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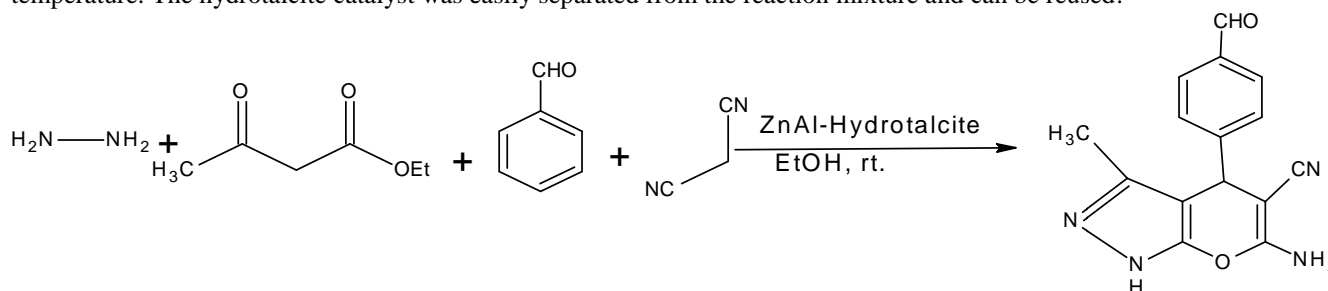
## Synthesis and Characterization of Zn-Al-Cl of Hydrotalcites and their Application in Four Component Synthesis of 4H-Pyrano[2,3C] Pyrazoles

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### ABSTRACT

Zn/Al hydrotalcite acts as an efficient heterogeneous basic catalyst for the synthesis of 4H-pyrano[2,3-c] pyrazoles via a multi-component reaction of hydrazine hydrate, ethyl acetoacetate, aldehydes, and malononitrile in ethanol at ambient temperature. The hydrotalcite catalyst was easily separated from the reaction mixture and can be reused.



**Keywords:** Heterogeneous catalyst, hydrotalcite, multi-component reactions.

### ARTICLE INFO

#### CONTENTS

1. Introduction . . . . .	188
2. Experimental . . . . .	188
3. Results and Discussion. . . . .	191
4. Conclusion . . . . .	192
5. Acknowledgement. . . . .	192
6. References . . . . .	192

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## 1. Introduction

Multi-component reactions (MCRs) have emerged as a means to achieve atom economy and benign synthesis by virtue of their convergence, productivity, easy execution, and generation of highly diverse and complex products from easily available starting materials in a single operation [1]. One-pot MCRs that involve economically and environmental friendly chemical processes have received attention as a strategy for “green” organic syntheses. The importance of MCRs in organic synthesis has been recognized and considerable efforts from both academic and researchers have been focused on the design and development of multi-component procedures for the generation of libraries of heterocyclic compounds [2].

4H- pyrano [2,3-c] pyrazoles [1] are important because of their pharmacological properties such as antimicrobial [3] and anti-inflammatory [4] activities. There has been a tremendous development in four multi-component reaction and efforts are still being made to find and develop new multi-component reaction. Multi-component reaction are now being tailored and fine-tuned for synthesizing various heterocyclic scaffolds for diverse application.

Heterogeneous catalysts are vital in green synthesis due to their easy recovery and subsequent reuse. My research work has been developing efficient and environmentally benign protocols using various heterogeneous catalysts [5–8]. Multi-component reactions play an important role in modern organic chemistry, because they generally exhibit higher atom economy and selectivity as well as produce fewer by-products compared to classical multi step syntheses [9]. Furthermore, MCRs are easy to perform, inexpensive, quick, consuming less energy and involves simple experimental procedures [10]. Otto first attempted synthesis of 4H-pyrano[2,3-c] pyrazole from 3-methyl-3-pyrazolin-5-one and arylidenemalononitrile using base catalyst [7]. From the literature, we observed that very few catalysts have been used for the synthesis of 4H-pyrano[2,3c]pyrazoles (e.g., triethylamine, [8] piperidine, [11] morpholine, [12] p-dodecylbenzenesulfonic acid, [13] hexadecyltrimethyl ammoniumbromide, [14] potassium fluoride dehydrate, [15] and electro-generated bases [16].

In these methodologies, two- or three-component strategies have been employed for the preparation of 4H-pyrano[2,3-c]pyrazoles. Michael addition of ethyl acetoacetate to the Knoevenagel product of malononitrile and benzaldehyde lead to the formation of 2-amino-3-cyano-4H-pyrano[2,3c] pyran [17]. 4H-pyrano[2,3-c]pyrazoles (Figure 2) are obtained when a mixture of 2, hydrazine hydrate, and a catalytic amount of piperazine is heated in water under combined microwave and ultrasound irradiation [18]. Our research group has been developing efficient and environmentally benign protocols using hydrotalcites as heterogeneous catalysts [19]. In continuation of our efforts to develop efficient and environmentally benign protocols for the synthesis of heterocycles, we report herein for the first time the use of a solid base, Zn/Al hydrotalcites, for the catalysis of an MCR of hydrazine hydrate.

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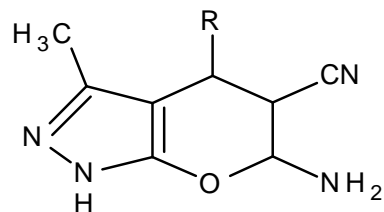


Figure 1

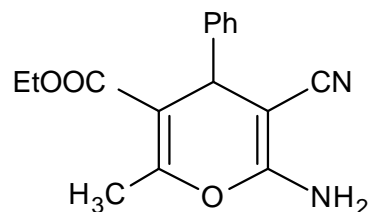


Figure 2

## 2. Experimental

### Materials and Methods

The hydrazine hydrate, ethyl acetoacetate, substituted aromatic benzaldehyde, malononitrile and metal salt used were purchased from Himedia and Rankem. The synthesized compounds were characterized by comparing the observed spectral data and physical properties with those of authentic sample. Melting points were determined on electrical melting points apparatus in an open capillary and were uncorrected. UV-Vis spectra were recorded on Chemitspectrascan 2600 double beam in acetonitrile, IR spectra were recorded on Shimadzu Prestige 21 spectrometer using KBr pellet, <sup>1</sup>H NMR spectra were recorded on BRUKER AVANCE II 400 NMR Spectra using CDCl<sub>3</sub> as an internal standard and Mass spectra were recorded on Agilent ION TRAP 6310 instrument.

### Catalysts preparation

Al-Zn-Cl was prepared by one pot co-precipitation reaction at 100 °C for 30 minutes and autogenous pressure in aqueous media to obtain small and high surface area particles [20]. In a typical reaction Zn and Al chloride (metallic ratio 3:1) were taken and corresponding ratio of sodium bicarbonate were added and pH was maintained at 8.5. After aging the slurry for 12 h. white precipitate obtained were dried [22].

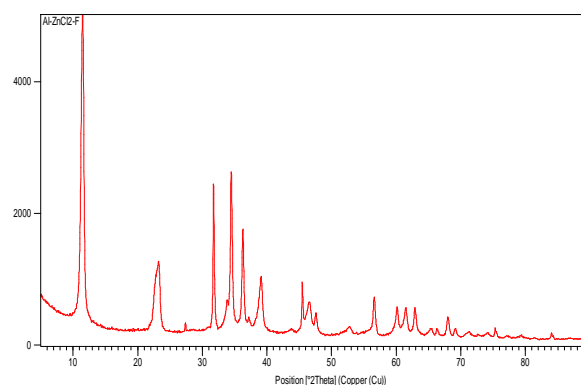


Figure 3: XRD pattern of Al-Zn-Cl Hydrotalcite

Powder X-ray diffraction (PXRD) measurements were performed on a PAN Alytical Xpert Pro X-ray Diffractometer using Cu Ka radiation ( $\lambda = 0.154 \text{ nm}$ ) at 40 kV, at a scanning rate of  $2^\circ \text{ min}^{-1}$ . Powder X-ray diffraction (PXRD) pattern of the powder catalyst was collected between  $5$  and  $85^\circ 2\theta$ , at a step width of  $0.02^\circ$  and a step time of  $1 \text{ s}$  using a PAN alytical Xpert Pro X-ray Diffractometer using Cu target and a graphite monochromator. However, the intensity of all the peak [(003), (006), (009), (012),(018),(110), (113) and (115)] decrease in the order of  $\text{Zn-Al-CO}_3$   $\text{Zn-Al-Cl}$  which indicates a decrease in crystallinity upon intercalation with anions other than Cl. The observed trend in the crystallinity is also corroborated by the decrease in average particle size from  $25.24 \text{ nm}$  for  $\text{Zn-Al-CO}_3$  and  $20.05$  for  $\text{Zn-Al-Cl}$ . For the hydrothermal treated sample  $\text{Zn-Al-HT}$  the basal reflection are recorded at  $8.15, 3.45$  and  $2.65^\circ$  ( $c = 25.44$ ), while the diffraction due to planes (110) is recorded at  $1.530^\circ$  ( $a = 3.07$ ). Hydrotalcite-like phase.

#### FT-IR

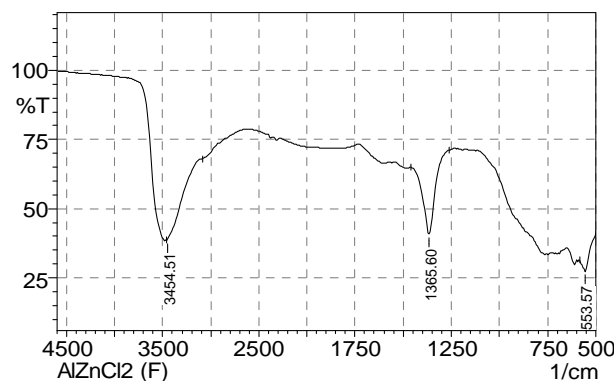


Figure 4

FT-IR analysis studies carried out in the order to analyze the nature of anion in the interlayer. The IR spectrum are shown in figure 4. Infrared spectrum in the Oh stretching region a broad around  $3454.51$ , in presence of Cl<sup>-</sup> anion was confirmed by the absorption peak about  $553.57 \text{ cm}^{-1}$ . A small band is observed at  $1365.60 \text{ cm}^{-1}$  just next to the water bending vibration at  $1155 \text{ cm}^{-1}$

#### TGA

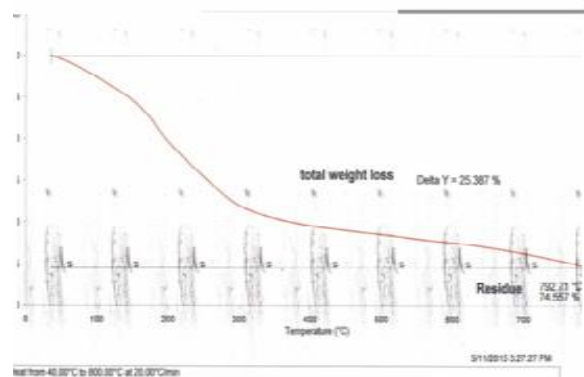


Figure 5

The TG showed a first weight loss below  $200^\circ\text{C}$ , which is ascribed generally to the loss of physically, adsorbed ant interlayer water. The second weight loss in the temperature range  $150-700^\circ\text{C}$  can be attributed to the decomposing to brucite-like layer and the removal of the interlayer anions. The broad DTG peak of  $\text{Zn-Al-Cl HT}$  reveals that the decomposing process is complex. It showed three weight loss process below  $200^\circ\text{C}$ , which are ascribed to loss of surface water and interlayer water. Two more stage of loss processes, one between  $200$  and  $400^\circ\text{C}$  and another  $450$  and  $600^\circ\text{C}$  are due to the removal of interlayer anions.

#### SEM

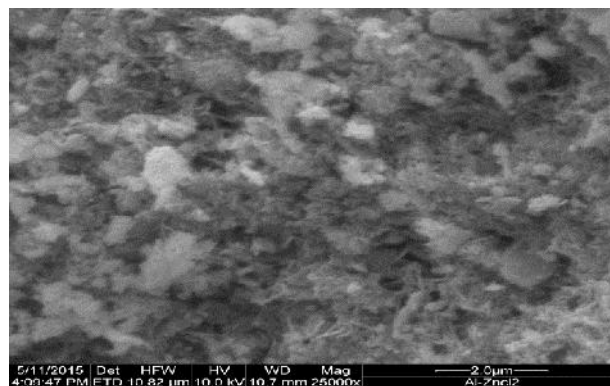
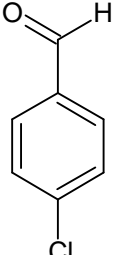
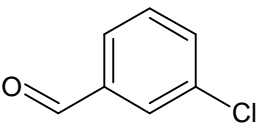
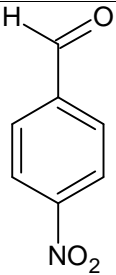
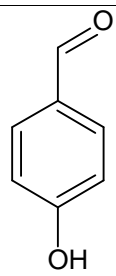
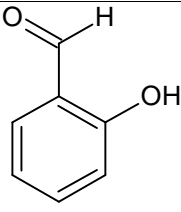
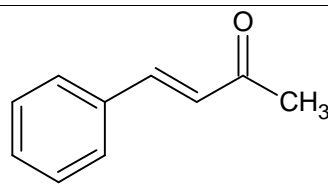
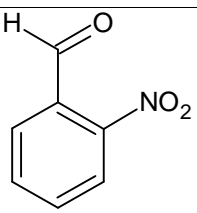
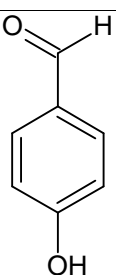


Figure 6

**Table 1:** Synthesis of pyranopyrazole derivatives via a multi-component reaction of hydrazine hydrate, ethyl acetoacetate, aromatic aldehyde and malononitrile in presence of  $\text{Zn/AlClHT}$  at room temperature

Entry	R <sup>1</sup>	Al- Zn--Cl Hydrotalcite	
		Time	Yield
1		1h	60

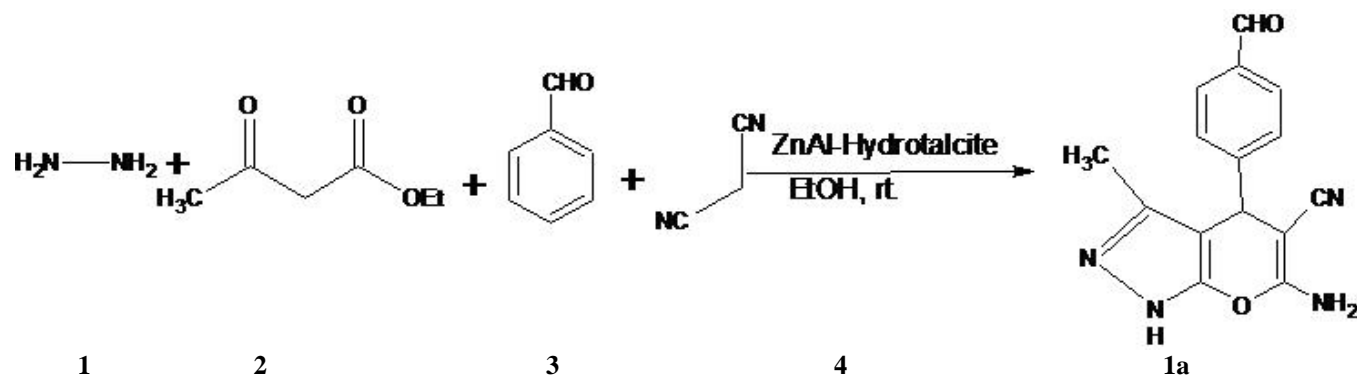
2		1h	98
3		1h	98
4		1.3h .	76
5		3h	45
6		2.3h	56
7		1.3h	42
8		1h	63
9		1h	48

10		1h	75
11		2h	27

**Notes:** Reaction condition: hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), aldehyde (2 mmol), malanonitrile (2 mmol), EtOH (5ml); HT=0.1g.

The morphology and structure of sample was studied by scanning and transition electron microscopies. SEM showed a homogeneous and laminar material, as expected for hydrotalcites. The energy dispersive X-ray detector

identified the presence of carbon, oxygen, magnesium, cobalt and aluminum with the molar ratio Zn:Al = 3:1, which is typical structure of the hydrotalcite-like materials.



**Table 2:** Reaction of hydrazine hydrate, ethyl acetoacetate, Chlorobenzaldehyde and malanonitrile in presence of Zn/Al Clor Li/AlNO<sub>3</sub> HT with different Zn/Al ratio and classical bases in EtOH at room temperature.

Entry	Catalyst	Yield (%)
1	Zn/Al(2:1)	42
2	Zn/Al(3:1)	98
3	Li/Al(3:1)	72
4	ZnO	63
5	MgO	75
6	CaO	43
7	Al <sub>2</sub> O <sub>3</sub>	55
8	TiO <sub>2</sub>	61
9	CuO	48
10	Fe <sub>2</sub> O <sub>3</sub>	75
11	Triton-X	66
12	Cetrimide	72
13	Sodium lauryl sulphate	62

**Notes:** Reaction condition: hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), aldehyde (2 mmol), malanonitrile (2 mmol), EtOH (5ml); Catalyst =0.1g. Time 1.3 room temperature.

#### Typical Reaction Procedure

Zn/Al HT(0.1 g.) and Ethanol (5 ml) were added to a mixture of hydrazine hydrate (2mmol), ethyl acetoacetate (2mmol), aldehyde(2mmol), malanonitrile (2mmol). The reaction mixture was stirred at room temperature at atmosphere pressure. After completion of the reaction. The reaction mixture was heated to dissolved the product in ethanol and filtered hot. The filtrate was allowed to stand at room temperature when the product separated. It was filtered and washed with water, followed by the mixture of ethyl acetate /hexane (30:70 v/v). The products were characterized by NMR, GC-MS and FT-IR.

### 3. Results and Discussion

In the present paper, we describe the use of (Zn/Al) hydrotalcites (HT) as a first heterogeneous catalyst for the

synthesis of 4H-pyrano[2,3c] pyrazoles. Zn-Al with molar ratio 2 and 3 were prepared by the reported procedures. (18) and were characterized by x-ray diffraction (XRD), Fourier transform infrared (FT-IR), transition electron microscope (TEM), scanning electron microscope (SEM), and Thermal gravimetric analysis (TGA). The reaction of hydrazine hydrate, ethyl acetoacetate (EAA), chlorobenzaldehyde, and malanonitrile was selected as model reaction for optimizing of various parameters. The reaction is carried out using different hydrotalcite (Zn/Al = 2, 3) and classical bases at room temperature (Table 1). The basicity of HT is sensitive to the Zn/Al ratio.

The total amount of basic sites of HT increase gradually with molar Zn/Al ratio but the proportion of basic sites (i.e., those catalyzing the reaction) decrease. The catalytic activity of the HT was more than that of corresponding calcined HT. It is known that that calcined HT contain basic site of pKa values up to 16.5. However, most of its basic site have 10.7 pKa 13.3, and only a few of them show strengths 13.3 pKa 16.9.[19] Thus, the total basicity of calcined HT is more than that of the corresponding uncalcined form. In the absence of catalyst, very little product was formed. Almost all the aldehydes resulted in good to excellent yield of the corresponding products. Studies revealed that aldehyde having electron withdrawing substituent's reacted faster and gave better yield of the product as compared to the aldehyde with electron donating substituent. Under the optimized condition, various substituted aromatic aldehyde were reacted to obtain the corresponding 4H-pyrano[2,3c] pyrazoles in good yield. The hydrotalcite is a heterogeneous catalyst and could easily separated from the reaction mixture by filtration. The recovered catalyst was used for successive run to test its reusability. It was observed there was a decrease in the yield of the products.

#### 4. Conclusion

In conclusion, we have developed an efficient protocol for the synthesis of pyranopyrazoles by a one-pot multi-component reaction of hydrazine hydrate, ethyl acetoacetate, aldehyde, malanonitrile using catalytical amount of Zn/Al hydrotalcites in ethanol at room temperature. The catalyst is simple and nontoxic. The reaction procedure is very mild and involves simple workup procedure to obtain the desired product to excellent yields.

#### 5. Acknowledgment

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