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A Facile Synthesis of 6-Amino-4-Aryl-3-Methyl-2,4-Dihydropyrano [2,3-C] Pyrazole-5-Carbonitriles in Aqueous Medium

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Abstract

A convenient four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles.They are widely used for industrial purposes and also exhibit a broad range of antimicrobial activity. They are synthesized by using ethylacetoacetate, hydrazine hydrate, malononitrile, and various aldehydes using Tetra n-butyl ammonium bromide (TBAB) as a catalyst and water as solvent under mild reaction conditions. This method has several advantages such as high yield, mild reaction condition, operational simplicity, easy work-up procedure with environment friendly nature.

Key words : Pyranopyrazoles, Tetra n-butyl ammonium bromide (TBAB) Aqueous medium, Multicomponent reactions, Organocatalyst, Rate enhancements.

Introduction

The more emphasis is given on the synthesis of organic compounds, Nowadays, by using readily available economically cheap starting materials maximum yield of product with environmental friendly method[1]. In this sense, multi-component reactions (MCRs) in aqueous medium have emerged as a great tool for synthetic transformation due to their easy handling, experimental simplification, less hazardous and minimum side product with high yield of desired product. It has advantages such as saves time, less energy and raw material required for the reactions, making the reaction economically attractive and ecofriendly[2].

As a reaction medium use as a water .It has several advantages such as environmentally benign, reduce in the formation of by-products and direct isolation of products by precipitation and filtration as they are often insoluble. Furthermore, Organic reaction

carried out in aqueous media have also made attention from chemist because of the concern about the environment, and considerable rate of reactions are more faster in water over those in organic solvents[2].

The Multifunctionalized pyran and its derivative shows various biological activities. 4H-Pyran is an important structural unit in heterocyclic compounds. In various heterocyclic compound pyranopyrazole is one of them heterocycles in which 4H- Pyran is an important structural unit. In recent years, Pyranopyrazoles have great importance due to their biological and pharmacological activities. Pyranopyrazoles constitute important fused heterocyclic compounds; thus in the last one decades their synthesis become very intresting work among the chemist especially in the field of medicinal/ pharmaceutical chemistry to their wide range of biological/pharmacological activities such as anticancer, antimicrobial[5,6], anti-inflammatory, insecticidal. They are also potential inhibitors of human chk1 kinase. The first procedure was to synthesize pyranopyrazole derivatives involves the reaction between 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene under basic conditions. Owing to the above mentioned properties, various methods were developed for the synthesis of these compounds. Recently, several catalysts have been reported for the one-pot syntheis of pyranopyrazole derivatives including glycine, *L*-proline and γ-alumina, and cetyltrimethylammonium chloride (CTACl). Taking into account the importance of pyranopyrazoles, the significant rate enhancement of MCRs in water herein, we wish to report the catalytic efficiency of Tetra n-butyl ammonium bromide for the synthesis of 6-amino-5-cyano-4-aryl-4*H*-pyrazolo[3,4 *b*] pyran derivatives **5** *via* the four-component reaction of hydrazine hydrate**1**, ethylacetoacetate **2**, aromatic aldehydes **3** and malononitrile **4** in aqueous medium (Scheme 1).

In recent years, Tetra n-butyl ammonium bromide (TBAB) has immerged as an extremely useful homogeneous catalyst in various organic transformation including conjugate addition of thiols to electron deficient alkenes, transthioacetalisation of acetals, trimethylsilylation of alcohols, synthesis of aryl-14H-dibenzoxanthene. TBAB is an inexpensive readily available ionic liquid with inherent properties like environmental compatibility, greater selectivity, operational simplicity non-corrosive nature and ease of reusability[4].

Materials and Methods

All chemicals were used of laboratory grade and used without purification. Reactions were monitored by thin layer chromatography (TLC), visualizing with ultraviolet. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on FT IR jasco 4100 KBr pellets with absorptions in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a BRUKER AVANCE DPX spectrometer using DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts (δ) are expressed in ppm, downfield from internal standard TMS and *J* values in hertz (Hz).

General procedure for the preparation of 6-Amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-C] pyrazole-5-carbonitriles or carboxylate (5a-m)

To start with, we took a mixture of hydrazine hydrate 1 (0.107 g, 2.0 mmol), ethyl acetoacetate 2 (0.260 g, 2.0 mmol),in water(5 ml) and allowed to stir for 5 min. To this mixture aromatic aldehyde derivatives 3 (2.0 mmol) and malononitrile 4 (0.132 g, 2.0 mmol) were added and allowed to refluxed under stirring for 25-30 min in the presence of Tetra n-butyl ammonium bromide (TBAB) (10 mol %). The precipitated solid was filtered, washed with water. The product obtained monitored by TLC . However, the products were further purified by recrystallization from ethanol.

All the synthesized compounds are reported in Table 3 and were confirmed by their physical constants and characterized by IR, ^1H and ^{13}C NMR and Mass. The spectroscopic data were in full agreement with the literature values.

Spectral data for prepared compounds :

6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano [2, 3-c] pyrazole-5-carbonitrile **(4a)** White crystals, mp. 245–246 °C; tmax (KBr): 3305, 3163 (NH2), 2187 (CN), 1644 (C=N), 1592,1518 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.10 (s, 1H, NH), 7.33–7.16 (m, 5H, atom), 6.88 (s, 2H, NH2), 4.59 (s, 1H, 4-H), 1.78 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d_6) δ161.3 (C6), 155.2 (C3), 144.9 (C8), 136.1 (C1'), 128.9 (C2',C6'),

127.9 (C3',C5') 127.2 (C4'), 121.3 (CN), 98.1 (C7), 57.6 (C5), 36.7 (C4), 10.2(CH_3) ppm. Mass:$C_{14}H_{12}N_4O$ MS(ESI+): m/z 253.11 $(M+H)^+$

6-Amino-4-(4-chlorophenyl)-3methyl-2,4-dihydropyrano[2,3-c]pyrazole-5- carbonitrile **(4b)**

Yellow solid, mp. 239-240 °C; tmax (KBr): 3315, 3063 (NH_2), 2117 (CN), 1649 (C=N), 1590,1520 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.15 (s, 1H, NH), 7.32–7.19 (m, 5H, arom), 6.92 (s, 2H, NH_2), 4.50 (s, 1H, 4-H), 1.72 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz,DMSO-d_6) δ162.3 (C6), 155.2 (C3), 143.9 (C8), 135.1 (C1'), 129.1 (C2',C6'), 127.9 (C3',C5') 127.8 (C4'), 122.5 (CN), 98.5 (C7), 56.8 (C5), 36.9(C4), 10.8(CH3) ppm. Mass:$C_{14}H_{11}N_4OCl$ MS(ESI+): m/z 287.11 $(M+H)^+$

6-Amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5 carbonitrile **(4c)**

Yellow solid, mp. 229-230 °C; tmax (KBr): 3263, 3102 (NH_2), 2217 (CN), 1685 (C=N), 1540,1565 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.05 (s, 1H, NH), 7.55–7.22 (m, 5H, atom), 6.77 (s, 2H, NH2), 4.51 (s, 1H, 4-H), 1.82 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d6) δ162.3 (C6), 151.2 (C3), 144.9 (C8), 135.1 (C1'), 128.9 (C2',C6'), 127.9 (C3',C5') 127.2 (C4'), 121.3 (CN), 98.1 (C7), 57.6 (C5), 36.9(C4), 10.8(CH3)ppm. Mass: $C_{14}H_{12}N_4O_2$ MS(ESI+): m/z 270.15 $(M+H)^+$

6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **(4d)**

White solid, mp.225-226 °C; tmax (KBr): 3185, 3010 (NH_2), 2205 (CN), 1715 (C=N), 1590,1520 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.56 (s, 1H, NH), 7.25–7.32 (m, 5H, arom), 6.45 (s, 2H, NH2), 4.65 (s, 1H, 4-H), 1.85 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d6) δ162.3 (C6), 151.2 (C3), 1445.8 (C8), 138.1 (C1'), 129.9 (C2',C6'), 125.9 (C3',C5') 125.2 (C4'), 128.3 (CN), 99.1 (C7), 59.6 (C5), 36.0(C4), 9.98(CH3) ppm. Mass:$C_{15}H_{14}N_4O_2$ MS(ESI+): m/z 273.21 $(M+H)^+$

6-Amino-3-methyl-4-(4methylphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **(4e)**

Yellow crystals, mp.219-220 °C; tmax (KBr): 3204, 3047 (NH_2), 2187 (CN), 1704 (C=N), 1540,1522 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.12 (s, 1H, NH), 7.47–7.08 (m, 5H, atom), 6.92 (s, 2H, NH2), 4.50 (s, 1H, 4-H), 1.72 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d_6) δ162.3 (C6), 151.2 (C3), 144.9 (C8), 135.1 (C1'), 124.9 (C2',C6'), 129.9 (C3',C5') 128.2 (C4'), 125.8 (CN), 98.4 (C7), 57.6 (C5), 36.9(C4), 11.5(CH3)ppm Mass:$C_{15}H_{14}N_4O$ MS(ESI+): m/z 267.05 $(M+H)^+$

6-Amino-4-(4-nitrophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **(4f)**

Brown crystals, mp. 249-250 °C; tmax (KBr): 3375, 3263 (NH_2), 2210 (CN), 1630 (C=N), 1570,1532 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.77 (s, 1H, NH), 7.78–7.26 (m, 5H, arom), 6.55 (s, 2H, NH2), 4.68 (s, 1H, 4-H), 1.79 (s, 3H, CH3); 13C NMR (63.9 MHz,DMSO-d_6) δ162.3 (C6), 151.2 (C3), 154.9 (C8), 134.1 (C1'), 128.9 (C2',C6'), 127.9 (C3',C5') 127.2 (C4'), 122.8 (CN), 94.1 (C7), 52.6 (C5), 36.2(C4), 11.5(CH_3)ppm. Mass:$C_{14}H_{11}N_5O_3$ MS(ESI+): m/z 298.14 $(M+H)^+$

6-Amino-4-(3-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **(4g)**

White powder, mp. 248-249 °C; tmax (KBr): 3407, 3173 (NH2), 2177 (CN), 1699 (C=N), 1595,1526 (Ar) cm^{-1}; 1H NMR(250 MHz, DMSO-d6) δ 12.84 (s, 1H, NH), 7.48–7.08 (m, 5H, atom), 6.72 (s, 2H, NH_2), 4.72 (s, 1H, 4-H), 1.85 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d_6) δ 162.3 (C6), 151.2 (C3), 144.9 (C8), 135.1 (C1'), 128.9 (C2',C6'), 127.9 (C3',C5') 127.2 (C4'), 121.3 (CN), 98.1 (C7), 57.6 (C5), 36.9(C4), 10.8(CH_3) ppm. Mass:$C_{14}H_{12}N_4O_2$ MS(ESI+): m/z 271.11 $(M+H)^+$

6-Amino-4-(3-nitrophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **(4h)**

Brown powder, mp. 229-230 °C; tmax (KBr): 3336, 3145 (NH_2), 2157 (CN), 1715 (C=N), 1601,1540 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 11.85 (s, 1H, NH), 7.11–6.98 (m, 5H, atom), 7.15 (s, 2H, NH2), 4.51 (s, 1H, 4-H), 1.68 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d_6) δ 162.3 (C6), 151.2 (C3), 144.9 (C8), 135.1 (C1'), 124.9 (C2',C6'), 129.9 (C3',C5') 127.2 (C4'), 121.3 (CN), 98.0 (C7), 57.4 (C5), 37.9(C4), 10.1(CH_3) ppm. Mass:$C_{14}H_{11}N_5O_3$ MS(ESI+): m/z 298.10 $(M+H)^+$

6-Amino-4-(2-methoxyphenyl)-3-methyl-2,4-

dihydropyrano[2,3-c]pyrazole-5-carbonitrile **(4i)**

White powder, mp.253-254 °C; tmax (KBr): 3305, 3063 (NH_2), 2187 (CN), 1644 (C=N), 1580,1521 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.18 (s, 1H, NH), 7.66–7.29 (m, 5H, atom), 7.85 (s, 2H, NH2), 4.77 (s, 1H, 4-H), 1.62 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz, DMSO-d_6) δ 162.3 (C6), 151.2 (C3), 144.9 (C8), 135.1 (C1'), 130.4 (C2',C6'), 121.9 (C3',C5') 124.2 (C4'), 131.3 (CN), 98.9 (C7), 57.1 (C5), 36.5(C4), 10.3(CH_3) ppm. Mass:$C_{15}H_{14}N_4O_2$ MS(ESI+): m/z 273.11 $(M+H)^+$.

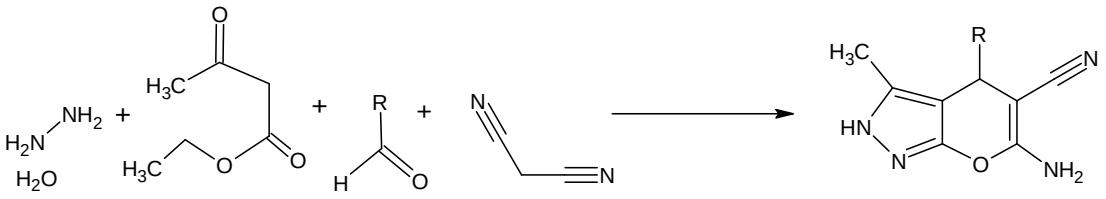
6-Amino-4-(2-nitrophenyl)-3-methyl-2, 4-dihydropyrano [2, 3-c] pyrazole-5-carbonitrile **(4j)**

Blackish powder,mp. 246-247 °C; tmax (KBr): 3363, 3036 (NH_2), 2214 (CN), 1649 (C=N), 1590,1520 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.68 (s, 1H, NH), 7.31–7.11 (m, 5H, atom), 7.25 (s, 2H, NH_2), 4.78 (s, 1H, 4-H), 1.89 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d_6) δ172.3 (C6), 151.1 (C3), 146.9 (C8), 138.1 (C1'), 138.9 (C2',C6'), 135.9 (C3',C5') 133.2 (C4'), 121.3 (CN), 94.1 (C7), 55.6 (C5), 36.9(C4), 10.8(CH_3) ppm. Mass:$C_{14}H_{11}N_5O_3$ MS(ESI+): m/z 298.17 $(M+H)^+$

6-Amino-4-(4-bromophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **(4k)** tmax (KBr): 3362, 3182 (NH_2), 2185 (CN), 1651 (C=N), 1621,1585 (Ar) cm^{-1}; ^1H NMR(250 MHz, DMSO-d_6) δ 12.18 (s, 1H, NH), 7.32–7.15 (m, 5H, atom), 6.91 (s, 2H, NH_2), 4.55 (s, 1H, 4-H), 1.75 (s, 3H, CH_3); ^{13}C NMR (63.9 MHz,DMSO-d_6) δ162.5 (C6), 151.8 (C3), 145.9 (C8), 135.8 (C1'), 127.9 (C2',C6'), 127.9 (C3',C5') 131.2 (C4'), 131.3 (CN), 97.1 (C7), 54.6 (C5), 37.7(C4), 9.95(CH_3) ppm. Mass:$C_{14}H_{11}N_4OBr$ MS(ESI+): m/z 333.15 $(M+H)^+$

Result and Discussion

The reaction (Scheme 1) between hydrazine hydrate, ethyl acetoacetate, malononitrile, and benzaldehyde (R = C6H5) was chosen as a model condensation reaction for optimizing the various reaction parameters: solvent, temperature, catalyst.



1 2 3 4 5

Scheme 1

Initially, the reaction was tried without any catalyst in solvent-free conditions at ambient temperature, but the reaction could not complete even after 24 h stirring (Table 1, entry 1). Interestingly, when 5 ml of water was added to the reaction mixture, an oily product was obtained (Table 1, entry 2). To increase the reaction rate and minimize the consumption of energy, we performed the model Tetra n-butyl ammonium bromide (TBAB) as catalysts in aqueous media under reflux conditions. From these preliminary studies, it was observed that the rate of the catalyzed reaction is higher than the corresponding uncatalyzed one at the same temperature. Table 1. entry 3).

Table 1. The Influence of temperature on one-pot condensation of ethylacetoacetate, hydrazine hydrate, benzaldehyde and malanonitrile.

Entry	Catalyst	Solvent	Temp °C	Time min	Yield%
1	Cat free	Neat	Room Temperature	120	-
2	Cat free	Water	Room Temperature	120	Oil
3	TBAB (10mol%)	Water	Reflux	25	92

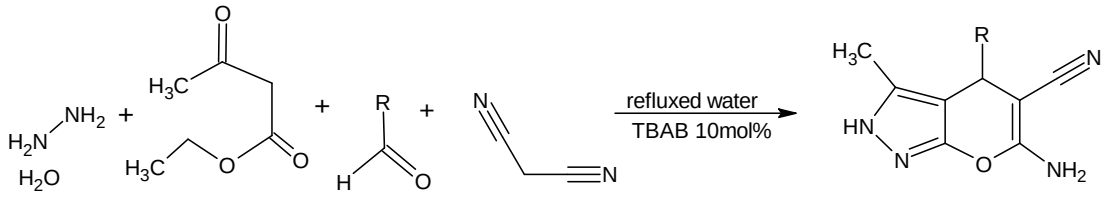
Table 2. The Influence of solvent on the model reaction in the presence of Tetra n-butyl ammonium bromide (TBAB) (10 mol%)

Entry	Catalyst	Temperature °C	Time, h	Yield%
1	Solvent free	90°C	4	88
2	CH_3CN	Reflux	5	58
3	DMSO	Reflux	1	50
4	H_2O	Reflux	25 min	92

The choice of a solvent is a crucial factor for multicomponent reactions, so different organic solvents were examined for the reaction (Table 2, entries 2-4) and we found that water was the solvent of choice which provided the highest rate and yield (Table 2, entry 4). Similar yield was also obtained under solvent free conditions but relatively longer reaction time was needed (Table 2, entry 1).

Reaction conditions: ethyl acetoacetate (2.0 mmol), hydrazine hydrate(2.0 mmol), benzaldehyde (2.0mmol) and malanonitrile (2.0 mmol). Isolated yield

With the optimized reaction conditions in hand and to study the efficiency of this catalyst, we extended our study with different aromatic aldehydes to prepare a series of pyranopyrazoles in good to excellent yields (Scheme 2, Table 3, 4a-m).



1 2 3 4 5

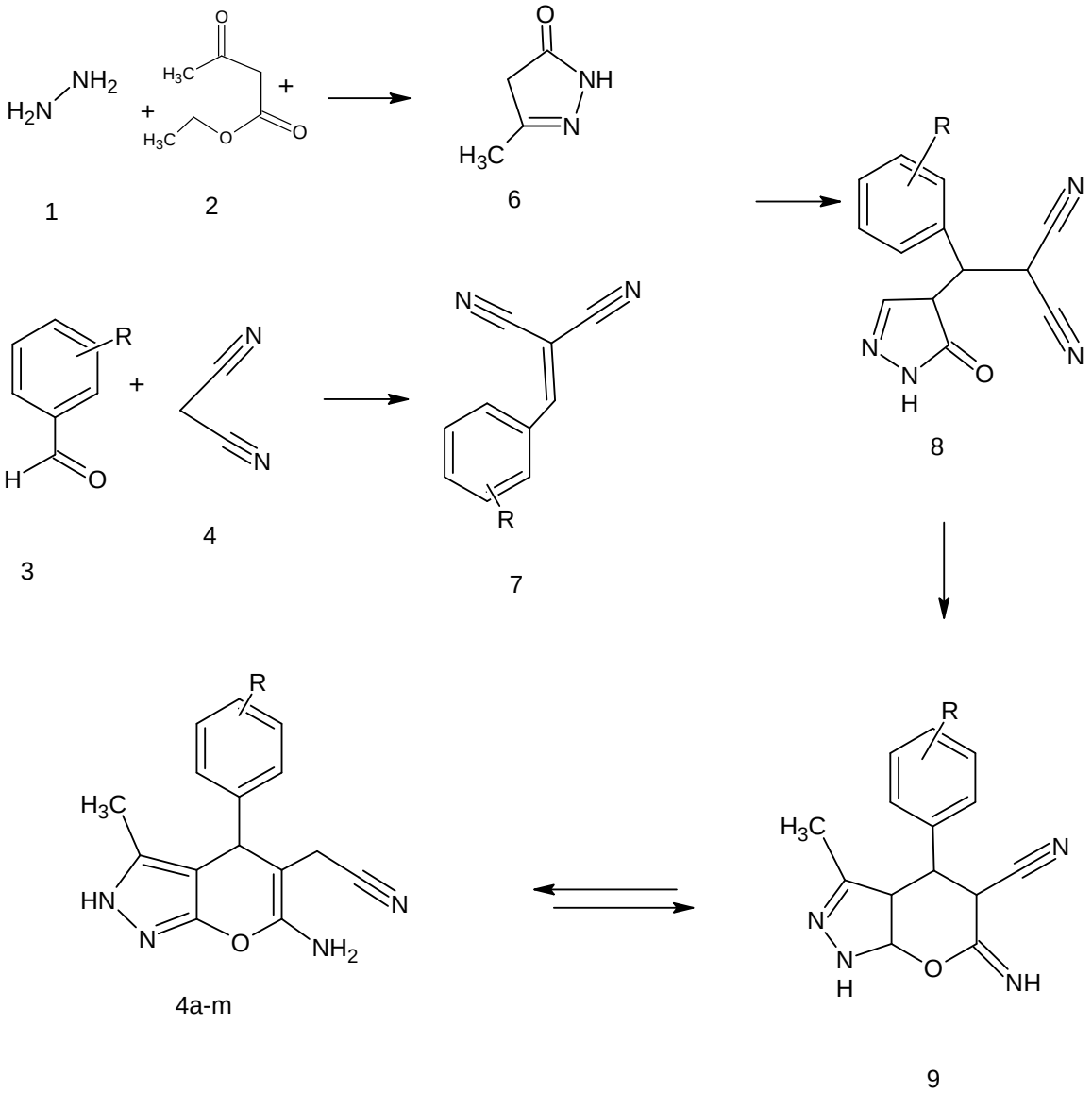
Scheme 2. Synthesis of pyranopyrazoles (4a-m)

Table 3. One-pot synthesis of pyranopyrazoles catalyzed by Tetra n-butyl ammonium bromide (TBAB)

Entry	Aldehyde	Time min	Product	Yield %	Melting point °C	
					Found	Reported
1	C_6H_5	60	4a	92	244-246	243-245
2	4-Cl-C_6H_4	60	4b	96	238-240	233-236
3	4-OH-C_6H_4	60	4c	93	229-230	224-226
4	4-MeO-C_6H_4	60	4d	88	224-226	208-211
5	4-CH_3-C_6H_4	60	4e	94	215-216	210-212
6	4-NO_2-C_6H_4	60	4f	93	248-251	245-248
7	3-OH-C_6H_4	60	4g	81	248-250	247-249
8	3-NO_2-C_6H_4	60	4h	84	215-218	214-217
9	2-MeO-C_6H_4	60	4i	96	253-254	248-251
10	2-NO_2-C_6H_4	60	4j	96	243-246	243-244
11	4-Br-C_6H_4	60	4k	90	180-182	182-185

Reactions were performed on a 2.0 mmol scale of all reactants with 10 mol % of Tetra n-butyl ammonium bromide in refluxed water (5 ml).

On the basis of the chemistry of pyranopyrazoles, we propose the possible foll owing mechanism: One molecule of hydrazine derivative **1** was firstly condensed with ethyl acetoacetate **2** to yield pyrazolone derivative **6**. On the other hand, aromatic aldehyde **3** condensed with malononitrile **4** to give α-cyanocinnamonitrile derivative **7**. The next step may involve Michael addition of the active methylene of **6** to an electron deficient carbon of dicyanoalkene **7**, which gives an intermediate **8** tautomerization to the intermediate followed by the nucleophilic attack of OH group on the cyano (CN) moiety to give the cyclic intermediate **9**, which is tautomerized to target pyranopyrazoles **4a-m**. In this process, Tetra n-butyl ammonium bromide (TBAB) could promote these reactions as phase transfer catalyst (Scheme 3).



Scheme 3. Plausible mechanism of pyranopyrazoles synthesis

Conclusion

We have been able to developed facile and ecofriendly method for the synthesis of biologically active pyranopyrazole via one pot condensation of various aromatic aldehydes, ethylacetoacetate, hydrazine hydrates and malanonitriles by using (TBAB) is an catalyst in aqueous media. Tetra butyl ammonium bromide (TBAB) is an easily available, inexpensive, environment friendly and efficient catalyst for the synthesis of Dihydropyrano [2,3-C] Pyrazole derivative by multicomponent condensation. The present method gives product very quickly, High yields, easy workup, cost effectivness and non-hazardous to environment. Further study with other catalyst is recommended.

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