Iodobenzene Diacetate on Alumina: Efficient Synthesis of 1,3,4-Oxadiazolyl-1,8-naphthyridines in Solventless System Using Microwaves

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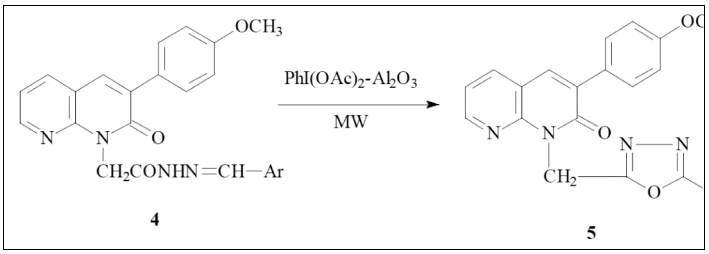

1-(5-Aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(*p*-methoxyphenyl)-1*H*-[1,8]naphthyridin-2-ones (**5**) were synthesized by the oxidative cyclization of [2-oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid arylidene-hydrazides (**4**) with alumina-supported iodobenzene diacetate (IBD) in solvent-free conditions under microwave irradiation. The products are obtained in good yields and in a state of high purity.

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Introduction.

The 1,3,4-oxadiazole [1-3] and 1,8-naphthyridine [4-6] classes of heterocycles are of current interest due to their broad spectrum biological activity. In recent years, the organic reactions on solid supports [7,8] and assisted by microwaves [9-11] in particular, have gained special attention because of their enhanced selectivity, milder reaction conditions and associated ease of manipulation. In view of this and in continuation of our work on microwave assisted organic transformation on 1,8-naphthyridine derivatives [12-15] we now report an efficient and high yielding protocol for the synthesis of 1,3,4-oxadiazolyl-1,8-naphthyridines (**5**) using Al_2O_3-PhI(OAc)$_2$ under solvent-free conditions and microwave irradiation.

Results and Discussion.

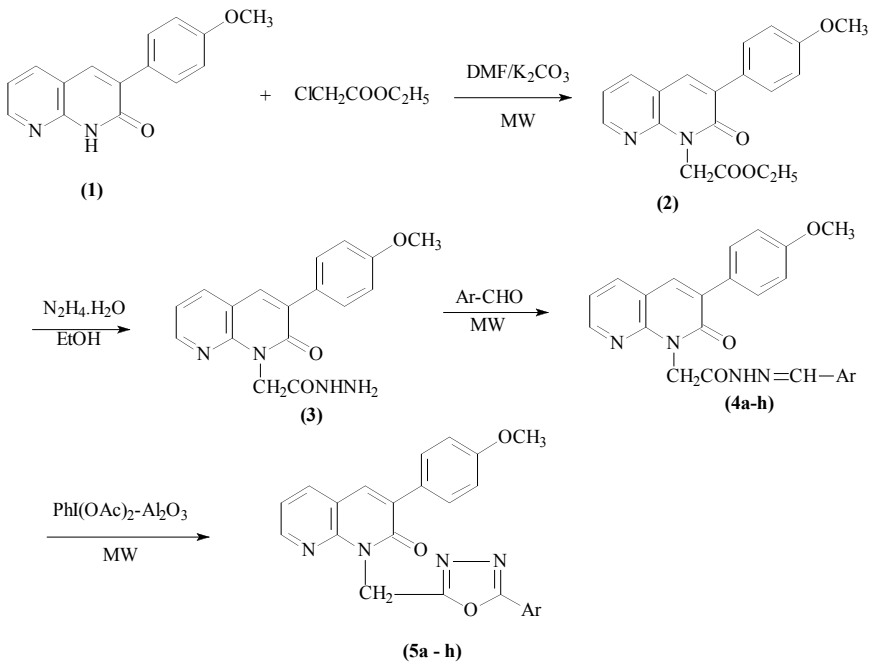
Alkylation of 1,2-dihydro-3-(*p*-methoxyphenyl)-1,8-naphthyridin-2-one (**1**) [16] with ethyl chloroacetate in DMF in the presence of anhydrous K_2CO_3 under microwave irradiation afforded ethyl [2-oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetate (**2**). The ester **2** on hydrazinolysis with refluxing hydrazine hydrate furnished [2-oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid hydrazide (**3**). Condensation of hydrazide **3** with various aromatic aldehydes in the presence of a catalytic amount of DMF under microwave irradiation resulted in the formation of the corresponding hydrazones, [2-oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid arylidenehydrazides (**4**).

Oxidative cyclization of hydrazones **4** with alumina-supported IBD (Al_2O_3-PhI(OAc)$_2$) [17] under microwave irradiation afforded the respective 1-(5-aryl-[1,3,4]-oxadiazol-2-ylmethyl)-3-(*p*-methoxyphenyl)-1*H*-[1,8]-naphthyridin-2-ones (**5**). The reaction proceeded smoothly providing good yield of the corresponding 1,3,4-oxadiazole as shown in the Table 1. The oxidative transformation is clean and efficient and is devoid of any by-products. Furthermore, the products obtained are of high purity by this procedure and no further purification was needed. The experimental procedure is very simple. The recyclability of the alumina support renders this process into truly ecofriendly green protocol.

Interestingly, this reaction proceeds only to a minor extent (9-15% in 5.0-7.0 minutes) when conducted under conventional conditions in an oil-bath preheated to 125 °C (temperature measured at the end of exposure during microwave experiment), which confirms the rate increase during microwave heating.

The structural assignments to these compounds **2-5** were based on their spectroscopic (IR and ^{1}H NMR) and analytical data. To the best of our knowledge this is the first report on the alumina-supported IBD mediated synthesis of 1,3,4-oxadiazoles under solvent-free conditions and microwave irradiation.

Scheme 1



Compounds **4** and **5**	Ar	Compounds **4** and **5**	Ar
a	C_6H_5	**e**	*p*-ClC_6H_4
b	*p*-$CH_3C_6H_4$	**f**	*o*-BrC_6H_4
c	*p*-$CH_3OC_6H_4$	**g**	*m*-$NO_2C_6H_4$
d	*o*-ClC_6H_4	**h**	3,4-(O-CH_2-O)C_6H_3

In conclusion, we have demonstrated a convenient, efficient, simple and mild procedure for the synthesis of 1,3,4-oxadiazoles using Al_2O_3-$PhI(OAc)_2$ in solvent-free conditions under microwave irradiation. In addition, high yield, short reaction time, pure products, simpler work-up and environmental acceptability are worthy advantages of this method.

EXPERIMENTAL

The melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra were recorded as KBr pellets on a Perkin-Elmer BX series FT-IR spectrophotometer. ^{1}H NMR were recorded on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ, ppm) using TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyser. For microwave irradiation a suitably designed LG MG 556P (2450 MHz) domestic microwave oven was used [18].

Synthesis of Ethyl [2-Oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]-acetate (**2**).

A mixture of 1,2-dihydro-3-(p-methoxyphenyl)-1,8-naphthyridin-2-one (**1**, 0.504 g, 20.0 mmol), ethyl chloroacetate (0.244 g, 20.0 mmol), anhydrous K_2CO_3 (0.196 g, 20.0 mmol) and DMF (15 ml) was exposed to microwave irradiation at 400 watts intermittently at 30 sec intervals for 4.0 minutes. After completion of the reaction, as indicated by TLC, the reaction was cooled and treated with chilled water. The solid that precipitated was collected by filtration, washed with water and recrystallized from ethanol to afford 0.331 g (98%) of pure **2**, mp 130-132 °C; ir (potassium bromide): 1736 (C=O), 1644 (C=O), 1607 (C=N) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.30 (t, J=7.0 Hz, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.22 (q, J=7.0 Hz, 2H, CH_2), 5.38 (s, 2H, N-CH_2), 8.12 (s, 1H, C_4-H), 8.55 (m, 1H, C_5-H), 7.89 (m, H, C_6-H), 9.13 (m, 1H, C_7-H), 6.90-7.72 (m, 4H, Ar-H).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.46; H, 5.33; N, 8.28. Found: C, 67.62; H, 5.38; N, 8.35.

Synthesis of [2-Oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic Acid Hydrazide (**3**).

A mixture of **2** (0.676 g, 20.0 mmol) and hydrazine hydrate (0.17 g, 30.0 mmol) in ethanol (30 ml) was refluxed on a water-bath for 5 hours. The reaction mixture was concentrated to one third of its volume and cooled. The resulting solid product was filtered and recrystallized from ethanol to give 0.301 g (93%) of pure **3**, mp 110-112 °C; ir (potassium bromide): 3420, 3305, 3170, ($NHNH_2$), 1648 (C=O), 1608 (C=N) cm^{-1}; ^{1}H nmr ($CDCl_3$ + DMSO-d_6): δ 3.36 (br, 2H, NH_2), 3.90 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2),

Table 1

Physical data of [2-Oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid arylidenehydrazides (**4**) and 1-(5-Aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(*p*-methoxy-phenyl)-1*H*-[1,8]naphthyridin-2-ones (**5**)

Compound	Reaction time (min)	M.P. (°C)	Yield (%)	Molecular formula	Elemental analysis Found / (Calcd) C	H	N
4a	1.5	170-172	95	$C_{24}H_{20}N_4O_3$	69.72 (69.90)	4.80 (4.85)	13.67 (13.59)
4b	1.0	140-42	98	$C_{25}H_{22}N_4O_3$	70.62 (70.42)	5.22 (5.16)	13.24 (13.15)
4c	1.5	198-200	96	$C_{25}H_{22}N_4O_4$	67.70 (67.87)	4.92 (4.98)	12.58 (12.67)
4d	1.5	218-220	94	$C_{24}H_{19}N_4O_3Cl$	64.71 (64.50)	4.33 (4.26)	12.62 (12.54)
4e	1.0	161-163	97	$C_{24}H_{19}N_4O_3Cl$	64.70 (64.50)	4.34 (4.26)	12.63 (12.54)
4f	1.5	229-231	94	$C_{24}H_{19}N_4O_3Br$	58.87 (58.66)	3.81 (3.87)	11.52 (11.41)
4g	1.0	220-222	95	$C_{24}H_{19}N_5O_5$	63.24 (63.02)	4.20 (4.16)	15.42 (15.32)
4h	1.5	200-202	96	$C_{25}H_{20}N_4O_5$	65.98 (65.79)	4.32 (4.39)	12.39 (12.28)
5a	5.5	>300	88	$C_{24}H_{18}N_4O_3$	70.44 (70.24)	4.45 (4.39)	13.77 (13.66)
5b	5.0	>300	94	$C_{25}H_{20}N_4O_3$	70.96 (70.75)	4.76 (4.72)	13.30 (13.21)
5c	6.0	>300	90	$C_{25}H_{20}N_4O_4$	68.43 (68.18)	4.60 (4.55)	12.64 (12.73)
5d	6.0	>300	87	$C_{24}H_{17}N_4O_3Cl$	64.98 (64.79)	3.86 (3.82)	12.71 (12.60)
5e	5.5	>300	92	$C_{24}H_{17}N_4O_3Cl$	64.97 (64.79)	3.87 (3.82)	12.72 (12.60)
5f	6.5	>300	88	$C_{24}H_{17}N_4O_3Br$	58.74 (58.90)	3.53 (3.47)	11.56 (11.45)
5g	7.0	>300	87	$C_{24}H_{17}N_5O_5$	63.51 (63.30)	3.80 (3.74)	15.47 (15.38)
5h	6.0	>300	90	$C_{25}H_{18}N_4O_5$	66.29 (66.08)	3.91 (3.96)	12.45 (12.33)

8.30 (m, 2H, C_4-H, C_5-H), 7.95 (m, 1H, C_6-H), 9.10 (m, 1H, C_7-H), 6.92-7.78 (m, 4H, Ar-H), 9.40 (s, 1H, CONH).

Anal. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.96; H, 4.94; N, 17.28. Found: C, 62.81; H, 4.98; N, 17.36.

Synthesis of [2-Oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic Acid Benzylidenehydrazide (**4a**).

A mixture of **3** (0.648 g, 20.0 mmol), benzaldehyde (0.212 g, 20.0 mmol) and DMF (5 drops) was subjected to microwave irradiation at 200 watts intermittently at 30 sec intervals for 1.5 minutes. On completion of reaction, as monitored by TLC, the reaction mixture was digested with cold water. The precipitate thus obtained was collected by filtration, washed with water and recrystallized from ethanol to furnish 0.392 g (95%) of pure **4a**, mp 170-172. Physical and spectral data of 4a are given in Tables 1 and 2. Other members of **4** are prepared by the same procedure.

Synthesis of 1-(5-Phenyl-[1,3,4]oxadiazol-2-ylmethyl)-3-(*p*-methoxyphenyl) -1*H*-[1,8]naphthyridin-2-one (**5a**)

Compound **4a** (0.824 g, 20.0 mmol) and IBD (0.71 g, 20.0 mmol) doped on neutral alumina (2 g) and mixed thoroughly and subjected to microwave irradiation at 800 watts intermittently at 30 sec intervals for 5.5 minutes. After complete conversion as indicated by TLC, the reaction mixture was cooled and extracted into dichloromethane and is neutralized with aqueous sodium bicarbonate solution. The dichloromethane layer is separated, dried over magnesium sulfate, filtered, and the crude product was recrystallized from methanol to give 0.36 g (88%) of pure **5a**, mp >300. Physical and spectral data of **5a** are given in Table 1 and 2. Other members of **5** are prepared by the same procedure.

Acknowledgements.

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Table 2

IR and ^{1}H NMR spectral data of [2-Oxo-3-(*p*-methoxyphenyl)-2*H*-[1,8]naphthyridin-1-yl]acetic acid arylidenehydrazides (**4**) and 1-(5-Aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(*p*-methoxyphenyl)-1*H*-[1,8]naphthyridin-2-ones (**5**)

Compound	IR cm^{-1} (KBr)	^{1}H NMR (δ, ppm) ($CDCl_3$ / $CDCl_3$ + DMSO-d_6)
4a	3438 (NH), 1692 (C=O), 1657 (C=O), 1609 (C=N)	3.92 (s, 3H, OCH_3), 5.85 (s, 2H, CH_2), 8.12 (m, 2H, C_4-H, C_5-H), 7.85 (m, 1H, C_6-H), 8.20 (m, 1H, C_7-H), 8.63 (s, 1H, N=CH), 6.98-7.80 (m, 9H, Ar-H), 11.02 (s, 1H, CONH)
4b	3436 (NH), 1694 (C=O), 1652 (C=O), 1609 (C=N)	2.40 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 5.80 (s, 2H, CH_2), 8.15 (m, 2H, C_4-H, C_5-H), 7.84 (m, 1H, C_6-H), 8.40 (m, 1H, C_7-H), 8.60 (s, 1H, N=CH), 6.89-7.78 (m, 8H, Ar-H), 11.05 (s, 1H, CONH)
4c	3434 (NH), 1690 (C=O), 1660 (C=O), 1605 (C=N)	3.88 (s, 6H, 2xOCH_3), 5.81 (s, 2H, CH_2), 8.02 (m, 2H, C_4-H, C_5-H), 7.82 (m, 1H, C_6-H), 8.32 (m, 1H, C_7-H), 8.63 (s, 1H, N=CH), 6.82-7.78 (m, 8H, Ar-H), 11.06 (s, 1H, CONH)
4d	3440 (NH), 1693 (C=O), 1658 (C=O), 1616 (C=N)	3.93 (s, 3H, OCH_3), 5.76 (s, 2H, CH_2), 8.22 (m, 2H, C_4-H, C_5-H), 8.01 (m, 1H, C_6-H), 8.50 (m, 1H, C_7-H), 9.02 (s, 1H, N=CH), 6.92-7.83 (m, 8H, Ar-H), 11.70 (s, 1H, CONH)
4e	3450 (NH), 1692 (C=O), 1659 (C=O), 1609 (C=N).	3.95 (s, 3H, OCH_3), 5.78 (s, 2H, CH_2), 8.00 (m, 2H, C_4-H, C_5-H), 7.81 (m, 1H, C_6-H), 8.56 (m, 1H, C_7-H), 8.62 (s, 1H, N=CH), 6.87-7.73 (m, 8H, Ar-H), 11.52 (s, 1H, CONH)
4f	3435 (NH), 1703 (C=O), 1652 (C=O), 1608 (C=N)	3.92 (s, 3H, OCH_3), 5.93 (s, 2H, CH_2), 8.26 (m, 2H, C_4-H, C_5-H), 8.00 (m, 1H, C_6-H), 8.60 (m, 1H, C_7-H), 9.08 (s, 1H, N=CH), 6.98-7.82 (m, 8H, Ar-H), 11.08 (s, 1H, CONH)
4g	3439 (NH), 1692 (C=O), 1652 (C=O), 1608 (C=N)	3.93 (s, 3H, OCH_3), 5.82 (s, 2H, CH_2), 8.21 (m, 2H, C_4-H, C_5-H), 7.99 (m, 1H, C_6-H), 8.56 (m, 1H, C_7-H), 8.78 (s, 1H, N=CH), 6.92-7.83 (m, 8H, Ar-H), 11.62 (s, 1H, CONH)
4h	3435 (NH), 1690 (C=O), 1658 (C=O), 1609 (C=N)	3.90 (s, 3H, OCH_3), 5.86 (s, 2H, CH_2), 6.02 (s, 2H, O-CH_2-O), 8.26 (m, 2H, C_4-H, C_5-H), 7.86 (m, 1H, C_6-H), 8.48 (m, 1H, C_7-H), 8.67 (s, 1H, N=CH), 6.89-7.78 (m, 7H, Ar-H), 11.53 (s, 1H, CONH)
5a	1658 (C=O), 1609 (C=N)	3.90 (s, 3H, OCH_3), 6.10 (s, 2H, CH_2), 8.18 (m, 2H, C_4-H, C_5-H), 7.90 (m, 1H, C_6-H), 8.42 (m, 1H, C_7-H), 6.90-7.69 (m, 9H, Ar-H)
5b	1656 (C=O), 1605 (C=N)	2.42 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 6.02 (s, 2H, CH_2), 8.23 (m, 2H, C_4-H, C_5-H), 8.02 (m, 1H, C_6-H), 8.42 (m, 1H, C_7-H), 6.92-7.86 (m, 8H, Ar-H)
5c	1660 (C=O), 1604 (C=N)	3.90 (s, 6H, 2xOCH_3), 6.00 (s, 2H, CH_2), 8.20 (m, 2H, C_4-H, C_5-H), 7.98 (m, 1H, C_6-H), 8.40 (m, 1H, C_7-H), 6.90-7.85 (m, 8H, Ar-H)
5d	1658 (C=O), 1607 (C=N)	3.92 (s, 3H, OCH_3), 6.03 (s, 2H, CH_2), 8.36 (m, 2H, C_4-H, C_5-H), 7.96 (m, 1H, C_6-H), 8.48 (m, 1H, C_7-H), 6.96-7.82 (m, 8H, Ar-H)
5e	1665 (C=O), 1612 (C=N)	3.90 (s, 3H, OCH_3), 5.98 (s, 2H, CH_2), 8.32 (m, 2H, C_4-H, C_5-H), 7.95 (m, 1H, C_6-H), 8.58 (m, 1H, C_7-H), 6.93-7.84 (m, 8H, Ar-H)
5f	1659 (C=O), 1610 (C=N)	3.88 (s, 3H, OCH_3), 6.03 (s, 2H, CH_2), 8.37 (m, 2H, C_4-H, C_5-H), 8.06 (m, 1H, C_6-H), 8.48 (m, 1H, C_7-H), 6.96-7.79 (m, 8H, Ar-H)
5g	1658 (C=O), 1610 (C=N)	3.92 (s, 3H, OCH_3), 6.08 (s, 2H, CH_2), 8.40 (m, 2H, C_4-H, C_5-H), 8.21 (m, 1H, C_6-H), 8.80 (m, 1H, C_7-H), 6.98-7.80 (m, 8H, Ar-H)
5h	1659 (C=O), 1609 (C=N)	3.90 (s, 3H, OCH_3), 6.02 (s, 2H, O-CH_2-O), 6.10 (s, 2H, CH_2), 8.37 (m, 2H, C_4-H, C_5-H), 8.02 (m, 1H, C_6-H), 8.56 (m, 1H, C_7-H), 6.95-7.80 (m, 7H, Ar-H)

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[17] IBD (0.355 g, 10.0 mmol) 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.

[18] The design involves piercing the roof of a domestic microwave oven and as such, proper sealing must be done in order to avoid the hazards of direct microwave exposure to the investigator.