SUPPORTING INFORMATION

Efficient Synthesis of Heterocycles and Carbocycles by Electrophilic Cyclization of Acetylenic Aldehydes and Ketones

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Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and a basic KMnO_4 solution [3 g of KMnO_4 + 20 g of K_2CO_3 + 5 mL of NaOH (5 %) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of ethyl ether, hexanes, ethyl acetate, and CH_2Cl_2 were purchased from Fisher Scientific Co. 2-Bromobenzaldehyde, 2-iodoacetophenone, phenylacetylene, 1-cyclohexenyl acetylene, 1-hexyne, PhSeBr , $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$, PhNMe_2 , phenol and Et_3N were purchased from Aldrich Chemical Co., Inc. The palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd.

Starting materials. The 2-(1-alkynyl)benzaldehydes were prepared by the Sonogashira coupling reaction of 2-bromobenzaldehyde with various terminal alkynes.¹

The same procedure was used to prepare 2-(phenylethynyl)acetophenone and 2-(phenylethynyl)pyridine-3-carboxaldehyde. All commercially available compounds were used as received.

General procedure for the synthesis of 4-iodo-1*H*-isochromenes. Into a solution of the 2-(1-alkynyl)benzaldehyde (0.25 mmol), K₂CO₃ (1.0 equiv) and the nucleophile (1.2 equiv) in CH₂Cl₂ (5.0 mL), I₂ (1.2 equiv) was added and the solution was stirred at room temperature until the total disappearance of the starting material as determined by TLC analysis. The reaction mixture was then quenched with satd aq Na₂S₂O₃ (5.0 mL) and water (5.0 mL). The resulting solution was extracted using diethyl ether. The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude product was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford pure compounds.

4-Iodo-1-methoxy-3-phenyl-1*H*-isochromene (2). The product was obtained as colorless crystals - mp 75 °C. The spectral properties were identical to those previously reported.²

1-*n*-Butoxy-4-iodo-3-phenyl-1*H*-isochromene (3). The product was obtained as a yellow oil: ¹H NMR (CDCl₃) δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.38-1.50 (m, 2H), 1.62-1.72 (m, 2H), 3.76-3.84 (m, 1H), 4.00-4.04 (m, 1H), 6.13 (s, 1H), 7.21 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.35 (td, *J* = 7.4, 1.1 Hz, 1H), 7.43-7.50 (m, 4H), 7.61-7.66 (m, 3H); ¹³C NMR (CDCl₃) δ 14.2, 19.6, 31.9, 68.9, 74.0, 99.1, 125.6, 127.8, 128.0, 128.2, 129.5, 129.9, 130.0, 130.2, 131.8, 137.8, 152.2; IR (neat, cm⁻¹) 3063, 3032, 2956, 2931, 2870, 1594, 1483; HRMS calcd for C₁₉H₁₈IO₂ 406.0430, found 406.0438.

4-Iodo-1-(2-iodobenzyloxy)-3-phenyl-1*H*-isochromene (4). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 3.02 (s, 6H), 6.21 (s, 1H), 6.74-6.77 (m, 3H), 7.24-7.36 (m, 7H), 7.53-7.58 (m, 3H); ^{13}C NMR (CDCl_3) δ 40.4, 72.9, 80.6, 112.1, 124.8, 126.2, 127.5, 128.3, 128.9, 129.2, 129.4, 130.4, 131.5, 133.4, 136.7, 150.6, 154.6; IR (neat, cm^{-1}) 3046, 1612, 1524; HRMS calcd for $\text{C}_{23}\text{H}_{20}\text{INO}$ 454.0668, found 454.0660.

1-(4-Dimethylaminophenyl)-4-iodo-3-phenyl-1*H*-isochromene (5). The product was obtained as a white solid (mp 51 $^{\circ}\text{C}$, dec). The spectral properties were identical to those previously reported.²

4-Bromo-1-methoxy-3-phenyl-1*H*-isochromene (6). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 3.67 (s, 3H), 6.05 (s, 1H), 7.26-7.29 (m, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.44-7.52 (m, 4H), 7.69-7.77 (m, 3H); ^{13}C NMR (CDCl_3) δ 56.3, 99.8, 100.0, 125.4, 125.7, 127.7, 128.1, 128.2, 129.5, 129.9, 130.0, 130.2, 135.3, 148.4; IR (neat, cm^{-1}) 3019, 2956; HRMS calcd for $\text{C}_{16}\text{H}_{13}\text{BrO}_2$ 316.0099, found 316.0105.

1-Methoxy-3-phenyl-4-phenylselenenyl-1*H*-isochromene (7). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 3.74 (s, 3H), 6.13 (s, 1H), 7.09 (d, J = 4.8 Hz, 1H), 7.15 (t, J = 5.4 Hz, 2H), 7.23-7.40 (m, 9H), 7.56-7.59 (m, 2H), 7.73 (d, J = 5.1 Hz, 1H); ^{13}C NMR (CDCl_3) δ 56.4, 76.9, 100.4, 125.7, 125.7, 126.6, 127.5, 127.6, 127.9, 128.4, 129.3, 129.4, 129.8, 130.0, 131.4, 133.6, 136.4, 157.1; IR (neat, cm^{-1}) 3063, 2968, 1021, 960; HRMS calcd for $\text{C}_{22}\text{H}_{18}\text{O}_2\text{Se}$ 394.0472, found 394.0479.

1-Methoxy-3-phenyl-4-*p*-nitrophenylsulfenyl-1*H*-isochromene (8). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 3.77 (s, 3H), 6.17 (s, 1H), 7.24-7.27 (m, 2H), 7.35-7.43 (m, 6H), 7.58-7.61 (m, 3H), 8.03 (d, J = 9.0 Hz, 2H); ^{13}C NMR (CDCl_3) δ

56.7, 100.5, 102.6, 123.8, 124.3, 125.6, 126.0, 127.7, 128.1, 128.2, 129.5, 129.9, 130.1, 130.2, 134.7, 145.3, 148.6, 158.8; IR (neat, cm^{-1}) 3093, 3065, 2930, 2833, 1594, 1510, 1337; HRMS calcd for $\text{C}_{22}\text{H}_{17}\text{NO}_4\text{S}$ 391.0878, found 391.0883.

3-*n*-Butyl-4-iodo-1-methoxy-1*H*-isochromene (10). The product was obtained as a pale yellow oil. The spectral properties were identical to those previously reported.²

3-*n*-Butyl-1-(4-dimethylaminophenyl)-4-iodo-1*H*-isochromene (11). The product was obtained as a white solid (mp 51 °C, dec): ^1H NMR (CDCl_3) δ 0.86 (t, J = 5.4 Hz, 3H), 1.22-1.38 (m, 2H), 1.44-1.53 (m, 2H), 2.50-2.80 (m, 2H), 2.97 (s, 6H), 5.99 (s, 1H), 6.66 (d, J = 5.6 Hz, 1H), 6.72 (d, J = 6.4 Hz, 2H), 7.11 (t, J = 5.6 Hz, 1H), 7.19 (d, J = 6.5 Hz, 2H), 7.29 (t, J = 5.7 Hz, 1H), 7.40 (d, J = 5.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.1, 22.5, 30.1, 32.7, 56.1, 63.9, 99.9, 115.6, 122.9, 124.3, 125.4, 126.0, 127.2, 127.3, 129.7, 130.1, 145.2, 148.6; IR (neat, cm^{-1}) 3062, 2955, 2926, 2858, 2806, 1736, 1612, 1524. HRMS calcd for $\text{C}_{21}\text{H}_{24}\text{INO}$ 433.0903, found 433.0913.

3-*n*-Butyl-1-methoxy-4-*p*-nitrophenylsulfenyl-1*H*-isochromene (12). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 0.89 (t, J = 7.3 Hz, 3H), 1.26-1.39 (m, 2H), 1.57-1.67 (m, 2H), 2.57-2.67 (m, 1H), 2.79-2.89 (m, 1H), 3.64 (s, 3H), 6.04 (s, 1H), 7.20-7.28 (m, 6H), 8.05 (d, J = 6.5 Hz, 2H); ^{13}C NMR (CDCl_3) δ 14.1, 22.5, 30.1, 32.7, 56.1, 63.9, 99.9, 122.9, 124.3, 125.4, 126.0, 127.2, 127.4, 129.7, 130.1, 145.2, 148.6; IR (neat, cm^{-1}) 3062, 2955, 1736, 1612, 1524; HRMS calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_4\text{S}$ 371.1192, found 371.1199.

3-(Cyclohex-1-enyl)-4-iodo-1-methoxy-1*H*-isochromene (14). The product was obtained as a yellow oil. The spectral properties were identical to those previously reported.²

3-(Cyclohex-1-enyl)-1-(4-dimethylaminophenyl)-4-iodo-1*H*-isochromene (15).

The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 1.56-1.66 (m, 4H), 2.03-2.17 (m, 4H), 2.96 (s, 6H), 5.98-5.99 (m, 1H), 6.02 (s, 1H), 6.68-6.72 (m, 3H), 7.12 (t, J = 6.0 Hz, 1H), 7.17 (d, J = 6.4 Hz, 2H), 7.30 (t, J = 5.7 Hz, 1H), 7.45 (d, J = 5.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 22.0, 22.6, 25.3, 27.0, 31.2, 57.0, 71.9, 80.5, 112.3, 117.6, 125.1, 127.3, 128.4, 128.8, 129.6, 131.9, 133.2, 133.7, 135.3, 157.6; IR (neat, cm^{-1}) 2927, 2855, 1613, 1523; HRMS calcd for $\text{C}_{23}\text{H}_{24}\text{INO}$ 457.0903, found 457.0913.

8-Iodo-5-methoxy-7-phenyl-5*H*-pyrano[4,3-*b*]pyridine (17). The product was obtained as a yellow oil: ^1H NMR (CDCl_3) δ 3.67 (s, 3H), 6.10 (s, 1H), 7.23-7.26 (m, 1H), 7.45-7.48 (m, 2H), 7.52 (d, J = 8.7 Hz, 1H), 7.68-7.70 (m, 2H), 8.72 (d, J = 3.0 Hz, 1H); ^{13}C NMR (CDCl_3) δ 56.5, 76.6, 100.3, 122.5, 122.6, 128.2, 130.0, 130.1, 133.7, 136.9, 148.3, 151.1, 156.4; IR (neat, cm^{-1}) 3029; HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{INO}_2$ 364.9913, found 364.9919.

Synthesis of 1,3-dihydro-3-[(*E*)-1-iodo-1-phenylmethylene]-1-methoxy-1-methylisobenzofuran (19). To a stirred mixture of 2-(phenylethynyl)acetophenone (0.25 mmol), K_2CO_3 (1.0 equiv) and MeOH (1.2 equiv) in CH_2Cl_2 (5 mL), I_2 (1.2 equiv) was added and the mixture was stirred until no starting material was observed by TLC. The reaction mixture was quenched with satd aq $\text{Na}_2\text{S}_2\text{O}_3$ (5.0 mL) and water (5.0 mL). The mixture was then extracted with diethyl ether and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (neutral aluminum oxide, hexane/EtOAc) to afford a pale yellow solid (*unstable*). The spectral properties were identical to those previously reported.²

General procedure for the synthesis of naphthalene derivatives 20 and 21

using I₂. To a solution of the 2-(1-alkynyl)benzaldehyde (0.25 mmol), 1.2 equiv of styrene or phenylacetylene and K₂CO₃ (0.25 mmol) in CH₂Cl₂ (5.0 mL), 1.2 equiv of I₂ was added and the reaction mixture was stirred for 30 min. The reaction mixture was then quenched with satd aq Na₂S₂O₃ and extracted with CH₂Cl₂. The organic extracts were dried over anhydrous Na₂SO₄ and concentrated to afford crude product, which was further purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.

Phenyl-(2-phenylnaphthalen-1-yl)-methanone (20). This compound was obtained as a colorless oil. The spectral properties were identical to those previously reported.³

1-Iodo-2-phenylnaphthalene (21). This compound was obtained as a colorless oil. The spectral properties were identical to those previously reported.³

References

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127.8318

128.0206

128.1666

129.5058

129.8940

129.9616

130.2394

131.7674

137.8434

152.2072