Synthetic Study and Biological Evaluation of new Heterocyclic Systems

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INTRODUCTION

The heterocyclic skeleton containing nitrogen atom is the basis of many essential pharmaceuticals and physiologically active natural products.

2(1H)-Pyridinone is nitrogen containing synthetically designed scaffold with a broad spectrum of biological activities. 2(1H)-Pyridinone moiety frequently found in a variety of interesting compounds has received remarkable attention due to its promising features as a key scaffold and in privileged building blocks.

It exists as tautomers. Other names of 2(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.

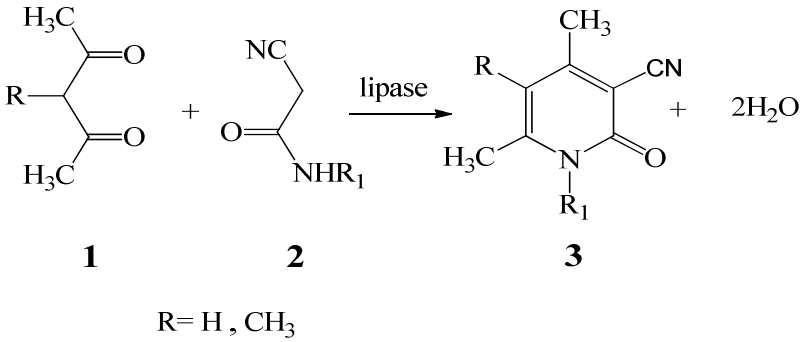
The most prominent feature of 2-pyridone is the amide group; a nitrogen with a hydrogen bound to it and a keto group next to it. In peptides, amino acids are linked by this pattern, a feature responsible for some important physical and chemical properties. In this and similar molecules, the hydrogen bound to the nitrogen is suitable to form strong hydrogen bonds to other nitrogen and oxygen containing species. The pyridinone structure is stable one, and there is a strong intermolecular hydrogen 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. This conclusion is based on the fact that the N-H distance is 1.02 A°, very nearly the normal covalent bond length of 1.00 A°, whereas the observed O-H distance greatly exceeds the normal covalent distance. This obviates the possibility that 2(H)-pyridinone exists as a hydrogen-bonded dimer.

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

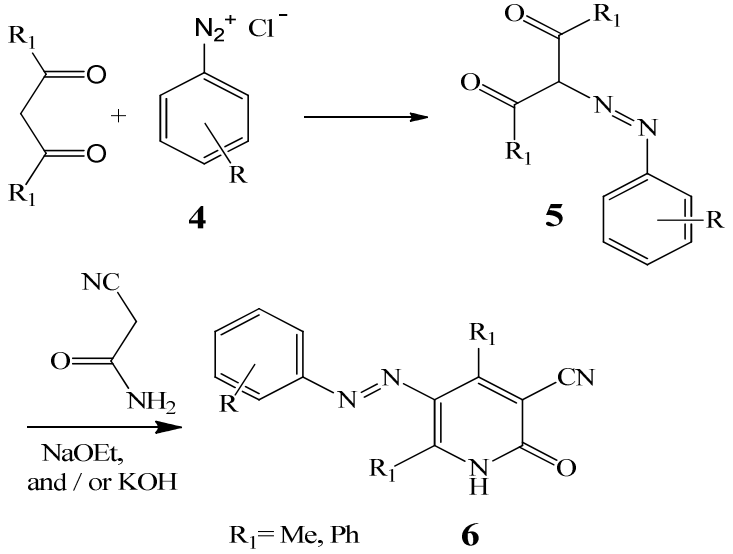
1.1. From unsymmetrical diketones

Lipases, including *Candida rugosa,* formerly *C. cylindracea,* were used to synthesize the substituted 3-cyano-2-pyridones [81, 82, 84, 85,103]. It has been shown that when an unsymmetrical diketone was used, different ratios of products were obtained in the chemical and enzymatic reactions [81]. Due to the high selectivity of lipases, practically only one, of two possible isomers, was obtained [81, 84]. In addition, the influence of N-substituted cyanoacetamides and 3- substituted acetylacetones on the enzymatic synthesis of 4,6-disubstituted-3-cyano-2-pyridones was studied and it was found that the introduction of alkyl groups into the molecule of acetylacetone had a greater impact on the reaction in comparison to the corresponding substituted cyanoacetamides [85,103] (cf. scheme 1).



Scheme 1

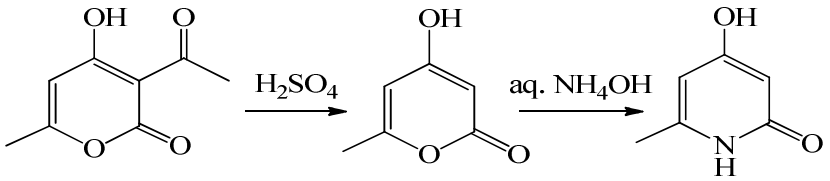
Dicarbonyl compound was coupled with arenediazonium chloride **4** to give intermediate **5** which then cyclized with cyanoacetamide in presence of sodium ethoxide to yield a pyridone azodye **6**. The use of KOH [83] instead of the previously employed sodium ethoxide [37, 86] was found to be more convenient (cf. scheme 2).



Scheme 2

1.2. From 2(1H)-pyrone derivatives

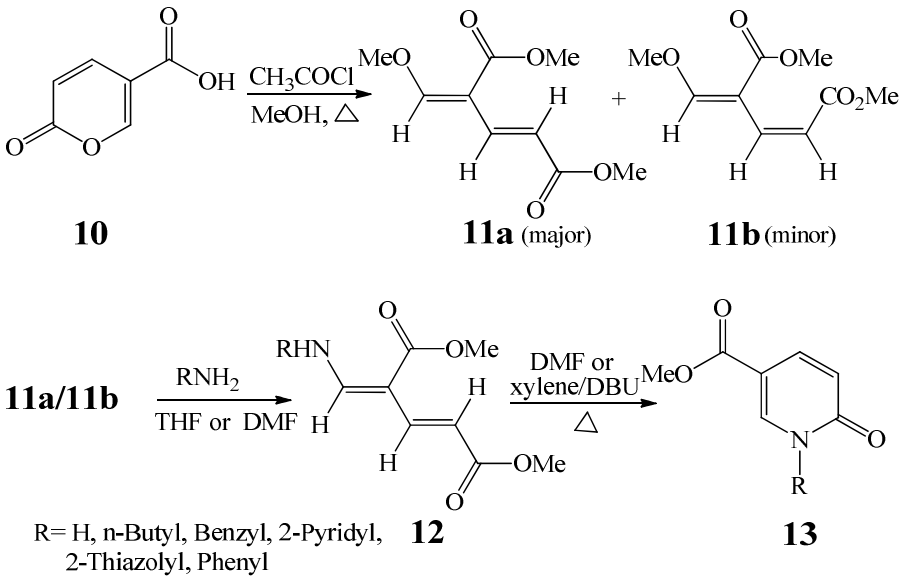
The hydrolysis of 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **7** [40] with sulfuric acid afforded compound **8** in 86% yield. Compound **8** was then reacted with aqueous ammonium hydroxide to produce the corresponding pyridone **9** in 80% yield [34] (cf. scheme 3).



7 **8** **9**

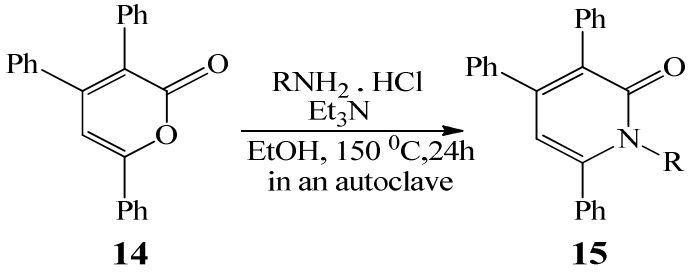
Scheme 3

Reaction of coumalic acid **10** with acetyl chloride in refluxing methanol afforded **11a**/**11b** as a mixture of geometrical isomers. **11a** was obtained as a major compound along with minor geometrical isomer **11b** [88]. This mixture of **11a**/**11b** was reacted with various amines to give dienamino esters **12**, which could be isolated or cyclized directly to produce the corresponding 5-carbomethoxy-2-pyridones **13** in high yield. [66] (cf. scheme 4).



Scheme 4

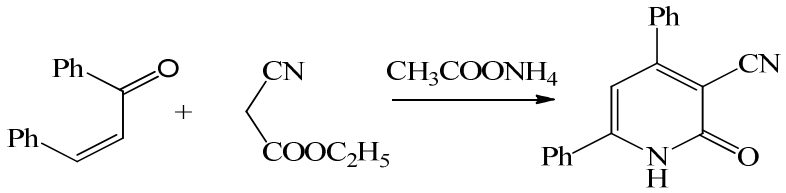
The pyridone derivatives were readily synthesized in good yields by the reaction of the corresponding pyrones **14** with primary amines [67] (cf. scheme 5).



Scheme 5

1.3. From chalcones

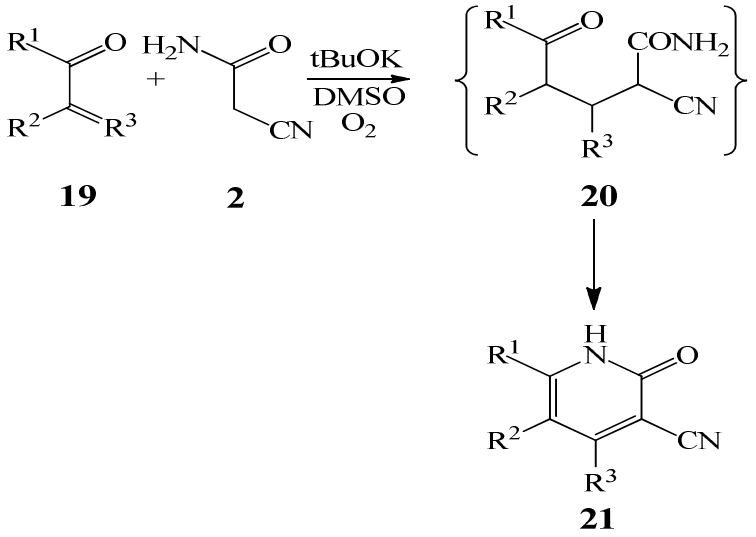
Compound **18** can be synthesized by refluxing corresponding chalcones **16** with ethyl cyanoacetate **17** [111] (cf. scheme 6).



16 **17** **18**

Scheme 6

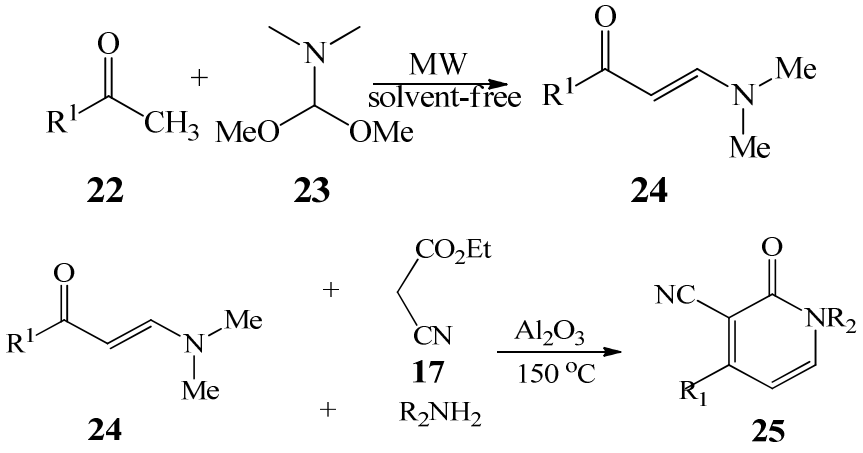
Pyridones **21** could be obtained by oxidation of α,β-unsaturated carbonyl compound **19** with cyanoacetamide **2** may be induced by the use of O_2 as an environmentally benign oxidant. Yields of pyridones **21** are good to excellent, and reaction times are short [56] (cf. scheme 7).



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

Scheme 7

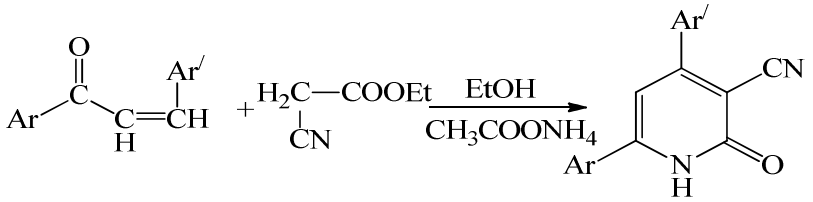
Substituted 3-cyano-2-pyridones have been synthetized from enaminones by multi-component reaction using a catalytic amount of basic alumina (Al_2O_3), Firstly, enaminones **24** were obtained from the reaction of methylacetone **22** with *N,N*-dimethylformamide-dimethylacetal (DMF-DMA) under solvent-free assisted by MW irradiations [61]. These intermediates **24** have been used as one of the key steps in the construction of the pyridone ring system. However, in second step of the synthesis of 2-pyridones. A new MCR has been developed using Al_2O_3 as a clean catalyst; A mixture of enaminone **24**, ethyl cyanoacetate **17**, and primary amine in the presence of catalytic amount of basic Al_2O_3 was heated at 150°C for 2-3h to afford the corresponding 2-pyridones **25** in excellent yields [59] (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

The condensation of the corresponding 1,3-diaryl-2-propen-1-ones **26** with ethyl cyanoacetate in boiling ethanol containing excessive ammonium acetate forms 3-cyanopyridone **27** [33] (cf. scheme 9).



26 **17** **27**

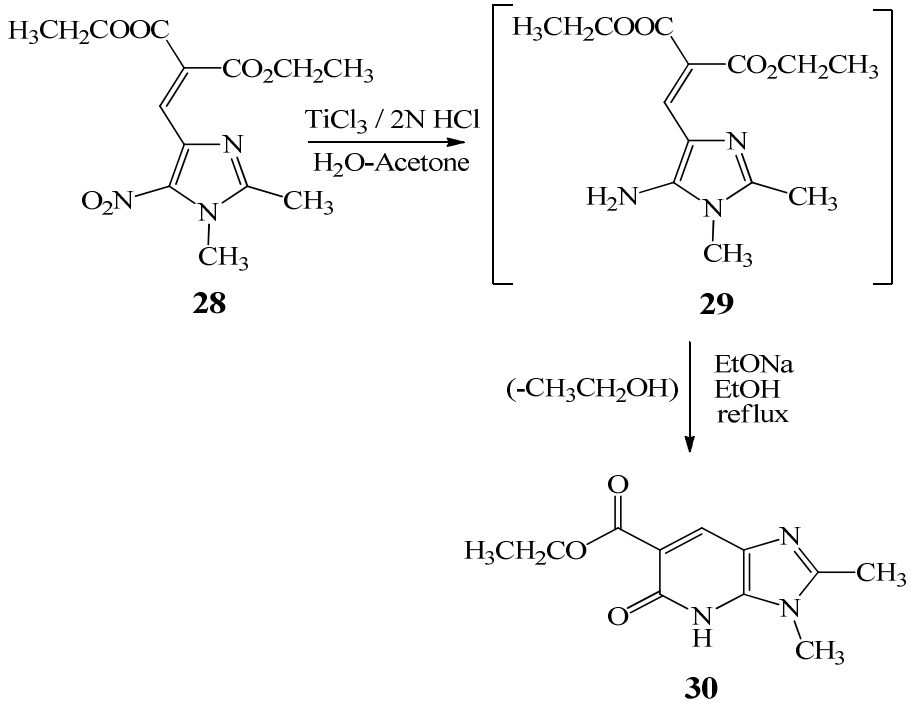
Ar= C_6H_4-OCH_3-4 C_6H_3-$(OCH_3)_2$-2,4 C_6H_3-$(OCH_3)_2$-3,4

$Ar^{/}$= C_6H_4-F-4 C_6H_4-Cl-4 C_6H_4-OH-4

Scheme 9

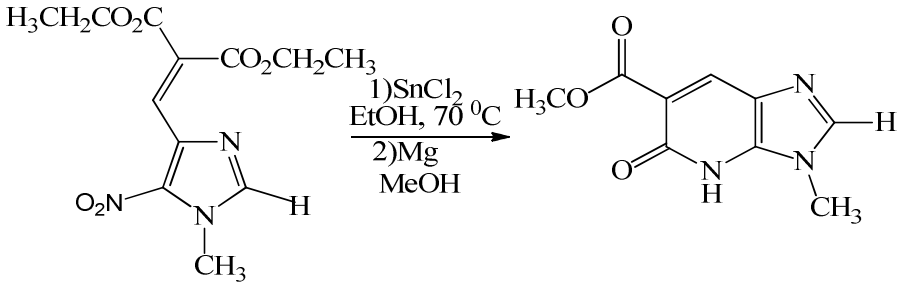
1.4. From nitroimidazole derivatives

The nitro group of diethyl 2-[(1,2-dimethyl-5-nitro-1*H*-imidazol-4- yl)methylene]malonate **28** was reduced in presence of weak reducing agent, titanium(III) chloride (30 wt % solution in 2N hydrochloric acid) in a H_2O-acetone mixture at room temperature. The resulting intermediate **29** was then heated in ethanolic sodium ethoxide solution to give the corresponding fused pyridone **30** [30] (cf. scheme 10).



Scheme 10

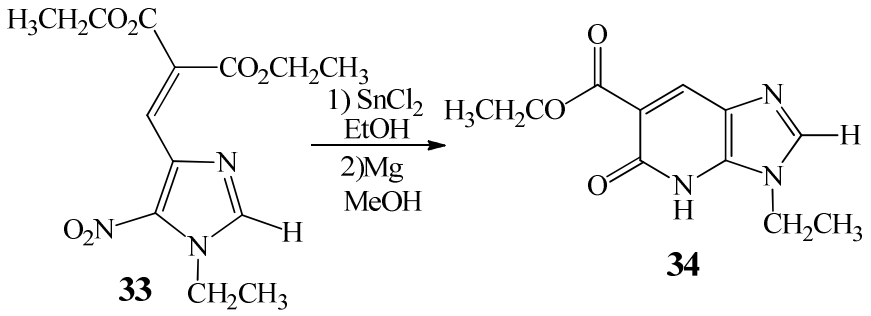
Unfortunately, this method was found to be not applicable to all nitroimidazoles. The 5-nitroimidazoles without alkyl substituents in the 2-position gave poor yields, so, it was necessary to find more general conditions and switched to other metal halides. Thus, it has been found that $SnCl_2$ in ethanol gave the best results. Reduction of compound **31** occurred with five equivalents of $SnCl_2$ in ethanol at 70 °C, then the corresponding amine was treated with two equivalents of magnesium (powder) in methanol at room temperature during 20 h leading to the corresponding bicyclic pyridone **32** in 92% yield [30] (cf. scheme 11).



31 **32**

Scheme 11

The imidazopyridone **32** was obtained as the methyl ester due to the transesterification reaction in methanol. These conditions were applied to the *N*-ethyl imidazole analogue of **31**, but gave the imidazopyridone **34** in poor yield [30] (cf. scheme 12).



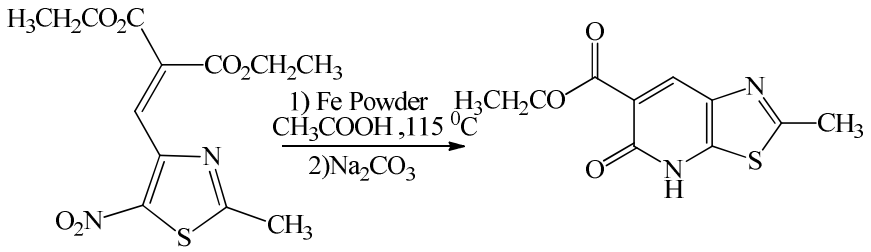
33 **34**

Scheme 12

1.5. From nitrothiazole derivatives

On the other hand, both the procedures previously described gave very poor yields of thiazolopyridone **36** when applied to the nitrothiazole **35**. Consequently Other

reaction conditions using iron in glacial acetic acid has been reported in previous publication [31]. Under these conditions, diethyl 2-[(2-methyl-5-nitrothiazol-4-yl)methyl-ene]malonate **35** afforded the target lactam **36** [30] (cf. scheme 13).



35 **36**

Scheme 13

1.6. From Baylis-Hillman acetate

The α,β-unsaturated methyl ester **39** was synthesized from the reaction of Baylis-Hillman acetate **37** and methyl acetoacetate **38** in 77% yields [44, 52, 53, 62- 64]. The ester **38** indeed produced 2-pyridone **44**, in low yield (16%), along with three other products, **41** (34%), **42** (7%) and **43** (5%), when subjected to the conditions previously employed for the synthesis of pyridine derivatives (NH_4OAc (3.0 equiv)/AcOH/reflux) [96]. Increasing the reaction temperature or varying the solvent (propionic or butyric acid) did not improve the results. The reaction gave much better yield of **44**(75%), while suppressing the formation of by-products **41**(4%), **42** (1-2%) and **43** (5%), when **39** was