-1-pyrazinyl-3-carboxamidopyrazole derivatives has been recently reported as a potent antibacterial agent with a very broad spectrum [12]. Recently, the components of the mitotic machinery have been targeted in an attempt to develop novel anticancer agents. These include critical signaling kinases such as the Aurora, PLK, and the cyclin-dependent kinase (CDK). The compound (AZD1152) is the first Aurora-B selective inhibitor to enter the clinical trials [13].

## 2. Results and discussion

The synthesis of 3-dimethyl-2-benzoyl propenenitriles **1(a-b)** is the vital key intermediate for the synthesis of various nitrogen heterocycles, such as pyrazole and pyrimidine derivatives. The literature reports suggest that 1,3,4-trisubstituted pyrazole derivatives are important compounds in the preparation of 1,5-diphenylpyrazole nonnucleoside derivatives, which are used as HIV-1 nonnucleoside reverse transcriptose inhibitors [15]. Similarly, 4-cyano pyrazole

derivatives showed significant biological activity by inhibiting alcohol dehydrogenase [16]. They also produce skeletal muscle relaxation on administration to animals [17].

In the literature, several methods have been reported for the synthesis of 5-amino pyrazole derivatives. Hasseneen and coworkers [18] have prepared pyrazole derivatives by the reaction of nitrile imine with fumaronitrile. Jachak and co-workers [19] also reported the synthesis of 4-cyano pyrazole derivatives by starting with cyanoacetaldehyde, DMF-DMA (*N*,*N*-Dimethylformamide dimethyl aceta) and hydrazines.

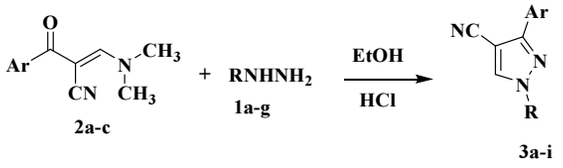
Recently, David Tupper [20] has reported the synthesis of 4-cyano pyrazole derivatives by starting with compounds similar to **1a.** These workers have prepared 4-cyano pyrazole derivatives along with 5-amino pyrazole derivative by refluxing 3-dimethylamino-2-benzoyl-propenenitrile **1a** with phenyl hydrazine or hydrazine in ethanol. However, the product was always a mixture of 4-cyano and 5-aminopyrazole derivatives. These workers have separated the mixture of pyrazoles by column chromatography and observed that the reaction of hydrazine or phenyl hydrazine took place with 3-dimethylamino-2-aroyl-propenenitrile to furnished pyrazole carbonitrile as major and aminopyrazoles as minor products.

Herein, the new route for the synthesis of 4-cyano pyrazole and 5-amino pyrazole derivatives has been described. It was demonstrated that the new procedure for the synthesis of 4-cyano and 5-aminopyrazole derivatives gave good yield. Also it was observed that treatment of **1** with hydrazine (or substituted hydrazine) in acidic medium gave 1,3-disubstituted 4-cyano-pryrazole derivatives **3**. Herein, the new route for the synthesis of 4-cyano pyrazole and 5-amino pyrazole derivatives has been described. It was demonstrated that the new procedure for the synthesis of 4-cyano and 5-aminopyrazole derivatives gave good yield. Also it was observed that treatment of **1** with hydrazine (or substituted hydrazine) in acidic medium gave 1,3-disubstituted 4-cyanopryrazole derivatives **3**. Tuper, Bray and his co-workers [20] reported that the 1,5-disubstituted–4-cyanopyrazole was obtained when compound **1** was refluxed in ethanol with hydrazine (or phenyl hydrazine).

### 2.1. Section I: Synthesis of 4-cyano pyrazole derivatives, 3a-i

Different methods were used for the synthesis of 4-cyano and 5-amino pyrazole derivatives. Tuper and Bray [20] performed these reactions without acid and base. Our observation was different from their studies.

The reactions of hydrazine or phenyl hydrazine with compound **2** in ethanol and catalytic amount of conc. HCl furnished 4-cyano pyrazole derivative **3(a-i)** as a single product (Experiment No. 1).



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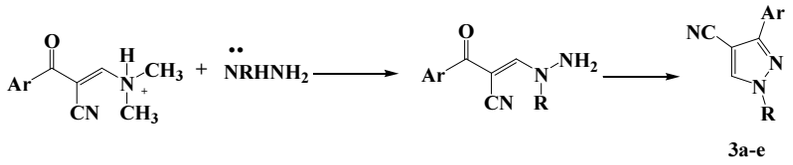
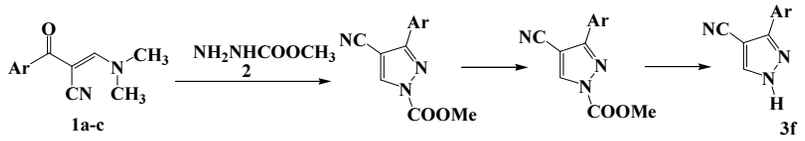



**3**: a, Ar= Ph, R=Ph; b, Ar=Ph, R=p-CH3Ph, c, Ar=Ph, R=p-CPh; d; Ar=Ph, R=p-NO2Ph; e, Ar=Ph, R=$OCH_3$Ph; f, Ar=Ph, R=H; g, Ar=Ph, R= $CH_2CH_2OH$; h, Ar=P-BrPh R= $CH_2CH_2OH$, I, Ar=P-BrPh R=Ph

The formation of 4-cyano pyrazole derivatives **3** can be rationalized as the acid protonated nitrogen of dimethylamino group and was replaced by hydrazine and then $NH_2$ of the hydrazine condenses with carbonyl carbon to form pyrazole ring. When the condensation of 3-dimethylamino-2-bezoyl-propenenitrile **1a** and N-methyl ester of hydrazine was carried out, the ester group has been hydrolyzed and decarboxylated to give 1H-pyrazole derivative **3f**.



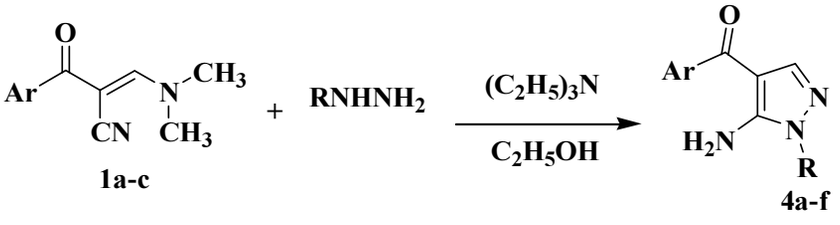

| Sr. No. | Name of the compound | Solvent | $N^1$-R | $C_3$-Ar | $C_5$-H |
|---|---|---|---|---|---|
| 1. | 1,3-diphenyl-1H-pyrazole-4-carbonitrile, **3a** | Lit [22] | | | |
| 2. | 3-phenyl-1-p-tolyl-1H-pyrazole-4-carbonitrile, **3b** | DMSO-$d_6$ | 2.35, s, 3H, CH3, 7.10-7.60 m, 4H, Ar-H | 7.10-7.60, m, 5H, Ar-H | 8.42, s |
| 3. | 1-(4-cholorphenyl)-3-phenyl-1H-pyrazole-4-carbonitrile **3c** | DMSO-$d_6$ | d ,7.60, d,4H, Ar-H | 7.16-7.50, m,Ar-H | 8.45, s |
| 4. | 1-(4-nitrophenyl)-3-phenyl-1H-pyrazole-4-carbonitrile, **3d** | Lit [19] | | | |
| 5. | 1-(4-methoxyphenyl)-3-phenyl-1H-pyrazole-4-carbonitrile, **3e** | DMSO-$d_6$ | 3.75 s CH3 6.90-5.77 m , 4H, Ar-H | 6.90- 5.77, m,Ar-H | 8.37, s |
| 6. | 3-phenyl-1H-pyrazole-4-carbonitrile, **3f** | DMSO-$d_6$ | 11.52, s, NH | 7.40- 7.95 m 5H, Ar-H | 8.00, s |
| 7. | 1-(2-hydroxyethyl)-3-phenyl-1H-pyrazole-4-carbonitrile **3g** | $CDCl_3$ | 3.67, t, 2H, $CH_2$,4.25 ,t 2H, $CH_2$ | 7.65, m, 5H, Ar-H | 8.08, s |
| 8. | 3-(4-bromophenyl)-1-(2-hydroxyethyl)-1H-pyrazole-4-carbonitrile, **3h** | $CDCl_3$ | 3.67, t, 2H, $CH_2$, 4.25 ,t 2H, $CH_2$ | 7.42 & 7.65 d, 4H Ar-H | 7.95, s |

**Table 1.** NMR of 4-cyano pyrazole 3a-j

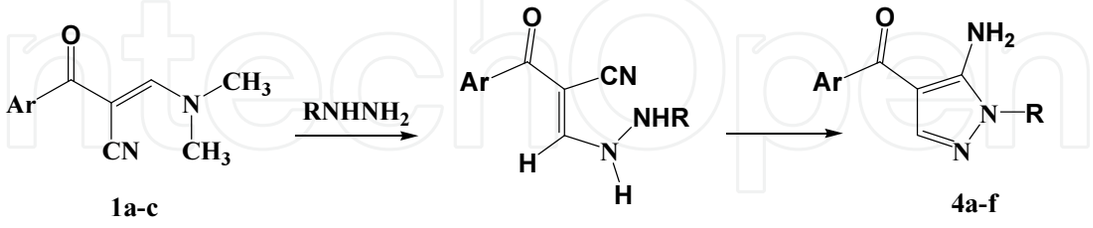
These compounds were characterized by IR, $^1$H NMR (Table No. 1). The IR of **3h** (R=$CH_2CH_2OH$) showed strong absorption at 2231 $cm^{-1}$due to CN and 3493 $cm^{-1}$ for OH. The $^1$H NMR in $CDCl_3$ of this compound showed clear triplet at δ 4.083 and 4.22 with J = 9.3 Hz. The aromatic protons showed para substituted pattern at δ 7.68 and 7.70 as doublet with coupling constant J=8.4 Hz. The $C_5$-H appeared as a sharp singlet at δ 7.89.

### 2.2. Section II: Synthesis of 5-Amino-4-aryl-substituted pyrazole derivatives, 4a-f

Compounds **1** and hydrazine or substituted hydrazine when refluxed in ethanol in the presence of triethylamine furnished 5-amino pyrazole derivatives **4(a-f)** in good yields (Experiment No. 2). This observation was again contradictory with Tupper's work [6]. These workers observed that when hydrazine and compound **1a** were refluxed with hydrazine or phenyl hydrazine in ethanol yielded the mixture of 4-cyano pyrazole and 5-amino pyrazole derivatives in 45–85% and 10–35% respectively. But it was observed that when base is used as a catalyst, the reaction completed within 1–2 hours, and 5-amino pyrazole derivative is only the product obtained. In this reaction, the condensation occurs by replacement of dimethylamino group and the ring closure reaction because of the attack of hydrazine moiety on nitrile function. The mechanism can be given as below.




**4**: a, Ar=Ph, R-Ph, b; Ar=Ph, R= CO-3-pyridyl; c, Ar=Ph, R= C (=S) NHPh, d, Ar=Ph, R= CO (p-ClPh); e; Ar=Ph,R= 2,4-($NO_2$)Ph, f; Ar= p-BrPh, R=Ph




Here the other product 4-cyano pyrazole was not formed in the basic medium. The benzoyl carbonyl is less reactive, and there is no chance for the condensation of hydrazine with it. The $^1$H NMR spectra (Table No. 2), IR of the compound **4(a-f)** characterizes all these 5-aminopyrazole derivatives. The elemental analysis was in agreement with the proposed structure. IR spectra **4f** show absorption bands at 3370 and 3320 $cm^{-1}$ due to $NH_2$ group and at 1748 $cm^{-1}$ due to the presence of carbonyl group. The $^1$H NMR of **4f** in $CDCl_3$ showed that the $NH_2$ split into two singlets at δ 7.57 and 7.76 exchangeable with $D_2O$. The 4-aromatic p-substituted

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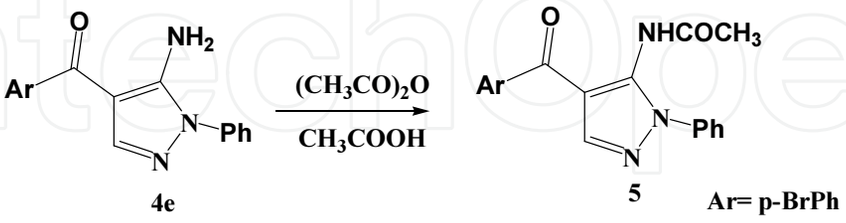
protons appears at 7.63 and 7.69 δ as doublet with J = 8 Hz. The 5-aromatic protons of the phenyl ring showed multiplet at δ 7.55–7.77, and the $C_3$-H appears as a singlet at δ 7.76. Thus the cyclization reaction provided synthesis for 4-cyano pyrazole and 5-amino pyrazole derivatives without a mixture of these two. The time required for the cyclization is also between 1 and 3 hours as compare to 2–18 hours as reported by Tupper and Bray [20].

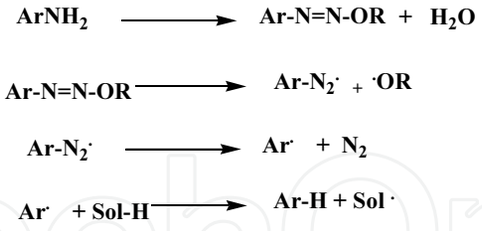



**4e** **5** **Ar= p-BrPh**

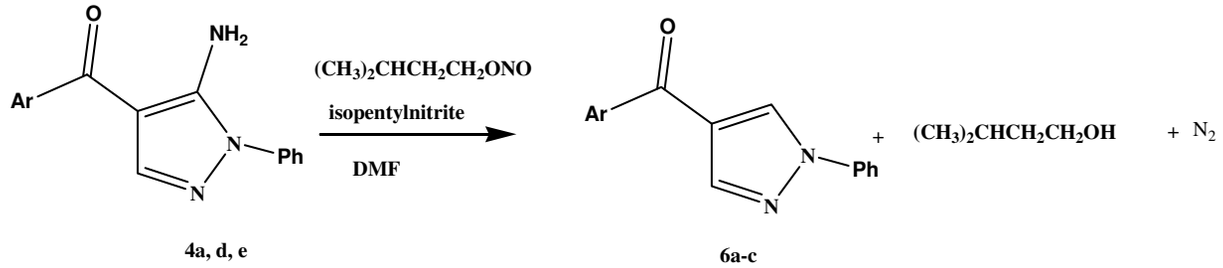
The presence of $NH_2$ in 5-amino pyrazole **4(a-f)** was confirmed by the formation of acetyl derivative. Thus compound **4e** on refluxing in acetic acid and acetic anhydride furnished acetyl derivative **5.**. The structure of **5** was characterized by IR and $^1$H NMR which is given in experimental part.

*2.2.1. Deamination of 5-aminopyrazole derivatives*

In the literature, the amino group in the pyrazole system can be removed by the method explained by Nishiwaki et al [23] and Doyle et al [21]. Doyle and his coworkers have performed the reductive deamination involving arylamines. Kornblum suggested that the aromatic primary amine group was diazotized and replaced by hydrogen donor [22].

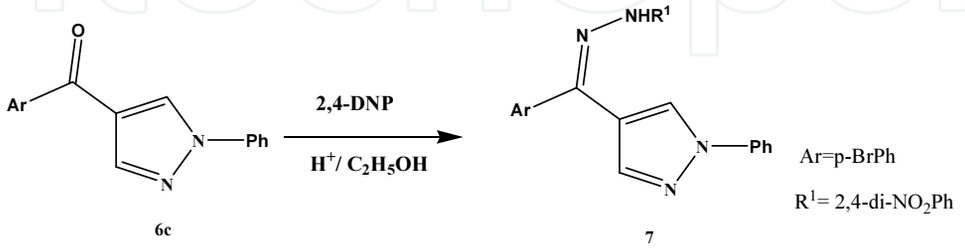



Thus the amino group in compounds **4a, d, e** in pyrazole on treatment with isopentylnitrile in DMF furnished deaminated pyrazole derivative **6a-c** in good yields.(ExperimentNo. 3).




**4a, d, e** **6a-c**

Compound 6**a-c** was characterized by $^1$H NMR, IR, and elemental analysis. The IR spectra did not show peak at δ 3370 and 3320 $cm^{-1}$ for $NH_2$ group, and the increase in carbonyl absorption from 1690 to 1720 cm–1 was due to the free carbonyl group that indicated the loss of $NH_2$ group. The $^1$H NMR of **6c,** R=Ph in $CDCl_3$ showed singlet for $C_3$-H and $C_5$-H at δ 8.12 and δ 8.34 as it was expected. The four aromatic protons showed para substituted pattern at δ 7.79, 7.77 as two doublets J = 8 Hz and five protons of phenyl ring showed multiplet at δ 7.22–7.75. After deamination, the product containing carbonyl function was characterized by the formation of 2,4-DNP derivatives.




6c 7

| Sr. No. | Name of the compound | Solvent | $N^1$-R | $C_4$-COAr | $C_3$-H | $C_5$-$NH_2$ |
|---|---|---|---|---|---|---|
| 1 | (5-Amino-1-phenyl-1H-pyrazole-4-yl)phenyl)methanone, **4a** | DMSO-$d_6$ | 7.40-7.75, m 5H Ar-H | 7.407.75,5H, m, Ar-H | 7.86, s | 7.40 &7.78 s |
| 2 | (5-Amino-1-(3-pyridylcarboxy)-1H-pyrazole-4-yl)phenyl) methanone, **4b** | DMSO-$d_6$ | 8.15-8.60, m, 4H | 7.40-7.75, m 5H, Ar-H | 7.97, s | 8.80 & 9.15, s |
| 3 | (5-Amino-1-(phenylsemicarbazide)-1H-pyrazole-4-yl) phenyl) methanone, **4c** | DMSO-$d_6$ | 7.28-7.93, m, 5H 12.05, bs, NH | 7.28-7.94, m, | 8.04, s | 9.2 & 11.82 s |
| 4 | (5-Amino-1-(4-chlorobenzene))-1H-pyrazole-4-yl) phenyl) methanone, **4d** | DMSO-$d_6$ | 7.25-7.78 m, 4H | 7.25-7.78, m, 5H | 7.92, s | 8.25 & 11.75 s |
| 5 | (5-Amino-1-(2,4-dinitrophenyl))-1H-pyrazole-4-yl) phenyl) methanone, **4e** | $CDCl_3$ | 8.23, 8.45, d & 9.23, s Ar-H | 7.28 &7.65 d 4H, Ar-H | 8.02, s | 8.30 & 11.80, s |
| 6 | (5-Amino-1-(4-bromobenzene))-1H-pyrazole-4-yl) phenyl) methanone, **4f** | $CDCl_3$ | 7.02-7.56, m, 5H, Ar-H | 7.26 & 7.63 d, 4H, ar-H | 7.92 s | 7.26 & 7.63 s, peak lost in $D_2O$ |

**Table 2.** NMR of 1-phenyl-4-benzoyl-5-aminopyrazole, 4a-f chemical shift in δ

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Thus compound **6c** on treatment with 2,4-dinitrophenylhydrazine in acidic medium furnished the hydrazone derivative **7** and supported the presence of carbonyl group in compound **6c.** (Experiment No. 5). The $^{1}$H NMR clearly indicated the singlet at δ 11.15. for NH protons and 3 hydrogen of phenyl group containing nitro group clearly observed at δ 8.09, 8.22, and 9.05.

## 3. Conclusion

The reaction of aroylpropenenitrile and substituted hyrazines in the presence of acid catalyst yielded 4-cyano pyrazoles and the same reaction in basic medium yielded 5-amino pyrazole derivatives as signal product in good yields.

To an equimolar solution (0.01 mol) of **1(a-b)** and substituted hydrazine **2(a-i)**, in ethanol (30 ml), concentrated hydrochloric acid (0.2 ml) was added, and the reaction mixture was refluxed for the time shown below. The solvent was removed in vacuo to get the residue of **3(a-j)**, which was recrystallized from the proper solvent.

**1,3-Diphenyl-4cyanopyrazoles, 3a**

Heating under refluxed for 3.5 hours, yield 65%, recrystallized from ethanol, m.p. 134°C (lit. [21] m.p. 135°C).

**1-p-Toloyl-3-phenyl-4-cyanopyrazole, 3b**

Heating under refluxed for 3 hours, yield 68%, recrystallized from ethanol, m.p. 123°C, IR(KBr):2230 and 1520 $cm^{-1}$.

**1-(p-Chlorophenyl)-3-phenyl-4-cyanopyrazole, 3c**

Heating under refluxed for 3 hours, yield 75%, recrystallized from ethanol, m.p. 141°C. IR (KBr): 2240, 1505 $cm^{-1}$.

**1-(4-nitrophenyl)-3-phenyl-1H-pyrazole-4-carbonitrile,3d**

Heating under refluxed for 3.5 hours, yield 70%, recrystallized from ethanol, m.p. 223°C, (lit. [19] m.p. 225°C).

**1-(4-methoxyphenyl)-3-phenyl-1H-pyrazole-4-carbonitrile,3e**

Heating under refluxed for 1 hour, yield 75%, recrystallized from ethanol, m.p. 125°C. IR (KBr): 2228 and 1510 $cm^{-1}$.

**3-phenyl-1H-pyrazole-4-carbonitrile, 3f**

Heating at 60°C for 6 hours, yield 60%, recrystallized from ethanol, m.p. 131°C (lit. [19] m.p. 134°C. IR (KBr): 3150, 2960, 2240, and 1510 $cm^{-1}$.

**1-(2-hydroxyethyl)-3-phenyl-1H-pyrazole-4-carbonitrile, 3g**

Heating under refluxed for 2.5 hours, yield 65%, recrystallized from ethanol, m.p. 106°C. IR (KBr): 2228, 1510 $cm^{-1}$.

**3-(4-bromophenyl)-1-(2-hydroxyethyl)-1H-pyrazole-4-carbonitrile, 3h**

Heating under refluxed for 2.5 hours, yield 63%, recrystallized from methanol, m.p. 135°C. IR (KBr): 2231, 1563, and 1533 $cm^{-1}$.

**3-(4-Bromophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile, 3i**

Heating under refluxed for 2 hours, yield 68%, recrystallized from methanol, m.p. 210°C. IR (KBr): 2210, 1600, 1580, and 1533 $cm^{-1}$.

### 3.1. Experiment 2

Synthesis of 1-substituted-4-benzoyl-5-aminopyrazoles, 4(a-h)

To an equimolar solution of **1a** or **1b** (0.01 mol), substituted hydrazines, **2a, j-n** in ethanol (30 ml) was taken in a reaction flask. Triethlyamine (0.2 ml) was added, and the reaction mixture was heated under reflux for the time shown below. The solvent removed in vacuo and the product obtained was filtered, recrystallized from the solvent shown for individual compound.

**(5-Amino-1-phenyl-1H-pyrazole-4-yl)phenyl)methanone, 4a**

Heating at 65°C for 1 hour, yield 65%, m.p. 178°C. IR (KBr): 3380, 3275, 1620, and 1540 $cm^{-1}$.

**(5-Amino-1-(3-pyridylcarboxy)-1H-pyrazole-4-yl)phenyl) methanone, 4b**

Heating under reflux for 1.5 hours, yield 45%, m.p. 149°C. IR (KBr): 3460, 3320, 3050, 1705, 1695, and 1630 $cm^{-1}$.

**5-Amino-1-(phenylsemicarbazide)-1H-pyrazole-4-yl) phenyl) methanone, 4c**

Heating under reflux for 1.5 hours, yield 450%, m.p. 127°C. IR (KBr): 3380, 3300, 3140, 1640, 1600, and 1550 $cm^{-1}$.

**(5-Amino-1-(4-chlorobenzene))-1H-pyrazole-4-yl) phenyl) methanone, 4d**

Heating under reflux for 1.5 hours, yield 45%, m.p. 199°C, recrystallized from ethanol. IR (KBr): 3370, 3320, 3040, 1690, 1630, 1590, and 1550 $cm^{-1}$.

**(5-Amino-1-(2,4-dinitrophenyl))-1H-pyrazole-4-yl) phenyl) methanone, 4e**

Heating under reflux for 2 hours, yield 60%, m.p. 217°C, recrystallized from ethanol. IR (KBr): 3443, 3221, 3050, 2922, 1741, 1631, 1605, and 1550 $cm^{-1}$.

**(5-Amino-1-(4-bromobenzene))-1H-pyrazole-4-yl) phenyl) methanone, 4f**

Heating under reflux for 1 hour, yield 50%, m.p. 186°C, recrystallized from ethanol. IR (KBr): 3370, 3320, 3040, 1690, 1630, 1590, and 1550 $cm^{-1}$.

### 3.2. Experiment 3

Deamination of 5-amonopyrazole derivatives: Preparation of 1-Substituted-4-benzoyl pyrazole, 6(a-d)

To a solution of **3a, d, or f** (0.01 mol) in anhydrous dimethylformamide (5 ml) maintained at 60–65°C, isopentylnitrite (0.01 5 mol) in anhydrous DMF (3 ml) was added over 10 minute. The mixture was stirred for 30 minutes. The solvent was removed under reduced pressure to get solid. The solid obtained was filtered washed with petroleum ether and recrystallized from proper solvent.

**1-Phenyl-4-benzoylpyrazole, 6a**

M.p. 124°C (lit [22]. m.p. 123–124°C); recrystallized from ethanol **1-(p-Chlorophenylsemicarbazole)-4-benzoylpyrazole, 6b** m.p. 235°C, recrystallized from ethanol, yield 65%. IR(KBr): 3320, 1660, 1591, 1573, and 1490 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) δ: 7.25–7.78 (m, 10H, Ar-H); 7.92 (s, 1H, $C_3$-H); 12.12 (bs 1H, NH). **1-Phenyl-4-benzoylpyrazole, 6c** yield 76%, and m.p. 198–199°C. Recrystallized from methyl alcohol. IR (KBr): 1720, 1626, 1582, and 1562 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ: 7.22–7.75 (m, 5H, Ar-H); 7.63 and 7.77 (d 4H, Ar-H); 8.13(s, 1H, C3-H); 8.43(s 1H C-5-H).

### 3.3. Experiment 4

**Synthesis of 2,4-dinitrophenylhydrazone derivative of 1-phenyl-4-benzoylpyrazole, 7.** In the mixture 1-phenyl-4-benzoylpyrazole (0.002 mol, 0.642 gm), 2,4-dinitro phenyl hydrazine (0.002 mol, 0.396 gm) in ethyl alcohol (20 ml), concentrated sulfuric acid (0.2 ml) was added. The reaction mixture was refluxed for 3 hours. The solvent was removed and solid obtained was filtered, washed with ethanol and recrystallized from ethanol: DMF (2:8), yield 400 mg, 76%, m.p. 220°C. IR (KBr): 3340, 1626, 1590, 15550, and 1480 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) δ: 7.25-7.51(m, 5H, Ar-H); 7.70 and 7.85 (d 4H, J=8.4 Hz, Ar-H); 7.95(s, 1H, $C_3$-H); 8.04(s 1H $C_5$-H); 8.25 & 8.40 (d 2H J=8.4 HzAr-H); 9.15(s, 1H Ar-H).

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## References

[1] Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., eds.; Pergamon Press: Oxford, 1984; Vol. 5, pp. 167–303. doi:10.1016/B978-008096519-2.00072-2.

[2] Elguero, J. In *Comprehensive Heterocyclic Chemistry II;* Katritzky, A. R., Rees, C. W., and Scriven, E. F. V., eds.; Pergamon Press: Oxford, 1996; Vol. 3, pp. 1–75. doi: 10.1016/ B978-008096518-5.00059-9.

[3] Kost, A. N. and Grandberg, I. I. In *Advances in Heterocyclic Chemistry;* Katritzky, A. R. and Boulton, A. J., eds.; Academic Press: New York, 1966; Vol. 6, pp. 347 ff.

[4] Lee, K. Y., Kim, J. M., and Kim, J. N. *Tetrahedron Lett.* 2003, 44, 6737–6740. doi:10.1016/ S0040-4039(03)01648-4.

[5] Wiley, R. H. and Wiley, P. *Pyrazolones, Pyrazolidones and Derivatives;* John Wiley and Sons: New York, 1964.

[6] Behr, L. C., Fusco, R., and Jarboe, C. H. In *The Chemistry of Heterocyclic Compounds, Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings;* Weissberger, A., ed.; Interscience Publishers: New York, 1967.

[7] David, D. P., Martin, D. J., and Charles, M. D. F. 5-Aminopyrazoles useful as selective inhibitors of the protein tyrosine kinase P56ick. WO 9740019 (A1), Nov. 30, 1997.

[8] Kordik, C. P., Luo, C., Zanoni, B. C., Lovenberg, T. W., Wilson, S. J., Vaidya, A. H., Crooke, J. J., Rosenthal, D. I., and Reitz, A. B. *Bioorg. Med. Chem. Lett.* 2001, 11, 2287–2290. doi:10.1016/S0960-894X(01)00449-8

[9] Nakazato, A. and Okuyama, S. *Drugs Future* 1999, 24, 1089–1098. doi:10.1358/dof. 1999.024.10.665576.

[10] Meegalla, S. K., Doller, D., Sha, D., Soll, R., Wisnewski, N., Silver, G. M., and Dhanoa, D. *Bioorg. Med. Chem. Lett.* 2004, 14, 4949–4953. doi:10.1016/j.bmcl.2004.07.033.

[11] Huppatz, J. L. *Aust. J. Chem.* 1985, 38, 221–230. doi:10.1071/ CH9850221.

[12] Shamroukh, A. H., Rashad, A. E., and Sayed, H. H. *Phosphorus, Sulfur Silicon Relat. Elem.* 2005, 180, 2347–2360. doi:10.1080/ 104265090921074.

[13] Carter, T. A., Wodicka, L. M., Shah, N. P., Velasco, A. M., Fabian, M. A., Treiber, D. K., Milanov, Z. V., Atteridge, C. E., Biggs, W. H., Edeen, P. T., Floyd, M., Ford, J. M., Grotzfeld, R. M., Herrgard, S., Insko, D. E., Mehta, S. A., Patel, H. K., Pao, W., Sawyers, C. L., Varmus, H., Zarrinkar, P. P., and Lockhart, D. J. *Proc. Natl. Acad. Sci. U. S. A.* 2005, 102, 11011–11016. doi:10.1073/pnas.0504952102.

[14] Ranjana Aggarwal, Vinod Kumar, Rajiv Kumar, and Shiv P. Singh *Beilstein J. Org. Chem.* 2011, 7, 179–197. doi:10.3762/bjoc.7.25.

[15] M. J. Genin, C. Biles, B. J. Keiser, S.M. Poppe, S.M. Swaney, W.G. Tarplay, V. Yagi, and D. L. Ramero; J. Med. Chem. 2000, 43, 1034–1040.

[16] Coenell N.W., Honsch C., Kim K. H., and Heneger K., Arch. Biochem. Biophys. 1983, 227, 81–90.

[17] Harry R. Snyder, Chem Abst. 66, 46424 (1967). U.S. Pat. 3,293,261 (1966).

[18] H. M. Hasseneen, H. A. Edd, N m. Elwan, and A. S. Shawali, Heterocycles, 27, 2857 (1988).

[19] M. Jachak, U. Kriessman, M. Mittlebach, and H. Junek, Monatshefte Chemie, 124, 199–207 (1999).

[20] David E. Tupper and Mark R. Bray, Synthesis 337, 1996.

[21] M. P. Doyle, J. F. Dellaria, Jr. B. Siegfried, and S.W. Bishop, J. Org. Chem. 42(22), 3494 (1977).

[22] N. Kornblum, Org. React. 2, 262 (1944).

[23] T. Nishiwaki, F. Fusko, and Emil Minamisono, J.C.S. Perkin I, 1871 (1974).

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