# Chloramine-T mediated synthesis of 1,2,4-triazolo[4,3-*a*] [1,8]naphthyridines under microwave irradiation

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An effective, practical and simple approach towards the synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines **8** from the corresponding aryl aldehyde 3-(*m*-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones **7** has been described, using chloramine-T in combination with microwave irradiation; the products are obtained in good yields and in a state of high purity.

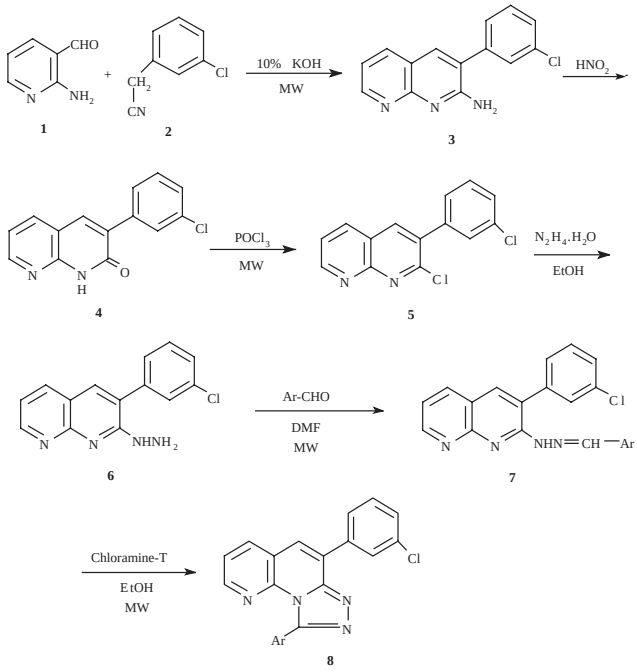
**Keywords:** chloramine-T, fused 1,8-naphthyridines, fused 1,2,4-triazoles, microwave irradiation

Compounds with heterocyclic rings fused on substituted 1,8-naphthyridines have become attractive targets in organic synthesis due to their significant biological activities.[1-3] The chemistry of fused 1,2,4-triazoles has received considerable attention from synthetic organic chemists due to their diverse pharmacological activities.[4-7] Several research groups have contributed to the development of methods of synthesis of fused 1,2,4-triazoles.[8-10] However, these procedures are time consuming and proceed in low yields. Therefore, a convenient and eco-friendly method for the synthesis of fused 1,2,4-triazoles is highly desirable. The versatile synthetic utility of aromatic *N*-halo-*N*-metallosulphonamide reagents is of current interest. The prominent member of this class of oxidants is sodium *N*-chloro-*p*-toluenesulphonamide (chloramine-T),[11-13] which is inexpensive and readily accessible. We have selected chloramine-T as an effective oxidising agent. Microwave-assisted organic reactions have recently received a great deal of attention and comprise a quickly developing area in synthetic chemistry.[14-18] Many reactions proceeded must faster under microwave irradiation and with higher yields compared to conventional heating. Microwave irradiation has also been applied to organic synthesis in open vessels using organic solvents such as ethanol, *N, N*-dimethylformamide (DMF), 1,2-dichloroethane (DCE), *o*-dichlorobenzene, *etc*. as energy transfer media which absorb microwave energy efficiently through dipole rotation. In view of this and in continuation of our interest in microwave-assisted organic transformations on 1,8-naphthyridine derivatives,[19-23] we report herein a new, inexpensive, practical and efficient method for the synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using chloramine-T under microwave irradiation (MW).

2-Aminonicotinaldehyde **1** on condensation with *m*-chlorophenylacetonitrile **2** in the presence of 10% KOH without any solvent under microwave irradiation resulted in the formation of 2-amino-3-(*m*-chlorophenyl)-1,8-naphthyridine **3,** which is converted into 1,2-dihydro-3-(*m*-chlorophenyl)-1,8-naphthyridin-2-one **4** by the reaction with $HNO_2$. Treatment of **4** with $POCl_3$ under microwave irradiation afforded 2-chloro-3-(*m*-chlorophenyl)-1,8-naphthyridine **5**, which on hydrazinolysis with refluxing hydrazine hydrate yielded 2-hydrazino-3-(*m*-chlorophenyl)-1,8-naphthyridine **6**.

Condensation of **6** with various aromatic aldehydes in the presence of DMF under microwave irradiation afforded the corresponding aryl aldehyde 3-(*m*-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones **7** in excellent yields.

The hydrazones **7** on oxidative cyclisation with chloramine-T in ethanol under microwave irradiation resulted in the formation of 1-aryl-4-(*m*-chlorophenyl)-1,2,4-triazolo[4,3-*a*] [1,8]naphthyridines **8** (Scheme 1). The reaction proceeds efficiently in good yields at ambient pressure within a few minutes. The transformation is very clean and rapid.




**Scheme 1**

The reaction conditions and work-up procedures are mild, simple and convenient. Furthermore, it is to be noted that highly pure products were obtained using this simple procedure and in most cases no further purification was needed. Interestingly, this reaction proceeds only to a minor extent (5–8% in 3.0–5.0 min) when conducted under conventional conditions in an oil-bath preheated to 110°C (highest observed temperature during irradiation) which confirms the rate increase during microwave heating. The structural assignments of compounds **3–8** were based on their elemental analyses and spectral (IR, $^1$H NMR and MS) data.

To the best of our knowledge this is the first report on rapid synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using chloramine-T as oxidising agent under microwave irradiation.

In conclusion, we have developed a highly practical procedure for the synthesis of 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines using chloramine-T under microwave irradiation. Moreover, high yields of the products, short reaction times, easy work-up, cheapness and non-toxicity of the reagent are noteworthy advantages of this method.

## Experimental

Melting points were determined in open capillaries using a Cintex apparatus and are uncorrected. Purity of compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) ($\nu_{max}$; $cm^{-1}$) were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer. $^1$H NMR spectra were recorded on a Varian

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**Table 1** Physical and analytical data of aryl aldehyde 3-(*m*-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones **7** and 1,2,4-triazolo [4,3-*a*][1,8] naphthyridines **8**

| Compd | Ar | Reaction time/min | Yield/% [m.p./°C] | Mol. formula | Microanalysis calculated [found]/% | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **7a** | $C_6H_5$ | 0.5 | 94 [135–137] | $C_{21}H_{15}N_4Cl$ | 70.29 [70.49] | 4.18 [4.23] | 15.62 [15.69] |
| **7b** | *p*-$CH_3OC_6H_4$ | 1.5 | 92 [140–142] | $C_{22}H_{17}N_4OCl$ | 67.95 [67.77] | 4.38 [4.42] | 14.41 [14.49] |
| **7c** | *p*-$CH_3C_6H_4$ | 1.0 | 98 [170–171] | $C_{22}H_{17}N_4Cl$ | 70.87 [70.99] | 4.56 [4.62] | 15.03 [15.12] |
| **7d** | *o*-$ClC_6H_4$ | 1.0 | 92 [160–163] | $C_{21}H_{14}N_4Cl_2$ | 64.12 [64.33] | 3.56 [3.62] | 14.24 [14.32] |
| **7e** | *p*-$ClC_6H_4$ | 0.5 | 96 [185–186] | $C_{21}H_{14}N_4Cl_2$ | 64.12 [64.34] | 3.56 [3.61] | 14.24 [14.31] |
| **7f** | *o*-$BrC_6H_4$ | 1.0 | 92 [162–163] | $C_{21}H_{14}N_4ClBr$ | 57.60 [57.78] | 3.20 [3.16] | 12.80 [12.88] |
| **7g** | *m*-$NO_2C_6H_4$ | 0.5 | 93 [190–192] | $C_{21}H_{14}N_5O_2Cl$ | 62.45 [62.65] | 3.47 [3.52] | 17.35 [17.43] |
| **7h** | *p*-$NO_2C_6H_4$ | 0.5 | 94 [215–216] | $C_{21}H_{14}N_5O_2Cl$ | 62.45 [62.64] | 3.47 [3.53] | 17.35 [17.45] |
| **7i** | 3,4-(O-$CH_2$-O-)$C_6H_3$ | 1.0 | 9.6 [224–226] | $C_{22}H_{15}N_4O_2Cl$ | 65.59 [65.78] | 3.73 [3.78] | 13.91 [13.99] |
| **8a** | $C_6H_5$ | 3.0 | 88 [254–256] | $C_{21}H_{13}N_4Cl$ | 70.69 [70.88] | 3.46 [3.52] | 15.71 [15.80] |
| **8b** | *p*-$CH_3OC_6H_4$ | 4.0 | 86 [200–201] | $C_{22}H_{15}N_4OCl$ | 68.31 [68.52] | 3.88 [3.92] | 14.49 [14.57] |
| **8c** | *p*-$CH_3C_6H_4$ | 3.0 | 92 [280–282] | $C_{22}H_{15}N_4Cl$ | 71.26 [71.45] | 4.04 [4.10] | 15.11 [15.21] |
| **8d** | *o*-$ClC_6H_4$ | 3.5 | 85 [225–226] | $C_{21}H_{22}N_4Cl_2$ | 64.45 [64.65] | 3.07 [3.12] | 14.32 [14.40] |
| **8e** | *p*-$ClC_6H_4$ | 3.0 | 90 [304–305] | $C_{21}H_{22}N_4Cl_2$ | 64.45 [64.64] | 3.07 [3.11] | 14.32 [14.42] |
| **8f** | *o*-$BrC_6H_4$ | 3.5 | 87 [210–212] | $C_{21}H_{12}N_4ClBr$ | 57.86 [57.99] | 2.76 [2.82] | 12.86 [12.95] |
| **8g** | *m*-$NO_2C_6H_4$ | 5.0 | 84 [280–283] | $C_{21}H_{12}N_5O_2Cl$ | 62.76 [62.94] | 2.99 [3.05] | 17.43 [17.52] |
| **8h** | *p*-$NO_2C_6H_4$ | 5.0 | 86 [320–322] | $C_{21}H_{12}N_5O_2Cl$ | 62.76 [62.95] | 2.99 [3.04] | 17.43 [17.53] |
| **8i** | 3,4-(O-$CH_2$-O-)$C_6H_3$ | 4.0 | 88 [220–222] | $C_{22}H_{13}N_4O_2Cl$ | 65.92 [66.12] | 3.25 [3.31] | 13.98 [14.07] |

Gemini 200 MHz spectrometer (chemical shifts in δ ppm) using TMS as internal standard. Mass spectra (EI-MS) were determined on a Finnigan MAT 8230 GC-MS spectrometer at 70 eV. Microanalyses were performed on a Perkin-Elmer 240 CHN elemental analyser. Irradiation was carried out in a domestic microwave oven (BPL 800 G, 2450 MHz).

*2-Amino-3-(m-chlorophenyl)-1,8-naphthyridine* **3:** A mixture of 2-aminonicotin-aldehyde **1** (0.01 mol), *m*-chlorophenylacetonitrile **2** (0.01 mol) and 10% KOH (5 drops) was exposed to microwave irradiation at 150 watts with pulses of 30 s, and gaps of 15 s for 2.0 min. 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 recrystallised from methanol to afford **3**, yield 98%, m.p. 225–227°C; IR: 3472, 3076 ($NH_2$), 1638 (C-$NH_2$), 1590 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 6.05 (s, 2H, $NH_2$), 7.74 (s, 1H, H-4), 8.00 (m, 1H, H-5), 8.76 (m, 1H, H-7), 7.08-7.52 (m, 5H, H-6, 4Ar-H); *m/z* (EI) 255 ($M^+$); Anal. Calcd. for $C_{14}H_{10}N_3Cl$ : C, 65.75; H, 3.91; N, 16.44; Found C, 65.92; H, 3.96; N, 16.52.

*1,2-Dihydro-3-(m-chlorophenyl)-1,8-naphthyridin-2-one* **4:** To a cold solution of **3** (0.01 mol) in 2 M HCl (25 ml) was added $NaNO_2$ solution (0.01 mol in 25 ml water) and the reaction mixture was 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 recrystallised from methanol to give **4**, yield 86%, m.p. 254–256°C; IR: 3447 (NH), 1660 (C=O), 1593 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.17 (s, 1H, H-4), 8.41 (m, 1H, H-5), 7.76 (m, 1H, H-6), 8.49 (m, 1H, H-7), 7.03–7.55 (m, 4H, Ar-H) 12.32 (s, 1H, NH); *m/z* (EI) 256 ($M^+$); Anal. Calcd. for $C_{14}H_9N_2OCl$: C, 65.50; H, 3.50; N, 10.92; Found C, 65.67; H, 3.55; N, 10.98.

*2-Chloro-3-(m-chlorophenyl)-1,8-naphthyridine* **5:** A mixture of **4** (0.01 mol) and $POCl_3$ (15 ml) was irradiated in a microwave oven at 80 watts with pulses of 10 s, and gaps of 15 s for 2.5 min. After completion of conversion as indicated by TLC, the reaction mixture was cooled and poured onto a mixture of crushed ice and $NaHCO_3$. The resultant precipitate was filtered, washed with water and recrystallised from ethanol to give **5**, yield 94%, m.p. 194–196°C; IR: 1594 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 8.42 (s, 1H, H-4), 8.56 (m, 1H, H-5), 7.73 (m, 1H, H-6), 9.18 (m, 1H, H-7), 7.40–7.59 (m, 4H, Ar-H); *m/z* (EI) 274 ($M^+$); Anal. Calcd. for $C_{14}H_8N_2Cl_2$: C, 61.09; H, 2.91; N, 10.18; Found C, 61.27; H, 2.95; N, 10.26.

*2-Hydrazino-3-(m-chlorophenyl)-1,8-naphthyridine* **6:** A mixture of **5** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (25 ml) was refluxed on a water-bath for 3 h. The reaction mixture was cooled, the solid that separated was filtered and recrystallised from ethanol to furnish **6**, yield 88%, m.p. 105–106°C; IR: 3420, 3297 (–$NHNH_2$), 1623 (C-$NHNH_2$), 1595 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.92 (br s, 2H, $NH_2$), 7.65 (s, 1H, H-4), 7.92 (m, 1H, H-5), 8.85 (m, 1H, H-7), 7.19–7.48 (m, 6H, H-6, NH, 4Ar-H); *m/z* (EI) 270 ($M^+$); Anal. Calcd. for $C_{14}H_{11}N_4Cl$: C, 62.10; H, 4.06; N, 20.70; Found C, 62.28; H, 4.11; N, 20.78.

*General procedure for the preparation of aryl aldehyde 3-(m-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones* **7:** A mixture of **6** (0.01 mole), aromatic aldehyde (0.01 mol) and DMF (5 drops) was subjected to microwave irradiation at 150 watts with pulses of 10 s and gaps of 15 s for 0.5–1.5 min, the completion of the reaction was monitored by TLC and poured onto crushed ice. The product which separated was filtered, washed with water and recrystallised from ethanol to afford **7**.

**7a:** IR: 3350 (NH), 1623 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.98 (m, 2H, H-4, H-5), 7.78 (m, 1H, H-6), 8.48 (m, 1H, H-7), 7.08–7.60 (m, 9H, Ar-H), 8.60 (s, 1H, N=CH), 10.36 (s, 1H, NH); *m/z* (EI) 358 ($M^+$).

**7b:** IR: 3365 (NH), 1624 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 3.82 (s, 3H, $OCH_3$), 7.72 (m, 2H, H-4, H-5), 7.58 (m, 1H, H-6), 8.25 (m, 1H, H-7), 6.85–7.37 (m, 8H, Ar-H), 8.48 (s, 1H, N=CH), 10.23 (s, 1H, NH); *m/z* (EI) 388 ($M^+$).

**7c:** IR: 3351 (NH), 1624 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.40 (s, 3H, $CH_3$), 7.70 (m, 2H, H-4, H-5), 7.63 (m, 1H, H-6), 8.32 (m, 1H, H-7), 6.92–7.40 (m, 8H, Ar-H), 8.43 (s, 1H, N=CH), 10.18 (s, 1H, NH); *m/z* (EI) 372 ($M^+$).

**7d:** IR: 3280 (NH), 1620 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.68 (m, 2H, H-4, H-6), 8.22 (m, 1H, H-5), 8.38 (m, 1H, H-7), 6.94–7.42 (m, 8H, Ar-H), 8.83 (s, 1H, N=CH), 10.20 (s, 1H, NH); *m/z* (EI) 392 ($M^+$).

**7e:** IR: 3360 (NH), 1625 $cm^{-1}$ (C=N); $^1H$ NMR ($CDCl_3$): δ 7.73 (m, 3H, H-4, H-5, H-6), 8.30 (m, 1H, H-7), 6.92–7.58 (m, 8H, Ar-H), 8.42 (s, 1H, N=CH), 10.18 (s, 1H, NH); *m/z* (EI+) 392 ($M^+$).

**7f:** IR: 3372 (NH), 1622 $cm^{-1}$ (C=N); $^1H$ NMR ($CDCl_3$): δ 7.64 (m, 2H, H-4, H-6), 8.20 (m, 1H, H-5), 8.32 (m, 1H, H-7), 6.98–7.40 (m, 8H, Ar-H), 8.78 (s, 1H, N=CH), 10.22 (s, 1H, NH); *m/z* (EI) 437 ($M^+$).

*General procedure for the preparation of 1-aryl-4-(m-chlorophenyl)-1,2,4-triazolo[4,3-a][1,8]naphthyridines* **8:** The mixture of the appropriate hydrazone (0.01 mol) and chloramine-T (0.01 mol) in ethanol (25 ml) was exposed to microwaves at 150 watts for successive irradiations of 30 s each with 15 s gaps for 3.0–5.0 min. After complete conversion as indicated by TLC, the reaction mixture was allowed to cool and the ensuing solid product was filtered, washed with water and recrystallised from ethanol to furnish **8**.

**8a:** IR: 1612 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 7.84 (s, 1H, H-5), 8.17 (m, 1H, H-6), 8.45 (m, 1H, H-8), 7.22–7.65 (m, 10H, H-7, 9Ar-H); *m/z* (EI) 356 ($M^+$).

**8b:** IR: 1610 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.83 (s, 3H, $OCH_3$), 8.13 (s, 1H, H-5), 8.30 (m, 1H, H-6), 7.79 (m, 1H, H-7), 8.41 (m, 1H, H-8), 6.82–7.84 (m, 8H, Ar-H); *m/z* (EI) 386 ($M^+$).

**8c:** IR: 1615 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 2.43 (s, 3H, $CH_3$), 7.78 (s, 1H, H-5), 8.16 (m, 1H, H-6), 7.60 (m, 1H, H-7), 8.45 (m, 1H, H-8), 7.22–7.45 (m, 8H, Ar-H); *m/z* (EI) 370 ($M^+$).

**8d:** IR: 1612 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.18 (m, 2H, H-5, H-6), 7.65 (m, 1H, H-7), 8.40 (m, 1H, H-8), 7.20–7.56 (m, 8H, Ar-H); *m/z* (EI) 390 ($M^+$).

**8e:** IR: 1614 (C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 8.15 (m, 2H, H-5, H-6), 7.80 (m, 1H, H-7), 8.52 (m, 1H, H-8), 7.22–7.63 (m, 8H, Ar-H); *m/z* (EI) 390 ($M^+$).

**8f:** IR: 1608 (C=N) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 7.79 (s, 1H, H-5), 8.13 (m, 1H, H-6), 7.74 (m, 1H, H-7), 8.38 (m, 1H, H-8), 7.23–7.60 (m, 8H, Ar-H); *m/z* (EI) 435 ($M^+$).

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