An efficient catalytic method for the synthesis of pyrido[2,3-d]pyrimidines as biologically
drug candidates by using novel magnetic nano particles as a reusable catalyst

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Abstract: A convenient method for the synthesis of pyrido[2,3-\textit{d}]pyrimidines by using the novel nanomagnetic silica-bonded S-sulfonic acid [Fe$_3$O$_4$@SiO$_2$@(CH$_2$)$_3$S-SO$_3$H] as an efficient and recyclable catalyst under solvent free condition is described. The major advantages of the present methodology are high yield, short reaction time, and reusability of the catalyst. Furthermore, the nanomagnetic silica-bonded S-sulfonic acid was fully characterized by using various techniques such as FT-IR, TG/DTG, DTA, EDX, μXRF, μXRF elemental mapping, XRD, HRTEM, SEM, XPS, and N$_2$ physisorption. The results obtained from this research support the idea of rational designs, syntheses, and applications of tasked-specific and reusable catalysts for the synthesis of various polynitrogenated heterocyclic compounds containing 1,4-dihydropyridine moieties.

Keywords: Tasked-specific catalyst, Reusable catalyst, Nano magnetic silica-bonded S-sulfonic acid, Solvent free conditions, Pyrido[2,3-\textit{d}]pyrimidines, Nitrogen heterocyclic compounds, 1,4-Dihydropyridines.
Introduction

Nowadays, the design of safer chemicals and chemical processes is of great interest. In this sense, catalytic processes play a major role in environmental protection by reducing toxic waste and reaction times while keeping high yield conditions. Solid acids are known as important catalysts in a wide range of reactions because of their high activity and recyclability. Among them, magnetic nano-catalysts are even more attractive due to their easy and fast separation from reaction media.

Nitrogenated heterocyclic compounds are invaluable candidates for the design and discovery of new biologically active compounds. Well-known examples are those molecules with 1,4-dihydropyridine (1,4-DHP) moieties which are considered as ‘distinguished scaffolds’ due to their bio- and pharmaceutical activities. Among them, 1,4-dihydropyridine derivatives are calcium channel blockers, cardiovascular agents for the treatment of hypertension, antivirals, antioxidants, and anti-tumors. Therefore, 1,4-DHPs are good candidates for drug components, having been their syntheses and applications extensively reviewed. Another remarkable feature of 1,4-DHPs as Hantzsch esters is their use as NAD(P)H (I) analogues (Figure 1) for the catalytic hydrogenation of unactivated aldehydes and 1,2,4-triazolinediones. Regarding synthetic methodologies towards 1,4-dihydropyridines, Li et al. have recently synthesized pyrido[2,3-d]pyrimidines via a one-pot three component reaction of aromatic aldehydes, malononitrile, and 2,6-diaminopyrimidin-4-one using [bmim]BF₄ as solvent at 80 °C. To the best of our knowledge, this is the only methodology towards pyrido[2,3-d]pyrimidines reported so far. Thus, the development of new and simple organic synthetic methods for the efficient preparation of this type of heterocycles is an interesting challenge in this field.
Niknam et al. have reported the synthesis and application of a bulky, amorphous silica-bonded S-sulfonic acid (SBSSA) as a reusable catalyst for the preparation of aromatic 1,1-diacetates,\textsuperscript{13} quinoxalines,\textsuperscript{14} 4,4′-(arylmethylene) bis (1H-pyrazol-5-ols),\textsuperscript{15} \(\alpha\)-amino nitriles,\textsuperscript{16} 1,8-dioxodecahydroacridines, 1,8-dioxooctahydroxanthenes,\textsuperscript{17} bis (indolyl) methanes,\textsuperscript{18} silylated alcohols,\textsuperscript{19} trisubstituted dimidazoles,\textsuperscript{20} 2,3-dihydroquinazolin-4(1H)-ones,\textsuperscript{21} and 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles.\textsuperscript{22}

A proper design, synthesis, and application of a given catalyst must consider important aims, such as recyclability, reusability, and proper tasked-specific behavior. Herein, following our recent interest on the rational design and synthesis of dihydropyridine derivatives for the development of new biomimetic reactions,\textsuperscript{23} we wish to report an operative and one-pot synthetic method for the preparation of pyrido[2, 3-\(d\)]pyrimidines using novel magnetic nano particles of [Fe\textsubscript{3}O\textsubscript{4}SiO\textsubscript{2}S(CH\textsubscript{2})\textsubscript{3}SO\textsubscript{3}H] as a recyclable and reusable catalyst under neat conditions (Schemes 1 and 2).

\textbf{Figure 1}: The molecular structure of NADH
Results and discussion

Fe₃O₄@SiO₂ nanoparticles and [Fe₃O₄@SiO₂@(CH₂)₃S-SO₃H] were synthesized following the procedure previously reported by our research group (Scheme 1).²⁴α To ensure construction of the recoverable magnetic nanoporous catalyst 2, this material was analyzed using different techniques
such as, Fourier transforms infrared spectroscopy (FT-IR), thermal gravimetric (TGA), derivative thermal gravimetric (DTG), differential thermal analysis (DTA), energy-dispersive X-ray spectroscopy (EDX), micro X-ray fluorescence (μXRF), μXRF elemental mapping, X-ray diffraction patterns (XRD), high resolution transmission electron microscopy (HRTEM), scanning electron microscopy (SEM), N$_2$ physisorption, and X-ray photoelectron spectroscopy (XPS) (Figures 2-9).

The FT-IR spectrum of the synthesized [Fe$_3$O$_4$@SiO$_2$@((CH$_2$)$_3$S)-SO$_3$H] nano catalyst 2 was investigated and compared with the precursor material [Fe$_3$O$_4$@SiO$_2$@((CH$_2$)$_3$SH)] 1 (Figure 2). As shown, both materials showed the corresponding Si-Si stretching absorption bands at 1077 and 1104 cm$^{-1}$, respectively. In the case of 2, the broad absorption band at 1077 overlapped the symmetric stretching absorption band from the SO$_2$ moiety.

On the other hand, catalyst 2 also showed two more absorption bands at 649 and 1206 cm$^{-1}$, corresponding to the stretching vibration of the S-O bond and the asymmetric stretching vibration of the SO$_2$ group (Figure 2b).

![Fig. 2. FT-IR spectrum of two final steps a) Fe$_3$O$_4$@SiO$_2$@((CH$_2$)$_3$SH) and b) Fe$_3$O$_4$@SiO$_2$@((CH$_2$)$_3$S-SO$_3$H)](image)
In order to monitor the thermal stability and behavior of \( \text{[Fe}_3\text{O}_4@\text{SiO}_2@(\text{CH}_2)_3\text{S-SO}_3\text{H}] \), the thermogravimetry (TG), derivative thermogravimetry (DTG), and the differential thermal analysis (DTA) were conducted being the attained data depicted in Figures 3 and 4. Regarding TGA, the first weight loss step, related to the removal of surface-adsorbed water and organic solvents, took place between 25 and 105 °C and involved a weight loss of 4 wt%. Finally, the second and main weight loss region for \( \text{[Fe}_3\text{O}_4@\text{SiO}_2@(\text{CH}_2)_3\text{S-SO}_3\text{H}] \) (between 105 to 700 °C) could be ascribed to the continuing decomposition of the sulfur moieties of the catalyst. The weight loss for this step was calculated to be 28.7% which was clearly correlated with \( \mu \text{XRF} \) results (see Figure 5). The remaining 71.3 wt% of catalyst was attributed to the \( \text{Fe}_3\text{O}_4@\text{SiO}_2 \). Moreover, the DTA analysis diagram showed a general negative downward slope between 25 °C to 700 °C in which, decomposition of catalyst and its precursor in nitrogen atmosphere were exothermic (Figure 4).

**Fig. 3.** Thermal gravimetric analysis (TG/DTG) analysis of nano \( \text{[Fe}_3\text{O}_4@\text{SiO}_2@(\text{CH}_2)_3\text{S-SO}_3\text{H}] \)
Next, micro X-ray fluorescence (µXRF), µXRF elemental mapping and energy-dispersive X-ray spectroscopy (EDX) analyses were used to determine the organic content and also the elemental composition of the nano-catalyst 2 (Figures 5a-f). As shown in Figure 5, the EDX and µXRF of 2 confirmed the presence of the expected elements in the catalyst structure, with a 29.44 wt% of sulfur content. Examination of the µXRF mapping images (Figures 5c-f) proved the presence of Si, Fe, and S elements in the catalyst with a good distribution over the catalyst surface.
Fig. 5. (a) Micro X-ray fluorescence (µXRF) quantitative results (b) SEM-EDX (c) µXRF image and µXRF elemental mapping images of (d) silisium (red), (e) sulfur (green), (f) iron (blue) of nano catalyst [Fe₃O₄@SiO₂@(CH₂)₃-S-SO₃H].
The particle size and shape as well as the morphology of nanoporous catalyst 2 were studied by XRD, SEM, and HRTEM (Figures 5-7 and Table 1). Characterization by X-ray diffraction (XRD) was performed to investigate the crystalline structure of [Fe₃O₄@SiO₂@(CH₂)₃S-SO₃H] in a range of 10 < 2θ < 80° (Figure 5). On the other hand, XRD patterns demonstrated diffraction lines of high crystalline nature at 2θ = 18.00°, 30.30°, 35.50°, 43.60°, 54.00°, 57.30°, 62.70° and 74.60° corresponding to Fe₃O₄ diffraction lines (111), (220), (311), (400), (422), (511), and (440) (Figure 6) [24a]. The peaks in range of 20 to 29 are related to Si [25], indicating this shift a proper progress in the catalyst preparation. Furthermore, the average crystalline size D (nm) of 2 could be estimated according to the Scherrer equation D = Kλ/(β cos θ), where λ is the X-ray wavelength of Cu kα (1.54Å), K is the Scherrer constant with a value of 0.9, β is the peak width at half maximum (FWHM) of the peak in radians, and θ is the Bragg diffraction angle. On the other hand, the averaged inter-planar distance [nm] of 2, 0.49279 nm (sing the similar highest diffraction line at 18.0°), was calculated according to the Bragg equation: dhkl = λ/(2sinθ), where K is a shape factor with the value of 0.9, θ is the Bragg diffraction angle, λ is the wavelength of Cu kα (1.5405 Å) as the X-ray source. Crystalline sizes from various diffraction lines using the Scherrer equation were found to be in the nanometer range (29.06 - 47.31 nm), which is in a close agreement with the scanning electron microscopy (SEM) results.
Fig. 6. XRD pattern of nano [Fe₃O₄@SiO₂@(CH₂)₃S-SO₃H]

Table 1. X-ray diffraction (XRD) data for nano catalyst [Fe₃O₄@SiO₂@(CH₂)₃S-SO₃H]

<table>
<thead>
<tr>
<th>Entry</th>
<th>2θ</th>
<th>Peak width [degree]</th>
<th>Size [nm]</th>
<th>Inter planar distance [nm]</th>
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<tr>
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<td>0.1</td>
<td>82.54</td>
<td>0.49279</td>
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<td>2</td>
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<td>84.4</td>
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<td>35.50</td>
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</tr>
<tr>
<td>4</td>
<td>43.60</td>
<td>0.1</td>
<td>87.81</td>
<td>0.20758</td>
</tr>
<tr>
<td>5</td>
<td>57.30</td>
<td>0.3</td>
<td>30.37</td>
<td>0.16078</td>
</tr>
</tbody>
</table>
Studies by SEM and HRTEM spectroscopy (Figure 7), helpful techniques to provide information about particle size and morphology of the materials, showed well-dispersed nanospherical particles with a high yield with an average size of 85 nm.

Fig. 7. (a) High resolution transmission electron microscopy (HRTEM) and (b) Scanning electron microscopy (SEM) of nano magnetic [Fe$_3$O$_4$@SiO$_2$@(CH$_2$)$_3$S-SO$_3$H]

Next, Nitrogen adsorption/desorption isotherm was carried out to obtain the information on the porosity and total surface area of the catalyst 2. As shown in Figure 8a, the studied catalyst exhibited type II isotherm according to the IUPAC definition and with H$_3$ type hysteresis loop, which indicated the presence of a nanoporous structure. The surface area and pore volume of the catalyst are listed in Table 2. Moreover, a narrow pore-size distribution was calculated from the adsorption branch on the basis of BJH model (Figure 8b).
Fig. 8. (a) N\textsubscript{2} physisorption isotherm and (b) BJH pore size distribution of the [Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2}@(CH\textsubscript{2})\textsubscript{3}S-SO\textsubscript{3}H]

Table 2. Textural properties of the [Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2}@(CH\textsubscript{2})\textsubscript{3}S-SO\textsubscript{3}H]

<table>
<thead>
<tr>
<th></th>
<th>$S_{\text{BET}}^a$</th>
<th>$S_{\text{BJH}}^b$</th>
<th>$V_m^c$</th>
<th>$V_t^d$</th>
<th>$D^e$</th>
</tr>
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<tr>
<td>(m$^2\cdot$g$^{-1}$)</td>
<td>(m$^2\cdot$g$^{-1}$)</td>
<td>(cm$^3\cdot$g$^{-1}$)</td>
<td>(cm$^3\cdot$g$^{-1}$)</td>
<td>(nm)</td>
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</tr>
<tr>
<td></td>
<td>44.36</td>
<td>31.56</td>
<td>0.10</td>
<td>0.08</td>
<td>3.05</td>
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</table>

$^a$S$_{\text{BET}}$: total surface area. $^b$S$_{\text{BJH}}$: surface area estimated by BJH model applied to the absorption branch of the isotherm. $^c$V$_m$: mesopore volume. $^d$V$_t$: total pore volume. $^e$D: pore diameters estimated by BJH model applied to the absorption branch of the isotherm.

X-ray photoelectron spectroscopy (XPS) studies were next performed over [Fe\textsubscript{3}O\textsubscript{4}@SiO\textsubscript{2}@(CH\textsubscript{2})\textsubscript{3}S-SO\textsubscript{3}H] in order to get insight about the surface composition and changes
associated with the chemical reaction of this catalyst (Figure 9). As expected, the peaks corresponding to S2p, O1s, C1s, Fe2p, and Si2p were clearly seen in the XPS survey spectrum of cat 2, which confirmed a 3-(trimethoxysilyl)-1-propanethiol moiety covalently bonded to Fe3O4@SiO2 (Figure 9a). As shown in Scheme 1, there are two types of sulfur containing groups, sulfide (-S-S-) as a covalent bridge bond and sulfate (-SO3) as an active catalytic site. Therefore, the high resolution XPS spectrum of S2p was used as a potential technique for the analysis of both internal and terminal sulfurs on catalyst 2. As shown in Figure 9b, the S2p spectrum comprises two singlet binding energy located at approximately 163.32 eV (S-S) and 168.88 eV (SO3H) with a relative peak area ratio (1:5) respectively. Each S2p peak could be de-convoluted into the two different peaks located at approximately 163.32, 168.88 eV, corresponding to 2p⁴/2 and 164.838, 169.94 eV, which corresponded to 2p¹/2 level. Interestingly, the relative area between S-S and S-O/S=O were not same indicating that the surface of catalysts was covered with thiosulphonate groups [25]. On the other hand, the XPS peak for chloride was not detected, (Figure 8b, orange lines), and only an orange residuals lines located at 522.68 eV were observed. Since the μXRF, EDX, and XPS had previously approved the presence of sulfur in the structure of catalyst, this result clearly suggested the absence of unreacted ClSO3H on the surface of the catalyst.
Fig. 9. XPS spectra of (a) Survey (inlet: Cl2p), and (b) S2p of nano catalyst 2.
After characterization of the catalyst, we studied its use in the synthesis of pyrido[2,3-d]pyrimidines under neat conditions. Initially, an optimization of the reaction conditions (catalyst loading, temperature, and solvent) was carried out for the condensation between 4-nitrobenzaldehyde, malononitrile and 2,4-diamino-6-hydroxypyrimidine at 100 °C. As shown in Table 3, the best results were obtained when the reaction was performed in the presence of 2 mg of the catalyst (Table 3, entry 1). No yield improvement was observed using higher catalyst loadings (Table 3, entries 2 to 6). Table 3 clearly displays that in the absence of catalyst and different temperature 25 and 100 °C, the product was produced in low yields (Table 3, entry 7 and 8). In addition, keeping the catalyst loading at 2 mg, lowers temperatures led to lower reaction yields (Table 3, entry 9 to 11).

**Table 3.** Condensation of 4-nitrobenzaldehyde, malononitrile and 2,4-diamino-6-hydroxypyrimidine under neat conditions. Catalyst loading and temperature study.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mg)</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yieldb (%)</th>
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</thead>
<tbody>
<tr>
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<td>2</td>
<td>100</td>
<td>20</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
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<td>22</td>
<td>92</td>
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<td>90</td>
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<tr>
<td>4</td>
<td>30</td>
<td>100</td>
<td>25</td>
<td>87</td>
</tr>
</tbody>
</table>

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*a* Condensation of 4-nitrobenzaldehyde, malononitrile and 2,4-diamino-6-hydroxypyrimidine under neat conditions. Catalyst loading and temperature study.
To compare the effect of the solution in comparison with solvent-free conditions, a mixture of 4-nitrobenzaldehyde, malononitrile and 2,4-diamino-6-hydroxypyrimidine as a typical reaction, by using 2 mg of nano [Fe₃O₄@SiO₂@(CH₂)₃S-SO₃H] as a catalyst in a good range of solvents such as H₂O, MeCN, EtOH, EtOAC and CH₂Cl₂ were investigated under reflux condition. The results are summarized in Table 4. The results display that solvent-free condition was the best of choice for this reaction (Table 4, entry 6).

Table 4. The effect of various solvents in the presence of 2 mg of [Fe₃O₄@SiO₂@(CH₂)₃S-SO₃H] as a catalyst in the one-pot condensation reaction of 4-nitrobenzaldehyde, malononitrile and 2,4-diamino-6-hydroxypyrimidine.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>50</td>
<td>100</td>
<td>20</td>
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<td></td>
<td>70</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>-</td>
<td>110</td>
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</tr>
<tr>
<td>8</td>
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</tr>
<tr>
<td>11</td>
<td></td>
<td>2</td>
<td>80</td>
<td>60</td>
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</table>

*Reaction conditions: 4-nitrobenzaldehyde (1 mmol; 151 mg), malononitrile (1 mmol, 66 mg) and 2,4-diamino-6-hydroxypyrimidine (1 mmol, 126 mg); bIsolated yield.
Reaction condition: 4-nitrobenzaldehyde (1 mmol; 151 mg), malononitrile (1 mmol, 66 mg) and 2,4-diamino-6-hydroxypyrimidine (1 mmol, 126 mg); Isolated yield.

After optimization of the reaction conditions, the efficiency and applicability of the method were studied via the reaction of malononitrile and 2,4-diamino-6-hydroxypyrimidine with various aromatic aldehydes in the presence of nano [Fe₃O₄@SiO₂@(CH₂)₃S-SO₃H]. The results are summarized in Table 5. Generally, all tested aldehydes including benzaldehyde as well as other aromatic aldehydes substituted with electron-donating and electron withdrawing groups afforded the desired pyrido[2,3-d]pyrimidine derivatives in good to excellent yields (84-94%) in short reaction times (8-23 min).

**Table 5.** Synthesis of pyrido[2,3-d]pyrimidine derivatives under neat conditions at 100°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>M.p (°C)</th>
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<tbody>
<tr>
<td>1</td>
<td>EtOAC</td>
<td>Reflux</td>
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<td>60</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>Reflux</td>
<td>90</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>Reflux</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>Reflux</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>Reflux</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>Reflux</td>
<td>20</td>
<td>92</td>
</tr>
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</table>

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Reaction condition: *a*4-nitrobenzaldehyde (1 mmol; 151 mg), malononitrile (1 mmol, 66 mg) and 2,4-diamino-6-hydroxypyrimidine (1 mmol, 126 mg); *b*Isolated yield.
1. HN\_2CN\_2\_N\_H\_2 6a 13 87 209-211

>300\textsuperscript{12}

2. HN\_2CN\_2\_N\_H\_2 6b 18 90 216-218

[\text{-}]

3. HN\_2CN\_2\_N\_H\_2 6c 13 92 213-215

[\text{-}]

4. HN\_2CN\_2\_N\_H\_2 6d 8 94 272-274

[\text{-}]

5. HN\_2CN\_2\_N\_H\_2 6e 11 92 227-229

>300\textsuperscript{12}
6 \[6f\] 12 90 229-231

7 \[6g\] 10 91 220-222

8 \[6h\] 14 89 235-237

9 \[6i\] 13 91 236-238

10 \[6j\] 12 90 266-268
11. 6k 16 89 233-235
[>300]\textsuperscript{12}

12. 6l 19 86 205-207
[-]

13. 6m 17 84 223-225
[>300]\textsuperscript{12}

14. 6n 22 86 164-166
[-]
A mechanistic proposal for the 2-catalyzed route towards the synthesis of pyrido[2,3-\(d\)]pyrimidine derivatives has been summarized in Scheme 3. According to the XPS results and previous works [12], the aldehyde, which is initially activated by the acidic surface sites of nano [Fe\(_3\)O\(_4\)@SiO\(_2\)@(CH\(_2\)_3S-SO\(_3\)H], suffer a Knoevenagel condensation with malononitrile to give intermediate A. Then, this excellent Michael acceptor undergoes a conjugate addition reaction by 2,4-diamino-6-hydroxypyrimidine to afford intermediate B that, after a 2-promoted intramolecular cyclization and a final tautomerization, affords the corresponding compounds 6 (Scheme 3).
Scheme 3. Proposed mechanism for the synthesis of pyrido[2,3-\(d\)]pyrimidines in the presence of \([\text{Fe}_3\text{O}_4@\text{SiO}_2@(\text{CH}_2)_3\text{SSO}_3\text{H}]\).

Catalyst recycling and recovering is an essential consideration regarding environmental, economic and industrial considerations. Apart from the magnetic isolation and separation of the catalyst upon reaction completion, the additional possibility to reuse it in several reaction cycles on the model
synthesis of 6a was also studied. Thus, after each cycle, the catalyst was magnetically separated from the reaction mixture and washed with a hot ethanol-water mixture and then, reused. As seen in Figure 10, the described catalyst can be reused up to 8 times without an important loss of activity.

![Fig. 10. Recyclability of nano[Fe₃O₄@SiO₂@(CH₂)$_3$S-SO$_3$H] in the synthesis 6a under neat conditions at 100 °C.](image)

**Conclusion**

In conclusion, we have described the first catalytic synthesis of pyrido[2,3-$d$]pyrimidines using the novel and recoverable nano magnetic [Fe₃O₄@SiO₂@(CH₂)$_3$S-SO$_3$H] catalyst which has been fully characterized. The major advantages of this methodology are high yields, short reaction times, and reusability of the catalyst. The described results from this research supports the idea of rational designs, syntheses and applications of tasked-specific and reusable catalysts for the synthesis of polynitrogenated heterocyclic compounds containing the 1,4-dihydropyridine moiety.

2. Experimental

2.1. General information
Solvents and reagents were used as obtained from Sigma-Aldrich, Alfa Aesar, and Merck companies without further purification. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. Rf values were measured using EtOAc as solvent. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Fourier transformed infrared (FTIR) spectra of the catalyst and the synthesized products were recorded on a FTIR spectrometer Perkin-Elmer spectrum 65 using KBr disks. High resolution mass spectra (GC/QTOF, EI, 70 eV) were obtained using an Agilent 7200 Network spectrometer. 1H NMR (300 and 400 MHz) spectra were obtained on a Bruker Avance 300 and a Bruker Avance 400 NMR spectrometers, under proton coupled mode using deuterated DMSO as a solvent, unless otherwise stated. 13C NMR (101 MHz) spectra were acquired on a Bruker Avance 400 NMR spectrometer in the proton decoupled mode at 20 °C in deuterated DMSO as solvent, unless otherwise stated. Chemical shifts are given in δ (parts per million) and the coupling constants (J) in Hertz. 19F NMR (282 MHz) spectra were recorded on a Bruker Avance 300 NMR spectrometer, in proton coupled mode. Data for 1H NMR spectra is reported as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br., broad), coupling constant (Hz), and integration. Thermogravimetric analyses (TGA) were carried out on a Mettler Toledo equipment (model TGA/SDTA851 and /SF/1100 TGDTA) under nitrogen atmosphere at 25°C and using a heating rate of 25 °C min⁻¹ up to 700 °C. Powder X-ray diffraction (XRD) pattern was recorded with an Ital structure ADD2000 model, using a monochromatized Cu Kα (λ = 0.154 nm) X-ray source in the range 10° < 2θ < 80°. High resolution transmission electron microscopy (HRTEM) images were obtained using a JEOL JEM-2010 microscope operating at an accelerating voltage of 200 kv. Sample was prepared by drop casting the dispersed particles onto a 200-mesh copper grid coated with a holey carbon film. Scanning electron microscopy (SEM) studies were performed using a TESCAN/MIRA with a
maximum acceleration voltage of the primary electrons between 10 and 15 kV. \( N_2 \) adsorption-desorption isotherms were measured at 77 K with a Quantachrome NOVA 4000e analyzer. The Brunauer-Emmett-Teller (BET) method was used to calculate the specific surface areas (\( S_{BET} \)). By using the Barrett-Joyner-Halenda (BJH) model, the pore volumes and pore size distributions were derived from the adsorption branches of isotherms. The micropore surface area (\( S_{BET \, \text{micro}} \)) was calculated using the \( V-t \) plot method. X-ray photoelectron spectroscopy (XPS, K-ALPHA, Thermo Scientific) was used to analyze the samples surface. All spectra were collected using Al-K radiation (1486.6 eV), monochromatized by a twin crystal monochromator, yielding a focused X-ray spot (elliptical in shape with a major axis length of 400µm) at 3 mA × 12 kV. XPS data were analyzed using Thermo Scientific Avantage Software. A smart background function was used to approximate the experimental backgrounds and surface elemental composition was calculated from background-subtracted peak areas. Charge compensation was achieved with the system flood gun that provides low energy electrons and low energy argon ions from a single source. A Gaussian/Lorenzian product function peak shape model (L/G Mix (%) = 30) was used. Micro X-ray fluorescence (µXRF) analyses were performed on an Edax, Orbis using 25 kV with image mapping resolution (128 × 100).

**Preparation of nano[Fe\(_3\)O\(_4\)@SiO\(_2\)@(CH\(_2\)_3S-SO\(_3\)H] catalyst**

Initially, iron oxide (Fe\(_3\)O\(_4\)) magnetic nanoparticles and the silica coated on iron oxide (Fe\(_3\)O\(_4\)@SiO\(_2\)) were synthesized according to previously reported procedures [24]. Thus, in a round-bottomed flask, 1.0 g of previously dried (under vacuum) silica coated magnetic nanoparticles was dispersed in 50 mL of anhydrous toluene and it was sonicated for 30 min. After this time, 3.5 mL of 3-(trimethoxysilyl)-1-propanethiol were added dropwise to the suspended solid nanoparticles, being the obtained mixture refluxed under mechanical stirring.
for 24 h. After this time, the prepared nanoparticles 1 were isolated by using an external magnet and dried at room temperature. Then, in a round-bottomed flask, 1.0 g of [Fe$_3$O$_4$@SiO$_2$@(CH$_2$)$_3$SH] (1) was sonicated for 30 min in anhydrous CH$_2$Cl$_2$ (50 mL). Next, 0.5 mL of chlorosulfonic acid were added dropwise to the reaction mixture at room temperature and the resulting solution was allowed to stir for 2 h until no more hydrogen chloride evolution was detected. Then, the resulting mixture was isolated by using an external magnet to afford [Fe$_3$O$_4$@SiO$_2$@(CH$_2$)$_3$S-SO$_3$H] (2) which was washed with ethanol and dried at room temperature (Scheme 1).

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

In a 10 mL round-bottomed flask, a mixture of aldehyde (1 mmol), malononitrile (1 mmol, 66 mg), 2,4-diamo-6-hydroxypyrimidine (1 mmol, 126 mg), and [Fe$_3$O$_4$@SiO$_2$@(CH$_2$)$_3$S-SO$_3$H] (2 mg) were stirred at 100 °C under neat conditions. After completion of the reaction (monitored by TLC), the mixture was allowed to cool to room temperature. Then, the resulted solid mixture was solved in DMF and the catalyst was recovered using a magnet. Products precipitated out of the DMF solution. Finally, the obtained crystals were washed with water to remove DMF (Table 1) (Scheme 2).

**2,7-Diamino-5-(4-nitrophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6a):**

Isolated as yellow solid, (283 mg, 87%), Rf: 0.16, Melting point: 209 – 211 °C; FT-IR: υ (cm$^{-1}$) = 3471, 3385, 3348, 3167, 2191, 1666, 1630, 1555, 1516, 1455, 1394, 1346, 1204; $^1$H NMR: δ 8.19 (d, $J$ = 8.7, 2H), 7.45 (d, $J$ = 8.7, 2H), 7.08 (br. s, 2H), 6.27 (br. s, 2H), 6.17 (br. s, 2H), 4.62 (s, 1H); $^{13}$C NMR: δ 163.2, 162.4, 162.2, 160.5, 152.8, 146.8, 128.7, 124.2, 120.4, 84.5, 57.1, 35.7; HRMS calcd. for C$_{10}$H$_5$N$_3$O$_2$ [M$^+$ - (C$_4$H$_6$N$_4$O)] 199.0382, found 199.0383.
2,7-Diamino-4-oxo-5-phenyl-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6b):
Isolated as khaki solid, (252 mg, 90%), Rf: 0.65, Melting point: 216 – 218 °C; FT-IR: \( \nu (\text{cm}^{-1}) = 3491, 3384, 3169, 2183, 1662, 1465, 1394, 1201, 1132; \) \(^1\)H NMR: \( \delta 7.33 – 7.26 \) (m, 2H), 7.25 – 7.17 (m, 3H), 6.91 (br. s, 2H), 6.15 (br. s, 2H), 6.09 (br. s, 2H), 4.41 (s, 1H); \(^{13}\)C NMR (75 MHz) \( \delta 163.2, 162.1 \) (2c), 160.3, 145.2, 128.9, 127.4, 127.2, 120.8, 85.7, 58.6, 35.9; HRMS calcd. for C\(_{10}\)H\(_8\)N\(_2\) [M\(^+\) - (C\(_4\)H\(_6\)N\(_4\)O)] 154.0531, found 154.0537.

2,7-Diamino-5-(3,4-difluorophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6c):
Isolated as lemon chiffon solid, (290 mg, 92%), Rf: 0.30, Melting point: 213 – 215 °C; FT-IR: \( \nu (\text{cm}^{-1}) = 3480, 3403, 3328, 3154, 2929, 2185, 1656, 1634, 1556, 1459, 1395, 1286, 1140, 799; \) \(^1\)H NMR: \( \delta 7.43 – 7.32 \) (m, 1H), 7.26 – 7.17 (m, 1H), 7.11 – 6.90 (m, 3H), 6.30 (br. s, 2H), 5.75 (br. s, 2H), 4.45 (s, 1H); \(^{13}\)C NMR: \( \delta 163.1, 162.3, 162.0 \) (dd, \( J = 246.0, 12.8 \) Hz), 148.65 (dd, \( J = 245.0, 12.6 \) Hz), 143.0 (t, \( J = 3.5 \) ), 144.50 (dd, \( J = 17.1 \) ), 116.0 (d, \( J = 17.1 \) ), 84.9, 57.7, 35.2; \(^{19}\)F NMR: \( \delta -136.58 \) (d, \( J = 22.5 \) Hz), -139.17 (d, \( J = 22.5 \) Hz); HRMS calcd. for C\(_{10}\)H\(_4\)F\(_2\)N\(_2\) [M\(^+\) - (C\(_4\)H\(_6\)N\(_4\)O)] 190.0343, found 190.0344.

2,7-Diamino-5-(2,6-difluorophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6d):
Isolated as floral white solid, (297 mg, 94%), Rf: 0.20, Melting point: 272 – 274 °C; FT-IR: \( \nu (\text{cm}^{-1}) = 3478, 3377, 3181, 2193, 1665, 1621, 1469, 1392, 1208, 995, 782, 563; \) \(^1\)H NMR: \( \delta 7.41 – 7.28 \) (m, 1H), 7.17 – 6.93 (m, 4H), 6.18 (br. s, 2H), 5.75 (br. s, 2H), 4.89 (s, 1H); \(^{13}\)C NMR: \( \delta 163.1, 162.3, 162.2 \) (dd, \( J = 240, 20 \) ), 161.3, 154.5, 129.8 (t, \( J = 10.6 \) ), 120.4, 119.0 (t, \( J = 15.9 \) ), 112.4 (d, \( J = 24.7 \) ), 83.4, 54.2, 26.2; \(^{19}\)F NMR (282 MHz) \( \delta -106.83, -114.09 \); HRMS calcd. for C\(_{10}\)H\(_4\)F\(_2\)N\(_2\) [M\(^+\) - (C\(_4\)H\(_6\)N\(_4\)O)] 190.0343, found 190.0350.
2,7-Diamino-5-(4-bromophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6e):

Isolated as moccasin solid, (329 mg, 92%), R_f: 0.16, Melting point: 227 – 229 °C; FT-IR: υ (cm⁻¹) = 3466, 3391, 3173, 2184, 1661, 1625, 1553, 1384, 1298, 1132; ¹H NMR: δ 7.53 – 7.47 (m, 2H), 7.19 – 7.12 (m, 2H), 6.97 (br. s, 2H), 6.20 (br. s, 2H), 6.12 (br. s, 2H), 4.43 (s, 1H); ¹³C NMR: δ 163.1, 162.2, 162.1, 160.3, 144.6, 131.7, 129.7, 120.7, 120.2, 85.2, 57.9, 35.4; HRMS calcd. for C₁₀H₅BrN₂ [M⁺ - (C₄H₆N₄O)] 231.9636 and 233.9616, found 231.9645 and 233.9620.

2,7-Diamino-5-(3-bromophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6f):

Isolated as linen solid, (323 mg, 90%), R_f: 0.30, Melting point: 229 – 231 °C; FT-IR: υ (cm⁻¹) = 3491, 3381, 3182, 2193, 1668, 1619, 1553, 1448, 1388, 1295, 1130, 1070, 786; ¹H NMR: δ 7.45 – 7.38 (m, 2H), 7.28 (t, J = 7.9, 1H), 7.16 (d, J = 7.5, 1H), 7.01 (br. s, 2H), 6.25 (br. s, 2H), 6.15 (br. s, 2H), 4.43 (s, 1H); ¹³C NMR: δ 163.1, 162.3, 162.1, 160.4, 148.0, 131.2, 130.1 (2c), 126.5, 122.0, 120.6, 85.0, 57.8, 35.5; HRMS calcd. for C₁₀H₅BrN₂ [M⁺ - (C₄H₆N₄O)] 231.9636 and 233.9616, found 231.9638 and 233.9615.

2,7-Diamino-5-(4-chlorophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6g):

Isolated as khaki solid, (mg, 91%), R_f: 0.65, Melting point: 220 – 222 °C; FT-IR: υ (cm⁻¹) = 3492, 3379, 3331, 3178, 2929, 2194, 1669, 1618, 1552, 1449, 1391, 1297, 1131, 828; ¹H NMR: δ 7.40 – 7.33 (m, 2H), 7.25 – 7.18 (m, 2H), 6.96 (br. s, 2H), 6.19 (br. s, 2H), 6.12 (br. s, 2H), 4.44 (s, 1H); ¹³C NMR: δ 163.1, 162.2, 162.1, 160.3, 144.2, 131.7, 129.3, 128.8, 120.7, 85.2, 58.0, 35.3; HRMS calcd. for C₁₀H₅ClN₂ [M⁺ - (C₄H₆N₄O)] 188.0141 and 190.0112, found 188.0145 and 190.0113.
2,7-Diamino-5-(2-chlorophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6h):
Isolated as papaya whip solid, (279 mg, 89%), Rf: 0.40, Melting point: 235 – 237 °C; FT-IR: \( \nu (\text{cm}^{-1}) = 3473, 3395, 3322, 3165, 2191, 1666, 1629, 1558, 1456, 1394, 1299, 1138, 1035, 750; \) \( ^1\)H NMR: \( \delta 7.41 – 7.23 \) (m, 4H), 6.97 (br. s, 2H), 6.15 (br. s, 2H), 5.74 (br. s, 2H), 4.76 (s, 1H); \( ^{13}\)C NMR (75 MHz) \( \delta 163.1, 162.2 \) (2c), 160.6, 140.7, 132.4, 131.4, 130.6, 129.3, 128.1, 120.3, 84.3, 56.1, 35.2; HRMS calcd. for C\(_{10}\)H\(_5\)ClN\(_2\) [M\(^+\) - (C\(_4\)H\(_6\)N\(_4\)O)] 188.0141 and 190.0112, found 188.0145 and 190.0112.

2,7-Diamino-5-(4-cyanophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6i):
Isolated as khaki solid, (277 mg, 91%), Rf: 0.17, Melting point: 236 – 238 °C; FT-IR: \( \nu (\text{cm}^{-1}) = 3451, 3413, 3337, 3204, 2885, 2731, 2227, 1633, 1594, 1442, 1395, 817; \) \( ^1\)H NMR: \( \delta 10.06 \) (br. s, 1H), 7.89 – 7.72 (m, 4H), 6.49 (br. s, 2H), 6.38 – 6.15 (m, 3H), 4.72 (d, \( J = 11.5 \), 1H); \( ^{13}\)C NMR: \( \delta 163.2, 162.6, 154.6, 145.6, 132.6, 129.2, 119.2, 114.9, 114.6, 110.6, 84.3, 42.6, 25.9; HRMS calcd. for C\(_{11}\)H\(_5\)N\(_3\) [M\(^+\) - (C\(_4\)H\(_6\)N\(_4\)O)] 179.0483, found 179.0486.

2,7-Diamino-5-(2,6-dichlorophenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6j):
Isolated as white solid, (314 mg, 90%), Rf: 0.22, Melting point: 266 – 268 °C; FT-IR: \( \nu (\text{cm}^{-1}) = 3479, 3377, 3319, 3181, 2193, 1670, 1621, 1469, 1394, 1208, 995, 782; \) \( ^1\)H NMR: \( \delta 7.55 \) (d, \( J = 7.8, 1H \)), 7.44 (d, \( J = 7.8, 1H \)), 7.35 (t, \( J = 8.0, 1H \)), 7.05 (s, 2H), 6.20 (s, 2H), 5.42 (br. s, 2H), 5.32 (s, 1H); \( ^{13}\)C NMR \( \delta 162.8, 162.3, 161.2, 135.8, 134.7, 131.8, 130.3, 129.2, 119.8, 82.7, 53.1, 33.6; HRMS calcd. for C\(_{10}\)H\(_4\)Cl\(_2\)N\(_2\) [M\(^+\) - (C\(_4\)H\(_6\)N\(_4\)O)] 221.9752 and 223.9722 and 225.9693 found 221.9754 and 223.9720 and 225.9694.
2,7-Diamino-5-(3-nitrophenyl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (6k):

Isolated as pale golden rod solid, (287 mg, 89%), Rf 0.16, Melting point: 233 – 235 °C; FT-IR: $\nu$ (cm$^{-1}$) = 3496, 3466, 3400, 3121, 2917, 2187, 1674, 1634, 1594, 1536, 1351, 1148, 787; $^1$H NMR: $\delta$ 8.18 – 8.05 (m, 2H), 7.72 – 7.52 (m, 2H), 7.08 (br. s, 2H), 6.31 (br. s, 2H), 6.17 (br. s, 2H), 4.63 (s, 1H); $^{13}$C NMR: $\delta$ 163.1, 162.4, 162.2, 160.6, 148.1, 147.6, 134.2, 130.6, 122.4, 121.9, 120.5, 84.7, 57.4, 35.5; HRMS calcd. for C$_{10}$H$_5$N$_3$O$_2$ [M$^+$ - (C$_4$H$_6$N$_4$O)] 199.0382, found 199.0383.

2,7-Diamino-5-(4-methoxyphenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6l):

Isolated as yellow solid, (266 mg, 86%), Rf 0.29, Melting point: 205 – 207 °C; FT-IR: $\nu$ (cm$^{-1}$) = 3400, 2186, 1659, 1626, 1556, 1455, 1384, 1034; $^1$H NMR: $\delta$ 7.11 (d, $J$ = 8.7, 2H), 6.87 – 6.83 (m, 4H), 6.11 (br. s, 2H), 6.06 (br. s, 2H), 4.35 (s, 1H), 3.72 (s, 3H); $^{13}$C NMR: $\delta$ 163.1, 162.4, 162.2, 160.6, 148.1, 147.6, 134.2, 130.6, 122.4, 121.9, 120.5, 161.9, 160.1, 158.5, 137.3, 128.5, 120.8, 114.2, 85.9, 58.8, 55.5, 35.1; HRMS calcd. for C$_{11}$H$_8$N$_2$O [M$^+$ - (C$_4$H$_6$N$_4$O)] 184.0637, found 184.0638.

2,7-Diamino-4-oxo-5-(p-tolyl)-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6m):

Isolated as ivory solid, (247 mg, 84%), Rf 0.18, Melting point: 223 – 225 °C; FT-IR: $\nu$ (cm$^{-1}$) = 3473, 3399, 3321, 3165, 2193, 2175, 1655, 1625, 1456, 1392, 1297, 1199, 1039, 792; $^1$H NMR: $\delta$ 7.09 (s, 4H), 6.87 (s, 2H), 6.10 (br. s, 2H), 6.07 (br. s, 2H), 4.36 (s, 1H), 2.25 (s, 3H); $^{13}$C NMR: $\delta$ 163.2, 162.1, 162.0, 160.1, 142.2, 136.3, 129.4, 127.4, 120.8, 85.8, 58.7, 35.6, 21.1; HRMS calcd. for C$_{11}$H$_8$N$_2$ [M$^+$ - (C$_4$H$_6$N$_4$O)] 168.0687, found 168.0684.

2,7-Diamino-5-(4-hydroxyphenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6n):
Isolated as papaya whip solid, (254 mg, 86%), Rf: 0.23, Melting point: 164 – 166 °C; FT-IR: υ (cm⁻¹) = 3446, 3345, 3184, 2195, 1660, 1618, 1552, 1463, 1388, 1260, 664; ¹H NMR: δ 9.28 (br. s, 1H), 6.99 (d, J = 8.5, 2H), 6.82 (br. s, 2H), 6.67 (d, J = 8.5, 2H), 6.05 (br. s, 4H), 4.28 (s, 1H); ¹³C NMR: δ 163.1, 162.0, 161.9, 160.0, 156.6, 135.5, 128.5, 120.9, 115.5, 86.1, 59.1, 35.2; HRMS calcd. for C₁₀H₆N₂O [M⁺ - (C₄H₆N₄O)] 170.0480, found 170.0483.

2,7-Diamino-5-(3-ethoxy-4-hydroxyphenyl)-4-oxo-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6o):
Isolated as beige solid, (303 mg, 89%), Rf: 0.33, Melting point: 205 – 207 °C; FT-IR: υ (cm⁻¹) = 3500, 3472, 3361, 3161, 2975, 2195, 1673, 1646, 1627, 1560, 1468, 1377, 1286, 1119, 1032; ¹H NMR: δ 8.77 (s, 1H), 6.82 (br. s, 3H), 6.69 (d, J = 8.1, 1H), 6.52 (dd, J = 8.1, 2.0, 1H), 6.05 (br. s, 4H), 4.26 (s, 1H), 4.05 – 3.88 (m, 2H), 1.31 (t, J = 7.0, 3H); ¹³C NMR: δ 163.2, 161.9 (2c), 159.9, 146.7, 146.1, 136.1, 120.9, 119.7, 116.1, 113.6, 86.0, 64.4, 59.0, 35.6, 15.2; HRMS calcd. for C₁₂H₁₀N₂O₂ [M⁺ - (C₄H₆N₄O)] 214.0742, found 214.0747.

2,7-Diamino-4-oxo-5-(thien-2-yl)-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (6p):
Isolated as papaya whip solid, (246 mg, 86%), Rf: 0.12, Melting point: 213 – 215 °C; FT-IR: υ (cm⁻¹) = 3486, 3376, 3152, 2193, 1669, 1622, 1556, 1451, 1398, 1126, 793, 728; ¹H NMR: δ 7.33 (dd, J = 5.1, 1.1, 1H), 7.07 – 6.95 (m, 3H), 6.93 – 6.88 (m, 1H), 6.35 (br. s, 2H), 6.12 (br. s, 2H), 4.82 (s, 1H); ¹³C NMR: δ 163.1, 162.1, 161.6, 160.5, 150.6, 127.0, 125.0, 124.7, 120.7, 86.0, 58.5, 31.4; HRMS calcd. for C₈H₄N₂S [M⁺ - (C₄H₆N₄O)] 160.0095, found 160.0097.

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