Cairo University

Faculty of Science
Department of Chemistry

SYNTHESIS OF SOME NEW AZA HETEROCYCLIC DERIVATIVES OF POTENTIAL BIOLOGICAL ACTIVITY

A Thesis

Submitted in Partial Fulfillment of the Requirements for the Ph. D. Degree of Science in Organic Chemistry

By

Hanan Ahmed Mohamed Mostafa
(M. Sc., Cairo University, 2006)

Department of Chemistry
Faculty of Science
Cairo University
Giza, Egypt
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APPROVAL SHEET FOR SUBMISSION

Title of the Ph. D. Thesis:

"Synthesis of Some New Aza Heterocyclic Derivatives of Potential Biological Activity"

Name of Candidate: ***Hanan Ahmed Mohamed Mostafa***

This Thesis has been approved for submission by the supervisors.

Supervisors:

1- Prof. Dr. Ahmad M. Farag

Professor of Organic Chemistry
Department of Chemistry
Faculty of Science, Cairo University
Signature:

2- Prof. Dr. Bahira Y. Hegazi

Professor of Applied Organic Chemistry
Department of Applied Organic Chemistry
National Research Center, Dokki, Cairo
Signature:

Prof. Dr. Mohamed A. Badawy

Chairman of Chemistry Department
Faculty of Science, Cairo University

ABSTRACT

Title of the Ph. D. **Thesis**:

"Synthesis of Some New Aza Heterocyclic Derivatives of Potential Biological Activity"

Name: ***Hanan Ahmed Mohamed Mostafa***

Degree: (Ph. D.), Faculty of Science, Cairo University, 2010.

This work has been carried out to investigate the utility of 5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide **(5)**, 5-(4-chlorophenyl) isoxazole-3-carbohydrazide **(6)**, 5-(1*H*-indol-3-yl)-1-phenyl-1*H*-pyrazole-3-carbohydrazide (**27)** and ethyl 2-oxo-2-(1-oxo-2,3-dihydro-1*H*-inden-2-yl) acetate **(41)** for the synthesis of some new heterocyclic compounds such as 2-{2-[5-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-3-carbonyl]-hydrazono}-*N*'-(4-fluorophenyl) propane-hydrazonoylchloride **(19)**; 2-{2-[5-(4-chlorophenyl) isoxazole-3-carbonyl]-hydrazono}-*N*'-(4-fluorophenyl)propanehydrazonoyl chloride (**20**), 5-(1*H*-Indol-3-yl)-1-phenyl-*N*-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)-1*H*-pyrazole-3-carboxamide **(28)** and 2-(2-(1-(1*H*-Indol-3-yl) ethylidene) hydrazinyl)-5-((4-chlorophenyl) diazenyl)-4-methylthiazole **(37c)**; 6-(3-hydroxy-1*H*-inden-2-yl)-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2*H*)-one **(45)**; 1,4-dihydro-1-phenylindeno [1,2-*c*] pyrazole-3-carbohydrazide **(47)**, *N*-phenyl-2-(1-phenyl-1,4-dihydroindeno [1,2-*c*] pyrazole-3-carbonyl) hydrazine-carbothioamide **(48)**; 1,4-dihydro-*N*'-(4-oxo-3-phenylthiazolidin-2-ylidene)-1-phenylindeno[1,2-*c*]pyrazole-3-carbohydrazide **(49)**; *N*'-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-1-phenyl-1,4-dihydroindeno [1,2-*c*] pyrazole-3-carbohydrazide **(58a)** and *N*'-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-1-(4-fluorophenyl)-1,4-dihydroindeno [1,2-*c*] pyrazole-3-carbohydrazide **(58b)** which have potent biological activities.

Key Words: Pyrazole, isoxazole, 1,3-thiazole, 1-indanone, 3-acetylindole, hydrazide, hydrazonyl halide.

SUPERVISORS

1- Prof. Dr. Ahmad M. Farag

2- Prof. Dr. Bahira Y. Hegazi

Prof. Dr. Mohamed A. Badawy

Chairman of Chemistry Department
Faculty of Science, Cairo University

Addendum

Beside the work carried out in this thesis, the candidate ***Hanan Ahmed Mohamed Mostafa*** has attended Post-graduate courses during the academic years 2008-2009 and 2009-2010 in the following topics:

1. Problem Seminars.
2. Symmetric & Asymmetric Catalysis in Organic Chemistry.
3. Special Topics in Organic Chemistry.
4. Electron Transfer in Organic Chemistry.
5. Stereochemistry.
6. Metal Catalyzed Organic synthesis.
7. Advanced Mechanistic Organic Chemistry.
8. Advanced Organic Chemistry.

She has also passed successfully an examination in the above mentioned topics.

Prof. Dr. Mohamed A. Badawy

Chairman of Chemistry Department
Faculty of Science, Cairo University

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The author

Hanan Ahmed Mohamed Mostafa

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TO

MY FATHER

MY MOTHER

MY HUSBAND

AND

My Children

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تشييد بعض المشتقات الغير متجانسة الحلقة المحتوية على النيتروجين ذات النشاط البيولوجى المتوقع

رسالة
مقدمـة من

حنان أحمد محمد مصطفى
ماجستير علوم (كيمياء)
جامعـة القاهرة ٢٠٠٦ م

للحصول على
درجة الدكتوراه فى فلسفه العلوم (كيمياء عضوية)

قسم الكيمياء ـ كلية العلوم
جامعـة القاهرة

ج. م. ع.
٢٠١٠م ـ ١٤٣١هـ

مستخلص

الاسم : حنان أحمد محمد مصطفى

عنوان الرسالة : تشييد بعض المشتقات غير المتجانسة الحلقة المحتوية على النيتروجين ذات النشاط البيولوجى المتوقع

الدرجة : دكتوراه الفلسفة فى العلوم (كيمياء عضوية)

تهدف هذه الرسالة الى امكانية استخدام مركبات الكربوهيدارزيد الجديدة **٥** او **٦** أو **٤٧** فى تحضير العديد من المركبات الجديدة ذات النشاط البيولوجى المتوقع. حيث تم معاملة مركبات الكربوهيدارزيد **٥** او **٦** مع الفنيل ازيوثايوسينات حيث أعطى مشتقات الثايوسيمى كاربازيد **٧** أو **٨** على الترتيب. بمعالجة **٧** أو **٨** مع كلورواستيك اسيد و بارا فلوروبنزلدهيد و مشتقات الفنسيل بروميد يعطى ٤-ثايزوليدنون **٩** و **١٠** و مشتقات الثيازول **١١** او **١٢** على الترتيب. فى حين عند معاملة مشتقات الثايوسيمى كاربازيد **٧** او **٨** بحمض الكبريتك المركز أعطى الثياديازول **١٣** أو **١٤** أيضا تم اختبار النشاط الكيميائى لمركبات الكربوهيدرازيد **٥** او **٦** تجاه بارا فلوروبنزلدهيد و الهيدرازونيل كلوريد و البيتاكتيو استر. تفاعل الملح **٢٩** مع الهيدازين يعطى الترايازوال **٣٠**. تفاعل الاخير مع الفنسيل بروميد يعطى الترايازولو ثايديازين **٣١**. أما تفاعل الملح **٢٩** مع بروميد الفنسيل و مشتقات الهيدرازونيل كلوريد يعطى مشتقات الثيازوال **٣٢** و **٣٣** على التوالى. أيضا استعرضنا تحضير مركبات البنزواميدازول **٤٢** و التيرايزينون **٤٥** عن طريق تفاعل مركب داى كيتو استر **٤١** مع الارثو فنيلين داى امين و الثايوسيمى كابزيد على الترتيب. أما تفاعل المركب **٤١** مع الفنيل هيدازين يليه التفاعل مع الهيدازين هيدرات فيعطى مركب الكربوهيدازيد الجديد **٤٧**. تفاعل مركب الكربوهيدارزيد **٤٧** مع الفنيل ازيوثايوسينات يعطى مشتق الثايوسيمى كاربازيد **٤٨**. معاملة المركب **٤٨** مع كلورواستيك اسيد أو التفاعل مع مشتقات الفنسيل بروميد يعطى ٤-ثايزوليدنون **٤٩** او مشتقات الثيازول **٥١** على الترتيب. وقد أظهرت بعض المركبات الجديدة أنشطة بيولوجية عالية كمضادات للفيروسات و مضادات للتسمم الخلوى وحماية الحامض النووى من الكسر داخل الخلايا السرطانية.

الكلمات الدالة:

بيرازول، 1,3-ثيازوال، 1,3,4 – ثياديازوال ، مضادات للفيروسات

السادة المشرفون :

١) **أ.د. أحمد محمود فرج**
أستاذ الكيمياء العضوية المتفرغ- كليه العلوم- جامعه القاهرة

٢) **أ.د. بهيرة يوسف حجازى**
أستاذ باحث - المركز القومى للبحوث

أ.د. محمد أحمد بدوي

رئيس مجلس قسم الكيمياء

Cairo University

Faculty of Science
Department of Chemistry

Name: Hanan Ahmed Mohamed Mostafa

Title Of Thesis:**Synthesis of Some New Aza Heterocyclic Derivatives of Potential Biological Activity.**

Examiners

1- Prof. Dr. Mamoru Koketsu
Professor of Organic Chemistry
Department of Materials Science and Technology
Faculty of Engineering
Gifu University
Gifu 501-1193 Japan

2- Prof. Dr. Holger Butenschön
Professor of Organic Chemistry
Institut für Organische Chemie
Universität Hannover
Schneiderberg 1B, D-30167 Hannover, Germany

3-Prof. Dr.Ahmed Mahmoud Farag
Professor of Organic Chemistry
Department of Chemistry
Faculty of Science, Cairo University

II. LITERATURE SURVEY

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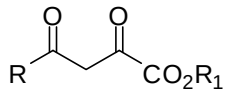
II.1 Introduction

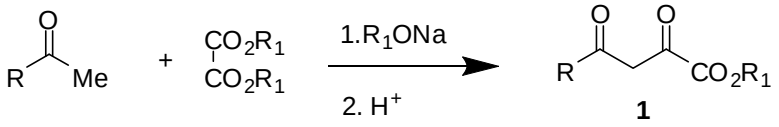
This review deals with the synthesis and reactions of 2,4-dioxoesters 1 which incorporates materials appearing in the Chemical Abstracts up to the mid of 2009. 2,4-Dioxoesters, the acylation products of methyl ketones with dialkyl oxalate, are valuable multi-purpose intermediates in organic synthesis and their preparation is well documented. 2,4-Dioxoesters are used in production e.g. pyrazole-3(5)-ethyl esters and their derivatives which are known to be important intermediates in the preparation of agrochemicals, microbicides, herbicides,[1] plant growth regulators and protectants[2], and also production of 3(2*H*)-furanone ring system which is the key skeletal element of many natural product antitumor agents.[3] Recently a review on utility of regio- and chemoselective features of benzoylpyuravtes in heterocyclic synthesis has been appeared.[4] The main purpose of this review is to present a survey of the literature on the synthesis of 2,4-dioxoesters and its reactions, some medicinal applications and provides useful and up-to-date data for medicinal chemists.



1

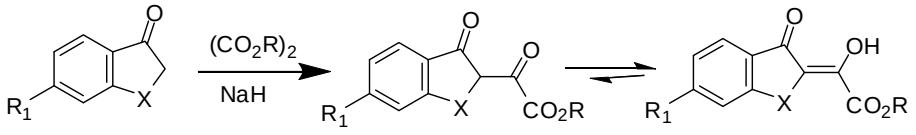
II.2. Methods of synthesis

2,4-Dioxoesters **1** were prepared by Claisen condensation of the appropriate methylketone with oxalic acid dialkyl esters in the presence of sodium alkoxides (Scheme 1) then acidified with dilute acid to give an excellent yields of the precursors **1**.[5-21]



Scheme 1 R= alkyl, aryl, heterocycle ; R_1 = Et, Me

Cyclic ketones **2** were condensed with dimethyl or diethyl oxalate to give the diketoester **3** which present in two tautomeric structures (Scheme 2).[22-26]



2 **3** **3`**

Scheme 2 X = $(CH_2)_{1-3}$, O ; R_1=R= Me, Et