STUDY THE BEHAVIOUR OF SOME UNSATURATED KETOACIDS TOWARD SOME NUCLEOPHILES AND SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS WITH NON-MIXED AND MIXED SYSTEM WITH EXPECTED BIOLOGICAL ACTIVITY

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Moktar Almbrok Ali Aburzeza

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مختـــار المبـروك علـى ابورزيـزة

للحصول على درجة

دكتوراه الفلسفة فى الكيمياء

(كيمياء العضوية)

قسم الكيمياء - كلية العلوم

جامعة عين شمس

٢٠١٢

SUMMARY

4-(4-acetamidophenyl)-4-oxo-but-2-enoic acid has been reacted with nitrogen nucleophiles e.g., 2-aryl-5-amino thiadiazole, and barbituric acid, and yielded the aza Michael adducts.The aza Michael adductes ware converted to the corresponding pyridazinone derivatives via the interaction with hydrazine hydrate in boiling ethanol.Some of the pyridazinone derivative was converted to the corresponding O-acyclic nucleoside when submitted to react with ethylchloroacetate in the presenc of K_2CO_3 anhydroues in boiling acetone, and converted to the corresponding furanones and ketones on treatment with boiling acetic anhydride. When aza Michael adduct was allowed to react with hydroxylamine hydrochloride in boiling pyridine afforded the corresponding oximes followed by loss of carbon dioxide. Interaction of 4-(4-acetamido phenyl)-4-oxo-but-2-enoic acid with aromatic hydrocarbon namely, *m*-xylene and *p*-xylene under Friedel-Crafts condition yielded the corresponding butanoic acids, their behavior toward hydrazine hydrate, acetic- anhydride and hydroxylamine have been investigated. The behavior of pyridazinone derivatives produced from butanoic acid derivatives and hydrazine hydrate e.g., ethyl chloroacetate and acetyl chloride have been described. The reaction of 4-oxo-but-2-enoic acid with sulphur nucleophiles e.g., thiophenol and carbon nucleophilese.g., barbituric acid under thia Michael and Michael reaction conditions respectively yielded the corresponding thia Michael and Michael adducts. Behavior of thia Michael

&Michael adducts toward hydrazines, hydroxylamines and acetic anhydride was investigated. Also 4-oxo-but-2-enoic acid was reacted with hydrogen peroxide in HCl presence of sodium hydroxide and yielded the corresponding oxirane derivative, its behavior towards 2-amino-5-phenyl-1, 3, 4-thiadiazole has been investigated and yielded 4-(4-acetamido- phenyl)-3-hydroxy-4-oxo-2-(5-phenyl-1,3,4-thiadiazole-2-yl) amino butanoic acid. The behavior of the butanoic acid derivative towards hydrazines, acetic anhydride, and hydroxylamine been also described . The reaction of the acid chloride of 4-oxo-but-2-enoic acid with anthranilic acid afforded the anthranil derivative which undergoes ring closure with acetic anhydride and yielded the semi acid anhydride. The behavior of semiacid anhydride towards hydrazine hydrate, hydroxyl-aminehydrochloride, formamide, ethylglycinate, semicarbazide, and thiosemicarbazide, has been investigated. All synthesized compound their structures were proved via physical tools e.g., IR, ^{1}H-NMR, and mass spectroscopy and chemical tools also. The routes of the reaction were traced via study the mechanisms of these reactions

ABSTRACT

The behavior of 4-(4-acetamidophenyl)-4-oxo-but-2-enoic acid towards nitrogen nucleophiles , sulphur nucleophiles ,oxygen nucleophiles and carbon nucleophiles has been investigated and yielded the corresponding aza, thia , and carba Michael . These Michael adducts used in synthesis of some interesting heterocyclic compounds with mixed and non mixed systems.

Key word:

Pyridazinones, oxazinones, furanones, oxirane, benzoxazinones

الملخص العربـــى

يتفاعل حمض ٤(٤ اسيتوامينو فينيل)-٤-اكسو-بيوتا-٢-اينويك مع ٢-امينـو-٥-اريـل ١و٢و٣-ثياديـازول والهيـدروكربونات الاروماتيـة النشـيطة مثـل ميتازيلين والبارازيلين وانتج نواتج ازامايكل وفريدل- كرافت وقد تم دراسة سلوك نواتج ازا مايكل والكلـة فريـدل- كرافت تجـاه الهيـدرازين وانهيدريـد حمـض الخليـك وكـدلك كلوريدالهيدروكسيل أمين وكذلك تم دراسة سلوك حمض٤-اكسو-بيوتا-٢-اينويك اتجاه الكواشف النيكليوفيليه الكبريتية مثل الثيو فينول والكواشف النيكلوفيليه الكربونية مثل حمض الباربتيوريك والفينول وانتج نواتج ثيا مايكل ومايكل وتم دراسة سلوك هده النواتج اتجاه الهيدرزينات وانهيدريد حمض الخليك وكلوريد الهيدروكسيل امين. كـدالك تـم دراسـة سـلوك حمـض ٤-اكسـو- بيوتـا ٢- اينويـك اتجـاه الكواشـف النيكليوفيلية الاكسجينيه مثل فوق اكسد الهيدروجين فى وسط قلوى واعطى مشتق الاكـزارين الـدى تـم بـدوره بالتفاعـل مـع ٢- امينـو-٥-فينيـل ٤،٣،١- ثياديـازول وانهيدريـد حمـض الخليـك وكلوريـد الهيدروكسـيل امـين – كـدلك تـم دراسـة تفاعـل كلوريدحمض ٤-اكسو- بيوتا-٢- اينويك مع حمض الانثرانيلك حيت انتج مشتق الانثرانيل الدى تم حلوقته باستخدام انهيدريد حمض الخليك الى مشتق البنزوكزازين الـدى تـم دراسـة سـلوكه تجـاه الكواشـف النيكلوفيليـه النتروجينيـه مثـل الهيـدرازين – الهيدروكسـيل امـين – الفورماميـد –ميتيـل جليسـينات- سـيمى كاربازيـد والثيوسـيمى كاربازيـد بهـدف دراسـة تبـات هـده الحلقـة بالنسـبة لشـطر الانيـون كـدلك تـم اتبـات التراكيـب الدقيقـة للمركبـات المصـنعة مـن خـلال الطـرق الكيميائيـة والطـرق الفيزيقيـة مثل طيف الأشعة تحت الحمراء – الرنين النووى المغناطيسى للبرتونات وطيف الكتلة. كذلك تم اقتفاء اثر التفاعلات من خلال تقديم اليات مقبوله علميا.

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INTRODUCTION

Due to their electrophilicity, β-aroylacrylic acid react with nucleophiles including primary and secondary amines **[Khachatryan , 2004]**. Also, β-aroylacrylic acids. are convenient polyelectrophilic reagents in the synthesis of heterocyclic rings, for which the addition reaction of N-, S-, P-, or C-nucleophile occurs exclusively at the α-carbonyl – electrophilic center of the molecule. Recently, β-aroylacrylic acid derivatives show high biological activity and exhibit a broad spectrum of physiological (fungicidal, antitumor, hypotensive, hypolipedemic, etc.)activities, antibacterial activity **[Kolos, 2007]** and in recovery of Alzheimer disease **[Maja, 2010]**. Also β- arolyacrylic esters are important intermediates in the field of medica science, agriculture and perfume **[Ken-ichi, 2006]**.

I. β-aroylacrylic Acid:

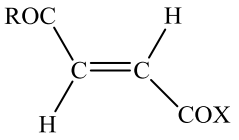
I.1. chemistry of β-aroylacrylic Acid:

It seems important to review the chemistry of β-aroylacrylic acid since the present investigation deals with the activity of β-aroylacrylic as suitable precursors in the preparation of the new pyridazinones and furanons and oxazinones.

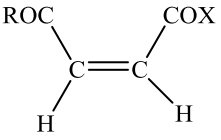
I.1.1 Structure:

It can be considered that β-benzoyl acrylic acid and its methyl ester are exist in three isomeric forms; Trans **E-(1)**, Cis

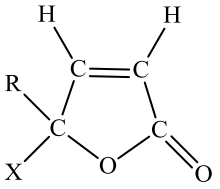
Z-(1) and the angelica lactone form (2) **[Chamoli, 1994].** Cf. scheme (1).



E-(1)



Z-(1)



(2)

a:R=C_6H_5,X=OH
b:R=C_6H_5,X=OCH_3

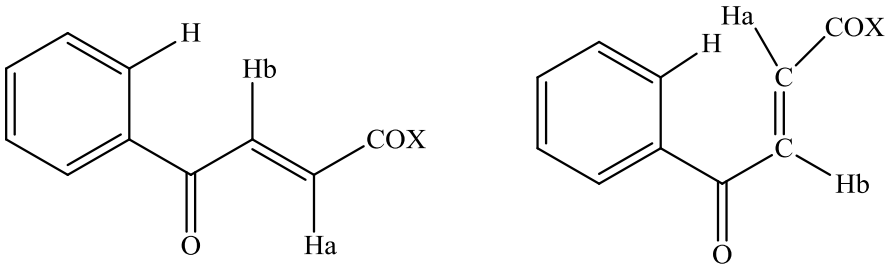
Scheme (1)

It has been reported that the compound obtained by Friedel-Craft's reaction of maleic anhydride with benzene afford benzoyl acrylic acid of the form **(1a) [Becker, 1955].** the infrared spectra show absorption between 1800, 1700, 1670 and 1635cm^{-1} and no absorption between 1800 and 1750 cm^{-1}. In the ultraviolet spectrum, band is observed at λ_{max} 238 mμ, λ_{max} 272 mμ. In the ^{1}H-NMR spectrum, the signal of a pair of sharp doublets at τ = 3.12 and 1.98 for the olefinic protons are observed.

The higher coupling constant value (J=15.4Hz) is a good evidence for existence of benzoyl acrylic acid in the Trans form **E-(1a).**

Since the benzene ring and remaining part of the molecule should be in the same plane as a result of conjugation, two isomers, **(3a)** and **(4a)** are possible.

However, inspection of the molecule model of **(1a)** shows that **(4a)** is not possible because of the strict hindrance between Ha and the o-hydrogen of the benzene ring. C.f. scheme (2).



(3) **(4)**

a:X=OH
b:X=OCH_3

Scheme (2)

In **(3a)** the deshielding effect of the benzene ring for Hb is expected to be presented on account of its proximity of the benzene ring, but no such effect is expected for Ha in **(4a).**

From the ^{1}H-NMR date for olefinic protons of methyl fumarate at τ= 3.17, the signal at τ= 3.12 is assigned to Ha and that at τ = 1.98 to Hb.

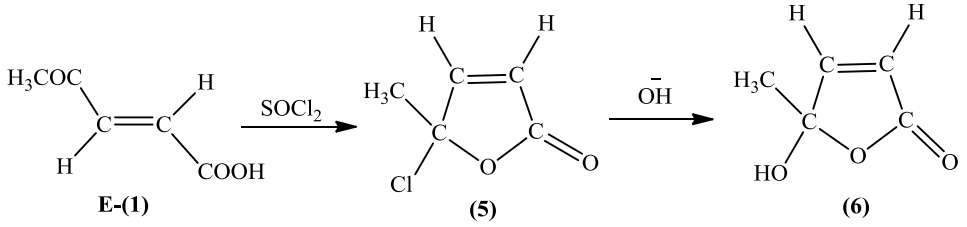
Since Hb is more deshielded by the benzene ring, this is good evidence for existence of the benzoyl acrylic acid in the transoid structure **(3)**.

In the ^{1}H-NMR spectrum of methyl benzoyl acrylate a pair of sharp doublets at τ=3.12 and τ=2.16 is observed. The infrared absorption spectrum of methyl benzoyl acrylate shows carbonyl absorption band at 1630 cm^{-1} but no absorption bands are observed

in the lactone carbonyl region. The ultraviolet absorption spectrum of the ester shows a λ_{max} 232 mμ, λ_{max} 270 mμ. The results suggest that methyl benzoyl acrylate exists in the form **(3b)**.

Treatment of methyl acrylate **E-(1b)** with aqueous sodium hydroxide gives the hydrolysed product **E-(1a)**. In the reaction mixture, the isomerized product is not detected. Thus benzoyl acrylic acid does not isomerized under basic condition.

It has been reported that acetyl acrylic **E-(1a)** is isomerized by thionyl chloride to 5-methyl-5-chloro-2,5-dihydro-2-oxofuran **(5)** which in turn is converted to **(6)** in an aqueous alkali **[Von, 1967].** C.f. Scheme (3).



Scheme(3)

Therefore it is interesting to examine the reaction of **E-(1a)** with thionyl chloride followed by reaction of methanol instead of an aqueous alkali. The ^{1}H-NMR spectrum of reaction mixture of **(1a)** with thionyl chloride followed by the reaction of methanol showed the signals corresponding to three substances, the normal esterified product **E-(1b),** and two anomalous products, 5-phenyl-5- methoxy-2,5-dihydro-2-oxofuran **(2b)**. and methyl-α-methoxy-β-benzoyl propionate **(7)**.