Ain Shams University
College of Women
For Arts, Science and Education
Chemistry Department

Synthesis and Biological Activity Of Some Pyridazine Derivatives

A Thesis Submitted for the Master Degree
In

Organic Chemistry

Presented By

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B.Sc. (2006)

To

Chemistry Department
College of Women for Arts, Science and Education
Ain Shams University

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Lecturer of Organic Chemistry

(2010)

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Approval of Chemistry Department Council / / 2010

Approval of Faculty Council **Approval of University Council**

/ / 2010 **/ / 2010**

QUALIFICATIONS

Name: Heba Kamal Abd El Mawgoud Abd El Kream

Scientific Degree: B.Sc.

Department: Chemistry

College: College of Women for Arts, Science and Education

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NOTE

The candidate has attended courses for one year, covering the following topics:

- Spectroscopy.
- Chemistry of heterocyclic compounds.
- Natural products.
- Petrochemicals.
- Organometallic compounds.
- Advanced reaction mechanisms.
- Photochemistry.
- Kinetics and catalysis chemistry.
- Quantum chemistry.
- Thermodynamics.
- Instrumental analysis.
- English language.

She has successfully passed a written examination in these courses, in partial fulfillment for the master degree of science.

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She also wishes to express her thanks to ***Dr. Ekhlass Mohammed Nassar****, Lecturer of Organic Chemistry, Chemistry Department, College of Women for Arts, Science and Education, Ain Shams University, for her help.*

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CONTENTS

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DEDICATION

To

my distinguished parents

I do appreciate my god

for giving me wonderfully parents

who are enlightening and always supporting me

in all my life.

I also thank my family

for continuous encouragement and help.

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The starting material, 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbonitrile **1**, was subjected to subsequent reactions to afford new condensed polycyclic compounds containing thieno[2,3-*c*]pyridazine moiety with anticipated biological activity. It was reacted with aromatic and heteroaromatic aldehydes, cyclohexanone, and phenyl isothiocyanate to afford 5-arylidene- and 5-heteroarylideneaminothienopyridazine derivatives $\mathbf{2_{a-h}}$, aminopyridazinothienoquinoline derivative **4**, and *N*,*N* `-phenylthiourea derivative **5**, respectively. Reaction of the enamino-nitrile **1** with benzyl chloride under different reaction conditions gave 5-benzyl-amino derivative **8** and aminopyrrolothienopyridazine derivative **9**. Also, reaction with hydroxylamine hydrochloride under different conditions led to 6-carboxamidoxime derivative **12** and aminopyrazolothienopyridazine hydrochloride derivative **13**. Diazotization of compound **1,** followed by coupling with 1- and 2-naphthol gave the corresponding azo derivatives $\mathbf{17_{a,b}}$. Heating compound **1** with hydrazine hydrate under reflux for 2 h afforded the 6-carboximidohydrazide derivative **19**. On the other hand, when the reaction was carried out under reflux for 6 h, aminopyrazolo-thienopyridazine derivative **20** was obtained.

The carboximidohydrazide derivative **19** was allowed to react with benzaldehyde, acetic anhydride, dimethylformamide, formic acid, acetyl-acetone, maleic anhydride and phthalic anhydride to furnish new fused polycyclic compounds **22**, **24**, **28**, **29**, **30**, **31** and **37**, respectively.

Structural assignment of the newly synthesised compounds was based on their IR, MS, ^{1}H-NMR, and elemental analyses.

Also, the biological activity of the newly synthesised compounds was screened.

This work aims to study synthesis, reactions, and biological activity of some pyridazine derivatives.

The starting material, 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbonitrile **1**, was synthesised following the literature procedure by refluxing a solution of the commercially available 4-cyano-5,6-diphenyl-pyridazine-3(2H)-thione with chloroacetonitrile in dry acetone in presence of catalytic amount of potassium carbonate.

The enamino-nitrile **1** was allowed to react with equimolecular quantity of aromatic and heteroaromatic aldehydes namely *p*-anisaldehyde, *p*-nitrobenzaldehyde, furfural, 5-methylfurfural, *N*-methyl-pyrrole-2-carboxaldehyde, 5-methyl-2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and 2-thiophenecarboxaldehyde in benzene to give good yields of the 5-arylidene- and 5-heteroarylideneaminothieno-pyridazine derivatives $\mathbf{2_{a-h}}$ **(Scheme 1)**.

On treatment of compound **1** with cyclohexanone in presence of one molar equivalent of anhydrous zinc chloride, a 1:1 complex of the amino derivative with zinc chloride was separated, which on treatment with 40 % NaOH followed by extraction with benzene gave 10-amino-3,4-diphenyl-6,7,8,9-tetrahydropyridazino[4`,3`:4,5]thieno[3,2-*b*]quinoline **4** **(Scheme 1)**.

Reaction of compound **1** with phenyl isothiocyanate in dimethyl-formamide in presence of triethylamine for 18 h at room temperature led to the corresponding *N*,*N* `-disubstituted thiourea derivative **5**, which was allowed to react with hydrazine hydrate 98 % in ethanol at reflux temperature for 3 h to give 7-amino-6-anilino-8-imino-3,4-diphenyl-pyrimido[4`,5`:4,5]thieno[2,3-*c*]pyridazine **6**. The latter compound

underwent acetylation with acetic anhydride to give the corresponding 7-acetylamino derivative **7 (Scheme 1)**.

Heating a mixture of compound **1** with benzyl chloride in ethanol at reflux temperature for 3 h gave the corresponding 5-benzylamino derivative **8**, which was cyclized to pyrrolothienopyridazine derivative **9** using sodium ethoxide in absolute ethanol. The latter compound was obtained directly upon treatment of compound **1** with benzyl chloride in presence of ethanolic sodium hydroxide. Reaction of compound **9** with nitrous acid followed the normal course of diazotization yielding clear diazonium salt solution, which reacted with 2-naphthol in ethanolic solution in presence of sodium acetate trihydrate as buffered solution to give the corresponding azo derivative **11 (Scheme 1)**.

Reacting equimolecular quantities of compound **1** and hydroxyl-amine hydrochloride in methanol in presence of ammonium hydroxide at room temperature for 24 h yielded the corresponding 6-carboxamidoxime derivative **12**. On the other hand, when the reaction was carried out in boiling pyridine containing triethylamine for 5 h, 3-amino-7,8-diphenyl-1H-pyrazolo[3`,4`:4,5]thieno[2,3-*c*]pyridazine hydrochloride **13** was obtained, which underwent diazotization with nitrous acid, followed by coupling with 2-naphthol to give the corresponding azo compound **15**. The latter compound underwent cyclization upon heating in glacial acetic acid for 3 h to give 3,4-diphenylnaphtho[2,1-*e*]pyridazino[4``,3``:4`,5`]-thieno[2`,3`:4,5]pyrazolo[3,2-*c*][1,2,4]triazine **16** by elimination of one molecule of water **(Scheme 2)**.

Diazotization of compound **1** was carried out, followed by coupling with 1- and 2-naphthol to give 5-[(4-hydroxynaphthalen-1-yl)diazenyl]-

and 5-[(2-hydroxynaphthalen-1-yl)diazenyl]-3,4-diphenylthieno[2,3-*c*]-pyridazine-6-carboxamide **17_a** and **17_b** , respectively. A solution of compound **17_b** and $CoCl_2.6H_2O$ in a mixture of CH_3OH and $CHCl_3$ was refluxed for 3 h to give the corresponding complex **18**, which possessing a 1:2 metal / ligand ratio **(Scheme 2)**.

Compound **1** was reacted with hydrazine hydrate 98 % in refluxing ethanol for 2 h to give 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboximidohydrazide **19**. On the other hand, when the reaction was carried out under reflux for 6 h, cyclization of the intermediate carboximidohydrazide derivative took place to give 3-amino-7,8-di-phenyl-1H-pyrazolo[3`,4`:4,5]thieno[2,3-*c*]pyridazine **20**. The same result was also obtained when the carboximidohydrazide derivative **19** was refluxed in absolute ethanol for 5 h. Compound **20** underwent acetylation upon heating in acetic anhydride under reflux for 5 h to give the corresponding 3-acetylamino derivative **21**. Reaction of the 3-amino derivative **20** with $NaNO_2$ / H_2SO_4 gave the diazotized aminopyrazolo-thienopyridazine, which on coupling with 2-naphthol in presence of sodium acetate trihydrate as buffered solution give compound **15 (Scheme 2)**.

Condensation of the 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carboximidohydrazide **19** with benzaldehyde was carried out in 1:1 molar ratio to give 6-(*N* `-benzylidene)carboximidohydrazide derivative **22**, which can be cyclized on boiling with acetic anhydride for 5 h to give 7-benzylideneamino-8-imino-6-methyl-3,4-diphenylpyrimido[4`,5`:4,5]-thieno[2,3-*c*]pyridazine **23** in good yield **(Scheme 3)**.

Refluxing the carboximidohydrazide derivative **19** with acetic anhydride for 5 h produced the corresponding monoacetyl derivative, which underwent smooth cyclization to give the corresponding fused pyrimidothienopyridazine followed by diacetylation of the amino group, to give 7-diacetylamino-8-imino-6-methyl-3,4-diphenylpyrimido-[4`,5`:4,5]thieno[2,3-*c*]pyridazine **24**. Reaction of the latter compound with ethanolic sodium hydroxide under reflux for 2 h afforded the mono-acetyl derivative **27 (Scheme 3)**.

The carboximidohydrazide **19** was refluxed in dimethylformamide for 12 h to afford 7-amino-8-imino-3,4-diphenylpyrimido[4`,5`:4,5]-thieno[2,3-*c*]pyridazine **28**. Alternatively, the latter compound was obtained upon treatment of compound **22** with dimethylformamide at reflux temperature for 8 h **(Scheme 3)**.

The expected 7-formylamino-8-imino-3,4-diphenylpyrimido[4`,5`: 4,5]thieno[2,3-*c*]pyridazine **29** was obtained in moderate yield by refluxing the 6-carboximidohydrazide **19** with formic acid for 3 h. Compound **29** was also obtained by formylation of compound **28** with formic acid at reflux temperature for 2 h **(Scheme 3)**.

Compound **19** was condensed with acetylacetone to give 5-amino-6-[(3,5-dimethyl-1H-pyrazol-1-yl)(imino)methyl]-3,4-diphenylthieno-[2,3-*c*]pyridazine **30 (Scheme 3)**.

The condensation reaction of the carboximidohydrazide **19** with maleic anhydride in boiling dimethylformamide afford 6-imino-10,11-di-phenylpyridazino[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[1,2-*b*]-pyridazin-3(4H)-one **31**, which underwent chlorination with phosphoryl chloride to give the corresponding 3-chloro derivative **32**. Treatment of

the latter compound with sodium azide give 6-imino-10,11-diphenyl-pyridazino[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[1,2-*b*]tetrazolo[5,1-*f*]-pyridazine **33**. Heating compound **32** with sodium ethoxide in absolute ethanol at reflux temperature afford 3-ethoxy-6-imino-10,11-diphenyl-pyridazino[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[1,2-*b*]pyridazine **34**. Heating the 3-chloro derivative **32** with equimolecular amount of *p*-anisidine and 4-amino-*N*-phenylbenzenesulphonamide in ethanol / THF (1:4) at reflux temperature afford the expected 6-imino-*N*-(4-methoxy-phenyl)-10,11-diphenylpyridazino[4``,3``:4`,5`]thieno[3`,2`:4,5]-pyrimido[1,2-*b*]pyridazin-3-amine **35** and 4-[(6-imino-10,11-diphenyl-pyridazino[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[1,2-*b*]pyridazin-3-yl)-amino]-*N*-phenylbenzenesulphonamide **36**, respectively **(Scheme 4)**.

Also, the condensation reaction of the carboximidohydrazide **19** with phthalic anhydride in boiling dimethylformamide gave the pentacyclic compound 8-imino-12,13-diphenylpyridazino[4``,3``:4`,5`]thieno-[3`,2`:4,5]pyrimido[2,1-*a*]phthalazin-5(6H)-one **37**, which underwent chlorination with phosphoryl chloride to give the corresponding 5-chloro derivative **38**. Heating the latter compound with sodium azide in ethanol at reflux temperature for 7 h afford 6-imino-10,11-diphenylpyridazino-[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[2,1-*a*]tetrazolo[1,5-*c*]phthalazine **39**. Refluxing compound **38** with sodium ethoxide in absolute ethanol for 3 h afford good yield of 5-ethoxy-8-imino-12,13-diphenylpyridazino-[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[2,1-*a*]phthalazine **40**. Heating the 5-chloro derivative **38** with equimolecular amounts of *p*-anisidine and 4-amino-*N*-phenylbenzenesulphonamide in ethanol / THF (1:4) at reflux temperature afford the expected 8-imino-*N*-(4-methoxyphenyl)-12,13-

diphenylpyridazino[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[2,1-*a*]-phthalazin-5-amine **41** and 4-[(8-imino-12,13-diphenylpyridazino[4``,3``:4`,5`]thieno[3`,2`:4,5]pyrimido[2,1-*a*]phthalazin-5-yl)amino]-*N*-phenyl-benzenesulphonamide **42**, respectively **(Scheme 4)**.

Structural assignment of the newly synthesised compounds was based on their infrared, mass spectrum, nuclear magnetic resonance, and the elemental analyses.

Also, the biological activity of the newly synthesised compounds was screened, which revealed that the synthesised compounds showed high and / or very high antimicrobial activity against the examined bacteria and fungi, respectively. It could be concluded from the results that the biologically active synthesised compounds are nearly as active as the standard antibacterial Ciprofloxacin against the both tested Gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*). On the other hand, the biologically active synthesised compounds are active as the standard Fungicide Nystin against the both tested fungi (*Candida albicans* and *Aspergillus niger*).

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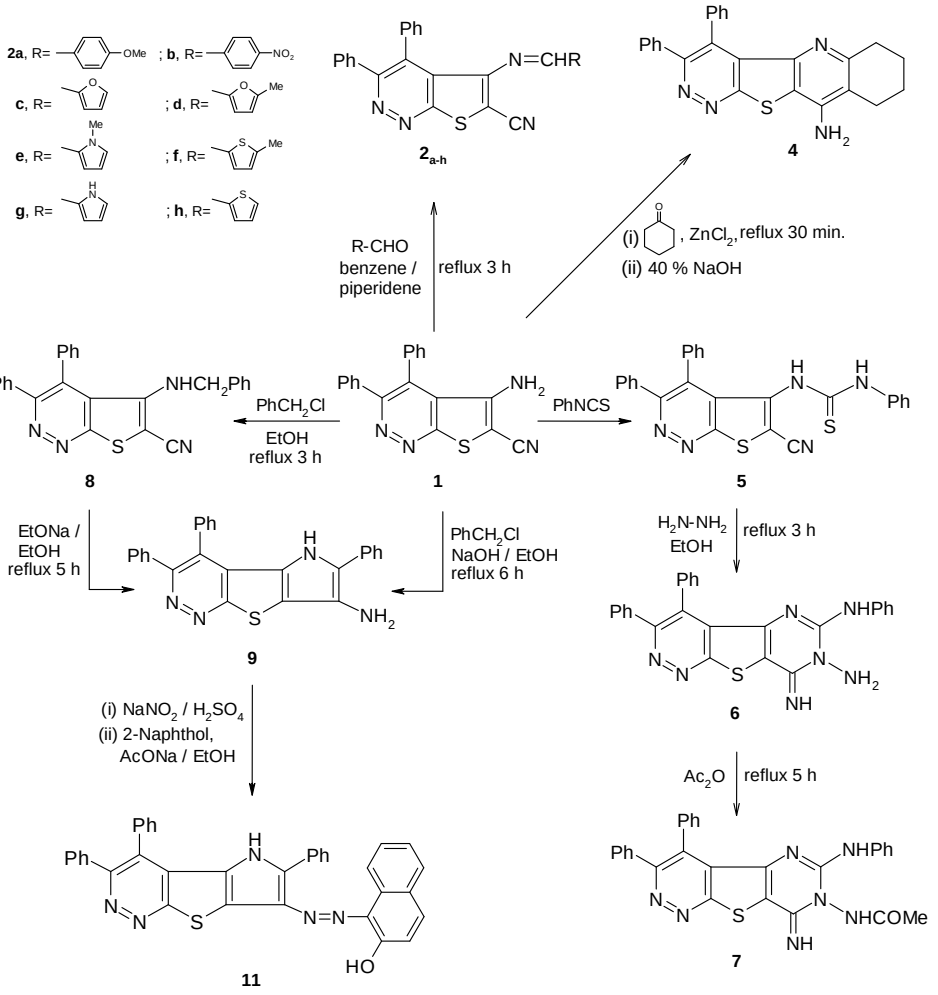
2a, R= OMe ; b, R= NO2
c, R= ; d, R= Me
e, R= Me ; f, R= Me
g, R= ; h, R=
2a-h
4
R-CHO
benzene /
piperidene
reflux 3 h
(i) , ZnCl2, reflux 30 min.
(ii) 40 % NaOH
8
1
5
PhCH2Cl
EtOH
reflux 3 h
PhNCS
EtONa /
EtOH
reflux 5 h
PhCH2Cl
NaOH / EtOH
reflux 6 h
9
H2N-NH2
EtOH
reflux 3 h
6
(i) NaNO2 / H2SO4
(ii) 2-Naphthol,
AcONa / EtOH
11
Ac2O
reflux 5 h
7

Scheme 1