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# Hydrotalcites as catalyst in suitable multicomponent synthesis of uracil derivatives

### Eliana Nope<sup>a</sup>,\*, Ángel G. Sathicq<sup>a</sup>, José J. Martínez<sup>b</sup>, Hugo Rojas<sup>b</sup>, Gustavo Romanelli<sup>a, c, \*</sup>

<sup>a</sup> Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA-CCT La Plata-CONICET-CIC-PBA), Universidad Nacional de La Plata, Calle 47 No 257, B1900AJK La Plata, Argentina

<sup>b</sup> Escuela de Ciencias Químicas, Facultad de Ciencias, Universidad Pedagógica y Tecnológica de Colombia UPTC, Avenida Central del Norte, Tunja, Boyacá, Colombia <sup>c</sup> Centro de Investigación en Sanidad Vegetal (CISaV) / Cátedra de Química Orgánica, Facultad de Ciencias Agrarias y Forestales, Universidad Nacional de La Plata, Calles 60 y 119 s/n, B1904AAN La Plata, Argentina

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#### ABSTRACT

Uracil compounds participate in a wide range of biological activities; however, reports on their synthesis using heterogeneous catalysts are scarce. In this work, the multicomponent synthesis of uracil derivatives assisted by layered double hydroxides (LDH) was studied under green chemistry conditions. The incorporation of  $Ni^{2+}$  or  $Co^{2+}$  was successfully performed by co-precipitation method. The yields to uracil derivatives are associated with the presence of weak basic sites and a better interaction of the reagents when the reaction is carried out in solvent-free conditions. The reaction pathway involves the formation of an enone between benzaldehyde and ethyl cyanoacetate, and subsequent reaction with urea, which is assisted by the presence of a basic catalyst. The scope of this synthesis is illustrated with nine examples.

#### 1. Introduction

Layered double hydroxides (LDHs), known as hydrotalcites, are materials composed of divalent ( $Me^{2+}$ ) and trivalent ( $Me^{3+}$ ) cations, whose structure is formed by Mg(OH)<sub>2</sub> layers, such as brucite. They are generally described as  $[Me^{2+}(1-x) Me^{3+} x(OH)_2]^{X+}(An^-)_{x/n}n^{H}_{2}O$ , where the isomorphic substitution of  $Me^{2+}$  by  $Me^{3+}$  cations results in positive net charge, which is compensated by the presences of interlaminar anions ( $An^-$ ) and crystallization water [1]. The properties of LDHs can be changed by reconstruction processes [2], by the isomorphic substitution of another  $Me^{2+}$  or  $Me^{3+}$  cation, forming ternary hydrotalcites [3] or through the modification of the ratio of metal cations [4]. These possibilities make these materials a very versatile system with desirable catalytic properties.

Several works have been published about the use of hydrotalcites in multicomponent reactions (MCRs) [3,5,6]. In several cases it was found that a change in the calcination process conditions, which results in the formation of mixed oxides, or a change in the ratio of metal cations is a useful parameter for a highly selective reaction [5,7,8]. The Biginelli reaction [9], together with the Hantzsch reaction [10], was the first multicomponent heterocyclic synthesis reported. In the Biginelli

synthesis, an aldehyde, urea, and an acetic acid ester react in acidic media to obtain 3,4-dihydropyrimidine-2(1 H)-ones in an MCR.

The mechanism of this reaction has been the subject of several studies because, depending on the reaction conditions, the synthesis of DHPM can take three different routes, which mainly involve the reaction medium, since the desired product can be obtained in acidic or basic conditions [11]. Currently, the environmental advantages of MCRs, such as high atom economy, no intermediate isolation and/or purification steps, with the consequent solvent and energy saving, and solventless reaction, among others, are well known and reported [12–14].

However, the use of Biginelli-type reaction to synthesize uracil derivatives is not very extended; in fact, there are a few examples in the literature [15–18]. Uracil-type molecules are a very important target in organic synthesis due to the wide array of biological activities. The most studied and reported properties of uracil derivatives are antitumor [19, 20] and antiviral [21,22] activity; however, they also possess a wide range of other properties as insecticidal [23], bactericidal [24], herbicidal [25] or antitubercular agents [15], among others.

There has been little focus on the synthesis of these compounds using heterogeneous catalysts. The Biginelli reaction generally proceeds in acid media [26]; however, uracil synthesis can be conducted in basic

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<sup>\*</sup> Corresponding authors at: Centro de Investigación y Desarrollo en Ciencias Aplicadas "Dr. Jorge J. Ronco" (CINDECA-CCT La Plata-CONICET-CIC-PBA), Universidad Nacional de La Plata, Calle 47 No 257, B1900AJK La Plata, Argentina.

E-mail addresses: eliana.nope@quimica.unlp.edu.ar (E. Nope), gpr@quimica.unlp.edu.ar (G. Romanelli).

media. There are few investigations reporting on the use of basic catalysts and in all cases the reaction is carried out under solvent conditions. Conventional catalysts such as NaOH in ethanol [27], K2CO3 in DMF or ethanol [16,28], and anhydrous acetic acid [29] have been reported with good yields but longer reaction times and with auxiliary processes for compound separation. The use of microwaves using K<sub>2</sub>CO<sub>3</sub> in ethanol [30] has recently been reported, although auxiliary substances such as acetic acid for extraction of the product are required. Therefore the search for environmentally friendly protocols is a requirement in the synthesis of these compounds. The basic properties of hydrotalcites can be modulated with the incorporation of other divalent or trivalent cations in the structure of brucite. Several examples have been described in Knoevenagel condensation and Michael addition using these basic solids [31,32]. However, the synthesis of uracil derivatives via the Biginelli multicomponent reaction, which may involve these reactions, has not been explored using hydrotalcites, in part because this type of reaction requires acidic sites, excess of solvent, and prolonged reaction times. In view of the advantages of these materials and considering that the Knoevenagel reaction and Michael addition are typical basic reactions, in this work we present a simple solvent-free protocol for the multicomponent synthesis of uracil derivatives, with excellent yields and good green parameters, using hydrotalcites with double divalent cation as materials that present high basicity due to the incorporation of another Me2+ in the brucite layer, which improves their basic and structural properties.

#### 2. Experimental

#### 2.1. General

Organic substrates and reagents were purchased from Aldrich, and used without further purification. The reaction yields were obtained from crystallized products. All the products were identified by comparison of analytical, thin layer chromatography (TLC) and nuclear magnetic resonance (<sup>1</sup>H and <sup>13</sup>C NMR) data with those reported.

#### 2.2. Synthesis of hydrotalcites

Layered double hydroxides (LDH) with a Mg/Al ratio of 3 were synthesized by co-precipitation method [6]. The hydrolysis was performed at 120 °C for 16 h, then the pH was adjusted at 9.8, and the mixture was subjected to an aging process for 24 h at 120 °C with constant agitation. The precipitate obtained was washed several times with deionized water and dried at 80 °C for 12 h. The solid obtained was called LDH–Mg. The incorporation of Ni<sup>2+</sup> and Co<sup>2+</sup> was performed applying the same methodology, using 1.53 g of Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O, 0.712 g of Al(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O, 1.71 g of Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O or 1.71 g of Co (NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O as precursor salts with a 3 Me<sup>2+</sup>:Al<sup>3+</sup> ratio. The materials can be described as  $[(MgNi)^{2+}_{1-x} Al^{3+}_x(OH)_2]^{x+}$  and  $[(MgCo)^{2+}_{1-x} Al^{3+}_x(OH)_2]^{x+}$ , and were labelled as LDH-MgNi and LDH-MgCo.

#### 2.3. Characterization of hydrotalcite

The solids were characterized by X-ray diffraction (XRD), N<sub>2</sub>-physisorption at 77 K, temperature programmed desorption of CO<sub>2</sub> (CO<sub>2</sub>-TPD), Fourier-transform infrared (FTIR) spectra, and basicity by titration of benzoic acid. The equipment and methodologies of the distinct characterization techniques have been reported in previous works [6]. The morphology of samples was observed using a Philips-505 scanning electron microscope (SEM).

#### 2.4. General procedure for the synthesis of uracil derivatives

All the reactions were performed in a reaction test tube, which was equipped with a condenser and immersed in an oil bath. A mixture of ethyl cyanoacetate (1 mmol), benzaldehyde (1 mmol), and urea or thiourea (1 mmol), and the selected catalyst (the amount of catalyst, which depended on the test performed, is specified in each of the tables of the results obtained), in solvent-free conditions, was thoroughly mixed and then heated at 80 °C for 6 h. The reaction was monitored by TLC using chloroform: methanol 9:1 mixture as the elution phase, to verify the reaction end point. On cooling, 3 mL acetone was added to the solid residue.

The reaction mixture was filtered to separate the catalyst, acetone was evaporated in a rotatory evaporator, and the crude product of 2,4dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile was dried under vacuum up to constant weight. The crude product was recrystallized from a water:ethanol mixture (ratio depending on the product) to give the pure uracil derivatives.

#### 2.5. Catalyst reutilization

The reusability of the catalyst was examined by running five consecutive tests, under the same reaction conditions (aldehyde (1 mmol); ethyl cyanoacetate (1 mmol); urea/thiourea (1 mmol); solvent-free; catalyst (LDH-MgCo, 50 mg); temperature, 80 °C; time, 6 h.; stirring). After each experiment, the catalyst was filtered (3 mL of acetone was previously added), washed with more acetone (2  $\times$  2 mL), dried under vacuum (25 °C), and then reused.

#### 2.6. <sup>1</sup> H NMR and <sup>13</sup> C NMR spectra of selected synthesized compounds

2,4-Dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (1)  ${}^{1}$ H RMN (400 Hz, DMSO-*d*<sup>6</sup>),  $\delta$  (ppm) 7.43 (3H, m), 7.69 (2H, m), 10.11 (2H, s).

<sup>13</sup>C RMN (100 Hz, DMSO-*d*<sup>6</sup>),  $\delta$  (ppm) 78.80, 120.56, 128.25, 128.49, 130, 139.35, 159.08, 165.36, 179.53.

6-(4-Chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (2)

<sup>1</sup>H RMN (400 Hz, DMSO-*d*<sup>6</sup>), *δ* (ppm) 7.53–7.47 (2H, m), 7.75–7.68 (2H, m), 10.14 (1H, s).

<sup>13</sup>C RMN (100 Hz, DMSO-*d*<sup>6</sup>),  $\delta$  (ppm) 78.76, 120.37, 128.36, 130.31, 134.69, 138.09, 158.92, 166.18, 171.19.

6-(2-Chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (3)

<sup>1</sup>H RMN (400 Hz, DMSO- $d^6$ ), δ (ppm) 7.32–7.29 (1H, m), 7.44–7.34 (3H, m), 7.52–7.46 (1H, dd, J = 7.52, J = 1.72 Hz), 10.10 (2H, s).

<sup>13</sup>C RMN (100 Hz, DMSO-*d*<sup>6</sup>),  $\delta$  (ppm) 81.15, 119.31, 127.35, 129.66, 129.84, 130.28, 130.88, 139.13, 159.07, 165.38.

6-(2,3-Dichlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4)

 $^{1}\mathrm{H}$  RMN (400 Hz, DMSO- $d^{6}$ ),  $\delta$  (ppm) 7.26 (1H, m), 7.75 (2H, s), 10.12 (2H, s).

<sup>13</sup>C RMN (100 Hz, DMSO-*d*<sup>6</sup>),  $\delta$  (ppm) 78.68, 120.53, 130.78, 130.85, 135.65, 135.68, 145.96, 158.93, 166.27.

6-(3-Nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (5)

<sup>1</sup>H RMN (400 Hz, DMSO- $d^6$ ), δ (ppm) 7.79–7.73 (1H, t, *J* = 7.98 Hz), 8.22–8.16 (1H, d, *J* = 7.76, *J* = 1.36 Hz), 8.35–8.29 (1H, dd, *J* = 8.21, *J*=2.53 Hz), 8.51 (1H, s), 10.24 (2H, s).

<sup>13</sup>C RMN (100 Hz, DMSO- $d^6$ ), δ (ppm) 78.91, 120.11, 123.13, 124.77, 130.10, 130.15, 134.89, 147.90, 158.90, 165.05, 169.82.

4-Oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (6)

<sup>1</sup>H RMN (400 Hz, DMSO-*d*<sup>6</sup>), δ (ppm) 7.48 (3H, m), 7.73 (2H, m), 11.61 (2H, s).

 $^{13}\mathrm{C}$  RMN (100 Hz, DMSO- $d^6$ ),  $\delta$  (ppm) 85.57, 119.38, 128.43, 128.66, 130.51, 138.16, 162.99, 167.81, 184.35.

4-Oxo-2-thioxo-6-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbon-itrile (7)

<sup>1</sup>H RMN (400 Hz, DMSO- $d^6$ ), δ (ppm) 3.82 (3H, s), 7.02 (2H, m), 7.78 (2H, m), 11.50 (2H, s).



Fig. 1. SEM micrographs of hydrotalcites.

 $^{13}\mathrm{C}$  RMN (100 Hz, DMSO- $d^6$ ),  $\delta$  (ppm) 55.77, 84.65, 119.73, 130.25, 130.48, 138.50, 163.22, 166.93, 183.01.

6-(4-Methoxyphenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (8)

<sup>1</sup>H RMN (400 Hz, DMSO- $d^6$ ), δ (ppm) 3.82 (3H, s), 7.05–6.99 (2H, m), 7.81–7.75 (2H, m), 11.50 (2H, s).

<sup>13</sup>C RMN (100 Hz, DMSO- $d^6$ ),  $\delta$  (ppm) 56.05, 84.60, 113.78, 119.75, 130.25, 130.49, 161.32, 163.17, 166.88, 183.01.

6-(Furan-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (9)

<sup>1</sup>H RMN (400 Hz, DMSO- $d^6$ ),  $\delta$  (ppm) 6.63 (dd, J = 3.49–1.72 Hz, 1 H), 7.17 (d, J = 3.34 Hz, 1 H), 7.85 (m, 1 H), 9.97 (s, 2 H).

<sup>13</sup>C RMN (100 Hz, DMSO-d<sup>6</sup>), δ (ppm) 75.76, 112.38, 113.96, 119.89, 145.23, 145.26, 151.94, 160.03, 166.36.

#### 3. Results and discussion

#### 3.1. Catalyst characterization

It is recognized that the co-precipitation method leads to the formation of a highly crystalline hydrotalcite-like layered structure. Thus, the formation of a lamellar structure was corroborated by the presence of characteristic XRD reflections (Fig. S1. Supplementary information). The isomorphic substitution of  $Mg^{2+}$  by  $Ni^{2+}$  or  $Co^{2+}$  is related to the distance between cations (a) and to the interlamellar distance (c). As can be seen, there is no significant variation in these parameters with the incorporation of  $Ni^{2+}$  or  $Co^{2+}$  cation because of the adequate formation of ternary hydrotalcite. Although the parameter *c* varies slightly with the presence of  $Ni^{2+}$  or  $Co^{2+}$  cation, this could be related to an increase in the interlamellar anion in the hydrotalcite structure, since when it has two divalent cations, the brucite layer generates a higher net positive charge, which requires a higher anion compensation charge [33].

FTIR spectroscopy is another useful analysis technique for the

characterization of hydrotalcite-type materials, since it involves the vibrations of the octahedral lattice, of the hydroxyl groups, and of the anions between the layers. The infrared spectrum of LDHs showed characteristic bands of hydrotalcite-type solids (Fig. S2. Supplementary information). The signals between 3400 and 3700  $\text{cm}^{-1}$  correspond to stretching vibrations of the hydrogen bond of the -OH groups and of the water molecules found in the interlamellar region [34,35]. The band at 1384 cm<sup>-1</sup> is attributed to the antisymmetric stretching mode of the carbonate anion of the interlamellar layer. The bands at 625 and 823  $cm^{-1}$  are related to the vibrational modes of  $CO_3^{2-}$  [1,36]. These attributions indicate that the carbonate ion is found as free anions and that they compensate for the positive charge of the laminar layers, which confirms the formation of carbonate anions in the structure of HDL [37]. In addition, small signals are observed around the 625 and 823 cm<sup>-1</sup> bands, which are assigned to the vibrational modes of surface bicarbonates [38].

The synthesis of hydrotalcite-type materials has been reported following different methodologies. The constant pH co-precipitation method has the greatest advantages, since it allows their preparation with a high level of purity and high crystallinity. The X-ray diffraction patterns of the synthesized solids showed a crystalline phase with reflections characteristic of the hexagonal lattice of hydrotalcite-type materials. However, this method can lead to the formation of highly agglomerated primary particles with different morphologies [39,40]. In this way, in the SEM micrographs of the synthesized materials (Fig. 1), the formation of agglomerated sheets composed of hexagonal-shaped grains is evident, forming layers that correspond to the hydrotalcite-like structure [38].

On the other hand, it is observed that the incorporation of another divalent cation changes the morphology of LDH-Mg, which presents the typical morphology of layered double hydroxides, that consists of aggregates of particles in the form of flakes, while LDH-MgNi and LDH-MgCo exhibit a spheroidal morphology called "sand rose" in which the



Fig. 2. EDS spectra for hydrotalcites.

#### Table 1

Textural,	structural	characteristics	determined	by	XRD	and	basic	properties
determine	ed by titrat	ion with 0.01 M	I benzoic aci	d.				

Catalyst	a (Å) <sup>a</sup>	c (Å) <sup>a</sup>	S <sub>BET</sub> (m <sup>2</sup> g <sup>-1</sup> )	Pore volume (cm <sup>3</sup> g <sup>-1</sup> )	Pore size distribution (nm) <sup>b</sup>	Basicity <sup>c</sup> (mmol/g)
LDH-Mg	0.307	2.32	17	0.11	8.2	0.016
LDH- MgNi	0.307	2.34	42	0.21	8.7	0.321
LDH- MgCo	0.307	2.34	28	0.13	8.4	0.163

<sup>a</sup> Lattice parameters.

<sup>b</sup> Pore size distribution is the value of differential pore volume.

 $^{\rm c}\,$  0.05 g hydrotal cite suspended in 2 mL phenolphthalein solution is titrated with 0.01 M benzoic acid.

aggregates are formed by strong interactions between the edge and the surface of sheets [41,42]. This type of morphology is induced by the co-precipitation conditions used during the synthesis process, specifically related to the concentration and addition of the alkaline solution, to reach a pH greater than 9, and is more predominant in LDH- MgNi [39]. Furthermore, it can be observed that the less regular grains are stacked together forming empty spaces in the mass of the catalyst, which may imply high porosity, thus modifying the textural properties of these materials [38,42]. This result is related to the XRD analysis, confirming the increase of the interlamellar anion in the hydrotalcite structure, which by presenting two divalent cations requires a higher compensation charge.

The elemental composition of the HDLs was confirmed by EDS



Fig. 3. Analysis of CO<sub>2</sub> desorption of LDH.

analysis and is shown in Fig. 2. In all the materials, all the elements expected in the composition of each material can be observed; an increase in intensity is also observed for the signal of carbon in HDL-MgNi and HDL-MgCo, which can be related to the increase in carbonate anions, as evidenced in the XRD results. Besides, the incorporation of Ni<sup>2+</sup> or Co2<sup>+</sup> in the hydrotalcite increased the surface area value due to a change in the pore volume, as can be seen in Table 1 (Fig. S3 Supplementary information). Generally, the surface area of these materials is around 100 (m<sup>2</sup>g<sup>-1</sup>), which, however, these values depends on the



Scheme 1. 2,4-Dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile synthesis.

## Table 2 Effect of different synthesized catalysts on 2,4-dioxo-6-phenyl-1,2,3,4-tetrahy-dropyrimidine-5-carbonitrile synthesis.

lds (%)

*Reaction conditions:* benzaldehyde (1 mmol); ethyl cyanoacetate (1 mmol); urea (1 mmol); absolute ethanol (2 mL); catalyst (100 mg); temperature, 78  $^{\circ}$ C; stirring.

<sup>a</sup> Reaction time for the maximal yields obtained.

 $^{\rm b}$  A 10 % of conversion was achieved, and the detected product was 2-propenoic acid, 2-cyano-3-phenyl-, ethyl ester.

synthesis method and the morphology obtained. Small areas are associated with "sand rose" type morphologies [39], therefore the values obtained in the synthesized materials are ascribed to this type of morphology, as described in the SEM analysis.

The basic properties of the synthesized materials were determined by titration with 0.01 M benzoic acid and temperature programmed desorption of carbon dioxide (CO<sub>2</sub>-TPD) The incorporation of Ni<sup>2+</sup> or  $Co^{2+}$  led to increases in the basicity of hydrotalcite, as is shown in Table 1. This result can be associated with a higher proportion of carbonate anions in the interlaminar layer [43], which is evident due to a larger pore volume. The CO<sub>2</sub>-TPD profiles are shown in Fig. 3. To study the basic sites using CO2-TPD only, we focused on desorption temperatures below 150 °C, disregarding the decomposition of the layered structure. The formation of weak basic sites is evident when  $Co^{2+}$  is incorporated into the brucite layer, which does not occur for LDH-Mg and LDH-MgNi. According to the literature, this formation of basic sites at low temperatures  $\sim 200$  °C is associated with bicarbonates formed in the surface Brönsted-type OH groups, which generates weak basicity [44]. Thus, although LDH-MgNi is the most basic, the solid LDH-MgCo evidences the presence of weak basic sites.

#### 3.2. Catalytic test and synthesis of uracil derivatives

Here we present the application of a heterogeneous system for the preparation of uracil derivatives with pyrimidine core in the presence of layered double hydroxides with double divalent cations. The optimum reaction conditions were examined employing a stoichiometric amount of benzaldehyde, ethyl cyanoacetate, and urea as test reaction substrates to obtain the 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile using solvent (ethanol or ethyl acetate) or a solventless reaction (Scheme 1).

The catalytic activity of LDH-Mg, LDH-MgNi, and LDH-MgCo materials in the reaction is displayed in Table 2. In all experiments, ethanol was used as solvent at reflux temperature (78 °C). First, a noncatalytic reaction using an equimolar amount of substrates (1 mmol, ratio: 1:1:1), and absolute ethanol (2 mL) was examined under the experimental conditions (78 °C, 12 h). A very low conversion of benzaldehyde (approx. 10 %) was observed, and a product was detected by TLC, which was isolated, purified, and characterized by mass spectrometry (Fig. 4).

The product (reaction intermediate) corresponds to the Knoevenagel-type condensation between benzaldehyde and ethyl cyanoacetate, as can be seen in reaction Scheme 2.

Then, the LDH catalysts (LDH-Mg, LDH-MgNi and LDH-MgCo) were checked under equivalent conditions (Table 2, entries 2, 3, and 4). In the three experiments, good yields to product 4 were obtained, indicating that the presence of one basic catalyst is necessary to improve the multicomponent reaction yields. In all cases, the formation of product 5 (Knoevenagel adduct) was evidenced in the shortest reaction times, which may indicate that the reaction proceeds through this intermediate. To confirm the identity of product 5, an experiment without the presence of catalyst was performed (Table 3, entry 12). It can be seen that benzaldehyde conversion was complete, no product 4 was detected, and pure intermediate 5 was isolated with 85 % yield. This corroborates that the Knoevenagel reaction takes place without the presence of basic sites, but the Michael addition between intermediate 5 and urea necessarily requires the presence of this type of site to favor the formation of uracil compound.

In such conditions, the yield attained using the LDH-MgCo catalyst



Fig. 4. Mass spectrum of 2-propenoic acid, 2-cyano-3-phenyl-, ethyl ester.



Scheme 2. Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate.

## Table 3 Effect of different variables using LDH-MgCo as catalyst in 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile synthesis.

Entry	Solvent	Catalyst amount (mg)	Temperature (° C)	Time (h)	Yields (%)
1	Ethanol	100	78	6	40
2	Ethyl	100	77	8	35
	acetate				
3	-	100	80	6	88
4	_	50	80	6	87
5	_	40	80	6	62
6	_	25	80	6	58
7	_	10	80	6	38
8	_	100	100	6	89
9	-	100	120	6	50
10	-	100 O	50	6	66
11	_	100	25	6	30
12 <sup>a</sup>	-	-	80	6	b

*Reaction conditions*: benzaldehyde (1 mmol); ethyl cyanoacetate (1 mmol); urea; catalyst (LDH-MgCo, 100 mg); stirring.

The bold values signifies optimal reaction conditions.

 $^{\rm a}$  Reaction performed without the catalyst. The conversion of benzaldehyde was 100 %.

<sup>b</sup> The isolated product was intermediate **5** (80 %).

(40 %, 78 °C, 6 h, entry 4) was slightly higher than for LDH-MgNi catalyst (38 %, 78 °C, 8 h, entry 3) and LDH-Mg catalyst (30 %, 78 °C, 12 h, entry 2). This fact can be explained considering the presence of weak basic sites in LDH-MgCo. Due to the shorter time of reaction with the highest yield to product 4, the LDH-MgCo catalyst was used in the next experiments.

As the reaction presented the best results with LDH–MgCo, we decided to optimize the reaction conditions with this catalyst. Three reaction variables were studied: solvent, reaction temperature, and catalyst amount (Table 3). The first parameter to be evaluated was the solvent effect. Entries 1, 2 and 3 (Table 3) show that the reaction is favored in solvent-free conditions compared to the reaction using ethanol or ethyl acetate as solvent. Generally, solvent-free reactions involve high concentrations or aggregations of charged species that can lead to some modifications in the reaction mechanisms resulting in the decrease of molecular dynamin and inducing special selectivity (stereo, regio- or enantioselectivity). Therefore both specific and weak interactions can appear, which are generally masked with the use of solvents, inducing additional effects on selectivity [45]. These interactions could be those that allow the selective formation of the Knoevenagel intermediate that drives the reaction.

The best reaction conditions were: benzaldehyde (1 mmol); ethyl cyanoacetate (1 mmol); urea (1 mmol); catalyst (LDH-MgCo, 100 mg), at 80 °C for 6 h. In these conditions a yield of 88 % was obtained (Table 3, entry 3). This could be due to a better interaction of the reagents with the catalyst. The reaction performed in solvent-free conditions improves the reaction suitability [46,47]

This behavior can be related to a probable specific interaction between the reagents and the catalyst that favors the formation of uracil. Although the Knoevenagel condensation product is formed without a catalyst, the presence of basic sites can contribute to the formation of the enolate intermediate of ethyl cyanoacetate on the surface of hydrotalcites, by interaction with the hydroxyl groups that occur in this material. However, in the presence of solvents, the formation of this type of intermediate is reduced (for example, using ethanol as solvent), because the more polar function is selectively masked [45]. Besides, taking into account that the reaction follows the Biginelli mechanism, which can take three reaction routes that involve the formation of three intermediates (iminium, enamine, and Knoevenagel) [48,49], the absence of solvent with the use of hydrotalcites allows the reaction to be highly selective towards the Knoevenagel condensation product that is formed between the aldehyde and ethyl cyanoacetate, which when reacting with urea leads to the formation of the uracil derivative in short reaction times. The formation of the first intermediate is key to determine the reaction route. Several investigations have reported that the reaction is driven by the formation of the iminium intermediate, which occurs between aldehyde and urea, but in these methodologies it is necessary to use solvents and acid catalysts [50]. It has also been found that all three mechanisms can occur at the same time under acidic conditions [11]. This indicates that the behavior in the Biginelli reaction is highly affected by the reaction conditions, so the synthesis of uracil derivatives is highly favored in the absence of solvent due to the basic character of hydrotalcites, which allows smoother reaction conditions.

The second parameter to be evaluated was the influence of temperature on the synthesis of compound 4. The results are shown in Table 3. Five experiments were performed (at 25, 50, 80, 100, and 120 °C) using LDH-MgCo (100 mg) as catalyst (Table 3, entries 3, 8, 9, 10, and 11). The results show that 50 and 100 °C are suitable temperatures for carrying out this transformation (Table 3, entry 3: 87 %, and entry 8: 89 % respectively). However, at room temperature (25 °C) and at 50 °C the reaction yields were low (Table 3, entry 11: 30 %, and entry 10: 60 % respectively). Even so, the reaction was selective towards the formation of the reaction product, and secondary products were not observed.

Then, when an increase of reaction temperature to  $120 \degree C$  (Table 3, entry 9) was tested, a low yield of 50 % was observed, and several unidentified secondary products were detected by TLC.

An increase in the reaction temperature decreases the interaction between ethyl cyanoacetate and the catalyst surface. Consequently, this can lead to the formation of by-products, which can be related to the presence of the different intermediates of the reaction, taking into account the three routes that the Biginelli mechanism can take and that can occur simultaneously. This behavior was also observed by Zhang et al. [51], in the absence of solvent using the acid catalyst YbCl<sub>3</sub>. As mentioned above, the reaction pathway leading to the formation of product 4 is the Knoevenagel condensation between the aldehyde and the ethyl cyanoacetate. Lima et al. found that when the Biginelli reaction is conducted at 120 °C, following the Knoevenagel route, it leads to the formation of a by-product that is identified as a Hantzsch ester, which is formed by the decomposition of urea that occurs at temperatures above 90 °C forming ammonia [52]. Therefore the yield in the reaction could be affected by the presence of this by-product under basic conditions, affecting the yield towards the product of interest.

From the different tests it is observed that a temperature of 100  $^{\circ}$ C and 100 mg of catalyst, and 80  $^{\circ}$ C and 50 mg of catalyst give comparable results (89 % vs. 87 % respectively). Therefore, for the next test, we chose the second set of variables since it implies lower catalyst cost and energy consumption.

Finally, the optimal amount of catalyst was evaluated. The results at 6 h are shown in Table 3, entries 3–7, and indicate that the yields decrease considerably when using less than 50 mg of catalyst. The use of

#### Table 4

Catalyst reuse. Effect on 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile synthesis.

Entry	Catalytic cycle	Yields (%)
1	1	87
2	2	84
3	3	83
4	4	82
5	5	81

*Reaction conditions*: benzaldehyde (1 mmol); ethyl cyanoacetate (1 mmol); urea (1 mmol); solvent-free; catalyst (LDH-MgCo, 50 mg); temperature, 80  $^{\circ}$ C; time, 6 h; stirring.

100 mg of catalyst gives comparable results to those obtained using 50 mg of catalyst. For this reason, 50 mg was used in the next experiments. This behavior may be related to a greater number of active sites that are necessary for the transformation of the reaction intermediate product of Knoevenagel condensation (product 5), which leads to the formation of product 4. Therefore a mass of catalyst <50 mg is not enough for this intermediate to be fully consumed, leading to the formation of uracil with high yields. In addition, a directly proportional behavior between the mass of the catalyst and the yield towards product 4 can be observed, which is characteristic of a catalytic process and cannot be associated with a loss of active sites [53,54].

To study the reuse of the catalyst in the reaction, the recovered catalyst was reused in the same conditions and proportions (80 °C, solvent-free conditions, 50 mg of LDH-MgCo, and 1:1:1 benzaldehyde, urea and ethyl cyanoacetate molar ratio, over five consecutive tests). For this purpose, the recovered catalyst was washed with acetone ( $2 \times 2$  mL), and dried in vacuum. The results, which are listed in Table 4, suggest no appreciable variations when the catalyst is reused five consecutive times.

To determine if the catalyst was leached out during the reaction, the hot filtration test was performed. For this, 50 mg of catalyst, 1:1:1 benzaldehyde, urea and ethyl cyanoacetate molar ratio were reacted for 3 h at 80 °C in the absence of solvent. When the reaction ended, hot acetone was added and the catalyst was separated, the product yield was 47 %. The filtrate was reacted under the same conditions for another 3 h; the yield towards the product was 49 %. This value falls within the experimental error and it is consequently demonstrated the catalyst exhibits good stability and does not significantly degrade during the reaction.

The scope and generality of this multicomponent reaction are illustrated by several examples using different aldehydes, ethyl cyanoacetate, and urea/thiourea, and the results are summarized in Table 5. According to the results of optimization experiments for the reaction conditions, the reactions were carried out in the presence of 50 mg catalyst, at 80 °C, in solvent-free conditions, and the corresponding 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitriles were obtained with very good yields, free of secondary products (Table 5, entries 1–5).

Alternatively, by replacing urea with thiourea, bioactive molecules corresponding to the 2,4-thioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile family [55] were also obtained (Table 5, entries 6–8). Finally, 2-furfuraldehyde was used as source of a formyl group (Table 5, entry 9) to obtain the respective products with very good yields. The workup and catalyst recovery are simple, and all reactions have very high selectivity toward the corresponding product 4.

After completion of the reaction (monitored by TLC), the catalyst was separated by filtration and washed with acetone. The crude product was easily isolated in almost pure state. Further purification was performed by recrystallization from a mixture of water and ethanol. The reaction solvent can be recovered by simple distillation and reused. The products are known compounds and were fully characterized by <sup>1</sup>H NMR and <sup>13</sup>C-NMR spectroscopies. The characterization details of all compounds are given in the experimental methods section.

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#### Table 5

Synthesis of different uracil derivatives with 1,2,3,4-tetrahydropyridine core.

Entry	Uracil dorivativa	Violda (0/) <sup>a</sup>	mp °C		
Entry	Uracii derivative	rields (%)	Found	Lit.	
1		85	275–277	276–278 [15]	
2		76	235–237	238–240 [15]	
3		73	295–296	293–295 [15]	
4		73	263–264	261–263 [60]	
5		78	243–245	-	
6		77	286–288	285–287 [61]	
7		74	259–260	260-261 [60]	
8		79	252–254	252 [61]	
9	H <sub>3</sub> CO NC NC NH NH O NH O	79	270-272	-	
	O N O				

*Reaction conditions*: Aldehyde (1 mmol); ethyl cyanoacetate (1 mmol); urea/ thiourea (1 mmol); solvent-free; catalyst (LDH-MgCo, 50 mg); temperature, 80  $^{\circ}$ C; time, 6 h.; stirring.

<sup>a</sup> The products were recrystallized from an ethanol/water mixture.

The structural assignments of compounds were based on spectral characterization. The compounds were reported previously in the literature, and the spectroscopy results obtained were compared with them. Figs. 5 and 6 show the DMSO- $d_6$  <sup>1</sup>H-NMR and <sup>13</sup>C-NMR of 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile. The <sup>1</sup>H-NMR showed the characteristic two signals around 7.3–7.7 ppm corresponding to aromatic proton, and a signal at 10.11 ppm corresponding to hydrogen of two -NH groups (Fig. 5). Meanwhile, <sup>13</sup>C-NMR showed the appearance of the signals from the aryl moiety at  $\delta$  128.25, 128.45,



Fig. 6. <sup>13</sup>C-NMR spectrum of 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile.



Scheme 3. Proposed pathway for uracil derivative formation (via enone formation assisted by LDH-MgCo based catalyst).



**Fig. 7.** Radial pentagon for 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile synthesis.

130.00, and 135.34 ppm, as well as from carbonyl at  $\delta$  159.09 and 166.36, the double bond carbons at  $\delta$  172.56 and 75.05 ppm, and nitrile at 120.57 (Fig. 6).

In the search for a pathway that clarifies the course of the reaction (it is noteworthy that in the literature there are only two reports on the synthesis of these compounds through this reaction and to date there are no studies on the reaction mechanism), it is observed that it could be rationalized as a variant of the Biginelli reaction, which involves the reaction between an aldehyde, a  $\beta$ -dicarbonyl compound, and urea. The multicomponent procedure for dihydropyrimidinone synthesis through Biginelli reaction is well known, and numerous works are reported in the literature [56].

A large number of investigations have focused on the use of acid-like catalysts, and only very few papers describe basic catalysts. Recently, Zhi-Liang Shen et al. [57] described the use of strong bases and proposed different pathways. Pathway 1 corresponds to the initial reaction of benzaldehyde and urea to form a bis ureide, and the reaction of these compounds with ethyl acetoacetate to give the corresponding dihydropyrimidinone.

Pathway 2 (via enone) is the direct reaction between benzaldehyde and ethyl acetoacetate, and subsequent reaction with urea to give the same product as pathways 1, which is assisted by the presence of a basic catalyst.

In view of our previous tests that showed the formation of reaction intermediate **5**, we performed an additional test between intermediate **5** and urea. The reaction conditions were as follows: intermediate **5**, 1 mmol; urea, 1 mmol; LDH-MgCo, 50 mg; temperature 80 °C; time, 6 h. Under these conditions, product **4** was formed. Therefore, we propose that the reaction be carried out following pathway 2 (via enone), which is assisted by the presence of a basic catalyst (Scheme 3).

A few years ago, Andraos and co-workers [58,59] proposed a series of green parameters to determine how green a process is. In this work we used five parameters (Atom Economy AE, Reaction Yield RY, Stoichiometry Factor SF, Material Recovery Parameter MRP, and Reaction Mass Efficiency RME) represented in a radial pentagon (Fig. 7). There we can see how much the process used in this work approaches ideality, mainly because it is a solventless and equimolar reaction and allows for catalyst recovery.

#### 4. Conclusion

We have described a novel base-mediated one-pot procedure for the preparation of a wide variety of novel 2,4-dioxo/thio-6-phenyl-1,2,3,4tetrahydropyrimidine-5-carbonitriles via a three-component condensation of aldehyde, ethyl cyanoacetate, and urea/thiourea using ternary hydrotalcites. The method is simple, convenient, efficient, and is expected to be a useful synthetic protocol for the synthesis of a wide range of novel drug-like uracil derivatives. The high yields obtained are associated with the weak basic sites of LDH-MgCo. This methodology requires a reaction time of approximately 6 h and a temperature of 80 °C to obtain good to excellent yields of nine derivatives (73 %-85 %). The basic catalysts are insoluble in polar media, which allows easy removal of the reaction products without affecting their catalytic activity. In addition, enone 5 is highly suggested as reaction intermediate. The applications of these catalysts in the valorization of the building blocks present in biomass such as furfural or 5-hydroxymethylfurfural through multicomponent reactions are in progress in our laboratory.

#### CRediT authorship contribution statement

Eliana Nope: Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. Ángel G. Sathicq: Supervision, Investigation, Formal analysis, Writing - original draft, Writing - review & editing. José J. Martínez: Methodology, Supervision, Formal analysis, Writing - original draft, Writing - review & editing. Hugo Rojas: Supervision, Formal analysis, Writing - review & editing. Gustavo Romanelli: Conceptualization, Methodology, Supervision, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition, Project administration.

#### **Declaration of Competing Interest**

The authors report no declarations of interest.

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#### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cattod.2020.12.029.

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