

# **A Base Promoted Cyclisation of *N*-Propargylaminopyridines. Synthesis of Imidazo[1,2-*a*]pyridine derivatives**

**Suren Husinec, Rade Markovic, Milos Petkovic, Veselin Nasufovic and Vladimir Savic**

*Institute of Chemistry, Technology and Metallurgy, Centre for Chemistry, PO Box 815, Njegosova 12, 11000 Belgrade Serbia; University of Belgrade, Faculty of Chemistry, Studentski Trg 12-16, 11000 Belgrade, Serbia and University of Belgrade, Faculty of Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia*

*vladimir.savic@pharmacy.bg.ac.rs*

## **SUPPLEMENTARY INFORMATION**

### **Table of contents**

|   |            |
|---|------------|
| <b>1. General.....</b>  | <b>S2</b>  |
| <b>2. Synthetic procedures.....</b>   | <b>S2</b>  |
| <b>3. Spectral data.....</b>  | <b>S5</b>  |
| <b>4. <sup>1</sup>H NMR, <sup>13</sup>C NMR and GC/MS spectra of selected compounds .....</b> | <b>S12</b> |

## 1. General

The NMR spectra were recorded on a Bruker Avance III (500 MHz) or Varian Gemini 2000 (200MHz) spectrometer. Chemical shift are given in parts per million ( $\delta$ ) downfield from tetramethylsilane as the internal standard and deuteriochloroform or DMSO-d<sub>6</sub> were used as a solvent. Mass spectral data were recorded using Agilent MSD TOF spectrometer coupled with Agilent 1200 HPLC or Agilent Technologies 5975C MS coupled with Agilent Technologies 6890N GC. IR spectra were recorded on a IR Termo Scientific NICOLET iS10 (4950) spectrometer. Flash chromatography employed silica gel 60 (230-400 mesh) while thin layer chromatography was carried out using alumina plates with 0.25 mm silica layer (Kieselgel 60 F<sub>254</sub>, Merck). The solvents were purified by distillation before use.

## 2. Synthetic procedures

### General procedures for the synthesis of *N*-Boc-2-aminopyridine:

**Method A:** To a solution of 2-aminopyridine (5 mmol) in *t*-BuOH ( 15 mL), Boc<sub>2</sub>O (5.5 mmol) was added in several portions and the mixture was heated at 35-40 °C (oil bath temperature) under nitrogen atmosphere for 16 h. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>, petrol ether/Et<sub>2</sub>O) to afford the product.

**Method B:** To a solution of 2-aminopyridine (5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> ( 15 mL), Boc<sub>2</sub>O (5.5 mmol) was added followed by Et<sub>3</sub>N (5.5 mmol) and the mixture was heated and stirred at 45 °C (oil bath temperature) under nitrogen atmosphere for 16 h. After being cooled to room temperature the solvent was evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>, petrol ether/Et<sub>2</sub>O) to afford the product.

**Method C:** To a solution of 2-aminopyridine (5 mmol) in THF ( 15 mL), NaH (7.5 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Boc<sub>2</sub>O (5.5 mmol) was then added and mixture was stirred at 70 °C (oil bath temperature) under nitrogen atmosphere for 16 h. The solvent was evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>, petrol ether/Et<sub>2</sub>O) to afford the product.

**Method D:** To a solution of 2-aminopyridine (5 mmol) in *t*-BuOH ( 15 mL), Boc<sub>2</sub>O (5.5 mmol) was added followed by DMAP (5.5 mmol) and the mixture was then heated at 70 °C (oil bath temperature) under nitrogen atmosphere for 16 h. After being cooled to room temperature, the solvent was evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>, petrol ether/Et<sub>2</sub>O) to afford the product.

**General procedures for the synthesis of *N*-Boc-*N*-propargyl-2-aminopyridines:**

**Method A:** To a solution of *N*-Boc-2-aminopyridine (5 mmol) in DMF ( 10 mL), NaH (5.5 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Propargyl bromide (5.5 mmol) was then added and mixture was stirred at room temperature under nitrogen atmosphere for 16 h. The reaction mixture was then diluted with H<sub>2</sub>O (20 mL) and extracted with Et<sub>2</sub>O (3×20 mL). The combined Et<sub>2</sub>O extracts were washed with H<sub>2</sub>O (2×30 mL), the organic phase dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The

solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>, petrol ether/Et<sub>2</sub>O) to afford the product.

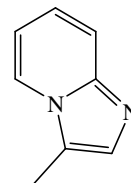
**Method B:** To a solution of *N*-Boc-2-aminopyridine (5 mmol) in THF ( 10 mL), NaH (5.5 mmol) was added and the mixture was stirred at room temperature for 0.5 h. Propargyl bromide (5.5 mmol) was then added and mixture was stirred at 70 °C (oil bath temperature) under nitrogen atmosphere for 16 h. After being cooled to room temperature, the solvent was evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>, petrol ether/Et<sub>2</sub>O) to afford the product.

**General procedure for imidazo[1,2-*a*]pyridines synthesis:**

To a solution of *N*-Boc-*N*-propargyl-2-aminopyridine (0,3 mmol) in THF ( 3 mL), *t*-BuOK (0.36 mmol) was added and the mixture was stirred at room temperature or at indicated temperature until t.l.c. monitoring showed absence of the starting material. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (SiO<sub>2</sub>, EtOAc/MeOH = 20/1) to afford the product.

### 3. Spectral data

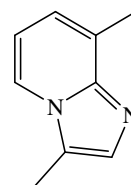
#### 3-Methylimidazo[1,2-*a*]pyridine (2)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a gray, amorphous solid in 70% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,42 (s, 3H), 6,77 (t, 1H), 7,10 (t, 1H), 7,38 (s, 1H), 7,57 (d, 1H), 7,81 (d, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 8,6; 111,6; 117,3; 119,5; 122,5; 122,7; 130,9; 144,8; IR (cm<sup>-1</sup>): 739, 1063, 1127, 1308, 1505, 3035; *m/z* = 131 (M<sup>+</sup>-1), 104, 78, 66, 51, 28;

C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>, required [M+H]<sup>+</sup>=133.07602; found [M+ H]<sup>+</sup>= 133.07616.

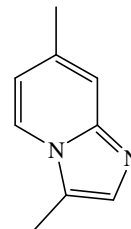
#### 3,8-Dimethylimidazo[1,2-*a*]pyridine (4a)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 53% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,41 (s, 3H), 2,57 (s, 3H), 6,70 (t, 1H), 6,90 (d, 1H), 7,35 (s, 1H), 7,69 (d, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 9,0; 16,8; 111,9; 120,1; 120,6; 121,9; 127,3; 130,5; 145,5; IR (cm<sup>-1</sup>): 752, 1135, 1308, 1492, 1632, 2913, 3035; *m/z* = 145 (M<sup>+</sup>-1), 131, 118, 93, 65;

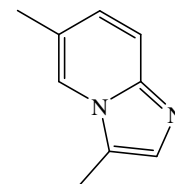
C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>, required [M+H]<sup>+</sup>=147.09167; found [M+ H]<sup>+</sup>= 147.09205.

### 3,7-Dimethylimidazo[1,2-*a*]pyridine (4b)



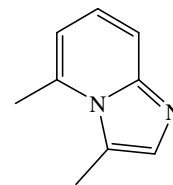
Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 52% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,37 (s, 3H), 2,41 (s, 3H), 6,63 (d, 1H), 7,30 (s, 1H), 7,33 (s, 1H), 7,72 (d, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 8,7; 20,9; 114,4; 115,8; 119,0; 121,9; 130,6; 133,8; 145,4; IR (cm<sup>-1</sup>): 728, 773, 1157, 1303, 1475, 1646, 2915; *m/z* = 145 (M<sup>+</sup>-1), 131, 118, 93, 65; C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>, required [M+H]<sup>+</sup>=147.09167; found [M+ H]<sup>+</sup>= 147.09128.

### 3,6-Dimethylimidazo[1,2-*a*]pyridine (4c)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 73% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,35 (s, 3H), 2,43 (s, 3H), 7,04 (d, 1H), 7,35 (s, 1H), 7,57 (d, 1H), 7,64 (s, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 8,8; 18,2; 116,4; 119,4; 120,5; 122,0; 126,9; 129,7; 143,6; IR (cm<sup>-1</sup>): 796, 1130, 1310, 1505, 1645, 2922; *m/z* = 145 (M<sup>+</sup>-1), 118, 93, 65; C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>, required [M+H]<sup>+</sup>=147.09167; found [M+ H]<sup>+</sup>= 147.09226.

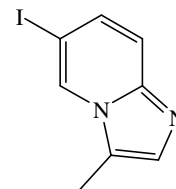
### 3,5-Dimethylimidazo[1,2-*a*]pyridine (4d)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 58% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,78 (s, 3H), 2,85 (s, 3H), 6,41 (t, 1H), 6,95 (t, 1H), 7,28 (s, 1H), 7,40 (d, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 13,6; 20,3; 112,1; 116,1; 121,6; 123,7; 133,2; 136,0; 147,4; IR (cm<sup>-1</sup>): 770, 1042, 1152, 1289, 1452, 1694, 2923; *m/z* = 145 (M<sup>+</sup>-1), 131, 118, 93, 65, 28;

C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>, required [M+H]<sup>+</sup>=147.09167; found [M+ H]<sup>+</sup>= 147.09149.

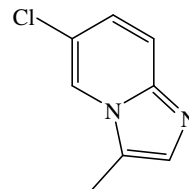
### 6-Iodo-3-methylimidazo[1,2-*a*]pyridine (4e)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 58% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,46 (s, 3H), 7,23-7,43 (m, 3H), 8,12 (s, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 8,9; 118,7; 119,9; 128,0; 128,7; 130,9; 131,9; 143,7; IR (cm<sup>-1</sup>): 794, 1131, 1142, 1303, 2918; *m/z* = 258 (M<sup>+</sup>), 205, 131, 103, 77, 63;

C<sub>8</sub>H<sub>7</sub>IN<sub>2</sub>, required [M+H]<sup>+</sup>=258.97267; found [M+ H]<sup>+</sup>= 258.97363.

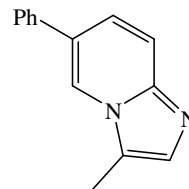
#### 6-Chloro-3-methylimidazo[1,2-*a*]pyridine (4f)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a yellow, amorphous solid in 53% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,47 (s, 3H), 7,15 (d, 1H), 7,44 (s, 1H), 7,63 (d, 1H), 7,92 (s, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 8,9; 117,9; 120,8; 124,9; 131,7; 143,3; IR (cm<sup>-1</sup>): 781, 1109, 1455, 1704, 2850, 2917, 3053; *m/z* = 165 (M<sup>+</sup>-1), 139, 112, 76, 63, 28;

C<sub>8</sub>H<sub>7</sub>ClN<sub>2</sub>, required [M+H]<sup>+</sup>=167.03705; found [M+ H]<sup>+</sup>= 167.03724.

#### 3-Methyl-6-phenylimidazo[1,2-*a*]pyridine (4g)

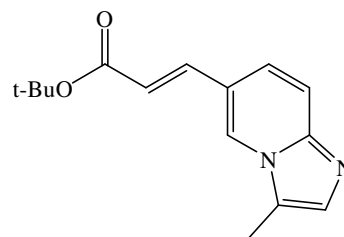


Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 59% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2,52 (s, 3H), 7,40-7,62 (m, 7H), 7,72 (d, 1H), 8,02 (s, 1H); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 9,1; 117,4; 120,1; 124,3; 126,9; 127,1; 127,9; 129,1, 131,3; 137,6; 144,3; IR (cm<sup>-1</sup>): 758, 1261, 1488, 1704, 3057; *m/z* = 207 (M<sup>+</sup>-1), 154, 127, 104, 77;

C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>, required [M+H]<sup>+</sup>=209.10732; found [M+ H]<sup>+</sup>= 209.10803.

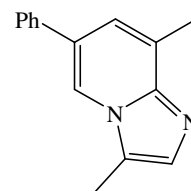


**(E)-*t*-Butyl 3-(3-methylimidazo[1,2-*a*]pyridin-6-yl)acrylate (4h)**



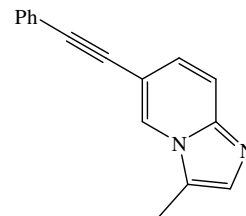
Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 51% yield. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 1,55 (s, 9H); 2,50 (s, 3H), 6,37 (d, 1H), 7,38 (d, 1H), 7,42 (s, 1H), 7,57 (d, 1H), 7,61 (d, 1H), 7,95 (s, 1H); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 9,0; 28,2; 29,7; 80,8; 118,0; 120,6; 120,7; 124,3; 132,2; 139,6; 165,9; **IR** (cm<sup>-1</sup>): 730, 1148, 1637, 1703, 2853, 2925; ***m/z*** = 258 (M<sup>+</sup>), 202, 185, 155, 41, 28; C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>, required [M+H]<sup>+</sup>=259.14410; found [M+ H]<sup>+</sup>= 259.14523.

**3,8-Dimethyl-6-phenylimidazo[1,2-*a*]pyridine (4i)**



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 63% yield. **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ 2,51 (s, 3H), 2,69 (s, 3H), 7,38-7,60 (m, 5H), 7,59 (d, 2H), 7,91(s, 1H); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ 9,3; 17,1; 118,1; 120,7; 123,3; 126,8; 127,1; 127,2; 127,7; 129,0; 130,8; 137,9; 144,8; **IR** (cm<sup>-1</sup>): 696, 758, 1027, 1078, 1488, 2916; ***m/z*** = 222 (M<sup>+</sup>), 169, 152, 115, 77, 28; C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>, required [M+H]<sup>+</sup>=223.12297; found [M+ H]<sup>+</sup>= 223.12359.

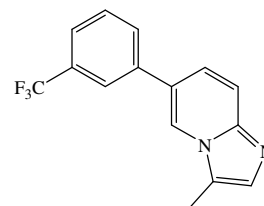
### 3-Methyl-6-(2-phenylethynyl)imidazo[1,2-*a*]pyridine (4j)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 72% yield. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 2,50 (s, 3H), 7,25-7,27 (m, 1H), 7,36-7,38 (m, 3H), 7,45 (s, 1H), 7,54-7,59 (m, 3H), 8,12 (s, 1H); **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ 9,0; 85,8; 90,4; 108,9; 117,5; 122,7; 125,8; 126,0; 128,5; 128,6; 131,6; 132,3; **IR** (cm<sup>-1</sup>): 796, 1023, 1254, 1412, 1630, 2917, 3056; **m/z** = 232 (M<sup>+</sup>), 179, 151, 116, 89, 28;

**C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>**, required [M+H]<sup>+</sup>=233.10732; found [M+ H]<sup>+</sup>= 233.10681.

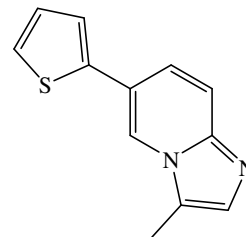
### 6-[3-(Trifluoromethyl)phenyl]-3-methylimidazo[1,2-*a*]pyridine (4k)



Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a brown, amorphous solid in 58% yield. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 2,56 (s, 3H), 7,45 (d, 1H), 7,49 (s, 1H), 7,63 (d, 1H), 7,67 (d, 1H), 7,77 (d, 2H), 7,83 (s, 1H), 7,06 (s, 1H); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 9,1; 117,8; 120,6; 120,7; 123,8; 123,8; 123,9; 124,0; 124,6; 124,7; 125,7; 129,7; 130,4; 131,5; 131,6; 131,8; 138,5; 144,2; **IR** (cm<sup>-1</sup>): 796, 1071, 1261, 2924; **m/z** = 276 (M<sup>+</sup>), 257, 223, 202, 138;

**C<sub>15</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>**, required [M+H]<sup>+</sup>=277.09471; found [M+ H]<sup>+</sup>= 277.09465.

**3-Methyl-6-(thiophen-2-yl)imidazo[1,2-*a*]pyridine (4l)**



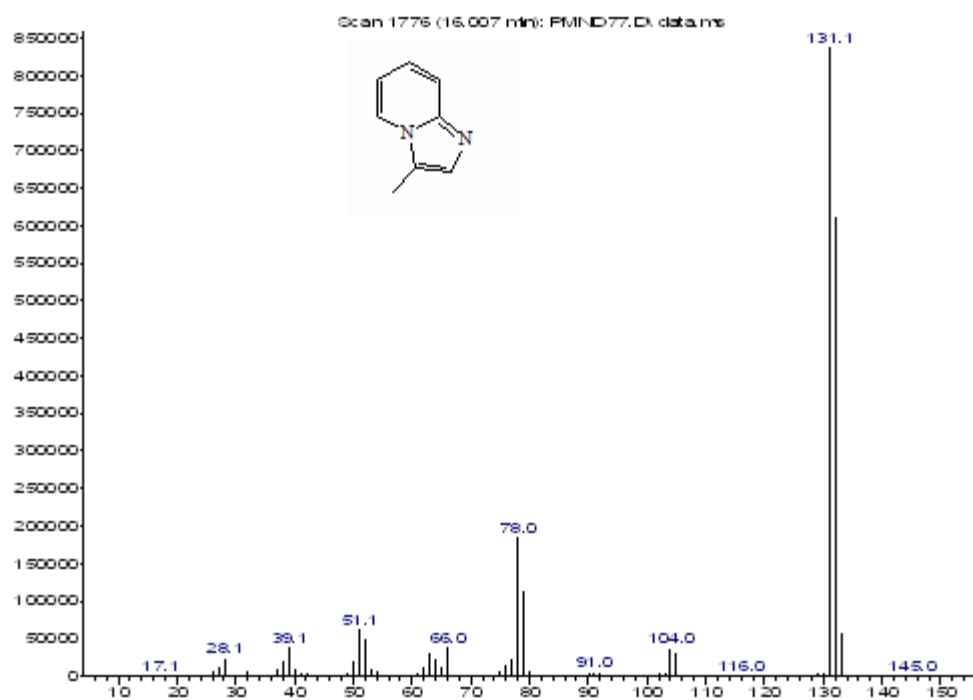
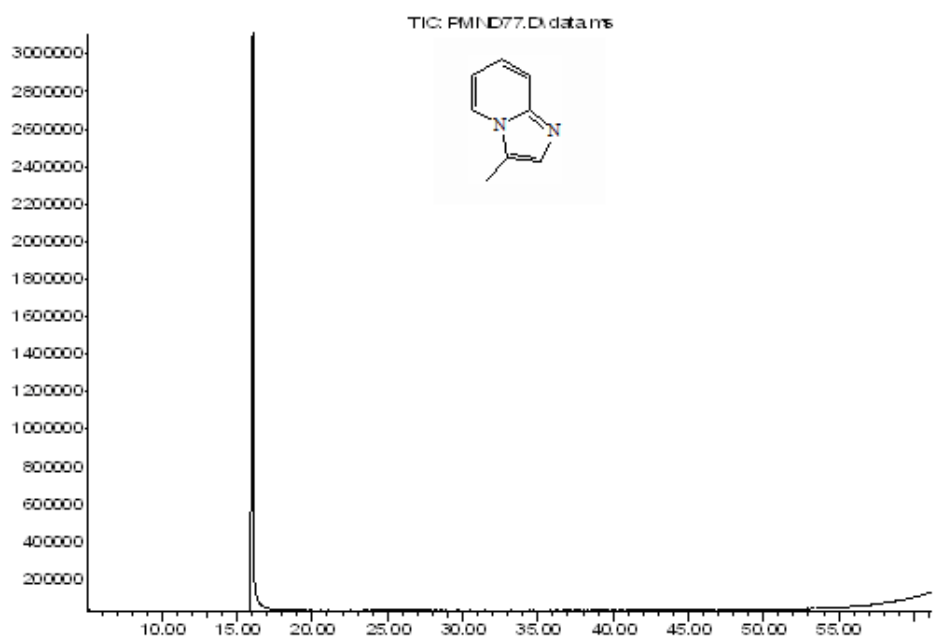
Flash chromatography (SiO<sub>2</sub>, 20:1 v/v EtOAc/MeOH) afforded the product as a green, amorphous solid in 68% yield. **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 2,52 (s, 3H), 7,12 (t, 1H), 7,30 (d, 1H), 7,32 (d, 1H), 7,41 (d, 1H), 7,43 (s, 1H), 7,64 (d, 1H), 8,07 (s, 1H).

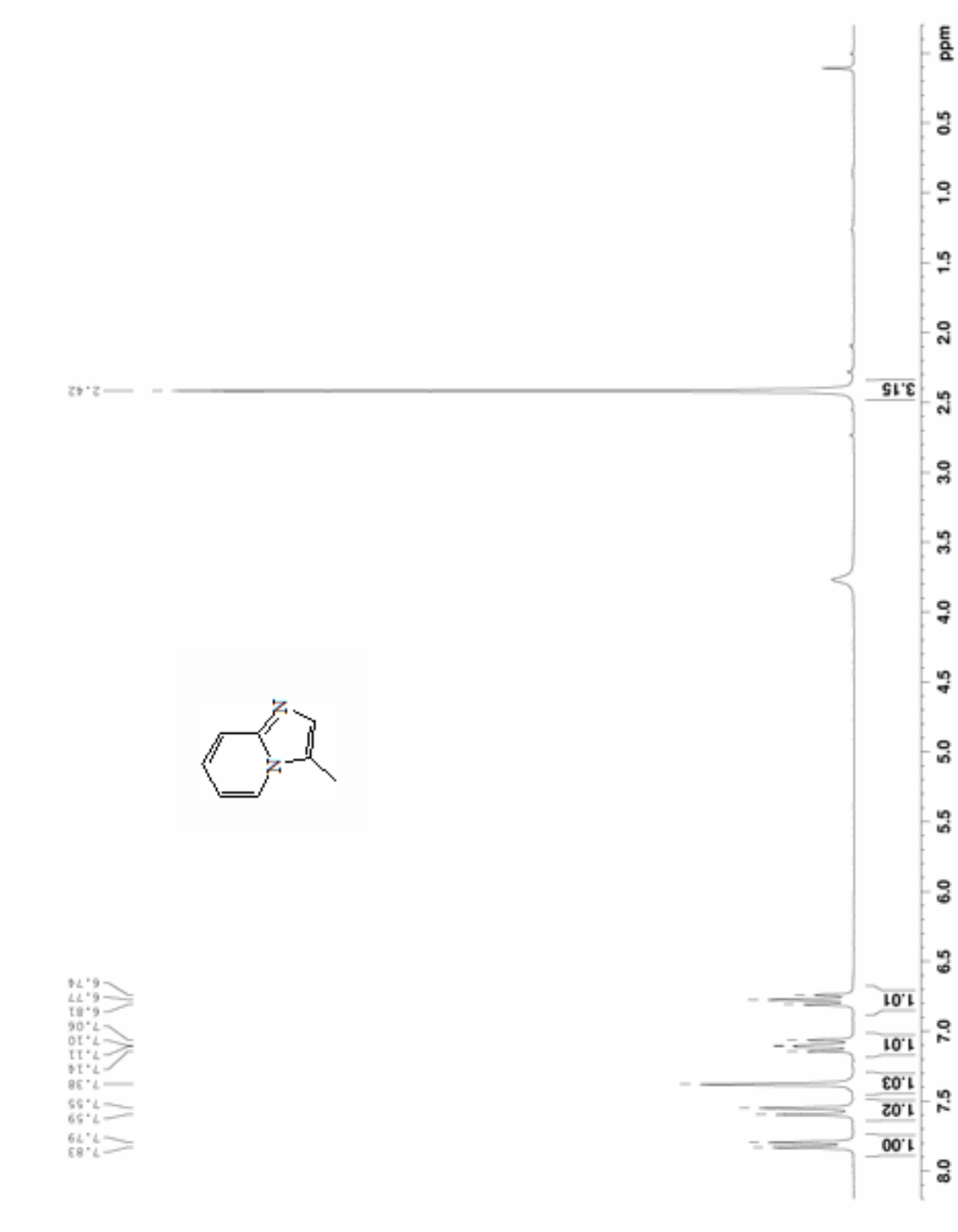
**<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ 9,1; 117,7; 119,0; 120,4; 120,6; 123,3; 123,9; 125,1; 128,2; 131,9; 140,4; 144,4; **IR** (cm<sup>-1</sup>): 790, 1016, 1259, 1500, 1715, 2923; ***m/z*** = 213 (M<sup>+</sup>-1), 160, 134, 107.

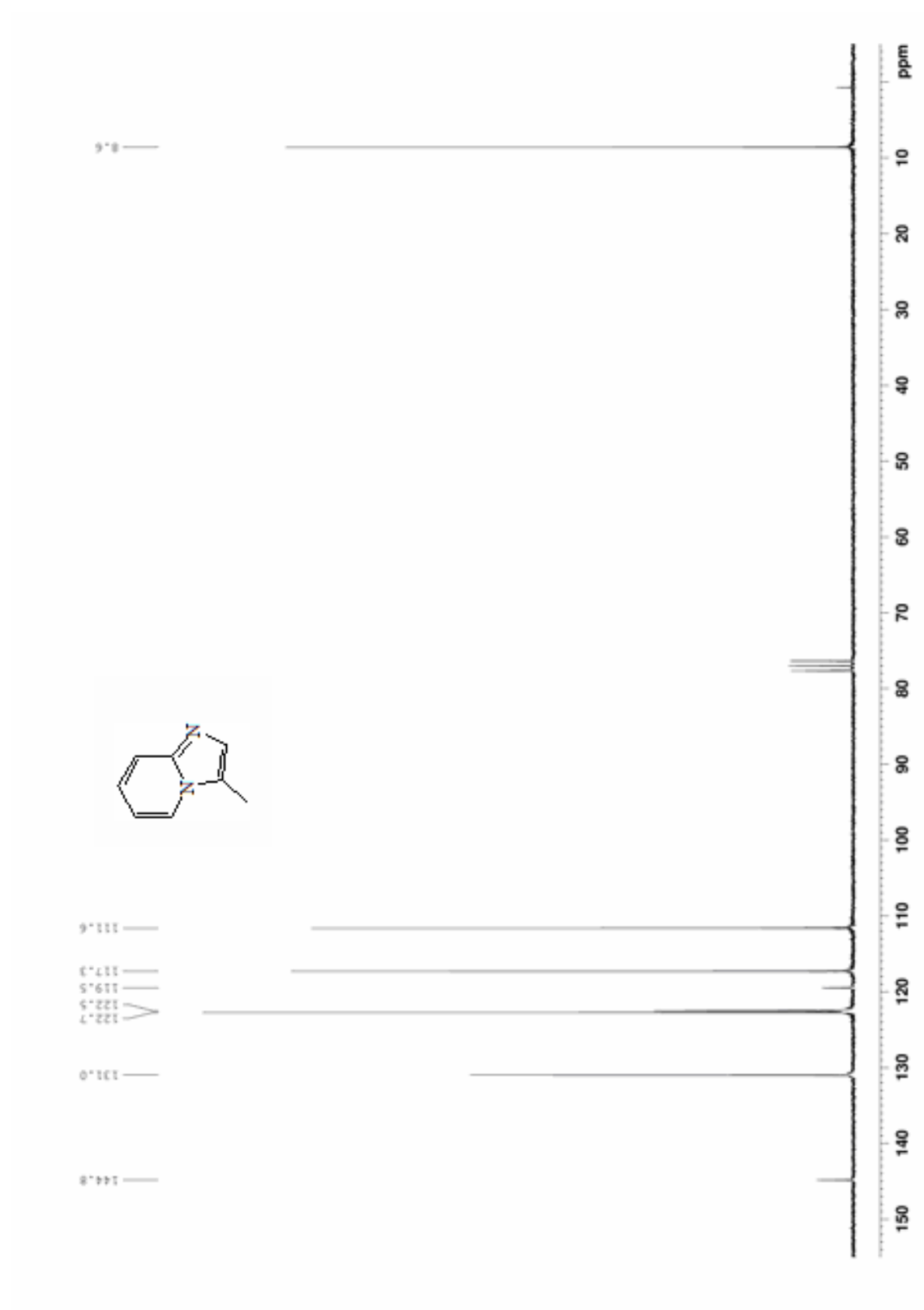
**C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>S**, required [M+H]<sup>+</sup>=215.06375; found [M+ H]<sup>+</sup>= 215.06408.

#### 4. $^1\text{H}$ NMR, $^{13}\text{C}$ NMR and GC/MS spectra of selected compounds

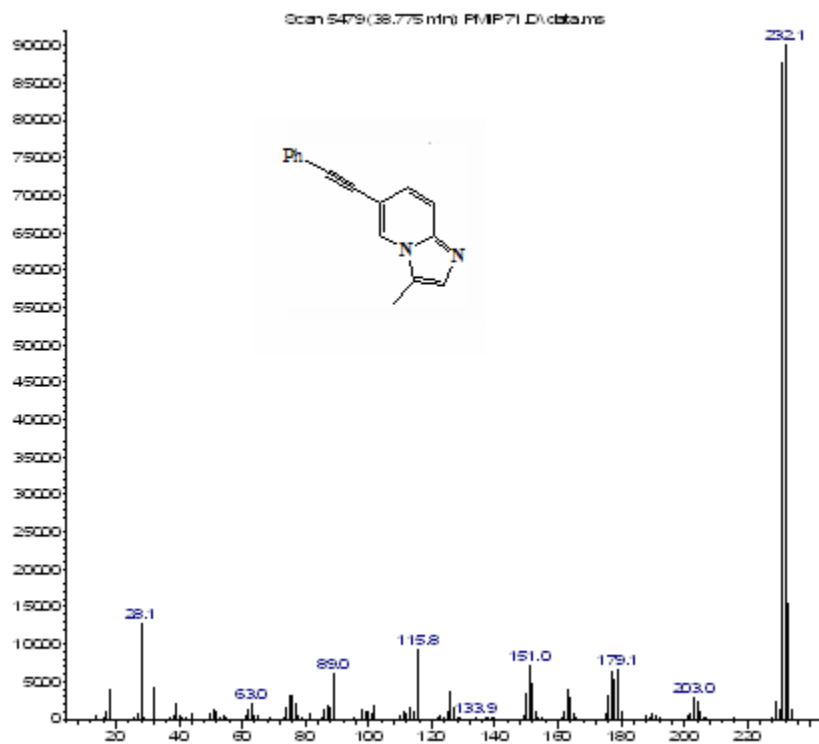
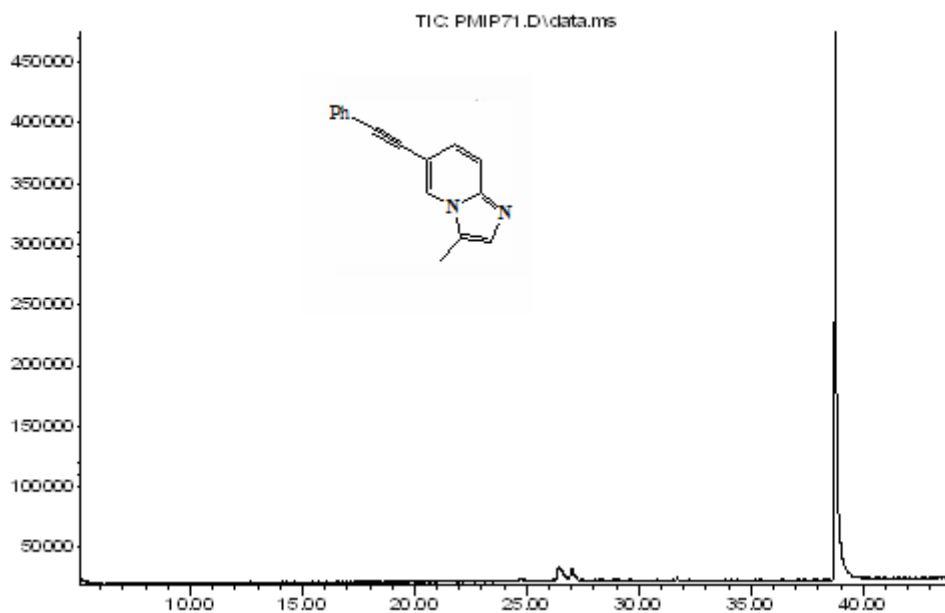
##### GC/MS, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR spectra of 3-methylimidazo[1,2-*a*]pyridine (2)





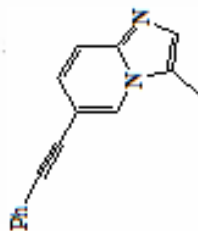
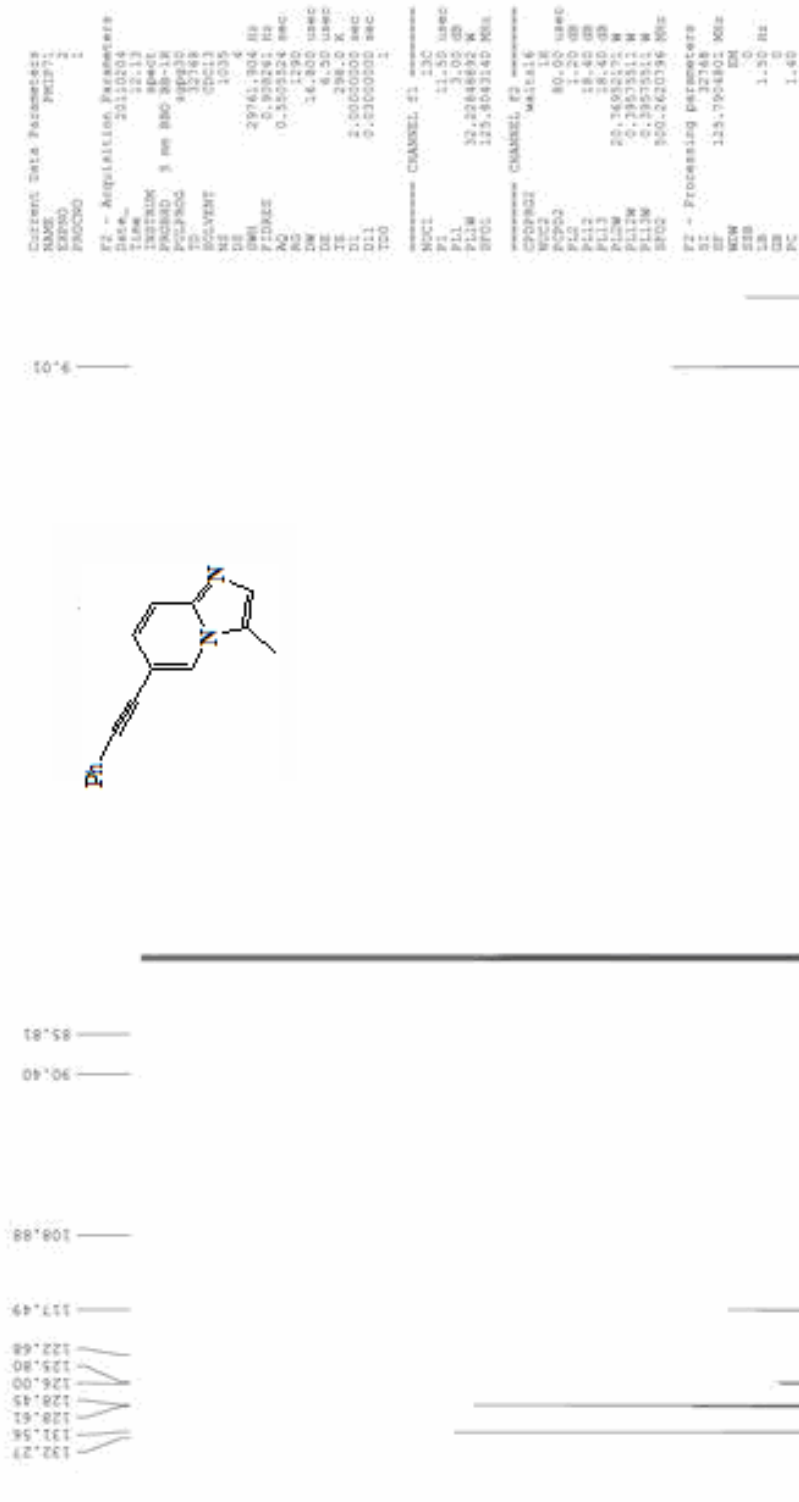


GC/MS,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of 3-methyl-6-(2-phenylethynyl)imidazo[1,2-*a*]pyridine (4j)









GC/MS,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of 3-methyl-6-(thiophen-2-yl)imidazo  
[1,2-*a*]pyridine (4l)

