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Facile and Efficient Synthesis of 1,3,4-Oxadiazole and its Hydrazones

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Abstract - This research includes the synthesis of new 1,3,4-Oxadiazole and its hydrazones starting from benzilic acid hydrazide (3) which have been prepared using known reactions from benzylic acid. The hydrazide (3) was heated with an alcoholic solution of potassium hydroxide and carbon disulfide under reflux conditions followed by acidification with hydrochloric acid to give a brownish crystalline 1,3,4-Oxadiazole 2-thiol (4) which on treatment with ethyl chloroacetate yielded a corresponding ester (5), which was condensed with hydrazine hydrate to give acid hydrazide (6). The hydrazones (7a-e) and (8a-e) were obtained by condensation of hydrazide (6) with substituted benzaldehyde and substituted acetophenone respectively. The structures of synthesized compounds have been identified on the principles of their FT-IR and 1H-NMR.Also the synthesized compounds purity were checked by TLC technique,

Keywords- benzilic acid ,oxadiazole, hydrazone, ethyl chloroacetate, substituted benzaldehyde , substituted acetophenone.

I. INTRODUCTION

Schiff bases are formed by the reaction of amino aromatic compounds with aldehyde or ketone compounds [1]. Hydrazone compounds are one of the types of Schiff bases which derived from hydrazides with various aldehydes or ketones it's have general structural formula $R1R2C=NNH_2$ and have been widely studied due to their facile and easily synthesis have been attracted much attention for their structures [2-4], coordination ability [5-7], and potential biological activities [8,9]. During recent years, many hydrazone compounds have displayed novel structures and extensive applications in luminescent probes, antibacterial and antitumor agents, fluorescence markers, optical materials, and anticonvulsant agents [10-12]. In the past years, we have done some work in the synthesis, structural characterization, and properties of hydrazone compounds, which show novel structures and luminescent properties [13, 14]. Hydrazones are useful intermediates towards the synthesis of a variety of heterocyclic compounds [15, 16]. 1,3,4-Oxadiazoles containing hydrazones also possessing a diversity of useful biological effects such as antimicrobial agents [17] antibacterial and moderate antifungal activities [18] Also done Comparison of hydrazones to antibacterial agents as oxadiazole compounds through antifungal activities and antioxidant activity. The hydrazones were the best of everything Biological activities of oxadiazole compounds [19].

II. EXPERIMENTAL SETUP

All reagents and chemicals are from BDH and Fluka, used without purification. Melting points were measured using: Electro thermal melting points apparatus type (not corrected). FT-IR spectra were recorded on Shimadzu FT-IR-8400 Infrared Spectrophotometer. ^{1}H-NMR spectra were recorded by Geo. 1400(500 MHz) using DMSO-d_6 as solvent. The methyl benzilate (2) was prepared by the usual esterification method, also benzilic acid hydrazide (3) was prepared using the reported method [20] starting from methyl benzilate**.**

Prepration of 5-(α،α-diphenyl –α-hydroxymethyl)-1,3,4-oxadiazoline -2-thiole (4). [21]

Dissolved benzilic acid hydrazide (3) (2.42 g., 0.01 moles) in ethanol (30mL) and added to a solution of potassium hydroxide (0.85 g, 0.015 mole) in ethanol (20 mL) and carbon disulfide (20 mL). The reaction mixture was refluxed for about (7 hrs.) until all hydrogen sulfide was evolved (tested by lead acetate solution). After the

concentration of the solution to a small volume, the residue was dissolved in water. The solution was added to ice-water, containing hydrochloric acid (5%, 15ml) the solid product was filtered, wash with cold water and the resulting precipitate was crystallized from aqueous ethanol to give the dark yellow product (,88%) m.p. (138-140 ºC).

Preparation of Ethyl2-((5-(hydroxydiphenylmethyl)-1,3,4-oxadiazol-2-yl) thio) acetate (5) [22]

A mixture of 1,3,4-oxadiazole (4) (0.01 mole) and ethyl chloroacetate (0.01 mole, 1.23 g) with potassium carbonate (0.28 g) in ethanol (25 ml) was refluxed on a steam bath for about (6 hrs.) Then cooled, and poured into an ice water to give the solid product which was filtered, and recrystallized with ethanol to pale yellow needles of compound (5) Yield 55%, m.p. (190-192ºC).

Preparation 2-((5-(hydroxydiphenylmethyl)-1,3,4-oxadiazol-2-yl) thio)acetohydrazide (6) [23]

To a suspension of the ester (5) **(**0.01 mole) in absolute ethanol (25 mL), was added hydrazine 0,02 moles, 98 %). The mixture was refluxed at 50–60 oC for (5 hrs,) and then the solid precipitate so formed was filtered and recrystallized from methanol to afford the hydrazide [6] as Yield %, m.p. (156 -158ºC).

Preparation of (Z)-N'-(substitutedbenzylidene-2-((5-(hydroxydiphenylmethyl)-1,3,4-oxadiazol-2-yl) thio)acetohydrazide (7a-e)[24]

General Procedure

To a well-stirred solution of the respectively substituted benzaldehyde (0.01 moles) in an absolute ethanol (10 mL) and glacial acetic acid (0.2 mL) was added the hydrazide (6) **(**0.01moles) in ethanol (20 mL) and the mixture was heated under reflux condition for (4hrs.). The resulting solution was concentrated and left to cool and the formed precipitated solid was filtered, dried and recrystallized from suitable solvent to give hydrazone compounds (7a-e). The physical properties are listed in table 1.

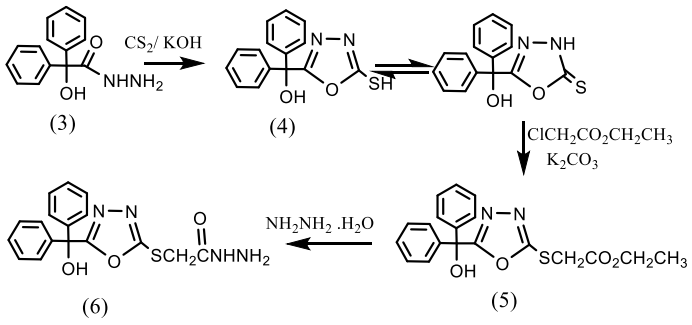
Preparation of (Z)-2-(5-(hydroxydiphenylmethyl)-1,3,4-oxadiazol-2-ylthio)-N'-(1-(-substituted nitro phenyl) ethylidene)acetohydrazide (8a-e)[25]

General Procedure

Substituted acetophenone (0,02 moles) was dissolved in ethanol (30ml) in a round -bottomed flask and heated on a water bath for (10 minutes). This hot solution was treated with a hot ethanolic solution (20 ml) of (0.02 moles) hydrazide (6) with few drops of glacial acetic acid and this mixture was refluxed for (4-5 hrs). The change in color of the solution indicates the formation of hydrazones (8a-e). It was then concentrated, cooled the solid thus separated out, was filtered, recrystallized from a suitable solvent, physical data are mentioned in table 2.

III. RESULTS AND DISSCUSION

The chemistry of benzilic acid and its hydrazone is very interesting due to the capability of both them functions has different significance in some areas. The target compounds, 5-(αα-diphenyl –α-hydroxymethyl)-1,3,4-oxadiazoline-2-thiole (4), ester and corresponding hydrazide (5,6) respectively were prepared as the following the routes shown in Scheme 1.

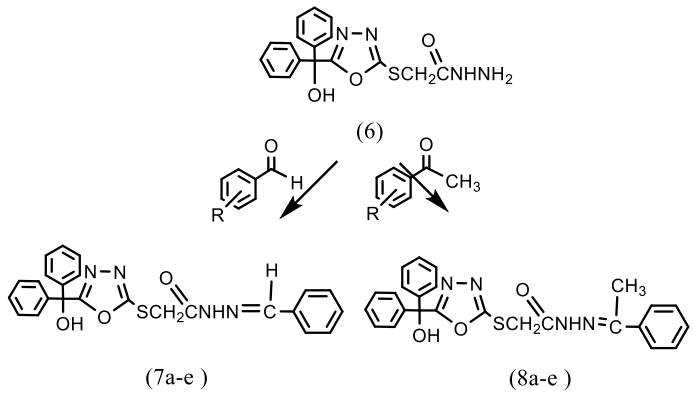


Scheme 1: synthesis of hydrazide (6)

The 1,3,4-oxadiazole-2-thiole (4) was synthesized in good yield (88 %) from benzilic acid hydrazide (3), On the reaction of compound (4) with ethyl Chloroacetate in the presence of potassium carbonate produced Ethyl2-((5-(hydroxydiphenylmethyl)-1,3,4-oxadiazol-2-yl) thio) acetate (5). which on treatment with hydrazine hydrate yielded the corresponding hydrazide (6). The structures of these compounds were identified by spectral (FT-IR and ^{1}H-NMR) and physical data in addition to monitoring the reactions using thin-layer chromatography. The IR spectrum for compound (4) disclosed the presence of C=N

at 1642 $cm^{-1,}$ C-O-C at 1285 cm^{-1} and 3423cm^{-1} due to the OH group in this compound, which may exist in two tautomeric forms (thiol and thion), the thion form of which is found to predominate, with no absorbance at around 2600 cm^{-1} of thiole form his is further supported by ^{1}H NMR spectrum which shows no absorbance for SH group i.e. the thione form was predominate which is also supported by some earlier reports [26,27] .IR spectrum for ester (5) shows two sharp absorption bands, one of which appearing at 1728 cm^{-1} was attributed to carbonyl frequency corresponding to acyl carbonyl, also bands at 1615 cm^{-1} for C=N group for cyclic oxadiazole and 2925 cm^{-1} for υ(C-H) aliphatic and at 3355 cm-1 due to OH group., while The ^{1}H-NMR spectrum of compound **(5)**, showed peaks at δ (1.23 ppm) integrated for three protons of CH_3 of ester group, CH_2 which attached with sulfur atom was appeared at (4.4ppm) while esteric CH_2 group was appear at (4.16ppm), in addition showed peaks at δ (5.44 ppm) and the range (7.23-7.87ppm) integrated for OH group and protons of aromatic part respectively.

IN The hydrazide (6) FT-IR spectrum shows characteristic absorption bands at: 3082 cm-1(C-H, of Ar.), 1628 (C=N), 1660-1665 cm^{-1} for carbonyl group, 3385 cm^{-1} (-OH),3345 cm^{-1} due to NH group and at 3455 cm^{-1} for NH_2 group. I ^{1}H- NMR spectrum for hydrazide (6) showed the significant peaks δ ppm 3.93(2H, -S- CH2-);4.35 (d,2H, NH2,), 5.44(s,1H, OH) ,8.15 for (NH). in addition to the aromatic proton signals at 7.19—7.25 for ten protons. The hydrazones (7a-e) and(8a-e) were synthesized by condensation of 2-((5-(hydroxydiphenylmethyl)-1,3,4-oxadiazol-2-yl) thio) acetohydrazide (6) with various aromatic aldehydes and substituted acetophenone respectevely , in absolute ethanol in the presence of glacial acetic acid as catalyst as shown in scheme 2.



Scheme 2 :Synthesis of hydrazones (7a-e)&(8a-e)

All hydrazone compounds were characterized by physical and spectroscopic (FT-IR, ^{1}H-NMR) data and purity were checked by TLC technique, The FTIR spectrum for hydrazones (7a-e) showed the following stretching bands; at the range (1649-1675 cm^{-1}) due to the (C=N of azomethane) bond,the range (1598-1612 cm^{-1}) for (cyclic C=N),(1649-1675 cm -1)for amidic carbonyl , at (3325-3377 cm^{-1}) stretching group for (NH), and at the range (3069-3086 cm^{-1}) due to (ArCH) group. The FT- IR data of the synthesized compound (7a-e) are listed in Table (3).

The FTIR spectrum for hydrazones (8a-e) showed the following stretching bands at the range (1627-1640 cm^{-1}) due to the (C=N of azomethane) bond,the range (1595-1611 cm^{-1}) for (cyclic C=N),(1658-1680 cm^{-1})for amidic carbonyl , at (3248-3375 cm^{-1}) stretching group for (NH), and at the range (3045 -3086 cm^{-1}) due to (ArCH) group. The FT- IR data of the synthesized compound (8a-e) are listed in Table (4).

Furthermore, ^{1}H-NMR spectra for hydrazones (7a and 7e), (8a and 8e) represented for these hydrazones are presented in Table 4. These data came in an agreement with those published in the literature for similar compounds, thus Hydrazones are distinguished by the presence of feature peaks especially a singlet proton for N=CH which appeared at the range (7.28-7.92 ppm). a singlet proton at the range (3-71-4.09 ppm) due to S-CH_2. In addition to the rest of the belonging to the other groups that showed that the results are correct and accurate, and which are shown in the table 5.

IV CONCLUSION

In conclusion, 1,3,4-oxadiazole bearing hydrazone compounds have been prepared and characterized starting from benzilic acid hydrazide, two series of hydrazone compounds, (7a-e) and (8a-e) have been successfully synthesized by several steps. First S-alkylation of 1,3,4-oxadiazole then converted to other S-hydrazide which condensation with aromatic aldehydes or substituted acetophenone respectively.

V. ACKNOWLEDGMENTS

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Table 1: The Physical data for compounds. (7a-e)

Comp. No.	X	M.p.**(°C)**	Yield %	Color	Crystallization solvent
7a	4- NO_2	178-180	88	Pale yellow	Methanol
7b	2,4- diCl	278-280	75	Brown	Ethanol
7c	4-Br	216-218	74	Dark yellow	Methanol
7d	2-NH_2 -3,4 diCH_3	233-235	68	Pale yellow	Methanol
7e	3-OCH_3	246-247	77	Yellow	Ethanol

Table 2: The Physical data for compounds. (8a-e)

Comp. No.	X	M.p. (°C) (Lit.)[12]	Yield %	Color	Crystallization solvent
8a	4-NO_2	183-185	78	White	Methanol
8b	4-Cl	175-176	60	Brown	aq.Ethanol
8c	4- Br	258-259 (259)	85	Pale yellow	Ethanol
8d	4-NH_2	235-237	69	White	Ethanol
8e	3-OCH_3	288-290 (287)	75	White	Acetone

Table 3: The FT-IR data of compounds (7a-e)

Comp. No.		FT.IR ν(cm^{-1})				
	C=N (azomethen)	C=N (cyclic)	C=O	NH	C-H-Ar	C-O-C asymm. (Symm.)
7a	1622	1598	1675	3255	3079	1485 (1366)
7b	1634	1604	1655	3365	3080	1510 (1375)
7c	1624	1596	1671	3337	3072	1520 (1344)
7d	1627	1605	1649	3369	3086	1530 (1348)
7e	1639	1612	1665	3377	3069	1541 (1334)

Table 4: The FT-IR data of compounds (8a-e)

Comp. No.	FT.IR $\nu(cm^{-1})$					
	C=N (azomethen)	C=N (cyclic)	C=O	NH	C-H-Ar	C-O-C asymm. (Symm.)
8a	1634	1611	1680	3354	3065	1535 (1352)
8b	1638	1610	1661	3339	3085	1519 (1365)
8c	1627	1595	1669	3248	3045	1528 (1354)
8d	1640	1608	1658	3375	3078	1528 (1345)
8e	1635	1599	1672	3345	3047	1538 (1326)

Table 5: The ^{1}H-NMR data of compounds (7a and 7e), (8a and 8e)

Comp. No.	^{1}H -NMR δ(ppm) DMSO-$_6$
7a	4.09(s,2H, S-CH_2),5.43(s,1H, OH),7.92(s,1H, NH) 8.1(s,,1H,N=CH),7.23-7.31(m, 10 H,ArH),7,9-8.22(m, 4H,ArH sub,).
7e	3.98(s,2H, S-CH_2),5.41(s,1H, OH),7.75(s,1H, NH) 8.21(s,,1H,N=CH),7.19 -7.25(m, 10H,ArH),7,82--8.18m, 4H,ArH sub,).
8a	0.95(s,3H,CH_3),3.71(s,2H,S-CH_2),3,78(s3H,OCH_3)5.43(s,1H,OH),7.28(s,1H,NH),6,95-7.25(m, 4 H, ArH sub,),7,14-7.52(m, 10H,ArH).
8e	1.15(s,3H,CH_3),4.01(s,2H,S-CH_2),3,82(s3H,OCH_3)5.39(s,1H,OH),7.35 (s,1H,NH),7.05-7.18(m, 4 H, ArH sub,),7,20-7.32(m, 10H,ArH).