Cairo University
Faculty of Science
Chemistry Department

SYNTHESIS AND CHARACTERIZATION OF SOME NEW HETEROCYCLIC COMPOUNDS CONTAINING N AND/OR S WITH EXPECTED BIOLOGICAL ACTIVITY

PRESENTED

BY

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ABSTRACT

Name: Labeeb Mohamed Shaif Mohamed

Title of Thesis: Synthesis and characterization of some new heterocyclic compounds containing N and/or S with expected biological activity.

Degree: Ph. D. Thesis, Faculty of Science Cairo University 2009–2010

This work has been carried out to investigate the chemical reactivity and synthetic potentiality of 2-thioxohydropyridine **11a-d** via their reaction with several active halogen-containing compounds to afford the corresponding 2-alkylthiopyridine in some cases and thieno[2,3-b]pyridine directly in most cases. Thieno[2,3-b]pyridine-2-carbohydrazides obtained through the reaction of 2-ethoxycarbonylthienopyridines with hydrazine hydrate which in turn, used to obtain the corresponding pyrimidinones **20-26(a-d)**, 1,3,4-oxdiazoles **28, 30(a-d),** pyrazolothienopyridine derivatives (**32a-d)** thienopyridine-3-amines **(34a-d),** pyrazolones **(36a-d),** pyrazolidine-3,5-diones **(38a-d)**. 3-Aminopyrazolopyridine obtained *via* the reaction of **11a-e** or **49a-e** with hydrazine hydrate which in turn, reacted with nitrous acid to give the diazonium salts **51a-e** which coupled with several active-hydrogen containing reagents to give the corresponding triazines. The structures of all newly synthesized heterocyclic compounds were elucidated by considering the data of IR, ^{1}H NMR (δppm), mass spectra as well as that of elemental analyses. Anti-Alzheimer, anti COX-2 and anti-Cancer activities were investigated for all newly synthesized heterocyclic compounds.

Key Words: 2-Cyanoethanethioamide, 6-Thioxo-1,6-dihydro-2,3'-bipyridine-5-carbonitrile, 6-(Alkylthio)-4-aryl-2,3'-bipyridine-5-carbonitriles, Thieno[2,3-b]pyridine, Thieno[2,3-b]pyridine-2-carbohydrazides, pyrimidinones, 3-aminopyrazolo[3,4-b]pyridine, *N*,*N*-Dimethyl-aminopyrazole, 3-phenyl-1,3-thiazol-2(3*H*)-ylidene,

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DEDICATION

TO

MY GODFATHER

MOHAMMAD DERHEM

TO

MY DEAR SISTER

NORYA MOHAMMAD AL HAJ

TO

MY FATHER AND MOTHER

TO

MY WIFE NEDAL

TO

MY DAUGHTER MISK

TO

MY SON AMEEN

WHO GAVE ME HELP AND SUPPORT

Labeeb Mohamed Shaif Mohamed

ACKNOWLEDGMENT

“I do thank God for all gifts He gave Me”

The author of the present thesis wishes to express his deep thanks and sincere gratitude to prof. Dr. Fawzy A. Attaby, Professor of Organic chemistry, Department of Chemistry, Faculty of Science, Cairo University, Dr. Azza M. Abdel-Fattah, Associated of Organic chemistry, Department of Chemistry, Faculty of Science, Cairo University, and Dr. Mohamed M. Elsayed, Associated Professor, Research Units, Hi-Care Pharmaceutical Co., Cairo, Egypt, not only for suggesting the work investigated, but also for kind supervision, advice and valuable criticism though out the work performed. My thanks extended to my best friend Mukhtar Abdul-Rahman Nasher from Taiz university.

Thanks are also due to all the members of the research group of Prof. Dr. Fawzy A. Attaby for their constant and support.

Labeeb M. Shaif M.

AIM OF THE PRESENT WORK

The present work aimed and was designed to fulfill the following objectives:

1- Continuation of the effort done by this group of research at Cairo University in the field of heterocyclic synthesis of derivatives with expected biological and medicinal activities.

2- Synthesis of several new heterocyclic derivatives containing N and/or S using the laboratory available chemicals and reagents.

3- Establishment of the structures of the newly synthesized heterocyclic compounds by considering the data of IR, ^{1}H NMR (δppm),, mass spectra and the elemental analyses.

4- Synthesis of some of these heterocyclic derivatives via alternative routes which was also, used as a tool to confirm the structures of the newly synthesized heterocyclic derivatives.

5- Study of the most probable mechanisms leading to the formation of the obtained heterocyclic products and comparison of our results with others of similar ring systems.

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SUMMARY OF THE ORIGINAL WORK

SUMMARY OF THE ORIGINAL WORK

The following is the summary of the original work investigated and included in the present thesis :

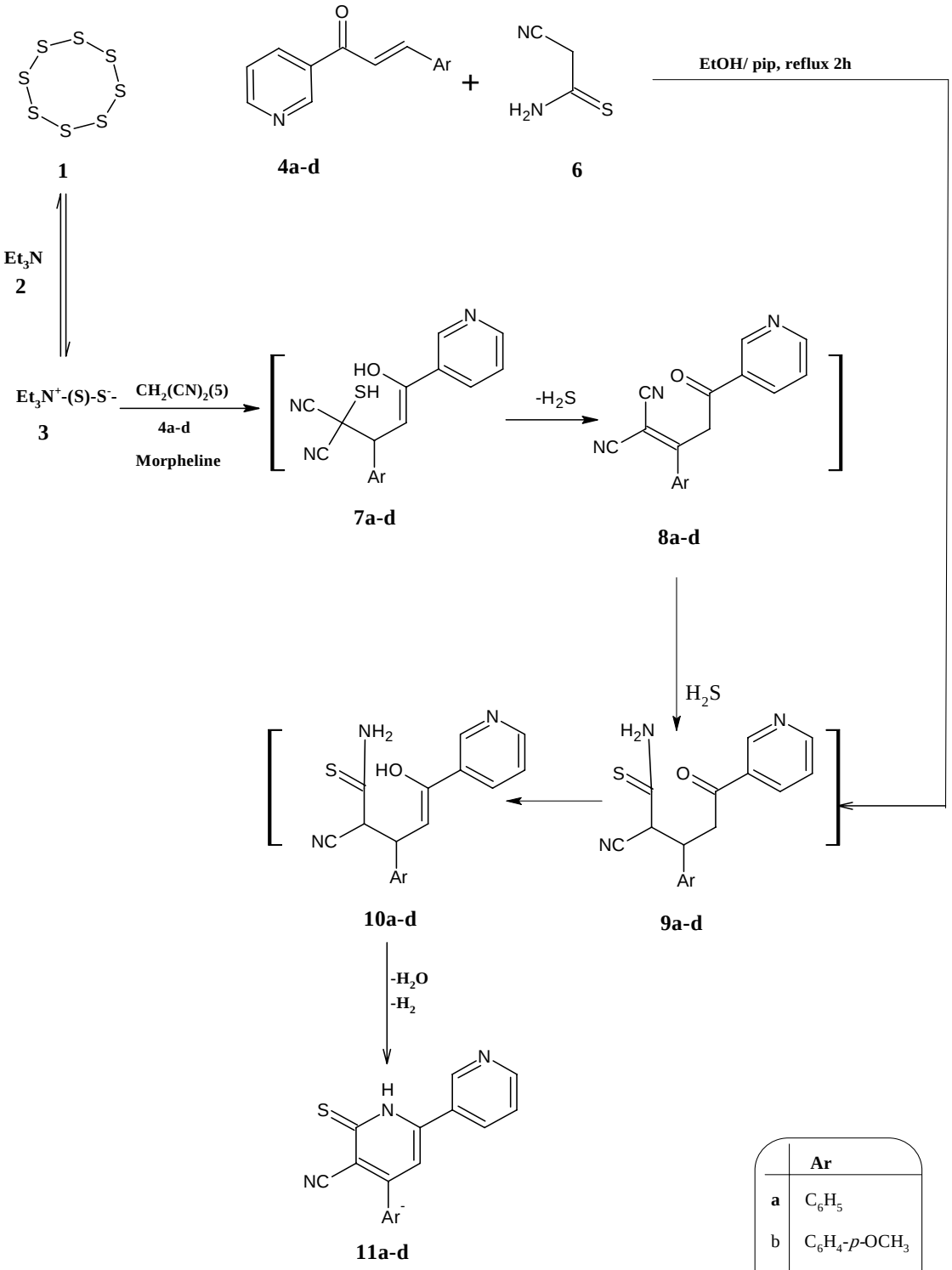
1. The starting materials of the present study were synthesized by reacting 2-cyanoethane-thioamide **(6)** with 3-(aryl or heterocyclic)-1-pyridin-3-ylprop-2-en-1-one **(4a-d)** to give the corresponding 2-thioxohydropyridine-3-carbonitriles **11a-d** as well as *via* the reaction of each of **4a-d**, malononitrile **(5),** dispersed sulfur **(3)**, morpholine. Compounds **11a-d** were used as the good starting materials for the present study (cf. Scheme 1 and Experimental Part).

2. Compounds **11a-d** were reacted with active halogen containing compounds **12a-h** in basic medium to afford the corresponding 2-alkylthio derivatives **13a-p,r,t,v.a'** which in turn, cyclized to their corresponding thieno[2,3-b]pyridines **14** in some cases while in most cases the thieno[2,3-b]pyridines **14** were obtained directly *via* the reaction of **11a-d** with **12a-h** in ethanolic sodium ethoxide (cf. Scheme 2 and Experimental Part).

3. Thieno[2,3-b]pyridine-2-carbohdrazides **15a-d** were obtained through the reaction of **13a-d** or **14a-d** with hydrazine hydrate. Synthons **15a-d** were reacted with anisaldehyde **(18)** or anisalidenemalononitrile **(16)** to give the corresponding hydrazones **17a-d**. Also, they reacted with formic acid **(19)**, triethylorthoformate **(21)**, DMF-DMA **(23)**, acetic anhydrate **(25)** to afford the corresponding pyrimidinone derivatives **20a-d**, **22a-d**, **24a-d** and **26a-d** respectively (cf, Scheme 3 and Experimental Part)).

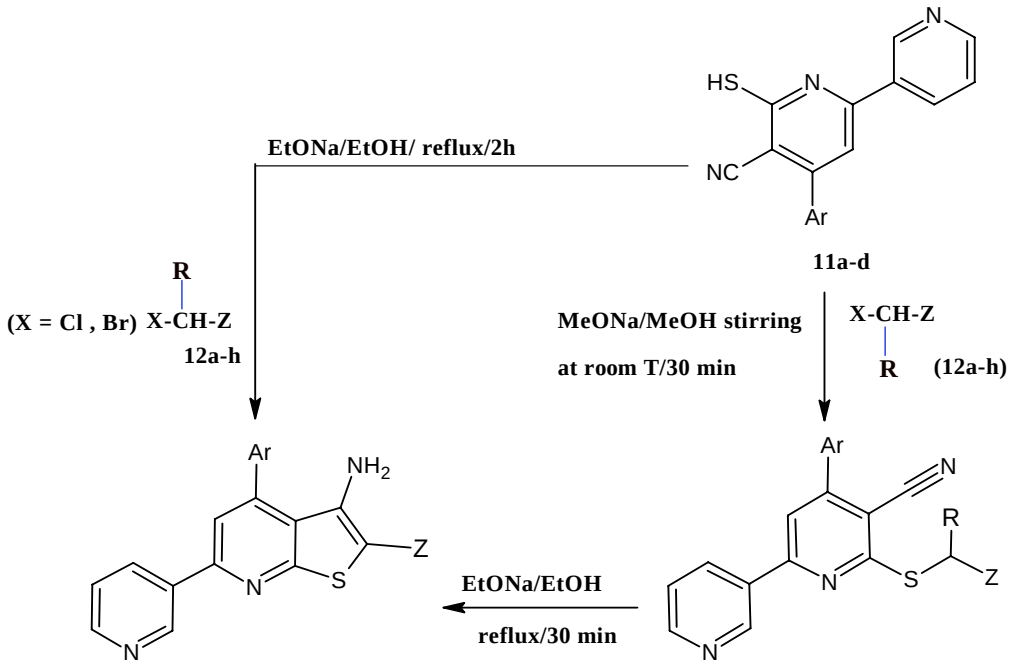
4. The synthetic potentiality of compounds **15a-d** was investigated through their reaction with carbon disulfide, phenylisothiocyanate and glacial acetic acid to give the corresponding 1,3,4-oxadiazoles **28a-d**, **30a-d** and pyrazolothienopyridine derivatives **32a-d** respectively (cf, Scheme 4 and Experimental Part).

5. The synthetic potentiality of compounds **15a-d** was investigated further through their reaction with acetylacetone **(33)**, ethyl acetoacetate **(35)** and diethylmaloneate **(37)** to give the corresponding thienopyridine-3-amines **(34a-d),** pyrazolones **(36a-d),** pyrazolidine-3,5-diones **(38a-d)** respectively (cf, Scheme 5 and Experimental Part).



	Ar
a	C_6H_5
b	C_6H_4-*p*-OCH_3
c	2-Thienyl
d	2-Furyl

Scheme 1



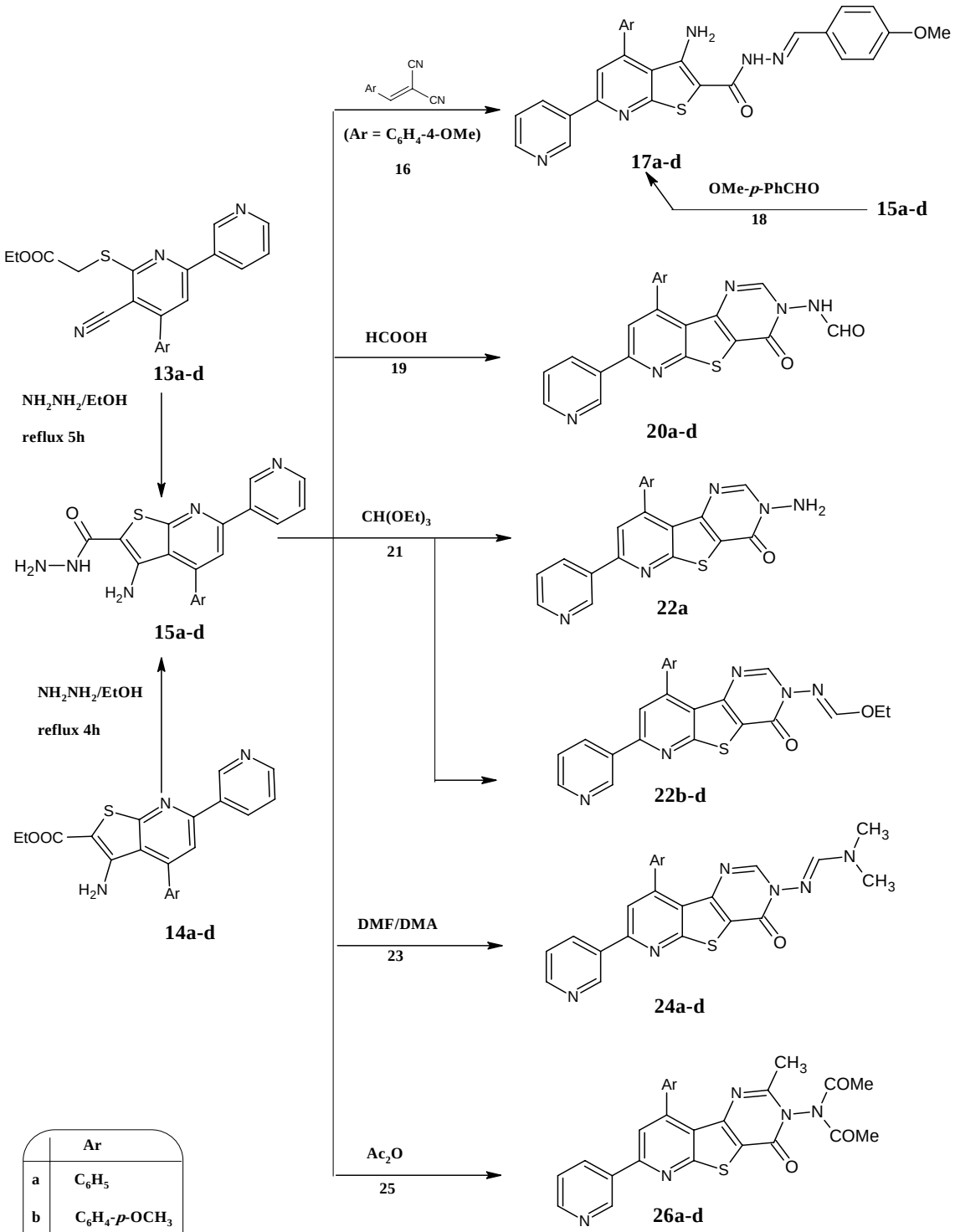
14a, b, c, d, e, f, g, h, i, j, k, l, [m], n, o, p, q, r, s, t, u, v, w, x, y, z, a', b'

13a, b, c, d, e, f, g, h, i, j, k, l, m, n, o ,p, [q], r,[s], t, [u], v, [w],[x], [y], [z],a', [b']

Scheme2

12	**X**	**Z**	**R**
a	Cl	COOEt	H
b	Cl	$CONH_2$	H
c	Br	COPh	H
d	Cl	COOH	H
e	Cl	CN	H
f	Br	COC_6H_4-4-Cl	H
g	Cl	COMe	H
h	Cl	COMe	COMe

13	**Ar**	**Z**	**R**	**14**	**Ar**	**Z**
a	C_6H_5	COOEt	H	a	C_6H_5	COOEt
b	C_6H_4-4-OCH_3	COOEt	H	b	C_6H_4-4-OCH_3	COOEt
c	2-thienyl	COOEt	H	c	2-thienyl	COOEt
d	2-furyl	COOEt	H	d	2-furyl	COOEt
e	C_6H_5	$CONH_2$	H	e	C_6H_5	$CONH_2$
f	C_6H_4-4-OCH_3	$CONH_2$	H	f	C_6H_4-4-OCH_3	$CONH_2$
g	2-thienyl	$CONH_2$	H	g	2-thienyl	$CONH_2$
h	2-furyl	$CONH_2$	H	h	2-furyl	$CONH_2$
i	C_6H_5	COPh	H	i	C_6H_5	COPh
j	C_6H_4-4-OCH_3	COPh	H	j	C_6H_4-4-OCH_3	COPh
k	2-thienyl	COPh	H	k	2-thienyl	COPh
l	2-furyl	COPh	H	l	2-furyl	COPh
m	C_6H_5	COOH	H	m	C_6H_5	COOH
n	C_6H_4-4-OCH_3	COOH	H	n	C_6H_4-4-OCH_3	COOH
o	2-thienyl	COOH	H	o	2-thienyl	COOH
p	2-furyl	COOH	H	p	2-furyl	COOH
q	C_6H_5	CN	H	q	C_6H_5	CN
r	C_6H_4-4-OCH_3	CN	H	r	C_6H_4-4-OCH_3	CN
s	2-thienyl	CN	H	s	2-thienyl	CN
t	2-furyl	CN	H	t	2-furyl	CN
u	C_6H_5	COPh-4-Cl	H	u	C_6H_5	COPh-4-Cl
v	C_6H_4-4-OCH_3	COPh-4-Cl	H	v	C_6H_4-4-OCH_3	COPh-4-Cl
w	2-thienyl	COPh-4-Cl	H	w	2-thienyl	COPh-4-Cl
x	2-furyl	COPh-4-Cl	H	x	2-furyl	COPh-4-Cl
y	C_6H_5	COMe	H, COMe	y	C_6H_5	COMe
z	C_6H_4-4-OCH_3	COMe	H, COMe	z	C_6H_4-4-OCH_3	COMe
a’	2-thienyl	COMe	H, COMe	a’	2-thienyl	COMe
b’	2-furyl	COMe	H, COMe	b’	2-furyl	COMe


Ar
CN
CN
(Ar = C6H4-4-OMe)
16
17a-d
OMe-p-PhCHO
18
15a-d
13a-d
NH2NH2/EtOH
reflux 5h
HCOOH
19
20a-d
CH(OEt)3
21
22a
22b-d
15a-d
NH2NH2/EtOH
reflux 4h
14a-d
DMF/DMA
23
24a-d
Ac2O
25
26a-d
Ar
a C6H5
b C6H4-p-OCH3
c 2-thienyl
d 2-furyl

Scheme (3)