Faculty of science
Chemistry department

Synthesis and chemical reactions of some pyrano[2,3-*c*]pyrazoles

Thesis Submitted By

Mohamad Nabil Abdulhameed Mohamad
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Approval sheet

Synthesis and chemical reactions of some pyrano[2,3-*c*]pyrazoles

Name of the candidate: Mohammad Nabil Abdulhameed Mohammad

This thesis has been approved for submission by supervisors:

Thesis Advisors **Approved**

Prof. Dr. Hassan M. F. Madkour
Faculty of Science, Ain Shams University

Dr. Omnia E. A. Mostafa
Faculty of Science, Ain Shams University

Dr. Eman A. El-Bordany
Faculty of Science, Ain Shams University

Dr. Ahmed K. Elziaty
Faculty of Science, Ain Shams University

Head of Chemistry Department

Prof. Dr: Ibrahim H. A. Badr

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Contents

Abstract

It has been reported that pyran derivatives possess antitumor activity [301], hypotensive effect [184], plant growth regulation effects [6], anticancer activity [120], antifungal effect [316]. The literature survey also reveals that enaminonitrile derivatives were used in the synthesis of many biologically active heterocyclic compounds [263]. On the basis of these reports, we extended our investigation in synthesizing heterocyclic systems and evaluate their antimicrobial activity.

Hence; 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile was prepared and utilized as a synthon in annulation reactions to get new fused heterocycles. The structural features of these new compounds were confirmed by spectral analysis as well as elemental analyses.

Summary

SUMMARY

The present investigation deals with the role of enaminonitriles in the synthesis of new heterocyclic systems from readily available materials, the biological activity (antimicrobial activity by diffusion disk method, minimum inhibitory concentration "MIC" and minimum bactericidal concentration "MBC") of these systems were also investigated.

Our target compound was obtained when 3-methyl-1*H*-pyrazol-5(4*H*)-one **1** was allowed to react with 2-(4-chlorobenzylidene)malononitrile **2** in refluxing ethanol in presence of few drops of piperidine; the Michael adduct 6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydro pyrano[2,3-*c*]pyrazole-5-carbonitrile **3** was isolated.

The behavior of starting compound **3** toward different electrophiles and nuleophiles had been studied. So, when pyranopyrazole **3** was heated in acetic anhydride at refluxing temperature the unexpected methyl oxazinone derivative **4** was obtained **[cf. scheme 1]**.

The reaction of our starting pyranopyrazole **3** with oxalyl chloride in dry toluene afforded the oxoacetyl

derivative **5** which has been allowed to react with appropriate alcohol or amine without purification in some coming reactions. Also the reaction of starting compound **3** with carbon disulphide gave the dithione derivative **6**, and when compound **3** was submitted to react with formic acid, the pyrimidinone derivative **7** was isolated **[cf. scheme 1]**.

The reaction of enaminonitrile **3** with sulphuric acid was investigated. Thus when compound **3** was stirred in concentrated sulphuric acid at 0 ^{o}C, the carboxamide derivative **8** was isolated.

The reaction of starting compound **3** with formamide at 100 ^{o}C afforded the aminopyrimidine derivative **9**. On the other hand, the reaction of starting compound **3** with benzoyl chloride in boiling toluene afforded the phenyloxazinone derivative **10** while the reaction of starting pyranopyrazole **3** with ethyl chloroacetate gave the unexpected ethyl acetate pyranopyrazole derivative **11**.

The reaction of pyranopyrazole **3** with chloroacetic acid gave the pyrrole carboxylic acid derivative **12** while when starting enaminonitile **3** reacted with diethyl malonate in dry methanol and sodium methoxide, the amino pyridine carboxylic acid derivative **13** was obtained. The reaction of starting compound **3** with urea and / or thiourea in refluxing

toluene gave the amino hydroxy pyrimidine derivative **14a** and / or amino pyrimidine thiol derivative **14b** respectively **[cf. scheme 2]**.

The reaction of starting enaminonitrile **3** with 4-chlorobenzaldehyde gave the corresponding Schiff base derivative **15**.

The reaction of pyranopyrazole **3** with refluxing trimethyl orthoformate and triethyl orthoacetate resulted in the corresponding formimidate derivative **16** and acetimidate derivative **17** respectively.

when oxazinone derivative **4** was allowed to react with formamide at 120 ^{o}C, the methyl pyrimidinone derivative **18** was obtained. On the other hand; compound **4** reacted with hydrazine hydrate in refluxing ethanol to give the acetamide derivative **19 [cf. scheme 3]**.

The oxoacetyl derivative **5** reacted directly with refluxing dry methanol and refluxing dry ethanol to afford the oxoacetate derivatives **20a** and **20b** respectively.

Also, when the oxoacetyl derivative **5** was allowed to react with anthranilic acid in dry pyridine, the reaction product was the oxoacetamidobenzoic acid derivative **21** which was cyclized in refluxing acetic anhydride to yield the benzooxazinyl oxazinone derivative **22 [cf. schemes 4]**.

The carboxamide derivative **8** was submitted to react with urea and / or thiourea in boiling toluene to give the pyrimidine diol **23a** and pyrimidine thiol **23b** derivatives respectively. On the other hand, reaction of **8** with formamide at 120 ºC led to the pyrimidinone derivative **7**, which has been identified as the same product resulted from reaction of the starting enaminonitrile compound **3** with formic acid **[cf. scheme 5]**.

Chlorination of pyrimidinone derivative **7** with phosphorous oxychloride afforded the chloropyrimidine derivative **24**. The later derivative **24** was reacted with hydrazine hydrate in refluxing ethanol to give the hydrazinopyrimidine derivative **25**. Also; chloropyrimidine derivative **24** reacted with sodium ethoxide; the resulted product was the ethoxypyrimidine derivative **26**.

When acetimidate derivative **17** was subjected to react with hydrazine hydrate in refluxing ethanol, it afforded the hydarzino methyl pyrimidine derivative **27** which reacted with carbon disulphide in dry pyridine to give the triazolopyrimidine thione derivative **28** while the reaction of **27** with refluxing acetic anhydride afforded the pyrimidine acetohydrazide derivative **29 [cf. scheme 6]**.

Tetrafused heterocyclic systems have been synthesized *via* hydarzinopyrimidine **27**. Thus, reaction of **27** with benzoyl chloride in refluxing toluene afforded the phenyl triazolopyrimidine derivative **30**, while the reaction of **27** with sodium nitrite in the presence of concentrated hydrochloride acid / glacial acetic acid mixture at 0 ^{o}C gave the tetrazolopyrimidine derivative **31 [cf. scheme 6]**.

Antibacterial and antifungal activities of some detected synthesized compounds were screened using the following methods and techniques:

1- Diffusion disk method.

2- Determination of the minimum inhibitory concentration (MIC) using tube dilution assay technique.

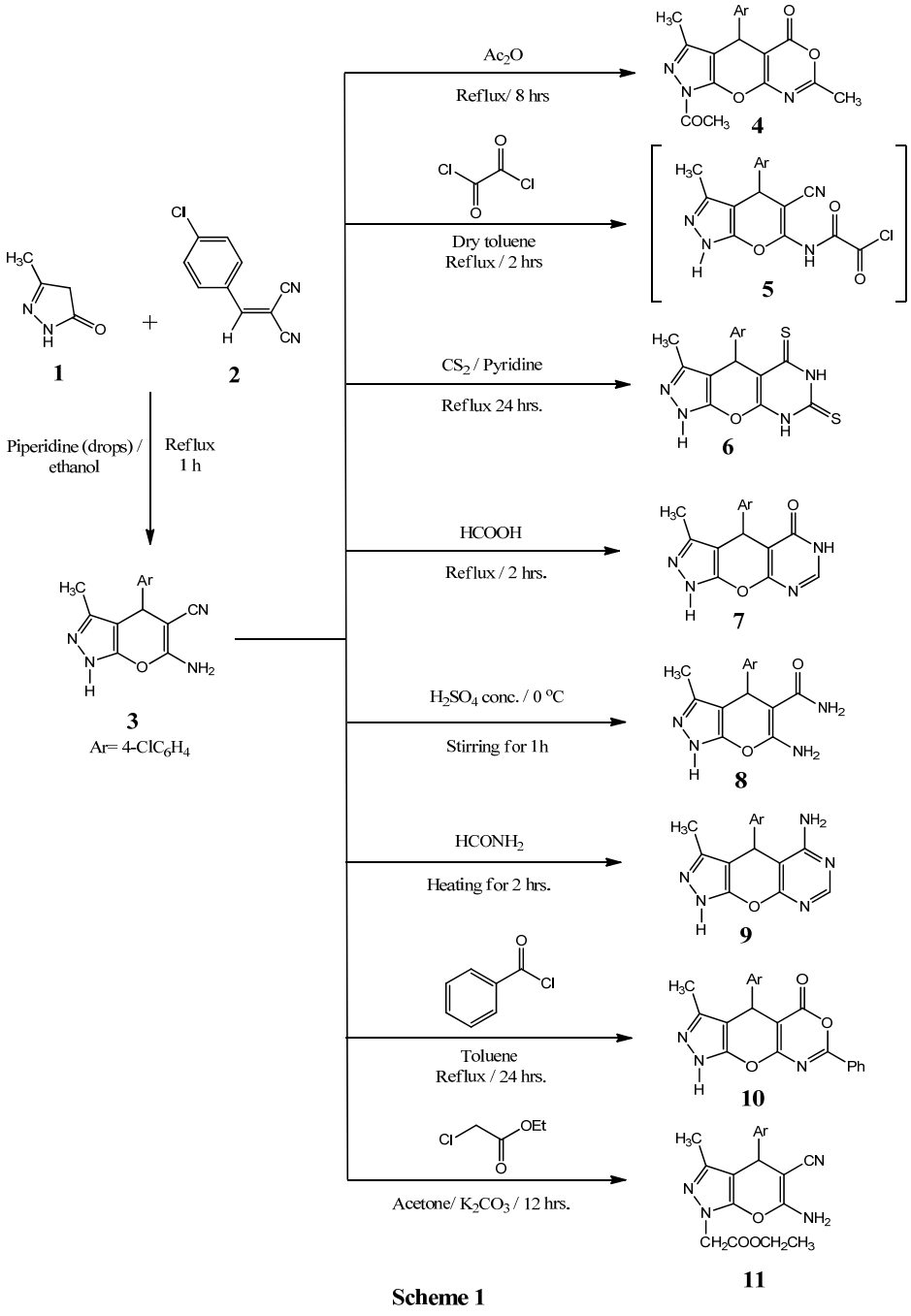
3- Determination of the minimum bactericidal concentration (MBC).

The experiments were performed using test bacterial organisms belonging to the Gram positive bacteria *(Staphylococcus aureus, Bacillus subtilis, Bacillus cereus and Kocuria rhizophila)* and Gram negative bacteria *(Salmonella typhimurium, Klebsiella pneumoniae and Pseudomonas aeruginosa)* respectively as well as *Candida albicans* as yeast and *Aspergillus niger* as mould. The active compounds were compared with

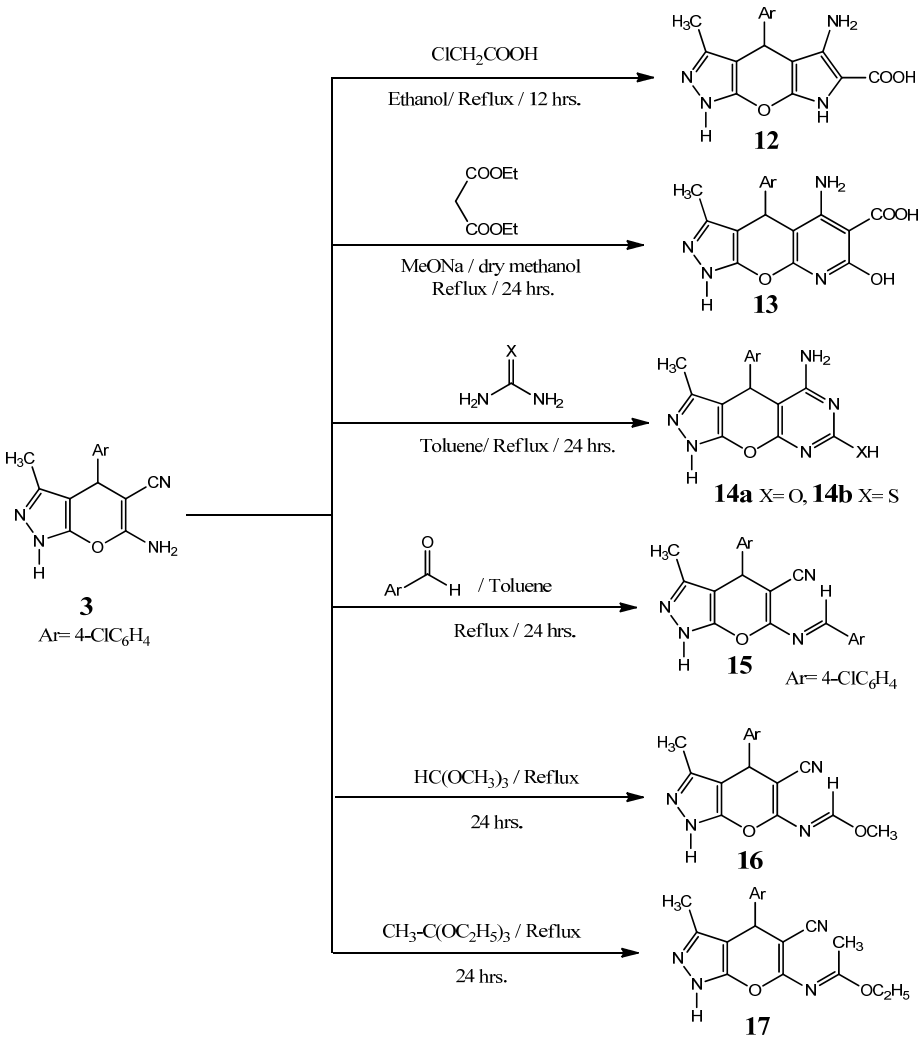
standard antibiotics Novobiocin and Chloramphenicol and the antifungal drug Nystatin.

The final results of biological activity can summarized as follows:

1- Compounds **3**, **6**, **7**, **9**, **12**, **13**, **14a** and **16** are active compounds.
2- The above compounds have activity towards the tested gram positive bacteria, yeast and mould varied according to each compound.
3- The mixture of compounds **3**+**9**, **9**+**16** and **6**+**16** were found to be active against tested gram negative bacteria.
4- Most of active compounds ranged from moderate to good bactericidal agents with more advantage to compound **9** which exceeds the compared antibiotics in some cases.


Piperidine (drops) / ethanol
Reflux 1 h
Ar= 4-ClC6H4
Ac2O
Reflux/ 8 hrs
Dry toluene
Reflux / 2 hrs
CS2 / Pyridine
Reflux 24 hrs.
HCOOH
Reflux / 2 hrs.
H2SO4 conc. / 0 °C
Stirring for 1h
HCONH2
Heating for 2 hrs.
Toluene
Reflux / 24 hrs.
Acetone/ K2CO3 / 12 hrs.

Scheme 1


ClCH2COOH
Ethanol/ Reflux / 12 hrs.
12
COOEt
COOEt
MeONa / dry methanol
Reflux / 24 hrs.
13
Toluene/ Reflux / 24 hrs.
14a X= O, 14b X= S
3
Ar= 4-ClC6H4
/ Toluene
Reflux / 24 hrs.
15
Ar= 4-ClC6H4
HC(OCH3)3 / Reflux
24 hrs.
16
CH3-C(OC2H5)3 / Reflux
24 hrs.
17

Scheme 2