Preparation of Number of Chalcone Compounds From 6-formyl-5-methoxy-1,3-benzoxathiol.

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Abstract:

A number of chalcones were prepared by condensing of acetyl arene with 6-formyl-5-methoxy-1,3-benzoxathiol under acidic conditions. Base-catalyzed Claisen-Schmidt condensation could not be used to prepare of chalcones due to the oxathiol ring sensitivity in both the starting material and products to the alkali. The percentage of the yields depended on the substituent's in the products isolated. The electron-withdrawing groups increase the reaction rate and product percentage, while the electron-donating groups decrease the reaction rate and product percentage .Where the low yields were observed for *o*-substituted compounds (B4 and B10), while the high yields were obtained for *m*- and *p*-substituted compounds due to the steric hindrance in *o*-substituted compound. The products were characterized by FT-IR , UV/VIS spectroscopy and melting points.

تحضير عدد من مركبات الجالكون من ٦ـ فورميل ـ٥ـ ميثوكسي ـ٣،١ـ بنزو اوكساثايول.

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ملخص البحث:

حضر عدد من الجالكونات بتكثيف اسيتايل أرين مع ٦- فورميل -٥- ميثوكسي -٣،١- بنزو اوكساثايول تحت ظروف حامضية .ان تكثيف كليزن –شميدت المحفز بالقاعدة لا يمكن استعماله في تحضير الجالكونات بسبب حساسية حلقة الاوكساثايول للقلويات في كل من المواد الأولية والنواتج . تعتمد نسبة الناتج على نوع المجاميع المعوضة في المركبات الناتجة حيث تزيد المجاميع الساحبة للالكترونات من نسبة الناتج وسرعة التفاعل بينما تقلل المجاميع الدافعة للالكترونات من سرعة التفاعل ونسبة الناتج. كما لوحظ بان نسبة الناتج للمركبات المعوضة عند موقع الارثو للمركبين (B4 و B10) تكون منخفضة بسبب الإعاقة الفراغية، بينما تكون نسبة الناتج عالية عندما يكون التعويض في مواقع البارا والميتا . شخصت النواتج بواسطة طيف الأشعة تحت الحمراء FT-IR ،UV/VIS و قياس درجة الانصهار.

Introduction

Aldol condensations represent an important class of carbon-carbon bond formation reactions both in nature and in synthetic chemistry. Chalcones which are α,β–unsaturated ketones prepared by crossed aldol condensation of an aromatic ketone and an aldehyde[1].

Chalcones are known to exhibit various biological activities[2]. They have been reported to possess antioxidant, antimalarial, antileishmanial, antiinflammatory, and antibacterial activity and antitumor[2,3].

The presence of a reactive α,β–unsaturated keto function in chalcone makes it biologically active, chalcones is found to be responsible for their antimicrobial activity, which may be altered depending on the type and position of substituent on the aromatic rings[3,4].Chalcone derivatives also possess anthelmintic, germicidal. antimicobial and carcenogenic activities[5].

Chalcones are also important compounds as Michael acceptors in organic synthesis. Michael addition reaction of appropriate carboanionic reagents to α,β-unsaturated carbonyl compounds such as chalcones is of synthetic interest for C-C bond formation[6]. Most of the chalcones are highly biologically active with a number of pharmacological and medicinal applications, chalcones have been used as anti AIDS agents[4].

Chalcone synthase activity was demonstrated in enzyme preparations from flowers of defined genotypes of dianthus caryophyllus L. (carnation)[7]

Chalcones are important intermediates in the synthesis of many pharmaceuticals. They are commonly synthesized via the Claisen-Schmidt condensation between acetophenone and benzaldehyde. This reaction is catalyzed by acids and bases under homogeneous conditions[8].

Oxathiole has been used in the treatment of acne due to its sulfur content. It is reported to possess cytostatic antipsoriatic, antibacterial and anti-mycotic properties , It is also added to some cosmetics[9]. Oxathiole is used in the treatment antitumor and anti cancer[10]. Substituted oxathiole fused chalcones were prepared by condensation of 4-acetyl-5-methoxy-2-oxo-benz[1,3]oxathiole with benzaldehydes under acidic conditions. These compounds were tested to be process cytotoxic, antibacterial, antifungal and tuberculostatic activity[11].

There are studies of chalcone synthesis under both acidic and alkaline conditions by Davey and Tivey[12].

In this research an oxathiole fused chalcones are prepared by condensation of appropriate 6-formyl-5-methoxy-1,3-benzoxathiol with acetyl arene under acidic conditions.

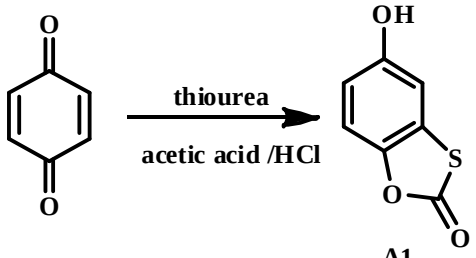
Experimental methods:

Melting points were recorded by Electrothermal 9300 melting point apparatus and are uncorrected . Infrared spectral data were obtained by

using F.T.I.R- Tensor 27-Bruker in the range of (200 – 4000) cm^{-1}**.** Electronic spectra were obtained by using Shimadzu UV/VIS Spectrophotometer UV-160 for 10^{-3} M solution of the compounds in (DMF or $CHCl_3$) using 1 cm cell quartz**.**

Preparation of 5-hydroxy-1,3-benzoxathiol-2-one(A1):[11,13]

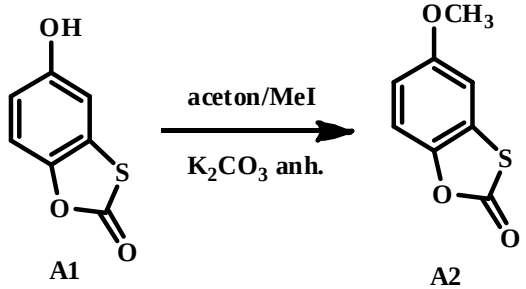
To a stirred solution of thiourea (60 gm , 0.79 mole) in (400 ml) 2N hydrochloric acid, a solution(50 gm,0.46 mole) benzoquinone in (250 ml) of glacial acetic acid was added. The mixture was stirred at room temperature for 30 min, during which time a mass of crystalline thiouronium salt precipitated (with most of the quinones). Upon heating on a steam bath, the salt was dissolved to give a clear solution. The mixture was heated for 1 hr, then chilled in an ice bath until crystallization was complete. The solid was collected, washed with water, and separated by filtration then air dried to provide (42 gm) of (A1), yield (84%), m.p. of 171 -173 °C.



A1

Preparation of 5-methoxy-1,3-benzoxathiol-2-one (A2): [11]

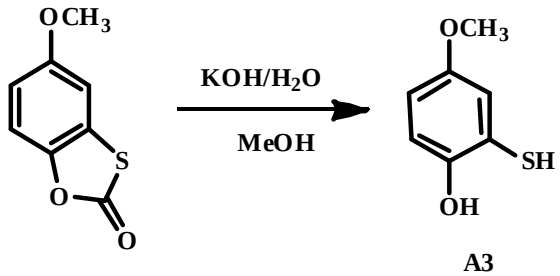
Anhydrous K_2CO_3 (100 gm) in (400 ml) acetone containing methyl iodide (50 gm, 0.352 mole) was added to (41 gm, 0.224 mole) of (A1) . The mixture was stirred overnight at (25 °C). The solids were removed by filtration, and the solvent removed under vacuum then air dried to provide (26.7 gm) of (A2) ,yield (65%) as a yellow powder (m.p. 66 -72°C). Recrystallization of the product from methanol gave a white solid with a m.p of (74-76)°C.



A1 A2

Preparation of 2-mercapto-4-methoxyphenol (A3): [14]

To a solution of KOH (30 gm) in (75 ml) warm H_2O, an equal volume of warm methanol was added followed by (16 g , 0.087 mole) of (A2). The mixture was refluxed for (3 h). After cooling to room temperature, the mixture was acidified with hydrochloric acid then extracted with (2x100 ml) CH_2Cl_2. The organic layer was separated ,dried with anhydrous magnesium sulfate ($MgSO_4$ anh.).

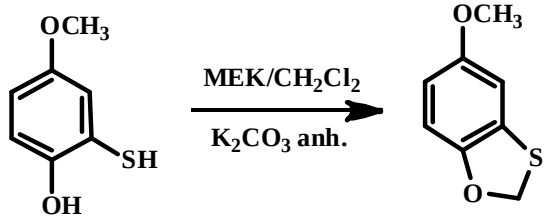


A2 A3

Removal of the solvent gave a yellow oily material which crystallized on standing. The product (A3), weighed 14 g, yield (87%) with m.p. of (57-58) °C.

Preparation 5-methoxy-1,3-benzoxathiol (A4): [14]

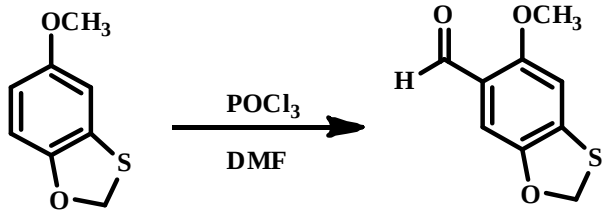
A solution of (10 gm, 0.064 mole) (A3) in (100 ml) methyl ethyl keton was added over the course of (2 h) to a vigorously stirred suspension of (25 gm) finely powdered anhydrous K_2CO_3 in (200 ml) methyl ethyl keton containing methylene Chloride (14 gm,0.098 mole). The refluxing was continued for (48 h). After cooling, the mixture was filtered and the filter cake washed with additional methyl ethyl keton (50 ml). The solvent of the combined washes and filtrate were evaporated under vacuum, and the product distilled to give (3 gm) (A4) yield (30%) with b.p of (122-126) °C.



A3 A4

Preparation 6-formyl-5-methoxy-1,3-benzoxathiol (A5): [14]

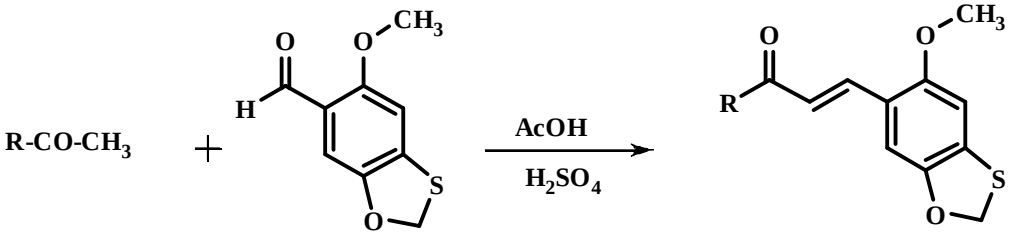
mixture of (3 ml) $POCl_3$ and (2 ml, 26 mmol) dimethylformamide (DMF) was heated quickly on the steam bath, then (2.5 gm, 0.0148 mole) of (A4) was added. The steam bath heating was continued for an additional (15 min) , the reaction mixture was poured into (100 ml) H_2O, and the mixture was stirred for few minutes. The solid material was collected by filtration, washed with H_2O, let to dry as possible, then recrystallized from methanol, to give (2.1 gm), yield (84 %) of 6-formyl-5-methoxy-1,3-benzoxathiol as brown needles with m.p. (119-120) °C.



A4 A5

General procedure for preparation the chalcone (B1-B10):

A mixture of 6-formyl-5-methoxy-1,3-benzoxathiol (A5) (196 mg, 1 mmol), suitable acetyl arene (1 mmol) and concentrated sulfuric acid (0.2 ml) in acetic acid (2 ml) was stirred at suitable temperature and time (Table - 1). The cold mixture was diluted with methanol (2-5ml) and the precipitated solid was filtered off. The crude product was crystallized from absolute ethanol except for compounds B1 and B7. The physical properties and the spectral data were listed in Table 1 and 2 respectively.

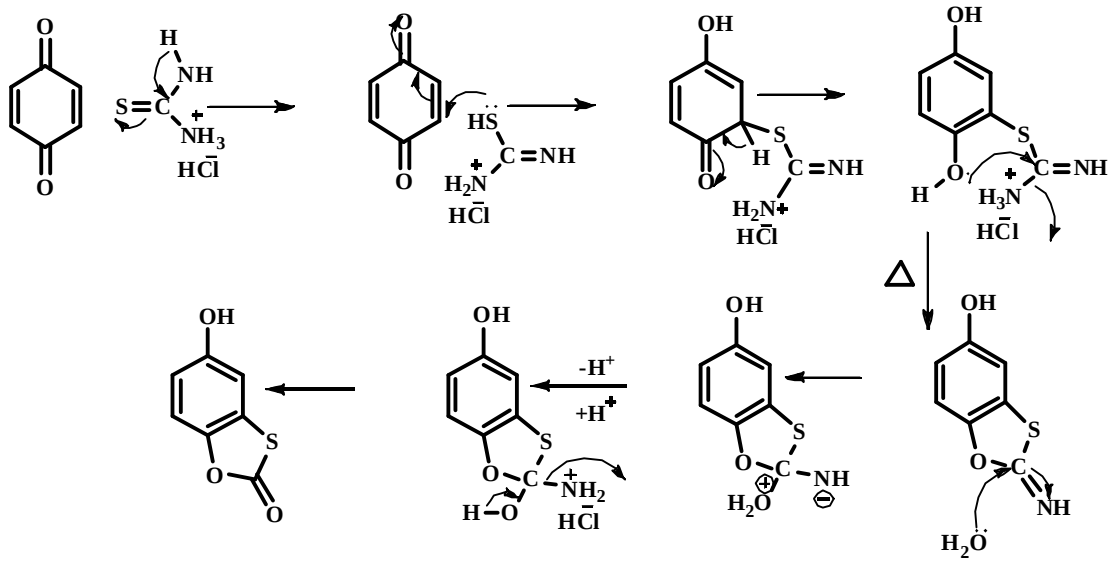


R= CH_3-, C_6H_5-, 4-$NO_2C_6H_4$-, 2-OHC_6H_4-, biPh-, 4-$NH_2C_6H_4$- , 2- Naphthyl- , 3,4-di$CH_3OC_6H_4$- , 4-FC_6H_4- , 2-$CH_3OC_6H_4$- .

Scheme 1. Synthesis of chalcones

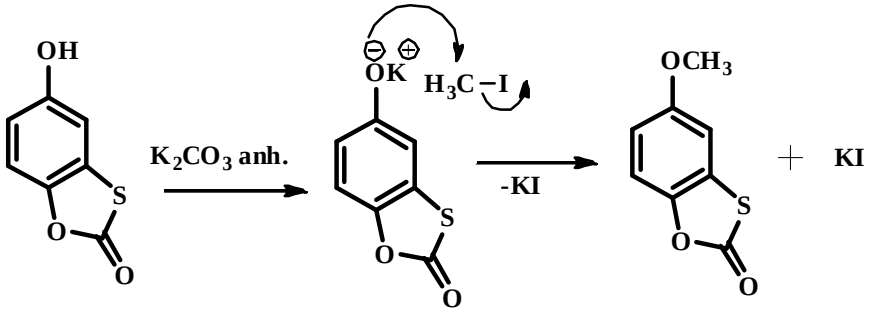
Result and discussion:

The oxathiolone ring in both the starting material and products was alkali-sensitive and for this reason the standard, base - catalyzed Claisen-Schmidt condensation could not be used. However, satisfactory results were obtained for reactions carried out in acetic acid with catalytic amount of sulfuric acid. The reaction mechanism of preparation starting material as shown as the following in the scheme (2):



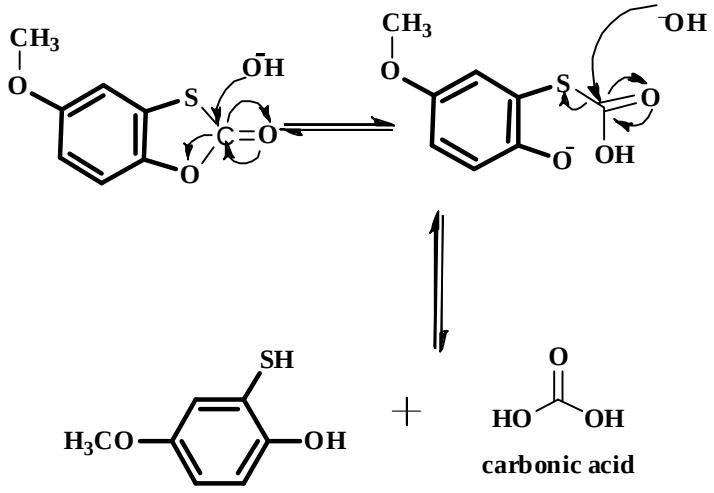
Scheme 2. mechanism of Preparation (A1)

The reaction mechanism of preparation (A2), scheme (3) include mechanism of the Williamson Synthesis[15], this method is suitable for the preparation of unsymmetric ether by alkylation of alkoxides will act as a base with primary alkyl halides, usually by an S_N2 mechanism. The term S_N2 means that two molecules are involved in the actual transition state.



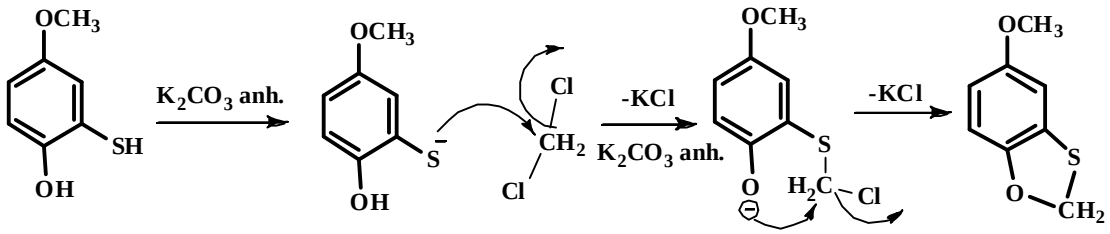
Scheme 3. mechanism of Preparation (A2)

The reaction mechanism of preparation (A3), scheme (4) [16] include 1st step: nucleophilic attack by the hydroxide ion to (C=O) of oxathiol ring, is formed S-(2-hydroxy-4-methoxyphenyl)hydroxyl thiocarbonate, 2ed step: nucleophilic attack by the hydroxide ion to (C=O) of thiocarbonate, is formed (A3) and carbonic acid.



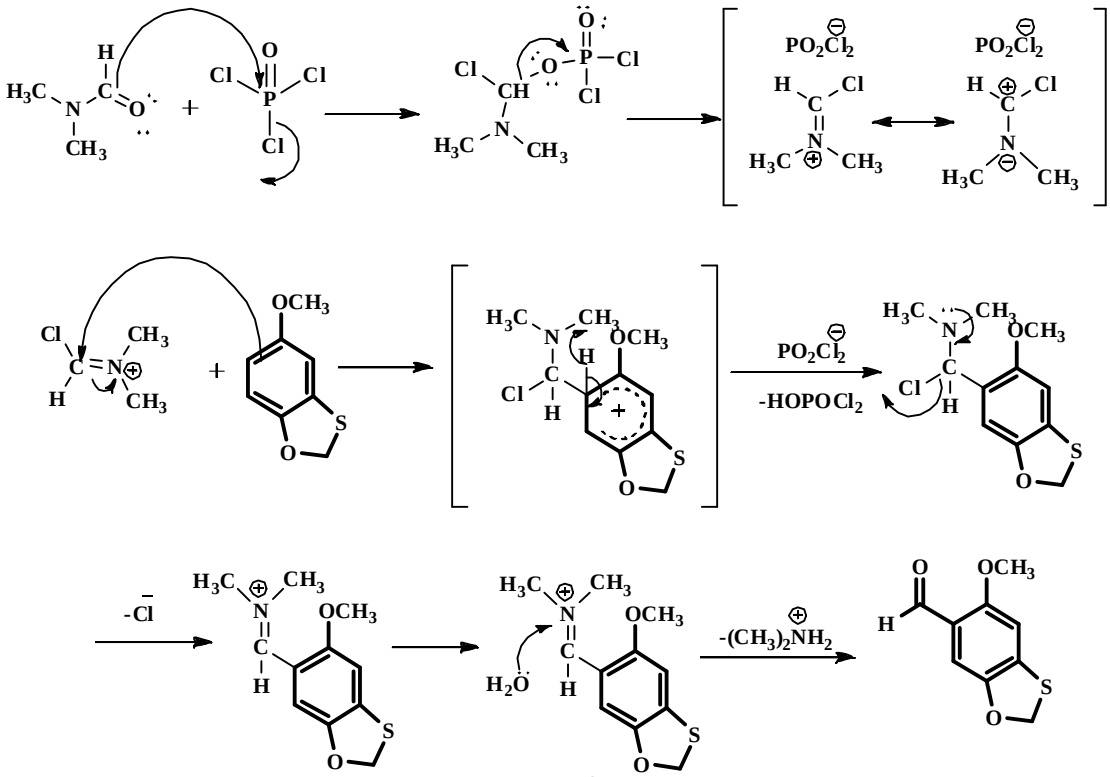
Scheme 4. mechanism of Preparation (A3)

The reaction mechanism of preparation (A4), scheme (5) include mechanism of the Williamson Synthesis[15].



Scheme 5. mechanism of Preparation (A4)

The reaction mechanism of preparation (A5), scheme (6) include formylating agent, also known as the Vilsmeyer-Haack reagent, is formed in situ from DMF and phosphorus oxychlorid [17], the vilsmeier reaction allows the formylation of electron-rich arenes. An electrophilic aromatic substitution leads to α-chloro amines, which are rapidly hydrolyzed during work up to give the aldehyde.



Scheme 6. mechanism of Preparation (A5)

The yields depended on substituent's in the products. Where the electron-withdrawing groups increase the reaction rate and the percentage of the yield, while the electron-donating groups decrease reaction rate and the percentage of the yield. The type and the substituent affects the reaction yields. Also the low yield were observed for ortho substituted compounds B4 and B10. While the high yields were achieved in *m*-and *p*-substituted compounds as seen in (Table-1). It is assumed that the low yields could be attributed to the steric hindrance of *o*-substituted compounds . Some physical properties characteristics of the synthesized compounds are shown in (Table-1).

In this study, 10 compounds were synthesized (Scheme 1). The structures of the obtained compounds was elucidated by spectral data. The infrared data were very informative and provided evidence for the formation of the expected structures (Table-2). υ C=O, υ C-O, υ C=C, υ C-H, υ C-S, υ NO_2, υ O-H and υ N-H, functions absorbed strongly in the expected regions. They show a characteristic IR absorption peak at 1746-

1701 cm^{-1} indicating the presence carbonyl group[3,11,18] (C=O), exhibited C-H stretching vibrations in the υ 2986-2916 cm^{-1} range which can be difficult to identify between two ethers groups in methoxy and oxathiole ring due to large variations in intensity. In addition, the absorption frequencies at υ 1263-1241 cm^{-1} (s), 1658-1621 (m), 889-880 (s), 3442 cm^{-1} (s) and 3293 cm^{-1} (s) indicating the presence of (C-O), (C=C), (C-S) , (O-H) and (N-H) groups[19], respectively. The UV spectra of chalcones (B1-B10), show maximum absorption at wave length (λ_{max}) at 350-288 nm (red shift) due to the conjugation of the two chromophore[20] (C=C and C=O) and presence oxochrom on aromatic ring.

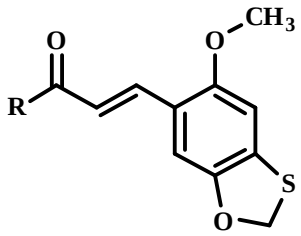
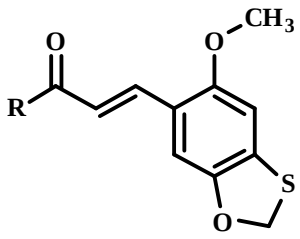


Table – 1 : Some physical properties of compounds (B1-B10)

No.	(R)	m.p	color	Solvent for crystallize	reaction time(h)	reaction heat(°C)	Yield %
B1-	CH_3-	187-189	yellow	cyclohexane	6	R.T	65
B2-	C_6H_5-	206-207	orange	abs ethanol	24	60	71
B3-	4-$NO_2C_6H_4$-	278-280	yellow	abs ethanol	24	60	79
B4-	2-OHC_6H_4-	227-229	orange	abs ethanol	24	60	45
B5-	biPh-	231-233	yellow	abs ethanol	24	60	75
B6-	4-$NH_2C_6H_4$-	222-224	Red	abs ethanol	6	90	60
B7-	2- Naphthyl	209-211	yellow	cyclohexane	24	R.T	57
B8-	3,4-diCH_3O C_6H_3-	218-220	yellow	abs ethanol	24	60	58
B9-	4-FC_6H_4-	201-204	creamy	abs ethanol	6	70	56
B10	2-$CH_3OC_6H_4$-	213-215	yellow	abs ethanol	8	80	43

Table – 2 : The spectral data of compounds (B1-B10)



NO.	(R)	FT.IR (KBR) Y CM^{-1}								UV(DMF , $CHCL_3$) Λ_{MAX} NM
		C-H	C=O	C-O	C=C	C-S	-NO_2	O-H	-NH	
B1-	CH_3-	2920	1730	1241	1621	884	------	------	------	288
B2-	C_6H_5-	2916	1740	1252	1645	887	------	------	------	311
B3-	4-$NO_2C_6H_4$-	2970	1733	1259	1642	881	1508(as) 1365(s)	------	------	315
B4-	2-OHC_6H_4-	2971	1701	1239	1653	885	------	3442	------	350
B5-	biPh-	2968	1731	1255	1640	883	------	------	------	317
B6-	4-$NH_2C_6H_4$-	2979	1729	1253	1654	886	------	------	3293	345
B7-	2- Naphthyl-	2972	1742	1249	1654	882	-----	------	-----	319
B8-	3,4-di$CH_3OC_6H_3$-	2986	1746	1263	1648	889	-----	------	-----	339
B9-	4-FC_6H_4-	2975	1736	1257	1646	880	-----	------	-----	332
B10-	2-$CH_3OC_6H_4$-	2981	1743	1250	1658	883	------	------	------	321

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