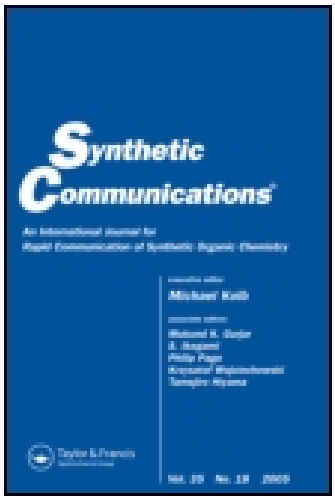

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MICROWAVE ASSISTED SYNTHESIS OF IMIDAZO[1,2-a]-[1,8]NAPHTHYRIDIN-1(2H)-ONES

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MICROWAVE ASSISTED SYNTHESIS OF IMIDAZO[1,2-*a*]-[1,8]NAPHTHYRIDIN-1(2*H*)-ONES

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ABSTRACT

Synthesis of 2-carboxyalkylamino-3-(*p*-chlorophenyl)-1,8-naphthyridines and their conversion into novel imidazo [1,2-*a*][1,8]naphthyridin-1(2*H*)-ones under microwave irradiation are described.

In recent years the use of microwave irradiation in organic reactions is rapidly increasing because of the short reaction time, operational simplicity and formation of cleaner reaction products. It has been commonly employed as thermal energy source in various organic reactions.[1] The use of domestic microwave oven in this regard is now a well-established procedure in MORE[2] chemistry. 1,8-Naphthyridines[3] and imidazoles[4] reported in the literature were found to possess varied biodynamic properties. In view of this and in continuation of our interest in developing simple and efficient routes for the synthesis of fused 1,8-naphthyridines,[5] we report herein the microwave assisted synthesis of a novel and hitherto unknown

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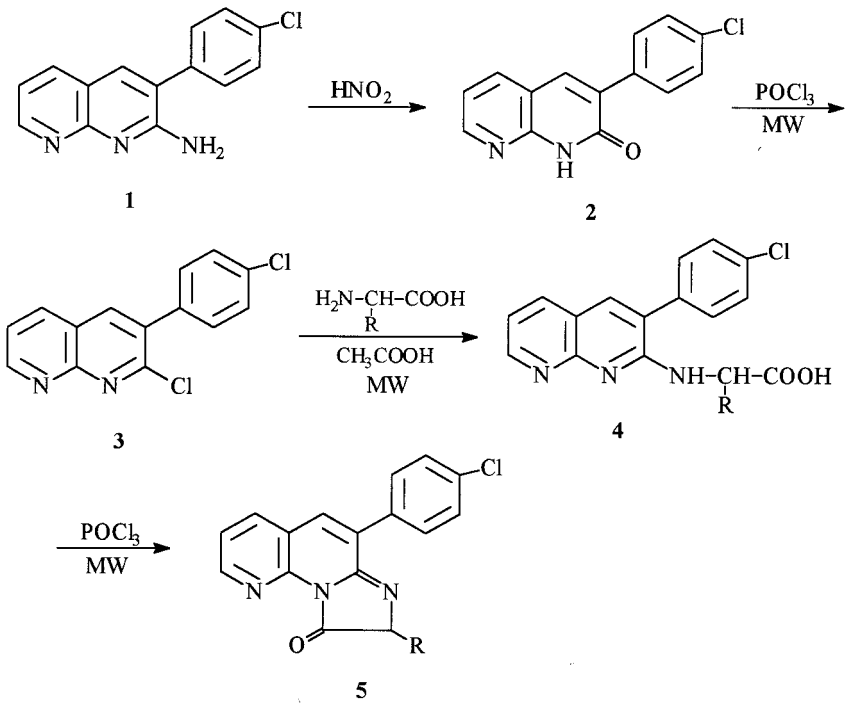
bridgehead nitrogen heterocyclic system viz., imidazo [1,2-*a*] [1,8]naphthyridin-1(2*H*)-ones.

The reaction of 2-amino-3-(*p*-chlorophenyl)-1,8-naphthyridine **1**[5f] with HNO_2 afforded 1,2-dihydro-3-(*p*-chlorophenyl)-1,8-naphthyridin-2-one **2**. Treatment of **2** with $POCl_3$ in microwave oven furnished 2-chloro-3-(*p*-chlorophenyl)-1,8-naphthyridine **3**.



Scheme 1.

Interaction of **3** with α-aminoacids in glacial acetic acid under microwave irradiation yielded the corresponding 2-carboxyalkylamino-3-(*p*-chlorophenyl)-1,8-naphthyridines **4**. Compounds **4** on treatment with $POCl_3$ under microwave irradiation resulted in the formation of imidazo-[1,2-*a*][1,8]naphthyridin-1(2*H*)-ones **5** (Scheme 1).

The microwave procedure for transformation of **4** to **5** owes its importance due to the fact that the reaction is completed within 5 min with improved yield as compared to conventional heating which requires 6–7 h.

Incidentally, this is the first observation of microwave irradiated synthesis of fused 1,8-naphthyridines.

In conclusions, the present method provides a highly efficient and practical synthesis of fused 1,8-naphthyridines with following advantages: significant shortening of the reaction time, simple reaction conditions and high yields of the products.

EXPERIMENTAL

IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz instrument and the chemical shifts were reported with Me_4Si as an internal standard. Mass spectra (MS) were measured on a Jeol JMS D-300 spectrometer. Microwave reactions were carried out in BPL make domestic microwave oven model No 800 G operating at 2450 MHz.

1,2-Dihydro-3-(*p*-chlorophenyl)-1,8-naphthyridin-2-one 2

To a cold solution of **1** (2.55 g, 0.01 mol) in 2N HCl (25 ml) was added $NaNO_2$ solution (0.01 mol in 25 ml water) and the reaction mixture stirred at room temperature for 0.5 h. It was then treated with chilled water. The solid that precipitated was filtered, washed with water and recrystallized from methanol to give **2** (2.20 g, 86%) as a pale yellow compound, m.p. 284°C. IR (KBr) 3448, 1672, 1607 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.27–7.83 (m, 5H, C_6-H, 4 Ar-H); 8.18 (m, 2H; C_4-H, C_5-H); 8.56 (m, 1H, C_7-H); 12.42 (s, 1H, NH). EIMS *m*/*z* M$^+$ 256 (100%). Anal. Calcd for $C_{14}H_9N_2OC1$: C, 65.50; H, 3.51; N, 10.92. Found: C, 65.72; H, 3.60; N, 10.82.

2-Chloro-3-(*p*-chlorophenyl)-1,8-naphthyridine 3

A mixture of **2** (2.56 g, 0.01 mol) and $POCl_3$ (20 ml) was irradiated in microwave oven for 3 min, the completion of the reaction was monitored by tlc. The reaction mixture was then added to crushed ice and $NaHCO_3$. The precipitated product was filtered, washer with water and recrystallized from ethanol to afford **3** (2.41 g, 88%) as a white compound, m.p. 262°C. IR (KBr) 1603 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.67–7.81 (m, 5H, C_6-H, 4Ar-H); 8.22 (m, 1H, C_4-H); 8.62 (m, 1H, C_5-H); 9.20 (m, 1H, C_7-H). EIMS *m*/*z* M$^+$ 274 (100%). Anal. Calcd. for $C_{14}H_8N_2Cl_2$: C, 61.09; H, 2.91; N, 10.18. Found: C, 61.28; H, 2.83; N, 10.26.

2-Carboxymethylamino-3-(*p*-chlorophenyl)-1,8-naphthyridine 4a

A mixture of **3** (2.74 g, 0.01 mol) and glycine (0.75 g, 0.01 mol) in glacial acetic acid (20 ml) was subjected to microwave irradiation for 4 min, the completion of the reaction was monitored by tlc and poured on crushed ice. The crude product was separated by filtration and recrystallized from methanol to furnish **4a** (2.82 g, 90%) as a white crystalline compound, m.p. 280°C. IR (KBr) 3420, 3150, 2960, 2887, 1672, 1608 cm^{-1}. ^1H NMR (DMSO-d_6) δ 3.82 (s, 2H, CH_2); 7.27–7.85 (m, 6H, C_6-H, 4Ar-H, NH); 8.18

Table 1. Analytical Data of the Compounds 4 and 5

Product No.	R	M.P. (°C)	Yield (%)	Mol.Form	Analysis Calc./Found C%	H%	N%
4a	H	280	90	$C_{16}H_{12}N_3O_2Cl$	61.24	3.83	13.40
					61.40	3.90	13.51
4b	CH_3	275	94	$C_{17}H_{14}N_3O_2Cl$	62.29	4.27	12.82
					62.43	4.32	12.95
4c	$(CH_3)_2CH$	273	92	$C_{19}H_{18}N_3O_2Cl$	64.13	5.06	11.81
					64.30	5.12	11.95
4d	$(CH_3)_2CHCH_2$	279	90	$C_{20}H_{20}N_3O_2Cl$	64.95	5.41	11.37
					64.78	5.50	11.48
4e	$CH_3CH_2CHCH_3$	276	91	$C_{20}H_{20}N_3O_2Cl$	64.95	5.41	11.37
					64.77	5.51	11.47
4f	$PhCH_2$	273	86	$C_{23}H_{18}N_3O_2Cl$	68.40	4.46	10.41
					68.61	4.53	10.54
4g	*p*-$HOC_6H_4CH_2$	280	88	$C_{23}H_{18}N_3O_3Cl$	65.79	4.29	10.01
					65.95	4.37	10.15
5a	H	232	86	$C_{16}H_{10}N_3OCl$	64.97	3.38	14.21
					64.81	3.45	14.29
5b	CH_3	195	90	$C_{17}H_{12}N_3OCl$	65.91	3.88	13.57
					65.73	3.95	13.66
5c	$(CH_3)_2CH$	240	87	$C_{19}H_{16}N_3OCl$	67.55	4.74	12.44
					67.71	4.80	12.52
5d	$(CH_3)_2CHCH_2$	> 300	86	$C_{20}H_{18}N_3OCl$	68.28	5.12	11.95
					68.40	5.20	11.86
5e	$CH_3CH_2CHCH_3$	230	84	$C_{20}H_{18}N_3OCl$	68.28	5.12	11.95
					69.39	5.19	11.84
5f	$PhCH_2$	215	83	$C_{23}H_{16}N_3OCl$	71.59	4.15	10.89
					71.77	4.20	10.78
5g	*p*-$HOC_6H_4CH_2$	270	85	$C_{23}H_{16}N_3O_2Cl$	68.74	3.98	10.46
					68.90	3.89	10.57

(m, 2H, C_4-H, C_5-H); 8.57 (m, 1H, C_7-H); 12.40 (s, 1H, COOH). EIMS *m*/*z* M^+ 313 (23.1%). Anal. Calcd for $C_{16}H_{12}N_3O_2Cl$: C, 61.24; H, 3.83; N, 13.40. Found: C, 61.40; H, 3.90; N, 13.51. Compound **4b–g** were similarly prepared (Table 1).

4-(*p*-Chlorophenyl)-imidazo[1,2-a][1,8]naphthyridin-1(2*H*)-one 5a

A mixture of **4a** (3.13 g, 0.01 mol) and $POCl_3$ (10 ml) was irradiated in microwave oven till the cyclization was over (about 5 min; by tlc) and poured on crushed ice. The product which separated on neutralisation with $NaHCO_3$ was filtered, washed with water and recrystallized from methanol to give **5a** (2.54 g, 86%) as a white compound, m.p. 232°C. IR (KBr) 1656, 1600 cm^{-1}. ^1H NMR (DMSO-d_6) δ 4.22 (s, 2H, CH_2); 7.42–7.84 (m, 5H, C_7-H, 4Ar-H); 8.59 (m, 1H, C_5-H); 8.73 (m, 1H, C_6-H); 9.14 (m, 1H, C_8-H). EIMS *m*/*z* M^+ 295 (9.9%). Anal. Calcd for $C_{16}N_{10}N_3OCl$: C, 64.97; H, 3.38; N, 14.21. Found: C, 64.81; H, 3.45; N, 14.29. Compounds **5b–g** were prepared similarly (Table 1).

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