Chapter – III

One-pot Synthesis of 1-(2-Methyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-ones from Anilines and N-Vinyl pyrrolidin-2-one through Imino Diels-Alder reaction using 4-nitro phthalic acid
Introduction

We have described the prevalence of 2-methyl-1,2,3,4-tetrahydroquinolines and 4-amino-1,2,3,4-tetrahydroquinolines in natural products and biologically active compounds in Chapter 1 and 2. Recently 2-methyl tetrahydroquinolines are found to be medicinally very important compounds and are patented. 1 2-methyl-1,2,3,4-tetrahydroquinoline was identified for the first time by gas chromatography-mass spectrometry in the parkinsonian and normal human brains. Sridharan et al have studied CAN-catalyzed three-component reaction between anilines (1) and alkyl vinyl ethers (2) and synthesized the 4-alkoxy-2-methyl-1,2,3,4-tetrahydroquinolines (3 and 4) (Scheme 1). 3

\[
\begin{align*}
\text{NH}_2 & \quad \begin{array} {c}	ext{OR} \end{array} \quad \text{CH}_2 & \quad \text{OR} \quad \text{CH}_3CN, \text{rt} \\
\text{R} & \quad \text{R} \quad \text{NH} & \quad \text{R} \quad \text{NH} \quad \text{CH}_3 \quad \text{R} \quad \text{NH} \quad \text{CH}_3 \\
\text{1} & \quad \text{2} & \quad \text{3} & \quad \text{4}
\end{align*}
\]

Scheme 1

In a part of medicinal chemistry programme, we required an efficient diastereoselective synthetic route to various tetrahydroquinolines. Catalytic three component imino Diels-Alder cyclo addition approaches to synthesis 1-(2-aryl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-ones (7) scaffold have been developed using anilines (1), aryl aldehydes (5) and N-vinyl pyrrolidin-2-one (6) (Scheme 2). 4
Our initial strategy was to synthesize 1-(2-aryl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-ones scaffold (7) based on the imino Diels-Alder reaction (Scheme 3). During our study of imino Diels-Alder reaction of benzaldehyde, 4-chloro aniline (1a) and N-vinyl pyrrolidin-2-one (6) as dienophile in presence of 50 mol% of 4-nitro phthalic acid (4-npa) in acetonitrile at ambient temperature, we have observed the formation of 1-(2-methyl-6-chloro-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one (8a). This unexpected result prompted us to develop a new method for the synthesis of 2-methyl-1,2,3,4-tetrahydroquinolines.
Present Work

A typical three component reaction of benzaldehyde, 4-chloro aniline (1a) and (6) as dienophile in presence of 50 mol% of 4-npa in acetonitrile at ambient temperature gave a clean product after column chromatographic purification. It was noticed that benzaldehyde remained unreacted and it was recovered in the chromatographic purification. The spectral data of this product did not corresponded to the expected product 3. Careful examination of the structure of this new product through $^1$H NMR spectral studies and by MS analysis confirms that the structure was 1-(2-methyl-6-chloro-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one (8a).

From this result it was found that instead of expected three component reaction, the reaction occurred between 4-chloro aniline (1a) and (6) to afford corresponding 2-methyl-1,2,3,4-tetrahydroquinoline (8a).

Further to ascertain this finding, the reaction was performed with the 4-chloroaniline (1a) and (6) in the absence of benzaldehyde (Scheme 4). In this case also the reaction proceeds smoothly and gave the desired product in excellent yield. The physical and spectral data of compounds obtained by either method have been compared and confirmed. This was found to be a straight forward approach for the preparation of 1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-ones, which not only preserves the simplicity but also conveniently gives the corresponding tetrahydroquinolines in excellent yields.
Further we examined the catalytic activity of various nitro phthalic acids in the model reaction of 4-chloro aniline (1a) with (6). Among them, 4-npa was found to be an efficient catalyst for the this reaction in CH3CN. The catalytic activity of 4-nitro phthalic acid in different reaction media has also been studied to investigate the solvent effect on reaction. The results are summarized in the Table 1 and shows that solvents such as CH3CN, MeOH, and EtOH are better solvents than toluene, CH2Cl2 and THF. Further, we examined the reaction in CH3CN/ H2O, MeOH/ H2O and EtOH/ H2O system. Remarkably, the reaction proceeded smoothly in CH3CN/H2O (3/1, v/v) system and obtained desired product in good yield. However, the CH3CN was found to be the best for the catalytic reaction in terms of yield and reaction time.

Similarly, several aryl amines reacted smoothly with 6 to give corresponding tetrahydroquinolines in 85-94 % yields (Table 2) in presence of 50 mol% of 4-npa in acetonitrile at 50 °C (Scheme 5). In all cases, the products (8) were obtained as cis-diastereoisomers. Their structural elucidations are based on ^1H NMR spectral data of the column purified products. The relative trans orientation of H2, H3 and H4 was established from the large vicinal coupling constants between H-4 and H-3 (J = 11.9) and H-2 and H-3 (J = 12.3).
Chapter III

Table 1. Effect of solvents in the synthesis of **8a**

<table>
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<tr>
<th>Entry</th>
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<th>Catalyst</th>
<th>Time / h</th>
<th>Yields$^b$ / %</th>
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<td>4-npa</td>
<td>3.0</td>
<td>92</td>
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<tr>
<td>2</td>
<td>CH$_3$CN</td>
<td>3-npa</td>
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<td>64</td>
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<td>CH$_3$CN</td>
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<td>60</td>
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<td>THF</td>
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$^a$ 50 mol% catalyst loaded  

$^b$ isolated yields

Scheme 5

Table 2. Synthesis of 2-methyl tetrahydroquinolines **8**

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<th>Yields$^a$ / %</th>
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<tr>
<td>2</td>
<td><strong>8b</strong></td>
<td>H</td>
<td>H</td>
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<td>3</td>
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<td>F</td>
<td>H</td>
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<td><strong>8f</strong></td>
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<td>H</td>
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<tr>
<td>7</td>
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<td>H</td>
<td>CH$_3$</td>
<td>3.5</td>
<td>90</td>
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<tr>
<td>8</td>
<td><strong>8h</strong></td>
<td>H</td>
<td>OCH$_3$</td>
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<tr>
<td>9</td>
<td><strong>8i</strong></td>
<td>H</td>
<td>F</td>
<td>4.0</td>
<td>90</td>
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</table>

$^a$ isolated yields
From these results, we have proposed the possible following mechanism to account for the reaction. An aromatic amine first reacts with NVP to afford N-vinylaniline and the second step proceeds via the imino Diels-Alder reaction between N-acetylidene phenylamine and another molecule of (6) (Scheme 6).

In conclusion, a very interesting and a facile synthesis of 1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-ones via 4-nitro phthalic acid catalyzed hetero (4+2) cyclization addition reaction between aryl amines and N-vinyl pyrrolidin-2-one have been described.
Experimental

General reaction protocol for the synthesis of 2-methyl-6-chloro-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8

A mixture of the 5 mmol of aryl amines (1), 12 mmol of N-vinyl pyrrolidin-2-one (6) and 2.5 mmol of 4-nitro phthalic acid in 5 cm³ acetonitrile were stirred at 50 °C for the appropriate time (Table 2). After completion of reaction as indicated by TLC, the reaction mixture was quenched with 20 cm³ saturated aqueous NaHCO₃ solution and extracted with 2 X 15 cm³ ethyl acetate. The combined organic layer were dried over anhydrous sodium sulphate, concentrated and the crude product was purified by column chromatography on silica gel (60-120 mesh, ethyl acetate-petroleum ether, 3:7) to afford 2-methyl-1,2,3,4-tetrahydroquinolines (8).

cis-1-(2-methyl-6-chloro-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8a

![cis-1-(2-methyl-6-chloro-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8a](image)

Colourless crystalline solid, M.p.: 150-152 °C; IR (KBr): $\tilde{\nu}$ = 3341 cm⁻¹; $^1$H NMR (400 MHz, CDCl₃): $\delta$ = 1.24 (d, 3H, $J = 6.2$ Hz, $H_{CH_3}$), 1.75 (ddd, 1H, $J = 12.3$, 5.5, 2.2 Hz, 3-H), 1.95 (ddd, 1H, $J = 11.6$, 5.9, 2.4 Hz, 3-H), 1.99-2.15 (m, 2H, 4'-H), 2.42-2.59 (m, 2H, 3'-H), 3.11-3.30 (m, 2H, 5'-H), 3.47-3.61 (m, 1H, 2-H), 4.5 (brs, 1H, NH), 5.5 (dd, 1H, $J = 11.9$, 5.9 Hz, 4-H), 6.48 (d, 1H, $J = 8.5$ Hz), 6.78 (s, 1H), 6.96 (dd, 1H, $J = 8.6$, 2.0 Hz) ppm; $^{13}$C NMR (400 MHz, CDCl₃): $\delta$ = 18.2, 22.0, 31.3, 33.5, 42.2, 47.0, 47.8, 116.0, 120.8, 122.7, 126.3, 129.0, 144.0, 175.8 ppm; MS: $m/z$ = 265 (M+1).
cis-1-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8b

Colourless crystalline solid, M.p.: 70-72 °C; IR (KBr): $\bar{\nu} = 3348$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.26$ (d, 3H, $J = 6.0$ Hz, H$_{CH3}$), 1.65 (ddd, 1H, $J = 12.1$, 5.7, 1.9 Hz, 3-H), 1.94 (ddd, 1H, $J = 12.0$, 5.79, 2.3 Hz, 3-H), 1.99-2.16 (m, 2H, 4'-H), 2.44-2.68 (m, 2H, 3'-H), 2.98-3.13 (m, 2H, 5'-H), 3.43-3.54 (m, 1H, 2-H), 4.34 (brs, 1H, NH), 5.65 (dd, 1H, $J = 11.5$, 5.8 Hz, 4-H), 6.67 (td, 1H, $J = 8.0$, 1.1 Hz), 6.8 (t, 1H, $J = 7.5$ Hz), 6.99 (m, 2H) ppm; $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta = 18.2$, 22.0, 31.3, 33.5, 42.2, 47.0, 47.8, 114.3, 117.9, 122.9, 127.7, 128.5, 145.0, 175.8 ppm; MS: $m/z = 231$ (M+1).

cis-1-(2-methyl-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8c

Pale yellow crystalline solid, M.p.: 90-92 °C; IR (KBr): $\bar{\nu} = 3341$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.24$ (d, 3H, $J = 6.2$ Hz, H$_{CH3}$), 1.75 (ddd, 1H, $J = 12.1$, 5.4, 2.0 Hz, 3-H), 1.98 (ddd, 1H, $J = 12.0$, 5.8, 2.2 Hz, 3-H), 2.01-2.19 (m, 2H, 4'-H), 2.41-2.57 (m, 2H, 3'-H), 3.04-3.16 (m, 2H, 5'-H), 3.41-3.61 (m, 1H, 2-H), 3.8 (s, 3H), 4.22 (brs, 1H, NH), 5.43 (dd, 1H, $J = 11.4$, 6.0 Hz, 4-H), 6.47 (d, 1H, $J = 8.7$ Hz), 6.67 (dd, 1H, $J = 8.7$, 2.7 Hz), 6.98 (d, 1H, $J = 2.9$ Hz) ppm; $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta = 17.8$, 22.0, 31.8, 33.4, 42.2, 46.7, 48.8, 56.7, 112.6, 115.2, 115.7, 124.3, 139.1, 152.7, 175.6 ppm; MS: $m/z = 261$ (M+1).

cis-1-(2,6-methyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8d

Pale yellow crystalline solid, M.p.: 95-96 °C; IR (KBr): $\bar{\nu} = 3422$ cm$^{-1}$; $^1$H NMR (400 MHz, DMSO): $\delta = 1.15$ (d, 3H, $J = 5.1$ Hz, H$_{CH3}$), 1.64 (q, 1H, $J = 11.9$ Hz, 3-H), 1.76 (ddd,
\(1H, J = 12.3, 5.6, 2.3 \text{ Hz}, 3'-H\), 1.97-2.12 (m, 2H, 4'-H), 2.21 (s, 3H), 2.25-2.45 (m, 2H, 3'-H), 2.95-3.22 (m, 2H, 5'-H), 3.39-3.55 (m, 1H, 2-H), 5.25 (dd, 1H, \(J = 11.6, 6.0 \text{ Hz}, 4'-H\)), 5.47 (brs, 1H, NH), 6.42 (m, 2H), 6.72 (d, 1H, \(J = 8.0 \text{ Hz}\)) ppm; \(^{13}\text{C NMR}\) (400 MHz, DMSO): \(\delta = 17.72, 20.2, 21.78, 30.74, 33.8, 41.6, 46.1, 47.4, 114.1, 124.2, 126.0, 128.1, 129.3, 144.1, 174.4 \text{ ppm}; MS: \(m/z = 245 (M+1)\).  

**cis-1-(2-methyl-6-fluoro-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8e**

![Image of compound 8e](image)

Colourless crystalline solid, M.p.: 138-140 °C; IR (KBr): \(\nu = 3258 \text{ cm}^{-1}\); \(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 1.22\) (d, 3H, \(J = 5.8 \text{ Hz}, H_{CH3}\)), 1.74 (ddd, 1H, \(J = 11.8, 5.6, 2.2 \text{ Hz}, 3'-H\)), 1.91 (ddd, 1H, \(J = 12.0, 5.6, 2.1 \text{ Hz}, 3'-H\)), 2.09-2.21 (m, 2H, 4'-H), 2.45-2.61 (m, 2H, 3'-H), 3.04-3.18 (m, 2H, 5'-H), 3.42-3.55 (m, 1H, 2-H), 4.25 (brs, 1H, NH), 6.58 (d, 1H, \(J = 8.5, 2.6 \text{ Hz}\)) ppm; \(^{13}\text{C NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 17.6, 21.6, 30.6, 33.2, 41.6, 46.3, 47.4, 116.0, 120.8, 122.7, 126.3, 129.0, 142.7, 174.7 \text{ ppm}; MS: \(m/z = 249 (M+1)\).  

**cis-1-(2-methyl-6-bromo-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8f**

![Image of compound 8f](image)

Colourless crystalline solid, M.p.: 131-133 °C; IR (KBr): \(\nu = 3332 \text{ cm}^{-1}\); \(^{1}\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 1.24\) (d, 3H, \(J = 6.2 \text{ Hz}, H_{CH3}\)), 1.75 (dd, 1H, \(J = 12.3, 5.5, 2.2 \text{ Hz}, 3'-H\)), 1.91-2.13 (m, 3H, 3'-H), 2.44-2.63 (m, 2H, 3'-H), 3.09-3.28 (m, 2H, 5'-H), 3.42-3.58 (m, 1H, 2, H), 4.45 (brs, 1H, NH), 5.38 (dd, 1H, \(J = 11.6, 5.8 \text{ Hz}, 4'-H\)), 6.58 (d, 1H, \(J = 8.3 \text{ Hz}\)), 6.81-7.12 (m, 2H) ppm; \(^{13}\text{C NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 18.2, 22.0, 31.3, 33.5, 42.2, 47.0, 47.8, 116.0, 120.8, 122.7, 126.3, 129.0, 144.0, 175.8 \text{ ppm}; MS: \(m/z = 310 (M+1)\).
cis-1-(2,8-methyl-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8g

Colourless crystalline solid, M.p.: 83-84 °C; IR (KBr): $\tilde{\nu} = 3415$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.28$ (d, 3H, $J = 5.8$ Hz, H$_{\text{CH3}}$), 1.71 (q, 1H, $J = 11.2$ Hz, 3-H), 1.78-1.89 (m, 1H, 3-H), 1.94-2.08 (m, 2H, 4'-H), 2.16 (s, 3H), 2.24-2.42 (m, 2H, 3'-H), 2.78-2.97 (m, 2H, 5'-H), 3.32-3.41 (m, 1H, 2-H), 3.78 (brs, 1H, NH), 4.99 (dd, 1H, $J = 11.1$, 5.9 Hz, 4-H), 6.42-6.51 (m, 1H), 6.95 (dd, 1H, $J = 7.9$, 1.5 Hz), 7.28 (dd, 1H, $J = 8.0$, 1.3 Hz) ppm; $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta = 17.81$, 20.5, 23.6, 31.4, 33.5, 40.7, 46.1, 47.4, 116.9, 121.6, 122.5, 125.7, 130.1, 143.3, 174.5 ppm; MS: $m/z = 245$ (M+1).

cis-1-(2-methyl-8-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8h

Colourless crystalline solid, M.p.: 78-80 °C; IR (KBr): $\tilde{\nu} = 3341$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.24$ (d, 3H, $J = 6.2$ Hz, H$_{\text{CH3}}$), 1.77 (ddd, 1H, $J = 11.9$, 5.3, 1.8 Hz, 3-H), 1.94-2.17 (m, 1H, 4'-H), 2.36-2.49 (m, 2H, 3'-H), 3.08-3.19 (m, 2H, 5'-H), 3.39-3.58 (m, 1H, 2-H), 3.76 (s, 3H), 4.09 (brs, 1H, NH), 5.42 (dd, 1H, $J = 11.7$, 6.2 Hz, 4-H), 6.62-6.83 (m, 2H), 6.99-7.11 (m, 1H) ppm; $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta = 17.4$, 22.5, 30.8, 33.4, 42.5, 46.5, 49.3, 56.1, 109.1, 116.4, 119.6, 123.3, 135.5, 146.7, 175.6 ppm; MS: $m/z = 261$ (M+1).

cis-1-(2-methyl-8-floro-1,2,3,4-tetrahydroquinolin-4-yl)pyrrolidin-2-one: 8i

Colourless crystalline solid, M.p.: 125-126 °C; IR (KBr): $\tilde{\nu} = 3365$ cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.23$ (d, 3H, $J = 6.2$ Hz, H$_{\text{CH3}}$), 1.79 (ddd, 1H, $J = 11.8$, 5.4, 2.1 Hz, 3-H), 2.02 (ddd,
1H, J = 11.5, 5.8, 2.2 Hz, 3-H), 2.04-2.18 (m, 2H, 4'-H), 2.38-2.55 (m, 2H, 3'-H), 3.18-3.37 (m, 2H, 5'-H), 3.49-3.63 (m, 1H, 2-H), 4.4 (brs, 1H, NH), 5.4 (dd, 1H, J = 11.5, 5.7 Hz, 4-H), 6.54-5.65 (m, 2H), 6.99 (d, J = 7.9 Hz, 1H) ppm; $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ = 17.2, 21.6, 31.8, 34.5, 43.1, 47.0, 47.4, 114.0, 118.8, 124.6, 124.9, 131.4, 145.9, 174.7 ppm; MS: $m/z = 249$ (M+1).
Chapter III

References


$^1$H-NMR spectrum of 8a
$^{13}$C-NMR spectrum of 8a

[Chemical structure image]

Current, Raw Parameters

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- **** CHANNEL 12 **

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- **** Processing parameters **

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Maximum Chromatogram of C:\CHEM32\1\DATA\DEC06\150141.D, Signt Id A

Mass spectrum of 8a

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<td>1.261e+004</td>
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MSD2 TIC, MS File (C:\CHEM32\1\DATA\DEC06\150141.D), MM-ES+APCI, Pos, Scan, Frag: 50, "TIC SIGNAL-2"

MSD2 SPC, time=1.376:1.513 of C:\CHEM32\1\DATA\DEC06\150141.D, MM-ES+APCI, Pos, Scan, Frag: 50, "TIC SIGNAL-2"
NMR Report

Current Data Parameters
NAME      GF509556-7015502
EXPMO     1
PROCNO    1

F2 - Acquisition Parameters
Date       20070201
Time       14.36
INSTRUM    spect
PROC96:    5 x BBO BB-15
PULPROG    zg30
TD         33852
SOLVENT    CDC13
NS         4
GS         0
SWF       8012.820 Hz
FIDRES     0.236702 Hz
AQ     2.1124168 sec
PG        14.7
DG       62.400 usec
DE        8.00 usec
TE       296.5 K
D1       2.00000000 sec
TDO      1

1H-NMR Spectrum of 8f

\[ \text{NMR Diagram} \]

10.5  10.0  9.5  9.0  8.5  8.0  7.5  7.0  6.5  6.0  5.5  5.0  4.5  4.0  3.5  3.0  2.5  2.0  1.5  1.0  0.5  0.0  ppm

0.000  0.000  1.000  0.000  0.060  1.125  1.065  2.131  2.364  2.104  2.364  2.781