Ain shams University
Faculty of Science
Chemistry Department

BEHAVIOR OF SOME PHTHALAZINONE DERIVATIVES TOWARD SOME CARBON ELECTROPHILES :"SYNTHESIS OF SOME NOVAL PHTHALAZINONE DERIVATIVES FOR ANTICANCER AND ANTIMICROBIAL EVALUATION"

A Thesis Submitted by

Mohammed Abed Kadhim

A thesis submitted for the degree of doctor of philosophy
In
Organic Chemistry

Supervised by

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قسم الكيمياء

سلوك بعض مشتقات الفثالزينون تجاة بعض الكواشف الالكتروفيلية الكربونية : " تخليق مشتقات الفثالزينون الجديدة وتقدير نشاطها الحيوي ضد السرطان والمكروبات"

رسالة مقدمة
للحصول على درجة دكتوراه الفلسفة في علوم الكيمياء
تخصص الكيمياء العضوية
من
محمد عبد كاظم
إلى
قسم الكيمياء
كلية العلوم
جامعة عين شمس

2015

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رسالة دكتوراه في الكيمياء العضوية

اسم الطالب :

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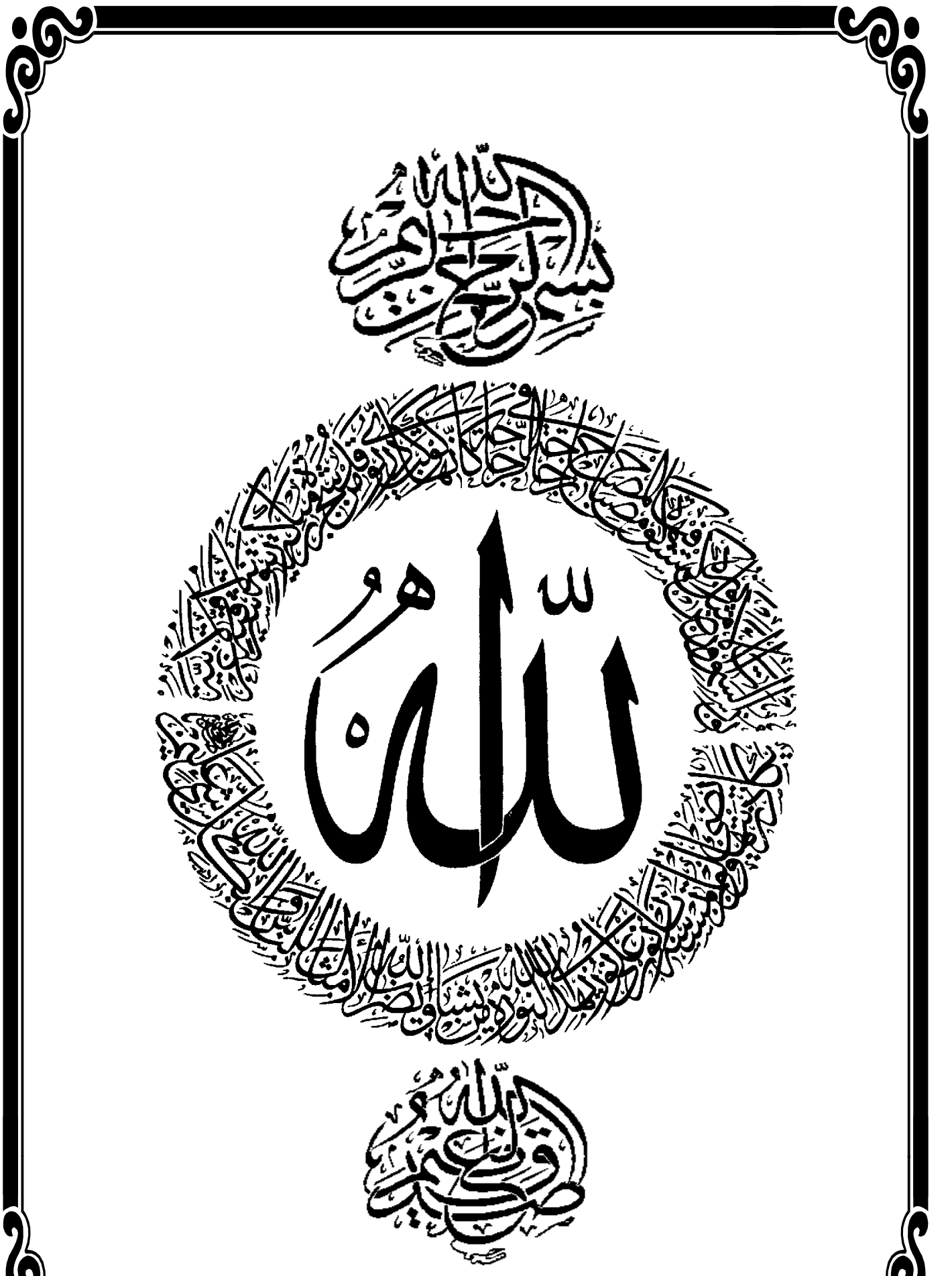

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AIM OF THE WORK

In the light of the long interest in the chemistry of phthalazine we noted the following :

1. Synthesis and studying the chemical behavior of 4-(5,6,7,8-tetrahydronaphthalen-2-yl) phthalazin-1(*2H*)-one **(2)** towards some carbon electrophiles .

2. Studying the chemical behavior of 2-(2-aminoethanol)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2*H*)-one **(9)** towards nitrogen nucleophiles.

3. Studying the chemical behavior of 2-(oxiran-2-ylmethyl)-4--(5,6,7,8-tetrahydronaphthalen-2-yl)phthalazin-1(2*H*)-one **(14)** towards carbon electrophiles .

4. Studying the chemical behavior of 2-(1-oxo-4-(5,6,7,8-trahydronaphthalen-2-yl)phthalazin-2(1*H*)-yl)acetohydrazide (**26)** towards carbon electrophiles ..

5. The new compounds were synthesized with the objective of studying their antimicrobial activity.

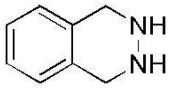
Introduction

In the past decades, the synthesis of heterocyclic compounds was a subject of great interest due to their wide applicability[1]. Heterocyclic compounds occur very widely in nature and essential to life. Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important.[2] Phthalazines are examples of nitrogen heterocycles that possess exciting biological properties.[3–5]They form the structural profile for several biologically active compounds and hence they are considered as important key elements. Several reports in the literature have focused on the pharmacology of phthalazine derivatives. These reports have resulted in a great number of contributions in diverse areas of interest.[6–11]Phthalazines have been reported to possess, anticonvulsant,[1]cardiotonic [2],[13]antimicrobial,[14]antitumor,[15–18]antihypertensive,[19,20],[21]antidiabetic,[22,23]antithrombotic antitrypanosomal,[24]anti-inflammatory,[25–31]and vasorelaxant activities.[20,32]Additionally, phthalazines have recently been reported to potentially inhibit serotonin reuptake and are considered as anti-depression agents.[33] Moreover, phthalazine derivatives represent key intermediate in the synthesis of various compounds with highly interesting pharmacological activities such as blood platelet aggregation inhibitors[34], poly(ADP ribose) polymerase inhibitors[35], and phosphodiesterase inhibitors[36]. In spite of the higher stabilities of 4-(2,4,6-trimethylphenyl)- 1(2*H*)-phthalazinone, it can be used as versatile building blocks in the synthesis of new phthalazine derivatives with high functionality at the heterocyclic system, which might have good biological and medicinal application.

Chemistry of phthalazines

It seems important to review the chemistry of phthalazines since the present investigation deals with the activity of phthalazines as suitable precursors in the preparation of the new phthalazine derivatives.

The fusion of a pyridazine ring with a benzene nucleus gives rise to a class of heterocyclic compounds known as phthalazines **1.**



1

Phthalazine derivatives are indexed under the following heading:

- Phthalazine
- 4,5-benzo-1,2-dihydropyridazine
- 2,3-benzodiazine
- β-phenodiazine

1. Primary synthesis of phthalazine derivatives

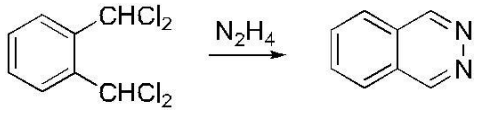
The primary synthesis of phthalazines (or hydrophthalazines) may be done by cyclocondensation of benzene (or cyclohexane) derivatives with acyclic synthons this provide one or more of the ring atoms needed to produce the phthalazine system, by analogous processing of other carbocyclic or pyridazine substrates, or by modification of other heterocyclic substrates in various ways.[37]

1.1. From a benzene derivative as substrate and one synthon

1.1.1. From 1,2-dialkylbenzenes

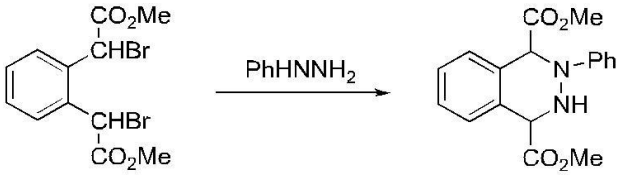
Phthalazine **3** was first prepared in 1893 by Gabril and Pinkus [38] by heating *α,α,α',α'*-tertachloro-*o*-xylene **(2)** and aqueous hydrazine under pressure for two hours at 150 ^{o}C. Similarly, it was prepared by refluxing the tetrabromo-*o*-xylene in water followed by addition of potassium hydroxide and hydrazine

sulphate.[39] In both cases, phthalazine was isolated as the hydrochloride from which the free amine was liberated by addition of base and then subsequent extraction with benzene.



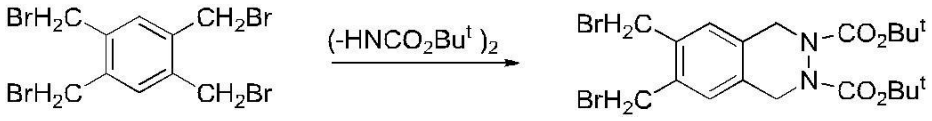
2 **3**

It was found that *o*-bis(*α*-bromo-*α*-methoxycarbonylmethyl)benzene **(4)** when refluxed with phenylhydrazine in benzene yielded dimethyl2-phenyl-1,2,3,4-tetrahydro-1,4-phthalazinedicarboxylate **(5).** [40]



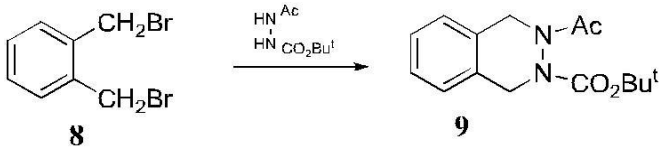
4 **5**

Meissner *etal.*[41] reported that the reaction of 1,2,4,5-tetra-bis(bromomethyl)benzene **(6)** with *N*,*N*-di(tertbutoxycarbonyl)hydrazine in boiling DMF gives 2,3di-tert-butyl 6,7-bis (bromomethyl)-1,2,3,4-tetrahydro-2,3-phthalazinedicarboxylate **(7)**.



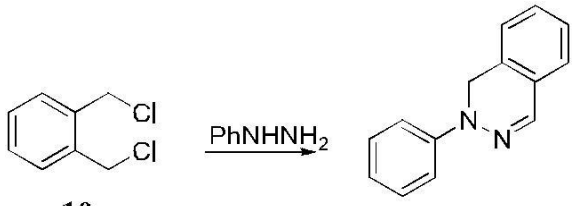
6 **7**

In a similar manner, [42] reaction of *o*-bis(bromomethyl)benzene **(8)** with *N*-acetyl-*N*'-(tert-butoxycarbonyl) hydrazine in boiling DMF gave tert-butyl 3-acetyl-1,2,3,4-tetrahydro-2-phthalazinecarboxylate **(9)**.



8 **9**

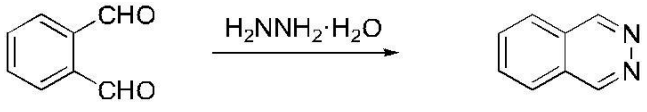
Recently, Yuhong and Varma [43] have reported the synthesis of 2-phenyl-1,2-dihydrophthalazine **(11)** by cyclocondensation of 1,2-bis(chloromethyl)benzene **(10)** with phenyl hydrazine in aqueous medium under microwave irradiation condition.



10 **11**

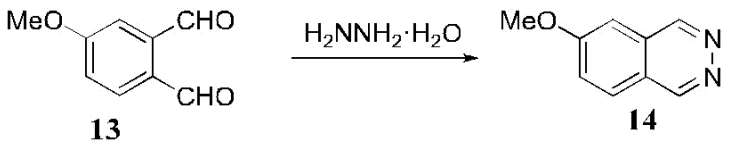
1.1.2. From 1,2-dialdehydobenzenes

Phthalazine **(3)** has been prepared by condensation of *o*-phthalaldehyde **(12)** with aqueous hydrazine sulphate [44,45]. Hirsch and Orphanos [46,47] allowed alcoholic solutions of **12** react with hydrazine at 0 ^{o}C to give **3** in high yield (96%).



12 **3**

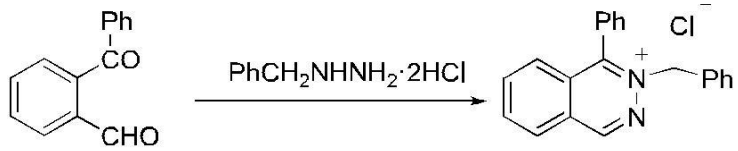
Tsoungas and Searcey [48] prepared 6-methoxyphthalazine **(14)** by reaction of 4 methoxy phthalaldehyde **(13)** with hydrazine in a broadly similar way.



13 14

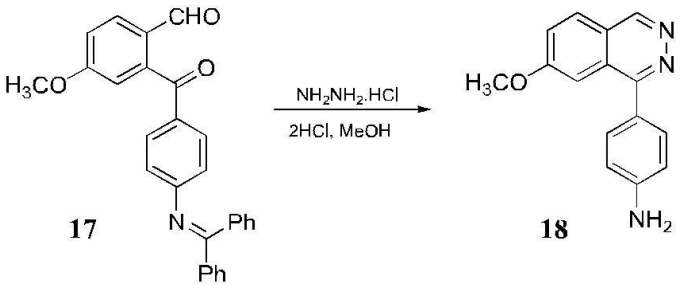
1.1.3. From 1-aldehydo-2-ketobenzenes

Johnson *et al*.[49] reported that, 2-benzophenonecarbaldehyde **(15)** reacts with benzylhydrazine dihydrochloride to yield 2-benzyl-1-phenylphthalazinium chloride **(16)**.



15 16

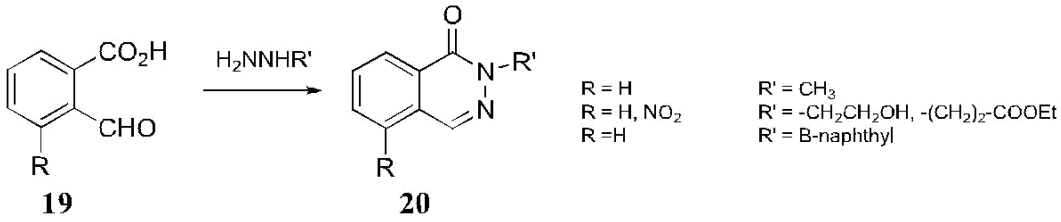
On the other hand, 4-(7-methoxyphthalazin-1-yl) aniline **(18)** was prepared by the reaction of 2-(4-(diphenylmethyleneamino)benzoyl)-4-methoxybenzaldehyde **(17)** with hydrazine hydrochloride in methanol. [50]



17 18

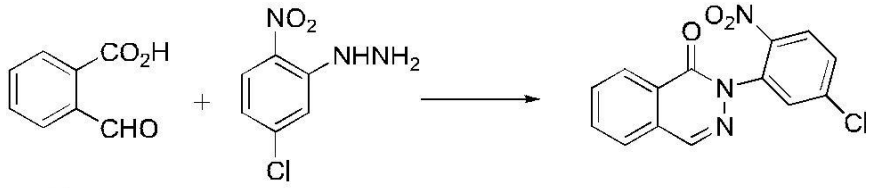
1.1.4. From 1-aldehydo-2-carboxybenzenes

Phthalaldehydic acid **(19)** condenses with alkylhydrazine [51,52] or arylhydrazine [53] by refluxing for 2-3 hours in ethanol to give 2-substituted-1-(2*H*)-phthalazinone (**20)**. Similarly, 3-nitrophthalaldehydic acid condenses with alkyl hydrazine to give **(20)**.[51]



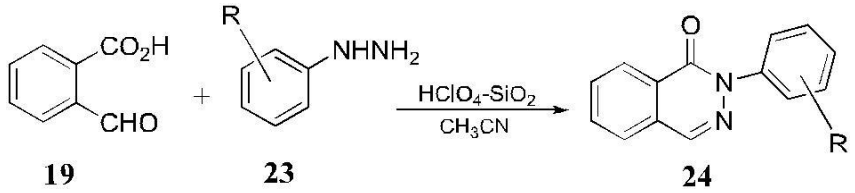
19 **20**

Kuznetsov and co-workrs [54] have reported the synthesis of 2-(2-ntitro-5-chlorophenyl)-1,2-dihydro-1-phthalazine **(22)** by condensation of phthalaldehydic acid **(19)** with 2-ntitro-5-chlorophenylhydrazine **(21)** in ethanol-sulphuric acid mixture.



19 **21** **22**

Recently, Heravi *et al.* [55] adopted a novel method for the synthesis of 1(2*H*)-phthalazinone derivatives **(24)** *via* the reaction of phthaladehydic acid **(19)** with various phenyl hydrazines **(23)** in acetonitrile using $HClO_4$-SiO_2 as a catalyst.



19 **23** **24**

In 2012, Linyan *et al.*[56] have reported the one-pot synthesis of a series of phthalazinones **(25)** using ultrathin Pt nanowires as catalysts under 1 bar of hydrogen *via* the reductive C–N coupling and intramolecular amidation of 2-carboxybenzaldehyde **(19)** with hydrazines.