IJPSR (2016), Vol. 7, Issue 5 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 December, 2015; received in revised form, 27 January, 2016; accepted, 13 February, 2016; published 01 May, 2016

SOLID SUPPORTED MICROWAVE ASSISTED RAPID SYNTHESIS OF 1, 3, 4 OXADIAZOLES

Bhagyashri Lole, Shubhangi Waghmale and Pravina Piste *

P.G. Department of Chemistry, Yashavantrao Chavan Institute of Science Satara, (Mah.) -415001, India

Key words:

Microwave, Hydrazones, 1, 3, 4 oxadiazoles, antibacterial activity

Correspondence to Author:
Associate Professor,

P.G. Department of Chemistry, Yashavantrao Chavan Institute of Science Satara, Dist.: Satara (Mah.) India-415001.

Email: ppiste321@gmail.com

ABSTRACT: We have carried out solid supported ,solvent free condition, microwave assisted rapid synthesis of 1- (2,5- substituted diphenyl)-1, 3, 4- oxadiazol -3(2H) - yl) ethanone (3a-3k) by cyclization of N'- (substituted phenyl methylidene) substituted benzohydrazide (2a-2k) in the presence of acetic anhydride and silica gel (solid support) for 3-4 minutes by microwave irradiation giving excellent yield in short reaction time are notable advantages of this method. The structure elucidations of all the synthesized compounds have been accomplished by elemental analysis, IR, NMR and Mass spectroscopic method. The synthesized compounds (3a-3k) were screened in vitro for their antibacterial activities against *S. aureus* (gram positive) and *E. coli* (gram negative) by cup plate method . Some of the products of series were found to have quite good activities as compared to the standard drug streptomycin. The introduction of -F, -NO2, -Cl (electron withdrawing) group enhancing antibacterial activity.

INTRODUCTION: The oxadiazole and its derivatives are the important class of heterocyclic compounds and have great importance due to their applications in medicinal chemistry for the drug discovery. [1a, b] The 1,3,4- oxadiazole exhibit wide range of biological activities such as antimicrobial [2], Antibacterial [3], anti-inflammatory [4, 5], anti tubercular [6], anticancer [7a, b], anthelmintic [8], antihypertensive [9]. anti HIV [10, 11] and anticonvulsant[12], etc. Various methods have been reported in literature for synthesis of 1, 3, 4- oxadiazoles [13, 14]. The most of the methods involve cyclization of acid hydrazides by using variety of reagents such as phosphorus oxychloride, carbon disulphide, thionyl chloride, tetrahydrofuran, etc. by adopting conventional and non conventional methods.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(5).2231-35

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (5).2231-35

The reactions on solid support without using solvent by microwave irradiation are recently in wide use for synthesis to create eco-friendly benign atmosphere [15]. So in present work, we have developed rapid and efficient method for synthesis of 1,3,4 oxadiazoles by microwave irradiation using silica gel as solid support.

Here in, we simply report the synthesis of 1, 3, 4 oxadiazole derivatives (3a-3k) from easily available materials such as acid hydrazides and substituted aldehydes by microwave irradiation. The synthesized compounds were screened for antibacterial activity against gram positive and gram negative bacterial strain and compared it with standard drug streptomycin.

MATERIALS AND METHODS:

All the chemicals used were of synthetic grade (S. D. Fine .Chem. Ltd. Mumbai, India). The melting points of the synthesized compounds reported were uncorrected and recorded by open capillary method. The Micro-oven used for the synthesis is of Little Chef MS-192 W. The purity was checked by TLC. The progress of the reaction was

monitored on percolated silica gel 60 F254 plates (Merck) using ethyl acetate: n-hexane (7:3) as an eluent and spot was detected by using iodine vapours. The structure of synthesized oxadiazole derivatives were confirmed by IR, H^1NMR and Mass Spectral analysis. IR spectra were recorded on Perkin-Elmer spectrum in KBr. H^1NMR spectra were recorded on 300MHz NMR spectrophotometer in $CDCl_3$ by using tetra methyl silane as reference standard. Mass spectrum was recorded on GC-MS spectrophotometer and elemental analysis (C, H, N) was carried out on carlo - Erba elemental analyser.

Experimental:

Synthesis of N'-(substituted phenylmethylidene) substituted benzohydrazide (2a-2k):-

A mixture of acid hydrazide (0.01 mol) and substituted aldehyde (0.01 mol) in presence of catalytic amount of glacial acetic acid was irradiated in microwave oven for 3 min. The resulting crude product was poured on ice. The product formed was filtered, washed with water, dried and recrystalized from ethanol (Table -I).

Synthesis of 1-(2,5-substituted diphenyl)-1, 3, 4-oxadiazol-3(2H)-yl) ethanone(3a-3k):-

Silica gel (3gm) was added to the mixture of hydrazone (0.01mol) and acetic anhydride (2ml) at room temperature. The reaction mixture was thoroughly mixed; the adsorbed material was dried in air and irradiated in microwave oven (192 W) at the intervals of 30s for four min. The reaction mixture was cooled and product was extracted with methanol and poured in ice cold water gave the crude product which was filtered washed with water and recrystalized from methanol to give corresponding 1,3,4 Oxadiazoles.

Scheme:

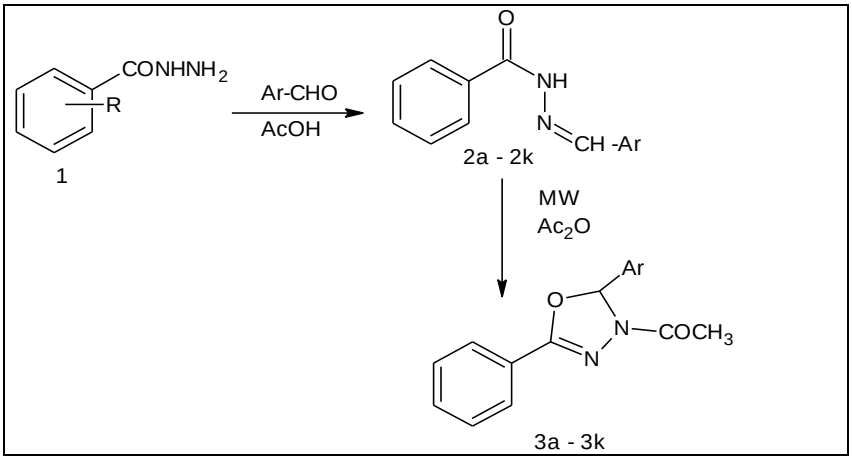

TABLE 1: PHYSICAL AND ELEMENTAL ANALYSIS OF SYNTHESIZED COMPOUNDS (2a-3k):

Entry	R	Ar	Yield %	MP °C	Elemental Analysis Calc.(found) %		
					C	H	N
2a	m-NO_2	p-ClC_6H_5	85	160	55.44	3.30	13.86
2b	-3,5 $(NO_2)_2$	o-OHC_6H_5	76	238	50.90	3.03	16.96
2c	2,4 di Cl	p-ClC_6H_5	81	198	51.37	2.75	8.56
2d	p-OH	p-FC_6H_5	78	238	65.36	4.28	10.89
2e	p-OH	p-ClC_6H_5	80	254	61.31	4.01	10.21
2f	p-OH	o-OH C_6H_5	82	282	65.62	4.68	10.93
2g	p-OH	p-OH C_6H_5	92	230	65.62	4.68	10.93
2h	p-OH	m-NO_2 C_6H_5	70	244	58.94	3.85	14.73
2i	p-OH	p-OCH_3 C_6H_5	75	196	66.66	5.18	10.37
2j	-3,5 $(NO_2)_2$	p-FC_6H_5	77	234	50.75	2.71	16.91
2k	-3,5 $(NO_2)_2$	p-OCH_3 C_6H_5	72	232	52.32	3.48	16.27
3a	m-NO_2	p-ClC_6H_5	64	222	55.65	3.47	12.17
3b	-3,5 $(NO_2)_2$	o-OHC_6H_5	62	142	50.79	3.17	14.81
3c	2,4-$(Cl)_2$	p-ClC_6H_5	75	218	52.03	2.98	7.58
3d	p-OH	p-FC_6H_5	72	184	64.21	4.34	9.36

3e	p-OH	p-ClC_6H_5	68	230	60.75	4.11	8.86
3f	p-OH	o-OH C_6H_5	60	246	64.42	4.69	9.39
3g	p-OH	p-OH C_6H_5	63	98	64.42	4.69	9.39
3h	p-OH	m-NO_2 C_6H_5	70	198	58.71	3.97	12.84
3i	p-OH	p-OCH_3 C_6H_5	65	218	65.38	5.12	8.97
3j	-3,5 $(NO_2)_2$	p-FC_6H_5	60	172	51.47	2.94	15
3k	-3,5 $(NO_2)_2$	p-OCH_3 C_6H_5	58	218	56.98	3.91	15.64

TABLE 2: SPECTRAL DATA OF SYNTHESIZED COMPOUNDS (3a-3k):

Comp.No.	IR(KBr) ,√ cm^{-1}	H^1NMR ($CDCl_3$),δ in ppm	Mass
3a	3082(Ar-CH), 1660 (>C=O), 1625 (>C=N, str.), 1442 (C-O-C).	7.4-8 (4H, m, Ar), 7.0-7.46 (4H, m, Ar), 8.56 (s ,1H ,-CH oxadiazole), 2.01 (s, 3H, -$COCH_3$).	--
3b	3208 (-OH str), 3120 (Ar-CH), 1640 (>C=O) , 1635(>C=N- str.), 1430 (C-O-C).	7.4-8 (3H, m Ar) 9.5(1H, s, -OH) 6.62-7.0 (4H, m Ar), 8.6 (s, 1H,-CH oxadiazole), 2.04 (s, 3H, -$COCH_3$).	--
3c	3057(Ar-CH), 1657 (>C=O), 1582 (>C=N-str.), 1492 (C-O-C).	7.0-7.46 (3H, m, Ar), 7.0-7.46 (4H, m, Ar) 8.52 (s, 1H, -CH oxadiazole), 1.98 (s, 3H, -$COCH_3$).	369
3d	3250 (-OH str), 3035(Ar-CH), 1627(>C=O), 1554 (>C=N- str.), 1457 (C-O-C).	6.62-7.0(4H, m, Ar), 7.08-7.4 (4H, m, Ar) 8.46 (s, 1H,-CH oxadiazole), 1.96 (s, 3H, -$COCH_3$), 9.5(s,1H, - OH).	299
3e	3250 (-OH str), 3070(Ar-CH), 1660(> C=O), 1590 (>C=N- str.), 1450 (C-O-C).	6.62-7.0(4H, m, Ar), 7.0-7.46 (4H, m, Ar) 8.54 (s, 1H, -CH oxadiazole), 2.02 (s, 3H, -$COCH_3$) 9.5(s,1H,- OH).	--
3f	3250 (-OH str), 3050(Ar-CH), 1630 (>C=O), 1640 (>C=N- str.), 1445 (C-O-C).	6.62-7.0(8H, m, Ar), 8.58 (s, 1H,-CH oxadiazole), 1.99 (s, 3H, -$COCH_3$) 9.5(s, 1H, -OH).	--
3g	3250(-OH str), 3050(Ar-CH), 1630(>C=O), 1640(>C=N- str.), 1445(C-O-C).	7.4-8 (4H, m, Ar), 6.62-7.0(4H, m, Ar), 8.58 (s, 1H, -CH oxadiazole), 2.02 (s, 3H, -$COCH_3$) 9.5(s, 1H,- OH).	--
3h	3250 (-OH str), 3120(Ar-CH), 1630(>C=O), 1580 (>C=N- str.), 1460 (C-O-C).	6.62-7.0(4H, m, Ar) 7.4-8 (4H, m, Ar), 8.62 (s, 1H -CH oxadiazole), 2.04 (s, 3H,- $COCH_3$) 9.5(s,1H, -OH).	--
3i	3250 (-OH str), 3080(Ar-CH), 1650(> C=O), 1645 (>C=N- str.), 1438 (C-O-C).	6.62-7.0(4H, m, Ar), 6.72-7.1(4H, m, Ar) 8.58 (s, 1H ,-CH oxadiazole), 2.1 (s, 3H, -$COCH_3$) 3.38 (s, 3H, -OCH_3), 9.5 (s,1H ,-OH).	--
3j	3035(Ar-CH), 1627 (>C=O), 1554 (>C=N-str.), 1457 (C-O-C).	7.4-8 (3H, m, Ar), 7.08-7.4 (4H, m, Ar), 8.52(s, 1H,-CH oxadiazole), 1.9 (s, 3H, -$COCH_3$).	--
3k	3080(Ar-CH), 1650 (>C=O), 1645(>C=N-str.) , 1438 (C-O-C).	7.4-8 (3H, m, Ar), 6.72-7.1(4H, m, Ar), 8.62 (s, 1H,- CH oxadiazole), 2.1 (s, 3H,- $COCH_3$), 3.38 (s, 3H,- OCH_3).	--

RESULTS AND DISCUSSION: Several methods are used for synthesis of oxadiazole derivatives but some of these methods have disadvantages such as hazardous reagent, catalyst, use of toxic chemicals, longer reaction time, lower yield etc. In the present work, we have developed the solvent free condition, microwave assisted methodology for synthesis of the oxadiazole derivatives emphasing greener approach. We have synthesized series of hydrazones and cyclization with acetic anhydride and silica gel as a solid support under microwave irradiation for 3-4 mins. targeted 1,3,4 oxadiazole derivatives (3a-3k).

The reaction was completed efficiently within few minutes and product obtained was in high yield with purity. The spectral data for synthesized compounds is shown in **Table 2**. The structures of the synthesized compounds were confirmed by IR, H^1NMR, Mass spectra. In H^1 NMR spectra of compounds (3a-3k) showing singlet at 2.0 ppm due to –$COCH_3$ and singlet at 8.5 ppm due to –CH of oxadiazole which is absent in compounds 2a-2k. IR spectra also supports above facts. It shows presence of absorption band at 1457 cm-1 indicates formation of oxadiazole ring in compounds (3a-3k) due to C-O-C which is absent in compounds 2a-2k. The compounds 3a, 3c and 3e shows M+ and M+2 peaks in 1:3 ratio in mass spectra which exhibiting presence of halogen i.e. chlorine.

All synthesized 1, 3,4 oxadiazole derivatives were screened for antibacterial activity. They are tested by using bacterial strains as Staphylococcus aureus (gram positive) and Escherichia coli (gram negative) .Streptomycin was used as standard reference. Antibacterial activity of synthesized compounds are shown in **Table 2**. The compounds 3b, 3c, 3j, 3k shows very good antibacterial activity as compared to standard drug streptomycin. It is observed that introduction of -F, -NO_2, -Cl (electron withdrawing) group enhancing

antibacterial activity. The remaining compounds show moderate antibacterial activity.

Antibacterial activity:

Antibacterial activities of synthesized 1, 3, 4 oxadiazole derivatives were investigated by cup plate method. The oxadiazole samples were tested in vitro against two bacterial strains - Escherichia coli (gram negative) and Staphylococcus aureus (gram positive) by measuring zone of inhibition at concentration of 10 mg/ml. The commercially available streptomycin was used as standard reference.

TABLE 3: ANTIBACTERIAL ACTIVITIES OF SYNTHESIZED OXADIAZOLE DERIVATIVES (3A-3K)

Compound	*E. Coli* (in mm)	*S.aureus*(in mm)
3a	9	9
3b	10	9
3c	12	8
3d	8	10
3e	9	9
3f	02	05
3g	8	9
3h	8	9
3i	9	10
3j	10	11
3k	12	12
Standard(10mg/ml) **(streptomycin)**	15	13

The compounds 3c and 3k shows good activity against *E.coli* while 3d, 3i, 3j and 3k compounds shows good activity against *S.aureus* and rest of them are showing moderate activity. The compounds 3c, 3k, 3d, 3i and 3j shows very good antibacterial activity as compared to standard drug streptomycin. It is observed that introduction of F, NO_2, Cl (electron withdrawing) group at meta and Para position in phenyl ring of oxadiazole moiety enhances the property.

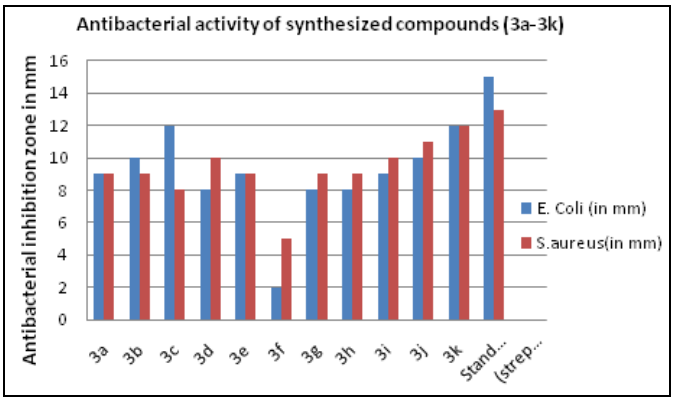

FIG.1: ANTIBACTERIAL ACTIVITY OF SYNTHESIZED COMPOUNDS (3a-3k)

CONCLUSION: We have developed the ecofriendly microwave assisted synthetic method for synthesis of 1, 3, 4 oxadiazole derivatives.
The merits of the protocol as:

1. No need of solvent
2. Short reaction time
3. Solid supported catalyst
4. Atom economy
5. Recovery of catalyst
6. Exhibiting good antibacterial activity

ACKNOWLEDGEMENT: Author thanks to Department of chemistry, Y.C. Institute of Science satara for providing research facility and Shivaji University, Kolhapur for providing spectral analysis.

REFERENCES:

1. a) EI-Nakkady, Hanna SS, Roaiah MM and Ghannam HM: J. Med. Chem. 2012;47 :387-398 b)Taher AT, Georgey HH, El-Subbagh HI: Eur. J. Med. Chem. 2012;47:445-451.
2. Shridhar M , Isloor AM, Peethambar SK, Kun Fun H : Synthesis and biological evaluation of newer analogues of 2,5-disubstituted 1,3,4-oxadiazole containing pyrazole moiety as antimicrobial agents . Arabian journal of Chemistry 2014;7:1185-1191.
3. Morjan RY, Mkadmh AM, Beadham I , Elmanama AA , Mattar MR, Raftery J, Robin G. , Awadallah AM, Gardiner JM : Antibacterial activities of novel nicotinic acid hydrazides and their conversion into N-acetyl-1,3,4-oxadiazoles . Bioorganic and Medicinal Chemistry letters 2014; 24:5796-5800.
4. Kumar B, Raj V, Kumar A and Singh V: Anti-inflammatory activity of 1, 3, 4-Oxadiazole derivatives compound. International Journal of Current Pharmaceutical Research 2012; 4(3):9-14.
5. Ullas P, Revanasiddappa BC and Subrahmanyam EVS: Analgesic and Anti-inflammatory activity of 1,3,4-oxadiazoles Derivatives. International Journal of pharmaceutical, chemical And Biological Sciences 2012; 2(3):202-205.
6. Dewangan D, Pandey A ,Sivakumar T,Rajavel R, Dubey R D: Synthesis of some novel2,5- disubstituted 1,3,4-oxadiazole and its analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activity. Int. J. Chem. Tech. Res. 2010; *2*:1397-1412.
7. a)Singh M , Tandona V: Eur. J. Med. Chem. 2011; 46 :659-669.b) Mavrova A T, Wesselinova D, Vassilev N, Tsenov J A, Eur. J. Med. Chem. 2011; 46:3362-3367.
8. Patel K, Chandran J E, Shah R, Vijaya, J, Sreenivasa G M: Synthesis, characterization and anthelmintic activity (*Perituma posthuma*) of new oxadiazole incorporated with

imidazole and pyrazole. Int. J. Pharm. Bio. Sci. 2010; 1,:1-13.

9. Bankar GR, Nampurath GK , Nayak PG, Bhattcharya S : A possible correlation between the correction of endothelial dysfunction and normalization of high blood pressure levels by 1,3,4-oxadiazole derivative, an L-type Ca^{2+} channel blocker in deoxycorticosterone acetate and N(G)-nitro-l-arginine hypertensive rats. Chem.Biol.Interact.2010; 183:327.
10. Johns BA, Weatherhead JG, Allen SH, Thompson JB, Garvey EP, Foster SA, Jeffrey JL, Miller WH :1,3,4-Oxadiazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 2: SAR of the C5 position. Bioorg . Med. Chem. Lett. 2009; 15, 19 (6): 1807-10.
11. El-Sayed WA, El-Essawy FA, Ali OM, Nasr BS, Abdalla MM, Abdel- Rahman AA: Anti-HIV activity of new substituted 1,3,4-oxadiazole derivatives and their acyclic nucleoside analogues. Z Naturforsch C. 2009; 64 (11-12):773-8.
12. Singh P and Jagra PK: Oxadiazoles: A novel class of anti-convulsant agents. Jangra Der Chemica Sinica 2010; 1(3):118-123.
13. Ramazani A, Zeinali NF, Abdian B, Rouhani M : One-pot, Three-component Synthesis of Fully Substituted 1,3,4-Oxadiazole Derivatives from(N Isocyanoimino) triphenylphosphorane, Aromatic Carboxylic acids and (1R)-(-)-Campherchinon. Bull. Korean Chem. Soc.2012; 33:453-458.
14. Ramazani A, Zeinali Nasrabadi F, Karimi Z, Rouhani M: Preparation of Fully Substituted 1,3,4-Oxadiazole Derivatives from N-Isocyanimino triphenyl phosphorane, (E)-Cinnamic Acids, Chloroacetone and Primary Amines. Bull.Korean Chem .Soc. 2011; 32:2700-2704.
15. Kategaonkar AH, Sadaphal SA, Shelke KA, Shingate BB, Shingare MS: Microwave assisted synthesis of pyrimido[4,5_d]pyrimidine derivatives in dry media. Ukrainica Bioorganica Acta 2009; 1:3-7.

How to cite this article:
Lole B, Waghmale S and Piste P: Solid Supported microwave assisted rapid Synthesis of 1, 3, 4 Oxadiazoles. Int J Pharm Sci Res 2016; 7(5): 2231-35.doi: 10.13040/IJPSR.0975-8232.7(5).2231-35.