1D AND 2D NMR STUDIES OF BENZYL O–VANILLIN

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ABSTRACT

The reaction of o–vanillin A with benzyl bromide B2 in acetone as the solvent and K2CO3 as a base in the presence of tetra–n–butylammonium iodide (TBAI) as catalyst formed benzyl o–vanillin, C. The complete assignments of C using PROTON, APT, DEPT–135, COSY, NOESY, HMQC and HMBC NMR in both CDCl3 and acetone–d6 are discussed, and the coupling constants J are reported in Hertz (Hz).

Keywords: 1H NMR; 13C NMR; 2D NMR; Benzyl o–Vanillin.

INTRODUCTION

The benzylolation of phenols and hydroxy benzaldehydes are early described, which it is called as Williamson reaction or Williamson ether synthesis [1–2]. It is used for a variety of heteroatomic functional groups as well as carbon nucleophiles, so this benzylolation is used to protect hydroxyl group. The benzylolation of o–vanillin A as phenol was chosen because of his high industrial, biological and pharmaceutical importance. Zaugg et al studied inhibition of sickle haemoglobin cells in whole blood by react the vanillins with amino groups of intracellular haemoglobin, which they found o–vanillin A significantly inhibit sickling at reduced partial pressures of oxygen [3]. Additionally, o–vanillin A and hydroxy benzaldehydes are extensively used as raw material to synthesized pancratistatin [4], coumarin[5], neoignan [6], EUK–8, EUK–134, JD–29 [7–9], narciclasine [9–10], aromatic C–ring in taxane [11], and albendazole derivatives [12], which have highly biological active. It is reported that the o–vanillin A induced mutations and it has also enhanced the chromosomal aberrations in vitro systems [13].

2–Benzyloxy–3–methoxybenzaldehyde or Benzyl o–vanillin C was early prepared [14–19] (Scheme 1), which it is used as a key for synthesizing a new anticancer drugs [16], and it is evaluated as anticancer drug against HL–60 cells [19]. In view of its importance, we have recently reported the crystal structure of C, determined by X–ray crystallography [20–22]. In this work, we have reported the complete assignments of C using PROTON, APT, DEPT–135, COSY, HMQC and HMBC NMR in both CDCl3 and acetone–d6.

EXPERIMENTAL SECTION

All NMR experiments were performed on Bruker Avance 400 UltrasoundTM NMR for 1H operating at 400.123 MHz, and Avance 300 NMR spectrometers for 13C operating at 71.478 MHz in CDCl3 and acetone–d6 at 298 K using Bruker XWINNMR software equipped with a 5 mm BBI inverse gradient and QNP probe, respectively [23–24]. Chemical shifts were reported downfield in parts per million (ppm) from a tetramethylsilane (TMS) reference, and coupling constants (J) were measured in Hertz (Hz). The concentration of solute molecule was 100 mg in 1.0 ml CDCl3 or acetone–d6.

RESULT AND DISCUSSION

Benzyl o–vanillin C was prepared following several published methods (Scheme 1). Merz et al and Krohn et al reacts benzyl chloride B1 with

\[
\begin{align*}
\text{H}_2\text{C}–\text{O} & \text{H} \quad \text{B1} \quad \text{X} = \text{Cl} \quad \text{B2} \quad \text{X} = \text{Br} \\
\text{OH} & \quad \text{A} \quad \text{B} \\
\text{C} & \quad \text{i, ii, iii, iv or v} \\
\end{align*}
\]

Scheme 1 Reagents and conditions: i. B1, NaOH, DMSO, 20 °C, 8 hr; ii. B1, KOH, EtOH, refl., 12 hr; iii. B2, K2CO3, DMF, rt, 24 hr; iv. B1, K2CO3, KI, THF, refl., 6 hr; v. B2, K2CO3, TBAI, acetone, rt, 3.5 hr.

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Table 1 $^1$H and $^{13}$C NMR chemical shifts and coupling constants of C in CDC$_3$ and acetone-d$_6$.

<table>
<thead>
<tr>
<th>Atom</th>
<th>CDC$_3$ J (Hz)</th>
<th>$^1$H NMR (ppm)</th>
<th>acetone-d$_6$ J (Hz)</th>
<th>CDC$_3$</th>
<th>acetone-d$_6$</th>
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<tbody>
<tr>
<td>CHO</td>
<td>10.22, d</td>
<td>0.72</td>
<td>10.24, d</td>
<td>0.77</td>
<td>190.80</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>3.82, s</td>
<td>-</td>
<td>3.98, s</td>
<td>-</td>
<td>56.52</td>
</tr>
<tr>
<td>CH$_2$</td>
<td>5.12, s</td>
<td>-</td>
<td>5.23, s</td>
<td>-</td>
<td>76.78</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>130.74</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>151.48</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>153.47</td>
</tr>
<tr>
<td>4</td>
<td>7.10–7.08, dd</td>
<td>8.09, 1.88</td>
<td>7.30–7.28, dd</td>
<td>7.87, 1.66</td>
<td>118.43</td>
</tr>
<tr>
<td>5</td>
<td>7.06–7.02, td</td>
<td>7.78, 0.64</td>
<td>7.20–7.15, td</td>
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<td>7.83, 1.96</td>
<td>7.38–7.35, dd</td>
<td>7.87, 1.86</td>
<td>119.47</td>
</tr>
<tr>
<td>1'</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>136.77</td>
</tr>
<tr>
<td>2'</td>
<td>7.35–7.33, dd</td>
<td>7.49, 1.93</td>
<td>7.47–7.45, dd</td>
<td>7.78, 1.76</td>
<td>129.01</td>
</tr>
<tr>
<td>3'</td>
<td>7.31–7.28, t</td>
<td>6.33</td>
<td>7.39–7.34, t</td>
<td>7.41</td>
<td>129.08</td>
</tr>
<tr>
<td>4'</td>
<td>7.32–7.28, t</td>
<td>8.01</td>
<td>7.42–7.39, t</td>
<td>4.67</td>
<td>128.94</td>
</tr>
</tbody>
</table>

On the other hand, we prepared C by reacting benzyl bromide B2 with A in acetone as the solvent and K$_2$CO$_3$ as a base [20, 25]. As previous methods needed considerable time to achieve a good yield, therefore, TBAI was added in an attempt to accelerate the reaction. TBAI seemed to do the trick and proved to be an excellent catalyst for the reaction, whereby the reaction conducted at room temperature took only 3.5 hours with 99.6% yield [22, 25]. Furthermore, C was obtained as single crystals with melting point of 35–35.5°C [20–22], Figure 1.

The title compound C was used and confirmed in the solution state, the conventional 1D $^1$H NMR, $^{13}$C NMR, APT, DEPT–135 along with 2D COSY, HMOC and HMBC to assign all proton and carbon chemical shifts. The splitting patterns for the aromatic protons of C were obtained from spectra acquired using 400 MHz $^1$H NMR. The $^1$H and $^{13}$C NMR chemical shift and coupling constants data in CDC$_3$ and acetone–d$_6$ are points of 45–47°C. Recently, Berger performed similar reaction using benzyl bromide B2 in DMF and K$_2$CO$_3$ as the base [18]. Although the reaction can be done at room temperature, it took 24 hours to complete with 96% yield. However, the product was obtained as an oily liquid. Lin et al. yielded C as 89% by using B1 and A in THF under reflux for 6 hours, they used K$_2$CO$_3$ as a base and KI as catalyst, the melting points of 58–59°C [19].

Figure 1 The molecular structure of Benzyl α–vanillin C, showing 50% probability displacement ellipsoids and atomic number. The dashed lines indicate intramolecular hydrogen bonds.

α–vanillin A in DMSO at 20°C using NaOH as a base for 4–8 hours [14,17], while Proftt and Cotterell et al used KOH as a base and refluxing the mixture in EtOH for 12 hours, the melting point of C 45°C [15–16]. Both reactions produce 95% yield in powder form with melting

Table 2 $^1$H–$^1$H COSY and $^1$H–$^{13}$C HMOC NMR of C in CDC$_3$ and acetone–d$_6$.

<table>
<thead>
<tr>
<th>Atom</th>
<th>CDC$_3$ J (Hz)</th>
<th>$^1$H NMR (ppm)</th>
<th>acetone–d$_6$ J (Hz)</th>
<th>CDC$_3$</th>
<th>acetone–d$_6$</th>
</tr>
</thead>
<tbody>
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<td>CHO</td>
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<td>190.17</td>
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</tr>
<tr>
<td>CH$_3$</td>
<td>H$_3$</td>
<td>-</td>
<td>H$_4$</td>
<td>66.52</td>
<td>66.52</td>
</tr>
<tr>
<td>CH$_2$</td>
<td>CH$_2$, CHO</td>
<td>H$_2$, H$_6'$</td>
<td>76.78</td>
<td>76.49</td>
<td></td>
</tr>
<tr>
<td>H$_2$</td>
<td>CH$_3$</td>
<td>CH$_3$, H$_6$</td>
<td>118.43</td>
<td>119.12</td>
<td></td>
</tr>
<tr>
<td>H$_3$</td>
<td>CHO</td>
<td>CHO, H$_4$, H$_6$</td>
<td>124.67</td>
<td>125.09</td>
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<tr>
<td>H$_4$</td>
<td>x</td>
<td>H$_5$, CHO</td>
<td>119.47</td>
<td>119.19</td>
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</tr>
<tr>
<td>H$_5$</td>
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<td>CH$_2$, CHO</td>
<td>128.94</td>
<td>129.10</td>
<td></td>
</tr>
<tr>
<td>H$_6$</td>
<td>-</td>
<td>-</td>
<td>129.08</td>
<td>129.59</td>
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</tr>
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</table>

x: not clear observation.
The chemical structure and the NMR numbering scheme of Benzyl o-vanillin C are shown in Figure 2. The structure was further substantiated by complete $^1$H and $^{13}$C NMR assignments in both solvents, which have not been previously reported for C, using 2D NMR COSY, HMQC and HMBC experiments. Figure 2 shows the chemical structure and the NMR numbering scheme of C.

1D NMR spectra

$^1$H NMR spectra

The $^1$H NMR spectra in CDCl$_3$ and acetone–d$_6$ of C were obtained and shown in Figure 3. The $^1$H NMR spectrum in acetone–d$_6$ shows similar splitting patterns.

Figure 3 $^1$H NMR spectrum of C in a) CDCl$_3$ and b) in acetone–d$_6$. 

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as those in CDCl₃ except that all the peaks shifted to more downfield. However, in acetone–d₆ clearer splitting patterns are observed. In CDCl₃ the ¹H NMR spectrum shows the chemical shift of the aldehyde proton at δ = 10.22 ppm as a doublet, (J = 0.72 Hz). The doublet may be due to coupling of aldehyde proton with H₅, which it is in a long-range couplings or zigzag configuration [26]. On the benzyl ring, two H₂ protons exhibited a signal at δ = 7.35–7.33 ppm as doublet of a doublet, (J = 7.49 and 1.93 Hz). The signal for H₄ (δ = 7.42–7.39 ppm) was overlapped with that of H₅ and is not clearly shown, although in acetone–d₆, it appears as a triplet (J = 4.67 Hz). H⁶ exhibited a signal at δ = 7.39–7.34 ppm (J = 7.41 Hz) as a triplet which was shown clearly in acetone–d₆.

Meanwhile, H₆ appears as doublet of a doublet due to coupling with H₅ and H₄ (δ = 7.38–7.35 ppm, J = 7.87 and 1.86 Hz). On the trisubstituted ring, H₄ exhibited doublet of a doublet at δ = 7.10–7.08 ppm, (J = 8.09 and 1.88 Hz) due to coupling of the proton to H₅ and H₆. Finally, H₅ exhibited a signal at δ = 7.06–7.02 ppm as triplet of a doublet, (J = 7.78 and 0.64 Hz) in CDCl₃, and at δ = 7.20–7.15 ppm as triplet of a doublet, (J = 7.91 and 0.76 Hz) in acetone–d₆ which is more clearly observed in Figure 3(b). The protons on methylene group of benzyl ring and the methyl protons exhibited signals at δ = 5.12 and 3.82 ppm, respectively.

¹³C NMR spectra

The ¹³C NMR spectrum of C was obtained and shown in Figure 4. In CDCl₃, the peak appears at δ = 190.80 ppm in the ¹³C NMR spectrum of C was assigned to the C=O group, while the quaternary

![Figure 4 ¹³C NMR spectrum of C in a) CDCl₃ and b) in acetone–d₆.](image-url)
carbon signals were observed at $\delta = 153.47$, 151.48, 136.77 and 130.74 ppm for C$_5$, C$_2$, C$_3$, and C$_1$, respectively. Other aromatic carbon signals of benzyl ring were observed at $\delta = 129.08$, 129.01 and 128.94 ppm for C$_3$, C$_2$ and C$_4$, respectively, while C$_6$, C$_9$ and C$_4$ at the trisubstituted aromatic carbon showed signals at $\delta = 124.67$, 119.47 and 118.43 ppm, respectively. The $^{13}$C NMR spectrum also shows CH$_2$ signal at $\delta = 76.76$ ppm and 56.52 ppm for OMe. Similar to $^1$H NMR spectra, $^{13}$C NMR spectrum in acetone-$_{d_6}$ shows the values of carbons being shifted to about 0.16–1.05 ppm downfield with the exception of C$_6$. Attached proton test (APT) and DEPT-135 NMR experiments in both solvents were also performed to confirm our postulation. Further confirmation was done by HMBC experiments. Table 1 summarises the $^1$H and $^{13}$C NMR in both solvents.

2D NMR spectra

$^1$H–$^1$H COSY NMR
The signals of C are assigned with an aid by the Correlation spectroscopy or COSY experiment which is a homonuclear 2D technique that explains which pairs of $^1$H nuclei in a molecule are coupled to one another. Figure 5 shows the $^1$H–$^1$H COSY NMR spectrum of C. The COSY spectrum confirmed the correlation assignments in both solvents CDCl$_3$ and acetone–$d_6$ of H$_4$ with methoxy group OMe at $\delta = 3.82$ and 3.98 ppm, respectively. While the homonuclear connectivities observed between CH$_2$ with H$_2$ in the benzyl ring and the aldehydic proton. From both spectra it can be seen that the one of the methylene protons is correlated with H$_2$, probably because the proton is H–bonded to the O atom in OMe. However, the $^1$H NMR for methylene protons only show a singlet at $\delta = 5.12$ ppm, indicating the both protons are equivalent. We propose that the rapid movement at the methylene carbon cause this phenomena providing the interchange between the two protons.

$^1$H–$^{13}$C HMBC NMR
Heteronuclear multiple quantum coherence or the 2D HMBC NMR spectrum was conducted to determine which hydrogens are connected to which carbons. The HMBC NMR spectrum for C was shown in Figure 6, and it confirms the attachments between the aromatic hydrogens and their corresponding carbons. The signals owing to C$_4$, C$_6$, C$_5$, C$_2$, C$_4$, and C$_3$ atoms are observed at $\delta = 118.43$, 119.47, 124.67 and 128–130 ppm in CDCl$_3$, and at $\delta = 119.12$, 119.19, 125.09, 129.10, 129.23 and 129.59 ppm in acetone–$d_6$, respectively. The one bond $^{13}$C–$^1$H connectivities are also well observed for OMe and CH$_2$ atoms whereby the cross peaks appear at the respective $\delta = 56.52$ and 76.76 ppm in CDCl$_3$, and at $\delta = 56.52$ and 76.49 ppm in acetone–$d_6$.

Figure 5 $^1$H–$^1$H connectivities in the COSY a) in CDCl$_3$, b) in acetone–$d_6$ and c) the most important correlations observed in COSY spectrum of C.
Figure 6 $^1$H-$^{13}$C connectivities of C in the HMQC a) in CDCl$_3$ and b) in acetone-$d_6$.

Table 2 summarises the values of COSY and HMQC experiments in both CDCl$_3$ and acetone-$d_6$.

CONCLUSION

We have reported the complete assignments of Benzyl o–van C using $^1$H, $^{13}$C, COSY and HMQC NMR in both CDCl$_3$ and acetone-$d_6$. Attached proton test (APT) and DEPT–135 NMR experiments in both solvents were also performed to confirm our postulation although the results were not discussed here. Further reactions using the compound to synthesise biologically important compounds are in progress.

ACKNOWLEDGEMENT

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REFERENCES

Crystal data for C$_{13}$H$_{14}$O$_3$, $M = 242.26$, monoclinic, space group $P2_1/c$, $a = 13.7203(3)$ Å, $b = 4.6599(10)$ Å, $c = 19.1552(5)$ Å, $\beta = 97.736(1)^\circ$, $V = 1213.55(5)$ Å$^3$, $Z = 4$, $D_c = 1.326$ g cm$^{-3}$, $\mu$ (Mo-K$\alpha$) = 0.092 mm$^{-1}$, $F(000) = 512$, $T = 297$ K, 3905 independent reflections. Data were collected on Bruker SMART APEX2 CCD area detector using o-scans [27], and the non-hydrogen atoms were refined anisotropically using full matrix least squares based on $F^2$ to give $R_1 = 0.0514$, $wR_2 = 0.1878$ for 2949 independent observed reflections ($F^2 > 2\sigma (F^2)$, $2\theta = 31.2^\circ$) and 164 parameters. The structure was solved and refined by SHELXTL against $F^2$ [28]. The software was used SHELXTL [28] and PLATON [29]. These data can be obtained free of charge from International Union of Crystallography IUCr cl2177 or The Cambridge Crystallographic Data Centre CCDC 627450. (Reference: doi:10.1107/S1600536806039250).

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