Novel Process For Synthesis of 2,3-dihydro-1,3,4-Thiadiazole Derivative

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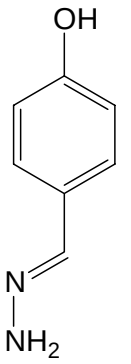
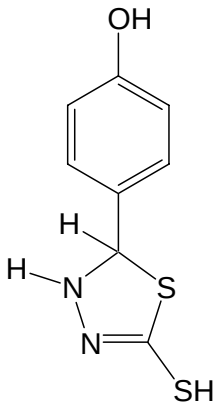
Abstract

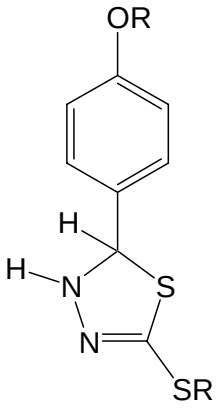
In this study a series of compounds (**3,4,5a,5b,5c,5d**) with 2,3-dihydro-1,3,4-thiadiazole were synthesized from p-hydroxy benzaldehyde. The mechanism of this studied was discussed. The chemical of the compounds were elucidated by their IR and ^{1}H-NMR spectral date.



(3)



(4)



(5)

R =

***a*= CH_3-------**

***b*= C_2H_5------**

***c*= C_3H_7-------**

***d*= *Ph*-CH_2-------**

keywords : 2,3-Dihydro-1,3,4-Thiadiazole, Novel, Benzaldehyde.

الخلاصة

في هذه الدراسة تم تحضير المركبات(**3,4,5a,5b,5c,5d**) والحاوية على الحلقة الغير متجانسة 2و3-ثنائي الهيدروجين-1و3و4-ثايادايزول من المركب بارا-هيدروكسي بنزلديهايد. تم مناقشة الميكانيكية لهذا التفاعل كون الطريقة حديثة، وقد تم إثبات تكوين المركبات باستخدام طيف الأشعة التحت الحمراء وطيف الرنين النووي المغناطيسي لنظير الهيدروجين.

Introduction:

1,3,4- Thiadiazoles attracted the great attention after the discovery of sulfa drugs and their potent representative bearing this heterocyclic ring . Several 1,3,4-Thiadiazoles have been found biologically active, e.g. they showed the anti-Cancer and antiviral activity[1-9] anti-inflammatory[6] anticonvulsant[8] H-2 antagonist[7] antibacterial[5].

Likewise a 1,3,4-thiadiazole nucleus which incorporates an N-C-S linkage exhibits a large number of biological activities [10].

As apart of our program amid to developing for synthesis of new compounds containing 1,3,4- Thiadiazoles heterocyclic rings, we reported here the facile and novel rout to synthesis of 2,3 – dihydro- 1,3,4-Thiadiazole heterocyclic ring and their derivatives through the intermolecular cyclization as shown in this novel synthesis that was illustrated in Scheme 1 and Scheme 2.

Experimental:

1-General:

The solvents used were purified by standard procedures. The melting point (m.p) was determined on an electrothermal digital melting point apparatus and uncorrected. The (^{1}H-NMR) spectra were recorded on 400MHz (JEOL, JNM-ECP400, FT-NMR system), (300MHz with AC300 instrument from Bruker company) spectrometer in $CDCl_3$. The spectral data is reported in delta (δ) units relative to TMS reference peak. Infrared (IR) spectra were recorded by using SHIMADZU FT-IR spectrometer(ν in cm^{-1}).

2. Procedure:

A. General procedure for synthesis compound (**3**)

(4-Hydrazonomethyl-phenol)

In stirred (30ml) of absolute ethanol added (lg, 0.008 mole) of p-hydroxy benzeldyde(**1**) with (0.4lg, 0.008 mole) of hydrazine hydrate (**2**). After the addition was complete, the reaction mixture was refluxed for 24hr then cooled. The solid that precipitate was filtered off, recrystalized by ethanol all data for this compound in table -1-

B. General procedure for synthesis compound (**4**).

(2-(4-Methoxy-phenyl)-5-methylsulfanyl-2,3-dihydro-[1,3,4]thiadiazole)

Compound (**3**) (lg, 0.0073 mole) were dissolved in absolute ethanol (30ml). Then the solution was added to the solution of (0.577 mole) of CS_2 with continuous stirring at 60 C^0. The reaction was then refluxed and monitored by TLC. After consumption of the starting material, added anhydrous sodium carbonate (0.78 mole) and (15ml) of cold distillated water, after 2hr of stirring added drop wise (3ml) of HCl (30%). The mixture was cooled to room temperature and separated the organic layer drying by $MgSO_4$. The mixture was cooled to room temperature to form yellow precipitate, The crude solid was then filtered and recrystalized from

ethanol to yield the compound (**4**). All data in table -1-

C. General procedure for synthesis compound (**5**).

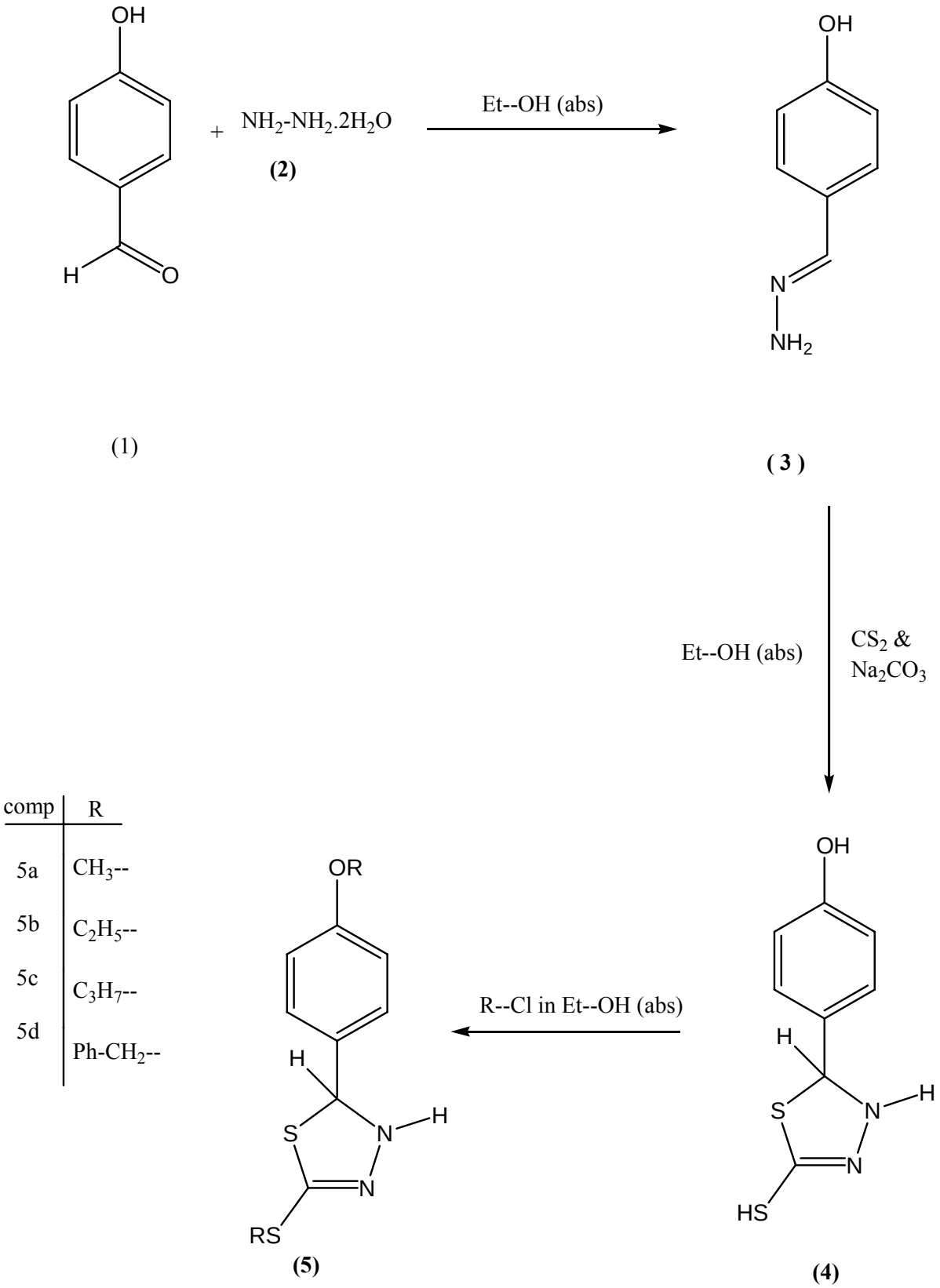
Compound (**4**) (0.5g, 0.0023) were dissolved in 20ml of absolute ethanol. Then the solution was added to (0.234g, 0.0046 mole-0.25g, 0.0046 mole-0.37g, 0.0046 mole-0.596g, 0.0046 mole) for (CH_3Cl, C_2H_5Cl, n-C_3H_7Cl and Ph-CH_2Cl) alkyl halide respectively continuous stirring at (r.t) in basic media. The reaction was then refluxed. The mixture was cooled to (r.t) we see yellow precipitate in the bottom of the (r.b.flask). The crude solid was then filtered and recrystalized from ethanol all data for derivatives in table -1- and their names are:

(5a): **2-(4-Methoxy-phenyl)-5-methylsulfanyl-2,3-dihydro-[1,3,4]thiadiazole**

(5b): **2-(4-Ethoxy-phenyl)-5-ethylsulfanyl-2,3-dihydro-[1,3,4]thiadiazole**

(5c): **2-(4-Propoxy-phenyl)-5-propylsulfanyl-2,3-dihydro-[1,3,4]thiadiazole**

(5d): **2-(4-Benzyloxy-phenyl)-5-benzylsulfanyl-2,3-dihydro-[1,3,4]thiadiazole**



Scheme (1): Explain the route of synthesis compound (3,4 and 5)

Results and discussion:

The synthesis of the target derivatives (**4**) began by condensing carbon disulfide with 4- Hydrazonomethyl-phenol under basic condition (Scheme1). The compound (**4**) was obtained in 61% yield, the IR and ^{1}NMR spectra was illustrated in fig 2 and 4 respectively.

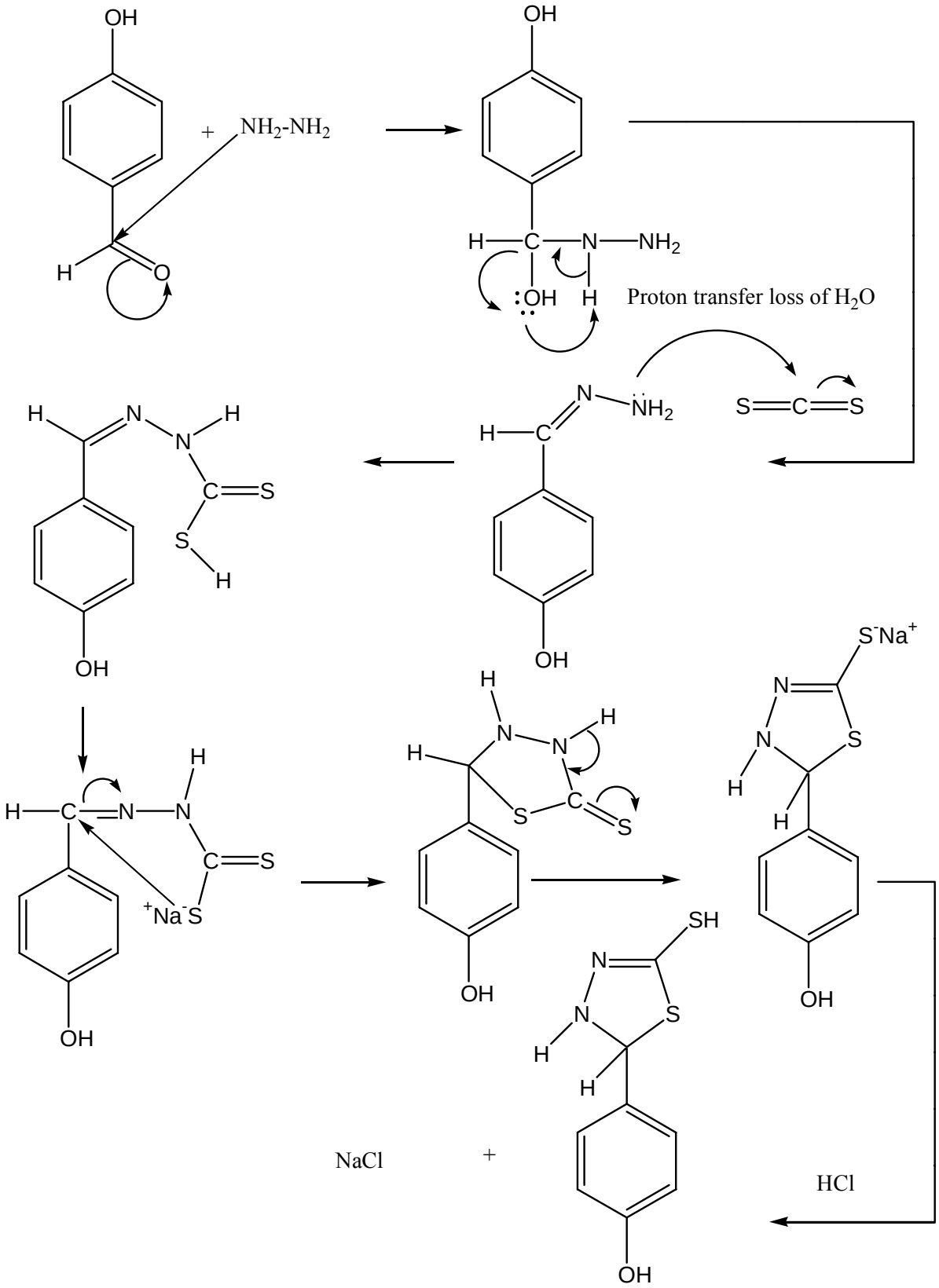
The mechanism of this reaction illustrated as shown in (Scheme 2).The (table1) reports the results of complete ^{1}H-NMR & IR spectra and it is important to point out , these spectral data was confirmed the structure of these compounds.

The presence of chemical shift (δ) at (4.93-4.95) δ and (7.7-7.9) δ indicated the appear of dihydro in heterocyclic 1,3,4-Thiadiazole ring in all derivatives **5a,5b, 5c** and **5d**, fig-3- as example for compound (**5c**).

The purity of the isolated compounds was checked by TLC in different solvents.

The characterization of the synthesized compound **(3)** is based on the infrared & ^{1}H-NMR data (Table 1), the IR spectra in fig-1- confirmed this compound.

The infrared spectra of compound (**3**) showed characteristic OH /NH_2 absorption in the region 3300-3100 cm^{-1}, which was eliminated by the formation of dihydro-1,3,4-Thiadiazole (**4**) heterocyclic ring and showed absorption peak in 2570-2630 cm^{-1} attributed to SH. The absence of NH and presence of S-H absorptions established that all the isolated 1,3,4-thiadiazole are in their thiole rather than in the hydrazine form as in fig illustrated below. In the ^{1}H-NMR spectra of these compounds the protons were observed in the expected region as shown in (Table 1).



Scheme 2 The mechanism for synthesis of compounds (3,4 and 5)

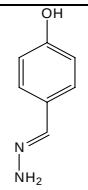
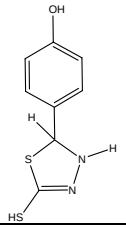
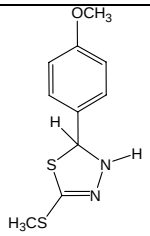
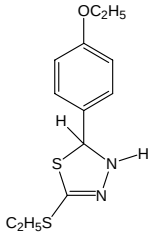
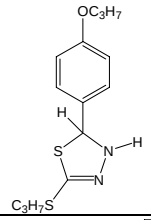
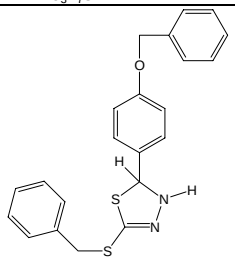
# of compounds	Structure	Yield % color	IR υ max (Cm^{-1})	^{1}H-NMR (δ)	m.p (C^0)
3		**75%** **Yellow**	3300, 3100	2.0(S,2H, NH_2), 5.1(S, 1H, OH), 6.8(d,2H,Ar), 7.4(d, 2H, Ar) 8.1(S, 1H, CH=N)	270-271
4		**61%** **yellow**	749, 1243, 1620, 3310, 2570	1.5(S,1H,SH), 4.95(S, 1H, SCH) 5.1(S, 1H, OH), 6.62(d, 2H, Ar), 7.21(d, 2H, Ar), 7.9(S, 1H, NH)	258-259
5a		**90%** **yellow**	760, 1252, 1640, 2562, 3315	2.1(S, 3H, S-CH_3), 3.73(S, 3H, O-CH_3), 4.95(S, 1H, SCH), 6.65(d, 2H, Ar), 6.95(d,2H, Ar), 7.8(S, 1H, NH)	244-245
5b		**82%** **yellow**	764, 1250, 1633, 1312, 2650	1.30(t, 3H, CH_3-CH_2-S), 1.61(t, 3H, CH_3-CH_2-O), 3.1(q,2H, CH_2-CH_2-S), 4.1(q, 2H, CH_3-CH_2-O), 5.0(S, 1H, SCH), 6.64(d,2H,Ar), 7.1(d,2H, Ar), 7.9(S,1H, NH)	147-148
5c		**71%** **Yellow**	755, 1253, 1650, 2556, 3320	0.97(t, 6H, CH_3), 1.74(m, 2H, CH_2-CH_2-O), 2.0(m, 2H, CH_2-CH_2-S), 3.93(t, 2H, CH_2-O), 4.959 S, 1H, SCH), 6.65(d, 2H, Ar), 6.95(d, 2H, Ar), 7.99 S, 1H, NH)	140-141
5d		**72.5%** **Yellow**	761, 1260, 1625, 2630, 3310	2.6(d, 2H, Ph-CH_2-CS), 4.93(S, 1H, SCH), 6.94(m, 4H, α-β system for benzene ring attack to the heterocyclic ring), 7.7(S, 1H, NH), 7.14(m, 10H, α-β system for two phenyl rings)	206-207

Table 1 Structure, IR, ^{1}H-NMR, yield and melting point data For all derivatives

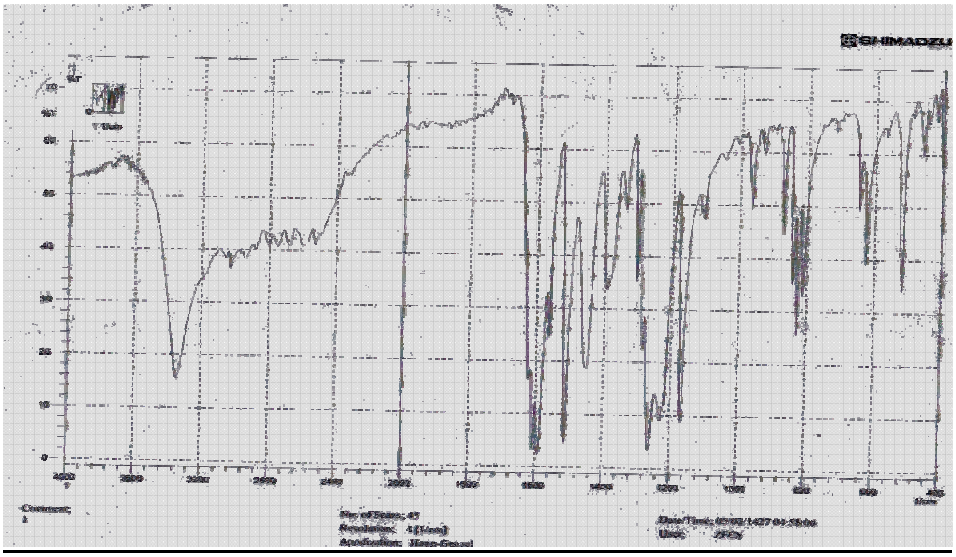


Fig -1- The IR spectra of compound (3)

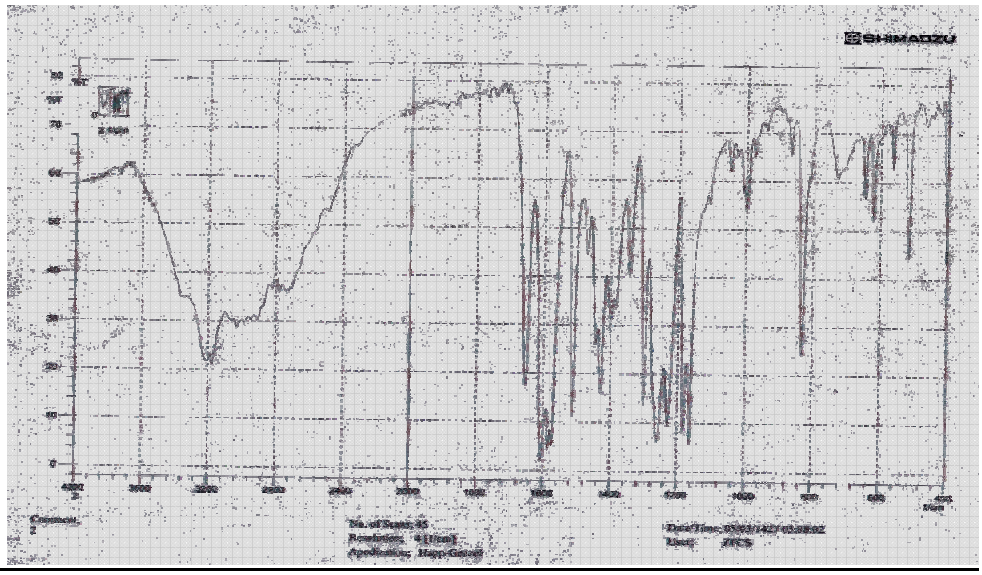


Fig -2- The IR spectra of compound (4)

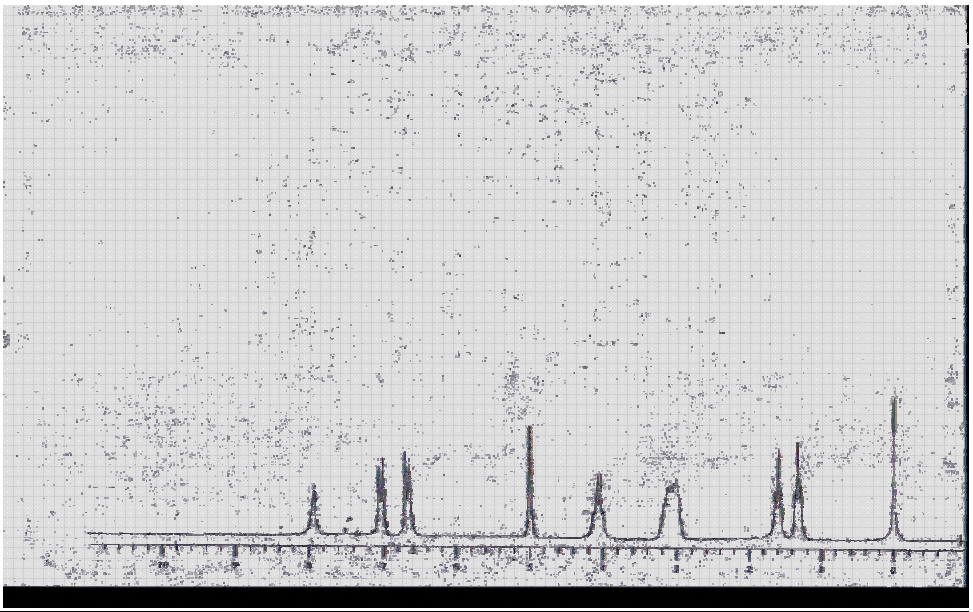


Fig -3- the ^{1}HNMR spectra of compound (5c)

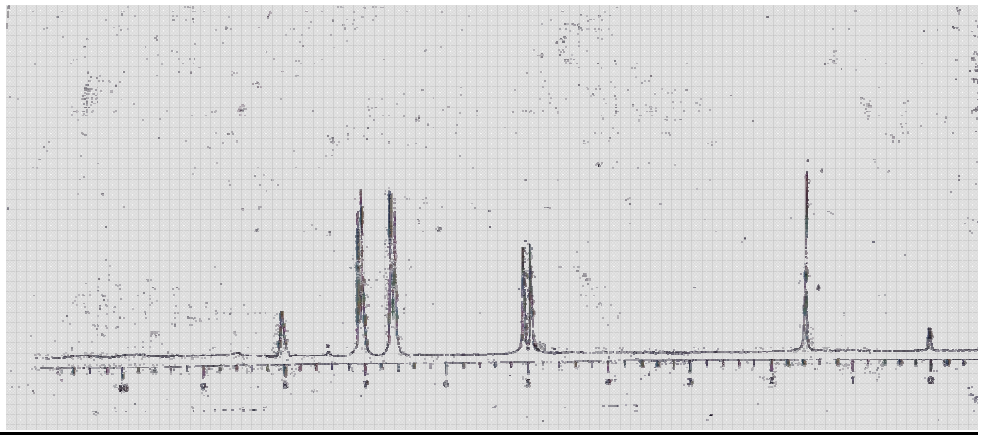


Fig -4- the ^{1}HNMR spectra of compound (4)

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