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# Starch-sulfuric acid (SSA) as a bio-degradable and recyclable solid acid catalyst for one-pot synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles

Rajesh H. Vekariya, Kinjal D. Patel and Hitesh D. Patel*

*Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad, Gujarat, India.*

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**Abstract:** Starch-sulfuric acid (SSA) catalyzed, one-pot, multi-component and an environmentally benign synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives has been achieved by reaction of ethyl acetoacetate, hydrazine hydrate, aryl aldehydes and malononitrile under solvent-free conditions. Upon completion of the reaction, the SSA could be recycled and reused several times with consistent catalytic efficiency. This protocol has several advantages including high yields, simple work-up process, avoiding the use of organic solvents, short reaction times, and use of an inexpensive and mild catalyst.

**Keywords:** 6-Amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives, Starch-sulfuric acid (SSA), One-pot, Solvent-free, Reusable catalyst.

## Introduction

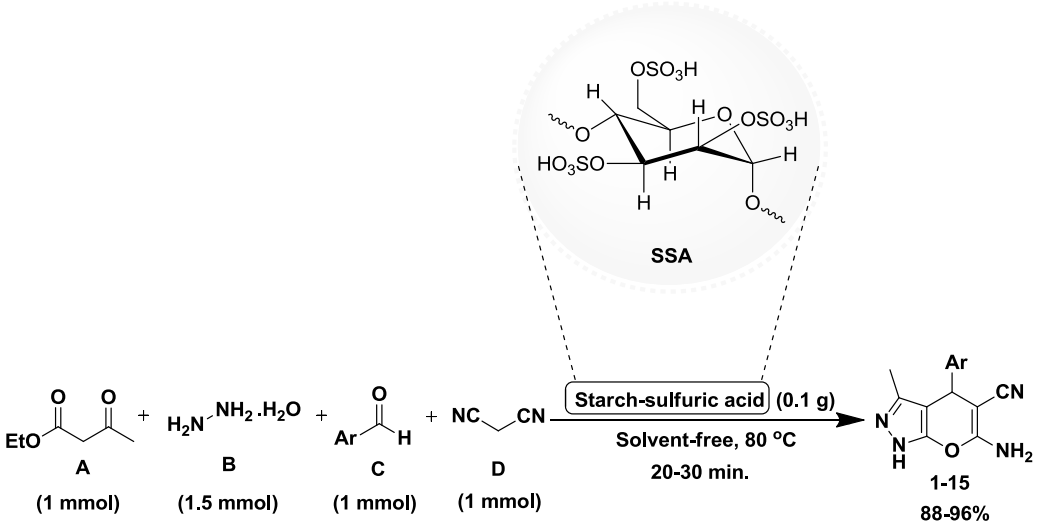
Recently, the expansion of green protocols that are environmentally benign and pollution free have received substantial levels of consideration because of the increasing tendency of the chemical industry towards greener unit processes. Now a days, Multi-component reactions (MCRs) have received much attention in the field of organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional synthetic methodologies [1]. Therefore, planning reactions that accomplish multi-bond formation in one operation is becoming one of the foremost challenges in the field of green organic synthesis [2]. Synthesis of biological active molecules as well as important organic intermediates through an MCR approach delivers a number of merits over conventional transformations, such as shorter reaction times, higher product yields, lower costs and environmental being [3-5].

4*H*-Pyrans analogue heterocyclic scaffolds signify a fortunate structural motif well distributed in naturally occurring compounds [6,7]. Furthermore, 4*H*-pyrane derivatives displays a broad spectrum of biological activities such as anticancer [8], anti-HIV [9], anti-inflammatory [10], antimalarial [11], antimicrobial [12], antiviral [13] and anti-proliferative [14]. These potent outlines of biological activities have encouraged widespread studies for the preparation of 6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole derivatives [15]. Condensed pyrazolo derivatives are also biologically important compounds and their chemistry has recently received considerable attention [16]. Several pyrano[2,3-*c*]pyrazoles are reported to have beneficial biological activities such as anti-inflammatory and analgesic [17]. In addition, the biological activity of

*Corresponding author. Tel: (+91) 079-26300969, Fax: (+91) 079-26308545, E-mail: drhiteshpatel1@gmail.com

fused azoles has led to exhaustive research on their synthesis [18].

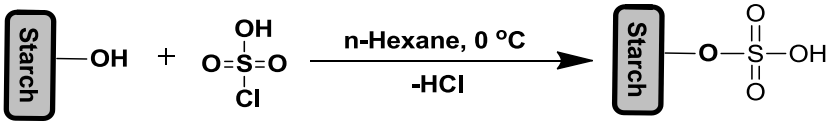
Owing to the growing environmental concerns, there is continued pressure on pharmaceutical as well as on chemical industries to reduce chemical waste. In this regard utilization of heterogeneous catalysts may offer the advantages of facile recovery and recycling of the catalyst, which reduced chemical pollutions [19, 20]. Recently, the direction of science and technology has been shifting toward more eco-friendly, bio-degradable and reusable catalysts [21, 22]. Natural biopolymers are attractive candidates in the search for solid support catalysts. It was therefore thought worthwhile to develop a new and mild method using an inexpensive biopolymer-based catalyst that can be easily separated, reused, and is not contaminated by the products [21]. The cellulose and starch are the most abundant natural polymers and have been widely studied during the past several decades because they are biodegradable materials and a renewable resource [23, 24]. Its unique properties make it an attractive alternative to conventional organic or inorganic supports in catalytic applications. Previously, SSA was utilized as catalyst for the synthesis of *α*,*α*'-benzylidene bis(4-hydroxycoumarin) derivatives [25], 3,4-dihydropyrimidinone derivatives [26], quinolines [27] and 1,5-diaryl-1*H*-pyrazoles [28]. Thus, in present study, we choose starch-sulfuric acid (SSA) as a catalyst, which is more efficient, economical and compatible with the environment. Herein, we wish to report the development of an environmentally friendly process for the preparation of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives via the one-pot, four-component synthesis catalyzed by starch-sulfuric acid (SSA) under solvent-free conditions (Scheme **1**).




**Scheme 1:** Synthesis of 1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles (1-15) catalyzed by SSA.

## Results and discussion

Starch-sulfuric acid (SSA) is readily prepared by drop wise addition of chlorosulfonic acid to a mixture of starch in *n*-hexane at 0 °C. It is important to note that this reaction is easy and clean without any work-up procedure because HCl gas is evolved from the reaction vessel immediately. This white reusable and nonhygroscopic solid acid is stable under the reaction conditions (Scheme **2**). Starch-sulfuric acid (SSA) is one of the important catalysts for the selective construction of heterocyclic ring systems, especially in the synthesis of 1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles. The catalyst decreases the production of chemical waste without using some highly toxic reagents in the synthesis of these products.




**Scheme 2:** Synthesis of starch-sulfuric acid (SSA).

The main objective of the current work was to develop an efficient and green protocol for the synthesis of 6-amino1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles under solvent-free conditions utilizing starch-sulfuric acid (SSA) as a solid and reusable catalyst. In order to optimize reaction conditions, we have chosen the condensation reaction of ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol, 80%), aromatic aldehydes (1 mmol) and malononitrile (1 mmol) as a model reaction. This model reaction was conducted under different conditions including temperature, solvents and the amount of the catalyst. The results are summarized in Table **1**. In the absence of SSA only 29 % yield of the product was obtained, with recovery of starting material, even after heating at 80 $^{o}$C for 1 h (Table **1**, Entry 1), whereas in the presence of SSA (0.05 g), under the same conditions the yield increased to 60 % (Table **1**, Entry 2). From this we concluded that the catalyst is essential for formation of the product in high yield in this transformation. On the basis of this result, further studies were conducted and it was found that 0.1 g SSA was optimum for this reaction, and gave the product in 96 % yield in just 20 min (Table **1**, Entry 3). The yields of product was also increased slightly by adding 0.075 g of SSA to the reaction mixture at room temperature (Table **1**, Entry 4). In addition higher amount of catalyst that is 0.15 g, can't be improved product yields and the reaction times (Table **1**, Entry 16).

**Table 1:** Optimization of the reaction conditions.

| Entry[b] | Solvent | Catalyst loading (g) | Temperature ($^{o}$C) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | Solvent-free | - | 80 $^{o}$C | 60 | 29 |
| 2 | Solvent-free | 0.05 | 80 $^{o}$C | 60 | 64 |
| **3** | **Solvent-free** | **0.10** | **80 $^{o}$C** | **20** | **96** |
| 4 | $H_2O$ | 0.10 | Reflux | 60 | 80 |
| 5 | MeOH | 0.10 | Reflux | 60 | 72 |
| 6 | EtOH | 0.10 | Reflux | 60 | 75 |
| 7 | MeCN | 0.10 | Reflux | 60 | 56 |
| 8 | $CH_2Cl_2$ | 0.10 | Reflux | 60 | 47 |
| 9 | EtOAc | 0.10 | Reflux | 60 | 41 |
| 10 | $CHCl_3$ | 0.10 | Reflux | 60 | 39 |
| 11 | Solvent-free | 0.10 | rt | 30 | 58 |
| 12 | Solvent-free | 0.10 | 40 $^{o}$C | 20 | 66 |
| 13 | Solvent-free | 0.10 | 50 $^{o}$C | 20 | 74 |
| 14 | Solvent-free | 0.10 | 60 $^{o}$C | 20 | 82 |
| 15 | Solvent-free | 0.10 | 70 $^{o}$C | 20 | 90 |
| 16 | Solvent-free | 0.15 | 80 $^{o}$C | 20 | 96 |

a = isolated yields

b = All studies were performed using ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol, 80%), aromatic aldehydes (1 mmol) and malononitrile (1 mmol) as a model reaction.

To evaluate the effects of different solvents on the reaction, the model reaction was conducted in a range of different solvents, including methanol, ethanol, acetonitrile, dichloromethane, ethyl acetate, chloroform and water in the presence of 0.1 g of SSA under reflux conditions (Table **1**, Entries 4-10). Aprotic solvents gave the desired product in lower yields, whereas protic solvents gave the product in good to excellent yields (Table **1**, Entries 5-7). Having optimized the solvent for the reaction, we proceeded to investigate the use of different temperatures including room temperature and 40, 50, 60 and 70 °C (Table **1**, Entries 11-15). The best result was obtained at the 80 °C (Table **1**, Entry 3).

To estimate the scope of this catalytic transformation, the optimized reaction conditions were subsequently applied to the reaction of ethyl acetoacetate, hydrazine hydrate and malononitrile with a variety of different aromatic aldehydes (Table **2**, Entries 1-15). A wide range of aromatic aldehydes with

electron donating and electron withdrawing substituents reacted successfully to give the corresponding products in high to excellent yields over short reaction time. In all cases, the reaction was found to be selective and afforded the desired products in high purity without any evidence of the formation of any side products. In addition, heterocyclic aldehyde like 2-furfuraldehyde could also reacted efficiently, which afforded product in excellent yields (Table **2**, Entry 10).

**Table 2:** Synthesis of synthesis of 1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles catalyzed by SSA.

| Entry | Ar | Time (min) | Yield (%)[a] | Mp ($^{o}$C) | Ref. |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | 20 | 96 | 244-246 | [29] |
| 2 | 4-OH-$C_6H_5$ | 25 | 94 | 224-225 | [29] |
| 3 | 4-$N(Me)_2$-$C_6H_5$ | 30 | 88 | 168-169 | [30] |
| 4 | 2-OH-$C_6H_5$ | 28 | 90 | 209-210 | [31] |
| 5 | 4-OMe-$C_6H_5$ | 30 | 91 | 210-212 | [29] |
| 6 | 3-$NO_2$-$C_6H_5$ | 30 | 90 | 193-194 | [29] |
| 7 | 2-Cl- $C_6H_5$ | 20 | 96 | 146-148 | [29] |
| 8 | 4-Cl-$C_6H_5$ | 22 | 95 | 233-234 | [29] |
| 9 | 4-Me-$C_6H_5$ | 28 | 88 | 206-209 | [29] |
| 10 | 2-furayl | 30 | 89 | 217-218 | [32] |
| 11 | 3,5-diOMe-4-OH-$C_6H_3$ | 25 | 94 | 198-201 | [34] |
| 12 | 4-Br-$C_6H_5$ | 24 | 96 | 179-181 | [29] |
| 13 | 3,4-diOMe-$C_6H_4$ | 28 | 91 | 186-189 | [33] |
| 14 | 4-$NO_2$-$C_6H_5$ | 22 | 95 | 250-251 | [29] |
| 15 | 3-OH-$C_6H_5$ | 25 | 89 | 225-228 | [31] |

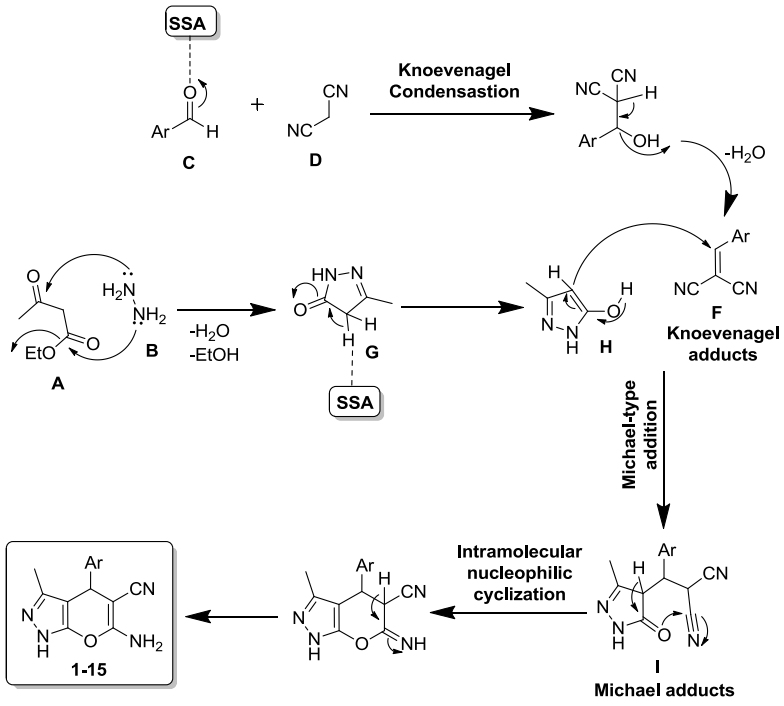
Reaction conditions: Ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol, 80%), aromatic aldehydes (1 mmol) and malononitrile (1 mmol) under solvent-free conditions at the 80 °C in the presence of SSA (0.1 g)
a = Isolated yield
b = Novel Compound

We have also proposed possible mechanism for the building of final products **(1-15)** (Scheme **3**). The nitrile anion **(E)** was formed by the removal of acidic hydrogen from malononitrile **(D)** catalyzed by SSA. 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 and hydrazine hydrate afforded compound **(G)**, which was enolised in the presence of SSA to formed compound **(H)**. Subsequently, the enolizable compound **(H)** condensed with the Knoevenagel adducts **(F)** via Michael addition, which results in the in situ formation of intermediate **(I)** (Michael adducts). Finally, which subsequently undergoes intramolecular nucleophilic cyclization (Thorpe–Ziegler type reaction) and tautomerization to afford the desired compounds **(1-15)**.

To evaluate the catalytic activity of SSA compared with other catalysts for the formation of compound **1**, comparative experiments were performed and the data are shown in Table **3**. Among the different catalysts tested, including $FeCl_3.6H_2O$, $InCl_3$, $ZnCl_2$, *p*-TSA, ceric ammonium nitrate (CAN) and SSA. However, SSA was found to be the most efficient in terms of the reaction times and product yields (Table **1**, Entries 1-6).

Next, we performed the recyclability study of the catalyst by carrying out the reaction of ethyl acetoacetate, hydrazine hydrate, benzaldehyde and malononitrile in the presence of catalytic amount of 0.1 g of SSA under solvent-free conditions at the 80 $^{o}$C. After completion of the reaction, the reaction mixture was extracted with ethyl acetate and the resulting solid was removed by filtration, and washed with ethanol. The recovered catalyst was collected dried in an oven at 80 $^{o}$C for 1 h prior before use. The results of recycling experiments are given in Figure **1**. Also, we have conformed the efficiency of recycle catalyst by elemental analysis. The conventional elemental

analysis showed the presence of sulfur, indicating sulfur had not leached out.




**Scheme 3:** Probable mechanistic pathway.

**Table 3:** Evaluation of catalytic activity of different catalysts for the condensation of benzaldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate under solvent-free conditions at the 80 $^{o}$C.

| Entry | Catalyst | Catalyst loading (g) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $FeCl_3.6H_2O$ | 0.1 | 30 | 58 |
| 2 | $InCl_3$ | 0.1 | 30 | 66 |
| 3 | $ZnCl_2$ | 0.1 | 30 | 72 |
| 4 | *p*-TSA | 0.1 | 30 | 60 |
| 5 | CAN | 0.1 | 30 | 68 |
| 6 | SSA | 0.1 | 20 | 96 |

a = isolated yields


**Figure 1:** Recyclability of SSA for the synthesis of compound 1.

## Conclusion

In summary, we have described an efficient and green protocol for the synthesis of 6-amino-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives using starch-sulfuric acid (SSA) as a bio-degradable and reusable catalyst under solvent-free conditions. SSA is superior to previously reported heterogeneous catalysts in view of its recovery, efficiency, nontoxicity, cheapness and environmentally friendly behavior. Due to their biodegradability and reusability profile it is consider as ideal for industrial applications. There are several striking features to this

methodology, including high yield of products with high purity, simple work-up process, avoiding the use of hazardous organic solvents and solvent-free conditions make the present method a valuable contribution in agreement with green chemistry principles.

## Experimental

*Apparatus and analysis:*

All chemicals, unless otherwise specified, were purchased from commercial sources and were used 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. Proton and carbon NMR spectra were recorded on Bruker AV 400 MHz spectrometer using DMSO as solvent and TMS as the internal reference. Mass spectra were recorded at Advion expression CMS, USA. Acetone is used as mobile phase, and electron spray ionization (ESI) is used as ion source. Elemental analyses were performed on a Micro Variant CHN elemental analyzer. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 $F_{254}$ aluminum sheets, visualized by UV light.

*Preparation of starch-sulfuric acid (SSA):*

At 0 $^{o}$C, chlorosulfonic acid (1.0 g, 9.0 mmol) was added drop wise into a magnetically stirred mixture of starch (5.0 g) in 20 mL *n*-hexane for 2 h. HCl gas was removed from the reaction vessel immediately. When addition was complete, the mixture was stirred additional for 2 h. The mixture was then filtered and washed with 30 mL diethyl ether and dried at room temperature to afford 5.2 g of starch-sulfuric acid as a white powder. The sulfur content of starch-sulfuric acid samples by conventional elemental analysis was 0.55 mmol/g. The number of $H^+$ sites on the SSA, determined by acid-base titration, was 0.50 meq/g. This value corresponds to approximately 90 % of the sulfur content, indicating that most of the sulfur species on the sample are in the form of the sulfonic acid groups.

*General method for the preparation of 6-amino-1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitriles (1-15):*

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

White solid. mp 245-246 $^{o}$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3405, 3390 ($NH_2$), 3315 (-NH-), 3065, 3028 (Aromatic), 2930 (-$CH_3$), 2205 (-CN), 1487 (-NH-). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 9.91, 35.41, 55.78, 113.25, 117.33, 125.17, 129.44, 135.70, 139.67, 156.65, 161.87. MS (ESI) *m/z* for (252.10): 253.1 $(M+1)^+$, 275.1 $(M+Na)^+$. Elemental Analysis (CHN): 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-dihydro pyrano[2,3-c]pyrazole-5-carbonitrile (2):*

Light yellow solid. mp 224-226 $^{o}$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3452 (C-OH), 3401, 3395 ($NH_2$), 3322 (-NH-), 3068, 3021 (Aromatic), 2921 (-$CH_3$), 2200 (-CN), 1477 (-NH-), 3450 (C-OH), 790 (*Para*-OH). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (268.10): 269.1 $(M+1)^+$, 291.2 $(M+Na)^+$. Elemental Analysis (CHN): 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-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (3):*

Light brown solid. mp 167-169 $^{o}$C IR $\nu_{max}$ (KBr) cm$^{-1}$: 3430 (C-N), 3409, 3380 ($NH_2$), 3318 (-NH-), 3067, 3018 (Aromatic), 2932 (-$CH_3$), 2212 (-CN), 1490 (-NH-), 810 (*Para*-N). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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; MS (ESI) *m/z* for (295.1): 296.0 $(M+1)^+$, 318.0 $(M + Na)^+$. Elemental Analysis (CHN): 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-(2-hydroxyphenyl)-3-methyl-1,4-dihydro pyrano[2,3-c]pyrazole-5-carbonitrile (4):*

Yellow solid. mp 209-211 $^{o}$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3452 (C-OH), 3407, 3392 ($NH_2$), 3317 (-NH-), 3067, 3030 (Aromatic), 2932 (-$CH_3$), 2207 (-CN), 1489 (-NH-), 740 (*Ortho*-OH). $^1$H NMR (400 MHz, DMSO-

$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (268.27): 268.1 $(M)^+$, 269.1 $(M+1)^+$, 291.1 $(M+Na)^+$. Elemental Analysis (CHN): 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-dihydro pyrano[2,3-c]pyrazole-5-carbonitrile (5):*

Light yellow solid. mp 211-212 $^o$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3411, 3385 ($NH_2$), 3320 (-NH-), 3070, 3022 (Aromatic), 2933 (-$CH_3$), 2206 (-CN), 1482(-NH-), 1351, 1560 (-$NO_2$), 775 (*Meta*-$NO_2$). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 9.86, 27.98, 55.18, 99.32, 111.68, 112.74, 121.11, 128.55, 127.53, 134.45, 135.18, 163.34. MS (ESI) *m/z* for (282.11): 282.1 $(M)^+$, 283.3 $(M+1)^+$. Elemental Analysis (CHN): 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. mp 193-195 $^o$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3411, 3385 ($NH_2$), 3320 (-NH-), 3070, 3022 (Aromatic), 2933 (-$CH_3$), 2206 (-CN), 1482(-NH-), 1351, 1560 (-$NO_2$), 775 (*Meta*-$NO_2$). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (297.1): 298.1 $(M+1)^+$, 319.9 $(M+Na)^+$. Elemental Analysis (CHN): 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. mp 147-148 $^o$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3409, 3394 ($NH_2$), 3319 (-NH-), 3068, 3032 (Aromatic), 2935 (-$CH_3$), 2209 (-CN), 1492 (-NH-), 1062 (C-Cl), 752 (*Ortho*-Cl). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (286.06): 286.1 $(M)^+$, 288.1 $(M+1)^+$. Elemental Analysis (CHN): 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. mp 233-235 $^o$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3400, 3391 ($NH_2$), 3317 (-NH-), 3066, 3017 (Aromatic), 2931 (-$CH_3$), 2211 (-CN), 1488 (-NH-), 1058 (C-Cl), 815 (*Para*-Cl). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (286.06): 286.1 $(M)^+$, 288.1 $(M+2)^+$. Elemental Analysis (CHN): 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. mp 207-209 $^o$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3413, 3396 ($NH_2$), 3321 (-NH-), 3072, 3024 (Aromatic), 2937 (-$CH_3$), 2212 (-CN), 1494 (-NH-), 800 (*Para*-$CH_3$). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (266.12): 266.2 $(M)^+$, 267.1 $(M+1)^+$. Elemental Analysis (CHN): 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-(furan-2-yl)-3-methyl-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (10):*

Brown solid. mp 217-219 $^o$C. IR $\nu_{max}$ (KBr) cm$^{-1}$: 3403, 3394 ($NH_2$), 3320 (-NH-), 3069, 3020 (Aromatic), 2935 (-$CH_3$), 2215 (-CN), 1491 (-NH-), 1200 (-O-). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 9.78, 34.21, 58.93, 104.82, 110.59, 113.25, 118.45, 138.66, 145.80, 154.66, 158.22, 163.13. MS (ESI) *m/z* for (242.08): 243.2 $(M+1)^+$, 365.1 $(M+Na)^+$. Elemental Analysis (CHN): 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 %.

*6-amino-4-(4-hydroxy-3,5-dimethoxyphenyl)-3-methyl -1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (11):*

Off-white solid. mp 199-201 $^oC$. IR $\nu_{max}$ (KBr) $cm^{-1}$: 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 (*Para*). $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (328.1): 329.1 $(M+1)^+$, 351.1 $(M+Na)^+$. Elemental Analysis (CHN): 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-(4-bromophenyl)-3-methyl-1,4-dihydro pyrano[2,3-c]pyrazole-5-carbonitrile (12):*

White solid. mp 179-180 $^oC$. IR $\nu_{max}$ (KBr) $cm^{-1}$: 3405, 3390 ($NH_2$), 3317 (-NH-), 3062, 3028 (Aromatic), 2930 (-$CH_3$), 2205 (-CN), 1626 (=C=N-), 1487 (-NH-), 1069 (C-Br), 810 (*Para*-Br). $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 9.66, 27.2, 40.57, 98.02, 113.88, 113.94, 120.81, 129.95, 131.53, 138.05, 139.18, 158.97. MS (ESI) *m/z* for (330.0): 330.2 $(M)^+$, 332.3 $(M+2)^+$. Elemental Analysis (CHN): 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-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (13):*

White solid. mp 187-189 $^oC$. IR $\nu_{max}$ (KBr) $cm^{-1}$: 3395, 3386 ($NH_2$), 3312 (-NH-), 3061, 3012 (Aromatic), 2927 (-$CH_3$), 2207 (-CN), 1483 (-NH-), 2592 (-$OCH_3$), 702 (*Meta*-$OCH_3$), 809 (*Para*-$OCH_3$). ). $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (312.12): 312.4 $(M)^+$, 313.4 $(M+1)^+$. Elemental Analysis (CHN): 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-nitrophenyl)-3-methyl-1,4-dihydro pyrano[2,3-c]pyrazole-5-carbonitrile (14):*

Yellow solid. mp 251-252 $^oC$. IR $\nu_{max}$ (KBr) $cm^{-1}$: White solid. IR $\nu_{max}$ (KBr) $cm^{-1}$: 3414, 3389 ($NH_2$), 3323 (-NH-), 3073, 3025 (Aromatic), 2936 (-$CH_3$), 2209 (-CN), 1485 (-NH-), 1354, 1563 (-$NO_2$), 818 (*Para*-$NO_2$). $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 9.71, 35.84, 55.84, 96.52, 120.47, 123.87, 128.81, 135.84, 146.34, 152.08, 154.63, 161.11. MS (ESI) *m/z* for (297.1): 397.2 $(M)^+$, 398.3 $(M+1)^+$. Elemental Analysis (CHN): 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-(3-hydroxyphenyl)-3-methyl-1,4-dihydro pyrano[2,3-c]pyrazole-5-carbonitrile (15):*

White solid. mp 259-260 $^oC$. IR *v*max (KBr) cm-1: 3410, 3395 (NH2), 3314 (-NH-), 3064, 3027 (Aromatic), 2935 (-CH3), 2210 (-CN), 1492 (-NH-), 3455 (C-OH), 778 (*Meta*-OH). $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta_H$ (ppm) 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-$d_6$): $\delta_C$ (ppm) 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. MS (ESI) *m/z* for (268.1): 269.2 $(M+1)^+$, 291.4 $(M+Na)^+$. Elemental Analysis (CHN): 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 %.

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