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A Solvent-free method for synthesis of dihydroangelicins using microwaves

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Abstract: dihydrofurocoumarins are a wide range of compounds, among them dihydroangelicins and dihydropsoralens, compounds present in various plant species with a varied biological activity. Several strategies have been developed for synthesize these compounds, and various catalysts were used for that purpose. In this work we report the synthesis of 8,9-dihydrofuran [2,3-h] coumarins using a strategy of alyloxycoumarins cycloaddition in sustainable conditions: absence of solvents, application of microwave radiation, and insoluble acid catalysis by means of heteropolyacids with Preyssler structure $H_{14}(NaP_5MoW_{29}O_{110})$]. With these conditions we replace the use of solvents and mineral acids with great impact to the environment with a solid easily recoverable heteropolyacid.

Keywords: Dihydroangelicins, dihydrofuocoumarins, microwave radiation, green chemistry, heteopolyacid, Preyysler structure.

1. INTRODUCTION

Dihydrofurocoumarins are a wide range or organic compounds that poseses a coumarin structure attached to a furan ring; geometric possibilities divide furocoumarins in two the main structures: dihydroangelicins and dihydropsoralens (Figure 1).

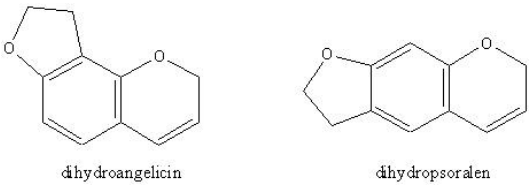

Figure 1 – Structure of dihydroangelicins and dihydropsoralens.

As part of the group of dihydroangelicins, several 4-phenyldihydroangelicins, mostly of plant origin, have show a variety of bioactivities useful for cancer treatments, working sucefully in human nasopharyngeal [1], bronchial [2], and liver cancer cells [3]. Aplications for these type of compounds, 5'-halomethyl-4-methyl-4 ', 5'-dihidroangelicins and 4,8-dimethyl-5'-(N-methylpyridinium)-4',5'-dihidropsoralens were described as potential agents for the treatment photochemotherapeutic skin diseases by psoralen and UV-A radiation [4].

Also, several dihydropyran and dihydrofurocoumarins have been reported with significant coronary vasodilating effect, being accompanied by an antispasmodic effect, associated to inhibition of adenosine monophosphate enzymephos phodiesterase [5].

Others enzymes, associated to others deceases, are also suceptibles to dihydroangelicines; for example dihydropsoralen (also called nodakenine) and decursinol showed a significant inhibitory effect of acetylcholinesterase, responsible for the hydrolysis of acetylcholine, a reaction related to Alzheimer's disease [6]. Chalepine shown good inhibition of glyceraldehyde-3-phosphate dehydrogenase, an enzyme present in the glycosomes parasite Trypanosoma cruzi, which causes Chagas disease [7]. 2'(S),3'(R)-2'-acetoxiisopropil-3'-acetoxy-2',3' dihydroangelicin next to columbianetine acetate and diacyldihydroangelicine have shown some fungicidal activity with Botrytis cinerea show weak fungicidal activity for linear dihydrocoumarins [8].

Various synthetic strategies have been developed for these compounds, like oxidative cyclization of aliloxicoumarins involving Claisen rearrangement and subsequent cyclization of allyloxycoumarin to form a dihydrofurane or dihydropirane ring. Conditions to perform this rearrangement generally involves temperatures above 150ºC, so that various conditions have been studied for this purpose like 24h reflux in solvents with high boiling point like N,N-diethylaniline, N,N-dimethylaniline, diphenyl ether [9] or ethylene glycol [10], requiring all of them a tedious isolation workup. Less vigorous conditions and reaction phases involves reagents like thiophenol [11], or heating under microwave radiation in NMF [9].

Cyclization step necessarily requires acid conditions, which have been tested using concentrated sulfuric acid and boron trifluoride etherate sulfuric acid [9].

Other method involves acetoxyiodocoumarins as starting reagents: One involves annulation of dienes with in presence

of Pd to form a substituted dihydroangelicine [12]. Other method involves reaction wirth Grignard's isopropylmagnesium chloride in THF at -100ºC for 1 hour, and subsequent addition of an α,β epoxyaldehide at 25ºC [13].

Also Fries reaction was used to perform dihydroangelicins, by means of treatment of 7-cloroacetoxyhetarenes with aluminum chloride, resulting in a rearrangement followed by intramolecular cyclization [14].

Other methods for preparing a dihydroangelicine moiety were reported, like photocycloaddition of furocoumarines [15] or by treatment of an o-hidroxydihydrofurancarbaldehide with acetic anhydride in presence of sodium acetate [16].

This work is part of our search of organic compounds with varied and important biological activity in the field of pesticides; here we carried out preparation of dihydroangelicins using green chemistry techniques from 7-allyloxycoumarins (Figure 2).

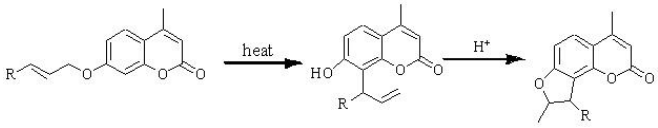

Figure 2 – Scheme of proposed green-synthesis of dihydroangelicins.

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2. MATERIALS AND METHODS

Chemicals were purchased from Aldrich, Fluka and Merck and were freshly used after purification by standard procedures (distillation and recrystallization). All the reactions were monitored by TLC on precoated silica gel plates (254 mm). Flash column chromatography was performed with 230 to 400 mesh silica gel. All the yields were calculated from pure products. All the products were identified by comparison of analytical data (mp, TLC, NMR) with those reported or with authentic samples prepared by conventional methods. Melting points of the compounds were determined in sealed capillary tubes and are uncorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker instrument 400 MHz model as $CDCl_3$ solutions, and the chemical shifts were expressed in d units with Me_4Si (TMS) as the internal standard. Microwave heating was perform using conventional house microwave oven.

In order to quantify how much 'greener' the presented methodology is, various green metric parameters were calculated for each reaction performed: Quantitative factors such as atom economy (AE), atomic efficiency factor (E) and semiquantitative EcoScale [17].

3. EXPERIMENTAL:

General procedure for preparation of 7-allyloxy-4-methylcoumarins: 7-allyloxycoumarins were prepared from classic techniques [9] from 7-hydroxy-4-methylcoumarin and allyl bromide in acetone solution in the presence of anhydrous potassium carbonate: 5 mmol of 7- hydroxy-4-methylcoumarin in 50 ml of acetone were dissolved, and to the solution 1.40 g of anhydrous potassium carbonate were added, and 7 mmol of the corresponding allyl bromide. The mixture was heated to reflux until disappearance of reagents in TLC. The solvent was evaporated under reduced pressure; then 50 ml of water was added to dissolve the salts; extracted with CH_2Cl_2 (3 x 10 ml), dried over anhydrous Na_2SO_4 and the solvent evaporated on a rotary evaporator. The crude product obtained was recrystallized from methanol.

General procedure for preparation of 8-allyl-7-hydroxy-4-methylcoumarins using solvent: 0.5 mmol of the corresponding 7-allyloxy-4-methylcoumarin were dissolved in 4 ml of corresponding solvent at reflux until disappearance of reagents in TLC. Then 3 ml of water was added, extracted with CH_2Cl_2 (2 x 2 ml), dried with Na_2SO_4 and the solvent was evaporated.

Solvent-free procedure for preparation of 8-allyl-7-hydroxy-4-methylcoumarins: 0.5 mmol of the corresponding 7-allyloxy-4-methylcoumarin were mixed with corresponding amount of silicagel, and the mixture was heated in nitrogen atmosphere) to desire temperature (using conventional heating or microwave heating) until disappearance of reagents in TLC. Then 3 ml of water was added, extracted with CH_2Cl_2 (2 x 2 ml), dried with Na_2SO_4 and the solvent was evaporated.

General procedure for preparation of dihydroangelicins: to 0.5 mmol of the corresponding 7-allyloxy-4-methylcoumarin, 1% mmol of catalyst was added, and then heated in nitrogen atmosphere to desire temperature (using conventional heating or microwave heating). After reaction, purification was made by column chromatography with (athyl acetate: petroleoum ether 1:2).

Characterization of prepared compounds:

7-allyloxy-4-methylcoumarin (1a): mp: 100-101ºC (lit mp [18] 104-105ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.34 (3H, s), 4.54 (2H, d, J = 12 Hz), 5.25 (1H, d, J = 12 Hz), 5.90-6.09 (2H, m), 6.10 (2H, s), 7.44 (2H, d, J = 16 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$), δ (ppm): 18.8, 69.4, 102.0, 112.2, 113.0, 113.9, 118.7, 125.7, 132.4, 152.8, 155.4, 161.5, 161.8.

7-crotyloxy-4-methylcoumarin (2a): mp: 83-84ºC (lit mp [19] 85ºC). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.74 (3H, d, J = 8 Hz), 2.37 (3H, s), 4.50 (2H, d, J = 16 Hz), 5.75-5.87 (2H, m), 6.10 (1H, s), 6.79-6.87 (2H, m), 7.48 (1H, t). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 18.1, 18.9, 69.4, 101.9, 112.1, 113.1, 119.9, 125.3, 125.7, 131.7, 153.0, 156.1, 161.6, 161.9.

7-cinnamyloxy-4-methylcoumarin (3a): mp: 179-181ºC (lit mp [20] 179-180ºC). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.38 (3H, s), 4.75 (2H, d, J = 16 Hz), 6.12 (1H, s), 6.32-6.45 (2H, m), 6.72-6.94 (2H, m), 7.26-7.52 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 18.9, 69.4, 102.0, 112.3, 113.0, 118.9, 123.3, 125.8, 126.7, 128.4, 128.9, 134.2, 136.3, 152.8, 155.5, 161.5, 161.8.

8-Allyl-7-hydroxy-4-methylcoumarin (1b): mp: 196-197ºC (lit mp [21] 198-199°C). ^{1}H NMR (400 MHz, DMSO- d6), δ (ppm): 2.38 (3H, s), 2.54 (2H, d), 4.98 (2H, d, J = 16 Hz), 5.92-5.99 (1H, m), 6.13 (1H, s), 6.91 (1H, d, J = 16 Hz), 7.50 (1H, d, J = 16 Hz). ^{13}C NMR (100 MHz, DMSO- d6), δ (ppm): 18.1, 26.5, 109.9, 111.9, 112.6, 115.0, 120.0, 123.9, 135.4, 152.6, 153.8, 158.7, 160.3.

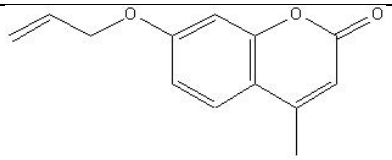
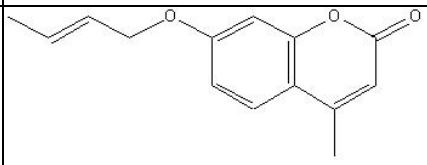
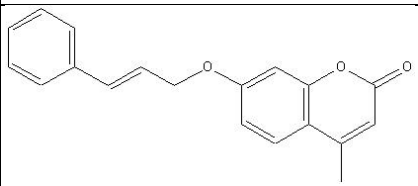
8-(1-methylallyl)-7-hydroxy-4-methylcoumarin (2b): mp: 205-205ºC (mp lit [19] 205ºC). ^{1}H NMR (400 MHz, DMSO-d6), δ (ppm): 1.74 (3H, d, J = 8 Hz), 2.38 (3H, s), 2.93-2.97 (1H, m), 4.98 (2H, d, J = 16 Hz), 5.92-5.99 (1H, m), 6.13 (1H, s), 6.97 (1H, d, J = 16 Hz), 7.49-7.53 (1H, d, J = 16 Hz). ^{13}C NMR (100 MHz, DMSO- d6), δ (ppm): 17.9, 23.0, 26.4, 110.0, 112.0, 112.3, 117.4, 123.8, 124.0, 138.0, 151.3, 153.8, 157.4, 160.2.

4,9-dimethyl-9,10-dihydroangelicin (1c): mp: 128-130ºC (lit mp [9] 129-130ºC). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.70 (3H, s), 1.51 (2H, d, J = 16 Hz), 2.40 (3H, d, J = 7 Hz), 4.60 (1H, d, J = 16 Hz), 6.11 (1H, m), 6.69-6.91 (1H, m), 7.26 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 18.9, 19.9, 32.0, 69.4, 101.9, 111.2, 118.8, 120.5, 125.7, 152.8, 155.3, 161.3, 163.1.

4,9,10-trimethyl-9,10-dihydroangelicin (2c): mp: 116-117ºC (no lit data). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.28 (3H, d, J = 6 Hz), 1.41 (3H, d, J = 6 Hz), 2.33 (3H, s), 3.04-3.70 (1H, m), 4.25-5.94 (1H, m), 6.04 (1H, s), 6.50-7.50 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 16.6, 19.2, 19.8, 32.1, 69.3, 101.5, 111.0, 117.9, 120.6, 125.7, 152.4, 155.3, 161.2, 162.9.

4. RESULTS AND DISCUSSIONS:

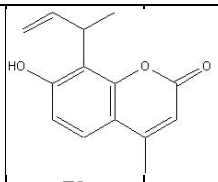
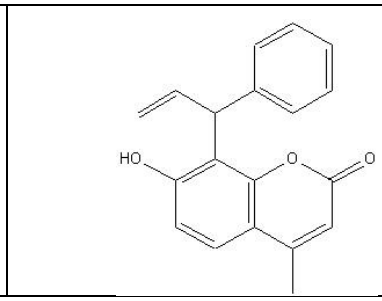
Table 1 summarized the results for the synthesis of 7-allyloxycoumarins (a).

Entry	Product	Yield (%)
1a		83
2a		64
3a		21

The main strategy to convert alliyloxycoumarins to 8-allyl-7-hydroxycoumarins was the thermal Claisen rearrangement. To define the best environmentally-well performed method, various reaction conditions were tested and EcoScale parameter was determined in each case. Results (conditions, yields and EcoScale factor) are summarized in table 2.

Table 2 - Thermal Claisen rearrangement conditions for synthesize 8-allyl-7-hydroxy-4-methylcoumarin*

Tests conditions	Yield (%)	Eco Scale	E factor
1-Reflux in nitrobenzene 24 h and further distillation	5	34.5	1770
2-Reflux in formamide 24 h and further extraction	15	49.5	1071
3-Reflux in DMF 7 h and further extraction	0	--	--
4-Reflux in DMF 6 h and further extraction	23	53.5	494
5-Microwave (800W) heating in DMF 25 min and further extraction	5	40.5	11726
6-Microwave (800W) heating in NMF 10 min and further extraction	17	46.5	3460
7-Solvent-free conventional heating (165ºC) 3 h on inert atmosphere and columns chromatography isolation	14	34	30085
8-Solvent-free conventional heating (174ºC) 48 h on inert atmosphere and extraction	63	68.5	140
9-Solvent-free conventional heating (150ºC) of a mixture with 4 times weight of silicagel, 2 h on inert atmosphere and extraction	12	53	442
10-Solvent-free conventional heating (200ºC) of a mixture with 4 times weight of silicagel, 2 h on inert atmosphere and column chromatography extraction	26	50	4723
11-Solvent-free conventional heating (180ºC) of a mixture with 6 times weight of silicagel, 2 h on inert atmosphere and extraction	37	65.5	149
12-Solvent-free conventional heating (180ºC) of a mixture with equal weight of silicagel, 2 h on inert atmosphere and extraction	67	80.5	75

13-Solvent-free microwave (800W) heating of a mixture with equal weight of silicagel, 100 min on inert atmosphere and extraction	67	 72	3b		0

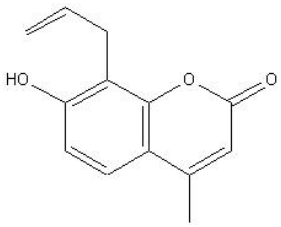
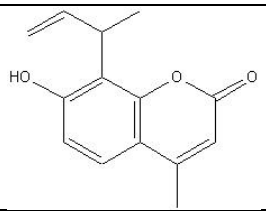
* Conditions: 0.5 mmol of 7-allyloxy-4-methylcoumarin. In the case of using solvents, volume is 4 mL. Conventional heatings were performed in a sand bath. Microwave heatings were performed in a 800W conventional oven.

Several considerations about the reaction should be made; on one hand a high temperature is needed for the reaction takes place, requiring values higher than 150ºC for a rearranged product [22]; moreover, in case of solvent-free conditions, it can be considered the formation of byproducts, mainly relating to the oxidation of the phenol, which generally takes place at temperatures above 160 ° C in presence of air oxygen [23], but this reaction was avoided often working under a inert atmosphere.

Tests 1-6 shows that working with solvents with high boiling points low yields were obtained and involves more isolation steps. The use of microwave irradiation over? allyloxycoumarin solutions does not alter the results as far as yields are concerned, although times are drastically reduced.

Best results were obtained in the absence of solvent under inert atmosphere. While comparing the reaction times shows drastic differences between the two systems, the application of microwave for 100 min in pulses of 10 min and 5 min intervals is operational and energy very high compared with 2 hours of conventional heating in presence of silica gel. Greenmetric parameters are also favorable. Such conditions were adopted to achieve optimal Claisen rearrangement to preparation of substituted 8 -allyl -7 - hydroxycoumarins. Results are given in table 3

Table 3 - Results for the synthesis of substituted 8-ally-7-hydroxycoumarins (b).

Entry	Product	Yield (%)
1b		67
2b		59

Starting from the same 7-allyloxycoumarins, test conditions for preparation of dihydroangelicins were studied to perform cycloaddition of 7-allyloxycoumarins.

In order to test different options for promoting agents for cyclization, which generally involves the presence of acidic or homolitic initiators, various conditions were tested. Results (conditions, yields and EcoScale factor) are summarized in table 4.

Table 4- Cycloadition conditions for synthesize 4,9-dimethyl-9,10-dihydroangelicine*

Tests conditions	Yield (%)	Eco Scale	e factor
$AlCl_3$ supported on silicagel 1% mmol, in refluxing toluene, 24h.	22	28	5221
$AlCl_3$ supported on alumina 1% mmol, in refluxing toluene, 24 h	0	--	--
$CoCl_2$ supported on silicagel 1% mmol, in refluxing toluene, 24 h.	0	--	--
$H_6P_2W_{18}O_{62}.2H_2O$ 1% mmol solvent-free conventional heating, inert atmosphere, 8 h	30	37	3825
$H_{14}NaP_5MoW_{29}O_{110}$ 1% mmol solvent-free conventional heating, inert atmosphere, 8 h	74	64	1529
$H_6P_2W_{18}O_{62}.2H_2O$ 1% mmol solvent-free 800W microwave heating, inert atmosphere, 60 min	70	62	1618
$H_{14}NaP_5MoW_{29}O_{110}$ 1% mmol solvent-free 800W microwave heating, inert atmosphere, 30 min	79	67.5	1432
Benzoyl peroxide in refluxing CCl_4	0	--	--

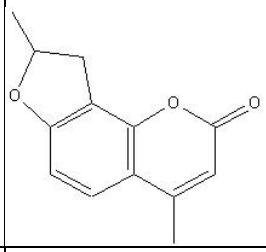
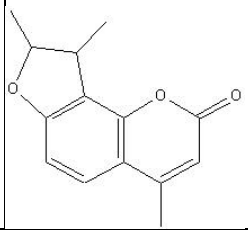
The use of weaker Lewis acids as catalysts do not favor reaction to give low yields or zero after a 24 h reaction. at reflux of toluene. For the particular case of aluminum

chloride, to be supported on silica gel shows a soft effect under a low yield obtained after 24 h, probably due to more acidic character of silica gel compared to alumina. The catalyst provided better working conditions refluxing toluene (110 ° C) is the heteropolyacid $H_{14}NaP_5MoW_{29}O_{110}$ (with Preyssler structure).

The use of benzoyl peroxide as initiator of homolytic reactions yielded no results after 24 h reaction.

About studies with acid catalysts in the absence of solvent good yields for HPAs are observed. Irradiation with microwave reduces reaction times drastically and giving a slightly higher yields. The analysis of the results led to adopt as working conditions to preparing substituted dihydroangelicins under microwave irradiation of aliloxicumarinas in the presence of 1% (mmol) of $H_{14}NaP_5MoW_{29}O_{110}$ as catalyst. Results are given in table 5.

Table 5 summarized the results for the synthesis of dihydroangelicines (c).

Entry	Product	Yield (%)
1c		79
2c		22

Regarding the effect of substituents on the same reaction conditions, it is observed that yields again are affected dramatically with increasing size of the substituent (table , entries 1-3) .

Finally, a test was performed using 8-allyl-7-hydroxy-4-methylcoumarin (the rearranged product 1b) as substrate under identical reaction conditions, giving a 12% yield of 1c.

Thus a synthesis of dihydroangelicins is made using sustainable conditions for the reaction: absence of solvents, applying microwave radiation and insoluble heteropoly acid catalysis with Preyssler structure. In addition, according to the selected reaction conditions, different products can be obtained.

Figure 3 show the plausible mechanism for the catalytic cycle representing the formation of dihydroangelicin from rearranged product under the selected conditions. Step 1: thermal Claisen rearrangement (in the absence of catalyst); Step 2: Cyclization of 8- allyl- 7- hydroxycoumarin to dihidroangelicina .

First step involves the rearrangement of the allyl group by thermal Claisen mechanism involving a pericyclic [3,3] sigmatropic rearrangement. Regarding the proposed cyclization of the rearranged product, catalytic cycle proposed first protonation of the olefinic carbon of 8-allyl-7-hydroxycoumarin by the HPA to form the most stable secondary carbocation that, as electrophile, attacks subsequently the oxygen atom of the phenolic hydroxyl of forming the furan cycle. The same catalyst (as anion) assists deprotonation to form the corresponding dihydroangelicin.

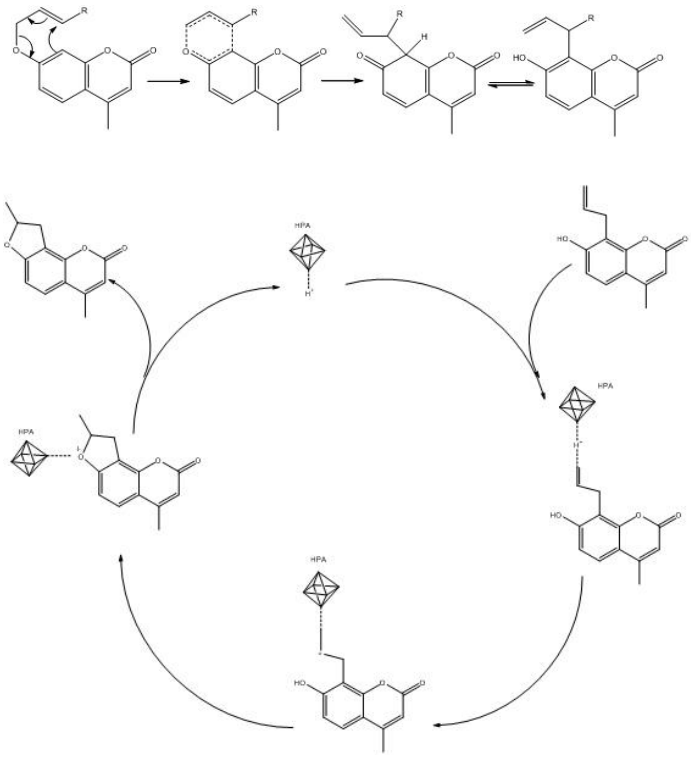


Figure 3 - Proposed mechanism for the catalytic cycle representing the formation of dihydroangelicins

CONCLUSION

A simple and environmentally friendly method can be achieved for the synthesis of compounds with potential pharmacological and agrochemical activity, replacing the use of solvents and mineral acids with great impact to the environment with a solid easily recoverable heteropolyacid.

The use of solvents and mineral acids are of great impact on the environment is replaced for a more bening methos. The advantages in this case the methodology involving: operational simplicity, work in absence of solvent, use of a reusable catalyst and good yields.

Comparison with dihydroangelicins preparation methods previously reported, shows the following differences:

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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Received: March 20, 2014 Revised: April 16, 2014 Accepted: April 20, 2014