Indian Journal of Chemistry
Vol. 55B, August 2016, pp 999-1006

Glycerol mediated green and one-pot synthesis of 6-amino-1,4-dihydropyrano [2,3-*c*]-pyrazole-5-carbonitriles under catalyst free conditions

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Received 24 August 2015; accepted (revised) 8 March 2016

A concise, facile and straightforward synthetic protocol has been described for the preparation of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives by a one-pot, three-component reaction of ethyl acetoacetate, hydrazine hydrate, aryl aldehydes and malononitrile in glycerol as a green and reusable reaction media under catalyst free condition. The corresponding 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles have been obtained with good to excellent yields (86-92%). This protocol is highly efficient due to its mild reaction conditions, operational simplicity, use of inexpensive, eco-friendly and green reaction media, catalyst-free conditions and absence of toxic organic solvents.

Keywords: 1,4-Dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives, one-pot, glycerol, catalyst free, green synthesis

The development and improvement of green methodologies for the synthesis of highly important organic intermediate is a challenging field for the organic chemists. Now a days, inflexible environmental concerns demand sustainable protocols that reduce the use of toxic and corrosive reagents and stop the stoichiometric formation of inorganic waste[1,2]. However, it has been also observed that the catalysts employed are not always eco-friendly and because of this, serious environmental pollution often results. Therefore, in the area of green synthesis, design of catalyst free reactions is an important goal for chemists[3].

On the other hand, utilization of organic solvents in an industrial scale leads to environmental pollution and causes many diseases and severe problems[4]. In this context, the use of eco-friendly solvents is particularly recommended because the majority of waste and pollution generated by the chemical processes is directly related to solvents[5-7]. With the ultimate goal of solving this environmental problem, several alternatives for the replacement of traditional organic solvents have been appraised during the last few years, which includes water[8], glycerol[9], polyethylene glycol[10], ionic liquids[11] and supercritical fluids[12]. Among them, glycerol is attracting considerable attention ever since the rapid development of the biodiesel industries, in which it is formed as the main by-product. In addition, the use of glycerol in the portfolio of available green solvents as a reaction solvent has attracted great attention in the recent past and has become an active area of research in green chemistry[13,14]. Glycerol (glycerin) is a colourless, odourless and viscous liquid. In fact, as suggested by Jerome and co-workers[15], glycerol can be considered as "organic water" since, like water, it is abundant, biodegradable, inexpensive, non-toxic, highly polar, immiscible with hydrocarbons, able to form strong hydrogen-bond networks and able to dissolve a wide range of organic and inorganic compounds. In addition, compared to water, it has the advantage of its higher boiling point, lower vapour pressure and also it is able to dissolve organic compounds usually immiscible with water. Thus, for the last few years many scientists have demonstrated a wide range of organic transformations using glycerol as a reaction media, which includes synthesis of 2-organoselanylpyridines[16], disulfides[17], 2-arylbenzothiazoles[18], benzimidazoles and benzodiazepines[19], pyrazolines[20], tetrazoles[21] and imidazoles[22]. Motivated by the above facts, the present work envisioned the design of green chemical approach involving glycerol mediated efficient synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles under catalyst-free conditions.

In medicinal chemistry, 4*H*-pyran analogue heterocyclic scaffolds signify a privileged structural motif and they are well distributed in naturally

occurring compounds[23]. Furthermore, 4*H*-pyran derivatives display a broad spectrum of biological activities such as anticancer[24], anti-HIV[25], anti-inflammatory[26], antimalarial[27] and antimicrobial[28]. These potent spheres of biological activity have encouraged widespread studies for the preparation of 6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives[29]. Condensed pyrazolo derivatives are also biologically important compounds and their chemistry has recently received considerable attention[30]. Several pyrano[2,3-*c*]pyrazoles have been described to have beneficial biological activities such as anti-inflammatory and analgesic[31]. In addition, the biological applications of fused azoles has led to exhaustive research on their synthesis[32].

Previously, this biologically important scaffold has been synthesized using various catalysts such as silica-supported tetramethylguanidine (SiO_2.TMG)[33], γ-alumina[34], per-6-amino-β-cyclodextrin (per-6-ABCD)[35], nano-ZnO[36], tetraethylammonium bromide (TEABr)[37], sodium benzoate[38], triethylamine[39], piperazine[40], piperidine[41], *N*-methylmorpholine[42] and L-proline[43]. However, these protocols have one or more drawbacks such as prolonged reaction time, use of organic solvents, strong acid or base catalysts, expensive catalyst and harsh reaction conditions. Thus, the development of novel environmentally friendly procedures for the synthesis of pyrano[2,3-*c*]pyrazoles in glycerol as a reusable reaction media is of significant interest. Our literature survey revealed that there is no report on the use of glycerol as an efficient reaction medium in the synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles.

For the first time, we disclose the application of glycerol as a sustainable reaction medium for the synthesis of a wide range of 1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles through the one-pot four-component process (Scheme I).

Results and Discussion

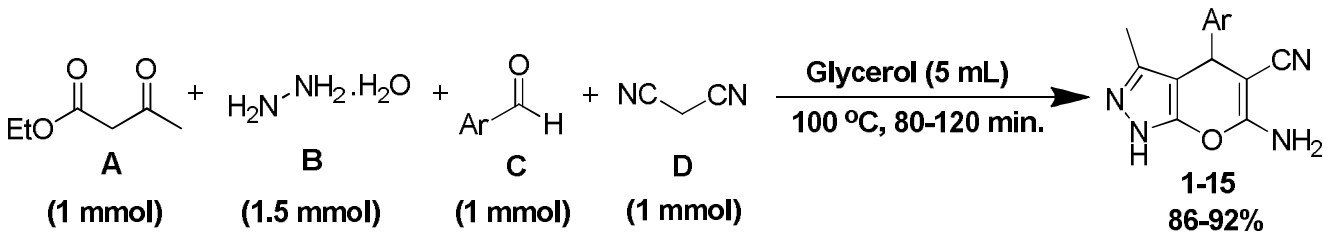
In the beginning, to achieving the optimized reaction conditions, we first performed the reaction between ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol, 80%), aromatic aldehydes (1 mmol) and malononitrile (1 mmol) as a model reaction. To improve the eco-compatibility of organic processes, several solvents were examined at variable temperatures. The results are summarized in Table I.

From Table I, we concluded that the trace amount of the product was obtained in the absence of solvent at RT under catalyst-free conditions (Table I, entry 1). In addition, it was revealed that the reaction afforded a lower yield of the product (29%) by increasing the temperature to 80°C under solvent as well as catalyst free conditions after prolonged reaction time (Table I, entry 2), which indicated that without any solvent, this reaction is sufficient. The rate of reaction goes on increasing on changing the solvent from ethanol and methanol (Table I, entries 3, 4) to water (Table I, entry 5) after a prolonged reaction time (120 min.).

Table I — Optimization of the reaction conditions

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]
1	–	RT	120	Trace
2	–	80	120	34
3	EtOH	Reflux	120	61
4	MeOH	Reflux	120	57
5	H_2O	Reflux	120	64
6	H_2O/EtOH	Reflux	120	72
7	DMF	Reflux	120	Trace
8	MeCN	Reflux	120	Trace
9	EtOAc	Reflux	120	Trace
10	CH_2Cl_2	Reflux	120	Trace
11	$CHCl_3$	Reflux	120	Trace
12	Glycerol	100	80	92
13	Glycerol	RT	80	48
14	Glycerol	50	80	55
15	Glycerol	60	80	62
16	Glycerol	70	80	69
17	Glycerol	80	80	78
18	Glycerol	90	80	87
19	Glycerol	110	80	92

a = Isolated yields



Scheme I — Glycerol mediated synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (1-15)

On other hand, a mixture of EtOH:H_2O (1:1, v/v) afforded a comparatively good yield of the product under similar reaction conditions (Table I, entry 6). Other organic solvents such as DMF, chloroform, ethyl acetate, dichloromethane and acetonitrile lead to trace amount of product yields (Table I, entries 7-11).When the reaction was carried out in glycerol at RT, then the yield of product was increased to some extent (Table I, entry 12). Finally, glycerol was able to significantly enhance the reaction in the forward direction at 100°C within shorter period of times and afforded product in excellent yield (Table I, entry 13). In the next step, the reaction was carried out at different temperatures in glycerol under catalyst-free condition. It was observed that, by increasing the temperature from 50°C to 100°C, the yields of product was improved (Table I, entries 12 and 14-18). In addition, result was not improved when the reaction as carried out at 110°C (Table I, entry 19). Hence, the best result was obtained by performing the reaction in the presence of glycerol at 100°C.

Then the generalization of the technique was evaluated using various aromatic aldehydes under optimized reaction conditions. The results showed that this protocol worked well for a wide range of aryl aldehydes possessing various functional groups including electron acceptor and electron donor substituents (Table II). In addition, heterocyclic aldehydes like 2-furfuraldehyde could also react efficiently, which afforded product in excellent yields (Table II, entry 15).

Table II — Glycerol mediated synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (1-15)

Entry	Ar	Time (min)	Yield (%)[a]	m.p. (°C)
1	C_6H_4	80	92	245-46[34]
2	4-OH-C_6H_4	100	88	224-26[34]
3	4-Br-C_6H_4	90	90	179-80[34]
4	2-OH-C_6H_4	110	86	209-11[35]
5	4-OMe-C_6H_4	100	91	211-12[34]
6	3-NO_2-C_6H_4	90	92	193-95[34]
7	2-Cl-C_6H_4	80	92	147-48[34]
8	4-Cl-C_6H_4	100	90	233-35[34]
9	4-Me-C_6H_4	110	89	207-09[34]
10	3-OH-C_6H_4	80	92	259-60[34]
11	4-NO_2-C_6H_4	100	91	251-52[34]
12	3,5-diOMe-4-OH-C_6H_2	100	90	199-201[a]
13	3,4-diOMe-C_6H_3	90	92	187-89[45]
14	4-$N(Me)_2$-C_6H_4	120	87	167-69[44]
15	2-Furayl	120	86	217-19[35]

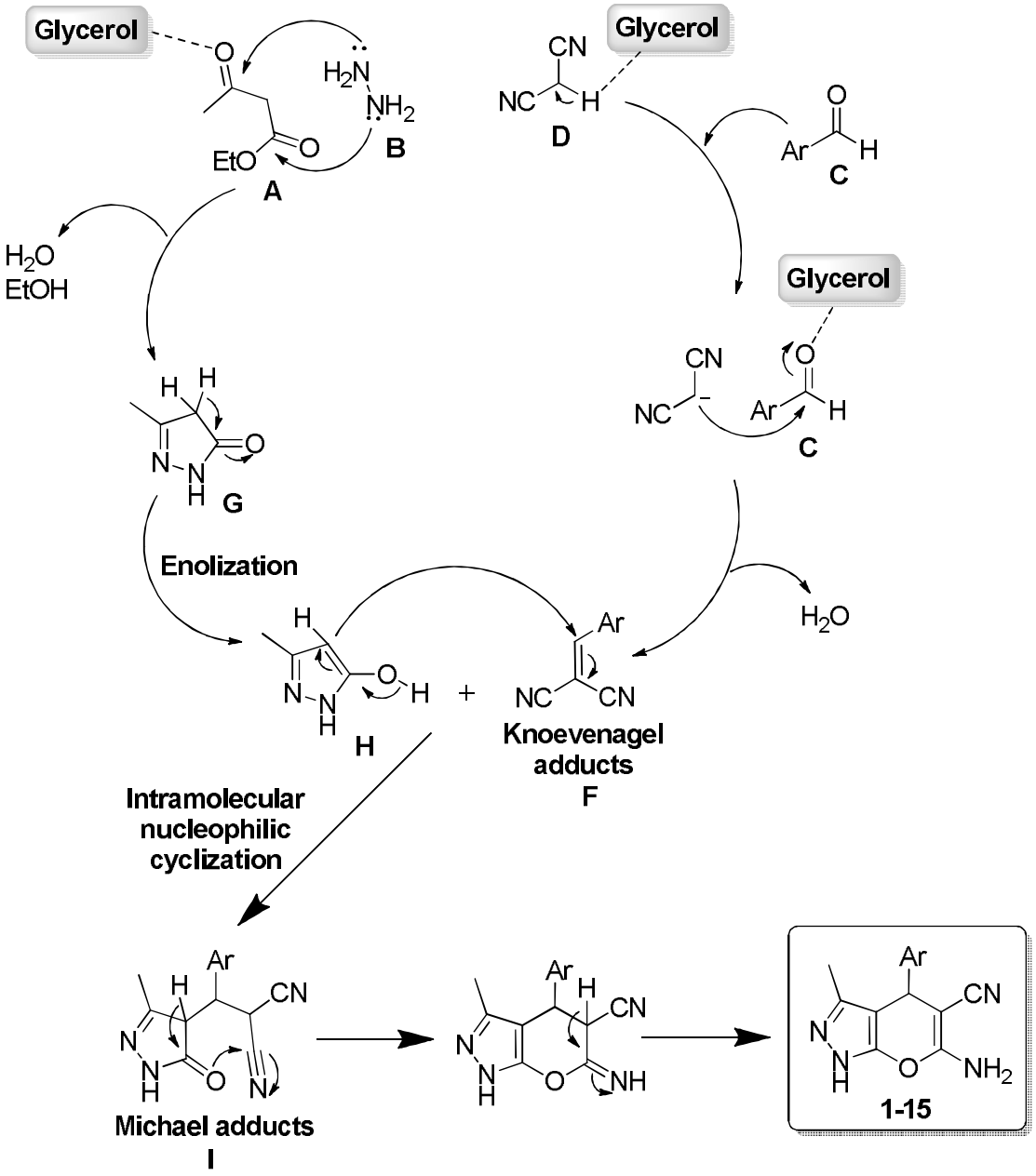
a = New compound

We have also proposed a possible mechanism for the construction of final products (1-15, Scheme II). The nitrile anion (E) was formed by the removal of acidic hydrogen from malononitrile (D) catalyzed by glycerol as the green reaction medium. Finally, the arylidene nitrile intermediates (Knoevenagel adducts, F) are formed through the Knoevenagel condensation reaction of the intermediate nitrile anion (E) with aldehydes (C). On other hand, the reaction of ethyl acetoacetate (A) and hydrazine hydrate (B) afforded compound (G), which was enolized into the compound (H). Subsequently, the enolized compound (H) condensed with the Knoevenagel adducts (F) *via* Michael addition, which results in the *in situ* formation of intermediate (I) (Michael adducts). Finally, this subsequently undergoes cyclization (Thorpe–Ziegler type reaction) and tautomerization to afford the desired compounds (1-15).

After extending the scope of synthesis of benzimidazoles, we checked the recyclability of glycerol in this reaction (Figure 1). After completion of condensation, the reaction mixture was extracted with hexane/ethyl acetate (95:5) and the glycerol phase was dried and reused. It was found that it could be reused five times without significant loss of efficiency.

Experimental Section

All chemicals, unless otherwise specified, were purchased from commercial sources and were analytical grade. The products were characterized by a comparison of their physical data and melting points with those of known samples or by their spectral data. Melting points were measured on an Optimelt MPA 100 melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Perkin-Elmer FT-IR 377 spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on Bruker AV 400 MHz spectrometer using DMSO-d_6 as solvent and TMS as the internal reference. Mass spectra were recorded on Advion Expression CMS, USA. Acetone was used as mobile phase, and electro-spray ionization (ESI) was used as ion source. Elemental analysis was performed on a CHN elemental analyzer. The progress of reaction was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F_{254} aluminum sheets, visualized by UV light.



Scheme II — The proposed mechanism for the glycerol mediated synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles

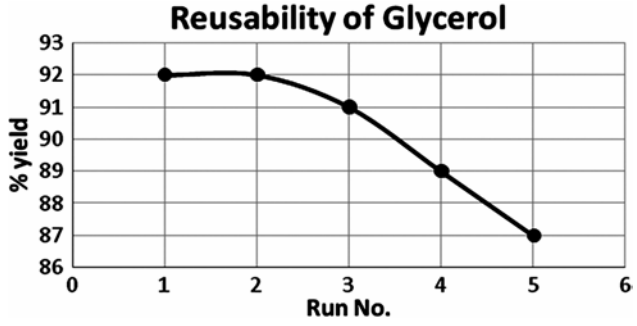


Figure 1 — Reusability profile of glycerol

General protocol for the preparation of 1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles, 1-15

A mixture of hydrazine hydrate (1.5 mmol, 80%), ethyl acetoacetate (1 mmol), aromatic aldehydes (1 mmol), malononitrile (1 mmol) and glycerol (5 mL) were taken in 25 mL Flat Bottom Flask (FBF). The reaction mixture was stirred at 100°C for appropriate time mentioned in Table II. The progress of the reaction was monitored by TLC analysis. When all the starting material had been consumed, the reaction mixture was washed with a mixture of

hexane/ethyl acetate 95:5 (10 mL) and the upper organic phases were separated from glycerol, dried with anhyd. $MgSO_4$, and the solvent evaporated under reduced pressure to afford crude product. The pure product was isolated by recrystallization from hot ethanol.The glycerol was dried under vacuum and reused for further reactions without further purification.

Spectral data of synthesized compounds

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile, 1: White solid. m.p. 245-46°C. IR (KBr): 3405, 3390 (NH_2), 3315 (-NH-), 3065, 3028 (Aromatic), 2930 (-CH_3), 2205 (-CN), 1487 cm^{-1} (-NH-); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.86 (s, 3H, CH_3), 4.65 (s, 1H, 4*H*), 6.45 (s, 2H, NH_2), 7.21-7.28 (m, 5H, Ar-H), 12.14 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.91, 35.41, 55.78, 113.25, 117.33, 125.17, 129.44, 135.70, 139.67, 156.65, 161.87; ESI-MS: *m/z* for (252.10): 253.1 $(M+1)^+$, 275.1 $(M+Na)^+$. Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.64; H, 4.78; N, 22.23%.

6-Amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, 2: Light yellow solid. m.p. 224-26°C. IR (KBr): 3452 (C-OH), 3401, 3395 (NH_2), 3322 (-NH-), 3068, 3021 (Aromatic), 2921 (-CH_3), 2200 (-CN), 1477 (-NH-), 3450 (C-OH), 790 cm^{-1} (*para*-OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.84 (s, 3H, CH_3), 4.84 (s, 1H, 4*H*), 6.77 (s, 2H, NH_2), 6.91 (s, 1H, OH), 7.21-7.23 (d, 2H, *J* = 8.40 Hz, Ar-H), 7.36-7.38 (d, 2H, *J* = 8.40 Hz, Ar-H), 12.07 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.91, 35.41, 55.78, 98.45, 121.25, 128.33, 129.17, 129.44, 130.70, 135.67, 144.47, 156.65, 161.87; ESI-MS: *m/z* for (268.10): 269.1 $(M+1)^+$, 291.2 $(M+Na)^+$. Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.72; H, 4.49; N, 20.86%.

6-Amino-4-(4-bromophenyl)-3-methyl-1,4-dihydro pyrano[2,3-*c*]pyrazole-5-carbonitrile, 3: White solid. m.p. 179-80°C. IR (KBr): 3405, 3390 (NH_2), 3317 (-NH-), 3062, 3028 (Aromatic), 2930 (-CH_3), 2205 (-CN), 1626 (=C=N-), 1487 (-NH-), 1069 (C-Br), 810 cm^{-1} (*para*-Br); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.15 (s, 3H, CH_3), 4.72 (s, 1H, 4*H*), 6.55 (s, 2H, NH_2), 7.44-7.46 (d, 2H, *J* = 8.48 Hz, Ar-H), 7.56-7.58 (d, 2H, *J* = 8.48 Hz, Ar-H), 10.93 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.66, 27.2, 40.57, 98.02, 113.88, 113.94, 120.81, 129.95, 131.53, 138.05, 139.18, 158.97; ESI-MS: *m/z* for (330.0): 330.2 $(M)^+$, 332.3 $(M+2)^+$. Anal. Calcd for $C_{14}H_{11}BrN_4O$: C, 50.77; H, 3.35; N, 16.92. Found: C, 50.72; H, 3.38; N, 16.89%.

6-Amino-4-(2-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, 4: Yellow solid. m.p. 209-11°C. IR (KBr): 3452 (C-OH), 3407, 3392 (NH_2), 3317 (-NH-), 3067, 3030 (Aromatic), 2932 (-CH_3), 2207 (-CN), 1489 (-NH-), 740 cm^{-1} (*ortho*-OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.92 (s, 3H, CH_3), 4.64 (s, 1H, 4*H*), 6.72 (s, 2H, NH_2), 7.00 (s, 1H, OH), 7.02-7.43 (m, 4H, Ar-H), 10.75 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.75, 28.62, 54.93, 89.43, 104.95, 115.49, 119.59, 120.86, 123.62, 127.57, 128.94, 136.48, 148.37, 158.60, 160.08, 162.78; ESI-MS: *m/z* for (268.27): 268.1 $(M)^+$, 269.1 $(M+1)^+$, 291.1 $(M+Na)^+$. Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.67; H, 4.53; N, 20.87%.

6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, 5: Light yellow solid. m.p. 211-12°C. IR ν_{max} (KBr): 3411, 3385 (NH_2), 3320 (-NH-), 3070, 3022 (Aromatic), 2933 (-CH_3), 2206 (-CN), 1482 (-NH-), 1351, 1560 (-NO_2), 775 cm^{-1} (*meta*-NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.79 (s, 3H, CH_3), 2.27 (s, 3H, OCH_3), 4.55 (s, 1H, 4*H*), 6.87 (s, 2H, NH_2), 7.30-7.32 (d, 2H, *J* = 7.96 Hz, Ar-H), 7.76-7.78 (d, 2H, *J* = 8.04 Hz, Ar-H), 12.11 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.86, 27.98, 55.18, 99.32, 111.68, 112.74, 121.11, 128.55, 127.53, 134.45, 135.18, 163.34; ESI-MS: *m/z* for (282.11): 282.1 $(M)^+$, 283.3 $(M+1)^+$. Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.58; H, 3.72; N, 23.55%.

6-Amino-3-methyl-4-(3-nitrophenyl)-1,4-dihydro pyrano[2,3-*c*]pyrazole-5-carbonitrile, 6: Dark Yellow solid. m.p. 193-95°C. IR (KBr): 3411, 3385 (NH_2), 3320 (-NH-), 3070, 3022 (Aromatic), 2933 (-CH_3), 2206 (-CN), 1482(-NH-), 1351, 1560 (-NO_2), 775 cm^{-1} (*meta*-NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.92 (s, 3H, CH_3), 4.79 (s, 1H, 4*H*), 6.72 (s, 2H, NH_2), 7.55 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.62 (d, 1H, *J* = 7.6 Hz, Ar-H), 8.00-8.03 (m, 2H, Ar-H), 11.23 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.50, 29.07, 56.51, 112.67, 121.22, 123.28, 128.43, 128.69, 135.74, 141.36, 146.36,151.31, 154.64, 161.90; ESI-MS: *m/z* for (297.1): 298.1 $(M+1)^+$, 319.9 $(M+Na)^+$. Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.58; H, 3.72; N, 23.55%.

6-Amino-4-(2-chlorophenyl)-3-methyl-1,4-dihydro pyrano[2,3-*c*]pyrazole-5-carbonitrile, 7: Off-white solid. m.p. 147-48°C. IR (KBr): 3409, 3394 (NH_2), 3319 (-NH-), 3068, 3032 (Aromatic), 2935 (-CH_3), 2209 (-CN), 1492 (-NH-), 1062 (C-Cl), 752 cm^{-1} (*ortho*-Cl); ^{1}H NMR (400 MHz, DMSO-d_6):δ_H 1.88 (s, 3H, CH_3), 4.96 (s, 1H, 4*H*), 6.75 (s, 2H, NH_2), 7.09-7.36 (m, 3H, Ar-H), 7.76-7.83 (m, 1H, Ar-H), 11.23 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.70, 29.12, 55.81, 88.83, 104.55, 115.19, 120.39, 121.06, 123.72, 126.17, 128.24, 137.98, 147.17, 158.60, 163.22; ESI-MS: *m/z* for (286.06): 286.1 $(M)^+$, 288.1 $(M+1)^+$. Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.63; H, 3.88;, N, 19.55%.

6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydro pyrano[2,3-*c*]pyrazole-5-carbonitrile, 8: Off-white solid. m.p. 233-35°C. IR (KBr): 3400, 3391 (NH_2), 3317 (-NH-), 3066, 3017 (Aromatic), 2931 (-CH_3), 2211 (-CN), 1488 (-NH-), 1058 (C-Cl), 815 cm^{-1} (*para*-Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.79 (s, 3H, CH_3), 4.64 (s, 1H, 4*H*), 6.96 (s, 2H, NH_2), 7.19-7.21 (d, 2H, *J* = 8.40 Hz, Ar-H), 7.37-7.39 (d, 2H, *J* = 8.40 Hz, Ar-H), 12.17 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.71, 35.51, 56.68, 97.15, 120.65, 128.43, 129.07, 129.34, 129.70, 130.00, 131.20, 135.67, 143.44, 154.65, 160.87; ESI-MS: *m/z* for (286.06): 286.1 $(M)^+$, 288.1 $(M+2)^+$. Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.63; H, 3.88; N, 19.55%.

6-Amino-3-methyl-4-(*p*-tolyl)-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile, 9: Off-white solid. m.p. 207-209°C. IR (KBr): 3413, 3396 (NH_2), 3321 (-NH-), 3072, 3024 (Aromatic), 2937 (-CH_3), 2212 (-CN), 1494 (-NH-), 800 cm^{-1} (*para*-CH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.77 (s, 3H, CH_3), 2.34 (s, 3H, *P*-CH_3), 4.65 (s, 1H, 4*H*), 6.85 (s, 2H, NH_2), 7.11-7.13 (d, 2H, *J* = 8.40 Hz, Ar-H), 7.32-7.34 (d, 2H, *J* = 8.40 Hz, Ar-H), 12.22 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 10.01, 22.56, 35.51, 56.68, 113.15, 117.65, 125.43, 128.07, 132.34, 135.70, 139.00, 154.62, 161.87; ESI-MS: *m/z* for (266.12): 266.2 $(M)^+$, 267.1 $(M+1)^+$. Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.63; H, 5.31; N, 21.05%.

6-Amino-4-(3-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, 10: White solid. m.p. 259-60°C. IR (KBr): 3410, 3395 (NH2), 3314 (-NH-), 3064, 3027 (Aromatic), 2935 (-CH3), 2210 (-CN), 1492 (-NH-), 3455 (C-OH), 778 cm^{-1} (*meta*-OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.95 (s, 3H, CH_3), 4.89 (s, 1H, 4*H*), 6.78 (s, 2H, NH_2), 6.96 (s, 1H, OH), 7.56 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.69 (d, 1H, *J* = 7.6 Hz, Ar-H), 8.07-8.09 (m, 2H, Ar-H), 11.23 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.48, 28.87, 58.09, 113.67, 122.22, 124.28, 129.43, 130.69, 136.74, 141.36, 147.36, 152.31, 155.64, 162.90; ESI-MS: *m/z* for (268.1): 269.2 $(M+1)^+$, 291.4 $(M+Na)^+$. Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.67; H, 4.53; N, 20.87%.

6-Amino-4-(4-nitrophenyl)-3-methyl-1,4-dihydro pyrano[2,3-*c*]pyrazole-5-carbonitrile, 11: Yellow solid. m.p. 251-52°C. IR (KBr): 3414, 3389 (NH_2), 3323 (-NH-), 3073, 3025 (Aromatic), 2936 (-CH_3), 2209 (-CN), 1485 (-NH-), 1354, 1563 (-NO_2), 818 cm^{-1} (*para*-NO_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.82 (s, 3H, CH_3), 4.84 (s, 1H, 4*H*), 7.08 (s, 2H, NH_2), 7.46-7.48 (d, 2H, *J* = 8.48 Hz, Ar-H), 8.20-8.22 (d, 2H, *J* = 8.48 Hz, Ar-H), 12.22 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.71, 35.84, 55.84, 96.52, 120.47, 123.87, 128.81, 135.84, 146.34, 152.08, 154.63, 161.11; ESI-MS: *m/z* for (297.1): 397.2 $(M)^+$, 398.3 $(M+1)^+$. Anal. Calcd for $C_{14}H_{11}BrN_4O$: C, 50.77; H, 3.35; N, 16.92. Found: C, 50.72; H, 3.38; N, 16.89%.

6-Amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, 12: Off-white solid. m.p. 199-201°C. IR (KBr): 3452 (C-OH), 3393, 3384 (NH_2), 3310 (-NH-), 3059, 3010 (Aromatic), 2925 (-CH_3), 2590 (-OCH_3), 2205 (-CN), 1481 (-NH-), 742 (*ortho*), 772 (*meta*), 805 cm^{-1} (*para*); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.86 (s, 3H, CH_3), 3.71 (s, 6H, 2 × OCH_3), 4.53 (s, 1H, 4*H*), 6.43 (s, 2H, NH_2), 6.85 (s, 2H, Ar-H), 8.28 (s, 1H, -OH), 12.08 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.88, 36.24, 55.93, 57.32, 97.63, 104.82, 120.89, 134.25, 134.45, 135.66, 147.80, 154.66, 160.73; ESI-MS: *m/z* for (328.1): 329.1 $(M+1)^+$, 351.1 $(M+Na)^+$. Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.54; H, 4.90; N, 17.06%.

6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, 13: White solid. m.p. 187-89°C. IR (KBr): 3395, 3386 (NH_2), 3312 (-NH-), 3061, 3012 (Aromatic), 2927 (-CH_3), 2207 (-CN), 1483 (-NH-), 2592 (-OCH_3), 702 (*meta*-OCH_3), 809 cm^{-1} (*para*-OCH_3); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.93 (s, 3H, CH_3), 3.83 (s, 6H, 2 × -OCH_3), 4.76 (s, 1H, 4*H*), 6.78 (s, 2H, NH_2),

7.54-7.56 (m, 2H, Ar-H), 7.96 (s, 1H, Ar-H), 11.53 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.75, 31.60, 56.84, 60.23, 99.12, 102.32, 104,56, 121.87, 124.56, 126.41, 134.64, 145.64, 153.05, 156.13, 163.04; ESI-MS: *m/z* for (312.12): 312.4 $(M)^+$, 313.4 $(M+1)^+$. Anal. Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.52; H, 5.18; N, 17.93%.

6-Amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, 14: Light brown solid. m.p. 167-69°CIR ν_{max} (KBr): 3430 (C-N), 3409, 3380 (NH_2), 3318 (-NH-), 3067, 3018 (Aromatic), 2932 (-CH_3), 2212 (-CN), 1490 (-NH-), 810 cm^{-1} (*para*-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.80 (s, 3H, CH_3), 2.77 (s, 6H, CH_3), 4.54 (s, 1H, 4*H*), 6.67 (s, 2H, NH_2), 6.57 (d, 2H, J = 8.4 Hz, Ar-H), 6.92 (d, 2H, J = 7.6 Hz, Ar-H), 11.88 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 10.07, 29.44, 57.71, 86.55, 104.21, 119.92, 125.19, 133.34, 133.25, 133.64, 140.95, 160.04, 163.15; ESI-MS: *m/z* for (295.1): 296.0 $(M+1)^+$, 318.0 $(M + Na)^+$. Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.09; H, 5.79; N, 23.70%.

6-Amino-4-(furan-2-yl)-3-methyl-1,4-dihydro pyrano[2,3-*c*]pyrazole-5-carbonitrile, 15: Brown solid. m.p. 217-19°C. IR (KBr): 3403, 3394 (NH_2), 3320 (-NH-), 3069, 3020 (Aromatic), 2935 (-CH_3), 2215 (-CN), 1491 (-NH-), 1200 cm^{-1} (-O-); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.89 (s, 3H, CH_3), 4.62 (s, 1H, 4*H*), 6.54 (s, 2H, NH_2), 6.85 (d, 1H, Furan-H), 7.05 (t, 1H, Furan-H), 7.34 (d, 1H, Furan-H), 12.18 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 9.78, 34.21, 58.93, 104.82, 110.59, 113.25, 118.45, 138.66, 145.80, 154.66, 158.22, 163.13; ESI-MS: *m/z* for (242.08): 243.2 $(M+1)^+$, 365.1 $(M+Na)^+$. Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.51; H, 4.14; N, 23.14%.

Conclusion

To conclude, we report for the first time the use of glycerol in the synthesis of various 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles. This protocol is very simple from the experimental point of view and would allow easy access to large families of 1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles under catalyst-free conditions. Short reaction time, good to excellent yields, safe process and simple workup make this a valuable contribution in accord with green chemistry principles. Further studies on the application of glycerol in organic synthesis are ongoing in our laboratory. Recovered glycerol can be directly reused without any purification for condensation reactions.

Acknowledgements

The authors are thankful to the Department of Chemistry, Gujarat University, for providing laboratory facilities and INFLIBNET, Ahmedabad for providing E-sources. The authors are also thankful to NFDD Centre for ^{1}H and ^{13}C NMR and Synzeal Laboratory for mass spectroscopy. R. H. Vekariya is thankful to UGC-BSR [F.7-74/2007 (BSR)] for financial assistance.

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