Microwave assisted Claisen-Schmidt condensation under solvent-free conditions

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A high yielding and fast method of Claisen-Schmidt condensation of 2-(4-acetophenylamino)-3-phenyl-1,8-naphthyridine 3 with various aromatic aldehydes under microwave irradiation using solid KOH in the absence of any solvent is described.

In recent years there has been a growing interest on the applications of microwave heating in organic chemistry due to its remarkable advantages such as decrease in the reaction time, cleaner reactions, easier work-up and better yields. It has been commonly employed as thermal energy source in various organic reactions. The use of domestic microwave oven in this regard is now a well-established procedure in more chemistry. It has been reported that the rate of a variety of organic reactions such as Diels-Alder, Michael addition, Claisen rearrangement, Doebner condensation, Knoevenagel condensation, Hantzsch synthesis could be enhanced by microwave irradiation. Solvent-free microwave assisted chemical reactions are gaining importance due to the advantages and environmentally friendly processes they offer, as compared to conventional reactions. One of the basic reactions in organic chemistry, is Claisen-Schmidt condensation for its significant utility in carbon-carbon bond formation, which is a pivotal process in organic synthesis. In view of this and in continuation of our interest on microwave assisted organic reactions, herein, we wish to report a simple, convenient and rapid microwave assisted Claisen-Schmidt condensation under solvent-free conditions using solid KOH as catalyst.

2-Amino-3-phenyl-1,8-naphthyridine, obtained by the condensation of 2-aminonicotinaldehyde with phenylacetanilide in boiling methanol containing a few drops of piperidine, on treatment with HNO2 gave 2-hydroxy-3-phenyl-1,8-naphthyridine, which on interaction with POC13 furnished the desired synthon, 2-chloro-3-phenyl-1,8-naphthyridine 1. Compound 1 on treatment with 4-aminocacetophenone 2 in gl. acetic acid under microwave irradiation yielded 2-(4-acetophenylamino)-3-phenyl-1,8-naphthyridine 3 in excellent yield (Scheme I).

Claisen-Schmidt condensation of 3 with various aromatic aldehydes in the presence of solid KOH under microwave irradiation in the absence of solvent resulted in the formation of 2-(4-cinnamoylphenylamino)-3-phenyl-1,8-naphthyridines 4 in very good to excellent yields. The reaction is fairly general, facile and efficient and devoid of any side products. 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. The process is environmentally benign. The results of the microwave irradiation condensation reactions are summarized in the Table I.

From the Table I it is evident that employing microwave irradiation for Claisen-Schmidt condensation of 3 with aromatic aldehydes results in excellent yields of α,β-unsaturated ketones within 1.0-3.5 min.

The structural assignments of 3 and 4 were based on their elemental analyses and spectral data.

In conclusion, we have demonstrated a solvent-free, environmentally benign, Claisen-Schmidt condensation under microwave irradiation in a very short time with excellent yields.

Experimental Section

Melting points were taken on Cintex melting apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer BX series FT-IR spectrophotometer using KBr discs; 1H NMR spectra on a Varian Gemini 200 MHz spectrometer using TMS as internal standard (chemical shifts in δ, ppm); and mass spectra at 70 eV on a Jeol JMS D-300 instrument. Purity of the compounds was checked by TLC. The reactions were carried out in a domestic microwave oven (BPL, 800 G, 800 W).

2-(4-Acetophenylamino)-3-phenyl-1,8-naphthyridine 3, 2-Chloro-3-phenyl-1,8-naphthyridine 1 (0.01 mole), 4-aminocacetophenone 2 (0.01 mole) and gl. acetic acid (25 mL) taken in a 100 mL Erlenmeyer flask were subjected to microwave irradiation at 450 watts for 4.0 min. The reaction mixture was cooled and poured into ice cold water. The resultant product was filtered, washed with water and recrystallized
\[
\begin{align*}
\text{Ar-CHO} & \quad \text{KOH} \\
\text{MW} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme I}
\end{align*}
\]

**Table I—Characterization data of compounds 3 and 4**

<table>
<thead>
<tr>
<th>Compd</th>
<th>Reaction period (min)</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Mol. formula</th>
<th>Found (%) (Calcd)</th>
<th>IR (cm(^{-1})) (KBr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>2.0</td>
<td>215</td>
<td>94</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>81.72 (81.50) 4.96 (4.92) 9.93 (9.84)</td>
<td>3465, 1645</td>
</tr>
<tr>
<td>4b</td>
<td>2.5</td>
<td>230</td>
<td>98</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>81.80 (81.63) 5.28 (5.22) 9.64 (9.52)</td>
<td>3420, 1640</td>
</tr>
<tr>
<td>4c</td>
<td>3.0</td>
<td>210</td>
<td>96</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>78.95 (78.77) 5.08 (5.03) 9.27 (9.19)</td>
<td>3390, 1640</td>
</tr>
<tr>
<td>4d</td>
<td>3.5</td>
<td>196</td>
<td>92</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>75.63 (75.41) 4.38 (4.33) 9.23 (9.10)</td>
<td>3440, 1645</td>
</tr>
<tr>
<td>4e</td>
<td>3.0</td>
<td>180</td>
<td>94</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>75.60 (75.41) 4.39 (4.33) 9.21 (9.10)</td>
<td>3460, 1650</td>
</tr>
<tr>
<td>4f</td>
<td>3.0</td>
<td>248</td>
<td>90</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>78.78 (78.56) 4.80 (4.74) 9.59 (9.48)</td>
<td>3410, 1645</td>
</tr>
<tr>
<td>4g</td>
<td>2.5</td>
<td>240</td>
<td>93</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>78.79 (78.56) 4.79 (4.74) 9.57 (9.48)</td>
<td>3425, 1640</td>
</tr>
<tr>
<td>4h</td>
<td>3.0</td>
<td>220</td>
<td>92</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>79.34 (79.15) 5.59 (5.53) 11.98 (11.91)</td>
<td>3385, 1650</td>
</tr>
<tr>
<td>4i</td>
<td>1.5</td>
<td>225</td>
<td>86</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>73.96 (73.73) 4.30 (4.24) 11.99 (11.86)</td>
<td>3405, 1645</td>
</tr>
<tr>
<td>4j</td>
<td>1.0</td>
<td>235</td>
<td>88</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>73.92 (73.73) 4.31 (4.24) 11.97 (11.86)</td>
<td>3415, 1642</td>
</tr>
<tr>
<td>4k</td>
<td>2.5</td>
<td>195</td>
<td>95</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>76.60 (76.43) 4.52 (4.46) 8.84 (8.92)</td>
<td>3450, 1640</td>
</tr>
<tr>
<td>4l</td>
<td>3.0</td>
<td>210</td>
<td>90</td>
<td>C(_2)H(_2)N(_3)O(_2)</td>
<td>82.31 (82.12) 5.15 (5.08) 9.38 (9.27)</td>
<td>3395, 1650</td>
</tr>
</tbody>
</table>
from ethanol to give 3, yield 92%; m.p. 250°C; IR (KBr): 3448 (NH), 1665 (C=O), 1603 cm⁻¹ (C=N); 
¹H NMR (CDCl₃): δ 2.58 (s, 3H, COCH₃), 7.84 (m, 1H, C₇-H), 8.02 (m, 1H, C₄-H), 8.58 (m, 1H, C₃-H).
7.15-7.75 (m, 10H, C₆-H, CH=CH, 14Ar-H), 12.18 (s, 1H, NH); MS: m/z 339 (M⁺, 100%), 324 (6.5), 296 (13.9), 295 (14.1), 220 (51.3), 206 (12.4).
Anal. Calcd for C₂₂H₁₇N₇O: C, 77.88; H, 5.01; N, 12.39. Found: C, 77.72; H, 5.07; N, 12.48%.

2-(4-Cinnamoylphenylamino)-3-phenyl-1,8-naphthyridine 4a. A mixture of 3 (0.01 mole), benzaldehyde (0.01 mole) and KOH (0.01 mole) were mixed together without any solvent in a 100 mL Erlenmeyer flask and placed in a microwave oven and irradiated at 450 watts for 2.0 min. The reaction mixture was allowed to attain room temperature and treated with cold water. The solid separated was filtered, washed with water and recrystallized from methanol to furnish 4a, yield 94%, m.p. 215°C; IR (KBr): 3465 (NH), 1645 (C=O), 1608 (C= C + CN), 980 cm⁻¹ (CH=CH, trans); ¹H NMR (CDCl₃ + DMSO-d₆): δ 7.82 (m, 1H, C₄-H), 7.98 (m, 1H, C₇-H), 8.61 (m, 1H, C₃-H), 7.16-7.79 (m, 17H, C₅-H, CH=CH, 14Ar-H), 12.18 (s, 1H, NH); MS: m/z 427 (M⁺, 79.9%), 296 (7.5), 222 (87), 220 (100), 205 (10.3), 131 (21.7), 103 (33.4), 77 (67.6).
Compounds 4b-1 were prepared similarly and their characterization data are given in Table I.

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References