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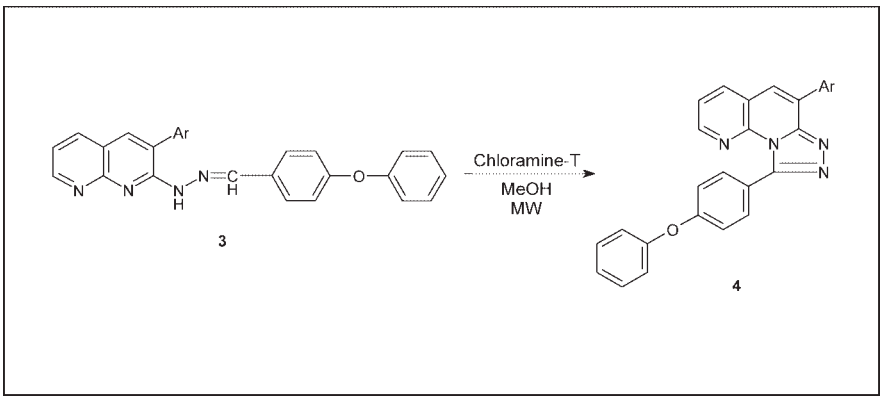
Received January 23, 2008
DOI 10.1002/jhet.33
Published online 11 February 2009 in Wiley InterScience (www.interscience.wiley.com).



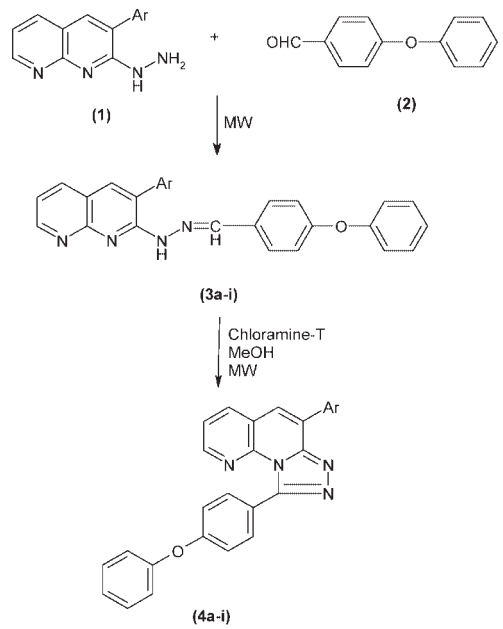
A simple and highly efficient procedure has been described for the synthesis of 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo [4,3-a] [1,8] napthyridines **(4)** by the oxidation of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones **(3)** with chloramines-T in methanol under microwave irradiation. The products were obtained in very good yields and excellent purities.

J. Heterocyclic Chem., **46**, 124 (2009).

INTRODUCTION

1,8-Naphthyridines constitute an important class of compounds possessing diverse biological activities [1–3]. Various 1,2,4-triazoles have been extensively explored for their applications in the field of biological and pharmacological activities [4–6]. Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and 1,2,4-triazole might result in compounds with interesting biological activity. Microwave-assisted organic synthesis has attracted considerable attention in recent years [7–10], due to enhanced reaction rates, high yields, improved selectivity, and cleaner products. 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. Chloramine-T (CAT) is a very versatile oxidizing agent and is of much importance in its synthetic utility [11,12]. In view of this and in continuation of our interest in microwave-assisted organic transformations on 1,8-napthyridine derivatives [13–17], we report herein, a convenient, practical and efficient method for the synthesis of 1,2,4-triazolo[4,3-*a*][1,8] naphthyridines using CAT in methanol under microwave irradiation.

Scheme 1



Compd **3** and **4**	Ar	Compd **3** and **4**	Ar
a	C_6H_5	**f**	2-FC_6H_4
b	4-$CH_3OC_6H_4$	**g**	3-FC_6H_4
c	2-ClC_6H_4	**h**	4-FC_6H_4
d	3-ClC_6H_4	**i**	4-$CF_3C_6H_4$
e	4-ClC_6H_4		

RESULTS AND DISCUSSION

Condensation of 3-aryl-2-hydrazino-1,8-napthyridines (**1**) with 4-phenoxybenzaldehyde (**2**) in the presence of catalytic amount of DMF under microwave irradiation afforded the respective 4-phenoxybenzaldehyde 3-aryl-1,8-napthyridin-2-ylhydrazones (**3**) in excellent yields.

Oxidative cyclization of hydrazones **3** with CAT in methanol under microwave irradiation resulted in the formation of 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo-[4,3-*a*][1,8]naphthyridines (**4**). The oxidative transformation is clean and efficient. The experimental procedure is very simple. The high yield transformation did not form any undesirable by-products. Furthermore, the products were obtained with a higher degree of purity by this procedure and in most cases no further purification was needed. Interestingly, this oxidative reaction proceeds only to a minor extent (5–8% in 3.5–4.5 min) when conducted under conventional conditions in an oil-bath preheated to 110°C (temperature measured at the end of exposure during microwave experiment) which confirms the rate augmentation during microwave heating (Scheme 1).

The structural assignments of compounds **3** and **4** were based on their spectroscopic (IR and ^{1}H NMR; Table 1) and analytical data (Table 2).

The significant advantages of this procedure are operational simplicity, short reaction time, pure products, inexpensive, and nontoxicity of the reagent and high yields.

EXPERIMENTAL

Melting points were measured 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) (ν_{max}: cm^{-1}) were recorded on a Perkin-Elmer BX series FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (Chemical shifts in δ, ppm) using TMS as internal standard. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. Microwave irradiation was carried out in a domestic microwave oven (LG MG 556p, 2450 MHz). The starting compounds **1** were prepared according to our reported

Table 1

IR and ^{1}H NMR spectral data of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones (**3**) and 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo-[4,3-*a*][1,8]naphthyridines (**4**).

Compd	IR cm^{-1} (KBr)	^{1}H NMR (δ, ppm) ($CDCl_3$)
3a	3377 (NH), 1623 (C=N)	7.63 (m, 2H, C_4—H, C_6—H), 7.82 (m, 1H, C_5—H), 8.44 (m, 1H, C_7—H), 8.59 (s, 1H, N=CH), 6.92—7.50 (m, 15H, NH, 14Ar—H)
3b	3330 (NH), 1622 (C=N)	3.90 (s, 3H, OCH_3), 7.92 (m, 2H, C_4—H, C_6—H), 8.15 (m, 1H, C_5—H), 8.52 (m, 1H, C_7—H), 8.85 (s, 1H, N=CH), 6.95–7.72 (m, 14H, NH, 13Ar—H)
3c	3431 (NH), 1627 (C=N)	7.60 (m, 2H, C_4—H, C_6—H), 7.78 (m, 1H, C_5—H), 8.45 (m, 1H, C_7—H), 8.59 (s, 1H, N=CH), 6.90–7.38 (m, 14H, NH, 13Ar—H)
3d	3390 (NH), 1625 (C=N)	7.65 (m, 2H, C_4—H, C_6—H), 7.87 (m, 1H, C_5—H), 8.53 (m, 1H, C_7—H), 8.65 (s, 1H, N=CH), 6.92–7.45 (m, 14H, NH, 13Ar—H)
3e	3425 (NH), 1623 (C=N)	7.62 (m, 2H, C_4—H, C_6—H), 7.89 (m, 1H, C_5—H), 8.43 (m, 1H, C_7—H), 8.62 (s, 1H, N=CH), 6.91–7.40 (m, 14H, NH, 13Ar—H)
3f	3360 (NH), 1628 (C=N)	7.67 (m, 2H, C_4—H, C_6—H), 7.80 (m, 1H, C_5—H), 8.25 (m, 1H, C_7—H), 8.78 (s, 1H, N=CH), 6.90–7.43 (m, 14H, NH, 13Ar—H)
3g	3353 (NH), 1625 (C=N)	7.65 (m, 2H, C_4—H, C_6—H), 7.85 (m, 1H, C_5—H), 8.47 (m, 1H, C_7—H), 8.66 (s, 1H, N=CH), 6.92–7.45 (m, 14H, NH, 13Ar—H)
3h	3345 (NH), 1626 (C=N)	7.60 (m, 2H, C_4—H, C_6—H), 7.88 (m, 1H, C_5—H), 8.14 (m, 1H, C_7—H), 8.63 (s, 1H, N=CH), 6.88–7.42 (m, 14H, NH, 13Ar—H)
3i	3360 (NH), 1626 (C=N)	7.75 (m, 2H, C_4—H, C_6—H), 8.00 (m, 1H, C_5—H), 8.22 (m, 1H, C_7—H), 8.78 (s, 1H, N=CH), 6.91–7.43 (m, 14H, NH, 13Ar—H)
4a	1603 (C=N)	8.12 (m, 3H, C_3—H, C_4—H, C_5—H), 8.45 (m, 1H, C_2—H), 7.02–7.70 (m, 14H, Ar—H)
4b	1608 (C=N)	3.89 (s, 3H, OCH_3), 8.10 (m, 3H, C_3—H, C_4—H, C_5—H), 8.40 (m, 1H, C_2—H), 7.00–7.65 (m, 13H, Ar—H)
4c	1605 (C=N)	7.70 (m, 2H, C_3—H, C_5—H), 8.15 (m, 1H, C_4—H), 8.50 (m, 1H, C_2—H), 7.02–7.52 (m, 13H, Ar—H)
4d	1608 (C=N)	7.82 (m, 2H, C_3—H, C_5—H), 8.20 (m, 1H, C_4—H), 8.48 (m, 1H, C_2—H), 7.00–7.54 (m, 13H, Ar—H)
4e	1604 (C=N)	7.78 (m, 2H, C_3—H, C_5—H), 8.18 (m, 1H, C_4—H), 8.45 (m, 1H, C_2—H), 7.02–7.56 (m, 13H, Ar—H)
4f	1605 (C=N)	7.63 (m, 1H, C_3—H), 8.05 (m, 1H, C_5—H), 8.15 (m, 1H, C_4—H), 8.47 (m, 1H, C_2—H), 7.00–7.53 (m, 13H, Ar—H)
4g	1610 (C=N)	7.80 (m, 2H, C_3—H, C_5—H), 8.16 (m, 1H, C_4—H), 8.45 (m, 1H, C_2—H), 7.02–7.66 (m, 13H, Ar—H)
4h	1606 (C=N)	8.13 (m, 3H, C_3—H, C_4—H, C_5—H), 8.44 (m, 1H, C_2—H), 7.00–7.65 (m, 13H, Ar—H)
4i	1607 (C=N)	8.20 (m, 3H, C_3—H, C_4—H, C_5—H), 8.48 (m, 1H, C_2—H), 7.03—7.82 (m, 13H, Ar—H)

Table 2

Physical and analytical data of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones (**3**) and 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo-[4,3-*a*][1,8]naphthyridines (**4**).

Compd	Reaction time (min)	MP (°C)	Yield (%)	Mol. formula	Elemental analysis Found/(Calcd)		
					C	H	N
3a	1.0	170–172	95	$C_{27}H_{20}N_4O$	77.75 (77.89)	4.86 (4.81)	13.53 (13.46)
3b	1.5	156–158	94	$C_{28}H_{22}N_4O_2$	75.50 (75.34)	4.97 (4.93)	12.64 (12.56)
3c	1.0	152–153	93	$C_{27}H_{19}ClN_4O$	71.77 (71.92)	4.26 (4.22)	12.50 (12.43)
3d	1.5	145–147	92	$C_{27}H_{19}ClN_4O$	71.78 (71.92)	4.28 (4.22)	12.49 (12.43)
3e	1.0	159–160	96	$C_{27}H_{19}ClN_4O$	71.76 (71.92)	4.27 (4.22)	12.51 (12.43)
3f	1.0	172–174	93	$C_{27}H_{19}FN_4O$	74.81 (74.65)	4.43 (4.38)	12.98 (12.90)
3g	1.5	148–150	94	$C_{27}H_{19}FN_4O$	74.79 (74.65)	4.44 (4.38)	12.97 (12.90)
3h	1.5	162–163	95	$C_{27}H_{19}FN_4O$	74.80 (74.65	4.42 (4.38)	12.96 (12.90)
3i	1.5	140–142	94	$C_{28}H_{19}F_3N_4O$	69.58 (69.42)	3.98 (3.93)	11.66 (11.57)
4a	3.5	208–210	90	$C_{27}H_{18}N_4O$	78.41 (78.26)	4.40 (4.35)	13.61 (13.53)
4b	4.5	200–202	87	$C_{28}H_{20}N_4O_2$	75.83 (75.68)	4.60 (4.50)	12.70 (12.61)
4c	4.0	228–230	86	$C_{27}H_{17}ClN_4O$	72.40 (72.24)	3.84 (3.79)	12.56 (12.49)
4d	4.0	214–216	85	$C_{27}H_{17}ClN_4O$	72.38 (72.24)	3.85 (3.79)	12.58 (12.49)
4e	3.5	230–232	92	$C_{27}H_{17}ClN_4O$	72.39 (72.24)	3.84 (3.79)	12.57 (12.49)
4f	3.5	206–208	87	$C_{27}H_{17}FN_4O$	75.15 (75.00)	3.99 (3.94)	13.05 (12.96)
4g	4.0	210–212	86	$C_{27}H_{17}FN_4O$	75.16 (75.00)	3.98 (3.94)	13.04 (12.96)
4h	3.5	238–240	90	$C_{27}H_{17}FN_4O$	75.14 (75.00)	3.99 (3.94)	13.03 (12.96)
4i	4.5	218–220	89	$C_{28}H_{17}F_3N_4O$	69.86 (69.71)	3.57 (3.53)	11.69 (11.62)

procedures [16–20]. The 4-phenoxylbenzaldehyde (**2**) was purchased from Aldrich Chemical Company.

General procedure for the synthesis of 4-phenoxybenzaldehyde 3-aryl-1,8-naphthyridin-2-ylhydrazones (3). A mixture of 1 (20.0 mmol), 4-phenoxy-benzaldehyde (2, 20.0 mmol) and DMF (5 drops) was subjected to microwave irradiation at 400 watts intermittently at 30 s intervals for the specified time (Table 2). On completion of reaction, as monitored by TLC, the reaction mixture was cooled and treated with cold water. The resulting solid product was collected by filtration, washed with water and re-crystallized from ethanol to give **3** (Table 2).

General procedure for the synthesis of 6-aryl-9-(4-phenoxyphenyl)-1,2,4-triazolo[4,3-*a*][1,8]napthyridines (4). To a solution of appropriate hydrazone **4** (20.0 mmol) in methanol (15 mL), CAT (20.0 mmol) was added. The reaction mixture was exposed to microwaves at 400 watts intermittently at 30 s intervals for specified time (Table 2). After complete conversion as indicated by TLC, the reaction mixture was cooled and digested with cold water. The solid then obtained was collected by filtration, washed with water and re-crystallized from ethanol to afford **4** (Table 2).

Acknowledgments. The authors thank the Directors, IICT, Hyderabad and IITM, Chennai, India for providing spectral and analytical data.

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