

Benha University  
Faculty of Science  
Chemistry Department



Date : June, 13<sup>th</sup> 2019  
Time : 2 hrs  
Organic compounds and its uses in  
different applied research (626 Ch)  
Pre-Master Students

الإجابة النموذجية لامتحان مادة المركبات العضوية واستخداماتها في البحوث

التطبيقية

كود المادة: (626 ك)

(ورقة امتحانية كاملة)

المستوى : تمهيدى ماجستير كيمياء عضوية

التاريخ : الخميس 2019 / 6 / 13

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قسم : الكيمياء

كلية : العلوم

## I. Write the different methods for synthesis of pyridopyrimidine? (20 mark)

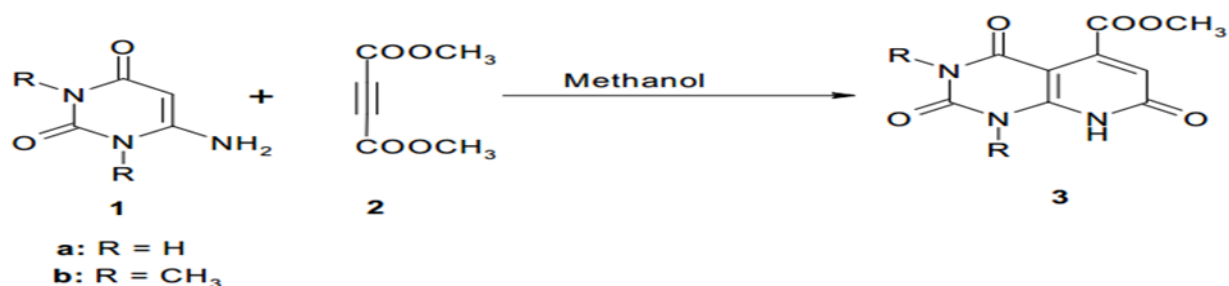
Synthesis of pyrido[2,3-d]pyrimidine derivatives was performed according to the following general strategies:

- (i) Fusion of the pyridine ring onto the pyrimidine ring system
- (ii) Fusion of the pyrimidine ring onto the pyridine ring system
- (iii) From Acyclic Intermediates

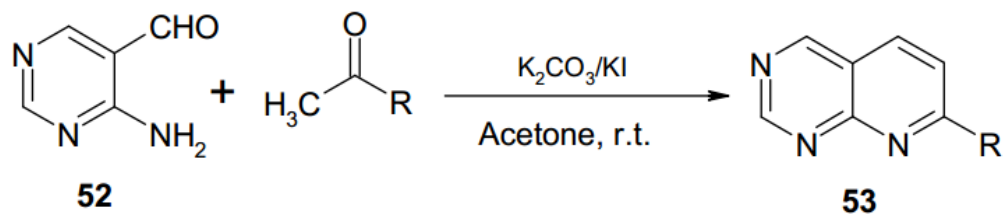
### (i) Fusion of the pyridine ring onto the pyrimidine ring system

#### Dimethyl acetylenedicarboxylate (DMAD):

Recently unsubstituted 6-aminouracil (1a) and its N-alkyl derivative 1b [62,63] have been found to react with dimethyl acetylenedicarboxylate (DMAD) (2) in protic media to give 5-carboxamido-7-oxopyrido[2,3-d]pyrimidines (3)



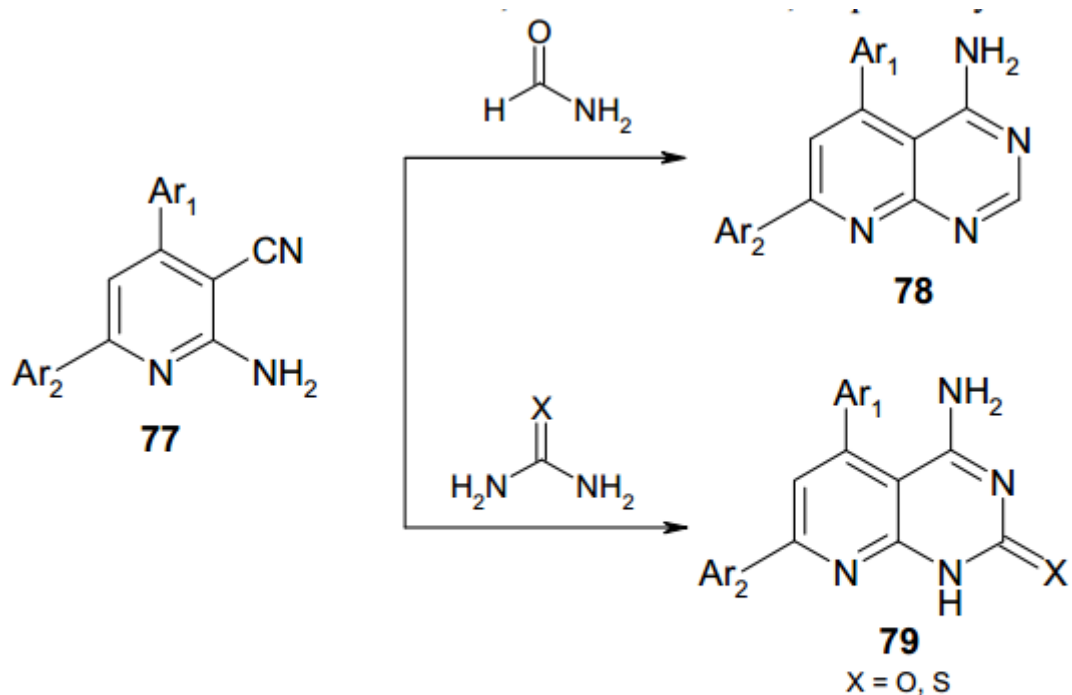
4-amino-5-formylpyrimidine 52 condensed with various aromatic ketone derivatives, in the presence of K<sub>2</sub>CO<sub>3</sub> and KI in acetone, to afford the corresponding 7-substituted pyrido[2,3-d]pyrimidine derivatives 53

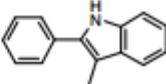


R = C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>4</sub>-4-Cl, C<sub>6</sub>H<sub>4</sub>-4-CH<sub>3</sub>, C<sub>6</sub>H<sub>4</sub>-4-OCH<sub>3</sub>, pyridinyl, thienyl, furanyl

**(i) Fusion of the pyrimidine ring onto the pyridine ring system**

2- Aminonicotinonitril:-A series of pyrido[2,3-d]pyrimidine derivatives viz 4-amino-pyrido[2,3-d]pyrimidines 78,[117-121] 4-aminopyrido[2,3-d]pyrimidins 79, [117,119,120] have been synthesized by the condensation reaction of 2-amino-4,6-disubstituted pyridine carbonitriles 77 with formamide, urea and thiourea, respectively.



Ar<sub>1</sub> = 2,4-dichlorophenyl, 4-methoxyphenyl,   
 Ar<sub>2</sub> = phenyl, 4-bromophenyl, 2-hydroxyphenyl

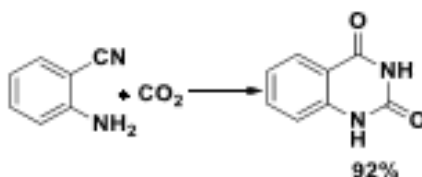
### (iii) Acyclic Intermediates

Synthesis of 5,6-dihydropyrido[2,3-d]pyrimidine derivatives directly from acyclic precursors, in which the pyrimidine and pyridine rings were constructed simultaneously, has been reported.

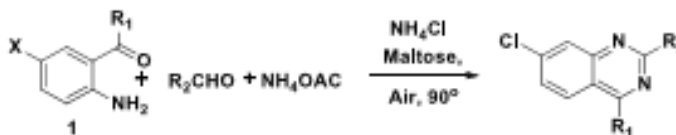
Ethyl cyanoacetate was reacted with ethyl acrylates forming diethyl 2-cyanoglutarates 112 which treated with guanidine in ethanol to afford 2-amino-5,6-dihydropyrido[2,3-d]pyrimidin-4,7-dione 113

## II. Explain the strategy for the synthesis of quinazoline derivatives? (20 mark)

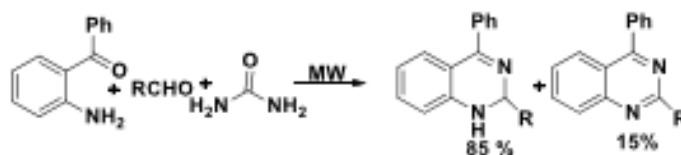
- simple and catalyst free route to synthesize potential quinazoline 2,4 (1H, 3H) diones in water from CO<sub>2</sub> and 2-amino benzonitrile. He also found an excellent yield by using water as a solvent as compared to organic solvents.



- An efficient and catalyst free synthetic route for the synthesis of quinazoline derivatives in high yields is given by Zhang et al. It is one pot three component reaction in which all the three reactants (2-aminoaryl ketones, aldehyde and ammonium acetate) .

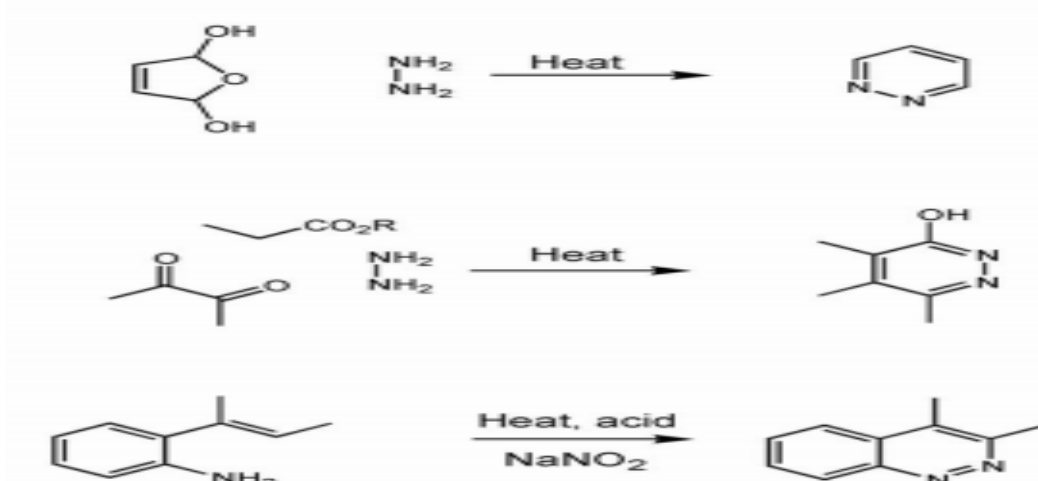


- a simple, clean, solvent free and catalyst free synthesis of 2,4-disubstituted-1,2-dihydroquinazoline with excellent yields within minutes. In this reaction, 2-aminobenzophenone, aldehydes and urea undergo microwave irradiation to give the final product. Urea is used as a source of ammonia.

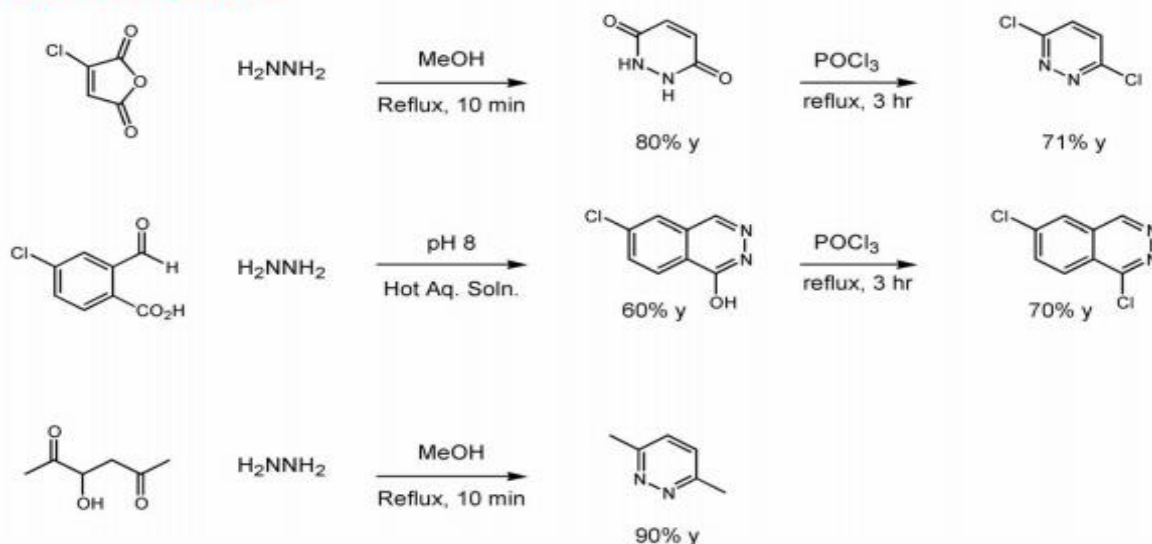


### III. Outline on the utility of dicarbonyl compounds in the synthesis of pyridazine derivatives? (20 mark)

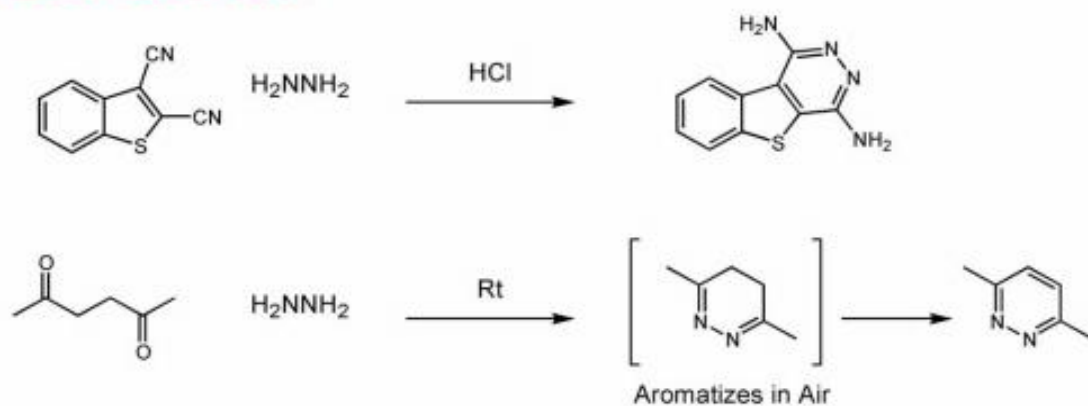
#### Synthesis of pyridazine;



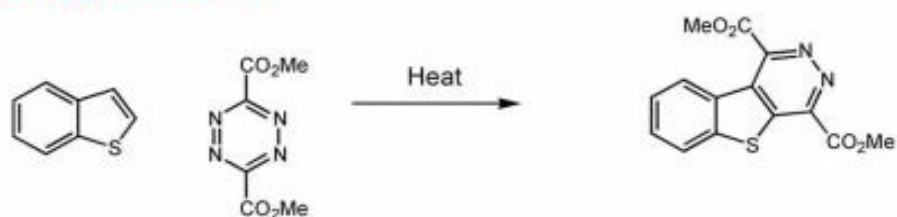
#### ■ Use of keto-acids etc.



■ Use of keto-acids etc.



■ From 1,2,4,5Tetrazines



IV. Discuss the application of :

[20 Mark]

a. Application of purine:

Purines and aminopurines are important compound classes with various physiological and pharmacological properties. For example,

1. purine derivatives are reported to act as nucleotide binding proteins that play a significant role in many biological processes.

2. Other representatives of this class have antirhinovirus 3 or antitumor activity as kinase inhibitors

Purine nucleoside derivatives have provided a productive area of chemical and biological research. For example, some purine

nucleoside analogues are used as antiviral (AZT, d4T, 3TC, etc.) [1a] and antitumor agents (AraC, FU, etc.). Furthermore, N-9 substituted purine nucleoside analogues are a very important class of heterocyclic compounds in biology, fulfilling functional roles as nucleic acids, coenzymes, and constituents in metabolic processes, energy storage, and cell signaling.

#### **b. Application of quinazoline:**

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities.

Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer, anti-inflammation, anti-bacterial, analgesia, anti-virus, anti-cytotoxin, anti-spasm, anti-tuberculosis, anti-oxidation, antimalarial, anti-hypertension, anti-obesity], anti-psychotic, anti-diabetes, etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods.

the potential anti-obesity activity of quinazoline derivatives, which were determined as MCHR1 antagonists.

#### **c. Application of pyridopyridazine:**

Pyridopyridazine compounds are important nitrogen atom containing heterocyclic compounds due to their pharmacological versatility. This heterocycle system characterized a structural feature for different types of bioactive compounds that exhibiting various types of biological activities which make it an attractive scaffold for the design and development of new drug molecules.

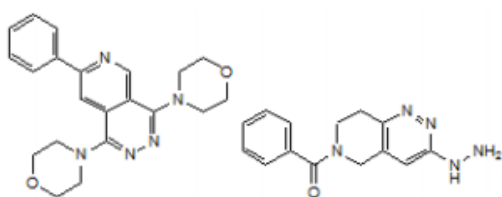
1- Anti-Inflammatory and Analgesic Activity;

Some pyrido[2,3-d]pyridazine-2(1H)-ones are useful in prophylaxis and management of protein kinase mediated inflammation and related diseases like rheumatoid arthritis, pulmonary diseases and pain.

## 2 -Antihypertensive Activity;

The antihypertensive drugs are of critical importance in order to control of Blood Pressure (B.P). A series of substituted-pyridopyridazines, some compounds

have excellent diuretic activity and different characters from known diuretics like thiazides, carbonic anhydrase inhibitors or furosemide.



Pyridopyridazine derivatives as antihypertensive agents.

## 3- Central Nervous System Activities;

A series of pyrido[2,3-d]pyridazines were selective ligands for GABA-A receptors and they are used in treatment of various central nervous system (CNS)

disorders like, anxiety, panic, phobia, psychoses (schizophrenia).

## 4-Antihistaminic Activity;

Allergic rhinitis is mediated by histamine (intracellular chemical messenger) which is released from several cells and particularly by mast cells. Some substituted pyrido[3,4-d]pyridazines 13a-c were found to have antihistaminic action and could be useful in treatment of allergic and inflammatory diseases of the respiratory tract like asthma, bronchitis, allergic rhinitis, chronic Obstructive Pulmonary Disease (OPD).

*All the best wishes,*

**Prof. Dr/ Aly Abdelmaboud Aly**