Synthesis of 1,8-naphthyridinyl-pyrazoles using microwave irradiation under solvent-free conditions

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Microwave irradiation of acetophenone 3-(2-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 2 on silica gel supported POCI₃-DMF (Vilsmeier-Haack reagent) under environmentally friendly solvent-free condition provides a fast, efficient and simple method for the synthesis of 3-aryl-4 formyl-1-[3-(2-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles 3 in good yields.

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The literature review shows that the Vilsmeier-Haack reaction of acetophenone phenylhydrazones resulted in the formation of pyrazole-4-carboxaldehyde. In Vilsmeier-Haack reaction, DMF-POCl₃ has a dual role of reagent as well as solvent. POCl₃ is a highly toxic solvent and its use is hazardous to health and is also pollutant of the environment. Recently the growing interest in the application of microwave irradiation in chemical reaction enhancement is due to high reaction rates and formation of cleaner products. The solvent-free reaction, in general, and on inorganic solid supports under this condition are especially appealing for providing an environmentally benign system. Pyrazole nucleus has wide applications in medicinal chemistry. The ring system plays an important role in many biological processes, and many therapeutic agents contain pyrazole moiety. 1,8-Naphthyridines represent a heterocyclic system of remarkable pharmacological efficiency. In the past two decades, a broad range of biological effects, including antibacterial, diuretic, anti-inflammatory and antitumor activities has been ascribed to these 1,8-naphthyridine derivatives. In view of this and in continuation of our interest on microwave assisted organic transformations, we now wish to report a facile and rapid protocol for the synthesis of 1,8-naphthyridinyl pyrazoles under POCI₃-DMF over silica gel under microwave irradiation.

Condensation of 2-hydrazino-3-(2-chlorophenyl)-1,8-naphthyridine 1 with different acetophenones in the presence of a catalytic amount of DMF under microwave irradiation afforded the corresponding acetophenone 3-(2-chlorophenyl)-1,8-naphthyridin-2-ylhydrazones 2 in excellent yields. The hydrazones 2 when subjected to the Vilsmeier-Haack reaction with POCl₃-DMF/SiO₂ under microwave irradiation gave 3-aryl-4-formyl-1-[3-(2-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles 3 (Scheme 1). The reaction proceeds efficiently in high yields at ambient pressure within a few minutes time and in the absence of solvent. The high yield transformation did not form any undesirable by-products. The purity of the product is high. The experimental procedure is very simple. The process is environmentally benign.

In order to know the role of microwave in rate enhancement of Vilsmeier-Haack reaction, similar reactions were carried out in an oil bath at ~110°C, where the reaction took longer time and low yields were observed.

The structures of the compounds synthesized (2 and 3) were assigned on the basis of their elemental analyses, IR, ¹H NMR and mass spectral data.

In conclusion, we have developed a solvent-free method for the facile synthesis of 1,8-naphthyridinyl pyrazoles using POCl₃-DMF over silica gel under microwave irradiation. The advantages of this environmentally benign and safe protocol include a simple reaction set-up not requiring specialized equipment, high product yields, short reaction times and the elimination of solvent.

Experimental Section

Melting points were recorded by means of a Cintex melting point apparatus and are uncorrected. The purity of the compounds was monitored by TLC on silica gel-G plates. IR spectra were recorded in KBr on a Perkin-Elmer spectrum BX series FT-IR spectrophotometer; ¹H NMR spectra on a Varian Gemini 200 MHz spectrometer and mass spectra on a Finnigan MAT 8230 GC-MS spectrometer. Microwave irradiations were carried out in LG MG-556 P domestic microwave oven.

General procedure for the synthesis of acetophenone 3-(2-chlorophenyl)-1,8-naphthyridin-2-
ylhydrazones 2. A mixture of 2-hydrazino-3-(2-chlorophenyl)-1,8-naphthyridine 1 (0.01 mole), appropriate acetophenone (0.01 mole) and DMF (5 drops) was subjected to microwave irradiation at 400 W for specified time (Table I). On completion of reaction (monitored by TLC), the reaction mixture was cooled and digested with water. The solid obtained was filtered and recrystallized from ethanol.

2a: IR (KBr): 3332 (NH), 1623 cm\(^{-1}\) (C=N); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.30 (s, 3H, CH\(_3\)), 7.85 (m, 2H, C\(_4\)-H, C\(_5\)-H), 7.60 (m, 1H, C\(_6\)-H), 8.27 (m, 1H, C\(_7\)-H), 6.93-7.45 (m, 9H, Ar-H), 9.90 (s, 1H, NH); MS: \(m/z\) 372 (M\(^+\)).

2b: IR (KBr): 3340 (NH), 1620 cm\(^{-1}\) (C=N); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.02 (s, 3H, CH\(_3\)), 2.42 (s, 3H, N=C-CH\(_3\)), 7.87 (m, 2H, C\(_4\)-H, C\(_5\)-H), 7.63 (m, 1H, C\(_6\)-H), 8.27 (m, 1H, C\(_7\)-H), 6.92-7.41 (m, 8H, Ar-H), 10.02 (s, 1H, NH); MS: \(m/z\) 386 (M\(^+\)).

2c: IR (KBr): 3325 (NH), 1618 cm\(^{-1}\) (C=N); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.48 (s, 3H, CH\(_3\)), 3.86 (s, 3H, OCH\(_3\)), 7.82 (m, 2H, C\(_4\)-H, C\(_5\)-H), 7.65 (m, 1H, C\(_6\)-H), 8.42 (m, 1H, C\(_7\)-H), 6.96 - 7.45 (m, 8H, Ar-H), 9.98 (s, 1H, NH); MS: \(m/z\) 402 (M\(^+\)).

2d: IR (KBr): 3327 (NH), 1622 cm\(^{-1}\) (C=N); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.36 (s, 3H, CH\(_3\)), 7.85 (m, 2H, C\(_4\)-H, C\(_7\)-H), 7.63 (m, 1H, C\(_6\)-H), 8.32 (m, 1H, C\(_7\)-H), 6.91 - 7.40 (m, 8H, Ar-H), 10.05 (s, 1H, NH); MS: \(m/z\) 406 (M\(^+\)).

General procedure for the synthesis of 3-aryl-4-formyl-1-[3-(2-chlorophenyl)-1,8-naphthyridin-2-yl]pyrazoles 3. To the Vilsmeier-Haack reagent (0.03 mole) at 0-5°C, compound 2 (0.01 mole) was added portionwise. After the addition was complete, the reaction flask was kept at room temperature for 5 min and silica gel (3 g) was added and properly mixed with the help of a glass rod, till free flowing powder was obtained. The powder is then irradiated in microwave oven at 400 W for specified time (Table I). After the completion of reaction as monitored by TLC, the reaction mixture was cooled, treated with chilled water and filtered. The solid obtained by the neutralization of the filtrate with...
Table 1 — Characterization data of compounds 2 and 3

<table>
<thead>
<tr>
<th>Compd</th>
<th>Reaction time (min)</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Found (%) (Calcd)</th>
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<tr>
<td>2a</td>
<td>0.5</td>
<td>145</td>
<td>94</td>
<td>C₂₂H₁₆N₄Cl</td>
<td>71.06 (70.87)</td>
</tr>
<tr>
<td>2b</td>
<td>0.25</td>
<td>150</td>
<td>98</td>
<td>C₂₂H₁₆N₄Cl</td>
<td>71.62 (71.41)</td>
</tr>
<tr>
<td>2c</td>
<td>0.5</td>
<td>155</td>
<td>96</td>
<td>C₂₂H₁₆N₄OCl</td>
<td>68.77 (68.57)</td>
</tr>
<tr>
<td>2d</td>
<td>0.25</td>
<td>165</td>
<td>97</td>
<td>C₂₂H₁₆N₄Cl₂</td>
<td>64.98 (64.86)</td>
</tr>
<tr>
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<td>0.5</td>
<td>174</td>
<td>94</td>
<td>C₂₂H₁₆N₄ClBr</td>
<td>58.78 (58.60)</td>
</tr>
<tr>
<td>2f</td>
<td>0.75</td>
<td>217</td>
<td>92</td>
<td>C₂₂H₁₆N₄OCl</td>
<td>68.15 (67.95)</td>
</tr>
<tr>
<td>2g</td>
<td>0.5</td>
<td>210</td>
<td>94</td>
<td>C₂₂H₁₆N₄OCl</td>
<td>63.45 (63.23)</td>
</tr>
<tr>
<td>2h</td>
<td>0.25</td>
<td>195</td>
<td>82</td>
<td>C₂₂H₁₆N₄Cl</td>
<td>70.35 (70.16)</td>
</tr>
<tr>
<td>3a</td>
<td>2.0</td>
<td>195</td>
<td>82</td>
<td>C₂₄H₁₅N₄OCl</td>
<td>70.88 (70.67)</td>
</tr>
<tr>
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<td>2.5</td>
<td>218</td>
<td>88</td>
<td>C₂₂H₁₆N₄OCl</td>
<td>68.18 (68.10)</td>
</tr>
<tr>
<td>3c</td>
<td>2.5</td>
<td>156</td>
<td>84</td>
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<td>64.92 (64.72)</td>
</tr>
<tr>
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<td>120</td>
<td>86</td>
<td>C₂₂H₁₆N₄OCl₂</td>
<td>59.15 (58.96)</td>
</tr>
<tr>
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<tr>
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<td>63.41 (63.23)</td>
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<tr>
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<td>C₂₂H₁₆N₄O₂Cl</td>
<td>63.43 (63.23)</td>
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<tr>
<td>3h</td>
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<td>82</td>
<td>C₂₂H₁₆N₄O₂Cl</td>
<td>70.35 (70.16)</td>
</tr>
</tbody>
</table>

NaHCO₃ was filtered, washed with water and recrystallized from methanol.

3a: IR (KBr): 1685 (C=O), 1605 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 8.32 (m, 2H, C₄-H, C₆-H) 8.80 (m, 1H, C₅-H), 9.23 (m, 1H, C₇-H), 7.02-7.83 (m, 10H, CH of pyrazole, 9Ar-H), 9.68 (s, 1H, CHO); MS: m/z 410 (M⁺).

3b: IR (KBr): 1690 (C=O), 1602 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 8.26 (m, 2H, C₄-H, C₆-H), 8.40 (m, 2H, C₅-H, C₆-H), 8.68 (m, 1H, C₅-H), 9.12 (m, 1H, C₇-H), 7.04-7.88 (m, 9H, CH of pyrazole, 8Ar-H), 9.66 (s, 1H, CHO); MS: m/z 424 (M⁺).

3c: IR (KBr): 1687 (C=O), 1607 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 3.88 (s, 3H, OCH₃), 8.46 (m, 2H, C₂-H, C₆-H), 8.74 (m, 1H, C₃-H), 9.20 (m, 1H, C₇-H), 7.00 - 7.81 (m, 9H, CH of pyrazole, 8Ar-H), 9.74 (s, 1H, CHO); MS: m/z 440 (M⁺).

3d: IR (KBr): 1686 (C=O), 1605 cm⁻¹ (C=N); ¹H NMR (CDCl₃): δ 8.37 (m, 2H, C₄-H, C₆-H), 8.76 (m, 1H, C₅-H), 9.18 (m, 1H, C₇-H), 7.15 - 7.93 (m, 9H, CH of pyrazole, 8Ar-H), 9.65 (s, 1H, CHO); MS: m/z 444 (M⁺).

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References