Faculty of Science
Chemistry Department

Access to Biologically Active Heterocyclic Systems from Carbonyl Compounds

Thesis

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Approval Sheet

Access to Biologically Active Heterocyclic Systems from Carbonyl Compounds

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Abstract

A novel series of tetrahydroquinolines containing acetohydrazide, oxopyrazole, oxothioxodihydropyrazole and thioxotriazole have been synthesized. A series of triazolo[4,3-a]quinoline, triazino[4,3-a]quinoline, thiadiazepino[5,6-b]quinoline and pyrazolquinoline have been synthesized from reaction of 2-hydrazinyltetrahydroquinoline-3-carbonitrile with formamide, formic acid, ethyl chloroacetate, carbon disulphide in alcoholic solution of potassium hydroxide, acetyl acetone and/ or ethyl cyanoacetate respectively. Antileishmanial, antibacterial, antifungal, antitumor and cytotoxicity activities of synthesized compounds were evaluated in *vitro*. Antileishmanial activity of the most synthesized compounds showed tremendous activity toward *L. major* leishmania. Most of the synthesized tetrahydroquinolines showed antibacterial activity against five bacterial strains (*S. Aureus*, *B. Subtilis, M. Luteus, E. aerogenase* and *E. coli*). On the other hand, the antifungal activities of compounds under investigation have significant activities towards four fungal strains *(C. Albicans, M. Canis, F. Solani* and *C. Glabrata*). Most of the test compounds exhibited significant level of tumor inhibition. Compounds **12** and **14** showed 100 % tumor inhibition that is comparable to standard drug Vincristine (100 % tumor inhibition). Tetrahydroquinolines

Abstract

under investigation showed cytotoxicity with LD_{50} values in the range 0.56-3.01 µg/ml compared to standard drug MS-222 with LD_{50} value of 4.30 µg/ml. The presence of a pyazole ring markedly improved the activity profiles of tetrahydroquinolines. All newly synthesized compounds were characterized by IR, ^{1}H-NMR, and MS.

CONTENTS

INTRODUCTION

Heterocycles containing nitrogen atom are the basis of manyessential pharmaceuticals and physiologically active natural products.

2(1H)-Pyridinone is nitrogen containing synthetically designed scaffoldhaving several biological activities. 2(1H)-Pyridinone moiety frequentlyfound in a variety of interesting compounds has received appreciable attention because ofits promising features as privileged building blocks.

Other names of2(1H)-pyridinone are 2-pyridone, 2(1H)-pyridone, 1-H-pyridine-2-one, 1, 2-dihydro-2-oxopyridine, 2-pyridinol, 1H-2-pyrid-one, 2-hydroxypyridine.

The most important structural feature of 2-pyridone is the amide group; a nitrogen witha hydrogen bound to it and a keto group next to it as in peptides and amino acids, a feature responsible for some important physical and chemicalproperties. In this pattern, the hydrogen bound to the nitrogen issuitable to form strong hydrogen bonding to other nitrogen and oxygen containingspecies. The pyridinone structure is stable one, due to a strong intermolecularhydrogen bonding between the nitrogen of one molecule and the oxygen of another.The hydrogen bonding is repeated throughout the structure linking molecules in endless helices. Thisconclusion is based on the fact that the N-H distance is 1.02 A°, very nearly thenormal covalent bond length of 1.00 A°, whereas the observed O-H distance greatlyexceeds the normal

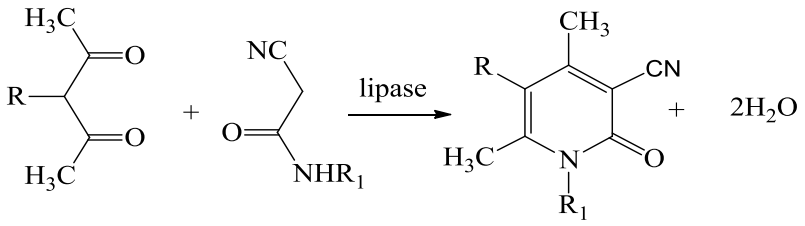
covalent distance. This indicates the possibility of existing 2(H)-pyridinone as a hydrogen-bonded dimer.

1. Synthesis of 2(1H)-pyridone derivatives:

2(1H)-pyridines could be prepared *via* one of the following dtarting materials.

1.1. Unsymmetricaldiketones

Lipases, including *Candida rugosa,* formerly *C. cylindracea,* were utilized to synthesize 3-cyano-2-pyridones [77, 78, 80, 81, 92].It has beenfound that starting with an unsymmetricaldiketonegave, different ratios of products in the chemical and enzymatic reactions[77].Because ofthe high selectivity of lipases, practically only one, of twopossible isomers, wasisolated[77, 80].Furthermore, theeffect of N-substituted cyanoacetamides and 3-substituted acetylacetones on the enzymatic synthesis of4,6-disubstituted-3-cyano-2-pyridones was investigated and ithas been found that the introduction of an alkyl group into themolecule of acetylacetone had a greater effect on thereaction in comparison to the corresponding substituted cyanoacetamides[81,92](cf. scheme 1).

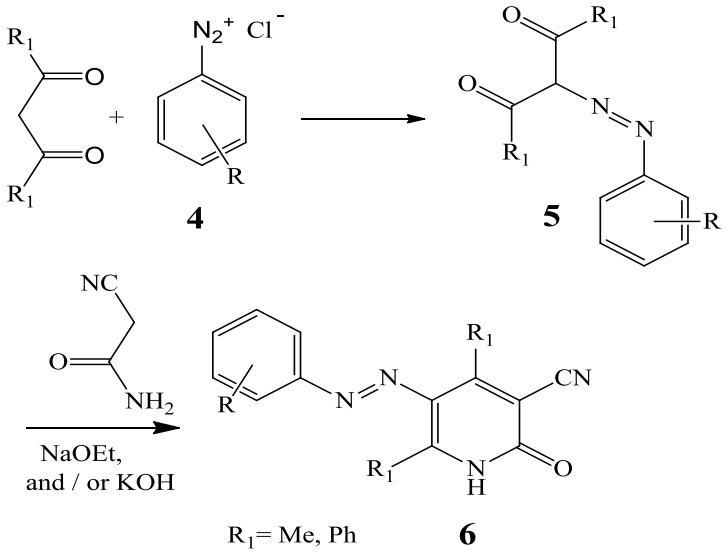


1 **2** **3**

R= H , CH_3

Scheme 1

When a dicarbonyl compound was allowed to couple with arenediazonium chloride **4**,the intermediate **5**firstly formed then cyclized with cyanoacetamide in presence of sodium ethoxide to yield an azodye**6**containing a pyridine moiety. The use of KOH [79] instead of sodium ethoxide[30,82] was found to be more suitable basic catalyst (cf. scheme 2).

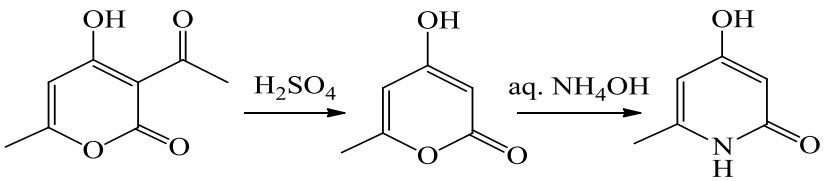


R_1= Me, Ph **6**

Scheme 2

1.2. 2H-pyran-2-one derivatives

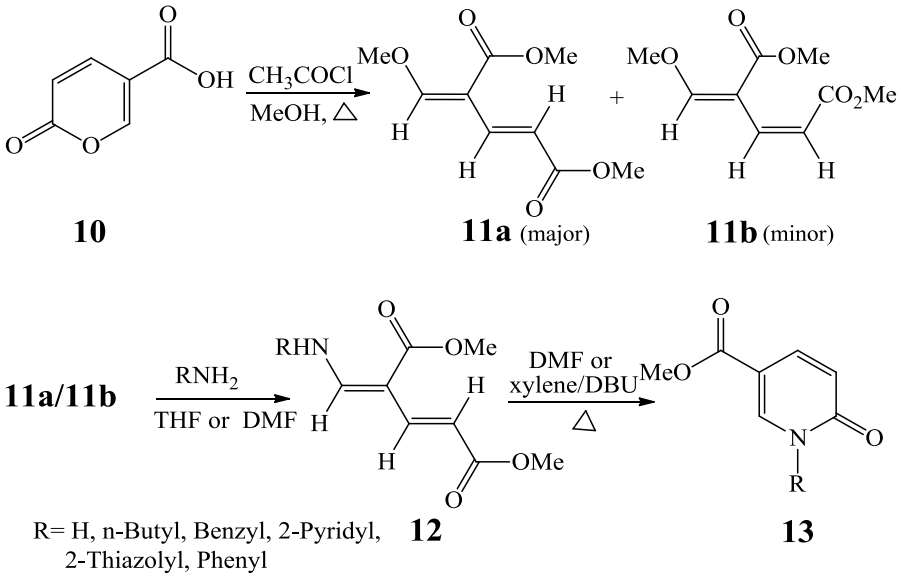
The deacetylationof3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one**7**[40] with dilute sulfuric acid gave α-pyrone**8**which then reacted with aqueous ammonium hydroxide to produce the corresponding pyridone**9**in 80% yield[34](cf. scheme3).



7 **8** **9**

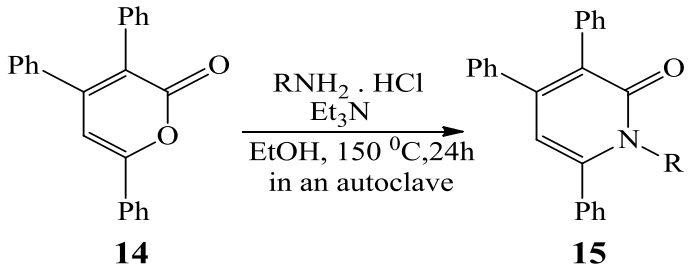
Scheme 3

Reaction of coumalic acid **10**with acetyl chloride in refluxing methanol gave a mixture of geometrical isomers**11a**/**11b**[85]. The mixture of **11a**/**11b** was allowed to react with various amines to give dienamino esters **12**, which cyclized directly to afford the corresponding 5- carbomethoxy-2-pyridones **13**in high yield. [58] (cf. scheme 4).



Scheme 4

The pyridone derivatives **15** were readily prepared in good yields *via* the reaction of the corresponding pyrones**14** with primaryaliphaic amines [59] (cf. scheme 5).

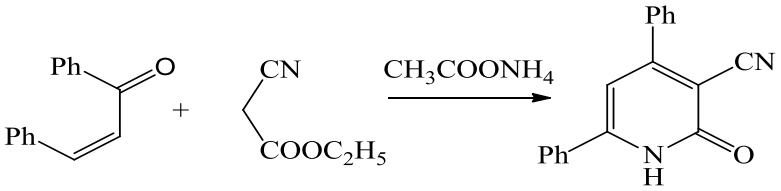


R= Me, Et, n-Pr, iso-Pr, n-Bu, iso-Bu, sec-Bu

Scheme 5

*1.3.*Chalcones

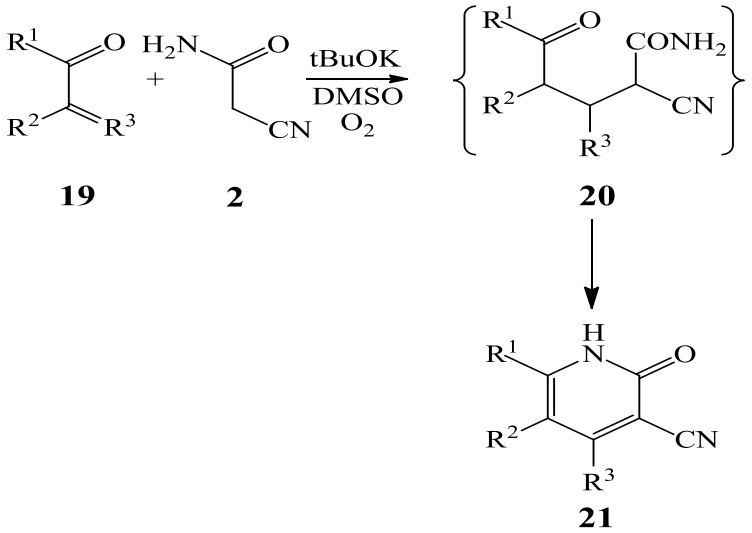
3-Cyano-2-pyridone**18**has been prepared by refluxing corresponding chalcones**16**with ethyl cyanoacetate**17**[101](cf. scheme6).



16 **17** **18**

Scheme 6

2-Pyridones **21** could be obtained by oxidation of α,β-unsaturated carbonyl compound**19**with cyanoacetamide**2** induced by the use of O_2 as an environmentally benign oxidant.This method is previliged by excellent yields of the produced pyridone, and reaction times are short [56] (cf. scheme 7).

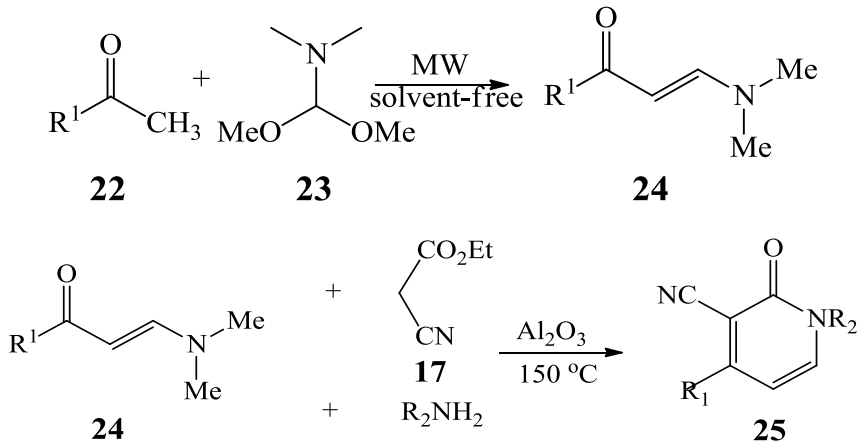


19 **2** **20** **21**

Scheme 7

3-Cyano-2-pyridones have been prepared from enaminones by multi-component reaction using a catalytic amount of basic

alumina (aluminium oxide). The enaminones**24**were obtained from the reaction of acetophenone derivative**22**with *N,N*-dimethylformamide-dimethylacetal (DMF-DMA) under solvent-free MW irradiations[54].However, in second step of the synthesis of 2-pyridones. A mixture of enaminone**24**, ethyl cyanoacetate**17**,and primary aliphatic amine in the presence of catalytic amount of basic Al_2O_3 was heated at 150°C for 2-3h toyield the corresponding 2-pyridones **25** in excellent yields [52] (cf. scheme 8).

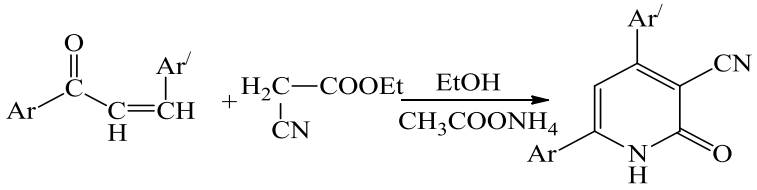


R_1=C_6H_5, p-ClC_6H_4, p-$CH_3C_6H_4$

R_2=CH_3, CH_2=CH-CH_2-, $C_6H_5CH_2$-, $(CH_3)_2$CH-

Scheme 8

Condensation of 1,3-diaryl-2-propen-1-ones **26** with ethylcyanoacetate in refuxing ethanol containing excessive ammonium acetate affored 3-cyanopyridone **27**[27](cf. scheme 9).

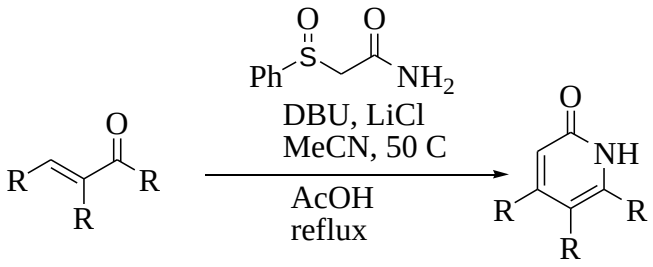


26 **17** **27**

Ar= C_6H_4-OCH_3-4 $Ar^{/=}$ C_6H_4-F-4
C_6H_3-$(OCH_3)_2$-2,4 C_6H_4-Cl-4
C_6H_3-$(OCH_3)_2$-3,4 C_6H_4-OH-4

Scheme 9

2-Pyridone **28** was prepared by means of an efficient protocol including the 1,4-addition of 2-(phenylsulfinyl) acetamide to α,β-unsaturated ketones followed by cyclization and sulfoxide elimination. [75] (cf.scheme10)



28

Scheme 10

1.4. Nitroimidazolederivatives

Diethyl2-[(1,2-dimethyl-5-nitro-1*H*-imidazol-4-yl)methylene]malonate**29**was reduced in presence of titanium tri chloride (30 wt% solution in 2N hydrochloric acid) in a water acetone mixture at room temperature. The resulting intermediate**30**was then heated in ethanolic sodium ethoxide