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THE SYNTHESIS OF (5-HYDROXY-5-(1-METHOXYPROPAN-2-YL) -4-METHYLFURAN-2(5H)-ONE, 5-(1-METHOXYPROPAN-2-YL) -4-METHYLFURAN-2(5H)-ONE) AND BIOLOGICAL ACTIVITY

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ABSTRACT

Butenolides are a class of lactones with a four carbon heterocyclic ring structure. They are sometimes considered as oxidized derivatives of furan. The simplest butenolide is 2-furanone, which is a common component of larger natural products and is sometimes referred to as simply "butenolide". A common biochemically important butenolide is ascorbic acid
(vitamin C).

The butenolide and their analogues represent a wide range of the natural compounds of medical and biological importance.

In the last decades, a great number of compounds of various structures, in general from Alkylidene butenolide were isolated and showed biological activities.

In this work we have studied the reactivity of some alkylidene butenolide and carried out their antibacterial activity.

Key words: Butenolides , addition 1,6 reagents organocuprates, biological activity.

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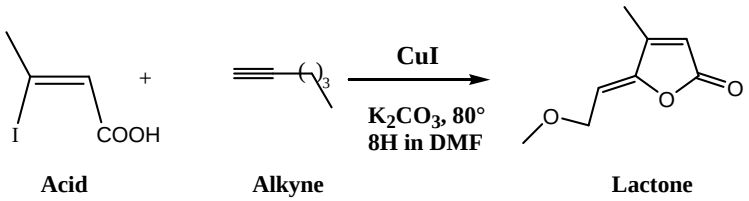
1. INTRODUCTION

In recent years there has been a great interest in preparing butenolides [1]containing compounds owing to the biological effect attributed to this class of natural products such as freelingyne, rubrolides, tetrenolin-furanosesquiterpenoid, Protoanemonin [2] . Among these bioactive compounds, there exist the alkylidenes butenolides, which have a large spectrum of biological activity[3-8].

2. EXPERIMENTAL SECTION

2.1. Preparation of Lactones

We have been interested in the preparation of some alkylidene butenolides using the method previously developed in our laboratory. In fact the method deals with the cycliztation of β-iodide-α,β-unsaturated acids using an alkyne with the presence of potassium carbonate and copper iodide , for this purpose we have used type of alkyne.



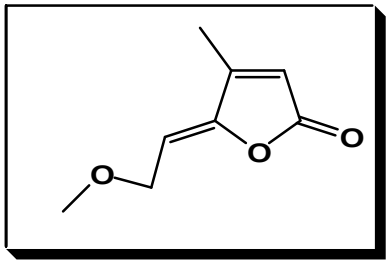
Acid **Alkyne** **Lactone**

We notice that very poor yields were obtained with (Z)-3-iodoacrylic acid, on the other side good yields were found with (Z)-3-iodobut-2-enoic acid. Hence we have opted to work on this acid.

Reactions with hexyne and octyne gave rise to two isomers: a furanone and a pyranone contrarily to the remaining akyne which gave only the corresponding furanone.

Under a nitrogen atmosphere the iodide acid was added to a stirred solution of calcium carbonate (2eq) in DMF, the resulting mixture was cooled down to –80°C for 10 minutes and then warmed up to room temperature, then the alkyne (1,5 eq) and the copper iodide (0.2 eq) were added respectively under nitrogen flux. After heating to 80°C and stirring overnight the solution was cooled to rt and quenched with saturated aqueous solution of NH_4Cl before being extracted three times with AcOEt. The combined organic layers were washed with saturated brine, dried over anhydrous $MgSO_4$ and then concentrated in vacuo. The residual oils were purified by flash

chromatography using an eluent system of petroleum ether/ether to give the corresponding lactones.



(Z)-5-(2-methoxyethylidene)-4-methylfuran-2 (5H)-one

RMN ^{1}H (300 MHz, $CDCl_3$)

δ=2.16(s, 3H), 3.39(s, 3H), 4.29(d, *J*=6.80 Hz, 2H), 5.41(t, *J*=6.80 Hz, 1H),5.98(s, 1H).

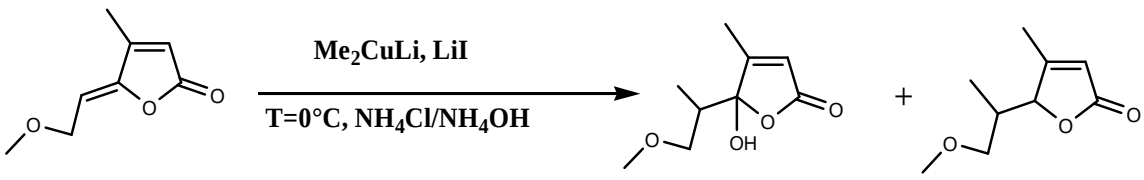
RMN ^{13}C (75 MHz, $CDCl_3$)

δ=12.16(1C), 58.96(1C), 66.87(1C), 108.30(1C), 117.81(1C), 150.63(1C), 154.74(1C), 169.48(1C).

2.2. Addition of cuprates

Once the lactones were in hand the next step consist of carrying out the cuprate addition using copper iodide.

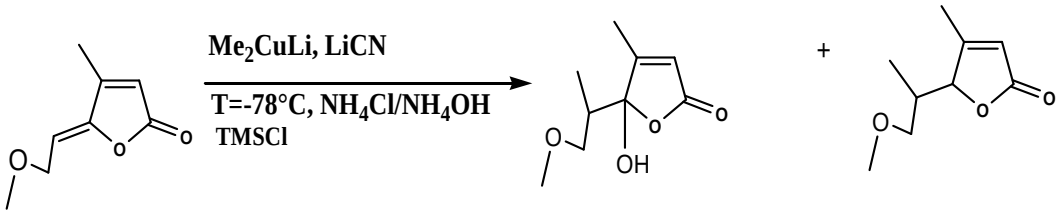
For the cuprate addition, the prescribed method is to add the mehyllithium on copper iodide in anhydrous ether at –5°C and then the lactone is added dropwise via canola before being quenched with NH_4Cl/NH_4OH (90/10) at 0°C and warmed till r.t, nevertheless this method reveals the presence of two isomers as shown blow



Butenolide 01 Butenolide 02

total yield 46%(74:46)

To improve the total output, the idea was to replace the copper iodide by other copper salts such as copper cyanide but there was almost no enhancement even by adding TMSCl as accelerator.



Butenolide 01 Butenolide 02

° **<50%**

2.3. Biological activity

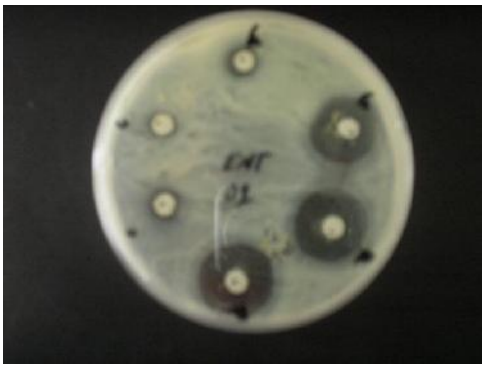
After the preparation of derivatives Alkylidene Butenolide, we went to see the biological characteristics, which can be carried by these chemical compounds.

Therefore, we studied the effect of these compounds on three types of bacteria harmful to human health, The bacteria used are; ***Proteus mirabilis, Enterobacter hafniae, Escherichia coli***, then we take three concentrations of each compound, the results recorded in the table1:

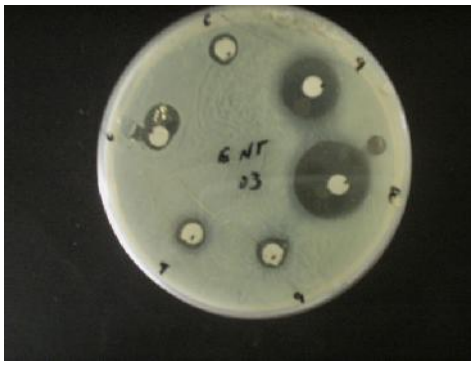
Table 1. Results of biological activity

Compound	Concentration (mmol/l)	Inhibition zone diameter(mm)		
		Escherichia coli	*Proteus mirabilis*	*Enterobacter hafniae*
Butenolide 01	**0.073**	**-**	**-**	**20**
	0.042	**-**	**-**	**18**
	0.015	**-**	**-**	**13**
Butenolide 02	**0.073**	**-**	**-**	**21**
	0.042	**-**	**-**	**10**
	0.015	**-**	**-**	**09**

- The following images show inhibition diameters for different concentrations of the compound:



A. B. of Butenolide 01



A. B. of Butenolide 02

Fig.1. shows the inhibition zone diameter for bacteria *Enterobacter hafniae*

3. GENERAL RESULT

Results obtained in the previous study, we can determine the sensitivity of various concentrations of each type of bacteria to each compound, table 2 illustrates this details.

Table 2. Sensitivity of the bacteria

Bacteria / Compounds	The degree of sensitivity of the bacteria		
	Enterobacter hafniae	*Proteus mirabilis*	*Escherichia coli*
Butenolide 01	**I**	-	-
Butenolide 02	**S**	-	-

4. CONCLUSION

According to the results obtained, we can determine the sensibility of each bacteria towards each compound.

The results presented in table 02 reveal that the compound *5-(1-methoxypropan-2-yl)-4-methylfuran-2(5H)-one* have inhibitory effect on one of the studied bacteria.

The goal of this work is to participate in the preparation of new derivative of butanilids and studying their antimicrobial activity against some kinds of bacteria.

According to the obtained resultants we can deduce:

-The derivative is obtained by adding organocupper reagent to butanolids at the position-1.6.

-The obtained butanolids from the addition-1.6 are new compounds.

-Most of the steps of reaction are simple and economic.

-The Chemical *compound 5-(1-methoxypropan-2-yl)-4-methylfuran-2(5H)-one* gave effective against type of bacteria; *Enterobacter hafniae.*

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