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Note

Microwave assisted synthesis of *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalimides under solvent-free conditions

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A simple, rapid and efficient protocol for the synthesis of *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalimides **3** has been achieved by the reaction of 2-amino-3-aryl-1,8-naphthyridines **1** with phthalic anhydride **2** in the presence of catalytic amount of DMF under microwave irradiation.

Keywords: 2-Amino-3-aryl-1,8-naphthyridines, phthalic anhydride, *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalamides, microwave irradiation

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The chemistry of 1,8-naphthyridine derivatives continues to draw the attention of synthetic organic chemists due to their varied biological and pharmacological activities[1-3]. Phthalimide derivatives constitute an important class of compounds possessing diverse type of biological properties including antimicrobial[4], antimalarial[4], antihypertensive[5,6] and antiviral[6] activity. Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and phthalimide might result in compounds with interesting biological activity. Microwave (MW) activation as non-conventional energy source has become a very popular and useful technology in synthetic organic chemistry[7-10]. Recently organic transformations accelerated under solvent-free microwave irradiation conditions gained wide popularity due to many practical advantages associated with enhanced reaction rates, high yields, improved selectivity and environment-friendly reaction conditions[8,9]. Due to the continued interest in the microwave assisted organic transformations of 1,8-naphthyridine derivatives[11-19], herein is reported a practical and efficient method for the synthesis of *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalimides **3** in solvent-free conditions under microwave irradiation.

Treatment of 2-amino-3-aryl-1,8-naphthyridines **1** with phthalic anhydride **2** in the presence of catalytic amount of DMF in absence of solvent under microwave irradiation afforded the corresponding *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalimides 3 (**Scheme I**), in excellent yields (92-98%) with short reaction time (3.0 – 4.0 min). The reaction is simple, clean, rapid and efficient and is devoid of any side products. The products were obtained with a high degree of purity by this procedure and no further purification was needed. It was observed that the neat mixtures of **1** and **2** did not reacted under microwave irradiation, but the reaction proceeds to completion within minutes on addition of few drops of high dielectric solvent such as DMF.

In a typical experimental procedure, equimolar quantities of 2-amino-3-phenyl-1,8-naphthyridine **1a**, phthalic anhydride **2** and catalytic amount of DMF was exposed to microwave irradiation at 600 W for 3.5 min. The reaction mixture was cooled to RT, digested with water and filtered off. After usual work-up *N*-(3-phenyl-1,8-naphthyridin-2-yl)phthalimide **3a** was obtained in 94% yield. The reaction is of general applicability and the different *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalimides **3** synthesized are given in **Table I**.

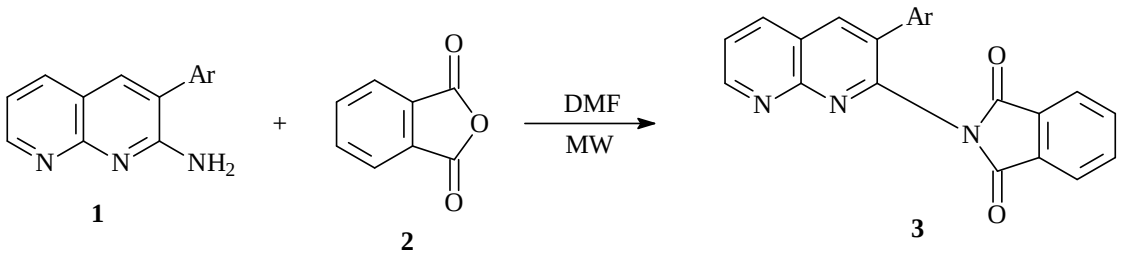
The reaction proceeds to only 5-8% in 3.0 – 4.0 min, when conducted under conventional conditions in an oil-bath preheated to 120^{o}C (measured immediately after microwave irradiation), thus demonstrating the advantage of the microwave heating method.

The structures of compounds **3** are assigned on the basis of their spectral (IR and ^{1}H NMR) and analytical data.

In conclusion, a simple, rapid and efficient method for the synthesis of 1,8-naphthyridinyl phthalimides under solvent-free microwave irradiation conditions has been demonstrated. The experimental simplicity, high yields, short reaction times, excellent purity and absence of solvent are the advantages of this method and thus, the method is environmentally benign.

Experimental Section

Melting points were obtained on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra (KBr) were recorded on Perkin-Elmer BX series FT-IR spectrometer. ^{1}H NMR spectra were recorded in



1 **2** **3**

a, Ar = C_6H_5
b, Ar = *p*-$CH_3OC_6H_4$
c, Ar = *o*-ClC_6H_4
d, Ar = *m*-ClC_6H_4
e, Ar = *p*-ClC_6H_4
f, Ar = *p*-BrC_6H_4
g, Ar = *p*-$NO_2C_6H_4$

Scheme I

Table I — Characterization data of *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalimides **3**

Compd	Mol. formula	Reaction Period (min)	m.p. (°C)	Yield (%)	Elemental analysis (N %)* Found (Calcd)	IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$) (δ, ppm)
3a	$C_{22}H_{13}N_3O_2$	3.5	130	94	11.90 (11.97)	1786, 1715, 1605	9.23 (m, 1H, C_7-H), 8.37 (m, 2H, C_4-H, C_5-H), 7.86 (m, 1H, C_6-H), 7.22-7.73 (m, 9H, Ar-H)
3b	$C_{23}H_{15}N_3O_3$	3.0	210	96	11.10 (11.02)	1786, 1716, 1609	8.94 (m, 1H, C_7-H), 8.13 (m, 2H, C_4-H, C_5-H), 7.84 (m, 1H, C_6-H), 7.02-7.67 (m, 8H, Ar-H), 3.88 (s, 3H, OCH_3).
3c	$C_{22}H_{12}N_3O_2Cl$	3.0	100	94	10.80 (10.89)	1790, 1730, 1607	9.26 (m, 1H, C_7-H), 8.42 (m, 2H, C_4-H, C_5-H), 7.83 (m, 1H, C_6-H), 7.25-7.70 (m, 8H, Ar-H)
3d	$C_{22}H_{12}N_3O_2Cl$	4.0	208	93	10.82 (10.89)	1787, 1721, 1608	9.25 (m, 1H, C_7-H), 8.36 (m, 2H, C_4-H, C_5-H), 7.88 (m, 1H, C_6-H), 7.23-7.75 (m, 8H, Ar-H)
3e	$C_{22}H_{12}N_3O_2Cl$	4.0	186	98	10.81 (10.89)	1786, 1714, 1604	9.22 (m, 1H, C_7-H), 8.33 (m, 2H, C_4-H, C_5-H), 7.90 (m, 1H, C_6-H), 7.26-7.80 (m, 8H, Ar-H)
3f	$C_{22}H_{12}N_3O_2Br$	3.0	120	95	9.86 (9.77)	1786, 1710, 1608	9.23 (m, 1H, C_7-H), 8.37 (m, 2H, C_4-H, C_5-H), 7.86 (m, 1H, C_6-H), 7.24-7.78 (m, 8H, Ar-H)
3g	$C_{22}H_{12}N_4O_4$	3.5	278	92	14.21 (14.14)	1789, 1716, 1605	8.87 (m, 1H, C_7-H), 8.39 (m, 2H, C_4-H, C_5-H), 7.98 (m, 1H, C_6-H), 7.30-7.84 (m, 8H, Ar-H)

* All the compounds gave satisfactory C, H analyses

$CDCl_3$ on a Varian Gemini 200 MHz spectrometer using TMS as internal standard. Irradiation was carried out in a domestic microwave oven (LG MG 556 P, 2450 MHz). The starting compounds **1a-g** were prepared in the laboratory[13-19].

General procedure for the synthesis of *N*-(3-aryl-1,8-naphthyridin-2-yl)phthalimides 3. A mixture of 2-amino-3-aryl-1,8-naphthyridine (**1**, 0.01 mole), phthalic anhydride (**2**, 0.01 mole) and DMF (5 drops) was subjected to microwave irradiation at 600 W intermittently at 30 s intervals for the specific time. After completion of the reaction as indicated by TLC, the reaction mixture was cooled and treated with cold water. The separated solid was filtered, washed with water and purified by recrystallization from methanol to afford **3** (**Table I**).

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