PREPARATION OF SOME NEW SCHIFF BASES FROM 5-NITROVANILLIN

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ABSTRACT

A series of Schiff bases were synthesized successfully based on the condensation reaction between 5-nitrovanillin and aromatic amines in moderate and high yields. The condensation underwent better in DCM solvent, acetic acid catalyst and anhydrous MgSO$_4$ as a drying agent and increased the yield up to 100 %. These new Schiff bases were determined with $^1$H, $^{13}$C NMR spectral analysis and compound 3a was studied further HSQC, HMBC, NOSY and MS spectra. The C=N bond exists in E conformation.

Keywords: antibacterial activity, nitrovanillin, Schiff base, vanillin.

1. Introduction

Schiff bases are characterized by the -N=CH- (imine) group which imports in elucidating the mechanism of transamination and racemization reaction in biological system [1, 2]. Schiff bases are active against a wide range of organisms for example; Candida Albicans, Escherichia coli Staphylococcus aureus, Bacillus polymxa, Trychophyton gypseum, Mycobacteria, Erysiphe graminis and Plasmopora viticola. To increase the bioactive properties, Schiff bases worked as ligands in complexes with metals showing the remarkably bioactive activities [3]. Metal-imine complexes have been widely investigated due to antitumor and herbicidal use. They can work as models for...
biologically important species [4]. Exploration and development of more effective antifungal agents is necessary, and the individual Schiff bases are considered to be promising antifungal medicines [5], [6].

Nitro aromatic compounds have been considered recently. For example, pyrrolnitrin and chloramphenicol are antibiotics; 1-nitroaknadine and aristolochic acid are natural products that are metabolites. Nitrofen is a pesticide while the 3-nitrotyrosine works as a signaling molecule [6].

![Chemical structures of various compounds](image)

**Figure 1. Some examples of nitro aromatic compounds**

B. R. Thorat et al. [7] reported a series of Schiff bases of 5-nitrovanillin but did not test any of their bioactivities. In Vietnam, Schiff bases of 5-nitrovanillin were investigated in 1999 [8], and showed considerable biological activities; however, some Schiff bases of 5-nitrovanillin have not been tested yet. In this paper, taking advantages of Schiff bases and nitroaromatic compounds, the combination of imine group and nitroaromatic compounds is not only hope to increase their bioactive properties but also provide good sources for synthesis of secondary amines, oxazolidine and others, Figure 1.

2. Content

2.1. Experimental section

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck were used as received, unless indicated. The $^1$H NMR and $^{13}$C NMR spectra were recorded on the Bruker Avance 500 NMR spectrometer in deuterated solvents. Chemical-shift data for each signal was reported in ppm units. Mass spectra were obtained from Mass Spectrometry.
Facility of The Vietnam Academy of Science and Technology on LC-MSD-Trap-SL spectrometer. Ethanol was redistilled after drying.

2.2. Synthetic procedure

Synthesis of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (2) [7,9]

Concentrated HNO$_3$ (2 mL) was carefully added to a cooled (5 °C) solution of vanillin (5 g, 33 mmol) and acetic acid (50 mL) over a period of 30 min. The gold colored precipitate that formed was filtered, washed with water, and allowed to dry (5.21 g, 80%): mp. 171 °C. $^1$H-NMR (CDCl$_3$, 500 MHz) $\delta$ (ppm): 9.87 (s, 1H), 8.1 (d, $J$ = 2.0 Hz, 1H), 7.6 (d, $J$ = 2.0 Hz, 1H), 3.96 (s, 3H). $R_f$ = 0.2 (n-hexan/ethyl acetate = 2/1).

2.2.2. Synthesis of Schiff bases

General procedure:

Method 1: To a solution of 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and amine (2.5 mmol) in absolute ethanol (10 mL) was added 2-3 drops of glacial acetic acid. The mixture was refluxed for 5-20 h. The progress of reaction was monitored with thin layer chromatography (TLC). After reaction completion, the mixture was concentrated and then added water (20 mL). The precipitate was filtered and washed well with water and cold ethanol. Re-crystallization in ethanol gave pure enough product for next reaction.

Method 2: To a solution of 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol), anhydrous magnesium sulfate (10 mmol, 1.2 g) and amine (2.5 mmol) in DCM (10 mL) was added 2-3 drops of glacial acetic acid. The mixture was refluxed for 2 h. Then filtration was used to get rid of MgSO$_4$. The mother liquid was washed with 3% HCl (5 mL x 3), dried over with Na$_2$SO$_4$ and then concentrated in vacuo. The title products were purified with flash column chromatography in eluent n-hexan and ethyl acetate (1/1).

Synthesis of 2-methoxy-4-[(E)-(naphthalen-1-ylimino)methyl]-6-nitrophenol (3a)

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 1-naphthylamine (2.5 mmol, 0.36 g, 143 g/mol) gave 3a as a redish brown powder (0.53 g, 82 %, 322 g/mol): m.p = 182 °C; $R_f$ = 0.73 (n-hexan/ethyl acetate = 2/1).

Synthesis of 2-methoxy-4-[(E)-(naphthalen-2-ylimino)methyl]-6-nitrophenol (3b)

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 2-naphthylamine (2.5 mmol, 0.36 g, 143 g/mol) gave 3b as a reddish brown powder (0.49 g, 76 %, 322 g/mol): m.p = 185 °C; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ (ppm): 11.07 (s, br, 1H), 8.42 (s, 1H), 8.28 (m, 1H), 8.04 (d, $J$ = 1.5 Hz, 1H), 8.00 (d, $J$ = 1.0 Hz, 1H), 7.85 (m, 1H), 7.73 (d, $J$ = 8.5 Hz, 1H), 7.52 (t, $J$ = 9.0 Hz, 2H), 7.45 (t, $J$ = 8.0 Hz, 1H), 7.03 (d, $J$ = 7.5 Hz, 1H), 4.06 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ (ppm): 157.3, 150.6, 149.0, 148.3, 134.0, 133.6, 128.6, 128.1, 127.7, 126.5, 126.3, 126.1, 125.9, 123.6, 118.6, 114.5, 112.8, 56.9. $R_f$ = 0.75 (n-hexan/ethyl acetate = 2/1).
Synthesis of 2-methoxy-6-nitro-4-[(E)-(4-hydroxyphenylimino)methyl]phenol (3c)

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 4-hydroxyaniline (2.5 mmol, 272 mg, 109 g/mol) gave 3c as a dark yellow powder (0.35 g, 78 %, 228 g/mol): m.p = 190 °C; \(^1\)H-NMR (CDCl\(_3\), 500 MHz) \(\delta\) (ppm): 9.60 (s, 1H), 8.59 (s, 1H), 8.05 (s, 1H), 7.66 (s, 1H), 7.25 (d, \(J = 8.5\) Hz, 2H), 6.82 (d, \(J = 8.5\) Hz, 2H), 3.90 (s, 3H); \(^1^3\)C-NMR (CDCl\(_3\), 125 MHz) \(\delta\) (ppm): 157.4, 150.6, 149.0, 148.2, 134.3, 133.2, 125.3, 119.8, 117.5, 116.5, 114.3, 56.8. \(R_f = 0.8\) (n-hexan /ethyl acetate = 2/1).

Synthesis of 4-[(E)-(2-hydroxyphenylimino)methyl]-2-methoxy-6-nitrophenol (3d)

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 2-hydroxyaniline (2.5 mmol, 0.3 g, 123 g/mol) gave 3d as a dark yellow powder (0.37 g, 62 %, 302 g/mol): m.p = 168 °C; \(^1\)H-NMR (DMSO, 500 MHz) \(\delta\) (ppm): 8.62 (d, \(J = 1.5\) Hz, 1H), 8.06 (d, \(J = 1.5\) Hz, 1H), 7.69 (s, 1H), 7.34 (d, \(J = 9.0\) Hz, 2H), 7.01 (d, \(J = 9.0\) Hz, 2H), 3.92 (s, 3H), 3.78 (s, 3H). \(^1^3\)C-NMR (CDCl\(_3\), 125 MHz) \(\delta\) (ppm): 158.7, 154.9, 152.8, 150.5, 148.7, 143.8, 139.9, 133.6, 128.3, 122.2, 118.2, 116.4, 114.8, 114.5, 114.2, 56.9, 55.7, 55.5. \(R_f = 0.8\) (n-hexan /ethyl acetate = 2/1).

Synthesis of 4-[(E)-(4-methoxyphenylimino)methyl]-2-methoxy-6-nitrophenol (3e)

Following the general procedure of method 2, using 5-nitrovanillin (0.34 g, 2 mmol, 152 g/mol) and 4-methoxyaniline (2.5 mmol, 0.27 g, 109 g/mol) gave 3e as a dark yellow powder (0.38 g, 67 %, 288 g/mol): m.p = 172 °C; \(^1\)H-NMR (CDCl\(_3\), 500 MHz) \(\delta\) (ppm): 8.60 (s, 1H), 8.08 (d, \(J = 2.0\) Hz, 1H), 7.82 (d, \(J = 2.0\) Hz, 1H), 7.27 (dd, \(J = 8.5, 1.5\) Hz, 1H), 7.22 (td, \(J = 8.0, 1.5\) Hz, 1H), 7.03 (br, 1H), 7.03 (dd, \(J = 8.0, 2.0\) Hz, 1H), 6.92 (td, \(J = 8.5, 1.0\) Hz, 1H), 4.05 (s, 3H). \(^1^3\)C-NMR (CDCl\(_3\), 125 MHz) \(\delta\) (ppm): 154.4, 152.1, 150.7, 149.1, 134.9, 133.7, 129.5, 127.5, 120.3, 118.6, 116.4, 115.3, 114.2, 56.9; \(R_f = 0.7\) (n-hexan /ethyl acetate = 2/1).

3. Results and Discussion

3.1. Synthesis

The five Schiff bases were synthesized successfully shown in the Scheme 1. These compounds were checked on Scifinder in the Leuven University (Belgium).
First of all, vanillin (1) was nitrated in cold condition and mixture reagent of HNO₃ and H₂SO₄ giving 5-nitro vanillin in 80 %. This compound was checked with ¹H NMR spectrum. Then, 5-nitro vanillin was condensed with aromatic amine gave Schiff bases 3a, 3b, 3c, 3d and 3e in moderate and good yield. Since they have long conjugation system, they are darkish yellow. The traditional method (method 1) gave yield lower than 50%. We also tried condition including MgSO₄ in DCM without acetic acid gave low yield too. Method 2 using MgSO₄ (5 eq.) and 1 drop of acetic acid was the best in our cases. In aniline case, the yield was about 100%, other cases their yields were 60 ÷ 85 %. The unreacted amine was washed with 3% HCl. Therefore, after work up the crude products can be used for next step without further purification.

3.2. Structure determination

To understand the structures of these Schiff bases, compound 3a, one of the most complicated compounds, was chosen to study ¹H NMR, ¹³C NMR, HMBC and MS spectra. First of all, the negative mass spectrum showed a base pick at m/z 321 au and the positive mass spectrum showed a peak at m/z 323 au. That indicated the molecular weight of compound 3a must be 322 g/mol matching with the designed product, expectedly, Figure 2.
Figure 2. Part of HMBC and MS spectra of compound 3a

Secondly, retention factor of compound 3a was much bigger than that of 5-nitrovanillin (2) (see experimental section). In addition, melting points of all Schiff bases were higher than that of 5-nitrovanillin due to molecular mass increased. Thirdly, \(^1\)H NMR spectrum of compound 3a indicated 14 protons including a broaden proton at \(\delta 11.08\) ppm was for H (OH), at \(\delta 8.48\) ppm for H8 and 3 protons at \(\delta 4.09\) ppm for H7. There were two doublet of doublet peaks at \(\delta 8.29\) and 7.86 ppm for either H16 or H15. There were doublet peaks at \(\delta 8.08\) and 8.03 ppm with splitting constant about 1.0 ± 2.0 Hz which were for H2 or H6. Another pair of doublets was at \(\delta 7.74\) ppm and \(\delta 7.04\) ppm with splitting constant about 8.5 Hz that must be for H10 or H12. A unique triplet at \(\delta 7.46\) ppm was H11 due to their ortho position of both H10 and H12. Unfortunately, H14 and H17 overlapped each other giving a multiplet although each was a doublet of doublet peak. \(^{13}\)C NMR spectrum of compounds 3a indicated 18 peaks associated with 18 carbon atoms. Certainly, peak at \(\delta 56.9\) ppm was assigned for C7. Others carbons were not identified on the \(^{13}\)C NMR spectrum. The HSQC cross peaks show the carbons bearing protons that combined with the HBMC cross peaks; therefore, all carbons and protons were assigned as shown in Table 1 and Figure 2. For instance, H7 had a cross peak with C3 that had a weak cross peak with H2 indicating the assignment of H2 from H6. Another example is that H10 and H12 were the doublet but H10 had a cross peak with C8 that bound the proton at \(\delta 8.45\) ppm.
Table 1. NMR spectral analysis of compound 3a (ppm, Hz)

<table>
<thead>
<tr>
<th>1H NMR</th>
<th>13C NMR</th>
<th>HSQC</th>
<th>HMBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>- -</td>
<td></td>
<td>C1 133.6</td>
<td>- C1xH2</td>
</tr>
<tr>
<td>H2 8.08 (d, J=1.5 Hz, 1H)</td>
<td>C2 118.6</td>
<td>H2xC2 118.6</td>
<td>H2xC6,  C4, C5, C3</td>
</tr>
<tr>
<td>- -</td>
<td></td>
<td>C3 150.7</td>
<td>- C3xH7</td>
</tr>
<tr>
<td>- -</td>
<td></td>
<td>C4 149.0</td>
<td>- C4xH2, H6</td>
</tr>
<tr>
<td>- -</td>
<td></td>
<td>C5 157.3</td>
<td>- C5xH2, H6</td>
</tr>
<tr>
<td>H6 8.03 (d, J=1.0 Hz, 1H)</td>
<td>C6 114.6</td>
<td>H6xC6 114.6</td>
<td>H6xC2, C4, C5</td>
</tr>
<tr>
<td>H7 4.09 (s, 3H)</td>
<td>C7 56.9</td>
<td>H7xC7 56.9</td>
<td>H7xC3,  C7x-</td>
</tr>
<tr>
<td>H8 8.45 (s, 1H)</td>
<td>C8 128.1</td>
<td>H8xC8 128.1</td>
<td>H8xC6, C2, C9,</td>
</tr>
<tr>
<td>- -</td>
<td></td>
<td>C9 148.4</td>
<td>- C9xH8, H11</td>
</tr>
<tr>
<td>H10 7.04 (d, J=8.5 Hz, 1H)</td>
<td>C10 126.5</td>
<td>H10xC10 126.5</td>
<td>H10xC12, C18</td>
</tr>
<tr>
<td>H11 7.46 (t, J=8.0 Hz, 1H)</td>
<td>C11 127.7</td>
<td>H11xC11 127.7</td>
<td>H11xC13, C9</td>
</tr>
<tr>
<td>H12 7.74 (d, J=7.5 Hz, 1H)</td>
<td>C12 112.8</td>
<td>H12xC12 112.8</td>
<td>H12xC14, C18</td>
</tr>
<tr>
<td>- -</td>
<td></td>
<td>C13 134.0</td>
<td>- C13xH11</td>
</tr>
<tr>
<td>H14 7.52 (m, 1H)</td>
<td>C14 126.3</td>
<td>H14xC14 126.3</td>
<td>H14x-C14xH16</td>
</tr>
<tr>
<td>H15 7.86 (dd, J=7.0, 2.0 Hz, 1H)</td>
<td>C15 125.9</td>
<td>H15xC15 125.9</td>
<td>H15xC17</td>
</tr>
<tr>
<td>H16 8.29 (dd, J=7.0, 2.5 Hz, 1H)</td>
<td>C16 123.6</td>
<td>H16xC16 123.6</td>
<td>H16xC14</td>
</tr>
<tr>
<td>H17 7.52 (m, 1H)</td>
<td>C17 126.0</td>
<td>H17xC17 126.0</td>
<td>H17x-C17xH15</td>
</tr>
<tr>
<td>- -</td>
<td></td>
<td>C18 128.6</td>
<td>- C18xH10, H12</td>
</tr>
<tr>
<td>H(O) 11.08 (br, s, 1H),</td>
<td>- -</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NMR spectral analysis of other compounds 3b, 3c, 3d and 3e was shown in the experimental section. All agreed with the expected products. Interestingly, compound 3d was observed the tautomerization around the imine bond in CDCl₃; consequently, 13C NMR spectrum was more complicated. Changing to DMSO solvent reduced that observation as shown.
In order to confirm E-conformation of the Schiff bases, NOSY spectrum of compound 3a was studied, Figure 3 and Figure 4. It was found that the conformation of 3a must be the E-3a. Because the cross peak a showed the H8 and H10 that were close to each other. In addition, the cross peak b improved that distance between H8 and H2 in space are short enough (see E-3a, in Figure 4). Interestingly, there were no data to see the naphthyl group flipped over to have a cross peak of H17 and H8 in the case of E-3a' in the NOSY spectrum.

Figure 3. A part of NOSY NMR spectrum of compound 3a

Figure 4. Some examples of E and Z conformations around C=N bond
4. Conclusion

Five new Schiff bases were synthesized by condensation reaction between 5-nitrovanillin and aromatic amines. The modification method of condensation reaction including drying reagent anhydrous MgSO$_4$, catalysis acetic acid in dry DCM was used to give high yield. Structures of Schiff bases were determined with spectroscopy methods such as NMR and MS. E conformation of C=N bond was determined with NOSY NMR spectrum.

REFERENCES


