Multi-components Reactions for the Synthesis of Condensed Heterocyclic Compounds

A Thesis submitted for the degree of Master of Science as a partial fulfillment for requirements of the Master of Science

Organic Chemistry

Aziza Mohamed Hussien Ahmed Hussien

Thesis advisors

Prof. Dr. Galal Hosni Sayed

Professor of Organic Chemistry, Faculty of Science, Ain Shams University

Prof. Dr. Mohamed Ali Hassan

Professor of Organic Chemistry, Faculty of Science, Ain Shams University

Dr. Abeer Mohamed El Sayed

Lecturer of Organic Chemistry, Faculty of Science, Ain Shams University

To

Department of Chemistry – Faculty of Science

Ain Shams University

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By

Aziza Mohamed Hussien Ahmed Hussien

Thesis advisors	Approved
Prof. Dr. Galal Hosni Sayed	••••••
Professor of Organic Chemistry, Faculty Shams University	y of Science, Ain
Prof. Dr. Mohamed Ali Hassan	•••••
Professor of Organic Chemistry, Faculty Shams University	y of Science, Ain
Dr. Abeer Mohamed El Sayed	•••••
Lecturer of Organic Chemistry, Faculty Shams University	of Science, Ain
Head of Ch	emistry Department

Prof. Dr. Hamed Ahmed Younes Derbala

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كلية العلوم قسم الكيمياء

شكر

خالص الشكر والتقدير للاساتذه الذين قاموا بالاشراف على الرساله وهم:

أ.د.جلال حسنى سيد

أستاذ الكيمياء العضويه المتفرغ - كلية العلوم- جامعة عين شمس أ.د.محمد على حسن

أستاذ الكيمياء العضويه المتفرغ- كلية العلوم- جامعة عين شمس دعبير محمد السيد

مدرس الكيمياء العضويه- كلية العلوم- جامعة عين شمس



كلية العلوم قسم الكيمياء

اسم الطالبه: عزيزه محمد حسين احمد حسين

الدرجه العلميه: ماجستير

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كلية العلوم

قسم الكيمياء

رسالة ماجستير في الكيمياء العضويه

اسم الطالبه: عزيزه محمد حسين احمد حسين

عنوان الرساله: تفاعلات متعدده المكونات لإصطناع مركبات غير متجانسة الحلقات المدمجه الدرجه العلميه: ماجستير العلوم في الكيمياء

لجنة الإشراف:

أ.د. جلال حسنى سيد كلية العلوم - جامعة عين شمس

أ.د. محمد على حسن كلية العلوم - جامعة عين شمس

د عبير محمد السيد كلية العلوم - جامعة عين شمس

لجنة التحكيم:

أ.د. محمد سعيد احمد عبد الحليم استاذ الكيمياء العضويه المتفرغ بهندسة عين شمس

أ.د.احمد محمود احمد فرج استاذ الكيمياء المتفرغ بعلوم القاهره

أ.د. جلال حسنى سيد استاذ الكيمياء العضويه المتفرغ بعلوم عين شمس

أ.د. محمد على حسن استاذ الكيمياء العضويه المتقرغ بعلوم عين شمس

الدراسات العليا:

ختم الاجازه: أجيزت الرساله بتاريخ / /

موافقة مجلس الكليه موافقة مجلس الجامعه

/ /

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الكيمياء العضويه

عزيزه محمد حسين احمد حسين

تحت اشراف

أ.د.جلال حسني سيد

أستاذ الكيمياء العضويه المتفرغ - كلية العلوم - جامعة عين شمس أ.د.محمد على حسن

أستاذ الكيمياء العضويه المتفرغ - كلية العلوم - جامعة عين شمس د. عبير محمد السيد

مدرس الكيمياء العضويه - كلية العلوم - جامعة عين شمس

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Multicomponent Reactions (MCRs)

The history of MCRs dates back to the second half of 19th century, it was only in the last decades that the concept of the multicomponent reactions has emerged as a powerful tool in synthetic chemistry for the rapid generation of molecular complexity and diversity with predefined functionality in chemical biology and drug discovery.

Multi-component reactions are chemical transformations in which three or more different starting materials react to give a final product in a one-pot procedure. Such reactions are one of the best tools in modern organic synthesis because they can generate a product with most of the atoms incorporated from the starting materials.¹ Also these reactions have received considerable attention in synthetic chemistry for the production of a broad spectrum of organic molecules.

In addition, water has emerged as a versatile solvent of organic reactions in the last two decades since it readily available, inexpensive, environmentally benign, neutral, and a natural solvent.² For these reasons, water has been used for multi-component reactions as well.³ Multi-component reactions in water are of outstanding value in organic synthesis and green chemistry.⁴

The multicomponent reactions are used in the synthesis of a large number of heterocyclic compounds:

1) Synthesis of imidazopyridine and pyridoimidazoindole derivatives:

Condensation between 2-amino-5-chloropyridine (1), 2-bromobenzalehyde (2) and 1-isocyano-4-methoxybenzene (3) in the presence of a catalytic amount of perchloric acid gave 2-(2-bromophenyl)-6-chloro-N-(4-methoxyphenyl)-imidazo[1,2-a]pyridine-3-amine (4) which can be converted to γ -chloro-5-(4-methoxyphenyl)-5H-pyrido[2',1':2,3]imidazo[4,5-b]indole (5) by treating (4) with water TMEDA and CuI in a sealed tube and under an inert atmosphere of argon.⁵

2)Synthesis of spiro[indoline-isoxazolo[4',3':5,6]-pyrido[2,3d]pyrimidine]triones:

The title compounds (6) were synthesized via a one-pot three component condensation reaction. The reaction was performed using barbituric acid (7) and an isatin (8) with an aminoisoxazole (9) in water in the presence of p-toluene sulfonic acid as a catalyst.⁶

3) Synthesis of new barbiturate salts:

Reaction of 2-aminopyridine (10), pyrimidinetetraonehydrates (11) and 4-hydroxycoumarin (12) in chloroform gave the barbiturate salt (13).⁷

4) Synthesis of tetrahydrobenzo [a] xanthene-11-ones:

Synthesis of 12-aryl/alkyl-8,9,10,12-tetrahydrobenzo[a]-xanthenes-11-ones (14) have been developed by one-pot reaction of dimedone (15b), with aldehydes (16) and β -naphthol (17) in the presence of InCl₃ under solvent-free conditions.⁸

5) Synthesis of spiro[indoline-3,5'-pyrroline]-2,2' -diones:

In the presence of p-toluenesulfonic acid as the catalyst the three-component reactions of arylamines (18), acetylenedicarboxylates (19), and isatins (8) gave 3'-hydroxyspiro[indoline-3,5'-pyrroline]-2,2'-dione derivatives (20).

$$ArNH_2 + \begin{pmatrix} CO_2CH_3 \\ CO_2CH_3 \\ 19 \end{pmatrix} + \begin{pmatrix} R \\ P-TsOH \\ EtOH \end{pmatrix} + \begin{pmatrix} CO_2CH_3 \\ HN \\ OAr \end{pmatrix} + \begin{pmatrix} CO_2CH_3 \\ OAr \\ O \end{pmatrix}$$

6) Synthesis of pyrazole derivatives:

4,4'-(Arylmethylene)bis(3-methyl-1H-pyrazol-5-ol) derivatives (24) were obtained via a one-pot three component reaction of hydrazine hydrate (21), ethyl acetoacetate (22), and aromatic aldehydes (e.g. m-nitrobenzaldehyde) (23) in water using pyridine trifluoroacetate or acetic acid at 70°C.¹⁰

$$NH_2$$
 + O O O + O 2N CHO O 4Me O 5H O 7N O 2 O 8H O 9N O 1 O 1 O 1 O 1 O 1 O 1 O 2 O 1 O 2 O 3 O 4 O 6 O 7 O 8 O 9 O 9N O 9 O 9N O 9

7) Synthesis of thiazines:

Aryl isothiocyanates (25), activated acetylene derivative (19) and isoquinoline (26) undergo a smooth 1:1:1 addition reaction in water at room temperature to produce thiazines (27).¹¹

Ar

- a; Ph
- b; 4-nitrophenyl
- c; 4-bromophenyl
- d; 3-bromophenyl

8) Synthesis of 2,6-bis(alkylamino)-benzofuro[5,6-b]furan-4,8-dione derivatives:

Reaction of 2,5-dihydroxycyclohexa-2,5-diene-1,4-diones (28), aldehydes (29) and isocyanides (30) in EtOH as the solvent at room temperature gave the desired titled compounds (31).¹²

R=aliphatic or aromatic

R'=cyclohexyl; 1,1,3,3-tetramethylbutyl or tert-butyl

9) Synthesis of thiazolidinones:

Synthesis of thiazolidinones (35, 36) can be achieved through the efficient multicomponent synthesis from the reaction of arenealdehydes (16) mercaptoacetic acid (32) and 2picolilamine (33) or 2-aminopyridine (34) under ultrasound irradiation.¹³