Efficient synthesis of 1,3,4-oxadiazolyl-1,8-naphthyridines under microwave irradiation

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An expeditious and convenient method for the synthesis of 1-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(*m*-chlorophenyl)-1*H*-[1,8]-naphthyridin-2-ones **5** from [2-oxo-3-(*m*-chlorophenyl)-2*H*-[1,8]naphthyridin-1yl]acetic acid arylidenehydrazides **4** using chloramine-T under microwave irradiation is described.

Keywords: microwave irradiation, 1,3,4-oxadiazoles, 1,8-naphthyridines, chloramine-T

1,8-Naphthyridine derivatives have attracted the attention of chemists mainly because of the broad spectrum of biological properties exhibited by this class of compounds.[1-3] 1,3,4-Oxadiazoles have interested many researchers in diverse fields. Though various routes for the synthesis of these compounds are known,[6-8] most of them involve long preparation times, high reaction temperatures, low yields and usage of expensive and toxic reagents. Therefore, the development and introduction of convenient and efficient methods for the preparation of 1,3,4-oxadiazoles is of practical importance and is still in demand. Microwave-assisted organic reactions have attracted considerable importance in organic synthesis because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of organic compounds.[9-11] In recent years, chloramine-T has emerged as a potential oxidising agent in different areas of organic synthesis[12-14] because it is non-toxic, easy to handle and readily available. In view of this and in continuation of our work on microwave assisted organic transformations on 1,8-naphthyridine derivatives[14-18] we now describe a convenient, efficient, inexpensive and high yielding protocol for the synthesis of 1,3,4-oxadiazolyl-1,8-naphthyridines using chloramine-T under microwave irradiation.

Alkylation of 3-(*m*-chlorophenyl)-1,8-naphthyridin-2(1*H*)-one **1**[18] with ethyl chloroacetate in DMF in the presence of anhydrous K_2CO_3 under microwave irradiation afforded ethyl [2-oxo-3-(*m*-chlorophenyl-2*H*-[1,8]naphthyridin-1-yl]acetate **2** in excellent yield. The ester **2** on hydrazinolysis with refluxing hydrazine hydrate furnished [2-oxo-3-(*m*-chlorophenyl)-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 afforded the corresponding hydrazones, [2-oxo-3-(*m*-chlorophenyl)-2*H*-[1,8]naphthyridin-1-yl)acetic acid arylidenehydrazides **4** in excellent yields.

Oxidative cyclisation of hydrazones **4** with chloramine-T in ethanol under microwave irradiation furnished the respective 1-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(*m*-chlorophenyl)-1*H*-[1,8]naphthyridin-2- ones **5** (Scheme 1). The oxidative transformation is facile, clean and efficient and is devoid of any by-products. The experimental procedure is very simple. Furthermore, the products were obtained with a high degree of purity by this procedure and no further purification was needed. The high yield of the oxadiazole in so short a time shows the potential advantage of microwave irradiation. By conventional heating method (oil bath) at 110°C (highest observed temperature during irradiation), the reaction was still incomplete after 3h.

The structure of compounds **2–5** were confirmed by their spectroscopic (IR and ^{1}H NMR) and analytical data. To the best of our knowledge this is the first report on microwave assisted chloramine-T promoted synthesis of 1,3,4-oxadiazoles.

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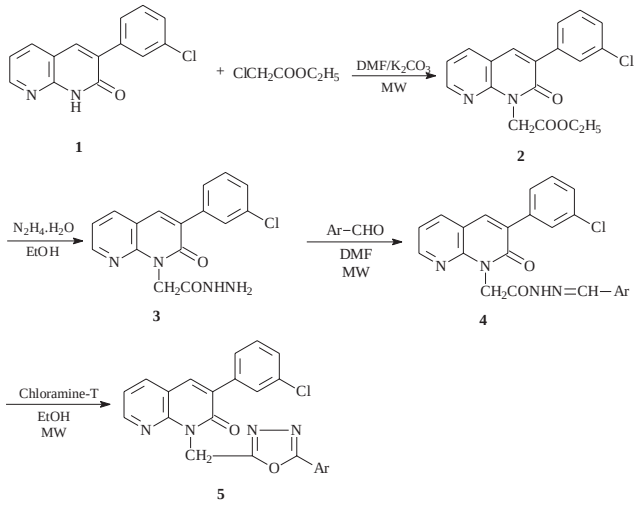

Scheme 1

In conclusion, we have demonstrated a convienient and highly efficient protocol for the synthesis of 1,3,4-oxadiazoles using chloramine-T under microwave irradiation. High yield, short reaction time, pure products, inexpensive and non-toxicity of the reagent are advantages of this procedure. The biological screening of the products **5** is in progress, and will be reported in future publications.

Experimental

Melting points were recorded on a Cintex melting point apparatus and are uncorrected. IR spectra (KBr) (ν_{max}; cm^{-1}) were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ, ppm) using TMS as internal standard. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyser. For microwave irradiation BPL 800 G (2450 MHz) domestic microwave oven was used. The purity of the compounds was checked using precoated TLC plates (Merk, 60F-254).

Ethyl [2-oxo-3-(m-chlorophenyl)-2H-[1,8]naphthyridin-1-yl] acetate **2 :** A mixture of 3-(*m*-chlorophenyl)-1,8-naphthyridin-2(1*H*)-one **1** (0.01 mol), ethyl chloroacetate (0.01 mol), anhydrous K_2CO_3 (0.01 mol) and DMF (10 ml) was subjected to microwave irradiation intermittently at 30 s intervals for 3.5 min. On completion of reaction, as monitored by TLC, the reaction was cooled and treated with chilled water. The solid that precipitated was filtered, washed with water and recrystallised from ethanol to give **2**, yield 96%, m.p. 160–162°C; IR: 1744, 1652, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 1.22 (t, *J* = 7.0 Hz, 3H, CH_3), 4.20 (q, *J* = 7.0 Hz, 2H, CH_2), 5.22 (s, 2H, N–CH_2), 8.30 (m, 2H, C_4-H, C_5–H), 8.00 (m, 1H, C_6–H), 8.52 (m, 1H, C_7–H), 7.20–7.72 (m, 4H, Ar–H); Anal. Calcd. For $C_{18}H_{15}N_2O_3Cl$: C, 63.07; H, 4.38; N, 8.18; Found C, 63.26; H, 4.44; N, 8.25.

[2-Oxo-3-(m-chlorophenyl)-2H-[1,8]naphthyridin-1-yl]acetic acid hydrazide **3:** A mixture of **2** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (30 ml) was refluxed on a water-bath for 5h. The reaction mixture was concentrated to one third of its volume, and cooled. The resulting solid product was filtered and recrystallised from ethanol to afford **3**, yield 90%, m.p. 181–182°C, IR: 3450, 3312, 3150,

1648, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.25 (br, 2H, NH_2), 5.27 (s, 2H, N–CH_2), 7.95 (s, 1H, C_4–H), 8.05 (m, 1H, C_5–H), 7.65 (m, 1H, C_6–H), 8.60 (m, 1H, C_7–H), 7.15–7.62 (m, 4H, Ar–H), 9.38 (s, 1H, CONH); Anal. Calcd. For $C_{16}H_{13}N_4O_2Cl$: C, 58.45; H, 3.96; N, 17.05; Found C, 58.65; H, 3.92; N, 17.14.

General procedure for the synthesis of [2-oxo-3-(m-chlorphenyl)-2H-[1,8]naphthyridin-1-yl]acetic acid arylidenehydrazides **4**: A mixture of **3** (0.01 mol), aromatic aldehyde (0.01 mol) and DMF (5 drops) was exposed to microwaves at 150 watts intermittently at 30 sec intervals for the specified time (Table 1). On completion of reaction, as monitored by TLC, the reaction mixture was digested with cold water. The precipitate thus obtained was filtered, washed with water and recrystallised from ethanol to give **4**.

4a : IR : 3432, 1680, 1655, 1628 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.25 (s, 2H, CH_2), 7.62 (m, 2H, H-4, H-5), 7.46 (m, 1H, H-6), 8.12 (m, 1H, H-7), 6.78–7.35 (m, 10H, N=CH, 9Ar-H), 9.80 (s, 1H, CONH).

4b : IR : 3450, 1682, 1654, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 2.20 (s, 3H, CH_3), 5.40 (s, 2H, CH_2), 7.78 (m, 2H, H-4, H-5), 7.62 (m, 1H, H-6), 8.20 (m, 1H, H-7), 6.80–7.52 (m, 9H, N=CH, 8Ar-H), 10.02 (s, 1H, CONH).

4c : IR : 3432, 1680, 1654, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.85 (s, 3H, OCH_3), 5.65 (s, 2H, -CH_2), 8.18 (m, 2H, H-4, H-5), 7.76 (m, 1H, H-6), 8.43 (m, 1H, H-7), 6.82–7.60 (m, 9H, N=CH, 8Ar-H), 10.18 (s, 1H, CONH).

4d : IR : 3433, 1685, 1654, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.80 (s, 2H, -CH_2), 8.22 (m, 2H, H-4, H-5), 8.05 (m, 1H, H-6), 8.51 (m, 1H, H-7), 7.00–7.78 (m, 9H, N=CH, 8Ar-H), 9.92 (s, 1H, CONH).

4e : IR : 3434, 1682, 1654, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.83 (s, 2H, CH_2), 8.20 (m, 2H, H-4, H-5), 7.94 (m, 1H, H-6), 8.52 (m, 1H, H-7), 7.18–7.80 (m, 9H, N=CH, 8Ar-H), 10.02 (s, 1H, CONH).

4f : IR : 3433, 1680, 1655, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.65 (s, 2H, CH_2), 8.17 (m, 2H, H-4, H-5), 8.00 (m, 1H, H-6), 8.47 (m, 1H, H-7), 7.20–7.79 (m, 9H, N=CH, 8Ar-H), 9.98 (s, 1H, CONH).

4g : IR : 3448, 1684, 1654, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.82 (s, 2H, CH_2), 8.24 (m, 2H, H-4, H-5), 7.97 (m, 1H, H-6), 8.55 (m, 1H, H-7), 7.12–7.73 (m, 9H, N=CH, 8Ar-H), 9.82 (s, 1H, CONH).

4h : IR : 3445, 1686, 1654, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.72 (s, 2H, CH_2), 6.02 (s, 2H, O-CH_2-O), 8.00 (m, 2H, H-4, H-5), 7.65 (m, 1H, H-6), 8.52 (m, 1H, H-7), 6.80–7.44 (m, 8H, N=CH, 7Ar-H), 10.05 (s, 1H, CONH)

General procedure for the synthesis of 1-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(m-chlorophenyl)-1H-[1,8]naphthyridin-2-ones **5** : To a solution of appropriate hydrazone **4** (0.01 mol) in ethanol (15 ml), chloramine-T (0.01 mol) was added. The reaction mixture was subjected to microwave irradiation intermittently at 30 sec intervals for specified time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with cold water. The solid thus obtained was filtered, washed with water and recrystallised from methanol to afford **5**.

5a : IR : 1654, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.04 (s, 2H, CH_2), 8.22 (m, 2H, H-4, H-5), 8.06 (m, 1H, H-6), 8.43 (m, 1H, H-7), 7.30–7.87 (m, 9H, Ar–H).

5b : IR : 1654, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 2.40 (s, 3H, CH_3), 6.00 (s, 2H, CH_2), 8.08 (m, 2H, H-4, H-5), 7.82 (m, 1H, H-6), 8.48 (m, 1H, H-7), 7.12–7.70 (m, 8H, Ar–H).

5c : IR : 1655, 1604 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.82 (s, 3H, OCH_3), 6.02 (s, 2H, CH_2), 8.10 (m, 2H, H-4, H-5), 7.90 (m, 1H, H-6), 8.52 (m, 1H, H-7), 6.82–7.80 (m, 8H, Ar–H).

5d : IR : 1650, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.03 (s, 2H, CH_2), 8.18 (m, 2H, H-4, H-5), 7.96 (m, 1H, H-6), 8.46 (m, 1H, H-7), 6.85–7.56 (m, 8H, Ar–H).

5e : IR : 1654, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.10 (s, 2H, CH_2), 8.00 (m, 2H, H-4, H-5), 7.83 (m, 1H, H-6), 8.52 (m, 1H, H-7), 6.82–7.50 (m, 8H, Ar–H).

5f : IR : 1656, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.08 (s, 2H, CH_2), 8.22 (m, 2H, H-4, H-5), 7.95 (m, 1H, H-6), 8.60 (m, 1H, H-7), 7.20–7.65 (m, 8H, Ar–H).

5g : IR : 1655, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.10 (s, 2H, CH_2), 8.32 (m, 2H, H-4, H-5), 8.15 (m, 1H, H-6), 8.68 (m, 1H, H-7), 7.15–7.79 (m, 8H, Ar–H).

5h : IR : 1654, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.10 (s, 4H, CH_2, O–CH_2–O), 8.21 (m, 2H, H-4, H-5), 7.95 (m, 1H, H-6), 8.55 (m, 1H, H-7), 7.20–7.70 (m, 7H, Ar–H).

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Table 1 Physical and analytical data of [2-oxo-3-(*m*-chlorophenyl)-2*H*-[1,8] naphthyridin-1-yl]acetic acid arylidenehydrazides **4** and 1-(5-aryl-[1,3,4]oxadiazol-2-ylmethyl)-3-(*m*-chlorophenyl)-1*H*-[1,8]naphthyridin-2-ones **5**

Compd	Ar	Reaction time (min)	Yield % (m.p.)	Mol. formula	Microanalysis (Found) C	H	N
4a	C_6H_5	1.0	90 (190–192)	$C_{23}H_{17}N_4O_2Cl$	66.27 (4.02)	(66.46) 13.45	4.08 (13.53)
4b	*p*-$CH_3C_6H_4$	1.5	98 (175–177)	$C_{24}H_{19}N_4O_2Cl$	66.90 (4.47)	(66.75) 13.01	4.41 (13.08)
4c	*p*-$CH_3OC_6H_4$	2.0	95 (210–213)	$C_{24}H_{19}N_4O_3Cl$	64.50 (4.30)	(64.71) 12.54	4.26 (12.59)
4d	*o*-ClC_6H_4	1.5	92 (218–220)	$C_{23}H_{16}N_4O_2Cl_2$	61.90 (3.59)	(61.73) 12.42	3.55 (12.50)
4e	*p*-ClC_6H_4	1.0	96 (215–216)	$C_{23}H_{16}N_4O_2Cl_2$	61.90 (3.60)	(61.72) 12.42	3.55 (12.51)
4f	*o*-BrC_6H_4	1.5	94 (160–162)	$C_{23}H_{16}N_4O_2ClBr$	55.70 (3.28)	(55.91) 11.30	3.23 (11.37)
4g	*m*-$NO_2C_6H_4$	1.0	92 (201–202)	$C_{23}H_{16}N_5O_4Cl$	59.80 (3.52)	(59.96) 15.17	3.47 (15.25)
4h	3,4-(O-CH_2-O) C_6H_3	1.5	96 (194–196)	$C_{24}H_{17}N_4O_4Cl$	62.54 (3.65)	(62.73) 12.16	3.69 (12.22)
5a	C_6H_5	4.0	85 (>300)	$C_{23}H_{15}N_4O_2Cl$	66.59 (3.68)	(66.70) 13.51	3.62 (13.58)
5b	*p*-$CH_3C_6H_4$	4.0	92 (>300)	$C_{24}H_{17}N_4O_2Cl$	67.21 (3.92)	(67.42) 13.07	3.97 (13.14)
5c	*p*-$CH_3OC_6H_4$	4.5	88 (>300)	$C_{24}H_{17}N_4O_3Cl$	64.79 (3.86)	(64.60) 12.60	3.82 (12.67)
5d	*o*-ClC_6H_4	4.0	86 (>300)	$C_{23}H_{14}N_4O_2Cl_2$	61.47 (3.17)	(61.67) 12.47	3.12 (12.54)
5e	*p*-ClC_6H_4	4.5	90 (>300)	$C_{23}H_{14}N_4O_2Cl_2$	61.47 (3.16)	(61.68) 12.47	3.12 (12.55)
5f	*o*-BrC_6H_4	5.0	87 (>300)	$C_{23}H_{14}N_4O_2ClBr$	55.93 (2.88)	(55.78) 11.35	2.84 (11.45)
5g	*m*-$NO_2C_6H_4$	5.0	84 (>300)	$C_{23}H_{14}N_5O_4Cl$	60.07 (3.10)	(60.26) 15.23	3.05 (15.30)
5h	3,4-(O–CH_2–O) C_6H_3	4.5	88 (>300)	$C_{24}H_{15}N_4O_4Cl$	62.81 (3.34)	(62.98) 12.21	3.27 (12.29)

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