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Synthesis of pyranopyrazoles using magnetic Fe_3O_4 nanoparticles as efficient and reusable catalyst

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ABSTRACT

Magnetic Fe_3O_4 nanoparticles as a heterogeneous catalyst, were found to be efficient for the synthesis of a series of pyranopyrazoles by a four component reaction of a mixture of hydrazine hydrate, ethyl acetoacetate, aldehydes/ketones and malononitrile in water at room temperature. The products were attributed to the nanosize of about 16 nm in which the catalyst could act as a nanoreactor. The present protocol offers the advantages of clean reaction, short reaction time, high yield, easy purification and economic availability of the catalyst.

1. Introduction

Green chemistry techniques continue to grow in importance and alternative processes aim to conserve resources and reduce costs. The replacement of conventional solvents with water, which is harmless to health and is available in large quantities, is an interesting basic approach along this line.[1–3] In recent years, the focus on green chemistry using environmentally benign reagents and conditions is one of the most fascinating developments in the synthesis of widely used organic compounds. The use of water as a promising solvent for organic reactions has received considerable attention in the arena of organic synthesis owing to its green credentials.[4–6] In addition, organic synthesis in aqueous media offers key advantages, such as rate enhancement and insolubility of the final products, which facilitates their isolation by simple filtration. Due to increasing environmental concerns, the development of clean synthetic procedures has become crucial and demanding research. In this sense, heterogeneous organic reactions have many advantages, such as ease of handling separation, recycling and environmentally safe disposal.[7,8] However, magnetic nanoparticles (MNPs) have received a great deal of attention because of their potential biomedical applications in fields, such as drug delivery,[9,10] magnetic resonance imaging,[11] bio-molecular sensors,[12] bio-separation[13] and magneto-thermal therapy.[14] Additionally, recent studies showed that magnetic nanoparticles are excellent catalysts for organic reactions.[8,15–17] Moreover, the magnetic properties make the complete recovery of the catalyst by means of an external magnetic field. These advantages become greater if such reactions can be conducted in aqueous media.

Multi-component reactions (MCRs) have emerged as a powerful tool for the construction of novel and complex molecular structures due to their advantages over conventional multi-step synthesis. The major advantages of MCRs include lower costs, shorter reaction times, high atom-economy and energy savings from the avoidance of time consuming and expensive purification processes. It is established that MCRs are generally much more environmentally friendly and offer rapid access to large compound libraries with diverse functionalities.[18–20] Pyrano[2,3-*c*]pyrazole molecule is an emerging class of heterocycles,[21a–e] which is widely explored as an important core of the emerging drugs with numerous medicinal activities including potential inhibitor of human Chk1 kinase,[22a] anti-inflammatory,[22b] anticancer, analgesic, molluscicidal[23] and antimicrobial.[24] The synthesis of substituted pyrano[2,3-*c*]pyrazole can be accomplished in several ways including the use of 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine.[25] Literature shows that methods employing piperazine,[26] β-cyclodextrin[27] and γ-alumina as catalysts have been developed for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles. Although the methods reported are effective, they are limited due to the levels of toxicity arising by the use of piperazine and piperidine.[25] In addition, these methods require expensive catalysts for the reaction.[27] The solvent required for the reaction,[27,28] makes the work up procedure tedious and cumbersome. Reported here is a simple,

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a simple, rapid and high yielding one pot four component reaction protocol for the synthesis of pyranopyrazole derivatives in water using magnetically recoverable Fe_3O_4 nanoparticles as heterogeneous catalyst at room temperature.

2. Results and discussion

Designing organic reactions in aqueous media is another progressing area in green chemistry. Water is an abundant and environmentally benign solvent. This protocol offers flexibility in tuning the molecular complexity and diversity. The reactions proceeded to completion almost instantaneously and pure product was obtained simply by recrystallization from ethanol without using any chromatographic techniques. The reaction between hydrazine hydrate **1**, ethyl acetoacetate **2**, ketones/aldehyde **3** and malononitrile **4**, stirred at room temperature for 1–5 min resulted in pyranopyrazoles **5a**–**p** (Table 1) in magnetically recoverable Fe_3O_4 nanoparticles as heterogeneous catalyst, but formed ketones after stirring for 5–15 min (Scheme 1).

Table 1
Synthesis of pyranopyrazoles **5a**–**p**

No	R	R^1	Time (min)	No	R	R^1	Time (min)
5a	Ph	H	1	**5i**	4-OH–Ph	H	4
5b	4-MeO–Ph	H	2	**5j**	2-OH–Ph	H	5
5c	2,5-MeO–Ph	H	3	**5k**	4-Br–Ph	H	3
5d	3,4,5-MeO–Ph	H	3	**5l**	4-F–Ph	H	3
5e	4-NO_2–Ph	H	4	**5m**	4-$(CH_3)_2$N–Ph	H	5
5f	3-NO_2–Ph	H	4	**5n**	Ph	CH_3	5
5g	4-Cl–Ph	H	3	**5o**	4-Br–Ph	CH_3	12
5h	3-Cl–Ph	H	5	**5p**	Ph	Ph	15

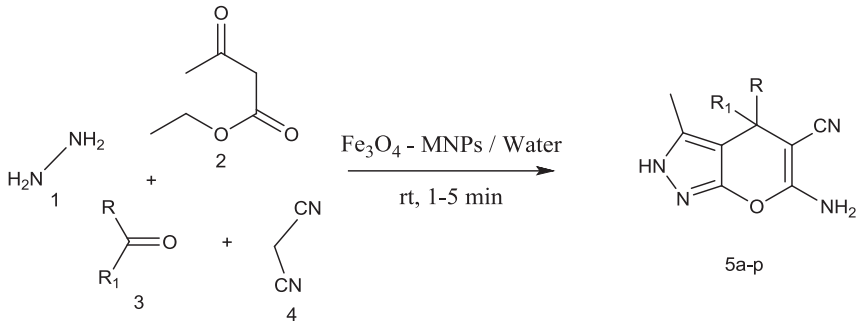
product in the shortest time was obtained using Fe_3O_4 nanoparticles, which may be due to greater diffusion of Fe_3O_4 nanoparticles in the reaction mixture. The recovered catalyst was found to be similar to the fresh Fe_3O_4 nanoparticles as shown in (Table 2).

The results represented in (Table 3) reports that the reaction in magnetically recoverable Fe_3O_4 nanoparticles produced the highest yield. Interestingly, when the reaction was carried out in the presence of 1 mol % Fe_3O_4-MNPs, it generated a 70% yield of product. Subsequent efforts were focused on optimizing conditions for formation of pyranopyrazoles by using different amounts of Fe_3O_4-MNPs to determine their effects on the reaction. As indicated, the best result was obtained with 6 mol % Fe_3O_4-MNPs. The reaction yield with increasing amount of Fe_3O_4-MNPs was not substantially increased.

Table 3
Amount of catalyst

Entry	Catalysts (mol %)	Yield (%)	Entry	Catalysts (mol %)	Yield (%)
1	1	70	**5**	5	95
2	2	78	**6**	6	97
3	3	82	**7**	7	97
4	4	90	**8**	8	97

The stability of magnetically recoverable Fe_3O_4 nanoparticles and its activity were investigated in recycling experiments for the reaction between hydrazine hydrate, ethyl acetoacetate, benzaldehyde and malononitrile under the optimized conditions. After each cycle, the catalyst was separated magnetically, washed with ethanol, dried at 50 °C under vacuum to remove residual solvents



Scheme 1. Four component synthesis of pyranopyrazoles **5a**–**p**.

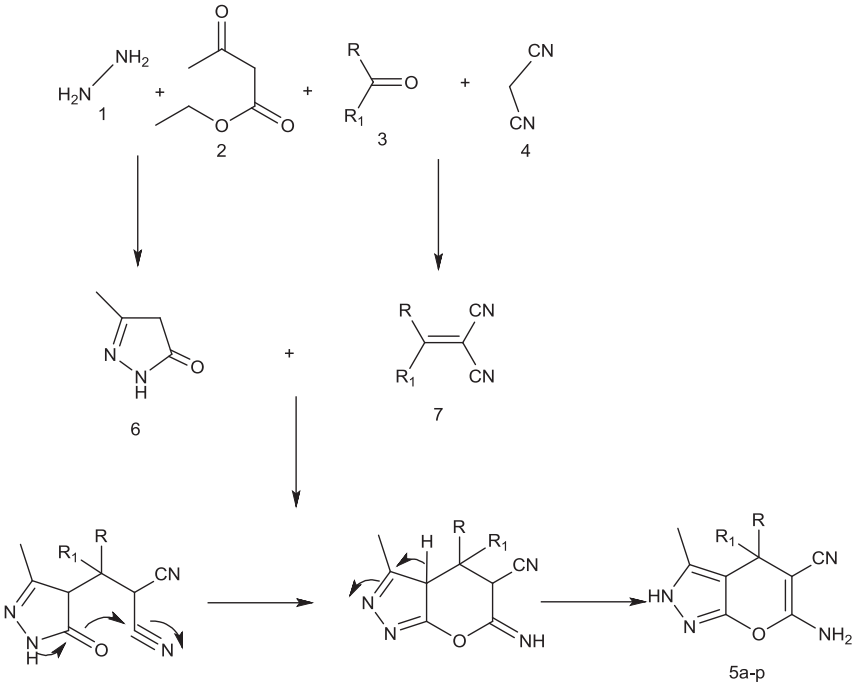
Table 2
The effect of different types of Fe_3O_4

No	Fe_3O_4		Fe_3O_4 NPs		Recovered Fe_3O_4 NPs		No	Fe_3O_4		Fe_3O_4 NPs		Recovered Fe_3O_4 NPs	
	Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)		Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
5a	1	73	1	97	1	97	**5i**	3	69	4	96	4	96
5b	3	71	2	95	2	95	**5j**	4	58	5	93	5	93
5c	2	65	3	97	3	97	**5k**	2	73	3	97	3	97
5d	2	68	3	93	3	93	**5l**	2	72	3	96	3	96
5e	2	70	4	94	4	94	**5m**	4	68	5	91	5	91
5f	3	63	4	96	4	96	**5n**	5	69	5	90	5	90
5g	2	74	3	93	3	93	**5o**	8	49	15	88	15	88
5h	2	66	5	94	5	94	**5p**	6	67	13	91	13	91

In the absence of a catalyst, the reaction mixture produced no product in water at room temperature but compound **5a** produced product after 8 h.[29a] Also, the reaction mixture worked up by using three types of catalysts were examined, i.e., Fe_3O_4, Fe_3O_4 nanoparticles and recovered Fe_3O_4 nanoparticles.[29b] The highest yield of

and used for the following cycle. Fe_3O_4 MNPs could be reused up to fourteen times without any significant loss of the initial catalytic activity. A very small loss in the amount of catalyst accompanied with a non-effective reduction in the initial catalytic activity from the 8th to 14th times has been recorded.

In order to investigate the effect of the solvent, the process above was also repeated in conventional organic solvents. Water, as the solvent, provided the best yields compared to common organic solvents.[29a] The use of ultra pure (milli-Q) water yielded more product than using the double distilled (DD) water. All the synthesized compounds were characterized by IR, NMR and elemental analysis. The reaction mechanism[29a,b] of the product is proposed to involve the following tandem reactions: pyrazolone **6** formation by reaction between **1** and **2**, Knoevenagel condensation between **3** and **4** (**7**), Michael addition of **6**–**7**, followed by cyclization and tautomerization, (Scheme 2).



Scheme 2. The reaction mechanism of synthesized pyranopyrazoles **5a**–**p**.

In an aqueous medium, the four component reaction protocol developed in the present study offers a fast and eco-friendly method for the synthesis of pyranopyrazoles. The protocol also offers flexibility in tuning the molecular complexity and diversity in a single step.

3. Experimental

3.1. General

All melting points are uncorrected and were recorded on Melt-Temp II melting point apparatus. IR spectra were measured as KBr pellets on a Shimadzu DR-8001 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini at 300 or 400 MHz using TMS as an internal reference and $CDCl_3$, $(CD_3)_2CO$ or DMSO-d_6 as a solvent. Mass spectra were performed on a Shimadzu GCMS-QP 1000 mass spectrometer at 70 eV. The elemental analyses were carried out on a Perkin–Elmer 240C Microanalyzer. All compounds were checked for their purity on TLC plates.

3.2. Preparation of the magnetic Fe_3O_4 nanoparticles (MNPs)

Fe_3O_4-MNPs were prepared using simple chemical coprecipitation described in the literature[30] with little modification. Typically, 20 mmol of $FeCl_3\cdot 6H_2O$ and 10 mmol of $FeCl_2\cdot 4H_2O$ were dissolved in 75 ml of distilled water in a three-necked bottom (250 ml) under Air atmosphere for 1 h. Thereafter, under rapid mechanical stirring, 10 ml of NaOH (10 M) was added into the solution within 30 min with vigorous mechanical stirring and ultrasound treatment under continuous Ar atmosphere bubbling. After being rapidly stirred for 1 h, the resultant black dispersion was heated to 85 °C for 1 h. The black precipitate formed was isolated by magnetic decantation, exhaustively washed with double-distilled water until neutrality, and further washed twice with ethanol and dried at 60 °C in vacuum.

3.3. General procedure for pyranopyrazoles (5a–p)

To a stirred aqueous mixture of hydrazine hydrate, 96% **1** (1 mmol) and ethyl acetoacetate **2** (1 mmol), ketones/aldehyde **3** (1 mmol), malononitrile **4** (1 mmol) and Fe_3O_4 nanoparticles (6 mol %) as catalyst were added successively at room temperature under an open atmosphere with vigorous stirring. After completion of the reaction, the reaction mixture was dissolved in ethanol and then the catalyst was separated magnetically. The magnetic Fe_3O_4 nanoparticles were washed three to four times with ethanol and then dried at 50 °C for 5 h. The product obtained was pure by TLC and NMR spectroscopy. However, the products were further purified by recrystallization from ethanol.

3.3.1. 6-Amino-2,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile ***5a***.[28a] Yield 97%, mp 167–196 °C; IR (KBr): ν 3372 (groups of NH, NH_2), 2190.74 (CN) cm^{-1}; ^{1}H NMR: δ 2.08 (s, 3H); 4.44 (s, 1H); 6.94 (s br, 2H); 7.17–7.44 (m, 5H); ^{13}C NMR: δ 11.4; 24.8; 70.4; 112.2; 126.3; 127.2; 129.3; 130.9; 140.2; 143.9; 152.3; 160.0; MS, *m*/*z* calcd for $C_{14}H_{12}N_4O$ $[M+H]^+$: 253.1089; found, 253.1092 (Rel Int. 100%).

*3.3.2. 6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (****5b****).*[28a] Yield 95%, mp 170–172 °C; IR (KBr): ν 3483.78 (NH_2), 3255.25 (NH), 2191.7 (CN) cm^{-1}; ^{1}H NMR: δ 2.07 (s, 3H); 3.70 (s, 3H); 4.61 (s, 1H); 7.16 (d, J=8.7 Hz, 2H); 7.95 (d,

J=8.4 Hz, 2H); 8.61 (s br, 2H); ^{13}C NMR: δ 11.5; 24.5; 55.4; 70.4; 114.7; 115.2; 127.8; 129.2; 140.5; 143.8; 153.3; 159.9; 160.0; MS, *m*/*z* calcd for $C_{15}H_{14}N_4O_2$ $[M+H]^+$: 283.1195; found, 283.1196 (Rel Int. 100%).

*3.3.3. 6-Amino-4-(2,5-dimethoxyphenyl)-2,4-dihydropyrano-[2,3-c] pyrazole-5-carbonitrile (**5c**).*[28b] Yield 97%; mp 222–224 °C; IR (KBr): ν 3382, 3240, 2168, 1608, 1450 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ_H 1.80 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.00 (s, 1H, 4*H*), 5.59 (s, 2H, NH_2), 6.51–6.52 (m, 1H, Ar–H), 6.60–6.69 (m, 1H, Ar–H), 6.74 (s, 1H, Ar–H) (ppm); ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ_C 9.9, 28.6, 55.0, 55.8, 58.5, 97.3, 111.5, 113.9, 114.7, 120.5, 132.5, 135.6, 150.5, 153.3, 155.0, 160.8 (ppm); MS (ES^+) calcd for $C_{16}H_{16}N_4O_3$ 312.1; found *m*/*z* 313.0 $(M+H)^+$, 335.0 $(M+Na)^+$.

*3.3.4. 6-Amino-4-(3,4,5-trimethoxyphenyl)-2,4-dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (**5d**).*[28b] Yield 93%, mp 230–232 °C; IR (KBr): ν 3381, 3246, 2170, 1610, 1455 cm^{-1}; ^{1}H NMR (DMSO-d_6+$CDCl_3$, 400 MHz): δ_H 1.85 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.48 (s, 1H, 4H), 6.03 (s, 2H, NH_2), 6.37 (s, 2H, Ar–H) ppm. ^{13}C NMR (DMSO-d_6+$CDCl_3$, 100 MHz): δ_C 9.6, 36.8, 54.5, 60.3, 96.9, 104.1, 105.4, 106.6, 120.5, 135.8, 139.2, 152.5, 154.8, 160.6 ppm. I MS (EI^+): calcd for $C_{17}H_{18}N_4O_4$ 342.13; found 342.90 $(M+H)^+$, 365.10 $(M+Na)^+$.

*3.3.5. 6-Amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile (**5e**).*[28a] Yield 94%, mp 192–194 °C; IR (KBr): ν 3383, 3272, 2198, 1620, 1451 cm^{-1}; ^{1}H NMR: 2.04 (s, 3H); 4.73 (s, 1H); 6.22 (s br, 2H); 7.48 (d, *J*=8.1 Hz, 2H); 8.17 (d, *J*=8.1 Hz, 2H); ^{13}C NMR: 11.4; 23.3; 70.7; 112.8; 127.9; 126.0; 130.0; 135.5; 141.9; 150.4; 154.2; 160.4 MS (ESI): *m*/*z* calcd for $C_{14}H_{11}N_5O_3$ $[M+H]^+$: 298.0940; found, 298.0989.

*3.3.6. 6-Amino-3-methyl-4-(3-nitrophenyl)-2,4,dihydropyrano-[2,3-c]pyrazole-5-carbonitrile (**5f**).*[28a] Yield 96%, mp 214–216 °C; IR (KBr): ν 3385, 3278, 2189, 1622, 1456 cm^{-1}; ^{1}H NMR: δ 2.03 (s, 3H); 4.75 (s, 1H); 6.38 (s br, 2H); 7.54–7.65 (m, 2H); 8.02–8.12 (m, 1H); 8.12 (s, 1H); ^{13}C NMR: δ 11.9; 26.3; 71.4; 112.4; 121.3; 127.6; 129.6; 133.1; 135.2; 141.6; 147.2; 151.4; 154.0; 160.1; MS (ESI): *m*/*z* calcd for $C_{14}H_{11}N_5O_3$ $[M+H]^+$: 298.0940; found, 298.0989.

*3.3.7. 6-Amino-4-(4-chlorophenyl)-2,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (**5g**).*[28a] Yield 93%, mp 174–175 °C; IR (KBr): ν 3380, 3281, 2193, 1622, 1454 cm^{-1}; ^{1}H NMR: 11.82 (s, 3H); 4.58 (s, 1H); 6.69 (s br, 2H); 7.18 (d, *J*=8.1 Hz, 2H); 7.31 (d, *J*=8.1 Hz, 2H); ^{13}C NMR: 111.7; 24.4; 70.4; 112.1; 126.7; 127.6; 130.1; 134.2; 141.4; 142.1; 153.6; 159.3; MS (ESI): *m*/*z* calcd for $C_{14}H_{11}ClN_4O$ $[M+H]^+$: 287.0699; found, 287.0699.

*3.3.8. 6-Amino-4-(3-chlorophenyl)-2,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (**5h**).*[28a] Yield 94%, mp 158–160 °C; IR (KBr): ν 3387, 3289, 2199, 1622, 1454 cm^{-1}; ^{1}H NMR: 2.05 (s, 3H); 4.46 (s, 1H); 6.56 (br, 2H); 7.04–7.14 (m, 2H); 8.52 (s, 1H); 8.59–8.61 (m, 1H): ^{13}C NMR: 11.5; 24.4; 70.4; 101.4; 126.9; 127.9; 129.7; 130.6; 133.0; 134.2; 142.2; 148.8; 153.4; 159.1; MS (ESI): *m*/*z* calcd for $C_{14}H_{11}ClN_4O$ $[M+H]^+$: 287.0699; found, 287.0699.

*3.3.9. 6-Amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (**5i**).*[28a] Yield 96%, mp 222–224 °C; IR (KBr): cm^{-1}, 878, 1271, 1368, 1583, 1645, 2222, 3056, 3350, 3410; ^{1}H NMR: 2.00 (s, 3H); 4.46 (s, 1H); 6.44 (s br, 2H); 7.01 (d, *J*=8.4 Hz, 2H); 6.07 (d, *J*=8.1 Hz, 2H); ^{13}C NMR: 12.0; 25.0; 71.0; 113.6; 119.5; 127.0; 130.2; 141.5; 143.8; 153.4; 154.5; 159.1; MS *m*/*z* (%): *m*/*z* calcd for $C_{14}H_{12}N_4O_2$ $[M+H]^+$: 269.1038; found, 269.1052.

*3.3.10. 6-Amino-2,4-dihydro-4-(2-hydroxyphenyl)-3-methylpyrano [2,3-c]pyrazole-5-carbonitrile (**5j**).*[28a] Yield 93%, mp 208–210 °C; IR (KBr): cm^{-1}, 1580, 1640, 2221, 3054, 3355, 3404; ^{1}H NMR: 2.05 (s, 3H); 4.73 (s, 1H); 5.60 (br, 2H); 6.94–7.18 (m, 2H); 7.72–7.95 (m, 2H); ^{13}C NMR: 11.4; 19.0; 71.4; 112.3; 119.1; 119.6; 122.3; 124.5; 126.7; 129.4; 130.2; 142.0; 154.8; 155.6; 159.8; MS (ESI): *m*/*z* calcd for $C_{14}H_{12}N_4O_2$ $[M+H]^+$: 269.1038; found, 269.1058.

*3.3.11. 6-Amino-4-(4-bromophenyl)-2,4-dihydro-3-methylpyrano [2,3-c]pyrazole-5-carbonitrile (**5k**).*[28a] Yield 97%, mp 180–183 °C; IR (KBr): cm^{-1}, 1644, 2220, 3054, 3287, 3391; ^{1}H NMR: 1.91 (s, 3H); 4.55 (s, 1H); 6.45 (br, 2H); 7.06 (d, *J*=8.4 Hz, 2H); 7.43 (d, *J*=8.1 Hz, 2H), ^{13}C NMR: 11.15; 24.16; 70.76; 112.12; 119.12; 128.37; 130.19; 134.99; 141.98; 143.92; 153.72; 159.11; MS (ESI): *m*/*z* calcd for $C_{14}H_{11}BrN_4O$ $[M+H]^+$: 331.0194; found, 331.0198.

*3.3.12. 6-Amino-4-(4-fluorophenyl)-2,4-dihydro-3-methylpyrano [2,3-c]pyrazole-5-carbonitrile (**5l**).*[28a] Yield 96%, mp 170–171 °C; IR (KBr): cm^{-1}, 1640, 2222, 3055, 3280, 3388; ^{1}H NMR: 1.97 (s, 3H); 4.58 (s, 1H); 6.47 (br, 2H); 7.01 (d, *J*=8.1 Hz, 2H); 7.18 (d, *J*=8.1 Hz, 2H); ^{13}C NMR: 12.0; 24.9; 70.9; 112.2; 126.4; 127.6; 130.5; 134.2; 141.4; 142.5; 154.5; 159.1; MS (ESI): *m*/*z* calcd for $C_{14}H_{11}FN_4O$ $[M+H]^+$: 272. 0995; found, 272.0998.

*3.3.13. 6-Amino-4-(4-(dimethylamino)phenyl)-2,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (**5m**).*[28a] Yield 91%, mp 162–165 °C; IR (KBr): cm^{-1}, 1641, 2199, 3050, 3284, 3408; ^{1}H NMR: 2.05 (s, 3H); 2.45 (s, 6H); 4.55 (s, 1H); 6.49 (s br, 2H); 6.72 (d, *J*=8.1 Hz, 2H); 7.71 (d, *J*=8.1 Hz, 2H); ^{13}C NMR: 11.5; 25.6; 40.8; 71.6; 111.1; 114.8; 126.9; 130.0; 137.5; 141.0; 153.0; 157.1; 159.4; MS (ESI): *m*/*z* calcd for $C_{16}H_{17}N_5O$ $[M+H]^+$: 296.1511; found, 296.1521.

*3.3.14. 2-[1-(3-Methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)-1-phenyl-ethyl]-malononitrile (**5n**).*[28a] Yield 90%, mp 200–202 °C; IR (KBr): ν 3380, 3320, 3190 (NH and NH_2), 2199 (CN) cm^{-1}; ^{1}H NMR: δ 1.72 (s, 3H); 2.12 (s, 3H); 6.33 (s br, 2H); 7.18–7.23 (m, 1H); 7.28–7.35 (m, 2H); 7.37–7.48 (m, 2H); ^{13}C NMR: δ 13.4; 27.8; 36.9; 75.4; 115.8; 122.6; 125.2; 129.6; 130.8; 140.4; 146.5; 152.3; 155.8; MS, *m*/*z* calcd for $C_{15}H_{14}N_4O$ $[M+H]^+$: 267.1245; found, 267.1248.

*3.3.15. 6-Amino-4-(4-bromophenyl)-2,4-dihydro-3,4-dimethylpyrano [2,3-c]pyrazole-5-carbonitrile (**5o**).*[28a] Yield 88%, mp 180–181 °C; IR (KBr): ν 3472.2 (NH), 3240 (NH_2), 2185.9 (CN) cm^{-1}; ^{1}H NMR: δ 1.78 (s, 3H); 2.15 (s, 3H); 6.58 (s br, 2H); 7.36 (d, *J*=8.4 Hz, 2H); 7.64 (d, *J*=8.7 Hz, 2H); ^{13}C NMR: δ 12.2; 26.7; 37.0; 75.4; 116.8; 120.2; 128.5; 130.8; 133.1; 140.5; 145.6; 152.5; 155.8; *m*/*z* calcd for $C_{15}H_{13}BrN_4O$ $[M+H]^+$: 345.0351; found, 345.0355 (Rel Int. 100%).

*3.3.16. 6-Amino-2,4-dihydro-3-methyl-4,4-diphenylpyrano[2,3-c]pyrazole-5-carbonitrile (**5p**).*[28a] Yield 91%, mp 210–211 °C; IR (KBr): ν 3402 (NH), 3240 (NH_2), 2222 (CN) cm^{-1}; ^{1}H NMR: 2.25 (s, 3H); 6.33 (br, 2H); 6.82 (m, 2H); 7.20 (m, 4H); 7.61 (m, 4H); ^{13}C NMR: 12.2; 49.4; 69.2; 115.7; 123.4; 127.3; 128.6; 131.2; 142.0; 147.4; 151.2; 159.9; MS, *m*/*z* (%), calcd for $C_{20}H_{16}N_4O$ $[M+H]^+$: 329.1402; found, 329.1403.

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