Microwave assisted heterocyclization: 
A rapid and efficient synthesis of 1,8-naphthyridinyl-1,3,4-oxadiazoles

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5-Aryl-2-[4-(3-phenyl-1,8-naphthyridin-2-ylamino)phenyl]-
1,3,4-oxadiazoles 4 have been synthesized by the reaction of 2-(4-
carboxyphenylamino)-3-phenyl-1,8-naphthyridine 3 with aromatic
acid hydrazides in the presence of POCl₃ under microwave irra­
diation and by conventional methods are described. The reaction
rate is enhanced tremendously under microwave irradiation as
compared to conventional method with improved yields.

In recent years the applications of microwave irradia­
tion in organic synthesis are increasing very rapidly due to advantages like short reaction time, suppres­
sion of side products, less polluting processes and at the same time excellent yields. 1,8-Naphthyridines and
1,3,4-oxadiazoles are interesting and important class of biodynamic heterocyclic moieties. So it was
presumed that incorporation of these heterocyclic systems would enhance biological properties. In view of
this and in continuation of our work on microwave assisted synthesis of 1,8-naphthyridines, we report
herein an efficient and clean procedure for the synthesis of 1,8-naphthyridinyl-1,3,4-oxadiazoles under mi­
crowave irradiation.

2-Chloro-3-phenyl-1,8-naphthyridine 1 was prepared from 2-amino-3-phenyl-1,8-naphthyridine by
treatment with HNO₂ and followed by reaction with POCl₃. Compound 1 on reaction with p-ami­
obenzoic acid 2 in gl. acetic acid under microwave irra­
diation afforded 2-(4-carboxyphenylamino)-3-phen­
yl-1,8-naphthyridine 3 in excellent yield. Treatment of 3 with aromatic acid hydrazides in the presence of
POCl₃ under microwave irradiation as well as conventional method yielded the corresponding 5-aryl-2-
[4-(3-phenyl-1,8-naphthyridin-2-ylamino)phenyl]-1,3,4-oxadiazoles 4 (Scheme 1).

The significance of our approach using microwave irradiation is that in classical approach heterocycliza­
tion of 3 to 4 requires 3.0 - 4.5 hr with constant heating at reflux temperature, while the same reaction was
completed in 3.0 - 5.5 min when carried out under microwaves with improved yield.

The structures of the compounds 3 and 4 were con­
firmed by their elemental analyses, IR, H NMR and mass spectroscopy.

Experimental Section
Melting points were taken on a Cintex melting point apparatus and are uncorrected. IR spectra were
recorded on a Perkin-Elmer BX series FT-IR spectrophotometer using KBr disc. H NMR spectra
were recorded on a Varian Gemini 200 MHz spectrometer using TMS as internal standard and mass spectra on a Jeol
p-aminobenzoic acid 2

with a funnel and subjected to microwave irradiation.

nyl-1,8-naphthyridine 3. A mixture of I

was checked by

was filtered off, washed with water and recrystallized from methanol to give 3, m.p. 21

yield 94%; IR (KBr): 

spectrometer. Purity of the compounds

was checked by TLC. The reactions were carried out in a BPL 800G domestic microwave oven.

Synthesis of 2-(4-carboxyphenylamino)-3-phenyl-1,8-naphthyridine 3. A mixture of I (0.01 mole), p-aminobenzoic acid 2 (0.01 mole) and gl. acetic acid (20 mL) was taken in a 100 mL conical flask covered in a "C, 73.90; H, 4.40; N, 12.32. Found: C, 73.72; H, 4.46; N, 12.44%.

Synthesis of 5-aryl-2-[4-(3-phenyl-1,8-naphthyridin-2-ylamino)phenyl]-1,3,4-oxadiazoles 4a-i

Method A (MWI). A 100 mL conical flask was charged with 3 (0.01 mole), appropriate aromatic acid hydrazide (0.01 mole) and POCl3 (10 mL) and capped with a funnel. The flask was kept in the microwave oven and irradiated at 300 Watts for the period indicated in Table I. The reaction mixture was cooled and poured into ice cold water. The solid thus separated was filtered off, washed with water and recrystallized from methanol to give 3, m.p. 210°C, yield 94%; IR (KBr): 3350 (NH), 1670 (C=O), 1605 cm-1 (C=N), 1552 (10.5), 296 (10.5), 263 (31.3), 221 (100), 220 (85.9), 194 (8.2), 193 (7.2). Anal. Caled for C2H8N4O3: C, 73.90; H, 4.40; N, 12.32. Found: C, 73.72; H, 4.46; N, 12.44%.

References


NOTES

Table I — Characterization data of compounds 4

<table>
<thead>
<tr>
<th>Compd*</th>
<th>m.p.</th>
<th>Method A</th>
<th>Method B</th>
<th>Mol. formula</th>
<th>N(%) Found</th>
<th>N(%) Calcd</th>
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<tbody>
<tr>
<td></td>
<td>(°C)</td>
<td>Yield (%)</td>
<td>Yield (%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Time (min)</td>
<td>Time (hr)</td>
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<td></td>
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<tr>
<td>4a</td>
<td>125</td>
<td>85/4</td>
<td>70/4</td>
<td>C25H16N4O</td>
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<td>(15.87)</td>
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<tr>
<td>4b</td>
<td>182</td>
<td>83/5.5</td>
<td>68/4.5</td>
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<td>15.52</td>
<td>(15.38)</td>
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<tr>
<td>4c</td>
<td>218</td>
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<td>76/4</td>
<td>C25H12N4O</td>
<td>15.53</td>
<td>(15.38)</td>
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<tr>
<td>4d</td>
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<td>(14.86)</td>
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<td>14.87</td>
<td>(14.72)</td>
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<td>4f</td>
<td>260</td>
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<td>14.85</td>
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<tr>
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<td>15.48</td>
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<tr>
<td>4h</td>
<td>220</td>
<td>90/4</td>
<td>73/3.5</td>
<td>C25H14N4O</td>
<td>15.46</td>
<td>(15.32)</td>
</tr>
<tr>
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<td>72/3</td>
<td>C25H18N4O</td>
<td>17.41</td>
<td>(17.28)</td>
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*All the new compounds showed satisfactory C and H analyses.