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Note

Efficient synthesis of 6-aryl-12*H*-pyrido-[2',3':4,5]pyrimido [1,2-*a*][1,8]naphthyridin-12-ones under microwave irradiation

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A straightforward and highly efficient procedure has been described for the synthesis of 6-aryl-12*H*-pyrido[2',3':4,5]-pyrimido[1,2-*a*][1,8]naphthyridin-12-ones **3** by the reaction of 3-aryl-2-chloro-1,8-naphthyridines **1** with 2-aminonicotinic acid **2** in glacial acetic acid 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.

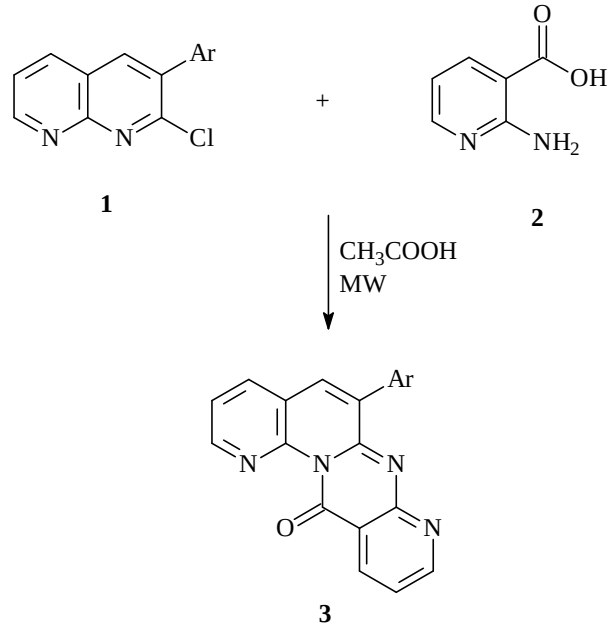
Keywords: 3-Aryl-2-chloro-1,8-napthyridines, 2-aminonicotinic acid, pyrido-[2',3':4,5]pyrimido[1,2,-*a*][1,8]naphthyridin-12-ones, microwave irradiation

1,8-Naphthyridines constitute an important class of compounds possessing diverse biological activities[1-3]. On the other hand, pyridines are very important class of heterocycles and have been widely used in pharmaceutical and agrochemical industry[4,5]. Further, pyrimidines have been extensively explored for their applications in the field of biological and pharmacological activities[6,7]. Therefore, it was envisaged that chemical entities with 1,8-naphthyridine, pyridine and pyrimidine might result in compounds with interesting biological activity.

Microwave-assisted organic synthesis has attracted attention in recent years[8-10], due to enhanced reaction rates, high yields, improved selectivity and eco-friendly conditions. Several methods have been developed for performing reactions with microwave irradiation in solution and under solvent-free conditions, but a homogeneous mixture is preferred to obtain uniform heating. The solvents with higher dielectric constants are superheated and the reactions take place rapidly. In view of this and in continuation of our interest in microwave-assisted organic transformations on 1,8-naphthyridine derivatives[11-14], we report herein, a convenient, practical and efficient method for the synthesis of a novel and hitherto unknown bridgehead nitrogen heterocyclic system, pyrido[2',3':4,5]pyrimido[1,2-*a*]-[1,8]naphthyridin-12-ones under microwave irradiation.

Treatment of 3-aryl-2-chloro-1,8-naphthyridines **1** with 2-aminonicotinic acid **2** in glacial acetic acid under microwave irradiation resulted in the formation of 6-aryl-12*H*-pyrido[2',3':4,5]pyrimido[1,2-*a*][1,8]-naphthyridin-12-ones **3** (**Scheme I**), in very good yields (86-92%) with short reaction time (3.0-4.5 min). The reaction is very clean and rapid. Furthermore, 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.

In a typical experimental procedure, an equimolar quantities of 3-phenyl-2-chloro-1,8-naphthyridine **1a** and 2-aminonicotinic acid **2** in glacial acetic acid was exposed to microwave irradiation at 400 W for 3.0 min. The reaction mixture was cooled to RT, digested with cold water and filtered off. After usual work-up



1 **2** **3**

	Ar		Ar
a	C_6H_5	**d**	3-ClC_6H_4
b	4-$CH_3OC_6H_4$	**e**	4-ClC_6H_4
c	2-ClC_6H_4	**f**	4-BrC_6H_4

Scheme I

Table I — Characterization data of 6-aryl-12*H*-pyrido[2',3':4,5]pyrimido[1,2-*a*][1,8]-naphthyridin-12-ones **3**

Compd	Reaction period (min)	m.p. °C	Yield (%)	Mol. Formula	N%* Found (Calcd)	IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$) δ, ppm
3a	3.0	260	90	$C_{21}H_{13}N_3O$	13.08 (13.00)	1654 1612	7.80 (m, 3H, C_3-H, C_5-H, C_{10}-H), 8.02 (m, 2H, C_4-H, C_{11}-H), 8.80 (m, 2H, C_2-H, C_9-H), 7.20-7.58 (m, 5H, Ar-H)
3b	3.5	242	86	$C_{22}H_{15}N_3O_2$	11.97 (11.90)	1665 1618	3.85 (s, 3H, OCH_3), 7.79 (m, 3H, C_3-H, C_5-H, C_{10}-H), 8.00 (m, 2H, C_4-H, C_{11}-H), 8.70 (m, 2H, C_2-H, C_9-H), 7.00-7.30 (m, 4H, Ar-H)
3c	4.0	285(d)	90	$C_{21}H_{12}N_3OCl$	11.83 (11.75)	1656 1615	7.47 (m, 3H, C_3-H, C_5-H, C_{10}-H), 7.98 (m, 2H, C_4-H, C_{11}-H), 8.65 (m, 2H, C_2-H, C_9-H), 7.18-7.38 (m, 4H, Ar-H).
3d	4.0	280	87	$C_{21}H_{12}N_3OCl$	11.84 (11.75)	1655 1610	7.78 (m, 3H, C_3-H, C_5-H, C_{10}-H), 7.97 (m, 2H, C_4-H, C_{11}-H), 8.60 (m, 2H, C_2-H, C_9-H), 7.20-7.45 (m, 4H, Ar-H)
3e	4.5	270(d)	92	$C_{21}H_{12}N_3OCl$	11.82 (11.75)	1672 1616	7.80 (m, 3H, C_3-H, C_5-H, C_{10}-H), 8.15 (m, 2H, C_4-H, C_{11}-H), 8.52 (m, 2H, C_2-H, C_9-H), 7.25-7.50 (m, 4H, Ar-H)
3f	3.0	278	88	$C_{21}H_{12}N_3OBr$	10.56 (10.47)	1660 1612	7.77 (m, 3H, C_3-H, C_5-H, C_{10}-H), 8.00 (m, C_4-H, C_{11}-H), 8.63 (m, C_2-H, C_9-H), 7.22-7.47 (m, 4H, Ar-H)

* All the compounds gave satisfactory C, H analyses

6-phenyl-12*H*-pyrido[2',3':4,5]pyrimido[1,2-*a*][1,8]-naphthyridin-12-one **3a** was obtained in 90% yield. The reaction is of general applicability and the different pyrido[2',3':4,5]pyrimido[1,2-*a*][1,8]-naphthyridin-12-ones **3** synthesized are given in **Table I**.

Interestingly, this reaction proceeds only to a minor extent (5-8% in 3.0–4.5 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.

This is the first report on rapid synthesis of a novel bridgehead nitrogen heterocyclic system, pyrido[2',3':4,5]pyrimido [1,2-*a*][1,8]-naphthyridines under microwave irradiation. The structures of compounds **3** were confirmed by their spectroscopic (IR and ^{1}H NMR) and analytical data.

In conclusion, a convenient and highly efficient protocol for the synthesis of pyrido[2',3':4,5]pyrimido[1,2-*a*][1,8]-naphthyridines under microwave irradiation is demonstrated. The significant advantages of this procedure are the simple operation, very good yields, high purity and short reaction times.

Experimental Section

Melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr,cm^{-1}) were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ ppm) using TMS as internal standard. Irradiation was carried out in a domestic microwave oven (LG MG 556p, 2450 MHz). 3-Aryl-2-chloro-1,8-naphthyridines **1** were prepared according to our reported procedures[11-16]. The 2-aminonicotinic acid **2** was purchased from Aldrich Chemical Company.

General procedure for the synthesis of 6-aryl-12*H*-pyrido-[2',3':4,5]pyrimido[1,2-*a*][1,8]naphthyridin-12-ones 3. A mixture of 3-aryl-2-chloro-1,8-naphthyridine (**1**, 0.01 mole) and 2-aminonicotinic acid (**2**, 0.01 mole) in glacial acetic acid (20 mL) was subjected to microwave irradiation at 400 W intermittently at 30 sec intervals for the specified time (**Table I**). 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 recrystallized from methanol to afford **3** (**Table I**).

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