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Studying the Esterification of Phenylacetic Acid with some Hydroxylated Derivatives Using Eco-Friendly Medias

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Abstract

In this research, the organic reaction of phenyl acetic acid and some Hydroxylated Derivatives in the absence of organic solvents to obtain phenyl acetic acid esters have been synthesized. The optimum reaction conditions were determined to produce phenyl acetic acid esters. The optimal condition (catalysts, temperature and solvents) to get a high selective compounds and high yields have been studied. When use of heterogeneous catalyst (Amberlyst-15) (10%mol), extra amount of reacted alcohol as a solvent and 110°C getting a required selectivity and high yield (about 80%) in comparison to the homogeneous catalysts (H₂SO₄, PTSA, CH₃SO₃H), in addition to the low selectivity of the final product. The reaction followed by using thin layer chromatography (T. L. C), the molecular structures have determined by spectroscopy methods: FT-IR, ¹H-NMR, ¹³C-NMR.

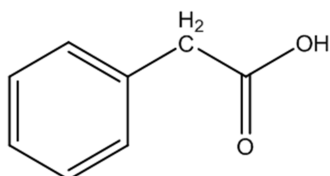
1. Introduction

Esterification is one of the most fundamental and important reactions used by industry because of the overwhelming applications of esters as intermediates in the synthesis of fine chemicals, drugs, plasticizers, perfumes, food preservatives, cosmetics, pharmaceuticals, solvents, and chiral auxiliaries. [1-4] Production capacity for esters varies anywhere from a few kilograms to several thousand kilograms per day. [5] Several synthetic routes have been adopted to make esters, but most of them do not meet the stringent specifications that are being applied in today's chemically conscious world.

The most traditional method of making an ester is the acidcatalyzed reaction of the concerned carboxylic acid with an alcohol, with one of them taken in molar excess to shift the equilibrium conversion favourably by using a homogeneous catalysts such as sulfuric acid, p-toluene sulphonic acid, HF, HCl, phosphoric acid, etc. The advantages of using solid heterogeneous catalysts are too well-known and among these are zeolites, ion-exchange resins, supported heteropoly acids, etc. [6-17]. The current work is concerned with the use of cation-exchange resins to develop an environmentally.

Phenylacetic acid is one of important organic chemical materials, which is widely used in the field of medicine, pesticide, aromatizer and so on. There exist several routes to synthesize phenylacetic acid, such as cyanobenzyl hydrolysis [18-22], phenylacetamide hydrolysis [23-25], electrochemical process [26-28], carbonyl process [29], etc, Phenylacetic acid (C₆H₅CH₂COOH) is an aromatic compound with two carbon

side chains that is found as an active auxin predominantly in fruits. Phenylacetic acid has biotechnological and pharmaceutical relevance because of its extensive applications in the production of β -lactam antibiotics, as an intermediate to produce pharmaceuticals such as penicillin G. Phenylacetic acid has extensive range of biological activity,



2-phenylacetic acid
 Chemical Formula: $C_8H_8O_2$
 Exact Mass: 136.05
 Molecular Weight: 136.15
 m/z: 136.05 (100.0%), 137.06 (8.8%)
 Elemental Analysis: C, 70.57; H, 5.92; O, 23.50

Figure 1. Chemical structure and some information of 2-phenylacetic acid.

antibacterial, analgesic, and virucidal properties, and is a plant growth regulator. Phenylacetic acid can be obtained by the fermentation of soya beans using *Bacillus Licheniformis*. [30-31] In the process of enzymatic hydrolysis of penicillin G by penicillin acylase, phenylacetic acid is obtained as a byproduct. [32] Phenylacetic acid strongly inhibits the activity of penicillin acylase. The simultaneous in situ or ex situ removal of phenylacetic acid is required to get higher productivity

Esters of PAA were also known as analgesics and inflammation inhibitors etc, [33-36]. Owing to the above mentioned biological activities of PAA derivatives and our own interest in their phenolic esters [37].

Thus, this method has a bright perspective. The influences of some factors on the yield of phenylacetic acid in the esterification it were mainly studied in this paper. Furthermore perfect solvent and effect of various factors were obtained. These haven't been reported in previous literature.

2. Experimental

2.1. Apparatus

Spectrum NMR proton and carbon device 400 MHz model Bruker by Switzerland company, optical absorption spectrum infrared device model FT-IR-4100 from the Japanese company Jasco.

2.2. Reagents and Materials

Phenylacetic acid, propan-1-ol, phenylmethanol, prop-2-en-ol, cyclohexanol, glycerol, n-hexane, ethyl acetate, toluene, dimethylsulfoxed, acetonitrile, *o*-xylene, diclormethan, from BDH, Amberlyst-15, methanesulfonic acid, para toluene sulfonic acid sulfuric acid, from Sigma

Aldrich

3. Experimental Procedure

A mixture of Phenylacetic acid, glycerol and catalyst different kinds of catalysts (sulfuric acid, methane sulfonic acid, p-toluenesulfonic acid, SiO_2-SO_3H and amberlyst-15) and different solvents (toluene, dimethylsulfoxed, water) were added, put in 100 mL neck glass reactor in oil bath equipped with a magnetic stirrer and a condenser as shown in figure 2.

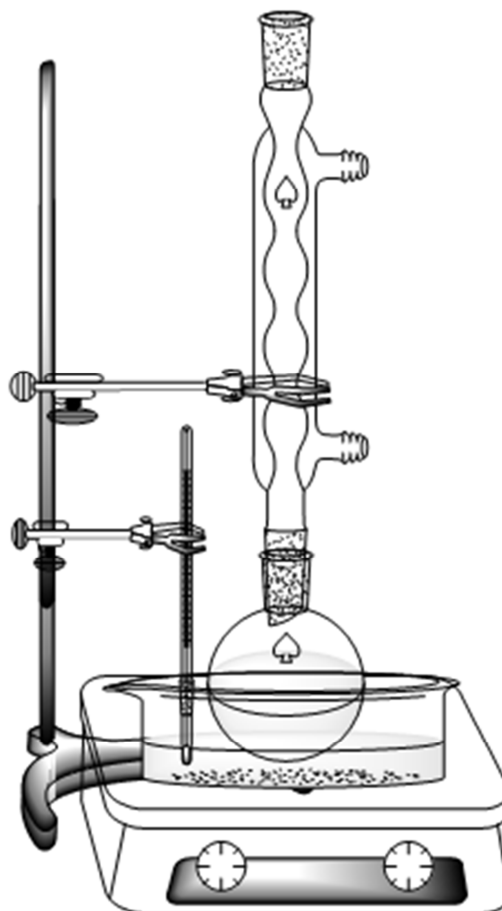


Figure 2. A tow-necked flask equipped with athermo meter.

In order to condense and reflux, the reaction is followed by thin layer chromatography (T. L. C) by n-hexan:ethylacetate (60:40), when stopped reaction and the catalyst go a way then evaporated the extra amount of alcohol, the residue product extract by dicloromethan:water, the extracts were dried over anhydrous Na_2SO_4 After removal of the solvent, the residue was purified by column chromatography mobile phase: n-hexan: ethylacetate to give desired ester and defined its proprieties, All of these reactions were performed at about $110^\circ C$ under stirring and reflowing. After the optimum conditions obtained, we used different alcohols to synthesized phenyl acetic acid esters like propan-1-ol, phenylmethanol, prop-2-en-ol, cyclohexanol.

4. Characterization

2,3-dihydroxypropyl 2-phenylacetate (1): (80%) was obtained as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.21-7.26 (m, 5H), 4.04-4.69 (s, 2H), 4.63-4.90 (d, $J = 7.0$ Hz, 2H), 3.04-4.07 (m, 1H), 3.94-3.96 (m, 2H), 3.35 (s, 3(-OH)) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 171, 134, 129, 126, 69, 65, 62 ppm.

Dodecyl 2-phenylacetate (2): (40%) was obtained as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.24 (m, 5H), 4.08 (t, $J = 7.0$ Hz, 2H), 3.61 (s, 2H), 1.62-1.57 (m, 2H), 1.25 (s, 18H), 0.88 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 171.7, 134.2, 129.2, 128.5, 127.0, 65.0, 41.5, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 28.6, 25.9, 22.7, 14.1 ppm.

Benzyl 2-phenylacetate (3): (55%) was obtained as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.25 (m, 10H), 5.13 (s, 2H), 3.67 (s, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 171.4, 135.8, 133.9, 129.3, 128.6, 128.5, 128.2, 128.1, 127.1, 66.6, 41.3 ppm.

Allyl 2-phenylacetate (4): (45%) was obtained as colorless clear viscous liquid. ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.26 (m, 5H), 5.94-5.86 (m, 1H), 5.29-5.20 (m, 2H), 4.60(d, $J = 5.5$ Hz, 2H), 3.65 (s, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 171.3, 133.9, 132.0, 129.3, 128.6, 127.1, 118.3, 65.5, 41.3 ppm.

Cyclohexyl phenylacetate (5): (76%) was obtained as

colorless clear viscous liquid. ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.24 (m, 5H), 4.80-4.74 (m, 1H), 3.59 (s, 2H), 1.82-1.79 (m, 2H), 1.71-1.66 (m, 2H), 1.54- 1.49 (m, 1H), 1.45-1.23 (m, 5H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 171.1, 134.4, 129.2, 128.5, 126.9, 73.0, 41.8, 31.5, 25.4, 23.6 ppm.

Propargyl 2-phenylacetate (6): (58%) was obtained as colorless clear viscous liquid. ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.26 (m, 5H), 4.69 (s, 2H), 3.68 (s, 2H), 2.47 (s, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ 170.8, 133.4, 129.3, 128.6, 127.3, 75.0, 52.3, 40.9 ppm.

L-(-)-Menthyl phenylacetate (7): (43%) was obtained as colorless clear viscous liquid. ^1H NMR (400 MHz, CDCl_3) ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.23 (m, 5H), 4.67 (dt, $J = 11.2, 4.4$ Hz, 1H), 3.60 (s, 2H), 1.99-1.94 (m, 1H), 1.77-1.61 (m, 3H), 1.51-1.31 (m, 2H), 1.04-0.93 (m, 2H), 0.90-0.86 (m, 4H), 0.83 (d, $J = 6.8$ Hz, 3H), 0.68 (d, $J = 7.2$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 171.2, 134.4, 129.2, 128.5, 126.9, 74.7, 47.0, 41.8, 40.8, 34.2, 31.4, 26.1, 23.4, 22.0, 20.7, 16.2 ppm.

5. Results and Discussion

Herein, we report an efficient method for the synthesis and esterification of phenyl acetic acid esters, reaction of phenyl acetic acid and some Hydroxylated Derivatives in the presence of catalytic amount of Amberlyst-15 afforded the corresponding hydroxyls derivatives as shown in (Figure 3).-

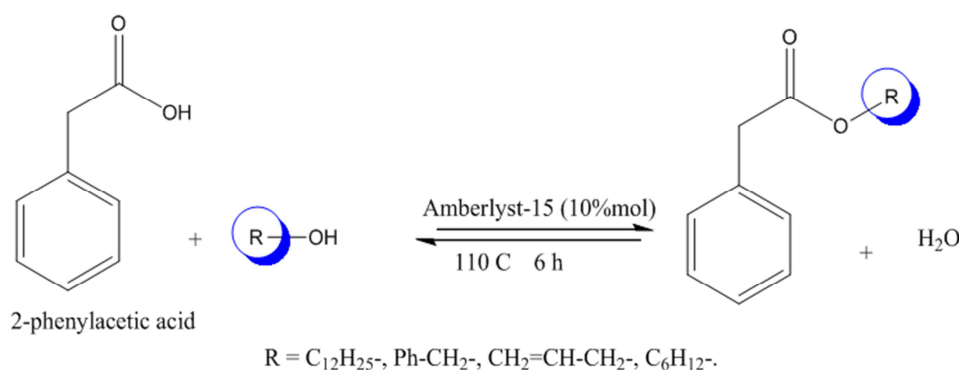
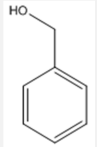
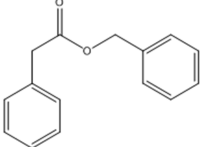
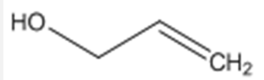
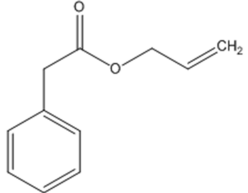
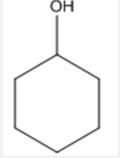
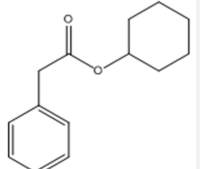
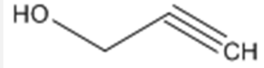
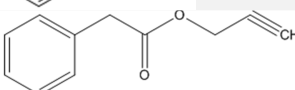
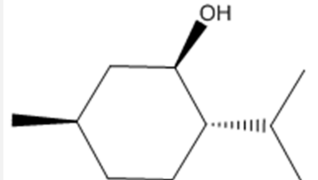
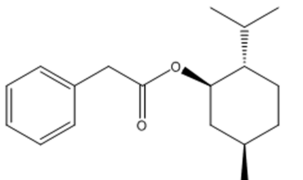


Figure 3. Esterification reaction of phenyl acetic acid and some hydroxylated derivatives to substituted phenyl acetic acid esters.

Table 1. Results of Amberlyst-15 catalyzed Esterification reaction of acetic acid and some hydroxylated derivatives at 110°C for 6 hours.

| Entry | Carboxylic Acid | Hydroxylated Derivatives | Products | State | Yields % |
|-------|-----------------|--------------------------|----------|--------------------------------|----------|
| 1 | | | | colorless clear viscous liquid | 80 |
| 2 | | | | colorless oil | 40 |

| Entry | Carboxylic Acid | Hydroxylated Derivatives | Products | State | Yields % |
|-------|-----------------|--|---|--------------------------------|----------|
| 3 | |  |  | colorless oil | 55 |
| 4 | |  |  | colorless clear viscous liquid | 45 |
| 5 | |  |  | colorless clear viscous liquid | 76 |
| 6 | |  |  | colorless clear viscous liquid | 58 |
| 7 | |  |  | colorless clear viscous liquid | 43 |

At first time, for the optimization of the reaction conditions, a mixture of phenyl acetic acid and some Hydroxylated Derivatives was investigated and its behavior was studied under a variety of conditions such as: Temperature, time of reaction, solvents, molar ratio of catalysts and type of catalysts.

The best result was achieved by carrying out the reaction of phenyl acetic acid and some Hydroxylated Derivatives (with 1:5) acid:alcohol molar ratio in the presence of (10%mol) of Amberlyst-15 at 110°C for 240 min. (The reaction mixture was monitored by T. L. C using (ethyl acetate:n-hexane - 2:3) under solvent-free conditions, with an excellent yield (nearly 80%).

The specific impacts of different molar amount of catalyst on the yield did not notice when the amount of catalyst was increased (Table 2):

Table 2. Effect of Amberlyst-15 percentage in esterification reaction of phenyl acetic acid.

| Entry | Amount of catalyst (mol. %) | Yield (%) |
|-------|-----------------------------|-----------|
| 1 | - | Traces |
| 2 | 3 | 55 |
| 3 | 5 | 68 |
| 4 | 10 | 80 |
| 5 | 15 | 80 |
| 6 | 20 | 80 |

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

Then and studying the effect of temperature, synthesis

was carried out at the temperature range of 50°C – 150°C (Table 3):

Table 3. Effect of temperature in esterification reaction of phenyl acetic acid.

| Entry | Temperature (°C) | Yield (%) |
|-------|------------------|-----------|
| 1 | 50 | 20 |
| 2 | 80 | 50 |
| 3 | 110 | 80 |
| 4 | 130 | 67 |
| 5 | 150 | 55 |

As indicated in Table 3, it is clear that by increasing the temperature until 110°C the yield improved from 20% to 80%, but by increasing the temperature more than 110°C, the yield was decreased until 55% at 150°C.

The time of reaction was optimized 240 min where the reaction was completely finished with the highest yield (monitored by T. L. C), But by increasing the time up to 240 min the yield was decreased, it is probably due to increasing the side products (Appearance several spot as checked by T. L. C), the results are summarized in Table 4:

Table 4. Effect of the time on esterification reaction of phenyl acetic acid.

| Entry | Time (min.) | Yield (%) |
|-------|-------------|-----------|
| 1 | 30 | 20 |
| 2 | 60 | 30 |
| 3 | 120 | 45 |
| 4 | 150 | 68 |
| 5 | 200 | 75 |
| 6 | 240 | 80 |
| 7 | 280 | 72 |

The effect of several solvent on the yield of phenyl acetic esters was studied. As indicated in the previous three tables (table 2, 3, 4), the yield was found to be significantly higher in solvent-free conditions. but we use extra amount of reacted alcohol. 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 [27].

Table 5. Effect of solvent on esterification reaction of phenyl acetic acid.

| Entry | Solvents | Yield (%) |
|-------|--------------------|-----------|
| 1 | Toluene | 55 |
| 2 | dimethyl sulfoxide | 30 |
| 3 | H ₂ O | 20 |
| 4 | - | 80 |

Several acidic catalysts were examined to compare them with Amberlyst -15 (Table 6). When using homogenous catalysts, the yield will be very low (Table 6, entries 1, 3, 4, 9). In other hand, when the Silic catalysts were used (Table 6, entries 2, 6), and enzymic catalyst (Table 6, entry 7) 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 6, entry 5) 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 6. Effect of type of catalyst on esterification reaction of phenyl acetic acid.

| Entry | Catalyst | Yield (%) |
|-------|-------------------------------------|-----------|
| 1 | H ₂ SO ₄ | 30 |
| 2 | SiO ₂ -SO ₃ H | 30 |
| 3 | CH ₃ -SO ₃ H | 45 |
| 4 | p-TSA | 50 |
| 5 | Amberlyst-15 | 80 |
| 6 | Zeolites | 25 |
| 7 | Novozym® 435 | 50 |
| 8 | A.C* | 40 |
| 9 | CH ₃ COOH | 33 |

A.C*: active carbon that activated by the sulfonic acid, and the efficiency of sulfonic groups was measured by the reverse calibration and was effective (0.0113 gr/mole).

The best result was achieved by caring out the reaction of phenyl acetic acid and hydroxylated derivatives in the presence of 10% of Amberlyst-15 at 110C° under solvent-free conditions and the product was obtained in very high yields 80%.

To our delight, Amberlyst-15 was successfully recycled at least 5 times without apparent decrease of activity and selectivity giving a yield at every cycle nearly 80%. After 5 cycles, the color of the Amberlyst-15 changed which is presumably due to the partial deposit of carbonaceous

materials but it does not impact the recyclability of Amberlyst 15.

6. Conclusion

In summary, there are developed a green method which has been mediated heterogeneous catalyst to synthesis of substituted to produce phenyl acetic acid esters via esterification reaction, the reaction time was around 240 min and yielded about (80%) using Amberlyst-15 as a green catalyst under solvent-free conditions. Moreover the low cost of the catalyst comparison with other traditional catalysts such as homogeneous catalysts by Re-used several times, also low toxicity of catalyst and simple experimental procedure, recyclability of the catalyst and high yields of the products are the advantages.

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