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Research Article

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Fischer Esterification of Glycerol by Phenylacetic Acids, Phenylacetic Anhydrides and Some of their Aromatic Derivatives

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ABSTRACT

In this research, the mono esters of glycerol have been synthesized by two methods :direct esterification at glycerol by phenylacetic acids in mediate of Amberlyst-15,10% mol and the other method base on transferring the acyl group from the phenylacetic anhydride to glycerol in mediate of acyl transfer agents and basic median of pyridine. The ester has been synthesized from anhydrides is more efficient than one from the carboxylic acid. The pKa of the Prepared esters have been determined and compared with the pKa of acids that used as starting materials.

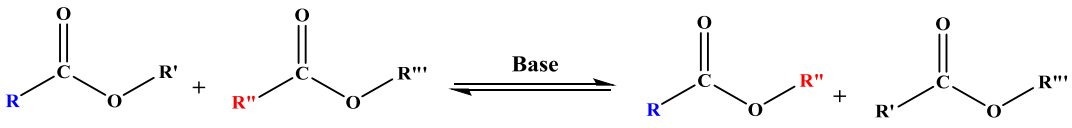
Keywords: Esterification; Glycerol; Phenylacetic anhydrides; Phenylacetic acids; Amberlyst-15

INTRODUCTION

Since the carboxylic acid drugs have bad effects at digestive system so our thought was to protect carboxylic group with conversion it to ester group that in body there is Lipase enzyme which can disseuated the ester to carboxylic acid and alcohol [1,2].

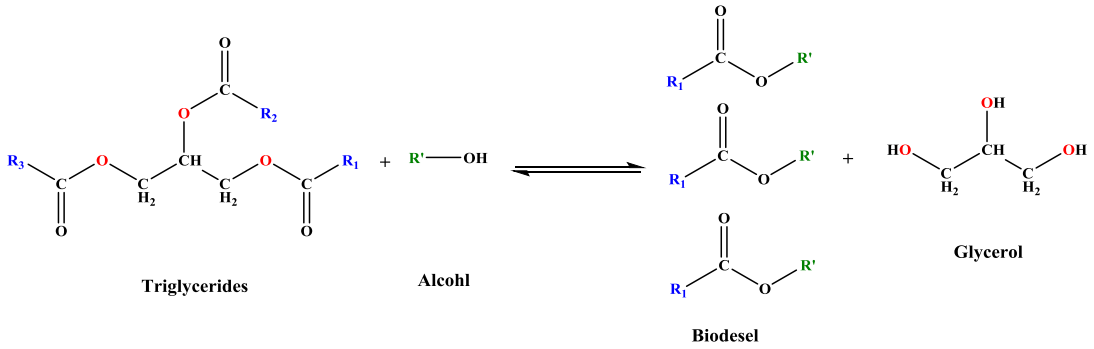
Esterification of carboxylic acids by alcohols has been classified as one of the most important reactions [3] due to the wide utility of esters in organic, bioorganic, medicine, pharmaceutical and food industries [4-6].

Many reactions and methods have been reported to synthesize a wide range of different esters [7] including undirect esterification reactions by two types: cross esterification that called also Ester- Ester exchange is the reaction between two esters where the exchange acyl group was accrued, between tri-ester with another tri-ester either between tri-ester with mono or di ester Scheme (1) that reaction is done by enzymatic or basic catalysts [8,9].



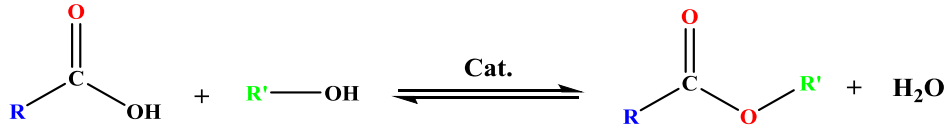
Scheme (1). Cross esterification, ester-ester exchange

The trans esterification is an ester reaction (often a tri-ester) with alcohol like methanol or ethanol, Where the reaction results are mono and di ester addition to the alcohol, trans esterification is one of the most important industrial reactions to the synthesis of bio-diesel (bio-fuels) [10,11] Scheme (2).



Scheme (2). Trans esterification

The direct esterification (fisher esterification): is condensation reaction between acid and alcohol Scheme (3) which is one of the most common and importance reactions for esters synthesis [12].



Scheme (3). Fisher esterification

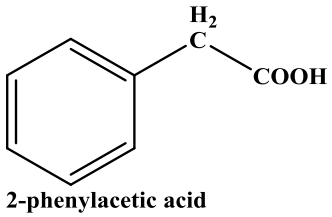
Esters can also be made from other carboxylic acid derivatives specially Acyl Halides and Acid Anhydrides are often called acyl transfer agents because they move the acyl group to the alcohol. Acyl transferring reactions are biologically interesting that:

• Protein Synthesis occurs by an acyl transfer reaction.

• Coenzyme A thio-esters participate in metabolic reactions by acyl transfer reactions

• Acyl-transfer reactions are among the most fundamental reactions in organic chemistry and biochemistry considering their importance in biochemical and synthetic processes, these reactions have been widely studied both in solution and in the gas phase [13-15]

On the other hand, esters of glycerol have great importance since Glycerol esterification were studied with many aliphatic and aromatic carboxylic acids including phenylacetic acid and its aromatic derivatives [16,17]. Phenylacetic acid is one of important organic chemical materials, which is widely used in the field of medicine, pesticide and aromatize [18]. Phenylacetic acid, it's alkaline and esters derivatives have antioxidant properties [19]. Phenyl acetic acid (Figure 1) 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. also Phenyl acetic acid has extensive range of biological activity and Structure-Activity Relations of PAAs were studied for the anti-inflammatory and analgesic actions. Similarly, several derivatives of phenyl acetic acids have been found to have promising biological activities [20-23].



2-phenylacetic acid

Chemical Formula: $C_8H_8O_2$, Molecular Weight: 136.15
Exact Mass: 136.05, m/z: 136.05 (100.0%), 137.06 (8.7%)
Elemental Analysis: C, 70.58; H, 5.92; O, 23.50

Figure 1. 2-phenylacetic acid

EXPERIMENTAL

Apparatus

Spectra NMR proton and carbon device 400 MHz model Bruker by Switzerland company, spectrum infrared device model FT-IR-4100 from the Japanese company Jasco, Digital pH Meter.

Reagents and Materials

All chemical material and catalysts, from Sigma Aldrich and Merck.

Experimental Procedure

Direct esterification: Reaction mixture of glycerol and acid with an interactive ratio 10:1 have been put in100 mL one neck glass flask in oil bath equipped with a magnetic stirrer and a reflex as shown in Figure 2. After the acid has been completly dissolved, the heterogeneous acid catalyst Amberst-15 has been added for 10% mole. The reaction process has been monitored by the thin layer chromatography T.L.C mobile phase n-hexane: ethyl acetate (6:4). The reaction ran 6 hours at 110° C then the catalyst has been removed by filtration. Removing the non-reactivated glycerol has been done by wash with brine. The product extract by ethyl acetate: water then the extracts has been dried over anhydrous Na2SO4. After removal of the solvent, the residue was purified by column chromatography that the eluent: n-hexan: ethylacetate to give desired ester and defined its proprieties

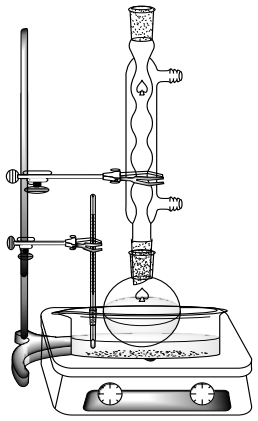


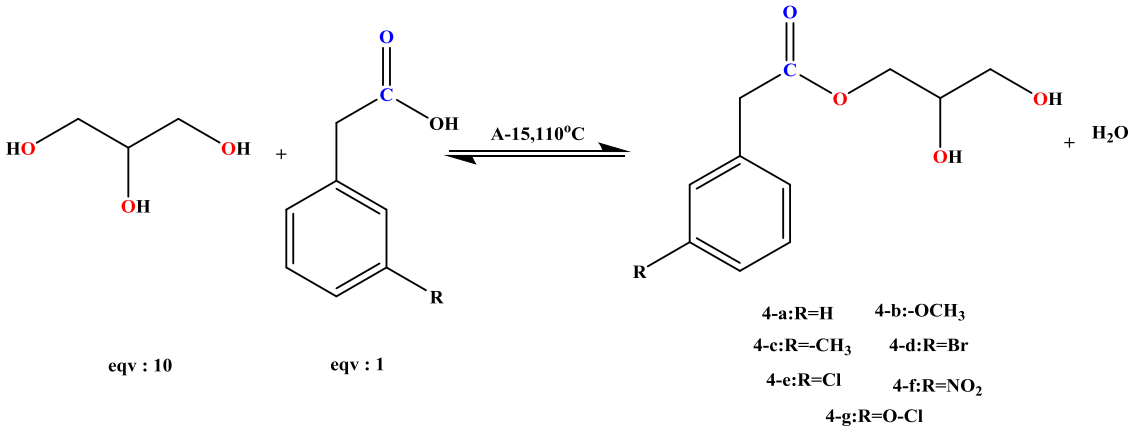
Figure 2. Box reactor for synthesis mono ester

Acyl transfer: The reaction mixture acid anhydride: glycerol has been prepared then adds to the reaction buffer equipped with a magnetic engine by an interactive ratio 1: 1 and then adds pyridine solution gradually by 5% mole. The reaction ran for 5 hours at 110 ° C then has been cooled to room temperature. The acidic aqueous solution has been added with a few drops of concentrated hydro chloride acid. The washing by the acidic solution has been done for three times. The product has been extracted from the ethyl acetate then has been purified by the column chromatography, and the eluent that used was n-Hexane: ethyl acetate.

RESULTS AND DISCUSSION

Esterification normally is a process used for preparation the esters by direct reaction between carboxylic acids and alcohols in presence of an acid catalytic. But Esters can also be made from acyl halides and acid anhydrides by reacting them with an appropriate alcohol in the presence of weak base.

In this work we have reported a conversion of glycerol to its corresponding esters with high selectivity. Two methods have been developed by us for its accomplishment, first: direct esterification "fisher esterification": in this type of reactions, glycerol reacts with one of phenylacetic acids. Since phenylacetic acid has been used as the substrate for esterification so it has reacted smoothly with glycerol in presence of Amberlst-15 as a catalytic scheme (4) in free condition of solvents that Glycerol has acted tow roles: reactive substance and solven.



Scheme (4). Direct esterification of glycerol and phenyl acetic acid

Several aromatic derivatives of phenylacetic acid that contained a replacement at the ortho or para positions of aromatic cycle have been used to synthesize mono esters of glycerol by fisher direct esterification in presence of Amberlyst-15 as a catalyst and obtained the results shown in the Table 1, where the highest yield has been reported by the methoxy group

Antioxidant power of *Catharanthus roseus*

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

Entry	**R**	Y%	**the appearance color**,
.1	H	65	Transparent oil
.2	$-OCH_3$	79	Pale yellow
.3	$-CH_3$	70	White
.4	Br	60	Transparent
.5	Cl	62	Pale yellow
.6	NO_2	55	Dark reddish yellow
.7	O-Cl	60	Light yellow

Esterification is a reversible reaction so removal of water shifts the equilibrium to the right and this is an endergonic (endothermic) reversible reaction with a high activation energy barrier in the absence of a catalyst. The reaction can be shifted to formation the ester by conducting the reaction under the vacuum distillation, as shown **(**Figure 3) where the ester is distilled in the beginning. This method has been proved to be a good effect in accelerating the formation of esters in high purity, but the amount of ester was little and did not improve the yield in the event of reaction without vacuum distillation

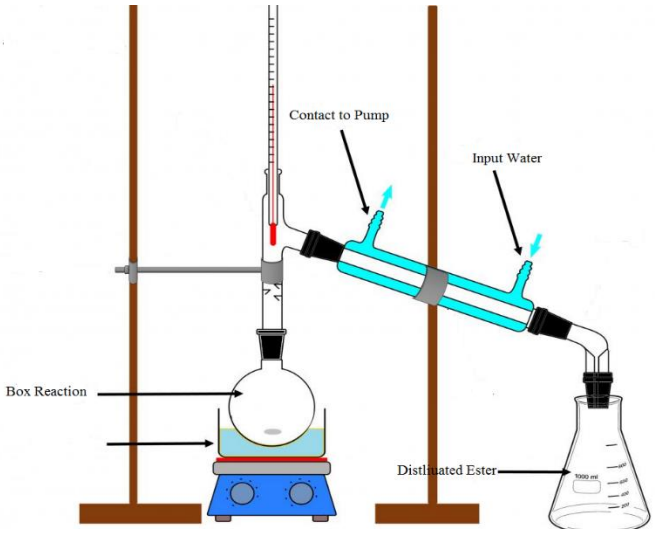
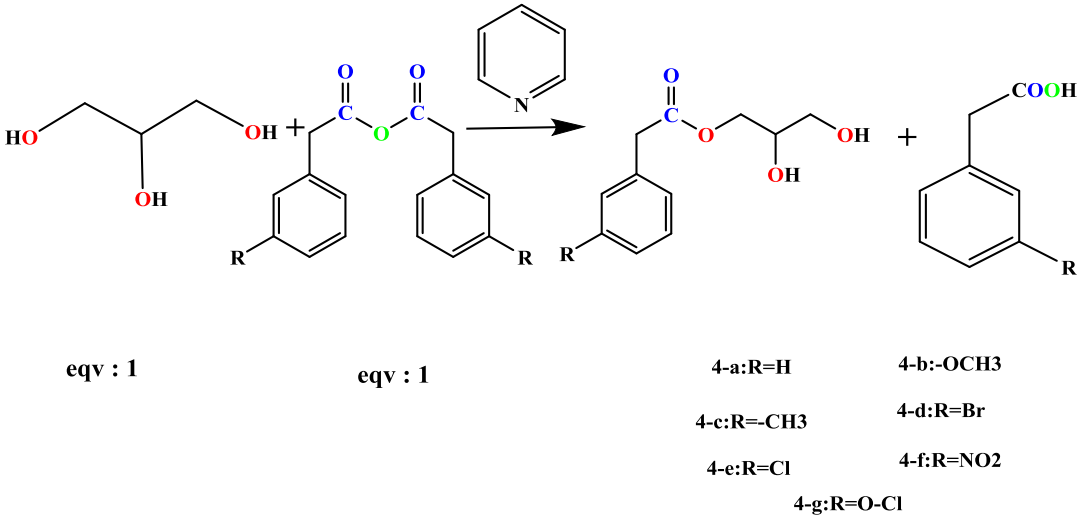


Figure 3. Box reactor vacuum distillation

Acyl transfer: where esterification has occured between glycerol and acid anhydride. Since the direct esterification is a reversible reaction so often a large amount of unreacted starting material remains. Therefore, using acid anhydrides as substrates instead of the acid itself made the reaction nonreversible. The esters can be made from acid Anhydrides scheme (5) by reacting them with glycerol in the presence of pyridine as catalysis.



Scheme (5). Phenyl acetic acid anhydride Acyl transfer reaction

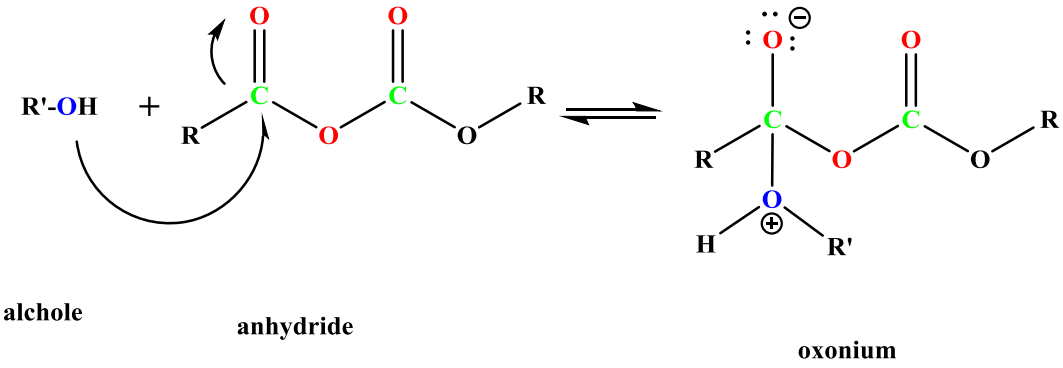
Ester synthesis from anhydrides is more efficient than the esters that from the carboxylic acid itself [24]. The results obtained are shown in Table 2.

Table 2. Phenyl acetic acid anhydride Acyl transfer esterification in pyridine

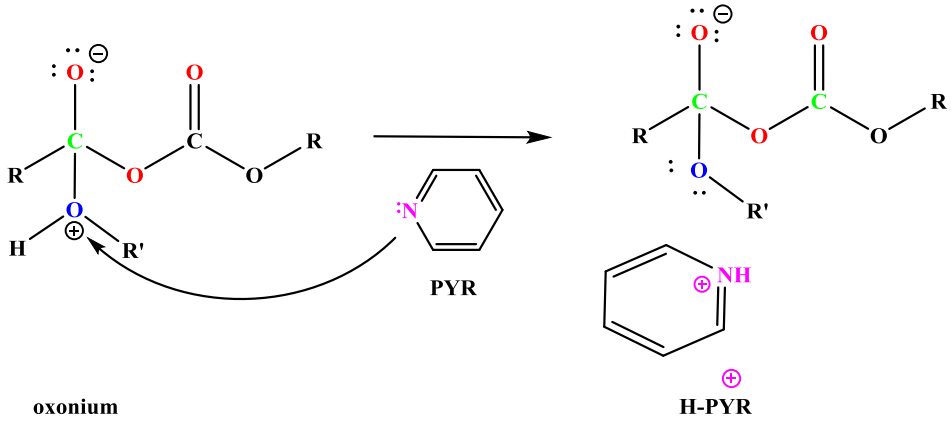
Entry	1	2	3	4	5	6	7
R	H	$-OCH_3$	$-CH_3$	Br	Cl	NO_2	O-Cl
Y%	75	90	80	65	65	60	69

The mechanism of acyl transfer reaction is done in four steps can be represented as follows: as scheme (6)

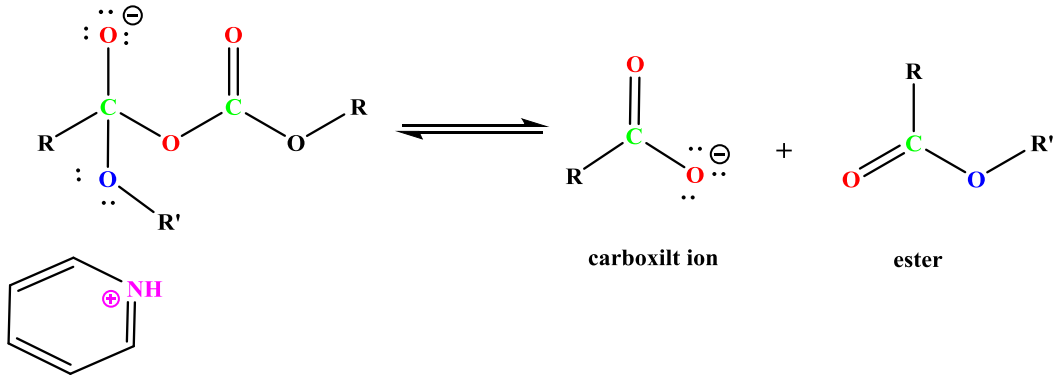
Step 1: Nucleophil1c Attacked by the alcohol:



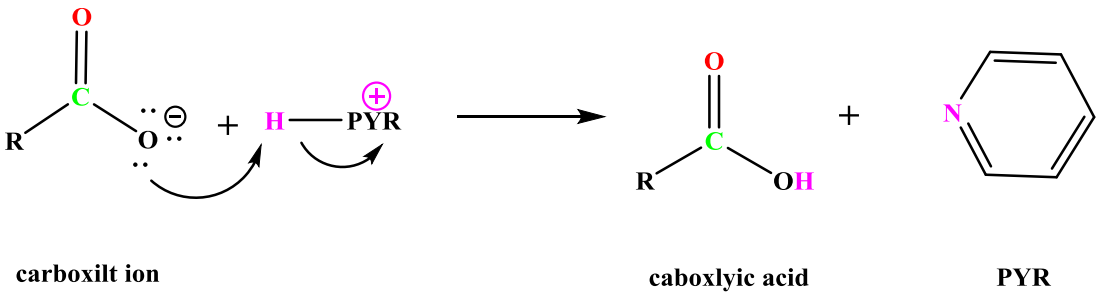
Step 2: Deprotonating by Pyridine:



Step 3: Leaving group removal:



Step 4: Protonating the carboxylate:



Scheme (6). Mechanism of acyl transfer reaction

After the previous esters were synthesized, the acidity value of the prepared esters has been determined and compared with the starting materials (the acid). On other hand the acidity value has been compared with the values of the theoretical constants obtained through the chemical drawing program (chem draw). Table 3 shows a correlation between theoretical and experimental values, as we know that esters have a lower acidity than acidity approval.

Table 3. pKa values of syntheses esters and acids

Entery	pKa, theoretically	pKa, Experimental
Phenyl acetic acid	4.281	-----
H	17.708 ,13.373	14.7
P-toyl acid	4.313	----
CH_3	13.374,17.708	15.3
p-methoxyphenyl acetic acid	4.332	-----
$-OCH_3$	13.377 ,17.710	15
p-bromo phenyl acetic acid	4.182	----
Br	13.373 ,17.708	15.6
p-chloro phenyl acetic acid	4.028	------
Cl	13.372 ,17.708	14.9
o- chloro phenyl acetic acid	4.181	------
O-Cl	13.341 17.703	14.4
p-nithro phenyl acetic acid	3.970	-----
NO_2	13.368 17.706	16,2

CHARECTARIZATION

2,3-dihydroxypropyl 2-phenylacetate
(80%) was obtained as colorless oil. FT-IR, (KBr,v,cm^{-1}) : 1260cm^{-1}: (C-O-C),1732cm^{-1}:(C=O, ester) 3416 cm^{-1}:(OH), 2952 cm^{-1}: (C_{SP2}-H,$_{stretch}$).
^{1}H-NMR:(400MHz,DMSO,TMS=0ppm,δ,ppm):7.19-7.2(m,5H),3.32-3.37 (dd, 2H, J^2=11,J^3=5.71Hz), 3.65-3.69 (m,1H) ,3.923.96 (dd,1H,J^2=11.1,J^3=6.5Hz) (diastereotopic protons), 4.05-4.09 (dd,1H,J^2=11.2,J^3=6.5Hz), 3.63 (S,2H),^{13}C-
NMR:(100.6MHz,DMSO,TMS=0ppm,δ,ppm):63.4:CH_2,70:CH,66.8:CH_2,171:C=O,40:CH_2,134.39:C,Ar,(126.75, 129.32, 128.29):CH,Ar

2,3-dihydroxypropyl 2-(4-methoxyphenyl)acetate
75%, oil product

FT-IR,(KBr,v,cm^{-1}):1225 cm^{-1}:(C-O-C),1734 cm^{-1}:(C=O ,ester),3396cm^{-1}:(OH),1441 cm^{-1}:($CH_{2\ Bent}$),2945 cm^{-1}:($CH_{2\ stretch}$) ^{1}H-NMR:(400MHz,DMSO,TMS=0ppm,δ, ppm): 4.07-4.09, (dd,2H,J^2=5.6,J^3=2.5Hz) 3.88-3.92 (m,1H),4.22-4.3 (d,2H,J=8.1Hz) , 3.55(S,2H) , 3.73 (S,3H),7.12-7.14(d,2H, J=7.2Hz),6.79-6.81(d,2H, J=7.2Hz) . ^{13}C-NMR:(100.6MHz, DMSO,TMS=0ppm,δ,ppm):63.86:CH_2,73.76:CH,67.57 : CH_2,171.96: C=O ,39.9: CH_2, 55.7: CH_3,(127,158.9):C,Ar (131.3, 114.68):CH,Ar.

2,3-dihydroxypropyl 2-(p-tolyl)acetate
70%, solid product, mp=44-45^{o}C
FT-IR,(KBr,v,cm^{-1}):1254cm^{-1}:(C-O-C),1729cm^{-1}:(C=O,ester),1343 cm^{-1}: ($CH_{3,Vibration}$),3400cm^{-1}:(OH),1410 cm^{-1}:(CH_2, bent),:2931 cm^{-1}:($CH_{2,\ stretch}$) ^{1}H-NMR:(400MHz,$CDCl_3$,TMS=0ppm,δ,ppm):3.49-3.54(dd,1H,J^2=11.6,J^3 = 6.2Hz),3.61-3.62(d,1H,J=3.6Hz),3.82-3.92(m,1H),4.14-4.15(d,2H,J=5.6Hz), 5.63(S,2H), 2.35(S,3H),7.16-7.18(d,2H),7.13-7.15(d,2H,J=8.2Hz). ^{13}C-NMR:(100.6MHz, $CDCl_3$,TMS=0ppm,δ,ppm):63.33:CH_2,69.82:CH, 65.53:CH_2, C=O:172,20.9:CH_3,(129.37, 129.14,):CH,Ar,(130.60,136.91):C,Ar

2,3-dihydroxypropyl 2-(4-bromophenyl)acetate
Transparent,60%
FT-IR,(KBr,v,cm^{-1}):1250 cm^{-1}:(C-O-C),1734 cm^{-1}: (C=O),3424 cm^{-1} :(OH), 1488 cm^{-1}:(CH_2 bent), 2929 cm^{-1} :($CH_{2stretch}$)
^{1}H-NMR:(400MHz,DMSO,TMS=0ppm,δ,ppm):3.30-3.40:(dd,2H,J2=16Hz,J3=2.5Hz),3.64-3.67(m,1H),3.99-4.1 (dd,2H,J2=11.1Hz,J3=4.3Hz),3.68 (S,2H),7.25-7.39(m ,4H), ^{13}C-NMR:(100.6MHz,DMSO,TMS=0ppm,δ,ppm): 62:CH_2, 65:CH_2,71:CH, 44: CH_2,171:C=O,(127.6,130.7):CH,Ar,(127,132.8): C,Ar.

2,3-dihydroxypropyl 2-(4-chlorophenyl)acetate
Pale yellow, 62%
.FT-IR,(KBr,v,cm^{-1}:1249 cm^{-1}:(C-O-C),1737 cm^{-1}:(C=O),3419 cm^{-1}: (OH), 1492 cm^{-1}:(CH_{2-Bent}),2924 cm^{-1}:($CH_{2stretch}$).^{1}H-NMR:(400MHz,DMSO,TMS=0ppm,δ,ppm):3.32-3.37:(dd,2H,J^2=14Hz,J^3=4.1Hz),4.24(m,1H), 3.98-4.03 (dd,2H,J^2=12Hz,J^3=4.3Hz), 3.71(2H,S), 7.36-7.39(m,2H),7.25-7.32(m,2H),^{13}C-NMR:(100.6MHz,DMSO,TMS=0ppm,δ, ppm) :62:CH_2,70:CH,65:CH_2, 40:CH_2, (132):C,Ar ,(130.74,127.61):CH,Ar

2,3-dihydroxypropyl 2-(4-nitrophenyl)acetate
Dark reddish yellow, 55%
.FT-IR,(KBr,v,cm^{-1}):1449 cm^{-1}:(C-O-C),1732 cm^{-1}:(C=O),3423 cm^{-1}:(OH), 1452 cm^{-1}:($CH_{2\ Bent}$), 2946 cm^{-1}.(CH_2 stretch).
^{1}H-NMR:(400MHz,DMSO,TMS=0ppm,δ,ppm):3.93-3.95 (d,1H,J=6.8Hz), 3.96-3.98 (d,1H,J=6.5Hz), 4.11-4.6(m,1H), 4.07-4.08 (d,1H,J=4.2Hz), 4.10-4.11(d,1H,J=4.2Hz), 3.68(S,2H), 7.19-7.35(m, 4H)
^{13}C-NMR:(100.6MHz, DMSO,TMS=0ppm,δ,ppm):62:CH_2,68.69:CH,65.45: CH_2,1700.71:C=O,39: CH_2,(128.53,126.46):CH,Ar,(133.58 ,142.32): C,Ar.

2,3-dihydroxypropyl 2-(2-chlorophenyl)acetate
Light yellow, 60%
FT-IR,(KBr,v,cm^{-1}):1242 cm^{-1}:(C-O-C),1735 cm^{-1}:(C=O),3449 cm^{-1}:(OH),
1436 cm^{-1}:(CH_2-$_{Bent}$),2926cm^{-1}:($CH_{2\text{-}strtch}$).
^{1}H-NMR:(400MHz,$CDCl_3$,TMS=0ppm,δ,ppm):3.51-5.55 (dd,2H,J=11.6Hz), 3.62-3.66(dd,2H,J=11.6Hz),3.96-4.19(m,1H) , 4.18-4.19(dd,2H,J=55.1Hz), 3.82(S,2H),7.38-7.40(m,1H),7.26(dd,1H,J=3.1Hz),7.24(m,1H),7.28-7.30:(m,2H),^{13}C NMR:(100.6MHz,$CDCl_3$,TMS=0ppm,δ,ppm):6 :CH_2, 70:CH,65:CH_2,171:C=O,38.78:CH_2,(134.47,132.07):C,Ar,(131.55,129.55,128.95, 127.02):CH,Ar.

CONCLUSION

Mono esters of glycerol were synthesized from phenyl acetic acid and some of its aromatic derivatives using amberlyst 15 as catalysts10% mol. These esters were synthesized from anhydride phenyl acetic acid using pyridine 5% as a catalyst. The use of anhydride was more effective in producing this type of esters On the other hand, it is possible to accelerate the synthesis of esters from their acids to approve by contact of the reaction vessel with a distillation device under the diluted pressure, and was made sure that the pKa of esters prepared less compared with the acids used as starting materials.

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