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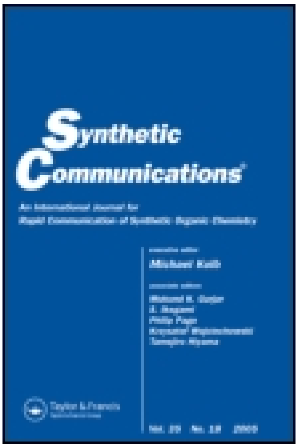

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Mg-Al Hydrotalcite as a First Heterogeneous Basic Catalyst for the Synthesis of 4H-Pyrano[2,3-c]pyrazoles Through a Four-Component Reaction

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Mg-Al HYDROTALCITE AS A FIRST HETEROGENEOUS BASIC CATALYST FOR THE SYNTHESIS OF 4H-PYRANO[2,3-c]PYRAZOLES THROUGH A FOUR-COMPONENT REACTION

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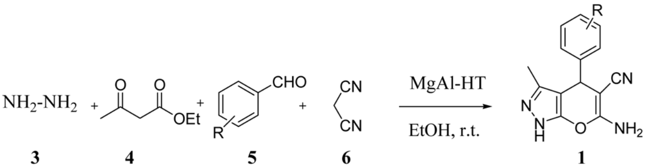
GRAPHICAL ABSTRACT



R = NO_2, Br, Cl, OMe, Me

Abstract *Mg/Al hydrotalcite acts as an efficient heterogeneous basic catalyst for the synthesis of 4H-pyrano[2,3-c]pyrazoles via a multicomponent reaction of aromatic 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

INTRODUCTION

Multicomponent 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 industrial researchers have been focused on the design and development of

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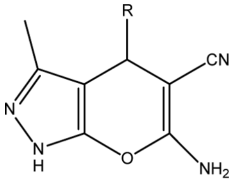

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Figure 1.

multicomponent 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. Furthermore, they show molluscicidal activity[5] and have been identified as a screening hit for Chk1 kinase inhibitor.[6] 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[2,3-c]pyrazoles (e.g., triethylamine,[8] piperidine,[9] morpholine,[10] p-dodecylbenzenesulfonic acid,[11] hexadecyltrimethylammonium bromide,[12] potassium fluoride dehydrate,[13] and electrogenerated bases[14]). 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 leads to the formation of 2-amino-3-cyano-4H-pyran (Fig. 1).[15] 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.[16]

Looking at these reactions, we thought it worthwhile to attempt a four-component, one-pot reaction, combining the essence of these reactions of **3**, **4**, **5**, and **6** to obtain **1**.

Heterogeneous catalysts are vital in green synthesis because of their easy recovery and subsequent reuse. Our research group has been developing efficient and environmentally benign protocols using hydrotalcites as heterogeneous catalysts.[17] 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, Mg/Al hydrotalcites, for the catalysis of an MCR of hydrazine hydrate

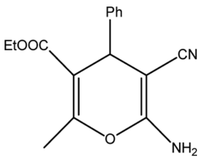

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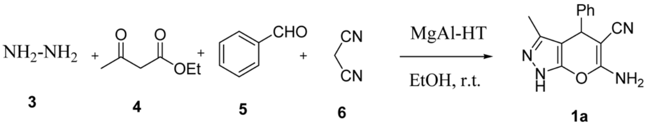
Figure 2.



Scheme 1.

(**3**), ethyl acetoacetate (**4**), aldehydes (**5**), and malononitrile (**6**) at room temperature (Scheme 1), making the synthesis highly effective and green.

RESULTS AND DISCUSSION

In the present paper, we describe the use of calcined (Mg/Al = 3) hydrotalcite (HT) as a first heterogeneous catalyst for the synthesis of 4H-pyrano[2,3-c]pyrazoles (Scheme 1). Mg–Al HT with Mg/Al molar ratio of 2, 3, and 5 were prepared by the reported procedures[18] and were characterized by x-ray diffraction (XRD), Fourier transform infrared (FT-IR), and differential scanning calorimetry (DSC).

The reaction of hydrazine hydrate, ethyl acetoacetate (EAA), 4-methoxybenzaldehyde, and malononitrile was selected as the model reaction for optimization of various parameters. The reaction was carried out using different HTs (Mg/Al = 2, 3, 5), calcined HTs (Mg/Al = 2, 3, 5), and classical bases at room temperature (Table 1). The HTs (Mg/Al = 2, 3, 5) were calcined at 500 °C to tune the basicity. The basicity of HT is sensitive to the Mg/Al ratio. The total amount of basic sites of HT increases gradually with the Mg/Al molar ratio but the proportion of basic sites (i.e., those catalyzing the reaction) decreases. The catalytic activity of the calcined HTs was more than that of the corresponding uncalcined HT. It is known that the calcined HT contains basic sites of pKa values up to 16.5. However, most of its basic sites have $10.7 \leq pKa \leq 13.3$, and only a few of them show strengths $13.3 \leq pKa \leq 16.5$.[19] Thus, the total basicity of calcined HT is more than that of the corresponding uncalcined form. In the absence of the catalyst, very little product was

Table 1. Reaction of hydrazine hydrate, EAA, 4-methoxybenzaldehyde, and malononitrile in the presence of Mg/Al HT with different Mg/Al ratios and classical bases in EtOH at room temperature

Entry	Catalyst	Yield (%)
1	Mg/Al: 2	41
2	Mg/Al: 3	57
3	Mg/Al: 5	50
4	Mg/Al: 3[a]	80
6	Na_2CO_3	17
7	MgO	55
8	Basic Al_2O_3	35
9	Piperidine	64

Notes. Reaction conditions: hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), benzaldehdye (2 mmol), malononitrile (2 mmol), EtOH (10 ml); catalyst = 0.1 g; time 1.5 h; room temperature.

[a] Hydrotalcite calcined at 500 °C.

Table 2. Reusability of Mg/Al HT (calcined at 500 °C)

Run	Yield (%)
1	80
2	77
3	77

Notes. Reaction conditions: hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), benzaldehdye (2 mmol), malononitrile (2 mmol), EtOH (10 ml); calcined HT = 0.1 g; time 1.5 h; room temperature.

Table 3. Synthesis of pyranopyarazole derivatives via a multicomponent condensation of hydrazine hydrate, ethyl acetoacetate, aromatic aldehydes, and malononitrile in the presence of Mg/Al HT at room temperature

Entry	Aldehyde	Time (h)	Isolated yield (%)
1	Benzaldehyde	1	87
2	2-Nitrobenzaldehyde	3	71
3	3-Nitrobenzaldehyde	3	64
4	4-Nitrobenzaldehyde	3	81
5	4-Bromobenzaldehyde	4	75
6	4-Chlorobenzaldehyde	4	86
7	4-Methoxybenzaldehyde	1.5	80
8	3,4,5-Trimethoxybenzaldehyde	3.5	70
9	2-Methylbenzaldehyde	5	62
10	Thiophenyl	2	79

Notes. Reaction conditions: hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), aldehdye (2 mmol), malononitrile (2 mmol), EtOH (10 ml); calcined HT = 0.1 g.

formed. For further reaction, the calcined HT (Mg/Al = 3) was used. The hydrotalcite is a heterogeneous catalyst and could easily be separated from the reaction mixture by filtration. The recovered catalyst was used for successive runs to test its reusability (Table 2). It was observed that there was a decrease in the yield of the product.

Under the optimized conditions, various substituted aromatic aldehydes were reacted to obtain the corresponding 4H-pyrano[2,3-c]pyrazoles in good yield (Table 3). It was observed that the aldehydes containing electron-withdrawing substituents reacted faster and gave a better yield of the product as compared to those containing electron-donating substituents.

In conclusion, Mg/Al (Mg/Al = 3) was found to be a simple and efficient solid base catalyst for the synthesis of 4H-pyrano[2,3-c]pyrazoles through an MCR of hydrazine hydrate, ethyl acetoacetate, aldehyde, and malononitrile. This is the first report of the synthesis of 4H-pyrano[2,3-c]pyrazoles through a four-component reaction in the presence of a solid catalyst.

EXPERIMENTAL

The Mg/Al HTs were prepared following the literature procedure. All products have been described previously and were fully characterized by FT-IR and ^{1}H NMR.

Typical Reaction Procedure

Ethanol (10 ml) and Mg/Al HT (0.1 g) were added to a mixture of hydrazine hydrate **1** (0.107 g, 2 mmol) and ethyl acetoacetate **2** (0.260 g, 2 mmol), aldehyde **3** (2 mmol), malononitrile **4** (0.132 g, 2 mmol). The reaction mixture was stirred at room temperature under an open atmosphere. After completion of the reaction, the reaction mixture was heated to dissolve 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 a mixture of ethyl acetate/hexane (20:80 v/v). The products were characterized by NMR and FT-IR.

Selected Data

6-Amino-3-methyl-4-phenyl-1,4-dihyropyrano[2,3-c]pyrazole-5-carbonitrile (Entry 1). IR (KBr) ν: 3368, 3307, 3170, 2197, 1648, 1610 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz) δ_H: 1.76 (s, 3H), 4.58 (s, 1H), 6.87 (s, 2H), 7.16–7.30 (m, 5H), 12.09 (s, 1H) ppm.

6-Amino-3-methyl-4-(4-nitrophenyl)-1,4-dihyropyrano[2,3-c]pyrazole-5-carbonitrile (Entry 4). IR (KBr) ν: 3472, 3230, 3120, 2192, 1648, 1621 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz) δ_H: 1.78 (s, 3H), 4.61 (s, 1H), 7.05 (s, 2H), 7.44 (d, 2H), 8.19 (d, 2H), 12.20 (s, 1H) ppm.

6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihyropyrano[2,3-c]pyrazole-5-carbonitrile (Entry 7). IR (KBr) ν: 3483, 3258, 3115, 2192, 1640, 1600 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz) δ_H: 1.77 (s, 3H), 3.72 (s, 3H), 4.52 (s, 1H), 6.84 (m, 4H), 7.06 (s, 2H), 12.07 (s, 1H) ppm.

6-Amino-3-methyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihyropyrano[2,3-c]-pyrazole-5-carbonitrile (Entry 8). IR (KBr) ν: 3379, 3285, 3142, 2186, 1643, 1599 cm^{-1}. ^{1}H NMR (DMSO, 300 MHz) δ_H: 1.85 (s, 3H), 3.62 (s, 3H), 3.70 (s, 6H), 4.57 (s, 1H), 6.45 (s, 2H), 6.87 (s, 2H), 12.09 (s, 1H) ppm.

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