ULTRASOUND PROMOTED EFFICIENT CONSTRUCTION OF POLYCYCLIC-FUSED PYRAZOLO[4,3-c]PYRIDINES VIA DOMINO REACTION

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Abstract – Ultrasonic-accelerated rapid protocol for the synthesis of polycyclic-fused pyrazolo[4,3-c]pyridines via SN2/Thorpe-Ziegler/Thorpe-Guareschi domino reactions of 4-acetyl-5-bromomethyl-1-phenyl-1H-pyrazole with salicylonitriles (2-mercaptobenzonitrile or 3-cyanopyridine-2(1H)-thiones). Ultrasound-based methodology performed better than the conventional process in rates and yields.

Pyrazole derivatives are an important class of heterocyclic compound for being key substructures in a variety of compounds with important biological properties. They are known to possess a wide spectrum of activities such as antimicrobial, antiinflammatory, antidepressant, antiviral, and antitumour activities. Many heterocyclic compounds containing the pyrazole ring display a broad spectrum of pharmacological and biological activities. Moreover, the pyrazole nucleus represent the core unit in a variety of drugs such as celecobix (Celebrex) and sildenafil (Viagra). Furthermore, the pyrazolopyridine moiety, which is a well-known nitrogen-containing fused-hetercycle, is a common and important feature of a variety of medicinal agents because of their wide range of biological and pharmaceutical properties such as antibacterial, antimicrobial, and oncogenic Ras inhibiting activities. Furthermore, these compounds can be used as promising luminescent materials and a fluorescent sensor. Owing to the attractive pharmacological properties of pyrazoles, new methodologies for the design of different pyrazoles have attracted the attention of the researchers. In recent years, the application of ultrasound irradiation in organic reactions has been rapidly increasing. A large number of organic reactions can be carried out in a higher yield, shorter reaction time and milder
conditions under sonication.\textsuperscript{15}

Recently, our group is actively engaged in the development of cascade synthesis of heterocycles and has developed a number of domino reactions to synthesize different heterocycles.\textsuperscript{16} Herein, we report the polycyclic-fused pyrazolo[4,3-c]pyridines 5 preparation via SN\textsubscript{2}/Thorpe-Ziegler/Thorpe-Guareschi domino reaction\textsuperscript{17} from 4-acetyl-5-bromomethyl-1-phenyl-1H-pyrazole with salicylonitriles (2-mercapto-benzonitrile or 3-cyanopyridine-2(1H)-thiones) under ultrasound irradiation (Scheme 1).

\textbf{Scheme 1. Synthesis of polycyclic-fused pyrazolo[4,3-c]pyridines}

In order to evaluate the potential of the synthesis procedure and to optimize the reaction conditions, the reaction of 4-acetyl-5-bromomethyl-1-phenyl-1H-pyrazole (1) and salicylonitrile (2) as a model was investigated. The results are summarized in Table 1.

\textbf{Table 1. Optimization of reaction conditions on the synthesis of 5a\textsuperscript{a}}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Conventional</th>
<th>Sonication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (h)\textsuperscript{b}</td>
<td>Yield (%)\textsuperscript{c}</td>
</tr>
<tr>
<td>1</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>100</td>
<td>9</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>100</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOK</td>
<td>DMF</td>
<td>100</td>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>DMSO</td>
<td>100</td>
<td>7</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>NMP</td>
<td>100</td>
<td>7</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>90</td>
<td>9</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>Cs\textsubscript{2}CO\textsubscript{3}</td>
<td>DMF</td>
<td>110</td>
<td>6</td>
<td>72</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 1 (1.0 equiv), 2 (1.0 equiv), base (2.0 equiv), solvent (20 mL).

\textsuperscript{b} Reaction progress monitored by TLC.

\textsuperscript{c} Isolated yield.

As indicated in Table 1, several bases (K\textsubscript{2}CO\textsubscript{3}, Cs\textsubscript{2}CO\textsubscript{3} and t-BuOK) were screened, and Cs\textsubscript{2}CO\textsubscript{3} was relatively efficient with 86% yield of 5a under ultrasound irradiation (entry 2). Solvent was investigated...
and DMF was found to be more effective than DMSO and NMP (entries 4 and 5). Further increase (110 °C) or decrease (90 °C) of reaction temperature did not push this domino reaction forward (entries 6 and 7).

To explore the scope and limitation of this reaction, we have extended the reaction of 4-acetyl-5-bromo-methyl-1-phenyl-1H-pyrazole (1) with a range of salicylonitriles (2) (2-mercaptobenzonitrile (3) or 3-cyanopyridine-2(1H)-thiones (4)) under optimum conditions (DMF/100 °C/Cs₂CO₃/ultrasound), furnishing the respective fused pyrazolo[4,3-c]pyridines (5a–h), and obtained results are summarized in Table 2.

Table 2. Synthesis of fused pyrazolo[4,3-c]pyridines 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>R</th>
<th>X</th>
<th>Y</th>
<th>Conventional</th>
<th>Sonication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)a</td>
</tr>
<tr>
<td>1</td>
<td>5a</td>
<td>H</td>
<td>O</td>
<td>C</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>7-Me</td>
<td>O</td>
<td>C</td>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>7-OMe</td>
<td>O</td>
<td>C</td>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>H</td>
<td>S</td>
<td>C</td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>7-Cl</td>
<td>S</td>
<td>N</td>
<td>9</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>H</td>
<td>S</td>
<td>N</td>
<td>7</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>6-Me</td>
<td>S</td>
<td>N</td>
<td>8</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>5h</td>
<td>8-Me</td>
<td>S</td>
<td>N</td>
<td>8</td>
<td>75</td>
</tr>
</tbody>
</table>

*a Isolated yields.

In order to verify the effect of ultrasound irradiation, all the reactions were carried out under the same conditions in absence of ultrasound irradiation (Table 2). The desired products were produced in much longer reaction time (5–9 h) and relatively lower yields (65–82%), while under ultrasonic irradiation the products were obtained in 2–4 h with the yields of 82–94%. The method to obtain the desired products under ultrasonic irradiation offers several significant advantages including faster reaction rates and higher yields. Thus, ultrasonic irradiation was found to have beneficial effect on the synthesis of polycyclic-fused pyrazolo[4,3-c]pyridine derivatives.

To the best of our knowledge, this new procedure provides the first example of an efficient and ultrasound promoted approach for the synthesis of furo- and thieno-fused pyrazolo[4,3-c]pyridine derivatives. This method is the most simple and convenient and would be applicable for the synthesis of different types of tetracyclic system heterocycles containing pyrazole, pyridine and benzofuran or...
benzothiophene unit with high regioselectivity. The structures of all the synthesized compounds were established by IR, NMR spectroscopy and elemental analysis.

The proposed mechanism of the process is summarized in Scheme 2. The present synthetic sequence was initiated by an alkylation of 4-acetyl-5-bromomethyl-1-phenyl-1H-pyrazole 1 with salicylonitriles (2) (2-mercaptobenzonitrile (3) or cyanopyridine-2(1H)-thiones (4)) giving to the ethers A. An intramolecular carbanion addition across the nitrile was brought about by ethers A via Thorpe-Ziegler reaction, and isomerization, resulting in the formation of amines C. Next, this then undergoes Thorpe-Guareschi reaction to yield the fused pyrazolo[4,3-c]pyridines 5.

\[
\begin{align*}
\text{Scheme 2. Proposed mechanism for the synthesis of compounds 5}
\end{align*}
\]

In conclusion, it has been successfully developed that S$_{\text{N}}$2/Thorpe-Ziegler/Thorpe-Guareschi domino reaction under ultrasonic condition, and a series of novel furo- and thieno-fused pyrazolo[4,3-c]pyridines were obtained. This method has the advantages of ultrasonic irradiation of convenient operation, mild reaction conditions, short reaction time and high efficiency.

**EXPERIMENTAL**

Melting points were determined in open capillaries and are uncorrected. The NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 MHz for $^1$H and 100 MHz for $^{13}$C) using TMS an internal reference. IR spectra were measured on Shimadzu FTIR-8300 spectrophotometer. C, H, and N analyses were performed by a HP-MOD 1106 microanalyzer. Ultrasonication was performed in a KQ-250E medical ultrasound cleaner with a frequency of 25 KHz and an output power of 250 W. The preparation of 4-acetyl-5-methyl-1-phenyl-1H-pyrazole was according to the literature procedure. All other chemicals used in this study were commercially available.
Synthesis of 4-acetyl-5-bromomethyl-1-phenyl-1H-pyrazole (1). To a solution of 4-acetyl-5-methyl-1-phenyl-1H-pyrazole (2.00 g, 10.0 mmol) in carbon tetrachloride (200 mL) containing azodiisobutyronitrile (AIBN) (150 mg, 0.91 mmol) was added N-bromosuccinimide (NBS) (1.78 g, 10.0 mmol) and refluxed for 4 h. After the reaction mixture was cooled, it was diluted with water (50 mL). The extract was dried over sodium sulfate and evaporated in vacuo to leave a residue which was recrystallized from propan-2-ol to give 1 (2.56 g, 92%). Red needles. Mp 152-154°C; IR (KBr, cm⁻¹): ν 1654 (C=O).

1H NMR (CDCl₃): δ 2.68 (s, 3H), 3.43 (s, 2H), 7.59-7.67 (m, 3H), 7.73-7.76 (m, 2H), 9.03 (s, 1H).


General procedure for the synthesis of pyrazolo[4,3-c]pyridine under conventional conditions. To a solution of 4-acetyl-5-bromomethyl-1-phenyl-1H-pyrazole (1) (279 mg, 1.0 mmol) in DMF (20 mL) was added salicylonitrile (2) (2-mercaptobenzonitrile (3) or 3-cyanopyridine-2(1H)-thiones (4)) (1.0 mmol) and cesium carbonate (651 mg, 2.0 mmol). The mixture was heated at 100 °C for appropriate time as shown in Table 2. After the reaction mixture was then cooled to rt, and then diluted with water (20 mL). The solid was filtered and recrystallized from HOAc to afford the corresponding products 5a-h.

4-Methyl-1-phenyl-1H-benzofuro[3,2-b]pyrazolo[5,4-d]pyridine (5a): Red needles. Mp > 300 °C; 1H NMR (CF₃CO₂D): δ 3.30 (s, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.66-7.68 (m, 4H), 7.72-7.80 (m, 3H), 8.17 (d, J = 8.0 Hz, 1H), 9.12 (s, 1H). 13C NMR (CF₃CO₂D): δ 16.3, 117.2, 117.3, 121.3, 123.1, 126.0, 126.4, 126.7, 130.0, 130.7, 131.8, 134.8, 135.2, 138.2, 138.7, 139.8, 151.8. Anal. Calcd for C₁₉H₁₃N₃O: C 76.24, H 4.38, N 14.04. Found: C 76.31, H 4.40, N 14.07.

4,7-Dimethyl-1-phenyl-1H-benzofuro[3,2-b]pyrazolo[5,4-d]pyridine (5b): Red needles. Mp > 300 °C; 1H NMR (CF₃CO₂D): δ 2.46 (s, 3H), 3.32 (s, 3H), 7.50 (s, 1H), 7.63-7.65 (m, 3H), 7.70-7.81 (m, 3H), 8.15 (d, J = 8.0 Hz, 1H), 9.15 (s, 1H). 13C NMR (CF₃CO₂D): δ 16.6, 23.4, 116.2, 117.0, 121.2, 123.1, 126.1, 126.3, 126.7, 130.3, 130.7, 131.5, 134.2, 135.0, 138.5, 138.9, 139.7, 151.5. Anal. Calcd for C₂₀H₁₅N₃O: C 76.66, H 4.82, N 13.41. Found: C 76.72, H 4.93, N 13.45.

4-Methyl-7-methoxy-1-phenyl-1H-benzofuro[3,2-b]pyrazolo[5,4-d]pyridine (5c): Red needles. Mp > 300 °C; 1H NMR (CF₃CO₂D): δ 3.36 (s, 3H), 3.98 (s, 3H), 7.28 (s, 1H), 7.60-7.66 (m, 3H), 7.76-7.84 (m, 3H), 8.24 (d, J = 8.0 Hz, 1H), 9.19 (s, 1H). 13C NMR (CF₃CO₂D): δ 23.2, 54.7, 115.4, 116.5, 121.9, 123.8,
126.0, 126.3, 126.6, 130.1, 130.9, 131.4, 134.6, 135.7, 138.5, 138.3, 139.2, 153.2. Anal. Calcd for C_{20}H_{15}N_{3}O_{2}: C 72.94, H 4.95, N 12.76. Found: C 73.02, H 4.97, N 12.80.

7-Chloro-4-methyl-1-phenyl-1H-benzofuro[3,2-b]pyrazolo[5,4-d]pyridine (5d): Red needles. Mp > 300 °C; ^1H NMR (CF_3CO_2D): δ 3.36 (s, 3H, CH_3), 7.28 (s, 1H), 7.62-7.68 (m, 3H), 7.74-7.82 (m, 3H), 8.31 (d, J = 8.0 Hz, 1H), 9.21 (s, 1H). ^13C NMR (CF_3CO_2D): δ 23.7, 116.1, 116.9, 120.8, 122.7, 125.7, 126.1, 126.8, 130.4, 130.8, 131.4, 134.8, 135.5, 135.8, 137.9, 139.4, 153.6. Anal. Calcd for C_{19}H_{12}ClN_{3}O: C 68.37, H 3.62, N 12.59. Found: C 68.42, H 3.67, N 12.63.

4-Methyl-1-phenyl-1H-benzothieno[3,2-b]pyrazolo[5,4-d]pyridine (5e): Red needles. Mp > 300 °C; ^1H NMR (CF_3CO_2D): δ 3.32 (s, 3H), 7.62-7.71 (m, 6H), 7.74-7.76 (m, 1H), 7.88 (d, J = 7.6 Hz, 1H), 8.44 (d, J = 7.6 Hz, 1H), 9.07 (s, 1H). ^13C NMR (CF_3CO_2D): δ 16.8, 117.1, 119.2, 123.4, 125.7, 127.6, 130.1, 132.7, 133.4, 134.1, 138.7, 139.7, 140.9, 144.2, 150.9, 156.5. Anal. Calcd for C_{19}H_{13}N_{3}S: C 72.36, H 4.15, N 13.32. Found: C 72.42, H 3.67, N 12.63.

4-Methyl-1-phenyl-1H-pyrido[2',3':5,4']thieno[3,2-b]pyrazolo[5,4-d]pyridine (5f): Red needles. Mp > 300 °C; ^1H NMR (CF_3CO_2D): δ 3.36 (s, 3H), 7.58-7.68 (m, 2H), 7.70-7.72 (m, 2H), 7.77 (t, J = 7.6 Hz, 1H), 8.22-8.25 (m, 1H), 9.13-9.14 (m, 1H), 9.17 (s, 1H), 9.71 (d, J = 8.0 Hz, 1H). ^13C NMR (CF_3CO_2D): δ 20.2, 115.2, 119.2, 126.7, 127.4, 128.2, 128.9, 129.2, 130.4, 131.1, 135.1, 140.0, 150.3, 157.3, 158.6. Anal. Calcd for C_{18}H_{12}NaS: C 68.33, H 3.82, N 17.71. Found: C 68.40, H 3.85, N 17.75.

4,8-Dimethyl-1-phenyl-1H-pyrido[2',3':5,4']thieno[3,2-b]pyrazolo[5,4-d]pyridine (5g): Red needles. Mp > 300 °C; ^1H NMR (CF_3CO_2D): δ 2.91 (s, 3H), 3.28 (s, 3H), 7.51-7.71 (m, 5H), 7.93-7.94 (m, 1H), 9.08 (m, 1H), 9.41-9.45 (m, 1H). ^13C NMR (CF_3CO_2D): δ 16.8, 19.4, 116.1, 119.0, 124.6, 124.9, 125.7, 130.5, 132.6, 133.6, 134.2, 138.8, 139.7, 140.0, 150.3, 156.2, 158.9. Anal. Calcd for C_{19}H_{14}NaS: C 69.07, H 4.27, N 16.96. Found: C 69.11, H 4.32, N 17.04.

4,6,8-Trimethyl-1-phenyl-1H-pyrido[2',3':5,4']thieno[3,2-b]pyrazolo[5,4-d]pyridine (5h): Red needles. Mp > 300 °C; ^1H NMR (CF_3CO_2D): δ 2.80 (s, 3H), 3.21 (s, 3H), 3.29 (s, 3H), 7.46-7.68 (m, 6H), 9.03-9.06 (m, 1H). ^13C NMR (CF_3CO_2D): δ 17.8, 18.9, 20.4, 110.0, 116.1, 118.7, 123.9, 125.9, 126.3, 130.5, 132.7, 134.1, 138.7, 139.8, 150.2, 156.2, 156.6, 157.4. Anal. Calcd for C_{20}H_{16}NaS: C 69.74, H 4.68, N 16.27. Found: C 69.79, H 4.72, N 16.32.

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