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Research Article

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Economic Microwave Irradiation Technique - Assist the Synthesis of Some Novel 2, 5 –Disubstituted-1, 3, 4- Oxadiazoles and Their Biological Activity

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ABSTRACT

The synthesis of 2-substituted -5-(α,α- diphenyl-α-hydroxymethyl)-1,3,4-oxadiazoles(5a-e)by heating benzilic acid hydrazide(3)either with several carboxylic acids in presence of phosphorus oxychloride, or refluxing this hydrazide with corresponding aldehydes to give substituted benzilyl hydrazones(4a–f) However, then oxidative cyclization of those hydrazones with ferric chloride to give the same products(5a–f). Assistance of microwave irradiation for synthesis of benzilyl hydrazones (4a–f) is introduced now a day. In the present study microwave promoted condensation reaction of aromatic aldehydes and benzilic acid hydrazide (3) are displayed, then cyclization by microwave irradiation. The structures of the prepared compounds were characterized through spectral and physical methods .Some of the synthesized products showed good biological activity.

Keywords: Heterocyclic, Hydrazones, Oxadiazole , Biological activity. Microwave irradiation

INTRODUCTION

Oxadiazole derivatives are robust pharmaceutical compounds with antiangiogenic and ant proliferative potential both *in vitro* and *in vivo* [1], as inhibitors of *Mycobacterium tuberculosis*[2] in addition to they are good against *E. coli, P. aeruginosa, S. aureus* and *S. pyogenes* as compared to standard Ampicillin [3]A modest and well-organized oxidative cyclization of aroyl hydrazones with aldehyde or ketone derivatives enables the synthesis of 1,3,4-oxadiazole derivatives in great incomes [4,5].

In addition, condensation of hydrazide derivatives with carboxylic acids followed by dehydrative cyclization give these important oxadiazole derivatives [6]. Microwave acceleration of oxadiazole derivatives synthesis has appeared as an appreciated alternative to conventional approaches in latest periods. These synthesis reactions are less period consuming and high yielding[7] and [8]. It is well-known that substituted -1,3,4-oxadiazole can be used as synthons for others biologically important compounds.So, it was of interest to investigate aspects of synthesis new series of Novel 2,5 –disubstituted-1,3,4- Oxadiazoles.

EXPERIMENTAL SECTION

Melting points were measured using electro thermal 9300 melting point appliance and are uncorrected. IR spectra were recorded on a Perkin- Elmer 590 B spectrophotometer using KBr disk. UV spectra were recorded on Shimadzu UV-160 spectrophotometer using methanol as a solvent ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400MHz spectrometer in DMSO-d_6 with TMS as the internal standard. Elemental analysis was performed on Carlo-Erba 1160 CHN analysis. All reagents and solvents were obtained from commercial suppliers and were used without further purification; the benzilic acid hydrazide was prepared by author [9], thus. The ester of benzylic acid (2) was prepared by the usual esterification method, benzilic acid hydrazide (3) was synthesized using reported method starting from ester (methyl benzilate) [9].

Synthesis of substituted benzilyl hydrazones (4a-f) Conventional Method (A)

To a hot ethanolic solution of benzilic acid hydrazide (3) (0.24gm, 1m mole), a solution of appropriate aromatic aldehydes (1m mole) in 20 ml of methanol is added and the reaction mixture is refluxed for (0.25–3 hrs.).On cooling the resulting product is filtered, dried and recrystallized from ethanol to give the substituted hydrazones (4a-f). Physical and spectral data are recorded in Tables 1 and 2 [10].

Microwave Irradiation Method (B)

An appropriate aromatic aldehyde (1m mole) is added to completely dissolved benzilic acid hydrazide (3) (0.24 gm, 1m mole) in 12 ml. ethanol. The reaction mixture is kept under microwave irradiation for 4 minutes at medium-low temperature. After completing the reaction (from the checked progress of reaction using thin layer chromatography spotting in dichloromethane as eluting solvent, immediately added the result mixture to cold-water bath. Orange yellow-colored crystals of compounds (4a-f) are recrystallized from methanol. % Yields are recorded in Table 1 [11].

Table 1: Physical data for synthesized compounds (4a-f)

Comp.No.	Ar	Reaction Time (hrs.)	m.p. °C	Yield% Conventional (MW)	Molecular formula	CHN Analysis % Found (Calcd.)		
						C%	H%	N%
4a	C_6H_5-	2	200-202	79 (96)	$C_{21}H_{18}N_2O_2$	75.98	5.55	8.29
						(76.36	5.45	8.48)
4b	3-ClC_6H_4	0.5	216-218	80 (94)	$C_{22}H_{17}ClN_2O_2$	69.0	4.61	7.49
						(69.13	4.66	7.68)
4c	4-ClC_6H_4	0.25	248-249	85 (94)	$C_{22}H_{17}ClN_2O_2$	69.96	4.62	7.52
						(69.13	4.66	7.68)
4d	4-$NO_2C_6H_4$	0.5	266-268	91 (97)	$C_{21}H_{17}N_3O_4$	66.88	4.61	10.93
						(67.02	4.53	11.02)
4e	4-HOC_6H_4	1	253-255	81 (95)	$C_{21}H_{18}N_2O_3$	72.64	5.31	8.00
						(72.83	5.20	8.09)
4f	2,4-ClC_6H_4	1	235-237	88 (94)	$C_{21}H_{16}Cl_2N_2O_2$	63.19	3.85	6.86
						(63.15	4.01	7.01)

Preparation of 2-substituted-5-(α, α-diphenyl-α-hydroxymethyl)-1,3,4-oxadiazoles (5a-f)

Conventional Method (C)

A mixture of one of benzilyl hydrazones(3) (4a-f) (0.001 mole) in dioxane (25 ml), a solution of ferric chloride (10 mg) in water and glacial acetic acid (10 ml) is stirred for one hour, diluted with water (200 ml) and kept at room temperature for 72 hrs. The product is filtered and crystallized from ethanol to give the matching 2,5-disubstituted -1,3,4-oxadizoles(5a-f).into ice-water and made basic by adding solution of sodium bicarbonate. The resulting solid is filtered, dried and crystallized from aqueous ethanol to give the title – oxadizoles (5a-f). Physical and spectral data are recorded in (Table 2 and 4) [12].

Microwave Irradiation method (D)

A mixture of one of compounds (4a-f) (0.001 mol) and 0.5 ml of acetic acid is irradiated in a microwave phial (30 ml) at 130 °C for 10 min. After completion of the reaction (monitored by thin layer chromatography, ethyl acetate/hexane, (5:2), the product is workup as method (C). % Yields are listed in (Table 2) [13].

Direct Method (E); (Authentic samples)

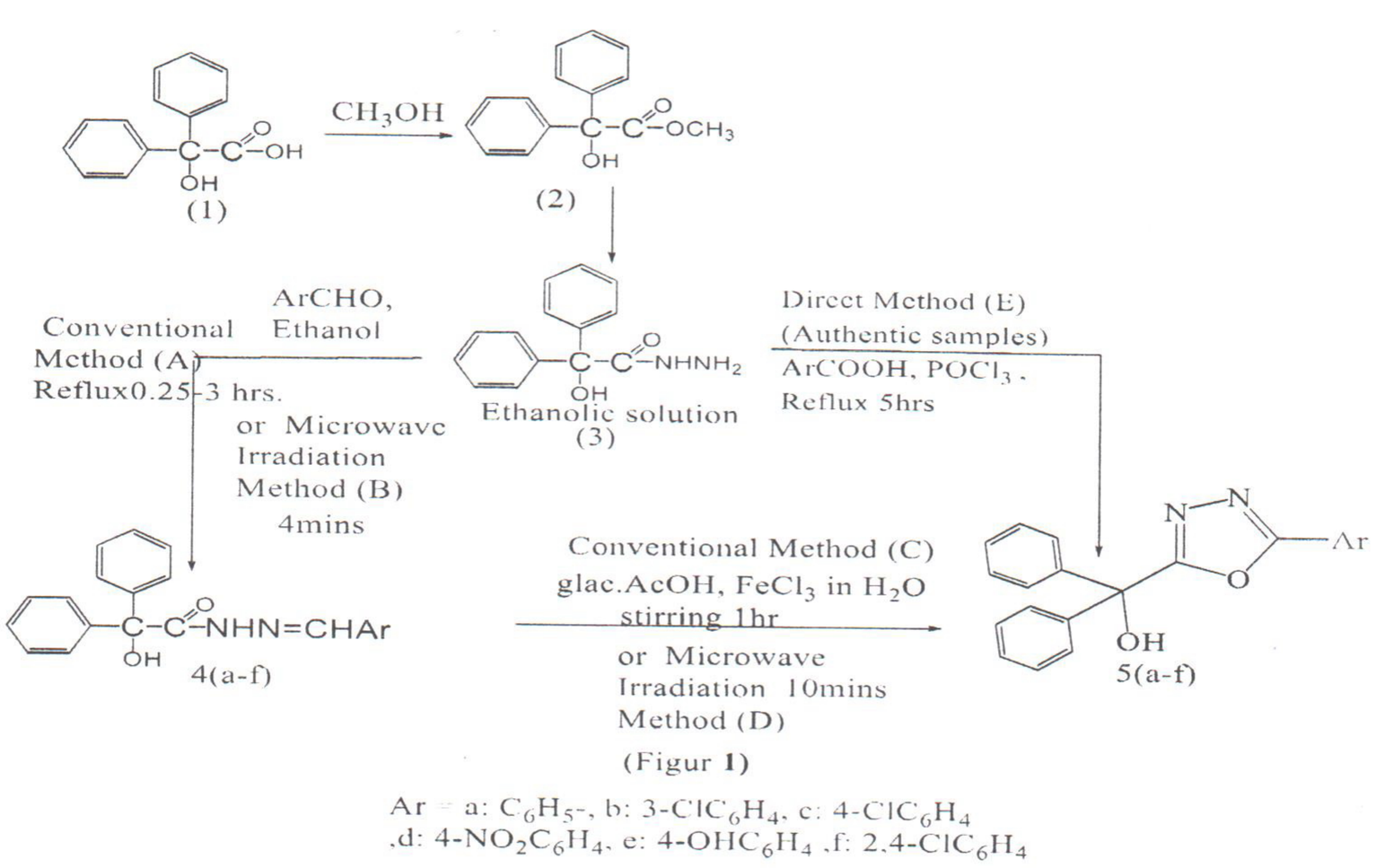
A mixture of benzilic acid hydrazide (3) (0.24 gm, 0.01 mole), appropriate aromatic carboxylic acids (0.01 mole) and phosphorus oxychloride (5 ml) are refluxed for five hours. After cooling, the reaction mixture is poured into ice-water and made basic by adding solution of sodium bicarbonate. The resulting product is filtered, dried and crystallized from aqueous ethanol to give the title – oxadizoles (5a-f). Physical data and spectral data are recorded in (Table 2 and 4) [2, 14].

Table2: Physical data for synthesized compounds (5a-f)

Comp.No.	Ar	Method	m.p. Ĉ	Yield% Conventional (MW)	Molecular formula	CHN Analysis % Found (Calcd.)		
						C%	H%	N%
5a	C_6H_5-	A	221-223	51 (95)	$C_{21}H_{16}N_2O_2$	76.69	4.71	8.55
						(76.82	4.87	8.53)
5b	3-ClC_6H_4	A,B	232-234	52 (91)	$C_{21}H_{15}ClN_2O_2$	69.83	4.02	7.63
						(69.51	4.13	7.72)
5c	4-ClC_6H_4	A,B	213-215	68 (91)	$C_{21}H_{15}ClN_2O_2$	69.44	4.16	7.55
						(69.51	4,13	7.72)
5d	4-$NO_2C_6H_4$	A,B	191-193	67 (93)	$C_{21}H_{15}N_2O_3$	67.41	3.88	11.17
						(67.56	4.02	11.26)
5e	4-OHC_6H_4	A	187-189	47 (92)	$C_{21}H_{16}N_3O_4$	73.29	4.29	8.19
						(73.25	4.65	8.13)
5f	2,4-ClC_6H_4	A.B	194-195	44 (97)	$C_{21}H_{14}Cl_2N_2O_2$	63.22	3.44	6.82
						(63.47	3.52	7.05)

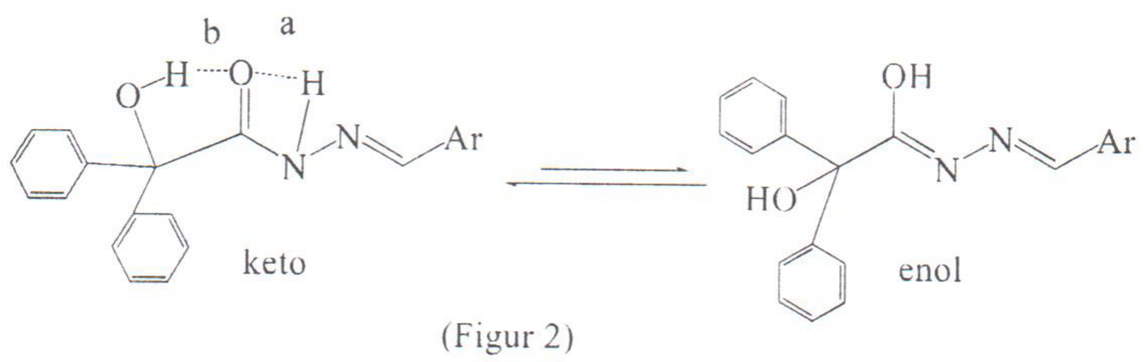
RESULTS AND DISCUSSION

All methods for synthesis of the target compounds is accomplished by the routes outlined in Schemes (1). Benzilic acid hydrazide reacts with suitable aromatic aldehydes to give the corresponding hydrazones (4a-f), Scheme (1). This reaction is carried out using two methods; the primer is method (A), a conventional method with 79-88% yield which is increased to 94-96% by using the former method (B) with microwave irradiation (only 10 minutes).



(Figur **1**)

UV, IR and 1H-NMR spectral data (Table 3), identified the structure of these hydrazones. UV spectrum shows λmax (CH_3OH) at (269-277 nm) due to the conjugation that cause bathochromic shift, Scheme (2).



(Figur 2)
Keto-enol toutomerization of (4a-f)

Ketone form is expected in this paper to be more stable due to it is stabilized by an internal hydrogen bond with amine proton (b) or benzylic hydroxyl proton (b) From the computational study, the total energy of keto form is (-4.4824), while that of enol form is (5.3617 kcal/mole. This indicates that the keto form is more stable by 9.8441 kcal/mole, and it is the main tautomeric form is the ketone.IR (cm^{-1}) spectra of these hydrazones. Table (3): 3285-3380(NH), (1635-1664 cm^{-1}) (C=O) and (1570-1593) (C=N). These results come with agreement of the published ones [15]. These low absorptions of carbonyl also due to the conjugation, which decrease the double bond property, the actual position of the C=O bond is affected by several factors; one of them is conjugation [16]. Conventional method (C) is the oxidative cyclization of benzilyl hydrazones (4a-f) to the target compounds (5a-f), which is carried out by stirring these hydrazones for one hour with glac. Acetic acid and aq. ferric chloride solution, or method (D) with microwave irradiation for ten minutes.

Table 3: Spectral Data for Synthesized Compounds (4a-F)

Comp. Number	IR(KBr) γ cm^{-1}			UV λmax (nm) MeOH	^{1} H-NMR δ (ppm) DMSO-d_6	13C-NMR δ (ppm) DMSO-d_6
	C=N	C=O	NH			
4a	1586	1660	3335	269	6.3(s,1H,OH);6.8-7.2(m,15H,3 Ph);8.1(s,1H,CH);10.2(s,1H,NH)	101.2, 126.3, 128.4, 129.3, 131.3, 133.6, 142.4, 143.3.
4b	1586	1642	3375	270	6.6(s,1H,OH);6.9(m,10H,2Ph);7.3-7.6(m,4H,ArH);8.1(s,1H,CH);10.1(s,1H,NH).	(101.4,125.8,127.4,128.5,Ph);8.1(s,1H,CH);10.2(s,1H,NH) 129.4,130.5,131.7,134.5,133.8,131.5142.8,143.6.
4c	1592	1635	3362	271	6.4(s,1H,OH);6.8-7.2(m,10H,2Ph);7.7(m,4H,ArH);8.4(s,1H,CH);10.1(s,1H,NH).	101.1,125.5,127.6,128.3,129.8,130.5,131.4,134.3,133.4,131.5,142.2,143.5.
4d	1570	1635	3380	274	6.3(s,1H,OH);7 (m,15H,2Ph);7.1-7.5(m,4H,ArH).8.1(s,1H,CH);10.4(s,1H,NH)	101.7,124,2,124.6,126.6,127.7,128.2,129.3,139.1,142.4,143.8,160.2.
4e	1590	1635	3368	278	5.7(s,1H,phenolicOH),6.4(s,H,OH);6.7-7.3(m,10H,2Ph):7.47.8(m,4H,ArH);8.3(s,1H,CH);10.0(s,1H,NH).	101.4,116.7,126.3,128.8,129.4,129.7,130.4,142.9,143.6,160.1.
4f	1595	1664	3285	277	6.4(s,1H,OH);6.5-7.2(m,10H,2Ph);7.3-7.6(m,3H,ArH);8.1(s,1H,CH);10.2(s,1H,NH).	101.7,126.2,128.2,129.3,130.2,131.2,142.45,143.7,160.6

Table 4: spectral data for synthesized compounds (5a-f)

Co.No.	IR(KBr) γ cm^{-1}		UV λmax (nm)	^{1} H-NMR δ (ppm) DMSO-d_6	^{13}C-NMR δ (ppm) DMSO-d_6
	C=N	C-O-C			
5a	1640	1245	241	6.4(s, 1H, OH) ;6.6-7.4(m, 15H, 3Ph).	91.3,121.9,126.1,127.5,127.8,128.2,129.8,130.1,131.7,143,5,163.3,164.8.
5b	1645	1248	243	6.2(s, 1H, OH) ;7.1 (m, 10H, 2Ph) ;7.2-7.5(m3H, ArH).	91.6,122.4,125.3,126.3,127.3,128.2,129.3,134.7,143.6,164.8.
5c	1650	1255	248	6.2(s, 1H, OH) ;7.0 (m, 10H, 2Ph) ;7.2-7.5(m3H, ArH).	91.5,122.2,125.2,126.3,127.6,128.2,129.3,134.4,143.3,164.5.
5d	1633	1250	252	6.5(s, 1H, OH) ;7.1 (m, 10H, 2Ph) ;7.1-7.6(m3H, ArH).	91.6,126.2,128.2,128.4,129.1,129.6,130.4,132.5,143.8,148.2,163.6.
5e	1640	1238	250	6.1(s, 1H, OH) ;6.5-6.9(m, 10H, 2Ph) ;7.4-7.8(m3H, ArH).	91.4,116.3,116.8,118.8,126.5,128.2,128.7, 129.5,143.4,158.3,163.2,164.5.
5f	1632	1246	247	6.3(s, 1H, OH) ;6.7-7.2(m, 10H, 2Ph) ;7.3-7.8(m3H, ArH).	90.9,126.2,127.5,128.5,129.6,130.2,133,6,135.5,135.8,143.4,163.5,166.1.

Finally, a preliminary study was conducted by which the insecticidal and antifungal activities of the synthesized hydrazones were in vitro bioassays showed that these compounds have moderate fungicidal activity against fungus

mycelium growth. Furthermore, hydrazones (4a and 4e) are a promising significant fungicide for further development. While oxadiazoles (5h and 5f) showed good insecticidal effect on larvae of kapra beetle and the adults of rose aphids.

CONCLUSION

From the experiment it was concluded that both the methods could be used for production of benzilyl hydrazones (4a-f) and oxadizoles (5a-f) but microwave irradiation has several advantages over conventional one. Microwave energy is additional effective revenue of cooking reactions. Chemical conversions that procured periods to complete can now be accomplished in few minutes. Microwave energy offers many assistances for carrying out preparation including improved reaction rates, income enhancements, and chemically cleaner. Finally, these hydrazones have moderate fungicidal activity against fungus mycelium growth, while oxadizoles showed good insecticidal effect.

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