CHAPTER 4

Urea Hydrogen Peroxide Initiated Synthesis of Pyranopyrazoles through Oxidative Coupling under Base and Metal-Free Conditions by Physical Grinding Method

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4.1 Introduction

Pyranopyrazoles are very important class of fused polycyclic organic compounds which have two heterocyclic pyrane and pyrazole core units. Pyranopyrazole and its derivatives are attractive target heterocyclic molecules due to its potency and wide range of biological and pharmacological activities including analgesic (Kamel 2015), anti-pyretic (Ismail et al. 2007), antimicrobial (Mamaghani et al. 2019), antioxidant, antitumor (Wang et al. 2000), fungicidal (Liu et al. 2012), insecticidal, antibacterial (Aslam et al. 2018), anti-HIV (Patil et al. 1993), herpetic (Gudmundsson et al. 2005), molluscicidal (Abdelrazek et al. 2007), antidepressants (Abdel-Aziz et al. 2009), cardiovascular, anticancer (Mohamed et al. 2010), anti-inflammatory (Zaki et al. 2014), hypoglycemic (Zonouz et al. 2012), Chk1 kinase 10 inhibitory (Gogai et al. 2009) shown in **Figure 4.1.**

Increasing demand of pyrazoles in the biological and pharmaceutical field scientists are always looking for new protocol for its synthesis. Therefore, a large number of methods have been reported in the presence of various homogenous/ heterogeneous, acidic or basic catalysts such as amberlyst A21 (Bihani et al. 2013), molecular sieves (Gujar et al. 2014), lipase (Bora et al. 2013), L-proline (Mecadon et al. 2011), meglumine (Guo et al. 2013),

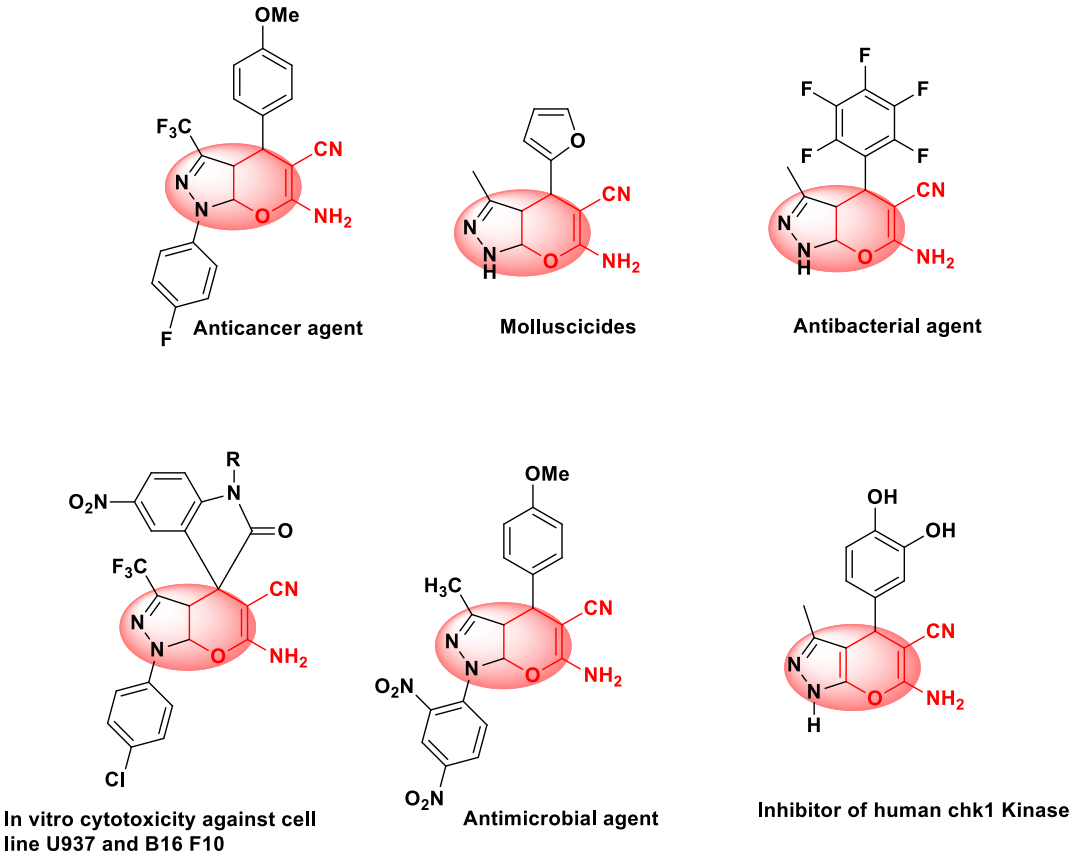


Figure 4.1 Structures of some biologically active 1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles

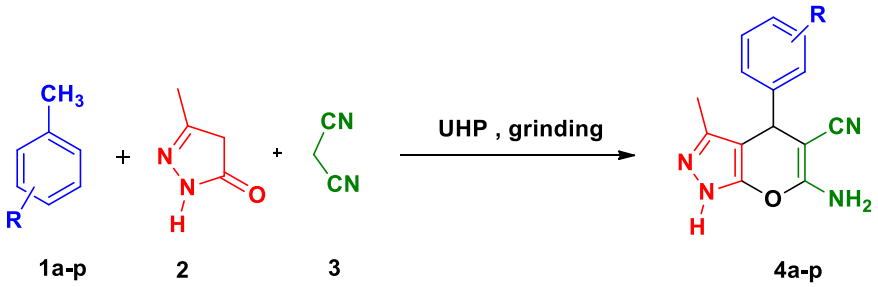
per-6-amino-β-cyclodextrin (Kanagaraj et al. 2010), sodium ascorbate (Kiyani et al. 2018), silica sodium carbonate (Eskandari et al. 2014), $CMCSO_3H$ (Ali et al. 2019), alpha-casein (Milani et al. 2019), theophylline (Mohamadpour 2019), saccharin (Mohamadpour et al. 2018), morpholinium glycolate (Shaikh et al. 2018), [Bmim]OH (Srivastava et al. 2013), $[Et_3NH][HSO_4]$ (Nimbalkar et al. 2017), sodium citrate (Laroum et al. 2017), bovine serum albumin (Dalal et al. 2016), cetyltrimethylammonium chloride (Wu et al. 2013),

cocamidopropyl betaine (Tamaddon et al. 2014), $H_5BW_{12}O_{40}$ (Heravi et al. 2018), RuIII@CMC/Fe_3O_4 (Chen et al. 2019), Fe_3O_4@Cu-β-CD (Mirhashemi et al. 2019), Polypyrrole/Fe_3O_4/CNT (Hojati et al. 2018), $Ag_3[PMo_{12}O_{40}]$ (Tamimi et al. 2019). Photo and electrochemical induced methods have also been reported for the synthesis of 1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (Tripathi et al. 2017, Upadhyay et al. 2017). However, more proficient and biocompatible catalysts are desirable which cover the issues of environmental safety and high atom economy.

The development of efficient, biocompatible and environmentally friendly protocol is getting incredible attention in synthetic organic chemistry. Successful implementation of the multicomponent single step approach allows low cost due to lesser material consumption, reduces reaction time, high atom economy compared to multi-step synthesis (Vachan et al. 2020, Paprocki et al. 2018). Moreover, the current research in organic chemistry is focused on the development of green methods to avoid environment pollution. In this context, recently many organic transformations were performed using green solvents, ionic liquids, deep eutectic solvents, solvent-free reactions etc (Pazoki et al. 2020, Zaharani et al. 2020, Saavedra et al. 2020, Gui et al. 2020).

We wish to report the simple and efficient environmentally benign synthesis of dihydropyrano[2,3-c]pyrazole which has a promising frontier field of research in medicinal, organic and combinatorial chemistry. Dihydropyrano[2,3-c]pyrazoles have been synthesized by methyl aryl derivatives, 4-methylpyrazolone and malanonitrile in the

presence of UHP via one-pot three-component reactions under physical grinding method at room temperature (**Scheme 4.1**).



Scheme 4.1 UHP initiated synthesis of dihydropyrano[2,3-c]pyrazoles

4.2 Results and Discussion

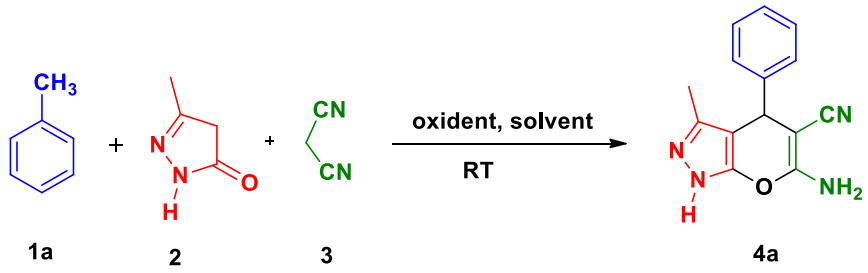
4.2.1 Optimization of Reaction Conditions

The stoichiometric ratio of toluene (**1a**), 4-methylpyrazolone (**2**) malononitrile (**3**) were chosen as a model reaction for the synthesis of dihydropyrano[2,3-c]pyrazole (**4a**). Different reaction parameters were optimized like solvents, oxidants and amount of the oxidant at room temperature.

To find an appropriate solvent different polar and non-polar solvents were tested in the presence of UHP (4 mmol). In non-polar solvents such as toluene, xylene, benzene no product was formed after 60 min (**Table 4.1, entries 1-3**). Polar-aprotic solvents such as 1,4-dioxane, acetonitrile, dichloroethane, DMSO gave the trace amount of the product dihydropyrano[2,3-c]pyrazoles (**4a**) even after 60 min (**Table 4.1, entries 4-7**). In the case of polar- protic solvents like methanol, ethanol and water gave the product (**4a**) in 35-60 %

yield (**Table 4.1, entries 8-10**). Just to avoid the solvent, the reaction was tried in solvent-free condition under grinding to our surprise it gave 88 % yield of the product in 15 min (**Table 4.1, entry 11**). The model reaction of toluene (**1a**), methylpyrazolone (**2**) malononitrile (**3**) was also investigated with different organic/ inorganic oxidising agents such as oxone, H_2O_2, TBHP, $K_2S_2O_8$ and benzoyl peroxide under grinding for 15 min at room temperature it gave the desired product (**4a**) but the yield of the product was poor (**Table 4.1, entries, 12-16**). Out of all tested oxidants UHP was found to be the best. The amount of the oxidant UHP was also examined, when the reaction was carried out in the absence of UHP, it did not provide the desired product even after an hour. Increasing the amount of UHP from 1 to 3 mmol, % yield of the reaction increases from 20-88 % (**Table 4.1 entries, 17-21**). There was no further increase in the % yield when more than 3 mmol of UHP was used.

Table 4.1 Optimization of reaction conditions[a]



Entry	Solvent	Oxidant (mmol)	Reaction condition	Time (min)	Yield (%)[b]
1	Toluene	UHP (4)	Stirring	60	NA
2	Xylene	UHP (4)	Stirring	60	NA

3	Benzene	UHP (4)	Stirring	60	NA
4	1,4- Dioxane	UHP (4)	Stirring	60	Traces
5	Acetonitrile	UHP (4)	Stirring	60	Traces
6	DCE	UHP (4)	Stirring	60	Traces
7	DMSO	UHP (4)	Stirring	60	Traces
8	Methanol	UHP (4)	Stirring	60	35
9	Ethanol	UHP (4)	Stirring	60	40
10	Water	UHP (4)	Stirring	60	60
11	-	UHP (4)	Grinding	15	88
12	-	Oxone (4)	Grinding	15	30
13	-	H_2O_2 (4)	Grinding	15	40
14		TBHP (4)	Grinding	15	50
15	-	$K_2S_2O_8$ (4)	Grinding	15	40
16	-	Benzoyl Peroxide (4)	Grinding	15	38
17	-	UHP (0)	Grinding	15	NA
18	-	UHP (1)	Grinding	15	20
19	-	UHP (2)	Grinding	15	60
20	-	UHP (3)	Grinding	15	88
21	-	UHP (6)	Grinding	15	89

[a] **Reaction conditions:** Toluene **1a** (1.0 mmol), methylpyrazolone **2** (1.0 mmol) malononitrile **3** (1 mmol) were grind/stirring together in the room temperature, [b] Isolated yield.

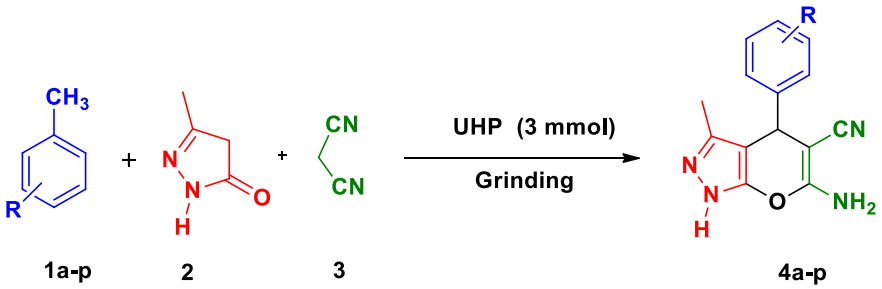
Toluene (**1a**, 1.0 mmol), methylpyrazolone (**2**, 1.0 mmol), malononitrile (**3**, 1.0 mmol) with UHP (3.0 mmol) under grinding at room temperature was found to be the optimum condition for the synthesis of dihydropyrano[2,3-c]pyrazole (**4a**).

4.2.2 Substrates Scope

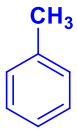
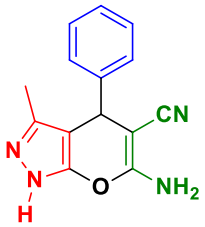
With the optimized conditions (**Table 4.1, entry 20**), the substrate scope of this methodology was explored with different methyl aryl derivatives. Coincidentally, methyl arenes with different electron donating as well as electron withdrawing groups such as 1-methoxy-4-methylbenzene (**1b**), p-xylene (**1c**), o-xylene (**1d**), N,N,4-trimethylaniline (**1e**), 2-methoxy-5-methylphenol (**1f**), 1-fluoro-4-methylbenzene (**1g**), 1-chloro-4-methylbenzene (**1h**), 1-chloro-3-methylbenzene (**1i**), 1-chloro-2-methylbenzene (**1j**), 1-bromo-4-methylbenzene (**1k**), 1-nitro-4-methylbenzene (**1l**), 1-methyl-3-nitrobenzene (**1m**), 1-methyl-2-nitrobenzene (**1n**), 2-methylnaphthalene (**1o**), 2-methylfuran (**1p**) malanonitrile (**2**) and 4-methylpyrazole (**3**) to give product *viz.*6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4b**), 6-amino-3-methyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4c**), 6-amino-3-methyl-4-(o-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4d**), 6-amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4e**), 6-amino-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4f**), 6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4g**), 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4h**), 6-amino-4-(3-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5carbonitrile

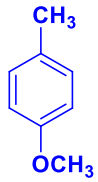
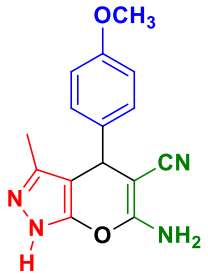
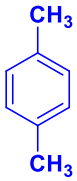
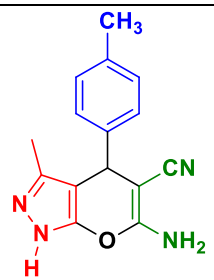
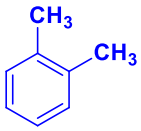
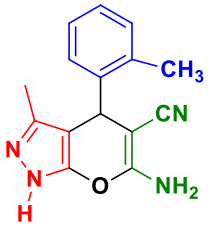
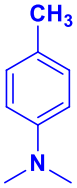
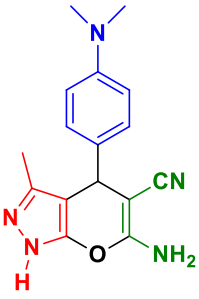
(**4i**), 6-amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4j**), 6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4k**), 6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4l**), 6-amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4m**), 6-amino-3-methyl-4-(2-nitrophenyl)-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (**4n**), 6-amino-3-methyl-4-(naphthalen-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4o**) and 6-amino-4-(furan-2-yl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**4p**) underwent subsequent transformation smoothly in good to excellent yields (80-88%). Interestingly, different positions of the substituent (ortho, meta and para) in aromatic ring did not affect the yield of the product.

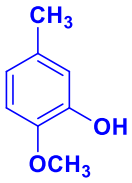
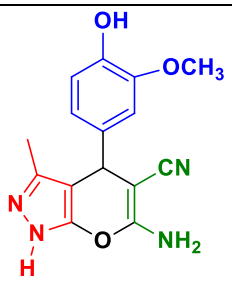
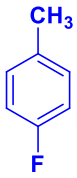
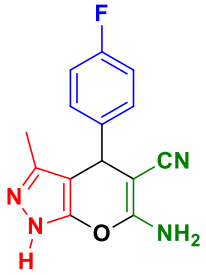
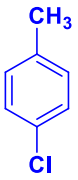
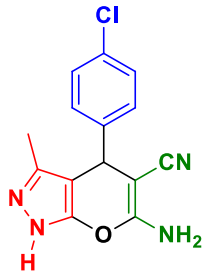
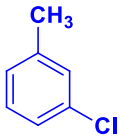
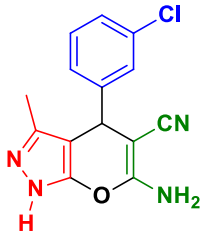
Table 4.2 Synthesis of dihydropyrano[2,3-c]pyrazole (4a-p)

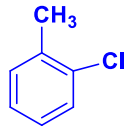
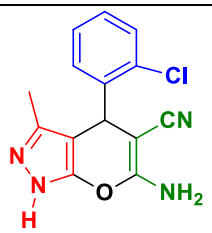
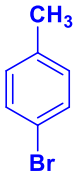
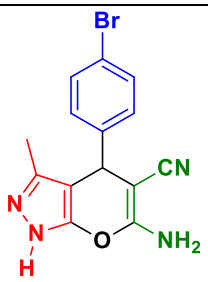
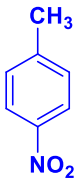
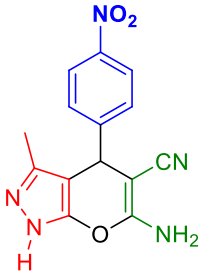
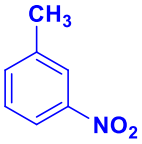
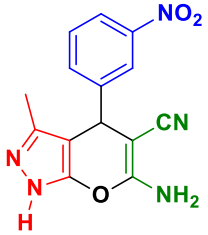


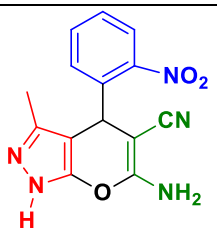
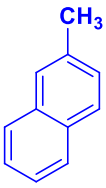
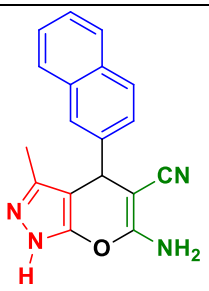
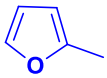
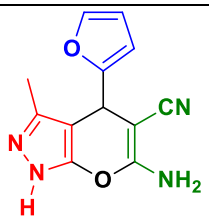
1a-p 2 3 4a-p

Entry	Reactant	Product	Time (min)	% Yield[b]
1	 1a	 4a	15	88

2	 1b	 4b	20	88
3	 1c	 4c	17	88
4	 1d	 4d	20	85
5	 1e	 4e	20	88

6	 1f	 4f	20	84
7	 1g	 4g	20	82
8	 1h	 4h	22	85
9	 1i	 4i	20	84

10	 1j  4j	20	82
11	 1k  4k	20	85
12	 1l  4l	20	84
13	 1m  4m	20	86

14	 1n	 4n	20	80
15	 1o	 4o	20	82
16	 1p	 4p	25	83

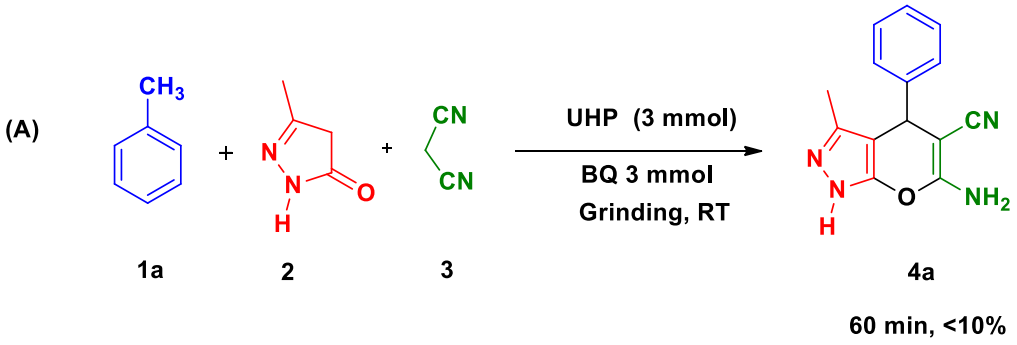
[a] **Reaction conditions**: Toluene **1a** (1.0 mmol), methylpyrazolone **2** (1.0 mmol) malononitrile **3** (1 mmol) and UHP (3 mmol) were grind together in the room temperature, [b] Isolated yield

4.3 Mechanistic Studies

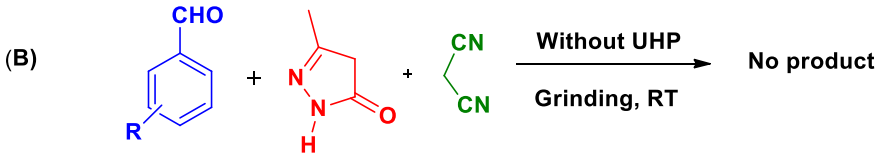
4.3.1 Controlled Experiments

In order to find the reaction mechanism, controlled experiments were carried out with model reaction, in presence of radical scavenger benzoquinone (BQ) under optimized reaction conditions (**Scheme 4.2, A**) less than 10% of the product was obtained. The result

shows that reaction goes via radical path. To investigate the role of urea-hydrogen peroxide complex in Knoevenagel condensation of benzaldehyde, methylpyrazolone and malanonitrile reaction was performed in the absence of UHP under grinding at room temperature in solvent-free condition (**Scheme 4.2, B**). This reaction did not provide the desired product even after 2 hrs. However, when the same reaction was carried out in the presence of UHP desired product was obtained in good yield (**Scheme 4.2, C**). These results indicate that UHP takes part not only in the oxidation of methyl arene to aldehyde but also in Knoevenagel-Micheal condensation reaction **Table 4.3.**



Scheme 4.2 Control experiments using benzoquinone as radical trapping agents



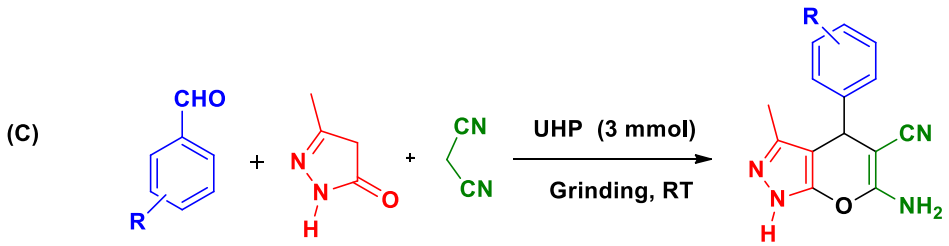
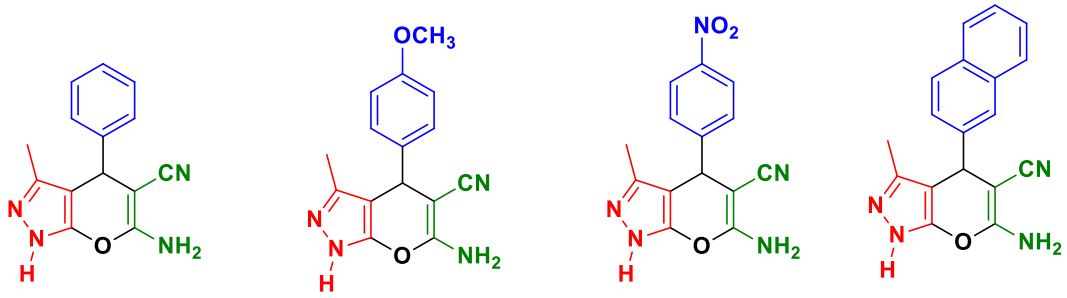


Table 4.3 Synthesis of pyranopyrazoles derivatives from aldehyde derivatives



[a] **Reaction conditions**: Benzaldehyde derivatives (1.0 mmol), methylpyrazolone **2** (1.0 mmol) malononitrile **3** (1 mmol) and UHP (3 mmol) were grind together in the room temperature, [b] Isolated yield.

4.3.2 Plausible Reaction Mechanism

On the basis of literature and our findings a plausible mechanism is predicted in **Figure 4.2**. The reaction is initiated by oxidation of methyl arene derivatives that selectively gave aldehyde derivatives which react with malanonitrile to from benzylidene adduct (**A**). In the second step, in the presence of OH radical methyl pyrazole gave radical intermediate (**B**). Then, (**B**) methyl pyrazole radical abstracts a hydrogen form benzylidene adduct to form intermediate (**C**). Intermediate (**C**) undergoes intermolecular cyclization and gives final product (**4**).

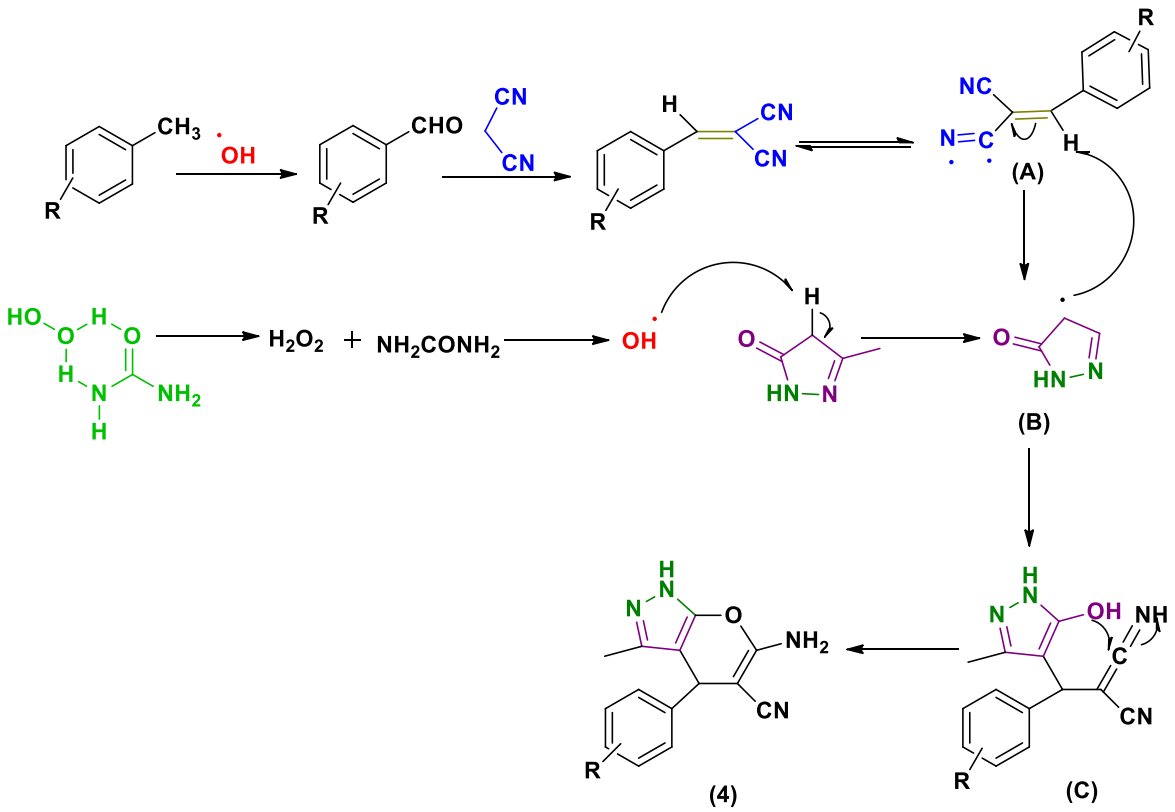


Figure 4.2 Plausible mechanism for the UHP induced dihydropyrano[2,3-c]pyrazole

4.4 Experimental

4.4.1 General procedure for the synthesis of the dihydropyrano[2,3-c]pyrazoles (4a-p)

Methyl arene (1 mmol), malanonitrile (1 mmol), 3-methylpyrazolone (1.0 mmol) and UHP (3 mmol) were grinded in mortar and pestle at room temperature. The progress of reaction was monitored by TLC. After completion of the reaction crushed ice was added into the reaction mixture and stirred for 15 min. The solid obtained was filtered and dried under vacuum, the crude product was recrystallized from ethanol to afford the pure products.

4.4.2 Spectral data of the compounds

6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a)

Yield 88 %; White solid; m.p. 210-211 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.10 (s, 1H), 7.33-7.20 (t, 2H), 7.24-7.21 (m, 1H), 7.18-7.16 (d, 2H), 6.87 (s, 2H), 4.59 (s, 1H), 1.78 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.04, 154.94, 144.63, 135.74, 128.61, 127.64, 126.91, 120.96, 97.82, 57.36, 36.41, 9.90.

6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4b) Yield 88 %; White solid; m.p. 210-211; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.07 (s, 1H), 7.09-7.07 (d, 2H), 6.88-6.86 (d, 2H), 6.82 (s, 2H), 4.54 (s, 1H), 3.73 (s, 3H), 1.78 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.16, 157.43, 154.23, 135.97, 135.02, 127.97, 120.32, 113.24, 97.37, 57.09, 54.47, 34.93, 9.24.

6-amino-3-methyl-4-(p-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4c)

Yield 88 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.08 (s, 1H), 7.11 (d, 2H), 7.04-7.03 (d, 2H), 6.85 (s, 2H), 4.53 (s, 1H), 2.26 (s, 3H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.62, 154.61, 141.35, 135.58, 135.40, 128.86, 127.22, 120.70, 97.58, 57.18, 20.92, 9.63.

6-amino-3-methyl-4-(o-tolyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4d)

Yield 85%; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.21 (s, 1H), 8.20 (s, 1H), 8.11 (d, 1H), 7.46 (s, 1H), 7.37 (d, 1H), 7.06 (s, 2H), 4.83 (s,

1H), 2.10 (s, 3H), 1.80 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.67, 154.18, 151.61, 151.28, 145.91, 145.10, 135.44, 128.33, 123.41, 122.50, 120.01, 96.08, 55.45, 35.42, 9.83, 9.25.

6-amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4e) Yield 88 %; White solid, m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.04 (s, 1H), 6.97 (d, 2H), 6.77 (s, 2H), 6.66 (d, 2H), 4.46 (s, 1H), 2.86 (s, 6H), 1.79 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.08, 154.31, 148.74, 135.01, 131.55, 127.49, 120.50, 111.83, 97.71, 57.51 38.83, 38.67, 34.89, 9.30.

6-amino-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4f) Yield 84 %; Off-white solid; m.p. 227-228 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): δ 12.09, 8.94 (s, 1H, OH), 6.77 (s, 2H), 6.72, 6.71-6.69 (m, 2H), 6.55 - 6.53 (m, 1H), 4.49 (s, 1H), 3.70 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.13, 147.77, 145.61, 136.22, 135.83, 121.39, 120.18, 115.85, 112.00, 98.35, 58.13, 56.05, 40.24, 40.07, 36.23, 10.25.

6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4g) Yield 82 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz DMSO-d6) δ (ppm): 12.13 (s, 1H), 7.21-7.19 (m, 2H), 7.15-7.12 (d, 2H), 6.91 (s, 2H), 4.63 (s, 1H), 1.78 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.44, 160.35, 159.51, 154.23, 140.17, 135.17, 128.86, 120.23, 114.77, 114.60, 97.01, 56.62, 34.96, 9.24.

6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4h) Yield 85 %; White solid; m.p. 252-253 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.15 (s, 1H), 7.38-7.36 (d, 2H), 7.20-7.18 (d, 2H), 6.95 (s, 2H, NH_2), 4.63 (s, 1H), 1.79 (s, 3H). **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm):161.37, 155.17, 143.95, 136.15, 131.70, 129.84, 128.93, 121.15, 97.66, 57.18, 36.01, 10.21.

6-amino-4-(3-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4i) Yield 84 %; White solid; m.p. 210-212 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.10 (s, 1H), 7.30 (d, 2H), 7.21 (d 1H), 7.16 (d, 2H), 6.87 (s, 2H), 4.59 (s, 1H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.40, 154.29, 143.96, 135.12, 127.96, 126.99, 126.26, 120.33, 97.17, 56.71, 39.33, 39.17, 39.00, 38.83, 38.67, 35.76, 9.25.

6-amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4j) Yield 82 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.15 (s, 1H), 7.40 (d, 1H), 7.31 (d, 1H), 7.25 (t, 1H), 7.18 (d, 1H), 6.93 (s, 2H), 5.06 (s, 1H), 1.76 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d6) δ (ppm): 161.82, 155.47, 141.36, 136.01, 132.49, 131.22, 130.05, 129.17, 128.29, 120.96, 97.36, 56.29, 33.97, 10.01.

6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4k) Yield 85 %; White solid; m.p. 249-250 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.15 (s, 1H), 7.51 (d, 2H), 7.14 (d, 2H), 6.94 (s, 2H), 4.62 (s, 1H), 1.80 (s, 3H); **^{13}C NMR (**125 MHz, DMSO-d_6**)** δ (ppm): 160.45, 154.24, 143.42, 135.24, 130.91, 129.28, 119.30, 96.66, 56.23, 38.50, 35.17, 9.28.

6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4l) Yield 84 %; White solid; m.p. 277-280 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 8.10-8.09 (d, 2H), 7.37-7.35 (d, 2H), 4.94 (s, 1H), 2.10 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.45, 154.24, 143.42, 135.24, 130.91, 129.91, 120.20, 119.30, 96.66, 56.23, 10.22.

6-amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4m) Yield 86 %; White solid; m.p. 210-212; ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.21 (s, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 7.77-7.57 (m, 2H), 7.04 (s, 2H), 4.88 (s, 1H), 1.81 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.61, 148.36, 147.29, 136.36, 134.84, 130.71, 122.37, 97.13, 56.64, 36.12, 10.22.

6-amino-3-methyl-4-(2-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4n) Yield 80 %; White solid; m.p. 187-188 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.21 (s, 1H), 7.85 (d, 1H), 7.66 (s, 1H), 7.49 (d, 1H), 7.33 (d, 1H), 7.03 (s, 2H), 5.11 (s, 1H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 160.71, 154.49, 148.68, 137.10, 135.28, 132.87, 130.80, 127.85, 123.11, 119, 95.90, 55.60, 30.96, 9.00.

6-amino-3-methyl-4-(naphthalen-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4o) Yield 82 %; White solid; m.p. 209-210 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 12.14 (s, 1H), 7.87 (d, 3H), 7.77 (s, 1H), 7.57-7.38 (m, 2H), 7.25 (d, 1H), 6.96 (s, 2H), 4.79 (s, 1H), 1.76 (s, 3H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ (ppm): 161.46,

155.38, 142.23, 136.38, 133.35, 132.67, 128.93, 128.14, 126.78, 126.55–126.05, 121.35, 97.94, 57.63, 37.04, 10.24.

6-amino-4-(furan-2-yl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4p)

Yield 83 %; Black solid; m.p. 218-220 ^{0}C; **^{1}H NMR** (500 MHz, DMSO-d_6) 12.17 (s, 1H), 7.54 (t, 1H), 6.96 (s, 2H), 6.37-6.39 (m, 1H), 6.18 (d, 1H), 4.78 (s, 1H), 1.98 (s, 3H), **^{13}C NMR** (125 MHz, DMSO-d_6) 161.9, 156.1, 155.2, 142.7, 136.3, 136.1, 121.0, 110.7, 106.1, 95.5, 54.4, 30.2, 10.0.

4.4.3 Spectral data of product 4a

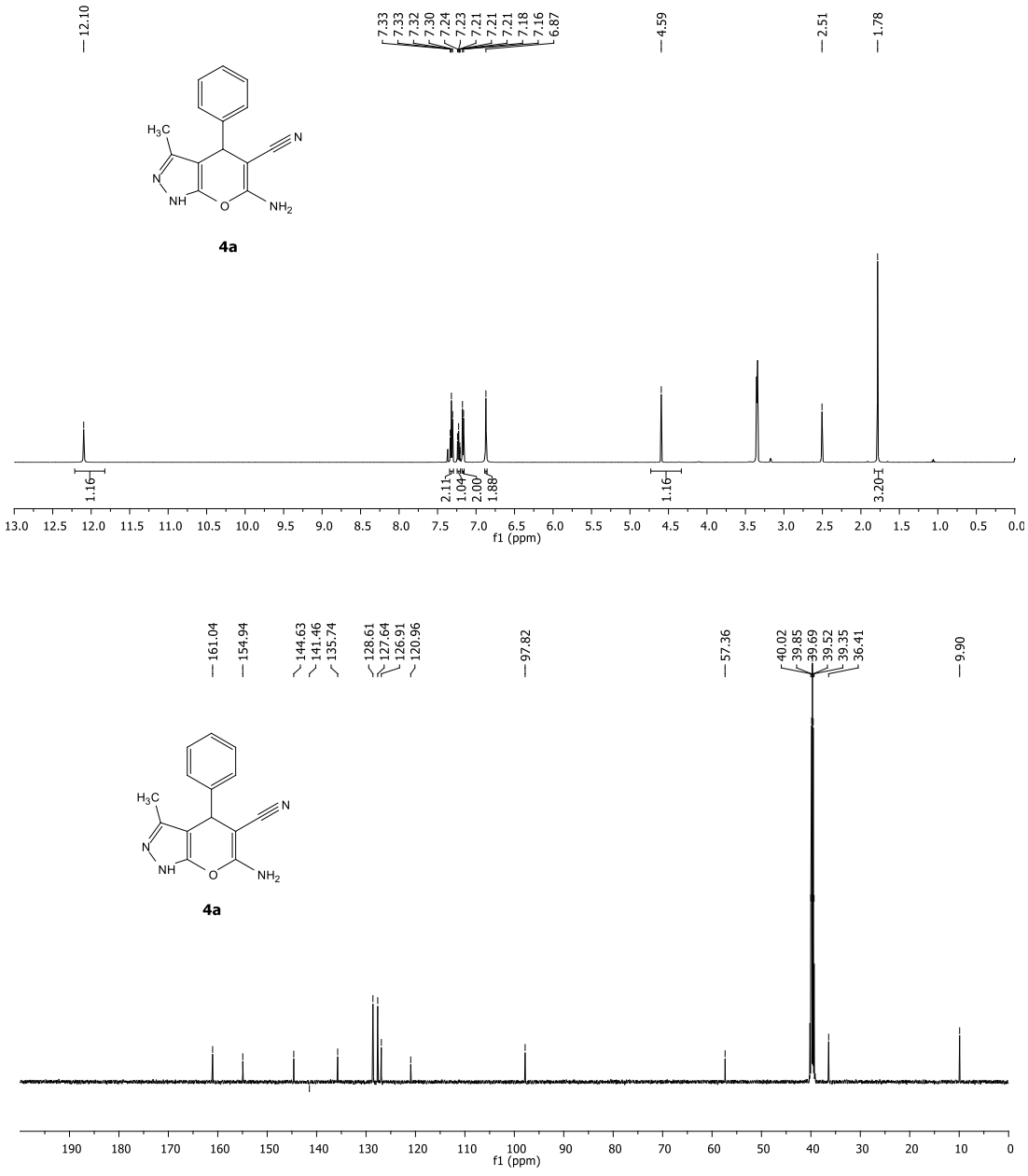


Figure 4.3 ^{1}H & ^{13}C NMR of 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (4a)

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