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Environmentally benign synthesis, antibacterial and anti-inflammatory activities of 3-aryl-1-{3-[2-(trifluoromethyl) phenyl][1,8]naphthyridin-2-yl}-1*H*-4-pyrazolecarbaldehydes

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A simple and efficient protocol for the transformation of 1-aryl-1-ethanone 1-{3-[2-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}hydrazones **3** to 3-aryl-1-{3-[2-(trifluoromethyl) phenyl][1,8]-naphthyridin-2-yl}-1*H*-4-pyrazolecarbaldehydes **4** is reported under microwave irradiation utilizing $POCl_3$-DMF over silica gel with high yields. The structures of the compounds **3** and **4** have been confirmed on the basis of their elemental analyses and spectral (IR, ^{1}H NMR and MS) data. The compounds **4** have been evaluated for their antibacterial and anti-inflammatory activities.

Keywords: Pyrazole, 1,8-naphthyridine, Vilsmeier-Haack reagent, solid support, microwave irradiation, antibacterial activity, anti-inflammatory activity

Pyrazoles generate a widespread interest due to diverse pharmacological and microbiological activities[1-3]. The literature review shows that the Vilsmeier-Haack reaction of acetophenone phenylhydrazone resulted in the formation of pyrazole-4-carboxaldehyde[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. Further the 1,8-naphthyridine ring system is an important pharmacophoric element in medicinal chemistry[6-8]. Fluorine containing heterocyclics are very fascinating targets for synthetic organic chemists because of their potentially high physiological activities[9,10]. Microwave-assisted organic reactions have attracted considerable attention in organic synthesis because of their simplicity, greater selectivity, and rapidity in operation, for synthesis of a variety of organic compounds[11-13]. In view of this facts and in continuation of our work on microwave-assisted organic transformations of 1,8-naphthyridine derivatives[14-16], we now describe a convenient, efficient and high yielding method for the synthesis of 3-aryl-1-{3-[2-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}-1*H*-4-pyrazolecarbaldehydes under solvent-free microwave irradiation conditions using silica gel as solid support.

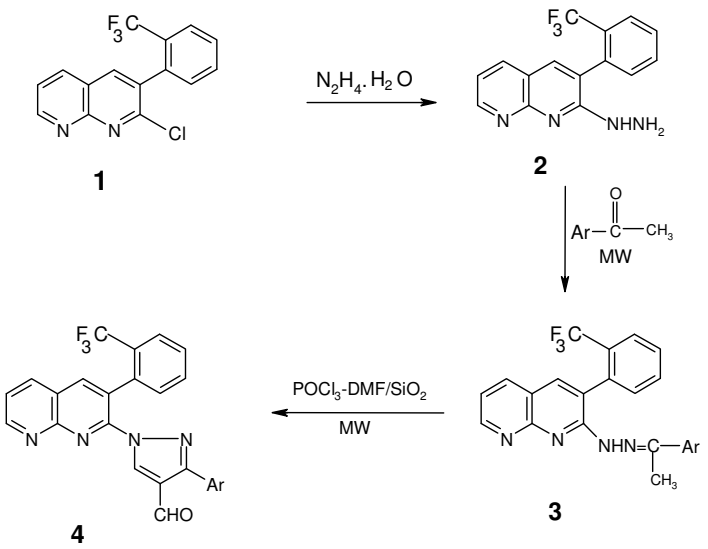
Results and Discussion

Condensation of 2-hydrazino-3-(2-trifluoromethyl-phenyl)-1,8-naphthyridine **2** with different acetophenones in the presence of catalytic amount of DMF under microwave irradiation resulted in the formation of 1-aryl-1-ethanone 1-{3-[2-(trifluoromethyl) phenyl][1,8]-naphthyridin-2-yl}hydrazones **3** in excellent yields. The hydrazones **3** on treatment with Vilsmeier-Haack reagent over silica gel ($POCl_3$-DMF/SiO_2) under microwave irradiation afforded the respective 3-aryl-1-{3-[2-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}-1*H*-4-pyrazolecarbaldehydes **4** in very good yields (**Scheme I**). The reaction is facile and efficient and is devoid of by-products. The purity of the products is high. The process is environmentally benign. The experimental procedure is very simple and convenient.

In a typical procedure, to the Vilsmeier-Haack reagent, prepared from DMF and $POCl_3$ at 0-5°C, hydrazone **3a** (Ar = C_6H_5) and silica gel was added and is exposed to microwaves at 400 W intermittently at 30 s intervals for 3.5 min. The reaction mixture was treated with cold water followed by simple processing furnished 3-phenyl-1-{3-[2-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}-1*H*-4-pyrazolecarbaldehyde **4a** (Ar = C_6H_5). The reaction is of general applicability and the various 1,8-naphthyridinyl pyrazoles **4** synthesized are given in **Table I**.

Interestingly, this reaction proceeds only to a minor extent (5-8% in 3.5-4.5 min) when conducted under conventional conditions in an oil-bath preheated to 120°C (measured immediately after microwave irradiation) which confirms the rate augmentation during microwave heating.

The structural assignments of compounds **3** and **4** were based on their spectral (IR, ^{1}H NMR and MS) and analytical data. The mild reaction conditions, simple operation, short reaction times, high product yields, excellent purity of the products and the elimination of the solvent are advantages of this method.



Ar	Ar
a: C_6H_5	**e**: 4-Br C_6H_4
b: 4–$CH_3C_6H_4$	**f**: 3-NO_2 C_6H_4
c: 4–$CH_3OC_6H_4$	**g**: 4-NO_2 C_6H_4
d: 4-Cl C_6H_4	**h**: 2-Naphthyl

Scheme I

Antibacterial activity

All the synthesized compounds **4** were subjected to their antibacterial activity against *Escherichia coli* and *Bacillus subtilis* following the filter paper disc technique of Vincent and Vincent[17] at 250 and 500 µg/disc concentrations. Gentamycin was used as a standard drug for comparison. The results are presented in **Table II**. From the activity data, it is established that all the compounds **4** were active against both the bacteria at the concentration of 250 µg/disc. However, the degree of inhibition varied both with the test compound as well as with the bacterium. Among the compounds tested **4b** and **4d** exhibited significant antibacterial activity. The remaining compounds showed either good or moderate antibacterial activity.

Anti-inflammatory activity

The anti-inflammatory activity of the compounds **4** was carried out using the carrageenan induced rat paw edema method[18], using Diclofenac sodium as reference drug for comparison. The results are given in **Table III**. Compounds **4c**, **4d** and **4e** showed very good anti-inflammatory activity. The remaining compounds displayed moderate anti-inflammatory.

Experimental Section

Melting points were measured on a Cintex melting point apparatus and are uncorrected. The homogeneity of the compounds was inferred from TLC on silica gel-G plates (Merck, 60F-254). IR spectra (KBr) were recorded on a Perkin-Elmer BX series 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 a VG 170708H spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN analyser. Microwave irradiations were carried out using domestic microwave oven (LG MG-556P, 2450MHz).

General procedure for the synthesis of 1-aryl-1-ethanone 1-{3-[2-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}hydrazones 3

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

3a: IR (KBr): 3356 (NH), 1622 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 7.78 (m, 1H, C_6-H), 7.84 (m, 2H, C_4-H, C_5-H), 8.30 (m, 1H, C_7-H), 6.85-7.65 (m, 9H, Ar-H), 9.82 (s, 1H, NH); MS (ES$^+$): *m/z* 407 $[M+H]^+$.

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

Compd	Reaction Time (min)	m.p. (°C)	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N
3a	1.0	93	92	$C_{23}H_{17}F_3N_4$	68.11 (67.97	4.25 4.22	13.84 13.79)
3b	0.5	142	94	$C_{24}H_{19}F_3N_4$	68.69 (68.56	4.57 4.55	13.37 13.33)
3c	1.0	157	93	$C_{24}H_{19}F_3N_4O$	66.19 (66.05	4.42 4.39	12.89 12.84)
3d	0.5	180	96	$C_{23}H_{16}ClF_3N_4$	62.78 (62.66	3.68 3.66	12.77 12.71)
3e	1.0	127	95	$C_{23}H_{16}BrF_3N_4$	57.05 (56.92	3.35 3.32	11.60 11.54)
3f	0.5	168	92	$C_{23}H_{16}F_3N_5O_2$	61.33 (61.20	3.60 3.57	15.56 15.51)
3g	0.5	139	94	$C_{23}H_{16}F_3N_5O_2$	61.34 (61.20	3.61 3.57	15.55 15.51)
3h	1.0	152	92	$C_{27}H_{19}F_3N_4$	71.17 (71.04	4.23 4.20	12.33 12.27)
4a	3.5	195	84	$C_{25}H_{15}F_3N_4O$	67.70 (67.57	3.43 3.40	12.65 12.61)
4b	3.5	208	85	$C_{26}H_{17}F_3N_4O$	68.27 (68.12	3.75 3.74	12.27 12.22)
4c	4.0	285	83	$C_{26}H_{17}F_3N_4O_2$	65.95 (65.82	3.64 3.61	11.86 11.81)
4d	3.5	231	86	$C_{25}H_{14}ClF_3N_4O$	62.86 (62.71	2.98 2.95	11.76 11.70)
4e	4.0	280	84	$C_{25}H_{14}BrF_3N_4O$	57.51 (57.38	2.74 2.70	10.76 10.71)
4f	4.5	205	82	$C_{25}H_{14}F_3N_5O_3$	61.49 (61.35	2.91 2.88	14.36 14.31)
4g	4.5	248	83	$C_{25}H_{14}F_3N_5O_3$	61.48 (61.35	2.91 2.88	14.37 14.31)
4h	4.0	227	84	$C_{29}H_{17}F_3N_4O$	70.58 (70.44	3.51 3.47	11.38 11.33)

Table II — Antibacterial activity data of compounds **4**

Compd	Inhibition zone (in mm) *E. coli* 250 µg/disc	*E. coli* 500 µg/disc	*B. subtilis* 250 µg/disc	*B. subtilis* 500 µg/disc
4a	9.0	15.5	6.0	10.5
4b	10.0	17.5	6.5	11.5
4c	9.5	16.5	6.0	10.5
4d	10.5	20.0	6.5	13.0
4e	9.5	17.0	5.5	11.0
4f	8.5	13.5	5.0	9.5
4g	9.0	14.5	5.5	10.0
4h	8.5	13.0	5.5	9.5
Gentamycin	12.0	22.0	8.0	15.0

3b: IR (KBr): 3328 (NH), 1623 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.17 (s, 3H, CH_3), 2.22 (s, 3H, N=C-CH_3), 7.78 (m, 1H, C_6-H), 7.82 (m, 2H, C_4-H, C_5-H), 8.36 (m, 1H, C_7-H), 6.92-7.64 (m, 8H, Ar-H), 9.84 (s, 1H, NH); MS (ES^+): *m/z* 421 $[M+H]^+$.

3c: IR (KBr): 3340 (NH), 1625 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.76 (m, 1H, C_6-H), 7.83 (m, 2H, C_4-H, C_5-H), 8.32 (m, 1H, C_7-H), 6.98-7.62 (m, 8H, Ar-H), 9.85 (s, 1H, NH); MS (ES^+): *m/z* 437 $[M+H]^+$.

3d: IR (KBr): 3345 (NH), 1624 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.17 (s, 3H, CH_3), 7.78 (m, 3H, C_4-H, C_5-H, C_6-H), 8.32 (m, 1H, C_7-H), 6.93-7.65 (m, 8H, Ar-H), 9.80 (s, 1H, NH); MS (ES^+): *m/z* 441 $[M+H]^+$.

3e: IR (KBr): 3334 (NH), 1622 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 7.73 (m, 3H, C_4-H, C_5-H, C_6-H), 8.30 (m, 1H, C_7-H), 6.95-7.68 (m, 8H, Ar-H), 9.80 (s, 1H, NH); MS (ES^+): *m/z* 485 $[M+H]^+$.

3f: IR (KBr): 3362 (NH), 1626 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.25 (s, 3H, CH_3), 7.67 (m, 1H, C_6-H), 7.78 (m, 2H, C_4-H, C_5-H), 8.37 (m, 1H, C_7-H), 7.03-7.60 (m, 8H, Ar-H), 9.85 (s, 1H, NH); MS (ES^+): *m/z* 452 $[M+H]^+$.

3g: IR (KBr): 3345 (NH), 1624 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.24 (s, 3H, CH_3), 7.80 (m, 1H, C_6-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.39 (m, 1H, C_7-H), 7.05-7.69 (m, 8H, Ar-H), 9.88 (s, 1H, NH); MS (ES^+): *m/z* 452 $[M+H]^+$.

Table III — Rat paw edema in mL[b] and % paw edema protection activity of compounds**4**

Compd	Paw Volume			
	1st h	2nd h	3rd h	4th h
4a	2.62±0.392 (4.37%)	2.45±0.305* (14.63%)	1.91±0.324*** (38.78%)	1.64±0.376*** (47.93%)
4b	2.52±0.268 (8.02%)	2.17±0.214*** (24.39%)	1.83±0.360*** (41.34%)	1.59±0.281*** (49.52%)
4c	2.48±0.256 (9.48%)	2.31±0.282** (19.51%)	1.95±0.310*** (37.50%)	1.48±0.286*** (53.01%)
4d	2.26±0.254 (17.51%)	2.11±0.263*** (26.48%)	1.85±0.384*** (40.70%)	1.31±0.281*** (58.41%)
4e	2.21±0.252 (19.34%)	2.13±0.264*** (25.78%)	2.09±0.274*** (33.01%)	1.54±0.292*** (51.11%)
4f	2.34±0.233 (14.59%)	2.19±0.274** (23.69%)	2.14±0.245** (31.41%)	1.97±0.315** (37.46%)
4g	2.44±0.397 (10.94%)	2.14±0.386*** (25.43%)	1.78±0.314*** (42.94%)	1.69±0.372*** (46.34%)
4h	2.29±0.272 (16.42%)	2.16±0.252*** (24.73%)	1.79±0.282*** (42.62%)	1.64±0.289*** (47.94%)
control	2.74±0.242 NA	2.87±0.254 NA	3.12±0.289 NA	3.15±0.291 NA
Diclofenac sodium	1.84±0.251*** (32.84%)	1.32±0.251*** (54.01%)	0.91±0.257*** (70.83%)	0.52±0.309*** (83.49%)

[a]Dose level: test compounds (100 mg/kg b.wt), Diclofenac sodium (10 mg/kg b.wt)
[b]Values are expressed as mean±SD (number of animals N= 6 rats)
Statistically significant compared to respective control values, ***P<0.001, **P<0.01, *P<0.05 (Dunnet's test)

3h: IR (KBr): 3352 (NH), 1622 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.22 (s, 3H, CH_3), 7.78 (m, 1H, C_6-H), 7.85 (m, 2H, C_4-H, C_5-H), 8.34 (m, 1H, C_7-H), 6.92-7.65 (m, 11H, Ar-H), 9.83 (s, 1H, NH); MS (ES^+): *m/z* 457 $[M+H]^+$.

General procedure for the synthesis of 3-aryl-1-{3-[2-(trifluoromethyl)phenyl][1,8]naphthyridin-2-yl}-1*H*-4-pyrazolecarbaldehydes 4

To the Vilsmeier-Haack reagent (0.03 mol) at 0-5°C, compound **3** (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 (3 g) 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 W intermittently at 30 s intervals for specified time (**Table I**). After the completion of reaction as monitored by TLC, the reaction mixture was cooled, treated with chilled water and filtered. The solid obtained by the neutralization of the filtrate with $NaHCO_3$ was filtered, washed with water and purified by recrystallization from ethanol to furnish **4** (**Table I**).

4a: IR (KBr): 1672 C=O), 1607 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.74 (m, 2H, C_4-H, C_6-H), 7.98 (m, 1H, C_5-H), 8.68 (m, 1H, C_7-H), 7.21-7.50 (m, 10H, CH of pyrazole, 9Ar-H), 9.68 (s, 1H, CHO); MS (ES^+): *m/z* 445 $[M+H]^+$.

4b: IR (KBr): 1671 (C=O), 1605 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 2.18 (s, 3H, CH_3), 7.80 (m, 2H, C_4-H, C_6-H), 8.01 (m, 1H, C_5-H), 8.64 (m, 1H, C_7-H),7.05-7.72 (m, 9H, CH of pyrazole, 8Ar-H), 9.65 (s, 1H, CHO); MS (ES^+): *m/z* 459 $[M+H]^+$.

4c: IR (KBr): 1668 (C=O), 1603 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 3.83 (s, 3H, OCH_3), 7.82 (m, 2H, C_4-H, C_6-H), 8.03 (m, 1H, C_5-H), 8.76 (m, 1H, C_7-H), 6.85-7.71 (m, 9H, CH of pyrazole, 8Ar-H), 9.67 (s, 1H, CHO); MS (ES^+): *m/z* 475 $[M+H]^+$.

4d: IR (KBr): 1668 (C=O), 1601 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.82 (m, 2H, C_4-H, C_6-H), 8.00 (m, 1H, C_5-H), 8.31 (m, 1H, C_7-H), 7.21-7.65 (m, 9H, CH of pyrazole, 8Ar-H), 9.63 (s, 1H, CHO); MS (ES^+): *m/z* 479 $[M+H]^+$.

4e: IR (KBr): 1670 (C=O), 1606 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.85 (m, 2H, C_4-H, C_6-H), 8.05 (m, 1H, C_5-H), 8.75 (m, 1H, C_7-H), 7.02-7.69 (m, 9H, CH of pyrazole, 8Ar-H), 9.68 (s, 1H, CHO); MS (ES^+): *m/z* 523 $[M+H]^+$.

4f: IR (KBr): 1670 (C=O), 1608 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.83 (m, 2H, C_4-H, C_6-H), 8.01 (m, 1H, C_5-H), 8.44 (m, 1H, C_7-H), 6.91-7.72 (m, 9H, CH of pyrazole, 8Ar-H), 9.65 (s, 1H, CHO); MS (ES^+): *m/z* 490 $[M+H]^+$.

4g: IR (KBr): 1668 (C=O), 1605 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.86 (m, 2H, C_4-H, C_6-H), 8.12 (m, 1H, C_5-H),

8.42 (m, 1H, C_7-H), 7.06-7.73 (m, 9H, CH of pyrazole, 8Ar-H), 9.67 (s, 1H, CHO); MS (ES^+): *m/z* 490 $[M+H]^+$.

4h: IR (KBr): 1672 (C=O), 1609 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ 7.90 (m, 2H, C_4-H, C_6-H), 8.08 (m, 1H, C_5-H), 8.54 (m, 1H, C_7-H), 7.00-7.78 (m, 12H, CH of pyrazole, 11Ar-H), 9.72 (s, 1H, CHO); MS (ES^+): *m/z* 495 $[M+H]^+$.

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