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

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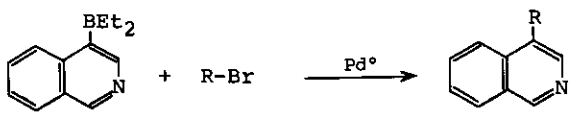
Abstract—— Syntheses of 4-substituted isoquinolines by the palladium-catalyzed cross-coupling reactions of diethyl(4-isoquinolyl)borane with organic halides are described.

Few general methods for the synthesis of the 4-substituted isoquinoline system, a common structural unit of several isoquinoline alkaloids, have been devised.[1] In connection with our previous work,[2] 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).[3]

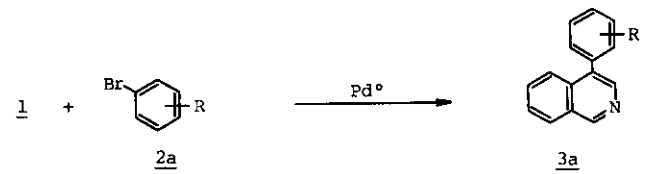



1 2 3

a; R = aryl
b; R = heteroaryl or alkenyl

The reaction of 1 (1 mol eq.) with aryl bromides (2a) (1.5 mol eq.) was conducted in the presence of powdered KOH (3 mol eq.), $Bu_4NBr$ (0.5 mol eq.) and $Pd(Ph_3P)_4$ (0.1 mol eq.) in THF at reflux under nitrogen to give 4-arylisoquinolines (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.[4]

Table 1 Preparation of 4-arylisoquinolines (3a)

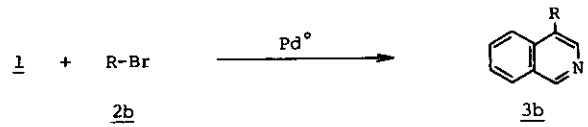



2a 3a

| R of 2a | React. time(h) | Yield of 3a (%)* | mp(°C) (Solvent) | mp(°C) of picrate (Solvent) | Formula | Analysis(%) Calcd(Found) C | H | N | $^1$H-NMR($CDCl_3$) δ |
|---|---|---|---|---|---|---|---|---|---|
| H | 6 | 70 | 78-80 (lit.[5] 82) | -------- | ------- | ---------- | | | 7.35-7.65(m, 7H), 7.70-8.00 (m, 2H), 8.42(s, 1H), 9.16 (s, 1H) |
| 2-OMe | 8 | 60 | 89-91 (acetone-hexane) | -------- | $C_{16}H_{13}NO$ | 81.68 (81.79 | 5.57 5.76 | 5.95 6.11) | 3.58(s, 3H), 6.95-7.60(m, 7H), 7.70-7.95(m, 1H), 8.40 (s, 1H), 9.14(s, 1H) |
| 2-$NO_2$ | 8 | 58 | oil | 227-229 (EtOH) | $C_{21}H_{13}N_5O_9$ | 52.61 (52.62 | 2.73 2.89 | 14.61 14.79) | 7.30-8.20(m, 8H), 8.39(s, 1H), 9.26(s, 1H) |
| 4-$NO_2$ | 6 | 64 | 162-163 (acetone-ether) | 214-216 (EtOH) | $C_{21}H_{13}N_5O_9$ | 52.61 (52.62 | 2.73 2.89 | 14.61 14.65) | 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) |
| 2-$NH_2$ | 6 | 61 | 115-117 (acetone-ether) | -------- | $C_{15}H_{12}N_2$ | 81.79 (82.02 | 5.49 5.58 | 12.72 12.59) | 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) |
| 2-COOMe | 6 | 55 | oil | 197-199 (EtOH) | $C_{23}H_{16}N_4O_9$ | 56.10 (56.11 | 3.28 3.20 | 11.38 11.36) | 3.40(s, 3H), 7.20-7.75(m, 6H), 7.80-8.15(m, 2H), 8.36 (s, 1H), 9.20(s, 1H) |
| 4-COOMe | 6 | 60 | 135-136 (acetone-hexane) | -------- | $C_{17}H_{13}NO_2$ | 77.55 (77.63 | 4.98 5.01 | 5.32 5.26) | 3.91(s, 3H), 7.40-8.25(m, 8H), 8.40(s, 1H), 9.20(s, 1H) |
| 2-$COCH_3$ | 5 | 45 | oil | 218-220 (EtOH) | $C_{23}H_{16}N_4O_8$ | 57.98 (58.09 | 3.39 3.25 | 11.76 11.72) | 2.00(s, 3H), 7.40-8.10(m, 8H), 8.32(s, 1H), 9.19(s, 1H) |
| 4-$COCH_3$ | 5 | 62 | 116-117 (acetone-hexane) | -------- | $C_{17}H_{13}NO$ | 82.57 (82.48 | 5.30 5.34 | 5.66 5.65) | 2.60(s, 3H), 7.40-8.20(m, 8H), 8.40(s, 1H), 9.18(s, 1H) |

* isolated yield by flash chromatography ( hexane : AcOEt = 4 : 1 )

Table 2 Preparation of 4-substituted isoquinolines (3b)




2b 3b

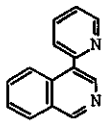
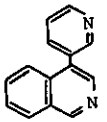
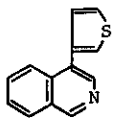
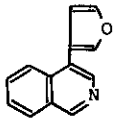
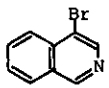
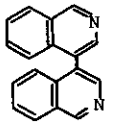
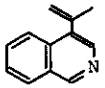
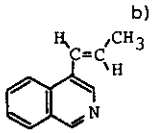
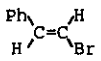
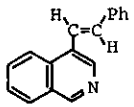
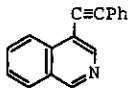
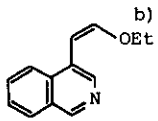
| R-Br (2b) | React. time (h) | Product (3b) | Yield (%) | mp (°C) of picrate (Solvent) | Formula | Analysis (%) Calcd (Found) C | H | N | $^1$H-NMR ($CDCl_3$) δ |
|---|---|---|---|---|---|---|---|---|---|
|  | 5 |  b) | 60 c) | 209-211 (EtOH) | $C_{20}H_{13}N_5O_7$ | 55.18 (55.31 | 3.01 2.91 | 16.09 16.12) | 7.20-8.40(m, 7H), 8.59 (s, 1H), 8.70-8.80(m, 1H), 9.22(s, 1H) |
|  | 5 |  b) | 64 c) | 238-240 (EtOH) | $C_{20}H_{13}N_5O_7$ | 55.18 (55.30 | 3.01 2.90 | 16.09 16.11) | 7.30-8.10(m, 6H), 8.42 (s, 1H), 8.64-8.76(m, 2H), 9.23(s, 1H) |
|  | 6 |  b) | 65 d) | 198-200 (EtOH) | $C_{19}H_{12}N_4O_7S$ | 51.82 (51.69 | 2.75 2.75 | 12.72 12.61) | 7.10-7.70(m, 5H), 7.80-8.00(m, 2H), 8.45(s, 1H), 9.06(s, 1H) |
|  | 5 |  b) | 48 d) | 182-183 (EtOH) | $C_{19}H_{12}N_4O_8$ | 53.78 (54.03 | 2.85 2.77 | 13.20 13.10) | 6.65(s, 1H), 7.50-7.80 (m, 4H), 7.80-8.10(m, 2H), 8.47(s, 1H), 9.13 (s, 1H) |
|  | 19 |  | 60 c) | 150-151 e) (lit.[6] 149) | -------- | | -------- | | 7.30-7.80(m, 6H), 7.90-8.20(m, 2H), 8.53(s, 2H), 9.33(s, 2H) |

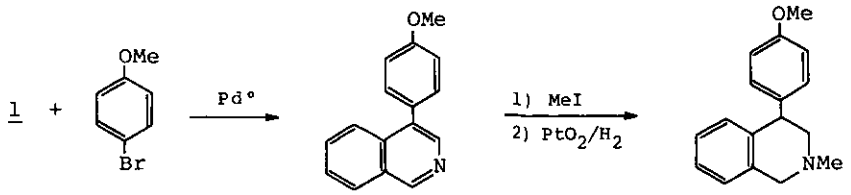
Table 2 Preparation of 4-substituted isoquinolines (3b) (continued)

| R-Br (2b) | React. time (h) | Product (3b) | Yield (%) | mp (°C) of picrate (Solvent) | Formula | Analysis Calcd (Found) C | H | N | $^1$H-NMR ($CDCl_3$) δ |
|---|---|---|---|---|---|---|---|---|---|
|  | 5 |  b) | 70 d) | 171-172 (EtOH) | $C_{18}H_{14}N_4O_7$ | 54.28 (54.32 | 3.54 3.53 | 14.07 13.93) | 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) |
| $CH_3CH=CHBr$ a) | 4 |  b) | 72 d) | 189-191 (EtOH) | $C_{18}H_{14}N_4O_7$ | 54.28 (54.13 | 3.54 3.52 | 14.07 14.15) | 1.91(d, 3H, J=6 Hz), 6.19 (qd, 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) |
|  | 6 |  | 65 d) | 78-80 e) (benzene) (lit.[7] 80-82) | -------- | | -------- | | 6.95-8.20(m, 11H), 8.62(s, 1H), 9.03(s, 1H) |
| PhC≡CBr | 6 |  | 77 d) | 63-65 e) (ether-hexane) (lit.[8] 60-62) | -------- | | -------- | | 7.20-7.90(m, 8H), 8.20(d, 1H, J=8 Hz), 8.65(s, 1H), 9.05(s, 1H) |
|  | 5 |  b) | 59 d) | 104-107/1 f) | $C_{13}H_{13}NO$ | 78.36 (78.19 | 6.58 6.69 | 7.03 6.91) | 1.35(t, 3H, J=7 Hz), 3.96 (q, 2H, J=7 Hz), 5.69(d, 1H, J=7 Hz), 6.43(d, 1H, J=7 Hz), 7.40-8.10(m, 4H), 8.98(s, 1H), 9.06(s, 1H) |

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 )

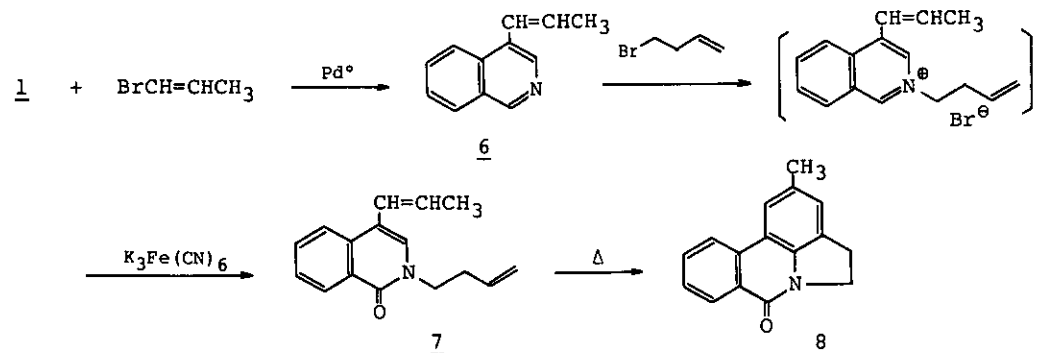
e) mp(°C) of base f) bp(°C) of base

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 $PtO_2$ in MeOH.




4 5

Transformation of 4-(1-propenyl)isoquinoline (6) to the pyrrolo[3,2,1-de]phenanthridine ring system could be accomplished.[9] 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 $K_3Fe(CN)_6$ 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.




6 7 8

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 δ-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), $Bu_4NBr$ (322 mg, 1 mmol), and $Pd(Ph_3P)_4$ (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 $MgSO_4$. 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 $Pd(Ph_3P)_4$ (230 mg, 0.2 mmol), powdered KOH (336 mg, 6 mmol) and $Bu_4NBr$ (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]. $^1$H-NMR($CDCl_3$) δ : 3.83(s, 3H), 6.98(d, 2H, J=8 Hz), 7.20-7.70 (m, 4H), 7.75-8.10(m, 2H), 8.41(s, 1H), 9.15(s, 1H). Anal. Calcd for $C_{22}H_{16}N_4O_8$: 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 $PtO_2$ (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). IR($CHCl_3$) : 1612, 1512, 1464 $cm^{-1}$. $^1$H-NMR($CDCl_3$) δ : 2.37(s, 3H), 2.40-2.80(m, 1H), 2.85-3.15(m, 1H), 3.60-3.70(m, 2H), 3.71(s, 3H), 4.10-4.35(m, 1H), 6.70-7.20(m, 8H). Anal. Calcd for $C_{17}H_{19}NO$ :

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 $K_3Fe(CN)_6$ (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 $^1H$-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 $cm^{-1}$. $^1H$-NMR($CDCl_3$) $\delta$ : 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

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