Synthesis and Characterization of some 1, 3, 4-oxadiazole Compounds Derived from 9H-Carbazole

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Abstract

In this paper, some novel 1, 3, 4-oxadiazole compounds were synthesized starting from 9H-carbazole. The reaction of 9H-carbazole (1)with ethyl chloroacetate yielded 9H-carbazol-9-ylacetate (2).These ester was converted to the corresponding 2- (9H-carbazol-9-yl) acetohydrazide(3)by reaction with hydrazine hydrate.While the second stage involves the reaction of hydrazide(3)with benzaldehyde or one of its substitutes, as well as with acetophenone or one of its substitutes to give hydrazones (4a-d)and (5a- d) respectively ,then the ring-closure of these hydrazones gave oxadiazole (6a-d) ,(7a-d) compounds respectively . The structures of all synthesized compounds were confirmed by physical properties and spectroscopy methods FT-IR and ^{1}H NMR spectroscopy.

Key Words: 9H-Carbazole, 1, 3, 4- oxadiazole, hydrazide, hydrazones, benzaldehyde,acetophenone.

Introduction

Carbazole and its derivatives are nitrogen-containing polycyclic heterocyclic aromatic compounds. Researchers have already reported that carbazole-containing heterocyclic compounds are found in many natural alkaloids (Fattorusso et al.,2008).The derivatives of carbazole moiety possess a wide spectrum of pharmacological activities such as anticonvulsant(Srivastava et al.,1999).antibiotics (Hagiwara et al.,2000).,antimalarial(K. Rana et al.,2004) antibacterial,(A. Nagaraj and C. Sanjeeva ,2008), anticancer(Katritzky et al.,1995).The Carbazole derivatives also has been exhibit in several industrial applications such photoelectrical materials (Morin et al.,2005) and photochromic (Kim et al.,2007). Heterocycles fused with carbazole rings have also been shown to be important for their biological activities such as antiviral and cytotoxic (Mark et al.,1989),novel neuroleptic and antipyretic agents (Ghoneim et al.,2006) various studies have been conducted on carbazoles, and especially in the synthesis of various compounds Heterocyclic compounds possess biological significance (Youssef, et al.,2017),(Lanza and Arnold,2015)and (Abdel-Mohsen et al.,2016).1,3,4-oxadiazole is a heterocyclic aromatic five-membered ring compound characterized by containing an oxygen atom with two nitrogen atoms at the 3 and 4 positions.Furthermore, various congeners of oxadiazoles have also been reported to exhibit antimicrobial, anti-malarial , analgesic and anticonvulsant (G.Nagalakshmi ,2007),also some derivatives of oxadizoles have antimalarial (Verma et al.2018), antidepressive (Tantray et al.,2018) and anticancer (Yadagiri et al.,2015)activities. Additionally were evaluated for HIV inhibitory and remarkable antipyretic activity (Cheptea et al.,2012) and showed highly selective and potent GSK-3β inhibitory activity *in- vitro*(Saitoh et al .,2009)and proved that these compounds can be used in the future in medicine and agriculture(M.Luczynski and A. Kudelko ,2022). Herein, we synthesized some derivatives 1, 3, 4-oxadiazole compounds starting from 9H-carbazole.

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Materials and Method

Melting points were determined in open capillary tubes and are uncorrected by using Stuart Melting Point Apparatus. The IR spectra (cm^{-1}) were recorded on Schimadzu FT-IR- 8400S .^{1}HNMR spectra (DMSO-d6) were recorded on ultra-shield 500 MHz Bruker (2003) NMR spectrometer using tetra methyl silane as internal standard . The reactions were monitored by TLC using 10% chloroform in benzene.

Synthesis of ethyl 4bH-carbazole-9(8aH)-carboxylate (2, 3)

To a solution of carbazole (2.01 g, 0.012 mol) in 20 mL of dry acetone, ethyl chloroacetate (1.472 g, 0.012 mol) was added dropwise in the presence of anhydrous potassium carbonate (0.09 g) and the resultant mixture refluxed for 10 hrs. Then the mixture was cooled and the thus obtained solid was filtered, dried and recrystallized from ethanol to give compound ester (2). Yield: 52 %; m.p.: 243–244°C IR (KBr, cm^{-1}): 3088 (C–H stretching of aromatic ring), 2984,2988 (C–H stretching of aliphatic group), 1745 (C=O stretching), 1046 (C–O–C stretching) for ethyl ester respectively. ^{1}H-NMR (500 MHz, DMSO-d6, ppm) including many signal as following singlet at 1.284 for(CH_3) protons,4.14 for (CH_2-CO)protons and 4.45 due to ($COCH_2$) protons and multiplet at the range 7.138-8.122 due to eight protons for aromatic system in the ester (2).

Synthesis of 4bH-carbazole-9(8aH)-carbohydrazide (5)

(0.01mol) of esters (2) were dissolved in (25ml) of ethanol then (20 ml) of hydrazine hydrate was added . The reaction mixture was heated to reflux over (5hrs.).After refluxing the mixture was cooled .The solvent was evaporated giving the solid as a pale yellow, dried and recrystallized from ethanol to give the hydrazide (4)(248-250°C,81%). IR (KBr, cm^{-1}): 3049(C–H stretching of aromatic ring), 3419, 3278 ($NHNH_2$ stretching), 1635 (C=O stretching); ^{1}H NMR (500 MHz, DMSO-d6, ppm)showed abroad at 4.82 for (CH_2CO-)protons, singlet at 11.253 for NH protons and singlet at 8.121 for two protons of NH_2 group while the eight protons of aromatic system appear at the range 7.13-8.102 as multiplet signal

Synthesis of (Z)-N'-(substituted benzylidene)-4bH-carbazole-9(8aH)-carbohydrazide (5a- d) and (Z)-N'-(1-(substituted phenyl)ethylidene)-4bH-carbazole-9(8aH)-carbohydrazide (6a -d).

A mixture of (0.01mol)substituted benzaldehyde or substituted acetophenone , (0.01mol)hydrazide(4) in an absolute ethanol (25 mL)) and glacial acetic acid (0.2 mL) were added .The mixture was heated under reflux conditions for (4 hrs.). The resulting, cool, and the formed precipitated solid was filtered, dried, and recrystallized from a suitable solvent to give hydrazone compounds (5a-d) and (6a-d) respectively. The physical properties are listed in Tables 1, 2.

Table 1: Physical data for compounds (5a-e).

Comp. No.	R	M.p.(°C)	Color	Yield %	Crystal. solvent
5a	4-Br	243-246	Light brown	55	Ethanol
5b	3-NO_2	173-179	gold	65	Methanol
5c	2-Cl	185-188	olive	77	Methanol
5d	3,4-OH	140-143	Light green	94	Acetone
5e	2,3OCH_3	136-138	brown	83	Ethanol

Table 2; Physical data for compounds (6a-d).

Comp. No.	R	M.p.(°C)	Color	Yield %	Crystal. solvent
6a	4-NH_2	112-113	Dark brown	97	Acetone
6b	4-CH_3	197-199	brown	91	Methanol
6c	2-OH	211-214	Light brown	57	Ethanol
6d	3-OCH_3	204-206	Light brown	55	Acetone

Synthesis of1-(2-(substituted phenyl)-5-(4bH-carbazol-9(8aH)-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanone(7a-e) and 1-(2-(substitutedphenyl)-5-(4bH-carbazol-9(8aH)-yl)-2-methyl-1,3,4-oxadiazol-3(2H)-yl)ethanone(8a-d)

Dissolved (0.001mol) from one of hydrazides (5a-d) or (6a-d) in (15ml) of acetic anhydride. The reaction mixture was heated to reflux over (4hrs.). After refluxing the mixture was cooled and poured into crushed ice and the formed precipitated solid was filtered, wash with cold water several times, dried, and recrystallized from a suitable solvent to give compounds (7a-d) and (8a-d) respectively. The physical properties are listed in Tables 3,4.

Table 3: Physical data for compounds (7a-e).

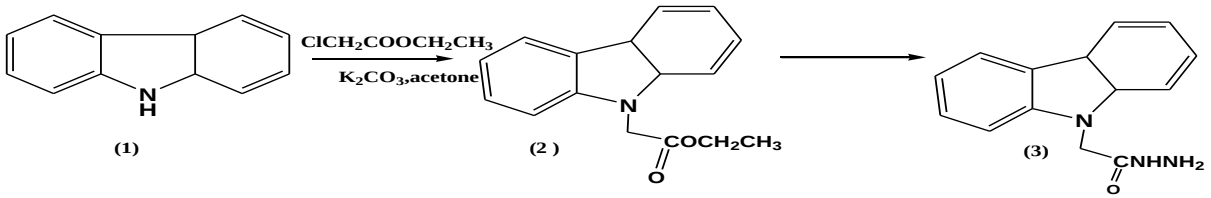
Comp. No.	R	M.P.(°C)	Color	Yield %	Crystal. solvent
7a	4-Br	57-59	Grey	62	Chloroform
7b	3-NO_2	85-87	Gold	53	Ethanol
7c	2-Cl	197-199	Light brown	57	Ethanol
7d	3,4-OH	112-114	Light brown	48	aq.Ethanol
7e	2,3-OCH3	191-193	Dark brown	39	Methanol

Table 4; Physical data for compounds (8a-d).

Comp. No.	R	M.p.(°C)	Color	Yield %	Crystal. solvent
8a	4-NH_2	61-63	olive	56	Acetone
8b	4-CH_3	205-207	Light brown	38	aq.ethanol
8c	2-OH	72-74	Dark grey	52	Ethanol
8d	3-OCH_3	57-59	Bright grey	94	aq,ethanol

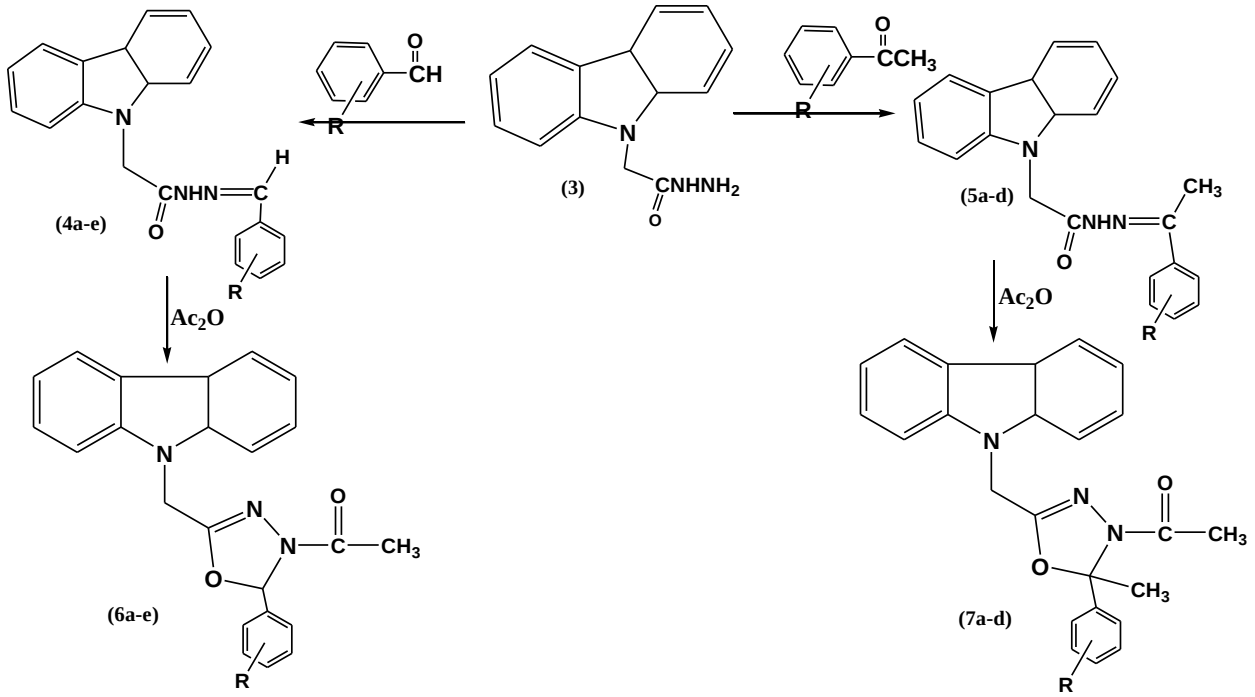
Discussion of the Results

The approved synthetic procedure for preparing the target compounds is set and shown in Schemes 1 and 2. Reaction of compound (1) with ethyl chloroacetate in the presence of potassium carbonate in dry acetone to obtain ethyl ester (2). The reaction of these compound with hydrazine hydrate in refluxing condition in ethanol gave 4bH-carbazole-9(8aH)-carbohydrazide (3) as shown in scheme 1



Scheme 1

Treatment of hydrazide (4)with substituted benzaldehyde or acetophenone gave the corresponding hydrazones(5a-e)and(6a-d) respectively ,which on cyclization by using acetic anhydride we get derivatives of 1,3,4- oxadiazole (7a-d) ,(8a-d) as shown in scheme2.



scheme2

Physical properties for hydrazones (5a-e) were reported in table 1. FT-IR spectra showed the following stretching bands; at the range (1654-1674 cm^{-1}) for (C=O) amidic bond, (3265-3293 cm^{-1}) due to the (NH) bond. While the hydrazones (6a-d) showed the following stretching bands; at the range (1639-1655cm^{-1}) for (C=O) amidic bond at the range (3289-3311 cm^{-1}) due to the (NH) bond. ^{1}H-NMR (δ (ppm) DMSO-d_6,500MHz) for compounds (5a-e) we noticed a peaks at the range(7.76-8.176 ppm) for N=CH proton ,(9.93-11.254 ppm) for NH protons and the aromatic protons showed peaks as a multiple signal as shown in table 5.Also The 1H-NMR spectra for compounds (6a-d) showed a peak between (*δ* 7.03–7.14 ppm) which was assigned to the N–H proton and a peak characteristic of CH_3 appeared between (*δ* 0.903–0.924 ppm) . In addition to other packages for these compounds, which are listed in the table6 .

Table 5: Spectral data for compounds (5a-e)

Table Comp. No.	FTIR (KBr) γcm^{-1}				^{1}H-NMR δ (ppm) DMSO-d_6
	C=O	CH Aliph.	CH Ar.	NH	
5a	1659	2949	3046	3265	4.22(d,2H,CH_2),8.176(s,1H,CH=N),7.138-8.70(m,8H,ArH), 6.88-7.133(m,4H, (sub. ArH),11.254(s, H, NH).
5b	1672	2898	3044	3281	4.28(bs,2H,CH_2),8.02(s,1H,CH=N),7.122,8.23(m,8H,ArH),6.88-7.09(m,4H, (sub. ArH),10.87(s, H, NH).
5c	1674	2928	3066	3293	4.251(bs,2H,CH_2),8.11(s,1H,CH=N),7.17-8.34(m,8H,ArH), 6.76-7.22(m,4H, (sub.ArH),11.123(s, H, NH).
5d	1664	2951	3057	3287	4.32(d,2H,CH_2),5.49(s,2H,2OH),7.87(s,1H,CH=N),7.644-8.44(m,8H,ArH),6,92-7.45(m,3H, (sub. ArH),9,95(s, H, NH).
5e	1654	2965	3058	3268	4.26(bs,2H,CH_2),3.78(s,6H,2OCH_3),7.76(s,1H,CH=N), 7.137-8.12 (m,8H,ArH),6.552-7.332(m,3H, (sub. ArH),11.244(s, H, NH).

Table

Table 6: Spectral data for compounds (6a-d)

Comp. No.	FTIR (KBr) γcm^{-1}			^{1}H-NMR δ (ppm) DMSO-d_6
	C=O	CH Ar.	NH	
6a	1641	3075	3311	0.91(bs,3H,CH_3),4. 21 (bs,2H,NH_2),4.29(bs,2H,CH_2),652(bs,2H, (sub. ArH),7.23(bs,2H, (sub. ArH),7.1(s,1H,NH),7.137-8.121(m,8H,ArH).
6b	1644	3082	3297	0.908(bs,3H,CH_3),2.38(s,3H,CH_3 sub.),7.03(s,1H,NH),7.1(bs,2H, sub. ArH),7.23(bs,2H, (sub. ArH),7.244-7,64(m,8H,ArH).
6c	1655	3084	3289	0.921(bs,3H,CH_3),4.18(d,2H,CH_2),5.34(s,1H,OH sub.),7.14(s,1H,NH),6.8(s,2H, (sub. ArH),7.18,7.42(bs,2H, (sub. ArH),7.54-7.89(m,8H,ArH).
6d	1639	3068	3302	0.924(bs,3H,CH_3),3.73(s,3 H,OCH_3 sub.),4.271(bs,2H,CH_2),7.11(s,1H,NH),6.72, ,6,78,7,04(s,3H,(sub. ArH), 7.26-8.55(m,8H,ArH).

Oxadiazoles (7a-e) and (8a-d) were obtained by reacting hydrazones(5a-e) and(6a-e) with acetic anhydride respectively. These compounds were determined based on their physical parameters such as melting points and solubility as well as chromatographic methods (TLC). The data in Tables (7 and 8) including spectroscopic methods (FT-IR, ^{1}H-NMR) for the compounds (7a-e) and (8a-d) are given. in supplementary materials to this paper. Where the FT-IR spectra showed new bands that return C=N groups at their expected range of frequencies, in addition to the absence of NH bands that were present in the hydrazones(5a-e)and (6a-d). The^{1}H-NMR spectra gave additional support about the validity of cyclization of hydrazones , that showed the appearance of a distinct signal for the CH bond of the oxadiazole ring and the absence of the signals belonging to the NH groups of hydrazones, which indicates the validity of the prepared compounds.

Table 7: Spectral data for compounds (7a-e)

Comp. No.	FTIR (KBr) γcm^{-1}				^{1}H-NMR δ (ppm) DMSO-d_6
	C=O	C=N	CH Ar.	C-O-C	
7a	1642	1608	3049	1248	2.02(bs,3H,CH_3,sub.),4.14(bs,2H,CH_2),6.65(s,1H,CH),7.01-7.6(m,8H,ArH),7.39,7.81(s,4H,sub.ArH)
7b	1639	1599	3067	1241	1.97(bs,3H,CH_3), sub.),4.24(bs,2H,CH_2),6,59(s,1H,CH),7.22-7.63(m,8H,ArH),7.41,7.92(s,4H,sub.ArH)
7c	1653	1610	3088	1259	2.11(bs,3H,CH_3),4.28(bs,2H,CH_2),6,64(s,1H,CH),7.07-7.58(m,8H,ArH),7.39,7.69(s,4H,sub.ArH)
7d	1658	1612	3052	1254	2.05(bs,3H,CH_3)4.21(bs,2H,CH_2),5.34(s,2H,2OH),6,61(s,1H,CH),7.11-7.62(m,8H,ArH),7.45,7.82(s,3H,sub.ArH)
7e	1644	1618	3077	1237	2.05(bs,3H,CH_3),3.73(s,2H,2CH_3),4.328(bs,2H,CH_2),6,61(s,1H, CH),7.05-7.49(m,8H,ArH),7.51,7.77(s,3H,sub.ArH)

Table 8: Spectral data for compounds (8a-d)

Comp. No.	FTIR (KBr) γcm^{-1}				^{1}H-NMR δ (ppm) DMSO-d$_6$
	C=O	C=N	CH Ar.	C-O-C	
8a	1659	2949	3046	3265	1.92(bs,3H,C-CH$_3$),2,19(s,3H,CO-CH$_3$),4.16(bs,2H,CH$_2$),4.22(bs,2H,NH$_2$),6,61(s,1H,CH),7.412-8.28(m,8H,ArH),6.38,6.97(m,4H,ArH).
8b	1672	2898	3044	3281	1.83(bs,3H,C-CH$_3$),2,01(s,3H,CO-CH$_3$),2,37(bs,3H,CH$_3$), 4.28(bs,2H,CH$_2$),6,63(s,1H,CH),7.02-7.28(m,8H,ArH),6.43.6.99(m,4H,ArH).
8c	1674	2928	3066	3293	1.87(bs,3H,C-CH$_3$),2,12(s,3H,CO-CH$_3$),4.26(bs,2H,CH$_2$),5.27(bs,2H,2OH), 6,64(s,1H,CH),7.06-8.32(m,8H,ArH),6.54.6.86(m,3H,ArH).
8d	1664	2951	3057	3287	1.95(bs,3H,C-CH$_3$),2,18(s,3H,CO-CH$_3$),3.86(bs,6H,2CH$_3$), 4.23(bs,2H,CH$_2$),6,6 (s,1H,CH),7.0-8.42(m,8H,ArH),6.54.6.95(m,3H,ArH).

Conclusions

We synthesized a new series of hydrazones(5a-d) and (6a-e). On cyclization of these hydrazones using acetic anhydride yielded a derivatives of 1,3.4-oxadiazole for carbazole(7a-e) and (8a-d). We characterized them by FT-IR and ^{1} H-NMR.

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