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ENVIRONMENTALLY BENIGN SYNTHESIS OF 3-ARYL-1-[3-(3-METHYLPHENYL) [1,8] NAPHTHYRIDIN-2-YL]-1*H*-4-PYRAZOLECARBALDEHYDES USING MICROWAVE IRRADIATION UNDER SOLVENT-FREE CONDITIONS AND THEIR BIOLOGICAL ACTIVITY

K. Mogilaiah*, Anjum Aara and K. Dhanaja
Department of Chemistry, Kakatiya University, Warangal-506 009
E-mail : mogilaiah_k@yahoo.co.in

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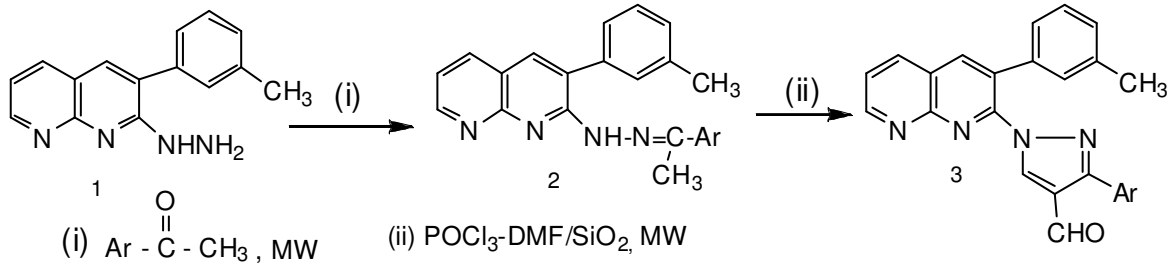
An efficient, rapid and environmentally friendly method for the synthesis of 3-aryl-1-[3-(3-methylphenyl) [1,8] naphthyridin-2-yl]-1*H*-4-pyrazolecarbaldehydes **3** is achieved by the Vilsmeier-Haack reaction of 1-aryl-1-ethanone 1-[3-(3-methylphenyl) [1,8] naphthyridin-2-yl] hydrazones **2** with $POCl_3$-DMF/SiO_2 under microwave irradiation. The yields are good and purity is high. The method is preparatively convenient and useful. The structures of the compounds **2** and **3** were established by their spectral (IR, ^{1}H NMR and MS) and analytical data. Compounds **3** have been screened for their antibacterial and anti-inflammatory activities.

Pyrazole is a versatile lead molecule for designing potential bioactive agents[1-3]. The Vilsmeier-Haack reaction of acetophenone phenylhydrazone resulted in the formation of pyrazole-4-carbaldehyde[4,5]. In Vilsmeier-Haack reaction, DMF-$POCl_3$ has a dual role of reagent as well as solvent. $POCl_3$ is a highly toxic solvent and its use is hazardous to health and is also pollutant of the environment. 1,8-Naphthyridines play a pivotal role in the field of heterocyclic chemistry[6-8]. Microwave induced organic reaction enhancement (MORE) chemistry has gained popularity as a non conventional technique for rapid organic synthesis, it is eco-friendly, economical and is believed to be a step towards green chemistry[9-11]. The solvent-free reaction[11], in general and on inorganic solid supports[12] under this condition are especially appealing for providing an environmentally benign system. Motivated by these facts and in continuation of our interest in microwave-assised organic transformations of 1,8-naphthyridine derivatives[13-15], herein we describe an efficient, rapid and environmentally benign protocol for the synthesis of 3-aryl-1-[3-(3-methylphenyl)] [1,8] naphthyridin-2-yl]-1*H*-4-pyrazolecarbaldehydes using $POCl_3$-DMF over silica gel under microwave irradiation.

Condensation of 2-hydrazino-3-(3-methylphenyl)-1,8-naphthyridine **1** with different acetophenones in the presence of catalytic amount of DMF under microwave irradiation furnished the respective 1-aryl-1-ethanone 1-[3-(3-methylphenyl) [naphthyridin-2-yl] hydrazones **2** in excellent yields.

The hydrazones **2** when subjected to the Vilsmeier-Haack reaction with $POCl_3$-DMF/SiO_2 under microwave irradiation gave 3-aryl-1-[3-(3-methylphenyl)] [1,8] naphthyridin-2-yl]-1*H*-4-



Ar

a: C_6H_5, b: 4-$CH_3C_6H_4$, c: 4-$CH_3OC_6H_4$, d: 4-ClC_6H_4, e: 4-BrC_6H_4, f: 3-$NO_2C_6H_4$, g: 4-$NO_2C_6H_4$, h: 2-Naphthyl

SCHEME-1

Table-1
Physical data of compounds **2** and **3**

Compd	Ar	Reaction time (min)	M.P. (^{0}C)	Yield (%)
2a	C_6H_5	0.5	95	96
2b	4-$CH_3C_6H_4$	0.5	142	97
2c	4-$CH_3OC_6H_4$	1.0	138	95
2d	4-ClC_6H_4	1.0	160	98
2e	4-BrC_6H_4	1.0	130	96
2f	3-$NO_2C_6H_4$	0.5	215	94
2g	4-$NO_2C_6H_4$	0.5	204	96
2h	2-Naphthyl	1.0	212	95
3a	C_6H_5	3.5	115	84
3b	4-$CH_3C_6H_4$	3.5	120	86
3c	4-$CH_3OC_6H_4$	3.0	98	84
3d	4-ClC_6H_4	3.0	150	87
3e	4-BrC_6H_4	3.5	105	85
3f	3-$NO_2C_6H_4$	4.0	132	82
3g	4-$NO_2C_6H_4$	4.0	110	84
3h	2-Naphthyl	3.5	145	85

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

pyrazolecarbaldehydes **3** (Scheme-1). Reactions are not time consuming and the yields of the products are good. The high yield transformation did not form any undesirable by-products. The purity of the product is high. The method is preparatively convenient and useful. The process is environmentally benign and the experimental procedure is very simple.

In a typical procedure, to the Vilsmeier-Haack reagent, prepared from DMF and $POCl_3$ at 0-5^0, hydrazone **2**a (Ar=C_6H_5) and silica gel were added and is exposed to microwaves at 400 watts intermittently at 30 sec intervals for 3.5 min. After usual work-up 1-[3-(3-methylphenyl)] [1,8] naphthyridin-2-yl]-3-phenyl-1*H*-4-pyrazolecarbaldehydes **3**a (Ar=C_6H_5) was obtained in 84% yield.

The generality of the facile Vilsmeier-Haack reaction was established by treating other hydrazones **2**b-h with $POCl_3$-DMF/SiO_2 under microwave irradiation to get the corresponding 3-aryl-1-[3-(3-methylphenyl)] [1,8] naphthyridin-2-yl]-1*H*-pyrazole-carbaldehydes **3**b-h (Ar=4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-naphthyl) (Table-1).

Interestingly, this reaction proceeds only to a minor extent (5-7% 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 increase during microwave heating.

The structures of the compounds **2** and **3** were assigned on the basis of their spectral (IR, ^{1}H NMR and MS) and analytical data. High yields of the products, easy work-up, short reaction times, excellent purity of the products and the elimination of the solvent are note-worthy advantages of this method.

Antibacterial activity

All the synthesized compounds **3** were evaluated for their antibacterial activity 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. Compounds **3**b, **3**d and **3**e exhibited significant antibacterial activity.

Anti-inflammatory activity

The anti-inflammatory activity of the synthesized compounds **3** was carried out following carrageenan-induced rat paw edema method[17], using Diclofenac sodium as reference drug for comparison. Among all the compounds **3**c, **3**d and **3**g displayed promising anti-infammatory activity at 4th hr.

Experimental

Melting points were recorded on a Cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was inferred from TLC on silica gel-G plates (Merk, 60F-254). IR spectra (KBr) were recorded on a Perkin-Elmer FT-IR spectrophotometer, ^{1}H NMR spectra on a Varian Gemini 300 MHz spectrometer (Chemical shifts in δ ppm) using TMS as internal standard and mass spectra on LCMS Agilent Technologies instrument. Elemental analyses were performed on a Perkin-Elmer 240 CHN analyzer. Microwave irradiation was carried out using domestic microwave oven (LG MG-556P, 2450MHz).

Synthesis of 1-aryl-1-ethanone 1-[3-(3-methylphenyl) [1,8] naphthyridin-2-yl] hydrazones 2: General procedure

A mixture of 2-hydrazino-3-(3-methylphenyl)-1,8-naphthyridine 1 (0.01 mol), appropriate acetophenone (0.01 mol) and DMF (5 drops) was subjected to microwave irradiation at 200 watts intermittently at 10 sec intervals for specified time (Table-1). On completion of the reaction (monitored by TLC), the reaction mixture was cooled to RT and digested with cold water. The solid obtained was filtered washed with water and purified by recrystallization from ethanol to obtain **2** (Table-1).

2a: IR (KBr): 3343 (NH), 1615 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 7.72 (m, 1H, C_6-H), 8.06 (m, 2H, C_4-H, C_5-H), 8.36 (m, 1H, C_7-H), 7.03-7.56 (m, 9H, ArH), 10.10 (s, 1H, NH); MS (LC-MS): m/z 353 $[M+H]^+$.

2b: IR (KBr): 3345 (NH), 1613 (C=N); ^{1}H NMR ($CDCl_3$): 2.23 (s, 3H, CH_3), 2.45 (s, 6H, 2xCH_3), 7.68 (m, 1H, C_6-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.21 (m, 1H, C_7-H), 6.97-7.54 (m, 8H, ArH), 10.05 (s, 1H, NH); MS (LC-MS): m/z 367 $[M+H]^+$.

2c: IR (KBr): 3339 (NH), 1612 (C=N); ^{1}H NMR ($CDCl_3$): 2.42 (s, 6H, 2xCH_3), 3.86 (s, 3H, OCH_3), 7.60 (m, 1H, C_6-H), 7.90 (m, 2H, C_4-H, C_5-H), 8.19 (m, 1H, C_7-H), 6.94-7.35 (m, 8H, ArH), 10.04 (s, 1H, NH); MS (LC-MS): m/z 383 $[M+H]^+$.

2d : IR (KBr): 3340 (NH), 1617 (C=N); ^{1}H NMR ($CDCl_3$): 2.43 (s, 6H, 2xCH_3), 7.62 (m, 1H, C_6-H), 7.84 (m, 2H, C_4-H, C_5-H), 8.22 (m, 1H, C_7-H), 7.21-7.55 (m, 8H, ArH), 10.02 (s, 1H, NH); MS (LC-MS): m/z 387 $[M+H]^+$.

2e : IR (KBr): 3336 (NH), 1617 (C=N); ^{1}H NMR ($CDCl_3$): 2.42 (s, 6H, 2xCH_3), 7.67 (m, 1H, C_6-H), 7.80 (m, 2H, C_4-H, C_5-H), 8.30 (m, 1H, C_7-H), 6.98-7.57 (m, 8H, ArH), 10.09 (s, 1H, NH); MS (LC-MS): m/z 431 $[M+H]^+$.

2f : IR (KBr): 3335 (NH), 1616 (C=N); ^{1}H NMR ($CDCl_3$): 2.44 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.65 (m, 1H, C_6-H), 7.83 (m, 2H, C_4-H, C_5-H), 8.28 (m, 1H, C_7-H), 7.20-7.60 (m, 8H, ArH), 10.05 (s, 1H, NH); MS (LC-MS): m/z 398 $[M+H]^+$.

2g: IR (KBr): 3333 (NH), 1615 (C=N); ^{1}H NMR ($CDCl_3$): 2.42 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 7.67 (m, 1H, C_6-H), 7.92 (m, 2H, C_4-H, C_5-H), 8.26 (m, 1H, C_7-H), 7.18-7.56 (m, 8H, ArH), 10.07 (s, 1H, NH); MS (LC-MS): m/z 398 $[M+H]^+$.

2h: IR (KBr): 3340 (NH), 1614 (C=N); ^{1}H NMR ($CDCl_3$): 2.43 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.70 (m, 1H, C_6-H), 8.02 (m, 2H, C_4-H, C_5-H), 8.32 (m, 1H, C_7-H), 7.15-7.52 (m, 11H, ArH), 10.10 (s, 1H, NH); MS (LC-MS): m/z 403 $[M+H]^+$.

Synthesis of 3-aryl-1-[3-(3-methylphenyl) [1,8] naphthyridin-2-yl]-1*H*-4-pyrazolecarbaldehydes 3 : General procedure

To the Vilsmeier-Haack reagent (0.03 mol) at 0-5^0, compound **2** (0.01 mol) was added portion wise. After the addition was complete, the reaction flask was kept at RT for 5 min and silica gel (3g) was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder is then irradiated in microwave oven at 400 watts intermittently at 30 sec. intervals for specified time (Table-1). After the completion of reaction as monitored by TLC, the reaction mixture was cooled to RT treated with chilled water and filtered. The solid thus separated by the neutralization of the filtrate with $NaHCO_3$ was filtered, washed with water and purified by recrystallization from ethanol to afford **3** (Table-1).

3a: IR (KBr): 1682 (C=O), 1610 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.93 (m, 3H, C_4-H, C_5-H, C_6-H), 8.23 (m, 1H, C_7-H), 7.26-7.62 (m, 10H, CH of pyrazole, 9Ar-H), 9.68 (s, 1H, CHO); MS (LC-MS): m/z 391 $[M+H]^+$.

3b : IR (KBr): 1618 (C=O), 1608 (C=N); ^1H NMR ($CDCl_3$): 2.25 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.96 (m, 3H, C_4-H, C_5-H, C_6-H), 8.26 (m, 1H, C_7-H), 7.22-7.60 (m, 9H, CH of pyrazole, 8Ar-H), 9.66 (s, 1H, CHO); MS (LC-MS): m/z 405 $[M+H]^+$.

3c: IR (KBr): 1699 (C=O), 1611 (C=N); ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.91 (m, 3H, C_4-H, C_5-H, C_6-H), 8.28 (m, 1H, C_7-H), 6.86-7.65 (m, 9H, CH of pyrazole, 8ArH), 9.64 (s, 1H, CHO); MS (LC-MS): m/z 421 $[M+H]^+$.

3d: IR (KBr): 1691 (C=O), 1609 (C=N); ^1H NMR ($CDCl_3$): 2.42 (s, 3H, CH_3), 7.67 (m, 3H, C_4-H, C_5-H, C_6-H), 8.30 (m, 1H, C_7-H), 7.27-7.62 (m, 9H, CH of pyrazole, 8Ar-H), 9.65 (s, 1H, CHO); MS (LC-MS): m/z 425 $[M+H]^+$.

3e: IR (KBr): 1692 (C=O), 1614 (C=N); ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 7.90 (m, 3H, C_4-H, C_5-H, C_6-H), 8.27 (m, 1H, C_7-H), 7.08-7.72 (m, 9H, CH of pyrazole, 8Ar-H), 9.68 (s, 1H, CHO); MS (LC-MS): m/z 469 $[M+H]^+$.

3f: IR (KBr): 1686 (C=O), 1611 (C=N); ^1H NMR ($CDCl_3$): 2.42 (s, 3H, CH_3), 7.94 (m, 3H, C_4-H, C_5-H, C_6-H), 8.25 (m, 1H, C_7-H), 7.15-7.68 (m, 9H, CH of pyrazole, 8Ar-H), 9.66 (s, 1H, CHO); MS (LC-MS): m/z 436 $[M+H]^+$.

3g: IR (KBr): 1677 (C=O), 1612 (C=N); ^1H NMR ($CDCl_3$): 2.41 (s, 3H, CH_3), 7.88 (m, 3H, C_4-H, C_5-H, C_6-H), 8.21 (m, 1H, C_7-H), 7.20-7.72 (m, 9H, CH of pyrazole, 8Ar-H), 9.68 (s, 1H, CHO); MS (LC-MS): m/z 436 $[M+H]^+$.

3h: IR (KBr): 1960 (C=O), 1610 (C=N); ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 7.93 (m, 3H, C_4-H, C_5-H, C_6-H), 8.24 (m, 1H, C_7-H), 7.18-7.76 (m, 12H, CH of pyrazole, 11ArH), 9.65 (s, 1H, CHO); MS (LC-MS): m/z 441 $[M+H]^+$.

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