A NOVEL SYNTHETIC APPROACH TO TERT-BUTYL ACETATES OF SOME NITROGEN HETEROCYCLES

5.1 Introduction

Nitrogen heterocycles are one of the most used frameworks for medicines, food flavorings, dyes, rubber chemicals, and adhesives. Synthesis of these heterocycles and their derivatives occupy an important place in the realm of natural and synthetic organic chemistry, due to their therapeutic and pharmacological properties. They have emerged as integral backbones of over 7000 existing drugs. Pyridine, a nitrogen containing compound is also an integral part of agrochemicals, preparative organic chemistry, and in coordination chemistry. In addition to these important biological applications, Nitrogen-heterocycles are ideal scaffolds for making libraries of drug-like compounds, and to generate libraries of inhibitors of HIV-1 protease. Thousands of nitrogen containing natural products exist in various plants and living things in nature. Compounds such as amphimedine (1) and aaptamine (2) were isolated from marine sponges. Similarly, Meridine (3), a nitrogen heterocycle was isolated from a marine organism *Amphicarpa meridiana*.

Some of the small molecules like Jasminine (4), a monoterpenic alkaloid isolated from *Jasminum gracile* and other *Oleaceae species* was characterized to be a pyridine ring fused to a six-membered lactam moiety. This singular 2,7-naphthyridin-3-one skeleton is also present in jasminidine (5) and dihydrojasminine (6), which co-occur with Jasminine in *Syringavulgaris* and *Osmanthus austrocaledonica*, respectively. Compounds 4 and 6 are responsible for the pleasant fragrance in the flowers of Jasmine.
Dimebolin Hydrochloride (7) (brand name Dimebon) is a synthetically made nitrogen containing antihistamine drug which has been used clinically since 1983.\textsuperscript{23} Research is continuing in both Russia and western nations into potential applications as a neuroprotective and potential nootropic.\textsuperscript{24} Recently dimebolin has attracted renewed interest after being shown to have positive effects on persons suffering from Alzheimer’s disease.\textsuperscript{25} Epibatidine (8) is an alkaloid that originally is found in the skin of a neotropical poisonous frog, *Epipedobates tricolor*, found in modern Ecuador. It was initially isolated by John Daly, and was found to be a powerful analgesic, about 200 times more potent than morphine.\textsuperscript{26}\textsuperscript{2}

Prompted by these observations, we decided to explore the synthesis of some of the nitrogen containing scaffolds. Our aim was to develop a one step organic transformation to achieve tert-butyl acetates of some nitrogen heterocycles having an active methyl group on the aryl ring, which could be useful building blocks in the early stages of natural products.
synthesis. Compounds possessing tert-butyl carboxylate functionality are useful building blocks in organic synthesis, preferably due to their ease of de-protection to the corresponding carboxylic acid under acidic medium.

5.2 Materials and methods

The starting materials needed such as suitably substituted nitrogen heterocycles with an active methyl group on the ring, di-tert-butyl dicarbonate and n-BuLi were purchased from commercial sources and used without any purification. The reaction of 1 with 1.1 equivalent of LDA (Lithium diisopropylamide) followed by quenching with Boc-anhydride (1.1 equiv) gave the respective tert-butyl acetates 2 in good yields (Scheme 5.1). The products synthesized are novel and $^1$H and $^{13}$C NMR spectra of these compounds were recorded on 400-MHz and 100-MHz Bruker spectrometer respectively and elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Melting points were recorded (uncorrected) on Buchi Melting Point B-545 instrument. Infrared spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer. Coupling constants were reported wherever it was necessary in hertz (Hz). Reactions were carried out in an oven dried three-necked round-bottomed flask.

5.3 Results and discussion

Our initial investigations were aimed at scrutinizing the feasibility synthesizing tert-butyl acetates of nitrogen-heterocycles having an active methyl group such as 2 or 4-methyl pyridine. From the literature, it was evident to use a two step protocol. In the first step, the carboxylic acid was prepared by the reaction of an active picoline such as 2 or 4-methyl pyridine with a strong base such as n-BuLi,$^{29}$ followed by quenching with carbon dioxide. Further, esterification of the carboxylic acid with tert-butanol, tert-butyl bromide or isobutylene provided the corresponding tert-butyl ester.

Hongmei Li and Jaume Balsells have demonstrated the synthesis of tert-butyl benzoates from haloarenes bearing multiple halogen substituents via selective metal-
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halogen exchange with lithium tri-n-butylmagnesium ate complex, followed by reacting with Boc-anhydride.\(^{30}\) Interestingly the broad scope and synthetic utility of this reagent as a carboxylating agent has not been explored for substrates that could not produce triarenemagnesium ate complexes. We decided to explore the possibility of using Boc-anhydride (di-tert-butyl dicarbonate) as a carboxylating reagent to produce the tert-butyl acetates of our desired nitrogen heterocycles. Herein, we report Boc-anhydride as a mild and efficient carboxylating reagent by demonstrating the synthesis of tert-butyl aryl acetates, substituted di-tert-butyl aryl malonates and tert-butyl benzoates by trapping the carbon nucleophiles generated by a non-nucleophilic base such as LDA (Lithium diisopropylamide) with Boc-anhydride (Scheme 5.1).

<table>
<thead>
<tr>
<th>Scheme 5.1</th>
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\[
\begin{align*}
\text{FG} & \quad \text{A} \\
\text{FG} & \quad \text{B}
\end{align*}
\]

LDA (1.1 equiv) \(\rightarrow\)
Boc\(_2\)O (1.1 equiv)
\(-78\,^\circ\mathrm{C}\)

\[
\begin{align*}
\text{FG} & \quad \text{A} \\
\text{FG} & \quad \text{B}
\end{align*}
\]

\(A = \text{Nitrogen}; \quad B = \text{Carbon or Nitrogen}\)

\(A = \text{Carbon}; \quad B = \text{Nitrogen}\)

\(\text{FG} = \text{Functional group}\)

Our initial investigations were aimed at scrutinizing the feasibility of trapping Boc-anhydride with carbanions generated by LDA. Accordingly, the nitrogen heterocycle 1a (Table 5.1) was treated with a freshly prepared solution of LDA (1.1 equiv) in THF at \(-78\,^\circ\mathrm{C}\) for 0.5 hours and to the resulting solution was added Boc-anhydride (1.1 equiv). To our satisfaction, the product formed was found to be the expected tert-butyl acetate 2a in 84% isolated yield (Entry 1, Table 5.1).
Table 5.1: Synthesis of tert-butyl acetates of nitrogen heterocycles having an active methyl group on the ring via Scheme 5.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (min.)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>30</td>
<td>2a</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>30</td>
<td>2b</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>45</td>
<td>2c</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>30</td>
<td>2d</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>45</td>
<td>2e</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>45</td>
<td>2f</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>45</td>
<td>2g</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>45</td>
<td>2h</td>
<td>0</td>
</tr>
</tbody>
</table>

Commercial LDA was found to provide quantitative yields when used in slight excess (1.4 equiv). Subsequently, we investigated the scope of this reagent as a tert-butyl carboxylating agent on other nitrogen heterocycles (Entries 2-8, Table 5.1) having an
active methyl group as shown in Scheme 5.1. This procedure was found to exhibit excellent scope, and the reaction condition was found to be optimal as we could obtain most of the products in good to excellent yields as depicted in Table 5.1. Surprisingly, 3-cyano-4-picoline did not react with LDA under this reaction conditions and only starting material was recovered from the reaction mixture (Entry 8, Table 5.1). While pyridine and quinoline substrates provided good yield of products, moderate yield was obtained for pyrazine (Entry 5, Table 5.1).

Interestingly, the use of excess of LDA (2.2 equiv) and Boc-anhydride (2.2 equiv) led to the formation of di-tert-butyl malonates (Entries 1-3, Table 5.2). It further emphasizes the synthetic utility of Boc-anhydride in producing the tert-butyl malonates of substrates possessing an active methyl group. Further use of excess of LDA (3.2 equiv) and Boc-anhydride (3.2 equiv) failed to introduce a third tert-butyl carboxylate group on substrates possessing an active methylene group. This could be attributed to the steric impediment on C2 carbon of the malonates (2i-2k). In all the cases we studied, the reaction was found to complete within an hour and provided good yield of products. Compounds possessing a fluoro-substituent on the ring were further characterized by $^{19}$F NMR at 376 MHz. The IR spectrum of compounds 2a-2k showed the typical carbonyl peak at $v_{\max}$ 1724-1740 cm$^{-1}$. The $^1$H NMR and $^{13}$C NMR spectra of selected compounds described in Table 5.1 and Table 5.2 are shown in figures 5.1 to 5.9. The compound characterization data for all the compounds described in Tables 5.1 and 5.2 are given in the experimental section of this chapter.

In summary, carbanions generated by a non-nucleophilic base (LDA) were effectively trapped with di-tert-butyl dicarbonate to provide the corresponding tert-butyl carboxylates in high yields. This reaction represents another useful way to prepare a variety of tert-butyl acetates and di-tert-butyl malonates of nitrogen heterocycles having an active methyl group.
on the aryl ring. The tolerance of functional groups such as bromo, chloro and fluoro on the aryl ring under these conditions adds a synthetic advantage to this protocol.

Scheme 5.2

\[
\begin{align*}
\text{B} & \xrightarrow{\text{LDA (2.2 equiv)}} \text{B} \\
\text{FG} & \xrightarrow{\text{Boc}_2\text{O (2.2 equiv)}} \text{Boc}_2\text{O} \\
\text{A} & \xrightarrow{-78 \degree \text{C}} \text{A}
\end{align*}
\]

A = Nitrogen; B = Carbon or Nitrogen
A = Carbon; B = Nitrogen
FG = Functional group

Table 5.2: Synthesis of di-tert-butyl malonates of nitrogen heterocycles having an active methyl group on the ring via Scheme 5.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (min.)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1F</td>
<td>30</td>
<td>2i</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>1i</td>
<td>45</td>
<td>2j</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>1k</td>
<td>45</td>
<td>2k</td>
<td>81</td>
</tr>
</tbody>
</table>
5.4 Experimental (general procedure for the preparation of tert-butyl acetates)

To a solution of diisopropylamine (0.12 mol) in THF (100 mL) at -78 °C was added n-BuLi (0.11 mol, 3 M solution in hexane) in drops over a period of 15 minutes and the resulting solution was stirred at -78 °C for additional 30 minutes. To the above LDA solution was added substrates 1a-1g (0.10 mol) in THF (20 mL) in drops and the reaction mixture was stirred for 0.5 hour. To this was added Boc-anhydride (0.11 mol) and the reaction mixture was slowly allowed to room temperature over a period of 1 hour, and diluted with water (200 mL). The product was extracted with diethyl ether (2 x 100 mL). The combined organic layer was washed with water (100 mL), brine (50 mL) and dried over sodium sulphate. The organic phase was concentrated under reduced pressure and the residue was purified by flash chromatography (1-5% EtOAc/hexane) to afford compounds 2a-2g as colourless liquids. The same protocol was used for the synthesis of 2i-2k, except for the fact that 0.05 mmol of 1i-1k were used.

**tert-Butyl(6-chloropyridin-2-yl)acetate (2a):** Colourless liquid; Rf (10% EtOAc/hexane) 0.60; [Found: C, 58.09; H, 6.25; N, 6.12. C_{11}H_{14}ClNO2 requires C, 58.03; H, 6.20; N, 6.15%]; ν_{max}(liquid film) 1726, 1584, 1439, 1134 cm⁻¹; ¹H NMR (400MHz, CDCl₃) 7.63-7.59 (1 H, t, J₅.1Hz, Ph), 7.23-7.21 (2 H, m, Ph), 3.73 (2 H, s, CH₂COO'Bu), 1.44 (9 H, s, COO'Bu); ¹³C NMR (100.6MHz, DMSO-d₆) 169.3, 155.7, 150.6, 139.0, 122.5, 122.4, 81.5, 44.5, 28.0; MS (ESI) 228 [M+H]^⁺.

**tert-Butyl(2-fluoropyridin-4-yl)acetate (2b):** Colourless liquid; Rf (10% EtOAc/hexane) 0.60; ν_{max}(liquid film) 1726, 1612, 1465, 1280, 854 cm⁻¹; [Found: C, 62.61; H, 6.74; N, 6.60. C_{11}H_{14}FNO₂ requires C, 62.55; H, 6.68; N, 6.63%]; ¹H NMR (400MHz, CDCl₃) 8.18-8.16 (1 H, d, J 5.1Hz, Ph), 7.12-7.10 (1 H, d, J 5.1Hz, Ph), 6.88 (1 H, s, Ph), 3.57 (2
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H, s, CH$_2$COO$'$Bu), 1.45 (9 H, s, COO$'$Bu); $^{13}$C NMR (100.6MHz, CDCl$_3$) 168.6, 165.1, 162.7, 149.1, 149.1, 147.5, 147.4, 129.1, 127.6, 122.5, 122.2, 110.3, 109.9, 81.9, 41.7, 41.7, 27.9; $^{19}$F NMR (376.5MHz, CDCl$_3$) -68.34 (1F, s); MS (ESI) 212 [M+H]$^+$. 

tert-Butyl(2-bromopyridin-4-yl)acetate (2c): Colourless liquid; R$_f$ (10% EtOAc/hexane) 0.60; $\nu_{\text{max}}$(liquid film) 1725, 1588, 1416, 1380, 1140, 834 cm$^{-1}$; [Found: C, 48.60; H, 5.23; N, 5.13. C$_{11}$H$_{14}$BrNO$_2$ requires C, 48.55; H, 5.19; N, 5.15%]; $^1$H NMR (400MHz, CDCl$_3$) 8.32-8.31 (1 H, d, $J$ 5.0Hz, Ph), 7.43 (1 H, s, Ph), 7.20-7.18 (1H, dd, $J$ 5.0, 1.2Hz, Ph), 3.51 (2 H, s, CH$_2$COO$'$Bu), 1.45 (9 H, s, COO$'$Bu); $^{13}$C NMR (100.6MHz, CDCl$_3$) 168.5, 149.9, 146.4, 142.3, 128.8, 123.6, 82.0, 41.4, 27.9; MS (ESI) 274 [M+2]$^+$. 

tert-Butyl(3,5-dimethylpyridin-2-yl)acetate (2d): Colourless liquid; R$_f$ (10% EtOAc/hexane) 0.65; $\nu_{\text{max}}$(liquid film) 1727, 1472, 1366, 1143, 884 cm$^{-1}$; [Found: C, 70.59; H, 8.70; N, 6.30. C$_{13}$H$_{17}$NO$_2$ requires C, 70.56; H, 8.65; N, 6.33%]; $^1$H NMR (400MHz, DMSO-$d_6$) 8.11 (1 H, s, Ph), 7.37 (1 H, s, Ph), 3.68 (2 H, s, CH$_2$COO$'$Bu), 2.22 (3H, s, PhMe), 2.19 (3H, s, PhMe), 1.37 (9 H, s, COO$'$Bu); $^{13}$C NMR (100.6MHz, CDCl$_3$) 170.0, 150.7, 147.0, 138.6, 131.6, 131.5, 81.0, 42.7, 28.0, 18.6, 17.9; MS (ESI) 222 [M+H]$^+$. 

tert-Butyl 2-pyrazin-2-ylpropanoate (2e): Colourless liquid; R$_f$ (10% EtOAc/hexane) 0.50; $\nu_{\text{max}}$(liquid film) 1726, 1403, 1367, 1142, 1081, 847 cm$^{-1}$; [Found: C, 63.51; H, 7.83; N, 13.39. C$_{11}$H$_{16}$N$_2$O$_2$ requires C, 63.44; H, 7.74; N, 13.45%]; $^1$H NMR (400MHz, CDCl$_3$) 8.58-8.58 (1 H, d, $J$ 1.4Hz, Ph), 8.53-8.52 (1 H, dd, $J$ 2.4, 1.6Hz Ph), 8.47-8.46 (1 H, d, $J$ 2.5Hz, Ph), 3.90-3.85 (1 H, q, PhCHMe), 1.56-1.55 (3 H, d, PhCHMe), 1.41 (9 H, s,
tert-Butyl(6-chloro-5-cyanopyridin-2-yl)acetate (2f): Colourless liquid; Rf (10% EtOAc/hexane) 0.65; $\nu_{\text{max}}$(liquid film) 1727, 1585, 1366, 1142, 1072, 785 cm$^{-1}$; [Found: C, 57.10; H, 5.23; N, 11.01. C$_{12}$H$_{13}$ClN$_2$O$_2$ requires C, 57.04; H, 5.19; N, 11.09%]; $^1$H NMR (400MHz, CDCl$_3$) 7.97-7.95 (1 H, d, $J$ 8Hz, Ph), 7.41-7.39 (1 H, d, $J$ 8Hz, Ph), 3.82 (2 H, s, CH$_2$COO'Bu), 1.46 (9 H, s, COO'Bu); $^{13}$C NMR (100.6MHz, CDCl$_3$) 168.0, 159.7, 152.0, 142.5, 122.6, 114.7, 108.9, 82.3, 44.7, 27.9; MS (ESI) 253 [M+H]$^+$. 

Di-tert-butyl(2-fluoropyridin-4-yl)malonate (2i): This compound was isolated in 93% yield as off-white solid by treating 2-fluoro-4-methylpyridine with LDA (2.2 equiv) for 45 min, followed by quenching the resultant reaction mixture with Boc-anhydride (2.2 equiv); Rf (10% EtOAc/hexane) 0.70; m.p. 45.5-47.2 °C; $\nu_{\text{max}}$(KBr) 1733, 1610, 1414, 1285, 1139, 849 cm$^{-1}$; [Found: C, 61.77; H, 7.19; N, 4.45. C$_{16}$H$_{22}$FNO$_4$ requires C, 61.72; H, 7.12; N, 4.50%]; $^1$H NMR (400MHz, CDCl$_3$) 8.22-8.21 (1 H, d, $J$ 5.1Hz, Ph), 7.23-7.21 (1H, m,
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Ph), 7.01 (1 H, s, Ph), 4.4 (2H, s, CH(COO'Bu)₂), 1.48 (18 H, s, CH(COO'Bu)₂); \(^{13}\)C NMR (100.6MHz, CDCl₃) 165.5, 164.9, 162.6, 147.6, 147.5, 147.4, 122.2, 122.1, 110.6, 110.2, 83.1, 59.2, 59.1, 28.0; \(^{19}\)F NMR (376.5MHz, CDCl₃) -67.73 (1F, s); MS (ESI) 312 [M+H]^+.

Di-tert-butyl (2-bromopyridin-4-yl)malonate (2j): White solid; Rᵥ (10% EtOAc/hexane) 0.75; m.p. 64.8-66.2 °C; \(^\nu\)max(KBr) 1739, 1731, 1588, 1456, 1369, 1134, 1085, 843 cm⁻¹; [Found: C, 51.67; H, 6.03; N, 3.70. C₁₆H₂₂BrNO₄ requires C, 51.62; H, 5.96; N, 3.76%]; \(^1\)H NMR (400MHz, CDCl₃) 8.37-8.35 (1 H, d, J 5.1Hz, Ph), 7.53 (1 H, s, Ph), 7.33-7.32 (1H, dd, J 5.1, 1.2Hz, Ph), 4.38 (1 H, s, CH(COO'Bu)₂), 1.47 (18 H, s, CH(COO'Bu)₂); \(^{13}\)C NMR (100.6MHz, CDCl₃) 165.5, 149.9, 144.8, 142.2, 128.8, 123.5, 83.2, 58.9, 27.8; MS (ESI) 374 [M+2]^+.

Di-tert-butyl (pyridin-2-yl)malonate (2k): Colourless liquid; Rᵥ (10% EtOAc/hexane) 0.70; \(^\nu\)max(liquid film) 1725, 1472, 1367, 1128, 757 cm⁻¹; [Found: C, 65.60; H, 8.03; N, 4.69. C₁₆H₂₃NO₄ requires C, 65.51; H, 7.90; N, 4.77%]; \(^1\)H NMR (400MHz, CDCl₃) 8.56-8.55 (1 H, m, Ph), 7.52-7.50 (1H, dd, J 7.9, 0.7Hz, Ph), 7.25-7.21 (1 H, m, Ph), 4.76 (1 H, s, CH(COO'Bu)₂), 1.47 (18 H, s, CH(COO'Bu)₂); \(^{13}\)C NMR (100.6MHz, CDCl₃) 166.8, 153.8, 149.1, 136.4, 123.6, 122.7, 82.2, 62.7, 27.7; MS (ESI) 294 [M+H]^+.
Figure 5.1 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2a)
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Figure 5.2 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2b)
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Figure 5.3 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2c)
Figure 5.4 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2d)
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Figure 5.5 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2e)
Figure 5.6 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2f)
Figure 5.7 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2g)
Figure 5.8 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2i)
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Figure 5.9 $^1$H NMR (400MHz) and $^{13}$C NMR (100.6 MHz) in CDCl$_3$ (2j)
References


