$PhI(OAc)_2$-Al_2O_3 Mediated Synthesis of 1,8-Naphthyridinyl-1,3,4-Oxadiazoles Under Microwave Irradiation

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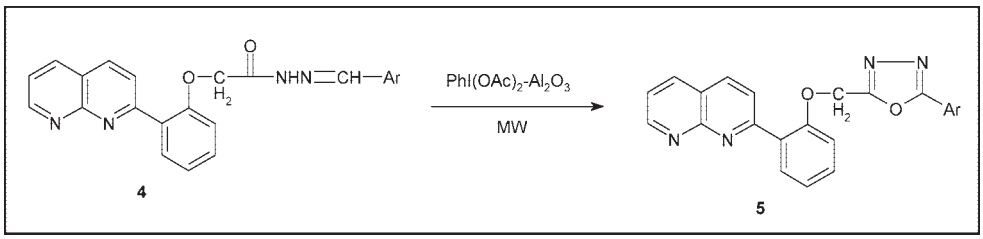

Alumina-supported iodobenzene diacetate [$PhI(OAc)_2$-Al_2O_3] is a highly efficient reagent for the oxidative cyclization of [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidene hydrazides **4** to 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)phenoxymethyl]-1,3,4-oxadiazoles **5** in solvent-free conditions under microwave irradiation. The products are obtained in good yields and in a state of high purity.

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INTRODUCTION

1,8-Naphthyridine derivatives acquired a special place in the heterocyclic field because of their diversified activities such as antibacterial [1], antitumor [2], antihypertensive [3], and anti-inflammatory [4]. 1,3,4-Oxadiazoles are biologically active [5,6], synthetically useful and important heterocyclic compounds. For these reasons the chemistry of 1,3,4-oxa-diazoles have been the subject of many investigations [7–10]. However, most of these investigations suffer from serious drawbacks which include the use of hazardous, highly toxic, long reaction times, low yields, drastic reaction conditions, and expensive or commercially unavailable reagents. In view of the rapidly increasing demands for green chemistry, an efficient and convenient method for the synthesis of 1,3,4-oxadiazoles is highly desirable.

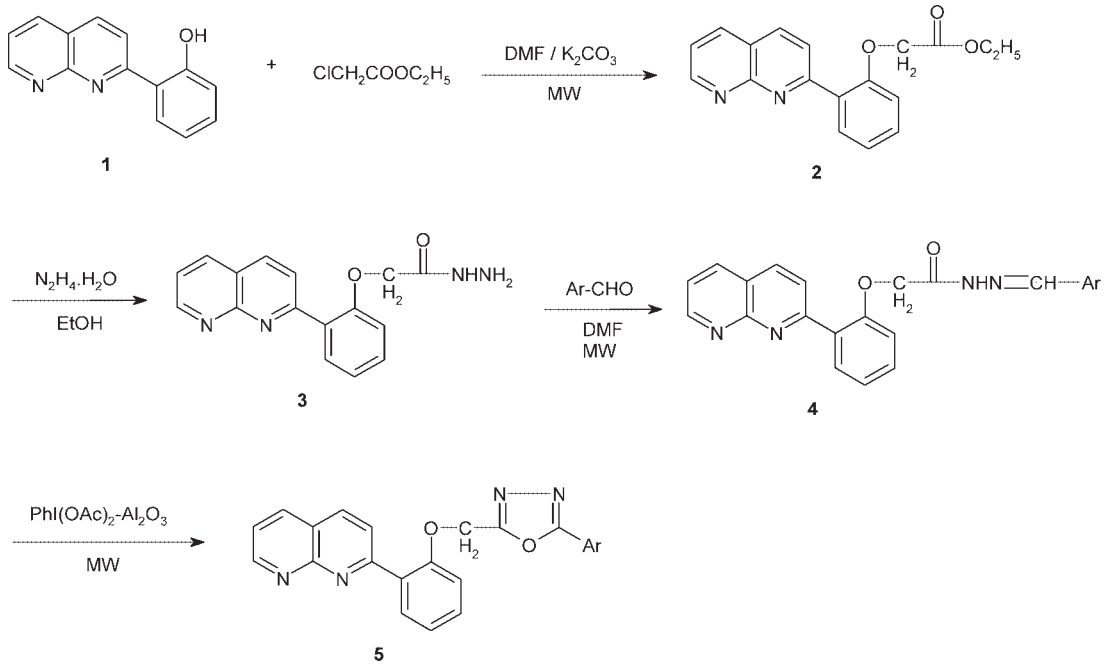
The versatile synthetic utility of organic hypervalent iodine reagents in general and iodobenzene diacetate (IBD) in particular is of current interest [11–13]. Microwave (MW) activation has become a very popular and useful technology in synthetic organic chemistry [14–16]. Recently, more interest has been focused on ''dry media'' synthesis using inorganic solid supports. The coupling of MW heating mode with the use of mineral solid support [17–19] such as alumina, silica, and clays have been used for the synthesis of several organic compounds with higher selectivity, yield and purity compared to traditional methods. In continuation of our interest in the MW assisted organic transformations of 1,8-naphthyrdines [20–23], we report herein, a practical and highly efficient method for the synthesis of 1,8-naphthyridinyl-1,3,4-oxadiazoles using alumina-supported IBD [$PhI(OAc)_2$-Al_2O_3] in solvent free conditions under MW irradiation.

RESULTS AND DISCUSSION

Alkylation of 2-(*o*-hydroxyphenyl)-1,8-naphthyridine **1** [24] with ethyl chloroacetate in DMF in the presence of anhydrous K_2CO_3 under MW irradiation resulted in the formation of ethyl [*o*-(1,8-naphthyridin-2-yl)phenoxy] acetate **2**, which on hydrazinolysis with refluxing hydrazine hydrate afforded [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid hydrazide **3**. Treatment of hydrazide **3** with aromatic aldehydes in the presence of catalytic amount of DMF under MW irradiation furnished the corresponding hydrazones, [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidenehydrazides **4** in excellent yields.

The hydrazones **4** on oxidative cyclization with alumina-supported IBD [$PhI(OAc)_2$-Al_2O_3] [25] in the absence of solvent under MW irradiation resulted in the formation of 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)phenoxymethyl]-1,3,4-oxadiazoles **5** (Scheme 1). The reaction proceeds efficiently in good yields at ambient pressure within a few minutes. The transformation is very clean and rapid. The reaction conditions and work-up procedures are mild, simple and convenient. Furthermore, it is to be noted that highly pure products were obtained using this simple procedure and in most cases no further purification was needed. The recyclability of the alumina support makes this an environmentally friendly ''green'' protocol. On comparing the rate enhancement effect of MW irradiation on the investigated reaction, the oxidative

Scheme 1



cyclization of hydrazone **4a** was chosen as a model reaction. The reaction gave compound **5a** in 10% yield in 5.0 min, when conducted under conventional conditions in an oil-bath preheated to 120°C (temperature measured at the end of exposure during MW experiment).

The structural assignments to compounds **2–5** were based on their spectral (IR and ^{1}H NMR) and analytical data. To the best of our knowledge this is the first report of the rapid synthesis of 1,3,4-oxadiazoles using $PhI(OAc)_2$-Al_2O_3 under solvent-free MW irradiation conditions.

In conclusion, the present procedure with $PhI(OAc)_2$-Al_2O_3 provides a very efficient method for the synthesis of 1,3,4-oxadiazoles under solvent-free conditions using MW irradiation. The notable advantages of this method are: operational simplicity, ready availability of reagents and general applicability, mild reaction conditions, short reaction times, good yields, and environmentally benign procedure.

EXPERIMENTAL

Melting points were measured on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra in KBr were recorded on a Perkin-Elmer BX series FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ, ppm) using TMS as internal standard. Elemental analyses (CHN) were performed on a Perkin-Elmer 240 CHN analyzer. Irradiation was carried out in a domestic MW oven (LG MG-556P, 2450 MHz).

Ethyl [*o*-(1,8-naphthyridin-2-yl)phenoxy]-acetate 2. A mixture of 2-(*o*-hydroxyphenyl)-1,8-naphthyridine **1** (0.01 mol), ethyl chloroacetate (0.01 mol), anhydrous K_2CO_3 (0.01 mol), and DMF (10 mL) was exposed to MWs at 400 watts intermittently at 30 s intervals for 4.5 min. After completion of reaction, as indicated by TLC, the reaction was cooled and poured onto crushed ice. The precipitate thus obtained was collected by filtration, washed with water and re-crystallized from ethanol to give **2**, yield 96%, mp 130°C; IR: 1755, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7.0 Hz, 3H, CH_3), 4.28 (q, J = 7.0 Hz, 2H, CH_2), 4.71 (s, 2H, O—CH_2), 8.28 (m, 3H, C_3—H, C_4—H, C_5—H), 7.98 (m, 1H, C_6—H), 9.13 (m, 1H, C_7—H), 6.90–7.59 (m, 4H, Ar—H); *Anal*. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.13; H, 5.19; N, 9.09. Found : C, 70.29; H, 5.24; N, 9.15%.

[*o*-(1,8-Naphthyridin-2-yl)-phenoxy]acetic acid hydrazide 3. A mixture of **2** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed on a water-bath for 6 h. The reaction mixture was cooled, the separated solid was collected by filtration and re-crystallized from ethanol to furnish **3**, yield 92%, mp 150°C; IR: 3450, 3275, 3082, 1675, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.92 (br, 2H, NH_2), 4.83 (s, 2H, CH_2), 8.22 (m, 3H, C_3—H, C_4—H, C_5—H), 7.95 (m, 1H, C_6—H), 9.12 (m, 1H, C_7—H), 6.97–7.54 (m, 4H, Ar—H), 9.56 (s, 1H, CONH); *Anal*. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.31; H, 4.76; N, 19.05. Found: C, 65.49; H, 4.80; N, 19.12%.

General procedure for the synthesis of [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidene hydrazides 4. A mixture of **3** (0.01 mol), aromatic aldehyde (0.01 mol), and DMF (five drops) was subjected to MW irradiation at 400 watts intermittently at 30 s intervals for the specified time (Table 1). On completion of the reaction, as monitored by TLC, the reaction mixture was digested with cold water. The resulting solid

Table 1

Physical and analytical data of [*o*-(1,8-naphthyridin-2-yl)phenoxy]acetic acid arylidenehydrazides **4** and 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)phenoxymethyl]-1,3,4-oxadiazoles **5**.

Entry	Ar	Reaction period (min)	M.p. (°C)	Yield (%)	Mol. formula	Found % (Calcd)		
						C	H	N
4a	C_6H_5	1.0	184	96	$C_{23}H_{18}N_4O_2$	72.43 (72.25)	4.76 (4.71)	14.74 (14.66)
4b	p-$CH_3C_6H_4$	0.5	176	98	$C_{24}H_{20}N_4O_2$	72.91 (72.73)	4.08 (5.05)	14.21 (14.14)
4c	p-$CH_3OC_6H_4$	1.5	234	94	$C_{24}H_{20}N_4O_3$	69.72 (69.90)	4.49 (4.85)	13.66 (13.59)
4d	p-ClC_6H_4	1.0	180	97	$C_{23}H_{17}ClN_4O_2$	66.45 (66.27)	4.02 (4.08)	13.49 (13.45)
4e	o-BrC_6H_4	1.5	200	94	$C_{23}H_{17}BrN_4O_2$	59.71 (59.87)	3.74 (3.69)	12.22 (12.15)
4f	m-$NO_2C_6H_4$	0.5	210	92	$C_{23}H_{17}N_5O_4$	64.80 (64.64)	3.94 (3.98)	16.46 (16.39)
4g	2,4-$Cl_2C_6H_3$	1.0	185	93	$C_{23}H_{16}Cl_2N_4O_2$	61.38 (61.20)	3.40 (3.55)	12.47 (12.42)
4h	2,6-$Cl_2C_6H_3$	1.5	223	92	$C_{23}H_{16}Cl_2N_4O_2$	61.36 (61.20)	3.41 (3.55)	12.49 (12.42)
5a	C_6H_5	5.0	>300	90	$C_{23}H_{16}N_4O_2$	72.76 (72.63)	4.26 (4.21)	14.80 (14.74)
5b	p-$CH_3C_6H_4$	4.5	>300	95	$C_{24}H_{18}N_4O_2$	73.27 (73.10)	4.61 (4.57)	14.29 (14.21)
5c	p-$CH_3OC_6H_4$	5.5	>300	92	$C_{24}H_{18}N_4O_3$	70.42 (70.24)	4.43 (4.39)	13.72 (13.66)
5d	p-ClC_6H_4	5.0	>300	93	$C_{23}H_{15}ClN_4O_2$	66.75 (66.59)	3.66 (3.62)	13.58 (13.51)
5e	o-BrC_6H_4	6.0	>300	90	$C_{23}H_{15}BrN_4O_2$	60.30 (60.13)	3.32 (3.27)	12.29 (12.20)
5f	m-$NO_2C_6H_4$	6.5	>300	88	$C_{23}H_{15}N_5O_4$	64.78 (64.94)	3.58 (3.53)	16.41 (16.47)
5g	2,4-$Cl_2C_6H_3$	5.5	>300	89	$C_{23}H_{14}Cl_2N_4O_2$	61.63 (61.47)	3.16 (3.12)	12.55 (12.47)
5h	2,6-$Cl_2C_6H_3$	6.5	>300	87	$C_{23}H_{14}Cl_2N_4O_2$	61.62 (61.47)	3.17 (3.12)	12.56 (12.47)

product was collected by filtration, washed with water, and re-crystallized from ethanol to afford **4**.

4a. IR: 3432, 1690, 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (s, 2H, CH_2), 8.18 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.10 (m, 1H, C_7—H), 6.92–7.55 (m, 10H, N=CH, 9Ar—H), 12.53 (s, 1H, CONH).

4b. IR: 3440, 1685, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 4.92 (s, 2H, CH_2), 8.27 (m, 3H, C_3—H, C_4—H, C_5—H), 7.94 (m, 1H, C_6—H), 9.12 (m, 1H, C_7—H), 6.90–7.58 (m, 9H, N=CH, 8Ar—H), 12.36 (s, 1H, CONH).

4c. IR: 3448, 1696, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.82 s, 3H, OCH_3), 4.91 (s, 2H, CH_2), 8.28 (m, 3H, C_3—H, C_4—H, C_5—H), 7.98 (m, 1H, C_6—H), 9.13 (m, 1H, C_7—H), 6.83–7.80 (m, 9H, N=CH, 8Ar—H), 12.42 (s, 1H, CONH).

4d. IR: 3420, 1702, 1609 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.94 (s, 2H, CH_2), 8.25 (m, 3H, C_3—H, C_4—H, C_5—H), 8.00 (m, 1H, C_6—H), 9.13 (m, 1H, C_7—H), 7.03–7.80 (m, 9H, N=CH, 8Ar—H), 12.89 (s, 1H, CONH).

4e. IR: 3450, 1705, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.92 (s, 2H, CH_2), 8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 7.93 (m, 1H, C_6—H), 9.14 (m, 1H, C_7—H), 7.00–7.73 (m, 9H, N=CH, 8Ar—H), 12.89 (s, 1H, CONH).

4f. IR: 3435, 1697, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.95 (s, 2H, CH_2), 8.17 (m, 3H, C_3—H, C_4—H, C_5—H), 7.91 (m, 1H, C_6—H), 9.08 (m, 1H, C_7—H), 6.90–7.49 (m, 9H, N=CH, 8Ar—H), 12.42 (s, 1H, CONH).

4g. IR: 3425, 1702, 1607 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.92 (s, 2H, CH_2), 8.24 (m, 3H, C_3—H, C_4—H, C_5—H), 7.95 (m, 1H, C_6—H), 9.10 (m, 1H, C_7—H), 6.98–7.62 (m, 8H, N=CH, 7Ar—H), 12.52 (s, 1H, CONH).

4h. IR: 3422, 1707, 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.90 (s, 2H, CH_2), 8.19 (m, 3H, C_3—H, C_4—H, C_5—H), 7.90 (m, 1H, C_6—H), 9.12 (m, 1H, C_7—H), 6.96–7.58 (m, 8H, N=CH, 7Ar—H), 12.73 (s, 1H, CONH).

General procedure for the synthesis of 5-aryl-2-[*o*-(1,8-naphthyridin-2-yl)-phenoxymethyl]-1,3,4-oxadiazoles 5. Compound **4** (0.01 mol) and $PhI(OAc)_2$ (0.01 mol) doped on neutral alumina (1 g) are mixed thoroughly and exposed to MWs at 800 watts intermittently at 30 s intervals for the specific time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with methanol (30 mL). The methanol solution was poured into ice-cold water (50 mL), the precipitated solid was collected by filtration and re-crystallized from ethanol to furnish **5** (Table 1).

5a. IR: 1605 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.46 (s, 2H, CH_2), 8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 8.00 (m, 1H, C_6—H), 9.15 (m, 1H, C_7—H), 7.04–7.60 (m, 9H, Ar—H).

5b. IR: 1602 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.30 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 8.18 (m, 3H, C_3—H, C_4—H, C_5—H), 7.98 (m, 1H, C_6—H), 9.14 (m, 1H, C_7—H), 7.00–7.56 (m, 8H, Ar—H).

5c. IR: 1604 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 3.87 (s, 3H, OCH_3), 5.41 (s, 2H, CH_2), 8.17 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.12 (m, 1H, C_7—H), 6.92–7.60 (m, 8H, Ar—H).

5d. IR: 1605 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.43 (s, 2H, CH_2), 8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 7.81 (m, 1H, C_6—H), 9.09 (m, 1H, C_7—H), 7.10–7.32 (m, 8H, Ar—H).

5e. IR: 1602 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.46 (s, 2H, CH_2), 8.23 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.03 (m, 1H, C_7—H), 7.20–7.74 (m, 8H, Ar—H).

5f. IR: 1603 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.42 (s, 2H, CH_2), 8.21 (m, 3H, C_3—H, C_4—H, C_5—H), 7.97 (m, 1H, C_6—H), 9.11 (m, 1H, C_7—H), 7.05–7.52 (m, 8H, Ar—H).

5g. IR: 1600 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.45 (s, 2H, CH_2), 8.19 (m, 3H, C_3—H, C_4—H, C_5—H), 7.92 (m, 1H, C_6—H), 9.13 (m, 1H, C_7—H), 6.94–7.56 (m, 7H, Ar—H).

5h. IR: 1601 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 5.43 (s, 2H, CH_2), 8.21 (m, 3H, C_3—H, C_4—H, C_5—H), 7.98 (m, 1H, C_6—H), 9.10 (m, 1H, C_7—H), 7.01–7.52 (m, 7H, Ar—H).

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[25] Iodobenzene diacetate (0.01 mol) per gram of neutral alumina is ground using a pestle and mortar; the recovered alumina after removal of the products is reused without any loss of activity.