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Eco-friendly Synthesis of Coumarin Derivatives via Pechmann Condensation Using Heterogeneous Catalysis

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Abstract
A coumarin derivatives has been synthesized via Pechmann condensation naphthol with a β-ketoester using Amberlyst-15 as a green and efficient catalyst.The optimal conditions are: molar ration of reagents (1:1), Amberlyst-15 (10mol.%, 0.2 g) at 110°C for 150min. in solvent-free conditions. The recyclability of amberlyst 15 adds an advantage to the studied reaction.These coumarins derivatives have biological activity and momentousness in the industrial fields
Keywords: Coumarins, Phenols, β-Ketoesters, Pechmann Reaction, Amberlyst-15

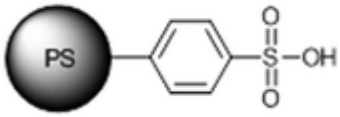
1. INTRODUCTION

Coumarins are an important class of benzopyrones wich consist of a benzene ring joind to a pyrone ring [1] . The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus. They are widely used as additives in food,perfumes, agrochemicals, cosmetics, pharmaceuticals [1] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable dye lasers [2]. They have varied bioactivities, such as, inhibitory of platelet aggregation[3], antibacterial [4], anticancer [5], inhibitory of steroid 5_-reductase [6] and inhibitory of HIV-1 protease [7]. Coumarins also act as intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols [8]. Their properties turn coumarins very interesting targets to organic chemists, and several strategies for their synthesis were already developed.

Coumarins can be synthesized by various methods such as Pechmann [9], Perkin [10], Knoevenagel [11], Reformatsky [12] and Witting [13] reactions. Pechmann condensation is one of the most common procedures for the preparation of coumarin and its derivatives.This method involves the reactions between a substituted phenol and a β-keto ester in the presence of an acidic catalyst. Simple starting materials are required here to produce various substituted coumarins in good yields.

Different acid catalysts like H2SO4, P2O5, FeCl3, ZnCl2, POCl3, AlCl3,HCl, H3PO4 and CF3-COOH acid are known to affect this condensation [14]. However, in the current context of environmental impact, these methods are not attractive as they require catalyst in excess, for example, sulfuric acid in 10–12 equivalents [15], trifluoroacetic acid in three to four equivalents [14b] and phosphorus pentoxide in five-fold excess [16]. Further, such reactions required long reaction time or heating the reaction mixtures above 150oC. In addition, aformation of undesired sideproducts alongside coumarins have been observed in these cases ,and in other cases gave lower yields[16b]. Recently, cation exchange resins [17] and solid acid catalysts [18] have been tried for this reaction. These reactions also have been attempted using microwave irradiation [19] for accelerated syntheses of different coumarins. In previous years a profound interest was shown in the use of ionic liquids [20] for organic synthesis and on green chemistry [21]so we report in this paper a solvent-free synthesis of coumarins using an inexpensive and non-polluting catalyst.

In recent years, heterogeneous catalysts are gaining more importance due to enviro-economic factor. The catalyst is generally is low cost and can be easily handled or removed. Thus there will be no undesirable wastes that caus environmental pollution. To the best of our knowledge, no report has been made about the use of heterogeneous catalyst for synthesis of coumarins via Pechmann condensation using Amberlyst-15 as heterogeneous catalyst.



PS= PolyStyrene
Figure (1): General formula of Amberlyst-15

It is a macro reticular polystyrene based ion exchange resin with strongly acidic sulfonic group. It serves as an excellent source of strong acid. It can also be used several times. Amberlyst 15, Hammett acidity function of -2, is reportedly sulfonated at 4.7 mmol g−1 corresponding approximately to one sulfonic acid group

per styrene monomer unit.[21a]

2. EXPERIMENTAL

2.1. Apparatus

^{1}H, ^{13}C NMR spectra were recorded on a Bruker 400 MHz, optical absorption spectrum infrared device model FT-IR-4100 from the Japanese company Jasco.

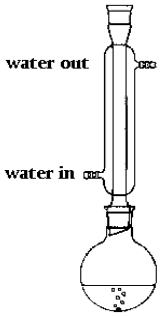
2.2- raw materials and reagnts

α-napthol**,** ethyl acetoacetate(sigma aldrich & merck**),** methan selfonic acid, sulforic acid and some solvents (99% by Merck) **,**Para toluene selfonic acid **,** amberlyst-15 (99% by sigma aldrech)

3. Experimental Procedure

General procedure

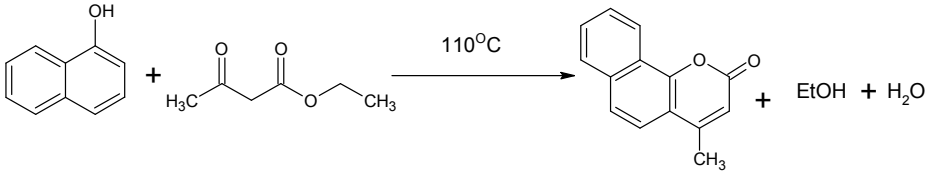
A mixture of α-napthol (1 mmol), ethyl acetoacetate (1.1 mmol) and acid catalyst (10 mol %) were added, then the reaction mixture was stirred in oil bath heated at 110°C for the desired time.



The reaction was monitored by thine layer chromatography (TLC). After completion of the reaction, mixture was filtered to remove the heterogeneous catalyst (or naturalized by Na2CO3 to remove the homogeneous catalyst), then filtrate was cooled to room temperature, after that, a hot methanol was added to cooled filtrate to result a solid (crude product) that it was filtered and then was recrystallized with ethanol to obtain pure product. The physical data (mp, NMR, IR) of these known compounds were found to be identical with those reported in the literature.

2. Results and Discussion

Herein, we report an efficient method for the preparation of coumarin derivatives using Amberlyst-15 as a catalyst in the Pechmann reaction.



Scheme 1. Synthesis of 4-methyl-2H-benzo[h]chromen-2-one (1) by using Amberlyst-15 as a catalyst

At first time, for the optimization of the reaction conditions, a mixture of α-napthol and ethyl acetoacetate was investigated as a model and its behavior was studied under a variety of conditions - such as:- Temperature, time of reaction, solvants molar ratio of catalyst and type of catalysts. The best result was achieved by carying out the reaction of α-napthol and ethyl acetoacetate (with 1: 1 mol ratio) in the presence of (0.2g,10%mol) of Amberlyst-15 at 110°C for 150 min -(The reaction mixture were monitored by TLC using(di chloro ethan : n.hexane-7:4)under solvent-free conditions, Scheme 1 , with an excellent yields (nearly 85%) of 1 were obtained.

The specific impacts of different molar amount of catalyst on the yield did not notice when the amount of catalyst was increased (Table 1):

Table1: effect of Amberlyst-15 percentage in Pechmann condensation of α-napthol (1 mmol) with ethyl acetoacetate (1 mmol) in solvent-free conditions at 110°C, for 150 min and It is found that 10 mol.%

Entry	Amount of catalyst (mol.%)	Yield (%)
1	-	Traces
2	10	87
3	20	88
4	30	86
5	40	85

the using of large quantities of Amberlyst-15 did not affect to the preparation of 1, so from an economic perspective, it is preferred using the least possible quantity of catalyst.

Then and to study the effect of temperature, synthesis of 1 was carried out at the temperature range of 40°C – 150°C (Table 2):

Table 2: effect of temperature in Pechmann condensationof α-napthol (1 mmol) with ethyl acetoacetate (1 mmol) and Amberlyst-15(10 mol%, 0.2g) in solvent-free conditions, for 150 min

Entry	Temperature (°C)	Yield (%)
1	40	20
2	80	40
3	110	88
4	130	80
5	150	55

As indicated in Table 2, it is clear that by increasing the temperature until 110°C the yield improved from 20% to 88%, but by increasing the temperature more than 110°C, the yield was decreased until 55% at 150°C, that is probably due to the formation of side products such as chromones, the self-condensation of ethyl acetoacetate, isomerization and cleavage of 4-methyl-2H-benzo[h]chromen-2-one (Appearance several spot as checked by TLC), in addition, the activity of catalyst was decreased at the high temperature because of low thermal stability of the vinyl based polymers [21b], so the temperature 110°C is an optimal temperature

The time of reaction was optimized 150 min where the reaction was completely finished with the highest yield (monitored by TLC), But by increasing the time up to 150 min the yield was decreased, it is probably due to increasing the side products (Appearance several spot as checked by TLC) , the results are summarized in Table 3:

Table 3: effect of the time on Pechmann condensationof α-napthol (1 mmol) with ethyl acetoacetate (1 mmol) and Amberlyst-15 (10mol.%, 0.2g) in solvent-free conditions at 110°C

Entry	Time (min.)	Yield (%)
1	30	20
2	60	30
3	100	70
4	150	86
5	200	75

The effect of several solvent on the yield of coumarin derivatives was studied. As indicated in the previous three tables (table 1, 2, 3), the yield was found to be significantly higher in solvent-free conditions. when this result was compared with other solvents. it is found that the non-polar solvents, like toluene, were better than polar solvent, it is due to reduce the formation of hydrogen bond (inter- and intra- molecular) in the phenol derivatives and also to form an azeotropic mixture (ethanol and water) which was producing during the reaction which facilitate removing them from the reaction media, in addition, that the polar solvents may cause the cleavage [22].

Table 4: Effect of solvent on Pechmann condensationof α-napthol (1 mmol) with ethyl acetoacetate (1 mmol) and Amberlyst-15(10mol.%, 0.2 g) at 110°C for 150min.

Entry	Solvants	Yield (%)
1	Toluene	85
2	THF	70
3	1,4-Dioxan	50
4	EtOH	20
5	MeOH	30
6	H2O	20
7	-	88

Several acidic catalysts were examined to compare them with Amberlyst 15 (Table 5). When using homogenous catalysts, it is necessary to use a large quantity of catalyst to have the same yield, but if the same molar percentage was used, the yield will be very low (Table 5, entaries 1, 4, 6). In other hand, when the Silic

catalysts were used (Table 5, entaries 2, 5), the yield was not improved, it may return to their high surface polarity which attract the water molecules that cause poisoning the active sites of catalyst. While non -polar surface catalyst (Amberlyst-15) (Table 5, entary 7) was stayed active and no poisoning active sites was observed, so the best yield was obtained, in addition, it is easy to isolate the catalyst from the reaction media without any supplementary treatment.

Table 5: effect of type of catalyst on Pechmann condensationof α-napthol (1 mmol) with ethyl acetoacetate (1 mmol) in solvent-free conditions at 110°C for 150min.

Entry	Catalyst	Yield (%)
1	H_2SO_4	30
2	SiO_2-SO_4H	30
3	CH3-SO_3H	45
4	*p*-TSA	50
5	HMS-SO_3H	10
6	$AlCl_3$	55
7	Amberlyst 15	88

To our delight, Amberlyst 15 was successfully recycled at least 5 times (figure.2.) without apparent decrease of activity and selectivity giving a yield at every cycle nearly 85%. After 5 cycles, the color of the Amberlyst 15 changed from (a) to (b) which is presumably due to the partial deposit of carbonaceous materials but it does not impact the recyclability of Amberlyst 15.[21]

(a)

(b)

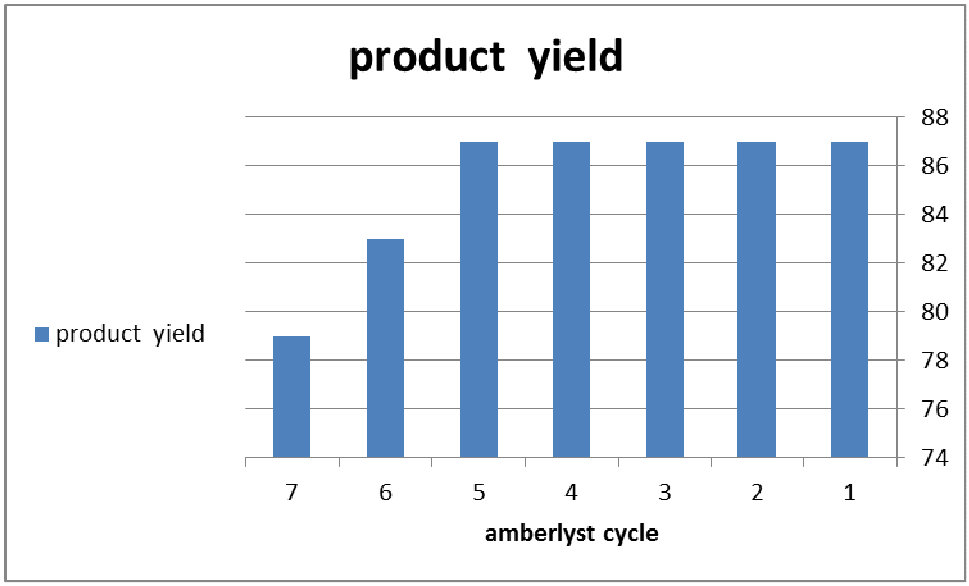


figure.2. Amberlyst-15 recycle study

Conclusion

In conclusion, we have developed a simple and efficient synthesis of substituted coumarins via Pechmann condensations using Amberlyst-15 catalyst under solvent-free conditions. Moreover the low cost of the catalyst, solvent-free condition, low toxicity of the catalyst, fast reaction times, simple experimental procedure, recyclablity of the catalyst and high yields of the products are the advantages.

3.3. Characterization of the products

4-methyl-2H-benzo[h]chromen-2-one(entry1a)(di chloro ethan : n.hexane-7:4)
IR(KBr) (v, cm-l):1718(C=O), 2978 (C_{sp3}-H), 3071(C_{sp2}-H), 1290 (C-O),1550+1610(C=Caromatic),1637 (C=Calken)
1H NMR(DMSO-d6, 400MHz) (δ, ppm): δ 2.566(s, 3H, CH3), 6.535(s, 1H, 3-H), 7.908(d, J=8,8Hz, 1H, 5-H), 7.827(dd, J=8,8Hz, 1H, 6-H), 8.068(m, 1H, 7-H), 7.774(m, 1H),8.399(m,1H)
13C NMR(DMSO-d6, 400MHz) δ19.12,114.2,115.55,121.68,122.04, 122.63, 124.45,127.30,128.41,129.12,134.809,150.09,154.75,160,20

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