

بسم الله الرحمن الرحيم





شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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**TANDEM *IN SITU* SYNTHESIS AND
REARRANGEMENT
OF CERTAIN HYDRAZONATE ESTERS**

A Thesis Submitted

By

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*As Partial Fulfillment of the
Requirements of
The M.Sc.Degree in Chemistry*

**Department of Chemistry
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Thesis Title :

**“TANDEM *IN SITU* SYNTHESIS AND
REARRANGEMENT OF CERTAIN HYDRAZONATE
ESTERS”**

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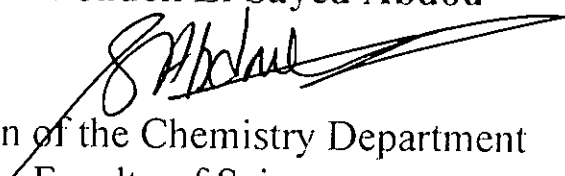
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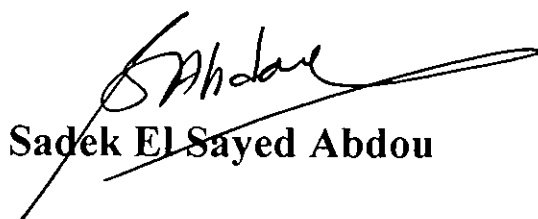
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In addition to the work carried out in this thesis, the candidate has studied and passed the following graduate courses:

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3. New trends in analytical chemistry.
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6. Heterocyclic chemistry.
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9. Organic photochemistry.
10. Quantum chemistry.
11. Carbohydrate chemistry.
12. Pericyclic reactions.
13. Techniques of molecular structure determination.
14. Designing organic synthesis.
15. Natural products chemistry.
16. Selected topics.
17. Mathematics.
18. German language



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ABSTRACT

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Title of thesis: Tandem *In Situ* Synthesis And Rearrangement Of Certain
Hydrazonate Esters.

Degree: M. Sc., Faculty of Science, University of Cairo, 2000 – 2001.

The first part of the original work of the thesis outlines a facile one-pot regioselective synthesis of [1,2,4]triazolo[4,3-a]-5(1H)-pyrimidinones *via* tandem Japp-Klingemann, Smiles rearrangement and cyclization reactions by azo coupling of various diazonium salts with the respective substitution products obtained from reaction of 6-phenyl-2-thiouracil with some active chloromethylene compounds.

The second part deals with synthesis of functionalized derivatives of novel pentaheterocyclic ring system namely pyrido[2,3-f: 6,5-f']di-[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one. The synthetic strategy is based on reaction of hydrazonoyl halides with pyridodipyrimidines. The mechanisms and regiochemistry of the studied reactions in both research projects were discussed.

Key words: Hydrazonoyl halides, Regioselectivity, Japp-Klingemann reaction, Smiles rearrangement, Thiohydrazonates, Thiohydrazides, 2-Thiouracils.

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Chapter I

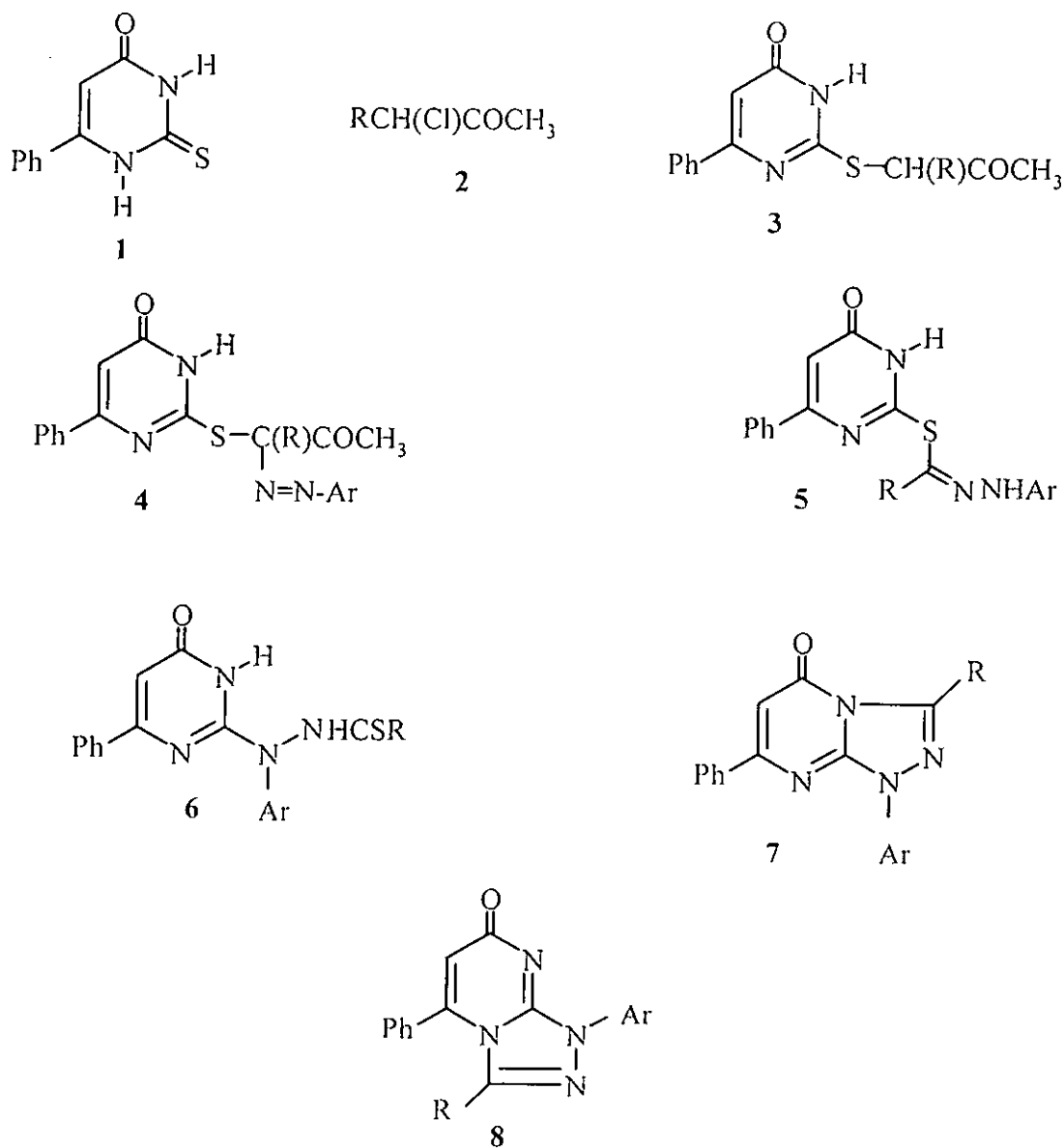
Statement and Objectives of the problem

CHAPTER I

STATEMENT AND OBJECTIVES OF THE PROBLEM

Tandem pericyclic reactions have attracted considerable attention within the past decade due to their utility in organic synthesis [96CR167] [96CR137] [93ACIE131] [92M1] [86CR831]. Other reactions in tandem have received little, if any, attention. Furthermore, many derivatives of [1,2,4]triazolo[4,3-a]pyrimidine have been reported to be useful as calcium-channel blocking vasodilators and they have antihypertensive [89GP711], cardiovascular [85FP834][95USP747], anxiolytic [80USP621] activities, as well as being components in photographic materials [91JKP934]. In the light of these facts, it was judicious to investigate the synthesis of some novel functionalized derivatives of [1,2,4]triazolo[4,3-a] pyrimidine **7** and/or **8** starting from the active [(4-oxo-6-phenyl-3H-pyrimidin-2-yl)thio] derivatives of N-phenyl 3-oxobutanamide, 2,4-pentanedione and ethyl 3-oxobutanoate **3A-C**, respectively, which have been unreported hitherto (Chart 1). Such required starting materials **3** will be prepared by reaction of **1** with the respective chloromethylene compounds **2**. In spite of the enormous body of literature dealing with the synthesis of target ring system namely 1H-[1,2,4]triazolo[4,3-a]pyrimidin-5-ones. Most of the methods reported for synthesis of such compounds, involve two or more reaction steps. In the present thesis, the author wishes to disclose the results of coupling of active [(4-oxo-6-phenyl-3H-pyrimidin-2-yl)thio]methine compounds **3** with diazotized anilines afforded directly and regioselectively the respective 1H-[1,2,4]triazolo[4,3-a]pyrimidin-5-ones **7** via three *in situ* tandem reactions : namely, Japp-Klingemann, Smiles rearrangement and cyclization reactions. Such a sequence of reactions provides a facile one-pot

regioselective synthesis of the target compounds 7. Both the mechanism and the regiochemistry of cyclization of the intermediate thiohydrazides 6 are to be elucidated.



Ar = XC₆H₄

R = A, PhNHCO; B, CH₃CO; C, EtOCO

X : a. H; b, 4-CH₃ ; c, 4-Cl; d. 4-NO₂

Chart 1

Furthermore, Shawali's interest has been focused during the past ten years on the various aspects of the chemistry of thiohydrazone esters **9** prepared from reactions of either heterocyclic thiones or thiophenols with hydrazoneyl halides **10** [80JHC833] [83H2239] [93CR2731] [95AHC377]. Such esters proved useful synthones for various fused bi- and tri-heterocycles. As a continuation of recent Shawali's studies [2000JPC599] [2000HAC87] [2000JPC96] [2001SC731], it was thought interesting to explore the synthesis of *bis*-thiohydrazone esters **12** and examine their utility for synthesis of novel functionalized pentaheterocyclic systems of type **13** and / or **14**. Such ring systems have also been unreported hitherto. In the present thesis, the author presents the results of the study of the reactions of a series of hydrazoneyl halides **10** with 5-substituted-1,3,7,9-tetrahydro-2,8-dithioxo-pyrido[2,3-d : 6,5-d']di-pyrimidin-4,6(1H,7H)-dione **11** (Chart 2) in an attempt to get the *bis*-thiohydrazone esters **12**. The objectives after such studies are on one hand to elucidate both the site selectivity and regioselectivity in reactions to be studied as the starting thione has more than one reactive sites and on the other hand to cast light on the utility of such reactions for synthesis of the target pentaheterocycles **13** and /or **14**.