

**CsOH/  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> CATALYZED MILD AND EFFICIENT METHOD FOR THE  
SYNTHESIS OF NOVEL MULTIFUNCTIONALIZED 4H-PYRAN DERIVATIVES  
VIA ONE-POT THREE- COMPONENT PROTOCOL**

**MMV Ramana<sup>\*</sup>, Rahul Betkar, Amey Nimkar, Prasanna Ranade, Balaji Mundhe**

*Department of Chemistry, University of Mumbai, Vidyanagari, Santacruz (E), Mumbai-400  
098, India*

*E-mail : ramanammv@yahoo.com*

**ABSTRACT**

A simple, mild, and environmentally benign multicomponent synthesis of polysubstituted 4H- pyran derivatives has been developed using recyclable CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> as heterogeneous basic catalyst. The 4H- pyran derivatives were synthesized by a one-pot three-component reaction of an aromatic aldehyde, malononitrile, and ethyl acetoacetate or isopropyl acetoacetate at room temperature in alcohol. The characterization of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyst was performed by using FT-IR, XRD, and TG-DTA techniques. The results revealed that the catalyst has high catalytic activity and good thermal stability.

**KEYWORDS**

4H- pyran, cesium hydroxide,  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>, multicomponent reaction, room temperature

**INTRODUCTION**

Polyfunctionalized 4H-pyrans are important class of organic compounds because of their significant antitumor<sup>i</sup>, anticoagulant<sup>ii</sup>, antibacterial<sup>iii</sup>, antiproliferative<sup>iv</sup>, antiviral<sup>v</sup>, sex pheromones<sup>vi</sup>, cancer therapy<sup>vii</sup>, and central nervous system activities<sup>viii</sup>. A number of 2-amino-4H-pyrans are widely utilized as cosmetics, pigments, and also act as potential biodegradable agrochemicals<sup>ix</sup>. Some of the 4H-pyran derivatives are used as photoactive materials<sup>x</sup> and potential calcium channel antagonists<sup>xi</sup>. Furthermore, 4H-pyrans are structural units in series of natural products<sup>xii</sup>. Therefore, synthesis of such compounds has attracted great interest for many organic chemists.

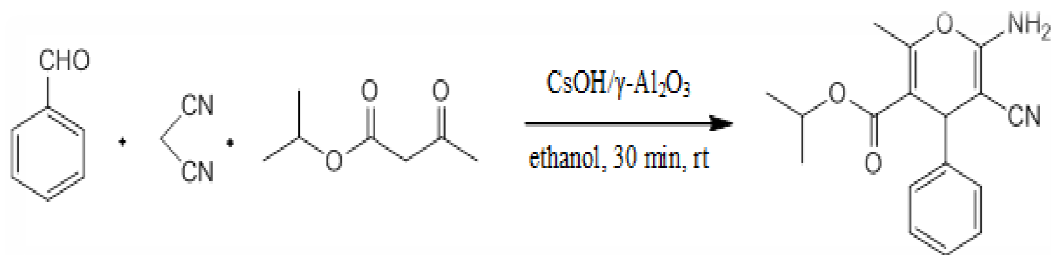
Multicomponent reactions (MCR) have been successfully utilized to synthesize number of biological and pharmacological active compounds<sup>xiii</sup>. MCR using environmentally benign solvents and catalysts is one of the most suitable protocol for developing variety of medicinal scaffolds.

Several procedures for the synthesis of 4H-pyrans have been reported. Generally, 4H- pyrans were synthesized by the reactions of aldehydes, active methylene compounds, and 1, 3-dicarbonyl compounds using bases such as piperidine<sup>xiv</sup>, triethylamine<sup>xv</sup>, pyridine<sup>xvi</sup>, 1,1,3,3-N,N,N,N-tetramethyl guanidinium trifluoroacetate as an ionic liquid<sup>xvii</sup>, diammonium hydrogen phosphate<sup>xviii</sup>, and N-methyl imidazole<sup>xix</sup>. Ultrasound<sup>xx</sup> and microwave heating<sup>xxi, xxii</sup> are also employed for the synthesis of 4H-pyran analogs. There are few reports for the synthesis of

4*H*-pyran derivatives using heterogeneous catalysts<sup>xxiii, xxiv</sup>. The above methods have several limitations such as long reaction time, low yield, use of toxic solvents, and bases. Therefore, there is a scope to develop ecofriendly alternative methods to synthesize important biological and pharmacological scaffolds.

## RESULTS AND DISCUSSION

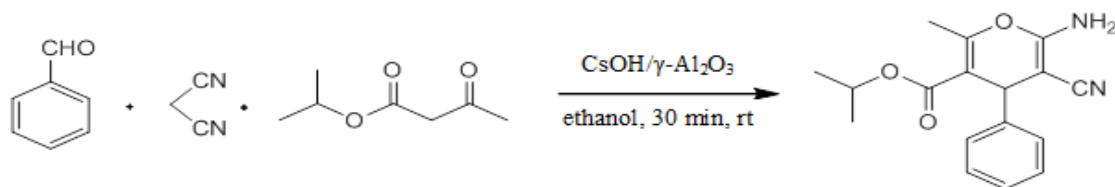
Recently, there has been increased interest in the design and use of green solid acid /base heterogeneous catalyst. The main advantage of heterogeneous catalyst is that it is easy to isolate liquid and gas phase reactants. Thus, we employed a rapid and efficient method for the synthesis of 4*H*-pyran derivatives via multicomponent reaction of aromatic aldehydes, ethyl/isopropyl acetoacetate, and malononitrile using recyclable CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> as heterogeneous basic catalyst at room temperature for the first time (**Scheme.1**).



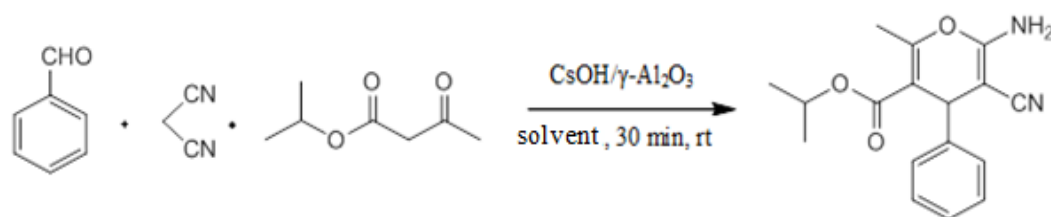
**Scheme.1:** multicomponent route to afford 4*H*- pyrans

CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalytic system offers many advantageous such as high yield, short reaction time, and easy work up. The characterization of catalyst was performed using XRD, TG-DTA, and IR techniques. The results indicate that CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> has good thermal stability. Thus, it can be used over wide range of temperatures.

In an initial experiment, we carried out a reaction between equivalent mixture of benzaldehyde (1.00 mmol), isopropyl acetoacetate (1.00mmol), and malononitrile (1.00mmol) in the presence of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> with different concentration of catalyst and using different solvents at room temperature. To optimize the reaction conditions, a set of experiments with different solvents and varying amount of catalyst were conducted. From the experiments, it can be seen that the efficiency of reaction was mainly affected by both the concentration of catalyst (**Table.1**) and solvents (**Table.2**). The best result was obtained when reaction was carried out in alcohol using 10 mol % of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub>. We also screened various basic catalysts for the reaction. Among these catalysts, CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> showed higher activity (**Table.3**). The decreasing catalyst loading from 10 mol % to 5 mol % decreases the yield of the product. However, no significant improvement of yield was observed even after increasing the catalyst loading from 10 mol % to 25 mol % (**Fig.1**)

**Table.1** Optimization of concentration of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyst

Entry	mol % of catalyst	Yield <sup>a</sup> (%)
1	5	61
2	10	93
3	15	91
4	20	90
5	25	90

<sup>a</sup> Isolated yield.**Table.2** Effect of solvents on the reaction

Entry	solvents	Yield (%) <sup>a</sup>
1	Methanol	81
2	Acetone	75
3	Ethanol	93
4	THF	70
5	DMSO	68

<sup>a</sup> Isolated yield.

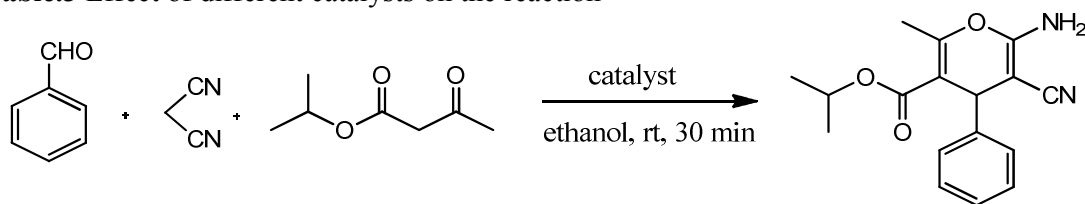
With these optimized conditions, we examined the generality of these conditions with different aromatic aldehydes to prepare a series of polysubstituted 4*H*-pyrans. All the reactions proceeded smoothly in 30 min to afford the products in good to excellent yield (**Table.4**).

Encouraged by these results, we decided to examine the catalytic activity of the recycled CsOH/  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>. The catalyst was recovered by simple filtration, washed with ethanol and dried at 100<sup>o</sup>C. The catalyst can be reused for atleast four times with slight loss of their activity (**Table.5**). Further, retention of the structure of catalyst was confirmed by comparing

the FT-IR spectra of fresh catalyst with that of the recovered catalyst. As shown in **Fig.2**, both the spectra are almost similar.

The FT-IR spectrum of CsOH/  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> calcined at 400<sup>0</sup>C for 1 h is shown in **Fig.2**. Along with bands of CsOH and Al<sub>2</sub>O<sub>3</sub>, few new bands are observed in the spectrum indicating CsOH is well chemisorbed on the surface of alumina. The band observed at 1045 cm<sup>-1</sup> and 1110 cm<sup>-1</sup> were attributed to the Al-O-Al symmetric stretching vibrations. The band at 881 cm<sup>-1</sup> and 920 cm<sup>-1</sup> were assigned to Al-O-Cs bonding. The bands between 1348 -1483 cm<sup>-1</sup> were related to the Cs-O bending vibrations. A broad band at 3500 cm<sup>-1</sup> was characteristic hydroxyl (-OH) group of water physisorbed onto the surface of alumina. The deformation mode of vibration of hydroxyl (-OH) group was observed at 1639 cm<sup>-1</sup>.

**Table.3** Effect of different catalysts on the reaction

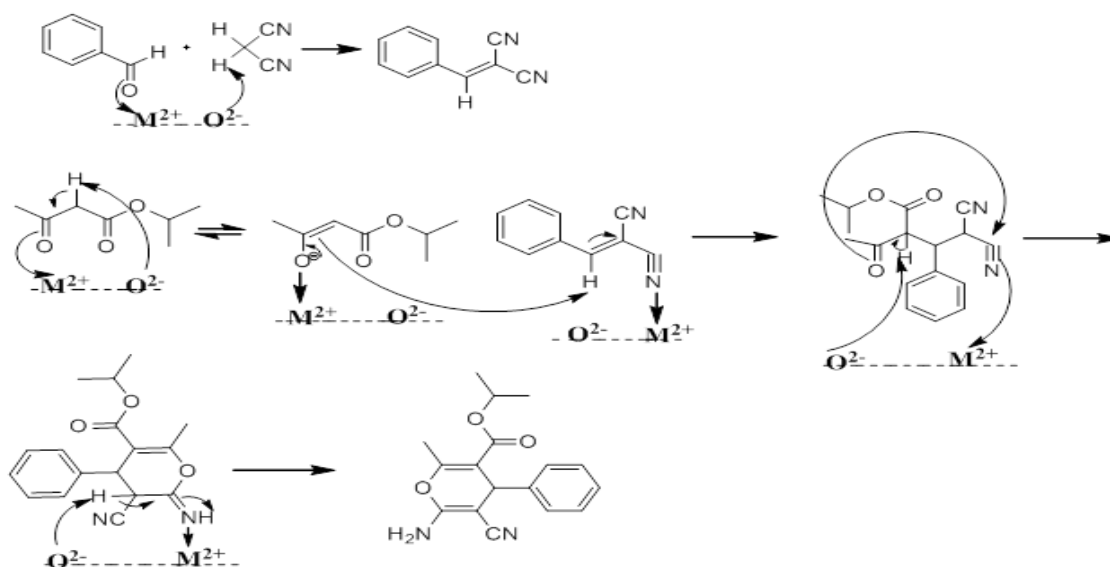


Entry	Catalyst	Yield (%) <sup>a</sup>
1	10 mol % KOH/ $\gamma$ -Al <sub>2</sub> O <sub>3</sub>	70
2	10 mol % KF/ $\gamma$ -Al <sub>2</sub> O <sub>3</sub>	81
3	10 mol % Cs <sub>2</sub> CO <sub>3</sub> / $\gamma$ -Al <sub>2</sub> O <sub>3</sub>	78
4	10 mol % CsF/ $\gamma$ -Al <sub>2</sub> O <sub>3</sub>	75
5	10 mol % CsOH/ $\gamma$ -Al <sub>2</sub> O <sub>3</sub>	93

**Fig.3** shows XRD patterns for  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> and CsOH loaded  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>. Peaks were obtained for  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> at  $2\theta = 20^{\circ}, 32^{\circ}, 37^{\circ}, 43^{\circ}, 46^{\circ},$  and  $67^{\circ}$ . The diffraction peaks of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> are in good agreement with International Centre for Diffraction Data Powder Diffraction File (PDF) 29-0063. A solid state reaction occurred between CsOH and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> during calcination and new phase Cs<sub>2</sub>O might be formed. The new phase Cs<sub>2</sub>O is basic in nature and provided catalytic activity for the reaction. XRD patterns for Cs<sub>2</sub>O were obtained at  $2\theta = 14^{\circ}, 22^{\circ}, 24^{\circ}, 27^{\circ}, 30^{\circ}, 52^{\circ}, 56^{\circ},$  and  $63^{\circ}$ . Thus, it was concluded that CsOH is well chemisorbed into the crystal structure of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>.

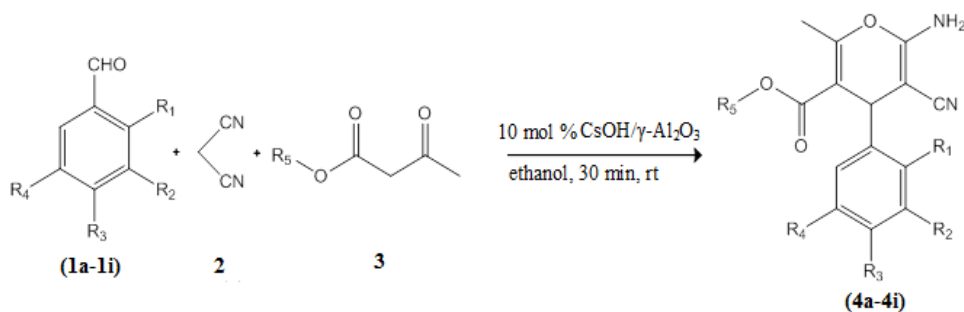
The TG-DTA curves of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> system (**Fig.4**) showed three endotherms at 100<sup>0</sup>C, 240<sup>0</sup>C and 710<sup>0</sup>C. Three main stages of weight losses are observed. The first and second weight loss at 100<sup>0</sup>C and 240<sup>0</sup>C are related to the loss of physisorbed and chemisorbed water respectively. The third weight loss at 740<sup>0</sup>C is probably due to the decomposition of Cs<sub>2</sub>O. These results show good thermal stability of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyst. Thus, it indicates that the catalyst can also be used at higher temperature reactions.

The plausible mechanism of reaction is shown in **Scheme.2**



**Scheme.2:** mechanism of the reaction

**Table.4** Synthesis of 4H-Pyran derivatives using CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> at room temperature<sup>a</sup>



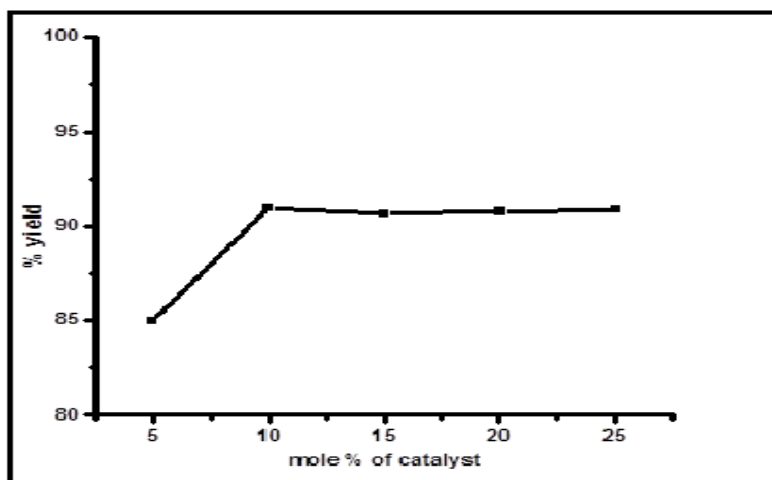
Product	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	Yield <sup>b</sup> (%)	M.P °C
4a	H	H	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	93	198-200
4b	H	CF <sub>3</sub>	H	CF <sub>3</sub>	CH <sub>3</sub> CH <sub>2</sub>	94	211-215
4c	H	H	F	H	CH(CH <sub>3</sub> ) <sub>2</sub>	92	198-199
4d	H	F	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	93	190-195
4e	H	F	F	H	CH(CH <sub>3</sub> ) <sub>2</sub>	94	200-205
4f	Cl	H	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	90	194-198
4g	H	Cl	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	88	195-197
4h	H	H	OCH <sub>3</sub>	H	CH(CH <sub>3</sub> ) <sub>2</sub>	91	185-188
4i	OH	H	OCH <sub>3</sub>	H	CH <sub>3</sub> CH <sub>2</sub>	83	218-220

<sup>a</sup>Reaction conditions: aldehyde(1mmol), malononitrile(1mmol), 1,3-dicarbonyl compound(1mmol), 10 mol % CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub>, ethanol(25 ml), rt, 30 min.

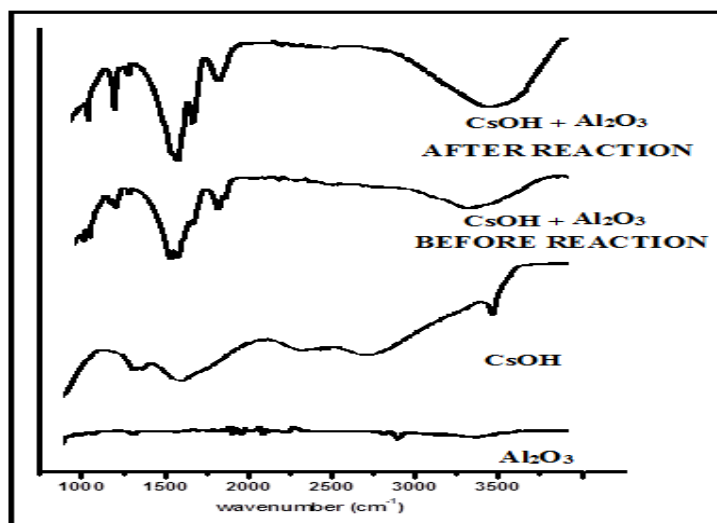
<sup>b</sup> Isolated yield

**Table.5** Recyclability of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyst

Product	No. of cycle	Yield (%)
4e	1	94
	2	93
	3	92
	4	91



**Fig.1** Optimization of CsOH/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub> concentration for the reaction.



**Fig.2** FT-IR spectra of (a)  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>, (b) CsOH, (c) CsOH/  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> before reaction and (d) CsOH/  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> after reaction calcined at 400<sup>0</sup>C.

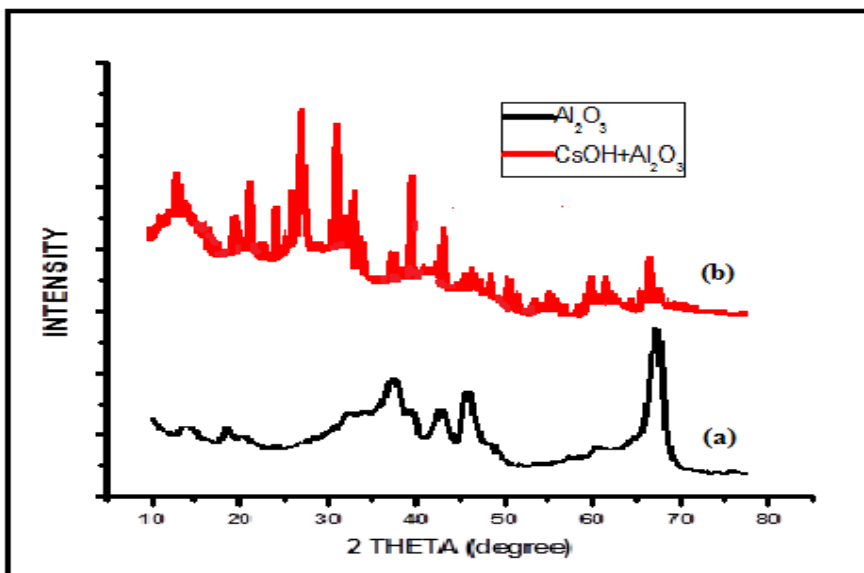


Fig.3 XRD pattern of (a)  $\gamma$ - $\text{Al}_2\text{O}_3$  and (b)  $\text{CsOH}/\gamma$ - $\text{Al}_2\text{O}_3$  calcined at  $400^\circ\text{C}$ .

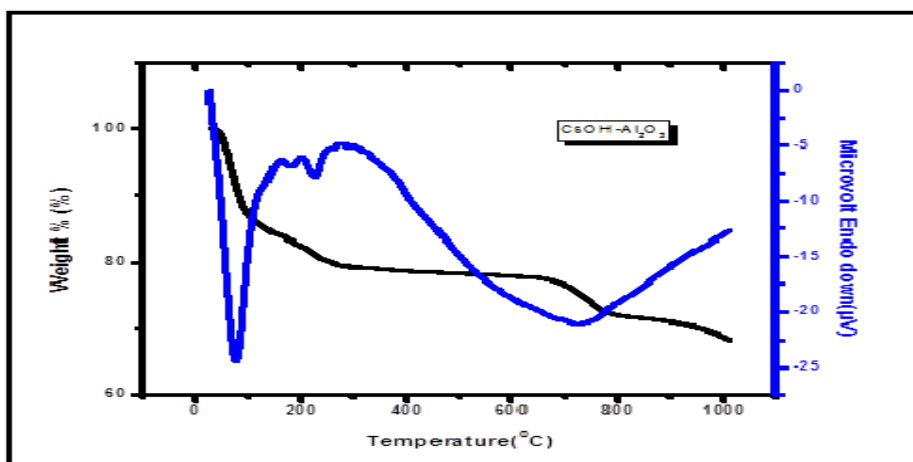


Fig.4 TG-DTA analysis of  $\text{CsOH}/\gamma$ - $\text{Al}_2\text{O}_3$  catalyst.

In conclusion, we have reported a mild and rapid method to synthesize polyfunctionalized *4H*-pyran analogs by using  $\text{CsOH}/\gamma$ - $\text{Al}_2\text{O}_3$  as a heterogeneous basic catalyst in ethanol at room temperature. The characterization of catalyst was performed by using FT-IR, TG-DTA, and XRD techniques. The results revealed that the catalyst has a good thermal stability and could be used for high temperature reactions. The catalyst could be reused for at least four runs after simple filtration and washing with ethanol. Thus, the developed protocol is highly efficient, economical, and environmentally benign.

## EXPERIMENTAL

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich (India) and used without purification. Melting points are uncorrected. UV-Vis absorption spectra were recorded on SHIMADZU UV-2401 PC spectrophotometer. IR spectra were recorded on Frontier Perkin Elmer IR spectrometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained on a Bruker AVANCE 300 MHz instrument in  $d_6$ -DMSO using TMS as internal standard.

Chemical shifts ( $\delta$ ) are expressed in ppm and coupling constants  $J$  are given in Hz. XRD pattern was measured on Shimadzu Maxima 7000 S X-ray Diffractometer. Thermal analyses (TG-DTA) were performed using Perkin Elmer Pyris Diamond Thermogravimetric Analyzer under inert reaction atmosphere ( $N_2$ ) with temperature control of  $10^0$  C  $min^{-1}$ . Elemental analysis (C, H, N) were carried out on elemental analyzer EA 3000, Euro Vector, Italy.

**Preparation of catalyst:** CsOH (1.1g) and (2.0)  $\gamma$ - $Al_2O_3$  were suspended in 25 ml methanol and stirred for 2 h at room temperature. Methanol was removed in vacuo and dried at  $100^0C$ . The obtained residue was calcined at  $400^0C$  for 4 h. Finally, the solid was crushed into particles for use as catalyst.

**General experimental procedure:** CsOH- $Al_2O_3$  (0.2g) was added to the mixture of aromatic aldehyde (1mmol), malononitrile (1mmol) and ethyl acetoacetate or isopropyl acetoacetate (1mmol) in 25ml ethanol and kept for stirring at room temperature for 30 min. Completion of reaction was monitored by TLC. After completion of reaction, mixture was filtered to remove the catalyst and washed 2-3 times with ethanol. The filtrate was poured into the ice cold water and filtered off the precipitate. The crude product was recrystallized from ethanol and dried to afford pure product.

#### Characterization of all Products

**Example 1:** Isopropyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (**4a**)

white solid; Yield: 93%; mp:198-200  $^{\circ}C$ ; UV (Methanol)  $\lambda_{max}$  (log  $\epsilon$ ): 290(4.12); IR ( $cm^{-1}$ ): 3458.63, 3403.25, 3324.0, 3264.18, 3224.38, 3200.69, 2981.19, 2937.10, 2197.06, 1677.91, 1641.76, 1608.55, 1578.89, 1469.61, 1362.82, 1264.31, 1175.04, 1069.17, 750.29;  $^1H$ -NMR ( $d_6$ -DMSO): 0.90-0.88(d, $J$ =6Hz,3H), 1.13-1.11(d, $J$ =6Hz,3H), 2.315(s,3H), 4.02-3.91(m,1H), 4.30(s,1H), 6.89(s,2H, $NH_2$ ),7.33-7.13(m,5H);  $^{13}C$ -NMR( $d_6$ -DMSO): 18.0, 20.8, 20.9, 38.1, 57.7, 60.1, 107.2, 119.6, 126.7, 127.1, 128.3, 144.8, 156.5, 158.4, 165.41; Elem.Anal.Calculated for  $C_{17}H_{18}N_2O_3$ :C,68.44; H,6.08; N,9.39. Found: C, 68.40; H, 6.10; N, 9.40%.

**Example 2:** Ethyl 6-amino-4-(3, 5-bis (trifluoromethyl) phenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (**4b**)

white solid; Yield: 94% ; mp:215-211  $^{\circ}C$ ; UV (Methanol)  $\lambda_{max}$  (log  $\epsilon$ ):294(4.06); IR ( $cm^{-1}$ ): 3407.06, 3340.94, 2973.30, 2195.08, 1679.18, 1645.18, 1605, 1455.8, 1370.99, 1275.04, 1168.77, 1125.99, 898.27, 680.97;  $^1H$ -NMR ( $d_6$ -DMSO): 0.99-0.97(d, $J$ =6Hz,3H), 2.3 (s,3H), 4.64(s,1H), 4.80-4.72(m,2H), 7.18(s,2H, $NH_2$ ), 7.88(s,2H), 8.01(s,1H);  $^{13}C$ -NMR( $d_6$ -DMSO): 18.20, 38.37, 55.91, 67.67, 105.56, 119.14, 121.42, 125.04, 130.11, 130.54, 148.73, 158.14, 158.44, 164.35; Elem.Anal.Calculated for  $C_{18}H_{14}F_6N_2O_3$ : C,51.44; H,3.36; N,6.67. Found: C, 51.55; H, 3.40; N, 6.60%.

**Example 3:** Isopropyl 6-amino-5-cyano-4-(4-fluorophenyl)-2-methyl-4*H*-pyran-3-carboxylate (**4c**)

White solid; Yield: 92%; mp: 199-198  $^{\circ}C$ ; UV (Methanol)  $\lambda_{max}$  (log  $\epsilon$ ):285(4.10); IR ( $cm^{-1}$ ): 3399.54, 3330.94, 3267.60, 3221.57, 3200.36, 2980.21, 2925.63, 2186.63, 1680.75, 1651.34, 1453.30, 1362.74, 1264.96, 1178.83, 1056.08, 747.76;  $^1H$ -NMR ( $d_6$ -DMSO): 0.90-0.88(d, $J$ =6Hz, 3H), 1.13-1.11(d, $J$ =6Hz,3H), 2.30(s,3H), 4.29(s,1H), 4.82-4.73(m,1H), 6.90(s,2H, $NH_2$ ), 7.17-7.13(dd, $J$ =12Hz,2H), 7.20-7.17(dd, $J$ =9Hz,2H);  $^{13}C$ -NMR( $d_6$ -DMSO): 18.0, 20.8, 20.9, 38.1, 57.0, 67.5, 107.1, 115.1, 119.5, 129.2, 141.1, 156.4, 158.3, 159.3, 164.7; Elem.Anal.Calculated for  $C_{17}H_{17}FN_2O_3$ : C,64.55; H,5.60; N,8.81. Found: C, 64.50, H, 5.45; N, 8.90%.

**Example 4:** Isopropyl 6-amino-5-cyano-4-(3-fluorophenyl)-2-methyl-4*H*-pyran-3-carboxylate (**4d**)

White solid; Yield: 93%; mp:195-190  $^{\circ}C$ ; UV (Methanol)  $\lambda_{max}$  (log  $\epsilon$ ):287(4.07); IR ( $cm^{-1}$ ): 3400.54, 3350.94, 3267.60, 3210.57, 3100.36, 2970.21, 2925.63, 2190.63, 1690.75, 1655.34, 92



1453.30, 1362.74, 1264.96, 1178.83, 1056.08, 747.76; <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 0.82-0.80(d,*J*=Hz,3H), 1.13-1.10(d,*J*=Hz,3H), 2.32(s,3H), 4.61(s,1H), 4.80-4.71(m,1H), 6.92(s,2H,NH<sub>2</sub>), 7.09(s,1H), 7.28-7.12(m,3H); <sup>13</sup>C-NMR(d<sub>6</sub>-DMSO): 18.00, 20.78, 21.34, 32.30, 55.82, 67.44, 105.73, 115.05, 115.34, 119.41, 124.56, 131.71, 157.55, 158.05, 158.59, 161.31, 164.55; Elem.Anal.Calculated for C<sub>17</sub>H<sub>17</sub>FN<sub>2</sub>O<sub>3</sub>: C,64.55; H,5.42; N,8.86. Found: C, 64.43, H, 5.50; N, 8.95%.

**Example 5:** Isopropyl 6-amino-5-cyano-4-(3, 4-difluorophenyl)-2-methyl-4*H*-pyran-3-carboxylate (**4e**)

White solid; Yield: 94%; mp:205-200 °C; UV (Methanol) λ<sub>max</sub> (log ε): 292(4.05); IR (cm<sup>-1</sup>): 3401.54, 3355.94, 3270.60, 3200.57, 3102.36, 2975.21, 2925.63, 2200.63, 1695.75, 1656.34, 1463.30, 1372.74, 1254.96, 1170.83, 1060.08, 750.76; <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 0.81-0.79(d,*J*=6Hz,3H), 1.14-1.12(d,*J*=6Hz,3H), 2.23(s,3H), 4.60(s,1H), 4.88(m,1H), 6.40(s,1H), 7.15(s,2H,NH<sub>2</sub>); 7.67-7.64(d,*J*=10Hz,1H); 7.90-7.75(d,*J*=9Hz, 1H), <sup>13</sup>C-NMR(d<sub>6</sub>-DMSO): 18.25, 20.0, 20.5, 38.9, 58.2, 68.0, 107.90, 116.00, 117.60, 119.70, 127.10, 141.40, 157.20, 158.76, 159.89, 162.12, 164.15; Elem.Anal.Calculated for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>N<sub>2</sub>O<sub>3</sub>: C,61.07; H,4.82; N, 8.38. Found: C, 60.87; H, 4.70; N, 8.40%.

**Example 6:** Isopropyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (**4f**)

White solid; Yield: 90%; mp:198-194 °C; UV (Methanol) λ<sub>max</sub> (log ε): 291(4.33); IR (cm<sup>-1</sup>): 3463.38, 3302.62, 3221.62, 3186.66, 2982.04, 2925.35, 2207.18, 1683.45, 1603.00, 1469.66, 1378.67, 1223.45, 1174.37, 1060.16, 748.23; <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 0.74-0.72(d,*J*=6Hz,3H), 1.12-1.10(d,*J*=6Hz,3H), 2.34(s,3H), 4.78-4.70(m,1H), 4.86(s,1H), 6.90(s,2H,NH<sub>2</sub>), 7.40-7.17(m,4H); <sup>13</sup>C-NMR(d<sub>6</sub>-DMSO): 17.95, 20.66, 21.32, 35.15, 55.98, 67.33, 106.06, 119.09, 127.66, 128.30, 129.14, 129.68, 132.00, 142.19, 157.65, 158.34, 164.51; Elem.Anal.Calculated for C<sub>17</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>: C,61.36; H,5.15; Cl,10.65; N,8.42. Found: C, 61.40; H, 5.10; Cl, 11.00; N, 8.60%.

**Example 7:** Isopropyl 6-amino-4-(3-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (**4g**)

White solid; Yield:88%; mp:197-195 °C; UV (Methanol) λ<sub>max</sub> (log ε): 290(4.30); IR (cm<sup>-1</sup>): 3403.25, 3324.00, 3264.18, 3224.38, 2981.19, 2937.10, 2200.00, 1677.91, 1641.76, 1608.55, 1578.89, 1469.61, 1374.85, 1264.31, 1175.04, 1120.56, 1060.17, 750.29; <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 0.90-0.88(d,*J*=6Hz,3H), 1.14-1.12(d,*J*=6Hz,3H), 2.31(s,3H), 4.31(s,1H), 4.82(m,1H), 6.97(s,2H,NH<sub>2</sub>), 7.35(m,3H), 7.38(s,1H); <sup>13</sup>C-NMR(d<sub>6</sub>-DMSO): 18.06, 20.94, 21.42, 38.56, 56.58, 67.64, 106.64, 119.46, 126.06, 126.74, 127.20, 130.31, 132.84, 147.44, 156.94, 158.41, 164.64; Elem.Anal.Calculated for C<sub>17</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>3</sub>: C,61.36; H,5.15; Cl,10.65; N,8.42. Found: C, 61.50; H, 5.25; Cl, 11.04; N, 8.55%.

**Example 8:** Isopropyl 6-amino-5-cyano-4-(4-methoxyphenyl)-2-methyl-4*H*-pyran-3-carboxylate(**4h**)

White solid; Yield: 91%; mp:188-185 °C; UV (Methanol) λ<sub>max</sub> (log ε):296(4.32); IR (cm<sup>-1</sup>): 3405.25, 3334.00, 3261.18, 3227.38, 2970.19, 2947.10, 2200.00, 2195.67, 1680.91, 1648.76, 1608.46, 1578.79, 1459.62, 1374.88, 1254.21, 1185.34, 11500.56, 1070.27, 850.79; <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 0.87-0.85(d,*J*=6Hz,3H), 1.17-1.15(d,*J*=6Hz,3H), 2.34(s,3H), 3.89(s,3H), 4.25(s,1H), 4.90(m,1H), 6.90(s,2H,NH<sub>2</sub>), 7.51-7.50(dd,*J*=3Hz,2H), 7.63-7.61(dd,*J*=6Hz,2H); <sup>13</sup>C-NMR(d<sub>6</sub>-DMSO): 17.90, 20.78, 21.45, 38.14, 57.82, 59.01, 67.34, 107.77, 110.66, 118.67, 119.78, 129.11, 130.80, 147.11, 158.78, 159.99, 164.55; Elem.Anal.Calculated for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.70; H, 6.20; N, 8.60%.

**Example 9:** Ethyl 6-amino-5-cyano-4-(2-hydroxy-4-methoxyphenyl)-2-methyl-4*H*-pyran-3-carboxylate (**4i**)

White solid; Yield: 83%; mp:220-218°C; UV (Methanol)  $\lambda_{\max}$  (log  $\epsilon$ ): 322(4.42); IR (cm<sup>-1</sup>): 3402, 3336.16, 3229.79, 2975.16, 2206.44, 1697.68, 1655.38, 1609.45, 1584.56, 1465.70, 1321.40, 1224.32, 1185.81, 1017.53, 865.68; <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO): 1.20-1.116(t, *J*=Hz, 3H), 2.49(s, 3H), 3.77(s, 3H), 4.09(m, 2H), 5.71(s, 1H), 6.83(s, 1H), 6.91-6.90(d, *J*=3Hz, 1H), 6.94-6.93(d, *J*=3Hz, 1H), 8.53(s, 2H, NH<sub>2</sub>), 9.32(s, 1H, OH); <sup>13</sup>C-NMR(d<sub>6</sub>-DMSO): 14.11, 21.7, 42.9, 55.69, 59.31, 80.12, 107.54, 111.46, 112.00, 113.09, 115.17, 126.37, 142.35, 147.44, 152.84, 151.20, 165.5; Elem.Anal.Calculated for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>: C,61.81; H,5.49; N,8.48. Found: C, 61.93; H, 5.60; N, 8.30%.

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