

# Synthesis of Substituted 1,3,4-Oxadiazoles Under Microwave Irradiation

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A series of substituted 1,3,4-oxadiazoles were synthesized by the cyclization of 2,6pyridine dicarboxylic acid, 5-(4'-carboxyl-phenyl)-2-furanylcarboxylic acid, or pphthalic acid, and aryl hydrazines in the presence of phosphorus oxychloride under the condition of microwave irradiation.

Keywords 1,3,4-oxadiazoles; microwave irradiation; synthesis

## INTRODUCTION

Substituted 1,3,4-oxadiazoles are widely applied in medicine and agriculture; for example, they are used as psychotropic drugs,<sup>1</sup> antiinflammatory<sup>2</sup> reagents, pesticides, and insecticidal,<sup>3</sup> fluorescence,<sup>4</sup> and plant growth reagents<sup>5</sup> etc. Meanwhile, pyridine and furan derivatives<sup>6</sup> also have attracted much attention due to their anticancer,<sup>2</sup> antihypertension,<sup>5</sup> and antifungal<sup>7</sup> activity.

The conventional methods of the synthesis of 1,3,4-oxadiazloes are as follows: (1) the cyclization of 1,4-disubstituted thiosemicarbazide in the presence of either  $I_2/NaOH^8$  or dicyclohexycarbodiimide (DCC),<sup>9,10</sup> and (2) the condensation of acid hydrazide with aromatic acids or cyanogen bromide under a severe condition. These methods are inconvenient as

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Address correspondence to Xicun Wang, Northwest Normal University, Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Lanzhou, 730070 Gansu, P.R. China. E-mail: wangxicun@nwnu.edu.cn they require heating of the reactants for an extended period of time. Moreover, the yield is frequently only moderate or low.

Microwave technique, meanwhile, has been widely used for a variety of organic reactions,<sup>11,12</sup> such as Claisen, cyclization, oxidation, Diels-Alder reaction, hydrolysis, esterification, etherification, and so on. Many reviews<sup>13-15</sup> have been published in favor of its considerable accelerations of the reaction rates and satisfactory yields.

#### **RESULTES AND DISCUSSION**

In view of this, we report herein the preparation of a new series of substituted 1,3,4-oxadiazoles using a microwave technique with the objective of obtaining new biologically active compounds. The synthetic route is shown in Scheme 1.



The reaction of 2,6-pyridine dicarboxylic acid, *p*-phthalic acid, and 5-(4'-carboxyl-phenyl)-2-furanylcarboxylic acid with aryl hydrazines catalyzed by pyridine on exposure to microwave irradiation in the presence of phosphorus oxychloride resulted in a series of substituted 1,3,4oxadiazoles. The results are shown in Tables I and II.

#### **EXPERIMENTAL**

Melting points were determined on a XT-4 thermal apparatus and the m.p. are uncorrected. <sup>1</sup>H NMR spectra were obtained on a Avanci-D2X-200 instrument using DMSO-d<sub>6</sub> as a solvent and TMS as internal standard. IR spectra were recorded using KBr pellets on a Nicolet AVATAR 360 FT-IR. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. The acids and aroyl hydrazines<sup>16</sup> were prepared according to literature methods.

			Vield	ΜР	Elemental Analysis % (Found)		
	Ar	Mol. formula	(%)	(°C)	С	Н	Ν
Id	$3-O_2NC_6H_4$	$C_{22}H_{12}N_6O_6$	86	>300	57.86(57.90)	2.74(2.65)	18.31(18.41)
Ig	$4\text{-}OCH_3C_6H_4$	$\mathrm{C}_{24}\mathrm{H}_{18}\mathrm{N}_4\mathrm{O}_4$	83	>300	67.66(67.60)	4.13(4.25)	13.19(13.14)
Ih	$2\text{-IC}_6\text{H}_4$	$\mathrm{C}_{22}\mathrm{H}_{12}\mathrm{N}_4\mathrm{O}_2\mathrm{I}_2$	75	>300	42.58(42.75)	2.01(1.96)	9.13(9.06)
Ii	$4\text{-IC}_6\text{H}_4$	$\mathrm{C}_{22}\mathrm{H}_{12}\mathrm{N}_4\mathrm{O}_2\mathrm{I}_2$	79	>300	42.79(42.75)	1.84(1.96)	8.99(9.06)
IIb	$2-ClC_6H_4$	$\mathrm{C}_{21}\mathrm{H}_{11}\mathrm{N}_{5}\mathrm{O}_{2}\mathrm{Cl}_{2}$	85	>300	57.68(57.82)	2.47(2.54)	16.16(16.05)
IId	$3-NO_2 C_6H_4$	$C_{21}H_{11}N_7O_6$	91	>300	55.03(55.15)	2.35(2.42)	21.58(21.44)
IIg	$4\text{-}OCH_3C_6H_4$	$C_{23}H_{17}N_5O_4$	87	>300	64.71(63.64)	3.98(4.01)	16.26(16.39)
IIIa	$C_6H_5$	$C_{26}H_{16}N_4O_3$	89	269-271	72.38(72.22)	3.70(3.73)	13.05(12.96)
IIIc	$4-ClC_6H_4$	$C_{26}H_{14}N_4O_3Cl_2$	72	>300	62.15(62.29)	2.69(2.81)	11.34(11.18)
IIIe	$4-NO_2 C_6H_4$	$C_{26}H_{14}N_6O_7$	74	279-281	59.63(59.78)	2.61(2.70)	16.14(16.09)
IIIf	$3-\mathrm{CH}_3\mathrm{C}_6\mathrm{H}_4$	$C_{28}H_{20}N_4O_3$	78	223 - 225	73.19(73.03)	4.35(4.38)	12.03(12.17)

TABLE I The Physical Data of 1,3,4-Oxadiazoles Under MicrowaveIrradiation

### **General Procedure for the Preparation of 1,3,4-Oxadiazoles**

A mixture of 5-(4'-carboxyphenyl)-2-furanylcarboxylic acid (1 mmol) or 2,6-pyridine dicarboxylic acid (1 mmol), aryl hydrazines (2 mmol), phosphorus oxychloride (6 mL), and 2 drops of pyridine was irradiated in a microwave oven (490 W) for 8 min. When it was cooled to r.t., some pieces of ice were added and the mixture stood for 2–4 h. The precipitate was

Entry	IR/cm <sup>-1</sup> C=N-N=C-O	$^{1}$ HNMR (DMSO-d <sub>6</sub> ) $\delta$
I-d	1623 1546 1487 1091	7. 62–8.31 (m, 12H, Ar-H)
I-g	$1614\ 1530\ 1446\ 1074$	3.93 (s, 6H, CH <sub>3</sub> ) 7.41–8.12 (m, 12H, Ar-H)
I-h	$1619\ 1534\ 1476\ 1083$	7.54–8.17 (m, 12H, Ar-H)
I-i	$1617\ 1538\ 1479\ 1085$	7.52–8.19 (m, 12H, Ar-H)
II-b	$1603\ 1530\ 1479\ 1095$	$8.32-8.51 (m, 3H, C_5H_3N) 7.63-8.24 (m, 8H, Ar-H)$
II-d	$1612\ 1533\ 1485\ 1091$	8.37–8.65 (m, 3H, C <sub>5</sub> H <sub>3</sub> N) 7.75–8.37 (m, 8H, Ar-H)
II-g	$1607\ 1529\ 1468\ 1089$	3.86 (s, 6H, CH <sub>3</sub> ) 8.39-8.52 (m, 3H, C <sub>5</sub> H <sub>3</sub> N) 7.58-8.18
		(m, 8H, Ar-H)
III-a	$1608\ 1537\ 1469\ 1087$	7.24–8.30 (m, 16H, Ar-H, and Fu-H)
III-c	$1613\ 1541\ 1457\ 1086$	7.25-8.23 (m,14H, Ar-H, and Fu-H)
III-е	$1607\ 1534\ 1466\ 1080$	7.33-8.41 (m,14H, Ar-H, and Fu-H)
III-f	$1612\ 1537\ 1465\ 1075$	$2.44~(s,6H,CH_3)$ 7.24–8.21 $(m,14H,Ar\text{-}H,andFu\text{-}H)$

TABLE II The IR and <sup>1</sup>H NMR Data of 1,3,4-Oxadiazoles UnderMicrowave Irradiation

collected by filtration and washed with a saturated sodium carbonate solution (2  $\times$  10 mL) and water (3  $\times$  10 mL). The product was recrystallized from DMF and EtOH.

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