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Dowex-50W Promoted Friedländer Synthesis of Substituted Quinolines under Solvent-Free Conditions

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Abstract - An efficient method for the synthesis of substituted quinolines using Dowex-50W ion exchange resin as reusable eco-friendly catalyst via Friedländer annulation under solvent-free conditions is described.

Quinoline derivatives have been well known not only in medicinal chemistry, because of their wide occurrence in natural products1 and drugs,2 but also in polymer chemistry, electronics and optoelectronics for their excellent mechanical properties.3 Versatile methods for the synthesis of the quinoline ring system have been developed.4 Friedländer annulation is one of the most simple and straightforward approaches for the synthesis of quinoline derivatives.

Homogeneous acidic catalysts such as H2SO4, HCl, AlCl3, and BF3, among others, are commonly used for organic synthesis carried out in laboratories and industries. However, the above-mentioned catalysts have several disadvantages because they are corrosive, toxic or volatile, and generate large amount of waste. In order to overcome all the drawbacks in the use of environmentally hazardous homogeneous catalysts, new solid acids such as: zeolites, clays, alumina, heteropolyacids, and acidic resins have been tested.5 Each catalyst has its own advantages and disadvantages. It is always interesting to develop a new environmental benign catalyst for organic transformation.

Recently, the use of ion exchange resins in organic synthesis has received great attention.6 It is easy to measure, safe to use, and readily removed at the end of the reaction. We report here using Dowex-50 ion
exchange resin as catalyst for the first time to synthesize substituted quinolines via Friedländer annulation under solvent-free conditions.

Treatment of 2-aminobenzophenone (1) and aryl ketones (2) with Dowex-50 as catalyst at 100 °C for 0.5 h caused cyclodehydration to give substituted quinolines (3) in good yields (Scheme 1). The results are given in Table 1. When the reaction is conducted in a conventional solvent, such as acetonitrile, the preparation of 2,4-dephenylquinoline (3a) needs refluxing for 10 h.

Table 1. Synthesis of substituted quinolines (3a-o)

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<td>4-BrC₆H₄</td>
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Scheme 1
This method is equally effective for cyclic ketone. Cyclopentanone, cyclohexanone and cycloheptanone were chosen to react with 2-aminobenzophenone (1a) to give the corresponding substituted quinolines (4, 5 and 6) in 81, 80 and 83% yields, respectively (Scheme 2).

Scheme 2

In conclusion, we have demonstrated a simple and efficient procedure for the Friedländer synthesis of substituted quinolines using Dowex-50W as catalyst under solvent-free conditions. The significant features of this method include operational simplicity, safe to use, and readily recovered at the end of the reaction.

ACKNOWLEDGEMENT
We gratefully acknowledge the National Council Science of Republic of China for financial support of this work.

EXPERIMENTAL
All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

Typical procedure for the synthesis of 2,4-diphenylquinoline (3a)
A mixture of acetophenone (2a) (240mg, 2.0mmol), 2-aminobenzophenone (1a) (197mg, 1.0mmol), and
Dowex-50W (100mg) was heated for 0.5 h at 100 °C. After cooling to room temperature, the reaction was dissolved in ethyl acetate and Dowex-50W was recovered by filtration. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel eluting with EtOAc-hexane (1:5) to give 3a.

2,4-Diphenylquinoline (3a)
Mp 110-111 °C (Lit., mp 112-113 °C). IR (KBr) v: 3050, 1584, 1541 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.45-7.59 (m, 9H), 7.74 (ddd, J = 1.2, 6.8, 15.2 Hz, 1H), 7.83 (s, 1H), 7.92 (dd, J = 0.8, 8.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.4 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 119.3, 125.6, 125.7, 126.3, 127.5, 128.4, 128.5, 128.8, 129.3, 129.4, 129.5 130.0, 138.3, 139.6, 148.7, 149.1, 156.8. MS (EI) m/z: 281 (M⁺), 280, 202, 176, 139, 125.

2-(4-Methylphenyl)-4-phenylquinoline (3b)
Mp 95-96 °C (Lit., mp 116-117 °C). IR (KBr) v: 3049, 1624, 1548 cm⁻¹. ¹H NMR (CDCl₃) δ: 2.43 (s, 3H), 7.34 (d, J = 8.0 Hz, 2H), 7.44-7.58 (m, 6H), 7.71-7.75 (m, 1H), 7.81 (s, 1H), 7.89 (dd, J = 1.0, 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 2H), 8.23 (d, J = 8.0 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 21.3, 119.1, 125.5, 126.0, 127.3, 128.3, 128.5, 129.3, 129.5, 129.9, 136.7, 138.4, 139.3, 148.7, 148.9, 156.7. MS (EI) m/z: 295 (M⁺), 294, 202, 145, 139.

2-(4-Methoxyphenyl)-4-phenylquinoline (3c)
Mp 78-79 °C (Lit., mp 77-79 °C). IR (KBr) v: 1736 cm⁻¹. ¹H NMR (CDCl₃) δ: 3.89 (s, 3H), 7.06 (ddd, J = 2.6, 2.6, 9.2 Hz, 2H), 7.44-7.58 (m, 6H), 7.69-7.75 (m, 1H), 7.79 (s, 1H), 7.89 (ddd, J = 0.8, 0.8, 8.4 Hz, 1H), 8.19 (ddd, J = 2.4, 2.4, 9.2 Hz, 2H), 8.24 (ddd, J = 0.6, 0.8, 8.4 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 55.3, 114.1, 118.8, 125.4, 125.5, 125.9, 128.3, 128.5, 128.8, 129.4, 129.5, 129.8, 130.1, 132.0, 137.4, 138.4, 148.7, 149.0, 156.3, 160.8. MS (EI) m/z: 311 (M⁺), 310, 268, 267, 140, 139, 132.

2-(4-Fluorophenyl)-4-phenylquinoline (3d)
Mp 63-64 °C. IR (KBr) v: 3056, 1593, 1546 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.19-7.24 (m, 2H), 7.47-7.57 (m, 6H), 7.72-7.76 (m, 1H), 7.78 (s, 1H), 7.91 (dd, J = 1.0, 8.4 Hz, 1H), 8.18-8.24 (m, 3H). ¹³C NMR (CDCl₃,100 MHz) δ: 115.4, 115.7, 118.7, 125.5, 126.2, 128.3, 128.4, 129.2, 129.3, 129.4, 129.5, 129.8, 135.5, 135.6, 138.1, 148.6, 149.1, 155.5, 162.4. MS (EI) m/z: 299 (M⁺), 298, 220, 202, 201, 139, 125. Anal. Calcd for C₁₂H₁₄NF: C, 84.26, H, 4.71, N, 4.68. Found: C, 84.39, H, 4.54, N, 4.53.
2-(4-Chlorophenyl)-4-phenylquinoline (3e)
Mp 104-105 °C (Lit., mp 106 °C). IR (KBr) : 3055, 1589, 1542 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.47-7.57 (m, 8H), 7.79 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.14-8.18 (m, 2H), 8.23 (d, J = 8.4 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 118.6, 125.6, 125.7, 126.5, 128.4, 128.6, 128.8, 128.9, 129.5, 129.6, 130.0, 136.5, 137.9, 138.2, 148.7, 149.4, 155.4. MS (EI) m/z: 317 (M⁺+2), 315 (M⁺), 314, 220, 202, 176, 139.

2-(4-Bromophenyl)-4-phenylquinoline (3f)
Mp 111-112 °C (Lit., mp 128-129 °C). IR (KBr) : 3029, 1584, 1539 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.48-7.57 (m, 6H), 7.64-7.67 (m, 2H), 7.73-7.87 (m, 2H), 7.91 (dd, J = 1.0, 8.4 Hz, 1H), 8.08-8.11 (m, 2H), 8.24 (d, J = 8.4 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 118.7, 123.8, 125.5, 125.7, 126.4, 128.4, 128.5, 129.0, 129.4, 129.6, 130.0, 131.8, 138.1, 138.3, 148.6, 149.3, 155.3. MS (EI) m/z: 361 (M⁺+2), 360 (M⁺+1), 359 (M⁺), 279, 278, 202, 139.

2-(2-Furyl)-4-phenylquinoline (3g)
Mp 98-99 °C (Lit., mp 109-111 °C). IR (KBr) : 3060, 1594, 1546 cm⁻¹. ¹H NMR (CDCl₃) δ: 6.60 (dd, J = 1.6, 3.6 Hz, 1H), 7.25 (m, 1H), 7.43-7.57 (m, 6H), 7.63 (dd, J = 0.6, 1.8 Hz, 1H), 7.74 (ddd, J = 1.0, 6.8, 8.4 Hz, 1H), 7.78 (s, 1H), 7.87 (dd, J = 1.2, 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 110.1, 112.1, 117.6, 125.6, 125.7, 126.1, 128.3, 128.4, 129.4, 129.5, 129.8, 138.0, 144.0, 148.4, 148.5, 148.9, 153.6. MS (EI) m/z: 271 (M⁺), 270, 243, 242, 241, 120.

4-Phenyl-2-(2-thienyl)quinoline (3h)
Mp 92-93 °C (Lit., mp 89-92 °C). IR (KBr) υ: 3054, 1585, 1543 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.16 (dd, J = 3.8, 5.0 Hz, 1H), 7.42-7.57 (m, 7H), 7.63-7.74 (m, 3H), 7.84 (ddd, J = 0.8, 8.4 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 117.8, 125.6, 125.7, 125.8, 126.0, 128.0, 128.4, 128.5, 128.6, 129.4, 129.5, 129.6, 138.0, 145.3, 148.5, 148.7, 151.7. MS (EI) m/z: 287 (M⁺), 286, 253, 202, 200.

2-(4-Nitrophenyl)-4-phenylquinoline (3i)
Mp 156-157 °C (Lit., mp 162-163 °C). IR (KBr) υ: 3055, 1588, 1547 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.52-7.58 (m, 6H), 7.77-7.81 (m, 1H), 7.86 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.37-8.42 (m, 4H). ¹³C NMR (CDCl₃,100 MHz) δ: 119.0, 120.8, 123.3, 123.9, 125.7, 126.0, 127.2, 128.1,
128.2, 128.6, 129.3, 129.4, 130.0, 130.2, 130.9, 137.8, 145.3, 148.2, 148.7, 149.8, 153.9. MS (EI) m/z: 326 (M⁺), 325, 280, 278, 202, 176, 139.

3-Methyl-2,4-diphenylquinoline (3j)
Mp 134-135 °C (Lit., mp 145-146 °C). IR (KBr) v: 3048, 1609, 1568 cm⁻¹. ¹H NMR (CDCl₃) δ: 2.17 (s, 3H), 7.32-7.34 (m, 2H), 7.40 -7.58 (m, 8H), 7.62 -7.68 (m, 3H), 8.20 (d, J = 8.4 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 18.5, 115.8, 126.1, 126.5, 126.9, 127.7, 127.9, 128.0, 128.2, 128.4, 128.6, 128.8, 129.2, 129.3, 137.5, 141.3, 146.1, 147.6, 160.6. MS (EI) m/z: 295 (M⁺), 294, 217, 189, 139.

2,3,4-Triphenylquinoline (3k)
Mp 190-191 °C (Lit., mp 189-190 °C). IR (KBr) v: 3052, 1603, 1547 cm⁻¹. ¹H NMR (CDCl₃) δ: 6.88-6.91 (m, 2H), 6.99 -7.02 (m, 3H), 7.14 -7.16 (m, 2H), 7.21 -7.23 (m, 3H), 7.26 -7.31 (m, 3H), 7.38-7.40 (m, 2H), 7.46 (ddd, J = 1.2, 6.8, 8.4 Hz, 1H), 7.59 (dd, J = 1.2, 8.4 Hz, 1H), 7.74 (ddd, J = 1.2, 6.8, 8.4 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H). ¹³C NMR (CDCl₃,100 MHz) δ: 126.2, 126.4, 126.5, 127.1, 127.2, 127.4, 127.5, 127.6, 129.2, 129.5, 129.8, 130.1, 131.2, 132.8, 136.8, 138.2, 141.0, 147.2, 147.5, 158.8. MS (EI) m/z: 357 (M⁺), 356, 278, 176, 171.

6-Chloro-2-(4-bromophenyl)-4-phenylquinoline (3l)
Mp 173-175 °C (Lit., mp 174-176 °C). IR(KBr) v: 3060, 1062, 1591 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.54-7.58 (m, 5H), 7.64-7.70 (m, 3H), 7.80 (s, 1H), 7.86 (d, J = 2.2 Hz, 1H), 8.08 (d, J = 11.2 Hz, 2H), 8.15 (d, J = 12.4Hz, 1H). MS (EI) m/z: 397 (M⁺+4), 395 (M⁺+2), 393 (M⁺), 358. Anal. Calcd for C₂₁H₁₃BrClN: C, 63.90, H, 3.32, N, 3.55. Found: C, 63.87, H, 3.14, N, 3.58.

6-Chloro-2-(4-chlorophenyl)-4-phenylquinoline (3m)
Mp 162-162 °C (Lit., mp 164-166 °C). IR(KBr) v: 3056, 1062, 1585 cm⁻¹. ¹H NMR (CDCl₃) δ: 7.49-7.58 (m, 7H), 7.64-7.70 (m, 3H), 7.80 (s, 1H), 7.86 (d, J = 2.8 Hz, 1H), 8.13 (d, J = 2.0 Hz, 2H), 8.16 (d, J = 3.2 Hz, 1H). MS (EI) m/z: 353 (M⁺+4), 351 (M⁺+2), 349 (M⁺), 314. Anal. Calcd for C₂₁H₁₃Cl₂N: C, 72.02, H, 3.74, N, 4.00. Found: C, 72.06, H, 3.78, N, 4.23.

6-Chloro-2-(4-methylphenyl)-4-phenylquinoline (3n)
Mp 132-134 °C (Lit., mp 132-134 °C). IR(KBr) v: 3046, 1602, 1581 cm⁻¹. ¹H NMR (CDCl₃) δ: 2.44 (s, 3H), 7.33 (d, J = 10.8 Hz, 2H), 7.52-7.57 (m, 5H), 7.66 (dd, J = 2.8, 12.0 Hz), 7.82 (s, 1H), 7.85 (d, J = 2.8 Hz, 1H), 8.09 (d, J = 11.2 Hz, 2H), 8.16 (d, J = 12.0 Hz, 1H). MS (EI) m/z: 331 (M⁺+2), 329 (M⁺),
294. Anal. Calcd for C\textsubscript{22}H\textsubscript{16}ClN: C, 80.11, H, 4.89, N, 4.25. Found: C, 80.18, H, 4.77, N, 4.35.

6-Chloro-2-(4-nitrophenyl)-4-phenylquinoline (3o)

Mp 219-220 °C (Lit.,\textsuperscript{14} mp 218-220 °C). IR(KBr) v: 3040, 1611, 1524 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}) δ: 7.53-7.58 (s, 5H), 7.72 (dd, J = 3.2, 12.0 Hz, 1H), 7.88 (s, 1H), 7.90 (d, J = 3.2 Hz, 1H), 8.20 (d, J = 12.4 Hz, 1H). MS (EI) m/z: 362 (M\textsuperscript{+}+2), 360 (M\textsuperscript{+}), 314, 278. Anal. Calcd for C\textsubscript{21}H\textsubscript{13}ClN\textsubscript{2}O\textsubscript{3}: C, 69.91, H, 3.63, N, 7.76. Found: C, 69.95, H, 3.72, N, 7.62.

2,3-Dihydro-9-phenyl-1H-cyclopenta[b]quinoline (4)

Mp 131-132 °C (Lit.,\textsuperscript{15} mp 130 °C). IR (KBr) v: 3058, 2923, 1569, 1485, 831 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ: 2.15-2.19 (m, 2H), 2.91 (t, J = 7.2 Hz, 2H), 3.24 (t, J = 7.6 Hz, 2H), 7.35-7.41 (m, 3H), 7.47-7.54 (m, 3H), 7.60-7.64 (m, 2H), 8.06-8.08 (m, 1H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ: 23.5, 30.3, 35.1, 125.4, 125.6, 126.2, 128.2, 128.4, 129.2, 133.6, 136.7, 142.6, 147.9, 167.4. EI-MS m/z: 245 (M\textsuperscript{+}), 244, 217, 168.

9-Pheyl-1,2,3,4-tetrahydroacridine (5)

Mp 137 °C (Lit.,\textsuperscript{15} mp 138 °C). IR (KBr) v: 3061, 2940, 2860, 1570, 1485, 1440, 1220, 765, 705 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ: 1.75-1.81 (m, 2H), 1.93 -1.99 (m, 2H), 2.59 (t, J = 6.8 Hz, 2H), 3.18 (t, J = 6.8 Hz, 2H), 7.20-7.35 (m, 4H), 7.46-7.55 (m, 3H), 7.63-7.65 (m, 1H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ: 22.4, 22.7, 27.8, 33.3, 125.8, 125.8, 126.6, 127.1, 127.9, 128.6, 128.8, 129.0, 136.5, 144.6, 147.9, 158.5; EI-MS m/z: 259 (M\textsuperscript{+}), 244, 230, 217, 202, 189, 121.

11-Phenyl-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline (6)

Mp 109-110 °C (Lit.,\textsuperscript{16} 105-107 °C). IR (KBr) v: 3054, 2927, 2851, 1571, 1485, 1443, 1196, 762, 708 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ: 1.61 (s, 2H), 1.86 (d, J = 2.4 Hz, 4H), 2.72 (t, J = 5.6 Hz, 2H), 3.38 (d, J = 3.6 Hz, 2H), 7.22-7.23 (m, 2H), 7.23-7.38 (m, 2H), 7.46-7.52 (m, 3H), 7.63 (t, J = 8.0 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ: 26.7, 28.1, 30.5, 31.6, 38.9, 126.0, 126.3, 126.8, 127.2, 128.4, 128.8, 129.1, 134.1, 136.9, 143.9, 146.9, 164.1. EI-MS m/z: 273 (M\textsuperscript{+}), 272, 258, 244, 231, 230.

REFERENCES


