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GREEN CATALYTIC SYNTHESIS OF PHENPROCOUMON

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ABSTRACT. The catalytic potential of triflate-based activated carbon composites has been investigated in phenprocoumon (C_3-alkylated compound) synthesis, through the alkylation of 4-hydroxycoumarin with phenyl-ethyl-carbinol. The main reaction products are O- and C_3-alkylated compounds. However, O-alkylated product is more easily produced to the detriment of the C_3-alkylated compound, the selective synthesis of the last being a challenge in these conditions. Both the conversion of 4-hydroxycoumarin and the selectivity to C_3-alkylated compound is highly influenced by the physico-chemical characteristics of the catalysts and the reaction conditions. The highest 4-hydroxycoumarin conversions (16.0-30.0%) and selectivity to phenprocoumon (94.0-99.7%) were achieved with triflate-based activated carbon composites, characterized by the existence of strong Brønsted acid sites, optimal Lewis/Brønsted acid ratio, and bimodal micro-/mesoporosity.

Keywords: *triflic acid; activated carbon, Friedel-Crafts alkylation, 4-hydroxycoumarin; phenprocoumon*

INTRODUCTION

Traditionally, the syntheses of fine chemicals and pharmaceutical intermediates are carried out in liquid-phase, either by using stoichiometric processes or homogeneous acid-base catalysis. Among these syntheses, the Friedel-Crafts alkylation is widely used in a great variety of commercially-important products. However, this process commonly encounters drawbacks such as problems of waste disposal, salt formation and difficulties for the catalyst separation and recycling.

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Two important examples which involve, as a key-step, the Friedel-Crafts alkylation are the synthesis of (all-*rac*)-[α]-tocopherol (Vitamin E) which displays important antioxidant properties, and the synthesis of vitamin K_1, an important compound in the control of blood clotting [1-5]. The processes use either trimethylhydroquinone (TMHQ) or menadiol acetate (MDA) as substrates and isophytol (IP) as alkylating agent. In both cases, the search for highly efficient, heterogeneous catalysts, which might replace presently used homogeneous catalysts, is a challenging task. In this context, we have recently shown that hydroxylated nanoscopic fluorides (MgF_2 and AlF_3), with bi-acidic (Lewis/Brønsted) properties, can be successfully applied as highly efficient catalytic alternative to the homogeneous ones [6, 7].

Coumarins are part of one of the most important classes of heterocyclic compounds, which possess a range of important biological activities such as anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, antibiotic, and cytotoxic [8-10]. In particular, 4-hydroxycoumarins and its C_3-alkylated derivatives are of great interest due to their use as anticoagulant rodenticides and antithrombotic agents (i.e., warfarin, difetialone, bromadiolone, coumatetralone, and flocoumafen). However, the selective C_3-alkylation of 4-hydroxycoumarin is one of the most difficult reactions in synthetic chemistry. As in the case of vitamins E and K_1, most of these methodologies use strong acids as homogeneous catalysts (*ie*, H_2SO_4, HCl, $Yb(OTf)_3$, $FeCl_3$ x $6H_2O$, $Bi(OTf)_3$, and TMSOTf) [11-14]. Therefore, these processes are also associated with problems such as high toxicity, corrosion, and difficulty in catalysts separation and recovery. Moreover, some of these catalytic systems have certain limitations such as long reaction time and low yields. Therefore, the development of novel heterogeneous catalytic methods for the selective C_3-alkylation of 4-hydroxycumarin with alcohols as alkylating agents, is highly desirable and of a great interest for pharmaceutical industry. In this context, sulfated tin oxide (SO_4^{2-}/SnO_2) has been found to be an efficient solid catalyst for the C_3-benzylation of 4-hydroxycoumarin with secondary benzyl alcohols as alkylating agents but also for the O-alkylation with secondary benzyl acetates [15]. However, information upon the catalyst recyclability and its reuse is totally missing.

Taking into account the above considerations and the high scientific and economic interest in the development of new efficient solid catalysts for alkylation processes, here we report the Friedel-Crafts alkylation of 4-hydroxycumarin with phenyl-ethyl-carbinol as alkylating agent, in the presence of acid-based solid catalysts, such as triflate-based activated carbons. The possibility of O-alkylated formation being formed is higher than the probability of C_3-alkylated product formation. However, as a function of the catalyst nature the C_3-alkylated product can be favoured to the detriment of O-alkylation, as the obtained results in this study demonstrated.

RESULTS AND DISCUSSION

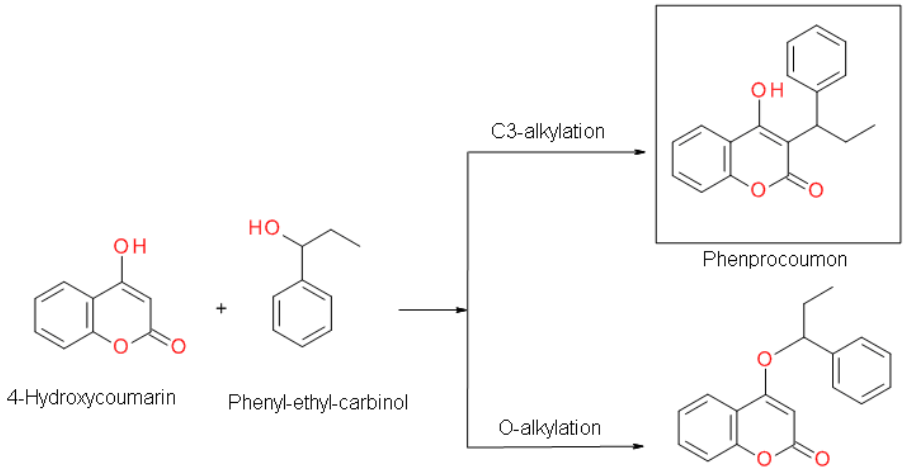
It is already known that the general mechanism of the catalytic Friedel-Crafts alkylations involves an initial interaction of the alkylating agent (E) with the acid catalyst to form an activated electrophile, E^+, which subsequently adds to the nucleophile aromatic ring with the formation of the Wheland intermediate (**1**) [16]. The subsequent elimination of proton forms the Friedel-Crafts alkylated product and restores the acid sites of the catalyst (Eq. 1):

$$E^+ + ArH \longrightarrow \underset{\mathbf{1}}{[E\text{-}Ar\text{-}H^+]} \longrightarrow E\text{-}Ar + H^+ \qquad \text{Eq. 1}$$

In these conditions, the activated electrophile (E^+) exists as a more or less tight ion pair, with a considerable degree of covalent bonding between the carbocation and the catalyst macroanion. Therefore, the nature of the catalyst has a considerable influence on the reactivity and selectivity of the alkylating agent, its relative stability being very important for determining the rate of alkylation. On the other hand, the reactivity of the aromatic nucleophile is governed by its ability to delocalize the positive charge in the Wheland intermediate (**1**) by inductive and resonance effects [16].

The application of the earlier developed hydroxylated nanoscopic fluorides [6, 7] failed in the development of a selective C_3-alkylation process of 4-hydroxycoumarin. This situation demonstrate that, indeed, the successful application of the Friedel-Crafts alkylation is strongly influenced by the reaction system features as the catalyst nature, the reaction conditions and the alkylating agent reactivity, their optimal combination being essential for the selective alkylation, in this case - for the selective synthesis of phenprocoumon (namely, C_3-alkylation in the detriment of O-alkylation). Scheme 1 shows the reaction pathways alkylation of 4-hydroxycoumarin with phenyl-ethyl-carbinol.

Initial catalytic tests (Table 1) were made by uses of different commercial carbon carriers (Ketjenblack EC-300J (KB), Vulcan XC-72R (V) and Black Pearls 2000 (BP)) impregnated with Nafion (*ie*, 40wt% and 80wt%). Obtained materials contained strong ~SO_3H groups with measured densities (meq/g_{cat}) of 0.29 and 0.45, respectively. Also, in order to modulate the optimum density of strong ~SO_3H Brønsted acid sites for the selective C_3-alkylation process to phenprocoumon, the Nafion content was varied from 10 wt% to 80wt% and the materials were calcined in nitrogen, at 200°C, for 4h, in order to make the surface layer more compact. Obtained samples contain 0.09-0.45 meq/g_{cat} of ~SO_3H groups.



Scheme 1. The O-/C_3-alkylation of 4-hydroxycoumarin with phenyl-ethyl-carbinol

As Table 1 shows, the catalysts became active only for a $–SO_3H$ sites densities of 0.45 meq_{SO3H}/g_{cat}.

Table 1. Catalytic performances of nafion-based catalysts

Entry	**Catalyst**	**Meq_{SO3H}/g_{cat}**	**X (%)**	**TOF (h^{-1})**	**TON**	**$S_{C\text{-}alkylated}$ (%)**	**$S_{O\text{-}alkylated}$ (%)**
1	V-40	0.29	0	0	0	0	0
2	KB-40	0.29	0	0	0	0	0
3	BP-40	0.29	1.6	0.6	1.1	100	0
4	V-80	0.45	5.6	1.2	2.5	100	0
5	BP-80	0.45	0.5	0.1	0.2	100	0
6	KB-80	0.45	0.1	0.02	0.04	100	0
7	BP-10-200*	0.09	0.2	0.2	0.4	0	100
8	BP-20-200*	0.17	1.1	0.6	1.3	0	100
9	BP-40-200*	0.29	0.8	0.3	0.6	0	100
10	BP-80-200*	0.45	0.9	0.2	0.4	0	100

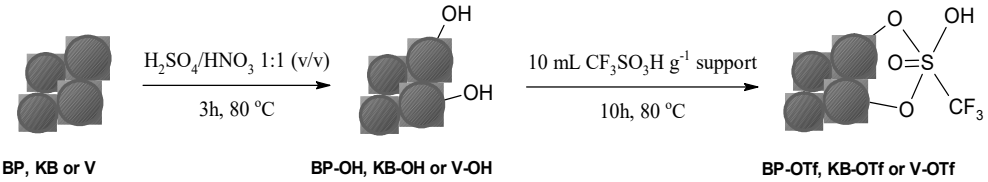
*KB - Ketjenblack EC-300J, V - Vulcan XC-72R, BP - Black Pearls 2000; * - samples calcined in nitrogen, at 200°C, for 4 h Reaction conditions: 1mmol 4-hidroxycoumarin, 1mmol phenyl-ethyl-carbinol, 50 mg catalyst, 10 ml methanol, 80°C, 2h*

Even so, alkylation reaction takes place with low conversions of 4-hydroxycoumarin. Very important, the selectivity toward C_3-alkylated product was 100%, irrespective of the conversion level. The highest conversion was obtained in the presence of V-48 sample (Table 1, entry 4). After 24h, in the

presence of the same catalyst, the 4-hydroxycoumarin conversion increased at 11.0%, while, changing the solvent from methanol to acetonitrile, after a similar reaction time, the conversion increased 17.1%. In both cases the selectivity remained 100% in the favour of C_3-alkylated product.

Unexpected, in the presence of calcined samples (Table 1, entries 7-10), O-alkylated compound was the only evidenced product (100% selectivity), even if the density of the $–SO_3H$ sites remained unchanged after the calcination process. At the moment it is not clear what provoked this inversion in the alkylation selectivity as the Nafion is considered as a stable compound up to 300°C [17]. However, since in the case of non-calcined samples part of Nafion was leached during the catalytic reactions, we may assume that the presence of Brønsted acid sites in the homogeneous phase favours the C_3-alkylation pathway in the detriment of the O-alkylation. Nevertheless, due to its chemical instability the catalytic system was abandoned.

A second type of tested acid-based composites involved the oxidation of the activated carbons followed by their impregnation with triflic acid (Scheme 2). Most probably, the functionalization of the activated carbons surface with triflate groups takes place through a similar mechanism to that proposed by Perego et al. [18] and confirmed by Coman et al. [19], in which triflic acid reacts with vicinal hydroxyl groups yielding a bipodally anchored triflate to the carrier surface. Moreover, the resulting water from the esterification reaction may be coordinated to the grafted triflate, generating a strongly hydrated triflic acid onto the activated carbon surface, less prone to leaching.



Scheme 2. The preparation of triflic acid-based activated carbon catalysts

Indeed, the FTIR analysis of the triflate-based AC samples (V-OTf, KB-OTf and BP-OTf) evidenced the successful anchoring of triflic acid. Therefore, in the IR spectra, the two bands located at 3410 cm^{-1} (νsOH) and 1695 cm^{-1} (νsC=O) indicate the successful oxidation of AC. However, very important are the bands located at 950 cm^{-1} and 1120 cm^{-1}, respectively, which correspond to the νsC-F and νsS=O of triflic acid, in agree with literature [20, 21]. For exemplification, the FTIR spectrum of V-OTf sample is given in Figure 1.

The XRD patterns of V-OTf sample before and after the grafting of triflic acid display the characteristic diffraction lines of the carbon materials, at 2θ of approximately 25° and 44°, respectively [22]. The presence of the diffraction line at around 24.85° (Figure 2) confirms that Vulcan carrier possesses an intermediate structure between amorphous and graphitic, called turbostratic structure, in agree with literature [23].

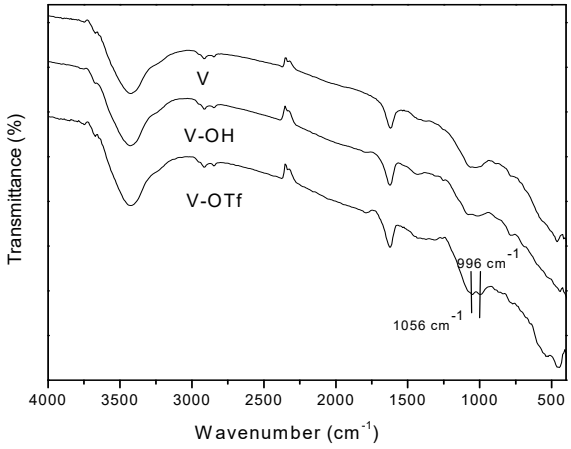


Figure 1. FTIR spectra of V, V-OH and V-OTf samples

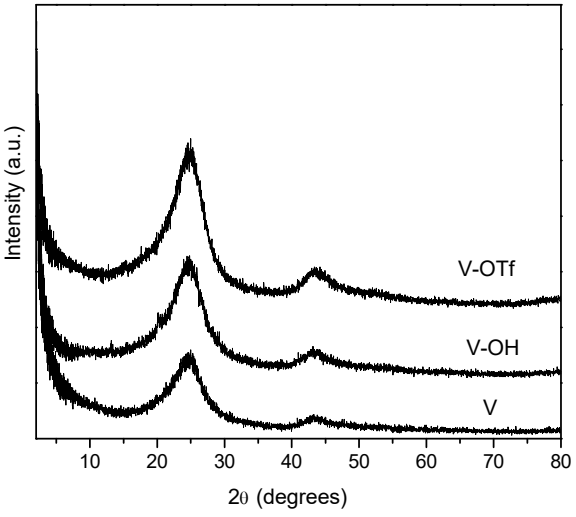


Figure 2. XRD patterns of V, V-OH and V-OTf samples

Due to its structure, black carbon Vulcan exhibits a high resistance to thermal decomposition. Indeed, the thermogravimetric (TG) analysis of the black carbon Vulcan (V) shows a mass loss of 53.74% at temperatures higher than 700°C. Oxidized sample (V-OH) loses only 34.58% from the initial mass while the sample modified with triflic acid (V-OTf) registered a total loss mass (100%) (Figure 3).

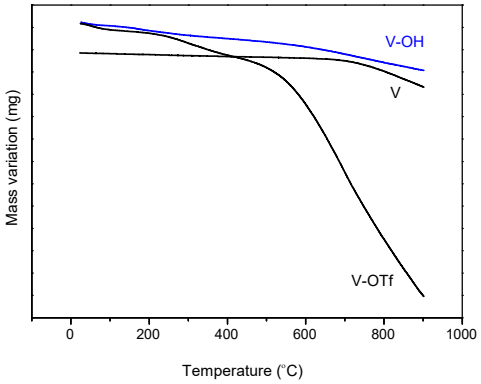


Figure 3. TG analysis of the V, V-OH and V-OTf samples

A water loss, accompanied by an endothermic effect, was observed in both V-OH and V-OTf samples, at temperatures lower than 100°C (Figure 4). An exothermic decomposition, with a maximum at 760°C was registered for the pristine carrier (sample V) while, the exothermic decomposition of the V-OH sample registered a maximum at 668°C. However, in the case of V-OTf sample, two exothermic effects, with maximum at 611 and 738°C, respectively, were registered.

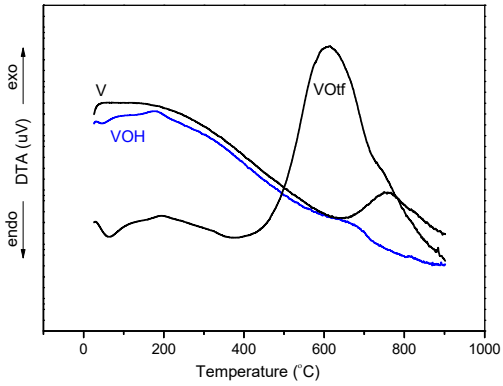


Figure 4. DTA analysis of the V, V-OH and V-OTf samples

Clearly, the functionalized V-OTf sample is less resistant to the thermal decomposition, this behavior being attributed to the partial destruction of its morphology during the treatment with triflic acid.

Pristine Vulcan sample had a relatively high surface area (S_{sp} = 254 m^2/g), a total pore volume of 0.67 cm^3/g and a bimodal meso-microporosity. After its oxidation and treatment with triflic acid a decrease of surface area till 225 m^2/g was registered, most probably due to a partially destruction of the carbon morphology, in agree with TG-DTA results.

In the case of triflate-based samples, the best results under reflux conditions were obtained in the presence of V-OTf catalyst and acetonitrile solvent. Therefore, after 24h of reaction the 4-hydroxycoumarin conversion reached 11.9%, with a total selectivity to the target product (C_3-alkylated product, namely phenprocoumon). Longer reaction times result in an increased conversion but a highly decreased selectivity to C_3-alkylated product (14.1%). The difference till 100% was completed by O-alkylated product, and low amounts of ethers produced from two molecules of phenyl-ethyl-carbinol.

Important improvements were, however, obtained when the alkylation reactions were rune in steel autoclave, under autogenic pressure (Table 2).

Table 2. Catalytic performances of the triflic acid-based catalysts under autogenic pressure

Entry	Catalyst	Time (h)	X (%)	$S_{C3\text{-alkylated}}$ (%)
1	V-OTf	12	28.2	99.7
2		24	30.1	98.7
3	KB-OTf	12	16.5	99.4
4		24	27.2	94.0
5	BP-OTf	12	23.3	95.8
6		24	28.2	94.4

Reaction conditions: 0.2 g 4-hydroxycoumarin, 0.2 g phenyl-ethyl-carbinol, 0.05 g catalyst, 5 ml acetonitrile, 150 ºC.

As Table 2 shows the presence of the V-OTf catalyst containing strong acid sites generated by the grafted triflate groups lead to a high increase of the conversion of 4-hydroxycoumarin (28.2%, Table 2, entry 1) after 12 h reaction yielding phenprocoumon (C3-alkylated products) with a remarkable 99.7% selectivity level. Unfortunately, a prolongation of the reaction time does not improve in high extend the conversion (30.1%, Table 2, entry 2) and lead to a decreased selectivity to phenprocoumon (98.7%, Table 2, entry 2), due to the formation of O-alkylated product. However, the

high selectivity to phenprocoumon has been well preserved during the V-OTf catalyst recycling, thus, confirming the presence of sulfonic species covalently bonded to the V carbon surface. Similar trends were observed irrespective of the used catalyst. Neither the change of the solvent nature or the variation of the reaction temperature was able to combine a high conversion of the 4-hydroxycoumarin with a high selectivity to phenprocoumon. Nevertheless, such performances can be obtained by adding higher amounts of catalyst in the reaction system.

At the moment, it is not entirely clear as to whether the total number of acidic sites has an influence upon the alkylation reaction, but it is obvious that both the presence of Brønsted acid sites and the Lewis/Brønsted acid site ratio are essential to promote the C_3-alkylation synthesis. It seems that the optimal acidic strength and the optimal combination of Lewis/Brønsted acid sites were generated in the sample V-OTf. Moreover, the decreasing alkylation rate is accompanied by an increasing of the C_3-alkylation selectivity. This effect may seem to be disadvantageous but catalytic syntheses with high selectivity into the target product are always preferred to those able to convert a substrate in high level to a large number of reaction products with individual low yields.

CONCLUSIONS

The synthesis of phenprocoumon is part of the organic synthesis from pharmaceutical industry which generates large amounts of waste, environmentally damaging.

A greener alternative to the classical methodology is the catalytic alkylation of 4-hydroxycoumarin with phenyl-ethyl carbinol. The O-/C_3-alkylation reaction rate ratio can be modulated in the favor of the C_3-alkylation by varying the chemical properties of the catalysts and the reaction conditions. The presented work showed that, irrespective of the catalysts nature, the 4-hydroxycoumarin conversions were from low to moderate levels. However, this cannot be considered a disadvantage as long as the selectivity to the target product can be improved till 100%. The developed systems bring a number of advantages in line with the principles of green chemistry, such as: the use of an alcohol (ie, phenyl-ethyl-carbinol) as alkylating agent, the use of substrate/reactant ratio of 1/1, the use of stable and recyclable solid catalysts, the synthesis of the target product (*ie*, C_3-alkylated product, phenprocoumon) with 100% selectivity. The above reaction system features eliminate a potential risk to the environment and simplify the product purification procedure, bringing essential advantages from the green chemistry point of view.

EXPERIMENTAL SECTION

Catalysts preparation

Commercial active carbon (AC) supports, purchased from Akzon Noble and Cabot, such as Ketjenblack EC-300J (KB, S_{sp} = 829 m^2/g; size particles of 30-40 nm), Vulcan XC-72R (V, S_{sp} = 254 m^2/g; size particles of 30 nm), and Black Pearls 2000 (BP, S_{sp} = 1475 m^2/g; size particles of 15 nm) were used for the preparation of the catalytic composites.

Nafion (ie, perfluorosulfonic polymer with terminal sulfonic groups) was deposited on each of the supports by wet impregnation, as follows: 3g of active carbon were dispersed in 150ml of 1-propanol. The obtained mixture was maintained under magnetic stirring for 30 minutes, at room temperature, and another 30 minutes under ultrasound radiation. Then, the corresponding amount of Nafion (10-80 wt%) was added under stirring and maintained for 30 minutes at room temperature, and another 30 minutes under ultrasound radiation. The solvent was evaporated at 85°C under vacuum and the obtained sample was dried at 110°C for 12h. Other serie of Nafion-based activated carbon composites, with different amounts of Nafion were calcined in nitrogen, at 200°C, for 4h.

The grafting of triflic acid onto V, KB and BP active carbons followed a procedure in two steps. In the first step, the activated carbon was oxidized with HNO_3 and H_2SO_4 under the following conditions: 1g of active carbon was kept in 50 ml of acid (25 ml of HNO_3 + 25 ml of H_2SO_4) under ultrasound radiation, for 1h, at 60°C, then washed to pH neutral and dried at 120°C, for 24 hours. Subsequently, the obtained material was treated with concentrated triflic acid (CF_3SO_3H, 10ml) and heated at 80°C for 10h. To remove the physical adsorbed residual triflic acid, the samples were washed with distilled water to neutral pH and dried at 120°C for 8 h. The obtained samples were abbreviated as V-OTf, KB-OTf and BP-OTf, respectively.

Catalysts characterisation

The obtained catalysts have been characterized by techniques such as TG-DTA, XRD and IR spectroscopy. TG-DTA characterization was performed with a TA Instruments SDT Q600, in the range of 25-900°C (10°C/min) and under nitrogen flow (20mL/min). XRD measurements were made with a Siemens D5000 diffractometer with CuK_α radiation (X = 1.5418 Å) with a scanning speed of 2 degrees/min, between 2° and 80°. FTIR spectra were measured with a Thermo-Nicolet FTIR apparatus, in the range of 500-4000 cm^{-1}, at room temperature (400 scans with a resolution of 4 cm^{-1}).

Catalytic tests

In a round bottom flask was added 10 ml of solvent (methanol or acetonitrile), 0.162 g (1 mmol) of 4-hydroxycoumarin and 0.136 g (1 mmol) of phenyl-ethyl-carbinol. Once the reactants have been dissolved, 50 mg of the catalyst was added, and the temperature has been raised at the boiling temperature typical of the solvent. The reaction is allowed to stir and reflux continuously for 2 - 48 h. Parallel tests have been made in steel autoclave, under autogenic pressure, as follow: 10 ml of solvent was added followed by the addition of 0.081 g - 0.162 g (0.5 mmol / 1.0 mmol) of 4-hydroxycoumarin and 0.136 g (1 mmol) of phenyl-ethyl carbinol. Once the reactants have been dissolved, 50 mg of the catalyst is added and the autoclave closed. The reaction is allowed to stir for 24 hours at the boiling temperature characteristic of the solvent.

After reaction, irrespective of the applied methodology, after the catalyst separation by filtration, the reaction products were analyzed by liquid chromatography (HPLC, Zorbax Eclipse Plus C18 column, eluent: AcCN:H_2O (75:25), wavelength: 274 nm) and identify by ^{1}H- and ^{13}C-RMN spectroscopy (Bruker Fourier, 300 MHz, standard: TMS (trimethyl silane), solvent: deuterated dimethyl sulfoxide (d-DMSO)).

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