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Мохамед Дарвиш Ораби
Магистрант кафедры органической химии
Колледж Науки
Хомс Сирия
Джума Мирза
Фармацевтический факультет
Арабский университет науки и техники
Варда Халил
Врач кафедры органической химии
Колледж Науки
Хомс Сирия
Гадир Аль - Хасан
Врач кафедры органической химии
Колледж Науки
Хомс Сирия
Алахмад Али
Аспирант в кафедре твёрдого тела
Нижегородский государственный университет
Россия, Нижний Новгород

SYNTHESIS OF NEW TWO ESTERS FROM KETOPROFEN WITH PROPAN-1,2-DIOL AND BUTANE - 1,3 DIOL

Annotation: *In this paper two new esters: 2-hydroxypropyl 2-(3-benzoylphenyl)propanoate (1) and 3-hydroxybutyl 2-(3-benzoylphenyl) propanoate (2) have been synthesized by fisher esterification reaction between butane - 1,3 diol or propan -1,2 diol and ketoprofen (1,2)، in the present: The optimal condition (catalysts and solvents) to get a high selective compounds and high yields have been studied. When use of heterogeneous catalyst (Amberlyst-15) and excess of propan-1,2-diol*

(eight time) which plays as a reactive and solvent getting a required selectivity and high yield in comparison to the homogeneous catalysts (H2SO4, CH3SO3H), in addition to the low selectivity of the final product.The reaction followed by thin layer chromatography (TLC). The structures have been determinade by spectroscopy methods: FT- IR, ^{1}H-NMR, ^{13}C-NMR.

Key words: *Пропан 1-2 диол, бутан 1-3 диол, реакция этерификации, амберлист-15, кетопрофен.*

СИНТЕЗ НОВЫХ ДВУХ ЭФИРОВ ИЗ КЕТОПРОФЕНА С ПРОПАН-1,2-ДИОЛОМ И БУТАНОМ - 1,3-ДИОЛОМ

Аннотация: *В этой статье два новых эфира: 2-гидроксипропил 2- (3-бензоилфенил) пропаноат (1) и 3-гидроксибутил 2- (3-бензоилфенил) пропаноат (2) были синтезированы реакцией этерификации Фишера между бутаном - 1,3-диолом или пропан -1,2 диол и кетопрофен (1,2) ‹в настоящем: оптимальные условия (катализаторы и растворители) для получения высокоселективных соединений и высоких выходов были изучены. При использовании гетерогенного катализатора (Amberlyst-15) и избытка пропан-1,2-диола (восемь раз), который играет роль реактива и растворителя, получая требуемую селективность и высокий выход по сравнению с гомогенными катализаторами (H2SO4, CH3SO3H), В дополнение к низкой селективности конечного продукта. Реакция сопровождается тонкослойной хроматографией (ТСХ). Структуры были определены методами спектроскопии: ИК-Фурье, 1H-ЯМР, 13C-ЯМР.*

Ключевые слова: *пропан 1-2 диола, путан 1-3 диола, реакция этерификации, Амберлист-15, кетопрофен.*

1. Introduction:

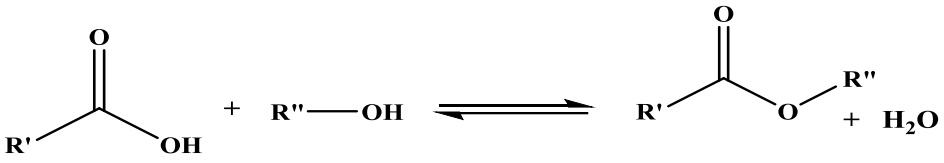
NSAIDs medicines are used as sedatives and in the treatment of acute Gouty arthritis (1),all kinds of cancer (colon, stomach) besides, heart diseases and capillaries,

diabetes, central and peripheral nervous system diseases, pain killers and antipyretics (2).

One of the important methods and effective machanisms followed to obtain prodrugs from non-steroidal anti inflammation is the mono-esters from them. They notably reduce the ulcerative side effects of some of these strong medical compositions. Thus the derivatives of papacetamol are made with aspirin to obtain the prodrugs (3), different alpha and aromatic derivatives of Indomethacin (4).

Ester derivatives were prepared for Indomethacin with methyl and trimethylsilyl (5). The preparation of these esters was studied by using various methods and catalyzers (6). where there was a synthesis of anti-oxidant esters that are non-steroidal anti-inflammatory especially the derivatives of indomethacin. They showed a synergistic effect and new use for the disappearance of carboxyl group in it (7,8,9).

The process of transforming NSAIDs to esters and amides to form COX-2 inhibitors is an easy and limited way because the ketoprofen esters and some of their amides are endured in the biological tissues (10). Therefore, the esterification of carboxyl acids (especially the medical ones) are considered the most important practical applications in protecting carboxyl group in medicine(e.g. ketoprofen). The side-effects of carboxyl acids mitigated on the stomach (11) and esterification of carboxyl groups takes place according to fischer interaction by using an acidic or basic media (12).



Scheme 1. General Interaction of Fischer Esterification.

Ketoprofen is one of the aromatic derivatives of Propanoic acid (13), which is used largely as one of the most important non-steroidal anti-inflammatory (NSAIDs) because of its antipyretic effect and its anti-inflammatory against arthritis, joints, inflammation and pain in muscles.

2. Experimental:

2.1. Apparatus

spectrum NMR proton and device 400 MHz model Bruker by Switzerland company, optical absorption spectrum infrared device model FT-IR-4100 from the Japanese company Jasco, rotary evaporator 4.91 model from the German company Normschiff, thin layer chromatographic of aluminum coated by Silica Gel 60F254 measuring 20 X 20 from the German company Merck, thin layer chromatographic of preparatory glass coated by Silica Gel 60F254 measuring 20 X 20 from the German company Merck.

2.2. Reagents and materials

Ketoprofen,Propan-1,2-diol,Butan-1,3-diol, and Amberlyst-15 (99% by sigma aldrech), Methan Selfonic Acid, Sulforic Acid and some Solvents (99% by Merck).

2.3 . Experimental Procedure

We added different molar ratios of Propan-1,2-diol to Ketoprofen acid (4:1, 6:1, 8:1, 10:1, 14:1) and different solvents (toluene, dimethylsulfoxed) and solventless by excess of Propan-1,2-diol into a tow-necked flask equipped with a thermometer thorn fractionating column, using dean-stark trap (figure-2) and cooler reflex.

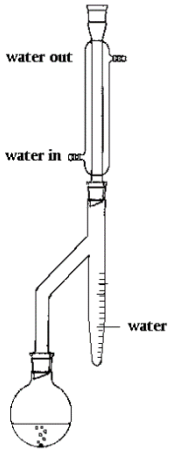
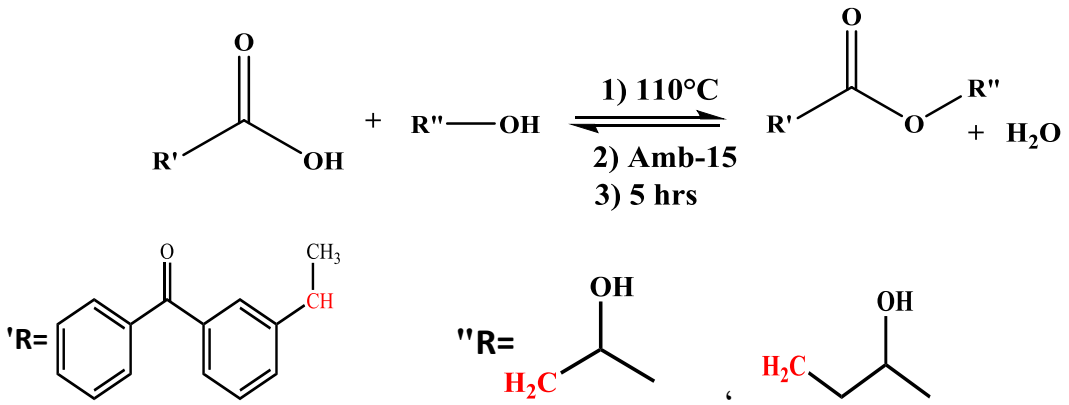


Figure 1. dean-stark trap using by fisher reterification reaction to remove of water.

Different kinds of catalysts (sulforic acid, methane sulfonic acid, and amberlyst-15) were added, respectively, to a tow-necked flask equipped with athermometer thorn fractionating column, using dean-stark trap and cooler reflex, we then added Ketoprofen,Propan-1,2-diol, and catalyst (the best molar ratio of Propan-1,2-diol to

Ketoprofen Acid is 8:1, solvent less and catalyst is amberlyst-15). All of these reactions were performed at about 110C° under stirring and reflowing. After the optimum conditions obtained, we used different Alcohols to synthesized α-mono ester like Propan-1,2-diol,Butan-1,3-diol.

3. Results and Discussion:



Scheme 2. Synthesis route of the main reaction.

Table 1. different alcohols to the Product.

Entry	Alcohols	Products
1	Propan-1,2-diol	2-hydroxypropyl 2-(3-benzoylphenyl)propanoate
2	Butan-1,3-diol	and 3-hydroxybutyl 2-(3-benzoylphenyl)propanoate

The optimal conditions for preparations of α-Mono ester Medicinal acids(α-MHPK), by esterification of Propan-1,2-diol and Ketoprofen Acid to produceα-Mono ester Medicinal acids. The catalytic effects of several catalytic systems were inspected in the esterification of Propan-1,2-diol with Ketoprofen Acid, these catalytic systems included sulfuric acid, methane sulfonic acid, and amberlyst-15 as shown in table(2), Entry(3) sulfuric acid did a remarkably bad job on this reaction in reverse, while methanesulfonic acid and amberlyst-15 had good catalytic activities. However, it was easy to remove amberlyst-15 after the reaction, because it was a heterogeneous catalyst. There for, amberlyst-15 was determined to be optimal catalyst for the esterification of

the Medicinal acids. The several acidic catalysts homo and heterogeneous has used table (2):

Table 2. effect of different catalysts to the Product yield% (α-MHPK).

Entry	H_2SO_4	CH_3SO_3H	Amberlyst-15	Time (hour)
1	17	22	11	2
2	28	41	24	3
3	**42**	52	38	4
4	33	**64**	49	5
5	30	59	**66**	6
6	27	53	61	7
7	24	48	55	8

Another table showed that the best one has a "heterogeneous acid catalyst" for Amberlyst-15 and the best time (5 hours), because after the formation of Di esters, the α-MHPK yield will therefore decrease. It appears when using other catalysts "H2SO4, CH3SO3H". In addition to an environmental perspective, the best acid catalyst was Amberlyst-15, because it was a heterogeneous acid catalyst table: it was easy to use once again after activating it.

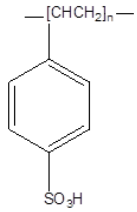


Figure 2. Catalytic formula (amberlyst-15).

Note the specific effects of the different molar quantity of the catalyst on yields when determining the amount of catalyst table (3).

Table 3. effect of different amount of catalyst (amberlyst-15).

Entry	amount of catalyst %mol	% yield
1	-------	12
2	5	63
3	10	**66**
4	20	55
5	40	38

So we conclude that when using large amounts of heterogeneous catalyst "Amberlyst-15" do not affect to the preparation α-MHPK, so from an economic perspective preferrcd using the least possible result.

After that the esterification reaction between Propan-1,2-diol and Ketoprofen acid with different solvents had been studied as shown table (4).

Table 4. effect of different solvents.

Entry	Solvent	% yield
1	Toluene	45
2	Dimethylsulfoxid	38
3	**Excess of Propan-1,2-diol**	**66**

Different solvents used to studying effects to the yield reaction. However, toluene was bad to the yield reaction, because it had a boiling point as a temperature reaction, and dimethylsulfoxyd was bad to remove it after reaction. Beside using the excess of Propan-1,2-diol was the best choice (ropan-1,2-diol played a reactant and solvent simultaneously) because Propan-1,2-diol was a rectant in this reaction. So the effect of the different molar ratios (Propan-1,2-diol:Ketoprofen acid) to the yield reaction had also been studied.

Table 5. effect of different molar ratios to the esterification yield.

Entry	Molar ratio (alcohol:acid)	yield%
1	4:1	52
2	6:1	58
3	**8:1**	**66**
4	10:1	62
5	14:1	61

The table (5) shown that the best molar ratio between Propan-1,2-diol and Ketoprofen acid in entry:3.

We found that when using a molar ratio (8:1) of Propan-1,2-diol to Ketoprofen acid, the yield reaction was the best, it was noted that when using alow percentage of Propan-1,2-diol, the yield reaction has decreased. The reaction was a secondary products was formed "Di esters", besides when using a very surplus of Propan-1,2-diol was also the yield reaction decrease, becauce that a few amount of product (α-MHPK)

was formed, there fore we conclude depending previous studies that the best molar ratio of the esterification reaction was (8:1) (Propan-1,2-diol:Ketoprofen acid) and when using an Amberlyst-15 (10%mol), time reaction 6 hours, yield was the formation of reaction product (α-MHPK) about 66%.

FT-IR Results:

α-MHPK was also confirmed by infrared spectroscopy, as shown in Figure (3). Figure (3) shows α-MHPK spectra, a clear absorption peak at 1735 cm -1 belonging to the carbonyl group. Also, there were two absorption peaks of 1282 and 1179 cm -1, which were the characteristic absorption bands of C-O-C stretching in α-MHPK. Characteristic belong to 2928 and 1452 cm -1 for methylene groups. In 3430cm-1 peak absorption plate of -OH was also observed, there were several distinct absorption ranges of the Aromate group near 722 and -3087cm-1, so α-MHPK was successfully synthesized.

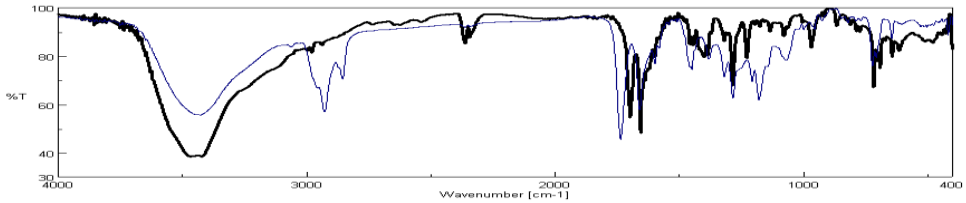


Figure 3. IR spectrum of α-MHPK (blue spectrum) and Ketoprofen acid (black spectrum).

1H-NMR Results: α-MHPK were further confirmed by 1H-NMR spectroscopy, as shown in figure (4).the spectrum corresponds to α-MHPK in figure (4), the characteristic peaks around 1 and 4.5ppm belonged to (1-5)H , respectively in the Propan-1,2-diol. The peaks around 6 and 7ppm represented aromate groups, and the other displacement of hydrogen was similar to that shown in figure (4). therefore, α-MHPK was successfully synthesized.

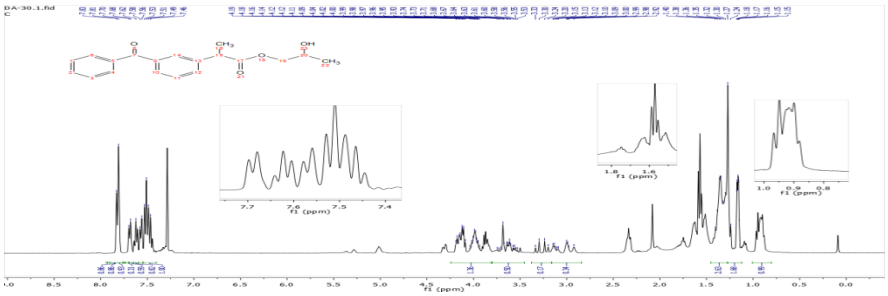


Figure 4. 1H-NMR spectrum of α-MHPK in CD3Cl.

FT-IR Results:

α-MHBK was also confirmed by infrared spectroscopy, as shown in Figure (5). Figure (5) shows α-MHBK spectra, a clear absorption peak at 1734 cm -1 belonging to the carbonyl group. Also, there were two absorption peaks of 1283 and 1137 cm -1, which were the characteristic absorption bands of C-O-C stretching in α-MHBK. Characteristic characteristics belong to 2927 and 1460 cm -1 for methylene groups. In 3441cm-1 peak absorption plate of -OH was also observed, there were several distinct absorption ranges of the Aromate group near 722 and 3062cm-1, so α-MHBK was successfully synthesized.

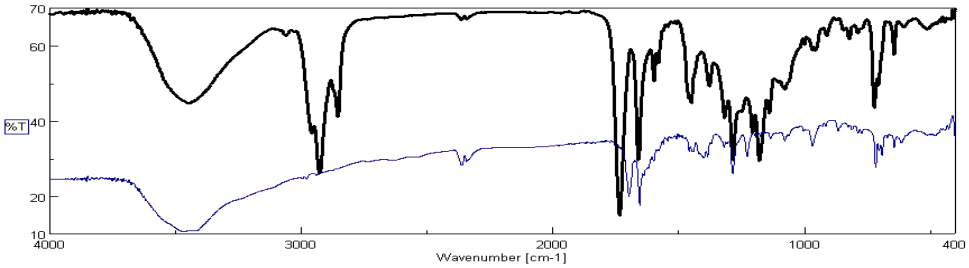


Figure 5. IR spectrum of α-MHBK (black spectrum) and Ketoprofen acid (blue spectrum).

1H-NMR Results: α-MHPK were further confirmed by 1H-NMR spectroscopy, as shown in figure (6).the spectrum corresponds to α-MHPK in figure (6), the characteristic peaks around 1 and 4.5ppm belonged to (1-6)H respectively in the Butan-1,3-diol. The peaks around 6 and 7ppm represented aromate groups, and the other displacement of hydrogen was similar to that shown in figure (6). therefore, α-MHPK was successfully synthesized.

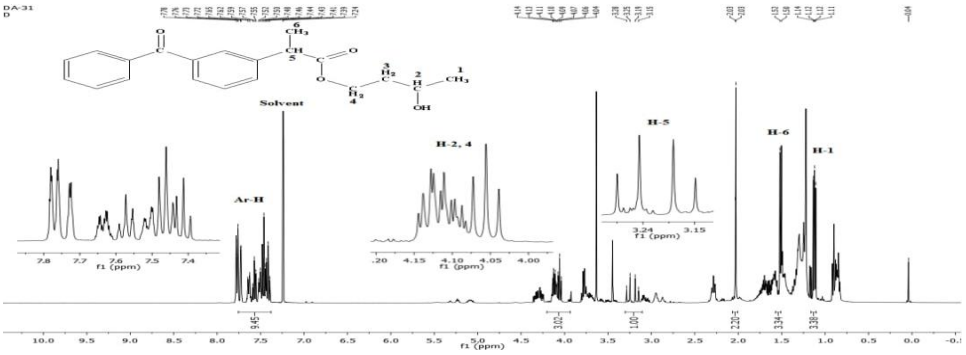
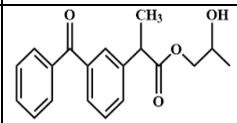
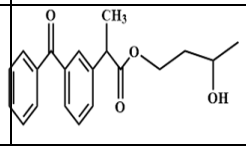


Figure 6. 1H-NMR spectrum of α-MHBK in CD3Cl.

Finally, when applying the previous conditions to prepare α-MHPK on the reaction of preparing some mono esters Medicinal acids , we had synthesized

successfully some of the mono esters Medicinal acids which had used in the many applications in Pharmaceutical Industries as shown in table(6).

Table 6. different products to the esterification.

Entry	Product	amount of catalyst (10%mol)	amount of acid	temperature	Time reaction	% yield
1		0.02021gr	0.254gr:0.001mol	110C°	5 hour	66
2		0.02021gr	0.254gr:0.001mol	110C°	5 hour	62

Antimicrobial Properties of NSAIDS(HPK and HBK):

The antimicrobial activity was reported in terms of the minimum inhibitory concentration (MIC) values, which are defined as the lowest concentration of an antimicrobial that visibly inhibits the growth of the bacteria after an overnight incubation.

Minimal inhibitory concentrations for each compound were investigated against Escherichia coli and coliform .

The test organism was laboratory strains used to test a range of concentration of two esters compounds for minimum inhibitory concentration determination . Antimicrobial activities determined by using agar dilution procedure and were tested with different concentrations of the compounds. The minimum inhibitory concentration (MIC) of synthesized HPK and HBK against Gram positive, Gram negative bacteria and fungus are summarized in Table 1. Gentomycin as standard drugs for comparison.

As shown in the table, antimicrobial activity against Escherichia coli was observed in the ligands their complexes tested at 50,100 µg/mL concentrations (Figure 7)

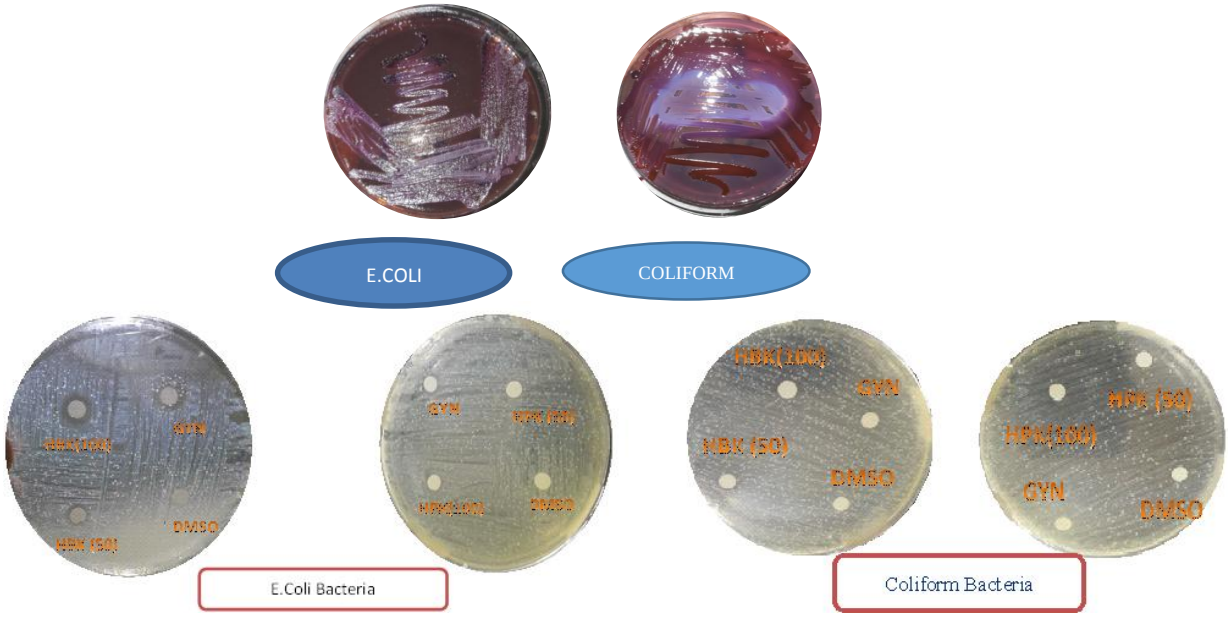


Figure 7. Antimicrobial activity against Escherichia coli was observed in tested at 50,100 µg/mL concentrations.

Table 7. Demonstrates the results of the biological study obtained for the prepared compounds.

	(C µg/ml)	Diameter inhibition (mm)	(C µg/ml)	Diameter inhibition (mm)	Diameter inhibition (mm) standard drugs
HBK E.COLI	100	6	50	4	7
HPK E.COLI	100	10	50	6	7
HBK COLIFORM	100	22	50	7	8
HPK COLIFORM	100	8	50	6	8

3. Conclusion:

In summary, the condition of organic esterification was successfully studied by synthesis of α-MHPK. When the molar ratio of Propan-1,2-diol to Ketoprofen acid was

(8:1), amberlyst-15 worked as a green catalyst, excess of Propan-1,2-diol used as a solvent "eight times", using dean stark-trap figure (2), for the removal of water, and the reaction time was around 5 hours, the esterification yielded about (66%). Under these conditions most of products table (6) was successfully synthesized, With little difference in the yields of interaction. The results proved that the optimum conditions to obtain high selective compounds with high yields (mono esters) by studying the affect of different catalysts and solvents have been investigated.

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