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Catalyst free, one-pot, facile synthesis of novel pyrazolo-1,4-dihydropyridine derivative form pyranopyrazoles

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ABSTRACT

One pot synthesis of pyrazolo-1,4-dihydropyridine derivatives from pyranopyrazoles using acidic solvent system is described. The targeted molecules were obtained in good to excellent yield without the use of expensive catalysts, toxic solvents and chromatographic separation. The generality and functional tolerance of this convergent and environmentally benign method is demonstrated.

1. Introduction

Hantzsch condensation discovered 1,4-dihydropyridines (1,4-DHP's) in 1882 [1]. The 1,4-DHP's has attracted more attention, thanks to its presence in the coenzyme, diphospho-pyridine nucleotide (DPNH) [2] and recognition as bio-active material. Many derivatives are commercialized in the market [3-7]. Fused 1,4-DHPs have also been able to make their presence felt largely due to ability to perform biological as well as pharmacological functions. 1,4-DHPs are an important class of Ca^{2+} channel blockers and are also known to be effective cardiovascular agents for the treatment of hypertension. Apart from these activities, DHPs are found to be as platelet-activity factor antagonists [8], calcium antagonists [9], anti-hypertensives [10], cerebral antischemic activity in the treatment of Alzheimer's disease and chemosensitizer acting in tumor therapy. Although the synthesis of pyrazolo-1,4-dihydropyridines using expensive starting material like 3-methyl-4,5-dihydro-1*H*-pyrazol-5-amine or 3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazol-5-amine, has considerably contributed to the development of new pyrazolo-1,4-DHPs [11-15], yet, the achieved molecule remains beyond the reach of most manufacturers, as it involves the usage of expensive starting material. The molecule also does not remain confined to the use of generally used methodologies and therefore, additional and exquisite methodologies need to be brought into use [14].

Therefore, recognizing the development of a clean, green and efficient procedure as the need of the hour, and persisting with our work on heterocyclics [16-18] and in continuation of our previous work (Scheme 1), we have been able to produce some pyrazolo-1,4-DHPs from easily available pyranopyrazoles (Figure 1) [16]. The present protocol is simpler as, use of harsh reaction condition scheme is not a pre-requisite to it (Scheme 2).

2. Experimental

2.1. Instrumentation

Materials were obtained from commercial suppliers and were used without further purifications. Melting points were recorded in open end capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance II 400 MHz spectrometer; chemical shifts (δ) are reported in ppm relative to TMS as internal standard. The mass spectrum and IR spectra were recorded at LC-MS Spectrometer Model Q-ToF Micro Waters and Perkin-Elmer Spectrum II infrared spectrophotometer, respectively.

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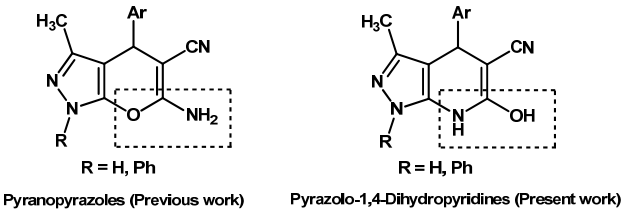
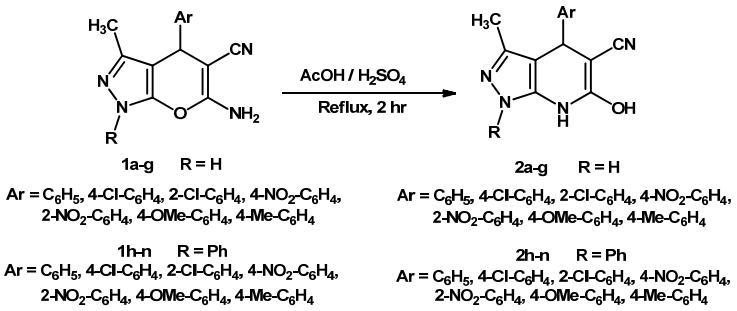


Scheme 1



Scheme 2

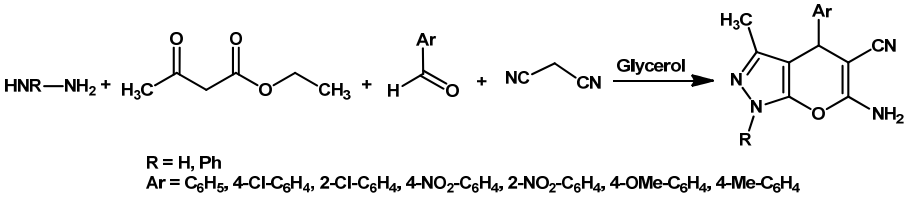


Figure 1. Synthesis of pyranopyrazoles using glycerol as green solvent.

Elemental analyses (C, H, and N) were performed using a Thermo Scientific elemental analyzer.

2.2. Synthesis

Pyranopyrazoles (**1a**-**n**) are prepared by using the given literature procedure [16]. In a conical flask, hydrazine hydrate/phenyl hydrazine (10 mmol), ethylacetoacetate (10 mmol), aromatic aldehyde (10 mmol) and malononitrile were added successively in glycerol (20 mL). Reaction mixture was stirred at 80 °C. After the completion of reaction (monitored by TLC), diluted the reaction mixture with ice cold water. Filtered the solid thus obtained and recrystallized with ethanol to afford compound **1a**-**n**.

6-Hydroxy-3-methyl-4-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2a**): In a conical flask pyranopyrazole (1 mmol) was taken in the mixture of acetic acid (3 mL) and sulphuric acid (0.1 mL) and reflux at 110 °C for the stipulated time Table 1. After the completion of reaction (*vide* TLC), reaction mixture was cooled to room temperature, solid separated out. Filtered and dried, recrystallized from ethanol to afford compound **2a** (Entry 1, Table 2). Yield: 88%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 3532 ν(O-H Str.), 3460 ν(N-H Str.), 3390 ν(N-H Str.), 2206 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.78 (s, 3H, CH_3), 4.53 (s, 1H, CH), 7.11-7.81 (m, 5H, Ar-H), 9.82 (s, 1H, OH), 12.14 (s, 1H, NH), 13.15 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.2, 156.9, 148.1, 139.5, 135.4, 122.1, 120.1, 114.1, 96.7, 77.9, 56.6, 52.6, 34.3, 9.7. MS (EI, *m/z* (%)): 253 (M$^+$, 12). Anal. calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.61; H, 4.78; N, 22.19%.

Similarly, other pyranopyrazoles **1b**-**n** were reacted to afford various pyrazolo-1,4-dihydropyridines derivatives **2b**-**n** (Table 2). Data obtained using advanced spectral techniques for some selected compounds have been summarized.

6-Hydroxy-3-methyl-4-(4-chlorophenyl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2b**): Yield: 84%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 3540 ν(O-H Str.), 3510 ν(N-H Str.), 3442 ν(N-H Str.), 2264 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.73 (s, 3H, CH_3), 4.51 (s, 1H, CH), 6.91-7.45 (m, 4H, Ar-H), 9.85 (s, 1H, OH), 12.01 (s, 1H, NH), 13.11 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):162.1, 153.3, 149.7, 144.2, 136.7, 133.0, 125.3, 120.9, 118.6, 98.3, 77.5, 53.2, 35.7, 9.7. MS (EI, *m/z* (%)): 288 (M$^+$, 10). Anal. calcd. for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.63; H, 3.84; N, 19.53%.

6-Hydroxy-3-methyl-4-(2-nitrophenyl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2e**): Yield: 85%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 3572 ν(O-H Str.), 3520 ν(N-H Str.), 3450 ν(N-H Str.), 2340 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.79 (s, 3H, CH_3), 4.76 (s, 1H, CH), 7.60-8.06 (m, 4H, Ar-H), 10.01 (s, 1H, OH), 12.19 (s, 1H, NH), 13.21 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):161.0, 154.7, 147.8, 146.5, 135.6, 134.0, 129.6, 121.7, 120.3, 96.3, 78.5, 56.4, 39.5, 9.7. MS (EI, *m/z* (%)): 298 (M$^+$, 13). Anal. calcd. for $C_4H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.53; H, 3.69; N, 23.54%.

6-Hydroxy-3-methyl-4-(4-methoxyphenyl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2f**): Yield: 81%. M.p.: 290-292 °C. FT-IR (KBr, ν, cm^{-1}): 3510 ν(O-H Str.), 3490 ν(N-H Str.), 3460 ν(N-H Str.), 2252 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.72 (s, 3H, CH_3), 3.68(s, 3H, OCH_3), 4.47 (s, 1H, CH), 7.21-7.80 (m, 4H, Ar-H), 9.92 (s, 1H, OH), 12.08 (s, 1H, NH), 13.06 (s, 1H, NH).

Table 1. Effect of temperature on the synthesis of compound **2a**.

Entry	Compound	Temperature (°C)	Time (h)	Yield [a] (%)
1	2a	70	9	20
2	2a	80	7	52
3	2a	90	4	70
4	2a	100	3	79
5	2a	110	2	88
6	2a	120 [b]	2	87
7	2a	130 [b]	2	82

[a] Yield refer to combined amounts of different crops.
[b] Reaction were carried out in silicon oil bath with the use of cold water in condenser.

^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):160.5, 157.9, 154.7, 136.1, 135.4, 128.3, 120.7, 113.4, 97.6, 78.5, 57.9, 54.7, 39.5, 35.6, 9.7. MS (EI, *m/z* (%)): 283 (M^+, 09). Anal. calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 11.34. Found: C, 63.79; H, 4.98; N, 11.33%.

6-Hydroxy-3-methyl-4-(4-methylphenyl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2g**): Yield: 82%. M.p.: >300 °C. FT-IR (KBr, ν, cm^{-1}): 3501 ν(O-H Str.), 3489 ν(N-H Str.), 3472 ν(N-H Str.), 2199 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.75 (s, 3H, CH_3), 2.21 (s, 3H, CH_3) 4.46 (s, 1H, CH), 7.01-7.42 (m, 4H, Ar-H), 9.72 (s, 1H, OH), 11.98 (s, 1H, NH), 12.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 159.0, 156.4, 150.2, 133.7, 130.8, 124.1, 123.0, 116.5, 95.2, 78.6, 56.4, 51.2, 40.2, 24.3, 9.7. MS (EI, *m/z* (%)): 267 (M^+, 10). Anal. calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.63; H, 5.28; N, 21.01%.

6-Hydroxy-3-methyl-1,4-diphenyl-4,7-dihydro-1H-pyrazolo [3,4-b]pyridine-5-carbonitrile (**2h**): Yield: 85%. M.p.: 228-230 °C. FT-IR (KBr, ν, cm^{-1}): 3490 ν(O-H Str.), 3430 ν(N-H Str.), 2221 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.90 (s, 3H, CH_3), 4.57 (s, 1H, CH), 7.21-7.48 (m, 10H, Ar-H), 10.07 (s, 1H, OH), 13.25 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 159.2, 144.2, 143.3, 141.2, 138.8, 135.1, 128.6, 123.4, 120.5, 113.4, 95.5, 77.5, 74.1, 58.2, 40.6, 39.3, 38.1, 36.6, 33.6, 12.4. MS (EI, *m/z* (%)): 329 (M^+, 13). Anal. calcd. for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.12; H, 4.89; N, 17.04%.

6-Hydroxy-3-methyl-4-(4-chlorophenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2i**): Yield: 82%. M.p.: 250-252 °C. FT-IR (KBr, ν, cm^{-1}): 3499 ν(O-H Str.), 3434 ν(N-H Str.), 2230 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.81 (s, 3H, CH_3), 4.49 (s, 1H, CH), 7.10-7.62 (m, 9H, Ar-H), 10.02 (s, 1H, OH), 13.29 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):159.3, 147.2, 144.7, 142.2, 138.2, 137.1, 129.7, 126.4, 122.6, 116.4, 97.4, 79.7, 78.1, 59.0, 41.3, 39.7, 39.1, 38.4, 35.6, 12.6. MS (EI, *m/z* (%)): 363 (M^+, 10). Anal. calcd. for $C_{20}H_{15}ClN_4O$: C, 66.21; H, 4.17; N, 15.44. Found: C, 66.19; H, 4.16; N, 15.41%.

6-Hydroxy-3-methyl-4-(2-chlorophenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2j**): Yield: 81%. M.p.: 220-222 °C. FT-IR (KBr, ν, cm^{-1}): 3498 ν(O-H Str.), 3480 ν(N-H Str.), 2229 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.87 (s, 3H, CH_3), 4.51 (s, 1H, CH), 7.11-7.69 (m, 9H, Ar-H), 10.06 (s, 1H, OH), 13.27 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):159.3, 147.5, 144.1, 143.0, 138.2, 136.9, 129.7, 125.8, 124.0, 118.4, 96.9, 78.9, 77.5, 58.9, 45.3, 40.7, 39.9, 38.1, 36.5, 12.6. MS (EI, *m/z* (%)): 363 (M^+, 09). Anal. calcd. for $C_{20}H_{15}ClN_4O$: C, 66.21; H, 4.17; N, 15.44. Found: C, 66.20; H, 4.15; N, 15.42%.

6-Hydroxy-3-methyl-4-(4-nitrophenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2k**): Yield: 88%. M.p.: 292-294 °C. FT-IR (KBr, ν, cm^{-1}): 3560 ν(O-H Str.), 3499 ν(N-H Str.), 2290 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.74 (s, 3H, CH_3), 4.90 (s, 1H, CH), 7.37-8.41 (m, 9H, Ar-H), 10.21 (s, 1H, OH), 13.36 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):159.6, 147.9, 145.7, 145.0, 143.9, 137.4, 134.4, 129.9, 129.0, 125.9, 122.1, 119.9, 97.4, 78.3, 57.2, 40.1, 39.3, 38.9, 36.4, 12.8. MS (EI, *m/z* (%)): 374 (M^+, 12). Anal. calcd. for $C_{20}H_{15}N_5O_3$: C, 64.34; H, 4.05; N, 18.76. Found: C, 64.33; H, 4.04; N, 18.76%.

6-Hydroxy-3-methyl-4-(2-nitrophenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2l**): Yield: 83%. M.p.: 286-288 °C. FT-IR (KBr, ν, cm^{-1}): 3559 ν(O-H Str.), 3440 ν(N-H Str.), 2263 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.80 (s, 3H, CH_3), 4.87 (s, 1H, CH), 7.32-8.11 (m, 9H, Ar-H), 10.20 (s, 1H, OH), 13.27 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):159.6, 147.8, 145.5, 144.8, 143.5, 136.9, 134.0, 130.2, 129.1, 124.6, 121.9, 119.7, 98.0, 78.1, 55.1, 41.2, 39.0, 37.9, 36.0, 12.7. MS (EI, *m/z* (%)): 374 (M^+, 14). Anal. calcd. for $C_{20}H_{15}N_5O_3$: C, 64.34; H, 4.05; N, 18.76. Found: C, 64.31; H, 4.00; N, 18.75%.

6-Hydroxy-3-methyl-4-(4-methoxyphenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2m**): Yield: 81%. M.p.: 265-267 °C. FT-IR (KBr, ν, cm^{-1}): 3520 ν(O-H Str.), 3425 ν(N-H Str.), 2219 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.81 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 4.56 (s, 1H, CH), 6.91-7.93 (m, 9H, Ar-H), 10.18 (s, 1H, OH), 13.17 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):159.1, 158.1, 145.2, 143.7, 137.6, 135.3, 128.9, 125.7, 119.8, 113.5, 99.4, 98.5, 78.5, 58.8, 54.8, 40.2, 39.8, 39.1, 38.2, 30.5, 12.5. MS (EI, *m/z* (%)): 359 (M^+, 08). Anal. calcd. for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.35; H, 5.05; N, 15.61%.

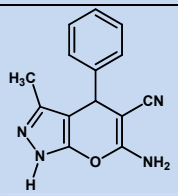
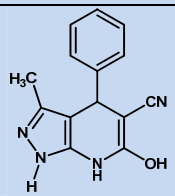
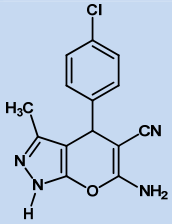
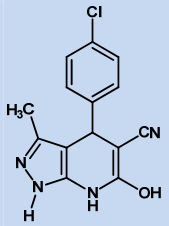
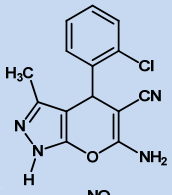
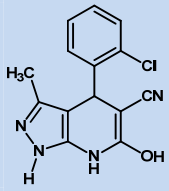
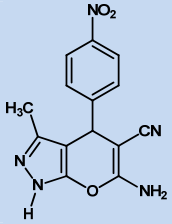
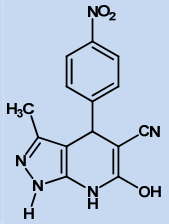
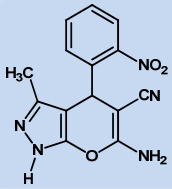
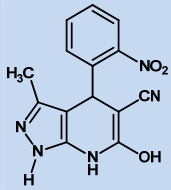
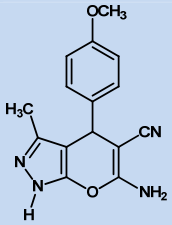
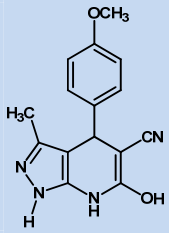
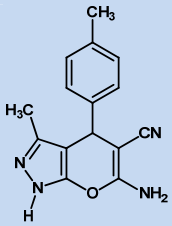
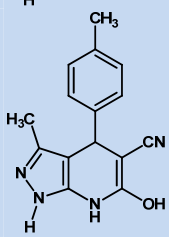
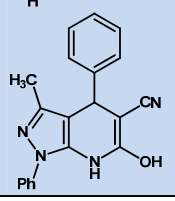
6-Hydroxy-3-methyl-4-(4-methylphenyl)-1-phenyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**2n**): Yield: 80%. M.p.:287-288 °C. FT-IR (KBr, ν, cm^{-1}): 3506 ν(O-H Str.), 3419 ν(N-H Str.), 2209 ν(C≡N Str.). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.79 (s, 3H, CH_3), 2.61(s, 3H, CH_3), 4.53 (s, 1H, CH), 7.41-8.24 (m, 9H, Ar-H), 10.09 (s, 1H, OH), 12.99 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):159.2, 145.2, 143.7, 140.2, 137.5, 136.0, 128.8, 127.4, 125.6, 119.8, 98.4, 78.7, 78.3, 58.9, 40.2, 39.8, 39.4, 38.9, 36.6, 20.6, 12.5. MS (EI, *m/z* (%)): 343 (M^+, 11). Anal. calcd. for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.66; H, 5.28; N, 16.36%.

3. Result and discussion

Reactions of pyranopyrazole **1a** with the mixture acetic acid and sulphuric acid were carried out at different temperatures (70-130 °C). It was observed that 110 °C is the optimal temperature for the synthesis of pyrazolo-1,4-dihydropyridines. Further, rise in temperature results in the decomposition of the reaction mixture (Table 1).

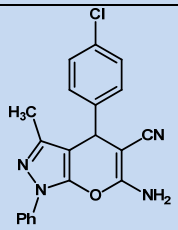
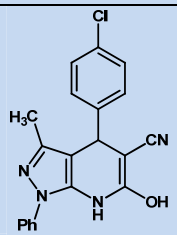
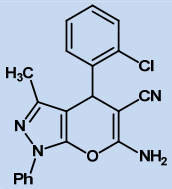
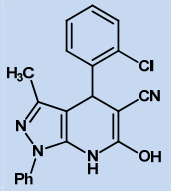
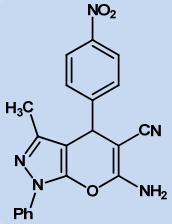
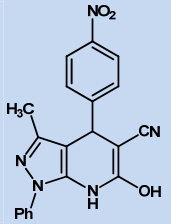
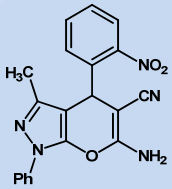
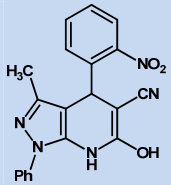
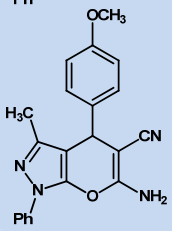
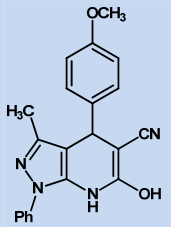
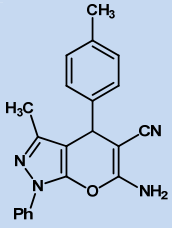
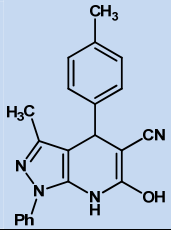
The structure of the compound **2a** was confirmed with the use of spectral techniques. In IR spectrum absorption at 3532 cm^{-1} represents the O-H stretching, absorption at 3460 and 3390 cm^{-1} for two N-H stretching, a sharp absorption peak at 2206 cm^{-1} represent C≡N stretching. In ^{1}H NMR spectra peaks two singletat 13.15 and 12.14 ppm are observed for two NH protons, a singlet for 9.82 ppm for OH proton, peaks for five aromatic protons are observed at 7.11-7.81 ppm, singlet at 4.53 ppm for –CH proton and a singlet for–CH_3 group is observed at 1.78 ppm. Spectral data of compound **2a** fully supports the structure assigned to it.Similarly, other pyrazolo-1,4-dihydropyridine derivatives**2b**-**n** have been synthesised from pyranopyrazoles **1b**-**n**in the mixture of acetic acid and sulphuric acid. The results are summarized in Table 2.

Table 2. Synthesis of pyrazolo-1,4-dihydropyridines from pyranopyrazoles.

S. No.	Entry of reactant	Reactant	Melting point of reactant (°C)	Entry of product	Product	Melting point of product (°C)	Yield [a]
1	1a		243-245	2a		>300	88
2	1b		233-235	2b		>300	84
3	1c		246-248	2c		>300	82
4	1d		249-252	2d		>300	90
5	1e		210-212	2e		>300	85
6	1f		208-210	2f		290-292	81
7	1g		240-242	2g		>300	82
8	1h		169-170	2h		228-230	85

[a] Yield refer to combined amounts of different crops.

Table 2. (Continued).

S. No.	Entry of reactant	Reactant	Melting point of reactant (°C)	Entry of product	Product	Melting point of product (°C)	Yield [a]
9	1i		175-176	2i		250-252	82
10	1j		143-145	2j		220-222	81
11	1k		195-197	2k		292-294	88
12	1l		199-200	2l		286-288	83
13	1m		175-177	2m		265-267	81
14	1n		176-177	2n		287-288	80

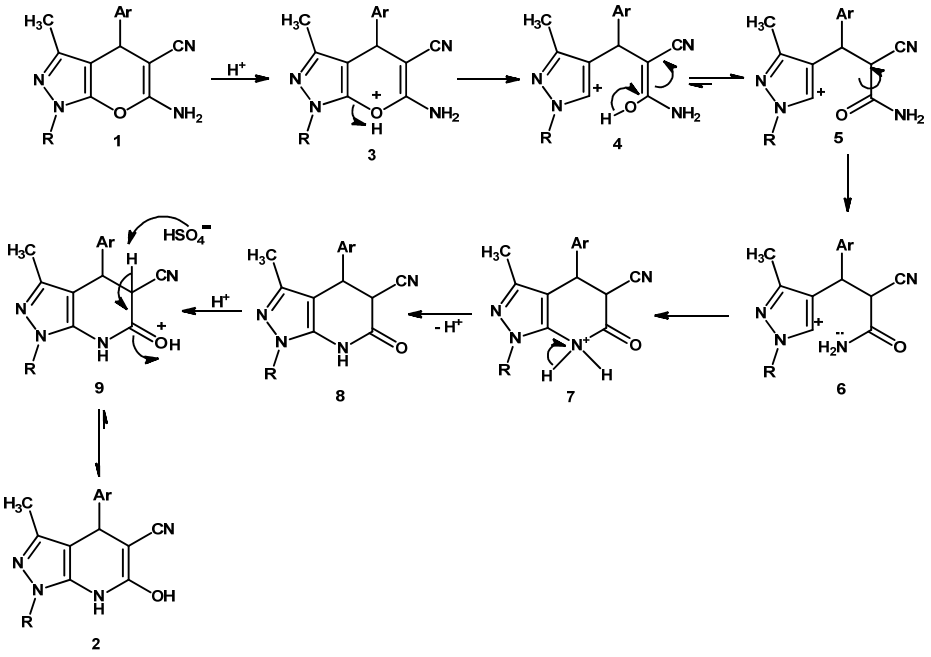
[a] Yield refer to combined amounts of different crops.

Reactions proceed smoothly with pyranopyrazoles carrying electron withdrawing as well as electron donating substituent's (Table 2). Efficacy of this method is fairly general and affords the resultant products in excellent yield (80-90%) and products are obtained by simple work up.

Attempt have been made to explain the plausible mechanism of the pyrazolo-1,4-dihydropyridine molecules (Scheme 3). In the acidic medium opening of pyran ring **1** occur *via* addition of H^+ ion to give compound **4** which upon tautomerism produced **5**, as C-C single bond rotation is possible in structure **5**, on rotating produced **6**. As we know C=0 bond length is smaller than C-NH_2, then the closing from NH_2 terminal is occurred to yield **7**. Further in acidic medium the keto form **8** is converted into more stable enol form **2** supported by the presence of absorption peak around 3550 cm^{-1} in IR and peak at around δ 10 ppm in ^1H NMR spectroscopy shows the presence of OH group and absence of peak 1650-1750 cm^{-1} confirm that enol form exist.

4. Conclusion

The present procedure is an effective method for production of pyrazolo-1,4-dihydropyridine, from easily obtainable initiating materials, in a single step with inherent flexibility and diversity. This method was efficacious to reduce labor, cost, waste production and also devoid of harsh reaction conditions. The target compounds were obtained in an acceptable yield with simple recrystallization as a purification step.



Scheme 3

Acknowledgements

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