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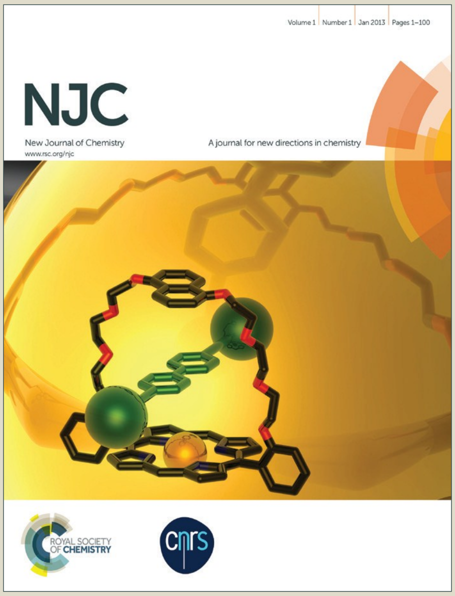

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ARTICLE

CsOH /γ-Al_2O_3: A heterogeneous reusable basic catalyst for one pot synthesis of 2-amino-4, 6-diaryl pyrimidines

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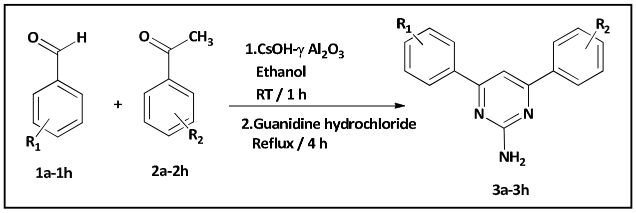
A new strategy for one pot synthesis of 2-amino-4, 6-diaryl pyrimidines using CsOH/γ-Al_2O_3 as a heterogeneous, reusable basic catalyst is presented. The developed synthetic protocol for pyrimidines is one pot three component reaction of acetophenones, aromatic aldehydes and guanidine hydrochloride in ethanol. The characterization of the catalyst CsOH/γ-Al_2O_3 was performed by using FT-IR, XRD, TG-DTA, SEM, BET surface area and CO_2-TPD analysis techniques. The analytical data proves that the catalyst has excellent reusability and also indicates its good thermal stability.

1. Introduction

Pyrimidines are important structural motif of various drug molecules as they exhibit diversified biological activities. Pyrimidine derivatives serve as antineoplastic,[1] antibacterial,[2] anti HIV,[3] antibiotics,[4] antifungals,[5] antituberculars.[6] Pyrimidine bases like thymine, cytosine, and uracil are essential building blocks of nucleic acids. Many of the established drugs containing pyrimidine nucleus are reported in literature namely 5-Fluorouracil as anticancer,[7] Idoxuridine as antiviral,[8] Zidovudine as anti HIV,[9] Trimethoprim as antibacterial.[10] Along with their direct application to human beings, certain pyrimidines are used as herbicides[11] and plant growth regulators.[12] Beyond their applications in the biological world, pyrimidines are widely employed in material chemistry due to their liquid crystalline property.[13] Also some pyrimidine derivatives show selective ion sensing property,[14] optoelectronic property,[15] and efficient Dye sensitized solar cells.[16]

Due to their importance, huge amount of work has been done for the synthesis of pyrimidines. 2-amino-4, 6-diaryl pyrimidines have been synthesized from chalcones,[17] β-diketones,[18] flavones[19] using different bases like K_2CO_3, KOH, NaOH and also via microwave irradiation.[20] Usually pyrimidine synthesis encounters long reaction time, low product yield, multistep synthesis. Therefore, there is scope to develop a rapid and green procedure for the synthesis of 2-amino-4, 6-diaryl pyrimidines.

In the past decade, one pot reactions have been the zest of chemists and now are practiced as one of the most important protocol in synthetic chemistry.[21-23] One pot reactions are always in limelight due to less reaction time, lessened amount of waste generated and high reaction rates. Application of catalyst in organic transformation is a key step towards an efficient synthesis of target molecule.[24] Use of heterogeneous catalytic media improves the isolation of product along with reusability of the catalyst.[25, 26] Hence, we have designed a new protocol for the synthesis of 2-amino-4, 6- diaryl pyrimidines from aromatic aldehydes, acetophenones and guanidine hydrochloride using heterogeneous basic catalyst CsOH/γ-Al_2O_3 (**Scheme 1**)



Scheme 1- Modified synthetic route to afford 2-amino-4, 6-diaryl pyrimidines.

Cesium hydroxide has been frequently employed as a basic catalyst for various chemical transformations.[27] The main disadvantage of using CsOH alone is the reusability of catalyst and hygroscopic nature. Alumina also served as a basic catalyst in various organic reactions.[28] Some initial experiments were carried out using alumina as a heterogeneous catalyst but there was no formation of product. Recently we have developed CsOH/γ-Al_2O_3 as a basic catalytic system for the synthesis of *4H*-pyran derivatives.[29] CsOH/γ-Al_2O_3 catalytic system has not been reported for the synthesis of 2-amino-4, 6-diaryl pyrimidines.

2. Experimental

2.1. Chemicals and instruments

Unless otherwise stated, all reagents were purchased from Sigma Aldrich (India) and used without purification. All melting

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Electronic Supplementary Information (ESI) available: [FT-IR, ^1H, ^{13}C and MS spectra of the selected compounds]. See DOI: 10.1039/x0xx00000x

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points were recorded on centrofix syndicate MP apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker AVANCE spectrometer (Bruker BioSpin AG, Fällanden, Switzerland; 300 MHz) using DMSO-d6/$CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) were expressed in terms of ppm. Infrared experiments were performed using Frontier Perkin Elmer IR spectrometer. XRD analysis of the catalyst was performed using Shimadzu Maxima 7000 S X-ray Diffractometer. Perkin Elmer Pyris Diamond Thermogravimetric Analyzer was used for TG-DTA studies. The analysis was carried out under inert atmosphere (N_2) with temperature control of 10°C min^{-1}. Scanning Electron Microscopy (SEM) analysis was carried out using FEI-Inspect 450 FEGSEM. Surfer Autosorb-1, Thermofisher Scientific was used for BET surface area analysis of the catalyst.

2.2. Preparation of CsOH/γ-Al_2O_3 catalyst

CsOH (1.0g) and γ-Al_2O_3 (2.0g) were stirred in 20.0 ml methanol for 2.0 hours at room temperature. Methanol was recovered under reduced pressure and the solid mass was dried at 100°C followed by calcination at 400°C for 4 hours. The obtained solid mass was crushed in to fine powder with the help of mortar and pestle.

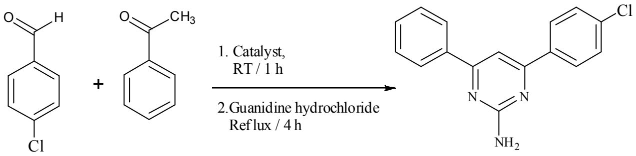
2.3. General procedure for pyrimidine synthesis

CsOH/γ-Al_2O_3 (10mol%) was added to the mixture of aromatic aldehyde (1 mmol) and acetophenone (1 mmol) in 30.0 ml ethanol. The reaction mixture was stirred at room temperature for 1 hour. After the completion of reaction (TLC control for formation of chalcone), guanidine hydrochloride (1 mmol) was added and refluxed for 4 hours. Catalyst was then filtered and reaction mixture poured in to ice cold water (30 ml). Crude solid product was collected by filtration and recrystallized from ethanol to afford pure product (**3a-3h**).

3. Results and discussion

A set of experiments was performed to determine the active catalytic component of the CsOH/γ-Al_2O_3 catalytic system. The reaction of acetophenone (1 mmol), 4-chlrobenzaldehyde (1 mmol) and guanidine hydrochloride (1 mmol) in one pot was carried out using only ethanol as a solvent. No product formation was observed in this case. (**Table 1**, Entry 1) Similarly, reactions were carried out using CsOH in ethanol and alumina in ethanol. Product formation was observed in case of CsOH in ethanol, but no regeneration of the catalyst as all the CsOH gets dissolved in ethanol. (**Table 1**, Entry 2) Alumina in ethanol did not lead to formation of product. (**Table 1**, Entry 3) Thus alumina is not the active component of the catalyst and is used as a support. A set of reactions were carried out with CsOH/γ-Al_2O_3 catalyst, with and without calcination at 400°C. In the case of catalyst without calcination, product formation was observed in the first cycle of the reaction, due to the basicity provided by CsOH. However when the catalyst was recovered and reused in second cycle there was traces of the product. This is due to the loss of CsOH during the recovery of the catalyst (washing with ethanol), as CsOH is adsorbed on the surface of alumina. (**Table 1**, Entry 4) When the catalyst was calcined at 400°C, product formation was observed with good yield both in fresh cycle and recycle of the catalyst. (**Table 1**, Entry 5) The above experiment clearly supports the requirement of the calcination of the catalyst as the active component cesium hydroxide is well incorporated into alumina support.

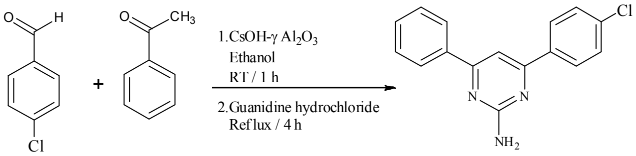
Table 1 Optimization of catalytic activity.



Entry	Reaction condition[a]	Yield[a] (%)
1	Ethanol	-
2	CsOH in Ethanol	70
3	Alumina in Ethanol	-
4	CsOH/γ-alumina in ethanol without calcination at 400°C	65
5	CsOH/γ-alumina in ethanol with calcination at 400°C	80

[a] Isolated yield

Table 2 Optimization of amount of CsOH/γ-Al_2O_3 catalyst loaded.



Entry	mol % of catalyst	Yield[a] (%)
1	5	58
2	10	80
3	15	75
4	20	75
5	25	72

[a] Isolated yield

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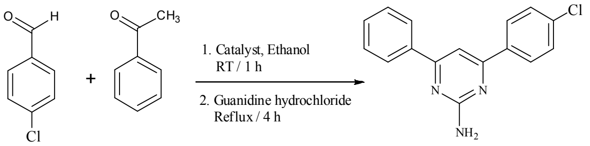
Optimization of reaction condition was carried out on the basis of the amount of catalyst loaded. Ranging from 5 mol% to 25 mol% of catalyst, a set of reactions was performed using acetophenone, 4-chloro benzaldehyde and guanidine hydrochloride in ethanol. Yield of the reaction was poor at the low amount of the catalyst loading. (**Table 2, entry 1**) However at higher loading of catalyst (10 mol %), yield increases up to 80%. (**Table 2, entry 2**) There was not much alteration in the yield, after further increase in concentration of the catalyst. Literature survey indicates that the maximum dispersion of the catalyst particles is obtained at particular fixed concentration.[30] Beyond this concentration, catalyst particles get agglomerated and do not participate in the reaction. Agglomeration of the catalyst will certainly decrease the surface area required for catalytic organic transformation.[31,32] Thus for CsOH/γ-Al_2O_3, maximum dispersion of the catalyst and catalytic activity was obtained at 10 mol% concentration. Similarly different solvents were screened for the pyrimidine synthesis, out of which ethanol gave the best results. The results from **Table 2** show that, efficiency of the reaction mainly depends on the amount of catalyst loaded. Various basic catalytic systems were also screened to select the most superior catalyst. Among these catalysts, CsOH/γ-Al_2O_3 catalytic system proved to be superior in terms of yield than other heterogeneous basic catalysts. (**Table 3**)

Table 3 Effect of different catalysts on the reaction



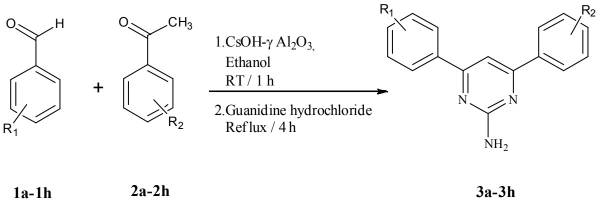
Entry	Catalyst (10 mol %)	Yield[a] (%)
1	KOH/ γ-Al_2O_3	65
2	KF/ γ-Al_2O_3	50
3	Cs_2CO_3/ γ-Al_2O_3	60
4	CsF/ γ-Al_2O_3	55
5	CsOH/γ-Al_2O_3	80

[a] Isolated yield

Molar composition of the catalyst was optimized by using CsOH and Al_2O_3 in 1:1 and 1:2 ratios respectively. When experiment was carried out at equimolar concentration of CsOH and alumina, hygroscopic nature of the catalyst was not diminished. Whereas at 1:2 molar composition of CsOH and alumina, the catalyst becomes non-hygroscopic, which is attributed to complete reactivity of CsOH with alumina.

Once the reaction conditions were optimized, a series of 2-amino-4, 6-diaryl pyrimidine derivatives **(3a-3h)** were synthesized. (**Table 4**) The reaction was carried out at a temperature of 80°C in ethanol using different aromatic aldehydes, acetophenones, and guanidine hydrochloride in the presence of CsOH/γ-Al_2O_3 catalytic system. Conventionally the reaction between acetophenone and aromatic aldehyde is carried out to afford chalcone which then condenses with guanidine hydrochloride to give 2-amino-4, 6-diaryl pyrimidines. The advantages of the current one pot synthetic protocol is high yield, short reaction time, mild reaction conditions and the need for separating the intermediate chalcone is avoided.

Table 4 Synthesis of 2-amino-4, 6-diaryl pyrimidine derivatives using CsOH/γ-Al_2O_3



Entry	R^1	R^2	Yield[b] (%)	M.P (^{0}C)
3a	H	H	75	118[33,34]
3b	4-Cl	H	80	160[33,34]
3c	3-Cl	H	72	118[33,34]
3d	4-F	H	74	132[33,34]
3e	4-CH_3	H	80	128[33,34]
3f	4-OCH_3	H	72	152[33,34]
3g	4-F	4-Br	72	154[33,34]
3h	4-Br	Ferrocene	80	188

[a] Reaction conditions: aldehydes (1 mmol), acetophenones (1 mmol), guanidine hydrochloride (1 mmol), 10 mol % CsOH/γ-Al_2O_3, ethanol (25 ml).

[b] Isolated yield.

Table 5 Recyclability of CsOH/γ-Al_2O_3 Catalyst

Product	No. of cycle	Yield[a] (%)
3b	1	80
	2	80
	3	78
	4	76
	5	76

[a] Isolated yield

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^1H, ^{13}C NMR and IR spectra of the pyrimidine derivatives (**3a-3h**) were consistent with the data reported in the literature.[33, 34] Reusability is one of the major aspect of using heterogeneous catalytic media. Catalyst was separated by simple filtration, washed with ethanol and dried at 400°C for one hour. Recycled catalyst was loaded successively up to 5 cycles without affecting its activity (**Table 5**).

After the synthesis of pyrimidine derivatives in good yields, characterization of the catalyst was performed by using various analytical and spectroscopic methods. In the FT-IR spectrum of CsOH/γ-Al_2O_3 catalyst calcined at 400°C, along with the CsOH and Al_2O_3 characteristic bands, new frequency bands were observed which are assigned as follows. Broad band at 3400 cm^{-1} attributed to (-OH) group of water physisorbed on surface of γ-Al_2O_3. Cs-O bending vibrations were observed at 1350-1480 cm^{-1}. The bands at 850-880 cm^{-1} and 910 cm^{-1} were assigned to Al-O-Cs bonding. (**Fig.1**)

Figure 2a and **Figure 2b** shows XRD pattern for γ-Al_2O_3 and CsOH/γ-Al_2O_3 catalyst after calcination at 400°C respectively. In **Figure 2a,** characteristic signals were obtained for γ-Al_2O_3 at 2θ = 32°, 37°, 43°, 46°, 67°. The diffraction peaks of γ-Al_2O_3 are in good agreement with International Centre for Diffraction Data Powder Diffraction file (PDF) 29-0063. Along with parent peaks of alumina, new diffraction peaks in XRD pattern of catalyst mainly attributed to formation of new phase Cs_2O during calcination of catalyst. XRD pattern for catalyst were obtained at 2θ = 19°, 23°, 26°, 29°, 33°, 37°, 49°, 51°, 64°, 67° (**Fig. 2b**). It was observed that the signals obtained for catalyst were almost similar to that of Cs_2O with slight shift in values and broadening of peaks (International Centre for Diffraction Data Powder Diffraction file (PDF) 00-009-0104). This shift in signals of catalyst compared with Cs_2O signals is due to presence of Alumina. Intensity peaks of alumina in the catalyst were also found lower due to presence of cesium hydroxide. Thus we can conclude that, after calcination, insitu formed Cs_2O is well incorporated in crystal structure of γ-Al_2O_3. XRD pattern of the catalyst after the 5th cycle of reuse shows unaltered diffraction pattern as that of fresh catalyst CsOH/γ-Al_2O_3 after calcination at 400°C. (**Fig. 2b**)

TG-DTA experiments were performed using Perkin Elmer Pyris Diamond Thermogravimetric Analyzer under inert reaction atmosphere (N_2) with temperature control of 10°C min^{-1}. **Figure 3** shows the TG-DTA curves of the catalytic system CsOH/γ-Al_2O_3 after calcination at 400°C. First and second endotherms at 100°C and 250°C were assigned to the loss of physisorbed and chemisorbed water respectively. The third weight loss at 750°C is due to volatilization of Cs_2O.[35,36] The results from TG-DTA curves indicate the wide operating range of temperatures for the catalytic system and are in accordance with our previous investigations.[29]

Figure 4a illustrates the SEM micrograph of γ-Al_2O_3. Alumina exhibits thick plate like morphology similar to flower shaped structure. **Figure 4b** reveals the surface morphology of the catalyst before reaction. Visual observations from **Fig.4** provide primary information about the incorporation of the cesium hydroxide on alumina which was strongly supported by Energy Dispersive X-ray analysis (EDAX) spectrum of the catalyst. (**Fig. Supp. info. S-20**) EDAX spectrum of the catalyst clearly indicates the presence of cesium, aluminium and

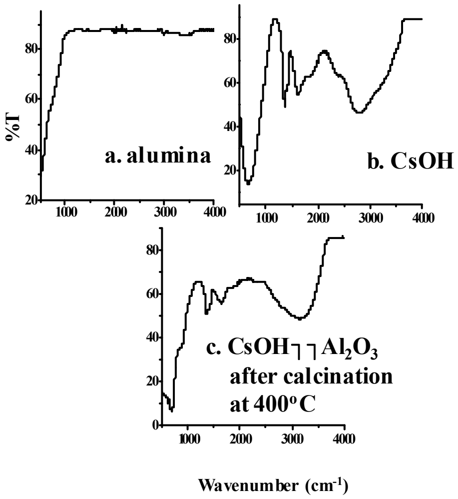

Fig.1 FT-IR spectra of (a) γ-Al_2O_3, (b) CsOH, (c) CsOH/ γ-Al_2O_3 catalyst after calcination at 400°C.

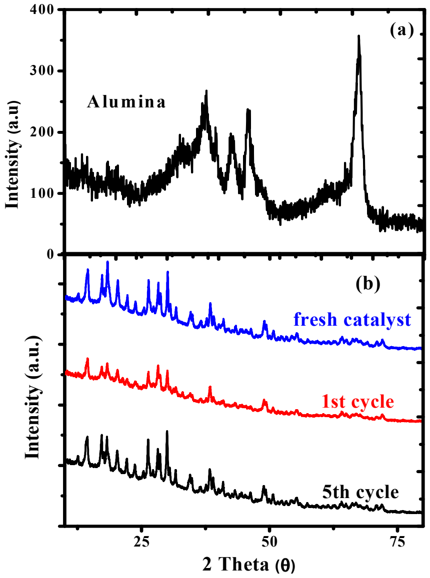

Fig.2 XRD patterns of (a) γ-Al_2O_3 and (b) CsOH/ γ-Al_2O_3 calcined at 400°C *i.* fresh catalyst *ii.* 1st cycle *iii.* 5th cycle of reuse.

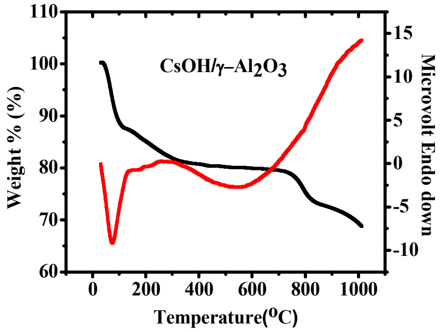

Fig.3 TG-DTA analysis of CsOH/ γ-Al_2O_3 catalyst

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oxygen. Thus, **Fig. 4b** shows the composite nature of catalyst unlike alumina. **Fig. 4c** and **Fig. 4d** represents the surface morphology of the reused catalyst after 1st and 5th cycle respectively. The EDAX spectrum for the same shows no alterations in the composition of the catalyst. (**Fig. Supp. info. S-20**)

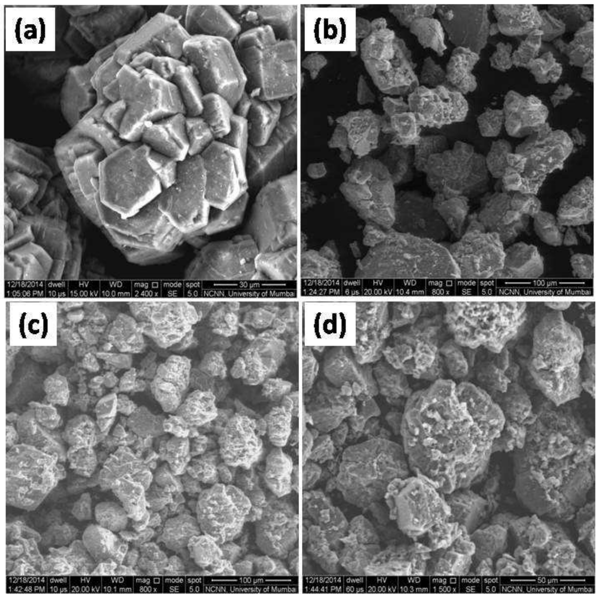

Fig.4 SEM images of (a) γ-Al_2O_3 (b) CsOH/ γ-Al_2O_3 before reaction (c) CsOH/ γ-Al_2O_3 after 1st recycle reaction (d) CsOH/ γ-Al_2O_3 after 5st recycle reaction.

BET surface area analysis of the catalyst was performed at liquid nitrogen temperature (78 K). Powdered catalyst sample (0.5 g) was placed in sample holder and allowed to degas for 2 hours at 150°C to remove contaminant gases and water vapors. Then the sample was analyzed for surface area properties and specific surface area of sample was calculated using BET adsorption equation. **Figure 5** relates to a nitrogen sorption isotherm of CsOH/γ-Al_2O_3 catalyst.

Catalyst exhibits type IV adsorption pattern. In the low pressure range ($P/P^0 < 0.4$), adsorption and desorption isotherm nearly superimpose each other and at higher pressure ($P/P^0 > 0.7$) isotherm increases. Type IV adsorption pattern indicates that initially nitrogen gas is chemisorbed on surface of the catalyst. After complete formation of monolayer of N_2 on catalytic surface, physisorption is initiated. At lower pressure chemisorption is preferred over physisorption.

Type IV isotherm shows small hysteresis loop like structure, indicating the presence of very small mesopore volume. The hysteresis effect and the slope of the plateau increased to yield Type IV isotherm with a significant increase in the nitrogen uptake through the entire pressure range indicating the presence of mesopores. Using the multiplot BET equation, specific surface area of the catalyst was calculated, which comes out to be 29.39 m^2/g. Figure (**Supp. info**. **S-21**) shows the multipoint BET plot of the CsOH/γ-Al_2O_3 catalyst. **Table 6** represents the BET experimental results of the catalyst CsOH/γ-Al_2O_3. According to BET theory, Monolayer adsorption suggests the chemisorption between surface of the catalyst and the adsorbate while further upcoming layers indicate the physisorption between catalyst and the adsorbate. BJH desorption pore size distribution curve of the catalyst was used to calculate maximum pore size distribution which is 10-50 A° (mesopores) radius (**Fig. 6**).

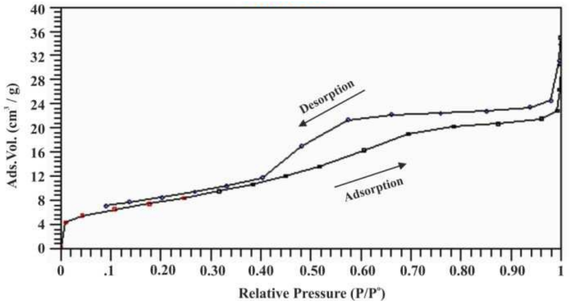

Fig.5 N_2 adsorption-desorption isotherm of CsOH/ γ-Al_2O_3 catalyst.

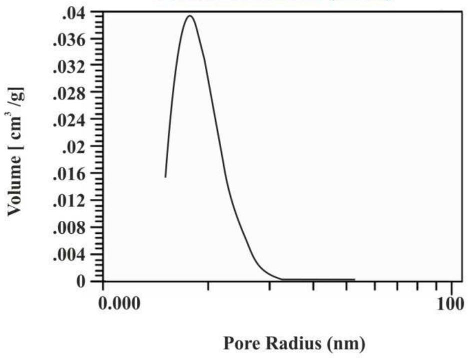

Fig. 6 BJH pore size distribution curve of CsOH/ γ-Al_2O_3 catalyst

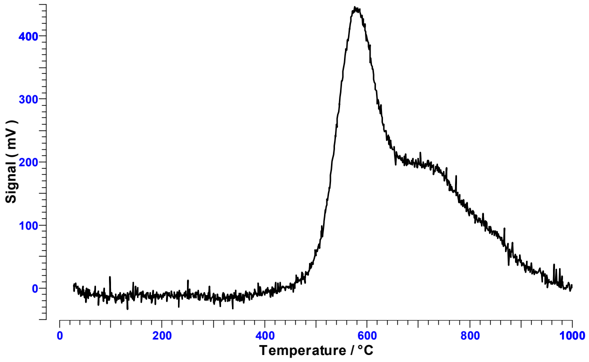

Fig. 7 CO_2-TPD analysis of the catalyst CsOH/γ-Al_2O_3

Table 6 BET experimental results of the catalyst CsOH/γ-Al_2O_3.

Constant C	Monolayer adsorption volume(cm^3/g)	BET surface area (m^2/g)	Avg.radius size (A°)
47.043	6.7563	29.3965	21.5644

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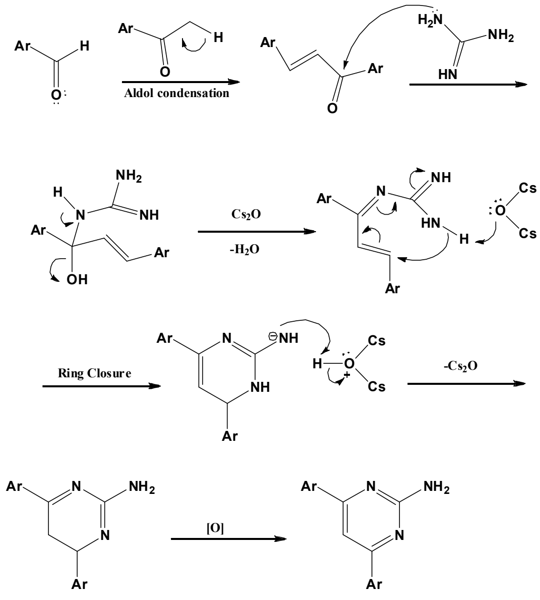
Fig. 7 depicts the TPD profile of CO_2 adsorbed on CsOH/γ-Al_2O_3 catalyst. In the lower temperature region, the catalyst has a small to moderate amount of CO_2 desorption at 100-300^{o}C and strong desorption peak at 600^{o}C. The result clearly indicates the presence of basic sites on the catalyst. The TPD plot of adsorbed CO_2 for γ-alumina shows the presence of weak basic sites at relatively lower temperatures.[37] Presence of cesium hydroxide shows the broad desorption signal at higher temperatures. Here we found that activities of the weak/moderate basic sites are responsible for the organic transformation.

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



Scheme 2 Plausible mechanism to afford 2, 4-diaryl pyrimidine using CsOH/ γ-Al_2O_3 catalyst

4. Conclusions

In conclusion, the developed one pot synthetic approach for 2-amino-4, 6- diaryl pyrimidine has several advantages compared to methods reported in the literature. It involves one pot process, short reaction time, high yields along with reusability of heterogeneous catalyst. Detailed studies of the catalyst for its characterization and properties has been accomplished utilizing FTIR, XRD, TG-DTA, SEM, EDAX, BET surface area analysis and CO_2-TPD analysis techniques. Structural features of the catalyst remain unaltered after the reaction and reusability was studied up to 5 cycles. Thus, the developed one pot synthetic protocol is simple, green and highly efficient.

Acknowledgement

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Graphical Abstract

CsOH /γ-Al_2O_3: A heterogeneous reusable basic catalyst for one pot synthesis of 2-amino-4, 6-diaryl pyrimidines.

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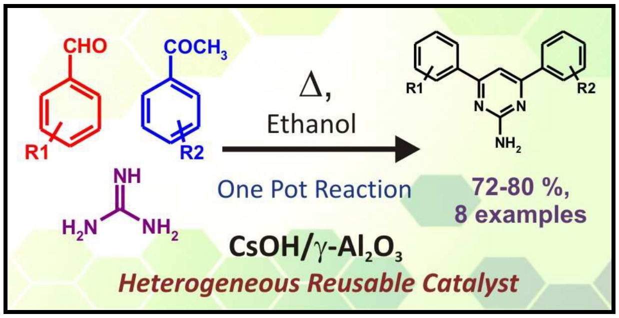

Pyrimidine derivatives were synthesized in one pot using a novel heterogeneous reusable catalyst and complete characterization of catalyst was performed.