Synthesis of imidazo[1,2-*a*][1,8]naphthyridines under microwave irradiation

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A convenient synthesis of 4-aryl-2-phenylimidazo[1,2-*a*][1,8]naphthyridines (**3**), by cyclocondensation of 3-aryl-1-(2-oxophenylethyl)-1,8-naphthyridin-2-ones (**2**) with ammonium acetate in glacial acetic acid under microwave irradiation, is described.

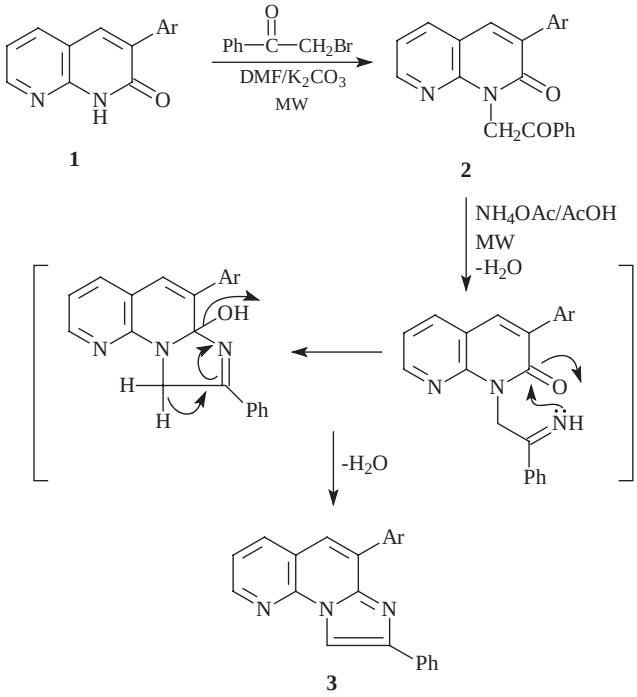
Keywords: 1,8-naphthyridines, fused imidazoles, microwave irradiation

1,8-Naphthyridines have been reported to possess antibacterial[1], antitumor[2], antiinflammatory[3], gastric antisecretory[4], antiallergic[5], local anaesthetic[6] and antihypertensive[7] activities. Imidazoles are very interesting compounds with wide-ranging biological activities.[8-10] Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and imidazole might result in compounds with interesting biological activity. Microwave irradiation is an energy source of which the popularity and synthetic utility in organic chemistry has increased considerably in recent years.[11-13] The rapid heating induced by such radiation avoids the harsh conditions and reagent decomposition of classical methods, leading to the formation of products under mild reaction conditions and normally with increased yields. In continuation of our interest in the microwave-assisted organic transformations of 1,8-naphthyridine derivatives[14-18], we report herein a practical method for the synthesis of imidazo[1,2-*a*]-[1,8]naphthyridines using ammonium acetate in glacial acetic acid under microwave irradiation.

Phenacylation of 3-aryl-1,8-naphthyridin-2(1*H*)-ones (**1**) with ω-bromoacetophenone in DMF in the presence of anhydrous K_2CO_3 under microwave irradiation resulted in the formation of 3-aryl-1-(2-oxo-2-phenylethyl)-1,8-naphthyridin-2-ones (**2**) in very good yields.

Cyclocondensation of **2** with ammonium acetate in glacial acetic acid under microwave irradiation furnished the respective 4-aryl-2-phenylimidazo[1,2-*a*][1,8]naphthyridines (**3**) (Scheme 1). The transformation is very clean and rapid and is devoid of any by-products, and the work-up procedure is simple and convenient. Furthermore, the products were obtained with a high degree of purity by this procedure and in most cases no further purification was needed. The reaction proceeds to only a minor extent (5–10% in 5.0–6.5 min) when conducted under conventional conditions in an oil-bath preheated to 120 °C, thus demonstrating the advantage of the microwave heating method. Nucleophilic addition of ammonia, produced *in situ* from ammonium acetate, to carbonyl carbon, followed by loss of two water molecules, as depicted in Scheme 1, is the net course of the reaction forming **3** from **2**. The structures of compounds **2** and **3** are assigned on the basis of their spectral (IR and ^{1}H NMR) and analytical data.

To the best of our knowledge this is the first report of the rapid synthesis of imidazo[1,2-*a*][1,8]naphthyridines using ammonium acetate in glacial acetic acid under microwave irradiation. The notable advantages of this procedure are the mild reaction conditions, simple operation, high yields and short reaction times. Study of the biological activity of the compounds **3** is in progress and will be reported in future publications.



1 **2** **3**

Scheme 1

Experimental

Melting points were measured on a Cintex melting point apparatus. The purity of the compounds was checked by TLC. IR spectra (KBr) were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ, ppm) using TMS as internal standard. Elemental analyses (CHN) were performed on a Perkin-Elmer 240 CHN analyzer. Irradiation was carried out in a domestic microwave oven (BPL 800 G, 2450 MHz). The requisite starting compounds **1** were prepared following the methods reported in the literature.[16-20]

3-Aryl-1-(2-oxo-2-phenylethyl)-1,8-naphthyridin-2(1H)-ones (**2**)

A mixture of 3-aryl-1,8-naphthyridin-2(1*H*)-one (**1**) (0.01 mol), ω-bromoacetophenone (0.01 mol), anhydrous K_2CO_3 (0.01 mol) and DMF (10 ml) was subjected to microwave irradiation at 400 watts intermittently at 30 sec intervals for the specified time (Table 1). On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with chilled water. The precipitate thus obtained was filtered, washed with water and recrystallised from methanol to afford **2**. (See Table 1 for yields, melting points, and analytical data.)

3-Phenyl derivative (**2a**): IR: 1654, 1597, 698 cm^{-1}. ^{1}H NMR: δ 6.02 (s, 2H, CH_2), 8.05 (m, 2H, C_4–H, C_6–H), 8.42 (m, 1H, C_5–H), 8.68 (m, 1H, C_7–H), 7.12–7.90 (m, 10H, Ar–H).

3-(p-Methoxyphenyl) derivative (**2b**): IR: 1654, 1607, 838 cm^{-1}. ^{1}H NMR: δ 3.84 (s, 3H, OCH_3), 6.00 (s, 2H, CH_2), 7.76 (m, 2H, C_4–H, C_6–H), 7.92 (m, 1H, C_5–H), 8.63 (m, 1H, C_7–H), 6.90–7.58 (m, 9H, Ar–H).

3-(o-Chlorophenyl) derivative (**2c**): IR: 1655, 1597, 756 cm^{-1}. ^{1}H NMR: δ 6.03 (s, 2H, CH_2), 7.96 (m, 2H, C_4–H, C_6–H), 8.07 (m, 1H, C_5–H), 8.68 (m, 1H, C_7–H), 7.08–7.72 (m, 9H, Ar–H).

3-(m-Chlorophenyl) derivative (**2d**): IR: 1664, 1594, 788 cm^{-1}. ^{1}H NMR: δ 6.07 (s, 2H, CH_2), 8.15 (m, 2H, C_4–H, C_6–H), 8.30 (m, 1H, C_5–H), 8.52 (m, 1H, C_7–H), 7.18–7.83 (m, 9H, Ar–H).

3-(p-Chlorophenyl) derivative (**2e**): IR: 1654, 1598, 830 cm^{-1}. ^{1}H NMR: δ 6.04 (s, 2H, CH_2), 7.86 (m, 2H, C_4–H, C_6–H), 8.06 (m, 1H, C_5–H), 8.60 (m, 1H, C_7–H), 7.08–7.60 (m, 9H, Ar–H).

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Table 1 Physical and analytical data of 4-aryl-1-(2-oxo-2-phenylethyl)-1,8-naphthyridin-2-ones (**2**) and 4-aryl-2-phenylimidazo[1,2-*a*][1,8]naphthyridines (**3**)

Compd	Ar	Reaction time/min	Yield/% [m.p.]	Mol. formula	Microanalysis calculated [found] %		
					C	H	N
2a	C_6H_5	4.0	88 [210–212]	$C_{22}H_{16}N_2O_2$	77.65 [77.81]	[4.75] 4.71	8.24 [8.32]
2b	*p*-$CH_3OC_6H_4$	5.0	92 [175–177]	$C_{23}H_{18}N_2O_3$	74.59 [74.78]	4.86 [4.81]	7.57 [7.65]
2c	*o*-ClC_6H_4	4.5	90 [147–150]	$C_{22}H_{15}ClN_2O_2$	70.49 [70.64]	4.01 [4.05]	7.48 [7.55]
2d	*m*-ClC_6H_4	5.0	91 [260–261]	$C_{22}H_{15}ClN_2O_2$	70.49 [70.66]	4.01 [4.04]	7.48 [7.56]
2e	*p*-ClC_6H_4	3.5	94 [220–222]	$C_{22}H_{15}ClN_2O_2$	70.49 [70.65]	4.01 [4.06]	7.48 [7.55]
2f	*p*-BrC_6H_4	4.0	92 [208–210]	$C_{22}H_{15}BrN_2O_2$	63.01 [63.20]	3.58 [3.52]	6.68 [6.76]
3a	C_6H_5	5.0	84 [220–221]	$C_{22}H_{15}N_3$	82.24 [82.36]	4.67 [4.62]	13.08 [13.16]
3b	*p*-$CH_3OC_6H_4$	6.5	86 [210–213]	$C_{23}H_{17}N_3O$	78.63 [78.78]	4.84 [4.88]	11.97 [11.91]
3c	*o*-ClC_6H_4	5.5	85 [218–220]	$C_{22}H_{14}ClN_3$	74.26 [74.42]	3.94 [3.98]	11.81 [11.92]
3d	*m*-ClC_6H_4	6.0	84 [130–132]	$C_{22}H_{14}ClN_3$	74.26 [74.43]	3.94 [3.98]	11.81 [11.93]
3e	*p*-ClC_6H_4	5.0	88 [235–236]	$C_{22}H_{14}ClN_3$	74.26 [74.42]	3.94 [3.99]	11.81 [11.90]
3f	*p*-BrC_6H_4	5.5	85 [128–129]	$C_{22}H_{14}BrN_3$	66.00 [66.14]	3.50 [3.54]	10.50 [10.58]

3-(p-Bromophenyl) derivative (**2f**): IR: 1654, 1600, 825 cm^{-1}. ^1H NMR: δ 6.02 (s, 2H, CH_2), 7.94 (m, 2H, C_4–H, C_6–H), 8.21 (m, 1H, C_5–H), 8.72 (m, 1H, C_7–H), 7.18–7.72 (m, 9H, Ar–H).

Imidazo[1,2-a][1,8]naphthyridines (**3**): A mixture of **2** (0.01 mol), ammonium acetate (0.1 mol) and glacial acetic acid (10 ml) was exposed to microwave irradiation at 400 watts intermittently at 30 sec intervals for the total period specified (Table 1). On completion of the reaction, as monitored by TLC, the mixture was digested with cold water. The solid thus obtained was filtered, washed with water and recrystallised from ethanol to give **3.** (See Table 1 for yields, melting points, and analytical data.)

2,4-Diphenyl derivative (**3a**): IR: 1637, 1602, 702 cm^{-1}. ^1H NMR: δ 7.95 (m, 2H, C_5–H, C_6–H), 7.72 (m, 1H, C_7–H), 8.89 (m, 1H, C_8–H), 7.15–7.60 (m, 11H, Ar–H).

4-(p-Methoxyphenyl)-2-phenyl derivative (**2b**): IR: 1636, 1608, 824 cm^{-1}. ^1H NMR: δ 3.82 (s, 3H, OCH_3), 8.05 (m, 2H, C_5–H, C_6–H), 7.80 (m, 1H, C_7–H), 8.78 (m, 1H, C_8–H), 7.00–7.58 (m, 10H, Ar–H).

4-(o-Chlorophenyl)-2-phenyl derivative (**3c**): IR: 1636, 1605, 742 cm^{-1}. ^1H NMR: δ 7.98 (m, 2H, C_5–H, C_6–H), 7.76 (m, 1H, C_7–H), 8.78 (m, 1H, C_8–H), 7.10–7.56 (m, 10H, Ar–H).

4-(m-Chlorophenyl)-2-phenyl derivative (**3d**): IR: 1636, 1600, 790 cm^{-1}. ^1H NMR: δ 8.02 (m, 2H, C_5–H, C_6–H), 7.81 (m, 1H, C_7–H), 8.90 (m, 1H, C_8–H), 7.05–7.70 (m, 10H, Ar–H).

4-(p-Chlorophenyl)-2-phenyl derivative (**3e**): IR: 1638, 1596, 842 cm^{-1}. ^1H NMR: δ 8.04 (m, 2H, C_5–H, C_6–H), 7.92 (m, 1H, C_7–H), 8.85 (m, 1H, C_8–H), 7.08–7.72 (m, 10H, Ar–H).

4-(p-Bromophenyl)-2-phenyl derivative (**3f**): IR: 1637, 1602, 833 cm^{-1}. ^1H NMR: δ 7.94 (m, 2H, C_5–H, C_6–H), 7.72 (m, 1H, C_7–H), 8.85 (m, 1H, C_8–H), 7.10–7.62 (m, 10H, Ar–H).

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