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# $\gamma$ -Alumina as a recyclable catalyst for the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles in aqueous medium

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# ABSTRACT

 $\gamma$ -Alumina as an expedient and recyclable catalyst for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in water via a four-component reaction is established. Comparative study of the efficacy of  $\gamma$ -alumina, basic alumina and KF-alumina is also discussed. The method presented is mild, environment friendly, inexpensive and functionality tolerable to give the products in good to excellent yields.

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Multi-component reactions (MCRs), by virtue of their flexibility to rapidly assemble three or more reactants and converting them into higher molecular weight compound in one-pot, have become a powerful synthetic strategy in recent years.<sup>1</sup> The synthetic utility of such protocols is further made more attractive when the reactions are carried out in aqueous medium.

Pyrano[2,3-c]pyrazoles constitute one of the privileged heterocyclic scaffolds known to exhibit important biological activities, such as analgesic,<sup>2a</sup> anti-tumor, anti-cancer,<sup>2b</sup> anti-inflammatory properties<sup>2c</sup> and also serve as potential inhibitors of human Chk1 kinase.<sup>3</sup> Furthermore, heterocyclic compounds bearing 4H-pyran units have played increasing roles in synthetic strategies to promising compounds in the field of medicinal chemistry.<sup>4</sup> Junek and Aigner<sup>5</sup> first established the synthesis of pyrano[2,3-c]pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine. Later on, a number of synthetic approaches have also been made for the synthesis 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazoles of employing triethylamine,<sup>6a,6b</sup> piperazine<sup>6c</sup> and piperidine<sup>6d</sup> as prominent catalysts. However, these syntheses have been achieved through a two-component or three-component reaction except for the works reported by Vasuki et al.<sup>6d</sup> and Gogoi and Zhao <sup>7</sup> where a four-component synthesis has been accomplished. Although, the reported methods are effective, they are confronted with certain drawbacks of environment compatibility by the use of toxic and expensive catalysts,<sup>6,7a</sup> which also lack recyclability.

Furthermore, alumina and alumina supported reagents, due to their surface property and well defined porosity, act as proficient catalysts and reagents for many important organic reactions.<sup>8</sup> More importantly, alumina is eco-friendly and inexpensive. Despite the available procedures we, therefore, decided to use the  $\gamma$ -alumina and improve further the existing methodologies pertaining to the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles.

Thus, in conjunction with our continued research aimed at the development of environmentally benign synthetic methodologies using solid-support catalysts,<sup>9</sup> we report herein the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihy-dropyrano[2,3-*c*]pyrazole-5-carbonitriles using  $\gamma$ -alumina as catalyst in water (Scheme 1).

In continuation of this method, we further carried out a comparative catalytic efficacy of  $\gamma$ -alumina, basic alumina and potassium fluoride loaded alumina (KF-alumina) with selected aldehydes for the same synthesis.



Scheme 1.





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Initially, the one-pot synthesis was optimized by heating a mixture of ethyl acetoacetate (1) (2.0 mmol), hydrazine hydrate (2) (2.5 mmol), 4-chlorobenzaldehyde (3e) (2.0 mmol) and malononitrile (**4**) (2.0 mmol) in the presence of  $\gamma$ -alumina (10 mol %) in water (10 mL) for 35 min which afforded 5e in 60% yield. The same reaction when carried out with 15 mol % of the catalyst gave 5e with an increased yield (71%). Thus, by varying the amount of  $\gamma$ -alumina, optimization was arrived at 30 mol % which significantly resulted in 90% yield of the product **5e** (Table 1). In another attempt, the catalyst recovered from the reaction after filtration and washing with boiling ethyl acetate was used further for the condensation of ethyl acetoacetate (1) (2.0 mmol), hydrazine hydrate (2) (2.5 mmol), 4-chlorobenzaldehyde (3e) (2.0 mmol) and malononitrile (4) (2.0 mmol). Interestingly, the reaction was observed to complete within 45 min giving 6e in 80% yield. The recvclability of the catalyst and the results are shown in Table 1.

Subsequently, a series of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles were prepared in the presence of  $\gamma$ -alumina (30 mol %) involving different aldehydes after simple work-up and purification (**5a**–**p**, Table 2).<sup>12</sup> Irrespective of the presence of electron withdrawing or donating substituents in the *ortho*, *meta* or *para* positions on the ring of various aromatic aldehydes the reactions proceeded smoothly to furnish the desired products in good yields (**5a**–**p**). Also, high yields of the products were obtained for the electron poor benzaldehydes,

 Table 1

 Optimization of the reaction condition and the catalyst recyclability with compound 5e

Entry	Reaction conditions	Yield <sup>a</sup> (%)
1	γ-Alumina (10 mol %), 35 min, refluxed	60
2	γ-Alumina (15 mol %), 35 min, refluxed	71
3	γ-Alumina (25 mol %), 35 min, refluxed	83
4	γ-Alumina (30 mol %), 35 min, refluxed	90
5	γ-Alumina (35 mol %), 35 min, refluxed	89
6	γ-Alumina (recycled once), 45 min, refluxed	80
7	$\gamma$ -alumina (recycled twice), 60 min, refluxed	50
8	$\gamma$ -alumina (recycled three times), 90 min, refluxed	20

<sup>a</sup> Isolated yields.

### Table 2

Synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles via Scheme 1

Entry	Substrate <b>3</b> (R <sup>1</sup> )	Product <b>5</b>	Time (min)	Yield <sup>a</sup> (%)	Mp <sup>c</sup> (°C)
1	C <sub>6</sub> H <sub>5</sub>	5a	50	80	244-246 <sup>6c</sup>
2	$4-CH_3C_6H_4$	5b	45	82	206–208 <sup>6d</sup>
3	$4-CH_3OC_6H_4$	5c <sup>b</sup>	60	79	210-212 <sup>6c</sup>
4	2-ClC <sub>6</sub> H <sub>4</sub>	5d	55	80	145-147
5	4-ClC <sub>6</sub> H <sub>4</sub>	5e	35	90	234–236 <sup>6c</sup>
6	3-BrC <sub>6</sub> H <sub>4</sub>	5f	40	84	222-224 <sup>6b</sup>
7	4-BrC <sub>6</sub> H <sub>4</sub>	5g	40	90	178-180 <sup>11</sup>
8	4-HOC <sub>6</sub> H <sub>4</sub>	5h <sup>b</sup>	75	74	224-226 <sup>6c</sup>
9	4-N(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	5i <sup>b</sup>	90	61	167–169 <sup>11</sup>
10	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	5j	60	72	220-222
11	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	5k	45	75	193-195 <sup>11</sup>
12	$4-NO_2C_6H_4$	51	40	85	251–253 <sup>6c</sup>
13	3-CH <sub>3</sub> O-4-HOC <sub>6</sub> H <sub>3</sub>	5m <sup>b</sup>	70	75	235–237 <sup>6c</sup>
14	2,5-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	5n	70	73	210-212
15	3,4-(CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	50	70	80	192–194 <sup>6d</sup>
16	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	5p	60	81	209–211 <sup>6d</sup>
17	1-Naphthyl	5q	55	79	200-202
18	9-Anthranyl	5r	60	85	206-208
19	Butyryl	5s	55	83	143-145
20	Propionyl	5t	60	70	130–132 <sup>6d</sup>

<sup>a</sup> Isolated yields.

<sup>b</sup> Purified by column chromatography.

<sup>c</sup> Literature references.

such as 2-nitrobenzaldehyde, 3-nitrobenzaldehyde and 4-nitrobenzaldehyde (entries 10–12, Table 2).

Similarly, the scope of this methodology was extended to polynuclear aldehydes such as 1-naphthaldehyde and 9-anthraldehyde. In each case, the reaction underwent smoothly resulting in similar good yields (products **5q** and **r**, entries 17 and 18, Table 2). The methodology was also found to be effective for the aliphatic aldehydes. Thus, butyraldehyde (**3s**) and propionaldehyde (**3t**) reacted cleanly with substrates **1**, **2** and **4** to give 6-amino-4-alkyl-3methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles **5s** and **t** in 83% and 70% yields, respectively (entries 19 and 20, Table 2). The products obtained were fully characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR, mass spectral and elemental analyses.<sup>13</sup>

Next, a comparative catalytic efficiency of  $\gamma$ -alumina, basic alumina and KF-alumina for the synthesis of **5** was examined by executing a series of reactions using 30 mol % each of the catalysts with reference to the optimized reaction condition. It was observed that the reactions performed with basic alumina exhibited low efficiency with most of the products requiring column chromatography purification. KF-alumina catalyzed reactions in ethanol as solvent, on the other hand, did show comparable efficiency with maximum yields almost equivalent to  $\gamma$ -alumina catalyzed reactions (Table 3). The comparative catalytic activity was found to display an order of  $\gamma$ -alumina > KF-alumina > basic alumina in the reaction. Here, the higher catalytic activity of  $\gamma$ -alumina may be attributed to its amphoteric nature and the surface area available for greater adsorption of the reactants on its surface.

Notably, reactions in the presence of  $\gamma$ -alumina catalyst were clean and all the products were obtained after simple filtration and purification by recrystallization from ethanol and water except for **5c**, **h**, **i** and **m** (entries 3, 8, 9 and 13, Table 2) which were purified by column chromatography. The spectral study revealed the formation of two enantiomers and the combined yields of the racemates are summarized in Table 2.

Although there is ambiguity on the reaction mechanism, we presume that the formation of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihy-dropyrano[2,3-*c*]pyrazole-5-carbonitriles takes place through a tandem Michael addition and Thorpe-Ziegler reaction as described in earlier reports.<sup>6d,7</sup> The amphoteric nature and high surface area of  $\gamma$ -alumina allow compound **6** to adsorb on its surface<sup>10</sup> to give complex **8c** (steps-B–D) which facilitates Michael addition of **8c** to compound **7** giving intermediate **9** (step-E). Subsequently, the Thorpe-Ziegler like intramolecular cyclization followed by tautomerization affords product **5** (Scheme 2).

In summary, we have devised a green and facile method for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles using  $\gamma$ -alumina as the recyclable catalyst and water as the solvent. A comparative study of

# Table 3

Comparative study of  $\gamma\text{-alumina, basic alumina and KF-alumina catalyst for the synthesis of <math display="inline">{\bf 5}$ 

Entry	Product 5	Time (min)	Yield <sup>a</sup> (%)			
			γ-Alumina	Basic alumina	KF-alumina	
1	5a	50	80	70	75	
2	5b	45	82	77	80	
3	5c	60	79 <sup>b</sup>	73 <sup>b</sup>	75 <sup>b</sup>	
4	5e	35	90	83	88	
5	5h	75	74 <sup>b</sup>	61 <sup>b</sup>	64 <sup>b</sup>	
6	5k	45	75	70 <sup>b</sup>	71 <sup>b</sup>	
7	51	70	85	60 <sup>b</sup>	70	
8	5m	70	75 <sup>b</sup>	67 <sup>b</sup>	72 <sup>b</sup>	
9	5q	55	79	71 <sup>b</sup>	74	
10	5r	60	85	72 <sup>b</sup>	78	
11	5s	70	83	78	78	

<sup>a</sup> Isolated yields.

<sup>b</sup> Purified by column chromatography.



Scheme 2. Proposed mechanism for the formation of pyrano[2,3-c]pyrazoles.

 $\gamma$ -alumina, basic alumina and KF-alumina with the  $\gamma$ -alumina displaying greater catalytic activity has also been shown. More importantly, the present procedure offers mild, efficient and environmentally benign strategy by the use of  $\gamma$ -alumina which overcomes the drawbacks of the reported methods.

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# Supplementary data

Supplementary data (spectroscopic analytical data, <sup>1</sup>H, <sup>13</sup>C NMR and mass spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.036.

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- 12. General experimental procedure for the synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles (5): To a pre-stirred mixture of ethyl acetoacetate (1) (0.26 mL, 2.0 mmol) hydrazine hydrate (2) (0.13 mL, 2.5 mmol) in water (10 mL) was added aldehydes (3) (2.0 mmol) and malononitrile (4) (0.13 g, 2.0 mmol) followed by pre-calcinated γ-alumina (30 mol %). The reaction mixture was then heated at 100 °C and allowed to stir for 35–90 min. On completion of the reaction (monitored by TLC), it was cooled and water was evaporated in vacuo. The residue was treated with boiling methanol-ethyl acetate (1:1) and filtered through a sintered funnel and washed thoroughly with the same solvent. The combined filtrate was evaporated in vacuo to afford the crude product which was recrystallized from ethanol/water (9.5:0.5), or purified by column chromatography over silica gel (100–200 mesh) using methanol/dichloromethane (2:8) as the eluent to afford pure compound 5.

Same procedure was followed for the reactions when basic alumina and KF-alumina (30 mol %) were used as catalysts during the comparative study.

13. Spectroscopic data for compound (**5k**): yellowish solid; IR ν<sub>max</sub> (KBr): 1076, 1169, 1348, 1407, 1527, 1600, 1653, 2196, 2932, 3118, 3217, 3469 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO): δ (ppm) 1.92 (s, 3H, CH<sub>3</sub>), 4.79 (s, 1H, 4H), 6.20 (s, 2H, NH<sub>2</sub>), 7.55 (t, 1H, *J* = 8.0 Hz, Ar–H), 7.62 (d, 1H, *J* = 7.6 Hz, Ar–H), 8.00–8.03 (m, 2H, Ar–H), 11.34 (s, 1H, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ (ppm) 9.70, 29.0, 56.5, 112.6, 120.2, 123.2, 128.4, 128.6, 135.7, 141.3, 146.3, 151.3, 154.6, 160.9; MS (ES<sup>+</sup>) calcd for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub> 297.1 found *m/z* 297.9 (M+H)<sup>\*</sup>, 319.9 (M+Na)<sup>\*</sup>; CHN calcd for C<sub>14</sub>H<sub>11</sub>N<sub>5</sub>O<sub>3</sub>: C, 56.56; H, 3.73; N, 23.56%; found: C, 56.69; H, 3.69; N, 23.43% (Lit.).<sup>11</sup> *For compound* (**5s**) yellow solid; IR ν<sub>max</sub> (KBr): 1149, 1222, 1401, 1467, 1527, 1613, 2203, 2932,3120, 3190, 3390 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ (ppm) 0.76–0.85 (m, 3H, CH<sub>3</sub>), 1.18–1.21 (m, 2H, CH<sub>2</sub>), 1.66–1.73 (m, 2H, CH<sub>2</sub>), 1.90 (s, 3H, CH<sub>3</sub>), 3.20–3.26 (m, 1H, 4H), 6.66 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ (ppm) 9.8, 13.7, 19.8, 31.3, 36.5, 96.6, 112.8, 112.9, 139.5, 159.5, 171.5; MS (ES<sup>+</sup>) calcd for C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O 218.1 found *m/z* 218.9 (M+H)<sup>\*</sup>, 240.9 (M+Na)<sup>\*</sup>; CHN calcd for C<sub>11</sub>H<sub>14</sub>N<sub>4</sub>O: C, 60.53; H, 6.47; N, 25.67%; found: C, 60.41; H, 6.39; N, 25.40%.