THE SYNTHESIS OF 4-SUBSTITUTED ISOQUINOLINE DERIVATIVES FROM DIETHYL(4-ISOQUINOLYL)BORANE

Minoru Ishikura, Izumi Oda, and Masanao Terashima
Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University,
Ishikari-Tobetsu, Hokkaido 061-02, Japan

Abstract——Syntheses of 4-substituted isoquinolines by the palladium-catalyzed cross-coupling reactions of diethyl(4-isoquinolyl)borane with organic halides are described.

Few general methods for the synthesis of the 4-substituted isoquinoline system, a common structural unit of several isoquinoline alkaloids, have been devised. In connection with our previous work, it was envisioned that the cross-coupling reaction of diethyl(4-isoquinolyl)borane with organic halides in the presence of palladium catalyst would provide a versatile method for the direct introduction of a substituent into the 4-position of isoquinoline. We wish to report here simple and regioselective preparation of various 4-substituted isoquinoline derivatives (3) via diethyl(4-isoquinolyl)borane (1).

\[
\begin{align*}
1 + R-Br & \xrightarrow{\text{Pd}^0} 3 \\
\text{a: } R &= \text{aryl} \\
\text{b: } R &= \text{heteroaryl or alkenyl}
\end{align*}
\]

The reaction of (1 mol eq.) with aryl bromides (2a) (1.5 mol eq.) was conducted in the presence of powdered KOH (3 mol eq.), Bu₄NBr (0.5 mol eq.) and Pd(PPh₃)₄ (0.1 mol eq.) in THF at reflux under nitrogen to give 4-arylsquoquinolines (3a) in moderate to good yields as summarized in Table 1. The formation of other 4-substituted isoquinoline derivatives (3b) was also successful under the same conditions as shown in Table 2. The present procedure for the preparation of 4-aryl-1,2,3,4-tetrahydroisoquinolines is straightforward and simple as compared with the known methods.
### Table 1: Preparation of 4-arylisoquinolines (3a)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>R of 2a</th>
<th>React. time(h)</th>
<th>Yield of 3a (%)</th>
<th>mp(℃) of picrate (Solvent)</th>
<th>mp(℃) of picrate (Solvent)</th>
<th>Formula</th>
<th>Analysis (%)</th>
<th>1H-NMR(CDCl₃) δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>6</td>
<td>70</td>
<td>78-80 (lit.5 82)</td>
<td>81.68</td>
<td>C₁₆H₁₅NO</td>
<td></td>
<td>7.35-7.65 (m, 7H), 7.70-8.00 (m, 2H), 8.42 (s, 1H), 9.16 (s, 1H)</td>
</tr>
<tr>
<td>2-OMe</td>
<td>8</td>
<td>60</td>
<td>89-91 (acetone-hexane)</td>
<td>81.79</td>
<td>C₁₆H₁₅NO</td>
<td></td>
<td>3.58 (s, 3H), 6.95-7.60 (m, 7H), 7.70-7.95 (s, 1H), 8.40 (s, 1H), 9.14 (s, 1H)</td>
</tr>
<tr>
<td>2-NO₂</td>
<td>8</td>
<td>58</td>
<td>oil</td>
<td>52.61</td>
<td>C₂₁H₁₃N₅O₉</td>
<td></td>
<td>7.30-8.20 (m, 8H), 8.39 (s, 1H), 9.26 (s, 1H)</td>
</tr>
<tr>
<td>4-NO₂</td>
<td>6</td>
<td>64</td>
<td>162-163 (acetone-ether)</td>
<td>52.61</td>
<td>C₂₁H₁₃N₅O₉</td>
<td></td>
<td>7.50-7.85 (m, 5H), 7.90-8.10 (m, 1H), 8.35 (d, 2H, J=9 Hz) 8.43 (s, 1H), 9.24 (s, 1H)</td>
</tr>
<tr>
<td>2-NH₂</td>
<td>6</td>
<td>61</td>
<td>115-117 (acetone-ether)</td>
<td>81.79</td>
<td>C₁₅H₁₂N₂</td>
<td></td>
<td>3.51 (br s, 2H), 6.70-7.35 (m, 4H), 7.40-7.70 (m, 3H), 7.70-8.10 (m, 1H), 8.42 (s, 1H), 9.16 (s, 1H)</td>
</tr>
<tr>
<td>2-COOMe</td>
<td>6</td>
<td>55</td>
<td>oil</td>
<td>56.10</td>
<td>C₂₃H₁₆N₄O₉</td>
<td></td>
<td>3.40 (s, 3H), 7.20-7.75 (m, 6H), 7.80-8.15 (m, 2H), 8.36 (s, 1H), 9.20 (s, 1H)</td>
</tr>
<tr>
<td>4-COOMe</td>
<td>6</td>
<td>60</td>
<td>135-136 (acetone-hexane)</td>
<td>77.55</td>
<td>C₁₇H₁₃N₂</td>
<td></td>
<td>3.91 (s, 3H), 7.40-8.25 (m, 8H), 8.40 (s, 1H), 9.20 (s, 1H)</td>
</tr>
<tr>
<td>2-COCH₃</td>
<td>5</td>
<td>45</td>
<td>oil</td>
<td>57.98</td>
<td>C₂₃H₁₆N₄O₈</td>
<td></td>
<td>2.00 (s, 3H), 7.40-8.10 (m, 8H), 8.32 (s, 1H), 9.19 (s, 1H)</td>
</tr>
<tr>
<td>4-COCH₃</td>
<td>5</td>
<td>62</td>
<td>116-117 (acetone-hexane)</td>
<td>82.57</td>
<td>C₁₇H₁₃NO</td>
<td></td>
<td>2.60 (s, 3H), 7.40-8.20 (m, 8H), 8.40 (s, 1H), 9.18 (s, 1H)</td>
</tr>
</tbody>
</table>

* isolated yield by flash chromatography (hexane : AcOEt = 4 : 1)
Table 2  Preparation of 4-substituted isoquinolines (3b)

\[
\begin{array}{ccccccc}
R-\text{Br} (2b) & \text{React. time} & \text{Product (3b)} & \text{Yield (%)} & \text{mp (°C) of picrate (Solvent)} & \text{Formula} & \text{Analysis (%)} & \text{H-NMR (CDCl₃) δ} \\
& (h) & & & & & & \\
\hline
\text{N-Br} & 5 & \text{b) } & 60 \text{ c) } & 209-211 \text{ (EtOH)} & C_{20}H_{13}N_2O_7 & 55.10 & 3.01 & 16.09 & 7.20-8.40 \text{ (m, 7H), 8.59 (s, 1H), 8.70-8.80 (m, 1H), 9.22 (s, 1H)} \\
\text{N-Br} & 5 & \text{b) } & 64 \text{ c) } & 238-240 \text{ (EtOH)} & C_{20}H_{13}N_2O_7 & 55.18 & 3.01 & 16.09 & 7.30-8.10 \text{ (m, 6H), 8.42 (s, 1H), 8.64-8.76 (m, 2H), 9.23 (s, 1H)} \\
\text{S-Br} & 6 & \text{b) } & 65 \text{ d) } & 198-200 \text{ (EtOH)} & C_{19}H_{12}N_2O_7 & 51.82 & 2.75 & 12.72 & 7.10-7.70 \text{ (m, 5H), 7.80-8.00 (m, 2H), 8.45 (s, 1H), 9.06 (s, 1H)} \\
\text{O-Br} & 5 & \text{b) } & 48 \text{ d) } & 182-183 \text{ (EtOH)} & C_{19}H_{12}N_2O_7 & 53.78 & 2.85 & 13.20 & 6.65 (s, 1H), 7.50-7.80 \text{ (m, 4H), 7.80-8.10 (m, 2H), 8.47 (s, 1H), 9.13 (s, 1H)} \\
\text{Br} & 19 & \text{b) } & 60 \text{ c) } & \text{---} & \text{---} & \text{---} & \text{---} & 7.30-7.80 \text{ (m, 6H), 7.90-8.20 (m, 2H), 8.53 (s, 2H), 9.33 (s, 2H)} \\
\text{(lit. 149)} & & & & & & & & \\
\end{array}
\]
<table>
<thead>
<tr>
<th>R-Br(2b)</th>
<th>React. time (h)</th>
<th>Product(3b)</th>
<th>Yield(%)</th>
<th>mp(°C) of picrate (Solvent)</th>
<th>Formula</th>
<th>Analysis</th>
<th>1H-NMR(CDC13) δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>C</strong></td>
<td><strong>H</strong></td>
</tr>
<tr>
<td>Br</td>
<td>5</td>
<td><img src="image1" alt="image" /></td>
<td>70 d)</td>
<td>171-172 (EtOH)</td>
<td>C_{18}H_{14}N_{4}O_{7}</td>
<td>54.28 3.54 14.07 (54.32 3.53 13.93)</td>
<td>2.18 (s, 3H), 5.06 (br s, 1H) 5.40 (br s, 1H), 7.20-7.60 (m, 2H), 7.70-8.00 (m, 2H), 8.31 (s, 1H), 9.05 (s, 1H)</td>
</tr>
<tr>
<td>CH3CH=CHBr a)</td>
<td>4</td>
<td><img src="image2" alt="image" /></td>
<td>72 d)</td>
<td>189-191 (EtOH)</td>
<td>C_{18}H_{14}N_{4}O_{7}</td>
<td>54.28 3.54 14.07 (54.33 3.52 14.15)</td>
<td>1.91 (d, 3H, J=6 Hz), 6.19 (q, 1H, J=6, 15 Hz), 6.90 (d, 1H, J=15 Hz), 7.30-8.10 (m, 4H), 8.48 (s, 1H), 9.02 (s, 1H)</td>
</tr>
<tr>
<td>PhC=CBr</td>
<td>6</td>
<td><img src="image3" alt="image" /></td>
<td>65 d)</td>
<td>78-80 e) (benzene)</td>
<td><strong>---------</strong></td>
<td><strong>---------</strong></td>
<td>6.95-8.20 (m, 1H), 8.62 (s, 1H), 9.03 (s, 1H)</td>
</tr>
<tr>
<td>PhC=CBr</td>
<td>6</td>
<td><img src="image4" alt="image" /></td>
<td>77 d)</td>
<td>63-65 e) (ether-hexane)</td>
<td><strong>---------</strong></td>
<td><strong>---------</strong></td>
<td>7.20-7.90 (m, 8H), 8.20 (d, 1H, J=8 Hz), 8.65 (s, 1H), 9.05 (s, 1H)</td>
</tr>
</tbody>
</table>

**Notes:**
- a) isomeric mixture
- b) oil
- c) isolated yield by flash chromatography (hexane : AcOEt = 1 : 1)
- d) isolated yield by flash chromatography (hexane : AcOEt = 4 : 1)
- e) mp(°C) of base
- f) bp(°C) of base
The reaction of 1 with p-methoxybromobenzene gave 4 (72% yield) which was converted into 5 in 68% yield upon treatment with methyl iodide followed by the catalytic hydrogenation with PtO₂ in MeOH.

Transformation of 4-(1-propenyl)isoquinoline (6) to the pyrrolo[3,2,1-de]phenanthridine ring system could be accomplished. Thus, treatment of 6 [derived from 1 and 1-bromo-1-propene in 72% yield (Table 2)] with 4-bromo-1-butene at 100°C followed by the oxidation with K₃Fe(CN)₆ under basic conditions produced dienamide (7) smoothly in 60% yield. Heating 7 in o-dichlorobenzene at 250°C under nitrogen produced 8 in 30% yield.

The present procedure provides general alternative to the known methods for the synthesis of 4-substituted isoquinoline derivatives.

EXPERIMENTAL

All melting points were determined with a Yanagimoto micro-melting-point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl before use. Infrared spectra were recorded with a Hitachi 270-30 spectrometer. Nuclear magnetic resonance spectra were determined with a
Hitachi R-40 and a JEOL FX-90Q spectrometers. Chemical shifts are reported relative to internal tetramethylsilane and given in \( \delta \)-value. Coupling constants are reported in Hertz and splitting patterns are designated as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on a JEOL JMS-D300 and a JEOL JMS-QH100 spectrometers. Flash chromatography was performed on silica gel 230-400 mesh ASTM obtained from Merck.

Typical Procedure for the Preparation of 4-Substituted Isoquinoline Derivatives:

4-Phenylisoquinoline — A mixture of 1 (394 mg, 2 mmol), bromobenzene (468 mg, 3 mmol), powdered KOH (336 mg, 6 mmol), \( \text{Bu}_4\text{NBr} \) (322 mg, 1 mmol), and \( \text{Pd(Ph}_3\text{P)}_4 \) (230 mg, 0.2 mmol) in THF (10 ml) under nitrogen was refluxed for 6 h. The mixture was diluted with AcOEt (60 ml), washed with brine (40 ml), and dried over \( \text{MgSO}_4 \). After removal of the solvent, the residue was purified by flash chromatography with hexane-AcOEt (4:1) as an eluent to give 287 mg (70% yield) of 4-phenylisoquinoline. (Table 1)

4-(4-Methoxyphenyl)isoquinoline (4) — Compound 4 was prepared in 72% yield by the reaction 1 (394 mg, 2 mmol) and p-methoxybromobenzene (558 mg, 3 mmol) in the presence of \( \text{Pd(Ph}_3\text{P)}_4 \) (230 mg, 0.2 mmol), powdered KOH (336 mg, 6 mmol) and \( \text{Bu}_4\text{NBr} \) (322 mg, 1 mmol) in THF (10 ml) under a nitrogen atmosphere in the same manner as described for 4-phenylisoquinoline. Mp 100-101°C (recrystallized from acetone-hexane), mp (picrate) 238-240°C (recrystallized from EtOH) [lit. 10 mp (picrate) 244°C]. \(^1\text{H-NMR}(\text{CDCl}_3) \delta : 3.83(\text{s, 3H}), 6.98(\text{d, 2H, } J=8 \text{ Hz}), 7.20-7.70(\text{m, 4H}), 7.75-8.10(\text{m, 2H}), 8.41(\text{s, 1H}), 9.15(\text{s, 1H}). \) Anal. Calcd for \( \text{C}_{22}\text{H}_{16}\text{N}_4\text{O}_8 \): C, 56.98; H, 3.47; N, 12.06. Found : C, 56.77; H, 3.40; N, 12.04.

4-(4-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (5) — A mixture of 4 (200 mg) and methyl iodide (2 ml) in MeOH (5 ml) was refluxed for 4 h, and then concentrated under reduced pressure. The residue was subjected to the catalytic hydrogenation with \( \text{PtO}_2 \) (10 mg) in MeOH (10 ml) and triethylamine (1 ml) under atmospheric pressure. After hydrogen up-take was ceased, the solvent and catalyst were removed, and the residue was purified by flash chromatography with hexane-AcOEt (2:1) as an eluent to give 146 mg (68% yield) of 5. Mp 121-122°C (recrystallized from acetone-ether). \( \text{IR} (\text{CHCl}_3) : 1612, 1512, 1464 \text{ cm}^{-1}. \) \(^1\text{H-NMR}(\text{CDCl}_3) \delta : 2.37(\text{s, 3H}), 2.40-2.80(\text{m, 1H}), 2.85-3.15(\text{m, 1H}), 3.60-3.70(\text{m, 2H}), 3.71(\text{s, 3H}), 4.10-4.35(\text{m, 1H}), 6.70-7.20(\text{m, 8H}). \) Anal. Calcd for \( \text{C}_{17}\text{H}_{19}\text{NO} : \)}
C, 80.60; H, 7.56; N, 5.53. Found: C, 80.42; H, 7.52; N, 5.47.

2-(3-Butenyl)-4-(1-propenyl)-1-isoquinolone (7) —— A mixture of trans-4-(1-propenyl)isoquinoline (6) (220 mg, 1.3 mmol) and 4-bromo-1-butene (255 mg, 1.9 mmol) was heated at 100°C for 4 h. After cooling, the mixture was dissolved in 20% NaOH solution (10 ml), and K$_2$Fe(CN)$_6$ (855 mg, 2.6 mmol) was added in portions. The mixture was stirred for 2 h, then extracted with AcOEt (50 ml), and the extract was dried over MgSO$_4$. After removal of the solvent, the residue was purified by flash chromatography with AcOEt-hexane (1:4) as an eluent to give 186 mg (60% yield) of 7 as a viscous oil. IR(neat) : 1650, 1622, 1544 cm$^{-1}$. High-resolution MS (m/z) : Calcd for C$_{16}$H$_{17}$NO 239.13092. Found 239.13063.

Product 7 thus obtained was regarded as a mixture of possible isomers (from $^1$H-NMR) and used directly for Diels-Alder reaction without further purification.

4,5-Dihydro-2-methyl-7H-pyrrolo[3,2,1-de]phenanthridin-7-one (8) —— A solution of 7 (100 mg) in o-dichlorobenzene (5 ml) was heated at 250°C for 5 days under a nitrogen atmosphere. After the mixture was concentrated under reduced pressure, the residue was purified by flash chromatography with hexane-AcOEt (1:1) as an eluent to give 30 mg (30% yield) of 8.Mp 215-217°C (recrystallized from acetone-hexane). IR(CHCl$_3$) : 1644, 1628, 1602, 1502, 1486 cm$^{-1}$. $^1$H-NMR(CDCl$_3$) δ : 2.48(s, 3H), 3.38(t, 2H, J=8 Hz), 4.49(t, 2H, J=8 Hz), 7.40-7.90(m, 4H), 8.19(dd, 1H, J=1, 8 Hz), 8.55(dd, 1H, J=1, 8 Hz). Anal. Calcd for C$_{16}$H$_{13}$NO : C, 81.68; H, 5.57; N, 5.95. Found : C, 81.60; H, 5.51; N, 6.05.

ACKNOWLEDGEMENT

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 59570902) from the Ministry of Education, Science and Culture of Japan, which is gratefully acknowledged.

REFERENCES


Received, 2nd February, 1987