

One-Pot Synthesis of 1,8-Dioxooctahydroxanthenes Catalyzed by Mg-Al Hydrotalcites

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Abstract

An environment friendly synthesis of 1,8-dioxooctahydroxanthenes derivatives using Mg-Al hydrotalcite as an efficient Lewis acid catalyst has been developed. Water was used as a green solvent and the reaction gave products in high yields in shorter reaction time and involved easy work up. The reaction works well with both electron deficient and electron rich aldehydes.

Keywords

Multicomponent Reactions, Green Reactions, Mg-Al Hydrotalcite, Xanthenes, Lewis Acid

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1. Introduction

Multicomponent reactions (MCRs) have emerged as a powerful tool for the synthesis of complex structures from simple substrates with high selectivity and high atom efficiency.¹⁻⁸ One-pot MCRs are the useful path for the facile generation of combinatorial libraries of various organic molecules of high synthetic and biological value.^{9,10} Xanthene and its derivatives are of considerable interest due to a plethora of biological and pharmaceutical activities like antiviral,¹¹ anti-inflammatory¹² and anti-bacterial activities.¹³ They also find their applications in photodynamic therapy,¹⁴ in laser technology^{15,16} and as pH sensitive fluorescent material for the visualization of bio-molecular assemblies.¹⁷ Numerous methods have been reported for the synthesis of 1,8-dioxooctahydroxanthenes. The reaction of aromatic aldehydes with 1,3-diketones has been promoted by various catalysts such as *p*-dodecylbenzenesulfonic acid in aqueous media,¹⁸ *p*-toluenesulfonic acid (*p*-TsOH) in organic solvents,¹⁹ benzyltriethylammonium chloride,²⁰ diammonium

hydrogen phosphate,²¹ MCM-41 functionalized sulfonic acid under ultrasonic irradiation²² and heterogeneous catalysts (NaHSO₄-SiO₂ and silica chloride),²³ InCl₃·4H₂O in ionic liquids,²⁴ Amberlyst-15,²⁵ polyaniline-*p*-toluenesulfonate salt²⁶ and PPA-SiO₂.²⁷ These methods have certain drawbacks which include prolonged reaction time, use of hazardous organic solvents, toxic catalysts and low catalytic efficiency.

Hydrotalcites (HTs) are the anionic clays which are layered double hydroxides whose structure is similar to brucite [Mg(OH)₂]. They are represented by a general formula [M_{1-x}²⁺M_x³⁺(OH)₂(Aⁿ⁻)_{x/n}·yH₂O], where M²⁺ and M³⁺ are divalent and trivalent cations respectively and Aⁿ⁻ is the interlayer charge balancing inorganic or organic anion. The divalent cation in most of the cases occupies the octahedral voids with anion and water in the interlayer's. Mg-AIHTs upon calcination are known to possess both acidic and basic sites.²⁸ In recent years, Mg-Al HTs have gained much attention as heterogeneous base catalysts for various chemical

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transformations such as the aldol and Claisen–Schmidt condensations or the Knoevenagel and Michael additions owing to their surface Lewis basic sites.²⁹⁻³¹ Recently, we have studied the effect of different phases of Mg-Al HTs formed by calcination on the Knoevenagel reaction of benzaldehydes and malononitrile.³² However, there has been no report about the use of Mg-Al HTs as heterogeneous Lewis acid catalysts. Mg-Al HTs exhibit Lewis acid sites similar to γ -Al₂O₃ when calcinated at higher temperatures²⁸. Herein we report Mg-Al hydrotalcite (HT) as a new efficient heterogeneous Lewis acid catalyst for preparation of 1,8-dioxooctahydroxanthenes which helps to overcome the problems inherent in the procedures reported earlier. To the best of our knowledge, this methodology has not been reported previously.

2. Materials and Methods

Mg-Al HT was prepared by the reported method.³³ All the reagents were purchased from commercial sources and used without further purification. The characterization of the HT samples was done using powder X-ray Diffraction analysis measured on PANalytical Xpert pro X-ray diffractometer using CuK α radiation (0.154178nm). Melting points (mp.s) were determined on Veego model no. VMP-D melting point apparatus and are uncorrected.

2.1. General Procedure for the Synthesis of Mg-Al Hydrotalcite

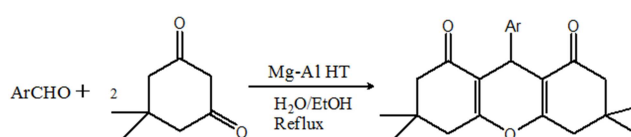
Mg-Al HT (Mg/Al = 0.33) was prepared using the co-precipitation method,³³ by the simultaneous addition of aqueous solutions (25mL) of Mg(NO₃)₂·6H₂O (0.033mol) and of Al(NO₃)₃·9H₂O (0.1 mol) to a solution (40mL) containing NaOH (0.27mol) and Na₂CO₃ (0.05mol) with vigorous stirring at room temperature for 8h (pH =8–10). The precipitate of HT was collected and washed with water until the pH of the filtrate was 7. The Mg-Al HT was dried at 80 °C for 16h followed by activation by calcination by heating the catalyst to 1050 °C in the furnace for 6 h and then slowly cooling it to room temperature.

2.2. General Procedure for the Synthesis of 1,8-Dioxooctahydroxanthenes

A mixture of a substituted benzaldehyde (1 mmol), dimedone

(280 mg, 2 mmol), Mg-Al HT (42 mg, 15 % w/w), and water or ethanol (10 mL) was stirred at reflux for the appropriate time (Table1). The progress of the reaction was monitored using silica gel TLC (EtOAc : hexane = 2:8). After completion of the reaction, the mixture was kept at room temperature and the resulting solid was collected. It was treated with hot ethanol (5 mL) and the mixture was filtered to recover the catalyst. The filtrate was concentrated and cooled to give the pure product in crystalline form.

3. Results and Discussions



Scheme 1. Synthesis of 1,8-Dioxooctahydroxanthenes

Several 1,8-dioxooctahydroxanthenes were synthesized under reflux conditions in water and ethanol. Table 1 shows that both electron-deficient and electron-rich aromatic aldehydes reacted with 2 equivalents of dimedone to afford the corresponding 1,8-dioxooctahydroxanthenes in high yields using Mg-Al HT as catalyst (Scheme 1). The catalytic activity may be attributed to the presence of mild acidic sites in Mg-Al HT (Mg/Al = 0.33) when calcined at 1050 °C. Aldehydes bearing electron-withdrawing groups gave higher yields than those substituted with electron-donating groups. The use of water and ethanol both resulted in excellent yields of 1,8-dioxooctahydroxanthenes ranging from 73-95%, although, reaction in water required less time. In order to test the scope of the reaction, formaldehyde and acetaldehyde were treated with dimedone in water and in ethanol, however, no product was formed even after stirring at reflux for eight hours. Interestingly, the reaction of benzaldehyde with acetylacetone did not yield any product under identical conditions, this failure may be due to the fact that acetylacetone exists mostly in its enol form (80%) and even more so in polar solvents. This fact may explain why it does not react because it is tied up to the acidic sites of the catalyst. Enolization is negligible in dimedone.³⁴

Table 1. Synthesis of 1,8-Dioxooctahydroxanthenes catalyzed by Mg-Al HT.

Aldehydes	Time (h)		Yield (%)		mp (°C)(Lit. mp)
	(Water)	(Ethanol)	(Water)	(Ethanol)	
C ₆ H ₅ CHO	3	4	85	87	204-205 (202-204) ¹⁶
2-Cl C ₆ H ₄ CHO	3.5	4	86	89	228-230 (228-230) ¹⁶
4-Cl C ₆ H ₄ CHO	3	3.5	84	86	225-226 (228-230) ¹⁶
4-F C ₆ H ₄ CHO	3	3.5	88	90	224-225 (224-226) ²²
4-NO ₂ C ₆ H ₄ CHO	3	3.5	92	95	226-227 (226-228) ¹⁶
3-NO ₂ C ₆ H ₄ CHO	3	4	89	90	168-170 (168-170) ¹⁶

Aldehydes	Time (h)		Yield (%)		mp (°C)(Lit. mp)
	(Water)	(Ethanol)	(Water)	(Ethanol)	
4MeOC ₆ H ₄ CHO	4	4.5	90	92	243-245 (242-244) ¹⁶
2-HO C ₆ H ₄ CHO	4	4.5	83	86	202-205 (205-206) ³⁵
4-Me C ₆ H ₄ CHO	4	4.5	80	81	218-220 (217-218) ¹⁶
Cinnamaldehyde	4.5	5	75	77	177-178 (175-177) ¹⁶
Furfuraldehyde	4.5	4.5	73	74	62-63 (62-64) ¹⁶
HCHO	8	8	-	-	
CH ₃ CHO	8	8	-	-	

4. Conclusion

In conclusion, a novel one-pot synthesis of 1,8-dioxooctahydroxanthenes using aromatic aldehydes and dimedone has been developed. It is notable that the catalyst is easy to prepare, less toxic than some of the earlier reported sulfonic acid catalysts and is environmental friendly. High yields, mild reaction conditions, short reaction times and the use of green solvent such as water are the notable advantages of this procedure. In addition the reaction works well with both electron deficient and electron rich aldehydes.

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