Ain Shams University
Girls College for Arts, Science and Education
Chemistry Department

Synthesis,Reactions and Biological Activity of New Isatin Derivatives

Thesis
Submitted for the Degree of Philosophy Doctor (Ph.D.) in Organic Chemistry

Chemistry Department
Girls College for Arts, Science and Education
Ain Shams University

By

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(2011)

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Ain Shams University
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DEDICATION

To

My Parents

I have to thank God for choosing

both of them to be my parents

Thanks for

Supporting me

To my brothers, sisters and friends

Thanks for helping me

جامعة عين شمس
كلية البنات للاداب و العلوم و التربية
قسم الكيمياء

" تشييد ,تفاعلات والفاعلية البيولوجية لمشتقات جديده للايزاتين"

رسالة مقدمة
للحصول على درجة دكتوراة الفلسفة فى العلوم
قسم الكيمياء

مقدمة من

هند محمود محمد اسماعيل
(مدرس مساعد بقسم الكيمياء)

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قسم الكيمياء

رسالة دكتوراة

اسم الطالبة : **هند محمود محمد اسماعيل**

عنوان الرسالة: **تشييد ,تفاعلات والفاعلية البيولوجية لمشتقات جديده للايزاتين**

الدرجة العلمية: **دكتوراة الفلسفة فى العلوم**

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تاريخ البحث: / /2011

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/ /2011م	**/ /2011م**
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جامعة عين شمس
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سنة التخرج:	2003
سنة المنح:	2011

كلية البنات للاداب و العلوم و التربية
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شكر

أشكر السادة الأساتذة الذين قاموا بالإشراف وهم:

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وكذلك الهيئات:
1- مركز التحاليل الدقيقة بكلية العلوم- جامعة القاهرة.

2- المعمل المركزي - مركز بحوث الصحراء.

3- المركز القومي للبحوث.

4- معهد الاورام - جامعة القاهره.

5- المركز الاقليمي للفطريات- جامعة الازهر.

Summary

In this study we reported the synthesis and reactivity of novel heterocyclic compounds containing both indole and oxindole moieties possessing significant biological activity.

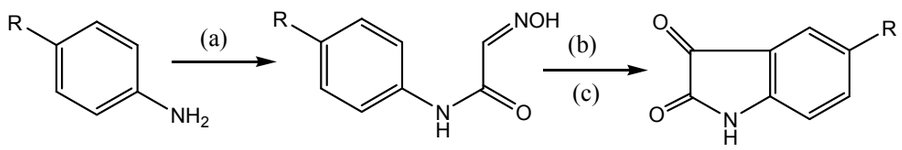
1.Synthesis of key starting materials

1.1:Synthesis of 5-Substituted isatins.

5-Substituted isatin were synthesized using Sandemyer methodology starting from the corresponding amines [**Scheme 1**].

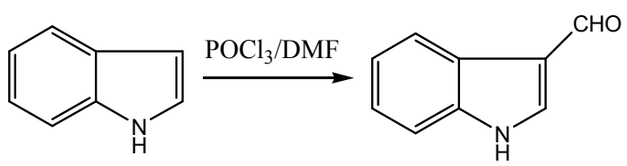
1.2:Synthesis of Indole 3-carbinal.

The formulation of commercially available indole with DMF/$POCl_3$ by Vismeyer - Hack reaction is carried out to obtain indole 3-carbinal in good yield [**Scheme 2**].



R, a = H, b = CH_3, c = Cl, d = NO_2, e = F.

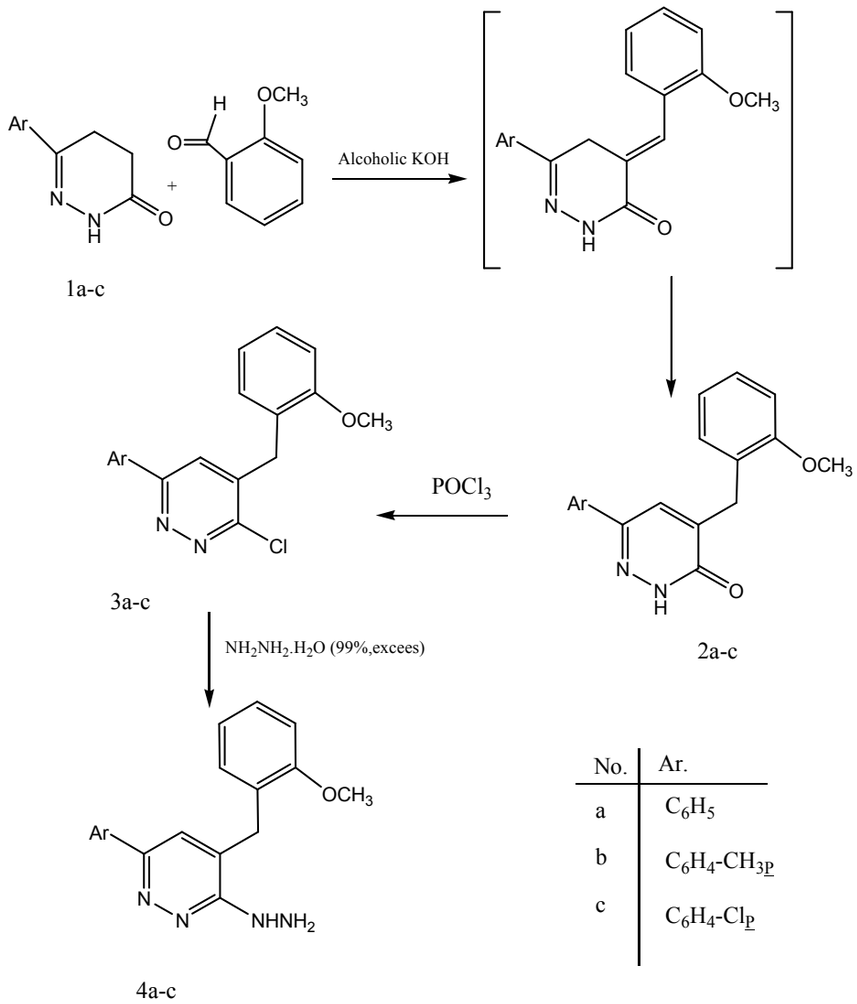
Scheme 1. a) $Cl_3CCH(OH)_2$,$H_2NOH.HCl$. ,b)H_2SO_4.,c)H_2O.



Scheme (2)

1.3:Synthesis of 1-(4-(2-Methoxybenzyl)-6-arylpyridazin-3-yl)hydrazine derivatives.

6-Aryl-4-(2-methoxyphenylmethyl)pyridazin-3(2H)-ones (2a-c) were synthesized via the base catalyzed condensation of 6-aryl-4,5-dihydropyridazin-3(2H) ones (1a-c) with 2-methoxybenzaldehyde.Reaction of (2a-c) with phosphorus oxychloride gave 3-chloropyridazines (3a-c), which on treatment with hydrazine hydrate gave 1-(4-(2-Methoxybenzyl)-6-arylpyridazin-3-yl)hydrazine derivatives (4a-c) in good yield [**Scheme 3**].



No.	Ar.
a	C_6H_5
b	C_6H_4-CH_{3P}
c	C_6H_4-Cl_P

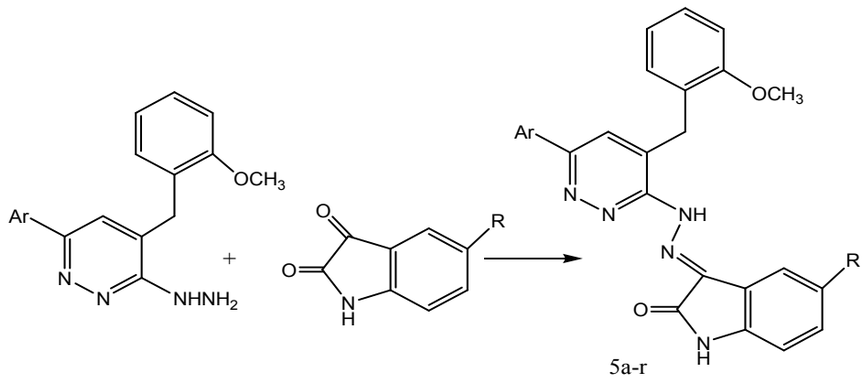
Scheme 3.Experimental protocol for the synthesis of 1-(4-(2-methoxybenzyl)-6-arylpyridazin-3-yl)hydrazines (4a-c).

These 3-hydrazino pyridazine compounds (4a-c) were used as key starting materials for the preparation of new hydrazone derivatives of expected biological activity.

2.Synthesis of new hydrazones

2.1: Synthesis of new hydrazone derivatives based on oxindole moiety.

Condensation reaction of 3-hydrazino pyridazine compounds (4a-c) with 5-substituted isatins to afford 6-aryl-3-{2-[4-(2-methoxybenzyl)pyridazin-3(2H)-ylidene]hydrazono}-5-substituted-indolin-2-ones (5a-r) [**Scheme 4**].



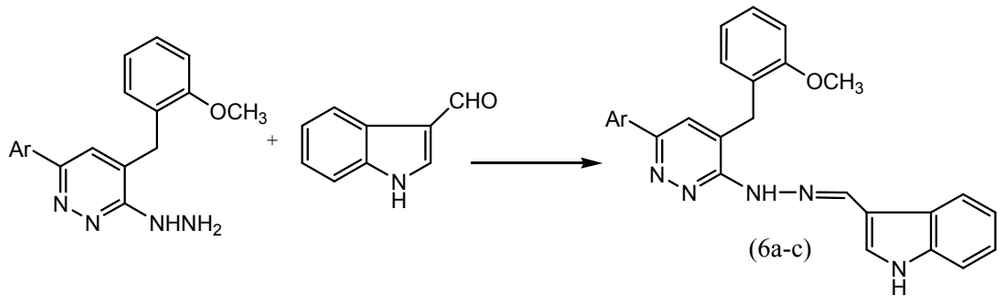
5a-r

Comp. No	R	Ar
5(a,b,c)*	H	C_6H_5, $C_6H_4CH_{3p}$, $C_6H_4Cl_p$
5(d,e,f)*	CH_3	C_6H_5, $C_6H_4CH_{3p}$, $C_6H_4Cl_p$
5(g,h,i)*	Cl	C_6H_5, $C_6H_4CH_{3p}$, $C_6H_4Cl_p$
5(j,k,l)*	OCH_3	C_6H_5, $C_6H_4CH_{3p}$, $C_6H_4Cl_p$
5m,n,o	NO_2	C_6H_5, $C_6H_4CH_{3p}$, $C_6H_4Cl_p$
5p,q,r	F	C_6H_5, $C_6H_4CH_{3p}$, $C_6H_4Cl_p$

Scheme (4)

2.2: Synthesis of new hydrazone derivatives based on indole moiety.

Also condensation reaction of 3-hydrazino pyridazine compounds (4a-c) with indole 3-carbinal in refluxing ethanol yielded the corresponding hydrazone derivatives 2-((1H-indol-3-yl) methylene)-1-(4-(2-methoxybenzyl)-6-arylpyridazin-3-yl) hydrazines (6a-c) [**Scheme 5**].



Ar,a = C_6H_5, b = $C_6H_4CH_{3p}$, c = $C_6H_4Cl_p$

Scheme (5)

3. Synthesis of new bis Schiff bases

The present study involved the synthesis of three different clases of bis Schiff base derivatives from condensation reaction of three different di-amines namely benzidine (4,4`-diamino-1,1`-biphenyl), 3,3'-dimethoxybenzidine and 2,6-diamino-pyridine with 5-substituted isatins or indole 3-carbinal.

Condensation of two moles of 5-substituted isatins and indole 3-carbinal with one mole of benzidine in ethanol at ambient temperature gave the desired bis Schiff bases named bis N-[(1,3-dihydro)-2H-indol-2-one] 4,4`-diamino-1,1`-biphenyl derivatives (7a-e) and bis-N-[(1H-indol-3yl)methylene]4,4`-diamino-1,1`-biphenyl (9a) respectively.

In the same manner condensation of two moles of 5-substituted isatins and indole 3-carbinal with one mole of 3,3'-dimethoxybenzidine in ethanol at ambient temperature gave the desired bis Schiff bases bis N-[(1,3-dihydro)-2H-indol-2-one]3,3'-dimethoxybenzidine derivatives (8a-e) and bis-N-[(1H-indol-3yl)methylene]3,3'-dimethoxybenzidine (9b) respectively.

Also reaction of two moles of 5-substituted isatins and indole 3-carbinal with one mole of 2,6-diaminopyridine yielded bis N-[(1,3-dihydro)-2H-indol-2-one]pyridine 2,6-diamine derivatives (10a-e) and bis N-[(1H-indol-3yl)methylene]pyridine 2,6-diamine (11) [**Scheme 6,7**].