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## Synthesis of 6-Amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in the Presence of Reusable Catalyst "Cellulose"

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Cellulose was applied as a reusable and green catalyst for the facile four-component synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives using hydrazine monohydrate, ethyl acetoacetate, malononitrile and aryl aldehydes, under solvent-free and thermal conditions. The use of non-toxic and inexpensive catalyst, short reaction time, clean work-up and good yields of the products are advantages of this method.

**Keywords:** Cellulose, Reusable catalyst, 1,4-Dihydropyrano[2,3-*c*]pyrazole, Solvent-free condition, Aryl aldehyde, Hydrazine monohydrate

### INTRODUCTION

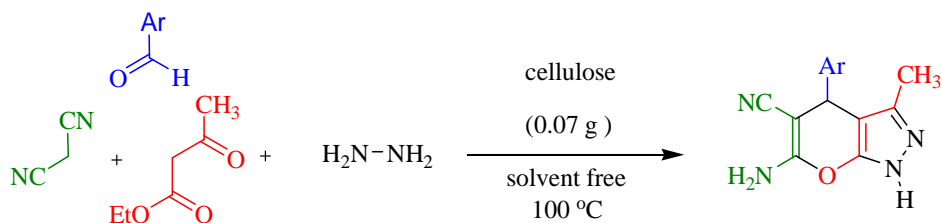
Polymer-inorganic particle composites have made considerable interest due to their combined properties derived from individual materials [1]. Cellulose is the structural component of primary and secondary cell walls of plants as minor and major constituents, respectively. As a chemical raw material, it is generally well known that it has been employed in the form of fibers or derivatives for nearly 150 years for a wide spectrum of products and materials in daily life. Multicomponent reactions (MCRs) have attracted lots of attention because of their exceptional synthetic and practical efficiency [2,3]. One of the important examples of MCRs is three-component synthesis of dihydropyrano[2,3-*c*]pyrazoles which are potential inhibitors of human Chk1 kinase [4]. Dihydropyrano[2,3-*c*]pyrazoles have been reported in literature as biologically important compounds possessing anticancer [5], antimicrobial [6], insecticidal [7] and molluscicidal activities [8,9]. Recently, some new catalysts have been

reported to facilitate four-component synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives such as TEAA (triethylammonium acetate) [10],  $H_3PO_4/Al_2O_3$  [11],  $\gamma$ -alumina, [12] nanosized magnesium oxide [13], trichloroacetic acid [14], ceric sulfate [14], imidazole [15], L-proline [16], ultra sound irradiation [17]. In continuation to our synthetic investigations [18-21], we describe a very green four-component synthesis for preparation of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles using cellulose as a reusable and biodegradable catalyst (Scheme 1).

### EXPERIMENTAL

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a Bruker Avance DRX 300 MHz instrument. The spectra were measured in  $DMSO-d_6$  relative to TMS (0.00 ppm). IR spectra were recorded on a

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*Scheme 1.* Synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles under thermal conditions in the presence of cellulose as a biodegradable and recover catalyst

JASCO FT-IR 460 plus spectrophotometer. Melting points were determined on an Electrothermal 9100 apparatus. TLC was performed on Silica-gel Polygram SILG/UV 254 plates.

### General Procedure for the Synthesis of 6-Amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile Derivatives

A mixture of hydrazine monohydrate (1 mmol) and ethylacetoacetate (1 mmol) was stirred at 0 °C, until 3-methyl-2-pyrazolin-5-one was precipitated and its formation completed (5 min). Then, it was warmed to room temperature. Next, aryl aldehyde (1 mmol), malononitrile (1 mmol) and cellulose (0.07 g) were added to mixture at 100 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and the crude solid product was dissolved in acetone. The mixture was filtered for separation of the catalyst. The catalyst was washed with (2 × 5 ml) of acetone. The recovered catalyst was dried in vacuum and used for the subsequent catalytic runs. The filtrate solution was evaporated and the crude product was recrystallized from ethanol to afford the pure pyranopyrazole derivatives in high yields. The desired pure products were characterized by comparison of their physical data.

All of the products are known. Selected spectroscopic data of some products are given below:

**6-Amino-1,4-dihydro-3-methyl-4-(2-chlorophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (Table 2, Entry 6).** IR (KBr,  $\text{cm}^{-1}$ ): 3776, 3391, 3357, 3314, 3169, 2803, 2710, 2351, 2190, 1489, 1408, 1350, 1052, 763;  $^1\text{H NMR}$  (300

MHz, (DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 1.78 (s, 3H, CH<sub>3</sub>), 5.05 (s, 1H, CH), 6.95 (s, 2H, NH), 7.15-7.57 (m, 4H), 12.14 (s, 2H, NH<sub>2</sub>).

**6-Amino-1,4-dihydro-3-methyl-4-(4-bromophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (Table 2, Entry 11).** IR (KBr,  $\text{cm}^{-1}$ ): 3470, 3227, 3120, 2194, 1735, 1650, 1595, 1560, 1401, 1353, 1107, 883, 810, 744, 543;  $^1\text{H NMR}$  (300 MHz, (DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 1.60 (s, 3H, CH<sub>3</sub>), 4.69 (s, 1H, CH), 6.96 (s, 2H, NH<sub>2</sub>), 7.15 (d, *J* = 8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H), 12.16 (s, 1H, NH).

**6-Amino-1,4-dihydro-3-methyl-4-(4-hydroxyphenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (Table 2, Entry 12).** IR (KBr,  $\text{cm}^{-1}$ ): 3766, 3491, 3357, 3214, 3169, 2803, 2710, 2351, 2190, 1489, 1408, 1350, 1052, 763;  $^1\text{H NMR}$  (300 MHz, (DMSO-*d*<sub>6</sub>):  $\delta$  (ppm) = 1.77 (s, 3H, CH<sub>3</sub>), 4.45 (s, 1H, CH), 6.62-6.98 (m, 6H, Ar, NH<sub>2</sub>), 9.23 (s, 1H, OH), 12.02 (s, 1H, NH).

## RESULTS AND DISCUSSION

To synthesize 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in a more efficient way, minimizing the time and amount of catalyst, the reaction of hydrazine monohydrate, ethylacetoacetate, benzaldehyde and malononitrile was selected as a model system. Catalyst reactivity was investigated at different temperatures (80, 100, 110 and 120 °C). The best result was obtained under molar ratios (1.0:1.0:1.0:1.0) of each reactants, in the presence of Cellulose (0.07 g) at 100 °C under solvent-free condition (Table 1).

**Table 1.** Optimization of Amount of Catalyst in the Synthesis of 6-Amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles under Thermal Solvent-free Condition

Entry	Catalyst (g)	Time (min)	Isolated yield (%)
1	0.03	25	70
2	0.05	20	75
<b>3</b>	<b>0.07</b>	<b>15</b>	<b>96</b>
4	0.10	13	96

**Table 2.** Preparation of 6-Amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles

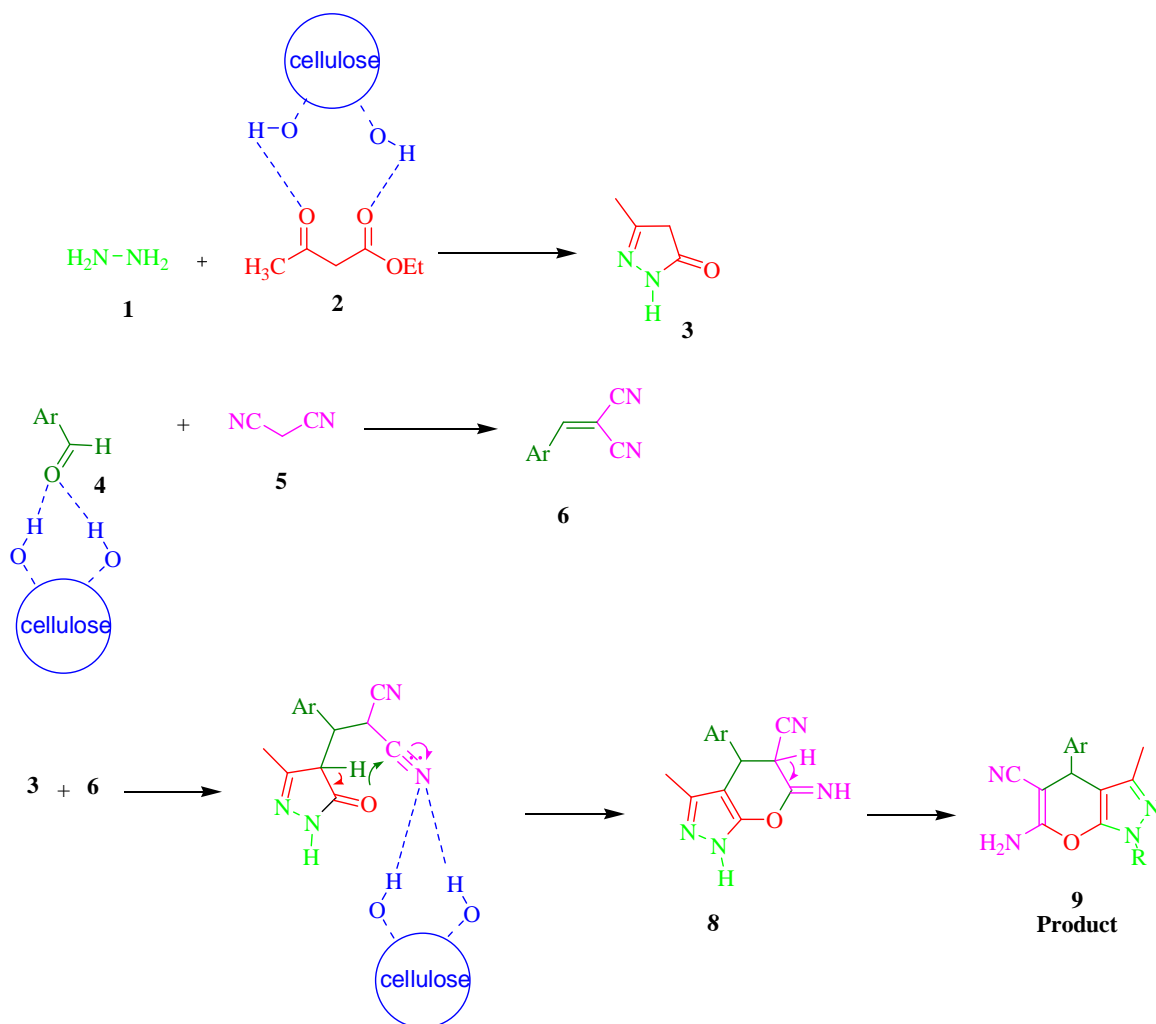
Entry	Ar	Time (min)	Isolated yield (%)	Found M.P.(°C)/[Lit.M.P (°C)][10-12]
1	C <sub>6</sub> H <sub>5</sub>	15	96	243-245/[244-246]
2	4-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	15	95	165-168/[167-169]
3	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	10	92	218-220/[220-222]
4	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	10	92	247-249/[249-252]
5	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	16	92	190-192/[193-195]
6	2-ClC <sub>6</sub> H <sub>4</sub>	17	90	143-145/[145-147]
7	4-ClC <sub>6</sub> H <sub>4</sub>	18	95	233-235/[234-236]
8	2,5-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	25	85	209-211/[210-212]
9	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	15	85	235-237/[235-237]
10	4-MeC <sub>6</sub> H <sub>4</sub>	20	84	204-206/[206-208]
11	4-Br	10	90	213-215/[213-215]
12	4-OH	10	95	218-220/[219-221]

With respect to optimized reaction, the scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted 6-amino-4-aryl-3-methyl-1,4-dihydropyran[2,3-*c*]pyrazole-5-carbonitriles using hydrazine monohydrate, ethyl acetoacetate, aryl aldehydes and malononitrile. The results are summarized in Table 2.

As can be seen, a variety of aryl aldehydes including electron withdrawing or releasing substituents (*ortho*-, *meta*- and *para*-substituted) participated well in this reaction and gave 6-amino-4-aryl-3-methyl-1,4-dihydropyran[2,3-*c*]pyrazole-5-carbonitriles in good to excellent yields.

As previously mentioned in literature [15,16], we proposed speculative mechanism for the synthesis of 1,4-dihydropyran[2,3-*c*]pyrazole in the presence of cellulose as a catalyst. First, pyrazolone **3** was formed by the reaction between **1** and **2**, Knoevenagel condensation between **4** and **5** produced 2-benzylidenemalononitrile **6**, Michael addition of **3** with **6**, and followed cyclization and tautomerization afforded the corresponding product. Cellulose can catalyze the probable reactions activated by hydrogen bonds. (Scheme 2).

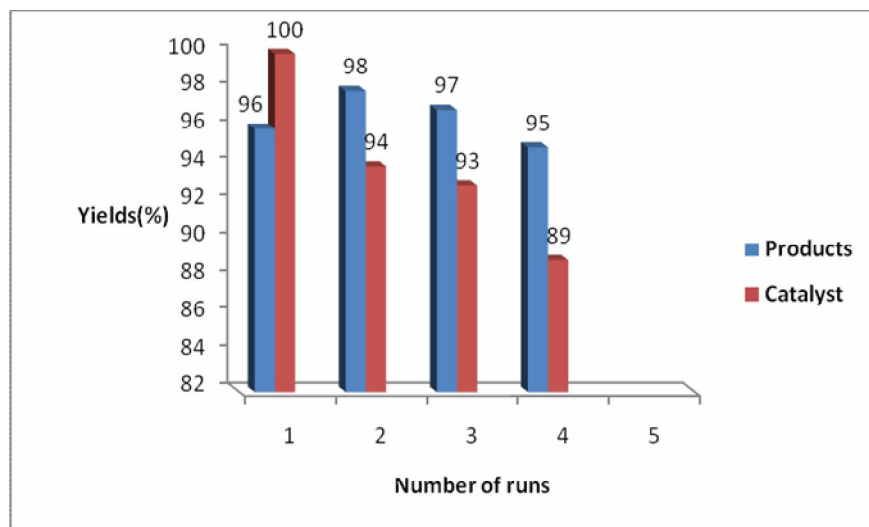
The accessibility of the present work in comparison with



Scheme 2. Proposed speculative mechanism for synthesis of 1,4-dihydropyran[2,3-*c*] pyrazole in the presence of cellulose as catalyst.

**Table 3.** Comparison the Result of Cellulose with other Catalysts Reported in the Literature for Preparation of 6-Amino-4-aryl-3-methyl-1,4-dihydropyran[2,3-*c*]pyrazole-5-carbonitriles

Entry	Catalyst	Conditions	Time (min)	Isolated yield (%)
1	(TEAA) ionic liquid (40 mol%)	r.t.	20	97
2	H <sub>3</sub> PO <sub>4</sub> /Al <sub>2</sub> O <sub>3</sub> (0.08 mol%)	Solvent free, 100 °C	7	97
3	γ-Alumina (15 mol%)	H <sub>2</sub> O, 100 °C	50	80
4	Nanosized MgO (62 mol%)	Acetonitrile, r.t.	10	97
5	Trichloroaceticacid (10 mol%)	Solvent free, 100 °C	5	85
6	Ce(SO <sub>4</sub> ) <sub>2</sub> (10 mol%)	Solvent free, 100 °C	5	80
7	Imidazole (50 mol%)	H <sub>2</sub> O, 80 °C	20	89
8	L-proline (5 mol%)	H <sub>2</sub> O, reflux	10	90
9	L-proline (5 mol%)	EtOH, reflux	10	87
10	Ultra sound irradiation	H <sub>2</sub> O, 50 °C	30	92
11	-	Boiling water	240	95
11	Cellulose	Solvent free, 100 °C	10	96 ( Present work)



**Fig. 1.** Reusability of cellulose as catalyst.

the reported results in the literature such as TEAA (triethylammonium acetate) [10],  $H_3PO_4/Al_2O_3$  [11],  $\gamma$ -alumina, [12] nanosized magnesium oxide [13], trichloroacetic acid [14], ceric sulfate [14], imidazole [15], L-proline [16], ultra sound irradiation [17], Boiling Water [22]. Some of the results have been accumulated in Table 3. The results show that Cellulose is a more efficient catalyst with respect to the reaction time exhibits broad applicability in similar yield.

We also investigated the recycling of the catalyst under solvent-free and thermal conditions using a model reaction of hydrazine monohydrate, ethylacetoacetate, benzaldehyde and malononitrile. After completion of the reaction, it was cooled to room temperature, and the crude solid product was dissolved in acetone. The mixture was filtered for separation of the catalyst. The catalyst was washed with (2 × 5 ml) acetone. The recovered catalyst was dried in vacuum and used for the subsequent catalytic runs. The catalytic system worked well up to four catalytic runs. The recovered catalyst was reused four times without any loss of its activities (Fig. 1).

## CONCLUSIONS

We have developed a green and straight forward protocol for the four-component synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles using cellulose as a green and available catalyst under solvent-free and thermal conditions. This procedure provides several advantages such as cleaner reactions, easier workup, reduced reaction times and eco-friendly promising strategy.

## ACKNOWLEDGMENTS

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