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Synthesis of pyrano [3, 2-B] pyran derivatives by a sequential one-pot reaction using tin tetrachloride supported on nano silica gel, a green protocol

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Tin tetrachloride supported on silica gel nanoparticles (SnCl4/SiO2 NPs) catalyzed efficient synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile and ethyl 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carboxylate derivatives have been achieved via a one-pot three component reaction between 5-hydroxy-2-hydroxymethyl-4H-pyran-4-one, an aromatic or aliphatic aldehyde and malononitrile or ethyl cyan acetate. This synthetic protocol is operationally simple and affords product with good to excellent yields at a short reaction time. The morphology of Nano catalyst was observed using a scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

Keywords: SnCl4/SiO2NPs; Solid acid; Kojic acid; Michael addition; Green chemistry; One-pot synthesis

INTRODUCTION

In recent years, Multi-Component Reactions (MCRs) as well as one-pot syntheses have a flourishing field of research in organic reactions. That is because they allow for simple and flexible assembly of three or more building blocks an atom efficient operation a product containing substantial elements of all the reactants. These reactions can avoid time-consuming and costly processes of intermediates purification as well as tedious steps of protection and de-protection of functional groups, thus enhancing the greenness of transformations. They are also widely applied in pharmaceutical chemistry to produce versatile structures and combinatorial libraries for drug discovery [1].

MCRs have many advantages such as simple procedures, convergence and atom economy that make them one of the significant topics in green chemistry.

Pyrans are one of the most important classes of structural motif commonly found in a wide variety of natural products, pharmaceutical molecules, and functional materials. Due to their various biological and medicinal activities, including anticancer [2, 3], anti-HIV [4], antibacterial [5], antiviral [6] and calcium channel antagonist activities [7], Pyrans and their derivatives have received much attention.

Kojic acid is another important heterocyclic compound in the pharmaceutical industry due to its accessibility, potential biological activity and high reactivity [8]. Moreover, biological assay has also utilized kojic acid derivatives specifically prepared for this purpose [9-13]. Consequently, wholesale demands of diverse Pyran derivatives in various fields provided a motive for the synthesis of new compounds.

According to the literature survey [14, 15], supported SnCl4 on SiO2 nanoparticles have been prepared and used effectively as a catalyst for various reactions. Application of solvent-free condition and solid acidic catalyst represents a powerful green technique.

Continuing our interest in sequential one-pot multi-component reaction and solid phase acidic nano catalyst (SnCl4/SiO2 NPs) [15], herein, we proposed a novel method for the synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile and ethyl 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carboxylate derivatives under solvent-free conditions.

RESULTS AND DISCUSSIONS

In order to find the optimum conditions for the synthesis of (pyrano [3, 2-b] pyran derivatives), we studied the reaction of Benz aldehyde, (1 mmol), malononitrile (1 mmol) and kojic acid (1 mmol) as the model substrates for the preparation of 4a.The results showed that the reaction cannot proceed in the absence of SnCl4/SiO2 NPs under solvent-free conditions (Table 1, entry 1). The transformation of Benz aldehyde with malononitrile and kojic acid proceeded smoothly with SnCl4/SiO2 NPs (0.004 g), and at the end of the reaction (about 15min later), the product was collected by hot ethanol and through filtration, and recrystallized from ethanol, affording the nicely crystalline 4a in good yield (95%, Table 1, entry 2). Decreasing the catalyst loading from 0.004 to 0.001 g, lowered the yield of the reaction significantly (Table 1, entries 15-17). The yield of 4a was not further improved with

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increased amount of the catalyst (Table 1, entries 18, 19).

Various solvents and catalysts were applied for the model reaction, and the results are showed in Table 1. In the presence of SnCl2.2H2O, Na2CO3, ZrCl4, pyridine, SbCl3, ZnCl2 and SnCl4 under solvent-free condition, the reactions time were prolonged (Table 1, entries 3-9). Different solvents, for example, CH2Cl2, EtOH, CH3CN, DMF and H2O were tested under reflux in the presence of SnCl4/SiO2 NPs as catalyst, but unexpectedly they resulted in low yields (Table 1, entries 10-14). Thus, it is clear from the experiments that the best condition for 4a could be entry 2, employing SnCl4/SiO2 NPs (0.004 g) as solid acid in solvent-free condition.

An interesting feature of this method is that the catalyst can be renewed at the end of the reaction and can be used several times without losing its activity. To recover the catalyst, after completion of the reaction, the catalyst can be removed and washed with chloroform and then dried at room temperature. This process repeated for two cycles and the yield of product 4a did not change significantly (Table 1, entries 20, 21).

By acid-base titration, we have found that 1 g of catalyst in water produced 3.24 mmol of H+ or Cl−. For determination of the loading amount of Sn on 1 g of 50% SnCl4/SiO2, we have added 10 mL aqueous solution of NaOH (0.16 M) to 1 g of catalyst and boiled it for 10 minutes. The remained silica gel has been isolated from the obtained Sn(OH)4 solution by filtration, and the Sn(OH)4 solution was evaporated to obtain a dry Sn(OH)4 powder. The calculated loading amount of Sn in the catalyst was 162 mg g−1 or 1.374 mmol g−1. According to above obtained data, SnCl4/SiO2 is a mixture of SiO2–SnCl3 (36%) and SiO2–SnCl2–SiO2 (64%) [14].

According to catalyst optimization table (Table1), the optimum amount of catalyst is 0.004 g (0.013 mmole H+) leads to a maximum amount of catalyst.

Table 1. Optimization of the reaction conditions for synthesis of 4aa

Entry	Catalyst (g)	Solvent	Time (h)	Yield[b] (%)
1	$SnCl_4/SiO_2$ NPs (0)	-	2	0
2	$SnCl_4/SiO_2$ NPs (0.004)	-	0.25	95
3	$SnCl_2.2H_2O$ (0.004)	-	0.25	Trace
4	Na_2CO_3(0.004)	-	0.25	19
5	$ZrCl_4$(0.004)	-	0.25	28
6	Pyridine (0.004)	-	0.25	Trace
7	$SbCl_3$(0.004)	-	0.25	16
8	$ZnCl_2$(0.004)	-	0.25	Trace
9	$SnCl_4$(0.004)	-	0.25	25
10	$SnCl_4/SiO_2$ NPs (0.004)	CH_2Cl_2	0.5	Trace
11	$SnCl_4/SiO_2$ NPs (0.004)	EtOH	0.5	52
12	$SnCl_4/SiO_2$ NPs (0.004)	CH_3CN	0.5	Trace
13	$SnCl_4/SiO_2$ NPs (0.004)	DMF	0.5	47
14	$SnCl_4/SiO_2$ NPs (0.004)	H_2O	0.5	62
15	$SnCl_4/SiO_2$ NPs (0.001)	-	0.25	73
16	$SnCl_4/SiO_2$ NPs (0.002)	-	0.25	80
17	$SnCl_4/SiO_2$ NPs (0.003)	-	0.25	85
18	$SnCl_4/SiO_2$ NPs (0.005)	-	0.25	95
19	$SnCl_4/SiO_2$ NPs (0.006)	-	0.25	96
20	$SnCl_4/SiO_2$ NPs (0.004) 2nd run	-	0.25	92
21	$SnCl_4/SiO_2$ NPs (0.004) 3rd run	-	0.25	89

a) Reaction condition: 1 mmol of Benz aldehyde, 1 mmol of kojic acid, and 1 mmol of malononitrile

b) Isolated yields.

In continuation of our investigations into the application of solid acids in organic synthesis [15-17], we prepared silica-supported tin tetrachloride and used it as a catalyst for the synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile and ethyl 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carboxylate derivatives. Silica-supported tin tetrachloride (SiO2-SnCl4) was prepared by the reaction of tin tetrachloride with activated silica gel, which was proved to be a solid acid of super acid strength. In IR spectrum of SnCl4/SiO2 nanoparticles (Fig 1), the hydroxyl bands were appeared at 3485 cm-1. The absorption bands for Si-O-Si, Si-OH and Sn-Cl were appeared in 1104, 811 and 473 cm-1, respectively [14, 18].

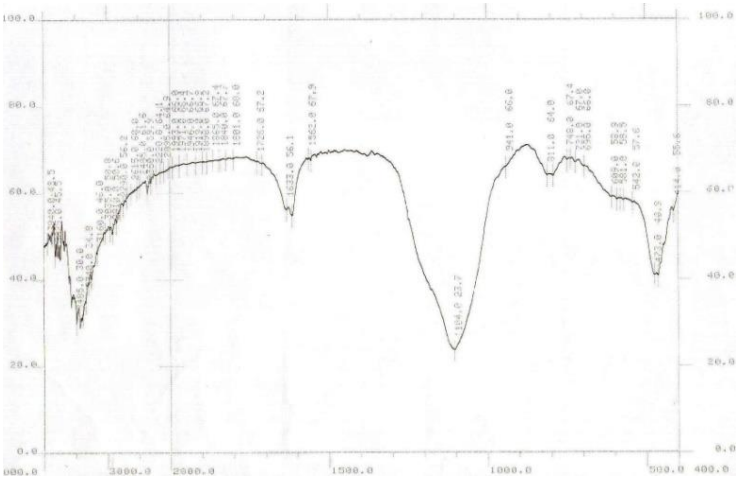


Fig 1. IR spectrum of SnCl4/SiO2nanoparticles

Powder X-ray diffraction was run and the strongest peaks of the XRD pattern correspond to the SiO2 plane with the other peaks were indexed as the (35), (53), and (67) planes of supported tin tetrachloride (Fig 2).

The dimensions of nano-SiO2 were observed using scanning electron microscope (SEM) (Figs3 and 4). The stable silica nanoparticles were made and used for preparation of catalyst (SnCl4/SiO2 NPs). The TEM analysis of catalyst (SnCl4/SiO2 NPs) was studied (Fig 5).

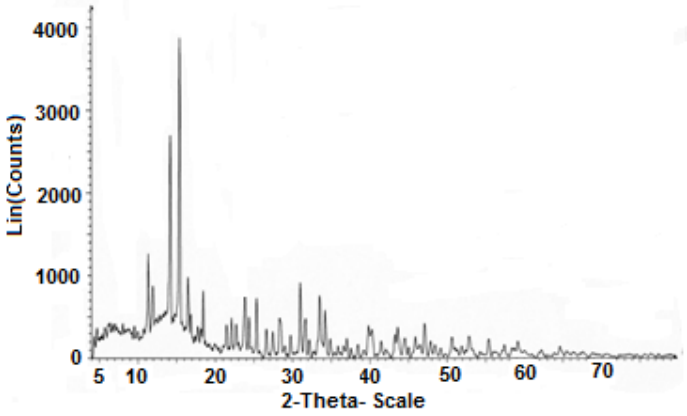


Fig 2. XRD spectrum of SnCl4/SiO2 nanoparticles

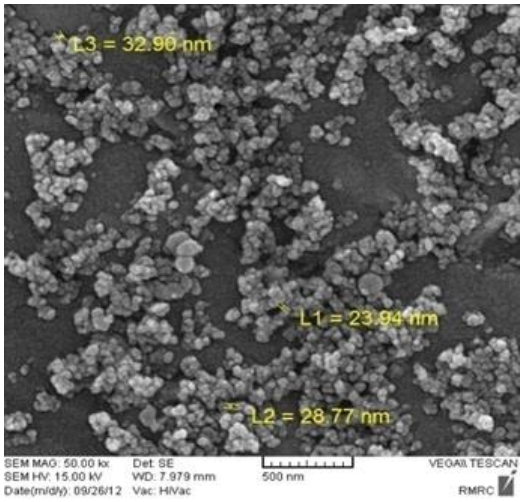


Fig 3. The SEM image of SiO2 nanoparticles.

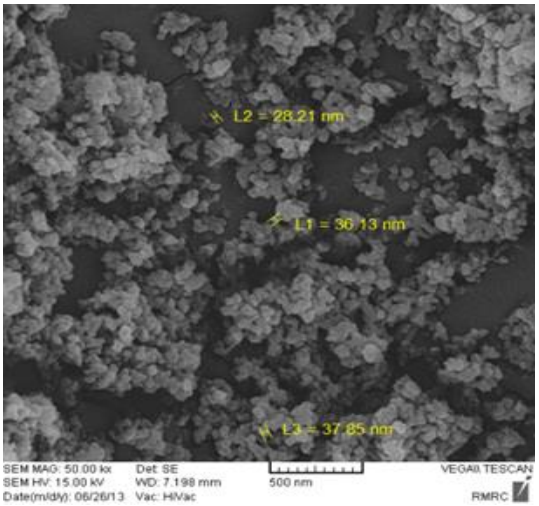


Fig 4. The SEM image of SnCl4/SiO2 nanoparticles.

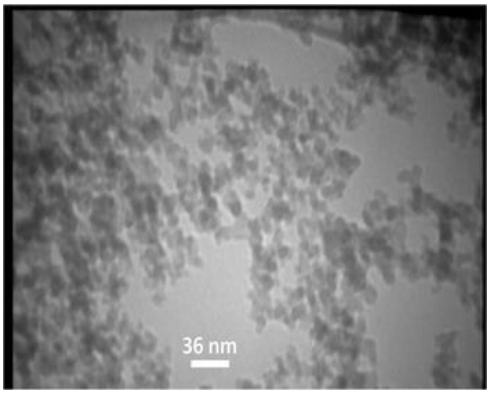
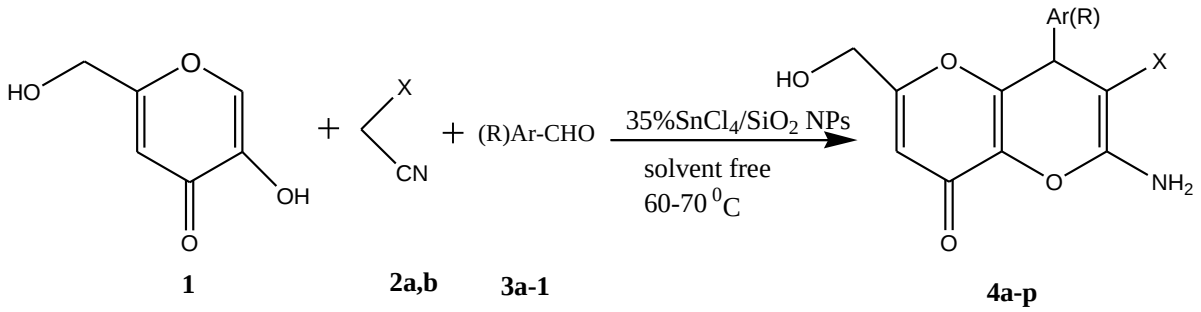


Fig 5. The TEM analysis of SnCl4/SiO2 nanoparticles

After catalyst preparation, we investigated the synthesis of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile and ethyl 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carboxylate derivatives by the three-component condensation of, kojic acid 1, malononitrile or ethyl cyan acetate 2 and an aromatic or aliphatic aldehyde 3, in the presence of 0.004 g SnCl4/SiO2 NPs as catalyst (Scheme 1).



Scheme 1. Synthesis of pyrano[3,2-b]pyran derivatives by condensation of kojic acid, malononitrile or ethyl cyan acetate and an aldehyde using SnCl4/SiO2 NPs as catalyst

Finally, a series of aromatic aldehydes were employed under similar environments to evaluate the substrate scope of this reaction. The results were summarized in Table 3. In all cases, aromatic aldehyde derivatives with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and leading to products with excellent yields. Aldehydes with electron-withdrawing groups reacted rapidly, while those containing electron-donating groups led to decrease in reactivity, requiring longer reaction times. According to the results, the method was applied to heterocyclic and aliphatic aldehydes. The results indicated that both heterocyclic and aliphatic aldehydes reacted with malononitrile and kojic acid under optimum reaction conditions and formed 4d-f products as well as aromatic aldehydes (Table 2, entries 4-6).

The 4a-p compounds were characterized by their elemental and spectral analysis. Spectral data of known compounds were compared with the literature data [17, 19, 5].

With the above-mentioned results in hand, a plausible mechanism of this reaction was proposed in Scheme 2. The initiation step of this chain process was begun with the interaction of aldehyde 3 and SnCl4/SiO2 NPs as a solid Lewis acid catalyst. The subsequent step was Knoevenagel condensation between the activated aldehyde and malononitrile or ethyl cyan acetate 2 to form intermediate 5. Then the Michael addition of kojic acid 1 to intermediate 5 would furnish intermediate 6. Finally, the product 4 was obtained by an intramolecular cyclization and tautomerism.

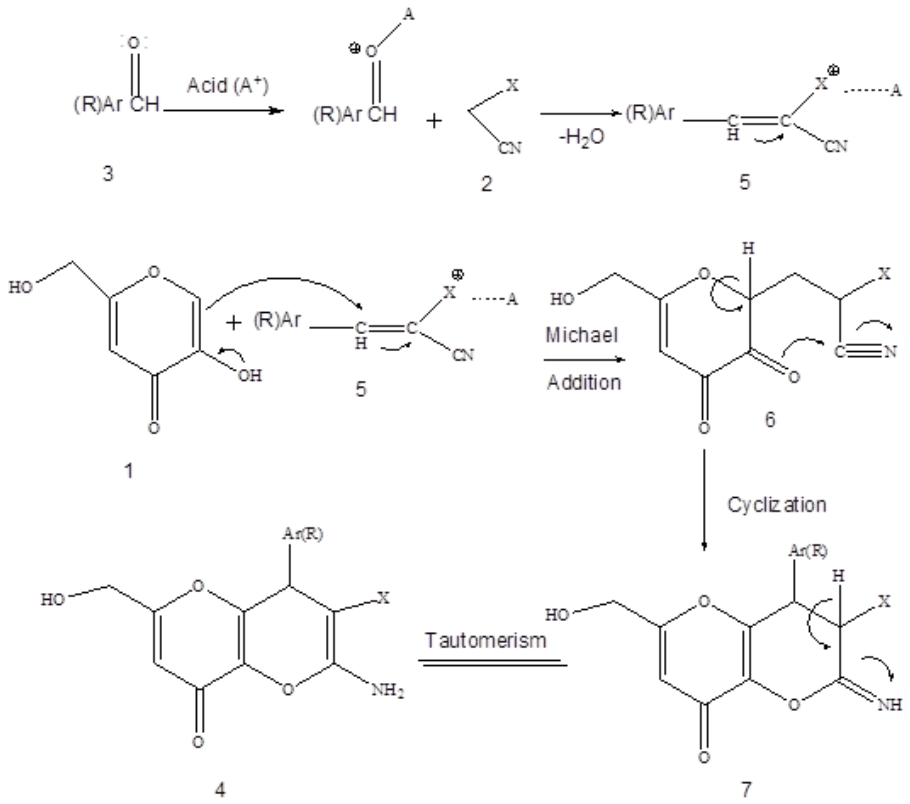
CONCLUSIONS

In conclusion, we elaborated an efficient, environmentally benign, atom-economical, starting from simple and readily available precursors for the preparation of 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile and ethyl 2-amino-4,8-dihydropyrano[3,2-b]pyran-3-carboxylate derivatives. SnCl4/SiO2 NPs as a solid Lewis acidic catalyst was successfully prepared and characterized using FTIR, XRD, SEM and TEM. The present method does not involve any hazardous organic solvent or catalyst. Therefore, this procedure could be classified as an environmental friendly medium.

Table 2. Synthesis of pyrano [3, 2-b] pyran derivatives

Entry	Ar (R)	X	Product	Time (min)	Yield[a] (%)	m.p. (ºC)	
						Found	Reported[Ref.]
1	C_6H_5	CN	4a	14	95	222-224	220-222[19]
2	2-ClC_6H_4	CN	4b	20	89	210-212	210-213[19]
3	2-FC_6H_4	CN	4c	12	94	206-208	207-208[19]
4	2-Furyl	CN	4d	20	89	224-226	223-225[19]
5	4-Pyridyl	CN	4e	18	90	232-234	233-235[19]
6	n-Butyl	CN	4f	20	90	185-186	184-186[17]
7	4-Cl-3-$O_2NC_6H_3$	CN	4g	10	96	245-247	245-247[17]
8	4-NCC_6H_4	CN	4h	12	94	240-242	239-241[17]
9	3-$O_2NC_6H_4$	CN	4i	10	95	258-260	258-260[17]
10	2-HO-3-$CH_3OC_6H_3$	CN	4j	17	92	250-252	248-250[17]
11	2-HOC_6H_4	CN	4k	17	92	249-251	-
12	4-$O_2NC_6H_4$	CN	4l	15	90	260-262	-
13	C_6H_5	CO_2Et	4m	30	90	193-195	194-196[5]
14	2-ClC_6H_4	CO_2Et	4n	22	94	198-200	197-199[5]
15	4-NCC_6H_4	CO_2Et	4o	20	92	197-198	196-198[5]
16	4-$O_2NC_6H_4$	CO_2Et	4p	15	95	203-205	203-205[5]

a) Isolated yields.



Scheme 2. Plausible mechanism for the formation of SnCl4/SiO2 NPs catalyzed 4a-p

EXPERIMENTAL

Materials and methods

All of compounds were analytical grade reagents and were used as received, without any further purification. The chemicals for this work were purchased from Fluka and Merck. Melting points were determined with an Electro thermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer. IR spectra were recorded on a Shimadzu IR-470 spectrometer. 1H and 13C NMR spectra were recorded on Bruker DRX-400 Avance spectrometer at solution in DMSO using TMS as internal standard. The size and morphologies of the nanoparticles were measured by obtaining TEM (Philips CM10) and SEM (VEGA//TESCAN), respectively. The powder X-ray diffraction studies were made on a SIMENS D5000 diffract meter using Ni-filtered Cu Kα radiation at a wavelength of 1.54.

Synthesis of tin tetrachloride supported on silica gel nanoparticles

The reagent was prepared by stirring a mixture 0.35g (0.16 ml) of SnCl4 and 0.65 g of nano silica gel in 5 ml of chloroform for 1 h at room temperature [14]. The slurry was dried slowly on a rotary evaporator at 40 °C. The obtained solid (SnCl4/SiO2 NPs) was dried at an ambient temperature for 2 h and then stored in a dry container. The dimensions of nanoparticles were observed with SEM and TEM. The sizes of nanoparticles are between 28 and 37 nm (Fig 4 and 5).

General procedure

A mixture of aromatic aldehyde (1 mmol), malononitrile or ethyl cyan acetate (1 mmol), kojic acid (1 mmol) and SnCl4/SiO2 NPs as catalyst (0.004 g) were placed in a round bottom flask. The materials were mixed and heated in 60-70 ºC. The progress of the reaction was followed by TLC (3:1: n-hexane: ethyl acetate). After completion of the reaction, ethanol was added to the mixture and was heated to resolve materials and subsequently was filtered to remove the catalyst. By evaporation of the solvent, the crude product was recrystallized from hot ethanol to obtain the pure compound.

Selected spectral data

2-Amino-4-(2-hydroxy phenyl)-6-hydroxy methyl-8-oxo-4,8-dihydro-pyrano [3,2-b]pyran-3-carbonitrile (4k)

Yellow, solid; m.p. 249-251 ºC; IR (KBr, cm-1): 3450 and 3330 (NH2, OH), 2225 (CN), 1656 (C=O) Cm-1; 1H NMR (400MHz, DMSO-d6): δ 4.08-4.21 (dd, 2H, J=16, J=6Hz, CH2), 5.19 (s, 1H, methine), 5.61 (t, 1H, J=6Hz, OH), 6.28 (s, 1H, =CH), 7.04 (d, 1H, J=8Hz, aromatic), 7.11 (d, 2H, J=3.4Hz, aromatic), 7.13 (s, 2H, NH2), 7.28-7.32 (m, 1H, aromatic), 9.28 (s, 1H, OH) ppm; 13C NMR (100MHz, DMSO-d6): δ 33.8, 50.4, 59.3, 108.8, 116.1, 119.4, 119.9, 124.9, 128.1, 128.9, 141.3, 148.9, 150.3, 161.4, 167.5, 173.7 ppm; Anal. Calcd. For C16H12N2O5: C, 61.54; H, 3.87; N, 8.97 Found: C, 61.48; H, 3.80; N, 8.89%.

***2-Amino-6-hydroxy methyl-4-(4-nitro phenyl)-8-oxo-4,8-dihydro-pyrano [3,2-b]pyran-3-carbonitrile (4l*)**

Dark red, solid; m.p. 260-262 ºC; IR (KBr, cm-1): 3390 and 3375 (NH2), 3315 (OH), 2225 (CN), 1645 (C=O), 1516 and 1343 (NO2); 1H NMR (400MHz, DMSO-d6): δ 4.16 (dd, 1H, J=16.4, J=6Hz, CH2), 4.20 (dd, 1H, J=16.4, J=6Hz, CH2), 5.17 (s, 1H, methine), 5.64 (t, 1H, J=6Hz, OH), 6.31 (s, 1H, =CH), 7.24 (s, 2H, NH2), 8.11 (d, 2H, J=8Hz, aromatic), 8.32 (d, 2H, J=8Hz, aromatic) ppm; 13C NMR (100MHz, DMSO-d6): δ 54.3, 59.8, 112.3, 114.8, 116.5, 118.1, 124.6, 130.0, 143.6, 148.1, 148.5, 158.9, 168.6, 172.3 ppm; Anal. Calcd. For C16H11N3O6: C, 56.30; H, 3.25; N, 12.31 Found: C, 56.28; H, 3.28; N, 12.25%.

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