Indian Journal of Heterocyclic Chemistry
Vol. 22, April-June, 2013, pp. 325-328

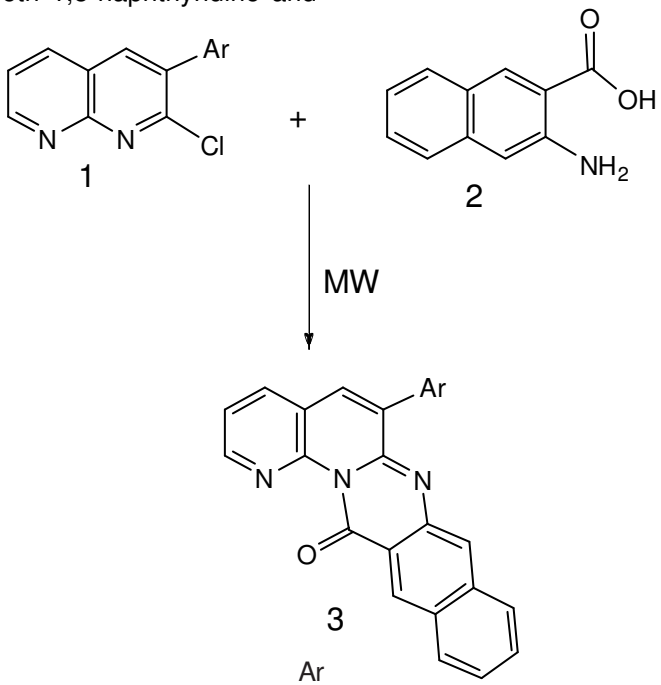
ENVIRONMENTALLY BENIGN SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NOVEL 6-ARYL-14*H*-BENZO [*g*] [1,8] NAPHTHYRIDINO [2,1-*b*] QUINAZOLIN-14-ONES

K. Mogilaiah*, Ch. Venkanna and D. Praveena
Department of Chemistry, Kakatiya University, Warangal-506 009
E-mail : mogilaiah_k@yahoo.co.in

Received 1 Nov. 2012; Accepted 23 June 2013

Microwave irradiation of 3-aryl-2-chloro-1,8-naphthyridines **1** with 3-amino-2-naphthoic acid **2** in the presence of catalytic amount of DMF provides a fast, efficient and simple method for the synthesis of 6-aryl-14*H*-benzo [*g*] [1,8] naphthyridino [2,1-*b*] quinazolin-14-ones **3** in excellent yields. The structures of compounds **3** were determined by their spectral (IR, ^{1}H NMR and MS) and analytical data. Compounds **3** have been screened for their antibacterial activity.

1,8-Naphthyridine derivatives have attracted considerable attention owing to their effective biological activity[1,2]. Quinazolines represent a heterocyclic system of remarkable pharmacological/ biological efficiency[3,4]. Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and quinazoline might result in compounds with interesting biological activity. Microwave (MW) activation as non-conventional energy source has become a very popular and useful technology in synthetic organic chemistry[5-7]. Recently organic



Ar
a: C_6H_5
b : 4-$CH_3OC_6H_4$
c: 2-ClC_6H_4
d: 3-ClC_6H_4
e: 4-ClC_6H_4
f: 2-FC_6H_4

Ar
g: 3-FC_6H_4
h : 4-FC_6H_4
i: 2-$CF_3C_6H_4$
j: 3-$CF_3C_6H_4$
k: 4-$CF_3C_6H_4$

SCHEME-1

Table-1
Physical data of compounds 3

Compd	Ar	Reaction time (min)	M.P. (^{0}C)	Yield (%)
3a	C_6H_5	2.5	190	94
3b	4-$CH_3OC_6H_4$	3.0	210	92
3c	2-ClC_6H_4	2.5	240	92
3d	3-ClC_6H_4	2.5	234	90
3e	4-ClC_6H_4	3.0	250	97
3f	2-FC_6H_4	2.5	243	93
3g	3-FC_6H_4	3.0	230	90
3h	4-FC_6H_4	3.0	265	96
3i	2-$CF_3C_6H_4$	2.5	225	93
3j	3-$CF_3C_6H_4$	2.5	205	92
3k	4-$CF_3C_6H_4$	3.0	252	95

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

transformations accelerated under solvent-free[6] microwave irradiation conditions gained wide popularity due to many practical advantages associated with enhanced reaction rates, high yields, improved selectivity and environment friendly reaction conditions. Due to the continued interest in the microwave-assisted organic transformations of 1,8-naphthyridine derivatives[8-10], herein is reported a practical and efficient method for the synthesis of a novel and hitherto unknown bridgehead nitrogen heterocyclic system, benzo [*g*] [1,8] naphthyridino [2,1-*b*] quinazolin-14-one in solvent-free conditions under microwave irradiation.

Treatment of 3-aryl-2-chloro-1,8-naphthyridines **1** with 3-amino-2-naphthioc acid **2** in the presence of catalytic amount of DMF without any solvent under microwave irradiation afforded the corresponding 6-aryl-14*H*-benzo [*g*] [1,8] naphthyridino [2,1-*b*] quinazolin-14-ones **3** (Scheme-1). The reaction proceeds efficiently in excellent yields at ambient pressure within a few minutes. The products were obtained with a high degree of purity by this procedure. The process is environmentally friendly. It was observed that the neat mixtures of **1** and **2** did not react 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 case, a mixture of 2-chloro-3-phenyl-1,8-naphthyridine **1**a, 3-amino-2-naphthoic acid **2** and DMF (5 drops) was exposed to microwave irradiation at 400 watts intermittently at 30 sec intervals for 25 min. After usual work-up 6-phenyl- 14*H*-benzo [*g*] [1,8] naphthyridino [2,1-*b*] quinazolin-14-one **3**a was obtained in 94% yield. The reaction is of general applicability and the various 6-aryl-14*H*-benzo [*g*] [1,8] naphthyridino [2,1-*b*] quinazolin-14-ones **3** synthesized are given in Table-1.

The reaction proceeds to only 5-8% in 2.5-3.0 min, when conducted under conventional conditions in an oil-bath preheated to 120^0 (measured 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,

Table-2
Antibacterial activity data of compounds 3

Compd	Inhibition zone (in mm) *E. coli* at 250µg/disc	*E. coli* at 500µg/disc	*B. subtilis* at 250µg/disc	*B. subtilis* at 500µg/disc
3a	8.0	17.5	6.5	11.0
3b	9.0	18.0	7.0	11.0
3c	8.5	18.5	7.5	11.5
3d	7.5	17.0	6.5	10.5
3e	11.5	21.0	7.5	14.0
3f	8.5	17.5	7.0	11.0
3g	8.0	16.5	6.5	10.0
3h	11.0	20.5	7.5	13.0
3i	8.0	17.5	7.5	11.5
3j	7.5	16.5	6.5	10.0
3k	10.5	20.0	7.5	13.5
Gentamycin	12.0	22.0	8.0	15.0

^{1}H NMR and MS) data. The mild conditions, short reaction times, high yields and excellent purities of the products are noteworthy advantages of this method.

Antibacterial activity

All the title compounds **3** were evaluated for their antibacterial activity against Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis* using filter paper disc method of Vincent and Vincent[11] at 250 and 500 µg/disc concentrations. Gentamycin was used as standard for comparison. The results are presented in Table-2.

Experimental

Melting points were measured in open capillaries 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 and ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer using TMS as internal standard. Mass spectra were recorded by using electron spray ionization technique (ESI) on the VG170708H mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. For microwave irradiation LG MG 556P (2450 MHz) domestic microwave oven was used.

Synthesis of 6-aryl-14*H*-benzo [*g*] [1,8] naphthyridino [2,1-*b*] quinazolin-14-ones 3 : General procedure

A mixture of 3-aryl-2-chloro-1,8-naphthyridines **1** (0.01 mol), 3-amino-2-naphthoic acid **2** (0.01 mol) and DMF (5 drops) was subjected to microwave irradiation at 400 watts intermittently at 10 sec intervals for the specified time (Table-1). On completion of reaction as indicated by TLC, the reaction mixture was cooled and treated with cold water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford **3** (Table-1).

Spectral data

3a: IR (KBr): 1655 (C=O), 1604 (C=N); ^{1}H NMR ($CDCl_3$): 7.73 (m, 2H, C_3-H, C_5-H), 7.96 (m, 1H, C_4-H), 8.58 (m, 1H, C_2-H), 7.19-7.50 (m, 11H, ArH); MS (ESI): m/z 374 $[M+H]^+$.

3b: IR (KBr): 1646 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 3.86 (s, 3H, OCH_3), 7.75 (m, 2H, C_3-H, C_5-H), 7.94 (m, 1H, C_4-H), 8.67 (m, 1H, C_2-H), 6.95-7.28 (m, 10H, ArH); MS (ESI): m/z 404 $[M+H]^+$.

3c: IR (KBr): 1653 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 7.82 (m, 2H, C_3-H, C_5-H), 8.00 (m, 1H, C_4-H), 8.65 (m, 1H, C_2-H), 7.20-7.58 (m, 10H, ArH); MS (ESI): m/z 408 $[M+H]^+$.

3d: IR (KBr): 1651 (C=O), 1602 (C=N); ^{1}H NMR ($CDCl_3$): 7.85 (m, 2H, C_3-H, C_5-H), 7.95 (m, 1H, C_4-H), 8.57 (m, 1H, C_2-H), 7.22-7.75 (m, 10H, ArH); MS (ESI): m/z 408 $[M+H]^+$.

3e: IR (KBr): 1673 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 7.70 (m, 2H, C_3-H, C_5-H), 7.98 (m, 1H, C_4-H), 8.62 (m, 1H, C_2-H), 7.20-7.46 (m, 10H, ArH); MS (ESI): m/z 408 $[M+H]^+$.

3f: IR (KBr): 1655 (C=O), 1604 (C=N); ^{1}H NMR ($CDCl_3$): 7.80 (m, 2H, C_3-H, C_5-H), 7.96 (m, 1H, C_4-H), 8.67 (m, 1H, C_2-H), 7.18-7.54 (m, 10H, ArH); MS (ESI): m/z 392 $[M+H]^+$.

3g: IR (KBr: 1667 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$): 7.78 (m, 2H, C_3-H, C_5-H), 8.00 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.20-7.68 (m, 10H, ArH); MS (ESI) : m/z 392 $[M+H]^+$.

3h: IR (KBr): 1672 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): 7.75 (m, 2H, C_3-H, C_5-H), 7.97 (m, 1H, C_4-H), 8.63 (m, 1H, C_2-H), 7.10-7.35 (m, 10H, ArH); MS (ESI): m/z 392 $[M+H]^+$.

3i: IR (KBr): 1652 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 7.78 (m, 2H, C_3-H, C_5-H), 7.94 (m, 1H, C_4-H), 8.65 (m, 1H, C_2-H), 7.15-7.56 (m, 10H, ArH); MS : (ESI): m/z 442 $[M+H]^+$.

3j : IR (KBr): 1654 (C=O), 1601 (C=N); ^{1}H NMR ($CDCl_3$): 7.82 (m, 2H, C_3-H, C_5-H), 8.00 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.22-7.60 (m, 10H, ArH); MS (ESI): m/z 442 $[M+H]^+$.

3k: IR (KBr): 1657 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 7.79 (m, 2H, C_3-H, C_5-H), 7.98 (m, 1H, C_4-H), 8.63 (m, 1H, C_2-H), 7.18-7.57 (m, 10H, ArH); MS (ESI): m/z 442 $[M+H]^+$.

Acknowledgement

The authors are thankful to the Director, IICT, Hyderabad for providing ^{1}H NMR and mass spectra.

References

1. P.L. Ferrarini, C. Mori, M. Badawneh, V. Calderone, R. Greco, C. Manera, A. Martinelli, P. Nieri and G. Saccomanni, *Eur. J. Med. Chem.,* **35** (2000), 815.
2. G. Grossi, M. Di. Braccio, G. Roma, V. Ballabeni, M. Tognolini and B. Barocelli, *Eur. J. Med. Chem.,* **40** (2005), 1135.
3. T.P. Tran, E.L. Ellsworth, M.A. Stier, J.M. Domagala, H.D.H. Showalter, S.J. Gracheck, M.A. Shapiro, T.E. Joannides and R. Singh, *Bioorg. Med. Chem. Lett.,* **14** (2004), 4405.
4. M. Decker, *Eur. J. Med. Chem.,* **40** (2005), 305.
5. S. Caddick, *Tetrahedron,* **51** (1995), 10403.
6. A. Loupy, A. Petit, J. Hamelin, F.T. Boullet, P. Jacquault and D.Mathe, *Synthesis* (1998), 1213.
7. P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron,* **57** (2001), 9225.
8. K. Mogilaiah, S. Kavitha, N. Srivani, K.S. Kumar and J.K. Swamy, *Indian J. Heterocyclic Chem.,* **19** (2010), 397.
9. K. Mogilaiah, J.K. Swamy and B. Sakram, *Indian J. Heterocyclic Chem.*, **20** (2011), 201.
10. K. Mogilaiah, A. Aara and P. K. Rao, *Indian J. Heterocyclic Chem.,* **22** (2012), 35.
11. J.C. Vincent and H.W. Vincent, *Proc. Soc. Exptl. Biol. Med.,* **55** (1944), 162.

3133/2012