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Nano-basic silica as an efficient catalyst for the multi-component preparation of pyrano[2,3-d]pyrimidine derivatives

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Abstract: A high-yield protocol is explored for the synthesis of pyrano[2,3-d]pyrimidines through the multi-component reaction of aromatic aldehydes, 1,3-Dimethylbarbituric acid, and malononitrile using nano-basic silica as an efficient catalyst. The method tolerates various electron-donating and electron-withdrawing groups on the aromatic ring. Nano-basic silica was characterized by field emission scanning electron microscope (FE-SEM) N_2 adsorption-desorption isotherm, dynamic light scattering (DLS), and X-ray powder diffraction (XRD) techniques. The particles of nano-basic silica have uniform spheres with sizes that are <100 nm. XRD pattern shows that nano-basic silica is amorphous. The specific surface area and pore volume distribution of nano-basic silica are $663 \text{ m}^2\text{g}^{-1}$ and $0.634 \text{ cm}^3\text{g}^{-1}$, respectively.

Keywords: 1,3-dimethylbarbituric acid; multi-component reaction; nano-basic silica; pyrano[2,3-d]pyrimidines.

Introduction

Over the years uracil and its fused derivatives, e.g. pyrano[2,3-*d*]pyrimidines, have gained considerable interest, because they are a class of natural and synthetic compounds possessing a great variety of biological and pharmaceutical activities. Thus, the discovery of such compounds in both natural products as well as *via* synthetic procedures has received significant challenges. Various pyrano[2,3-*d*]pyrimidine derivatives that have been found so far show interesting anti-tumor,

hepatoprotective, anti-bronchitis, and anti-AIDS activities (Metolcsy, 1971; Pershin et al., 1972; Regnier et al., 1972; Suguira et al., 1973; Heber et al., 1993; Furuya and Ohtaki, 1994; Hirota et al., 1994; Musstazza et al., 2001).

Therefore, great research attention has been devoted to the synthesis of such compounds, and at present, the multi-component reaction of aromatic aldehydes, barbituric acids, and malononitrile under different conditions is the simplest and newest approach for their synthesis. Many different bases have been found to be viable catalysts for this reaction (Devi et al., 2003; Bagley et al., 2004; Seeliger et al., 2007; Elinson et al., 2011; Azarifar et al., 2012; Khurana and Vij, 2013; Elinson et al., 2014; Khazaei et al., 2015). Despite these procedures, the established method for the reaction systems based on the uses of homogeneous catalysts are often plagued by many inherent problems, including corrosion, difficulties related to catalyst recycling, and generation of waste. Thus, the use of heterogeneous catalysts remains in demand.

In continuation of our reports on the synthesis of heterocyclic compounds (Ghashang, 2012a,b, 2016; Dehbashi et al., 2013; Shafiee et al., 2013; Ghashang et al., 2014, 2015a,b, 2016a,b; Shafiee et al., 2014; Momayezan et al., 2015; Baziar and Ghashang, 2016; Taghrir et al., 2016; Zare et al., 2016), we were encouraged to examine the efficiency of a nano-basic silica as a green, environmentally friendly catalyst in preparation of pyrano[2,3-*d*]pyrimidines (Scheme 1).

Results and discussion

We investigated the morphological evolution of the catalyst using the field emission scanning electron microscope (FE-SEM) image of the sample. As shown in Figure 1, the particles of nano-basic silica are relatively homogeneous in size and shape; they are uniform spheres with sizes of <100 nm.

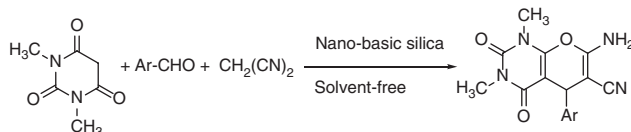
Dynamic light scattering (DLS) was used to determine the particle size distributions of the nanoparticles of nano-basic silica dispersed in ethanol (1 g l^{-1} was sonicated in 20 ml of ethanol for 2 h). According to the

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DLS-measurement, the size distribution of the nano-particles is almost less than 100 nm, with an average of 88 nm (Figure 2). Figure 3 shows the X-ray powder diffraction (XRD) pattern of nano-basic silica. The XRD pattern shows a hump at 2θ ranging from 20–30, thus indicating the amorphous state of the nano-particles.

Using the Brunauer–Emmett–Teller (BET) method, we investigated the nitrogen adsorption/desorption isotherm to determine the specific surface area and pore volume



Scheme 1: Preparation of pyrano[2,3-d]pyrimidines using nano-basic silica.

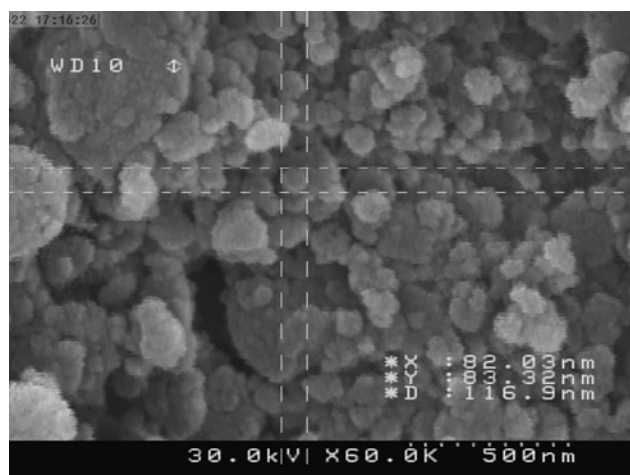


Figure 1: FE-SEM micrograph of nano-basic silica.

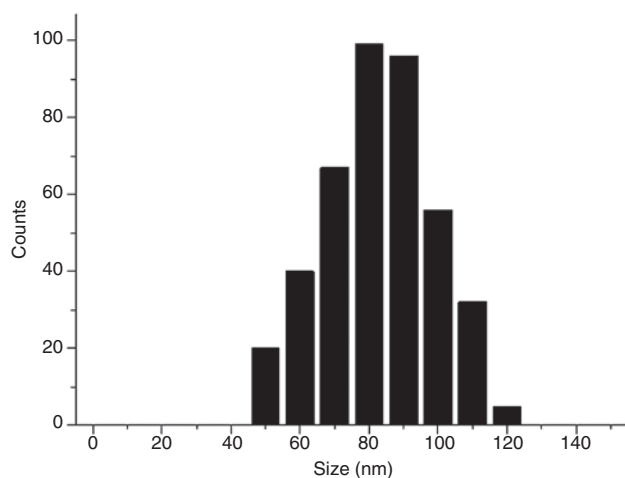


Figure 2: Particle size distribution of nano-basic silica.

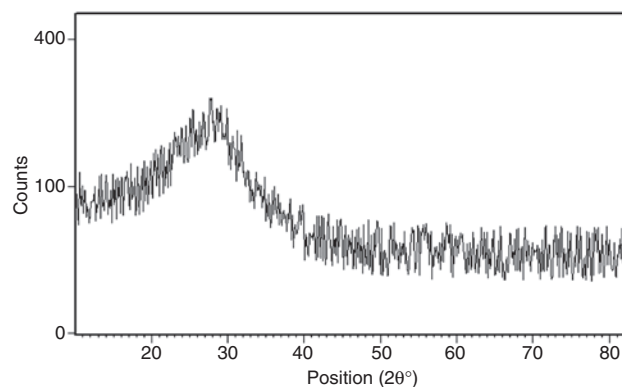


Figure 3: XRD pattern of nano-basic silica.

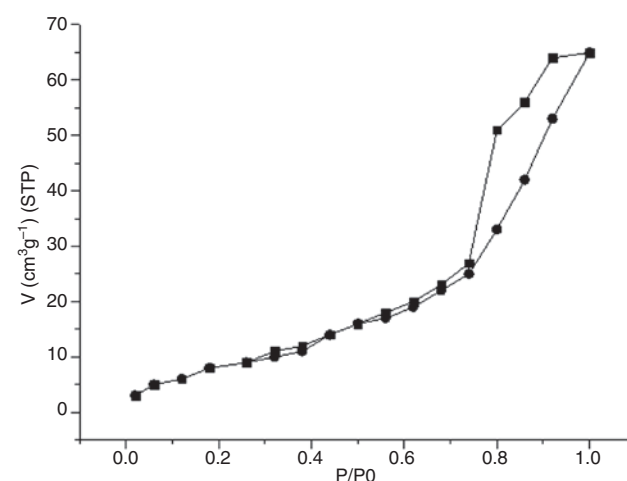


Figure 4: Nitrogen adsorption/desorption isotherm of nano-basic silica at 77K.

distribution at $663 \text{ m}^2\text{g}^{-1}$ and $0.634 \text{ cm}^3\text{g}^{-1}$, respectively. The isotherm of nano-basic silica was classified as type IV with hysteresis loops of H1 type (Figure 4), indicating the mesoporous nature of the sample.

The catalytic activity of the as-prepared nano-basic silica was examined by the condensation reaction of aromatic aldehydes, 1,3-dimethylbarbituric acid, and malononitrile to afford pyrano[2,3-d]pyrimidines. First, to optimize the reaction conditions, the condensations of benzaldehyde, 1,3-dimethylbarbituric acid, and malononitrile were examined in different polar and non-polar solvents as well as a solvent-free condition at reflux or at 90°C (Table 1). The reaction yields no product at room temperature, in the absence of a catalyst and also in non-polar solvents, such as hexane, CH_2Cl_2 , and Et_2O . The main reason for these results is that the temperature has an essential role in the progress of the reaction. Using polar solvents, such as EtOH, EtOAc,

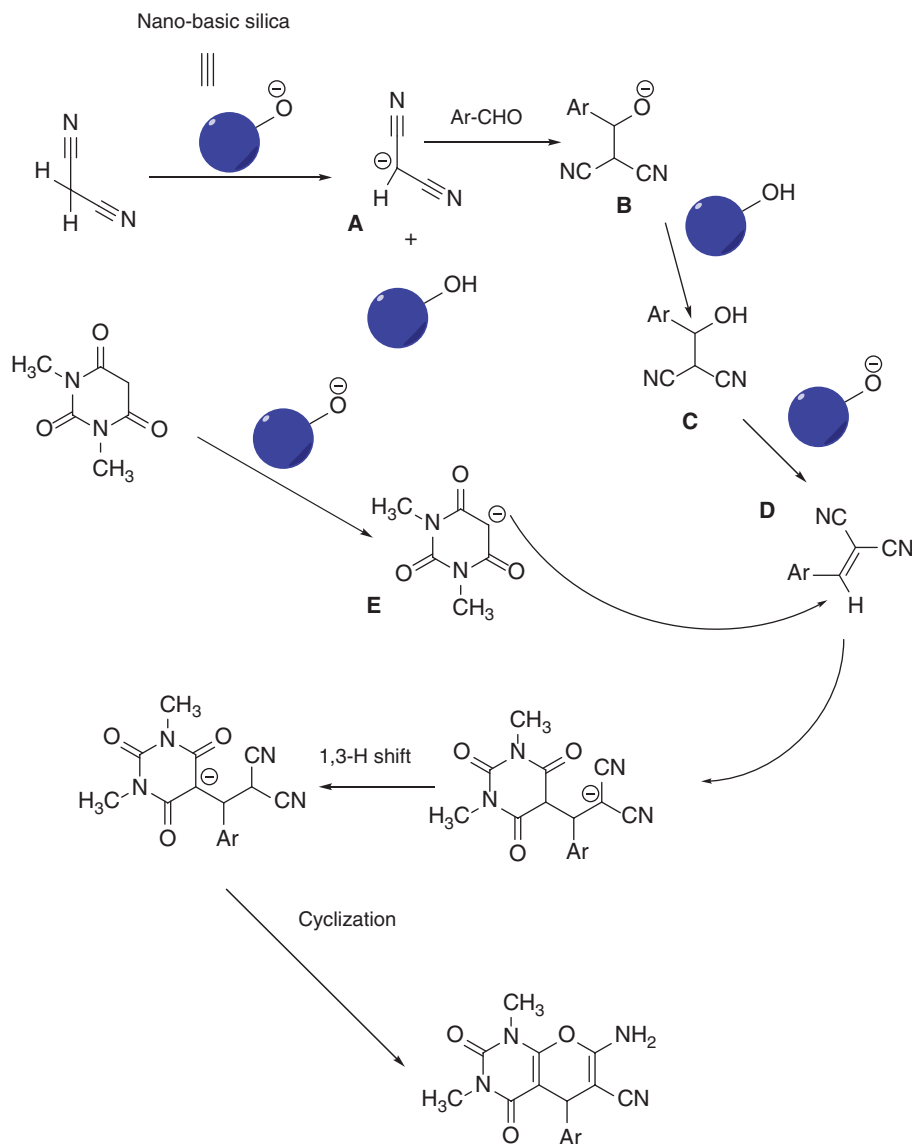
Table 1: Optimization of the reaction conditions.

Entry	Catalyst amount (mol%)	Solvent (5 ml)	Temperature (°C)	Time (h)/Yield (%) ^a
1	25	Hexane	Reflux	2/0
2	25	EtOAc	Reflux	2/32
3	25	EtOH	Reflux	2/61
4	25	H ₂ O	Reflux	2/66
5	25	Et ₂ O	Reflux	2/0
6	25	CH ₂ Cl ₂	Reflux	2/0
7	25	—	90	1.1/92
8	10	—	90	2/78
9	50	—	90	1/88
10	75	—	90	0.8/85
11	25	—	r.t.	2/0
12	—	—	90	2/0

^aIsolated yield.

and CH₃CN, can lead to poor yields. Finally, we observed that solvent-free, thermal heating to 90°C is the optimal choice to generate an excellent product yield (89%) in 2 h. Increasing the catalyst amounts do not improve the product yield. Thus, the optimum condition is a solvent-free and thermal condition (90°C) using 25 mol% of the catalyst.

The proposed reaction mechanism of the three-component reaction of aromatic aldehydes, 1,3-dimethylbarbituric acid and malononitrile catalyzed by nano-basic silica is shown in Scheme 2. At the beginning of the reaction, two active methylene groups (a CH₂ group in 1,3-dimethylbarbituric acid and malononitrile) reacted with basic silica to form carbanions **A** and **E**. Carbanion **A** quickly attaches to the carbonyl group of aromatic

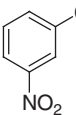
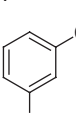
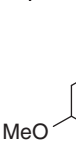
**Scheme 2:** Proposed reaction mechanism.

aldehyde, resulting in **B** and **C** intermediates. The formed intermediate **C** eliminates one molecule of water to form benzylidene malononitrile **D** (generally known as Knoevenagel condensation of benzaldehyde with malononitrile). The condensation of **E** with **D** and the continuing reaction progress *via* an intramolecular cyclization leads to the formation of the desired products.

Subsequently, the scope of the reaction for different aldehydes was studied using the optimized reaction conditions (see Table 2). Both aldehydes with various substituents participated smoothly in the reaction, providing the desired products in high to excellent yields. However,

aromatic aldehydes bearing electron-withdrawing groups (e.g. nitro and halide), showed better reactivity and the reactions were completed in shorter time. On the one hand, the presence of electron-withdrawing groups, such as nitro, has a powerful deactivating effect on the positive carbon of aldehydes. Thus, it decreased the activation energy of the carbanion addition to a carbonyl group (Scheme 2) and increased the rate of the reaction. On the other hand, electron-withdrawing groups decreased the energy of the LUMO orbital, and the nucleophilic addition of carbanion **D** to benzylidene malononitrile **D** is faster when compared with that of electron-donating

Table 2: Preparation of pyrano[2,3-d]pyrimidines using nano-basic silica as catalyst (25 mol%).

Entry	Aldehyde	Time (h)	Yield (%) ^a	M.p. [°C] (Lit. M.p.)	References
1		1.1	92	218–220 (219–222)	Elinson et al., 2014
2		1.4	75	206–208 (202–203)	Elinson et al., 2014
3		0.9	89	210–212 (206)	Khazaei et al., 2015
4		0.6	93	207–209 (204)	Khazaei et al., 2015
5		1.2	79	210–212 (211–212)	Khazaei et al., 2015
6		1	89	231–233 (235)	Khazaei et al., 2015
7		0.9	96	228–230 (229–232)	Elinson et al., 2014
8		1	73	246–248 (247–248)	Khazaei et al., 2015
9		1.5	77	241–243 (238–239)	Azarifar et al., 2012
10		2	69	263–265 (–)	–

^aIsolated yield; all products were characterized by NMR analysis.

groups. Moreover, compared to those at the *para* position, aldehydes substituted at the *ortho* position, such as 2-chloro and 2,4-dichloro (Table 2, Entries 5,9), produced a good yield but converted to the product in longer reaction times. This can be attributed to the steric hindrance of *ortho* position.

Conclusion

Nano-basic silica was prepared from the reaction of NaOH with nano-silica and then characterized by FE-SEM, DLS, XRD, and BET techniques. The results show that the particles are homogeneous in size and shape, with an average size of 88 nm. The sample has specific surface area and pore volume distribution of $663 \text{ m}^2\text{g}^{-1}$ and $0.634 \text{ cm}^3\text{g}^{-1}$, respectively. Using the prepared nano-basic silica as catalyst, a number of pyrano[2,3-d]pyrimidines were synthesized in high yields through the multi-component reaction of 1,3-dimethylbarbituric acid, aromatic aldehydes, and malononitrile. The study provides a procedure with the advantage of operational simplicity and a satisfactory substrate scope.

Experimental section

All reagents were purchased from Merck Company (Mumbai, India) and used without further purification. FE-SEM images were obtained on HITACHI S-4160, Japan. N_2 adsorption measurements of the catalyst were carried out using micro metrics adsorption equipment (Quantachrome instrument, Model Nova 2000, USA), N_2 (99.99%) as the analysis gas and the catalyst samples were slowly heated to 120°C for 3 h under nitrogen atmospheric. The total pore volume was obtained from the maximum amount of nitrogen gas adsorbed at partial pressure $P/P_0 = 0.999$. DLS measurement was done using a Zetasizer Nano ZS instrument (Zetasizer Nano ZS, Model ZEN3600, Malvern Instruments, Malvern, UK). The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument (Bruker BioSpin, Fällanden, Switzerland). The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). Elemental analyses (C, H, N) were carried out on a Perkin-Elmer 2400 analyzer (Perkin Elmer, Norwalk, CT, USA). Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus (Mount Holly, NJ, USA). TLC was performed on silica gel Polygram SIL G/UV 254 plates (Merck, Darmstadt, Germany).

Preparation of basic silica nanopowders

To a suspension of silica nanopowders (10 g, 30–50 nm) in pure water (100 mL), 5 g of NaOH was added under vigorous magnetic stirring. The mixture was continuously stirred at a temperature of 100°C

until water was completely evaporated. The resulting precipitate was washed with water several times and dried in an oven at 100°C for 1 h.

General procedure for the synthesis of pyrano[2,3-d]pyrimidine derivatives

A mixture of aldehydes (1 mmol), 1,3-dimethylbarbituric acid (1 mmol), malononitrile (1 mmol), and nano-basic silica (25 mol%) was heated in 90°C for the appropriate time. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was dissolved in hot ethanol. The catalyst was removed by simple filtration. The solvent was concentrated, and the crude products were purified by crystallization from EtOH. The spectral data of selected compounds are given below.

7-amino-1,3-dimethyl-2,4-dioxo-5-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 1): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.04$ (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.63 (s, 1H, CH), 7.14–7.30 (m, 7H) ppm; Elemental analysis: Found: C, 61.85; H, 4.48; N, 17.98%; $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_3$; requires: C, 61.93; H, 4.55; N, 18.06%.

7-amino-1,3-dimethyl-2,4-dioxo-5-(p-tolyl)-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 2): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 2.27$ (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.61 (s, 1H, CH), 7.08 (d, $J = 7.9$, 2H), 7.18 (d, $J = 7.9$, 2H), 7.27 (s, 2H, NH_2) ppm; $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): $\delta = 21.4$, 29.3, 31.2, 39.6, 62.5, 119.4, 127.0, 127.5, 129.3, 138.6, 145.2, 152.4, 158.8, 161.6, 162.5 ppm; Elemental analysis: Found: C, 62.90; H, 4.93; N, 17.22%; $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_3$; requires: C, 62.95; H, 4.97; N, 17.27%.

7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 3): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.04$ (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.75 (s, 1H, CH), 7.23–7.37 (m, 6H) ppm; Elemental analysis: Found: C, 55.64; H, 3.71; N, 16.16%; $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{O}_3$; requires: C, 55.74; H, 3.80; N, 16.25%.

7-amino-1,3-dimethyl-5-(3-nitrophenyl)-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, product 4): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.05$ (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 5.07 (s, 1H, CH), 7.33 (s, 2H, NH_2), 7.63–7.96 (m, 3H), 8.11 (d, $J = 7.7$ Hz, 1H) ppm; Elemental analysis: Found: C, 54.06; H, 3.63; N, 19.66%; $\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}_3$; requires: C, 54.09; H, 3.69; N, 19.71%.

7-amino-5-(2,4-dichlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 5): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.04$ (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.87 (s, 1H, CH), 7.17–7.61 (m, 5H) ppm; Elemental analysis: Found: C, 50.59; H, 3.14; N, 14.64%; $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{N}_4\text{O}_3$; requires: C, 50.68; H, 3.19; N, 14.78%.

7-amino-5-(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 6): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.03$ (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.34 (s, 1H, CH), 7.20–7.48 (m, 6H) ppm; Elemental analysis: Found: C, 49.29; H, 3.25; N, 14.27%; $\text{C}_{16}\text{H}_{13}\text{BrN}_4\text{O}_3$; requires: C, 49.38; H, 3.37; N, 14.40%.

7-amino-5-(4-fluorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 7): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.02$ (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.26 (s, 1H, CH), 7.08–7.23 (m, 6H) Elemental analysis: Found: C, 58.63; H, 4.08; N, 17.12%; $\text{C}_{16}\text{H}_{13}\text{FN}_4\text{O}_3$; requires: C, 58.54; H, 3.99; N, 17.07%.

7-amino-5-(3-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 8): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.04$ (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 4.71 (s, 1H, CH), 7.19–7.36 (m, 6H) ppm; Elemental analysis: Found: C, 55.68; H, 3.87; N, 16.17%; $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{O}_3$; requires: C, 55.74; H, 3.80; N, 16.25%.

7-amino-5-(2-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 9): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.04$ (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 4.73 (s, 1H, CH), 7.21–7.30 (m, 5H), 7.39 (d, $J = 7.7$ Hz, 1H) ppm; $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): $\delta = 27.6$, 29.3, 33.4, 57.3, 88.0, 118.7, 127.7, 128.6, 129.7, 132.1, 136.0, 141.2, 150.0, 151.2, 157.9, 160.8 ppm; Elemental analysis: Found: C, 55.89; H, 3.95; N, 16.21%; $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{O}_3$; requires: C, 55.74; H, 3.80; N, 16.25%.

7-amino-1,3-dimethyl-2,4-dioxo-5-(3,4,5-trimethoxyphenyl)-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-6-carbonitrile (Table 2, Entry 10): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): $\delta = 3.04$ (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 3.83 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 4.27 (s, 1H, CH), 6.45 (s, 2H), 7.31 (s, 2H, NH_2) ppm; $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6): $\delta = 27.9$, 29.6, 33.7, 56.1, 57.5, 58.1, 88.3, 106.1, 119.1, 136.2, 136.5, 150.2, 151.5, 158.2, 160.3, 161.4 ppm; Elemental analysis: Found: C, 57.23; H, 5.24; N, 13.89%; $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_6$; requires: C, 57.00; H, 5.04; N, 13.99%.

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