Chemical Methodologies 6(2022) 773-782

Chemical Methodologies

Journal homepage: http://chemmethod.com

Original Research Article

Eco-friendly, Rapid Synthesis of Some 4-Hydroxybenzoic Acid Hydrazide Derivatives

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ARTICLE INFO

Article history
Submitted: 2022-05-07
Revised: 2022-06-15
Accepted: 2022-07-19
Manuscript ID: CHEMM-2207-1572
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Elham Ezzatzadeh

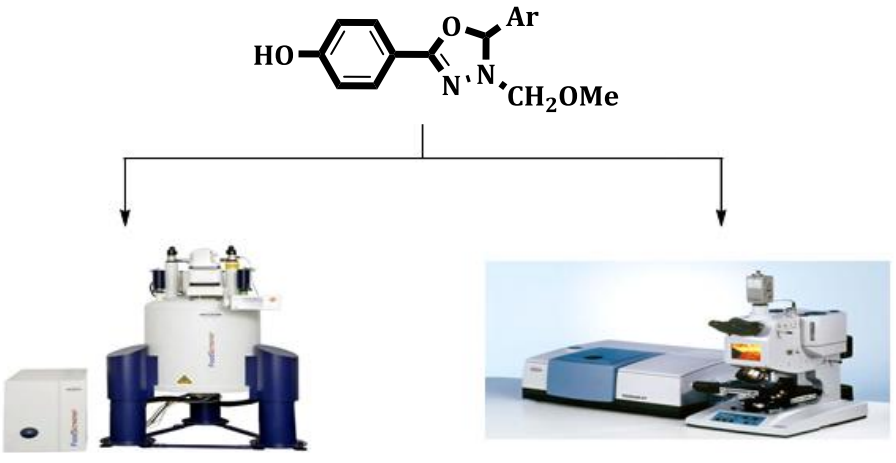
DOI:.10.22034/CHEMM.2022.350693.1572

KEYWORDS
Green chemistry
Eco-friendly synthesis
Schiff bases
1,3,4-Oxadiazole
Microwave synthesis

ABSTRACT

In this study, some azomethine compounds were prepared from 4-hydroxybenzoic acid hydrazide with some primary amine derivatives in different ways from the usual methods. The method used in research is utilizing water as solvent instead of any other organic solvent. In addition, lab-made microwave was used instead of hot plate or reflux method. P-hydroxy ethyl benzoate was treated directly with hydrazine hydrate in microwave oven which gave hydrazide derivative in a very short time; hydrazide derivative (**1**) was reacted with some carbonyl compounds (aldehyde derivatives) to produce of some Schiff base derivatives (compounds **2-14**). None of these azomethine derivatives exceeded 10 minutes in lab-made micro wave and using water as solvent. Compounds (**2-14**) were treated with acetic anhydride in microwave oven to synthesized of some 1,3,4-oxadiazole derivatives (**15-23**). All compounds high yield, short time, low cost in comparison with traditionally methods. The prepared compounds were characterized by melting points, ^{1}H-NMR, and FT-IR.

GRAPHICAL ABSTRACT



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Introduction

Microwave irradiation method is a better than heating method (reflux) and it is also a better method than the ones using organic solvents such as ethanol, methanol, dimethyl formamide, chloroform, acetone, benzene, and dimethylsulfoxide [1].

Traditional methods may cause damages to the health of humans, animals, and the surrounding environment because of the all classical reactions producing fumes that are harmful to health and environment [2]. Green chemistry is one of the most important sciences in environmental field [3]. It can be defined as a branch of science which utilizes a set of principles for the invention, design, development, and implementation of chemical processes that reduce or eliminate the use and generation of hazardous substances [4]. There are many advantages in a chemical synthesis in green chemistry such as high yield, rapid synthesis, reduce the damage of the environmental, declines waste to even waste disposal in the correct way, all chemical wastes should be better disposed without causing any damage to the environment and organisms [5].

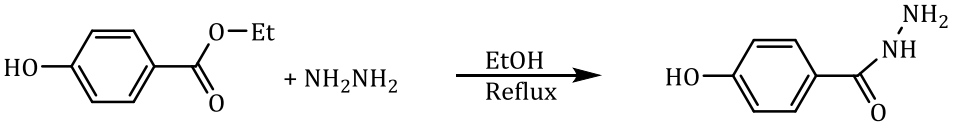
Recently, new methods have been used to prepare some organic compounds such as microwave synthesis for preparing some chemical compounds, Schiff bases, some heterocyclic rings, macro cycle compounds, and some inorganic compounds (complexes). Some researchers were synthesis of some pyrazole, pyridine derivatives under microwave irradiation [6, 7] were synthesized by some derivative of *N*-benzylidene-6-methoxybenzo[d]thiazol-2-amine under microwave method. Some researchers prepared some azomethine derivatives containing fluoro atom under microwave irradiation [8].

Oxadiazole derivatives are important in heterocyclic compounds and their importance is due to their applications in pharmaceutical fields [9, 10]. The well-known methods of preparing oxadiazole derivatives are classic methods, but in this research, the irradiation of microwave was utilized for preparing *N*-acetyl 1,3,4-oxadiazole derivatives.

Materials and Methods

Preparation of p-hydroxybenzohydrazide [11]

A mixture of ethyl 4-hydroxybenzoate (0.1 mol, 0.166 g) with hydrazine hydrate in (25 mL) of ethanol all mixture compounds were reflux under (60-70 °C) for 2 hours, the precipitate was filtered and recrystallized from methanol (yield 65%, m.p=263 (°C lit m.p=262 °C) (Scheme 1).

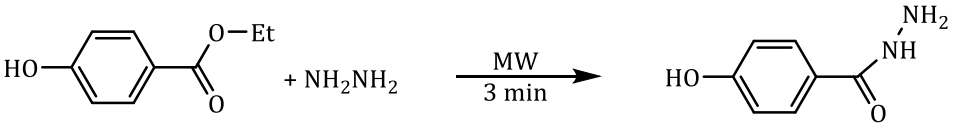


1, 4-hydroxybenzohydrazide

Scheme 1: Preparation of p-hydroxybenzohydrazide

Preparation of 4-hydroxybenzohydrazide under lab-made microwave irradiation

2 mL of hydrazine hydrate with 0.166 g of ethyl p-hydroxybenzoate were placed in a conical flask, and then it was transferred to a lab-made microwave at 180 watts for 3 minutes the product was filtered and collected the precipitate without recrystallization, (yield 93%, m.p=265 °C) (Scheme 2).

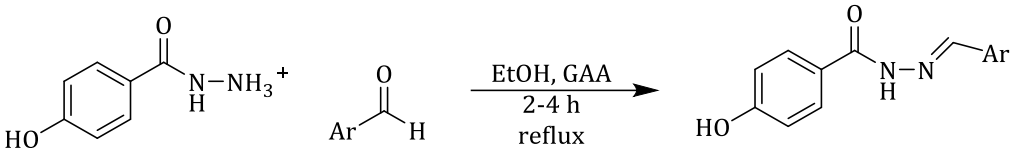


1, 4-hydroxybenzohydrazide

Scheme 2: Preparation 4-hydroxybenzohydrazide under microwave irradiation

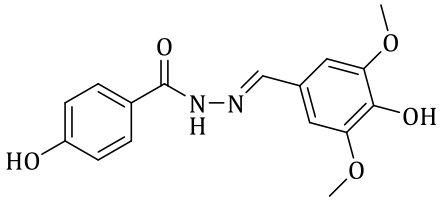
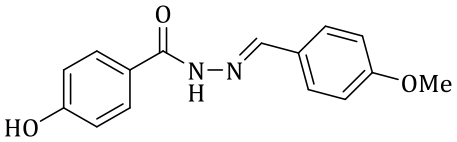
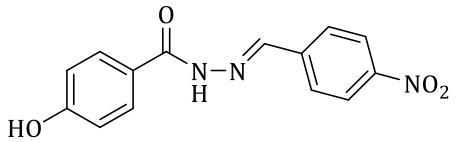
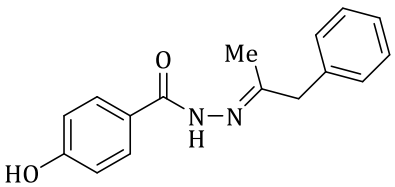
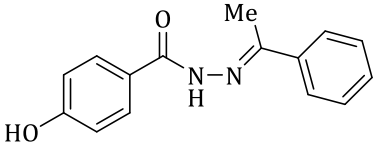
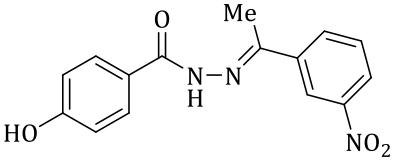
*Preparation of some Schiff base of N′-substituted-4-hydroxybenzohydrazide (**2-14**) [12, 13]*

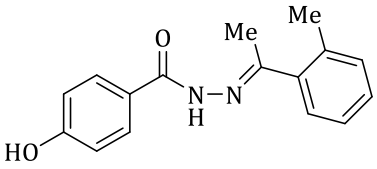
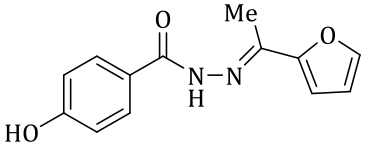
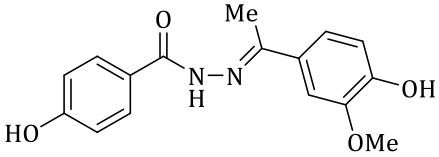
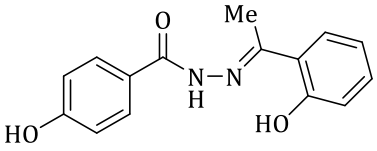
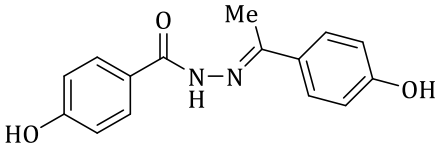
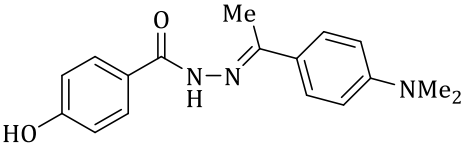
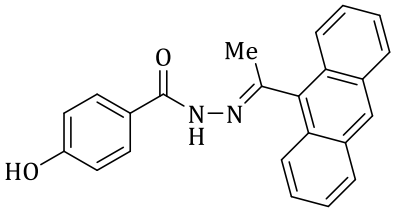
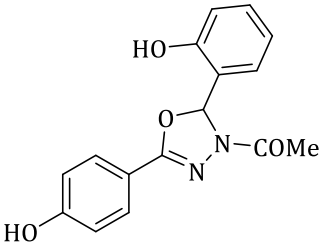
Some derivatives of aromatic aldehyde (0.01 mol) with a 4-hydroxybenzohydrazide were refluxed for 3-7 hours in 50 mL of ethanol the mixture (Scheme 3). The reaction was monitored by thin layer chromatography to determine the end time of the reaction. Then, the product was filtered and washed with cold methanol and recrystallized from a suitable solvent (Table 1).

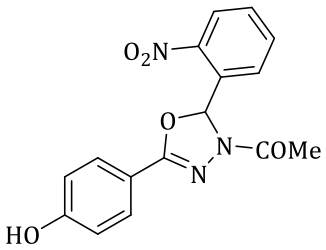
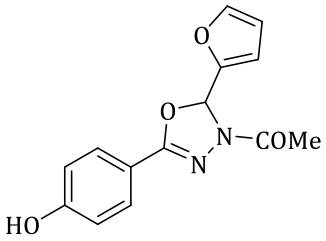
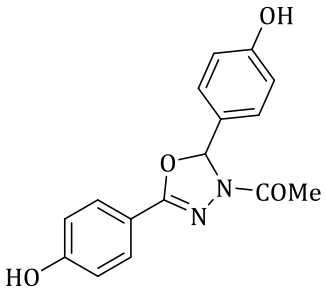
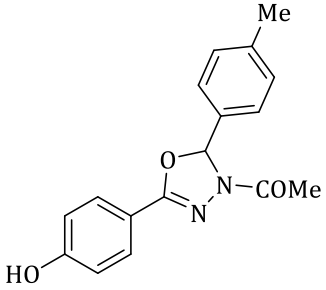
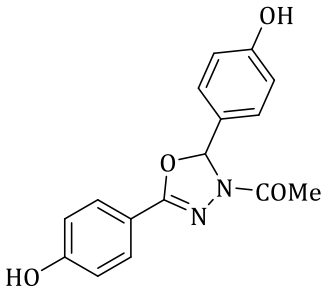


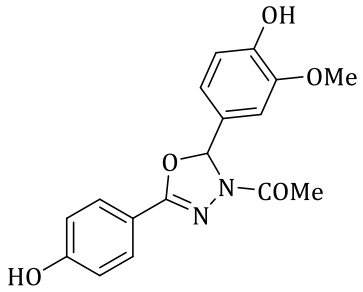
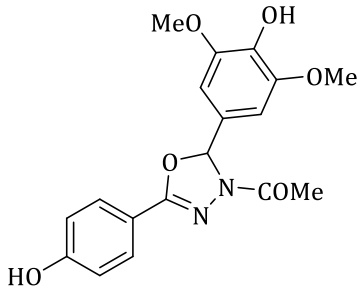
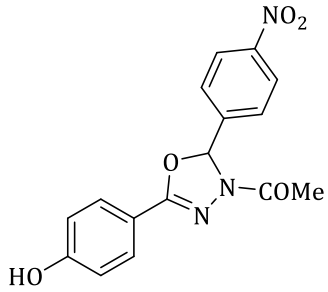
Scheme 3: Synthesis of Schiff bases

Table 1: Nomenclature and physical properties of all synthesized compounds

No.	Nomenclature and Structures	Solvent	time	M.P (°C)	Method
2	4-hydroxy-*N*′-(4-hydroxy-3,5-dimethoxybenzylidene)benzohydrazide 	water	7 min	230-232	MW
		ethanol	2 hrs.	231-233	reflux
3	4-hydroxy-*N*′-(4-methoxybenzylidene)benzohydrazide 	water	10 min	222-224	MW
		methanol	3 hrs.	223-225	reflux
4	4-hydroxy-*N*′-(4-nitrobenzylidene)benzohydrazide 	water	8 min	295-296	MW
		methanol	2 hrs.	294-296	reflux
5	*N*′-benzyl-4-hydroxy-*N*′-methylbenzohydrazide 	water	2 min	264-266	MW
		methanol	2.5 hrs.	263-265	reflux
6	4-hydroxy-*N*′-(4-methylbenzylidene)benzohydrazide 	Water	7 min	260-262	MW
		ethanol	3 hrs.	260-262	reflux
7	4-hydroxy-*N*′-(3-nitrobenzylidene)benzohydrazide 	water	5 min	295-297	MW
		ethanol	3 hrs.	294-296	Reflux
8	4-hydroxy-*N*′-(2-methylbenzylidene)benzohydrazide	water	6 min	220-222	

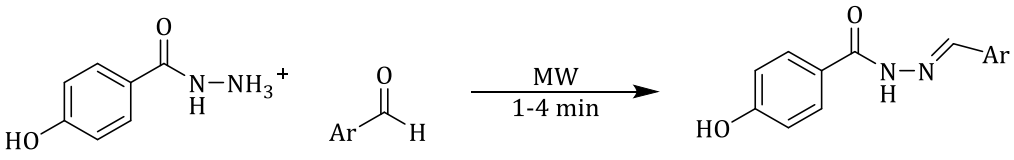
					MW
		methanol	3 hrs.	221-223	reflux
9	*N*′-(furan-2-ylmethylene)-4-hydroxybenzohydrazide	water	12 min	245-247	MW
		free	4 hrs.	244-246	reflux
10	4-hydroxy-*N*′-(4-hydroxy-3-methoxybenzylidene)benzohydrazide	Water	5 min	220-221	MW
		ethanol	4 hrs.	220-222	reflux
11	4-hydroxy-*N*′-(2-hydroxybenzylidene)benzohydrazide	water	7 min	255-258	MW
		ethanol	3.5 hrs.	255-257	reflux
12	4-hydroxy-*N*′-(4-hydroxybenzylidene)benzohydrazide	water	6 min	261-263	MW
		ethanol	3 hrs.	261-263	reflux
13	*N*′-(4-(dimethylamino)benzylidene)-4-hydroxybenzohydrazide	water	6 min	232-234	MW
		ethanol	3 hrs.	232-235	reflux
14	*N*′-(anthracen-9-ylmethylene)-4-hydroxybenzohydrazide	water	5 min	280-282	MW
		ethanol	4.5 hrs.	281-283	reflux
15	1-(2-(2-hydroxyphenyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone	Acetic anhydride	30 min	121-124	MW
		Acetic anhydride	6 hrs.	121-123	reflux
16	1-(5-(4-hydroxyphenyl)-2-(3-nitrophenyl)-1,3,4-	Acetic	32 min	190-192	MW

	oxadiazol-3(2*H*)-yl)ethanone 	anhydride			
		Acetic anhydride	7 hrs.	191-193	reflux
17	1-(2-(furan-2-yl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone 	Acetic anhydride	40 min	174-176	MW
		Acetic anhydride	8 hrs.	174-176	reflux
18	1-(5-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone 	Acetic anhydride	40 min	158-160	MW
		Acetic anhydride	8 hrs.	157-159	reflux
19	1-(5-(4-hydroxyphenyl)-2-p-tolyl-1,3,4-oxadiazol-3(2*H*)-yl)ethanone 	Acetic anhydride	39 min	95-97	MW
		Acetic anhydride	8.5 hrs.	97-99	reflux
20	1-(2,5-bis(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone 	Acetic anhydride	37 min	181-183	MW
		Acetic anhydride	7.5 hrs.	181-183	reflux
21	1-(2-(4-hydroxy-3-methoxyphenyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone	Acetic anhydride	21 min	187-189	microwave
		Acetic anhydride	8 hrs.	188-189	reflux

					
22	1-(2-(4-hydroxy-3,5-dimethoxyphenyl)-5-(4-hydroxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone 	Acetic anhydride	32 min	220-221	Microwave
		Acetic anhydride	7 hrs.	219-221	reflux
23	1-(5-(4-hydroxyphenyl)-2-(4-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone 	Acetic anhydride	29 min	106-109	Microwave
		Acetic anhydride	7.5 hrs.	105-107	reflux

*Preparation of some Schiff base of N'-substituted-4-hydroxybenzohydrazide under lab-made microwave (**2-14**) [14]*

A mixture of hydrazide with some aromatic aldehyde were placed in a container with (3 mL) of ethanol the reaction mixture was placed in a lab-made microwave (180-360) watts at 3-8 minutes according to the type of aromatic aldehyde (Scheme 4). Then, the product was washed with cold water, filtered, and collected (Table 1).



2-14

Scheme 4: Synthesis of Schiff base under microwave irradiation

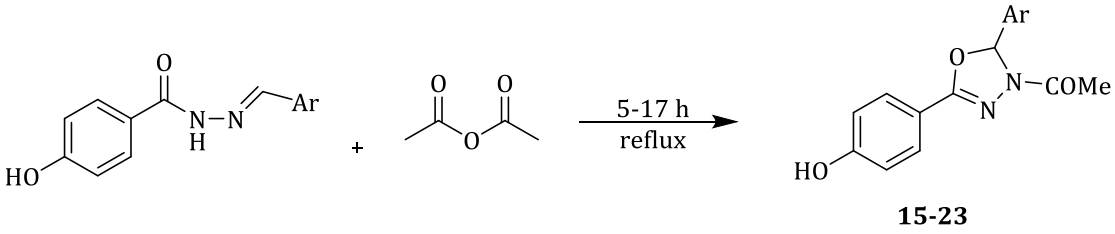
*Synthesis of 1-(5-(4-hydroxyphenyl)-2-Aryl-1,3,4-oxadiazol-3(2H)-yl)ethenone (**15-23**)*

Acetic anhydride (50 mL) as solvent and reactant was reacted with some Schiff bases (**2-10**) in a round flask (150 mL) the mixture reaction was refluxed for 5-17 hours, with monitored the reaction by thin layer chromatography (Scheme 5). The precipitate was filtered and recrystallized from a suitable solvent, all physical properties and yields can be reviewed in Table 1.

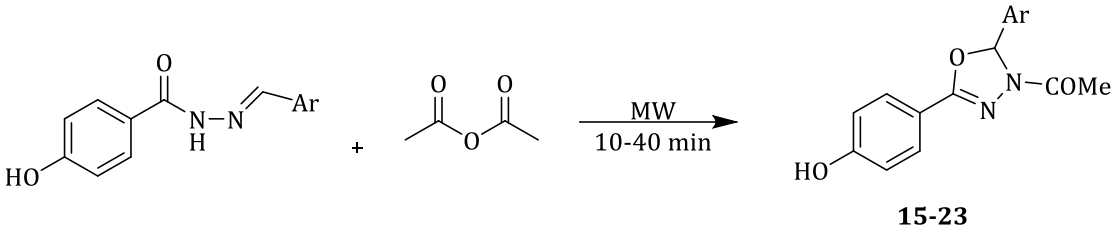
Synthesis of 1-(5-(4-hydroxyphenyl)-2-Aryl-1,3,4-oxadiazol-3(2H)-yl)ethanone(15-23) under lab-made microwave

Under irradiation of lab-made microwave, the mixture reaction of Schiff base with 5 mL of acetic

anhydride in a beaked 25 mL moved to oven and shed radiation for this reaction (10-40) minutes. The reaction mixture was allowed to be cooled and poured onto the ice water, after filtration has been recrystallized from a suitable solvent (Scheme 6). The calculation of yield and melting point are listed in Table 1.



Scheme 5: Synthesis of 1-(5-(4-hydroxyphenyl)-2-Aryl-1,3,4-oxadiazol-3(2H)-yl)ethenone



Scheme 6: Synthesis of 1-(5-(4-hydroxyphenyl)-2-Aryl-1,3,4-oxadiazol-3(2H)-yl)ethanone under microwave irradiation

Results and Discussion

In this research, two methods were used for preparing some derivatives of substituted of p-hydroxy benzoic acid hydrazide, all prepared compounds have been characterized by using melting points, Fourier transform infrared, and ^{1}H-NMR.

Acid hydrazide of hydroxy benzoic acid was prepared under reflux and microwave irradiation. Through these two methods, it was concluded that the microwave method is better than the usual method because it has the advantage of having a shorter time, higher yield, low cost, and less amount of solvent. Infrared spectroscopy results for compound **1** showed new band at 1649 cm^{-1} due to of carbonyl of hydrazide, which was added to that appeared a new band at 3217 and 3321 cm^{-1} for amine of hydrazide.

A series of compounds (**2-14**) were prepared from the reaction of acid hydrazide (**1**) with some derivatives of aromatic aldehyde under room temperature, reflux, and microwave irradiation. It was noted that all of these methods gave similar characterized results, but the difference in time, yield, and solvent. Reflux method revealed prepared compounds with longer time reaction and low yield with comparison with microwave irradiation. Preparation of compounds (**2-14**) under microwave irradiation revealed good results as it proved to be the best method than the usual one especially time, yield, cost, and solvent, all derivative compounds (**2-14**) prepared under lab-made microwave at (**4-8**) minutes with yield between 90-97% without recrystallization and water as solvent, but the time reaction of reflux method with 2-5 hours, yielded (60-75%) with recrystallized from a suitable solvents. The results of infrared spectroscopy showed a new band at 1590-1615 cm^{-1} due to of imine groups and disappearance band at 3217 and 3321 cm^{-1} of primary amine, all data of these compounds is depicted in Table 2, ^{1}H-NMR of compounds (**2-14**) showed peak at 9.92-1.11 ppm for hydroxyl group in phenol and a singlet signal at 8.50-8.70 ppm for CH=N for azomethine group, signal at 11.31-11.94 ppm for NH peak. *N*-acetyl 1,3,4-oxadiazole derivatives can be prepared from Schiff bases of acid hydrazide with acetic anhydride this reaction is

known and characterized by a long reaction time, but in this research, microwave method was used for preparing *N*-acetyl 1,3,4-oxadiazole derivatives (**15-23**) (Table 3).

This method has several advantages. It can be counted with some points, short-time reaction, lower energy consumption, high yield, and high purity for the product. The FT-IR spectroscopy showed a good evidence for prepared of oxadiazole ring, all spectrums of infrared spectroscopy showed a new band at 1704-1755 cm^{-1} for C=O amide, disappeared of azomethine and NH bands at 3230-3383 $cm^{-1,}$ respectively. ^{1}H-NMR of compounds **15-23** reveals disappearance peaks of CH=N and NH at 8.50-8.70, 11.31-11.94 ppm, respectively and new peak at 2.19-2.41 ppm for methyl group. All data for proton NMR of compounds **15-23** are listed in Table 4 and 5.

Table 2: FT-IR of compounds **2-14**

Compounds	OH	C=O	NH	C=N	CH aliph	CH Ar	Others
2	3281	1638	3325	1619	2935	3195	OH (3325)
3	3243	1620	3383	1599	2963	3085	C-O (1219)
4	3150	1655	3338	1604	2931	3081	NO_2 (1338, 1549)
5	3195	1609	3315	1590	2909	3139	-
6	3205	1627	3277	1603	2919	3031	-
7	3208	1644	3305	1601	2970	3091	NO_2 (1349, 1560)
8	3109	1633	3230	1607	2943	3031	-
9	3137	1634	3250	1620	2943	3084	-
10	3270	1636	3270	1601	2929	3075	OH (3506)
11	3135	1638	3319	1615	2972	3080	OH (3531)
12	3194	1606	3272	1588	2958	3049	OH (33080
13	3185	1642	3358	1603	2906	3055	-
14	3110	1639	3204	1606	2990	3039	-

Table 3: FT-IR of compounds **15-23**

Component	OH (cm^{-1})	C=O (Oxadiazole) (cm^{-1})	C=N (Oxadiazole) (cm^{-1})	CH aliph (cm^{-1})	CH Ar (cm^{-1})	Others (cm^{-1})
15	3181	1748	1655	2924	3004	OH (3347)
16	3100	1753	1666	2952	3035	NO_2 (1353,1521)
17	3113	1752	1656	2936	3064	-
18	3102	1753	1662	2969	3036	-
19	3225	1748	1688	2936	3030	-
20	3220	1749	1628	2939	3038	OH (3319)
21	3266	1757	1625	2947	3030	OH (3293)
22	3166	1755	1629	2942	3079	OH (3257)
23	3109	1704	1630	2921	3047	NO_2 (1344,1595)

Table 4: ^{1}H-NMR of Schiff base derivatives

Component	N-H (ppm)	OH (ppm)	CH=N	Others
2	11.50	10.10	8.59	OH (9.09 ppm)
4	11.94	10.18	8.50	-
5	11.31	9.92	-	(-CH_3), (-CH_2) 1.82,4.35
11	11.40	11.11	8.58	(OH) 10.17
14	11.88	9.62	8.70	-

Table 5: ^{1}H-NMR of 1,3,4-oxadiazole derivatives

Component	OH (ppm)	-(CH_3)	H-aromatic	Others
15	9.85	2.27	m (7.19-7.91)	(-OH) s, 9.67
19	8.99	2.29	m (6.95-7.95)	(-CH_3) s, 2.39
20	9.92	2.19	m (7.43-7.99)	(-OH) s, 9.54
22	9.92	2.25	m (7.17-7.47)	(-OCH_3), s 1.88
23	10.15	2.41	m (8.03-8.44)	-

Conclusion

All synthesized compounds in this research were prepared by two methods traditional and non-classical methods. The non-classical method means the preparation of compounds under lab-made microwave. The results indicate the advantage of using irradiation microwave by comparing reflux method for the following reasons:

Microwave irradiation is featured, short time, small amount of solvent, high yield, high purity, and eco-friendly. For preparing Schiff bases in this research, water was used as solvent instead of ethanol or methanol, the use of water in this method is a good point because it is cheap, safe for the environment, and short time needed for doing the reaction.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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HOW TO CITE THIS ARTICLE

Huda H. Saeed, Ismaeel Y. Majeed. Eco-friendly, Rapid Synthesis of Some 4-Hydroxybenzoic Acid Hydrazide Derivatives. *Chem. Methodol.*, 2022, 6(10) 773-782

https://doi.org/10.22034/CHEMM.2022.350693.1572

URL: http://www.chemmethod.com/article_153728.html