Versatile and Convenient Methods for the Synthesis of C-2 and C-3 Functionalised 5-Azaindoles

Myriam Lefoix, Jean-Philippe Daillant, Sylvain Routier, Jean-Yves Mérou, Isabelle Gillaizeau, Gérard Coudert* Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d’Orléans, Rue de Chartres, BP 6759, 45067 Orléans Cedex 2, France
Fax +33(2)38417281; E-mail: jean-yves.merour@univ-orleans.fr; E-mail: gerard-coudert@univ-orleans.fr
Received 26 April 2005; revised 17 June 2005

Abstract: Functionalisation at C-2 and C-3 of N-protected-5-azaindole leads to a variety of very useful new substituted 5-azaindole derivatives in fair to good yields.

Keywords: 5-azaindole, lithiation, stannylation, 2-substituted-5-azaindole, 3-substituted-5-azaindole

A considerable number of plant alkaloids or marine organisms contain indole as the structural core. The obvious importance of bioactive indole derivatives in living organisms has spurred chemists to design and synthesise a myriad of indole-containing pharmaceutical agents. The corresponding azaindolic (pyrrolopyridine) derivatives are not so well represented, while the 7-azaindole framework appears in the variolins family (e.g. I) and in tricyclic heterocycles isolated from an antarctic sponge; to the best of our knowledge, the 4-, 5-, and 6-azaindole skeletons have not been found so far in nature. Nevertheless, the evident biological interest, the bioisosteric replacement of the phenyl by a pyridine moiety, of such derivatives has inspired chemists to synthesise azaindole-containing compounds.

For instance fused or non-fused 7-azaindole containing products are now in continuous development due to the commercial availability of 7-azaindole. A ligand for dopamine D1 receptors possessing a 7-azaindole framework has been described. In the area of cancer chemotherapeutics, a 7-aza analogue of the alkaloid olivacine was prepared in our group. In addition, we reported the synthesis of 7-azacarbazoles and more recently we described an original way to synthesise symmetrical and unsymmetrical 7-azaindolocarbazoles with potential anti-tumour activity.

Surprisingly, in the 5-azaindole series, the pioneering work of Bisagni, Dormoy and Heymes who reported the synthesis of 11-aminoazaelipticine derivatives III and the industrial preparation of pazaellipticine IV, respectively, was not followed by other similar work. The 5-azaindole moiety is sometimes introduced as a substituent in more elaborate structures as described for the 2-substituted 5-azaindole derivative V, an inhibitor of coagulation factor Xa. As well, some patents have displayed the potential of azaindoles in medicinal chemistry.

In the course of a program aimed at designing 5-azaindole containing biologically active derivatives we were faced, as others before us, with a lack of background information concerning the reactivity of this heterocyclic system and the difficulty to easily prepare such substituted derivatives. Substituted 5-azaindoles were synthesised almost exclusively from functionalised pyridine precursors. Consequently herein, we wish to describe efficient procedures for the regioselective functionalisation of C-2 and C-3 of the 5-azaindole ring system with a view to preparing more elaborate structures.

The 5-azaindole unit I was prepared from commercially available 3-picoline N-oxide, according to Dormoy’s method and was protected as the benzenesulfonyl derivative in 84% yield using a standard procedure (Scheme 1). Reactions at C-2 were previously investigated by Bisagni and Dormoy who first described the formation of the 2-
lithioderivative of 1-sulfonyl-5-azaindole 2 and its reaction with some electrophiles. According to them, treatment of 2 with a slight excess of LDA (1.2 equiv) in THF at −20 °C in the presence of TMEDA (1.0 equiv) efficiently gave the 2-lithioderivative, which was further trapped with a range of electrophiles (2 equiv), leading to the required 2-substituted derivatives in fair to good yields. (Scheme 2, Table 1). One clear advantage of using LDA instead of BuLi as a base to lithiate 1-sulfonyl-5-azaindole is that the former is well-tolerated by various functional groups.

Scheme 2

Table 1  C-2 Functionalisation of 5-Azaindole 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>Electrophile</th>
<th>E</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ClSn(CH₃)₂</td>
<td>Sn(CH₃)₂</td>
<td>0.5 h</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>I₂</td>
<td>I</td>
<td>0.5 h</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>CHO</td>
<td>3 h</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>ICH₃</td>
<td>CH₃</td>
<td>2 h</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>Acetophenone</td>
<td></td>
<td>4 h</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>B(OOMe)₂</td>
<td>B(OH)₂</td>
<td>5 h</td>
<td>71</td>
</tr>
</tbody>
</table>

* Reactions were performed using LDA (1.2 equiv) except for compound 8 (1.4 equiv).

Compounds 5 and 7 were obtained previously by Dormoy in 52% and 48% yields, respectively; these lower yields are probably a result of the use of an excess of BuLi (1.8 equiv) by the authors. In fact, under such experimental conditions, we observed the formation of 2,3-disubstituted derivatives as a by-product. Compounds 3 and 8 obtained in satisfactory yield are very useful compounds in palladium-catalysed cross-coupling reactions by Stille or Suzuki methodologies; moreover, the 5-azaindole moiety could be introduced by Heck or Sonogashira reactions on appropriate substrates using the 2-lododerivative 4.

Alternatively, functionalisation of the C-3 position of the 5-azaindole moiety was carried out. Only two examples, concerning the preparation of the methyl glyoxal azaindole and the synthesis in low yield of a 3-stannyl derivative, were described. In order to develop a general method, we first prepared the 3-iodo-N-protected azaindoles 10–12. Treatment of 5-azaindole 1 with potassium hydroxide in DMF, followed by addition of iodine, led to the 3-iodo-5-azaindole 9 in 91% yield (previously reported in 42% yield); the latter is more stable compared to the 3-iodoindole. Protection of 9 with Boc₂O in THF, in the presence of DMAP as base, gave the Boc-protected derivative 10 in quantitative yield. 1-Benzenesulfonyl-5-azaindole 11 was also obtained in 78% yield by the reaction of the sodium anion of 9 with benzylsulfonyl chloride. Similarly the MOM protecting group was introduced on 9 using MOMCl and sodium hydride in THF, affording 12 in 77% yield (Scheme 3). The use of a strong base (NaH) for the introduction of the MOM and benzensulfonyl groups might possibly explain the lower yields observed for compounds 11 and 12.

Scheme 3

Then, we undertook the preparation of the 3-stannyl derivative by reacting compounds 10–12 with hexamethylditin in the presence of a catalytic amount of dichlorobis(triphenylphosphine)palladium and anhydrous lithium chloride. The required organostannanes were obtained in 90%, 97% and 95% yields, respectively. It should be mentioned that replacement of the hexamethylditin reagent by the less toxic hexabutylditin was disappointing; the corresponding N-Boc-3-tributylstannyl-5-azaindole was obtained in only 24% yield (this compound was previously reported in low yield by halogen–metal exchange) together with the N-Boc-5-azaindole, after loss of the iodine atom.

In order to assess the diversity of the reaction, we investigated the halogen–lithium exchange of the 3-iododerivative 10 with a range of electrophiles, with a view to obtaining the 3-lithio derivative regioselectively (Scheme 4). Compound 10 was treated with BuLi at −78 °C in THF for 30 minutes and gave the corresponding 3-lithioderivative, which was then quenched with various electrophilic species, affording after work-up the required 3-substituted azaindoles 16–23 in good yields except for compound 20 (Table 2). Isomerisation of the lithio species to the 2-position was never observed, contrary to the indole series.

Scheme 4
We have prepared, in excellent yield, the carboxylic acid 16 (92% yield) and the aldehyde 17 (70% yield); the stanny derivative 13 (93% yield) and the boronate ester 22 (88% yield) thus obtained represent attractive intermediates for the construction of more complex structures possessing a 5-azaindole subunit. Current work on the Stille reaction with compound 13 is underway.

In conclusion we have developed two optimised protocols allowing easy and efficient substitution of positions 2 or 3 of 5-azaindole. These procedures are quite general and the observed yields are generally high, which will allow the design and synthesis of complex 5-azaindole alkaloid analogues. The synthesis of 2,3-disubstituted compounds from the previously monosubstituted 5-azaindole is in progress. Elaboration of biologically active products from stannyl, boronic or iodo derivatives 3, 4, 8, 10, 13 and 22 using palladium-catalysed cross-coupling reactions is also under investigation.

Melting points were determined using a Büchi capillary instrument and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FTIR paragon 1000 spectrometer. NMR spectra were recorded in CDCl₃ or DMSO-d₆ (at 300 K if not specified) on a Bruker Avance DPX 250. Chemical shifts are given in ppm relative to TMS as internal standard. MS were recorded on Perkin-Elmer SCIEX API 300 using ion spray methodology. TLC were run on pre-coated silica gel plates (Merck 60F254) and the spots were visualised using a UV lamp. Flash chromatography was carried out on a column using flash silica gel 60 Merck (40–63 μm) as the stationary phase. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. HRMS were performed by the Centre Régional de Mesures Physiques de l’Ouest de Rennes. Electronic impact analyses were performed on a Micromass MS/MS ZAB Spec TOF with an EBE TOF geometry. Petroleum ether (PE) had a boiling point range 40–60 °C.

1-Benzensulfonyl-1H-pyrrolo[3,2-c]pyridine (2)
To a suspension of NaH (0.76 g, 19.0 mmol, 60% dispersion in mineral oil) in THF (60 mL), under Ar at 0 °C, was added a soln of 5-azaindole 1 (1.50 g, 12.7 mmol) in THF (15 mL). The reaction mixture was stirred for 30 min at r.t., then cooled to 0 °C and C₆H₅SO₂Cl (1.78 mL, 14.0 mmol) was added slowly. The mixture was stirred at r.t. until the starting material had been completely consumed (TLC). The mixture was poured into H₂O (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were washed with brine (50 mL), dried over MgSO₄ and filtered. The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography (EtOAc) to furnish 2 as a white solid (2.7 g, 84%).

**Table 2 C-3 Functionalisation of the 3-Iodo-5-azaindole**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Electrophile (equiv)</th>
<th>BuLi (equiv)</th>
<th>Time (h)</th>
<th>E</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>ClSn(CH₃)₃ (1.5)</td>
<td>1.1</td>
<td>2</td>
<td>Sn(CH₃)₃</td>
<td>93</td>
</tr>
<tr>
<td>16</td>
<td>CO₂ (excess)</td>
<td>1.1</td>
<td>2</td>
<td>COOH</td>
<td>92</td>
</tr>
<tr>
<td>17</td>
<td>DMF (3.0)</td>
<td>1.1</td>
<td>2</td>
<td>CHO</td>
<td>70</td>
</tr>
<tr>
<td>18</td>
<td>ICH₃ (1.5)</td>
<td>1.4</td>
<td>4</td>
<td>CH₃</td>
<td>80</td>
</tr>
<tr>
<td>19</td>
<td>Allylbromide (1.1)</td>
<td>1.4</td>
<td>4</td>
<td>CH₂CH=CH₂</td>
<td>71</td>
</tr>
<tr>
<td>20</td>
<td>4-Methoxybenzaldehyde (2.0)</td>
<td>1.4</td>
<td>5</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>21</td>
<td>Acetophenone (1.3)</td>
<td>1.4</td>
<td>5</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>22</td>
<td>(2.0)</td>
<td>1.4</td>
<td>2</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>23</td>
<td>Acetone (2.0)</td>
<td>1.4</td>
<td>2</td>
<td></td>
<td>63</td>
</tr>
</tbody>
</table>

Functionalisation of Position 2 of N-Benzensulfonyl-5-azaindole 2; General Procedure A
To a soln of compound 2 (200 mg, 0.77 mmol) and N₃N₃N₃N₄-tetraethylhydrazine (0.12 mL, 0.77 mmol) in THF (5 mL), under Ar at -20 °C, LDA (0.480 mL, 1.54 mmol; 2 M soln, THF–heptane–ethylbenzene) was added dropwise. The reaction mixture was stirred for 30 min at -20 °C, followed by the slow addition of
the electrophile (1:2–2 equiv). The mixture was stirred at –20 °C until the starting material had been consumed (TLC). The mixture was poured into H2O (20 mL) and extracted with EtOAc (20 mL). The organic layers were washed with brine (20 mL), dried over MgSO4 and filtered. The solvent was evaporated in vacuo to give the crude product which was purified by flash chromatography.

1-Benzensulfonyl-2-trimethylstannyl-1H-pyrrolo[3,2-c]pyridine (3)

The reaction was carried out as described in general procedure A using C6H5Sn(CH₃)₂ as the electrophile (308 mg, 1.6 mmol, 2 equiv). Purification by flash chromatography (PE–EtOAc, 8:2) furnised 3 as a white solid (309 mg, 95%).


1-Benzensulfonyl-2-methyl-1H-pyrrolo[3,2-c]pyridine (6)

The reaction was carried out as described in general procedure A using CH₃I as the electrophile (0.10 mL, 1.5 mmol, 2 equiv). Purification by flash chromatography (PE–EtOAc, 6:4) furnised 6 as a yellow-brown solid (184 mg, 86%).

Mp 105 °C; Rf 0.2 (PE–EtOAc, 2:8).

IR (KBr): 726, 817, 1093, 1172, 1409 cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 2.56 (s, 3 H, CH₃), 6.78 (d, 1 H, H-6, J₆,₇ = 5.8 Hz), 8.61 (d, 1 H, H-7, J₆,₇ = 5.8 Hz), 1.72 (s, 1 H, H-4).

13C NMR (62.5 MHz, CDCl₃): δ = 126.0 (CH), 130.2 (2 × CH), 131.9 (Cq), 142.3 (Cq), 144.0 (CH), 144.7 (CH-7), 145.2 (Cq).


1-Benzensulfonyl-2-(1-hydroxy-1-phenylethyl)-1H-pyrrolo[3,2-c]pyridine (7)

The reaction was carried out as described in general procedure A using acetophenone as the electrophile (0.09 mL, 1.5 mmol, 2 equiv). Purification by flash chromatography (PE–EtOAc, 8:2) furnised 7 as a white solid (229 mg, 79%).

Mp 142–143 °C; Rf 0.15 (PE–EtOAc, 3:7).

IR (KBr): 1448, 1597, 2980, 3060, 3518 cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 1.96 (s, 3 H, CH₃), 5.38 (br s, 1 H, OH), 7.02 (s, 1 H, H-3), 7.21–7.28 (m, 1 H, CH₂), 7.42–7.45 (m, 1 H, CH), 7.94 (d, 1 H, H-7, J₆,₇ = 5.8 Hz), 8.47 (d, 1 H, H-7, J₆,₇ = 5.8 Hz), 8.89 (s, 1 H, H-4).

13C NMR (62.5 MHz, CDCl₃): δ = 27.3 (CH₃), 109.9 (CH-6), 121.6 (CH-3), 127.4 (2 × CH), 128.0 (Cq), 129.5 (2 × CH), 134.7 (CH), 138.0 (Cq), 142.6 (CH-4), 142.7 (Cq), 144.6 (CH-7).

MS (IS): m/z (%) = 379 (100) [MH]^+.


1-Benzensulfonyl-2-formyl-1H-pyrrolo[3,2-c]pyridine (8)

The reaction was carried out as described in general procedure A using B(OH)₂ as the electrophile (0.10 mL, 1.5 mmol, 2 equiv). The reaction was quenched with H₂O (15 mL) and the aqueous layer was then acidified to pH 1 with HCl (3 N). After standing, the product precipitated and was then filtered to afford 8 as an unstable white solid (185 mg, 84%).

IR (KBr): 1089, 1175, 1683 cm⁻¹.

1H NMR (250 MHz, CDCl₃): δ = 7.49 (s, 1 H, H-3), 7.86 (m, 2 H, CH), 7.37 (7.3 Hz, 8.13 (d, 1 H, H-6, J₆,₇ = 5.4 Hz), 8.65 (d, 1 H, H-7, J₆,₇ = 5.4 Hz), 9.01 (s, 1 H, H-4), 10.49 (s, 1 H, CHO).

13C NMR (62.5 MHz, CDCl₃): δ = 109.9 (CH-6), 117.0 (CH-3), 123.4 (Cq), 127.0 (2 × CH), 129.9 (2 × CH), 135.1 (CH), 137.8 (Cq), 138.2 (Cq), 142.8 (Cq), 147.2 (CH-7), 147.5 (CH-4), 182.3 (C=O).

HRMS (EI): m/z calc'd for C₁₄H₁₁N₂O₃S [M]^+: 263.03608; found: 263.0361.
was stirred for 10 min at r.t. and then a soln of I2 (3.19 g, 12.6 mmol) in DMF (6 mL) was added. After 15 min at r.t., the mixture was poured into a sat. soln of Na2S2O5 (1.29 g) and an aq soln of 28% NH4OH (13 mL) in H2O (192 mL). The precipitate was filtered and washed with H2O to afford 9 as a pale yellow solid which was dried over P2O5 (2.8 g, 91%).

Mp 178–179 °C (dec.); Rf 0.4 (PE–EtOAc, 6:4).

IR (KBr): 3082, 3421 cm–1.

1H NMR (250 MHz, MeOD): δ = 7.43 (dd, 1 H, H-6, J6,7 = 0.9 Hz), 7.49 (s, 1 H, H-2), 8.20 (d, 1 H, H-7, J6,7 = 5.8 Hz), 8.53 (s, 1 H, H-4).

13C NMR (62.5 MHz, CDCl3): δ = 116.8 (s, C(CH3)3), 129.8 (2 × C), 131.0 (CH-2), 139.3 (Cq), 145.2 (CH-4), 145.3 (CH-7).

MS (IS): m/z (%) = 345 (92) [MH]+, 289 (100) [MH – H]+, 245 (29) [MH – Br]+.

HRMS (EI): m/z calc’d for C12H13IN2O2 [MH]+: 344.00218; found: 344.0021.

1-Benzensulfonfyl-3-iodo-1H-pyrrolo[3,2-c]pyridine (11)

To a suspension of NaH (51 mg, 1.28 mmol, 60% dispersion in mineral oil) in DMF (5 mL), under Ar at 0 °C, was added a soln of 9 (250 mg, 1.02 mmol) in DMF (15 mL). The reaction mixture was stirred for 30 min at r.t., then cooled to 0 °C and MOMCl (0.064 mmol) was added slowly. The mixture was stirred for 15 min, then poured into H2O (10 mL) and extracted with EtOAc (20 mL). The organic layers were washed with brine (15 mL), dried over MgSO4 and filtered. The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography (EtOAc) to furnish 11 as a white-brown solid (226 mg, 77%).

Mp 78–79 °C; Rf 0.5 (CH2Cl2–MeOH, 9:1).

IR (KBr): 1083, 1119, 3022 cm–1.

1H NMR (250 MHz, CDCl3): δ = 3.26 (s, 3 H, OCH3), 5.43 (s, 2 H, NCH2O), 7.30 (s, 1 H, H-2), 7.33 (d, 1 H, H-6, J6,7 = 6.0 Hz), 8.43 (d, 1 H, H-7, J6,7 = 6.0 Hz), 8.74 (s, 1 H, H-4).

13C NMR (62.5 MHz, CDCl3): δ = 56.1 (CH3), 56.4 (OCH3), 77.3 (NCH2O), 105.0 (CH-6), 127.4 (Cq), 132.9 (CH-2), 140.6 (Cq), 142.5 (CH-7), 144.7 (CH-4).

Synthesis 2005, No. 20, 3581–3588 © Thieme Stuttgart · New York
1H NMR (250 MHz, CDCl3): δ = −9.0 [Sn(CH3)3], 28.2 [C(CH3)], 84.7 [C(CH3)], 110.2 (CH-6), 114.3 (Cn), 132.3 (CH-2), 132.9 (Cq), 140.9 (Cq), 143.9 (CH-4), 144.8 (CH-7), 149.2 (t-BuOOC).

MS (IS): m/z (%) = 382 (37) [MH]+, 322 (100) [MH – t-Bu]+, 282 (60) [MH – Boc]+.

HRMS (EI): m/z calcd for C18H23N2O5Sn [M + Na]+: 405.0601; found: 405.0598.

1-Benzensulfanyl-3-trimethylstannyl-1H-pyrrolo[3,2-c]pyridine (14)

Stannylation was carried out as described in general procedure B.

Purification by flash chromatography (PE–EtOAc, 6:4) furnished 14 as a white solid (410 mg, 97%).

Mp 142–143 °C; Rf 0.3 (PE–EtOAc, 6:4).

IR (KBr): 1187, 1375 cm−1.

1H NMR (250 MHz, CDCl3): δ = 0.41 [s, 9 H, Sn(CH3)3], 52.2 (JH,11Sn = 57.5 Hz), 7.35 (s, small amount of isotopes, 1 H, H-2), 6.52–7.35 (m, 3 H, ArH), 7.89 (dd, 1 H, H-6, H-7, JH,6,7 = 5.6 Hz), 8.16 (d, 1 H, H-2, JH,6,7 = 5.6 Hz), 8.80 (s, 1 H, H-4).

13C NMR (65.25 MHz, CDCl3): δ = −8.8 [Sn(CH3)3], 108.4 (CH-6), 116.1 (Cn), 127.0 (2 CH, 129.6 (2 × CH, Cq), 131.8 (CH-2), 134.4 (CH), 138.2 (Cq), 140.5 (Cq), 143.9 (CH-7), 145.2 (CH-4).

MS (HN): m/z (%) = 427 (100) [MH]+.

HRMS (EI): m/z calcd for C18H15N2O2S2Sn [M – 0.2 (CH2Cl2–MeOH, 9:1). Purification by flash chromatography (PE–EtOAc, 6:4) furnished 18 as a white solid (108 mg, 80%).

Mp > 250 °C; Rf 0.2 (PE–EtOAc, 6:4).

IR (KBr): 1673, 1743, 2837–2978 cm−1.

1H NMR (250 MHz, CDCl3): δ = 1.67 [s, 9 H, C(CH3)3], 2.32 (s, 3 H, CH3), 2.74 (s, 1 H, H-2), 7.93 (d, 1 H, H-6, JH,5,6 = 5.5 Hz), 8.47 (d, 1 H, H-7, JH,6,7 = 5.5 Hz), 8.82 (s, 1 H, H-4).

13C NMR (62.5 MHz, CDCl3): δ = 95.1 (CH), 28.2 (CH-2), 84.4 [C(CH3)], 109.9 (CH-6), 125.3 (CH-7), 127.6 (Cq), 139.9 (Cq), 142.1 (CH-4), 144.2 (CH-7), 149.2 (t-BuOOC).

MS (IS): m/z (%) = 233 (59) [MH]+, 177 (100) [MH – t-Bu]+, 133 (61) [MH – Boc]+.

HRMS (EI): m/z calcd for C19H14N2O3 [M+]: 232.12118; found: 232.1221.

1-tert-Butyloxy carbonyl-3-formylpyrrolo[3,2-c]pyridine (17)

Halogen–metal exchange was carried out as described in general procedure C using DMF as the electrophile (0.13 mL, 1.7 mmol, 2 equiv). Purification by flash chromatography (PE–EtOAc, 4:6) furnished 17 as a white solid (100 mg, 70%).

IR (KBr): 1673, 1743, 2837–2978 cm−1.

1H NMR (250 MHz, CDCl3): δ = 1.74 [s, 9 H, C(CH3)3], 7.99 (d, 1 H, H-6, JH,5,6 = 5.8 Hz), 8.26 (s, 1 H, H-2), 8.58 (d, 1 H, H-7, JH,6,7 = 5.8 Hz), 9.52 (s, 1 H, H-4), 10.10 (s, 1 H, CHO).

13C NMR (62.5 MHz, CDCl3): δ = 28.0 [C(CH3)], 86.9 [C(CH3)], 110.0 (CH-6), 120.9 (Cq), 122.5 (Cq), 136.4 (CH-2), 140.3 (CH-3), 145.0 (CH-4), 145.8 (CH-7), 148.1 (t-BuOOC), 185.0 (CHO).

HRMS (EI): m/z calcd for C19H14N2O3 [M + Na]+; 246.10044; found: 246.1014.

1-tert-Butyloxy carbonyl-3-methylpyrrolo[3,2-c]pyridine (18)

Halogen–metal exchange was carried out as described in general procedure C using CH1I as the electrophile (0.07 mL, 1.2 mmol). Purification by flash chromatography (PE–EtOAc, 4:6) furnished 18 as a white solid (108 mg, 80%).

1H NMR (250 MHz, CDCl3): δ = 1.67 [s, 9 H, C(CH3)3], 2.32 (s, 3 H, CH3), 2.74 (s, 1 H, H-2), 7.93 (d, 1 H, H-6, JH,5,6 = 5.5 Hz), 8.47 (d, 1 H, H-7, JH,6,7 = 5.5 Hz), 8.82 (s, 1 H, H-4).

13C NMR (62.5 MHz, CDCl3): δ = 95.1 (CH), 28.2 (CH-2), 84.4 [C(CH3)], 109.9 (CH-6), 125.3 (CH-7), 127.6 (Cq), 139.9 (Cq), 142.1 (CH-4), 144.2 (CH-7), 149.2 (t-BuOOC).

HRMS (EI): m/z calcd for C19H14N2O3 [M+]: 232.12118; found: 232.1221.

1-tert-Butyloxy carbonyl-3-(prop-2-enyl)pyrrolo[3,2-c]pyridine (19)

Halogen–metal exchange was carried out as described in general procedure C using allyl bromide as the electrophile (0.10 mL, 1.2 mmol). Purification by flash chromatography (PE–EtOAc, 4:6) furnished 19 as a brown oil (106 mg, 71%).

IR (KBr): 1146, 1732, 2976 cm−1.

1H NMR (250 MHz, CDCl3): δ = 1.56 [s, 9 H, C(CH3)3], 3.50 (dd, 2 H, Hc, Jc,d = 1.2, Jd,e = 6.7 Hz), 5.13–5.24 (m, 2 H, Ha, Ha¢), 5.96–6.09 (m, 1 H, Hb), 7.37 (s, 1 H, H-2), 7.95 (d, 1 H, H-6, JH,5,6 = 5.6 Hz), 8.47 (d, 1 H, H-7, JH,6,7 = 5.6 Hz), 8.85 (s, 1 H, H-4).

13C NMR (62.5 MHz, CDCl3): δ = 28.2 [C(CH3)], 29.4 (CH2), 84.7 [C(CH3)], 110.1 (CH-6), 116.9 (CH-a), 118.4 (Cq), 123.6 (CH-2), 135.3 (CH-b), 140.2 (Cq), 142.6 (CH-4), 144.3 (CH-7), 149.3 (t-BuOOC).

MS (HN): m/z (%) = 259 (75) [MH]+, 203 (85) [MH – t-Bu]+, 159 (100) [MH – Boc]+.

HRMS (EI): m/z calcd for C19H14N2O3 [M+]: 258.13683; found: 258.1380.
1-tert-Butyloxycarbonyl-3-(hydroxy-(4-methoxyphenyl)methyl)pyrrolo[3,2-c]pyridine (20)

Halogen–metal exchange was carried out as described in general procedure C using 4-methoxybenzaldehyde as the electrophile (0.14 mL, 1.2 mmol). Purification by flash chromatography (PE–EtOAc, 1:1) furnished 20 as a yellow oil (97 mg, 47%).

IR (KBr): 1743, 2751–3587 cm–1.

13C NMR (62.5 MHz, CDCl3): δ = 8.58 (s, 1 H, H-4).

1H NMR (250 MHz, CDCl3): δ = 1.56 [s, 9 H, C(CH3)3], 3.64 (s, 3 H, OCH3), 7.47 (s, 1 H, H-2), 7.94 (d, 1 H, 6-H, J6,7 = 5.7 Hz), 8.37 (d, 1 H, H-7, J5,6 = 5.7 Hz), 9.10 (s, 1 H, H-4).


References


