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Cobalt supported on alumina as green catalyst for Biginelli reaction in mild conditions: effect of catalyst preparation method

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Abstract: Cobalt supported on alumina (10 wt% Co/Al_2O_3) was synthesized by three different methods; sol-gel (SG), microemulsion (ME) and impregnation (IMP). The materials were characterized by the Brunauer-Emmett-Teller (BET) method, X-ray diffraction (XRD), X-ray fluorescence, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analysis. Their catalytic activity was investigated toward the formation of Biginelli reaction products, 3,4-dihydropyrimidin(1*H*)-ones (DHPMs). The catalysts were found to be efficient for this reaction with yields between 50% and 71% and can be reused without great loss of efficiency. Among the catalytic systems, that prepared by the SG method is the most active with 71% of DHPMs yield under solvent free conditions at 100°C for 1 h of reaction time.

Keywords: alumina support; Biginelli reaction; catalysis; cobalt materials; dihydropyrimidinones; green chemistry.

1 Introduction

Green chemistry considers the design of a process that reduces the use of hazardous substances, by-products formation and energy consumption [1]. Catalysis could be the fundamental tool [2] and the technological key to achieve the objectives of a sustainable process in pollution prevention [2–4]. This latter is one of the 12 pillars of ecological chemistry [5]. Nowadays, more than 90% of all industrial processes are based on catalysis [2, 6].

The use of catalysts in organic synthesis has received much attention particularly for the synthesis of various heterocycles such as Biginelli reaction products named 3,4-dihydropyrimidin(1*H*)-one (DHPMs) [7, 8]. These are currently the subject of intense focus due to their wide spectra of biological activities [9–12] such as anticancer, antifungal and anti HIV [13]. The Biginelli reaction is a new approach to “green chemistry” because it is a multicomponent reaction in which three or more starting chemicals are used as inputs for product formation, thus minimizing the number of intermediate steps [14, 15]. Biginelli multicomponent reaction is a cyclocondensation of aldehyde, β-ketoester, and urea/thiourea under acidic conditions [16]. It is usually performed in an homogeneous system in the presence of acid as HCl [17], H_2SO_4 [18], NH_2SO_3H [19], HBF_4 [20], CCl_3CO_2H [21] and ionic liquids as $BMImBF_4$ [22], [hmim]HSO_4 [23] and [C_3SO_3HDoim]HSO_4 [24]. These acids are corrosive, pollutant and unrecoverable. So, the development of environmentally friendly approaches is still desirable in order to bypass all these drawbacks.

The utility of heterogeneous catalysis has been demonstrated in a wide variety of organic syntheses. Then, in a heterogeneous system, the catalyst can be easily separated from the reaction mixture and regenerated compared to the homogeneous system. Moreover, solid catalysts are usually resistant to degradation in an appropriate pH range and at the reaction temperature. Therefore, a solid catalyst has a great potential for clean synthesis which is important from an economic and environmental point of view. Thus, several Lewis acid solids such as $MgCl_2.6H_2O$ [25], Zn $(OTf)_2$ [26], TaBr5 [27], Mo/γAl_2O_3 [28], $CuCl_2/SiO_2$ [29], Fe_3O_4/PAA-SO_3H [30], $Cu(NH_2SO_3)_2$ [31], MPc (M=Co and Fe) [32], $CoCl_2$ $6H_2O$ [33], $NiCl_2$ $6H_2O$ [34, 35] and ZnO [36] were tested as catalysts in organic synthesis.

In this context, the synthesis of 3,4-dihydropyrimidine-2(1H)-ones via the Biginelli reaction under mild and

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solvent-free conditions was carried out in the presence of cobalt supported on alumina catalyst. Alumina support, a practically inert compound, permits stabilization of the active species by providing an opportunity to disperse over a large surface area. Otherwise, several attractive features such as Co-support interaction strength, good mechanical properties, adjustable pore structure and high resistance to attrition were reported [37–39]. It should be emphasized that the cobalt species are not dangerous compared to those of mercury, lead, cadmium, arsenic and chrome. So, some authors evidenced the green environmental aspect of cobalt-based catalysts. These latter were tested in the adipic acid production to substitute nitric acid [40, 41]. Biological studies showed the high interest of cobalt in vitamin B12 enzyme in the transport of substrates in the human body [42]. Therefore, cobalt can be considered as a green element.

The used method to support the active species is an important factor for a successful reaction towards better catalytic activity. So, in this work, the effect of catalyst preparation method (impregnation [IMP], sol-gel [SG] and reverse microemulsion [ME]) on catalytic activity was investigated. The materials were characterized by different techniques (the Brunauer-Emmett-Teller [BET] method, X-ray diffraction [XRD], X-ray fluorescence, scanning electron microscopy [SEM] and transmission electron microscopy [TEM] analysis).

2 Materials and methods

2.1 Catalysts preparation

Cobalt supported on alumina with a loading (5–15% wt) was synthesized with different methods: IMP, SG and reverse ME. $Co(NO_3)_2 \cdot 6H_2O$ was used as the cobalt precursor. For samples prepared by the SG and ME methods, aluminum nitrate salt $Al(NO_3)_3 \cdot 9H_2O$ (Riedel-Haën, Hanover, Germany) was used as the precursor of Al_2O_3 support. In the IMP procedure, an aqueous solution of Co nitrate was added dropwise to γ-Al_2O_3 (Merck, Darmstadt, Germany) followed by drying at room temperature. In the SG method, 0.2 mol of citric acid was added to an aqueous solution constituted of 0.01 mol of $Co(NO_3)_2$ and 0.17 mol of $Al(NO_3)_3$. The solution was then stirred at 80°C until the gel formation. In the ME procedure, an aqueous solution (A) containing 0.17 mol $Al(NO_3)_3.9H_2O$, 0.01 mol $Co(NO_3)_2.6H_2O$, 300 ml cyclohexane, 62 ml butanol-1 and 0.15 mol cetyltrimethylammonium bromide (CTAB) surfactant was maintained under vigorous magnetic stirring for 1 h (reverse ME). A second aqueous solution (B) containing 80 ml ammonium hydroxide (2.05 M) and 300 ml cyclohexane, 62 ml butanol-1 and 0.15 mol CTAB surfactant was maintained under vigorous magnetic stirring for 1 h. Then, (A) and (B) solutions were mixed under vigorous magnetic stirring for 24 h. The resulting solid was filtered and washed repeatedly with methanol. The prepared solids by different methods were dried for 24 h at 110°C and calcined under air at 500°C for 4 h with a heating rate of 4°C/min.

The samples were noted as XCoAl-x, where X designates X%wt of Co and x the preparation process (IMP, SG and reverse ME).

2.2 Characterization

Nitrogen adsorption-desorption isotherms were obtained using a Micrometrics ASAP 2020 apparatus. Before physisorption measurements, samples were evacuated at 250°C. The Barrett, Joyner and Halenda (BJH) method was used to determine the mean pore size.

The real composition of the solids was determined by elemental analysis based on fluorescence X with an XSRS 3400 SIEMENS fluorescence spectrometer.

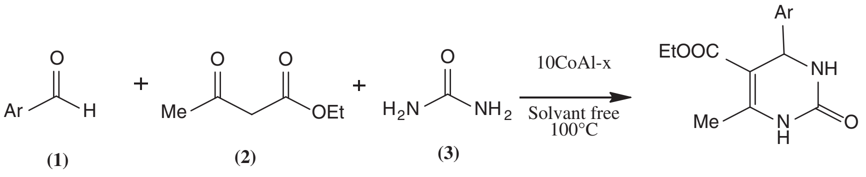
Powder XRD patterns of the catalysts were recorded on a SIEMENS D5000 powder diffractometer using Cu-Kα radiation. Crystalline phases were identified through Highscore plus software database.

Sample morphology was examined by both SEM and TEM using Philips XL30 ESEM and CM10 microscopes, respectively.

2.3 Catalytic test

Catalytic activity of cobalt supported on alumina was examined in the Biginelli reaction under mild and solvent free conditions.

In a 25 ml single-neck round bottom flask, a mixture of benzaldehyde (1) (2 mmol), ethyl acetoacetate (2) (2 mmol), urea (3) (3 mmol) and 0.2 g of catalyst was kept under regular stirring at 100°C for 1 h (Scheme 1). Completion of the reaction was monitored by thin layer chromatography. The reaction product was washed with boiled ethanol and then filtered to remove the catalyst. DHPM product was purified and recrystallized in hot ethanol, then placed in an ice bath to obtain a pure product. The isolated catalyst was dried at 100°C overnight and was reused in the next runs without further purification. Identification of DHPM is obtained via its melting temperature, infrared (IR) spectroscopic analysis and ^1H and ^{13}C nuclear magnetic resonance (NMR).



Scheme 1: Biginelli reaction over 10CoAl-x systems.

IR spectra were recorded on Fourier transform spectrometer Shimadzu FTIR-type 8400 and the NMR ones on a Bruker FT-NMR AVIIIHD500. Chemical shifts were expressed in parts per million (ppm) relative to Trimethylsilyl (δ=0 ppm) and coupling constant J in Hertz (Hz). NMR multiplicities are reported using the following abbreviations: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

3 Results and discussion

3.1 Catalysts characterization

BET surface area, pore and micropore volume, micropore area and pore size obtained for the samples are summarized in Table 1. It appears that the preparation method has a great influence on these parameters. The specific surface area, pore volume, micropore volume and micropore areas of 10CoAl-ME are much higher than those obtained for 10CoAl-IMP and 10CoAl-SG (329 against 51 and 11 m^2/g, 47×10^{-2} against 9×10^{-2} and 1×10^{-2} $cm^3\cdot g^{-1}$, 9.12×10^{-3} against 5.16×10^{-4} and 5.03×10^{-4} $cm^3\cdot g^{-1}$ and 27.02 against 2.22 and 1.44 m^2/g, respectively). These differences can be related to the fact that the ME method favors the increase of specific surface area, pore volume, micropore volume and micropore areas of materials compared to other procedures, as reported in the literature [43]. Low specific surface area, low values of pore volume, micropore volume and micropore areas obtained with the IMP method were already underlined by some authors in the case of Co supported on alumina [44]. On the contrary, Pajonk [45] obtained higher surfaces parameters by the SG method. For all systems, the presence of hysteresis loops in nitrogen isotherms suggests the existence of mesopores with an average pore size of 72.3 Å, 57.6 Å and 42.5Å for 10CoAl-IMP, 10CoAl-ME and 10CoAl-SG, respectively. Their nitrogen adsorption isotherms could be ascribed to type IV (one example in Figure 1). The chemical analysis of samples is listed in Table 2.

The obtained results were in good accordance with the expected ones for cobalt, alumina and oxygen. In this way, the Co_{exp}/Co_{theo} atomic ratios obtained were 1, 0.90 and 0.72 for IMP, SG and ME, respectively.

The XRD profiles of the cobalt supported on alumina prepared by different methods are shown in Figure 2. Similar XRD patterns were observed for both 10CoAl-ME and 10CoAl-IMP (Figure 2A) with intense lines assigned to the $CoAl_2O_4$ spinel phase, crystallized in a cubic structure (2θ=31°, 36°, 38°, 44°, 56°, 59° and 65°) and characteristic lines of the Co_3O_4 phase, crystallized in a cubic phase (2θ=31°, 3°8, 51°, 56°, 58°, 67°). $NiAl_2O_4$ spinel was already observed in the case of nickel supported on alumina [46]

Table 1: Brunauer-Emmett-Teller (BET) surface areas, pore volume, and pore diameter of catalysts.

Catalysts	BET surface area ($m^2\cdot g^{-1}$)	Pore volume ($cm^3\cdot g^{-1}$)	Micropore volume ($cm^3\cdot g^{-1}$)	Micropore area ($m^2\cdot g^{-1}$)	Pore size (Å)
10CoAl-SG	11	1×10^{-2}	5.03×10^{-4}	01.44	42.5
10CoAl-ME	329	47×10^{-2}	9.12×10^{-3}	27.02	57.6
10CoAl-IMP	51	9×10^{-2}	5.16×10^{-4}	02.22	72.3

BET, Brunauer-Emmett-Teller.

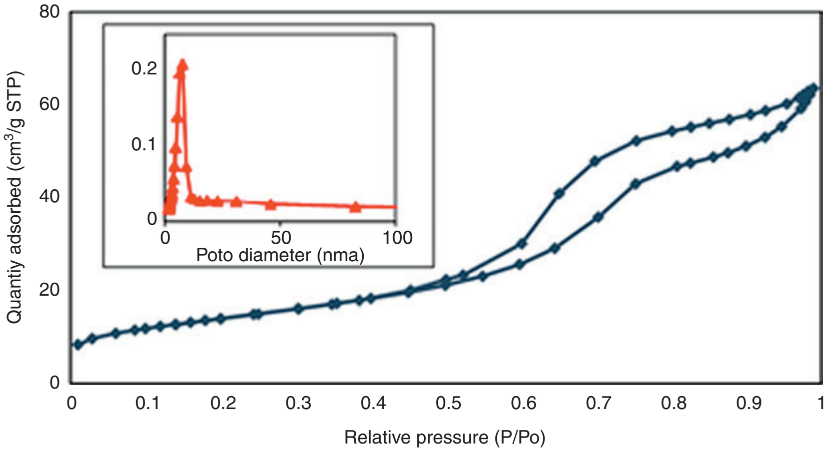


Figure 1: N_2 adsorption isotherms and BJH pore size distribution of 10CoAl-impregnation (IMP).

Table 2: Chemical analysis of 10CoAl-x.

Catalysts	Composition (wt%)			Molar ratio	
	Co	Al	O	Co	Co_{exp}/Co_{theo}
CoAl-SG	8.1	40	39	0.10 (0.11)	0.90
CoAl-ME	6.4	37	36	0.08 (0.11)	0.72
CoAl-IMP	9.4	43	42	0.11 (0.11)	1.00

Expected values are indicated in parentheses.
IMP, impregnation; ME, microemulsion; SG, sol-gel.

and the Co_3O_4 phase was also observed in the case of Co supported on Al_2O_3 prepared by IMP and ME [47, 48]. For the IMP cobalt sample, another peak at $2\theta = 39°$ was observed, which was attributed to CoO. It was noted that the observed peaks at $2\theta = 36°$, $56°$, $65°$ and $67°$ can be also assigned to Al_2O_3. The XRD pattern of 10CoAl-SG exhibits an amorphous phase (Figure 2B). It was underlined that the material crystallinity is sensitive to the calcination temperature [49, 50]; an increase in the latter can favor the oxide formation. Furthermore, a well-dispersed cobalt species on the support was observed when the system was amorphous [51].

SEM images of calcined 10CoAl-IMP, 10CoAl_–SG and 10CoAl-ME at 500°C are represented in Figure 3. Micrographs of the materials are different. That of 10CoAl-IMP reveals a smoother surface on which particles are arranged fairly regularly with aggregates morphology, whereas 10CoAl-SG has a lamellar texture with a bright burst. With the ME method, a heterogeneous porous morphology was observed. These results are in accordance with those of BET and BJH surface parameters.

The detailed microstructure of 10CoAl-ME was further investigated by TEM and the result is shown in Figure 4. The TEM micrograph reveals uniform distribution of cobalt nanoparticles over the alumina support, indicating good dispersion.

3.2 Biginelli reaction

The preliminary catalytic tests performed with $Co(NO_3)_2{\cdot}6H_2O$ or $Al(NO_3)_3{\cdot}9H_2O$ (entries 12 and 13) showed that the Biginelli reaction takes place in the homogenous phase and high DHPM yields were obtained (85% and 89%, respectively). Figures 5 and 6 show the ^1H and ^{13}C NMR results.

The catalytic performances of supported alumina cobalt systems prepared with different methods (SG, ME and IMP) were investigated for the 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyridin-2(1H)-one (DHPM) synthesis under free solvent conditions from benzaldehyde, ethyl acetoacetate and urea with a ratio of 2 : 2 : 3, via the Biginelli reaction.

In order to optimize the reaction parameters, several tests were carried out under various conditions. Obtained catalytic results are summarized in Table 3. The Biginelli reaction, only in the γ-Al_2O_3 support presence led to a low DHPM yield (40%) after 1 h of reaction time (Table 3, entry 1).

The effect of cobalt content on the support has been investigated using the IMP preparation method. The catalytic results showed that a cobalt amount increase from 5 wt% up to 10 wt% led to DHPM yield increase from 50% to 56%, while with 15 wt% of cobalt content, the DHPM yield was only 57% (entries 2–4, Table 3). From these observations, the other catalytic tests were carried out with 10 wt% of cobalt. It is important to note that the

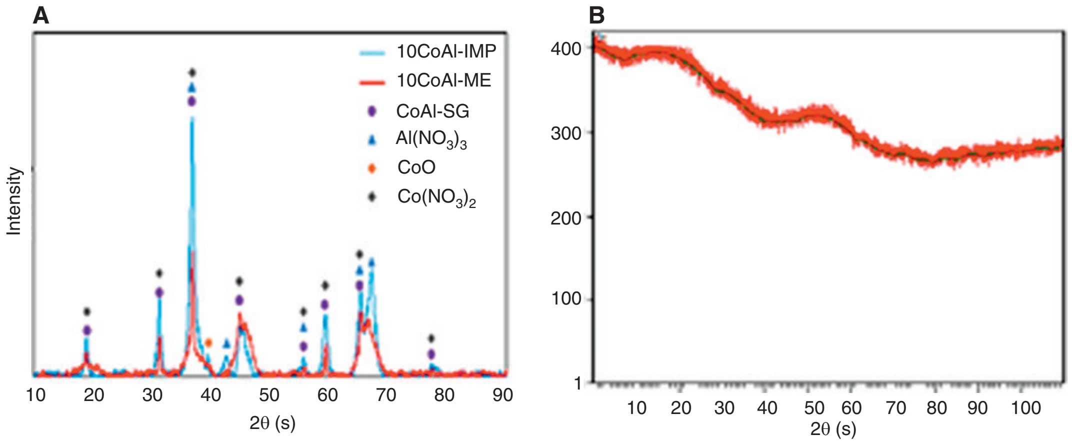


Figure 2: X-ray powder diffraction patterns of calcined materials at 500°C: (A) 10CoAl-impregnation (IMP) and 10CoAl-microemulsion (ME); (B) 10CoAl-sol-gel (SG).

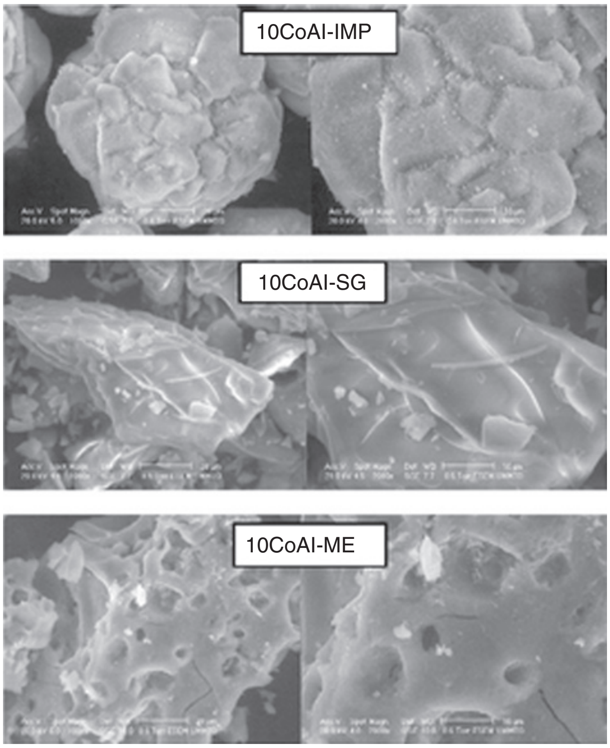


Figure 3: Scanning electron microscopy (SEM) images of calcined materials at 500°C: 10CoAl-impregnation (IMP), 10CoAl-sol-gel (SG) and 10CoAl-microemulsion (ME).

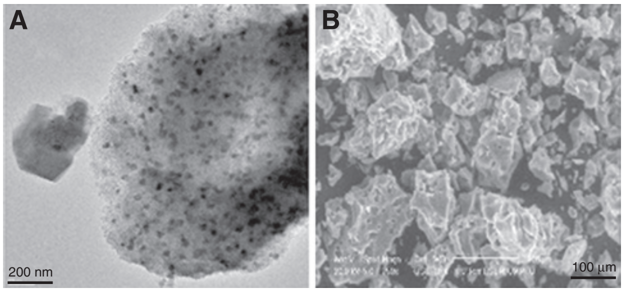


Figure 4: Representative transmission electron microscopy (TEM) (A) and scanning electron microscopy (SEM) (B) images obtained for 10CoAl-microemulsion (ME) catalyst. Scale bars: (A) 200 nm; (B) 100 µm.

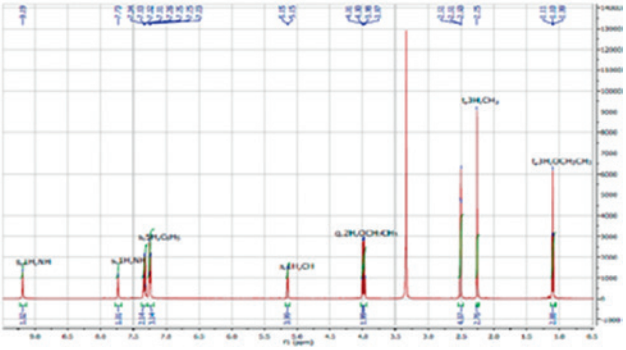


Figure 5: ^{1}H nuclear magnetic resonance (NMR) of produced 3,4-dihydropyrimidin(1H)-one (DHPM) over 10CoAl-sol-gel (SG) system.

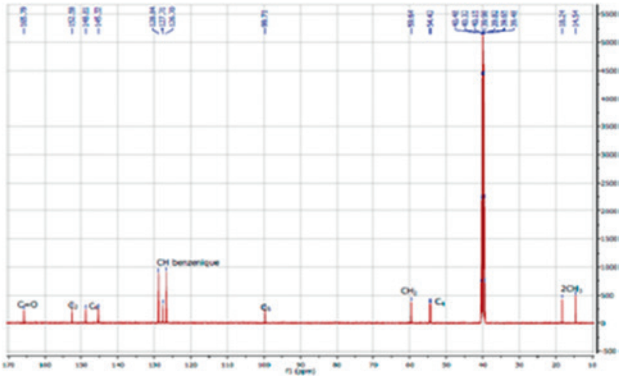


Figure 6: ^{13}C nuclear magnetic resonance (NMR) of produced 3,4-dihydropyrimidin(1H)-one (DHPM) over 10CoAl-sol-gel (SG) system.

performance of 10CoAl-x catalysts depended on the preparation method. In this sense, DHPM yields decreased in the following order: SG (71%) > ME (62%) > IMP (56%) (entries 3, 5, and 6). These observations have already been reported by other authors on Co/Al_2O_3 systems [44, 52–56]. Therefore, the low catalytic activity of Co/Al_2O_3 prepared by IMP compared to systems prepared by the SG and ME techniques can be related to the strong interaction between Co particles and Al_2O_3 support reducing the number of active Co sites and the difficulty to obtain homogenous cobalt particles distribution by conventional IMP [44]. Moreover, it was observed that the reagent nature, operation conditions (pH…) and synthesis method used can influence the distribution and the active species nature [53]. A pH modification can alter the particle size [57]. The citric acid use in the case of the IMP method favors a “fully” dispersed active species [58].

The influence of the reaction time (45 min, 60 min, 75 min and 90 min) on DHPM yield, on the 10CoAl-SG system was studied. The increase of reaction time led to higher DHPM yield (71%) (entries 7, 5, 8 and 9). The results showed that DHPM yield increases with time and reaches a maximum of 71% after 60 min. From these results, the reaction time was fixed to 1 h.

The influence of catalyst weight (0.05 g, 0.1 g and 0.2 g) was also investigated with the 10CoAl-SG system. DHPM yield increased from 63% up to 71% with the increase of catalyst weight from 0.05 g up to 0.2 g (entries 11, 10 and 5). It is important to note that up to 0.2 g, a bad agitation was observed following to the formation of a compact reagent mixture.

Table 3: 3,4-Dihydropyrimidin(1*H*)-one (DHPM) yield via Biginelli[a] reaction in presence of CoAl-x.

Entry	Catalysts	Amount of catalyst (g)	Time	Yields[b] (%)
1	γAl_2O_3	0.2	1 h	40
2	5CoAl-IMP	0.2	1 h	50
3	10CoAl-IMP	0.2	1 h	56
4	15CoAl-IMP	0.2	1 h	57
5	10CoAl-SG	0.2	1 h	71, 48[c]
6	10CoAl-ME	0.2	1 h	62
7	10CoAl-SG	0.2	45 min	63
8	10CoAl-SG	0.2	75 min	67
9	10CoAl-SG	0.2	90 min	66
10	10CoAl-SG	0.1	1h	65
11	10CoAl-SG	0.05	1h	63
12	$Co(NO_3)_2\ 6H_2O$	0.2	1h	85
13	$Al\ (NO_3)_3\ 9H_2O$	0.2	1h	89

[a] Reaction conditions: benzaldehyde (2 mmol), ethylacetoacetate (2 mmol) and urea (3 mmol) at 100°C for 1 h under solvent free conditions. Compounds were characterized by matching infrared (IR), nuclear magnetic resonance (NMR) spectral and melting point data with the literature.

[b] Isolated yields after recrystallization.

[c] Isolated yield with: benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (1.5 mmol) at 100°C for 1 h under solvent free conditions.

IMP, impregnation; ME, microemulsion; SG, sol-gel.

The results compiled in Table 3 also show that when the reactant ratio (benzaldehyde:ethyl acetoacetate:urea) changed from 1 : 1 : 1.5 to 2 : 2 : 3, the DHPM yield increased from 48% up to 71% for a catalyst mass of 0.2 g (entries 5c and 5b).

The reusability of both 10CoAl-SG and 10CoAl-ME was investigated under optimal operating conditions (catalyst: 0.2 g, reaction temperature: 100°C, reaction time: 1 h). Used samples were recovered by filtration, washed with ultra-pure water, dried overnight at 100°C and reused in the next runs without further purification. DHPM yields are given in Table 4. After three reaction cycles, DHPM yield decreased by 6% and 0% in the presence of 10CoAl-SG and 10CoAl-ME, respectively.

Table 4: Recyclability of 10CoAl-sol-gel (SG) and 10CoAl-microemulsion (ME) catalysts for the synthesis of 3,4-dihydropyrimidin(1*H*)-one (DHPM).

Test number	DHPMs yields (%)	
	10CoAl-SG	10CoAl-ME
1	71	62
2	67	59
3	64	52

DHPM, 3,4-dihydropyrimidin(1*H*)-one; ME, microemulsion; SG, sol-gel.

This study showed that the 10CoAl-SG system is the most active for the Biginelli reaction. However, the high activity obtained is difficult to correlate to surface parameters because the catalytic sample studied exhibits low BET area surface, low pore volume and low micropore volume and different morphology compared to 10CoAl-IMP and 10CoAl-ME systems.

Physical data for 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyridin-2(1H)-one (DHPM). Mp 201–205°C. IR (KBr): $\nu_{max} = 3245\ cm^{-1}$, $3100\ cm^{-1}$, $2960\ cm^{-1}$, $1720\ cm^{-1}$, $1630\ cm^{-1}$, $1540\ cm^{-1}$, $1490\ cm^{-1}$. ^1H NMR (Figure 5) (500 MHz, DMSO-d_6): $\delta = 9.19$ (s, 1H, NH), 7.73 (s, 1H, NH), 7.34 (s, 5H, C_6H_5), 5.15 (s, 1H, J = 2.87 Hz, CH), 4.01 (q, J = 6.5 Hz, 2H, OCH_2CH_3), 2.51 (s, 3H, CH_3), 1.11 (t, J = 6.5 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (Figure 6) (125 MHz, DMSO-d_6): $\delta = 165.7$ (COOEt), 152.5 (C2), 148.8 (C6), [145.3, 128.8, 127.7, 126.7] C arom, 99.7 (C5), 59.6 (OCH_2CH_3), 54.4 (C4), 18.2 (CH_3), 14.5 (OCH_2CH_3) ppm.

4 Conclusion

In this study, the Biginelli reaction under solvent free conditions was performed on cobalt supported on alumina systems prepared by SG, ME or IMP method.

The results obtained showed that all Co/Al_2O_3 systems were active in this reaction and gave good 3,4-dihydropyrimidin-2(1*H*)-one yield (56–71%). Among them, Co/Al_2O_3 prepared by SG led to a higher yield. 10CoAl-SG and 10CoAl-ME catalysts remained active after three reaction cycles, which demonstrates that they can be reusable.

From the results obtained, it can be concluded that heterogeneous systems can be a good alternative to green synthesis of the Biginelli reaction product in mild and solvent free conditions compared to homogeneous systems that are corrosive and pollutant, despite their higher catalytic activity.

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