Synthesis and Characterization of 1,3,4-Oxadiazoles Derived From 9-Fluorenone

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Abstract:

In the present work, 9-fluorenone-2-carboxylic acid methyl ester (**1**) was prepared from 9-fluorenone-2-carboxylic acid and then converted into the acid hydrazide (**2**). Compound (**2**), is the key intermediate for the synthesis of several series of new compounds such as substituted 1,3,4-oxadiazole derivatives (**3**-**6**) were synthesized from the condensation of different substituted benzoic acids with compound (**2**) using $POCl_3$ as condensing agent. Treatment of compound (**2**) with formic acid gave the N-formyl hydrazide (**7**), which upon refluxing with phosphorous pentoxide in benzene yielded the corresponding 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole (**8**). Reaction of hydrazide (**2**) with phenyl isocyanate to give N-phenyl semicarbazide derivative (**9**), then this compound (**9**) convert to 5-(9-fluorenone-2-yl)-N-phenyl-1,3,4-oxadiazole-2-amine (**10**) via intramolecular cyclization by syrup H_3PO_4. Also the hydrazide (**2**) was treated with CS_2/KOH afforded 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-thiol (**11**). Compound (**11**) was used to react with various alkyl halides and secondary amines to give 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-alkyl thiol (**12**-**15**) and 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-N-alkyl (**16**-**19**) derivatives respectively.

Keywords: 9-Fluorenone, Acid hydrazide derivatives, 1,3,4-Oxadiazole.

Introduction:

9-fluorenone (IUPAC name 9H-fluoren-9-one) is member of polycyclic aromatic hydrocarbon (PAH), which was widely used in the applications of thermo and light sensitizer, liquid crystal chemistry, luminescence chemistry, spectrophotoetric analysis, molecular chemistry and biochemorphology industry [1,2]. Heterocyclic compounds containing the five-membered nucleus possess a diversity of useful biological effects. For example, 1,3,4-oxadiazole (two nitrogen and one oxygen heteroatom) have been found to possess a wide spectrum of biological activities such as antibacterial [3,4], antifungal [5,6], anthelmintic [7], anti-tubercular [8], anti-infective [9], anticancer [10], anti-HIV [11], antioxidant [12], analgesic [13,14], anti histaminic [15], insecticidal [16], anti-inflammatory [17], anticonvulsant [18,19] and also reported as enzyme tyrosinase inhibitors [20]. 1,3,4-oxadiazole have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis [21]. Among the methods employed in synthesis of

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1,3,4-oxadiazole, condensation of hydrazide and its derivatives as the starting materials with variety of substituted acids and bases are commonly used [22]. In continuation of interest in the chemistry of 9-fluorenone, 1,3,4-oxadiazole derivatives of this compound have been prepared by conventional synthetic techniques.

Materials and Methods:

General

All reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm pre-coated silica-gel F254 plates, spots were detected with iodine vapour. The IR spectra were recorded in (Department of Chemistry, College of Science, Baghdad of University) on (SHIMDZU) FT-IR 8400 spectrophotometer; solid samples were run in KBr discs, Liquid samples were run as smears. UV spectra were recorded with UV-Visible spectrophotometer (CARY) UV-100 Conc. Melting point were determined on a Gallenkamp meting point apparatus with sample contained in open capillary glass tube in an electrically heated metal block apparatus and were un corrected. ^{1}H-NMR spectra were recorded in (Al-Albyt university, Jordan) on ultra shield 300 MHz NMR spectrophotometer in acetone-d_6 solutions and with tetra methylsilane (TMS) as an internal standard.

Preparation of 9-fluorenone-2-carboxylic acid methyl ester (1)

A mixture of 9-fluorenone-2-carboxylic acid (0.1 mol) and an excess of methanol (10 ml) with sulfuric acid (1 ml) were refluxed on water-bath for (24 hrs), then reaction mixture was cooled and the resulting solid (**1**) was washed with methanol and recrystallized from benzene to give compound (**1**).

Preparation of 9-fluorenone-2-carboxylic acid hydrazide (2) [8]

To a solution of compound (**1**) (0.01 mol) in ethanol (30 ml), hydrazine hydrate (99%) (0.02 mol) was added then the resulting mixture was refluxed on water-bath for (3 hrs).The formed precipitate was filtered and recrystallized from chloroform to give the hydrazide derivative (**2**).

Preparation of 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-aryl (3-6) [17]

A solution of compound (**2**) (0.01mole) in phosphorus oxychloride (5 ml) was added in portions with stirring to a solution of appropriate substituted benzoic acid (0.01mole) and ethanol (20 ml) were taken in a round-bottom flask. The mixture was refluxed for (8 hrs). The solution was cooled to room temperature and poured into crushed ice and then neutralized with (10%) $NaHCO_3$ solution, then the solid product was filtered, washed with water and recrystallized from a suitable solvent gave the compounds (**3-6**).

Preparation of N-formyl-9-fluorenone-2-carboxylic acid hydrazide (7) [23]

A solution of (**2**) (0.01 mol) in formic acid (20 ml) was refluxed for (30 min). The solvent was evaporated and the residue was crystallized from benzene afford (**7**).

Preparation of 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole (8) [23]

To a solution of (**7**) (0.01 mol) in ethanol (15 ml), phosphorous pentoxide (0.01 mol) was added. The

mixture was refluxed for (3 hrs). The solvent was evaporated, water (10 ml) was added and the mixture was extracted with chloroform. The solvent was evaporated and the residue was recrystallized from benzene to give compound (**8**).

Preparation of N-phenyl-(9-fluorenone-2-carboxylic acid) semicarbazide (9)

To a solution of compound (**2**) (0.02 mol) in absolute ethanol (15 ml) phenyl isocyanate (0.04 mol) was added with continuous stirring and the mixture was refluxed for (4-5 hrs), then reaction mixture was cooled and the resulting solid (**9**) was recrystallized from chloroform.

Preparation of 5-(9-fluorenone-2-yl)-N-phenyl-1,3,4-oxadiazole-2-amine (10)

Compound (**9**) (0.01 mol) was dissolved in syrup of phosphoric acid (10 ml), heated at 120°C for (1hr), kept overnight and then poured into an ice-cold water. The resulting solid (**10**) was filtered and recrystallized from methanol.

Preparation of 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-thiol (11) [24]

Compound (**2**) (0.02 mol) was added to a solution of KOH (0.02 mol) in absolute ethanol (20 ml) and the resulting mixture was cooled to 0ºC. Distilled carbon disulfide (0.04 mol) was added dropwise to the stirred mixture, which was refluxed for (6 hrs). The solvent was removed under reduced pressure, the residue was dissolved in water (50 ml) and then filtered. The filtrate was cooled, neutralized to pH (5-6) using glacial acetic acid and the separated product was filtered, washed with water, dried and recrystallised from benzene to give (**11**).

Preparation of 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-alkyl thiol (12-15) [8]

To a stirred solution of (**11**) (0.01mol) and NaOH (0.01mol) in water (15 ml), a mixture of a suitable alkyl halide (0.01 mol) and methanol (10 ml) was added dropwise. The resulting mixture was stirred at room temperature for (7 hrs). The precipitate formed was filtered off and recrystallized from an appropriate solvent to give (**12-15**) in good yields.

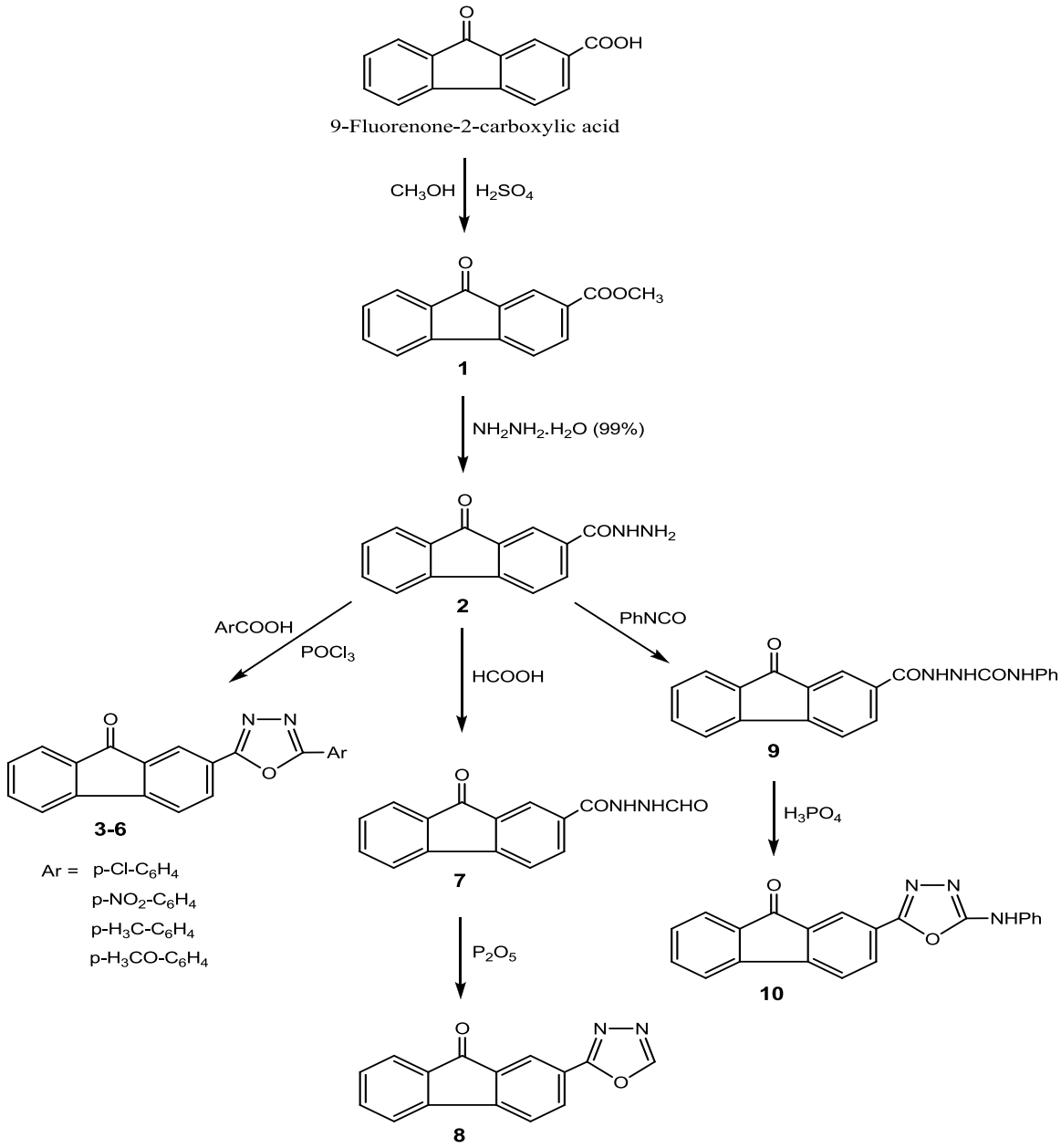
Preparation of 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-N-alkyl (16-19) [25]

To a stirred solution of compound (**11**) (0.02 mol) in dry dioxane (15 ml) was added to a solution of the appropriate secondary amine (0.01 mol) in dry dioxane (10 ml). The mixture was refluxed for (5 hrs). After cooling, the precipitate was filtered and crystallized from a suitable solvent afford compounds (**16-19**).

Results and Discussion:

To achieve the desired heterocyles, the sequence of reactions shown in Scheme (1,2) was followed. The esterification reaction of 9-fluorenone-2-carboxylic acid with methanol in the presence of sulfuric acid gave 9-fluorenone-2-carboxylic acid methyl ester (**1**), which was indicated by the disappearance of the broad band for OH stretching absorption for COOH group in 9-fluorenone-2-carboxylic acid and appearance bands at 2944 cm^{-1} and 2861 cm^{-1} due to (C-H) stretching for (CH_3) group. The key intermediate for the synthesis of substituted 1,3,4-oxadiazole

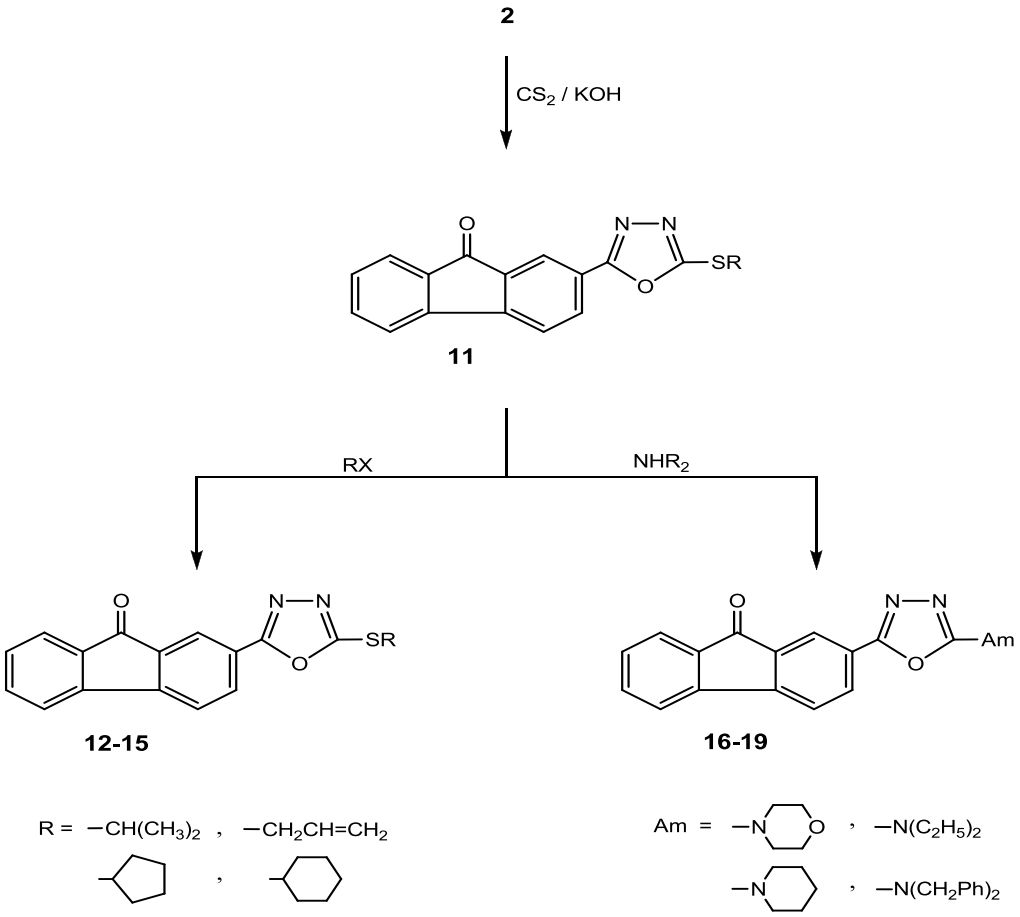
derivatives is 9-fluorenone-2-carboxylic acid hydrazide (**2**) which was prepared by the reaction of compound (**1**) with hydrazine hydrate (99%). The FT-IR spectrum of acid hydrazide (**2**) showed absorption band in the region of 3272 cm^{-1} characteristic of (NH_2) group and at 3141 cm^{-1} of (NH) group. The C=O stretching was observed at 1685 cm^{-1} for amide group. Condensation of acid hydrazide (**2**) with various substituted benzoic acids in presence of $POCl_3$ yielded 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-aryl (**3**-**6**) in moderate to good yield, was confirmed by its FT-IR spectra that showed bands between (1222-1249) and (1098-1109) due to (C-O-C) asymmetric and symmetric stretching respectively, in addition to the band at (1657-1671) cm^{-1} for the (C=N) stretching, combined with the disappearance of the NH_2, NH and C=O amide stretching bands. The ^{1}H-NMR spectrum of compound (**6**) showed a strong singlet signal at 3.5 ppm attributed to the three protons of the methoxy group (OCH_3) and a multiplet signals at (7.1-8.3) ppm assigned to the aromatic protons. Further, N-formyl-9-fluorenone-2-carboxylic acid hydrazide (**7**) was obtained from reaction of (**2**) with formic acid [23,24]. The structure of compound (**7**) was confirmed by the presence of two amidic carbonyl stretching bands at 1710 cm^{-1} and 1668 cm^{-1} (CO-NH-NH-CHO), in addition to the band at 2796 cm^{-1} assigned to (C-H) stretching. Treatment of compound (**7**) with phosphorous pentoxide in benzene afforded 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole (**8**), which displayed two bands at 1231 cm^{-1} and 1113 cm^{-1} for the (C-O-C) asym. and sym. stretching, in addition to the band at 1669 cm^{-1} for the (C=N) stretching. In another 1,3,4-oxadiazole preparation, condensation of acid hydrazide (**2**) with phenyl isocyanate to give N-phenyl-(9-fluorenone-2-carboxylic acid) semicarbazide (**9**). The IR spectra of this compound showed a broad band at 1693 cm^{-1} which was assigned to amide (I) and amide (II) bands. When compound (**9**) was treated with H_3PO_4 at (120)°C, it was affected by intramolecular cyclization through the loss of H_2O and giving the expected 5-(9-fluorenone-2-yl)-N-phenyl-1,3,4-oxadiazole-2-amine (**10**), was indicated by the presence in their IR spectra of the ether (C-O-C) stretching bands at 1236 cm^{-1} and 1089 cm^{-1}, in addition to the band at 1668 cm^{-1} attributed to the (C=N) stretching, its ^{1}H-NMR spectra for this compound showed a signal at 6.5 ppm attributed to the (N-H) proton and a multiplet signals at (7.2-8.2) ppm belong to the aromatic protons (Scheme 1).



Scheme 1

Compound 5-(9-fluorenone-2-yl)-1,3,4-oxadiazole-2-thiol (**11**) was synthesized by the ring closure reaction of acid hydrazide (**2**) with CS_2 in presence of KOH [24] which exists in a tautomeric thiol-thione equilibrium, as indicated by the (C=S) stretching band at 1165 cm^{-1}, S-H stretching at 2615 cm^{-1} and (N-H) stretching at 3191cm^{-1} [26]. Moreover, the compound (**11**) was conveniently alkylated by condensing it with different alkyl halides to give (**12-15**) derivatives. The FT-IR spectra showed bands between (2941-2954) and (2848-2855) cm^{-1} assigned to (C-H) asym. and sym. stretching respectively, combined with the disappearance of the (S-H) stretching band. The ^{1}H-NMR spectrum of compound (**15**) showed a multiplet signals (1.2-2.1) ppm and (2.7-3.0) ppm attributed to

the ten protons and one proton of the cyclohexyl and a multiplet signals at (7.1-7.8) ppm belong to the aromatic protons. While treatment of (**11**) with secondary amines resulted in compounds (**16**-**19**) by nucleophilic displacement of the (SH) group [25], which was indicated by the disappearance of the (S-H) vibration band, its ^{1}H-NMR spectra for compound (**19**) showed a signal at 5.1 ppm attributed to the (CH_2) protons and a multiplet signals at (7.1-8.1) ppm belong to the aromatic protons (Scheme 2). Table (1) represent the physical data of compounds (**1**-**19**). Characteristic absorption bands of FT-IR and U.V spectra of compounds (**1**-**19**) are listed in Table (2). Table (3) represent the ^{1}H-NMR spectra for compounds (**6**, **10**, **15** and **19**).



Scheme 2

Table (1): Physical properties of the prepared compounds (1-19)

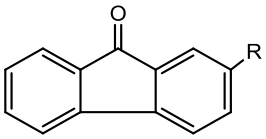
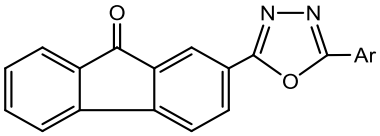
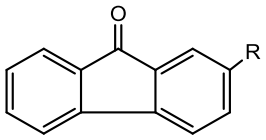
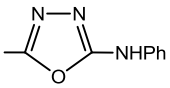
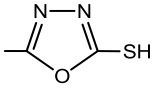
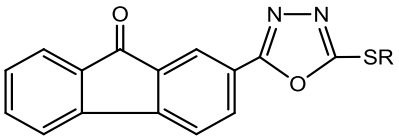
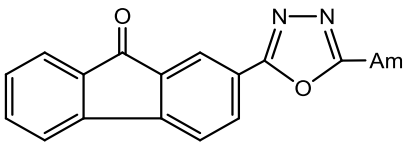
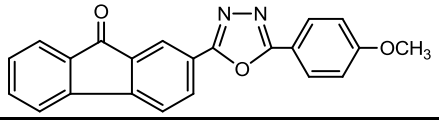
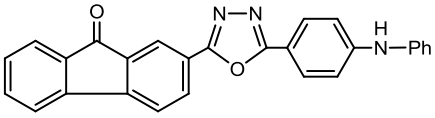
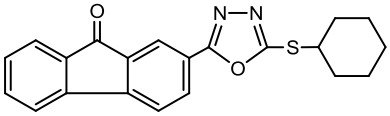
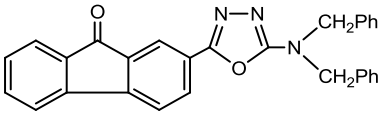
Compound structure	Comp. No.	R / Ar / Am	Color of crystal	m.p. °C	Yield %	Solvent of Rec.
	**1**	-$COOCH_3$	Yellow	182-183	81	Benzene
	2	-$CONHNH_2$	Yellow	90-92	80	Chloroform
	**3**	p-Cl-C_6H_4	Pale-yellow	118-120	70	Benzene
	4	p-NO_2-C_6H_4	Yellow	163-165	68	Toluene
	5	p-CH_3-C_6H_4	Yellow-brown	144-146	72	Toluene
	6	p-OCH_3-C_6H_4	Yellow-brown	182-184	70	Benzene
	**7**	-CONHNHCHO	Yellow	67-69 Dec.	75	Benzene
	8		Yellow-reddish	203-205	60	Benzene
	9	-CONHNHCONHPh	Pale-yellow	123-125	74	Chloroform
	10		Yellow-brown	191-193 Dec.	67	Methanol
	11		Yellow	114-116	74	Benzene
	**12**	-$CH(CH_3)_2$	Pale-yellow	88-90	73	Chloroform
	13	-$CH_2CH=CH_2$	Brown	160-162	71	Chloroform
	14		Dark-yellow	127-129	70	Chloroform
	15		Light yellow	155-157	70	Methanol
	**16**		Dark-yellow	224-226 Dec.	69	Toluene
	17	-$N(C_2H_5)_2$	Deep yellow	169-171 Dec.	70	benzene
	18		Pale-yellow	77-79	68	Chloroform
	19	-$N(CH_2Ph)_2$	Deep yellow	184-186	69	Chloroform

Table (2): Characteristic absorption bands of FT-IR and U.V spectra of compounds (1-19)

Comp. No.	FTIR spectral data cm^{-1}							U.V. (λ_{max}) nm
	υ(C=O) Ketone	υ(C-H) Aromatic	υ(C-H) Aliphatic	υ(C=C) Aromatic	υ(C=N) Imine	υ(C-O-C) Ether	Others (υ)	
1	1722	3061 3040	2944 2861	1559	-	-	1749 (C=O) ester	351
2	1720	3066 3005	-	1593	-	-	3272, 3141 (N-H) hydrazide 1685 (C=O) amide	353
3	1719	3059 3042	-	1563	1671	1239 1107	1091 (C-Cl)	357
4	1716	3062 3051	-	1589	1668	1222 1109	1554, 1338 ($C-NO_2$)	359
5	1723	3060 3038	2949 2834	1569	1669	1237 1098	-	353
6	1720	3059 3040	2946 2841	1573	1657	1249 1105	-	352
7	1721	3063 3034	-	1582	-	-	1710, 1668 (C=O) amidic 2796 (C-H) aldehyde	366
8	1719	3062 3041	-	1592	1669	1231 1113	2959 (C-H) olefinic	359
9	1720	3065 3033	-	1589	-	-	3331, 3224 (N-H) amide I and II 1693 (C=O) amide I and II	369
10	1720	3066 3034	-	1588	1668	1236 1089	3328 (N-H) amine	364
11	1716	3096 3070	-	1593	1658	1238 1111	2615 (S-H) Thio enol form 1165 (C=S) Thio keto form 3191 (N-H) amine	360
12	1719	3065 3031	2941 2853	1576	1668	1239 1112	-	364
13	1716	3097 3032	2954 2855	1570	1663	1249 1118	1627 (C=C) olefinic	367
14	1721	3059 3030	2952 2849	1588	1662	1241 1110	-	364
15	1719	3060 3037	2942 2848	1593	1663	1240 1112	-	358
16	1720	3066 3042	2953 2851	1574	1664	1236 1098	1261 (C-N) imine	360
17	1721	3064 3041	2946 2848	1581	1663	1243 1110	1264 (C-N) imine	366
18	1719	3061 3042	2945 2844	1586	1669	1238 1094	1282 (C-N) imine	361
19	1720	3062 3022	2941 2852	1591	1665	1241 1097	1268 (C-N) imine	360

Table (3): ^{1}H-NMR spectra for compounds (6, 10, 15 and 19)

Comp. No.	Compound structure	δH aromatic ppm	δH other bands ppm
6		7.1-8.3 (m,11H,Ar-H)	3.5 (s,3H, OCH_3)
10		7.2-8.2 (m,16H,Ar-H)	6.5 (s,1H, NH)
15		7.1-7.8 (m,7H,Ar-H)	1.2-2.1 (m,10H, cyclohexyl) 2.7-3.0 (m,1H, cyclohexyl)
19		7.1-8.1 (m,17H,Ar-H)	5.1 (s,4H,CH_2)

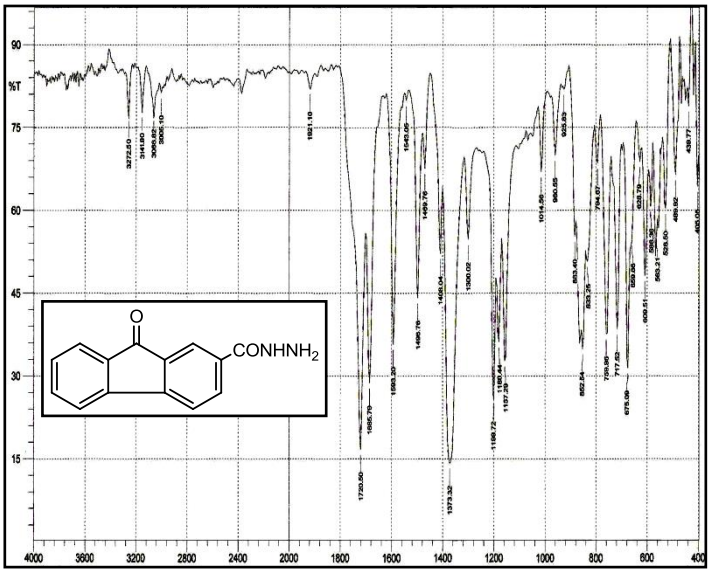


Fig.(1): FT-IR spectrum for compound (2)

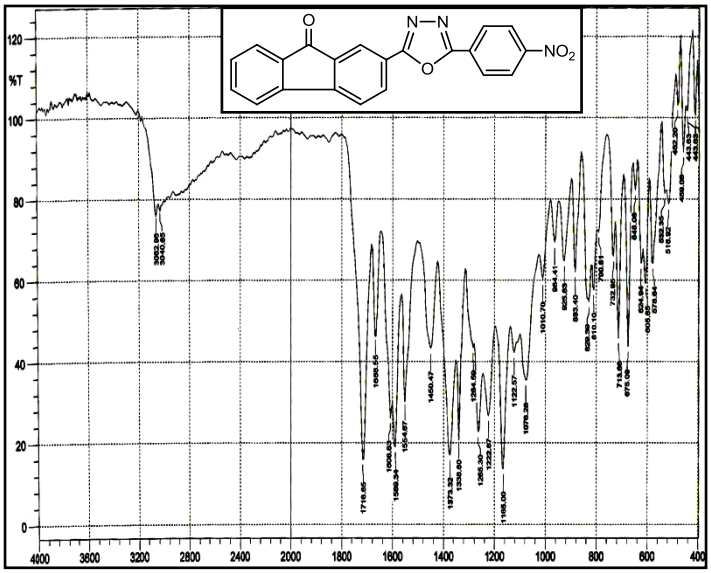


Fig.(2): FT-IR spectrum for compound (4)

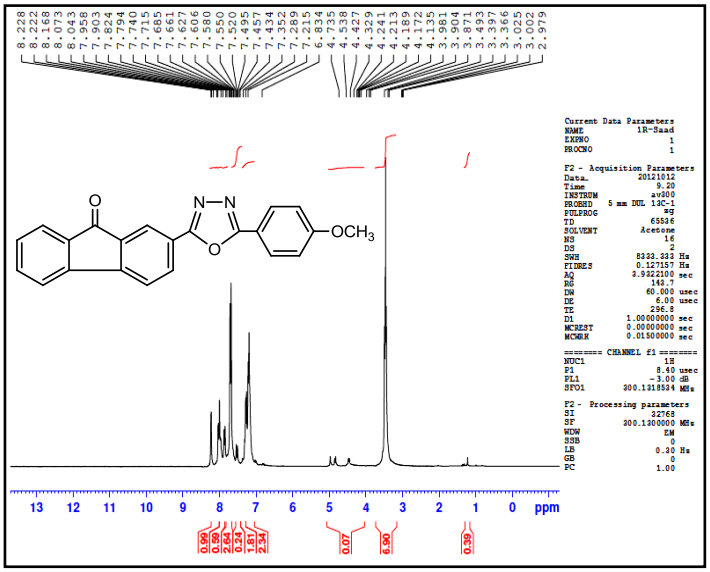


Fig.(3): ^{1}H-NMR spectrum for compound (6)

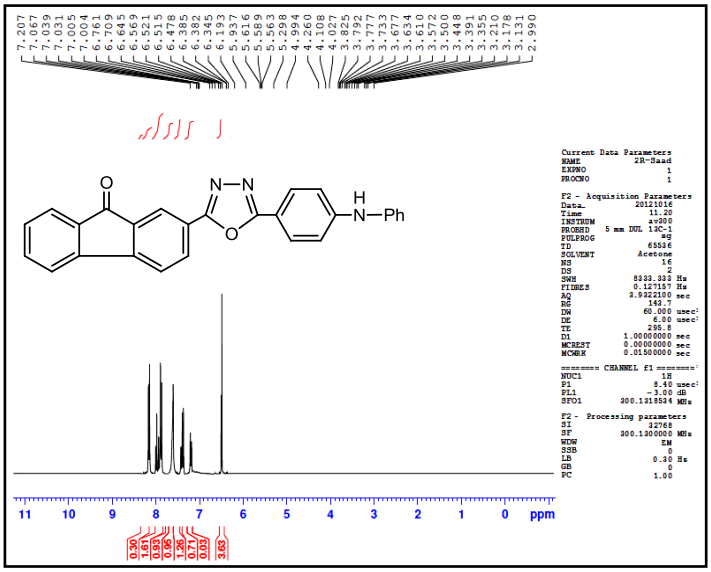


Fig.(4): ^{1}H-NMR spectrum for compound (10)

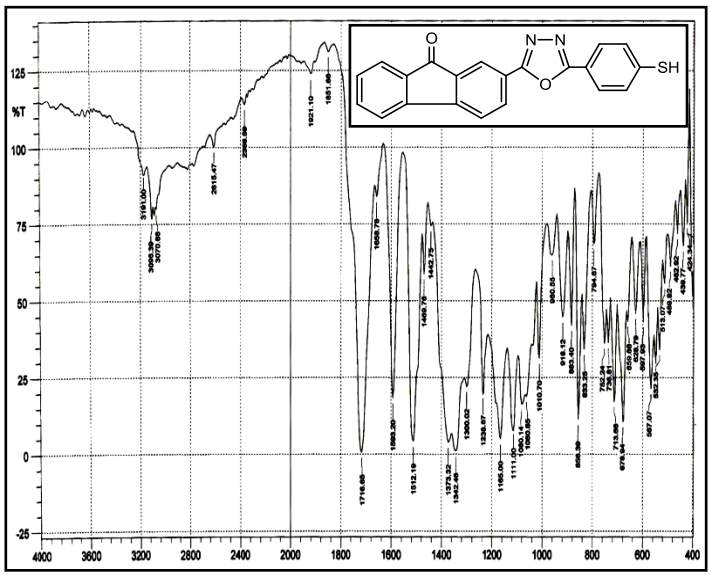


Fig.(5): FT-IR spectrum for compound (11)

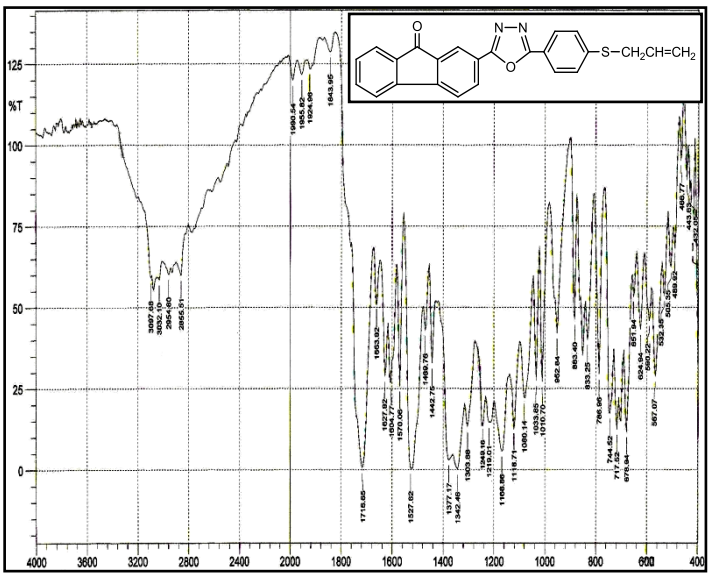


Fig.(6): FT-IR spectrum for compound (13)

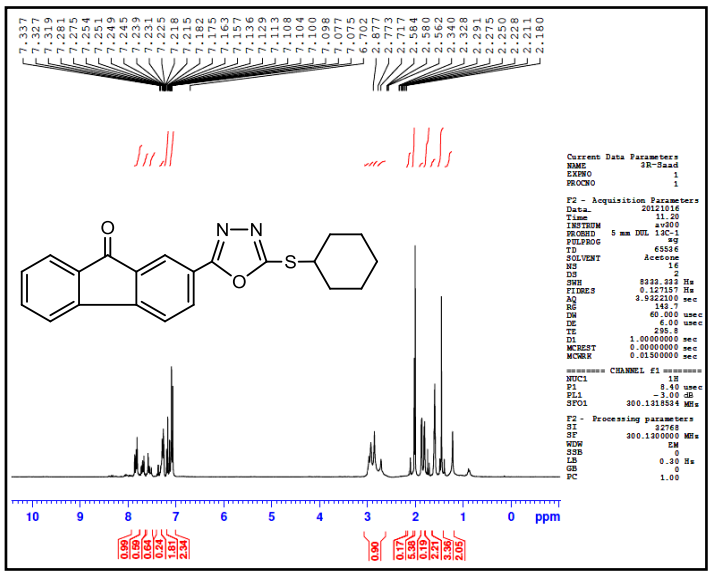


Fig.(7): ^{1}H-NMR spectrum for compound (15)

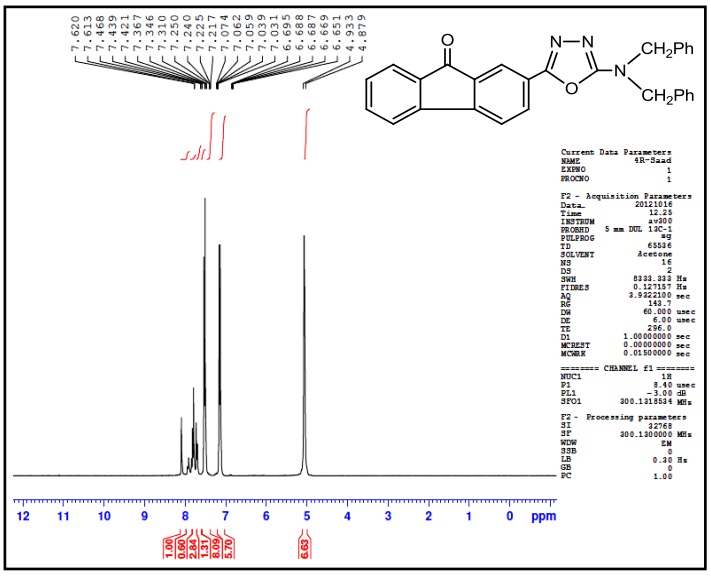


Fig.(8): ^{1}H-NMR spectrum for compound (19)

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تخليق وتشخيص 4،3،1-اوكسادايازولات مشتقة من 9-فلورينون

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الخلاصة:

في العمل الحالي، 9-فلورينون-2-كربوكسيليك اسيد مثيل استر (**1**) حضر من 9-فلورينون-2-كربوكسيليك اسيد وبعد ذلك حول إلى اسيد هايدرازيد (**2**)، مركب (**2**) هو المفتاح الوسطي لتخليق عدة سلاسل لمركبات جديدة مثل تعويض 4،3،1-اوكسادايازول (**3-6**) من تكاثف مركبات البنزويك اسيد المختلفة مع المركب (**2**) باستعمال $POCl_3$ كعامل مكثف. معاملة المركب (**2**) مع حامضِ الفورميك اعطى N- فورميل هايدرازيد (**7**)، الذي صعد مع مع خامس أكسيد الفوسفور في البنزين نتج عن المقابلة 5-(9-فلورينون-2-ايل)- 4،3،1-اوكسادايازول (**8**). مفاعلة الهايدرازيد (**2**) مع فينيل إيزوسيانات لإعطاء مشتق N-فينيل سيميكاربازايد (**9**)، ثم هذا المركب (**9**) حول الى 5-(9-فلورينون-2-ايل)-N- فينيل-4،3،1-اوكسادايازول-2-امين (**10**) عن طريق التداخل الضمني بواسطة حامض الفوسفوريك. ايضا الهايدرازيد (**2**) تم مفاعلته مع كبريتد الكاربون وهيدروكسيد البوتاسيوم لاعطاء 5-(9-فلورينون-2-ايل)- 4،3،1-اوكسادايازول-2-ثايول (**11**). المركب (**11**) استعمل للتفاعل مع هاليدات الكيل و امينات ثانوية مختلفة لاعطاء 5-(9-فلورينون-2-ايل)-4،3،1-اوكسادايازول-2-الكيل ثايول (**12-15**) و 5-(9-فلورينون-2-ايل)-4،3،1-اوكسادايازول-2-N-الكيل (**16-19**) على التوالي.