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Process Intensification with Bifunctional Heterogeneous Catalysts: Selective One-Pot Synthesis of 2′-Aminochalcones

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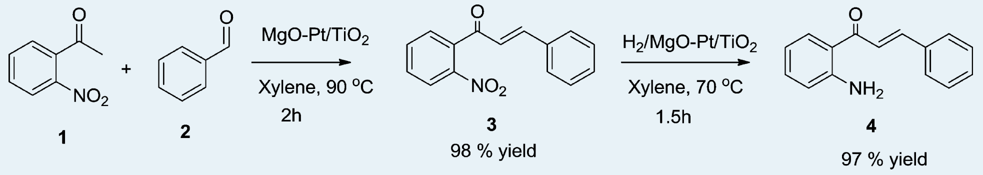
Supporting Information



ABSTRACT: 2′-Aminochalcones of pharmaceutical and commercial interest have been obtained in high yields and selectivities through a one-pot process using a bifunctional heterogeneous catalyst bearing base and metal active sites. This is a physical mixture material formed by a high-surface-area MgO and Pt on TiO_2. The process involves as the first step the Claisen−Schmidt condensation between *o*-nitroacetophenone and benzaldehyde derivatives on the basic catalytic function. This is followed by a chemoselective hydrogenation of the nitro group in the presence of the carbonyl and double-bond carbon−carbon groups within the molecule. Using the bifunctional catalyst and the reaction system proposed here, it is possible to produce, under mild reaction conditions and short reaction times, 2′-aminochalcones with higher yields and selectivities than those obtained by conventional multistep methods.

KEYWORDS: *heterogeneous catalysis, 2′-aminochalcones, fine chemicals, cascade process, bifunctional catalyst*

1. INTRODUCTION

Chalcones (1,3-diaryl-2-propen-1-ones), which belong to the flavonoid family, are abundant in edible plants where they serve different physiological functions such as UV photoprotectors, insect repellents, and attractants of pollinators.[1] A huge number of chalcone derivatives have attracted increasing attention because of their potential pharmacological applications such as anticancer (inhibiting tubulin polymerization), diuretic, choleretic, spasmolytic, bactericidal, antiinflammatory, antimalarial, and antifungal properties.[2] Among them, 2′-aminochalcone derivatives are interesting compounds because they exhibit antitumor activity[3] and because of their high UV−visible extinction coefficient are useful as photoprotectors in sunscreen formulations as well as in textile polymers or fibers.[4]

The most general method of obtaining chalcones is by Claisen−Schmidt condensation between substituted acetophenones and substituted benzaldehydes in the presence of conventional homogeneous bases, such as aqueous alkali metal hydroxide solutions.[1] In recent years, heterogeneous catalysts have gained importance mainly because of environmental and economical factors. Then, a variety of solid acid catalysts such as zeolites,[5] silica−H_2SO_4,[6] and Montmorillonite KSF (clay)[7] and base heterogeneous catalysts such as MgO,[8] Al/Mg mixed oxides,[9] activated $Ba(OH)_2$,[10] basic activated carbons (Na- and Cs-Norit),[11] hydroxyapatite,[12] and KF-supported alumina[13] have been evaluated for the synthesis of chalcones.

However, the synthesis of 2′-aminochalcones by Claisen−Schmidt condensation between *o*-aminoacetophenones and benzaldehyde derivatives is not an easy-to-perform process because in the presence of strong bases, besides the typical possible side reactions such as the Cannizaro reaction and the self-aldol condensation of acetophenones, oligomerization reactions of amino compounds can also take place easily, considerably decreasing the final yield of the 2′-aminochalcones.[14,15] For example, a 52−72% yield of 2′-aminochalcone has been reported, starting from *o*-aminoacetophenone and benzaldehyde in aqueous or ethanolic solutions of NaOH or KOH (10−15 wt %) and 5−25 °C.[14,16] A higher yield (94%) were reported by Lee et al.,[17] although a higher concentration of a strong base (25 wt % MeONa), a lower temperature (0 °C), and a toxic solvent such as THF were required. To overcome these difficulties, other strategies have been reported. For instance, a 68−84% yield of 2′-aminochalcones can be obtained by protecting the amino group of the acetophenone by acetylation with acetic anhydride before the condensation reaction. However, in this case, an additional process of hydrolysis of the resulting 2′-acetamidochalcones was required.[18] Another procedure for obtaining 2′-aminochalcones consists of reducing the corresponding 2′-nitrochalcone. Nevertheless, the presence of different reducible

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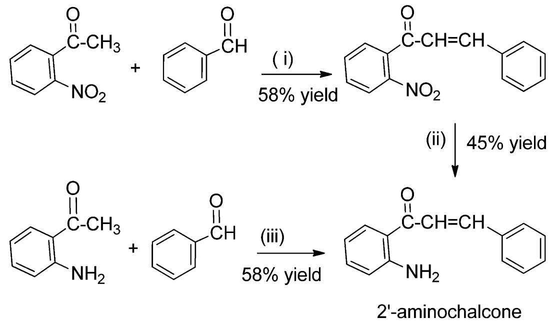
functions such as the C═C bond and carbonyl group within the molecule makes the process difficult, giving a low selectivity to the corresponding 2′-aminochalcone. For instance, different homogeneous catalysts have been employed for the reduction of 2′-nitrochalcones such as iron−acetic acid, ferrous hydroxide, sodium hydrogen sulfide, and stannous chloride−hydrochloride acid.[19] Thus, in the presence of the most satisfactory catalyst, stannous chloride in hydrochloride acid, 2′-nitrochalcone was reduced to 2′-aminochalcone with a 45% yield. After this reduction process, an additional step using excess aqueous ammonia followed by extraction with boiling acetone is required. Moreover, this route requires as a previous step the synthesis of the corresponding 2′-nitrochalcone through the Claisen−Schmidt condensation between *o*-nitroacetophenones and benzaldehydes. Unfortunately, this condensation under a homogeneous catalysis (NaOH) gives a low yield of the corresponding 2′-nitrochalcone (∼60%).[20] Then, if both steps are combined for the production of 2′-aminochalcones, maximum yields of about 25% can be obtained using a conventional homogeneous catalyst (Scheme 1).

Scheme 1. Synthesis of 2′-Aminochalcone from Nitro or Aminoacetophenones and Benzaldehyde Using Conventional Methods



As described above, these methods suffer from unsatisfactory yields, use expensive and sometimes corrosive reagents, give residual wastes salts and effluent-polluting chemicals, and require various purification steps with the corresponding energy consumption. Therefore, there is an incentive to develop a catalytic process able to produce 2′-aminochalcones by environmentally friendly methods while minimizing the number of reaction steps.

In this work, we have studied for the first time the possibility to produce 2′-aminochalcones through a one-pot process using a bifunctional heterogeneous catalyst that combines basic and metal functions.[21] The process involves as a first step the Claisen−Schmidt condensation between *o*-nitroacetophenone and benzaldehyde derivatives catalyzed by the basic sites with the selective hydrogenation of the nitro into the amino group on the metal sites (Scheme 2).

2. EXPERIMENTAL SECTION

2.1. Materials and Methods. Benzaldehyde was purified by distillation (≥99.5%). Biphenyl (99.5%), *o*-nitroacetophenone (95%), *o*-aminoacetophenone (98%), *o*-xylene (≥99%), magnesium nitrate hexahydrated (≥99%), aluminum nitrate nonahydrate (≥98%), sodium carbonate (≥99.5%), and sodium hydroxide (≥95%) were purchased from Aldrich. Gold(III) chloride trihydrate (99.9%), platinum(II) acetylacetonate (97%), and palladium(II) acetylacetonate (99%) were purchased from Aldrich. Titanium dioxide P-25 Degussa and aluminum oxide nanopowder were purchased by Evonik Industries and NanoScale Materials, respectively.

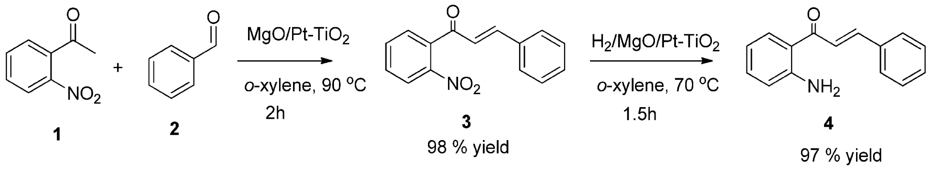
Al/Mg hydrotalcite was prepared by following a previously reported procedure.[9b] An Mg−Al hydrotalcite with a Mg/Al ratio of 3 was prepared from gels produced by mixing two solutions: solution A containing 2.25 moles of $Mg(NO_3)_2$ and 0.75 mol of $Al(NO_3)_3$ in an Al + Mg concentration of 1.5 mol/L for a ratio of 0.25 and another solution B of 6.75 moles of NaOH and 2 moles of Na_2CO_3 dissolved in the same volume of solution A. Both solutions are coadded at a rate of 1 mL min^{-1} under vigorous mechanical stirring at room temperature. The suspension was left for 18 h at 60 °C. The hydrotalcite was filtered and washed until pH 7 was achieved, and the solid was dried at 60 °C. The hydrotalcite was calcined at 450 °C in dry nitrogen for 6 h in order to obtain the corresponding Al/Mg mixed oxide (HTc) with a surface area of 267 $m^2\ g^{-1}$. The hydrated Al/Mg mixed oxide (HTr) was obtained by directly adding 36 wt % water over the HTc just before the reaction (S_{BET} = 30 $m^2\ g^{-1}$).

A MgO sample with a surface area of 670 $m^2\ g^{-1}$ was purchased from NanoScale Materials. Prior to each experiment, the catalyst was calcined at 450 °C for 10 h first in a stream of air and finally in a stream of nitrogen to remove any absorbed impurities and carbonates. The KF−Al_2O_3 sample with 40 wt % KF was supplied by Aldrich.

Au−TiO_2 (1.5 wt %) was supplied by Strem Chemicals, Inc. Pt−TiO_2 (0.2 wt %) and Pt−Al_2O_3 (0.2 wt %) samples were prepared by incipient wetness following previously reported procedure.[22] Pt−TiO_2 catalyst (0.2 wt %) was prepared by supporting nanosized crystals of Pt on TiO_2 and decorating the exposed (111) and (110) Pt crystal faces with TiO_2 from the support by activation under hydrogen flow (100 mL min^{-1}) at 450 °C for 3 h. The same pretreatment was used for Pt−Al_2O_3.

Pd−MgO (0.5 wt %) and Pt−MgO (0.5 wt %) with different Pt loadings were prepared by the impregnation of the support with the corresponding amount of a solution of palladium(II) acetylacetonate or platinum(II) acetylacetonate, respectively, in water-free toluene (12.5 mL) that was added to 1 g of an oxide support. The mixture was stirred for 12 h at room temperature, and the solvent was removed at reduced pressure and dried overnight under vacuum. The samples were calcined for 3.5 h at 550 °C with an N_2 flow of 100 mL min^{-1} and actived by

Scheme 2. One-Pot Process for the Synthesis of 2′-Aminochalcone Using a MgO/Pt−TiO_2 Catalyst



calcination at 450 °C with a mixture of hydrogen and nitrogen (H_2/N_2 90/10 at a flow rate of 100 mL min^{-1}) for 2 h.

Au−MgO (0.5 wt %) was prepared following the Pd−MgO procedure but using $HAuCl_4 \cdot 3H_2O$ as a source of Au. The catalyst was actived at 250 °C with a mixture hydrogen and nitrogen (H_2/N_2 90/10 at a flow rate of 100 mL min^{-1}) for 3 h.

Au(1 wt %)−Pt−MgO(100 ppm) was prepared by the impregnation of the support with an aqueous solution (25 mL) of platinum(II) acetylacetonate (1 mg) and $HAuCl_4 \cdot 3H_2O$ (40 mg), which was added to 2 g of oxide support. The mixture was stirred for 12 h at room temperature, and the solvent was removed at reduced pressure. The sample was calcined for 3.5 h at 450 °C with an N_2 flow of 100 mL min^{-1} and then reduced with hydrogen (H_2 flow rate of 100 mL min^{-1}) for 2 h. A Au(0.7 wt %)−Pt(0.45 wt %) sample was prepared following the same methodology.

The amount of metal supported was determined by ICP analysis in a Varian SpectrAA-10 Plus. The average metal size of the different catalysts was measured with TEM images that were acquired by using a JEM 1010 transmission electron microscopy operated at 100 kV. The samples were prepared directly by dispersing the powders onto carbon copper grids. Physicochemical characteristics of metal-supported catalysts are summarized in Table 1.

Table 1. Physicochemical Characteristics of Metal-Supported Catalysts

catalyst	metal content (wt %)	metal particle size (nm)
Pd−MgO	0.5	3−5
0.05Pt−MgO	0.05	1.5
0.1Pt−MgO	0.1	1.7
0.2Pt−MgO	0.2	2.4
0.5Pt−MgO	0.5	3
1Pt−MgO	1	8.7
Au−MgO	0.5	8.5
Au−Pt−MgO(1)[a]	1	12.3
Au−Pt−MgO(2)[b]	0.7	12.1
Au−TiO_2	1.5	3−6
Pt−TiO_2	0.2	1.5
Pt−Al_2O_3	0.2	4

[a]The catalyst contains 100 ppm Pt. [b]The catalyst contains 0.45 wt % Pt with a crystal size of 2.3 nm.

Powder X-ray diffraction patterns were collected with a Philips X'PERT diffractometer equipped with a proportional detector and a secondary graphite monochromator. Data were collected stepwise over the $2° \leq 2\theta \leq 40°$ angular region with steps of 0.02° 2θ, a 20 s/step accumulation time, and Cu KR (λ = 1.54178 Å) radiation.

2.2. Reaction Procedure. *2.2.1. Synthesis of 1-(2-Nitrophenyl)-3-phenylprop-2-en-1-one (2′-Nitrochalcone, **3**) (General Procedure).* The Claisen−Schmidt condensation was performed in a 3 mL autoclave containing 30 mg of basic catalyst under a nitrogen atmosphere. Then a solution of *o*-nitroacetophenone (165 mg, 1 mmol) and benzaldehyde (106 mg, 1 mmol) in 0.5 mL of *o*-xylene was added, and 1,1′-biphenyl was used as an internal standard. The reaction mixture was heated to 90 °C under vigorous stirring. After reaction, the catalyst was filtered off, and the solvent was eliminated by heating under reduced pressure. The 2′-nitrochalcone (**3**) was crystallized in ethanol as white needles.

*2.2.2. Reduction of 2′-Nitrochalcone (**3**) to 1-(2-Aminophenyl)-3-phenylprop-2-en-1-one (2′-Aminochalcone, **4**) (General Procedure).* In a 3 mL autoclave we placed the catalyst (Pt−TiO_2, 30 mg) and a solution of 2′-nitrochalcone (0.5 mmol, 126 mg) and 1,1′-biphenyl as an internal standard (72 mg, 0.5 mmol) in 0.5 mL of *o*-xylene. The autoclave was pressurized at 9 bar of hydrogen and held at 70 °C under vigorous stirring.

*2.2.2.1. One-Pot Procedure: Preparation of 1-(2-Aminophenyl)-3-phenylprop-2-en-1-one (**4**).* Typically, a solution of *o*-nitroacetophenone (165 mg, 1 mmol), benzaldehyde (106 mg, 1 mmol), 1,1′-biphenyl as an internal standard (72 mg, 0.5 mmol), and 0.5 mL of *o*-xylene was added to a physical mixture of calcined MgO (30 mg) and 0.2 wt % Pt−TiO_2 (30 mg). The reaction mixture was heated to 90 °C under vigorous stirring. When the maximum yield of 2′-nitrochalcone was achieved (98%), the temperature was set to 70 °C and the autoclave was pressurized at 9 bar of hydrogen. After reaction, the catalyst was collected by vacuum filtration, and the product mixture was analyzed by GC-MS.

In all reactions, samples were taken at regular intervals, diluted with acetonitrile, and analyzed by GC equipped with a Biorad column (30 m × 0.25 mm × 0.25 μm) and an FID as the detector. In all cases, the molar balance was ≥95%.

2.2.2.2. Recycling of the MgO/Pt−TiO_2 Physical Mixture. After reaction, the catalyst was recovered by filtration and calcined at 450 °C for 7 h in the presence of air, followed by a stream of nitrogen (3 h). Before each cycle, the catalyst was actived at 450 °C under hydrogen flux for 3 h. The amount of reactants was readjusted to the acatalyst weight to maintain the initial ratios.

2.2.2.3. Synthesis of 2′-Aminochalcones under Homogeneous Catalysis. The synthesis of 2′-aminochalcones using a homogeneous catalyst was performed following the procedure described in ref 15. Typically, 2′-aminoacetophenone (2 mmol) was added to a solution of benzaldehyde (2 mmol) in 15 mL of ethanol containing 15 wt % NaOH and stirred at 25 °C for 16 h.

The 2′-nitrochalcone and 2′-aminochalcone derivatives that were synthesized were isolated by liquid chromatography using silica gel and a mixture of hexane−ethyl acetate with different polarities as the eluent. The compounds were further purified by recrystallization in ethanol. The identification of the products was carried out by MS-GS (Agilent MDS-5973 with an HP5 capillary column) and NMR spectroscopy with a Bruker Avance 300 spectrometer working at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. The ^{1}H and ^{13}C NMR spectra of the products were recorded using $CDCl_3$ as the solvent and TMS as the internal reference. A coupling constant of approximately of 16 Hz for the CH═CH protons in the ^{1}H NMR spectrum of the 2′-aminochalcones indicates the trans geometry for the chalcone.

ESI−HRMS (electrospray ionization−high-resolution mass spectrometry). Samples were diluted in acetonitrile and analyzed by means of a Waters ACQUITY XevoQToF spectrometer (Waters Corp.) through direct infusion of the liquid sample in an ESI interface. The ESI source was operated in positive ionization mode with the capillary voltage at 1.5 kV. The temperature of the source and desolvation were set at 100 and 400 °C, respectively. The cone and desolvation gas flows were 100 and 800 L h^{-1}, respectively. All data collected in centroid mode were acquired by using the Masslynx software (Waters Corp.). Leucine enkephalinephalin was used as the lock mass generating an $[\mathrm{M + H}]^+$ ion (m/z = 556.2771) at a concentration of 2 ng mL^{-1} and a flow rate of 50 mL min^{-1} to ensure accuracy during the MS analysis.

*2.2.2.4. Spectral Characteristics Data. 2.2.2.4.1. trans-1-(2-Nitrophenyl)-3-phenylprop-2-en-1-one (**3**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 8.19 (ddd, 8.10, 1.32, 0.38 Hz, 1H); 7.77 (td, 7.54, 1.32 Hz, 1H); 7.66 (ddd, 9.04, 7.54, 1.51 Hz, 1H); 7.53–7.47 (m, 3H); 7.42–7.35 (m, 3H); 7.24 (d, 16.20 Hz, 1H); 7.01 (d, 16.20 Hz, 1H). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 192 (C), 146 (C), 146 (CH), 136 (C), 134 (CH), 133 (C), 131 (CH), 130 (CH), 129 (CH), 128 (2CH), 126 (CH), 124 (CH). MS m/z (%) 253 ($\mathrm{M^+}$, 6), 207 (36), 191 (4), 147 (16), 119 (16), 105 (67), 77 (93), 51 (36), 28 (28).

*2.2.2.4.2. trans-3-(4-Chlorophenyl)-1-(2-nitrophenyl)prop-2-en-1-one (**3a**).* ^{1}H NMR($\mathrm{CDCl_3}$, 300 MHz): δ 8.2 (dd, 8.2, 1 Hz, 1H); 7.8 (td, 7.5, 1.2 Hz, 1H); 7.7 (ddd, 8.1, 7.5, 1.5 Hz, 1H); 7.5 (dd, 7.8, 1.5 Hz, 1H); 7.4 (dt, 8.4, 2.1 Hz, 2H); 7.3 (dt, 8.4, 2.1 Hz, 2H); 7.2 (d, 16.2 Hz, 1H); 6.95 (d, 16.2 Hz, 1H). ^{13}C NMR ($\mathrm{CDCl_{3,}}$ 75 MHz): δ 192(C), 145 (CH), 139 (C), 138 (C), 137 (CH), 136 (CH), 130 (CH), 128 (CH), 125 (CH), 118 (C), 115 (C).

*2.2.2.4.3. trans-3-(4-Fluorophenyl)-1-(2-nitrophenyl)prop-2-en-1-one (**3b**).* ^{1}H NMR (n, 300 MHz): δ 8.1 (dd, 8.2, 1 Hz, 1H); 7.75 (td, 7.5, 1.1 Hz, 1H); 7.63 (8.0, 1.05 Hz, 1H); 7.45 (dd, 7.5, 1.4 Hz, 1H); 7.3–7.1 (m, 4H); 7 (td, 8.31, 2.46 Hz, 1H); 6.8 (d, 16.2 Hz, 1H). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 193(C), 164 (C), 161 (C), 146 (CH), 144 (CH), 136 (C), 134 (CH), 130 (CH), 127 (C), 128 (CH), 127 (C), 125 (CH), 124 (CH), 117 (CH), 115 (CH), 114 (CH). MS m/z (%) 260 (6), 223 (10), 207 (67), 191 (9), 165 (4), 147 (31), 124 (100), 122 (99), 119 (25), 95 (81), 75 (28), 44 (24), 28 (33).

*2.2.2.4.4. trans-4-(3-(2-Nitrophenyl)-3-oxoprop-1-en-1-yl)-benzonitrile (**3c**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 8.15 (dd, 8.2, 1 Hz, 1H); 7.75 (td, 7.5, 1.2 Hz, 1H); 7.7–7.65 (m, 3H); 7.55 (d, 16.56 Hz, 2H); 7.45 (dd, 7.4, 1.5 Hz, 1H); 7.2 (d, 16.3 Hz, 1H); 6.95 (d, 16.3 Hz, 1H). ^{13}C NMR ($\mathrm{CDCl_{3,}}$ 75 MHz): δ 192(C), 146 (C), 142 (CH), 138 (C), 136 (C), 134 (CH), 132 (CH), 130 (CH), 128 (CH), 125 (CH), 118 (C), 115 (C).

*2.2.2.4.5. trans-3-(4-Methoxyphenyl)-1-(2-nitrophenyl)-prop-2-en-1-one (**3d**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 8.20 (dd, 8.13, 1.08 Hz, 1H); 7.75 (td, 7.47, 1.26 Hz, 1H); 7.64 (td, 7.53, 1.56 Hz, 1H); 7.50 (dd, 7.47, 1.44 Hz, 1H); 7.45 (dt, 8.64, 1.86 Hz, 1H); 7.20 (d, 16.2 Hz, 1H); 6.9–6.86 (m, 3H); 3.81 (s, 3H). ^{13}C NMR ($\mathrm{CDCl_{3,}}$ 75 MHz): δ 193 (C), 162 (CH), 146 (C), 136 (C), 134 (CH), 130 (CH × 2), 129 (CH), 127 (C), 124 (CH × 2), 114 (CH), 55 ($\mathrm{CH_3}$).

*2.2.2.4.6. trans-1-(2-Nitrophenyl)-3-(p-tolyl)prop-2-en-1-one (**3e**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 8.18 (dd, 8.1, 1.2 Hz, 1H); 7.76 (td, 7.5, 1.2 Hz, 1H); 7.65 (dd, 7.5, 1.5 Hz, 1H); 7.50 (dd, 7.2, 1.5 Hz, 1H); 7.39 (d, 8.1 Hz, 2H); 7.22 (d, 16.2 Hz, 1H) 7.21 (d, 7.8 Hz, 2H); 6.96 (d, 16.2 Hz, 1H); 2,37 (s, 3H). ^{13}C NMR ($\mathrm{CDCl_{3,}}$ 75 MHz): δ 193 (C), 147 (C), 146 (CH), 142 (C), 136 (C), 134 (CH), 131 (C), 130 (CH × 2), 129 (CH), 128 (CH × 2), 125 (CH), 124 (CH), 21 (CH3). MS m/z (%) 267 ($\mathrm{M^+}$, 4), 252 (7), 223 (100), 207 (49), 179 (67), 146 (22), 121 (49), 105 (60), 93 (39), 77 (51), 51 (24), 28 (54), 18 (51).

*2.2.2.4.7. trans-1-(2-Aminophenyl)-3-phenylprop-2-en-1-one (**4**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 7.875 (dd, 8.29, 1.32 Hz, 1H); 7.75 (d, 15.45 Hz, 1H); 7.65–7.59 (m, 3H); 7.44–7.39 (m, 3H); 7.31 (dd, 15.45, 1.51 Hz, 1H); 6.72 (td, 8.29, 1.13 Hz, 2H); 6.51 (s.a, 2H). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 192 (C), 150 (C), 143 (CH), 135 (C), 134 (CH), 131 (CH), 130 (CH), 129 (CH), 128 (3CH), 126 (C), 123 (CH), 117 (CH), 116 (CH). MS m/z (%) 222 ($\mathrm{M^+} - 1$, 89), 194 (12), 146 (100), 120 (15), 92 (21), 65 (24), 39 (7).

2.2.2.4.8. 1-(2-Aminophenyl)-3-phenylpropan-1-one. ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 7.66 (dd, 8.01, 1.41 Hz, 1H); 7.25–7.1 (m, 6H); 6.57 (d, 8.34 Hz, 1H); 6.54 (td, 7.08 Hz, 1H); 6.1 (broad, 2H); 3.25 (t, 8.4 Hz, 2H); 3 (t, 8.34 Hz, 2H).^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 201 (C), 150 (C), 142 (C), 141 (C), 134 (CH), 131 (CH), 129 (CH), 128 (CHx2), 127 (CH), 126 (CH), 117 (CH), 116 (CH), 41 ($\mathrm{CH_2}$), 30 ($\mathrm{CH_2}$).

*2.2.2.4.9. trans-1-(2-Aminophenyl)-3-(4-chlorophenyl)-prop-2-en-1-one (**4a**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 7.75 (dd, 8.43, 1.53 Hz, 1H); 7.55 (q, 15.6 Hz, 2H); 7.45 (dt, 84, 1,7.1 Hz, 2H); 7.30 (dt, 8.49, 1.83 Hz, 2H); 7.20 (td, 8.37, 1.5 Hz, 1H); 6.61 (tt, 7.14, 1.14 Hz, 1H); 6.62 (dd, 8.28, 1.26 Hz, 1H); 6.27 (broad, 2H). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 191 (C), 151 (C), 141 (CH), 136 (C), 134 (CH), 133 (C), 131 (CH), 129 (CH × 2), 123 (CH), 119 (C), 117 (C), 116 (C). MS m/z (%) 256 ($\mathrm{M^+} - 1$, 33), 146 (100), 120 (9), 92 (13), 65 (12), 39 (3).

*2.2.2.4.10. trans-1-(2-Aminophenyl)-3-(4-fluorophenyl)-prop-2-en-1-one (**4b**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 7.7 (dd, 8.4, 1.14 Hz, 1H); 7.55 (q, 15.6 Hz, 2H); 7.35–7 (m, 5H); 6.65–6.6 (m, 2H); 6.26 (s, 2H).^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 191 (C), 164 (C), 161 (C), 151 (C), 141 (CH), 136 (C),134 (CH), 131 (CH), 130 (CH), 124 (CH), 118 (C), 117 (CH × 2), 116 (CH), 115 (CH), 114 (CH). MS m/z (%) 240 ($\mathrm{M^+} - 1$, 39), 212 (6), 146 (100), 120 (16), 92 (13), 65 (13), 39 (4). MS m/z (%) 240 ($\mathrm{M^+} - 1$, 39), 212 (6), 146 (100), 120 (16), 92 (13), 65 (13), 39 (4).

*2.2.2.4.11. trans-4-(3-(2-Aminophenyl)-3-oxoprop-1-en-1-yl)benzonitrile (**4c**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 7.76 (dd, 8.7, 1.5 Hz, 1H); 7.63 (s, 4H); 7.61 (s, 2H); 7.40 (d, 15.51 Hz, 1H); 7.24 (td, 8.3, 1.5 Hz, 1H); 6.63 (m, 2H); 6.3 (broad, 2H). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 191 (C), 151 (C), 140 (CH), 139 (C), 135 (CH), 133 (CH), 131 (CH), 128 (CH), 126 (CH), 119 (C), 118 (C), 117 (CH), 116 (CH), 113 (C).

*2.2.2.4.12. trans-1-(2-Aminophenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (**4d**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 7.80 (dd, 8.4, 1.56 Hz, 1H); 7.65 (d, 15.51 Hz, 1H); 7.50 (dt, 9.63, 2.88 Hz, 2H); 7.40 (d, 15.51 Hz, 1H); 7.20 (dd, 7.05, 1.44 Hz, 1H); 6.8 (dt, 9.63, 2.88 Hz, 2H); 6.62 (td, 7.1, 1.14 Hz, 1H); 6.61 (dd, 8.25, 1.24 Hz, 1H); 6.20 (broad, 2H); 2,30 (s, 3H). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 192(C), 161 (C), 151 (C), 143 (CH), 134 (CH), 131 (CH), 130 (CH), 128 (C), 121 (CH), 119 (C), 117 (CH), 116 (CH), 114 (CH), 55 ($\mathrm{CH_3}$). MS m/z (%) 252 ($\mathrm{M^+} - 1$, 100), 236 (31), 209 (22), 180 (13), 164 (10), 146 (99), 120 (22), 92 (31), 65 (25), 39 (6).

*2.2.2.4.13. trans-1-(2-Aminophenyl)-3-(p-tolyl)prop-2-en-1-one (**4e**).* ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ 7.80 (dd, 8.4, 1.5 Hz, 1H); 7.65 (d, 15.54 Hz, 1H); 7.50 (d, 15.54 Hz, 1H); 7.45 (s, 1H); 7.20 (td, 8.4, 1.5 Hz, 2H); 7.15 (d, 8.1 Hz, 2H); 6.62 (td, 8.28, 1.14 Hz, 1H); 6.61 (dd, 8.28, 1.2 Hz, 1H); 6.22 (broad, 2H); 2,30 (s, 3H). ^{13}C NMR ($\mathrm{CDCl_3}$, 75 MHz): δ 192(C), 151 (C), 142 (CH), 140 (C), 136 (CH), 135 (C), 132 (CH), 129 (CH), 128 (CH), 122 (CH), 119 (CH), 117 (C), 115 (CH), 21($\mathrm{CH_3}$). MS m/z (%) 236 ($\mathrm{M^+} - 1$, 81), 146 (100), 115 (16), 92 (13), 65 (18), 39 (4).

3. RESULTS AND DISCUSSION

The study was started by selecting an adequate solid base catalyst able to perform the first step efficiently, i.e., the Claisen−Schmidt condensation between *o*-nitroacetophenone and benzaldehyde to obtain the corresponding 2′-nitrochalcone, which was taken as a reaction model (Scheme 2).

The mechanism generally accepted for the Claisen−Schmidt condensation in basic media involves the formation of the anion of *o*-nitroacetophenone. It is followed by an attack of the carbonyl group of benzaldehyde to give the aldol intermediate, which dehydrates to the corresponding 2′-nitrochalcone. Thus, different solids with basic sites able to abstract the proton in the methyl group of acetophenone, such as an Al/Mg mixed oxide (HTc), a rehydrated Al/Mg mixed oxide (HTr), and MgO, were selected as catalysts. Al/Mg mixed oxides possess strong Lewis basic sites associated with $O^{2-}M^{+2}$ ion pairs[23] that are able to perform the Claisen−Schmidt condensation[9] and related aldol condensations.[24] However, it has been demonstrated that when the Al/Mg mixed oxide is hydrated with a controlled amount of water, its catalytic activity can be considerably increased for a variety of aldol-type condensations.[25] The increased activity of the hydrated Al/Mg oxides is attributed to the partial restoration of the layered structure of the hydrotalcite in which some of the CO_3^{2-} compensation anions in the interlayer space are replaced by OH^- anions that act as strong Bronsted basic sites.[26]

We have previously shown that Al/Mg mixed oxides produced from the calcination of Al/Mg hydrotalcites (HTc) and particularly their hydrated forms (with a 36 wt % water content, HTr) are excellent and reusable catalysts for the synthesis of chalcones through the Claisen−Schmidt condensation between acetophenone and benzaldehyde derivatives.[9c] Then, in order to test the catalytic activity of these materials for the aldol condensation of *o*-nitroacetophenone and benzaldehyde, an Al/Mg hydrotalcite (Mg/Al molar ratio of 3) was calcined at 450 °C to obtain the corresponding Al/Mg mixed oxide (HTc). By the hydration of this material with 36 wt % CO_2-free water, the hydrated sample was obtained (HTr). In Figure 1 the XRD of the samples is given. The as-synthesized Al/Mg hydrotalcite (Figure 1b) presents the typical bands of this layered material that disappear after calcination, showing the typical bands of the Al/Mg mixed oxide (Figure 1c). After hydration, the Al/Mg mixed oxide partially recovers its initial lamellar structure (Figure 1d).

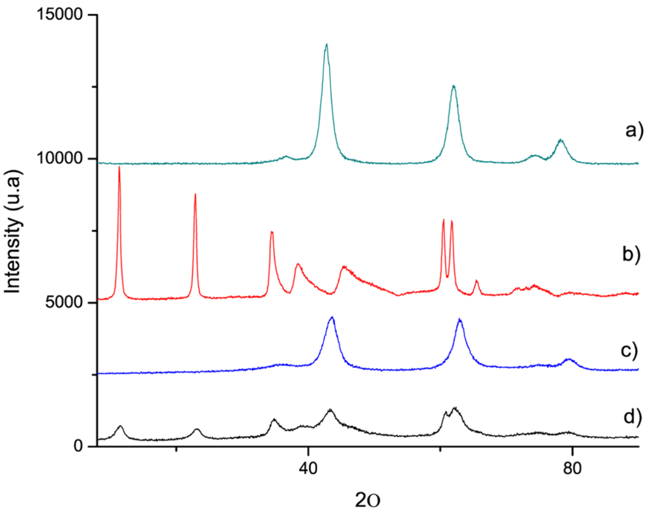


Figure 1. Powder X-ray diffraction (XRD) patterns of (a) MgO, (b) Al/Mg hydrotalcite, (c) Al/Mg mixed oxide (HTc), and (d) rehydrated HTc (HTr) samples.

The Claisen−Schmidt condensation was carried out using equimolar amounts of *o*-nitroacetophenone and benzaldehyde in *o*-xylene as a solvent at 90 °C and in the presence of 10 wt % of either HTc or the corresponding hydrated sample (HTr). As can be observed in Figure 2, only maximum yields of 77 and 40% *trans*-2′-nitrochalcone were achieved, respectively (Table 2), which can be attributed to catalyst deactivation. To confirm this point and after the condensation reaction, catalysts were washed with dichloromethane and reused in a second cycle. As can be seen in Figure S1 (Supporting Information), an important decrease in catalytic activity was observed for both catalysts, confirming that a strong deactivation of the samples is taking place during the reaction. Neither benzoic acid or benzylic alcohol were detected in the reaction media, indicating that the Cannizaro reaction does not take place under these conditions and that the production of benzoic acid is not the cause of the catalyst deactivation (Figure 2). Moreover, in the case of the rehydrated HTr sample, we performed the XRD analysis of the used catalyst (Figure S2), and it was confirmed that the lamellar structure of the starting material is preserved after use, indicating that deactivation is not due to changes in the catalyst structure. Then, the catalyst decay should be attributed to a strong adsorption of reactants and/or product

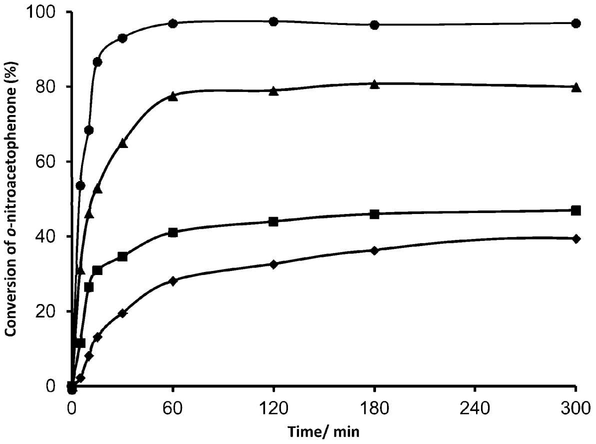


Figure 2. Kinetic curves of aldol condensation between *o*-nitroacetophenone and benzaldehyde in the presence of MgO (●), HTc (▲), HTr (■), and KF-Al_2O_3 (◆).

Table 2. Results of the Claisen−Schmidt Condensation of Benzaldehyde and *o*-Nitroacetophenone Using Different Solid Base Catalysts[a]

entry	catalyst	$r_o \times 10^2$ (mmol min^{-1})	$r_o \times 10^4$ (mmol min^{-1} m^{-2})	conv (%) **1**	yield (%) **3**	selec (%) **3**
1	MgO	10.60	1.6	99	98	99
2	HTc	6.00	2.2	78	77	99
3	HTr	1.33	4.4	41	40	99
4	KF-Al_2O_3	0.44		34	29	86

[a] Reaction conditions: Molar ratio of benzaldehyde/*o*-nitroacetophenone = 1, 10 wt % catalyst, *o*-xylene as a solvent, at 90 °C, results given at 1 h.

on the catalyst surface. In fact, the solid−liquid extraction of the two samples with a Soxhlet apparatus showed that the organic material that was extracted was composed mainly of 2′-nitrochalcone.

Because adsorption is an exothermic process, an increase in temperature should favor desorption. To determine this, we carried out the reaction at 120 °C using HTc as catalyst, but unfortunately, only a 25% yield of 2′-nitrochalcone was detected after 8 h of reaction because of the oligomerization of the enone, which is favored at higher temperature.

The TG analysis of the used catalysts after Soxhlet extraction showed that the amount of organic material adsorbed on HTr (10 wt %) was similar to the amount of organic material detected on the HTc catalyst (11%). However, considering the differences in surface area of both catalysts (267 and 30 m^2/g for HTc and HTr, respectively), the amount of organic material retained per m^2 on HTr is about 10 times higher than on HTc. These results can explain the fast deactivation observed with the hydrated sample and can be related to its greater polar character.

Because of the strong deactivation exhibited by the hydrotalcite-based catalysts (HTc and HTr), MgO was tested as catalyst because it presents strong Lewis basicity with good activity for aldol-type condensations.[27] The basic sites able to abstract protons are those associated with $Mg^{2+}O^{2-}$ ion pairs, in which O^{2-} acts as a Lewis basic site. Furthermore, we have previously demonstrated that the aldol condensation is a reaction sensitive to the structure of MgO: the basic sites associated with corners and edges, which are the most basic, are the most active sites,[28] and the number of such sites can be increased by decreasing the crystal size of MgO. Considering these results, we selected an MgO sample with a crystallite size of 3 nm and a 670 m^2/g surface area to perform the aldol condensation between *o*-nitroacetophenone and benzaldehyde. As can be seen in Figure 2 and Table 2, MgO results in the most active catalyst when compared to HTc and HTr. However, if the surface area is taken into consideration, it can be seen that the initial activity of the HTr sample bearing Bronsted basic sites is considerably superior to the Lewis basic catalyst, which is in good agreement with previously reported results.[9c] However, MgO shows a much slower deactivation rate being possible to achieve 98% yield of the corresponding chalcone within a 1 h reaction time. For comparison purposes, the reaction was also performed using KF/Al_2O_3, which is recognized as a strong Lewis base catalyst. In this case, a lower initial reaction rate and a higher deactivation rate were observed.

Considering that the 2′-nitrochalcone has pharmacological interest because it is a potent inhibitor of the biosynthesis of the release of Interleukin-1 and is currently used for the treatment of chronic inflammatory diseases (such as rheumatoid arthritis and septic shock),[20] we can conclude that MgO is an excellent catalyst for producing 2′-nitrochalcone in a selective way. Notice that the yield achieved using NaOH as homogeneous catalyst was considerably lower (59% after 2 h).

To study the reusability of the MgO catalyst after the reaction, the catalyst was filtered and submitted to a solid−liquid extraction (Soxhlet equipment) using dichloromethane as a solvent for 10 h. When the catalyst was used in a second experiment, only 5% of nitrochalcone was achieved after 8 h of reaction, indicating that an important deactivation of the catalysts occurs during the reaction, which can be attributed to strong adsorption of the organic material on the catalyst surface. In fact, the thermogravimetric analysis of MgO showed that 22 wt % of organic material with respect to the weight of the catalyst remains adsorbed on the solid after Soxhlet extraction. The greater amount of organic material retained on MgO with respect to HTc and HTr samples should be attributed to its higher surface area (670 m^2/g). However, the organic material can be burned off by calcination at 450 °C in air, and the catalyst can be reused in five consecutive cycles, practically maintaining its initial catalytic performance (Figure 3).

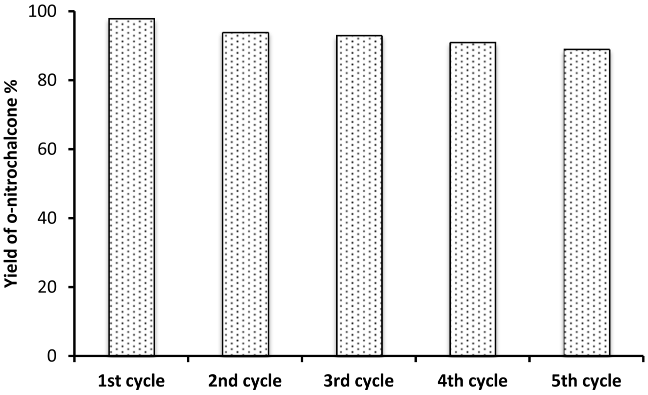


Figure 3. Reuses of MgO in the Claisen−Schmidt condensation of *o*-nitroacetophenone and benzaldehyde after catalyst calcination at 450 °C.

3.1. Reduction of 2′-Nitrochalcone to 2′-Aminochalcone.

As mentioned above, the final objective of this work is directed to opening a new reaction route to produce the most interesting 2′-aminochalcones directly from *o*-nitroacetophenone and benzaldehyde derivatives by means of a one-pot process. The process will involve the basic catalyzed Claisen−Schmidt condensation to give 2′-nitrochalcone, followed by the selective hydrogenation of the nitro group of the 2′-nitrochalcone.

It has recently been reported that Pd, Pt, and Au nanoparticles supported on different metal oxides can be chemoselective catalysts for reducing nitro into amino groups in a variety of organic compounds.[22,29] According to the previous results, a series of bifunctional metal−MgO catalysts were prepared and tested for the hydrogenation step (Scheme 2). (The characteristics of the catalysts are given in the Experimental Section.)

The reduction process was first carried out using Pd on MgO (0.5 wt % Pd−MgO) at 70 °C and 9 bar of hydrogen pressure and using *o*-xylene as a solvent (Table 3, entry 1). Under these conditions, a moderate yield of 2′-aminochalcone was obtained (43%), whereas a compound assigned by MS-GC to the nitrosochalcone intermediate was formed in considerable amounts (Figure S3, Supporting Information). Moreover, the reduction of the C═C bond of the 2′-aminochalcone to give 1-(2-aminophenyl)-3-phenylpropanone also occurs to a considerable extent. This not surprising if one takes into account that Pd−MgO is a selective catalyst for the reduction of the C═C bond in *α*,*β*-conjugated enones.[28] When 1 wt % Pt−MgO was tested as a catalyst for the reduction of 2′-nitrochalcone (Table 3, entry 2), low activity (TOF) and selectivity for the desired product **4** was obtained (58%), again as a result of the competitive hydrogenation of the C═C bond of the 2′-

Table 3. Results of the Hydrogenation of 2′-Nitrochalcone (**3**) in the Presence of Different Metal-Supported Catalysts[a]

entry	catalyst	S/C	TOF (h^{-1})[b]	*t* (h)[c]	conv (%) **3**	yield (%) **4**	selc (%) **4**[d]
1	Pd−MgO	550	1130	0.50	100	43	43
2	1Pt−MgO	233	555	0.33	100	58	58
3	0.5Pt−MgO	421	1897	0.33	100	69	69
4	0.2Pt−MgO	647	1830	0.42	100	70	70
5	0.1Pt−MgO	1209	4029	1	100	71	71
6	0.05Pt−MgO	2248	3705	1.83	100	31	31
7	Au−MgO	250	167	8	28	5	17
8	Au−Pt−MgO(1)	276	35	8	100	25	25
9	Au−Pt−MgO(2)	234	1490	0.33	100	69	69
10	Au−TiO_2	229	76	5	100	96	96
11	Pt−Al_2O_3	1176	3868	0.33	100	51	51
12	Pt−$TiO_{2(d)}$	980	1565	0.42	96	90	94
13[e]	Pt−$TiO_{2(nd)}$	1000	1108	5	100	83	83

[a] Reaction conditions: 2′-nitrochalcone (0.5 mmol) and *o*-xylene (0.5 mL) at 70 °C and 9 bar H_2. Substrate/catalyst ratio (S/C) (mol/mol). [b] TOF is calculated as the initial rate (mmol h^{-1}) of disappearance of **3** divided by mmols of metal. [c] Time at which the maximum yield of 2′-aminochalcone was detected. [d] In all cases, 1-(2-aminophenyl)-3-phenylpropanone formed by the hydrogenation of the C═C bond of the 2′-aminochalcone and intermediate 2′-nitrosochalcone were the byproducts (Figures S3−S15, Supporting Information). [e] Pt−TiO_2 activated at 200 °C in the presence of hydrogen.

aminochalcone that takes place to a considerable extent. In a first approximation to increase the hydrogenation selectivity, we have attempted to modify the metal crystal size by changing the platinum content. Then, four samples with different Pt loadings (0.5 wt % Pt−MgO, 0.2 wt % Pt−MgO, 0.1 wt % Pt−MgO, and 0.05 wt % Pt−MgO) were prepared and tested in the reduction reaction. As can be seen in Table 3 (entries 2−6), the decrease in particle size significantly improves the catalytic activity and the selectivity for 2′-aminochalcone. Thus, when the metal crystal size was reduced from 8.7 to 3 nm, the selectivity for 2′-aminochalcone was considerably increased (entries 2 and 3), achieving a yield for 2′-aminochalcone of 69% with the sample with a Pt content of 0.5 wt % (entry 3), and remains similar at lower Pt content (entries 4 and 5). Further diminution of the Pt content (entry 6) decreases the selectivity to 2′-aminochalcone because in this case the 2′-nitrosochalcone intermediate was the main product formed (Figure S8, Supporting Information).

In previous work, we studied the selective hydrogenation of nitrostyrene in the presence of Au nanoparticles on different supports such as TiO_2, Fe_2O_3, SiO_2, and carbon. It was found that gold on TiO_2 and Fe_2O_3 were chemoselective catalysts for the reduction of the nitro group, whereas when inert supports such as silica and carbon were used, the chemoselectivity decreased.[30]

Here, we have explored the possibility of gold on MgO (Au−MgO) as a catalyst for the cascade synthesis of 2′-aminochalcone. Results in Table 3, entry 7 clearly indicate that gold on MgO is even less active and selective for the formation of 2′-aminochalcone than Pd/MgO or Pt/MgO. With the aim of improving the hydrogen dissociation, a bimetallic Au−Pt−MgO catalyst bearing 100 ppm of Pt on the Au/MgO catalyst was prepared and tested in the reaction (entry 8). In this case, neither the activity nor selectivity could be improved, achieving similar results to those observed when using 0.05 wt % Pt−MgO sample (entry 6). When the crystal size of Pt was increased (2.3 nm) by preparing a sample of Au−Pt−MgO bearing 0.45 wt % Pt, a higher selectivity for 2′-aminochalcone was achieved (69%); however, the yield of 2′-aminochalcone was not high (69%; Table 3, entry 9; Figure S11) and was similar to those obtained with samples 0.2Pt−MgO and 0.5Pt−MgO (Table 2, entries 3 and 4).

The results obtained so far, preclude the use of the metal on MgO (M-MgO in were M is Pt, Pd or Au) to catalyze the desired one-pot process for the synthesis of 2′-aminochalcones. At this point, we thought that another possibility for performing the one-pot process could be based on a physical mixture catalyst formed by a highly chemoselective catalyst for reducing nitro groups and MgO as a basic catalyst. To do that, gold nanoparticles supported on TiO_2 (Au/TiO_2)[29,30] were first studied for the chemoselective hydrogenation of 2′-nitrochalcone. Results given in Table 3 (entry 10) indicate a good activity and selectivity of the Au/TiO_2 catalyst, although a high catalyst/substrate ratio and longer reaction time were required.

However, it has been previously reported[22] that nanocrystals of Pt decorated with TiOx species can selectively reduce the nitro groups in a wide range of substituted nitro aromatic compounds under mild reaction conditions. The catalyst was prepared by supporting nanosized crystals of Pt on TiO_2 and decorating the exposed (111) and (110) Pt crystal faces with TiO_2 from the support simply by treating the material at 450 °C in the presence of hydrogen. Therefore, we thought that this material would be an excellent candidate for performing the reduction of 2′-nitrochalcone. As shown in Table 3, the higher temperature pretreated Pt−TiO_2 (entry 12) resulted in an active and selective catalyst giving 94% selectivity at almost complete conversion under mild reaction conditions. It is interesting that with a conventional hydrogenation catalyst such as Pt/Al_2O_3 or with nondecorated Pt−TiO_2 (activated at 200 °C) (Table 3, entries 11 and 13) complete conversion can be achieved, though the selectivities for 2′-aminochalcone are sensibly lower.

The reusability of the decorated Pt−TiO_2 was studied by regenerating the catalyst by calcination at 450 °C under hydrogen and performing the reduction of 2′-nitrochalcone during five consecutive cycles without an appreciable loss of activity (Figure S16). Additionally, the catalyst could also be regenerated by simply washing with dichoromethane. In Figure S17 it can be observed that the catalytic activity was practically maintained during four consecutive cycles.

Several reaction parameters such as the amount of metal on the catalyst may influence the catalytic activity in the one-pot synthesis of 2′-aminochalcone. To study the optimal amount of metal catalyst in the hydrogenation of 2′-nitrochalcone using Pt−TiO_2, we carried out the hydrogenation with different molar ratios of 2′-nitrochalcone/Pt (S/C). The plot of the initial rate formation of 2′-aminochalcone versus S/C (Figure 4) indicates good activity when working between 1000 and 2700 mol of reactant per mol of Pt. Working at S/C molar ratios of 2700 and 5000 mol mol^{-1}, we found that the maximum selectivities for 2′-aminochalcone of 95 and 90% were achieved, respectively. Therefore, an S/C molar ratio of 2700 was chosen for the subsequent experiments.

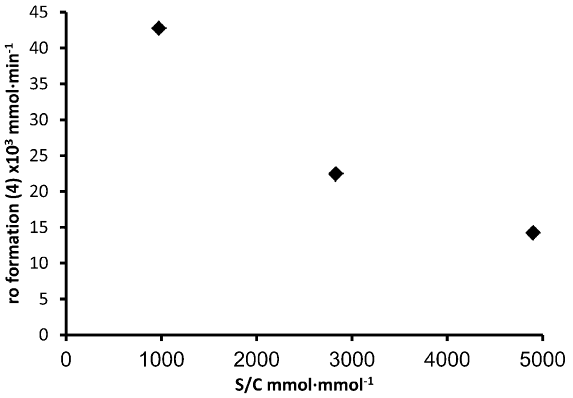


Figure 4. Initial hydrogenation reaction rate of 2′-nitrochalcone into 2′-aminochalcone with Pt−TiO_2 versus the S/C molar ratio.

3.2. One-Pot Process.

In consideration of the above findings, a bifunctional catalyst containing MgO and Pt−TiO_2 has been used for the condensation and reduction steps, respectively, for the one-pot synthesis of 2′-aminochalcones. This catalyst matches the reaction conditions required for the two reactions. With this in mind, we prepared a bifunctional catalyst by combining different weight ratios of MgO and 0.2 wt % Pt−TiO_2 components. The results presented in Table 4 showed that the physical mixture (MgO/Pt−TiO_2) prepared at a 1:1 wt ratio is the most active catalyst, giving a 98% yield with 99% selectivity for 2′-nitrochalcone in a 2 h reaction time. When the weight ratio of MgO/TiO_2 was 1:2, a decrease in the reaction rate was observed, which could be attributed to a competitive adsorption of reactants on TiO_2, which is not basic enough to promote the condensation reaction (Table 4, entry 5). When the catalyst was formed with 2:1 a weight ratio of MgO/Pt−TiO_2, high yield and selectivity for 2′-nitrochalcone could also be achieved; however, longer reaction times (3 h) were required. In this case, the excess MgO promotes the Cannizaro reaction producing benzylic alcohol and benzoic acid, which were detected in small amounts in the reaction media. The formation of benzoic acid promotes the deactivation of the basic component of the catalyst, with a 3 h reaction time necessary to obtain results similar to those obtained in 2 h when the weight ratio of the two components of the catalysts was 1:1.

Table 4. Results of the Claisen−Schmidt Condensation of *o*-Nitroacetophenone and Benzaldehyde Using the Physical Mixture MgO/Pt−TiO_2 Catalyst[a]

entry	catalyst	MgO/Pt−TiO_2 (wt ratio)	*t* (h)	yield 3 (%)	selec 3 (%)
1[b]	MgO		1	98	99
2[c]	MgO/Pt−TiO_2	1/1	2	98	99
3[c]	MgO/Pt−TiO_2	1/2	8.25	55	100
4[c]	MgO/Pt−TiO_2	2/1	3	97	97
5[b]	TiO_2		8	1	100

[a]Reaction conditions: benzaldehyde (1 mmol), *o*-acetophenone (1 mmol), and *o*-xylene (0.5 mL) at 90 °C. [b]10 wt % catalyst. [c]20 wt % physical mixture (MgO and Pt−TiO_2) catalyst with respect to the total weight of reactants.

With the 1:1 MgO/TiO_2 physical mixture catalyst and a substrate-to-Pt molar ratio of 2700, the one-pot reaction was performed (Figure 5). The procedure was as follows: The condensation of *o*-nitroacetophenone and benzaldehyde was carried out at 90 °C in *o*-xylene as a solvent, and when a 98% yield of 2′-nitrochalcone was achieved, the reaction temperature was decreased to 70 °C and the reactor was pressurized at 9 bar of hydrogen. After 1.5 h of reaction time, a yield of 97% (98% selectivity) of 2′-aminochalcone was achieved, with a 95% final yield for the process. These results show that the one-pot procedure presented here (Scheme 2) is highly effective for the synthesis of 2′-aminochalcones and it is possible to achieve a 3-fold higher yield than when using previously reported methods (25%) that involve a multistep process (Scheme 1) .

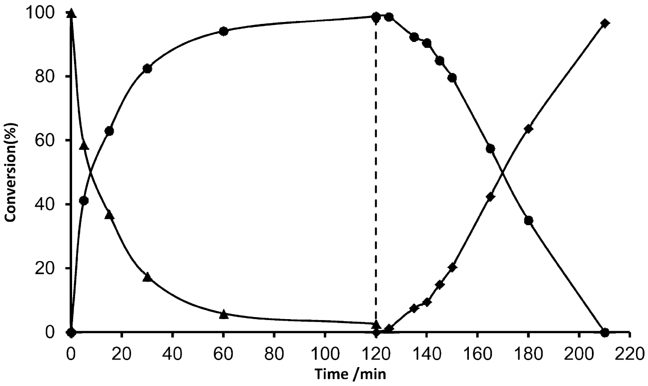


Figure 5. Kinetics of the one-pot reaction using a physical mixture of MgO and Pt−TiO_2. *o*-Nitroacetophenone (▲), 2′-nitrochalcone (●), and 2′-aminochalcone (◆). Reaction conditions: *o*-nitroacetophenone (1 mmol) and benzaldehyde (1 mmol) in 0.5 mL of *o*-xylene. First step: 90 °C under a N_2 atmosphere. Second step: 70 °C at 9 bar hydrogen. Catalysts: MgO (30 mg) and Pt−TiO_2 (30 mg).

To show if there is a possible benefit in selectivity when the physical mixture of MgO/Pt−TiO_2 is used in the one-pot process, we have performed an additional experiment under the same reaction conditions but carrying out the two reaction steps in separated vessels. Thus, the synthesis of 2′-nitrochalcone was performed first only with MgO, and when the reaction was completed, the catalyst was filtered off and the resulting reaction product was hydrogenated with the Pt−TiO_2 catalyst. The results presented in Figure S18 show that whereas the catalytic activity for the hydrogenation increases with respect to that for the one-pot system, the chemoselectivity is sensibly lower (87 instead of 98%). From these results, we speculate that the increase in selectivity observed during the one-pot process could be due to a selective deactivation of Pt by undetectable amounts of impurities formed during the reaction. That assumption could explain the decrease in activity and the increase in selectivity during the one-pot process.

3.3. Stability and Reuse of the Catalyst.

Finally, the recyclability of the MgO/Pt−TiO_2 catalyst was tested by performing successive reuses of the catalyst in the one-pot reaction. After the reaction, the catalyst was recovered, calcined, and used in subsequent runs as explained in the Experimental Section. Results of the conversion, yield, and selectivity for 2′-aminochalcone are displayed in Figure 6, and as can be seen, no loss of activity was observed after three consecutive cycles. Additionally, XRD analysis of the fresh and used catalyst was performed, and as can be observed in Figure S19, the structure of each catalyst is preserved after use and calcination.

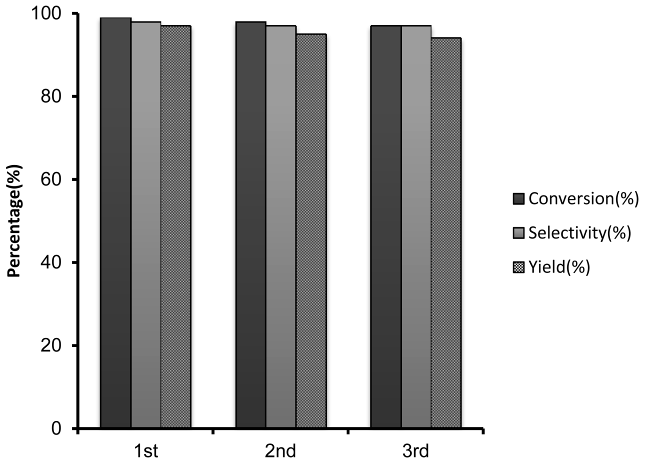


Figure 6. Reuses of the MgO/Pt–TiO_2 catalyst in the one-pot process.

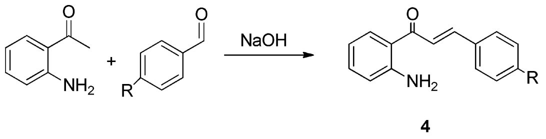
3.4. Scope of the Catalytic System.

Different 2′-aminochalcones were synthesized by reacting substituted benzaldehydes and *o*-nitroacetophenone in the presence of physical mixture MgO/Pt–TiO_2 (Table 5). In general, it is observed that electron-withdrawing groups (i.e., Cl, –CN) in the aromatic ring of benzaldehyde favor the Claisen–Schmidt condensation with respect to electron-donating groups, in good agreement with previously reported results.[9a,31] The higher yield of 2′-nitrochalcone compared to those obtained with nitrochalcones bearing electron-withdrawing groups cannot be attributed to electronic effects but is probably related to geometric effects associated with diffusional problems or/and geometrical restrictions in the adequate adsorption configuration caused by the presence of larger substituents on the aromatic ring.

It is interesting that the hydrogenation of the nitrile group (entry 4) and the hydrodehalogenation of halogenated derivatives (entries 2 and 3) were not observed and that the chemoselective hydrogenation of the 2′-nitrochalcones is maintained for all reactants. Then, results from Table 5 show that good to moderate yields of 2′-aminochalcones can be obtained in short reaction times using the one-pot protocol.

For comparison purposes, the synthesis of 2′-aminochalcones starting from *o*-aminoacetophenone and substituted benzaldehydes was carried out in the homogeneous phase using NaOH as a catalyst. As can be observed in Table 6, yields and selectivities of the corresponding 2′-aminochalcones were in all cases lower, and longer reaction times than those obtained through the one-pot process presented here were required.

Table 6. Synthesis of 2′-Aminochalcones by the Claisen–Schmidt Condensation of 2′-Aminoacetophenone and Benzaldehyde Derivatives Using NaOH as a Homogeneous Catalyst[a]



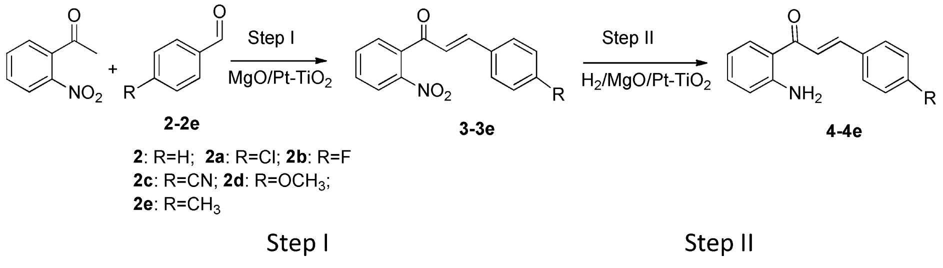
entry	R	*t* (h)	conversion (%)[b]	yield (%) 4[b]	selectivity (%) 4
1	H	4	100	60	60
2	Cl	16	75	50	66
3	CN	16	80	55	68
4	OCH_3	16	88	61	69
5	CH_3	18	90	51	55

[a] Reaction conditions: 2′-aminoacetophenone (2 mmol) benzaldehyde derivative (2 mmol) in 15 mL of ethanol containing 15 wt % NaOH at 25 °C. [b] Data of conversion and yields from GC analysis.

4. CONCLUSIONS

Chalcones are molecules of industrial interest, and different procedures and catalysts have been developed through the years. This is especially true for the synthesis of 2′-aminochalcones. The synthesis reported until now requires a multistep process with low final yields of the desired products. A catalyst has been prepared here that can perform the synthesis of 2′-aminochalcones in one pot starting from easily

Table 5. One-Pot Synthesis of Different 2′-Aminochalcones Using the MgO/Pt–TiO_2 Catalyst[a]



	step I			step II			
R	*t* (h)	yield (%)[c] 3–3e	select (%) 3–3e	*t* (h)	yield (%) 4–4e[c]	selec (%) 4–4e	total yield (%)[c]
H	2	98	99	1.5	97	98	95 (84)
Cl	3.5	90	97	0.5	73	71	65 (58)
F	2	93	99	0.75	65	68	60 (53)
CN[b]	2	83	100	0.75	93	92	77 (67)
OCH_3[b]	7	80	98	1.15	91	90	73 (67)
CH_3	8	80	98	0.75	71	92	57 (49)

[a] Reaction conditions. First step: *o*-nitroacetophenone (1 mmol), benzaldehyde derivative (1 mmol), 30 mg of MgO, 30 mg of 0.2% PtTiO_2, 0.5 mL of *o*-xylene, 90 °C, N_2 atmosphere. Second step: 70 °C, 9 bar of H_2. [b] 90 °C was the reaction temperature in the second step. [c] Data from GC analysis. Isolated yield in parentheses.

accessible *o*-nitroacetophenone and benzaldehydes. When the one-pot process is used, a bifunctional catalyst that is a physical mixture material formed by high-surface-area MgO together with Pt on TiO_2 is optimized. With this catalyst, the process involves the Claisen−Schmidt condensation between *o*-nitroacetophenone and benzaldehyde on the basic catalytic function in the first step, followed by chemoselective hydrogenation of the nitro group in the presence of the carbonyl and double-bond carbon−carbon groups within the molecule.

With the bifunctional catalyst and the reaction system proposed here, under mild reaction conditions it is possible to produce 2′-aminochalcones in high yields and selectivities in a one-pot reaction system. This result considerably improves the values reported previously with the multistep synthesis procedure.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs5011713.

Kinetic data (PDF)

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Notes

The authors declare no competing financial interest.

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