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Synthesis of Some New Fused Heterocyclic Rings Derived from 3-Benzofuranone

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ABSTRACT

In the present work, the synthesis of some new fused heterocyclic rings derived from 3-benzofuranone was achieved. 3-Benzofuranone (1) was prepared by the action of polyphosphoric acid on phenoxyacetic acid. 3-Benzofuranone was treated with benzaldehyde and furfural in alkaline medium to afford 2-arylidene-3-benzofuranone (aurones) (2, 3). The reactions of the synthesized aurones with hydrazine hydrate, phenyl hydrazine, hydroxylamine hydrochloride, acetamide, urea and thiourea gave substituted pyrazoline (4, 5), 3-phenyl pyrazoline (6, 7), isoxazole (8, 9), 2-pyridinone and pyrimidin-2-one(thione) (12-15) respectively fused with 3-benzofuran. The structures of the synthesized compounds were confirmed by IR and physical methods.

تحضير عدد من المركبات الجديدة الحلقية غير المتجانسة المندمجة المشتقة من 3-بنزوفيورانون

الملخص

تم في هذا البحث تحضير عدد من المركبات الجديدة الحلقية غير المتجانسة المندمجة المشتقة من 3-بنزوفيورانون. حضر المركب 3-بنزوفيورانون (1) من خلال تفاعل حامض فينوكسي الخليك مع حامض الفوسفوريك المتعدد. تم مفاعلة 3-بنزوفيورانون مع كل من البنزالديهايد والفورفورال في وسط قاعدي للحصول على مركبات 2-اريليدين-3-بنزوفيورانون (آرون) (2، 3). حولت الآرونات المحضرة من خلال تفاعلها مع الهيدرازين المائي والفنيل هيدرازين وهيدروكلوريد الهيدروكسيل امين والاسيتاميد واليوريا والثايوريا للحصول على معوضات البايرازولين (4، 5) و3-فنيل بايرازولين (6، 7) والايزوكسازول (8، 9) و2-بيريدينون والبريميدين-2-اون(ثايون) (12-15) على التوالي والمندمجة مع 3-بنزوفيوران. شخصت المركبات المحضرة باستخدام طيف الاشعة تحت الحمراء والطرق الفيزياوية.

INTRODUCTION

3-Benzofuranone or coumaran-3-one derivatives (coumaranones) (Dictionary of Organic Compounds, 1982) have a broad diffusion in the nature and, they have important biological activities.

2,6-Dihydroxy-3(2H)-benzofuranone was isolated from *Pterocarpus marsupium*, and was also evaluated for hypoglycemic activity in fasted rats. The titled compound showed significant activity at 10 mg/Kg p.o. dose. (Council of Scientific and Industrial Research, 2005).

Furthermore, coumaranones were known as antioxidant in fruits and vegetables as 4,6-dihydroxy-3(2H)-benzofuranone which was isolated from quercetin and kaempferol (Jorgensen et al., 1998). Similarly (Krishnamachari et al., 2002), it was found that naturally occurring substituted 3-benzofuranone in quercetin was active in scavenging reactive oxygen species (ROS).

7-Hydroxy-2,4–dimethyl–3(2H)-benzofuranone was isolated from *Microsphaeropsis olivacea* grown in liquid and solid media. The isolated compound presented a moderate activity towards the enzyme acetylcholinesterase (AChE) and its cytotoxicity against human lung fibroblasts (Hormazabal et al., 2005).

The synthesis of 3-benzofuranone derivatives draw the attention of many researchers because of their various biological activities as mentioned above. 3-Benzofuranone was synthesized by the cyclodehydrochlorination of the corresponding phenoxyacetyl chloride by means of aluminum chloride (Elderfield, 1963; Pamer and Scollick, 1968; Schoepfer et al., 2002), as well as, the cyclodehydration of the corresponding phenoxyacetic acid by action of polyphosphoric acid, concentrated sulfuric acid and phosphorus pentaoxide (Kalinowski and Kalinowski, 1948; Hastings and Heller, 1972).

It was (Bose and Yates, 1952), have reported that coumaranone is formed when αdiazo-o-methoxyacetophenone is treated with hydrochloric acid as a catalyst, and they thought that the reaction proceeds through α-chloro-o-methoxyacetophenone as an intermediate. Recently, the mechanism of the latter reaction was reported, and has been found that 2, 4, 6-trimethoxy diazoacetophenone undergoes rapid hydrolysis in aqueous solutions in the presence of perchloric acid to give 4, 6-dimethoxy-3(2H)-benzofuranone (Kresge and Popik, 2004).

Furthermore, interamolecular Dieckmann cyclization was employed to synthesis of 3-benzofuranone via the reaction of ethyl (2-ethoxycarbonyl-5-methoxy-3-methyl) phenoxy acetate with sodium to give ethyl 3-hydroxy-6-methoxy methyl benzofuran-2-carboxylate (Brewer and Elix, 1972).

In other wise, 2-benzylidene-3-benzofuranone and its substituted (aurones) (Katritzky and Rees, 1984) were considered. Aurones have been found to occur in nature, they have been isolated as glycosides from the flower petals of certain *Compositae*, especially the genus *Coreopsis*. Because of their bright golden yellow colors, these substances are important contributors to the pigmentation of the flowers in which they occur (Geissman and Harborne, 1956).

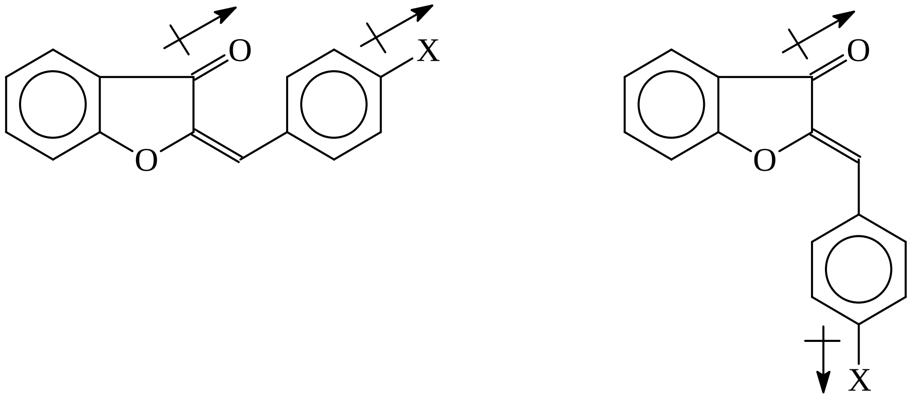
4,6-Dihydroxy-2- [α,α-(4-hydroxyphenyl)hydroxyl]methylene-3(2H)benzofuranone was isolated from the methanol extract of *Diospyros melanoxylon* leaves, the structure was elucidated by a combination of chemical and spectroscopic analysis (Mallavadhani and Mahapatra, 2005).

3`,4`,6-Trihydroxy-2-(phenyl methylene)-3(2H)-benzofuranone which is obtained from natural source was tested for its potential to inhibit growth of *Cryptosporidium parvum*. The compound was active in vitro at concentration 25-100 nM (Kayer et al., 2001).

Kayser et al. (2002), analyzed a series of aurones for their ability to inhibit respiratory functions of mitochondria of *Leishmania* parasites, and they found that these compounds inhibited parasite enzyme activity at 25 nM by over ninety percent.

The routes for the synthesis of aurones were reported in many papers, the most important one is the reaction of 3-benzofuranone with arylaldehydes in basic solution (Hastings and Heller, 1972; King et al., 1975; Vebrel et al., 1998; Schoepfer et al., 2002).

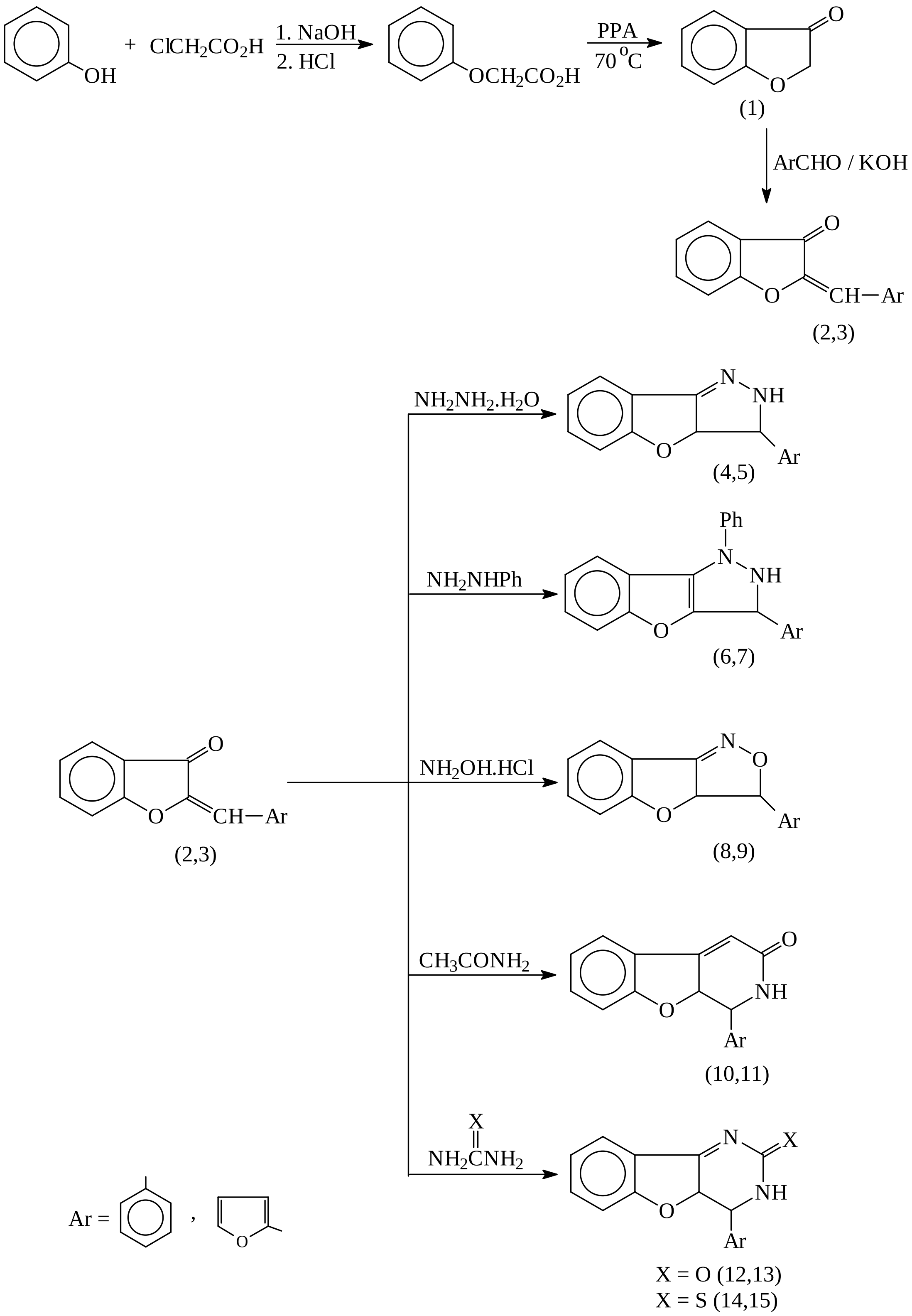
The structure of aurones was investigated using X-ray, IR, NMR and dipole moment measurements, these techniques established that aurones are planer molecules and confirms that the (Z)-configuration assigned to naturally occurring and synthetic aurones (Hastings and Heller, 1972; King et al., 1975; Katritzky and Reez, 1984).



(E) (Z)

X = H, Cl

The previous preview, and in view of the importance of the fused heterocyclic compounds, has encouraged to further work to synthesis some new fused heterocyclic compounds derived from 3-benzofuranone via aurones, which may have a significant biological activity. Scheme (1), gathering a series of reactions which were accomplished in this paper.


OH
+ ClCH2CO2H
1. NaOH
2. HCl
OCH2CO2H
PPA
70 oC
O
(1)
ArCHO / KOH
CH—Ar
(2,3)
NH2NH2.H2O
N
NH
Ar
(4,5)
NH2NHPh
Ph
(6,7)
NH2OH.HCl
(8,9)
CH3CONH2
(10,11)
X
NH2CNH2
X = O (12,13)
X = S (14,15)
Ar =

Scheme 1

EXPERIMENTAL

All chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs.

Phenoxyacetic acid was synthesized according to the described procedure in Vogel's (1980). m.p. = 97-99 °C, Lit. = 98-99 °C.

Melting points, yields and IR spectral data of synthesized compounds were tabulated in Tables (1 and 2).

Synthesis of 3(2H)-benzofuranone (1): (Hastings and Heller, 1972)

Phenoxyacetic acid (5 gm) was stirred with polyphosphoric acid (75 ml) at (70 °C) for (90 min). The reaction was quenched by pouring the mixture carefully onto a minimum quantity of crushed ice. The solid was filtered off, dissolved in ether, and washed with (10%) sodium carbonate solution. The ethereal layer was dried over $MgSO_4$, filtered and followed by evaporation of the solvent. The residue was recrystallized from ethanol, giving the ketone (58%), (m.p. = 98-100 °C, Lit. = 100 °C) (Amick, 1975).

Synthesis of 2-arylidene-3-benzofuranone (2,3): (Schoepfer et al., 2002)

To a solution of 3-benzofuranone (1) (0.02 mol, 2.68 gm) and benzaldehyde or furfural (0.02 mol) in ethanol (50 ml), potassium hydroxide (0.03 mol, 1.68 gm) was added at room temperature. The reaction mixture was stirred for (2 hrs.) and then left in the refrigerator to the next day. The resulting solid was filtered off, washed with cold water and recrystallized from ethanol, Tables (1 and 2).

1-Aryl-2,8a-dihydro-1H-8-oxa-2,3-diaza-cyclopenta[a] indene (4 and 5): (El-Rayyes and Bahtiti, 1989)

Aurone (2 or 3) (0.005 mole) was dissolved in (50 ml) ethanol, and (0.005 mole, 0.25 ml) hydrazine hydrate was added. The reaction mixture was refluxed for (12 hrs.). The solvent was evaporated under reduced pressure and the solid was collected and recrystallized from ethanol, Tables (1 and 2).

Synthesis of 1-phenyl-3-aryl-2,3-dihydro-1H-8-oxa-2,3-diaza-cyclopenta[a] indene (6,7): (Joshi and Jauhar, 1965)

A mixture of aurone (2 or 3) (0.005 mol), glacial acetic acid (10 ml) and phenyl hydrazine (0.005 mol, 0.54 gm) was refluxed for (4 hrs.). The reaction mixture was allowed to reach room temperature for (1 hr.), cold water was added, and the produced solid was filtered off, washed with cold water and recrystallized from ethanol, Tables (1,2).

Synthesis of 3-aryl-3,3a-dihydro-benzo[3,2a] isoxazole (8,9): (Ibrahim and Vlladimir, 1987)

A mixture of aurone (2 or 3) (0.02 mol), hydroxylamine hydrochloride (0.02 mol, 1.4 gm), potassium hydroxide (2 gm) and water (5 ml) in ethanol (50 ml) was refluxed for (24 hrs.). The reaction mixture was cooled in an ice bath, the solid was filtered off and recrystallized from ethanol-water, Tables (1 and 2).

General procedure to synthesis of:
1-Aryl-1,9a-dihydro-2H-benzo[4,5] furo[2,3c] pyridine-3-one (10,11), and 4-Aryl-4,4a-dihydro-3H-benzo[4,5] furo[3,2-d] pyrimidin-2-one (12,13) or -2-thione (14,15): (Marzinzik and Felder, 1998)

A small piece of sodium metal was dissolved in (25 ml) absolute ethanol and then (0.01 mol) of acetamide, urea or thiourea was dissolved. In other flask, aurone (2 or 3) was dissolved in (25 ml) absolute ethanol. The solutions were mixed and refluxed for (24 hrs.). The reaction mixture was cooled and the solid was filtered off and recrystallized from ethanol, Tables (1 and 2).

Table 1: Physical properties of compounds (1-15).

Comp. No.	**Yield %**	**m.p. °C**
1	58	98-100*
2	80	223-225
3	77	115-118
4	90	238-241
5	64	78-81
6	55	134-136
7	73	137-140
8	81	250-252
9	78	123-125
10	63	235-238
11	60	223-225
12	71	248-250
13	84	220-222
14	70	190-193
15	58	169-171

* Lit. (Hastings and Heller, 1972) = 100 °C.

RESULTS AND DISCUSSION

A series of fused heterocyclic compounds were synthesized using 2-arylidene-3-benzofuranone (aurones) as a starting materials, which was prepared from the reaction of 3-benzofuranone with aromatic aldehyde in presence of alcoholic potassium hydroxide solution, as mentioned in Scheme (1).

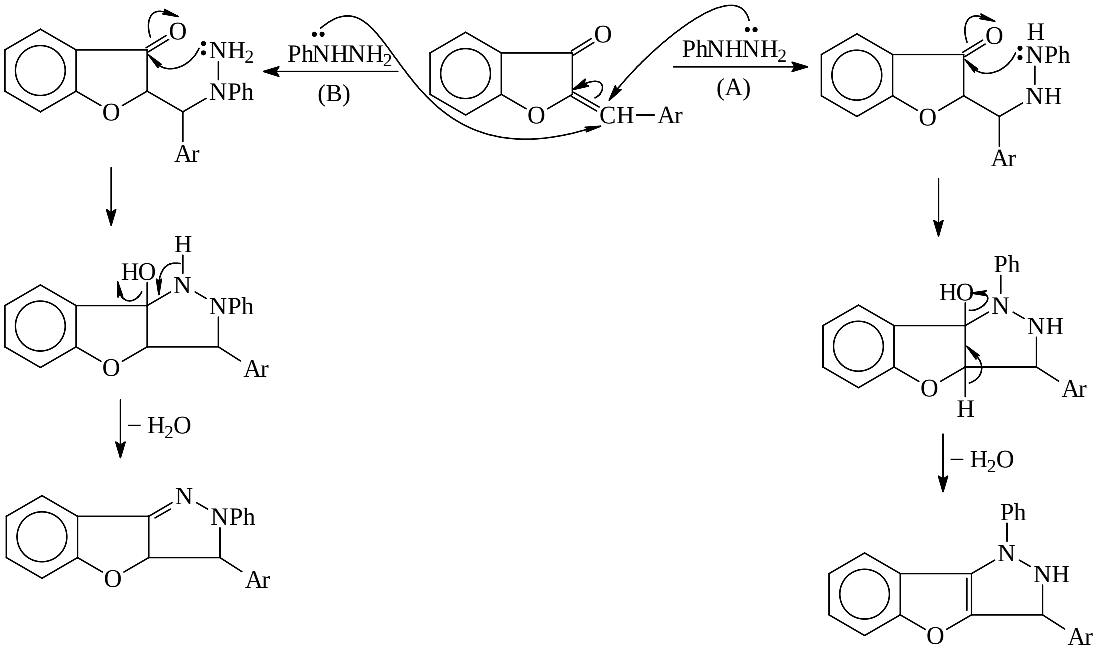
3-Benzofuranone was synthesized by heating phenoxyacetic acid with polyphosphoric acid at 70 °C (intramolecular cyclodehydration). The structure of synthesized compound was confirmed by IR spectra as well as melting point measurement and gave +ve test with 2,4-dinitrophenyl hydrazine reagent. IR spectra showed absorption at (1790 cm^{-1}) which was due to (C=O) group. This value is high, and it due to the fact that the cyclic ketones absorb at higher field comparing with alicyclic (cyclic strain effect).

3-Benzofuranone was converted to aurones (2, 3), by its reaction with benzaldehyde and furfural in alcoholic potassium hydroxide solution respectively. IR spectrum of compounds (2, 3) showed bands at (1619, 1612 cm^{-1}) for (C=C) and (1665, 1670 cm^{-1})

for (C=O). The decreasing of carbonyl absorption in aurones is due to the conjugation with (C=C) group.

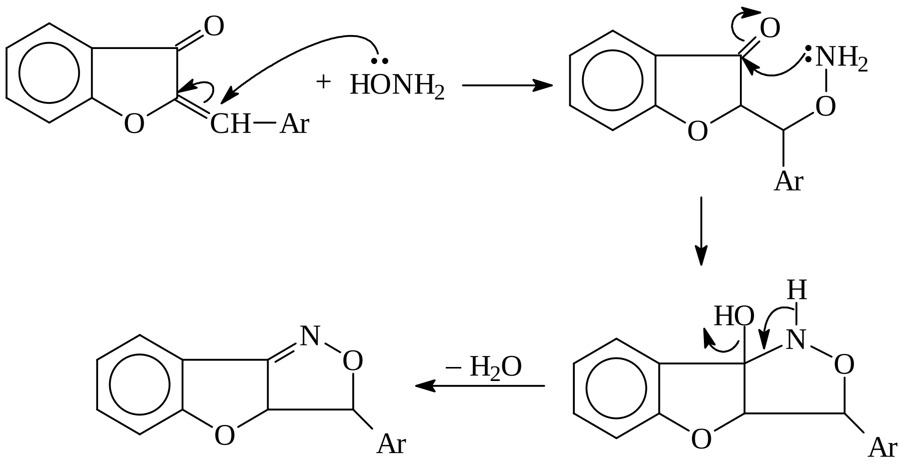
Pyrazoline derivatives (4, 5) were synthesized by the reaction of aurones (2, 3) with hydrazine hydrate in ethanol. IR spectrum of compounds (4, 5) showed bands at (1602, 1609 cm^{-1}) due to (C=N) and bands at (3421, 3346 cm^{-1}) for (N-H) group.

The reaction of aurones (2, 3) with phenyl hydrazine in glacial acetic acid gave compounds (6, 7) respectively. The reaction may undergo through two expected mechanisms, as shown below:



IR spectra of compounds (6 and 7) showed bands at (1598, 1597 cm^{-1}) due to aliphatic (C=C) and absorptions at (3286, 3290 cm^{-1}) due to (N-H) stretching. IR data (absorption of N-H) revealed that the mechanism of the reaction proceed through rout (A).

Isoxazole derivatives (8 and 9) were synthesized according to Ibrahim and Vlladimir (1987), procedure, by the reaction of aurones (2, 3) with hydroxylamine hydrochloride in ethanolic potassium hydroxide solution. The reaction undergoes through (OH) attack of hydroxylamine on β-carbon in aurone (Michael addition) followed by condensation of (NH_2) group with (C=O) of aurone.



The structure of compounds (8 and 9) was confirmed by IR spectra which show the absorptions at (1620, 1635 cm^{-1}) for (C=N), and sharp band at (1235, 1233 cm^{-1}) due to (N-O) stretching.

Aurones (2 and 3) were reacted with acetamide in alcoholic potassium hydroxide to give pyridinone derivatives (10 and 11). The suggested mechanism including the attack of (NH$_2$) group in acetamide to β-carbone in chalcon followed by Aldol condensation between (CH$_3$) group in acetamide residue with carbonyl group of aurone. IR spectra showed bands at (1650, 1660 cm^{-1}) for (C=O), (1593, 1579 cm^{-1}) for (C=C) aliphatic and broad bands at (3387, 3405 cm^{-1}) due to (N-H) stretching.

Finally, pyrimidin-2-one(thione) derivatives (12-15) were synthesized according to the previous method. IR data was listed in Table (2).

Note: All the synthesized compounds showed strong absorption band in the IR spectra at the region (1008-1131 cm^{-1}) corresponding to (Ar-O-C) stretching.

Table 2: IR data of the synthesized compounds (1-15).

Comp. No.	**ν (cm^{-1}) KBr**					
	N-H	**C=O**	**C=N**	**C=C aliph.**	**C=S**	**Ar-O-C**
1	-	1790	-	-	-	1100
2	-	1665	-	1619	-	1046
3	-	1670	-	1612	-	1010
4	3421	-	1602	-	-	1046
5	3346	-	1609	-	-	1114
6	3286	-	-	1598	-	1117
7	3290	-	-	1597	-	1131
8	-	-	1620	-	-	1083
9	-	-	1635	-	-	1054
10	3387	1650	-	1593	-	1083
11	3405	1660	-	1579	-	1108
12	3458	1660	1620	-	-	1008
13	3420	1664	1614	-	-	1083
14	3380	-	1619	-	1251	1085
15	3384	-	1616	-	1236	1070

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