“Studies on chemical reactivity of some furanone derivatives”

“A thesis submitted as a partial
fulfillment for requirements of the master
of science”

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Under supervision of

“Prof. Dr. Ahmed Ismail Hashem ”

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A Thesis Submitted for M. Sc. Degree in Organic Chemistry

Presented by

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(B. Sc. 2002)

Department of Chemistry

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Ain Shams University

Cairo, Egypt

2015

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Ahmed Abdel-aziz Mohamed Elshaikh

APPROVAL SHEET

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Abstract

In this investigation, two furanone derivatives, one of the 2(3*H*)-type and the other of the 2(5*H*)-type, were synthesized and used as starting materials for the construction of other heterocyclic systems of synthetic and biological importance. The original work of this thesis is presented in two parts:

Part (1): Synthesis and reactions of some 2(3*H*)- and 2(5*H*)- furanone derivatives: A comparative study

3-Cyano-4,5-diphenyl-2(5*H*)-furanone **1** and 3-cyano-4,5-diphenyl-2(3*H*)-furanone **2** were prepared and their reactions with some nitrogen nucleophiles were studied. It was possible to obtain pyrrolone, pyridazinone, thiazolidinone and tetrazole derivatives.

Part (2): Utilization of 4,5- diphenyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile (10) as a precursor of other pyrrole derivatives

The title compound was utilized as a starting material to construct pyrrole derivatives bearing heterocyclic rings at positions -2 and -3. The reactions of this compound with some reagents led to the construction of a thiazolone nucleus at positions -2, a thiazolidinone ring at position -3, and a tetrazole ring at position -3. Also, the thiol group in the starting compound was converted into a sulphonamide group.

Keywords: Furanone, nucleophilic reagents, thiazolone, thiazolidinone, pyrrolone, tetrazole, sulphonamide.

Summary

Furanones represent a group of heterocyclic systems of special importance. 2(3*H*)-Furanones are the precursors of a wide variety of heterocyclic systems, and the nucleus of 2(5*H*)-furanones is the core skeleton of many natural products.

In this investigation, two furanone derivatives, one of the 2(3*H*)-type and the other is its 2(5*H*)-isomer, are used as starting materials for the construction of some heterocyclic compounds of synthetic and biological importance. The original work of this thesis is presented in two parts:

Part (1): Synthesis and reactions of some 2(3*H*)- and 2(5*H*)- furanone derivatives: A comparative study

Early, it was reported that condensation of benzoin with ethyl cyanoacetate in the presence of sodium ethoxide led to the formation of 3-cyano-4,5-diphenyl-2(5*H*)-furanone**1**. On reinvestigating this reaction, it was possible to isolate this compound together with another product namely 3-cyano-4,5-diphenyl-2(3*H*)-furanone**2**. The formation of the latter product is explained on the basis of isomerization of **1** under the basic reaction conditions. Such isomerization is believed to occur via the intermediacy of two carbanion intermediates which are stabilized by both the cyano group at position 3- and the phenyl group at position 5-. The formation of the furanone **2** in a smaller yield compared

with **1** led the author to determine the relative stabilities of these two isomers. Calculations revealed that the 2(5*H*)-furanone **1** is more stable than the 2(3*H*)-isomer **2** by 24.5 kJ mol^{-1}.

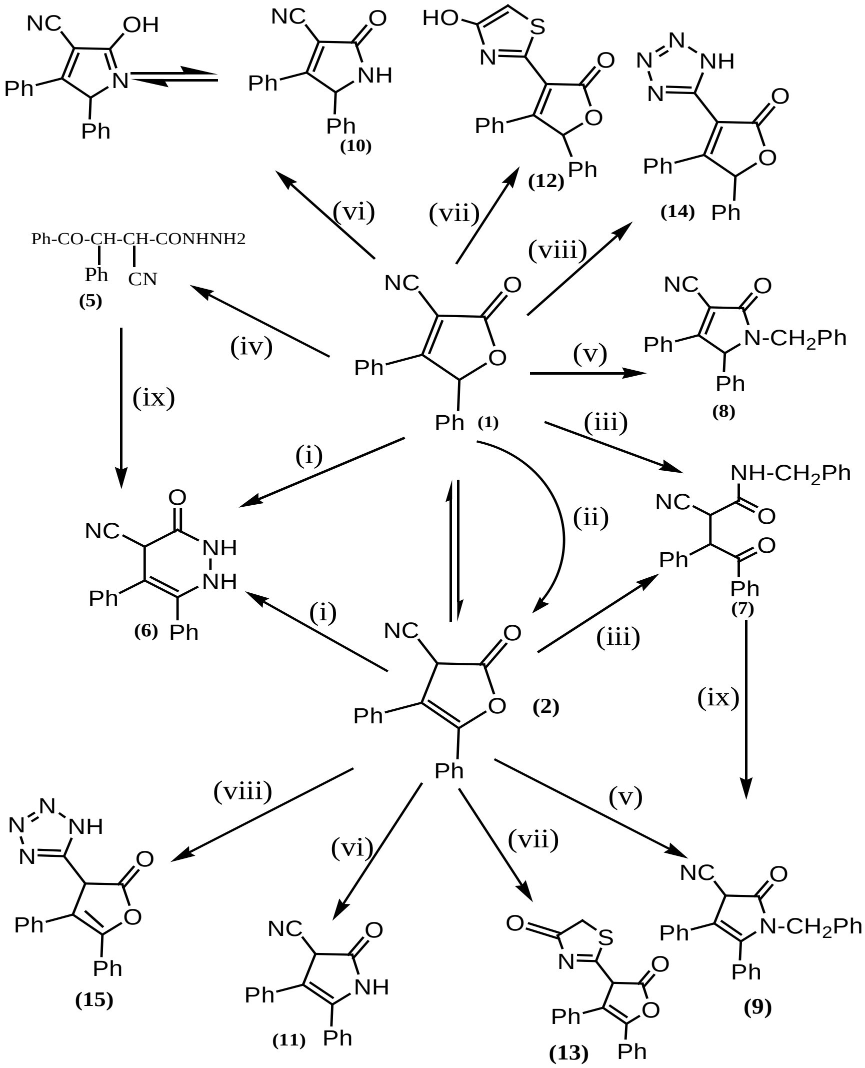
The reactions of the two isomeric furanones **1 & 2** with some nitrogen nucleophiles e.g. hydrazine hydrate, benzylamine and ammonium acetate were studied in order to explore the effect of the relative positions of the double bond and carbonyl group on their behavior.

It is to be mentioned that the two furanones gave the same products with hydrazine hydrate and benzylamine. This behavior was explained in terms of isomerization of the 2(5*H*)-isomer to the 2(3*H*)-isomer prior to ring opening and then cyclization of the open-chain product. The unfavored 1,4-addition of these nucleophiles to the α,β-unsaturated carbonyl moiety of **1** is explained in terms of steric and electronic effects of the phenyl group at position 4.

Fusion of the furanones **1** and **2** with ammonium acetate gave the corresponding pyrrolones **10, 11** respectively.

The presence of cyano group at position 3 in both the 2(5*H*)- and 2(3*H*)-furanones promoted the interest of the author to construct thiazolidinone and tatrazole rings at this position. Thus **1** and **2** reacted with thioglycolic acid to give the thiazolidinone derivatives **12** and **13** respectively. The tetrazolyl derivatives **14** and **15** were obtained by reacting the 2(5*H*)- and 2(3*H*)-furanones respectively with sodium azide in the presence of ammonium chloride.

The structures of all products obtained were elucidated from their analytical and spectroscopic data. All the foregoing reactions are illustrated by **Scheme 2**.



(i) N_2H_4/EtOH/reflux; (ii) N_2H_4/EtOH/stirring; (iii)$PhCH_2NH_2$/EtOH/Reflux; (iv)N_2H_4/EtOH/$80^{O}C$; (v)$PhCH_2NH_2$/fusion; (vi) Amm.acetate/fusion; (vii) thioglycolic acid/pyridine; (viii) sod.azide/NH_4Cl; (ix) HCl/AcOH

Scheme (2)

Part (2): Utilization of 4,5- diphenyl -2-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile (10) as a precursor of other pyrrole derivatives

The wide spectrum of biological activity of pyrrole derivatives and their pharmacological applications led the author to utilize the title compound as a starting material for the synthesis of other pyrrole derivatives. The pyrrolone**10**, obtained from fusion of the furanone **1** with ammonium acetate (cf. Part 1, Scheme 2), reacted with phosphorus pentasulphide in boiling toluene to give the thione/thiol tautomers **20a,b**.

Alkylation of **20** by ethyl iodide in alc.KOH led to the formation of the ethylthio derivative **21**.

The presence of the –SH and –CN functionalities at positions -2 and -3 respectively encouraged the author to construct a thiazolidinone ring at position 3 and a thiazolone ring at position 2 . The conversion of the –CN group into thiazolidinone ring was affected by the reaction of **20** with thioglycolic acid to give thiazolidinone derivative (**22**). On the other hand, the conversion of –SH group into a thiazolidinone derivative was achieved by three steps:

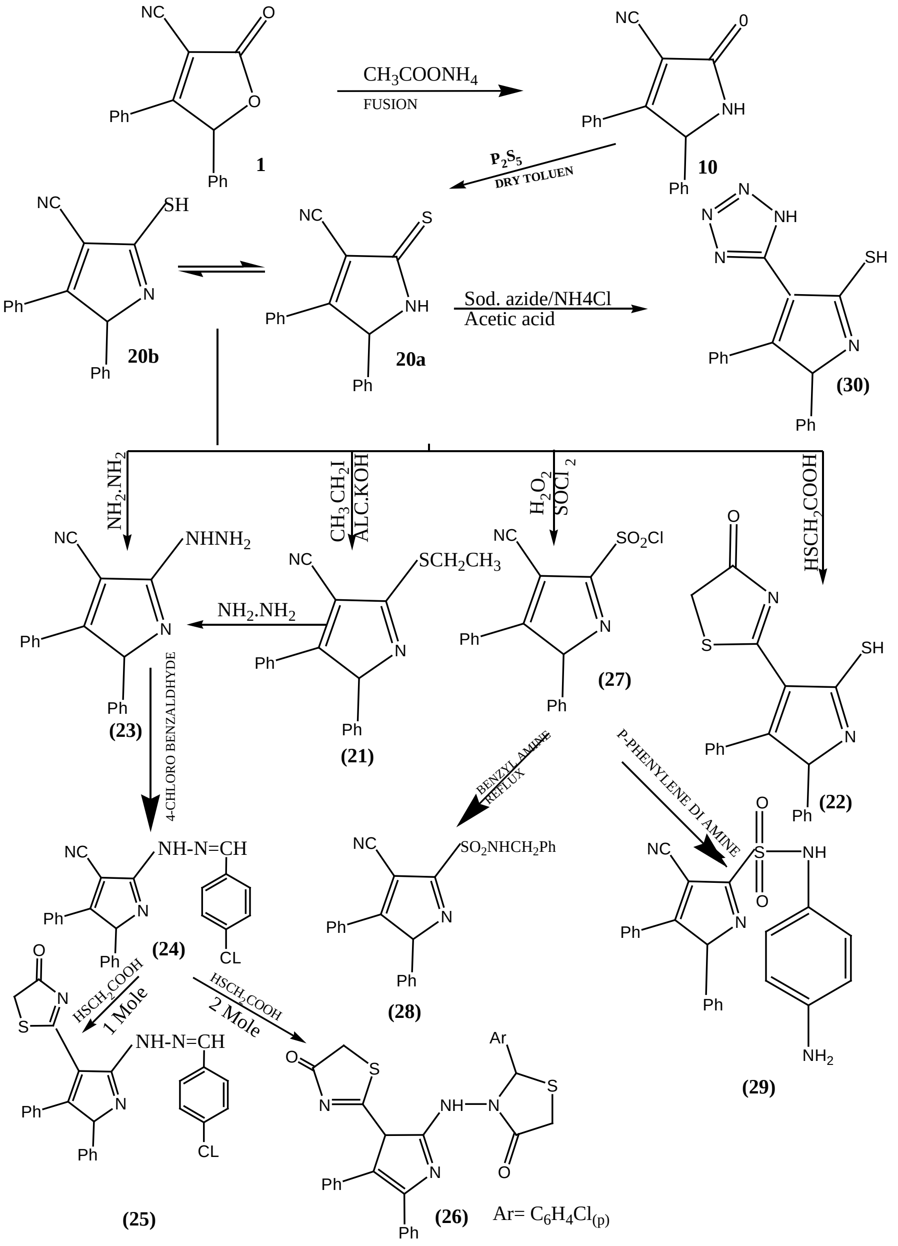
(i)Treatment of the tautomer **20** or its ethylthio derivative **21** with hydrazine hydrate resulted in replacement of the –SH or the $–SC_2H_5$ groups to give the 2-hydrazino derivative (**23**), (ii)the latter compound was condensed with 4-chlorobenzaldehyde to give the corresponding hydrazone derivative (**24**), (iii) treatment of the hydrazone derivative with thioglycolic acid led to the formation of (**25**).

It is to be mentioned that when the hydrazone derivative (**24**) was reacted with thioglycolic acid (1:1 mole), conversion of the –CN group only occurred to give (**25**). But, using two moles of thioglycolic acid led to the construction of a thiazolone ring at positions 2 and a thiazolidinone ring at position 3 to give (**26**). Evidently this indicates that the –CN carbon is more susceptible to attack by this nucleophile than the hydrazone carbon.

The diverse therapeutic effects of sulphonamides initiated the interest of the author to convert the –SH group at position -2 of the thione/thiol tautomer **(20)** into a sulphonamide group. This conversion was affected by treatment of **20** with hydrogen peroxide / thionyl chloride mixture to give the sulphonyl chloride derivative (**27**) which reacted with the primary amines: benzylamine and p-phenylenediamine to give the sulphonamide derivatives (**28,29**) respectively.

The study was also extended to construct a tetrazolyl group at position 3 by treating the thione/thiol tautomer with sodium azide in the presence of ammonium chloride to give the tetrazolyl derivative (**30**).

The structures of the products obtained in this part were also elucidated from their analytical and spectroscopic data. All the reactions studied in this part are illustrated by Scheme (5).



Scheme (5)

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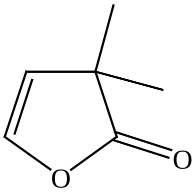
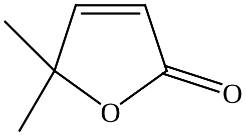
Arabic Summary

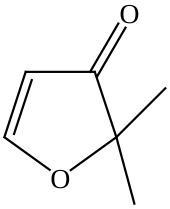
There are three types of furnaones: 2(3H), 2(5H), and 3(2H)-furanones(1-3)(Rao, 1976).



(1)



(2)



(3)

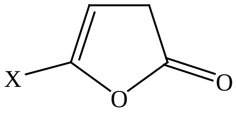
The term butenolide was first employed by Klobb for describing these compounds ***(Klobb, 1898)***. Chemical abstracts currently has adopted the furanone system of naming these compounds. Thus $\Delta^{\beta,\gamma}$-butenolides are the 2(3*H*)-furanones and $\Delta^{\alpha,\beta}$-butenolides are the 2(5*H*)-furanones. In spite of this standardization of naming these compounds, the butenolide nomenclature still continues to be employed in the literature ***(Rao, 1976)***.

In this chapter, a literature survey of the chemical reactions of the first two types is presented:

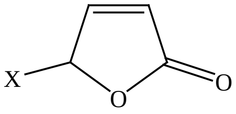
I. Isomerization

2(3H)-Furanones:

Generally, 2(5*H*)-furanones**(5)** are thermodynamically more stable than their tautomers, the 2(3*H*)-furanones**(4)**. This higher stability was explained on the basis of SCF-MO calculations which showed that the energy of **(5a)** is less than that of its tautomer **(4a)** by 53 KJ/mole ***(Bodar et al., 1970)***. Isomerization of **(4)** to **(5)** was effected by triethylamine in benzene ***(Guntrum et al., 1986)*** or even by heating at 100°C in an atmosphere of nitrogen ***(Blaschette et al., 1989)***.



(4)



(5)

a : X = H
b : X = CH_3
c : X = CMe_3
d : X = NMe_2

Calculations for both molecules proved that the total energy of **(5a)** is lower than that of **(4a)*****(Dianxun et al., 1994)***. It was concluded that, at room temperature, 2(3*H*)-furanone**(4a)**, which is an unstable molecule can gradually be converted into the 2(5*H*)-furanones**(5a)**.

5-(Diethoxymethyl)-2(3*H*)-furanone **(6)** was converted to 5-formyl-2(5H)-furanone**(8)** by the action of 0.2 N HCl in acetone ***(Wang et al., 1989)***. Isomerization of the hydroxymethylene derivative **(9)** to its tautomer **(10)** was carried out by addition of $AlCl_3$ (Scheme 1) ***(Wang et al., 1989)***.