SYNTHESIS AND STRUCTURAL ANALYSIS OF NOVEL ISOMERIC AMIDINO-SUBSTITUTED 2-AMINOPHENOLS

Lucija Ptiček, Mario Cetina, Marija Mudrešić, Livio Racané

Department of Applied Chemistry, Faculty of Textile Technology, University of Zagreb, Prilaz baruna Filipovića 28a, 10000 Zagreb, Croatia
Contents

• Amidines
• Background (benzothiazoles)
• Synthetic approach (benzoxazoles)
• Synthesis of isomeric 2-aminophenols

• Pinner reaction
• Amidine synthesis
• X-ray crystal analysis
• Further research and goals

25th Croatian meeting of chemists and chemical engineers, Poreč, 2017.
Amidines (Am)

• Nitrogen analogues of carboxylic acids
• Strong organic bases
• Protonated at physiological pH value (7.4)
• Acyclic and cyclic
• Unsubstituted, N- or N’-substituted, N,N’-disubstituted, N,N- disubstituted, N,N,N’-trisubstituted, N,N,N’,N’-tetrasubstituted cation
Background

• Interesting due to their potential for diverse pharmaceutical uses
• Substituted benzothiazoles are associated with antimicrobial, antifungal and antitumor activity
• Amidines are often a part of important medical and biochemical agents


25th Croatian meeting of chemists and chemical engineers, Poreć, 2017.
Background

- Antiproliferative effect of compounds 3a – 3f on growth of tumor cells in vitro.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Cell lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>IC_{50}^{\mu M}</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;100</td>
</tr>
<tr>
<td>3c</td>
<td>3.07</td>
</tr>
<tr>
<td>3d</td>
<td>&gt;100</td>
</tr>
<tr>
<td>3e</td>
<td>30.9</td>
</tr>
<tr>
<td>3f</td>
<td>10.14</td>
</tr>
</tbody>
</table>

Synthetic approach – amidino-substituted benzoxazoles

- Efficient general method for benzoxazole preparation?
- Condensation reaction of amidino-substituted 2-aminophenols with aldehydes, carboxylic acids and carboxylic acid derivatives

\[
\text{Ar} \left[ \begin{array}{c} \text{O} \\ X \end{array} \right]_{n=1-2} + \text{N} \left[ \begin{array}{c} \text{O} \\ \text{H}_2\text{N} \\ \text{AmH} \end{array} \right] \xrightarrow{} \text{Ar} \left[ \begin{array}{c} \text{O} \\ \text{N} \text{AmH} \end{array} \right]_{n=1-2}
\]

\(X = \text{H, OH, Cl}\)
Synthesis of isomeric cyano-substituted 2-aminophenols

25th Croatian meeting of chemists and chemical engineers, Poreč, 2017.
Pinner reaction

- Partial solvolysis of a nitrile to yield an imidate (imino ether) by acid catalyzed addition of alcohol to nitrile
- Treatment of nitrile with gaseous hydrochloride acid in a mixture of anhydrous alcohol produces the hydrochloride salt of an imidate
- Pinner salts can react with various nucleophiles
Pinner reaction: step I

3a

\[ \text{NC} - \text{C} - \text{OH} \xrightarrow{\text{R-OH/HCl(g) r.t.}} \text{Cl} - \text{N}^+ - \text{H}_2\text{N} - \text{Cl} \]

\[ 4a^1 - 4a^3 \]

3b

\[ \text{NC} - \text{C} - \text{OH} \xrightarrow{\text{R-OH/HCl(g) r.t.}} \text{Cl} - \text{C} - \text{NH}_2 \]

\[ 4b^1 - 4b^3 \]

\[ R^1 = -\text{CH}_2\text{CH}_2\text{OCH}_3 \]

\[ R^2 = -\text{CH}_3 \]

\[ R^3 = -\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_3 \]

3c

\[ \text{O} - \text{N} - \text{NH}_2 \xrightarrow{\text{R-OH/HCl(g) r.t.}} \text{Cl} - \text{N}^+ - \text{H}_2\text{N} - \text{Cl} \]

\[ 4c^1 - 4c^2 \]

25th Croatian meeting of chemists and chemical engineers, Poreč, 2017.
Pinner reaction: step II from 2-amino-4-cyanophenol

\[ R-\text{NH}_2 + \begin{array}{c} \text{HO-} \\ \text{Cl} \text{H}_2\text{N} \end{array} \times \text{NH}_2 \times \text{Cl} \times \text{O} \text{EtOH abs.} \text{reflux 2 - 4 h} \rightarrow \begin{array}{c} \text{O} \\ \text{H}_2\text{N} \end{array} \times \text{HAm} \]

5a-f

5a; R = H
5b; R = \[ \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array} \]
5c; R = \[ \begin{array}{c} \text{NH}_2 \\ \text{NH}_2 \end{array} \]
5d; R = \[ \begin{array}{c} \text{NH} \\ \text{NH} \end{array} \]
5e; R = \[ \begin{array}{c} \text{Ph} \\ \text{H}_2\text{N} \end{array} \]
5f; R = \[ \begin{array}{c} \begin{array}{c} \text{Ph} \\ \text{H}_2\text{N} \end{array} \end{array} \]

6a-f

6a; Am = \[ \begin{array}{c} \text{NH}_2 \\ \text{NH} \end{array} \]
6b; Am = \[ \begin{array}{c} \text{NH}_2 \\ \text{NH} \end{array} \]
6c; Am = \[ \begin{array}{c} \text{NH} \\ \text{NH} \end{array} \]
6d; Am = \[ \begin{array}{c} \text{NH} \\ \text{NH} \end{array} \]
6e; Am = \[ \begin{array}{c} \text{NH} \\ \text{Ph} \end{array} \]
6f; Am = \[ \begin{array}{c} \text{NH} \\ \text{Ph} \end{array} \]
Pinner reaction: step II from 2-amino-4-cyanophenol

25th Croatian meeting of chemists and chemical engineers, Poreč, 2017.
Pinner reaction: step II from 2-amino-5-cyanophenol

\[
R\cdot\text{NH}_2 + \text{Cl}^- \text{Cl}^- \text{H}_3\text{N}^+ \xrightarrow{\text{EtOH abs. reflux 2 - 4 h}} \text{HAm}^+ \]

5a-f

5a; R = H
5b; R = \begin{array}{c} \text{CH}_3 \\ \text{CH}_3 \end{array}
5c; R = \text{NH}_2
5d; R = \text{NH}_2

7a-d

7a; Am = \begin{array}{c} \text{NH} \\ \text{NH} \end{array}
7b; Am = \begin{array}{c} \text{NH} \\ \text{NH} \end{array}
7c; Am = \begin{array}{c} \text{N} \\ \text{N} \end{array}
7d; Am = \begin{array}{c} \text{N} \\ \text{N} \end{array}

25th Croatian meeting of chemists and chemical engineers, Poreč, 2017.
X – ray structural analysis

- **7d**: zwitterionic form
- **6g**: mesylate salt form

<table>
<thead>
<tr>
<th>Selected bonds</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7d</td>
</tr>
<tr>
<td>C7 – N2</td>
<td>1.322 (3)</td>
</tr>
<tr>
<td>C7 – N3</td>
<td>1.322 (3)</td>
</tr>
<tr>
<td>C1 – O1</td>
<td>1.303 (3)</td>
</tr>
</tbody>
</table>
Current research and goals

• Preparation of isomeric amidino-substituted benzoxazole derivatives by condensation reaction in PPA and investigation of their biological activity

\[
\text{Ar} \left[ \begin{array}{c} \text{O} \\ \text{COH} \end{array} \right]_{n=1-2} + \text{AmH} \rightarrow \text{PPA} \rightarrow \text{Ar} \left[ \begin{array}{c} \text{O} \\ N \end{array} \right]_{n=1-2}
\]

Am = a, b, c, d, e, f, g

a, b, c, d, e, f, g

25th Croatian meeting of chemists and chemical engineers, Poreč, 2017.
Thank you for your attention!

This work was funded by the Croatian Science Foundation (project HRZZ-5596).