Indian Journal of Heterocyclic Chemistry
Vol. 23, April-June, 2014, pp. 393-398

ECO-FRIENDLY SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 6-ARYL-10-NITRO-12*H*-[1,8] NAPHTHYRIDINO [2,1-*b*] QUINAZOLIN-12-ONES

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Received 12 Nov. 2013; Accepted 24 April 2014

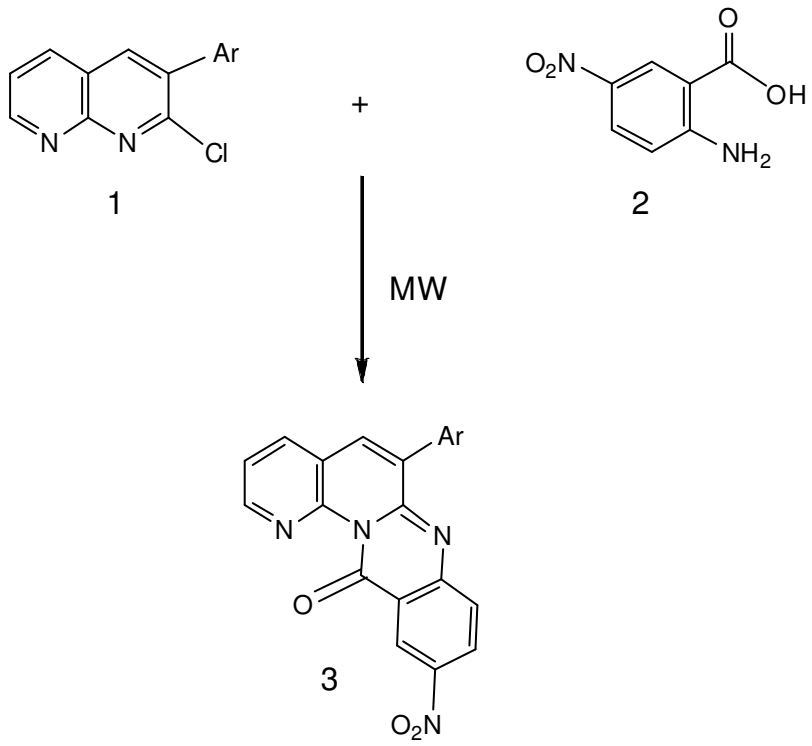
A highly efficient, simple and rapid method for the synthesis of 6-aryl-10-nitro-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones **3** by the cyclocondensation of 3-aryl-2-chloro-1,8-naphthyridines **1** with 2-amino-5-nitrobenzoic acid **2** in the presence of catalytic amount of DMF under microwave irradiation has been described. The yields are very good and purity is high. The structures of compounds **3** were established by their elemental analyses and spectral (IR, ^{1}H NMR and MS) data. Compounds **3** have been screened for their antibacterial activity.

1,8-Naphthyridines generate a wide spread interest due to their pharmacological and microbiological activities[1-3]. Quinazolines represent one of the most active class of compounds possessing a wide spectrum of biological activity[4,5]. Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and quinazoline might result in compounds with interesting biological activity. Microwave-induced Organic Reaction Enhancement (MORE) chemistry reactions are extremely fast, cleaner than conventional reactions and lead to higher atom economy (less chemical waste)[6-8]. Because of short time requirement, ease of workability and eco-friendliness, microwaves provide an alternative green approach to environmentally unacceptable procedures using toxic and expensive reagents. In view of this and in continuation of our interest in microwave-assisted organic transformations of 1,8-naphthyridine derivatives[9-11], we present herein, a convenient, practical and efficient method for the synthesis of 6-aryl-10-nitro-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones in solvent-free conditions under microwave irradiation.

Cyclocondensation of 3-aryl-2-chloro-1,8-naphthyridines **1** with 2-amino-5-nitrobenzioc acid **2** in the presence of catalytic amount of DMF without any solvent under microwave irradiation afforded the corresponding 6-aryl-10-nitro 12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones **3** (Scheme-1), in very good yields (90-96%) with short reaction time (2.0-3.5 min). The reaction is simple, clean, rapid and efficient and is devoid of any side products. The products were obtained with high degree of purity by this procedure. The process is environmentally benign. The experimental procedure is very simple. It was observed that the neat mixture of **1** and **2** did not reacted under microwave irradiation, but the reaction proceeds to completion within minutes on addition of few drops of high dielectric solvent such as DMF.

In a typical experimental procedure, equimolar quantities of 2-chloro-3-phenyl-1,8-naphthyridine **1**a, 2-amino-5-nitrobenzoic acid **2** and catalytic amount of DMF was exposed to microwave irradiation at 400 watts intermittently for 30 sec. intervals for 2.0 min. the reaction mixture was cooled to RT, digested with water and filtered off. After usual work-up 6-phenyl-10-nitro-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-one **3**a was obtained in 92% yield. The reaction is of general applicability and the various 6-aryl-10-nitro-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones **3** synthesized are given in Table-1.

The reaction proceeds to only 5-7% in 2.0-3.5 min, when conducted under conventional conditions in an oil-bath preheated to 120^0 (measured



	Ar		Ar
a	C_6H_5	h	4-ClC_6H_4
b	4-$CH_3C_6H_4$	i	2-FC_6H_4
c	2-$CH_3OC_6H_4$	j	3-FC_6H_4
d	3-$CH_3OC_6H_4$	k	4-FC_6H_4
e	4-$CH_3OC_6H_4$	l	2-$CF_3C_6H_4$
f	2-ClC_6H_4	m	3-$CF_3C_6H_4$
g	3-ClC_6H_4	n	4-$CF_3C_6H_4$

SCHEME-1

Table-1
Physical data of compounds **3**

Compd	Ar	Reaction time (min)	M.P. (°C)	Yield (%)
3a	C_6H_5	2.0	225	92
3b	4-$CH_3C_6H_4$	2.5	236	93
3c	2-$CH_3OC_6H_4$	2.5	184	91
3d	3-$CH_3OC_6H_4$	2.0	178	90
3e	4-$CH_3OC_6H_4$	2.5	195	94
3f	2-ClC_6H_4	3.0	220	92
3g	3-ClC_6H_4	2.5	215	90
3h	4-ClC_6H_4	3.5	245	96
3i	2-FC_6H_4	2.5	223	92
3j	3-FC_6H_4	3.0	228	90
3k	4-FC_6H_4	3.5	235	95
3l	2-$CF_3C_6H_4$	3.0	210	92
3m	3-$CF_3C_6H_4$	2.5	198	90
3n	4-$CF_3C_6H_4$	3.5	223	94

All the compounds gave satisfactory C,H,N elemental analyses.

immediately after microwave irradiation), thus demonstrating the advantage of the microwave heating method.

The structural assignments of compounds **3** were based on their elemental analyses and spectral (IR, ^{1}H NMR and MS) data. The experimental simplicity, short reaction times, high yields, excellent purity and absence of solvent are the advantages of this method and thus, the method is environmentally benign.

Antibacterial activity

The antibacterial activity of the title compounds **3** was examined against the bacteria *Escherichia coli* and *Bacillus subtilis* by filter paper disc technique of Vincent and Vincent[12] at 250 and 500 μg/disc concentrations. Standard antibacterial Gentamycin was also screened under similar conditions for comparison. The results are presented in Table-2.

Table-2
Antibacterial screening results of compounds **3**

Compd	Inhibition zone (in mm)			
	E.coli at		*B. subtilis* at	
	250 μg/disc	500 μg/disc	250 μg/disc	500 μg/disc
3a	7.5	15.0	6.0	9.5
3b	8.5	17.5	6.5	10.5
3c	7.5	15.5	5.5	8.5
3d	7.0	14.0	5.0	7.5
3e	8.0	16.5	6.0	10.5
3f	8.0	18.0	7.0	11.0
3g	7.5	15.5	6.0	10.0
3h	11.0	20.5	7.0	13.5
3i	9.0	17.0	6.5	10.5
3j	7.5	16.0	6.0	9.5
3k	10.5	20.0	7.0	12.5
3l	7.5	16.5	7.0	11.5
3m	7.0	16.0	6.0	9.5
3n	10.0	19.5	7.0	13.0
Gentamycin	12.0	22.0	8.0	15.0

Experimental

Melting points were determined on a Cintex melting point apparatus and are uncorrected. Homogeneity of the compounds was checked by precoated TLC plates (Merck, 60F-254). IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using TMS as internal standard and mass spectra on a VG 170708H spectrometer. Microwave irradiation was carried out in a domestic microwave oven (LG MG 556P, 2450 MHz). The 2-amino-5-nitrobenzoic acid **2** was purchased from Aldrich Chemical Company.

Synthesis of 6-aryl-10-nitro-12*H*-[1,8] naphthyridino [2,1-*b*] quinazolin-12-ones 3: General procedure

A mixture of 3-aryl-2-chloro-1,8-naphthyridines **1** (0.01 mol), 2-amino-5-nitrobenzoic acid **2** (0.01 mol) and DMF (5 drops) was subjected to microwave irradiation at 400 watts intermittently at 30 sec intervals for the specified time (Table-1). After completion of reaction as indicated by TLC, the reaction mixture was allowed to attain RT and digested with cold water. The solid that precipitated was filtered, washed with water and recrystallized from methanol to afford **3** (Table-1).

Spectral data

3a: IR (KBr): 1657 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): δ 8.03 (m, 2H, C_3-H, C_5-H), 8.55 (m, 1H, C_4-H), 8.72 (m, 1H, C_2-H), 6.80-7.85 (m, 8H, ArH); MS : m/z 369 (M+1).

3b: IR (KBr): 1660 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 2.26 (s, 3H, CH_3), 8.05 (m, 2H, C_3-H, C_5-H), 8.60 (m, 1H, C_4-H), 8.70 (m, 1H, C_2-H), 6.85-7.88 (m, 7H, ArH); MS : m/z 383 (M+1).

3c: IR (KBr): 1667 (C=O), 1609 (C=N); ^{1}H NMR ($CDCl_3$): 3.84 (s, 3H, OCH_3), 8.03 (m, 2H, C_3-H, C_5-H), 8.57 (m, 1H, C_4-H), 8.68 (m, 1H, C_2-H), 6.76-7.80 (m, 7H, ArH); MS : m/z 398 [M$^+$].

3d: IR (KBr): 1673 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$): 3.86 (s, 3H, OCH_3), 8.02 (m, 2H, C_3-H, C_5-H), 8.63 (m, 1H, C_4-H), 8.78 (m, 1H, C_2-H), 6.80-7.83 (m, 7H, ArH); MS : m/z 398 (M$^+$).

3e: IR (KBr): 1670 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$): 3.85 (s, 3H, OCH_3), 8.04 (m, 2H, C_3-H, C_5-H), 8.60 (m, 1H, C_4-H), 8.82 (m, 1H, C_2-H), 6.82-7.95 (m, 7H, ArH); MS : m/z 398 (M$^+$).

3f: IR (KBr): 1672 (C=O), 1610 (C=N), ^{1}H NMR ($CDCl_3$): 8.00 (m, 2H, C_3-H, C_5-H), 8.56 (m, 1H, C_4-H), 8.70 (m, 1H, C_2-H), 6.83-7.84 (m, 7H, ArH), MS : m/z 401 (M-1).

3g: IR (KBr): 1668 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): 8.03 (m, 2H, C_3-H, C_5-H), 8.54 (m, 1H, C_4-H), 8.67 (m, 1H, C_2-H), 6.80-7.82 (m, 7H, ArH); MS : m/z 401 (M-1).

3h: IR (KBr): 1678 (C=O), 1612 (C=N); ^{1}H NMR ($CDCl_3$): 8.10 (m, 2H, C_3-H, C_5-H), 8.65 (m, 1H, C_4-H), 8.76 (m, 1H, C_2-H), 6.70-7.82 (m, 7H, ArH); MS : m/z 401 (M-1).

3i: IR (KBr): 1665 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 8.02 (m, 2H, C_3-H, C_5H), 8.65 (m, 1H, C_4-H), 8.78 (m, 1H, C_2-H), 6.80-7.72 (m, 7H, ArH); MS : m/z 387 (M+1).

3j: IR (KBr): 1676 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$): 8.00 (m, 2H, C_3-H, C_5-H), 8.63 (m, 1H, C_4-H), 8.83 (m, 1H, C_2-H), 6.75-7.64 (m, 7H, ArH); MS : m/z 387 (M+1).

3κ: IR (KBr): 1672 (C=O), 1609 (C=N); ^{1}H NMR ($CDCl_3$): 8.03 (m, 2H, C_3-H, C_5-H), 8.59 (m, 1H, C_4-H), 8.81 (m, 1H, C_2-H), 6.78-7.80 (m, 7H, ArH); MS : m/z 386 (M$^+$).

3l: IR (KBr): 1658 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): 8.02 (m, 2H, C_3-H, C_5-H), 8.65 (m, 1H, C_4-H), 8.82 (m, 1H, C_2-H), 6.75-7.78 (m, 7H, ArH); MS : m/z 436 (M$^+$).

3m: IR (KBr): 1665 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 8.00 (m, 2H, C_3-H, C_5-H), 8.72 (m, 1H, C_4-H), 8.90 (m, 1H, C_2-H), 6.65-7.75 (m, 7H, ArH); MS : m/z 436 (M$^+$).

3n: IR (KBr): 1670 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 8.04 (m, 2H, C_3-H, C_5-H), 8.68 (m, 1H, C_4-H), 8.78 (m, 1H, C_2-H), 6.80-7.83 (m, 7H, ArH); MS : m/z 437 (M+1).

Acknowledgement

The authors are thankful to the Director, IICT, Hyderabad for providing ^{1}H NMR and mass spectra. One of us (PKR) is grateful to CSIR, New Delhi for the award of a Junior Research Fellowship.

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