Available Online at
http://www.ijcpa.in
January-March 2016

International Journal of
CHEMICAL AND PHARMACEUTICAL
ANALYSIS

eISSN: 2348-0726 ; pISSN : 2395-2466

Research Article | Volume-3 | Issue-2 | Article ID: 797

SYNTHESIS AND CHARACTERIZATION OF Zn-Al-Cl_2 OF HYDROTALCITES AND THEIR APPLICATION IN FOUR COMPONENT SYNTHESIS OF 4H-PYRANO[2,3c] PYRAZOLES

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Received: 28 July 2015 / Revised: 10 November 2015 / Accepted: 19 February 2016 / Available online : 31 March 2016

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; multicomponent reactions.

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 hetrocyclic compounds. [2] 4H- pyrano [2,3-c] pyrazoles [1] are important because of their pharmacological properties such as antimicrobial [3] and anti-flammantory[4] activities. There has been a tremendous development in four multi-component reaction and efforts are still being made to find and develop new multicomponent reaction. Muticomponent 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] Multicomponent 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 arylidene malononitrile using base catalyst[7] From the literature, we observed that very few catalysts have been usedfor the synthesis of 4H-pyrano[2,3c] pyrazoles(e.g.,triethylamine,[8] piperidine,[11] morpholine,[12] p-dodecylbenzenesulfonic acid, [13] hexadecyltrimethylammoniumbromide,[14] potassium fluoride dehydrate, [15] and electrogenerated 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 malanonitrile and benzaldehyde lead to the

formation of 2-amino-3-cyno-4H-pyrano[2,3c] pyran.[17] 4H-pyrano[2,3-c]pyrazoles(Fig.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.

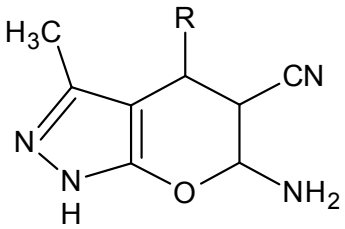


Figure 1

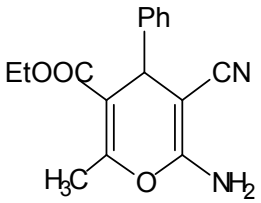


Figure -2

2. 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 Chemito spectrascan 2600 double beam in acetonitrile, IR spectra were recorded on Schimadzu Prestize 21 spectrometer using KBr pellate, ^{1}HNMR spectra were recorded on BRUKER AVANCE II 400 NMR Spectra using $CDCl_3$ as an internal standard and Mass spectra were recorded on Agilent ION TRAP 6310 instrument.

2.1 Catalysts preparation

Al-Zn-Cl was prepared by one pot co-precipitation reaction at 100 $^{\circ}$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.[21]

Al-Li-NO_3 was prepared by mixing salt solution containing Li^{2+} and Al^{3+}in Li/Al (metallic ratio 3:1). The solution pH was raised to 8.0 using 25% NaOH. The thick red slurry was heated at 120 $^{\circ}$C and at autogenous pressure in an autoclave. After completion the precipitate was aged for 12 h and filtered and washed with deionized water.

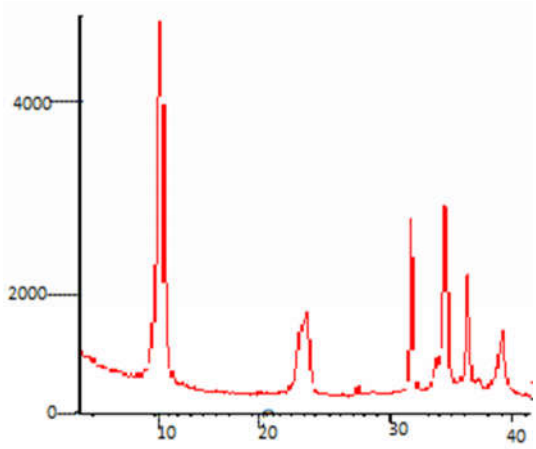


Fig.3 PXRD pattern of Al-Zn-Cl Hydrotalcite

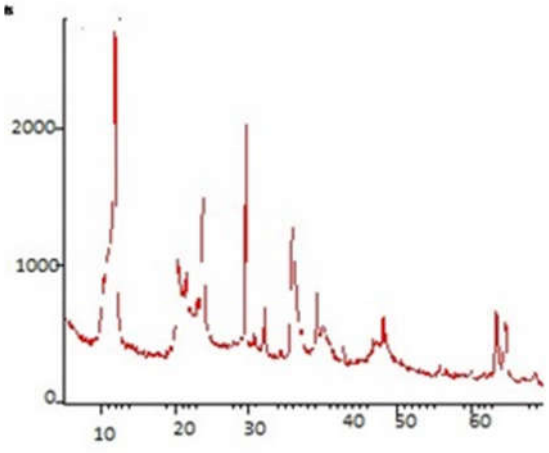


Fig. 4 PXRD pattern of Al -Li--NO_3 Hydrotalcites

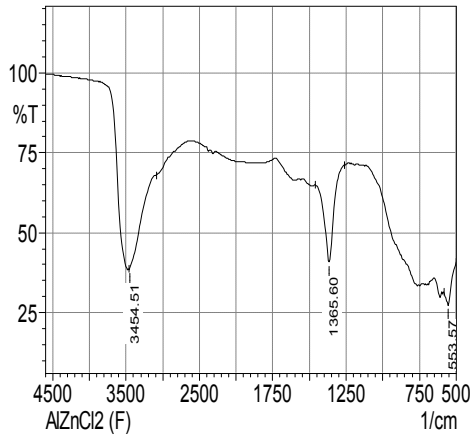


Fig. 5: FTIR of Al-Zn-Cl Hydrotalcites

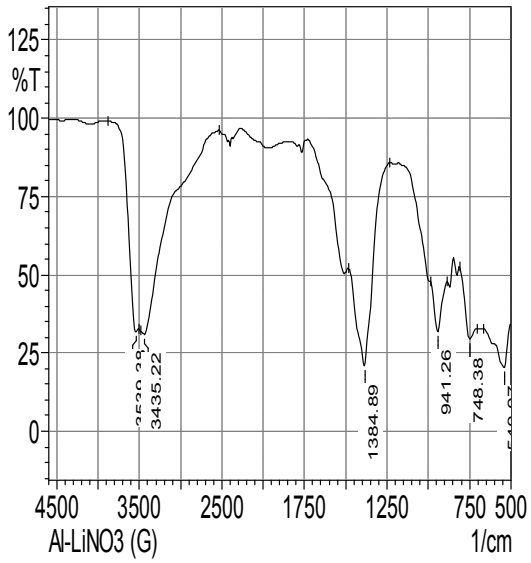


Fig. 6: FTIR of Al -Li--NO_3 Hydrotalcites

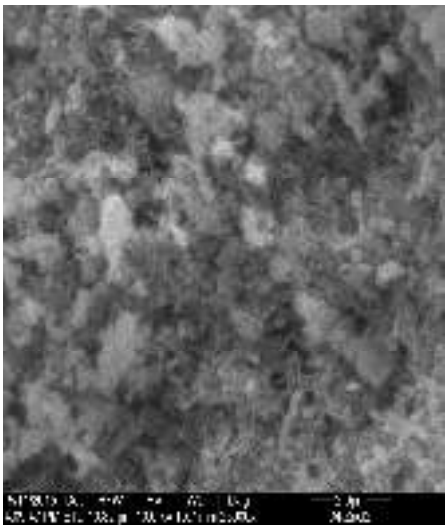


Fig.7: SEM –image of Al-Zn-Cl hydrotalcites

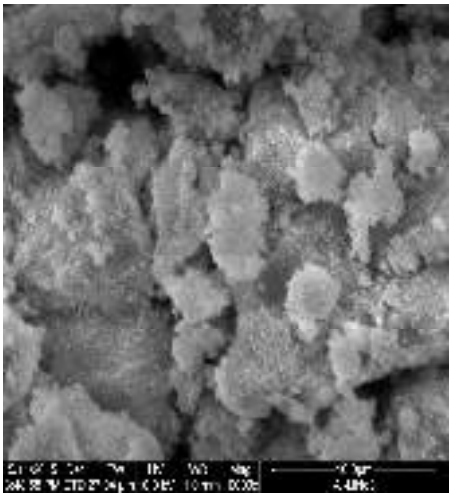


Fig.8: SEM –image of Al -Li--NO_3 hydrotalcite

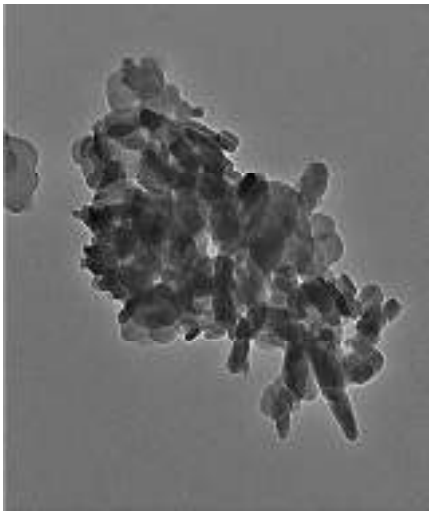


Fig. 9: TEM –image of Al -Li--NO_3hydrotalcite

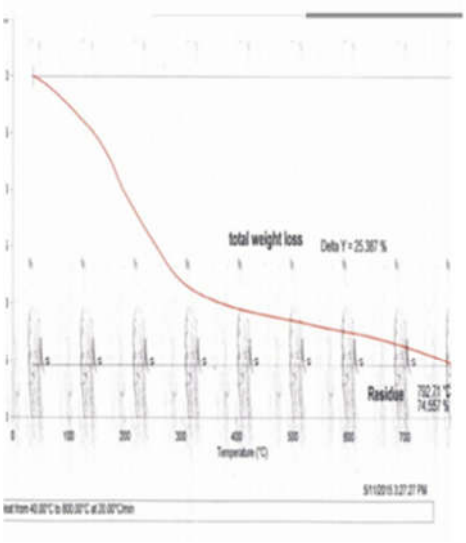


Fig.10: TGA – of Al-Zn-Cl hydrotalcite

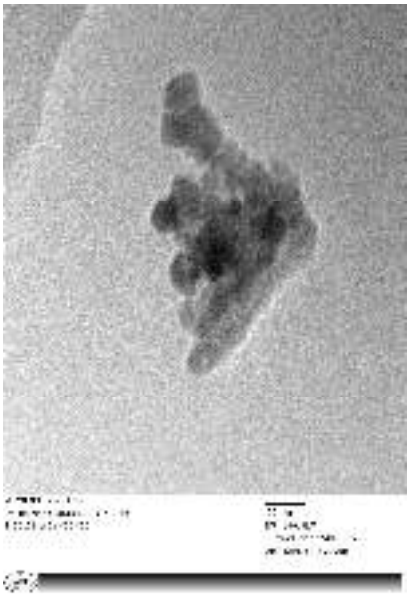


Fig.11: TEM of Al-Zn-Cl hydrotalcite

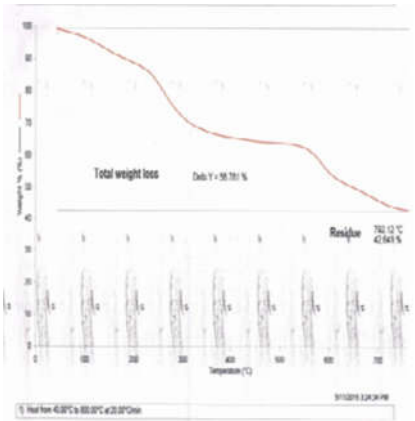
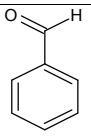
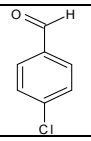
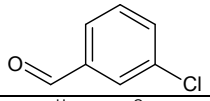
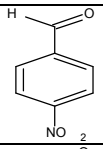
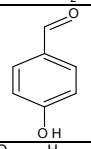
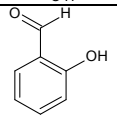
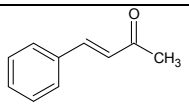
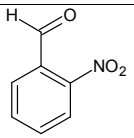
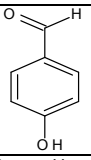
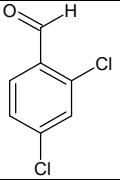
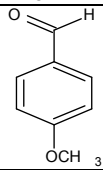
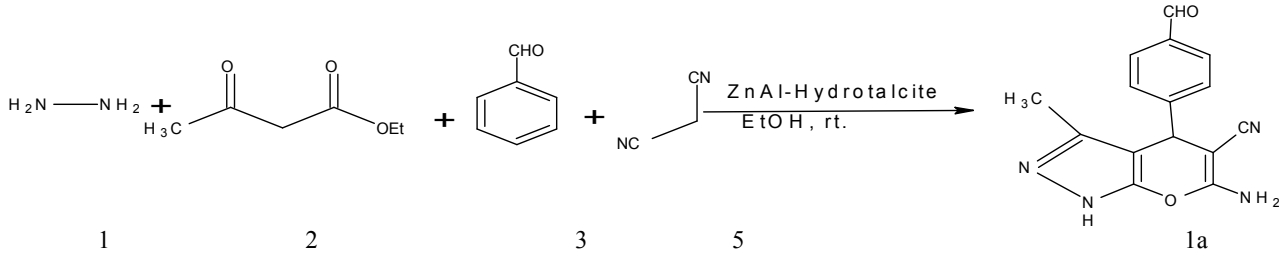


Fig.12: TGA of Al -Li--NO_3 hydrotalcite

Table 1: Synthesis of pyranopyrazole derivativesvia a multicomponent reaction of hydrazine hydrate, ethyl acetoacetate , aromatic aldehyde and malononitrile in presence of Zn/AlCl or Li/$AlNO_3$ HT at room temperature.

Entry	R^1	Al- Zn--Cl Hydrotalcite		Al -Li--NO_3Hydrotalcite	
		Time	Yield	Time	Yield
1		1h	60	1.3	58
2		1h	98	1h	98
3		1h	98	1h	98
4		1.3h .	76	2h	78
5		3h	45	4h	32
6		2.3h	56	3h	40
7		1.3h	42	1h	35
8		1h	63	1h	70
9		1h	48	1	33
10		1h	75	2	72
11		2h	27	2h	32

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



1 2 3 5 1a

Table 2. Reaction of hydrazine hydrate, ethyl acetoacetate, Chlrobenzaldehyde and malononitrile in presence of Zn/Al Clor Li/$AlNO_3$ 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)	98
4	ZnO	63
5	MgO	75
6	CaO	43
7	Al_2O_3	55
8	TiO2	61
9	CuO	48
10	Fe_2O_3	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.

2.2 Typical Reaction Procedure

Zn/Al HT (0.1g.) and Ethanol (5ml) were added to a mixture of hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), 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 product 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 3were 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), chlrobenzaldehyde, and malanonitrile was selected as modal reaction for optimizing of various parameters. The reaction is carried out using different hydrotalcite (Zn/Al =2, 3) and classical bases at room temperature (Table1).The basicity of HT is sensitive to the Zn/Al ratio. The total amount of basis 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 $10.7 \leq pKa \geq 13.3$, and only a few of them show strengths $13.3 \leq pKa \leq 16.9$.[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 optimize 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 separate 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 multicomponent reaction of hydrazine hydrate, ethyl acetoacetate , aldehyde , malononitrile 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

Authors are thankful to Ministry of Higher Education of Madhya Pradesh, M.P. to provide JRF to Jugraj Jatav, SAIF Chandigarh, and DRDE Gwalior for providing analytical facilities.

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