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Microwave assisted novel synthesis and antibacterial evaluation of 1-(2-methyl-2,5-substituted diphenyl-1,3,4-oxadiazol-3(2*H*)-yl)ethanone derivatives

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ABSTRACT

In continuation of our interest regarding microwave assisted synthesis, we have carried out Novel synthesis of 1-(2-methyl-2, 5 substituted diphenyl-1, 3, 4-oxadiazol-3(2H)-yl) ethanone derivatives ***(4a–4i)*** *by cyclisation of N'-[(1Z)-1-(substituted phenyl) ethylidene] benzohydrazide derivatives* ***(3a-3i)*** *in presence of acetic anhydride on solid support silica gel under the microwave radiation. All the synthesized compounds were characterised on the basis IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis also synthesized compounds were screened for their antibacterial activity against Gram positive and Gram negative bacteria.*

Key words: Oxadiazole, solid support silica, Microwave, Antibacterial activity.

INTRODUCTION

1, 3, 4-Oxadiazole, a privileged structure represents a key motif in heterocyclic chemistry and is important in medicinal chemistry because of its ability to exhibit a wide range of pharmacological activities [1] especially antimicrobial [2], cytotoxic [3], antifungal [4] and anticancer activities [5]. They are also useful as inhibitors of bacterial phenylalanyl t-RNA synthetase [6] human neutrophil elastase[7] antagonists[8,9], y-secretase inhibitor[10] antikinetoplastid activity[11] and orientation in the γ-amino butyric acid binding site [9] .They are extensively utilised as synthons or precursor in various organic syntheses such as for the preparation of spiro-fused ß-lactam oxadiazolines [12]. Microwave-assisted organic synthesis has obtained central position in the area of heterocyclic research, generally due to the short reaction times, eco-friendly nature and high yields of the resulting products as compared to that of the any conventional methods. Microwave-assisted organic synthesis is mainly based on the efficient heating of materials by the microwave dielectric heating effect (through dipolar polarization and ionic conduction) [13].Reactions on solid support without using solvent usually with open vessel in domestic microwave ovens are currently in use for synthetic chemist to create eco-friendly atmosphere [14, 15]. Using this approach, we have reported here Microwave assisted synthesis of novel series of 1-(2-methyl-2,5-substituted diphenyl-1, 3, 4-oxadiazol-3(2*H*)-yl)ethanone derivatives, using solid support without use of the solvent, newly synthesized compounds were evaluated for their antibacterial activity against Gram positive and Gram negative bacteria.

EXPERIMENTAL SECTION

Solvents and reagents were commercially sourced from Sigma Aldrich and used without further purification. Melting points were determined in an open capillary and are uncorrected. Products were recrystalized from ethanol as a solvent. The purity of compound checked by the TLC on silica gel G plates. The microwave used for the synthesis is of ONIDA Company and domestic type. The Infrared spectra were obtained on Perkin Elmer FT-IR spectrometer. The samples were examined as KBr discs 5%w/w. All the compounds were analysed for C, H and N on Carlo-Erba elemental analyser.^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avon 300MHz

spectrometer using $CDCl_3$/ DMSO as solvent and TMS as internal standard, the chemical shift are reported in ppm. Multiplicities are indicated by's' (singlet),'d' (doublet),'t' (triplet),'q (quartet),'m' (multiplet), bs (broad singlet).

General procedure for the Synthesis of (substituted) Aryl Hydrazides (2a – 2f):
A mixture aryl ester (0.02mol) and Hydrazine hydrate (0.02 mol) was taken in borocil beaker and irradiated to the microwave radiation for 2-3 minutes [16]. After completion of reaction, resulting mixture treated with ice cold water to give desired hydrazide.

General procedure for the Synthesis of N'-[(1Z)-1-(substituted phenyl) ethylidene] substituted benzohydrazide (3a-3i)
A mixture of aryl hydrazide (2 mmol), substituted acetophenone (2 mmol) and glacial Acetic acid was subjected to the microwave irradiation at 30 microwave power intermittently at 30s intervals for 3 min. On completion of reaction as monitored by TLC the reaction mixture was cooled and treated with chilled water the precipitate thus obtained was filtered washed with water and recrystalized from ethanol [17] .

General procedure for the Synthesis of 1-(2-methyl-2, 5-(substituted) diphenyl-1, 3, 4-oxadiazol-3(2H)-yl) ethanone(4a-4i)
Silica gel (1g) was added to the N'-[(1Z)-1-(substituted phenyl) ethylidene] substituted benzohydrazide (1a-1f, 1.58 mmol) and Ac_2O (6ml) at room temperature. The reaction mixture was thoroughly mixed and adsorbed material was dried in air and irradiated in microwave oven intermittently at 30 s intervals for the time 4 minutes . The completion of the reaction was monitored by TLC using n-hexane: ethyl acetate (6:4) as mobile phase. The reaction mixture was cooled and the product was extracted with methanol. Dilution of methanol solution with ice cold water gave the crude product which was filtered, washed with water and recrystallized from methanol to give 4a-4i.

Spectral data of representative compounds:
2, 4-dichlorobenzohydrazide (2c)
IR (KBr): υ_{max}=3305(-NH), 3261.04, 3212.83(-NH), 3031.55 (Ar-H), 1678.73 (>C=O), 1623.78(Ar-C=C-), 794.53(C-Cl) cm^{-1}.
^{1}HNMR (300MHz, $CDCl_3$):*δ*=4.1(s, 2H, -NH_2), 7.2-7.6(m, 3H, Ar-H), 9.5 (s, 1H, -NH)ppm.
^{13}CNMR (75MHz, $CDCl_3$):*δ* = 128.08, 130.15, 133.12, 134.82, 137.88, 138.50, 163.01(>C=O).

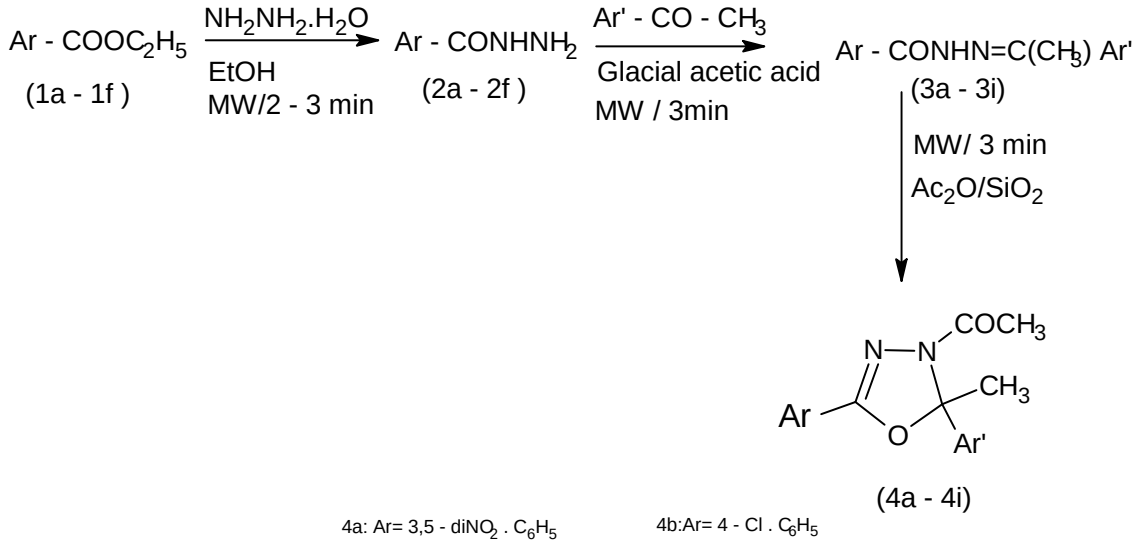
***N*'-[(1*Z*)-1-(4-aminophenyl) ethylidene]-2, 4-dichlorobenzohydrazide (3c)**
IR(KBr): υ_{max}=3345.89(-NH), 3232.11, 3212.83(-NH_2), 2998.77(Ar-H), 2815.56(C-H),1643.05 (>C=O), 1587.13(Ar-C=C-),1511.92(-C=N-),829.24 (C-Cl)cm^{-1}.
^{1}HNMR (300MHz, DMSO): δ =2.1(s, 3H, -CH_3), 5.0(s, 2H, -NH_2), 6.4-7.6(m, 7H, Ar-H), 10.6 (s, 1H, -NH) ppm.
^{13}CNMR (75MHz, DMSO): δ=14.14, 118.50, 131.15, 131.20, 131.44, 131.94, 132.89, 133.45, 134.38, 135.12, 141.50, 149.17, 162.50(>C=O).

***N*-{4-[3-acetyl-5-(2, 4-dichlorophenyl)-2-methyl-2, 3-dihydro-1, 3, 4-oxadiazol-2-yl]phenyl} acetamide (4c)**
IR(KBr):υ_{max}=3129.90(-NH),3000(Ar-H),2977.55(C-H),1689.22(>C=O),1643.10(>C=O),1583.27(Ar-C=C-), 1525.42(-C=N-), 1367.28(C-O-C), 798.39 (C-Cl) cm^{-1}.
^{1}HNMR (300MHz, DMSO): δ= 1.9(s, 3H,-CH_3), 2.0(s, 6H, -CH_3), 7.3-7.8(m, 7H, Ar-H), 10.0(s, 1H, -NH)ppm.
^{13}CNMR(75MHz,DMSO):δ=22.60, 22.72, 24.46, 100.62, 118.58, 127.59, 127.77, 127.86, 128.39, 129.53, 133.48, 135.28, 136.20, 141.10,154.99, 168.90(>C =O), 168.99(>C=O).

1-[5-(2, 4-dichlorophenyl)-2-methyl-2-phenyl-1, 3, 4-oxadiazol-3(2*H*)-yl]ethanone (4d)
IR (KBr):υ_{max}=3017.696(Ar-H), 2924.092(C-H), 1669.440(>C=O), 1584.815(Ar-C=C-), 1517.016(-C=N-), 1371.781(C-O-C), 759.155(C-Cl) cm^{-1}.
^{1}HNMR (300MHz, $CDCl_3$):δ=1.5(s, 3H,-CH_3), 2.3(s, 3H,-CH_3), 7.2-7.8(m, 8H,-Ar-H)ppm.
^{13}CNMR(75MHz,$CDCl_3$): δ=22.11, 24.21, 99.83, 127.93, 128.44, 129.35, 129.53, 130.04, 130.18, 130.21, 132.42, 132.67, 135.95,137.52,137.54,156.76,169.77ppm.
MS (EI): m/z = 349(M+).

1-[2-(2-hydroxyphenyl)-2-methyl-5-(4-methylphenyl)-1, 3, 4-oxadiazol-3(2*H*)yl] ethanone (4e)
IR (KBr): υ_{max} =3247.696(-OH), 3014.125(Ar-H), 2919.092 cm^{-1},1670.183(> C=O), 1609.986 (Ar-C=C-),1522.962 (-C=N-),1380.077 (-C-O-C-),750(C-Cl) cm^{-1}.
^{1}HNMR (400MHz, $CDCl_3$):δ=1.4(s, 3H,-CH_3), 2.4(s, 6H,-CH_3), 6.8-7.7(m, 8H, Ar-H), 12.7(s,1H , -OH)ppm.
^{13}CNMR(100MHz,$CDCl_3$): δ=21.58, 22.85, 24.12, 100.60, 118.23, 118.61, 118.99, 127.33,127.64, 129.55, 129.81, 131.59, 132.82,143.01,155.12,168.92(>C=O) ppm.
MS (EI): m/z = 310(M+).

Scheme



4a: Ar= 3,5 - diNO_2 . C_6H_5
Ar'= 4 -CH_3CONH . C_6H_5

4b:Ar= 4 - Cl . C_6H_5
Ar'=4 - CH_3CONH . C_6H_5

4c: Ar=2,4 - diCl . C_6H_5
Ar'=4 - CH_3CONH . C_6H_5

4d:Ar=2,4 - diCl . C_6H_5
Ar'=C_6H_5

4e:Ar=4 -CH_3 . C_6H_5
Ar'=2 - OH . C_6H_5

4f:Ar=4 - CH_3 .C_6H_5
Ar'=4 - CH_3CONH . C_6H_5

4g:Ar= 3 - NO_2.C_6H_5
Ar'=4 - CH_3CONH . C_6H_5

4h:Ar=2 - OH . C_6H_5
Ar'= 2 - OH . C_6H_5

4i:Ar=2 - OH . C_6H_5
Ar'=4 - CH_3CONH . C_6H_5

RESULTS AND DISCUSSION

Looking towards the therapeutic applications of the 1, 3, 4–oxadiazole derivatives we have synthesized novel series of 1-(2-methyl-2,5 substituted diphenyl-1, 3, 4-oxadiazol-3(2*H*)-yl)ethanone derivatives **(4a-4i)** by cyclisation of *N* '-[(1*Z*)–1-(substituted phenyl)ethylidene] benzohydrazide derivatives **(3a -3i)** in presence of acetic anhydride on solid silica support under the microwave radiation as presented in the reaction scheme. Synthesis of benzohydrazide derivatives **(3a-3i)** were carried out by condensation reaction of the different aryl hydrazides with substituted acetophenones in presence of glacial acetic acid under the microwave radiation within 3min.All the synthetic steps were carried out using microwave radiation.

Proposed mechanism for the synthesis of oxadiazole **(4a-4i)** involves oxidative cyclization reaction of **(3a -3i)** involving attack of the enolic oxygen of the enol tautomer on the azomethine imine moiety [18] as shown in **fig.1**

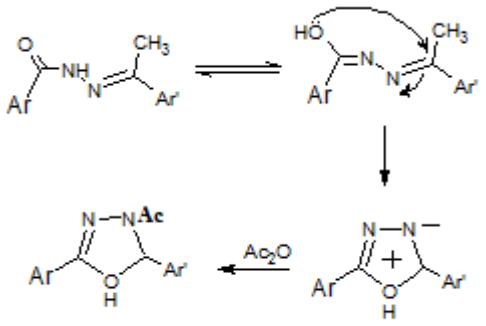


Fig.1 Mechanism for formation of 1, 3, 4-oxadiazole

Structures of all synthesized derivatives were confirmed by the IR, ^{1}HNMR, ^{13}CNMR and Mass spectral data. IR spectra of N'-[(1Z)-1-(substituted phenyl) ethylidene]substituted benzohydrazide **(3a-3i)** shows presence of Characteristic N-acyl hydrazone -NH stretch at 3345.89 cm^{-1} and hydrazinamide carbonyl stretch at 1643.05 cm^{-1}

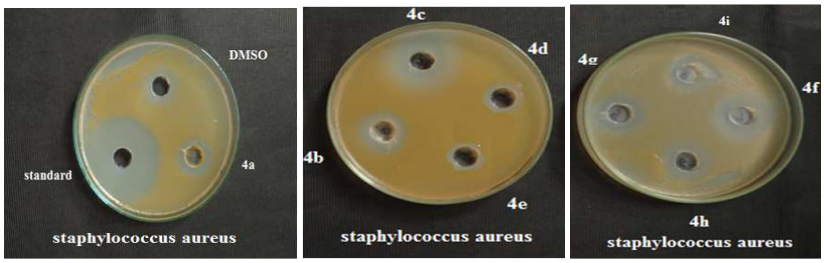
which is present at lower wave number with respect to the starting aryl hydrazide (1678.73 cm^{-1}).In ^{1}HNMR spectra of **(3a-3i),** presence of hydrazinamide -NH at δ 10.6 ppm. Multiplets of aromatic protons present at δ 6.4-7.4 ppm.

Formation of compounds 1-(2-methyl-2, 5 substituted diphenyl-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone derivatives **(4a–4i)** was evident from IR spectrum by replacement of hydrazinamide carbonyl stretch by an acetinamide carbonyl stretch at 1689.22-1670 cm^{-1}. In addition to that new absorption band present at 1367 cm^{-1} corresponds to the oxadiazole ring C-O-C stretch. In ^{1}HNMR spectra of compounds **(4a–4i)** there is a presence of singlet at δ 2.07-2.4 ppm due to acetinamide $–CH_3$ group, another singlet present at δ 1.4-1.9 ppm is due to the $–CH_3$ group attached to oxadiazole ring. In addition to that multiplets of aromatic proton present at δ 7.3-7.8 ppm.^{13}CNMR spectra of the synthesized compounds also shows respective signals as per structures of the compounds.

Synthesized compounds were screened for their antibacterial activity against *E.coli* and *S.aureus* using cup plate method at 100 µg/ml using streptomycin standard. Result of the screening reported in (Table 2).Out of the synthesized compounds 4b, 4c, 4d, 4e, 4f, 4g, 4h, and 4i. shows good activity against *E.coli*. However compounds 4b, 4c, 4f, 4g, 4h, 4i shows good activity against *S.aureus*. Results of the screening indicates that compounds with chloro (4c, 4d), hydroxyl (4e,4h,4i),nitro(4g) and tolyl (4f) groups exhibits maximum inhibitory activity. Remaining compounds shows moderate activity.

Antibacterial activity of 1-(2-methyl-2, 5-substituted diphenyl-1, 3, 4-oxadiazol-3(2*H*)-yl) ethanone (4a- 4i)

Against *Staphylococcus aureus*



Against *Escherichia coli*

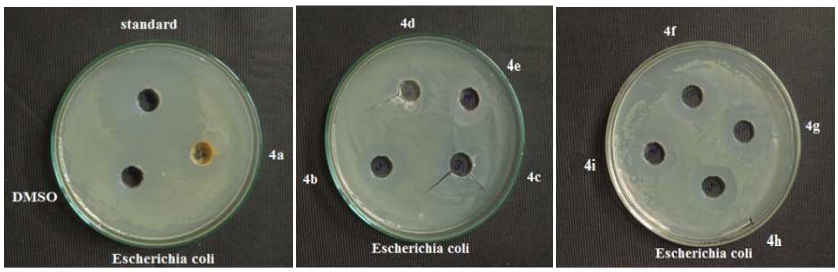


Table 1: Antibacterial activity of synthesized compound (4a – 4i)

Compound No. (100 µg/ml)	Antibacterial activity (mm)	
	E.coli	***S.aureus***
4a	15	15
4b	**17**	**17**
4c	**17**	**18**
4d	**17**	15
4e	**19**	15
4f	**18**	**19**
4g	**20**	**17**
4h	**20**	**18**
4i	**18**	**18**
Streptomycin	**22**	**23**

Table 2: Physical and Elemental analysis of synthesized compound (4a-4i):

Comp. No.	Molecular Formula	MP ^{0}C	Yield %	Elemental analysis (%)		
				C	H	N
4a	$C_{19}H_{17}N_5O_7$	242	76	53.38	3.99	16.37
4b	$C_{19}H_{18}N_3O_3Cl$	260	78	61.36	4.81	11.31
4c	$C_{19}H_{17}N_3O_3Cl_2$	197	76	56.3	4.17	10.35
4d	$C_{17}H_{14}N_2O_2Cl_2$	140	74	58.46	4.05	8.05
4e	$C_{18}H_{18}N_2O_3$	170	75	69.69	5.82	9.01
4f	$C_{20}H_{21}N_3O_3$	180	70	68.38	5.99	11.96
4g	$C_{19}H_{18}N_4O_5$	190	68	59.65	4.72	14.61
4h	$C_{17}H_{16}N_2O_4$	340	69	65.35	5.11	8.95
4i	$C_{19}H_{19}N_3O4$	218	65	64.56	5.36	11.85

CONCLUSION

Novel series of 2, 5-substituted diphenyl- 1, 3, 4-oxadiazole derivatives were prepared in good yields using silica solid support and microwave method. Short reaction time, higher yield and purity are the merits of the current protocol. All synthesized compounds show promising antibacterial potential as compared to that of reference standard streptomycin.

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