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SOLVENT-FREE MICROWAVE-ASSISTED SYNTHESIS OF NOVEL 6-ARYL-8-PHENYL-8,11-DIHYDROPYRAZOLO [3′,4′:4,5] PYRIMIDO [1,2-*a*] [1,8] NAPHTHYRIDIN-11-ONES AND THEIR ANTIBACTERIAL ACTIVITY

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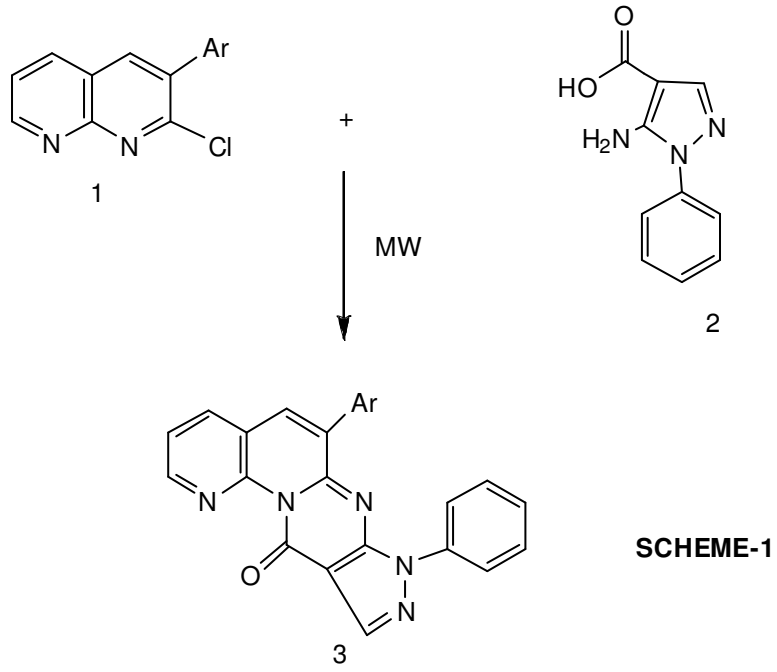
A straightforward and efficient protocol for the synthesis of novel 6-aryl-8-phenyl-8,11-dihydropyrazolo-[3′,4′:4,5] pyrimido [1,2-*a*] [1,8] naphthyridin-11-ones **3** has been achieved by the reaction of 3-aryl-2-chloro-1,8-naphthyridines **1** with 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid **2** in the presence of a catalytic amount of DMF in solvent-free conditions under microwave irradiation. The products are obtained in very good yields and in a state of high purity. The structural assignments of compounds **3** were based on their elemental analyses and spectral (IR and ^{1}H NMR) data. The compounds **3** have been screened for their antibacterial activity.

1,8-Naphthyridines have been reported to exhibit interesting and diverse biological and pharmacological activity[1-3]. On the other hand, pyrazoles are among the most active class of compounds possessing a wide spectrum of biological activity[4-6]. Further, the pyrimidine ring system is an important pharmacophoric element in medicinal chemistry[7,8]. Therefore, it was envisaged that chemical entities with 1,8-naphthyridine, pyrazole and pyrimidine might result in compounds with interesting biological activity.

Environment-friendly chemical process is the vital part of the current chemical research and development. In recent years reports on the microwave-assisted synthesis under solvent-free reaction conditions is promising alternative to conventional methods as these reactions represent a clean, efficient, safe, economical and eco-friendly procedure[10-12] and is believed to be a step towards green chemistry. In view of this and because of sustained interest in microwave-assisted organic transformations based on 1,8-naphthyridine derivatives[13-15], herein is reported an efficient and convenient method for the synthesis of a novel and hitherto unknown bridgehead nitrogen heterocyclic system, pyrazolo [3′,4′:4,5] [1,2-*a*] [1,8] naphthyridin-11-ones in solvent-free conditions under microwave irradiation.

Cyclocondensation of 3-aryl-2-chloro-1,8-naphthyridines **1** with 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid **2** in the presence of catalytic amount of DMF without any solvent under microwave irradiation resulted in the formation of 6-aryl-8-phenyl-8,11-dihydropyrazolo-[3′,4′:4,5] pyrimido [1,2-*a*] [1,8] naphthyridin-11-ones **3** (Scheme-1). The reactions proceed 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 needed. The experimental procedure is very simple. The procedure is environmentally benign. Further, we observed that neat mixture of **1** and **2** did not react on microwave irradiation, but the reaction completed within minutes on addition of few drops of high dielectric solvent such as DMF.

In a typical experimental procedure, a mixture of 3-phenyl-2-chloro-1,8-naphthyridine **1**a, 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid **2** and DMF (5 drops) was exposed to microwave irradiation at 400 watts intermittently at 30 sec. intervals for 3.0 min. The reaction mixture was cooled to room temp, digested with cold water and filtered off. After usual work-up 6,8-diphenyl-8,11-dihydropyrazolo-[3′,4′:4,5] pyrimido [1,2-*a*] [1,8] naphthyridin-11-one **3**a was obtained in 92% yield. The reaction is of general applicability and the different pyrazolo-[3′,4′,4:5] pyrimido [1,2-*a*] [1,8] naphthyridin-11-ones **3** synthesized are presented in Table-1.



SCHEME-1

	Ar		Ar
a	C_6H_5	j	3-BrC_6H_4
b	3-$CH_3C_6H_4$	k	4-BrC_6H_4
c	4-$CH_3C_6H_4$	l	2-FC_6H_4
d	2-$CH_3OC_6H_4$	m	3-FC_6H_4
e	3-$CH_3OC_6H_4$	n	4-FC_6H_4
f	4-$CH_3OC_6H_4$	o	2-$CF_3C_6H_4$
g	2-ClC_6H_4	p	3-$CF_3C_6H_4$
h	3-ClC_6H_4	q	4-$CF_3C_6H_4$
i	4-ClC_6H_4	r	2-Naphthyl

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

Compd	Ar	Reaction time (min)	M.P. (°C)	Yield (%)
3a	C_6H_5	3.0	220	92
3b	3-$CH_3C_6H_4$	3.5	238	93
3c	4-$CH_3C_6H_4$	3.0	265	94
3d	2-$CH_3OC_6H_4$	3.5	242	92
3e	3-$CH_3OC_6H_4$	4.0	247	90
3f	4-$CH_3OC_6H_4$	4.0	235	94
3g	2-ClC_6H_4	3.0	268	92
3h	3-ClC_6H_4	3.0	282	91
3i	4-ClC_6H_4	3.5	270	96
3j	3-BrC_6H_4	3.5	256	92
3k	4-BrC_6H_4	4.0	262	95
3l	2-FC_6H_4	3.0	236	92
3m	3-FC_6H_4	3.5	245	90
3n	4-FC_6H_4	4.0	280	96
3o	2-$CF_3C_6H_4$	3.0	240	92
3p	3-$CF_3C_6H_4$	3.5	232	90
3q	4-$CF_3C_6H_4$	3.5	253	95
3r	2-Naphthyl	4.0	275	94

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

Interestingly, this reaction proceeds only to a minor extent (5-8% in 3.0-4.0 min) when conducted under conventional conditions in an oil-bath preheated to 120^0 (measured immediately after microwave irradiation), which confirms the rate augmentation during microwave heating.

To the best of our knowledge this is the first report of the rapid synthesis of a novel bridgehead nitrogen heterocyclic system, pyrazolo-[3′,4′:4,5] pyrimido [1,2-*a*] [1,8] naphthyridin-11-ones under solvent-free microwave irradiation conditions.

The structures of the compounds **3** were established by their spectral (IR and ^{1}H NMR) and analytical data. The significant advantages of this procedure are : short reaction times, high yields,

Table-2
Antibacterial acreening 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	8.5	18.0	7.0	11.5
3b	7.5	14.5	5.5	9.0
3c	9.0	16.5	6.5	10.5
3d	8.0	15.5	6.0	9.5
3e	9.0	17.0	6.5	10.5
3f	9.5	18.5	7.0	11.5
3g	9.0	19.0	7.0	12.0
3h	8.0	18.0	6.5	11.5
3i	11.5	21.5	7.5	14.5
3j	8.0	16.0	6.0	10.0
3k	9.0	17.0	6.5	11.0
3l	9.0	18.0	7.0	11.5
3m	8.5	17.0	6.5	11.0
3n	11.5	21.0	7.5	14.0
3o	8.5	18.0	7.0	12.0
3p	8.0	17.0	6.5	11.0
3q	11.0	20.5	7.5	14.0
3r	9.0	17.5	7.0	11.5
Gentamycin	12.0	22.0	8.0	15.0

simple experimental work-up procedure, excellent purity of the products and minimum environmental impact.

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[16] at 250 and 500 μg/disc concentrations. Standard antibacterial Gentamycin was also screened under similar conditions for comparison. The results are given in Table-2.

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 and ^{1}H NMR spectra on a Varian Gemini 400 MHz spectrometer using TMS as internal standard. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Microwave irradiation was carried out in a domestic microwave oven (LG MG 556P, 2450 MHz). The 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic acid **2** was purchased from Aldrich Chemical Company.

Synthesis of 6-aryl-8-phenyl-8,11-dihydropyrazolo-[3′,4′:4,5] pyrimido [1,2-*a*] [1,8] naphthyridin-11-ones 3: General procedure

A mixture of 3-aryl-2-chloro-1,8-naphthyridine **1** (0.01 mol), 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylic 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 the reaction as indicated by TLC, the reaction mixture was cooled and treated with cold water. The solid that precipitated was filtered, washed with water and purified by recrystallization from ethanol to afford **3** (Table-1).

Spectral data

3a: IR (KBr): 1653 (C=O), 1604 (C=N); ^{1}H NMR ($CDCl_3$): δ 7.75 (m, 2H, C_3-H, C_5-H), 7.82 (s, 1H, C_{10}-H), 7.96 (m, 1H, C_4-H), 8.73 (m, 1H, C_2-H), 7.21-7.48 (m, 10H, ArH).

3b: IR (KBr): 1660 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 2.22 (s, 3H, CH_3), 7.80 (m, 2H, C_3-H, C_5-H), 8.00 (s, 1H, C_{10}-H), 8.25 (m, 1H, C_4-H), 8.52 (m, 1H, C_2-H), 7.24-7.52 (m, 9H, ArH).

3c:IR (KBr): 1665 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 2.30 (s, 3H, CH_3), 7.85 (m, 2H, C_3-H, C_5-H), 7.98 (s, 1H, C_{10}-H), 8.15 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.22-7.54 (m, 9H, ArH).

3d: IR (KBr): 1657 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$): 3.85 (s, 3H, OCH_3), 7.80 (m, 2H, C_3-H, C_5-H), 8.00 (s, 1H, C_{10}-H), 8.15 (m, 1H, C_4-H), 8.53 (m, 1H, C_2-H), 7.12-7.30 (m, 9H, ArH).

3e: IR (KBr): 1660 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): 3.86 (s, 3H, OCH_3), 7.76 (m, 2H, C_3-H, C_5-H), 8.03 (s, 1H, C_{10}-H), 8.08 (m, 1H, C_4-H), 8.56 (m, 1H, C_2-H), 7.05-7.25 (m, 9H, ArH).

3f: IR (KBr): 1663 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$): 3.84 (s, 3H, OCH_3), 7.73 (m, 2H, C_3-H, C_5-H), 8.06 (s, 1H, C_{10}-H), 8.17 (m, 1H, C_4-H), 8.48 (m, 1H, C_2-H), 6.99-7.27 (m, 9H, ArH).

3g: IR (KBr): 1655 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 7.76 (m, 2H, C_3-H, C_5-H), 7.92 (s, 1H, C_{10}-H), 8.05 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.20-7.53 (m, 9H, ArH).

3h: IR (KBr): 1665 (C=O), 1609 (C=N); ^{1}H NMR ($CDCl_3$): 7.83 (m, 2H, C_3-H, C_5-H), 7.94 (s, 1H, C_{10}-H), 8.27 (m, 1H, C_4-H), 8.57 (m, 1H, C_2-H), 7.25-7.58 (m, 9H, ArH).

3i: IR (KBr): 1674 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 7.70 (m, 2H, C_3-H, C_5-H), 7.80 (s, 1H, C_{10}-H), 7.95 (m, 1H, C_4-H), 8.62 (m, 1H, C_2-H), 7.18-7.45 (m, 9H, ArH).

3j: IR (KBr): 1667 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$): 7.62 (m, 2H, C_3-H, C_5-H), 7.88 (s, 1H, C_{10}-H), 8.00 (m, 1H, C_4-H), 8.72 (m, 1H, C_2-H), 7.20-7.52 (m, 9H, ArH).

3k: IR (KBr): 1670 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): 7.74 (m, 2H, C_3-H, C_5-H), 7.86 (s, 1H, C_{10}-H), 7.97 (m, 1H, C_4-H), 8.78 (m, 1H, C_2-H), 7.25-7.78 (m, 9H, ArH).

3l: IR (KBr): 1675 (C=O), 1611 (C=N); 1H NMR ($CDCl_3$): 7.60 (m, 2H, C_3-H, C_5-H), 7.86 (s, 1H, C_{10}-H), 7.95 (m, 1H, C_4-H), 8.74 (m, 1H, C_2-H), 7.17-7.40 (m, 9H, ArH).

3m: IR (KBr): 1672 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 7.52 (m, 2H, C_3-H, C_5-H), 7.85 (s, 1H, C_{10}-H), 7.97 (m, 1H, C_4-H), 8.66 (m, 1H, C_2-H), 7.09-7.45 (m, 9H, ArH).

3n: IR (KBr): 1674 (C=O), 1602 (C=N); ^{1}H NMR ($CDCl_3$): 7.73 (m, 2H, C_3-H, C_5-H), 7.80 (s, 1H, C_{10}-H), 7.94 (m, 1H, C_4-H), 8.60 (m, 1H, C_2-H), 7.12-7.26 (m, 9H, ArH).

3o: IR (KBr): 1660 (C=O), 1605 (C=N); ^{1}H NMR ($CDCl_3$): 7.68 (m, 2H, C_3-H, C_5-H), 7.78 (s, 1H, C_{10}-H), 7.95 (m, 1H, C_4-H), 8.68 (m, 1H, C_2-H), 7.22-7.63 (m, 9H, ArH).

3p : IR (KBr) : 1666 (C=O), 1608 (C=N); ^{1}H NMR ($CDCl_3$): 7.88 (m, 2H, C_3-H, C_5-H), 7.99 (s, 1H, C_{10}-H), 8.01 (m, 1H, C_4-H), 8.75 (m, 1H, C_2-H), 7.22-7.64 (m, 9H, ArH).

3q: IR (KBr): 1655 (C=O), 1606 (C=N); ^{1}H NMR ($CDCl_3$): 7.86 (m, 2H, C_3-H, C_5-H), 7.88 (s, 1H, C_{10}-H), 7.98 (m, 1H, C_4-H), 8.69 (m, 1H, C_2-H), 7.24-7.73 (m, 9H, ArH).

3r : IR (KBr): 1670 (C=O), 1607 (C=N); ^{1}H NMR ($CDCl_3$): 7.72 (m, 2H, C_3-H, C_5-H), 7.82 (s, 1H, C_{10}-H), 7.96 (m, 1H, C_4-H), 8.65 (m, 1H, C_2-H), 7.20-7.68 (m, 12H, ArH).

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