

## Microwave-Assisted Synthesis of 2,5-Disubstituted-1,3,4-Oxadiazoles

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Received November 12, 2003; Accepted November 21, 2003

**Abstract:** Recent advances in technology have now made microwave energy a more efficient means of heating reactions. Chemical transformations that took hours, or even days, to complete can now be accomplished in minutes. Microwave energy offers numerous benefits for performing synthesis including increased reaction rates, yield enhancements, and cleaner chemistries. 2,5-Disubstituted-1,3,4-oxadiazoles were synthesized under microwave irradiation and by conventional heating and were structurally characterized by <sup>1</sup>H-NMR, EI, IR, UV and elemental analysis.

**Key Words:** Microwave-irradiation, Phosphorous oxychloride, 2,5-Disubstituted-1,3,4-oxadiazole.

Microwave radiation provides an alternative to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat. The use

of heating. The microwave technology has been applied to a number of useful research and development processes such as polymer technology, organic synthesis, application to waste

**Table 1. Comparison between Microwave-Assisted and Conventional Method of Synthesis of 2,5-Disubstituted-1,3,4-Oxadiazole in Terms of Yield and Time**

Entry	R'	Microwave		Conventional	
		Time (min)	Yield (%)	Time (h)	Yield (%)
a	C <sub>6</sub> H <sub>5</sub>	12	92	6	81
b	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	9	96	5	86
c	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	12	92	6	76
d	<i>m</i> -BrC <sub>6</sub> H <sub>4</sub>	12	87	6	71
e	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	12	85	6	68
f	3-Pyridinyl	12	89	9	75
g	CH <sub>2</sub> Cl	7	87	5	78
h	CHCl <sub>2</sub>	7	85	4	77
i	CCl <sub>3</sub>	6	91	4	76
j	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	13	81	7	69
k	3,4,5-Trimethoxy benzoyl	15	79	9	63
l	1-C <sub>10</sub> H <sub>7</sub>	12	83	9	69
m	2-C <sub>10</sub> H <sub>7</sub>	12	81	8	72

of microwave irradiation has introduced several new concepts in chemistry, since the absorption and transmission of the energy is completely different from the conventional mode

treatment; drug release/targeting; ceramic and alkane decomposition [1-5].

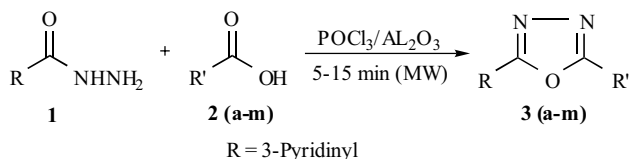
We believe that the time saved by using microwaves is potentially important in traditional organic synthesis but could be of even greater importance in high speed combinatorial and medicinal chemistry as well as industrial scale production of chemicals.

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In continuation of our work in the synthesis of therapeutically important molecules [6], we report here the microwave-assisted synthesis of 2,5-disubstituted-1,3,4-oxadiazole. Conventionally, syntheses of this class of compounds have been achieved in 5-7 h [7-10] (Table 1).

The substituted oxadiazoles are heterocyclic compounds, which serve both as biomimetic and reactive pharmacophores and many are key elements with potential biological activities [11-13] such as pesticidal [14], anti-peripheral vasomotility [15], CNS stimulant, anti-inflammatory, hypotensive [16], insecticidal [17], bactericidal [18], hypoglycemic [19,20], analgesic, anticonvulsive, antiemetic, diuretic [21], muscle relaxant [22,23], herbicidal [24,25] and fungicidal activity [26,27].

A number of commercially available hydrazides were treated with different carboxylic acids **2 (a-m)** in the presence of phosphorous oxychloride to afford 2,5-disubstituted-1,3,4-oxadiazoles **3 (a-m)** (scheme-1). To establish the general validity of our newly developed method, several selected one-pot microwave-assisted syntheses were carried out. This method appeared to be rapid and economical, with a wide range of applications. The reaction was found to proceed smoothly under microwave irradiation within 6-15 min whereas under reflux conditions, 4-9 h were required (Table 1) [28]. The products were isolated by simple cold aqueous work-up followed by either solvent extraction or precipitation and were finally purified by column chromatography wherever necessary, to afford pure 2,5-disubstituted-1,3,4-oxadiazole.



Scheme 1.

In conclusion, this method provides an excellent approach for the safe, rapid, inexpensive and simple synthesis of medicinally important 2,5-disubstituted-1,3,4-oxadiazoles in a single step. The present method is an important addition to microwave-assisted synthetic methodologies.

## ACKNOWLEDGEMENTS

One of us, Mr. Zia-Ullah is thankful to the Higher Education Commission (HEC) Pakistan for granting "Merit Scholarship for Ph.D. Studies in Science and Technology."

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- [28] **Typical experimental procedure: Synthesis of 3a.** The mixture of 3-pyridyl hydrazide (0.50 g, 3.65 mmol), benzoic acid (0.44 g, 3.65 mmol) and alumina (1.50 g) were finely ground with a mortar and pestle. Phosphorous oxychloride (0.50 ml, 5.47 mmol) was added to this mixture in a Pyrex glass vial, which was placed in a screw capped Teflon vessel. Microwave irradiation (MW domestic type oven 900 W with a frequency 2450 MHz, Dawlance, Pakistan) was applied for 12 min (four pulses each of 3 min). After the completion of reaction (TLC analysis), the mixture was poured into ice-cold water. The precipitate was

filtered and washed with 10% solution of NaHCO<sub>3</sub> to afford **3a** (0.75 g, 92%) as a yellowish white solid. FTIR (KBr)  $\nu_{\max}$ : 3073, 1667, 1557, 1287, 832, 659 cm<sup>-1</sup> UV (CH<sub>3</sub>OH)  $\lambda_{\max}$  (log $\epsilon$ ) 204 (7.50). R<sub>f</sub> = 0.34 (ethyl acetate/acetone = 9:1). <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$ : 7.50–7.44 (m, 3H, H-3"/4"/5"), 7.63 (dd, 2H,  $J = 7.8, J = 2.3$  Hz, H-2"/6"), 8.59–8.56 (m, 1H, H-4'), 8.81 (dd,

1H,  $J = 4.9, J = 8.3$  Hz, H-5'), 9.13 (dd, 1H,  $J = 4.9, J = 1.6$  Hz, H-6'), 9.21 (d, 1H,  $J = 2.14$  Hz, H-2'). EI-MS  $m/z$ : 223 (M<sup>+</sup>, 21), 145 (31), 106 (100), 77 (79), 78 (65), 68 (35), 51 (72). Anal. Calcd. for C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>O: C, 69.95; H, 4.06; N, 18.82, O, 7.17. Found: C, 69.99; H, 3.91; N, 18.81; O, 7.18.