تشييد والنشاط البيولوجي لبعض الأنظمة غير متجانسة الحلقة الملتحمة الجديدة المحتوية علي الكبريت والنيتروجين

"رساله مقدمه للحصول على درجة دكتوراة الفلسفة فى العلوم فى الكيمياء بكلية العلوم "

"الكيمياء العضوية"

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كلية العلوم

جامعة عين شمس

2015

كلية العلوم

قسم الكيمياء

شكر

خالص الشكر والتقدير للأساتذة الذين قاموا بالإشراف على الرسالة وهم :

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الدرجة العلمية : دكتوراة الفلسفه في العلوم

القسم التابع له : الكيمياء العضوية

أسم الكلية : العلوم

الجامعة : عين شمس

سنة التخرج : 2007

سنة المنح : 2015

كلية العلوم

قسم الكيمياء

رسالة دكتوراة الفلسفة فى العلوم فى الكيمياء

أسم الطالب : أسماء عمر أبو القاسم الرايس

عنوان الرسالة : " تشييد والنشاط البيولوجي لبعض الأنظمة غير متجانسة الحلقة الملتحمة الجديدة المحتوية علي الكبريت والنيتروجين "

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الدراسات العليا :

ختم الإجازة : أجيزت الرسالة بتاريخ / / 2015م

موافقة مجلس الكلية موافقة مجلس الجامعة

/ / 2015م / / 2015م

Synthesis and Biological Activity of New Fused Sulfur and Nitrogen Heterocyclic Systems

Submitted
For the Degree of
Doctor of philosophy [ph.D]
(In Chemistry)

"Organic Chemistry"

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(M.Sc. Chemistry)

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Acknowledgement

First, *foremost, and all thanks to Allah by whose grace this work had been completed and by whose grace all my life is arranged in the best.*

I am deep indebted to ***Prof. Dr. Hassan. M. F. Madkour,*** *Professor of Organic Chemistry, Faculty of Science, Ain Shams University; he was always kind enough to suggest t bhe lines of research and follow the progress of the work with keen interest, guidance and valuable criticism. Thanks for all, not only from me but also from everybody will learn from me.*

I would like to express my sincere gratitude and indebtedness to ***Prof. Dr. Mahmoud F. Farhat,*** *Professor of Organic Chemistry, Faculty of Science, Ain Shams University; for his kind help, encouragement, supervision and continuous advice and for his valuable help.*

Also, I wish to acknowledge my sincere gratitude to ***Dr. Marwa Sayed Salem****, Lecturer of Organic Chemistry, Faculty of Science, Ain Shams University; to follow the progress of the work with keen interest and guidance.*

Finally*, my great and deep gratitude for my family, friends, my colleagues in the laboratory and for all people who help me to finish this work.*

ASMA OMER ERRAYES

Aim of the Work

In continuation of our previous work [103,104, 236] in the utility of activated nitriles in synthesis of a wide variety of heterocyclic systems, we aimed at design and synthesis pyrimidine derivatives from relatively simple starting materials.

Pyrimidines have gained considerable attention because of their role in biological systems, particularly in nucleic acids, which contain pyrimidines and purines as the main nucleobases. It has been noticed that introduction of an additional ring to the pyrimidine core tends to exert profound influence in conferring novel biological activities in these molecules [1, 221, 230]. Consequently, the aza analogs of purines, mainly the triazolopyrimidines, also are important [60]. The study of compounds incorporating the triazolopyrimidine has been developed due to their varied effects in diverse domains. Triazolopyrimidines (TPs), a subtype of purine analogs, have been the subject of chemical and biological studies due to their interesting pharmacology including antihypertensive, cardiac stimulant, antimalarial, antifungal, anti-HBV, antimicrobial, anticancer, antipyretic, analgesic, antiinflammatory, potential herbicidal, antioxidant and leishmanicidal activities [47, 82, 110, 123, 124, 130, 139, 219, 243, 265, 266, 271, 278, 321, 329, 330].

Pyrimidines are of great importance in fundamental metabolism, being an integral part of DNA and RNA, found in the three bases uracil, thymine and cytosine of the six present in the nucleotides. [133]They are found to possess diverse biological properties as bactericides, fungicides, viricides, insecticide, and meticides [120] and antioxidants. [104] Many derivatives of pyrimidine have been used as therapeutic agents. [97] Several triazolo and pyrazolopyrimidine derivatives are found to possess antifungal and antilieishmanial activity. [324] Certain pyrimidines are known to display antimalarial [268] antifilarial activities and also are potent inhibitors of cancer cell proliferation. [48, 165, 187]In the recent years, a lot of attention has been drawn by the pyrimidine derivatives due to their diverse range of activities, especially calcium channel blocker property. [135]

The most general and widely used route to synthesize pyrimidines involves the combination of a reagent containing the N-C-N skeleton namely (urea, thiourea and guanidine) with C-C-C unit such as 1,3-diketones and diesters.

In continuation of our previous work, [186]thiourea is employed as the N-C-N unit and condensed with arylidene ethyl cyanoacetate to complete the pyrimidine ring namely 6-(benzo[d][1,3]dioxol-5-yl)-4-oxo-2-thioxo-1,2,3,4-tetra-hydropyrimidine-5-carbonitrile **1** which will be utilized to design and construct a variety of heterocyclic compounds in order to screen their antioxidant activity.

"Part I"

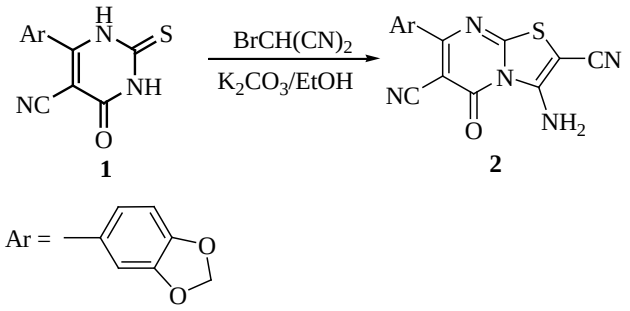
Synthetic utility of 4-oxo-2-thioxo-tetrahydropyrimidine derivative in heterocyclic synthesis

The present work aimed at utilization of thioxotetrahydropyrimidine **1** [186]as a scaffold for synthesis of different heterocyclic compounds and study of their biological activities especially their antioxidant potency.

(i) Synthesis of thiazolopyrimidines:

a) Reaction with bromomalononitrile:

When tetrahydropyrimidine**1**[186] was submitted to reactwithbromomalononitrile in aqueous alcoholic potassium carbonate solution,enaminonitrile**2** was obtained **[cf. Scheme 1]**. The structural features of enaminonitrile**2** were identified on the basis of coupling band exhibited at ν 3391 and 3291 cm^{-1} due to the amino NH_2 functionality and disappearance of $\nu_{C=S}$. ^{1}H-NMR spectrum revealed D_2O-exchangeable singlet at δ 8.48 ppm due to amino group.



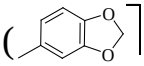
Scheme 1

The structure of **2** was confirmed by spectroscopic tools:

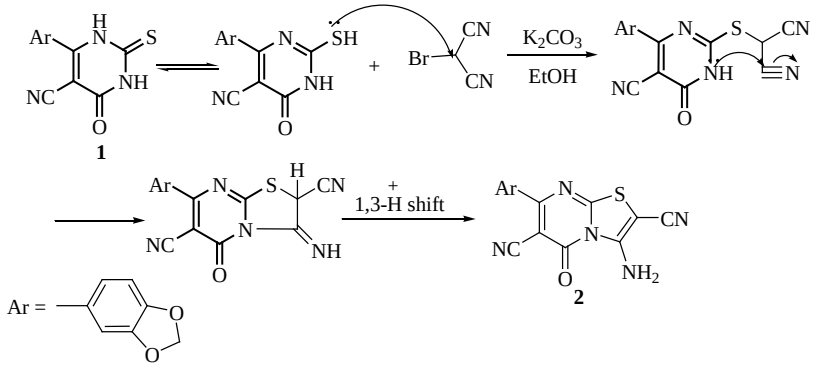
i- The IR spectrum exhibited the absorption bands: 3391, 3291 ν_{NH2}, 3081 ν_{CH} aromatic, 2909 ν_{CH} aliphatic, 2201 $\nu_{C\equiv N}$, 1687 $\nu_{C=O}$**[cf. Fig.1]**.

ii- The ^{1}H-NMR spectrum (DMSO-d_6, 300 MHz) exhibited the following signals (δ/ppm): 8.48 (s, 2H, NH_2, D_2O-exchangeable), 7.63-7.11 (m, 3H, Ar-H) and 6.17 (s, 2H, O-CH_2-O*).* **[cf. Fig.2and 3]**.

iii- The ^{13}C-NMR spectrum (75 MHz, DMSO-d_6) exhibited the following signals: 102.2 (O-CH_2-O), 107.88, 108.38, 112.89, 115.65, 124.60, 127.99, 129.26, 147.67, 150.83, 151.28, 161.35, 165.19 (C=O) **[cf. Fig.4]**.

iv- The mass spectrum showed the following fragments (m/e, % relative intensity):339 (M+2]$^{\cdot+}$, 13.53), 338 (M+1]$^{\cdot+}$, 20.13), 337 (M$^{\cdot+}$, 70.33), 321(M-NH_2]$^{\cdot+}$, 4.40), 216 (M-3,4-methylenedioxyphenyl]$^{\cdot+}$, 4.40) 121 ( , 11.57) and 70 (CN-CH_2-CH_2-NH_2]$^{\cdot+}$, 100.0)**[cf. Fig.5]**.

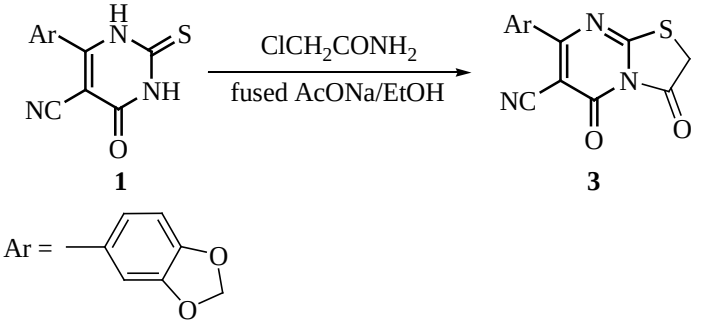
A plausible mechanism of the formation of enaminonitrile**2**is shown in scheme 2.



Scheme 2

b) Reaction with chloroacetamide:

Thiazolopyrimidine derivative **3** has been obtained *via* reaction of tetrahydropyrimidine**1** with chloroacetamide in boiling ethanol containing fused anhydrous sodium acetate. The structural features of thiazolopyrimidine derivative **3** were established by elemental analysis as well as spectral data **[cf. scheme 3]**:



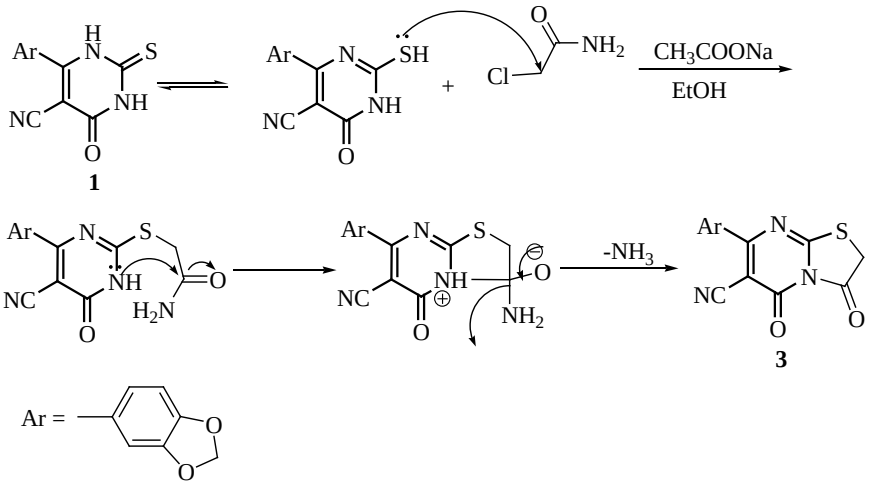
1 **3**

Scheme 3

i. The IR spectrum exhibited strong absorption bands at: 3033 ν_{CH} aromatic, 2919 ν_{CH} aliphatic, 2224 $\nu_{C\equiv N}$, 1724 & 1695 $\nu_{C=O}$, 1654$\nu_{C=N}$.**[cf. Fig.6]**.

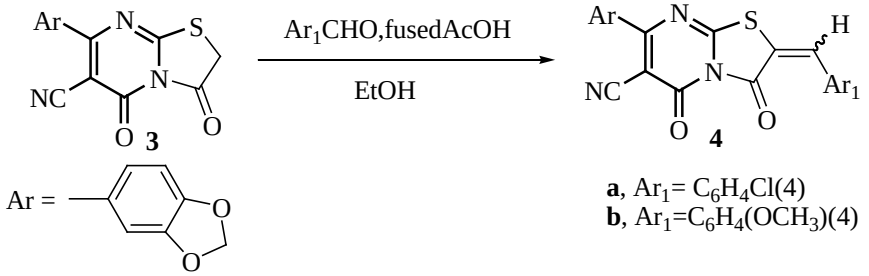
ii. The ^{1}H-NMR spectrum (DMSO-d_6, 300 MHz) exhibited the following signals (δ/ ppm): 7.61-7.10 (m, 3H, Ar-H), 6.16 (s, 2H, O-CH_2-O) and 4.13 (s, 2H, S-CH_2-C=O). **[cf. Fig.7]**.

A possible mechanism of the formation of compound **3**is shown in scheme 4.



Scheme 4

The structure of compound **3**has been also confirmed chemically *via* condensation reaction with substituted aromatic aldehydes namely, 4-chlorobenzaldehyde and/or 4-methoxybenzaldehyde to afford the corresponding benzylidene derivatives **4a,b**,respectively **[cf. scheme 5]**.



Scheme 5

The structure of **4a** was confirmed by spectroscopic tools.

i. The IR spectrum exhibited absorption bands: 3127 ν_{CH} aromatic, 2828 ν_{CH} aliphatic, 2227 $\nu_{C\equiv N}$, 1721 & 1665 $\nu_{C=O}$. **[cf. Fig.8]**.

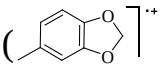
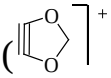
ii. The ^{1}H-NMR spectrum (DMSO-d_6, 300 MHz) exhibited the following signals (δ/ ppm): 7.26-7.08 (m, 7H, Ar-H), and 6.19(s, 2H, O-CH_2-O),6.11(s, 1H, -CH=C-S).**[cf. Figs.9]**.

The structure of **4b** was confirmed from its spectral data.

i. The IR spectrum exhibited the absorption bands: 3141 ν_{CH} aromatic, 2980 ν_{CH} aliphatic, 2205 $\nu_{C\equiv N}$, 1713 & 1662 $\nu_{C=O}$.**[cf. Fig.10]**.

ii. The ^{1}H-NMR spectrum (DMSO-d_6, 300 MHz) exhibited the following signals (δ/ ppm): 9.87 (s, 1H, -CH=C-S), 7.31-6.94 (m, 7H, Ar-H), 6.07 (s, 2H, O-CH_2-O) and 3.87 (s, 3H, -OCH_3)**[cf. Fig.11]**.

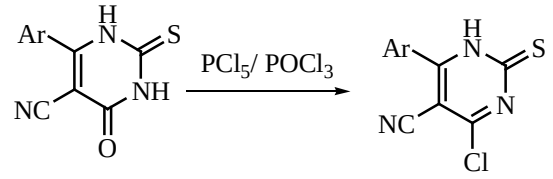
iii. The ^{13}C-NMR spectrum (75 MHz, DMSO-d_6) exhibited the following signals: 77.89 (OCH_3), 101.26 (O-CH_2-O), 107.42, 107.49, 108.33, 108.42, 120.15, 122.49, 122.51, 132.64, 146.72, 148.37, 158.55, 165.86 (2C=O & C=N), 170.90. **[cf. Fig.12]**.

iv. The mass spectrum showed the following fragments (m/e, % relative intensity):432 $(M+1]^{\cdot+}$, 20.13), 431 ($M^{\cdot+}$, 70.33), 307(4.40), 226 (4.40), 121 ( , 11.57)and 69 ( ,100.0)**[cf. Fig.13]**.

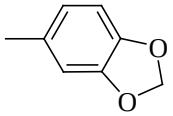
(ii) Utility ofchloropyrimidine derivative to construct fused heterocyclic systems

Chlorination of tetrahydropyrimidine**1** with a mixture of phosphorus pentachloride and phosphorus

oxychloride as a chlorinating reagent gave the chloropyrimidine derivative **5**.The structure of compound **5** was assigned from its spectroscopic data, a qualitative and quantitative elemental analysis which indicates the presence of chlorine. **[cf. scheme 6]**.



1 **5**

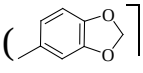
Ar = 

Scheme 6

The structures of **5** were confirmed by its spectral data.

i. The IR spectrum exhibited the absorption bands: 3202 ν_{NH}, 3151 ν_{CH} aromatic, 2987 ν_{CH} aliphatic, 2225 $\nu_{C\equiv N}$, 1652 $\nu_{C=N}$, 1243$\nu_{C=S}$. **[cf. Fig.14]**.

ii. The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) exhibited the following signals (δ/ ppm): 13.07 (br.s, 1H, -NH, D_2O-exchangeable), 7.22-7.07 (m, 3H, Ar-H) and 6.14 (s, 2H, O-CH_2-O). **[cf. Fig.15]**.

iii. The mass spectrum showed the following fragments (m/e, % relative intensity): 291 ($M^{\cdot+}$, not observed), 279 ($M–CH_2+2H]^{\cdot+}$) (55.34), 254 (61.17), 227 (64.08), 204 (52.43), 171 (68.93), 155 (73.79), 121 ( , 73.79), and 57 (100). **[cf. Fig.16]**