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Synthesis and Characterization of some Substituted 1, 2, 5-oxadiazine Derived from 9H- carbazole

Maha M. Tawfiq **Salim J. Mohammed**
Department of Chemistry/ College of Science/ University of Mosul

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corresponding author:
Maha M. Tawfiq
Chemimaha96@gmail.com

ABSTRACT

Hydrazones possess unit an azomethine (–NHN=CH) group and are considered derivatives of aldehydes and ketones compounds in which the oxygen atom has been replaced by the NNH_2 In this paper, we study synthesis of the novel of some new 1, 2,5-oxadiazine derivatives were prepared starting with carbazole (1) as a synthon, which on reaction with chloroacetyl chloride in absolute ethanol yielded ethyl 1-(9*H*-carbazole-9-yl)2-chloroethanone (2). This compound (2) on reaction with hydrazine hydrate giving 1-(9H-carbazol-9-yl)-2-hydrazinylethanone (3) followed treatment the later compound with either substituted benzaldehyde or substituted acetophenone will give substituted hydrazones (4a-e) and (5a-d) respectively. These hydrazone compounds on were allowed to react with an acetic acid anhydride to give the corresponding 1, 2, 5-oxadiazine compounds (6a-e) and (7a-d). The purity of substituted hydrazones and the corresponding 1,2,5-oxadiazine compounds were tested by thin-layer chromatography (TLC). All newly synthesized compounds in this study were confirmed by physical and spectral (FT-IR, nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) analysis.

Keywords: Carbazole, Hydrazones, Schiff bases, Oxadiazine, Acetic Anhydride.

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INTRODUCTION

Carbazole has a tricyclic structure, consisting of two benzene rings located on either side of a five-membered nitrogen-containing ring (Zhang *et al*., 2010). The structure of the compounds is based on that of indole, but in which a second benzene ring is fused to the arcuate ring at position 2-3 of indole (Fattorusso and Taglialatela, 2008). Many researches have been conducted on carbazole and its derivatives. The carbazole molecule consists of two six-membered benzene rings fused on either side by a five-membered nitrogen-containing ring (Nandy *et al*., 2014). Thus, hydrazones are types of Schiff bases and very important chemical compounds because of their ease of obtaining and preparing them directly, as well as to their stability towards hydrolysis. Hydrazones were prepared from the condensation of substituted aldehydes or ketones with hydrazine derivatives and have the general formula R-NH-N=C-R1 (Xin Su and Ivan Aprahamian, 2014). Hydrazones and their derivatives are also very important compounds in organic and medicinal chemistry due to their biological activity which includes: anticancer (Yang *et al*., 2021), antiviral (Alam *et al*., 2014) (Popiolek *et al*., 2020), antibacterial (Al-Daher and Omer, 2019), antifungal (Siemann *et al*., 2002; Rollas *et al*., 2007; Aslan *et al*., 2012; Backes *et al*., 2014; Alsaeedi *et al*., 2015; Ghiya *et al*., 2016; Segretti *et al*., 2016; Bhat *et al*., 2018; Zhou *et al*., 2019; Shaaban *et al*., 2020; Mohammed, 2022), antidepressant properties (Abid *et al*., 2017) and in the treatment of many diseases such as Alzheimer's disease and infections (Murtaza *et al*., 2016 and Fernandes *et al*., 2017). Also, some hydrazones are used as ligands in preparing some complexes (Al-Daher and Mohammed, 2018).

Oxadiazine are the molecules with oxygen and two nitrogen's resting in different positions of the cyclic structure. six-membered heterocyclic rings having three heteroatoms are very less in nature, but they possess various biological applications. Derivatives of 1,2,5-oxadiazine exhibited various biological applications such as anti-inflammation (Sava *et al*., 1985 and Xia *et al*., 2008) against malaria (Eissa *et al*., 2019) and tuberculosis (Holdiness, 1987; Zheng *et al*., 2009; Ajani *et al*., 2010) anti-cancer (Mohareb *et al*., 2010) plant growth regulator, anti-convulsive activity, anti-bacterial, nematocidal, cardiovascular, anti-HIV. Oxadiazine derivatives are used as an intermediate to synthesized some of the β-lactam antibiotics or prodrugs (Shet *et al*., 2010; Mohareb and Schatz, 2011; Shubakara *et al*., 2014; Gurlananjappa and Kariappa, 2017).

EXPERIMENTAL

Chemicals and solvents used during the research are commercially available, Aldrich and Fluka companies. Melting points are recorded in open capillaries tubes by using Stuart SMP30 melting point apparatus. Infrared spectra were recorded by using (Shimadzu FT-IR-ATR) (Japan) infrared spectrophotometer. Measurements were performed in Salahaddin University, Erbil. ^{1}H-NMR spectra were recorded by using (Bruker 400MHZ) with tetramethyl silane as internal standard in ((DMSO.d_6).

Synthesis of 1-(9H-carbazole-9-yl) chloroethanone (2) (Al-Majidi, 2013)

Dissolved (0.002 moles) of carbazole (1) in dry acetone (40 ml) then (0.002 moles) of chloroacetylchloride was added. The mixture was refluxed for (6hrs.), and then solvent was evaporating under reduced pressure. The resulting solid was dried, to give the precipitate a clear color (brown), m.p. (138-140 ^{o}C), yield (75%).

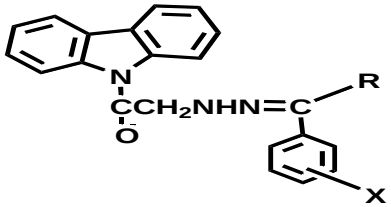
Synthesis of 1-(9H- carbazole- 9- yl) -2- hydrazinylethanone (3) (Al-Majidi and Al-Quaz, 2010)

Dissolved (0.001 moles) of 1-(9H-carbazol-9-yl)-2-chloroethan-1-one (2) in absolute ethanol (25 ml), with (20 ml) of hydrazine hydrate (85%) was added. The mixture was refluxed for (5hrs.), and then the solvent was evaporated to half volume. The formed precipitate was isolated by filtration, dried to give pure compound with a Light brown clear color, m.p. (231-232 ^{o}C), yield (80%).

Synthesis of benzylidene hydrazinyl and phenylethylidene hydrazinyl (4a-e) (5a-d) (Al-Kaissy *et al*., 2013)

A mixture of (0.001moles) of hydrazinylethanone (3**)** and (0.001moles) of substituted benzaldehyde or acetophenone were dissolved in (30ml) of absolute ethanol. A few drops of glacial acetic acid were added. The mixture was refluxed for about (4hrs.), and then the solvent was evaporating under reduced pressure. The resulting solid was dried, to give precipitate of hydrazones (4a-e) (5a-d) respectively. The physical data are recorded in (Table 1).

Table 1: Physical Properties for compounds (4a-e) (5a-d)

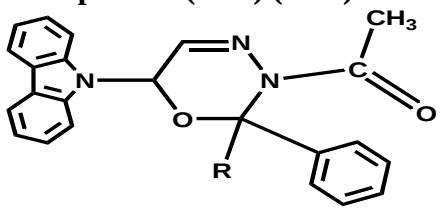


Compd. No.	R	X	m.p ^{o}C	Yield %	Color
4a	H	P-Br	243-246	51	Light brown
4b	H	m-NO_2	173-179	42	Gold
4c	H	o-Cl	186-188	58	Olive
4d	H	3,4-OH	140-143	94	Light green
4e	H	2,3-OCH_3	136-138	83	Brown
5a	CH_3	p-NH_2	112-113	97	Dark brown
5b	CH_3	p-CH_3	197-199	91	Brown
5c	CH_3	o-OH	211-214	57	Light brown
5d	CH_3	m-OCH_3	204-206	55	Light brown

Synthesis of substituted 1,2,5-oxadiazine compounds (6a-e) (7a-d) (Joshi *et al*., 2008)

Dissolved (0.001moles) of hydrazones (4a-e) (5a-d) in (15ml) of acetic anhydride. The mixture was heated in refluxed system for (4hrs.), at 100 °C. The resulting mixture poured on crushed ice with stirring. The formed precipitate was isolated by filtration, washed with water, dried, to give precipitate of 1,2,5-oxadiazine compounds (6a-e) (7a-d) respectively. The physical data are recorded in (Table 2).

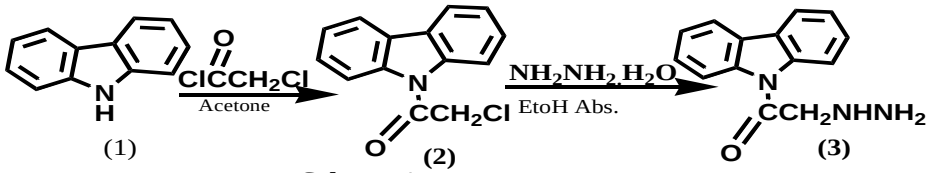
Table 2: Physical Properties for compounds (6a-e) (7a-d)



Compd. No.	R	X	m.p ^{o}C	Yield %	Color
6a	H	P-Br	57-59	62	Grey
6b	H	m-NO_2	85-87	54	Gold
6c	H	o-Cl	197-199	57	Light brown
6d	H	3,4-OH	112-114	42	Light brown
6e	H	2,3-OCH_3	191-193	44	Dark brown
7a	CH_3	P-NH_2	61-63	43	Olive
7b	CH_3	p-CH_3	205-207	51	Light brown
7c	CH_3	o-OH	72-74	52	Dark grey
7d	CH_3	m-OCH_3	55-57	94	Bright grey

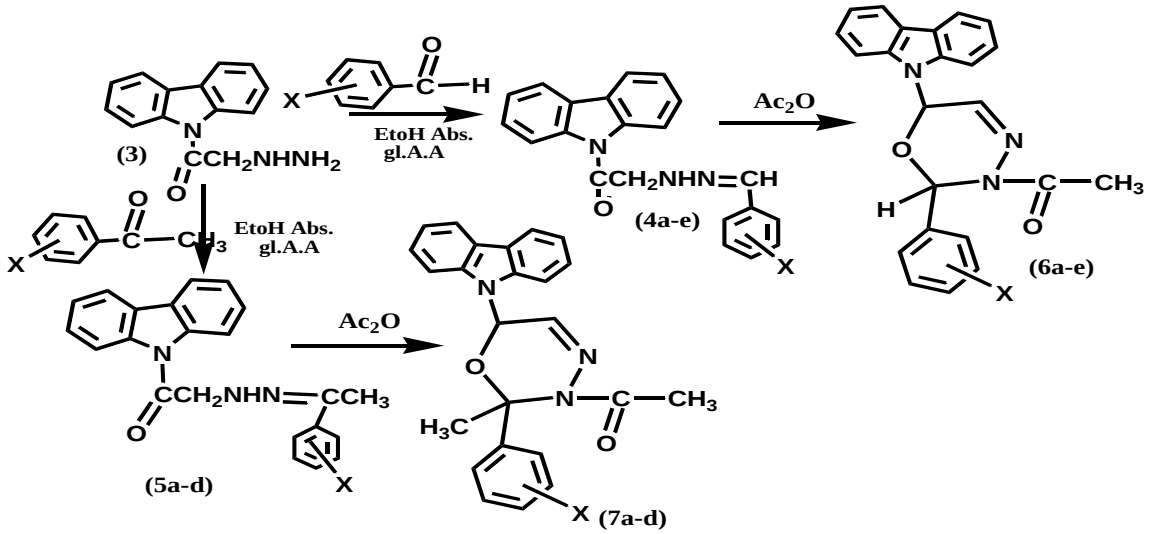
RESULTS AND DISCUSSION

In this research, reaction of carbazole (1) with chloro acetylchloride to give an ester namely1-(9H-carbazole-9-yl) chloroethanone (2) followed on reaction with hydrazine hydrate afforded the corresponding hydrazide (3) as shown in the scheme (1).



Scheme 1

Treatment of hydrazide (M3) with substituted benzaldehyde or acetophenone gave the corresponding hydrazones (M4a-e) (M5a-d) respectively, which on reaction with acetic anhydride giving the corresponding 1, 2, 5-oxadiazine compounds (6a-e) and (7a-d) as shown in scheme (2).



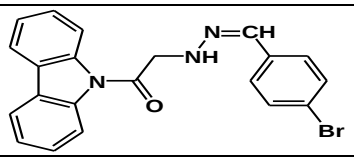
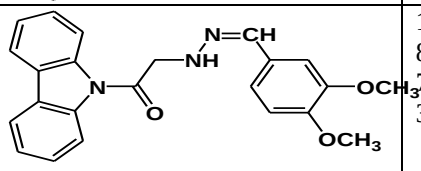
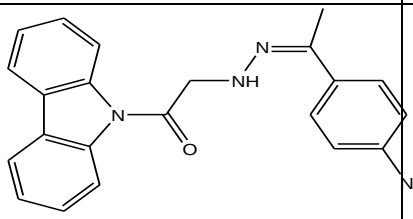
Scheme 2:Synthesis of hydrazones and 1,2,5-oxadiazine compounds

The structures of the target hydrazones (4a-e) (5a-d) were elucidated using (FT-IR, ^{1}H-NMR, ^{13}C-NMR). The FT-IR spectra for compounds (4a-e) (5a-d) showed the following stretching bands; (1620 -1681cm^{-1}) due to the (C=N) bond for hydrazones, (1740-1810 cm $^{-1}$) for (C=O) group, (3008-3418 cm $^{-1}$) for the (NH) bond (NH) group. The ^{1}H-NMR spectra for compounds (4a, 4e, 5a) in (DMSO-d_6) representation for these hydrazones showed the peaks for (CH=N, NH, and aromatic protons) and other groups in these compounds is in full agreement with the proposed structures which confirmed in (Table 3). While ^{13}C-NMR for compounds (4a, 4e, 5a) in (DMSO-d_6) representation for these hydrazones showed the signal for carbon atoms in these compounds as shown in (Table 4).

Table 3: FT-IR data of compounds (4a-e) (5a-d)

Compd. No.	C=N	C=O	NH	Other
4a	1622	1790	3049	C-Br (570)
4b	1640	1780	3049	NO_2 (1519) asym (1340) sym
4c	1681	1775	3417	C-Cl(756)
4d	1653	1790	3051	OH(1394)
4e	1625	1792	3008	OCH_3(1068)
5a	1647	1730	3226	----------
5b	1620	1740	3418	----------
5c	1645	1755	3049	OH (1327)
5d	1643	1750	3149	----------

Table 4: The ^{1}H-NMR and ^{13}C-NMR spectral data of compounds (4a,4e,5a)

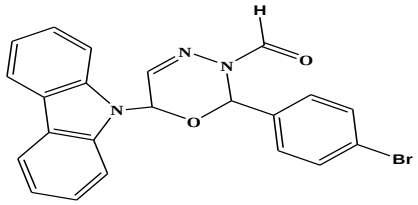
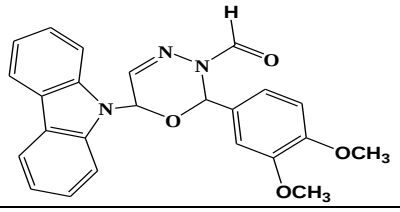
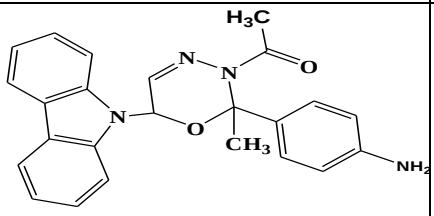
Compd. No.	Structure	^{1}H-NMR, (ppm), DMSO-d_6	^{13}C-NMR, (ppm), DMSO-d_6
4a		3.468(s,2H,CH_2),7.138-8.716(m,13H,ArH+CH), 11.254(s,1H,NH).	168.3(C=O),51.4(CH_2NH), 144.3(N=CH),115.6,116.3,1181.5,119.2,120.3,121.4,131.7(ArC).
4e		11.245(s,1H,NH), 8.871(s,1H,CH) 7.135-8.871[m,11H,ArH] 3.903,(s,6H,2OCH_3).	165.4(C=O), 50.5(CH_2NH), 143.3(N=CH), 55.1-60.3(OCH_3),111.2,113.5,116.9,119.4 119.8,132.6,153.5(ArC).
5a		1.049(s,3H,CH_3),3.461(bs,2H,CH_2), 5.538(bs,2H,NH_2) 7.137-8.121(m,12H,ArH), 11.254, [s,3H,NH],	196(C=O),51.8(CH_2NH), 167.8(N=C),17.2(C-CH_3), 151.8(C-NH_2),11.3,116.5,118.8, 119.6, 120.4,121.3,122.6, 130.0(ArC).

The structure of compounds (6a-e) (7a-d) have been identified based on their FT-IR, ^{1}H-NMR, and ^{13}C-NMR. The FT-IR spectra were characterized by the presence at the range (1224-1301cm^{-1}) due to (C-N) bands, the range (1645-1695 cm^{-1}) due to (C=N) bands also at the range (1700-1790 cm^{-1}) refer to (C=O) amide groups besides at the range (1004-1076 cm^{-1}) due to (C-O-C) bands. The assignment of the vibration v (cm^{-1}) of the IR absorption bands spectra was illustrated in (Table 5). Whereas the chemical shifts that appeared in the ^{1}H-NMR show signals due to exhibition of protons of (N-CH) as singlet at the range (5.0 -5.2 ppm) and at the range (2.04-3.19 ppm) of (**N**-C=O-CH_3) in addition the other obtained values for compounds (6a-e) (7a-d) are listed in (Table 6). In the ^{13}C-NMR spectra of compounds (6a-e) (7a-d) showed different signals for all carbon atoms which mentioned in (Table 6). The range σ (90-97ppm) due to (N-CH), σ (152.7-159.3 ppm) assigned to (C=N-N). The carbons atom of carbonyl group was appeared at the range σ (166.5-169.7 ppm) while the signals of the carbon of aromatic ring (Ar-C) all signal appears.

Table 5: FT-IR data of compounds (6a-e) (7a-d)

Compd. No.	C-N	C=N	C=O	C=C	C-O-C	Others
6a	1238	1685	1762	1595	1024	C-Cl (794)
6b	1236	1680	1721	1595	1020	NO_2 (1521) asym (1342) sym
6c	1240	1688	1750	1595	1022	C-Cl (725)
6d	1236	1695	1747	1590	1076	OH (1375)
6e	1298	1691	1757	1593	1004	OCH_3(1068)
7a	1301	1681	1770	1595	1014	NH(3061) asym (928)sym
7b	1238	1668	1750	1597	1028	—
7c	1238	1645	1700	1590	1025	OH (1390)
7d	1224	1683	1790	1594	1045	OCH_3(1045)

Table 6: The ^{1}H-NMR and ^{13}C-NMR spectral data of compounds (6a, 6e and 7a)

Compd. No.	Structure	^{1}H-NMR, (ppm), DMSO-d6	^{13}C-NMR, (ppm), DMSO-d_6
6a		1.917(s,3H,CH_3),5.23(bs, 1H,CH),6.28(bs,2H,CH_2), 7.409-8.836 (m, 12H, -ArH),	92.5(CH),164.7(C=N-N), 168.59(N-C=O), 110.4,111.3,113.4,116.2,117.8,118.3,119.2,123.4,127.3 ,130(Ar-C).
6e		1.915(s,3H,CH3),3.805(s, 6H,2OCH_3),7.38-8.40 [m, 12H, ArH,], 5.03 [s,1H,CH]CH=N) .	94(CH), 166.4(C=N-N), 168.8(N-C=O), 117-130(Ar-C), 23.4(CH3),19.1(Ar-CH_3)
7a		1.914(s,3H,CH_3),2.089(s, 3H,CH_3),4.56(bs,2H,CH_2) ,7.412-8.282(m,12H,ArH).	90(N-CH), 154.7(C=N-N), 167(N-C=O), 115-127(Ar-C), 22.9(CH3).

CONCLUSION

We conclude that in this research we studied the synthesis of some new 1,2,5-oxadiazine derivatives that were prepared starting with carbazole, which when treated with chloroacetyl chloride gave the ester (2). When reacted with hydrazine hydrate, the hydrazide(3) compound was prepared, which was reacted with either substituted benzaldehyde or substituted acetophenone, giving us hydrazone-hydrazide. When these compounds are reacted with acetic acid anhydride, the final products are obtained, represented by the compounds 1, 2, 5-oxadiazine, corresponding . The purity of all compounds prepared in the study was tested by thin layer chromatography (TLC), and finally these compounds were identified by physical and spectroscopic analysis.

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تحضير وتشخيص بعض معوضات 5,2,1–اوكسادايازين المشتقة من H9 كاربازول

مها محمد توفيق **سالم جاسم محمد**

قسم الكيمياء/ كلية العلوم/ جامعة الموصل

الملخص

تمتلك الهيدرازونات مجموعة الازوميثين NHN = CH– وتعتبر من مشتقات الألدهيدات والكيتونات والتي تم فيها استبدال ذرة الأكسجين بـ NNH_2. في هذه البحث، تم دارسة تحضير بعض مركبات 5,2,1–أوكساديازين الجديدة وتم تحضير المشتقات ابتداءا من الكاربازول كمادة أولية، والذي عند التفاعل مع كلورو كلوريد الاسيتيل في الإيثانول المطلق كمذيب ينتج (2) 2-chloroethanone (9H-carbazole-9-yl) -1 ethyl. هذا المركب (2) عند التفاعل مع الهيدرازين المائي سيعطي (3) (H-carbazol-9-yl) -2-hydrazinylethanone يتبع ذلك معاملة الهيدرازيد الناتج إما معوضات البنزالديهايد أو معوضات الأسيتوفينون البديل سوف ينتج مشتقات الهيدرازونات (4a-e) (5a-d) على التوالي. ثم اجراء التفاعل لمركبات الهيدرازون هذه مع أنهيدريد حمض الخليك لإعطاء مركبات 1،2،5–أوكساديازين المقابلة (6a-e) and (7a-d) تم التأكد من نقاوة هذه المركبات ومتابعة سير التفاعلات بواسطة كروماتوغرافيا الطبقة الرقيقة (TLC)، وتم تشخيص المركبات المصنعة حديثًا في هذه الدراسة عن طريق التحليل الفيزيائي والطيفي المتضمن الاشعة تحت الحمراء (FT-IR)، الرنين المغناطيسي النووي (^{1}H NMR and ^{13}C NMR) لبعض هذه المركبات.

الكلمات الدالة: الكاربازول، الهيدرازونات، قواعد شيف، الأوكسادايازين، أنهيدريد حامض الخليك.