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GREEN SYNTHESIS AND CHARACTERIZATION OF VARIOUS (2-NAPHTHYL)[1,2,4] TRIAZOLO [4,3-A][1,8] NAPHTHYRIDINES

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Abstract

A simple and highly efficient procedure has been described for the synthesis of 9-aryl-6-(2-naphthyl)[1,2,4]triazolo[4,3-a][1,8]naphthyridines **8** by the oxidation of the corresponding aryl aldehyde 1-[3-(2-naphthyl) [1,8]naphthyridin-2-yl]hydrazones **7** using silica gel supported ferric chloride in solvent-free conditions under microwave irradiation. The products are obtained in very good yields and in a state of high purity. The structure of compounds **3-8** were confirmed by their spectral studies.

Keywords: 1,8-Naphthyridine, 1,2,4-triazole, SiO₂-FeCl₃, solvent-free conditions, microwave irradiation.

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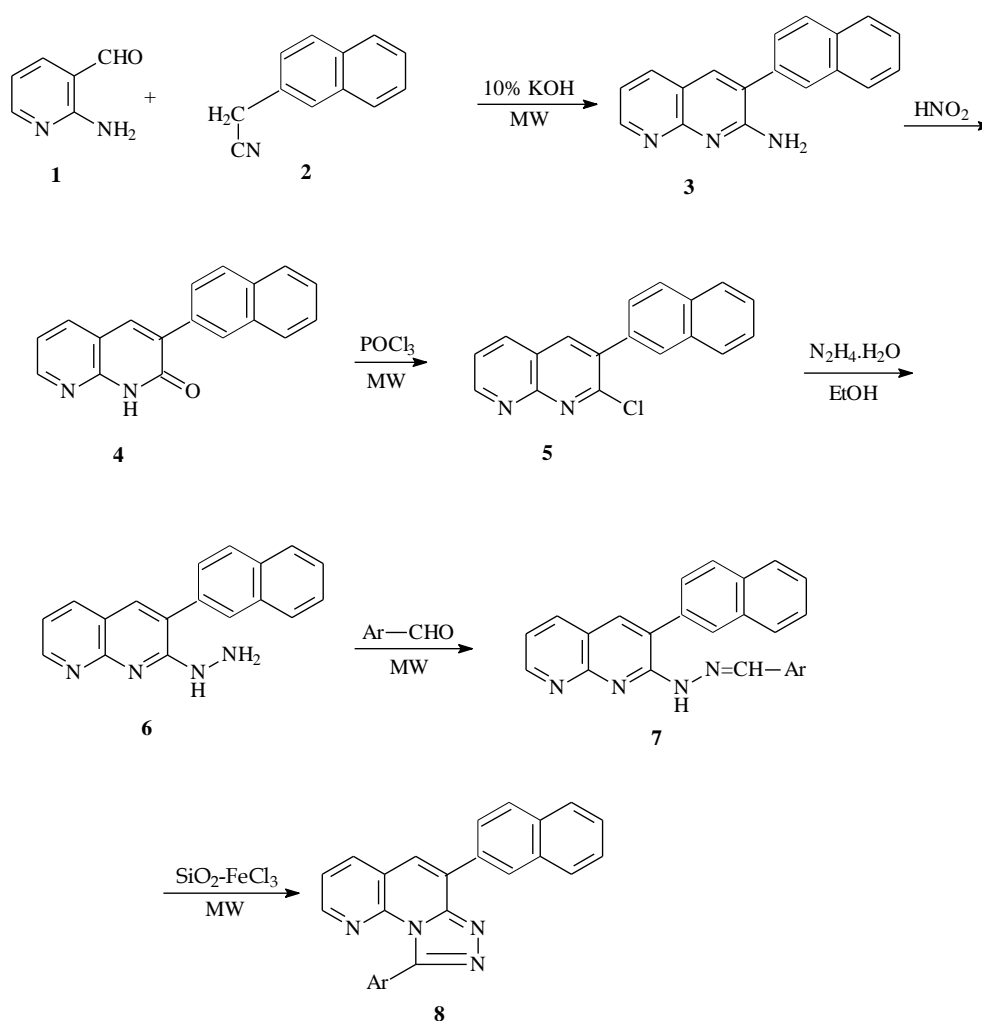
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Introduction:

1,8-Naphthyridines are an important group of heterocyclic compounds possessing a variety of biological activities¹⁻³. Fused 1,2,4-triazoles are of interest to many researchers in diverse fields⁴⁻⁶. Though various routes for the synthesis of these compounds are known⁷⁻¹², the majority of them involve longer preparation time, high reaction temperature, low yields and usage of toxic reagents. Therefore, development and introduction of convenient and efficient method for the preparation of fused 1,2,4-triazoles is a practical importance and is still in demand. In recent years, microwave irradiation, as a high

energy technique, has been used in organic synthesis¹³⁻¹⁵. The application of microwave (MW) heating under solvent-free reaction conditions¹⁴ and on inorganic solid support^{16,17} is promising alternative to polluting reactions and has been a current field of interest. In view of this and in continuation of our interest in the microwave-assisted organic transformations of 1,8-naphthyridine derivatives¹⁸⁻²⁰, we report herein a convenient, efficient and high yielding protocol for the synthesis of 9-aryl-6-(2-naphthyl)[1,2,4]triazolo [4,3-a][1,8]naphthyridines using silicagel supported ferric chloride ($\text{SiO}_2\text{-FeCl}_3$) in solvent-free conditions under microwave irradiation.



Ar	Ar
a: C ₆ H ₅	f: 4-F C ₆ H ₄
b: 4-CH ₃ C ₆ H ₄	g: 2-NO ₂ C ₆ H ₄
c: 4-CH ₃ OC ₆ H ₄	h: 3-NO ₂ C ₆ H ₄
d: 2-Cl C ₆ H ₄	i: 4-NO ₂ C ₆ H ₄
e: 4-Cl C ₆ H ₄	j: 3,4-(CH ₃ O) ₂ C ₆ H ₃

Scheme I

2-Aminonicotinaldehyde **1** on condensation with 2-naphthylacetonitrile **2** in the presence of 10% KOH without any solvent under MW irradiation afforded 3-(2-naphthyl)[1,8]naphthyridin-2-amine **3**, which is converted into 3-(2-naphthyl)-1,2-dihydro[1,8]naphthyridin-2-one **4** by reaction with HNO₂. Treatment of **4** with POCl₃ under MW irradiation furnished 2-chloro-3-(2-naphthyl)[1,8]naphthyridine **5**, which on hydrazinolysis with refluxing hydrazine hydrate resulted in the formation of 1-[3-(2-naphthyl)[1,8]naphthyridin-2-yl]hydrazine **6**.

Condensation of **6** with various aromatic aldehydes in the presence of catalytic amount of DMF under MW irradiation afforded the corresponding aryl aldehyde 1-[3-(2-naphthyl)[1,8]naphthyridin-2-yl]hydrazones **7** in excellent yields.

The hydrazones **7** on oxidative cyclization with silica gel supported ferric chloride (SiO₂-FeCl₃) in solvent-free conditions under MW irradiation furnished the respective 9-aryl-6-(2-naphthyl)[1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **8** (Scheme I) in very good yields (88-94%) with short reaction time period (3.5-5.0 min). The oxidative transformation is simple, rapid and efficient and is devoid of any side products. The process is environmentally benign. The experimental procedure is very simple.

In a typical experiment, **7a** (Ar = C₆H₅) was mixed with SiO₂-FeCl₃ and the mixture was exposed to MW irradiation at 800 W intermittently at 30 sec intervals for 4.0 min. The reaction mixture was cooled to RT and digested with methanol. After usual work-up 9-phenyl-6-(2-naphthyl)[1,2,4]triazolo[4,3-*a*][1,8]naphthyridine **8a** (Ar = C₆H₅) was

obtained in 90% yield. When the reaction was carried out under conventional conditions for the same time as above (4.0 min) at 120°C (temperature measured at the end of exposure during microwave experiment), the product was obtained only in 5% yield.

The generality of the above transformation was checked by treating other hydrazones **7** with SiO₂-FeCl₃ under MW irradiation and in all cases respective 9-aryl-6-(2-naphthyl)[1,2,4]triazolo[4,3-*a*][1,8]naphthyridines **8** were obtained in 88-94% yields (Table I).

Experimental Section

Melting points were measured in open capillaries on a Cintex melting point apparatus and are uncorrected. Purity of the compounds was checked using precoated TLC plates (Merk, 60F-254). ¹H NMR spectra on a Varian Gemini 300 MHz spectrometer (chemical shifts in δ ppm). Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Microwave irradiation was carried out in a domestic microwave oven (LGMG 556P, 2450 MHz). The 2-naphthylacetonitrile **2** was purchased from Aldrich Chemical Company.

3-(2-Naphthyl)[1,8]naphthyridin-2-amine **3**.

A mixture of 2-aminonicotinaldehyde **1** (0.01 mol), 2-naphthylacetonitrile **2** (0.01 mol) and 10% KOH (5 drops) was exposed to MW irradiation at 200 W intermittently at 30 sec for 2.5 min. On completion of the reaction, as monitored by TLC, the reaction mixture was cooled, the solid thus obtained was filtered, washed with water and purified by recrystallization from methanol to afford **3**, yield 97%; m.p. 310°C. ¹H NMR (CDCl₃ +

DMSO-*d*₆): δ (s, 2H, NH₂), (s, 1H, C₄-H), (m, 1H, C₅-H), (m, 1H, C₇-H), (m, 8H, C₆-H, 7Ar-H). Anal. Calcd for C₁₈H₁₃N₃: C, 79.68; H,

4.83; N, 15.49. Found: C, 79.81; H, 4.85; N, 15.54%.

Table I — Physical and analytical data of compounds **7** and **8**

Entry	Reaction time (min)	m.p. °C	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
7a	0.5	184	95	C ₂₅ H ₁₈ N ₄	80.32 (80.19)	4.87 4.85	15.01 14.96
7b	1.0	194	97	C ₂₆ H ₂₀ N ₄	80.53 (80.39)	5.23 5.19	14.46 14.42
7c	1.0	171	94	C ₂₆ H ₂₀ N ₄ O	77.33 (77.21)	5.00 4.98	13.90 13.85
7d	0.5	165	95	C ₂₅ H ₁₇ N ₄ Cl	73.57 (73.44)	4.22 4.19	13.74 13.70
7e	1.0	186	98	C ₂₅ H ₁₇ N ₄ Cl	73.56 (73.44)	4.21 4.19	13.76 13.70
7f	0.5	188	96	C ₂₅ H ₁₇ N ₄ F	76.65 (76.52)	4.40 4.37	14.32 14.28
7g	0.5	183	95	C ₂₅ H ₁₇ N ₅ O ₂	71.74 (71.59)	4.10 4.09	16.76 16.70
7h	0.5	175	95	C ₂₅ H ₁₇ N ₅ O ₂	71.72 (71.59)	4.12 4.09	16.75 16.70
7i	0.5	145	97	C ₂₅ H ₁₇ N ₅ O ₂	71.73 (71.59)	4.11 4.09	16.74 16.70
7j	1.0	196	96	C ₂₇ H ₂₂ N ₄ O ₂	74.78 (74.64)	5.12 5.10	12.94 12.89
8a	4.0	224	90	C ₂₅ H ₁₆ N ₄	80.75 (80.63)	4.36 4.33	15.08 15.04
8b	4.0	210	92	C ₂₆ H ₁₈ N ₄	80.94 (80.81)	4.71 4.69	14.55 14.50
8c	4.5	255	90	C ₂₆ H ₁₈ N ₄ O	77.73 (77.60)	4.53 4.51	13.97 13.92
8d	4.0	235	90	C ₂₅ H ₁₅ N ₄ Cl	73.92 (73.80)	3.75 3.72	13.82 13.77
8e	3.5	248	94	C ₂₅ H ₁₅ N ₄ Cl	73.94 (73.80)	3.74 3.72	13.81 13.77
8f	4.0	242	92	C ₂₅ H ₁₅ N ₄ F	77.03 (76.91)	3.89 3.87	14.40 14.35
8g	4.0	252	88	C ₂₅ H ₁₅ N ₅ O ₂	72.08	3.63	16.83

					(71.94	3.62	16.78)
8h	4.5	245	88	C ₂₅ H ₁₅ N ₅ O ₂	72.07	3.64	16.82
					(71.94	3.62	16.78)
8i	5.0	258	90	C ₂₅ H ₁₅ N ₅ O ₂	72.06	3.65	16.83
					(71.94	3.62	16.78)
8j	4.0	208	91	C ₂₇ H ₂₀ N ₄ O ₂	75.12	4.69	12.99
					(74.99	4.66	12.95)

3-(2-Naphthyl)-1,2-

dihydro[1,8]naphthyridin-2-one 4. To a cold solution of **3** (0.01 mol) in 2 M HCl (25 mL) was added NaNO₂ solution (0.01 mol in 25 mL water) and the reaction mixture was stirred at room temperature for 0.5 hr and treated with chilled water. The solid that separated was filtered, washed with water and purified by recrystallization from methanol to give **4**, yield 95%; m.p. 183°C. ¹H NMR (CDCl₃): δ (m, 1H, C₆-H), (s, 1H, C₄-H), (m, 1H, C₅-H), (m, 1H, C₇-H), (m, 7H, Ar-H), (brs, 1H, NH). Anal. Calcd for C₁₈H₁₂N₂O: C, 79.40; H, 4.44; N, 10.29. Found: C, 79.54; H, 4.47; N, 10.33%.

2-Chloro-3-(2-naphthyl)[1,8]naphthyridine

5. A mixture of **4** (0.01 mol) and POCl₃ (10 mL) was subjected to MW irradiation at 200 W intermittently at 30 sec intervals for 2.0 min. After completion of reaction, as indicated by TLC, the reaction mixture was cooled and poured onto a mixture of crushed ice and NaHCO₃. The solid that separated was filtered, washed with water and purified by recrystallization from ethanol to afford **5**, yield 94%; m.p. 208°C. ¹H NMR (CDCl₃): δ (m, 1H, C₆-H), (s, 1H, C₄-H), (m, 1H, C₅-H), (m, 1H, C₇-H), (m, 7H, Ar-H). Anal. Calcd for C₁₈H₁₁N₂Cl: C, 74.36; H, 3.81; N, 9.63. Found: C, 74.49; H, 3.83; N, 9.68%.

1-[3-(2-Naphthyl)[1,8]naphthyridin-2-

yl]hydrazine 6. A mixture of **5** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed on a water bath for 4.0 hr. The reaction mixture was cooled and treated with cold water. The solid that separated was filtered, washed with water and purified by recrystallization from ethanol to furnish **6**, yield: 95%; m.p. 176°C. ¹H NMR (CDCl₃): δ (brs, 2H, NH₂), (m, 2H, C₄-H, C₆-H), (m, 1H,

C₅-H), (m, 1H, C₇-H), (m, 8H, NH, 7Ar-H). Anal. Calcd for C₁₈H₁₄N₄: C, 75.51; H, 4.93; N, 19.57. Found: C, 75.65; H, 4.95; N, 19.61%.

General procedure for the synthesis of aryl aldehyde

1-[3-(2-naphthyl)[1,8]naphthyridin-2-yl]hydrazones 7. A mixture of **6** (0.01 mole), aromatic aldehyde (0.01 mole) and DMF (5 drops) was subjected to MW irradiation at 200 W intermittently at 10 sec intervals for the specified time (**Table I**). On completion of the reaction, as monitored by TLC, the reaction mixture was cooled and digested with cold water. The solid thus obtained was filtered, washed with water and purified by recrystallization from ethanol to afford **7** (**Table I**).

7a: ¹H NMR (CDCl₃): δ 7.88 (m, 2H, C₅-H, C₆-H), 8.15 (s, 1H, C₄-H), 8.34 (m, 1H, C₇-H), 8.45 (m, 1H, N=CH), 7.00-7.83 (m, 12H, Ar-H), 10.32 (s, 1H, NH).

7b: ¹H NMR (CDCl₃): δ 2.40 (s, 3H, CH₃), 7.85 (m, 2H, C₅-H, C₆-H), 8.14 (s, 1H, C₄-H), 8.36 (m, 1H, C₇-H), 8.42 (s, 1H, N=CH), 6.98-7.72 (m, 11H, Ar-H), 10.30 (s, 1H, NH).

7c: ¹H NMR (CDCl₃): δ 3.85 (s, 3H, OCH₃), 7.84 (m, 2H, C₅-H, C₆-H), 8.15 (s, 1H, C₄-H), 8.35 (m, 1H, C₇-H), 8.42 (s, 1H, N=CH), 6.90-7.80 (m, 11H, Ar-H), 10.24 (s, 1H, NH).

7d: ¹H NMR (CDCl₃): δ 7.90 (m, 2H, C₅-H, C₆-H), 8.15 (s, 1H, C₄-H), 8.38 (m, 1H, C₇-H), 8.42 (s, 1H, N=CH), 7.02-7.83 (m, 11H, Ar-H), 10.28 (s, 1H, NH).

7e: ¹H NMR (CDCl₃): δ 7.85 (m, 1H, C₆-H), 8.13 (s, 1H, C₄-H), 8.37 (m, 1H, C₇-H), 8.40 (s, 1H, N=CH), 7.00-7.80 (m, 11H, Ar-H), 10.30 (s, 1H, NH).

7f: ¹H NMR (CDCl₃): δ 7.88 (m, 2H, C₅-H, C₆-H), 8.16 (s, 1H, C₄-H), 8.27 (m, 1H, C₇-H),

8.38 (s, 1H, N=CH), 7.02-7.83(m, 11H, Ar-H), 10.28 (s, 1H, NH).

7g: ¹H NMR (CDCl₃): δ 7.90 (m, 2H, C₅-H, C₆-H), 8.15 (s, 1H, C₄-H), 8.32 (m, 1H, C₇-H), 8.45 (s, 1H, N=CH), 7.00-7.82 (m, 11H, Ar-H), 10.28 (s, 1H, NH).

7h: ¹H NMR (CDCl₃): δ 7.86 (m, 2H, C₅-H, C₆-H), 8.17 (s, 1H, C₄-H), 8.36 (m, 1H, C₇-H), 8.42 (s, 1H, N=CH), 6.98-7.75 (m, 11H, Ar-H), 10.32 (s, 1H, NH).

7i: ¹H NMR (CDCl₃): δ 7.88 (m, 2H, C₅-H, C₆-H), 8.18 (s, 1H, C₄-H), 8.35 (m, 1H, C₇-H), 8.44 (s, 1H, N=CH), 7.05-7.86 (m, 11H, Ar-H), 10.30 (s, 1H, NH).

7j: ¹H NMR (CDCl₃): δ 3.86 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 7.85 (m, 2H, C₅-H, C₆-H), 8.18 (s, 1H, C₄-H), 8.37 (m, 1H, C₇-H), 8.52 (s, 1H, N=CH), 7.05-7.78 (m, 10H, Ar-H), 10.30 (s, 1H, NH).

General procedure for the synthesis of 9-aryl-6-(2-naphthyl)[1,2,4]triazolo[4,3-a][1,8]naphthyridines 8. Compound **7** (0.01 mol) and silica gel supported ferric chloride (SiO₂-FeCl₃) (2g) are mixed thoroughly and exposed to MW irradiation at 800 W intermittently at 30 sec intervals for the specified time (**Table I**). After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with methanol (30 mL). The methanol solution was poured into ice cold water (50 mL), the separated solid was filtered, washed with water and purified by recrystallization from ethanol to furnish **8** (**Table I**).

8a: ¹H NMR (CDCl₃): δ 8.20 (m, 2H, C₃-H, C₅-H), 8.45 (m, 1H, C₄-H), 8.80 (m, 1H, C₂-H), 7.23-8.02 (m, 12H, Ar-H).

8b: ¹H NMR (CDCl₃): δ 2.48 (s, 3H, CH₃), 8.18 (m, 2H, C₃-H, C₅-H), 8.45 (m, 1H, C₄-H), 8.78 (m, 1H, C₂-H), 7.25-8.00 (m, 11H, Ar-H).

8c: ¹H NMR (CDCl₃): δ 3.92 (s, 3H, OCH₃), 8.17 (m, 2H, C₃-H, C₅-H), 8.40 (m, 1H, C₄-H), 8.76 (m, 1H, C₂-H), 7.04-8.02 (m, 11H, Ar-H).

8d: ¹H NMR (CDCl₃): δ 8.22 (m, 2H, C₃-H, C₅-H), 8.45 (m, 1H, C₄-H), 8.74 (m, 1H, C₂-H), 7.18-8.04 (m, 11H, Ar-H).

8e: ¹H NMR (CDCl₃): δ 8.20 (m, 3H, C₃-H, C₅-H), 8.47 (m, 1H, C₄-H), 8.78 (m, 1H, C₂-H), 7.25-8.02 (m, 11H, Ar-H).

8f: ¹H NMR (CDCl₃): δ 8.22 (m, 2H, C₃-H, C₅-H), 8.46 (m, 1H, C₄-H), 8.76 (m, 1H, C₂-H), 7.22-8.04 (m, 11H, Ar-H).

8g: ¹H NMR (CDCl₃): δ 8.19 (m, 2H, C₃-H, C₄-H), 8.45 (m, 1H, C₅-H), 8.78 (m, 1H, C₂-H), 7.24-8.03 (m, 11H, Ar-H).

8h: ¹H NMR (CDCl₃): δ 8.17 (m, 2H, C₃-H, C₄-H), 8.44 (m, 1H, C₅-H), 8.82 (m, 1H, C₂-H), 7.20-8.00 (m, 11H, Ar-H).

8i: NMR (CDCl₃): δ 8.22 (m, 2H, C₃-H, C₄-H), 8.47 (m, 1H, C₅-H), 8.80 (m, 1H, C₂-H), 7.23-8.05 (m, 11H, Ar-H).

8j: ¹H NMR (CDCl₃): δ 3.92 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 8.38 (m, 2H, C₃-H, C₅-H), 8.48 (m, 1H, C₄-H), 8.77 (m, 1H, C₂-H), 7.00-8.02 (m, 10H, Ar-H).

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