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ORGANIC CHEMISTRY | RESEARCH ARTICLE

A highly efficient and sustainable synthesis of dihydropyrano[2,3-c]pyrazoles using polystyrene-supported p-toluenesulfonic acid as reusable catalyst

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Abstract: A simple, expedient, and ecofriendly protocol for the one-pot synthesis of dihydropyrano[2,3-c]pyrazole derivatives using polystyrene-supported p-toluenesulfonic acid as a highly active and reusable heterogeneous catalyst in water has been developed. The core advantages of the present protocol are excellent yields, mild reaction conditions, broad substrate scope, and easy work-up procedure. This new protocol exemplifies the operationally simple synthesis of dihydropyrano[2,3-c]pyrazoles in a time-efficient and cost-effective manner.

Subjects: Medicinal & Pharmaceutical Chemistry; Organic Chemistry; Polymers & Plastics

Keywords: dihydropyrano[2,3-c]pyrazoles; polystyrene-supported p-toluenesulfonic acid; green chemistry

1. Introduction

The heterocyclic pyranopyrazole motif is a privileged pharmacophore scaffold found in many biologically active compounds of diverse origins, from natural products to synthetic sources. Among these, a large number of dihydropyrano[2,3-c]pyrazole derivatives have been reported to exhibit



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PUBLIC INTEREST STATEMENT

In this article, we described the operationally simple synthesis of bioactive dihydropyrano[2,3-c]pyrazoles using polystyrene-supported p-toluenesulfonic acid as a highly active and reusable heterogeneous catalyst in water. Remarkable advantages of the method include excellent yields, mild reaction conditions, broad substrate scope, easy work-up procedure, shorter reaction time, and cost-effectiveness. This green protocol may serve as a key for developing diverse molecules for medicinal chemistry.

diverse biological activities such as antimicrobial, anti-inflammatory, analgesic, antitumor, and molluscicidal activities (Abdelrazek, Metz, & Metwally, 2006; El-Tamany, El-Shahed, & Mohamed, 1999; Kuo, Huang, & Nakamura, 1984; Siddekha, Nizam, & Pasha, 2011; Wang et al., 2000; Zaki, Soliman, Hiekal, & Rashad, 2006). Moreover, they also act as potential inhibitors of human chk1 kinase (Foloppe et al., 2006).

A four-component coupling of aromatic aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate has been used to create dihydropyrano[2,3-c]pyrazole derivatives. The previously reported methods include catalysts, such as heteropolyacids, cocamidopropyl betaine, triethyl ammonium bromide, piperazine, piperidine, polyphosphoric acid supported on $\text{Ni}_{0.5}\text{Zn}_{0.5}\text{Fe}_2\text{O}_4$ nanoparticles, disulphonic acid imidazolium chloroaluminate, sodium benzoate, and per-6-amino- β -cyclodextrin (Chavan, Babar, Hoval, & Bandgar, 2011; Kanagaraj & Pitchumani, 2010; Kiyani, Samimi, Ghorbani, & Esmaili, 2013; Kumar et al., 2013; Moeinpour & Khojastehnezhad, 2014; Moosavi-Zare et al., 2013; Peng, Song, & Dou, 2006; Tamaddon & Alizadeh, 2014; Vasuki & Kumaravel, 2008). Most of these synthetic protocols reported suffer from high catalyst loading, prolonged reaction time, harsh reaction conditions, poor recyclability, and low yields. Therefore, the development of a new catalytic route which implements green chemistry practices is an active area of research for synthetic methodologies.

The desire for the greener synthesis of biologically active molecules has stimulated the progress of polymer-supported catalytic reactions which endeavor to emulate nature in the construction of intricate molecules. The use of polymer-supported catalysts in organic synthesis offer many advantages in sustainable chemistry because they are inexpensive, readily available, non-toxic, stable, easier for handling, non-corrosive, retrievable, and show high selectivity. They also provide tunable Lewis acidity along with easier work-up procedures for reactions (Bakherad, Bahramian, & Jajarmi, 2014; Chang, Lee, & Bae, 2014; Chen, Sun, Wang, & Cheng, 2012; Font, Jimeno, & Pericàs, 2006; Hodge, 1997; Jadhav et al., 2013; Matsukawa, Fukazawa, & Kimura, 2014; Matsukawa, Harada, & Yasuda, 2012; Ohtaka et al., 2011; Rahmatpour, 2012; Rahmatpour & Mohammadian, 2013; Schweizer, Becht, & Le Drian, 2010; Xu, Shi, & Wang, 2013). Absence of transition metals makes these protocols attractive for the synthesis of pharmaceutical products. Polystyrene (PS) resin is one of the most commonly used polymer supports in organic synthesis. Recently, several PS-supported catalysts such as GaCl_3 , diethanolamine-based ionic liquids, PPh_3 , Pd catalyst, oligoethylene glycols, DABCO, TBD, nanoparticles, superacidic fluoroalkyl sulfonic acid, and hydroxyproline, TiCl_4 , etc. bring various organic transformations (Chang et al., 2014; Chen et al., 2012; Font et al., 2006; Jadhav et al., 2013; Matsukawa et al., 2012, 2014; Ohtaka et al., 2011; Rahmatpour, 2012; Rahmatpour & Mohammadian, 2013; Schweizer et al., 2010; Xu et al., 2013). Among various types of catalysts, PS-supported p-toluenesulfonic acid (PS-PTSA) is a highly crosslinked polystyrene resin functionalized with a p-toluenesulfonic acid end group. The use of PS-PTSA as catalyst for the synthesis of biologically active hydroxyproline derivatives, diversified pyrrole derivatives, mannich-type reactions, hydrolysis of thioesters and transprotection of thiols from thioesters to thioethers, and nucleophilic substitution of alcohols have been reported (Iimura, Manabe, & Kobayashi, 2003; Iimura, Nobutou, Manabe, & Kobayashi, 2003; Reddy & Jeong, 2012; Sanz, Martinez, Miguel, Alvarez-Gutierrez, & Rodriguez, 2006; Shinde, Lee, Jeong, & Jeong, 2015). To the best of our knowledge, PS-PTSA has not yet been used for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives.

In continuation of our effort toward the development of ecofriendly synthetic protocols, (Gujar, Chaudhari, Kawade, & Shingare, 2014; Labade, Pawar, & Shingare, 2011; Labade, Shinde, & Shingare, 2013; Niralwad, Shingate, & Shingare, 2011; Shinde, Kategaonkar, Shingate, & Shingare, 2011) it was thought worthwhile to disclose a new and expeditious route for the synthesis of dihydropyrano[2,3-c]pyrazoles using polystyrene-supported p-toluenesulfonic acid due to its many practical benefits which attracted our interest.

2. Results and discussion

In search of the best experimental reaction conditions for the synthesis of dihydropyrano[2,3-*C*]pyrazoles, reaction of *p*-methylbenzaldehyde (**1a**), malononitrile (**2**), ethylacetoacetate (**3**), and hydrazine hydrate (**4**) was selected as a model reaction (Scheme 1).

Initially, in absence of a catalyst, trace amount of product was detected at room temperature, and the reaction proceeds at reflux with low yield (24%) in aqueous medium (Table 1, entries 1–2). During this investigation, efforts were mainly focused on polystyrene-supported catalysts in aqueous media. Initially, we studied the effect of PS on reaction, but the corresponding product **5a** was obtained in 24% yield (Table 1, entry 3). From further studies, it was observed that *p*-toluenesulfonic acid (PTSA), triethylamine (TEA), and diisopropylethylamine (DIEA) gave the desired product albeit in low yields, i.e., 58, 49, 35% respectively (Table 1, entry 4–6). In contrast, it was exciting to find PS-PTSA accelerated the model reaction to afford the desired product in 91% yield (Table 1, entry 8) at reflux. Encouraged by these results, we then investigated polystyrene-supported base catalysts. For this purpose, when we utilized polystyrene-supported triethylamine (PS-TEA) and polystyrene-supported diisopropylethylamine (PS-DIEA) in the model reaction, 74% and 69% yield of the desired product was obtained (Table 1, entries 9–10), respectively. The catalytic activity of PS-TEA and PS-DIEA was significantly lower than that of PS-PTSA. Therefore, PS-PTSA was chosen as catalyst for the synthesis of dihydropyrano[2,3-*c*]pyrazoles, despite the fact that we compare polystyrene-supported acid and base catalyst at every step. Next we planned to optimize its loading since catalyst concentration is a significant factor that completely affects the reaction rate and product yield. To study

Scheme 1. Standard model reaction.

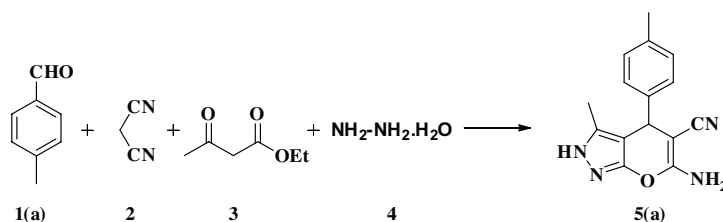


Table 1. Screening of catalyst and effect of concentration of catalyst on model reaction^a

Entry	Catalyst	Temperature (°C)	Concentration of catalyst (mol%)	Time (min)	Yield ^b (%)
1	—	RT	—	180	Trace
2	—	Reflux	—	20	24
3	PS	Reflux	15 (mg)	20	24
4	PTSA	Reflux	15	20	58
5	TEA	Reflux	15	20	49
6	DIEA	Reflux	15	20	35
7	PS-PTSA	RT	15 (mg)	100	43
8	PS-PTSA	Reflux	15 (mg)	20	91
9	PS-TEA	Reflux	15 (mg)	20	74
10	PS-DIEA	Reflux	15 (mg)	20	69
11	PS-PTSA	Reflux	1 (mg)	20	55
12	PS-PTSA	Reflux	5 (mg)	20	68
13	PS-PTSA	Reflux	10 (mg)	20	83
14	PS-PTSA	Reflux	20 (mg)	20	94
15	PS-PTSA	Reflux	25 (mg)	20	94

^aReaction condition: 4-methylbenzaldehyde (2 mmol), malononitrile (2 mmol), ethylacetoacetate (2mmol), hydrazine hydrate (2 mmol), water (10 ml).

^bIsolated yields.

this, the reaction was performed at different concentrations of PS-PTSA, i.e. 1, 5, 10, 15, 20, and 25 mg, and gave the product in 55, 68, 83, 91, 94, and 94% yield, respectively (Table 1, entries 8, 11–15). Thus, it was clear that reaction rate increased with increasing catalyst concentration up to 20 mg without any significant difference on further increasing the catalyst concentration. It means 20 mg of catalyst was sufficient for catalyzing the reaction effectively.

Different solvents were also examined using polymer-supported catalysts on model reaction at reflux for 20 min to obtain desired product **5a** in 21–94% yield (Table 2, entries 1–7). It can be seen that the reaction using water as the solvent resulted in higher yield (Table 2, entry 1) for PS-PTSA and reaction using ethanol as the solvent led to higher yield (Table 2, entry 2) for PS-TEA and PS-DIEA than those using other solvents and solvent-free reactions. Furthermore, the reaction efficiency was also assessed with varying reaction temperatures ranging from RT to reflux temperature (table 2, entries 9–15) of the respective solvent for catalysts, finding that the yield of product **5a** was improved as the temperature was increased. Therefore, the best reaction conditions were obtained when respective solvent of catalysts was used at reflux temperature (Table 2, entries 1 and 2).

To further extend the scope of PS-PTSA-catalyzed reaction, we screened various electronically divergent aryl aldehydes under the optimized reaction conditions which lead to dihydropyrano[2,3-*c*]pyrazole derivatives in good-to-excellent yields, i.e. 82–94% (Table 3, entries 1–14). Interestingly, some heteroaryl aldehydes also underwent the reaction smoothly (Table 3, entries 15–16). Formation of the products were confirmed by ¹H NMR, ¹³C NMR, and mass spectrometry.

Next, a comparative catalytic efficiency of PS-PTSA, PS-TEA, and PS-DIEA for the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives were studied by performing a series of reactions using each of the catalysts with reference to their optimized reaction condition (Table 4). PS-TEA-catalyzed reactions in ethanol as solvent did show comparable efficiency with maximum yields almost equal to PS-PTSA-catalyzed reactions in water. It was observed that the reactions performed with PS-DIEA in ethanol showed low efficiency. The comparative catalytic activity was found to display an order of PS-PTSA > PS-TEA > PS-DIEA in the reaction.

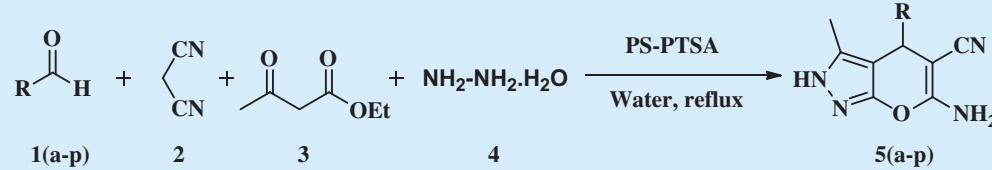
Table 2. Screening of solvents and effect of temperature on model reaction^a

Entry	Solvent	Temperature (°C)	Time (min)	Yield ^b (%)		
				PS-PTSA	PS-TEA	PS-DIEA
1	Water	Reflux	20	94	82	76
2	Ethanol	Reflux	20	61	88	81
3	Methanol	Reflux	20	66	70	62
4	Acetone	Reflux	20	54	42	28
5	DCM	Reflux	20	43	30	21
6	THF	Reflux	20	50	55	47
7	Acetonitrile	Reflux	20	68	63	60
8	–	100	20	59	65	50
9	Water	RT	100	48	–	–
10	Water	40	20	54	–	–
11	Water	60	20	65	–	–
12	Water	80	20	82	–	–
13	Ethanol	RT	100	–	40	33
14	Ethanol	40	20	–	51	45
15	Ethanol	60	20	–	67	62

^aReaction condition: 4-methylbenzaldehyde (2 mmol), malononitrile (2 mmol), ethyl acetoacetate (2 mmol), hydrazine hydrate (2 mmol), catalysts (20 mg), solvent (10 ml).

^bIsolated yields.

Table 3. Synthesis of dihydropyrano[2,3-C]pyrazoles^a



Entry	Product	R	Time (min)	Yield ^b (%)	M.P. ^c (°C)
1	5a	4-Me-Ph	20	94	175-177
2	5b	Ph	15	92	164-166
3	5c	4-OMe-Ph	20	91	211-213
4	5d	4-F-Ph	15	90	169-171
5	5e	4-Br-Ph	15	89	176-178
6	5f	4-Cl-Ph	15	93	244-246
7	5g	4-OH-Ph	20	91	222-224
8	5h	4-(Me ₂ N)-Ph	15	90	225-227
9	5i	3,4-(OMe) ₂ -Ph	20	88	188-190
10	5j	3-Cl-Ph	15	90	159-161
11	5k	2-Cl-Ph	20	89	144-146
12	5l	3-NO ₂ -Ph	20	86	190-192
13	5m	2-NO ₂ -Ph	20	82	221-223
14	5n	2-OH-Ph	20	85	208-210
15	5o	2-Thienyl	25	87	223-225
16	5p	2-Furanyl	25	88	176-178

^aReaction condition: aldehydes (2 mmol), malononitrile (2 mmol), ethylacetoacetate (2 mmol), hydrazine hydrate (2 mmol), PS-PTSA (20 mg), water (10 ml).

^bIsolated yields.

^cMelting points match with literature values.

The reusability of polystyrene-supported catalysts were also performed under the optimized conditions of respective polystyrene-supported catalysts for the synthesis of **5a**. The recovered polystyrene-supported crude catalyst after completion of reaction was washed with diethyl ether to obtain pure catalyst, dried in an oven, and reused for further catalytic cycles directly. It was observed that the catalysts maintained their activity with no significant drop in the yield up to five runs (Figure 1). The gradual decrease in catalytic activity may be due to blocking of some active sites on the catalyst surface by the residues of the reaction.

Figure 1. Recycling and reuse of catalyst.

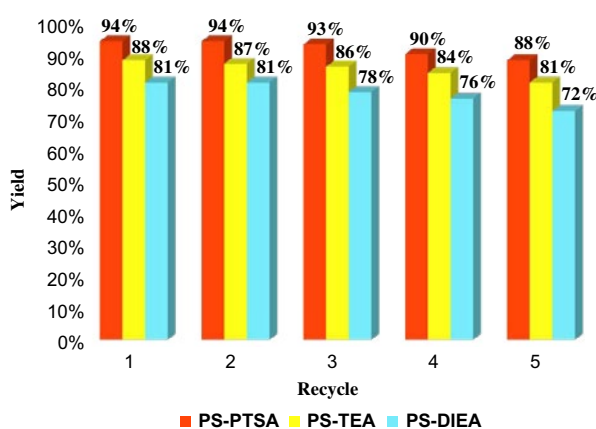
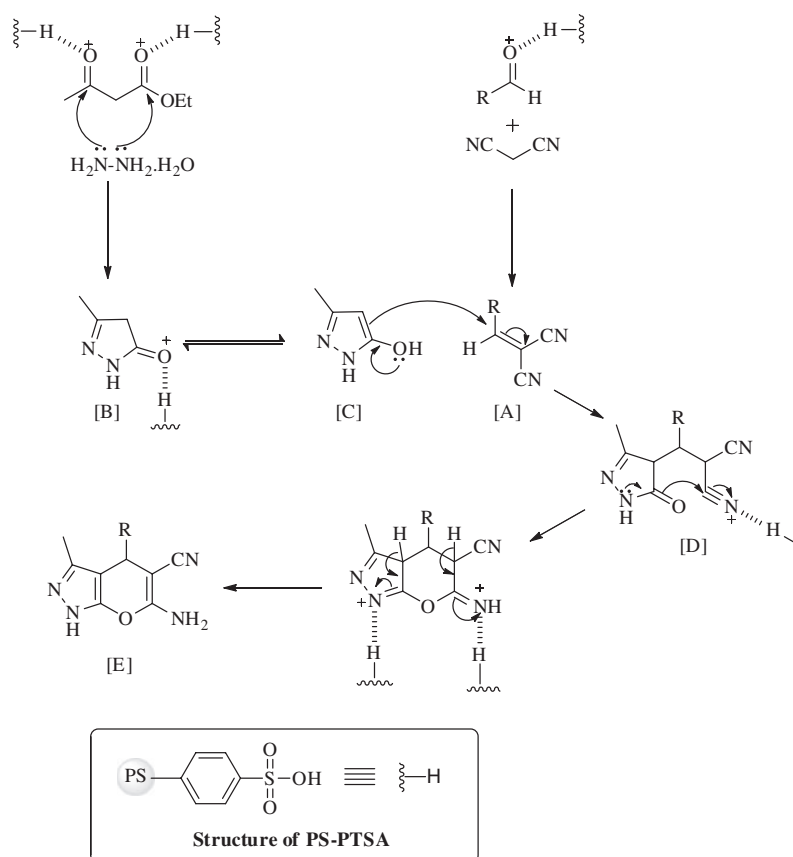


Figure 2. A plausible mechanism of reaction.



Mechanistically, the reaction occurs via initial formation of arylidenemalononitrile [A] by the Knoevenagel condensation between PS-PTSA activated carbonyl group of aldehyde and malononitrile and pyrazolone [C] by the nucleophilic attack of $-\text{NH}_2$ groups of hydrazine on PS-PTSA activated carbonyl groups of ethyl acetoacetate. Finally, Michael addition of pyrazolone [C] to arylidenemalononitrile [A] leads to formation of intermediates [D], which on further intramolecular cyclization yield pyranopyrazole [E] (Figure 2).

3. Conclusion

In conclusion, polystyrene-supported p-toluenesulfonic acid was found to be highly efficient heterogeneous catalyst in aqueous media for the one-pot reaction of aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate to afford the corresponding dihydropyrano[2,3-c]pyrazole derivatives. Also, comparative study of PS-PTSA, PS-TEA, and PS-DIEA has been carried out which display catalytic activity in order of PS-PTSA > PS-TEA > PS-DIEA in the reaction. The present protocol offers several remarkable advantages, such as mild reaction conditions, shorter reaction time, excellent yield of products, broad substrate scope, simple operational procedure, high catalytic activity. Furthermore, catalyst can be easily recovered and reused without a significant decrease in catalytic activity.

4. Experimental

4.1. General experimental procedure for the synthesis of dihydropyrano[2,3-c]pyrazoles 5(a-p) using PS-PTSA

A mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), ethyl acetoacetate **3** (2 mmol), hydrazine hydrate **4** (2 mmol), and PS-PTSA (20 mg) in water (10 mL) was stirred vigorously at reflux. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane, 2:8). After completion of the reaction (Table 3), the reaction mixture was cooled to RT and ethyl acetate (30 ml) was added and

filtered to recover the catalyst. Thus, obtained portion of organic layer (ethyl acetate) was dried over Na_2SO_4 and concentrated on rotary evaporator under reduced pressure to achieve the desired product. This crude product (5a) was purified by recrystallization from 10% aqueous ethanol as a solvent.

4.2. General experimental procedure for the synthesis of dihydropyrano[2,3-*c*]pyrazoles 5(a-p) using PS-TEA

A mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), ethyl acetoacetate **3** (2 mmol), hydrazine hydrate **4** (2 mmol), and PS-TEA (20 mg) in ethanol (10 mL) was stirred vigorously at reflux. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane, 2:8). After completion of the reaction (Table 4), ethanol was added at 60°C to dissolve the product completely and filtered to recover the catalyst. The ethanolic solution was concentrated on rotary evaporator under reduced pressure and allowed to stand to get crystalline product.

4.3. General experimental procedure for the synthesis of dihydropyrano[2,3-*c*]pyrazoles 5(a-p) using PS-DIEA

A mixture of aldehyde **1** (2 mmol), malononitrile **2** (2 mmol), ethyl acetoacetate **3** (2 mmol), hydrazine hydrate **4** (2 mmol), and PS-DIEA (20 mg) in ethanol (10 mL) was stirred vigorously at reflux. Progress of the reaction was monitored by TLC (ethyl acetate:*n*-hexane, 2:8). After completion of the reaction (Table 4), ethanol was added at 60°C to dissolve the product completely and filtered to recover the catalyst. The ethanolic solution was concentrated on rotary evaporator under reduced pressure and allowed to stand to get crystalline product.

4.4. Spectral data for representative compound

6-amino-1,4-dihydro-4-(4-methylphenyl)-3-methylpyrano[2,3-*c*]pyrazole-5-carbonitrile (**5a**): ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.78 (s, 3H, -CH₃), 2.26 (s, 3H, -CH₃), 4.54 (s, 1H), 6.82 (s, 2H, -NH₂), 7.04 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 12.06 (s, 1H, -NH); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 9.80, 20.67, 35.88, 57.37, 97.76, 120.88, 127.40, 129.03, 135.50, 135.75, 141.53, 154.8, 160.81; ES-MS: *m/z* 265.2 [M-H]⁺.

Table 4. Comparative study of PS-PTSA, PS-TEA and PS-DIEA catalysts

Entry	Product	R	Time (min)	Yield ^a (%)		
				PS-PTSA	PS-TEA	PS-DIEA
1	5a	4-Me-Ph	20	94	88	81
2	5b	Ph	15	92	90	85
3	5c	4-OMe-Ph	20	91	83	78
4	5d	4-F-Ph	15	90	86	75
5	5e	4-Br-Ph	15	89	82	78
6	5f	4-Cl-Ph	15	93	92	87
7	5g	4-OH-Ph	20	91	85	73
8	5h	4-(Me ₂ N)-Ph	15	90	80	74
9	5i	3,4-(OMe) ₂ -Ph	20	88	84	73
10	5j	3-Cl-Ph	15	90	85	79
11	5k	2-Cl-Ph	20	89	82	70
12	5l	3-NO ₂ -Ph	20	86	80	77
13	5m	2-NO ₂ -Ph	20	82	77	71
14	5n	2-OH-Ph	20	88	76	76
15	5o	2-Thienyl	25	87	81	70
16	5p	2-Furanyl	25	88	80	65

^aIsolated yields.

6-amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (**5c**): ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.76 (s, 3H, -CH $_3$), 3.71 (s, 3H, -OCH $_3$), 4.51 (s, 1H), 6.79 (s, 2H, -NH $_2$), 6.84 (d, 2H, J = 8.0 Hz), 7.04 (d, 2H, J = 8.0 Hz), 12.04 (s, 1H, -NH); ^{13}C NMR (DMSO- d_6 , 100 MHz): δ 11.1, 24.6, 56.2, 62.0, 114.4, 114.9, 127.5, 128.7, 140.0, 143.4, 152.9, 158.8, 166.3; ES-MS: m/z 283.2 [M + H] $^+$.

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