Synthesis of 9-aryl-6-(4-trifluoromethylphenyl)-1,2,4-triazolo[4,3-a][1,8]naphthyridines using Cu(OAc)$_2$ under microwave irradiation and their antibacterial activity

K Mogilaiah*,$^a$ K Shiva Kumar$^a$, A Nageswara Rao$^a$ & H Ramesh Babu$^b$

$^a$Department of Chemistry, Kakatiya University, Warangal 506 009, India
$^b$Department of Physical Sciences/Chemistry, Kakatiya Institute of Technology and Science, Warangal 506 015, India
E-mail: mogilaiah_k@yahoo.co.in

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An effective, practical and simple approach towards the synthesis of 9-aryl-6-(4-trifluoromethylphenyl)-1,2,4-triazolo[4,3-a][1,8]naphthyridines 8 from the corresponding aryl aldehyde 3-(4-trifluoromethylphenyl)-1,8-naphthyridin-2-ylhydrazones 7 has been achieved, using Cu(OAc)$_2$ in combination with microwave irradiation. The products are obtained in good yields and in a state of high purity. The structural assignments of compounds 3-8 are based on their elemental analyses and spectral (IR, $^1$H NMR and mass spectroscopy) data. The compounds 8 have been screened for their antibacterial activity.

Keywords: 1,2,4-Triazole, 1,8-naphthyridine, Cu(OAc)$_2$, microwave irradiation, antibacterial activity

The chemistry of fused 1,2,4-triazoles has generated intensive scientific interest due to their pharmacological and biological applications$^{1,2}$. The synthesis of a fused 1,2,4-triazole system is possible by two distinct routes either by treatment of a suitably substituted 1,2,4-triazole with appropriate reagents to give rise either to the fused 1,2,4-triazole system as such or an intermediary product which may be cyclized subsequently$^3$ or more conventionally by starting from a suitable α-hydrazone heterocycle and creating the triazole unit thereon. The later method for the formation of fused 1,2,4-triazoles has been discussed in a review$^4$ and is the one more frequently employed for the synthesis. The wide applicability of this approach was recognized by a number of workers and a variety of fused 1,2,4-triazoles were prepared by a proper choice of conditions and reagents$^5-9$. However, these methods are not very satisfactory due to drawbacks such as low yields, expensive reagents, longer reaction time at higher reaction temperature and tedious work-up procedures. Therefore, the development of further convenient and efficient methods for the synthesis of fused 1,2,4-triazoles is of practical importance. Fused 1,8-naphthyridines constitute an important class of compounds possessing diverse biological and pharmacological activities$^{10-12}$. Trifluoromethylated organic compounds have been the subject of much attention in recent years owing to their unique physical and biological properties$^{13,14}$.

Microwave-assisted organic synthesis has attracted much attention in recent years$^{15-17}$, due to enhanced reaction rates, high yields, improved selectivity and eco-friendly conditions. 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. In view of this and in continuation of our work on microwave assisted organic transformations of 1,8-naphthyridine derivatives$^{18,20}$, we report herein, a simple, practical and effective method for the synthesis of 1,2,4-triazolo[4,3-a][1,8]naphthyridines using Cu(OAc)$_2$ under microwave irradiation (MW).

Results and Discussion

2-Aminonicotinaldehyde 1, on condensation with 4-trifluoromethyl-pheny lacetonitrile 2 in the presence of 10% KOH without any solvent under microwave irradiation afforded 2-amino-3-(4-trifluoromethylphenyl)-1,8-naphthyridine 3, which is converted into 1,2-dihydro-3-(4-trifluoromethylphenyl)-1,8-naphthyridin-2-one 4 by the reaction with HNO$_2$. Treatment of 4 with POC$_3$ under microwave irradiation yielded 2-chloro-3-(4-
trifluoromethylphenyl)-1,8-naphthyridine 5, which on hydrazinolysis with refluxing hydrazine hydrate furnished 2-hydrazino-3-(4-trifluoromethyl-phenyl)-1,8-naphthyridine 6.

Condensation of 6 with various aromatic aldehydes in the presence of catalytic amount of DMF under microwave irradiation resulted in the formation of the corresponding aryl aldehyde 3-(4-trifluoromethylphenyl)-1,8-naphthyridin-2-ylhydrazones 7 in excellent yields.

Oxidative cyclization of hydrazones 7 with Cu(OAc)$_2$ in glacial acetic acid under microwave irradiation afforded the respective 9-aryl-6-(4-trifluoromethylphenyl)-1,2,4-triazolo-[4,3-a][1,8] naphthyridines 8 (Scheme I). The transformation is very clean and rapid. The reaction conditions and work-up procedures are mild, simple and convenient. The high yield

![Scheme I](image-url)
transformation did not form any undesirable by-products. Furthermore, the products were obtained with a high degree of purity by this procedure and no further purification was needed. The experimental procedure is very simple.

In a standardized procedure, a mixture of 7a (Ar = C₆H₅), Cu(OAc)₂ and glacial acid was irradiated under microwave irradiation at 400 W for 3.5 min. The reaction mixture was cooled and poured into ice-cold water. After usual work-up, a compound was obtained in 90% yield. The compound was assigned the structure 9-phenyl-6-(4-trifluoromethylphenyl)-1,2,4-triazolo[4,3-a][1,8]naphthyrindine 8a (Ar = C₆H₅) based on analytical and spectral data.

The generality of this facile oxidative transformation was established by treating other hydrazones 7 with Cu(OAc)₂ under similar conditions to get the corresponding 1,2,4-triazolo[4,3-a][1,8]naphthyrindines 8 (Ar = 4-CH₃C₆H₄, 4-CH₃OC₆H₄, 2-CIC₆H₄, 4-CIC₆H₄, 2,4-Cl₂C₆H₃, 3-NO₂C₆H₄, 3,4-(CH₂O)₂C₆H₃) in good yields (Table I and Table II).

Table I — IR, ¹H NMR and mass spectral data of compounds 7 and 8

<table>
<thead>
<tr>
<th>Compd</th>
<th>IR (KBr) cm⁻¹</th>
<th>¹H NMR (200 MHz, CDCl₃ + DMSO-d₆) (δ, ppm)</th>
<th>LC-MS [M+H]+ (m/z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>3378 (NH), 1624 (C=N)</td>
<td>7.80 (m, 3H, C₆-H, C₅-H, C₇-H), 8.34 (m, 1H, C₇-H), 8.46 (s, 1H, N=CH), 6.98-7.72 (m, 9H, Ar), 10.28 (s, 1H, NH)</td>
<td>393.1</td>
</tr>
<tr>
<td>7b</td>
<td>3333 (NH), 1621 (C=N)</td>
<td>2.39 (s, 3H, CH₃), 7.82 (m, 2H, C₆-H, C₅-H), 8.33 (m, 1H, C₇-H), 8.43 (s, 1H, N=CH), 6.95-7.70 (m, 9H, C₆-H, 8 Ar-H), 10.26 (s, 1H, NH)</td>
<td>407.4</td>
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<tr>
<td>7c</td>
<td>3356 (NH), 1622 (C=N)</td>
<td>3.86 (s, 3H, OCH₃), 7.82 (m, 3H,C₆-H, C₅-H,C₇-H), 8.37 (m, 1H, C₇-H), 8.40 (s, 1H, N=CH), 6.82-7.75 (m, 8H, Ar), 10.23 (s, 1H, NH)</td>
<td>423.3</td>
</tr>
<tr>
<td>7d</td>
<td>3376 (NH), 1621 (C=N)</td>
<td>7.82 (m, 2H, C₆-H, C₅-H), 8.20 (m, 1H, C₇-H), 8.28 (m, 1H, C₇-H), 8.40 (s, 1H, N=CH), 6.98-7.70 (m, 8H, Ar), 10.20 (s, 1H, NH)</td>
<td>427.2</td>
</tr>
<tr>
<td>7e</td>
<td>3355 (NH), 1624 (C=N)</td>
<td>7.78 (m, 3H, C₆-H, C₅-H,C₇-H,C₈-H), 8.37 (m, 1H, C₇-H), 8.4 (s, 1H, N=CH), 8.00-7.72 (m, 8H, Ar), 10.31 (s, 1H, NH)</td>
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<td>7f</td>
<td>3377 (NH), 1622 (C=N)</td>
<td>7.80 (m, 2H, C₆-H,C₅-H), 8.20 (m, 1H, C₇-H), 8.35 (m, 1H, C₇-H), 8.75 (s, 1H, N=CH), 7.00-7.67 (m, 7H, Ar), 10.18 (s, 1H, NH)</td>
<td>461.2</td>
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<tr>
<td>7g</td>
<td>3378 (NH), 1629 (C=N)</td>
<td>7.85 (m, 2H,C₆-H,C₇-H), 8.22 (m, 1H, C₇-H), 8.40 (m, 1H, C₇-H), 8.70 (s, 1H, N=CH), 7.10-7.70 (m, 8H, Ar), 10.65 (s, 1H, NH)</td>
<td>438.3</td>
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<td>7h</td>
<td>3358 (NH), 1627 (C=N)</td>
<td>3.90 (s, 3H, OCH₃), 3.97 (s, 3H, OCH₃), 7.72 (m, 1H, C₆-H), 7.80 (m, 2H, C₅-H, C₇-H), 8.25 (m, 1H, C₇-H), 8.40 (s, 1H, N=CH), 6.80-7.65 (m, 7H, Ar), 10.10 (s, 1H, NH)</td>
<td>453.2</td>
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<tr>
<td>8a</td>
<td>1614 (C=N)</td>
<td>8.00 (m, 1H, C₆-H), 8.27 (s, 1H, C₇-H), 8.43 (m, 2H, C₅-H, C₇-H), 7.10-7.84 (m, 9H, Ar)</td>
<td>391.1</td>
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<tr>
<td>8b</td>
<td>1610 (C=N)</td>
<td>2.49 (s, 3H, CH₃), 8.02 (m, 2H, C₆-H, C₅-H), 8.40 (m, 2H, C₅-H, C₇-H), 7.25-7.86 (m, 8H, Ar)</td>
<td>405.3</td>
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<td>8c</td>
<td>1610 (C=N)</td>
<td>3.88 (s, 3H, OCH₃), 7.99(m, 1H, C₇-H), 8.20 (s, 1H, C₅-H), 8.49 (m, 2H, C₅-H, C₇-H), 7.02-7.80 (m, 8H, Ar)</td>
<td>421.3</td>
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<tr>
<td>8d</td>
<td>1612 (C=N)</td>
<td>7.75 (m, 1H, C₅-H, C₇-H), 8.25 (m, 1H, C₅-H, C₇-H), 7.30-7.60 (m, 8H, Ar)</td>
<td>425.1</td>
</tr>
<tr>
<td>8e</td>
<td>1610 (C=N)</td>
<td>7.98 (m, 2H, C₆-H, C₅-H), 8.53 (m, 2H, C₅-H, C₇-H), 7.10-7.83 (m, 8H, Ar)</td>
<td>425.1</td>
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<tr>
<td>8f</td>
<td>1611 (C=N)</td>
<td>8.13 (m, 1H, C₅-H), 8.25 (m, 2H, C₅-H, C₇-H), 8.42 (m, 1H, C₇-H), 7.35-7.65 (m, 7H, Ar)</td>
<td>459.1</td>
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<tr>
<td>8g</td>
<td>1612 (C=N)</td>
<td>7.82 (m, 2H, C₅-H,C₇-H), 8.40 (m, 2H, C₅-H, C₇-H), 7.20-7.72 (m, 8H, Ar)</td>
<td>436.3</td>
</tr>
<tr>
<td>8h</td>
<td>1612 (C=N)</td>
<td>3.82 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 8.25 (m, 1H, C₅-H, C₇-H), 8.45 (m, 1H, C₇-H), 6.92-7.82 (m, 7H, Ar)</td>
<td>451.2</td>
</tr>
</tbody>
</table>
Interestingly, this oxidative reaction proceeds only to a minor extent (6-10% in 3.0-4.5 min) when conducted under conventional conditions in an oil-bath preheated to 120°C (temperature measured at the end of exposure during microwave experiment) which confirms the rate augmentation during microwave heating.

The structure of compounds 3-8 were confirmed by their spectroscopic (IR, 1H NMR and MS) and analytical data.

To the best of our knowledge this is the first report on microwave-assisted Cu(OAc)$_2$ mediated synthesis of 1,2,4-triazolo[4,3-$\alpha$][1,8]-napthyridines.

In conclusion, we have devised a simple and efficient method for the synthesis of 1,2,4-triazolo[4,3-$\alpha$][1,8]-napthyridines using Cu(OAc)$_2$ under microwave irradiation. The method also has several other advantages such as simple experimental procedure, short reaction time, pure products, high yields, cheapness and non-toxicity of the reagent.

### Antibacterial activity

All the synthesized compounds 8 were tested for their antibacterial activity against Escherichia coli and Bacillus subtilis following the filter paper disc technique of Vincent and Vincent $^{11}$ at 250 and 500 µg/disc concentrations. Gentamycin was used as a standard drug for comparison. The results are given in Table III. The antibacterial activity data indicate that all the compounds 8 were active against both Gram-negative and Gram-positive bacteria at the concentration of 250 µg/disc. The activity of the compound depends upon the nature and position of the substituent at the phenyl group. Compounds 8b, 8d, 8e and 8h showed promising antibacterial activity. The most active compound of the series was 8e, which exhibited activity comparable to that of Gentamycin.

### Experimental Section

All melting points were determined on a Cintex melting point apparatus and are uncorrected.
Homogeneity of the compounds was checked using precoated TLC plates (Merck, 60F-254). IR spectra (KBr) were recorded on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer; $^1$H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer (chemical shifts in $\delta$ ppm) and mass spectra on a PE-SCIEX API 3000 LC-MS/MS System. Microwave irradiation was carried out on a domestic microwave oven (LGMC 556P, 2450 MHz). The 4-trifluoromethylphenylacetonitrile was purchased from Aldrich Chemical Company.

### 2-Amino-3-(4-trifluoromethylphenyl)-1,8-naphthyridine, 3

A mixture of 2-aminonicotinaldehyde 1 (0.01 mol), 4-trifluoromethylphenylacetonitrile 2 (0.01 mol) and 10% KOH (5 drops) was exposed to microwave irradiation at 400 W intermittently at 30 sec intervals for 2 min. After completion of the reaction as indicated by TLC, the reaction mixture was cooled and treated with chilled water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford 3. Yield 98%. m.p.296°C. IR (KBr): 3378 (NH), 1658 cm$^{-1}$ (C=N); $^1$H NMR (200 MHz, CDCl$_3$+DMSO-$d_6$): $\delta$ 7.18-7.68 (m, 5H, Ar-H); LC-MS: m/z 291.1 [M+H]+. Anal. Calcd for C$_{15}$H$_9$N$_2$OF$_3$: C, 62.07; H, 3.52; N, 14.60%. Found: C, 62.22; H, 3.18; N, 9.71%.

### 2-Chloro-3-(4-trifluoromethylphenyl)-1,8-naphthyridine, 5

A mixture of 4 (0.01 mol) and POCl$_3$ (10 mL) was subjected to microwave irradiation at 200 W intermittently at 30 sec intervals for 1.5 min. On completion of the reaction, as monitored by TLC, the reaction mixture was cooled and poured onto a mixture of crushed ice and NaHCO$_3$. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford 5. Yield 95%. m.p.270°C. IR (KBr): 1608 cm$^{-1}$ (C=N); $^1$H NMR (200 MHz, CDCl$_3$+DMSO-$d_6$): $\delta$ 8.45 (1H, C$_3$-H), 7.96 (m, C$_2$-H), 9.14 (m, 1H, C$_7$-H), 7.60-7.85 (5H, C$_6$-H Ar-4H); LC-MS: m/z 309.1[M+H]+. Anal. Calcd for C$_{15}$H$_9$N$_2$ClF$_3$: C, 58.36; H, 2.61; N, 9.07. Found: C, 58.52; H, 2.64; N, 9.14%.

### 2-Hydrazino-3-(4-trifluoromethylphenyl)-1,8-naphthyridine, 6

A mixture of 5 (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed on a water bath for 3.5 h. The reaction mixture was cooled, the solid that separated was filtered, washed with water and purified by recrystallization from ethanol to furnish 6. Yield 94%. m.p.198°C. IR (KBr): 3295, 3178 (-NHNH$_2$), 1616 (C-NHNH$_2$), 1589 cm$^{-1}$ (C=N); $^1$H NMR (CDCl$_3$+DMSO-$d_6$): $\delta$ 2.90 (2H, NH$_2$), 7.75 (m, 2H, C$_2$-H, C$_5$-H), 7.96 (m, C$_3$-H, C$_4$-H), 8.84 (m, 1H, C$_7$-H), 7.18-7.68 (5H, 5H, C$_6$-H Ar-4H); LC-MS: m/z 305.1 [M+H]+. Anal. Calcd for C$_{15}$H$_9$N$_3$F$_3$: C, 59.21; H, 3.64; N, 18.41. Found: C, 59.39; H, 3.69; N, 18.49%.

### General procedure for the synthesis of aryl aldehyde 3-(4-trifluoro - methylphenyl)-1,8-naphthyridine-2-yldrazones, 7

A mixture of 6 (0.01 mol), aromatic aldehyde (0.01 mol) and DMF (5 drops) was exposed to microwave at 200 W intermittently at 30 sec intervals for the specified time (Table I). On completion of the reaction, as monitored by TLC, the reaction mixture was cooled and digested with cold water. The
precipitate thus obtained was filtered, washed with water and purified by recrystallization from ethanol to afford 7 (Table II).

**General procedure for the synthesis of 9-aryl-6-(4-trifluoro methylphenyl)-1,2,4-triazolo[4,3-\(a\)] [1,8]-naphthyridines, 8**

The mixture of the appropriate hydrazone 7 (0.01 mol) and Cu(OAc)\(_2\) (0.015 mol) in glacial acetic acid (15 mL) was exposed to microwaves at 400 W intermittently at 30 sec intervals for the specified time (Table I). After complete conversion as indicated by TLC, the reaction mixture was cooled and treated in the cold water. The product which separated was filtered, washed with water and purified by recrystallization from ethanol to furnish 8 (Table II).

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**References**