

REVIEW ARTICLE

Hydrotalcites in Organic Synthesis: Multicomponent Reactions

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Abstract: Background: The use of solid bases as heterogeneous catalysts allows the replacement of conventional bases in Organic Chemistry, being of utmost importance. Lamellar double hydroxides or hydrotalcites are materials having excellent basic properties and high surface areas. As their surface properties have been used as bifunctional catalysts allowing the incorporation of metals and depending on the calcination temperature, these materials may exhibit Lewis or Brønsted basic sites. Additionally, they are widely used in various organic synthesis reactions.

Objective: This contribution has been aimed to provide a compilation of the application of hydrotalcites as basic materials in organic synthesis, with a particular emphasis on multicomponent reactions.

Conclusion: Hydrotalcites act as heterogeneous catalysts that conduct highly efficient processes in short reaction times and with the advantage of their easy recovery and reuse without significant loss of their catalytic activity. In addition, due to the modification of their structural and chemical properties, they are catalysts with multiple applications in organic synthesis such as Michael addition reactions, dehydrogenation reactions of alcohols, Knoevenagel condensations, reduction reactions, oxidations, epoxidations, multicomponent reactions, among others. Multicomponent reactions are of major interest since they allow obtaining compounds that have high biological activity and are generated through processes in a single step by combining three or more starting reagents under solvent-free conditions.

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1. INTRODUCTION

The replacement of homogeneous catalysts of basic or acidic character by solids as heterogeneous catalysts in organic reactions is becoming increasingly important. Homogeneous catalysts are more commonly used in organic synthesis since they present high catalytic activity and high selectivity towards the products of interest. However, the use of expensive and toxic reagents, high temperatures in the reaction process, as well as the difficulty of separation and reuse of the catalyst, are the main disadvantages of this system. Various investigations have been conducted with the use of solid-state catalysts, leading to reactions in a heterogeneous phase that has advantages such as mild reaction conditions, easy separation and reuse of the catalyst, resulting in a catalytic activity greater than or equal to that of conventional catalysts [1].

Hydrotalcite-type compounds are a class of anionic minerals belonging to the family of clays, which are used as antacids, exchangers and ion absorbers, catalysts and catalytic supports with high surface area, basic surface properties, and structural stability. They are known as lamellar double hydroxides (LDH) with the general formula $[\text{Me}^{2+}_{(1-x)}\text{Me}^{3+}_x(\text{OH})_2]^{x+}(\text{A}_{x/n})^{n-} \cdot n\text{H}_2\text{O}$, where Me^{2+} and Me^{3+} are divalent and trivalent cations respectively, and A^{n-} is

the anionic compensation charge. Their structure consists of brucite ($\text{Mg}(\text{OH})_2$) layers where the substitution of divalent cations with trivalent cations results in a positive net charge that is compensated by interlaminar anions and crystallization waters found in the interlaminar layer [2]. These materials can be synthesized by various techniques depending on the specific requirements and properties of the compounds to be reacted, but generally synthesized by the coprecipitation method at a constant pH [3]. Synthesis conditions such as temperature, pH and metal composition have been extensively studied because their structure and surface properties, as well as the resulting mixed oxides of these compounds in the calcination process, depend strongly on the chemical composition and the synthesis process [4]. In catalysis, the surface area, the interaction between two or more oxide components, and the size of the resulting metal oxides strongly influence the speed and selectivity of the chemical reactions [5].

Hydrotalcites have been widely used as catalysts having a high basic area after calcination. The calcination process is generally characterized by endothermic transitions that depend on several factors such as the nature and relative quantity of cations, the type of anion, the calcination atmosphere, and the structure obtained by the synthesis method. The mixed oxides formed after the calcination of the lamellar double hydroxides show some interesting properties in the field of catalysis, such as large surface area, a synergistic effect between their elements (which favors the development of their basic properties) and also a shape memory effect

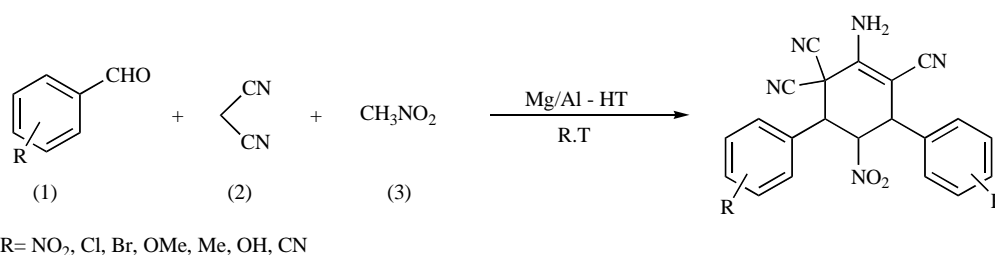
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that allows the regeneration of the original structure. These mixed oxides have been widely used as catalysts for organic reactions and in the production of pharmaceuticals, soaps, and fragrances [6, 7].

The basic and acidic properties of hydrotalcites make them bifunctional catalysts that can act in different chemical transformations, for example, in reactions such as gas phase displacement in water, aldol condensation reactions, alkylations, Knoevenagel condensations, double-bond isomerizations, among others [8]. One approach to the processes based on the principles of green chemistry consists of the reduction of synthesis processes that require several reaction steps and purification stages, which are important criteria for the efficiency and viability of the processes. A new perspective in organic synthesis is the multicomponent reaction that has emerged as a highly valuable synthetic tool in the context of the discovery of modern drugs [9]. These reactions combine at least three reagents to generate a single product that preferably contains all starting atoms and has interesting applications in the therapeutic field and in bioorganic chemistry [10]. In this minireview, a compilation of the application of hydrotalcites as materials with strong basic character, acid-base sites and support of metal nanoparticles in organic synthesis is made, but special emphasis is given to the multicomponent reactions since they allow obtaining compounds with biological properties of great importance under solvent-free conditions and with short reaction times.

2. MULTICOMPONENT REACTION CATALYZED BY HYDROTALCITES

Multicomponent reactions (MCR) are defined as reactions that occur in a single step and involve more than two starting reactants that react to form a single product that normally contains the essential parts of the starting materials and requires an equilibrium and a sequence of reversible and irreversible steps [11]. Several investigations have been carried out in the field of multicomponent reactions using hydrotalcite (HT) as a heterogeneous catalyst. Kshirsagar and coworkers studied the reaction between benzaldehyde (1), malononitrile (2) and nitromethane (3) (Scheme 1) using Mg/Al hydrotalcite under solvent-free conditions, obtaining high yields. They also found that the catalytic activity of the calcined HT is greater than that of the uncalcined HT, and the HT with a Mg/Al = 5 ratio is the best catalyst for this reaction. Since nature, density and strength of the basic sites depend on the content of Al, this ratio increases the catalyst basicity. Although the catalyst shows a decrease in the yield of the product in the reuse studies, the XRD analyses of the fresh calcined HT (Mg/Al = 5) and HT used in the reaction show that there is no change in the structure and morphology of this material. This is the first report on the single-step synthesis of cyclohexenes functionalized through a reaction of three components in the presence of a solid catalyst. Under the optimized conditions, various substituted aromatic aldehydes were reacted to obtain the corresponding products (Table 1) [12].

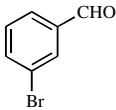
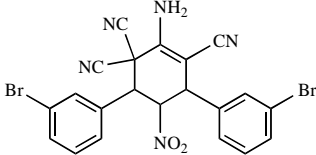
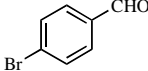
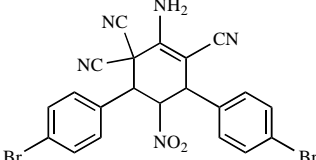
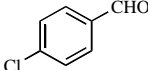
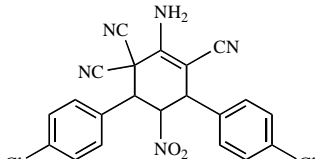
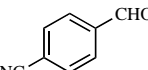
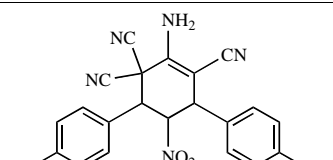
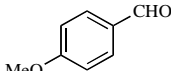
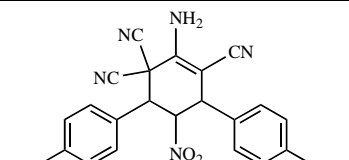
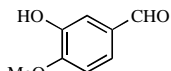
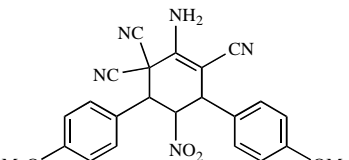
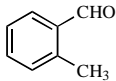
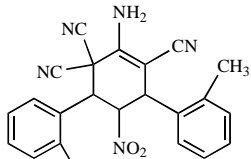


Scheme 1.

Table 1. Reaction of aldehyde, malononitrile, and nitromethane in the presence of Mg–Al HT [(Mg/Al = 5) calcined at 500°C] at room temperature.

Entry	Aldehyde	Product	Time (h)	Yield (%)
1			5	72
2			5.5	66
3			4	87

Table 1. contd...

Entry	Aldehyde	Product	Time (h)	Yield (%)
4			4	48
5			4	90
6			4.5	80
7			5	81
8			7	72
9			10	30
10			7.5	67

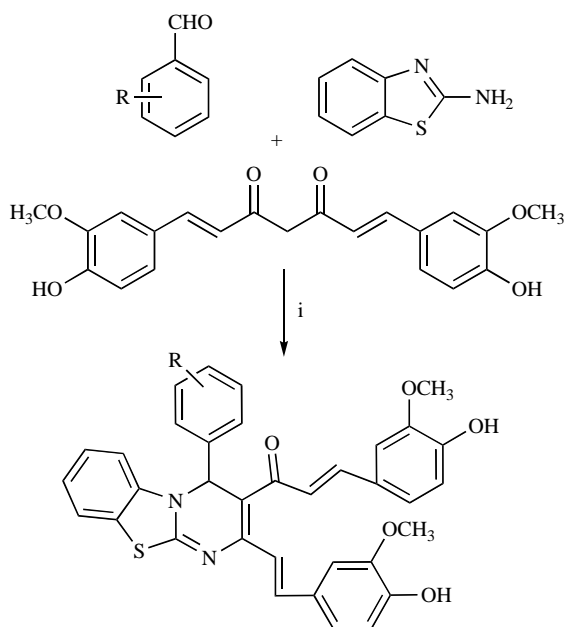
Reaction conditions: Aldehyde (5 mmol), malononitrile (5 mmol), nitromethane (3 mmol), HT (0.05 g), room temperature (29°C).

Calcined Mg/Al (3:1) hydrotalcite was studied in cycloaddition reactions of 5,6-dihydro-4H-1,2-oxazines and 1,4,5,6-tetrahydropyridazines. This methodology presents advantages such as the elimination of the use of solvents and inorganic bases, and also allows the recovery and reuse of the catalyst [13]. Mg/Al-CO₃ hydrotalcite calcined at 500°C is an effective catalyst for the synthesis of 4H-pyrimido [2,1-b] benzothiazole derivatives of curcumin (Scheme 2) under solvent-free conditions by developing a rapid and environmentally benign method [14].

Copper (II) hydrotalcite was also studied for the synthesis of β -hydroxytriazoles in water through the reaction of three components, namely, epoxides (1), sodium azide (2), and terminal alkynes (3) (Scheme 3) at room temperature [15]. The catalytic activity of Mg-

V/CO₃ was studied in the synthesis of multisubstituted pyridines through a multicomponent reaction in a single step, obtaining high yields in short reaction times [16]. A new multicomponent reaction between Meldrum's acid (1), various aromatic aldehydes (2), nitromethane (3) and various alcoholic solvents (4) (Scheme 4) was studied in the direct synthesis of β -aryl- γ -nitroesters using metal oxides derived from hydrotalcite, obtaining yields ranging from 15% to 95%. These oxides act as a heterogeneous catalyst that promotes the process in a single step [17].

The coupling of benzaldehyde (1), amines (2) and phenylacetylene (3) (Scheme 5) in refluxing THF using HT-AuCl₄ hydrotalcite synthesized by the ion exchange technique allows the preparation of propargylamine by the activation of the C-H bond with good yields.



Scheme 2. Conditions (i) heating at 70°C using hydrotalcite as catalyst.

Nevertheless, in the reuse cycles of the recovered catalyst, it was found that in the third cycle of reaction, the catalyst loses its catalytic activity, probably due to the formation of Au⁽⁰⁾ species. However, this is a highly efficient and simple process for obtaining several propargylamines with excellent yields [18].

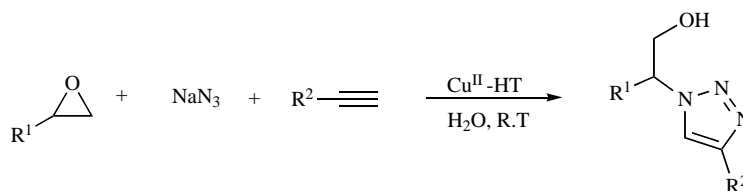
3. SYNTHESIS OF PYRANS

In recent years, 4H-pyrans and their derivatives have attracted considerable attention in the field of organic chemistry. These com-

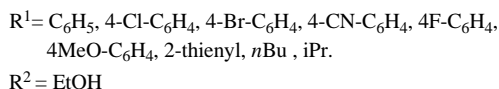
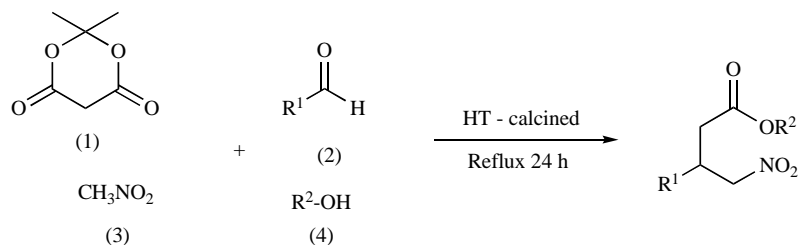
pounds have a broad spectrum of biological activities and are used as anticoagulants, anticancer agents, and as cognitive enhancers for the treatment of neurodegenerative diseases such as Alzheimer's, Huntington's disease, Parkinson's and Down syndrome, as well as for the treatment of schizophrenia [19]. The synthesis of 4H-pyran compounds and their derivatives involves a reaction between an aldehyde and a Michael acceptor (malononitrile) and a β-dicarbonyl compound in the presence of a basic catalyst such as piperidine, morpholine or metal alkoxides using volatile solvents, leading to long reaction times and the difficult catalyst recovery [20]. The reaction mechanism initially proceeds by Knoevenagel condensation where the strong basic sites of the catalyst promote the reaction by abstracting a proton from the active methylene compound, which reacts with the aldehyde forming an alkene intermediate followed by a Michael-type addition resulting in the 4H-pyran compound [21]. Several heterogeneous catalysts with basic properties have been studied in this reaction [22-24].

Recently, Babu and coworkers studied the Mg/La catalyst in the synthesis of 4H-pyran derivatives (Scheme 6) using aromatic aldehydes such as 4-chloro, 4-nitro, 3-nitro and 4-cyano-benzaldehydes (Table 2, entries 2-5) that react rapidly with high yields compared to 4-hydroxy, 4-methyl, 4-methoxy and 4-acetoxy benzaldehyde derivatives (Table 2 entries 6-9). This hydrotalcite also has a strong basic character due to the presence of La₂O₃ affording high yields in short reaction times at the reflux temperature of methanol [25].

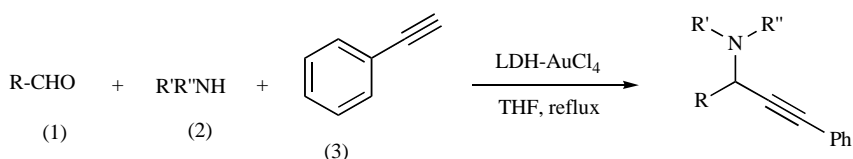
Calcined hydrotalcite (Mg/Al = 3) was described as a heterogeneous catalyst for the synthesis of 4H-pyran [2,3-c] pyrazole. Using hydrazine hydrate (1), ethyl acetoacetate (2), aldehydes (3) and malononitrile (4) (Scheme 7), it was observed that the aldehydes containing electron-withdrawing substituents react more readily with better yields compared to those containing electron-donating substituents (Table 3). The HTs (Mg/Al = 2, 3, 5) were calcined at 500°C to adjust the basicity, since the basicity is sensitive to the Mg/Al ratio, and the number of HT basic sites gradually increases



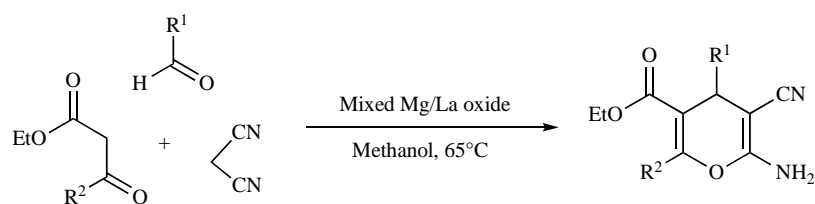
Scheme 3. Synthesis of b-hydroxy 1,4-disubstituted 1,2,3-triazoles using Cu^{II}-HT as catalyst in water.



Scheme 4. Multicomponent synthesis of γ-nitroesters.



Scheme 5.



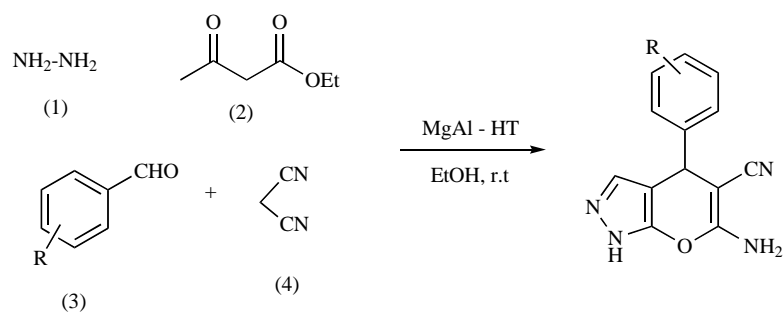
Scheme 6. Synthesis of polyfunctionalized 4H-pyrans via one-pot condensation of an aldehyde, malononitrile, and ethyl acetoacetate using mixed Mg/La oxide.

Table 2. Mg/La catalyzed synthesis of 4H-pyran derivatives^a.

Entry	R ¹	R ²	Time (h)	Yield (%)
1	Ph	Me	1	83
2	4-NO ₂ -C ₆ H ₄	Me	1	88
3	3-NO ₂ -C ₆ H ₄	Me	1	86
4	4-Cl-C ₆ H ₄	Me	1	92,89 ^b
5	4-CN-C ₆ H ₄	Me	1	90
6	4-OH-C ₆ H ₄	Me	2	79
7	4-Me-C ₆ H ₄	Me	1.5	87
8	4-OMe-C ₆ H ₄	Me	1.5	82
9	4-CH ₃ -COO-C ₆ H ₄	Me	3	60
10	CH ₃ -CH ₂	Me	3	52
11	4-Cl-C ₆ H ₄	CH ₂ COOEt	1	87
12	4-Me-C ₆ H ₄	CH ₂ COOEt	1	76
13	4-OH-C ₆ H ₄	CH ₂ COOEt	1.5	15
14	C ₆ H ₅	OEt	1.5	78

^aReaction conditions: aldehyde derivative (1 mmol); malononitrile (1.1 mmol); active methylene diketo compound (1.1 mmol).

^bYield obtained after the fourth recycle.



R= NO₂, Cl, Br, OMe, Me

Scheme 7.

with this ratio, but the proportion of basic sites (those that catalyze the reaction) decreases. Therefore, calcined HTs exhibit higher activity than uncalcined HTs [26]. Vijay V. Dabholkar *et al.* also found the same result with the Mg/Fe hydrotalcite calcined at 500°C, where the removal of the hydration water molecules from the catalyst due to calcination leads to the formation of mixed phases of metal oxides such as finely dispersed MgFe₂O₄ and MgO with the surface increase. Thus, Lewis basicity in the HT increases and Brønsted basicity decreases and protic and aprotic organic solvents (Table 4) such as ethanol and DMF favor the reaction with yields of 85% towards 4H-pyran derivatives [27].

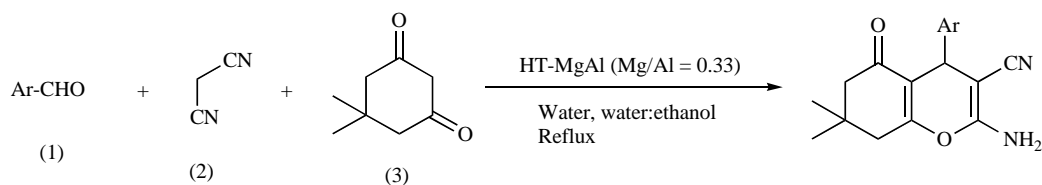
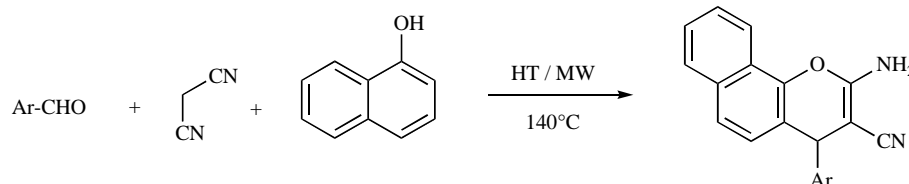
The synthesis of 4H-tetrahydrobenzo-[b]-pyran was studied using calcined hydrotalcite (Mg/Al = 0.33) at 1050°C under a tricomponent reaction between benzaldehyde (1), malononitrile (2) and dimedione (3) (Scheme 8). Using water as a solvent and a mixture of water/ethanol 1:1, various aromatic aldehydes were studied. Aldehydes substituted with electron donor groups exhibit lower yields with longer reaction times compared to the aldehydes containing electron withdrawing groups. The solvent used at 1:1 water/ethanol mixture is more efficient and shows high yields in short reaction times. Apart from the eco-friendly advantages and the high catalytic efficiency, the catalyst allows the easy insulation of the

Table 3. Synthesis of pyranopyrazole 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-Bromobenzaldehyde	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

Table 4. Reaction of benzaldehyde, malononitrile, hydrazine hydrate and ethyl acetoacetate in the presence of C-Mg-Fe HT-3 in different solvents at ambient temperature.

Entry	Solvent	Yield of Product (%)
1	H ₂ O	40
2	EtOH	78
3	MeOH	74
4	DMF	72
5	EtOH:DMF (1:1)	85
6	EtOH:DMF (2:1)	70
7	EtOH:DMF (1:2)	76
8	DMSO	65
9	Without solvent	25

**Scheme 8.** Synthesis of 4H- tetrahydrobenzo[b]pyran derivatives using Mg-Al HT.**Scheme 9.**

product and its recovery and reuse. HT Mg-Al can be reused in several reaction cycles after dissolving the product in hot ethanol and washing several times with ethanol, largely maintaining its catalytic activity [28].

2-Amino-chromene derivatives (Scheme 9) were synthesized using hydrotalcite with different ratios (Mg/Al = 2, 3 and 5) under microwave irradiation at 140°C and under solvent-free conditions

so that occurs maximum microwave absorption at reagents. It was found that under these conditions, the reaction is completed in only 7 min compared to the reaction in the presence of a solvent. The uncalcined HT (Mg/Al = 3) presents the best yields, since in the calcination at high temperatures Lewis basicity increases, while the Brønsted basicity decreases because the hydroxyl groups in the brucite layer are removed as water after calcination. In this reaction, the Brønsted-type basicity is essential. Several substituted aromatic

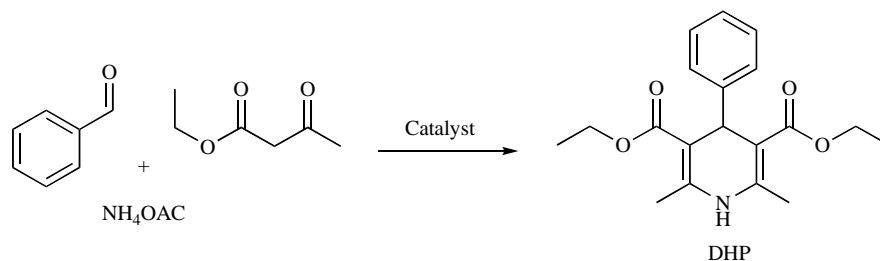
aldehydes were studied, showing that aldehydes containing substituents that attract electrons in the para position react more rapidly and afford high yields [29].

4. HANTZSCH SYNTHESIS

The classical synthesis of 1,4-dihydropyridines (1,4-DHPs) by the Hantzsch reaction involves the condensation of an aldehyde with ethyl acetoacetate and ammonium acetate in alcohol under reflux. However, this procedure shows low yields and long reaction times [30]. 1,4-DHPs are a class of important compounds in the field of pharmaceuticals, which are found in numerous bioactive compounds including various antihypertensive, hepatoprotective, antitumor, antidiabetic agents, among others. They are commercially used as calcium channel blocking compounds such as

nifedipine, nitrendipine, and nimodipine for the treatment of cardiovascular diseases [11, 31, 32].

Antonyraj *et al.* used acetonitrile and ethanol as solvents in the synthesis of 1,4-DHP (Scheme 10), obtaining yields of 45% in ethanol at 1 h and 61% in acetonitrile in 6.5 h with MgAl₂-HT. This could be explained due to a cooperative behavior of the acid-base sites because stronger concentrations of Lewis acid sites (Al³⁺) generate stronger Brønsted basic sites. Furthermore, the variation of the divalent metal ions by the substitution of Mg²⁺ by Ni²⁺ or Co²⁺ in a binary hydrotalcite (with the atomic composition M(II)/Al = 3) dramatically decreases the yield of 1,4-DHP. Various DHPs were synthesized using different aldehydes, whose yields are summarized in Table 5. The multicomponent synthesis of 1,4-DHP using hydrotalcite as a basic solid catalyst suggests its application in catalytic processes oriented to the pharmaceutical industry [33].

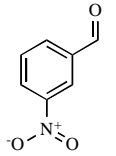
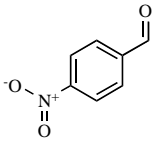
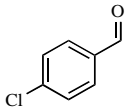
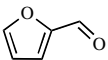



Scheme 10. Hantzsch reaction.

Table 5. DHP synthesis for various aldehydes over MgAl₂-HT^a.

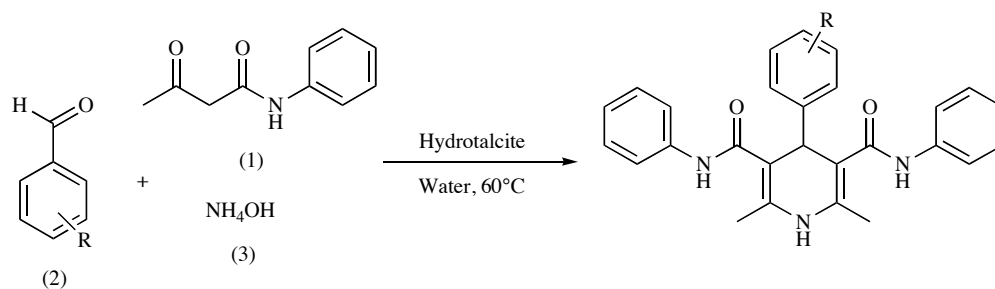
Entry	Aldehyde	Nitrogen Source	Mole Eq. of N-source	Yield %
1		NH ₄ OOCCH ₃	1	61
2		NH ₄ OOCCH ₃	2	73
3		NH ₄ OOCCH ₃	2	32 ^b
4		Liq. NH ₃	2	43
5		(NH ₄) ₂ CO ₃	1	18
6		NH ₄ OOCCH ₃	1	45

Table 5. contd...

Entry	Aldehyde	Nitrogen Source	Mole Eq. of N-source	Yield %
7		NH ₄ OOCCH ₃	2	56
8		NH ₄ OOCCH ₃	2	57
9		NH ₄ OOCCH ₃	2	53
10		NH ₄ OOCCH ₃	2	75
11		NH ₄ OOCCH ₃	2	57

^a 0.0039 M aldehyde, 0.0078 M of ethylacetoacetate, solvent–acetonitrile (10mL); 50 mg catalyst; 6.5 h.

^b Reusability of the catalyst obtained from the experiment in entry 3.



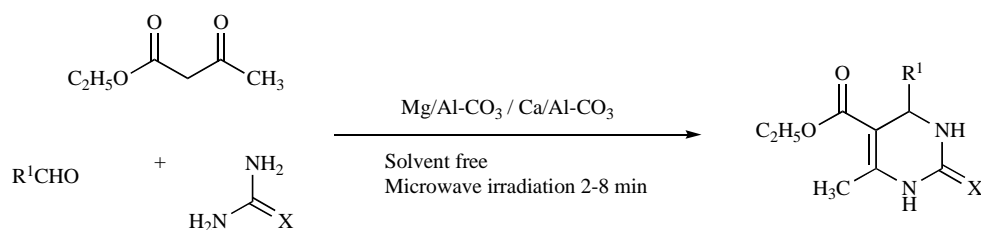
Scheme 11. Multicomponent reaction catalyzed by hydrotalcite.

Pagadala *et al.* studied the synthesis of 1,4-dihydropyridines using various homogeneous catalysts and hydrotalcite as a heterogeneous catalyst by means of the Hantzsch reaction. The reaction was carried out between acetoacetanilide (1), aromatic aldehydes (2) and ammonium hydroxide (3) (Scheme 11). The results show that when using NaOH and [Bmim]BF₄ in ethanol, water or dichloromethane (DCM) as reaction solvents, the reaction does not lead to some expected products. However, under solvent-free conditions at 60°C a yield of 55% was obtained using the ionic liquid [Bmim]BF₄ as a catalyst. The best yields were obtained using Zn/V-CO₃ hydrotalcite as a heterogeneous catalyst in an aqueous medium at 60°C. These results show that the use of Zn/V-CO₃ hydrotalcite as catalyst significantly improves product yields, and the zinc and vanadium loading on the hydrotalcite provides the possibility of altering properties such as acidity, pore size, and surface area. Possibly, the catalyzed reaction continues through a cyclic transition state in the interlaminar space of the catalyst, which, because of its bifunctional acid-base character, allows the mediation of the Hantzsch reaction and the Michael addition of carbonyl compounds [34].

5. BIGINELLI SYNTHESIS

The Biginelli reaction is a simple and direct procedure for the synthesis of 3,4-dihydropyrimidinones (3,4-DHPM) by means of the condensation of three components, namely, an aliphatic or aromatic aldehyde, a β-keto ester compound, and urea, and is catalyzed by mineral acids. DHPMs represent a heterocyclic system of remarkable pharmacological efficacy, including antiviral, antibacterial and anti-inflammatory activities [35]. On the other hand, it has been found that this condensation presents good yields when the Lewis acid is replaced by a strong Brønsted base [36, 37].

Heterogeneous catalysts such as hydrotalcites have been studied as catalysts with strong Brønsted-type basicity in the Biginelli synthesis (Scheme 12). Mg/Al-CO₃ and Ca/Al-CO₃ were studied under solvent-free conditions and under microwave irradiation with a reaction time of 2-8 min, obtaining good yields at 80°C. The hydrotalcites (Mg/Al-CO₃ and Ca/Al-CO₃) calcined at 500°C for 6 h showed lower catalytic activity, since in the calcination Lewis basicity increases while Brønsted basicity decreases, Brønsted-type basicity being necessary for this reaction. Under the optimization

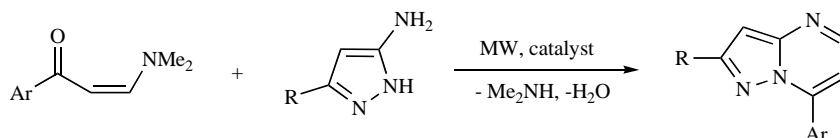


Scheme 12. Synthesis of dihydropyrimidinones. X = O, S.

Table 6. Hydrotalcite catalyzed synthesis of 3,4-dihydropyrimidinones in solvent-free conditions^a.

Entry	R ¹	X	Mg-Al-CO ₃ hydrotalcite		Ca-Al-CO ₃ hydrotalcite	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1	C ₆ H ₅	O	2	86	6	67
2	4-(CH ₃ O)-CH ₄	O	6	82	8	63
3	4-(CH ₃)-CH ₄	O	8	71	6	59
4	4-(Cl)-CH ₄	O	6	79	8	62
5	4-(Nme ₂)-CH ₄	O	8	80	8	66
6	4-(NO ₂)-CH ₄	O	6	83	8	67
7	4-(OH)-CH ₄	O	8	72	8	61
8	2-(OH)-CH ₄	O	8	76	6	63
9	C ₆ H ₅	S	6	78	6	66
10	4-CH ₃ OC ₆ H ₄	S	6	76	6	62

^aReaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1 mmol), 80°C, solvent-free thermal conditions without microwave irradiation.



Scheme 13. Synthesis of pyrazolo[1,5-a]pyrimidine derivatives.

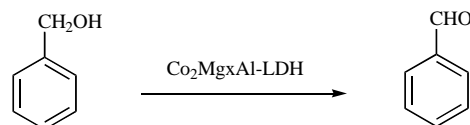
conditions, other aldehydes were studied (Table 6), showing that substituted aromatic aldehydes containing both donor groups and electron acceptors provide high yields with high purity, which shows that the electronic effects do not play a significant role in the yield of the synthesized product [38]. These results were also reported by Dabholkar and coworkers using hydrotalcite Mg/Fe at 550°C under solvent-free conditions; after the reaction, the catalyst can be used at least four times without significant loss of its catalytic activity [39].

6. USE OF HYDROTALCITES IN ORGANIC SYNTHESIS

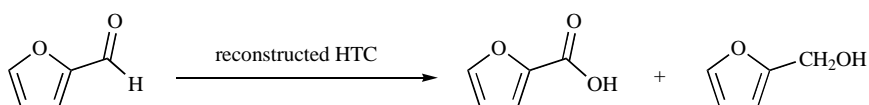
The development of environmentally benign protocols for fine chemistry synthesis is attracting more attention every day. Several authors have studied hydrotalcites as heterogeneous catalysts in various chemical reactions. Mg/Al as the solid catalyst was studied in the Michael addition reaction of aminopyrazoles to enaminone derivatives under solvent-free conditions using microwave irradiation (Scheme 13), showing that the catalyst acts as a bifunctional catalyst where the acid (Al³⁺) sites to act on the adsorption of the addition step and the Brønsted basic sites (OH) facilitate nucleophilic addition via deprotonation/re-protonation processes [40]. Also calcined and uncalcined Mg/Al hydrotalcites with a molar ratio of 0.6 catalyze the Michael additions of 2-methylcyclohexane-1,3-dione, 2-acetylcyclopentanone and 2-acetylcyclohexanone to methyl vinyl ketone with high selectivity, and an optimum balance

of the acid-base properties can make the calcined aluminum-rich hydrotalcite an excellent catalyst in the Michael addition to numerous 1,3-diones [41].

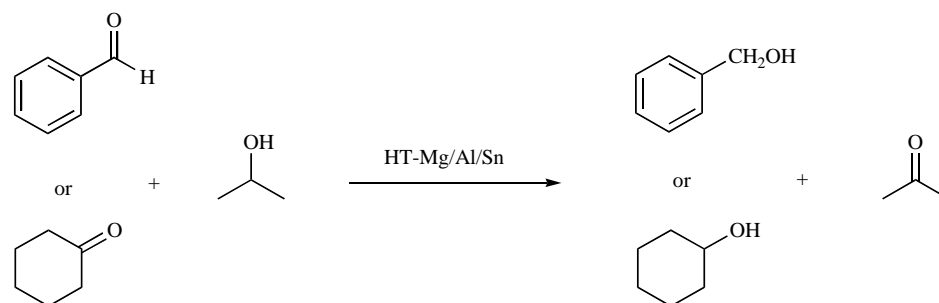
Co₂Mg_xAl-LDH hydrotalcites with different Mg²⁺ contents were used in the selective oxidation of benzyl alcohol to benzaldehyde (Scheme 14), obtaining better catalytic activities after the addition of different amounts of Mg²⁺ ions. Although the efficiency in terms of product performance is not the best in comparison with other reaction systems, this study can be used to design more efficient catalysts, since the addition of Mg²⁺ ions not only influences the number of basic sites but also promotes the oxidation process of Co²⁺ to Co³⁺ [42]. Thao *et al.* found that Co²⁺ in the octahedral layer of hydrotalcite acts as an active site for styrene oxidation, whereas the intra-lamellar ions of Co²⁺ act as the basic sites and are responsible for the formation of benzaldehyde. The conversion of styrene amounts to about 70%-90%, and the selectivity to the desired products (benzaldehyde + styrene oxide) is approximately 92%-99% [43].



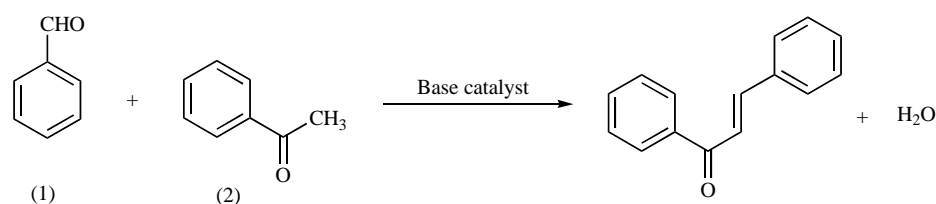
Scheme 14.



Scheme 15. Cannizzaro reaction.



Scheme 16. Meerwein-Ponndorf-Verley (MPV) reaction.



Scheme 17.

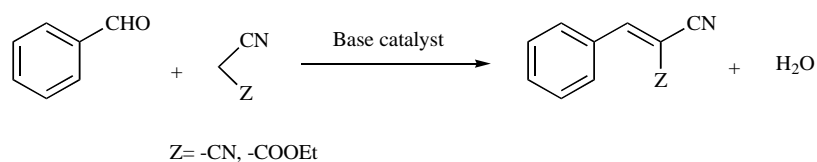
The catalysts of Co-Al and Ni-Al type hydrotalcite with different ratios ($M^{2+}/Al^{3+} = 0.5-3.0$) were evaluated in the selective reduction reaction of nitrogen oxide (NO) with propane, propylene and n-decane in the presence of O_2 . The catalytic activity was greater at an M^{2+}/Al^{3+} ratio = 0.5, which is related to the high dispersion of the Ni or Co cations that are stabilized by a significant amount of Al^{3+} ions. When propane and n-decane were used as reducing agents, the conversion of both catalysts was characterized by temperature dependence, because the catalyst takes part in the concurrent hydrocarbon oxidation reaction [44].

Rehydration of the mixed oxide of Mg-Al (calcined hydrotalcite) with water results in the formation of reconstructed hydrotalcite having OH groups instead of carbonates in the middle layer. The amount of water in the mixture influences the degree of rehydration and the total reconstruction of the hydrotalcite structure is only observed when biphasic (water-organic solvent) reaction conditions are used. Kikhtyanin and coworkers demonstrated that the Brønsted basic sites of calcined reconstructed HT catalyze the transformation of furfural in the Cannizzaro reaction (Scheme 15), and furfuryl alcohol and furfuryl furoate are formed during the reaction. However, furoic acid is not detected among the reaction products because it remains adsorbed at the basic sites of the catalyst forming furoates at the surface, which leads to a gradual deactivation of the catalyst, where by the Cannizzaro reaction would result in the deactivation of the catalyst, making it difficult to recover and reuse without an oxidative regeneration step [45].

The Meerwein-Ponndorf-Verley (MPV) reaction between aldehydes and ketones with 2-propanol as a hydrogen donor using Mg/Al and Mg/Al/Sn hydrotalcites calcined at 450°C (Scheme 16) shows that the presence of tin in the hydrotalcite provides the better results due to the increase of the acidity by the Sn^{4+} ion, and it can be assumed that these solids have strong Lewis basic sites (O^{2-} ions) and Lewis acid sites (coordinately unsaturated Al^{3+} and Sn^{4+} ions). Therefore, mixed oxides containing Al^{3+} and Sn^{4+} ions adsorb 2-propanol more efficiently than magnesium oxide and lead to higher conversions [46].

The Claisen-Schmidt condensation between benzaldehyde (1) and acetophenone (2) (Scheme 17) has been carried out in the presence of rehydrated and calcined hydrotalcites as basic solid catalysts. The results show that a mixed Al-Mg oxide with an Al/(Al + Mg) molar ratio of 0.25 shows excellent catalytic activity for this type of condensation, and it also allows obtaining several chalcones that present pharmacological, anti-inflammatory, antineoplastic activities with excellent activity and selectivity in all cases [47]. Guida and coworkers investigated the catalytic activity of Mg/Al hydrotalcite in the intramolecular condensation of acetonylacetone for the synthesis of chalcones, finding that the solvent influences the rate of reaction due to its acidity, and the water reacts with the catalyst to hydroxylate the surface, creating active basic sites where high amounts of water inhibit the reaction. These results explain why ethanol (95%) is the best solvent for this reaction. In addition, the calcination temperature of the catalyst also influences the reaction rate, and hydrotalcite calcined at 500°C presents the best yields [48].

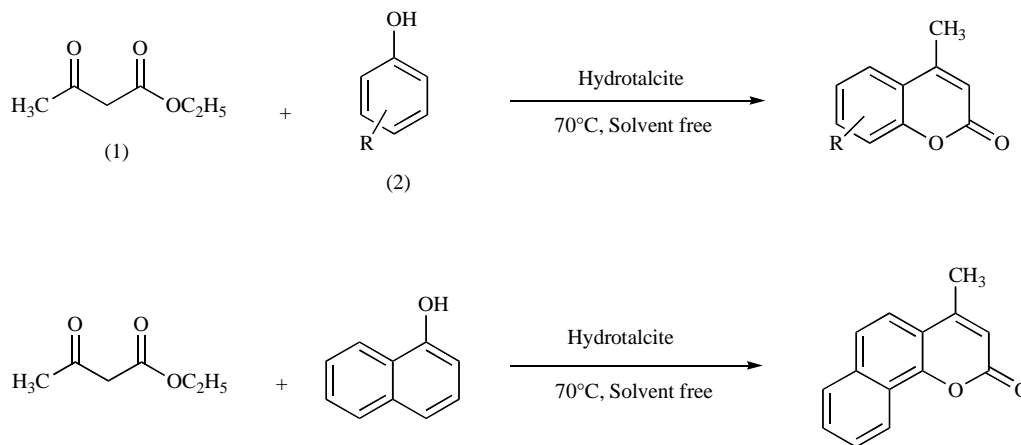
Knoevenagel condensation of carbonyl compounds containing an active methylene group is one of the most important methods for preparing substituted alkene derivatives (Scheme 18). Climent *et al.* studied the preparation method of Mg/Al hydrotalcites, showing that the mixed oxides derived from the hydrotalcites synthesized by ultrasound considerably improve the surface area of the calcined hydrotalcite as well as the number of active sites showing greater activity. This is explained assuming that not only changes the total number of the basic sites exposed to the reactants, but also increases the fraction of the strongest sites corresponding to O^{2-} located at the corners of the crystals. Using this catalyst it is possible to obtain yields of 96% with a selectivity of 99% in 15 minutes of reaction [27]. NiAl- CO_3 hydrotalcite also catalyzes the Knoevenagel condensation of different aldehydes (Table 7), demonstrating that this solid-base catalyst is a practical alternative to Knoevenagel condensation soluble bases with the following advantages: (a) high catalytic activity, (b) solvent-free conditions, (c) mild reaction conditions, (e) use of a non-toxic catalyst, and (f) recyclable nature of the catalyst [49].



Scheme 18.

Table 7. Knoevenagel condensation of aldehydes with ethylcyanoacetate and malononitrile, carried out at 60°C in solvent-free conditions.

Entry	Aldehyde	Ethylcyanoacetate		Malononitrile	
		Time (h)	Yield (%)	Time (h)	Yield (%)
1	Benzaldehyde	24	35	0.5	97
2	4-Hydroxy-3-methoxybenzaldehyde	5	74	1	70
3	3-Hydroxy-4-methoxybenzaldehyde	7	92	24	84
4	4-Methylbenzaldehyde	24	53	1	93
5	2-Methylbenzaldehyde	5	76	1	96
6	4-Methoxybenzaldehyde	6	70	1.5	84
7	Salicylaldehyde	24	79	4	53
8	3-Phenylprop-2-enal	24	82	1	93
9	Cyclohexanecarbaldehyde	5	80	3	83
10	Hexanal	1	60	0.5	95



Scheme 19. Preparation of coumarin derivatives.

Calcined Mg-Al-CO₃ and Ca-Al-CO₃ hydrotalcites were studied in the synthesis of coumarin derivatives, using ethyl acetoacetate (1) and phenols/naphthol (2) at 70°C (Scheme 19) as environmentally friendly and reusable heterogeneous catalysts under solvent-free conditions. The reaction was completed within a few minutes with excellent yield (Table 8). This study revealed that the catalytic activity of the calcined hydrotalcite shows a striking correlation with its corresponding basic properties, and the metal content composition affects the yield of target molecules (Table 9) [50].

The synthesis of alkenes through the Wittig reaction catalyzed by Mg/Zn hydrotalcite calcined at 500°C using dioxane as solvent shows a significant increase in its catalytic activity compared to uncalcined hydrotalcite, demonstrating that basicity is sufficient to produce phosphonium ylide because the decreased content of aluminum leads to increased activity and the number of the stronger basic sites of the calcined hydrotalcites increases with the increasing content of aluminum in the brucite layers. The structural recon-

struction of the calcined hydrotalcites due to the memory effect depends strongly on the temperature as well as on their chemical composition. The reconstruction process is complex and results in the formation of materials with different structural and surface characteristics than the initial hydrotalcites [51].

Microwave-assisted synthesis of 2-benzimidazolethiol from 1,2-benzenediamine (1) and carbon disulfide (2) (Scheme 20) using reconstructed hydrotalcite shows the corresponding mono- and dialkylated derivatives of 2-benzimidazolethiol in good yields in short reaction times. This protocol offers several advantages, such as the use of a reusable and efficient heterogeneous base for alkylation reactions [52].

The synthesis of substituted 1H-tetrazoles using Zn/Al hydrotalcite in the reaction of benzonitrile (1) with sodium azide (2) (Scheme 21) presents yields between 69% and 91% with the advantage of easy recovery and reuse of the catalyst [53].

Table 8. Hydrotalcite (Mg–Al-HT) catalyzed synthesis of coumarin derivatives.

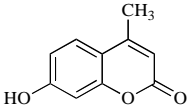
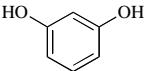
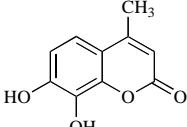
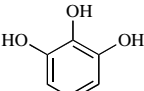
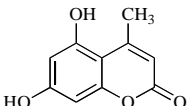
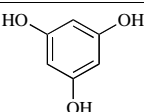
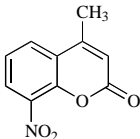
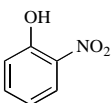
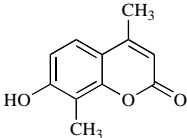
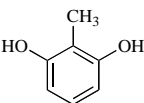
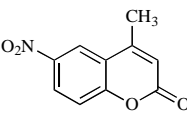
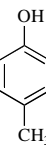
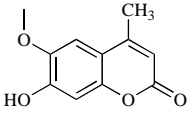
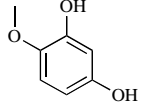
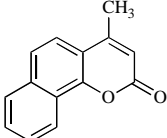
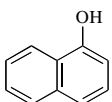
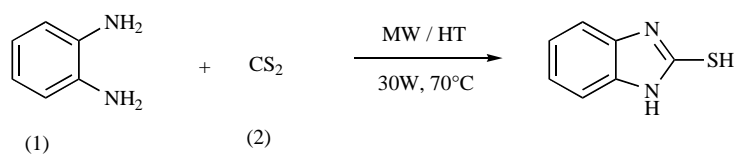
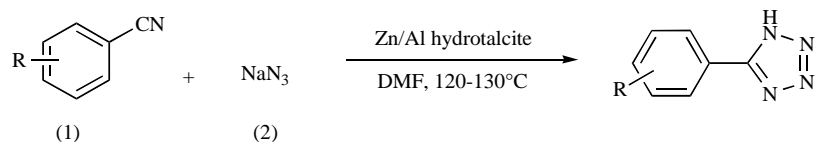
Entry	Product	Phenol	Time (min)	Yield(%)
1			30	97
2			40	92
3			35	89
4			35	91
5			50	83
6			25	93
7			30	95
8			45	95

Table 9. Effect of metal composition of hydrotalcite on the yield of coumarin^a.

Entry	Hydrotalcite Ratio	Time (min)	Yield (%)
1	(2:1) Mg–Al–CO ₃	70	84
2	(3:1) Mg–Al–CO ₃	30	97
3	(4:1) Mg–Al–CO ₃	70	79
4	(2:1) Ca–Al–CO ₃	80	74
5	(3:1) Ca–Al–CO ₃	60	90
6	(4:1) Ca–Al–CO ₃	90	78
7	MgO	150	21
8	CaO	180	15

^a Reaction conditions: solvent-free conditions, heating at 70°C.

**Scheme 20.** Synthesis of 2-benzimidazolethiol.**Scheme 21.** Zn/Al hydrotalcite catalyzed synthesis of 5-substituted 1H-tetrazoles.**Table 10.** Cu/Al-HTB (Cu:Al, 2.5:1) catalyzed amination of aryl chlorides with cycloalkylamines^a.

Entry	Aryl chloride	Product	Time (h)	Yield (%)
1			9	71
2			8	91
3			8	89
4			8	56
5			8	88
6			9	59
7			6	93

^aReaction conditions: 20 wt% catalyst, 3.6 mmol (1.1 equiv.), K₂CO₃, 3.17 mmol aryl chloride, 2/mL amine, temperature 100°C.

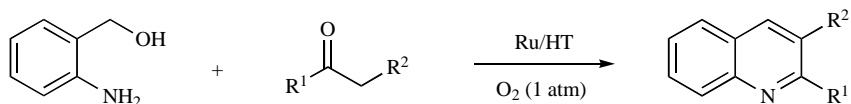
The amination between aryl chloride with primary and secondary aromatic amines catalyzed by Cu/Al-HT and K₂CO₃ allows working with a variety of functional groups (Table 10) and does not require an expensive additive. Several aryl chlorides were coupled with benzylamine, dibenzylamine, and cycloalkylamines to produce the corresponding N-arylated products in good yields (45% - 93%) [54].

7. HYDROTALCITES AS BIFUNCTIONAL CATALYSTS

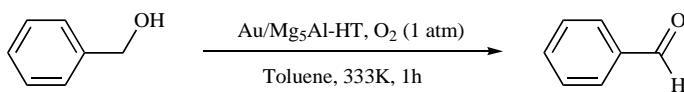
One of the most relevant properties of hydrotalcites is that they have high surface areas so they are also used as catalytic supports: in this way, several metals have been supported in these materials obtaining bifunctional catalysts. Ru/HT act as an efficient bifunctional catalyst for the synthesis of substituted quinolines from 2-aminobenzyl alcohols and various carbonyl compounds under oxygen and without homogeneous bases (Table 11). In the reaction, Ru acts on the oxidation of the 2-aminobenzyl alcohol to 2-amino benzaldehyde under an O₂ atmosphere followed by the aldol reaction with ketones which are catalyzed by basic sites of HT [22, 55].

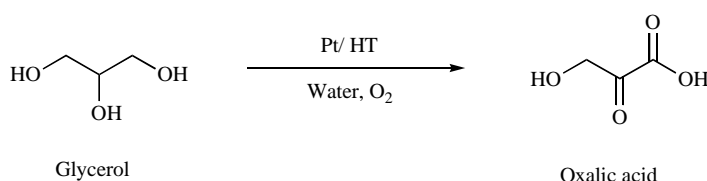
HT-supported gold nanoparticles (NP-Au) were used for the synthesis of the aerobic oxidation of methyl esters and imines of primary alcohols in a catalyzed tandem reaction under conditions free of homogeneous bases (Scheme 22). The catalytic performance of this reaction can be adjusted through the atomic ratio of the Mg/Al support, showing that at a ratio of Mg/Al = 5 the best yields are obtained, and there is a cooperation between the NPA-Au and the basic sites of hydrotalcite, which not only benefits the oxidation of the starting alcohol, but also the following stages of the tandem reaction, which are promoted by the basic support (HT), including the formation of hemiacetal as an intermediate compound and its subsequent oxidation [56].

Mitsudome *et al.* found that the catalytic activity of Au nanoparticles on basic supports increases with the decreasing size of Au nanoparticles in the aerobic oxidation of alcohols under mild reaction conditions (40°C, in air). This system offers significant benefits such as high catalytic efficiency, requires no additives, uses atmospheric O₂ and allows easy catalyst recovery [57]. Gold nanoparticles of less than 5 nm were studied in the selective oxidation of glycerol in water with molecular oxygen under mild reaction

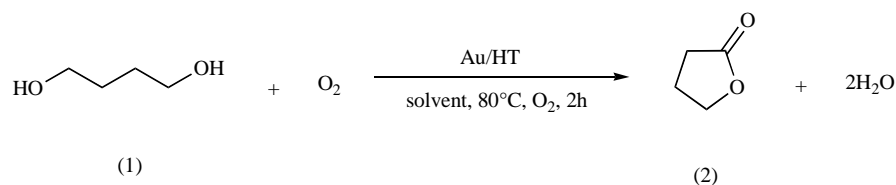
Table 11. Quinoline synthesis from various ketones^a.

Entry	Ketone	Product	Yield of Quinoline ^b (%)
1	R=H	R=H	84
2	R= 4-Cl	R= 4-Cl	83
3	R= 4-F	R= 4-F	90
4	R= 3-CF ₃	R= 3-CF ₃	78
5	R= 2-Me	R= 2-Me	35
6	R= 3-Me	R= 3-Me	94
7	R= 4-Me	R= 4-Me	83
8	R= 4-OMe	R= 4-OMe	79
9	R=4-NO ₂	R=4-NO ₂	83
10			89
11			74
12			74
13			88
14			77
15			80

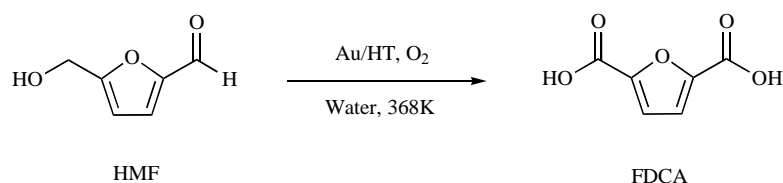
^a2-Aminobenzylalcohol (1 mmol), ketone (1.2 mmol), Ru/HT-N (0.3 g, Ru: 3.0 mol %), toluene (5 mL), 20 h, 100°C, O₂ (1 atm).^bYield was determined by HPLC and GC using an internal standard based on 2-aminobenzyl alcohol.**Scheme 22.** Benzyl alcohol oxidation.



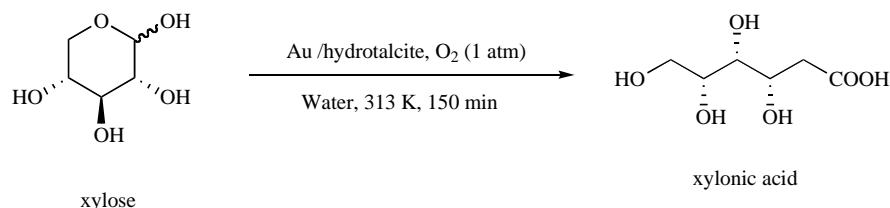
Scheme 23. Glycerol oxidation in water.



Scheme 24. Oxidation of 1,4-butanediol using supported gold catalysts.



Scheme 25. HMF oxidation in water using supported gold catalysts in the presence of oxygen without addition of homogeneous base.



Scheme 26. Aqueous oxidation of xylose into xylonic acid using Au/HT catalyst under 1 atm of molecular oxygen.

conditions. XANES spectra indicate that calcination at temperatures above 100°C leads to the generation of Au metal which is the catalytically active site for this reaction [58]. Akihiro Tsuji and co-workers studied Pt/HT in this same reaction (Scheme 23) finding similar results and concluded that the catalytic activity is related to the precise control of the concentration of Pt⁰ and the basicity of the HT support [59].

Au/HT leads to the formation of γ -butyrolactone (2) with an excellent performance through the aerobic oxidative lactonization reaction of 1,4-butanediol (1) (Scheme 24) without the need for high temperatures, additives, and high catalytic loading, using various diols that use molecular oxygen as the primary oxidizing agent [60]. Hydrotalcites containing transition metals as support of gold nanoparticles (Au/M-HT, M = Cr, Zn, Mn, Co, Ni, Fe) exhibit excellent catalytic activity for the oxidation of alcohols in the liquid phase. The Au/MgCr catalyst shows the best yields due to the synergy between gold nanoparticles and transition metals, which not only involves the basic surface sites of hydrotalcites but also includes Cr cations involved in the dehydrogenation of alcohol [61].

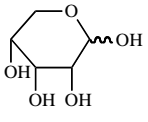
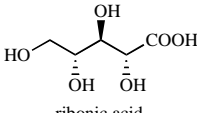
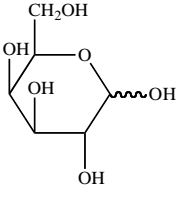
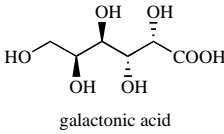
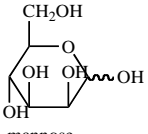
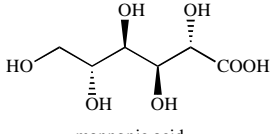
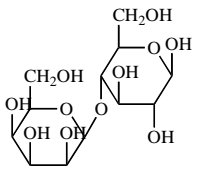
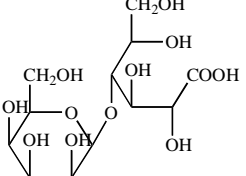
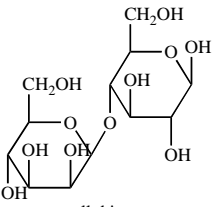
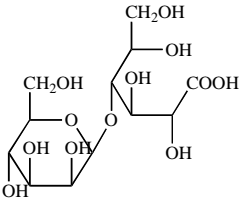
The selective oxidation of 5-hydroxymethylfurfural (HMF) to furan dicarboxylic acid (FDCA) (Scheme 25), using molecular oxygen in water and in the absence of a homogeneous base using Au/HT, shows that the role of HT as a basic support for oxidation could be attributed to the formation of intermediate hemiacetals from aldehydes such as HMF and FFCA and the formation of metal

alcoholate species through the HMFCFA metal-hydride change [62]. The hydrotalcite-supported gold nanoparticles show good activity as heterogeneous catalysts for the oxidation of monosaccharides (xylose, ribose, galactose and mannose) and disaccharides (lactose and cellobiose) in the corresponding aldonic acids (Scheme 26, Table 12) using atmospheric pressure of molecular oxygen, water as the solvent of reaction, and without the addition of external bases, with high yields [63]. These investigations open a catalytic pathway for the synthesis of fine chemicals based on biomass derivatives.

Hydrotalcite as support of gold nanoparticles (Au/HT) also has been studied as a heterogeneous catalyst in the dehydrogenation of amides from alcohols and amines, presenting high efficiency under mild reaction conditions with yields of 98% [64], in the deoxygenation of epoxides for the formation of alkenes in the presence of H₂ or CO/H₂O as reducing agents, showing 99% selectivity and high atom efficiency. In addition, the catalyst can be reused without loss of catalytic activity or selectivity [65, 66]. Ag/HT hydrotalcite has also been studied in this reaction, showing a simple purification process due to catalyst separation and reuse without any loss in its catalytic activity [67].

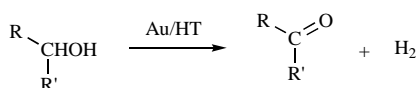
Au nanoparticles supported on HT can efficiently catalyze the dehydrogenation of alcohols in carbonyl compounds (Scheme 27): however, the size of Au nanoparticles play a key role in the dehydrogenation reaction. Fang *et al.* found that small size Au nanopar-

Table 12. Aqueous oxidation of aldose sugars into the corresponding aldonic acids using Au/HT catalyst under 1 atm of O₂^a.

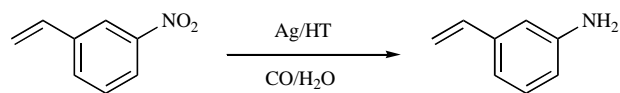
Entry	Substrate	Product	Time (min)	Yield %
1	 ribose	 ribonic acid	150	90
2	 galactose	 galactonic acid	120	87
3	 mannose	 mannonic acid	120	80
4	 lactose	 lactobionic acid	180	96
5	 cellobiose	 cellobionic acid	180	92

^aReaction conditions: 1.7 wt% Au/HT 50 mg, substrate 0.5mmol, H₂O 7 mL, O₂ flow (10 mL min⁻¹), 313 K.

ticles (0.5 nm) are more active than the larger particle size (45 nm) [68].

**Scheme 27.**

Hydrotalcite-supported silver nanoparticles (Ag/HT) act as an effective heterogeneous catalyst for the reduction of nitroaromatics using CO/H₂O as the reducing reagent (Scheme 28), showing a complete chemoselective reduction. This methodology could be a good tool for the synthesis of functionalized anilines [69].

**Scheme 28.** Reduction of nitroaromatics.

CONCLUSION

Hydrotalcites or double lamellar oxides are used as catalysts or catalytic supports having high surface areas, basic surface proper-

ties, and structural stability that depend on the synthesis conditions such as temperature, pH, atomic ratio, and metallic composition. The calcination process leads to the formation of mixed oxides with Lewis or Brønsted basic sites that are favored depending on the calcination temperature, have high surface area and a shape memory effect that allows regeneration to their original structure. In these materials, the metal composition plays a key role given that, depending on the metal and its atomic ratio, a bifunctional acid-base catalyst can be obtained. As support hydrotalcites also allow obtaining bifunctional materials by mainly supporting transition metals that generally lead to oxidation or reduction processes. In this way, hydrotalcites present a wide spectrum of applications as heterogeneous catalysts in organic synthesis and have been studied in different reactions such as Michael addition reactions, dehydrogenation reactions of alcohols, Knoevenagel condensations, reduction reactions, oxidations, epoxidations, alkylations, multicomponent reactions, among others. Multicomponent reactions are of major interest since they allow obtaining compounds that have high biological activity and are generated through processes in a single step by combining three or more starting reagents under solvent-free conditions. In general, these materials act as heterogeneous catalysts that conduct highly efficient processes in short reaction times and with the advantage of their easy recovery and reuse with-

out significant loss of their catalytic activity. In addition, due to the modification of their structural and chemical properties, they are catalysts with multiple applications in organic synthesis.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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