

A FACILE MICROWAVE ASSISTED SYNTHESIS AND SPECTRAL ANALYSIS OF 2-FURYL-5-SUBSTITUTED-1,3,4-OXADIAZOLES

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Article Received on: 30/09/13 Revised on: 31/10/13 Approved for publication: 17/11/13

DOI: 10.7897/2230-8407.041115

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ABSTRACT

An efficient synthesis for the preparation of some 2-furyl-5-substituted-1,3,4-oxadiazoles by using both conventional and microwave method has been devised. The obtained results revealed that, microwave assisted technique is efficient, eco-friendly and in-expensive method which not only gives higher yield but also reduces the reaction time significantly. The resulting compounds were characterized by IR, ¹H-NMR and Mass spectral analysis.

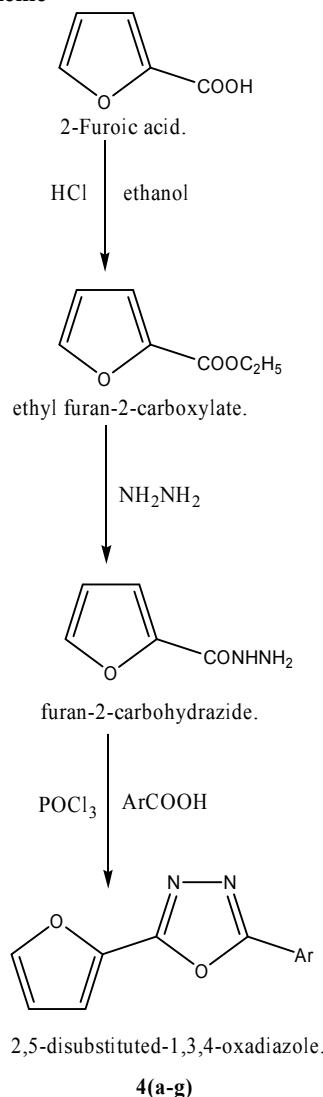
Keywords: Oxadiazoles, Microwave assisted synthesis, Spectral analysis

INTRODUCTION

Synthetic organic chemists explore new methods for chemical transformation. In recent years a lot of work has been carried out to use microwave irradiation as an alternative to conventional heating which provide higher yield and cleaner product. 1,3,4-oxadiazole belongs to an important class of heterocyclic compounds possessing wide spectrum of pharmacological activities such as muscle relaxant, anti-mitotic, antibacterial, anti-inflammatory, anticonvulsant, CNS stimulant, antihypertensive, antimicrobial, insecticidal, anticancer, anti tuberculostrict, antiviral, anti parkinsonian, anti proliferative, anti protozoal, analgesic and antihistaminic activities. Keeping the above in view, 2-furyl-5(substituted)-1,3,4-oxadiazoles has been synthesized using microwave irradiation and conventional methods. The IR, ¹H-NMR and Mass spectra of the synthesized compounds are investigated and discussed in relation to their molecular structures.¹⁻¹⁰

MATERIALS AND METHODS

All the chemicals used in the reaction were of AR grade. Sigma Aldrich make were used in all the reactions. Melting point was determined by open capillary method using the 'Tempo' make melting point apparatus and are corrected. The purity and homogeneity of the compounds as well as completion of reaction times was checked by thin layer chromatography (TLC) using Silica gel-G as adsorbent and solvent system used is benzene : chloroform : methanol (5:4:1). The spots were visualized by iodine vapors and visualized with U.V. light. All the compounds were purified by preparative TLC/Column chromatography. The IR spectra of all the compounds were recorded in FT-IR (Model: Shimadzu IR Affinity-1) using KBr pellets in the region of 4000-500 cm⁻¹. The ¹H NMR spectra were recorded in Bruker Avaze III at a frequency of 400 MHz and the Mass spectra were recorded on Varian 1200 L Single Quadrupole.

Synthetic Scheme

General Procedure for the Preparation of 1,3,4-Oxadiazole (4.a to 4.g)¹¹⁻¹⁵

Conventional Method**Preparation of Furan-2-carboxylic acid ester**

In a 500 ml round bottom flask, a mixture of furoic acid (11.2 g, 0.1 mol), 60 ml of ethanol and 1.4 ml of conc. H₂SO₄ were refluxed for 10 hours on a steam bath. The solution was cooled and poured slowly with stirring on to 200 g of crushed ice; Added sufficient ammonia solution to render the resulting solution alkaline. Generally, some ester separates as oil but most of it remains dissolved in the alkaline solution. The solution was extracted five times with 25 ml ether the combined ether extract was dried with anhydrous MgSO₄. Ether was removed by evaporation on a water bath and the residue was collected.

Preparation of furan-2-carboxylic acid hydrazide

A mixture of ester and hydrazine hydrate in 1:1 portion and ethanol (30 ml) were taken in a round bottom flask and refluxed for 4-6 hours. Excess of ethanol was removed by distillation. On cooling the product (acid hydrazide) separates out. It was filtered and collected. Re crystallization was carried out with methanol.

Preparation of 2-furyl-5-aryl-1,3,4-oxadiazole

A mixture of acid hydrazide (1.26 g, 0.01 mol) and various aromatic acid (0.01 mol) in phosphorous oxychloride (5 ml) were refluxed for 5-6 hours. The contents were cooled and poured into crushed ice. It was neutralized with sodium bicarbonate solution and the resulting solid was filtered, dried and re crystallized from methanol.¹⁶⁻¹⁸

Microwave method**Preparation of furan-2-carboxylic acid ethyl ester**

In a double necked flask, a mixture of 11.2 g furoic acid and 60 ml ethanol were refluxed by microwave irradiation at 360W for 12 minutes. The reaction is catalyzed using 1 ml HCl.

Preparation of 2-furoic acid hydrazide

A mixture of ethyl-2-furoate (2 g) and hydrazine hydrate (6.9 ml) were directly irradiated under microwave without any solvent for 60-100 sec. at 360W. The yield of the hydrazide is 79-90 %.

Preparation of 2-furyl-5(substituted)-1,3,4-oxadiazole derivatives

A mixture of furoic acid hydrazide (0.01 mole), aromatic acid (0.01 mole) and phosphorous oxychloride were taken in a double necked round bottom flask. The reaction mixture is irradiated for 6 minutes at 210 watts. The reaction mixture is cooled and poured into crushed ice. It was then neutralized with sodium bicarbonate and the resulting solid was filtered, dried and re crystallized with methanol.¹⁹⁻²³

RESULTS AND DISCUSSION

The oxadiazoles were prepared using the proposed synthetic scheme by both conventional and microwave irradiation method. The reaction yield, melting point, R_f value and other physical data of the synthesized analogues are given in the table.

Physical property data of synthesized oxadiazoles (4.a to 4.g)

Compound	Derivatives	Mol. Formula	M.P. (°C)	R _f values	Conventional method		Microwave method	
					Yield	Time (h)	Yield	Time (minutes)
4.a)	p-chlorobenzoic acid.	C ₁₂ H ₇ N ₂ O ₂ Cl	111-102	0.56	68.2 %	5	82.7 %	10
4.b)	p-nitrobenzoic acid.	C ₁₂ H ₇ N ₃ O ₄	230-231	0.62	62.3 %	4	72.4 %	7
4.c)	3,5-dinitrobenzoic acid.	C ₁₂ H ₆ N ₄ O ₆	147-148	0.69	68.8 %	5	74.5 %	8
4.d)	Benzoic acid	C ₁₂ H ₈ N ₂ O ₂	95-96	0.52	60.1 %	4.5	77.6 %	10
4.e)	o-aminobenzoic acid	C ₁₂ H ₉ N ₃ O ₂	107-108	0.49	74.1 %	4	75.2 %	7
4.f)	p-hydroxybenzoic acid.	C ₁₂ H ₈ N ₂ O ₃	121-122	0.55	72.2 %	4.5	92.1 %	10
4.g)	Salicylic acid.	C ₁₂ H ₈ N ₂ O ₃	120-121	0.53	60.6 %	5	82.3 %	9

Characterization

Formation of Oxadiazoles (4.a to 4.g) was confirmed by IR, ¹H NMR and Mass spectral data. The characterization data of the synthesized compounds has been given as below:-

4.a) 2-furyl-5-(p-chlorophenyl)-1,3,4-oxadiazole

IR (KBr) (cm⁻¹): 3001.54 (C-H), 1620.27 (C=N), 1481.33 (C=C), 1095 (C-O), 840.96 (di substitution at para position), 740.67 (C-Cl). H¹NMR (DMSO-d₆, 400 MHz), δ (ppm): 8.098-7.694 (m, 4H, CH), 7.692-7.690 (d, 1H, CH), 7.469-7.452 (t, 1H, CH), 6.838-6.834 (d, 1H, CH). GC-MS (m/z): 246 (M⁺).

4.b) 2-furyl-5-(p-nitrophenyl)-1,3,4-oxadiazole.

IR (KBr) (cm⁻¹): 3070.68 (C-H), 1635.64 (C=N), 1527.62 (C-C), 1450.47 (C=C), 1527 and 1350 (N=O), 1103.28 (C-O), 1018.41(C-O-C), 840.96 (disubstitution at para position). H¹NMR (DMSO-d₆, 400 MHz), δ (ppm): 8.094-7.695 (m, 4H, CH), 7.691-7.689 (d, 1H, CH), 7.461-7.458 (t, 1H, CH), 6.833-6.830 (d, 1H, CH). GC-MS (m/z): 302 (M⁺).

4.c) 2-furyl-5-(3,5-dinitrophenyl)-1,3,4-oxadiazole.

IR (KBr) (cm⁻¹): 3109.25 (C-H), 1604.77 (C=N), 1519.91 (C-C), 1442.75 (C=C), 1519 and 1350 (N=O), 1172.28 (C-O), 1026.13(C-O-C), 864.11 (1,3,5-trisubstitution). H¹NMR (DMSO-d₆, 400 MHz), δ (ppm): 8.097-7.694 (m, 4H, CH), 7.692-7.690 (d, 1H, CH₂), 7.462-7.457 (t, 1H, CH), 6.834-6.830 (d, 1H, CH). GC-MS (m/z): 257 (M⁺).

4.d) 2-furyl-5-phenyl-1,3,4-oxadiazole.

IR (KBr) (cm⁻¹): 3062.96 (C-H), 1635.66 (C=N), 1506.32 (C-C), 1480.23 (C=C), 1081.14 (C-O), 1018.41(C-O-C), 840.26 (disubstitution at para position). H¹NMR (DMSO-d₆, 400 MHz), δ (ppm): 8.092-7.694 (m, 4H, CH), 7.692-7.690 (d, 1H, CH), 7.463-7.458 (t, 1H, CH), 6.831-6.830 (d, 1H, CH). GC-MS (m/z): 212 (M⁺).

4.e) 2-furyl-5-(o-aminophenyl)-1,3,4-oxadiazole.

IR (KBr) (cm⁻¹): 3335.55 and 3400 (N-H), 3100.24 (C-H), 1630.27 (C=N), 1530.77 (C-C), 1485.33 (C=C), 1281.73 (C-N), 1085.57 (C-O), 1027.13(C-O-C). H¹NMR (DMSO-d₆, 400 MHz), δ (ppm): 8.090-7.693 (m, 4H, CH), 7.691-7.690 (d, 1H, CH), 7.463-7.457 (t, 1H, CH), 6.831-6.830 (d, 1H, CH). GC-MS (m/z): 227 (M⁺).

4.f) 2-furyl-5-(p-hydroxyphenyl)-1,3,4-oxadiazole.

IR (KBr) (cm⁻¹): 3500-3200 (O-H), 3035.25 (C-H), 1620.32 (C=N), 1520.27 (C-C), 1452.55 (C=C), 1281.73, 1107.72 (C-O), 1044.62(C-O-C), 840.77 (disubstitution at para position). H¹NMR (DMSO-d₆, 400 MHz), δ (ppm): 8.094-7.693 (m, 4H, CH), 7.692-7.691 (d, 1H, CH), 7.462-7.456 (t, 1H, CH), 6.831-6.830 (d, 1H, CH). GC-MS (m/z): 228 (M⁺).

4.g) 2-furyl-5-(o-hydroxyphenyl)-1,3,4-oxadiazole.

IR (KBr) (cm⁻¹): 3500-3200 (O-H), 3110.33 (C-H), 1640.22 (C=N), 1505.89 (C-C), 1452.42 (C=C), 1281.73, 1070.88 (C-O), 1022.62(C-O-C), 740.67 (disubstitution at para position).

$^1\text{H NMR}$ (DMSO- d_6 , 400 MHz), δ (ppm): 8.097-7.694 (m, 4H, CH), 7.692-7.690 (d, 1H, CH), 7.462-7.457 (t, 1H, CH), 6.834-6.830 (d, 1H, CH). GC-MS (m/z): 228 (M^+).

CONCLUSION

The data from the table confirms that there was as a significant difference in time taken for the preparation of oxadiazoles by the conventional method which ranges from 4-5 hours. While oxadiazoles preparation using microwave method takes only 7-10 minutes for the completion of reaction. Also, there was significant difference in the yield of the oxadiazoles prepared by conventional and microwave assisted synthesis. Conventional method gave poorer yields of oxadiazoles ranging from 60.1-70.1 %, while microwave method provides better yield ranging from 72.4-92.1 %. These data revealed that microwave assisted technique is efficient, eco-friendly and inexpensive method which not only give higher yield but also reduces the reaction time significantly. The titled compounds were characterized by physiochemical properties like melting point and R_f value. The structures of the synthesized compounds were confirmed by IR, $^1\text{H NMR}$ and Mass spectra. The spectral data also supported the assigned structure by showing the characteristic absorption peaks.

ACKNOWLEDGMENTS

The authors are thankful to Principal, Dr. Sr. Betty Carla and Prof. Bhanumathy L., Dept. of Pharmaceutical Chemistry, St. Joseph's College of Pharmacy, Cherthala, Kerala, India for providing Laboratory facilities, guidance and financial support.

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Cite this article as:

Alex Martin. A facile microwave assisted synthesis and spectral analysis of 2-furyl-5-substituted-1,3,4-oxadiazoles. Int. Res. J. Pharm. 2013; 4(11):64-66 <http://dx.doi.org/10.7897/2230-8407.041115>

Source of support: Nil, Conflict of interest: None Declared