استخدام الأحماض β- الكيتونية فى تشييد بعض الأنظمة غير متجانسة الحلقة المختلطة وغير المختلطة

رساله مقدمه للحصول على درجه الماجستير فى العلوم كجزء
مكمل لمتطلبات رساله الماجستير بكليه العلوم
الكيمياء العضويه

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Utility of β- Keto Acids in Synthesis of Some Interesting Mixed and Non-Mixed Heterocyclic Systems

A Thesis Submitted for the degree of master of
Science as a partial fulfillment for equirements
Of the Master of Science

Organic Chemistry

Al-Shimaa Omar Ali Mahmoud

(B.Sc.Chemistry, Honour Degree)

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2013

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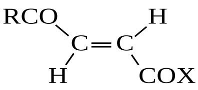
CONTENTS

Chemistry of β-Aroylacrylic Acids

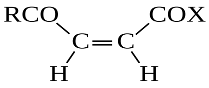
4-Aryl-4-oxobut-2-enoic acids (β-aroylacrylic acids) and their derivatives represent an important class of compounds with wide spectrum of biological activities including antibacterial activity [33, 41, 44, 99, 171], anti-ulcer and cytoprotective properties [20], kynurenine-3-hydroxylase [78, 174], and antiproliferative activity toward Human cervix carcinoma (HeLa) [54, 90]. Moreover, the β-aroylacrylic acids have been attracting increasing attention in view of their high reactivity as building blocks for the synthesis of wide variety of compounds of various classes due to their selective transformations with different reagents.

I. Structure

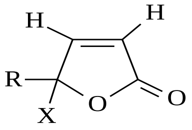
It can be considered that β-benzoylacrylic acid and its methyl ester exist in three isomeric forms[25], the trans E-**(1)**, the cis form Z-**(1)** and the angelica lactone form **(1b)**.



E-(1)



Z-(1)



(1b)

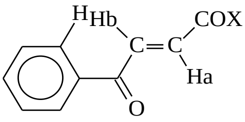
X= OH or OMe

It has been reported that the compound obtained by Friedel-Crafts reaction of maleic anhydride with benzene was (E)-β-benzoylacrylic acid of the form E-**(1)** [79].

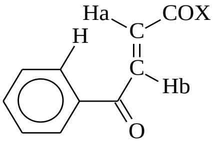
The infrared spectra showed absorption bands at

1700, 1670 and 1635 cm^{-1} and no absorption band was observed in the lactone carbonyl region between 1800 and 1750 cm^{-1}. In the ultraviolet spectrum, band was 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 $\tau = 3.12$ and 1.98 for the olefinic protons were observed. The higher coupling constant value (J=15.4 Hz) is a good evidence for the existence of β-benzoylacrylic acid in the trans form E-**(1).**

Since benzene ring and the remaining part of the molecule should be in the same plane as a result of conjugation, two isomers, E-**(1a)** and E-**(1b)** are possible. However, inspection of the molecular model of E-**(1)** showed that E-**(1b)** is not probable because of the steric hindrance between H_a and the o-hydrogen of the benzene ring.



E-(1a)



E-(1b)

X= OH or OMe

In E-**(1a)** the deshielding effect of the benzene ring for H_b is expected to be present on account of its proximity of the benzene ring, but no such effect is expected for H_a in E-**(1b)**. Since H_b is more deshielded by the benzene ring, this is a good evidence for the existence of benzoylacrylic acid in the trans structure E-**(1a)**.

In the ^{1}H-NMR spectrum of methyl benzoylacrylate a pair of sharp doublets at $\tau = 3.12$ and $\tau = 2.16$ was observed. The infrared absorption spectrum of methyl benzoylacrylate showed carbonyl absorption bands at 1725 and 1670 cm^{-1} and the olefinic double bond at $1630 cm^{-1}$, but no absorption band is observed in the lactone carbonyl region.

The ultraviolet absorption spectrum of the ester showed a λ_{max} value of 232 mμ and a λ_{max} value of 270 mμ. The results suggested that methyl benzoylacrylate was in the E-**(1b)** form (X=OMe).

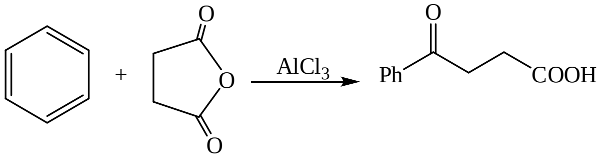
II. General Methods for The Synthesis of β-Aroylacrylic Acids

Generally, the synthesis of β-aroylacrylic acids is based on Friedel-Crafts acylation reaction of aromatic hydrocarbons with maleic anhydride in the presence of Lewis acid. A different number of methods have been also reported for the synthesis of β-aroylacrylic acids.

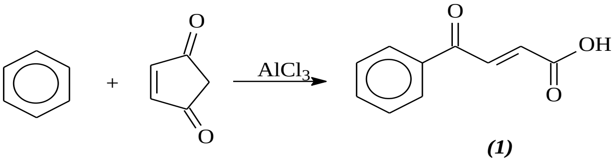
II.1. Friedel-Crafts Reaction

One of the most general and oldest known methods for the synthesis of β-aroylacrylic acids is Friedel-Crafts acylation reaction. The Friedel-Crafts reaction between an aliphatic dibasic anhydride and aromatic compound results in the formation of an aroyl fatty acid with the aroyl group situated at the last carbon atom of the aliphatic chain. Since the lesser known dibasic anhydride is succinic anhydride, the number of the methylene groups between the carboxyl group and the carbonyl group cannot be less than two.

Burcker [36], introduced the reaction in 1882, where he condensed succinic anhydride with benzene in the presence of $AlCl_3$ and obtained β-benzoylpropionic acid.



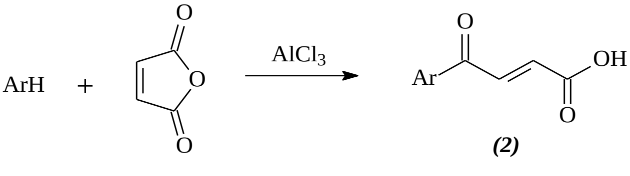
In the same year Von Pechmann [143] prepared β-benzoylacrylic acid **(1)** by using maleic anhydride instead of succinic anhydride.



(1)

The reaction between aromatic compounds and maleic anhydride has generally given lower yields and less pure products than the comparable reaction with succinic anhydride.

Domenick Papa [141] prepared a series of β-aroylacrylic acids **(2)**. A reasonably large number of aromatic compounds have been condensed with maleic anhydride. Substitution occurs generally in the expected position with the formation of only one isomer.

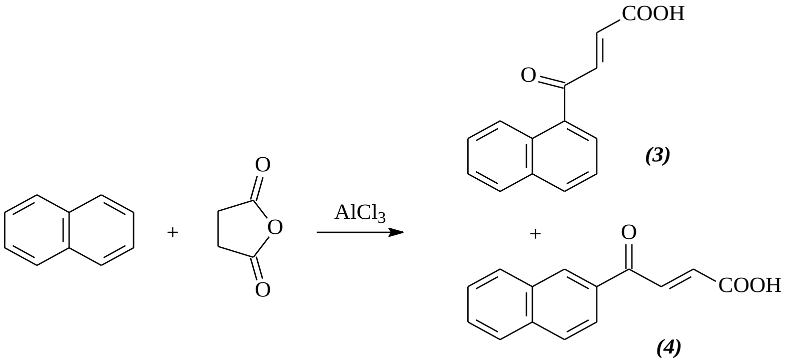


(2)

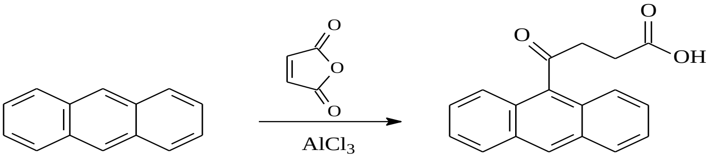
Recently, Darkulic et al.[54] prepared a series of 27 β-aroylacrylic acids *via* the Friedel-Crafts acylation of different aromatic hydrocarbons with maleic anhydride according to Papa [141].

β-benzoylacrylic acid **(1)** was obtained by reaction of one mole of maleic anhydride with excess benzene in 95% yield by heating 1.5 hours at 60°C [133], 91% yield by heating 23 hours in the steam bath [141], in 80-85% yield by refluxing one hour [79].

Methylene chloride or dichloroethane can be used as solvent in the reaction of maleic anhydride (one mole) with benzene (one mole) [12]**.** From the reaction between maleic anhydride and naphthalene, two acids **(3)** and **(4)** have been isolated [141].



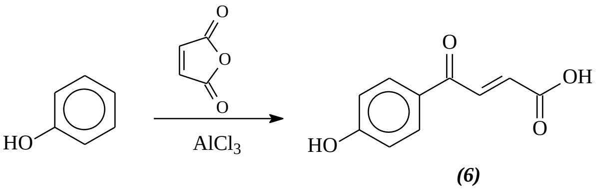
Anthracene in contrast to its behavior on succinoylation is reported to form 9-acid **(5)** [133].



(5)

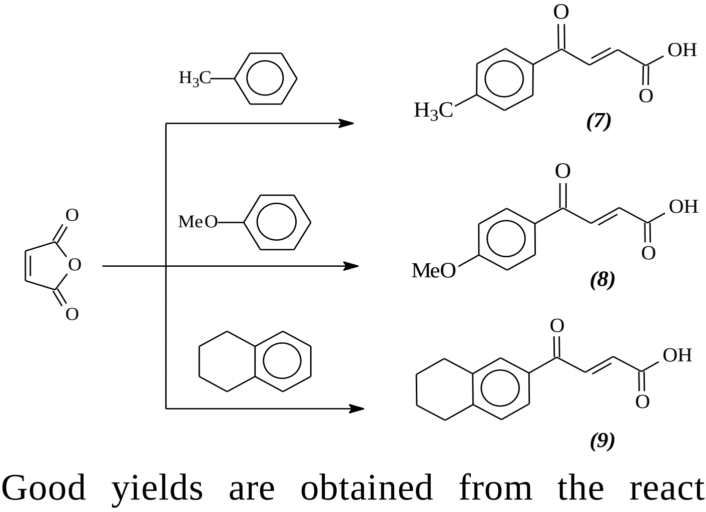
Acenaphthene forms the corresponding acid in only 32% yield. In the early investigation of the reaction between the alkyl benzenes and maleic anhydride, the alkyl benzenes were used both as reactants and solvent and the yields of pure products were very low [110].

Phenol, maleic anhydride and aluminum chloride in benzene yield 25% of β-p-hydroxybenzoylacrylic acid **(6)** [23].

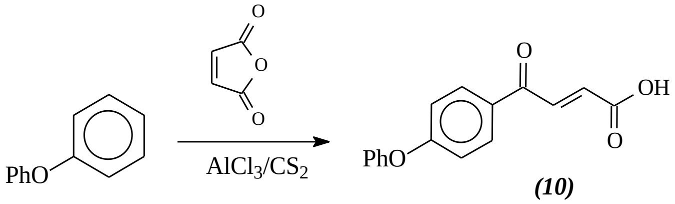


(6)

It has been shown that toluene, anisole and tetraline can readily be condensed with maleic anhydride in tetrachloroethane solution to give β-(p-toluoyl)-, (p-anisoyl)- and 3,2-tetralinoylacrylic acids **(7)**, **(8)** and **(9)** in 60-70% yields, respectively [12, 23, 73, 110, 133, 141].



Good yields are obtained from the reaction of maleic anhydride with the cresolmethylethers, veratrole and hydroquinone dimethylether in nitrobenzene as a solvent [45]. Reaction in carbon disulphide gives lower yields [152]. Diphenylether also reacts with maleic anhydride to give 4-phenoxybenzoylacrylic acid **(10)** [152].



Resorcinol dimethylether, however forms the expected acid **(11)** only to a small extent [154]. The main product of the reaction is a substituted succinic anhydride **(12)** formed by the addition of resorcinol dimethylether to maleic anhydride. The anhydride **(12)** is partly hydrolyzed to the substituted maleic acid **(13)**. A fourth product is the acid **(14)** formed by the addition of the ether to the acrylic acid **(11)**.