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Note

Microwave assisted synthesis of 1,3,4-oxadiazolyl 1, 8-naphthyridines under solvent-free conditions using solid support

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A convient synthesis of 1-(4-acetyl-5-aryl-5-methyl-[1,3,4]oxadiazol-2-ylmethyl)-3-(4-chlorophenyl)-1*H*-[1, 8]naphthyridin-2-ones**,** by cyclization of acetophenone [2-oxo-3-(4-chlorophenyl)-2*H*-[1,8]-naphthyridin-1-yl]methylcarbonylhydrazones with acetic anhydride using silica gel as solid support under microwave irradition is described. The structural assignments of the compounds are based on their elemental analyses and spectral data.

Keywords: 1,3,4 Oxadiazole, 1,8 naphthyridine, acetophenones, hydrazone, acetic anhydride, silica gel, solid support, microwave irradition, solvent-free condition

The chemistry of 1,3,4-oxadiazoles has received considerable attention from synthetic organic chemists due to their diverse biological activities[1-3]. Several research groups have contributed to the development of methods of synthesis of 1,3,4-oxadiazoles[4-6]. However, these procedures are time consuming and proceed in low yields. Therefore, a convenient and eco-friendly method for the synthesis of 1,3,4-oxadiazoles is highly desirable. Further, 1,8-naphthyridine derivatives have become attractive targets in organic synthesis due to their significant pharmacological activities[7-10]. The solvent-free organic reactions assisted by microwaves in particular, have gained special attention in recent years[11-13]. The use of microwave irradiation in organic synthesis can increase the purity of the resulting products, enhance the chemical yield and shorten the reaction time. Solvent-free reaction leads to a clean, eco-friendly and economic technology. Reactions on solid support without using solvent usually with open vessel in domestic microwave ovens are currently in use for synthetic chemist to create eco-friendly atmosphere[14,15]. In view of these facts, and in continuation of the interest in the microwave-assisted organic transformations of 1,8-naphthyridine derivatives[16-18], we present herein a rapid and efficient method for the synthesis of 1,3,4-oxadiazoyl 1,8-naphthyridines in solvent-free conditions under microwave irradiation using silica gel as solid support.

The starting compound, [2-oxo-3-(4-chlorophenyl)-2*H*-[1,8]-naphthyridin-1-yl]acetic acid hydrazide **2** was prepared by the hydrazinolysis of ethyl-[2-oxo-3-(4-chlorophenyl)-2*H*-[1,8]naphthyridin-1-yl]acetate **1**, which was in turn obtained by the alkylation of 1,2-dihydro-3-(4-chlorophenyl)-2*H*-[1,8]naphthyridin-2-one with ethyl chloroacetate in DMF in the presence of anhydrous K_2CO_3 under microwave irradiation[18].

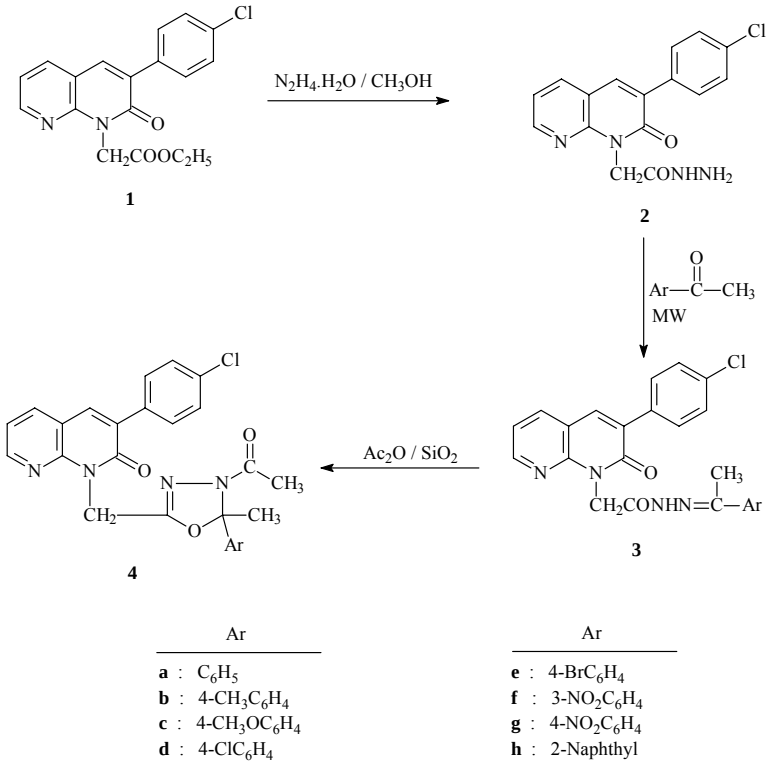
Condensation of **2** with various acetophenones in the presence of catalytic amount of DMF under microwave irradiation furnished the corresponding hydrazones, acetophenone [2-oxo-3-(4-chlorophenyl)-2*H*-[1,8]naphthyridin-1-yl]methylcarbonylhydrazones **3** in excellent yields.

The hydrazones **3** on treatment with acetic anhydride under microwave irradiation using silica gel as solid support resulted in the formation of the desired 1-(4-acetyl-5-aryl-5-methyl-[1,3,4]oxadiazol-2-ylmethyl)-3-(4-chloro-phenyl)-1*H*-[1,8]naphthyridin-2-ones **4** (**Scheme I**).

The cyclization reactions progressed efficiently to completion giving very good yields at ambient pressure within a few minutes. The products were obtained with a high degree of purity by this procedure and no further purification was required. The experimental procedure is very simple. The process is environmentally benign.

In a typical case, a mixture of hydrazone **3a** (Ar = C_6H_5) and Ac_2O deposited on silica gel, was exposed to microwave irradiation at 400 W intermittently at 30 s intervals for 4.0 min. The reaction was allowed to attain RT and extracted with methanol. After usual work-up 1-(4-acetyl-5-phenyl-5-methyl-[1,3,4]oxadiazol-2-ylmethyl)-3-(4-chloro-phenyl)-1*H*-[1,8]naphthyridin-2-one **4a** (Ar = C_6H_5) was obtained in 85% yield.

The reaction proceeds to only a minor extent (5-10% in 4.0 5.5 min) when conducted under conventional conditions in an oil-bath preheated to 120°C (highest observed temperature during irradia-



Scheme I

tion) thus demonstrating the advantage of the microwave heating method.

The reaction is general applicability and the different 1,3,4-oxadiazolyl 1,8-naphthyridines **4** synthesized are given in **Table I**.

The structures of the compounds **3** and **4** were confirmed by their elemental analyses, IR and ^1H NMR spectroscopy.

In conclusion, we have divised a simple and useful method for the synthesis of 1,3,4-oxadiazoles under mild and environmentally safe reaction conditions. The experimental simplicity, high yields, short reaction times, mild reaction conditions, high purity and absence of solvent are the noteworthy advantages of the present procedure.

Table I — Physical characterization data of compounds **3** and **4**

Compd	Ar	Reaction Time (min)	m.p. (°C)	Yield (%)
3a	C_6H_5	1.5	244	94
3b	4-$CH_3C_6H_4$	2.0	236	96
3c	4-$CH_3OC_6H_4$	2.0	210	94
3d	4-ClC_6H_4	1.0	246	98
3e	4-BrC_6H_4	1.0	232	96
3f	3-$NO_2C_6H_4$	1.0	200	95
3g	4-$NO_2C_6H_4$	1.0	174	97
3h	2-Naphthyl	1.5	208	95
4a	C_6H_5	4.0	210	85
4b	4-$CH_3C_6H_4$	5.5	192	87
4c	4-$CH_3OC_6H_4$	5.0	184	86
4d	4-ClC_6H_4	3.5	205	88
4e	4-BrC_6H_4	4.0	198	86
4f	3-$NO_2C_6H_4$	4.5	180	84
4g	4-$NO_2C_6H_4$	5.5	120	86
4h	2-Naphthyl	4.5	184	85

Experimental Section

Melting points were recorded by means of a Cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra were recorded in KBr pellets on a Perkin-Elmer Spectrum BX series FT-IR spectrophotometer. ^1H NMR Spectra on a Varian Gemini 400 MHz spectrometer using TMS as internal standard and mass spectra on a VG Micromass 7070H spectrometer. Elemetal analyses were performed on a Perkin-Elmer 240 CHN elemetal analyser. Microwave irradiation

was carried out in an LG MG-556p domestic microwave oven.

General procedure for the synthesis of acetophenone[2-oxo-3-(4-chlorophenyl)-2*H*-[1,8]naphthyridin-1-yl]methylcarbonylhydrazones 3. A mixture of [2-oxo-3-(4-chlorophenyl)-2*H*-[1,8]naphthyridin-1-yl]-acetic acid hydrazide **2** (0.01 mole), acetophenone (0.01 mole) and DMF (5 drops) was subjected to microwave irradiation at 200 W intermittently at 30 s intervals for the specified time (**Table I**). On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with chilled water. The precipitate thus obtained was filtered, washed with water and recrystallized from ethanol to afford **3**.

3a: IR (KBr): 3432 (NH), 1647 (ring C=0), 1629 (CONH), 1592 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 5.85 (s, 2H, CH_2), 7.95 (m, 1H, C_6-H), 8.10 (s, 1H, C_4-H), 8.28 (m, 1H, C_5-H), 8.58 (m, 1H, C_7-H), 6.90-7.80 (m, 9H, Ar-H), 9.38 (s, 1H, CONH); MS: *m/z* 430 (M^+). Anal. Calcd for $C_{24}H_{19}N_4O_2Cl$: C, 66.90; H, 4.31; N, 13.00. Found: C, 66.74; H, 4.35; N, 13.07%.

3b: IR (KBr): 3430 (NH), 1652 (ring C=0), 1625 (CONH), 1590 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.28 (s, 3H, N=C-CH_3), 5.82 (s, 2H, CH_2), 7.98 (m, 1H, C_6-H), 8.18 (s, 1H, C_4-H), 8.26 (m, 1H, C_5-H), 8.53 (m, 1H, C_7-H), 7.00-7.92 (m, 8H, Ar-H), 9.45 (s, 1H, CONH); MS: *m/z* 444 (M^+). Anal. Calcd for $C_{25}H_{21}N_4O_2Cl$: C, 67.49; H, 4.72; N, 12.60. Found: C, 67.64; H, 4.76; N, 12.26%.

3c: IR (KBr): 3440 (NH), 1653 (ring C=0), 1628 (CONH), 1580 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 5.90 (s, 2H, CH_2),

7.98 (m, 1H, C_6-H), 8.25 (s, 1H, C_4-H), 8.50 (m, 1H, C_5-H), 8.65 (m, 1H, C_7-H), 7.05-7.90 (m, 8H, Ar-H), 9.40 (s, 1H, CONH); MS: *m/z* 460 (M^+). Anal. Calcd for $C_{25}H_{21}N_4O_3Cl$: C, 65.15; H, 4.56; N, 12.16. Found: C, 65.32; H, 4.61; N, 12.23%.

3d: IR (KBr): 3428 (NH), 1654 (ring C=0), 1625 (CONH), 1586 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 7.90 (m, 1H, C_6-H), 8.15 (s, 1H, C_4-H), 8.25 (m, 1H, C_5-H), 8.50 (m, 1H, C_7-H), 7.18-7.80 (m, 8H, Ar-H), 9.36 (s, 1H, CONH); MS: *m/z* 464 (M^+). Anal. Calcd for $C_{24}H_{18}N_4O_2Cl_2$: C, 61.93; H, 3.87; N, 12.04. Found: C, 61.75; H, 3.92; N, 12.11%.

3e: IR (KBr): 3425 (NH), 1652 (ring C=0), 1626 (CONH), 1585 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 5.80 (s, 2H, CH_2), 7.92 (m, 1H, C_6-H), 8.12 (s, 1H, C_4-H), 8.20 (m, 1H, C_5-H), 8.48 (m, 1H, C_7-H), 7.20-7.86 (m, 8H, Ar-H), 9.42 (s, 1H, CONH); Anal. Calcd for $C_{24}H_{18}N_4O_2ClBr$: C, 56.52; H, 3.53; N, 10.99. Found: C, 56.78; H, 3.57; N, 11.07%.

3f: IR (KBr): 3434 (NH), 1654 (ring C=0), 1630 (CONH), 1588 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.23 (s, 3H, CH_3), 5.86 (s, 2H, CH_2), 7.92 (m, 1H, C_6-H), 8.17 (s, 1H, C_4-H), 8.28 (m, 1H, C_5-H), 8.52 (m, 1H, C_7-H), 7.17-7.82 (m, 8H, Ar-H), 9.38 (s, 1H, CONH); Anal. Calcd for $C_{24}H_{18}N_5O_4Cl$: C, 60.56; H, 3.78; N, 14.72. Found: C, 60.72; H, 3.82; N, 14.80%.

3g: IR (KBr): 3450 (NH), 1654 (ring C=0), 1628 (CONH), 1586 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.26 (s, 3H, CH_3), 5.92 (s, 2H, CH_2), 7.95 (m, 1H, C_6-H), 8.10 (s, 1H, C_4-H), 8.28 (m, 1H, C_5-H), 8.50 (m, 1H, C_7-H), 7.20-7.80 (m, 8H, Ar-H), 9.40 (s, 1H, CONH); Anal. Calcd for $C_{24}H_{18}N_5O_4Cl$: C, 60.56; H, 3.78; N, 14.72. Found: C, 60.74; H, 3.81; N, 14.79%.

3h: IR (KBr): 3435 (NH), 1653 (ring C=0), 1627 (CONH), 1587 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 5.82 (s, 2H, CH_2), 7.98 (m, 1H, C_6-H), 8.15 (s, 1H, C_4-H), 8.26 (m, 1H, C_5-H), 8.54 (m, 1H, C_7-H), 7.18-7.87 (m, 1H, Ar-H), 9.46 (s, 1H, CONH); Anal. Calcd for $C_{28}H_{21}N_4O_2Cl$: C, 69.93; H, 4.37; N, 11.65. Found: C, 70.10; H, 4.42; N, 11.72%.

General procedure for the synthesis of 1-(4-acetyl-5-aryl-5-methyl-[1,3,4]oxadiazol-2-ylmethyl)-3-(4-chlorophenyl)-1*H*-[1,8]naphthyridin-2-ones 4. Silica gel (3 g) was added to the mixture of hydrazone **3** (0.01 mole) and Ac_2O (2 mL) at RT. The reaction mixture was thoroughly mixed and adsorbed material was dried in air and irradiated in microwave oven at 400 W intermittently at 30 s intervals for the time indicated in **Table I**. The reaction mixture was cooled and the product was extracted with methanol. Dilution of methanol solution with ice-cold water gave the crude product, which was filtered, washed with water and recrystallization from methanol to give **4**.

4a: IR (KBr): 1734 ($COCH_3$), 1654 (C=0 naphthyridine), 1586 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 2.32 (s, 3H, $COCH_3$), 5.42 (s, 2H, CH_2), 7.82 (m, 2H, C_4-H, C_6-H), 7.93 (m, 1H, C_5-H), 8.50 (m, 1H, C_7-H), 7.18-7.68 (m, 9H, Ar-H); MS: *m/z* 472 (M^+). Anal. Calcd for $C_{26}H_{21}N_4O_3Cl$: C, 66.03; H, 4.44; N, 11.85. Found: C, 66.62; H, 4.49; N, 11.92%.

4b: IR (KBr): 1724 ($COCH_3$), 1654 (C=0 naphthyridine), 1582 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.45 (S, 3H, $COCH_3$), 5.45 (s, 2H, CH_2), 7.93 (m, 2H, C_4-H, C_6-H), 8.12 (s, 1H, C_5-H), 8.52 (m, 1H, C_7-H), 7.16-7.72 (m, 8H, Ar-H); MS: *m/z* 486 (M^+). Anal. Calcd for

$C_{27}H_{23}N_4O_3Cl$: C, 66.60; H, 4.72; N, 11.51. Found: C, 66.67; H, 4.76; N, 11.58%.

4c: IR (KBr): 1722 ($COCH_3$), 1652 (C=0 naphthyridine), 1585 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.35 (s, 3H, $COCH_3$), 3.85 (s, 3H, OCH_3), 5.38 (s, 2H, CH_2), 7.90 (m, 1H, C_4-H, C_6-H), 8.15 (s, 1H, C_5-H), 8.60 (m, 1H, C_7-H), 7.15-7.80 (m, 8H, Ar-H); MS: *m/z* 502 (M^+). Anal. Calcd for $C_{27}H_{23}N_4O_4Cl$: C, 64.47; H, 4.57; N, 11.14. Found: C, 64.62; H, 4.61; N, 11.22%.

4d: IR (KBr): 1730 ($COCH_3$), 1654 (C=0 naphthyridine), 1580 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.33 (s, 3H, $COCH_3$), 5.35 (s, 2H, CH_2), 7.88 (m, 2H, C_4-H, C_6-H), 8.12 (s, 1H, C_5-H), 8.48 (m, 1H, C_7-H), 7.10-7.78 (m, 8H, Ar-H); MS: *m/z* 506 (M^+). Anal. Calcd for $C_{26}H_{20}N_4O_3Cl_2$: C, 61.53; H, 3.94; N, 11.04. Found: C, 61.70; H, 3.98; N, 11.12%.

4e: IR (KBr): 1732 ($COCH_3$), 1652 (C=0 naphthyridine), 1588 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 2.30 (s, 3H, $COCH_3$), 5.40 (s, 2H, CH_2), 7.95 (m, 2H, C_4-H, C_6-H), 8.08 (m, 1H, C_5-H), 8.52 (m, 1H, C_7-H), 7.14-7.80 (m, 8H, Ar-H); Anal. Calcd for $C_{26}H_{20}N_4O_3ClBr$: C, 56.57; H, 3.62; N, 10.15. Found: C, 56.75; H, 3.66; N, 10.22%.

4f: IR (KBr): 1724 ($COCH_3$), 1654 (C=0 naphthyridine), 1580 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.56 (s, 3H, $COCH_3$), 5.80 (s, 2H, CH_2), 7.80 (m, 2H, C_4-H, C_6-H), 8.24 (m, 1H, C_5-H), 8.50 (m, 1H, C_7-H), 7.12-7.70 (m, 8H, Ar-H); Anal. Calcd for $C_{26}H_{20}N_5O_5Cl$: C, 60.29; H, 3.86; N, 13.53. Found: C, 60.47; H, 3.90; N, 13.60%.

4g: IR (KBr): 1728 ($COCH_3$), 1653 (C=0 naphthyridine), 1582 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.25 (s, 3H, $COCH_3$), 5.82 (s, 2H, CH_2), 7.90 (m, 1H, C_6-H), 8.20 (m, 2H, C_4-H, C_5-H), 8.53 (m, 1H, C_7-H), 7.18-7.80 (m, 8H, Ar-H); Anal. Calcd for $C_{26}H_{20}N_5O_5Cl$: C, 60.29; H, 3.86; N, 13.53. Found: C, 60.46; H, 3.91; N, 13.59%.

4h: IR (KBr): 1734 ($COCH_3$), 1652 (C=0 naphthyridine), 1588 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, CH_3), 2.35 (s, 3H, $COCH_3$), 5.60 (s, 2H, CH_2), 7.90 (m, 2H, C_4-H, C_6-H), 8.20 (m, 1H, C_5-H), 8.48 (m, 1H, C_7-H), 7.15-7.85 (m, 11H, Ar-H); Anal. Calcd for $C_{30}H_{23}N_4O_3Cl$: C, 73.92.29; H, 4.72; N, 11.50. Found: C, 74.08; H, 4.76; N, 11.58%.

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