Pergamon

Tetrahedron 55 (1999) 13193–13200

TETRAHEDRON

A Direct Anionic Cyclization of 2-Alkynylbenzonitrile to 3-Substituted-1(2*H*)-isoquinolones and 3-Benzylideneisoindol-2-ones Initiated by Methoxide Addition

Ming-Jung Wu*[,a], Li-Juan Chang[a], Li-Mei Wei[b] and Chi-Fong Lin[a]

[a]School of Chemistry, Kaohsiung Medical College, Kaohsiung, Taiwan

[b]Department of Applied Chemistry, Fooyin Institute of Technology, Kaohsiung County, Taiwan

Received 20 May 1999; revised 25 August 1999; accepted 9 September 1999

Abstract: Treatment of 2-(2-alkylethynyl)benzonitrile with sodium methoxide in refluxing methanol for 12 h gave 3-alkyl-1(2*H*)-isoquinolone in modest yield. Under the same reaction conditions, methanolysis of 2-(2-arylethynyl)benzonitrile lead to the formation of 3-alkylidene isoindol-1-one. Partial hydrolysis of 2-(1-hexynyl)benzonitrile to the corresponding benzamide, followed by treatment of the benzamide with sodium methoxide in refluxing methanol gave 3-pentylidene isoindol-1-one in 49% yield. This suggests that the benzamide is not involved in this cyclization reaction.

INTRODUCTION

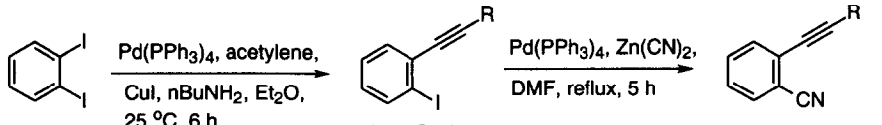
The development of an efficient method for the synthesis of isoquinolone ring systems has become an important research area in both synthetic and medicinal chemistry. Interest in isoquinolone ring systems stems from its presence in many plant alkaloids and drugs[1] and its usefulness as an intermediate in the synthesis of many alkaloids.[2] Many naturally occuring or synthetic isoquinolone derivatives also show various biological activities.[3] Although many synthetic approaches toward isoquinolone ring systems have been reported,[4] we report herein an efficient synthesis of 3-substituted isoquinolinones in one step *via* methanolysis of 2-alkynylbenzonitriles.

RESULTS AND DISCUSSION

The synthesis of 2-alkynylbenzonitriles **3a-g** starting from 1,2-diiodobenzene (**1**) in two steps is outlined in Scheme 1. Palladium-catalyzed coupling of 1,2-diiodobenzene (**1**) with 1-alkynes using tetrakis(triphenylphosphine)palladium (0) (0.03 equiv) as the catalyst afforded 2-alkynyliodobenzenes **2a-g** in 25-66% yields. Compounds **2a-g** were then coupled with zinc cyanide using a palladium catalyst under refluxing DMF for 5 h to give 2-alkynylbenzonitriles **3a-g** in 30-82% yields.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00812-1

Scheme 1



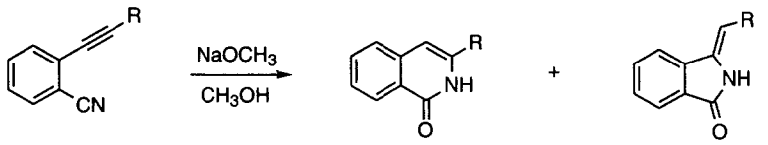
1

2a, R = nC_4H_9, 62%
2b, R = nC_5H_{11}, 66%
2c, R = CH_2Ph, 44%
2d, R = CH_2OTHP, 43%
2e, R = $CH_2CH_2CH_2OH$, 53%
2f, R = Ph, 25%
2g, R = *p*-$CH_3C_6H_4$, 50%

3a, R = nC_4H_9, 70%
3b, R = nC_5H_{11}, 58%
3c, R = CH_2Ph, 30%
3d, R = CH_2OTHP,68%
3e, R = $CH_2CH_2CH_2CH$, 82%
3f, R = Ph, 54%
3g, R = *p*-$CH_3C_6H_4$, 33%

Treatment of 2-alkynylbenzonitriles **3a-d** and **3h**[5] with sodium methoxide, generated by adding 5 atom-mol of fresh cut sodium metal into dry methanol, in refluxing methanol for 12 h gave the corresponding 3-substituted isoquinolones **4a-d** and **4h** as the major products. In the entries of methanolysis of benzonitriles **3c** and **3h**, 1-methoxyisoquinoline derivatives **6c** and **6h** were also isolated in 11% and 17% yields, respectively, in addition to the formation of products **4c** (35%) and **4h** (34%). When arylethynylbenzonitriles **3f** and **3g** were employed under the same reaction conditions, benzylideneisoindolones **5f** and **5g** were obtained in 49% and 30% yield, respectively. The structure of **5g** was unambiguously determined by X-ray crystallography.[6] After methanolysis of **3g** under the described conditions, **7g** was also isolated in 33% yield in addition to the formation of **5g**. These results are summarized in Scheme 2.

Scheme 2

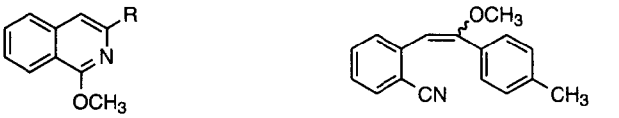


3a, R = nC_4H_9
3b, R = nC_5H_{11}
3c, R = CH_2Ph
3d, R = CH_2OTHP
3f, R = Ph
3g, R = *p*-$CH_3C_6H_4$
3h, R = $CH_2CH_2CH_2OTHP$

4a, 28%
4b, 34%
4c, 35%
4d, 41%

4h, 34%

5f, 49%
5g, 30%



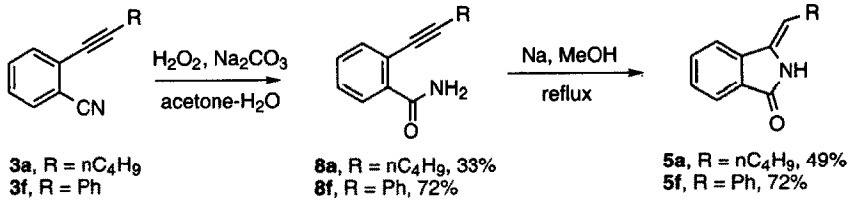
6c, R = CH_2Ph,11%
6h, R = $CH_2CH_2CH_2OTHP$, 17%

7g, 33%

Partial hydrolysis of benzonitriles **3a** and **3f** according to the literature procedure[4i] gave benzamides **8a** and **8f** in 33% and 72% yield, respectively. Treatment of **8a** with sodium methoxide in refluxing methanol for 12h gave pentylideneisoindol-1-one (**5a**) in 49% yield, no isoquinolone **4a** was observed in this reaction. Under the same reaction conditions, methanolysis of **8f** gave **5f** in 72% yield. (Scheme 3) These results suggest that 2-alkynylbenzamide, such as **8a**, is not the intermediate of the formation of isoquinolone **4a**. A plausible mechanism for these cyclization reactions is proposed in Scheme 4. The addition of methoxide to the nitrile group generates an iminium anion which then undergoes 6-*endo* cyclization to give an aromatized isoquinoline intermediate when R is an alkyl group. Protonation of the intermediate give 1-methoxyisoquinoline which was

then hydrolyzed to isoquinolone **4** during acid workup. When R is an aryl group, the iminium anion would undergo a 5-*exo* transition state to give an isoindol intermediate in which the α-anion is stabilized by the aryl group. Again, protonation and hydrolysis of the intermediates would lead to isoindolone derivatives. The isolation of the intermediates, 1-methoxyisoquinolines **6c** and **6h**, is another strong evidence to support the proposed mechanism.

Scheme 3

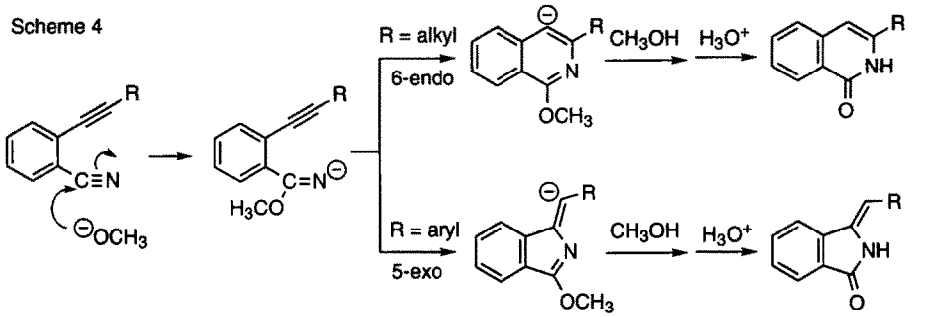


3a, R = nC_4H_9
3f, R = Ph

8a, R = nC_4H_9, 33%
8f, R = Ph, 72%

5a, R = nC_4H_9, 49%
5f, R = Ph, 72%

Scheme 4



In conclusion, methanolysis of 2-(2-alkylethynyl)benzonitriles with sodium methoxide in refluxing methanol provided a novel method for the synthesis of 3-substituted isoquinolones albeit in modest yield and methanolysis of 2-(2-arylethynyl)benzonitriles under the same conditions gave 3-benzylidene isoindolones. Further synthetic applications of this novel cycloaromatization to more complex heterocyclic ring systems are currently under investigation.

EXPERIMENTAL SECTION

General procedure for coupling of 1-alkyne with 1,2-diiodobenzene. To a degassed solution of 1-alkyne (11.4 mmol) in Et_2O (25 mL) containing CuI (0.27g, 1.4 mmol) and *n*$BuNH_2$ (1.73 g, 23.6 mmol) in Et_2O (25 mL) was added a degassed solution of 1,2-diiodobenzene (3.0 g, 9.1 mmol) containing $Pd(PPh_3)_4$ (0.32 g, 0.3 mmol) in Et_2O (25 mL). The resulting reaction mixture was stirred for 6 h and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic extracts were washed with saturated aqueous Na_2CO_3 solution (40 mL) and dried over anhydrous $MgSO_4$. After filtration and removal of solvent *in vacuo*, the residue was purified by column chromatography on silica gel (hexanes as eluent) to give the desired products.

2-(1-Hexynyl)-1-iodobenzene (2a). Obtained in 62% yield as a yellow oil. IR (neat) 2198 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.40 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.25 (dt, 1H, *J* = 7.6, 1.2 Hz), 6.94 (dt, 1H, *J* = 7.6, 1.8 Hz), 2.48 (t, 2H, *J* = 7.0 Hz), 1.48-1.69 (m, 4H), 0.69 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.5, 132.4, 130.5, 128.6, 127.6, 100.9, 94.8,82.8, 30.5, 22.0, 19.2,

13.6; MS(EI) relative intensity: 284 (M^+, 100), 241 (58), 142 (59); HRMS calcd for $C_{12}H_{13}I$ 284.0063, found 284.0061.

2-(1-Heptynyl)-1-iodobenzene (2b). Obtained in 66% yield as a yellow oil. IR (neat) 2198 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.82 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.40 (dd, 1H, J = 8.0, 1.6 Hz), 7.26 (dt, 1H, *J* = 7.6, 1.2 Hz), 6.94 (dt, 1H, *J* = 7.6, 1.6 Hz), 2.47 (t, 2H, *J* = 7.2 Hz), 1.35-1.70 (m, 6H), 0.93 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 132.4, 130.5, 128.6, 127.6, 101.0, 94.8, 82.9, 31.1, 28.2, 22.2, 19.5, 14.0; MS(EI) relative intensity: 298 (M^+, 100), 269 (38), 241 (42), 142 (75); HRMS calcd for $C_{13}H_{15}I$ 298.0220, found 298.0223.

2-(3-Phenyl-1-propynyl)-1-iodobenzene (2c). Obtained in 44% yield as a yellow oil. IR (neat) 2197 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.84 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.45-7.51 (m, 3H), 7.25-7.36 (m, 4H), 6.98 (dt, 1H, *J* = 8.0, 1.6 Hz), 3.92 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 136.2, 132.6, 130.1, 128.9, 128.5, 128.1, 127.7, 126.6, 100.8, 91.6, 84.8, 25.9; MS(EI) relative intensity: 318 (M^+, 100), 248 (21), 191 (36), 189 (43); HRMS calcd for $C_{15}H_{11}I$ 317.9906, found 317.9913.

2-(3-(2-Tetrahydropyranyloxy-1-propynyl)-1-iodobenzene (2d). Obtained in 43% yield as a yellow oil. IR (neat) 2198 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.52 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.24-7.32 (m, 1H), 6.95-7.03 (m, 1H), 5.01-5.04 (m, 1H), 4.55 (s, 2H), 3.85-3.96 (m, 1H), 3.52-3.63 (m, 1H), 1.51-1.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 132.9, 129.6, 129.4, 127.8, 100.8, 96.7, 89.1, 87.6, 62.0, 54.4, 30.1, 25.2, 18.9. MS(EI) relative intensity: 342 (M^+, 7), 258 (47), 241 (100); HRMS calcd for $C_{14}H_{15}IO_2$ 342.0118, found 342.0121.

2-(5-Hydroxy-1-pentynyl)-1-iodobenzene (2e). Obtained in 53% yield as a yellow oil. IR (neat) 3400, 2198 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.81 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.39 (dd, 1H, *J* = 8.0, 1.8 Hz), 7.25 (td, 1H, *J* = 7.6, 1.2 Hz), 6.95 (td, 1H, *J* = 7.6, 1.8 Hz), 3.87 (t, 2H, *J* = 6.2 Hz), 2.60 (t, 2H, *J* = 6.9 Hz), 1.83-1.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.5, 132.4, 130.1, 128.8, 127.7, 100.9, 93.6, 83.4, 61.6, 31.0, 16.1; MS(EI) relative intensity: 286 (M^+, 100), 277 (18), 244 (24), 131 (26); HRMS calcd for $C_{11}H_{11}IO$ 285.9855, found 285.9845.

2-(2-Phenylethynyl)-1-iodobenzene (2f). Obtained in 25% yield as a yellow oil. IR (neat) 2218 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.92-7.94 (m, 1H), 7.69-7.71 (m, 2H), 7.58-7.61 (m, 1H), 7.41-7.44 (m, 3H), 7.35 (dt, 1H, *J* = 7.6, 1.2 Hz), 7.01-7.05 (m, 1H). These data are in accord with literature values.[7]

2-(2-(4-Methylphenyl)ethynyl)-1-iodobenzene (2g). Obtained in 50% yield as a white solid. mp 88-90 °C; IR (neat) 2218 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.87 (dd, 1H, J = 8.0, 1.1 Hz), 7.15-7.54 (m, 6H), 7.00 (td, 1H, *J* = 8.0, 1.8 Hz), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 138.7, 132.4, 132.3, 131.5, 130.0, 129.1, 128.3, 127.8, 119.8, 101.1, 21.6; Anal. Calcd for $C_{15}H_{11}I$: C, 56.62; H, 3.47. Found: C, 56.73; H, 3.55.

General procedure for coupling of 2-(1-alkynyl)iodobenzene with zinc cyanide. To a stirred solution of 2-(1-alkynyl)iodobenzene (5.6 mmol) in dry DMF (40 mL) was added $Pd(PPh_3)_4$ (0.25 g, 0.22 mmol), followed by $Zn(CN)_2$ (0.82 g, 1.25 mmol). The resulting reaction mixture was degassed, heated to reflux and stirred for 5 h at this temperature. After cooling to room temperature, the reaction mixture was quenched with 2 N aqueous NH_4OH and extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography on silica gel (hexanes as eluent) to give the desired products.

2-(1-Hexynyl)-benzonitrile (3a). Obtained in 70% yield as a yellow oil. IR (neat) 2229 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.46-7.51 (m, 2H), 7.31-7.35 (m, 1H), 2.48 (t, 2H, *J* = 6.6 Hz), 1.46-1.67 (m, 4H), 0.95 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.4, 132.2, 128.1, 127.5, 117.7, 115.2, 97.9, 30.4, 21.9, 19.2, 13.5; MS(EI) relative intensity: 183 (M^+, 49), 182 (77), 168 (100); HRMS calcd for $C_{13}H_{13}N$ 182.0970, found 182.0964.

2-(1-Heptynyl)-benzonitrile (3b). Obtained in 58% yield as a yellow oil. IR (neat) 2229 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.60 (dd, 1H, *J* = 7.4, 1.0 Hz), 7.46-7.51 (m, 2H), 7.29-7.40 (m, 1H), 2.48 (t, 2H, *J* = 7.0 Hz), 1.31-1.73 (m, 6H), 0.92 (t, 3 H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.5, 132.2, 132.1, 128.1, 127.5, 117.7, 115.3, 98.0, 31.0, 28.1, 22.2, 19.5, 13.9; MS(EI) relative intensity: 197 (M^+, 20), 196 (31), 182 (37), 168 (58), 140 (100); HRMS calcd for $C_{14}H_{15}N$ 197.1206, found 197.1203.

2-(3-Phenyl-1-propynyl)-benzonitrile (3c). Obtained in 30% yield as a yellow oil. IR (neat) 2229 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.84 (dd, 1H, *J* = 8.1, 1.0 Hz), 7.25-7.51 (m, 7H), 6.98 (td, 1H, *J* = 7.5, 1.6 Hz), 3.92 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.6, 132.5, 132.4, 132.2, 128.6, 128.0, 127.9, 127.6, 126.8, 117.8, 115.3, 94.8, 79.0, 25.8; MS(EI) relative intensity: 217 (M^+, 11), 191 (91), 189 (100), 165 (55); HRMS calcd for $C_{16}H_{11}N$ 217.0892, found 217.0895.

2-(3-(2-Tetrahydropyranyloxy-1-propynyl)benzonitrile (3d). Obtained in 68% yield as a yellow oil. IR (neat) 2229 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52-7.66 (m, 3H), 7.36-7.49 (m, 1H), 4.94-4.97 (m, 1H), 4.56 (s, 2H), 3.84-3.90 (m, 1H), 3.55-3.62 (m, 1H), 1.53-1.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 132.7, 132.2, 129.4, 128.1, 127.7, 124.5, 116.0, 97.7, 71.6, 62.3, 30.3, 29.7, 25.3, 19.1. MS(EI) relative intensity: 241 (M^+, 0.3), 141 (28), 140 (100); HRMS calcd for $C_{15}H_{15}NO_2$ 241.1104, found 241.1096.

2-(4-Hydroxy-1-pentynyl)-benzonitrile (3e). Obtained in 82% yield as a yellow oil. IR (neat) 3400, 2229 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.61 (d, 1 H, *J* = 7.4 Hz), 7.30-7.51 (m, 3H), 3.87 (t, 2H, *J* = 6.2 Hz), 2.63 (t, 2H, *J* = 6.8 Hz), 1.82-1.96 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.4, 132.3, 132.1, 127.9, 127.7, 117.9, 115.3, 112.3, 97.0, 61.2, 30.9, 16.1; MS(EI) relative intensity: 185 (M^+, 49), 167 (100), 166 (62), 140 (64); HRMS calcd for $C_{16}H_{11}NO$ 185.0841, found 185.0832.

2-(2-Phenylethynyl)benzonitrile (3f). Obtained in 54% yield as a yellow oil. IR (neat) 2227 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.55-7.69 (m, 5H), 7.36-7.43 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 132.6, 132.3, 131.9, 129.2, 128.4, 128.1, 127.2, 122.0, 117.5, 115.3, 96.0, 85.5. These data are in accord with literature values.[4i]

2-(2-(4-Methylphenylethynyl)-benzonitrile (3g). Obtained in 33% yield as a white solid. mp 81-82 °C; IR (neat) 2218 cm^{-1}; IR (neat) 2228 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.34-7.69 (m, 7H), 7.21 (dd, 1H, *J* = 7.9, 0.8 Hz), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.5, 132.6, 132.3, 132.0, 131.9, 129.2, 127.9, 127.5, 118.9, 117.6, 115.2, 96.4, 85.1, 21.6; Anal. Calcd. for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.44. Found: C, 88.47; H, 5.08; N, 6.36.

2-(5-Tetrahydropyranyloxy-1-pentynyl)benzonitrile (3h). To a solution of **3e** (0.08 g, 0.43 mmol) in CH2Cl2 (5 mL) was added subsequently 3,4-dihydro-2H-pyran (0.04 mL, 0.48 mmol) and PPTS (11 mg, 0.04 mmol). The resulting solution was stiired at room temperature for 5 h, quenched with 50% aqueous Na2CQ3 solution (5 mL) and extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried over anhydrous MgSO4. Filtration and concentration gave the crude product which was purified by flash chromatography on silica gel (20% EtOAc in hexanes as eluent) to give 3h (0.11 g, 97%) as a colorless liquid. IR (neat) 2231 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.61 (dd, 1H, J = 8.6, 1.0 Hz), 7.47-7.52 (m, 2H), 7.32-7.36

(m, 1H), 4.63 (t, 1H, J = 3.6 Hz), 3.85-3.93 (m, 2H), 3.51-3.60 (m, 2H), 2.60-2.64 (m, 2H), 1.50-1.97 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.5, 132.3, 132.2, 127.9, 127.6, 117.7, 115.3, 98.9, 97.2, 77.4, 65.8, 62.2, 30.7, 28.7, 25.4, 19.5, 16.5.

General Procedure for methanolysis of 2-alkynylbenzonitrile. To a solution of 2-akynylbenzonitrile (1.1 mmol) in 25 ml of methanol was added freshly cut sodium metal (5.5 mmol-atom), the resulting solution was heated to reflux and stirred at this temperature for 12 h. After cooling to room temperature, the methanol was removed in vacuo. To the residue, water was added and extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes as eluent) to give the products.

3-Butylisoquinolin-1-one (4a). Obtained in 28% yield as a white solid. mp 141 °C (EtOAc-hexane) (Lit.[8] mp 139-140 °C); IR (neat) 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 10.5 (br s, 1H), 8.37 (d, 1H, *J* = 7.5 Hz), 7.62 (t, 1H, *J* = 7.5 Hz), 7.38-7.52 (m, 2H), 6.30 (s, 1H), 2.62 (t, 2H, *J* = 7.5 Hz), 1.66-1.78 (m, 2H), 1.25-1.50 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz).

3-Pentylisoquinolin-1-one (4b). Obtained in 34% yield as a white solid. mp 108 °C (EtOAc-hexane) (Lit.[8] mp 106-108 °C); IR (neat) 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 10.5 (br s, 1H), 8.37 (dt, 1H, *J* = 8.0, 0.7 Hz), 7.58-7.66 (m, 1H), 7.38-7.49 (m, 2H), 6.31 (s, 1H), 2.62 (t, 2H, *J* = 7.6 Hz), 1.67-1.80 (m, 2H), 1.22-1.44 (m, 4H), 0.91 (t, 3H, *J* = 7.0 Hz).

3-Benzylisoquinolin-1-one (4c) and **1-methoxy-3-benzylisoquinoline (6c)**. Compound **4c** was obtained in 35% yield as a white solid. mp 128 °C (EtOAc-hexane) (Lit.[9] mp 190-191 °C); IR (neat) 1622 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.73-7.78 (m, 2H); 7.26-7.54 (m, 8H), 6.76 (s, 1H), 3.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.1, 140.1, 135.4, 134.4, 130.8, 128.8, 127.4, 127.3, 126.4, 122.9, 121.1, 96.9, 55.5; Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.67; H, 5.56; N, 5.95. Found: C, 81.98; H, 6.08; N, 5.67. Compound **6c** was obtained in 11% yield as a yellow oil. IR (neat) 1614, 1564 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.19 (dd, 1H, *J* = 8.4, 1.1 Hz), 7.23-7.61 (m, 7H), 6.97 (d, 1H, *J* = 0.8 Hz), 4.13 (d, 2H, *J* = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.3, 151.5, 140.0, 138.6, 130.2, 129.3, 128.3, 126.1, 125.8, 125.7, 124.0, 118.2, 112.4, 53.5, 44.2; MS(EI) relative intensity: 249 (M^+, 100), 248 (84), 234 (63); HRMS calcd for $C_{17}H_{15}NO$ 249.1155, found 249.1165.

3-(2-Tetrahydropyranyloxymethyl)isoquinolin-1-one (4d). Obtained in 41% yield as a white solid. mp 150-151 °C; IR (neat) 1623 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.55 (br s, 1H), 8.36-8.40 (m, 1H), 7.61-7.69 (m, 1H), 7.43-7.52 (m, 2H), 6.43 (s, 1H), 4.68-4.73 (m, 1H), 4.62 (dd, 1H, *J* = 13.1, 1.2 Hz), 4.53 (dd, 1H, *J* = 13.1, 0.8 Hz), 3.91-3.99 (m, 1H), 3.55-3.64 (m, 1H), 1.51-1.96 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.3, 139.8, 137.8, 136.8, 132.8, 127.5, 126.8, 126.2, 104.8, 99.3, 66.2, 63.2, 30.4, 25.2, 19.6; Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.35; H, 6.72; N, 5.31.

3-Benzylideneisoindol-1-one (5f). Obtained in 49% yield as a white solid. mp 187-188 °C; IR (neat) 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (br s, 1H), 7.88 (d, 1H, *J* = 7.6 Hz), 7.79 (d, 1H, *J* = 7.6 Hz), 7.64 (td, 1H, *J* = 7.6, 1.2 Hz), 7.52 (t, 1H, *J* = 7.6 Hz), 7.41-7.47 (m, 4H), 7.29-7.33 (m, 1H), 6.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.0, 138.2, 134.9, 133.1, 132.2, 129.2, 128.7, 128.5, 127.7, 123.5, 119.8, 105.9; Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.30; H, 4.98; N, 6.30.

3-(4-Methylbenzylidene)isoindol-1-one (5g) and **2-(2-methoxy-2-(4-methylphenyl))-ethenylbenzonitrile (7g)**. Compound **5g** was obtained in 30% yield as a white solid. mp 209 °C; IR (neat) 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (br s, 1H), 7.88 (dt, 1H, *J* = 7.6, 1.0 Hz), 7.78 (dt, 1H, *J* =

8.0, 0.8 Hz), 7.63 (td, 1H, J = 6.6, 1.2 Hz), 7.51 (td, J = 6.6, 1.2 Hz), 7.35 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.0 Hz), 6.53 (s, 1H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 137.8, 132.4, 132.2, 132.1, 129.9, 129.0, 128.3, 123.5, 119.7, 106.0, 21.3. The structure was unambiguously determined by X-ray crystallography.[6] Compound **7g** was obtained in 33% yield as a yellow oil and a mixture of E/Z isomers. IR (neat): 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, 1H, J = 8.0 Hz), 7.45-7.63 (m, 4H), 7.22-7.26 (m, 3H), 7.19 (s, 0.67H), 7.17 (s, 0.33H), 6.33 (s, 0.67H), 5.96 (s, 0.33H), 3.88 (s, 1H), 3.64 (s, 2H), 2.40 (s, 2H), 2.33 (s, 1H); MS(EI) relative intensity: 249 (M^+, 56), 119 (100); HRMS calcd for $C_{17}H_{15}NO$ 249.1155, found 249.1155.

3-(2-Tetrahydropyranyloxypropyl)isoquinolin-1-one (4h) and **3-(2-Tetrahydropyranyloxypropyl)-1-methoxyisoquinoline (6h)**. Compound **4h** was obtained in 34% yield as a white solid. mp 113-114 °C; IR (neat) 1647 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.44 (br s, 1H), 8.36 (dd, 1H, J = 7.2, 0.8 Hz), 7.59 (td, 1H, J = 6.8, 1.5 Hz), 7.35-7.46 (m, 2H), 6.32 (s, 1H), 4.61 (t, 1H, J = 3.4 Hz), 3.80-3.91 (m, 2H), 3.45-3.56 (m, 2H), 2.76 (t, 2H, J = 7.3 Hz), 1.48-2.08 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 141.5, 138.6, 132.4, 127.2, 125.6, 125.5, 124.4, 103.9, 99.1, 66.4, 62.5, 30.6, 30.2, 28.4, 25.4, 19.6; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.36; N, 4.87. Found: C, 70.92; H, 7.37; N, 4.89. Compound **6h** was obtained in 17% yield as a yellow oil. IR (neat) 1614, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64-7.75 (m, 2H), 7.26-7.41 (m, 2H), 6.67 (s, 1H), 4.56-4.60 (m, 1H), 3.79-4.04 (m, 1H), 3.90 (s, 3H), 3.59-3.76 (m, 2H), 3.37-3.50 (m, 1H), 3.08 (t, 2H, J = 6.3 Hz), 1.46-1.80 (m, 8H); MS(EI) relative intensity: 285 (M^+, 0.2), 245 (10), 217 (70), 186 (100); HRMS calcd for $C_{18}H_{23}NO_2$ 285.1730, found 285.1735.

General Procedure for Partial Hydrolysis of Benzonitriles to Benzamides. To a solution of benzonitrile (0.16 mmol) in acetone (2 mL) was added subsequently 3N aqueous Na_2CO_3 soution (2 mL) and 15% aqueous H_2O_2 solution (2 mL). The resulting suspension was stirred at room temperature for 14 days. Acetone was then removed *in vacuo*. The residue was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (2 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of the solvent, the residue was purified by flash chromatography on silica gel (30% EtOAc in hexanes as eluent) to give the products.

3-Pentylideneisoindol-1-one (5a). Starting from amide **8a** and following the general methanolysis procedure gave **5a** in 49% yield as a white solid. mp 125-126 °C; IR (neat) 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (br s, 1H), 7.84 (dd, 1H, J = 7.6, 0.8 Hz), 7.65 (dd, 1H, J = 7.0, 0.8 Hz), 7.57 (td, 1H, J = 7.6, 1.0 Hz), 7.46 (td, 1H, J = 7.6, 1.0 Hz), 5.63 (t, 1H, J = 8.0 Hz), 2.33 (t, 2H, J = 7.4 Hz), 1.40-1.58 (m, 4H), 0.95 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 137.6, 134.3, 133.2, 131.9, 128.5, 123.4, 119.4, 108.2, 31.6, 27.0, 22.4, 13.9; Anal. Calcd for $C_{13}H_{15}NO{\cdot}1H_2O$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.43; H, 7.24; N, 5.80.

2-(1-Hexynyl)benzonitrile (8a). Obtained in 33% yield as a white solid. mp 107 °C (Lit.[4j] 105-107 °C); IR (neat) 2220, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (dd, 1H, J = 7.2, 2.4 Hz), 7.67 (br s, 1H), 7.48 (td, 1H, J = 5.6, 2.4 Hz), 7.35-7.42 (m, 2H), 6.47 (br s, 1H), 2.28 (t, 2H, J = 7.0 Hz), 1.58-1.65 (m, 2H), 1.45-1.52 (m, 2H), 0.95 (t, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 134.0, 133.7, 130.9, 130.2, 128.1, 121.0, 112.3, 97.8, 79.6, 30.4, 22.1, 19.3, 13.5; Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.12, H, 7.62, N, 6.79.

2-(2-Phenylethynyl)benzonitrile (8f). Obtained in 72% yield as a white solid. mp 163 °C (Lit.[4j] 155-157 °C); IR (neat) 2220, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.10-8.15 (m, 1H), 7.38-7.65 (m, 8H), 6.60 (br s, 2H). These data are in accord with literature values.[4j]

Acknowledgment: We thank the National Science Council of the Republic of China for financial support of this work.

REFERENCES

1. (a) Pelletier, S. W. Chemistry of the Alkaloids, Van Nostrand Reinhold Co., New York, **1970**, P. 77. (b) Shamma, M.; Moniot, J. L. Isoquinoline Alkaloid Research, Plenum Press, New York, **1978**, P. 57.
2. See for examples: (a) Dyke, S. F. *Tetrahedron*, **1971**, *27*, 281. (b) Brown, D. W.; Dyke, S. F. *Tetrahedron* **1966**, *22*, 2429. (c) Iida, H.; Kawano, K.; Kihuchi, T.; Yoshimizu, F. *Yakugaku Zasshi*, **1976**, *96*, 176; *Chem. Abstr.*, **1976**, *84*, 135898.
3. (a) Sulkowski, T. S.; Wille, M. A. *U. S. Patent* **1969**, 3452027, American Home Products Corp.; *C. A.* **1969**, *71*, 112830. (b) Coyne, W. E.; Cusic, J. W. *U. S. Patent* **1971**, 3600394, Searle & Co.; *C. A.* **1971**, *75*, 118241. (c) Kubo, K.; Ito, N.; Sozu, I.; Isomura, Y.; Homma, H. *Japan Kokai Tokkyo Koho* **1979**, *79*, 163585; *C. A.* **1980**, *93*, 8037; *Japan Kokai Tokkyo Koho* **1979**, *79*, 92997; *C. A.* **1980**, *92*, 111036; *Ger. Offen.* **1979**, 2828528; *C. A.* **1979**, *90*, 168468. (d) Wakabayashi, T.; Watanabe, K. *Japan Kokai Tokkyo Koho* **1978**, *78*, 119879; *C. A.* **1979**, *90*, 152028.
4. Selected examples: (a) Connors, R.; Tran, E.; Durst, T. *Can. J. Chem.* **1996**, *74*, 221. (b) Sugimoto, A.; Shinba-Tanaka, H.; Ishikawa, M. *Synthesis* **1995**, 431. (c) Grignon-Dubois, M.; Meola, A. *Synth. Commun.* **1995**, *25*, 2999. (d) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803. (e) Fisher, L. E.; Caroon, J. M.; Jahangir; Russel Stable, S.; Lundberg, S.; Muchowski, J. M. *J. Org. Chem.* **1993**, *58*, 3643. (f) Cobas, A.; Cuitian, E.; Castedo, L. *J. Org. Chem.* **1993**, *58*, 3113. (g) Fisher, L. E.; Muchowski, J. M.; Clark, R. D. *J. Org. Chem.* **1992**, *57*, 2700. (h) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem. Sec B.* **1989**, *28*, 67. (i) Couture, A.; Grandclaudon, P. *Synthesis* **1986**, 576. (j) Sakamoto, T. An-Naka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1986**, *34*, 2754. (k) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1985**, *33*, 626. (l) Stanoeva, E.; Haimova, M.; Ognyanov, V. *Liebigs Ann. Chem.* **1984**, 389. (m) Kitamura, T,; Kobayashi, S.; Taniguchi, H. *Chem. Lett.* **1984**, 1523. (n) Mali, R. S.; Kulkarni, B. K.; Shankaran, K. *Synthesis* **1982**, 329. (o) Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett.* **1982**, *32*, 1957. (p) Beugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 729.
5. Compound **3h** was prepared in 77% yield by the reaction of **3e** with 3,4-dihydro-2*H*-pyran (1.1 equiv) using pyridinium *p*-toluenesulfonate as a catalyst (0.1 equiv) in dichloromethane for 5 h.
6. X-ray crystallographic data of compound **5g** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Cryatallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
7. Du, C.-J. F.; Hart, H. *J. Org. Chem.* **1987**, *52*, 4311.
8. Wilson, J. W.; Anderson, E. L.; Ullyot, G. E. *J. Org. Chem.* **1951**, *16*, 800.
9. Belgaonkar, V. H.; Usgaonkar, R. N. *Indian J. Chem.* **1975**, *13*, 336.