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M. Sc Thesis

Entitled

NEW APPROACHES ON THE SYNTHESIS OF AZOLES, AZINES, THIOPHENES AND THEIR FUSED DERIVATIVES

Presented

BY

SAMAR MOHAMED SAMI SHARAF
(B. Sc., Chemistry)

For Partial Fulfilment of M.Sc. Degree

Chemistry Department
Faculty of Science
Cairo University
Giza, EGYPT

2001

APPROVAL SHEET FOR SUBMISSION

Title: **of [M.S.C.] Thesis**

New approaches on the synthesis of Azoles , Azines . Thiophenes and their fused derivatives .

Name Of candidate: Samar Mohammed Sami Sharaf .

This thesis has been approved for submission by the supervisors

1- **Prof. Dr**. Rafat Milad Mohareb

Signature

2- **Prof. Dr**. Adiba H.Floota

Signature

ABSTRACT

Name : Samar Mohammed Sami Sharaf .

Title of thesis: New approaches on the synthesis of Azoles , Azines , Thiophenes and their fused derivatives .

Degree M.S.c. unpublished Master of Science Thesis, Faculty of Science – Cairo University, 2001:

This work has been carried out to investigate the use of 2 amino – 3 cyano – 4,5,6,7, tetrahydrobenzo [b] thiophene **1** as a starting material react with diethylmalonate **2** to form amide derivatives **3**. The reactivity of compound **3** towards chemical reagents studied to form pyridines , pyrimidines and pyridazines with potential biological activity , the structure of the newly synthesized products were established on the basis of microanalytical data as well as spectral data.

Key words, Heterocyclic , Thiophene , Pyrazole ,Pyridine . pyrimidine , fused heterocyclic .

Supervisors:

Prof. Dr. Mohammed Halmy Elnagdi

Chairman of Chemistry Department
Faculty of Science – Cairo University

Cairo University
Faculty of Science
Chemistry Department

To whom it may concern besides the work carried out in this thesis, the candidate Samar Mohamed Sami Sharaf has attended post-graduate studies for the partial fulfillment of M.Sc. degree in the following topics:

1- Biochemistry
2- Carbohydrate
3- Design
4- Dyes
5- Electrochemistry
6- Heterocyclic Chemistry
7- Mathematics
8- Molecular Structure
9- Pericyclic
10- Photochemistry
11- Physical Organic Chemistry
12- Polymer Chemistry
13- Quantum Chemistry
14- Spectroscopy
15- Selected Topics
16- Volumetry
17- Foreign Language (German)

She has also passed successfully an examination on the above mentioned Topics.

Prof. Dr. M. Halmy Elnagdi

Chairman of Chemistry Department
Faculty of Science-Cairo University

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CONTENTS

ENGLISH
SUMMARY

The Reaction of 2-Amino-3-cyano-4,5,6,7-Tetrahydrobenzo[b]-thiophene with Diethyl Malonate: Synthesis of Coumarine, Pyridine and Thiazole Derivatives

The reaction of **1** with **2** in an oil bath at 140°C gave two products each with the molecular formula $C_{14}H_{16}N_2SO_3$. Their separation was based on the greater solubility of one of them over the other in ethanol. The ethanol soluble product was identified to be compound **3** based on analytical and spectral data.

The ethanol insoluble product (low yield) was identified to be the tetrahydrobenzo[b]thieno[5,4:2,3]-pyridine derivative **4**. Compound **3** showed interesting reactivity towards a variety of chemical reagents. Thus, it reacted with benzenediazonium chloride at $0\,^{o}C$ to give the corresponding hydrazo derivative **5**. The latter reacted with hydrazine hydrate to give the 5-hydroxy-1,2,3-triazole derivative **6**. The structure of compound **6** was based on analytical and spectral data. The reaction of compound **3** with benzaldehyde gave the benzal derivative **7**. The latter reacted with hydrazine hydrate and phenylhydrazine to give the 3-hydroxypyrazole derivatives **8a** and **8b**, respectively. The reaction of **3** with salicylaldehyde gave the coumarin derivative **9**, the formation of which took place through first a condensation followed by ethanol elimination.

The reactivity of compound **3** towards cyanomethylene reagents was studied. Thus, with either malononitrile **(10a)** or ethyl cyanoacetate **(10b)**, the corresponding 2-pyridinyl-4,5,6,7-tetrahydrobenzo[b]thiophene derivatives **11a** and **11b** respectively were formed. Compound **11a** underwent ready cyclization when heated in a boiling water bath with sodium ethoxide solution to give the annulated compound which was identified as the tetrahydrobenzo[b]thieno[5,4:4,5]pyrimidino[3,2:1,2]-pyridine derivative **12**

Compound **3** reacted with bromine in hot acetic acid solution to give the monobromo derivative **13.** The latter reacted with potassium cyanide in ethanol solution to give the tetrahydrobenzo[b]thieno[5,4:2,3]-pyridine derivative **15**. Compound **15** was formed through the intermediate formation of **14** followed by cyclization.

The reaction of compound **13** with thiourea gives the 2-aminothiazole derivative **16**, the structure of which was established on the basis of analytical and physical data. Compound **16** underwent ready cyclization when heated in ethanolic sodium hydroxide solution to give the tetrahydrobezo[b]thieno[5,4:2,3]pyridino[6,5;4,5]thiazolidene derivative **18**. Formation of the latter product took place through the intermediate formation of **17** followed by ester hydrolysis and decarboxylation.

Compound **3** reacted with thioglycolic acid to give the thiazole derivative **19**. The latter product underwent ready cyclization when heated in dimethylformamide solution containing a catalytic amount of triethylamine to give the tetrahydrobenzo[b]thieno[5,4:4,5]pyrimidino-[6,1:2,3]thiazole derivative **20**. Moreover, the reaction of compound **3** with cinnamonitrile derivatives was studied. Thus, the reaction of **3** with either α-cyanocinnamonitrile **(21a)** or α-ethoxycarbonylcinnamonitrile

(21b) gave the 2-pyridino-tetrahydrobenzo[b]thiophene derivatives **22a** and **22b**, respectively. The latter products underwent ready cyclization when heated in sodium ethoxide solution to give the tetrahydrobenzo[b]-thieno[5,4:4,5]pyrimidino[3,2:1,2]pyridine derivatives **23a** and **23b** respectively. The structures of compounds **22a,b** and **23a,b** were based on analytical and spectral data.

Recently, our research group studied the reaction of active methylene reagents with phenyl isothiocyanate in basic dimethylformamide/KOH solution, followed by heterocyclization with α-halocarbonyl compounds to give either thiophene or thiazole derivatives. The nature of the products depends on the α- halocarbonyl compound used.