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SYNTHESIS OF 7-ALKOXYQUINOLINES, COUMARINS, AND RESORUFINS

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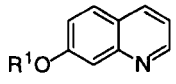
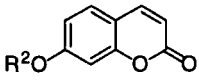
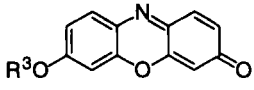
Abstract: Synthesis of the title compounds by treatment of the sodium salts of 7-quinolinol, 7-hydroxycoumarin, and resorufin with alkyl halides is described.

7-Alkoxyquinolines, coumarins, and resorufins are widely used as specific indicators of activity of cytochrome P450 isozymes.[1] We required a number of these compounds for use in characterizing the activity of mutant enzymes. Although most of the needed compounds were known, the reported syntheses were cumbersome and inefficient.[2-5] We report herein simple and efficient syntheses of 7-alkoxyquinolines **1a-1g**, coumarin **2**, and resorufin **3**.







1a $R^1 = CH_3$
1b $R^1 = CH_2CH_3$
1c $R^1 = (CH_2)_2CH_3$
1d $R^1 = (CH_2)_3CH_3$
1e $R^1 = (CH_2)_4CH_3$
1f $R^1 = (CH_2)_5CH_3$
1g $R^1 = (CH_2)_6CH_3$

2 $R^2 = (CH_2)_6CH_3$

3 $R^3 = (CH_2)_6CH_3$

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Previously we had prepared 7-alkoxycoumarins and resorufins via the Williamson ether synthesis in EtOH, THF, and DMSO solvents according to the literature. Yields for the resorufin derivatives were low.[2-5] The greater expense for 7-quinolinol as compared to 7-hydroxycoumarin and resorufin prompted an investigation of alternative conditions for these alkylations.

Treatment of 7-quinolinol with 2.5 equivalents of sodium hydride in *N,N*-dimethylformamide at 0 °C, followed by addition of 2 equivalents of a primary alkyl iodide, provided the corresponding 7-alkoxyquinoline after aqueous workup and column chromatography on silica gel. Product yields were good to excellent, ranging from 73-99% (see Table). Given these results we examined the alkylation of the sodium salts of 7-hydroxycoumarin and resorufin with 1-iodoheptane in DMF. Good yields of products were also obtained in these cases.

General Procedures. All reactions were run under an argon atmosphere. 7-Quinolinol was purchased from ACROS Organics and was used without further purification. All other reagents were purchased from Aldrich Chemical Company and were used without further purification. Reaction product solutions were concentrated *in vacuo* using a rotary evaporator at 30-40 mm Hg. Analytical thin-layer chromatography (TLC) employed Merck glass-backed pre-coated plates (0.25 mm, silica gel 60, F-254). Visualization of spots was effected by (a) UV illumination, (b) exposure to iodine vapor, or (c) treatment of the plate with a 5% solution of phosphomolybdic acid in ethanol or a 2.5% solution of anisaldehyde in ethanol containing 6% H_2SO_4 and 2% acetic acid followed by charring on a hot plate. Reaction product solutions were concentrated using a rotary evaporator at 30-40 mm Hg. Gravity-driven column chromatography was performed on Merck silica gel 60 (70-230 mesh). Melting points were determined on a MEL-TEMP capillary apparatus and are uncorrected. IR spectra were obtained using KBr

Table. Yields of 7-Alkoxyquinolines, Coumarins, and Resorufins.

Product	Solvent	Yield, %	Reference
1a	EtOH	20	3
	DMF	73	tw[a]
1b	DMF	99	tw
1c	DMF	96	tw
1d	DMF	96	tw
1e	DMF	96	tw
1f	DMF	97	tw
1g	DMF	99	tw
2	DMF	79	tw
3	DMSO	44	6
	DMF	66	tw

[a]This work.

plates. NMR spectra were recorded in $CDCl_3$ solution. Proton and ^{13}C magnetic resonance spectra were recorded at 300 MHz and 75 MHz, respectively, using the residual proton signal from solvent (7.24 ppm) and the center line of the chloroform-*d* triplet (77.0 ppm) as internal references. Mass spectra were obtained from the Mass Spectrometry Lab in the Department of Chemistry at The University of Arizona, Tucson, Arizona. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

7-Heptoxyquinoline (1g). To a slurry of NaH (207 mg, 8.62 mmol) in dry DMF (10 mL) at 0 °C was added 7-quinolinol (500 mg, 3.45 mmol) in dry DMF (20 mL). The mixture was stirred for 1 hour and then allowed to warm to room temperature. Iodoheptane (1.13 mL, 6.90 mmol) was added and the mixture was stirred for 3 days while progress of the reaction was monitored by TLC (EtOAc). The reaction mixture was then poured into ice water and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (25 mL), brine (25 mL),

dried ($MgSO_4$), and concentrated. The residue was subjected to column chromatography on silica gel 60 (70-230 mesh) eluted with 35% EtOAc/hexanes to yield **1g** as a white solid, mp 40-41 °C, R_f 0.70 (EtOAc). The yield was 832 mg (3.42 mmol, 99%). IR 2939, 2850, 1616, 1443, 1259, 1009, 833 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J = 6.6 Hz), 1.29-1.38 (6H, m), 1.45-1.51 (2H, m), 1.82-1.87 (2H, m), 4.10 (2H, t, J = 6.6 Hz), 7.16-7.25 (2H, m), 7.40 (1H, d, J = 3.0 Hz), 7.67 (1H, d, J = 9.0 Hz), 8.04 (1H, d, J = 9.0 Hz), 8.81 (1H, d, J = 3.0 Hz). ^{13}C NMR δ 14.0, 22.6, 26.0, 29.0, 29.1, 31.7, 68.2, 107.7, 118.8, 120.1, 123.4, 128.7, 135.7, 149.8, 150.3, 160.2. EI mass spectrum (70 eV) *m/z* (relative intensity) 243 (5), 145 (100), 117 (12), 89 (8), 57 (16), 43 (17), 41 (32), 29 (22).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.68; H, 8.55; N, 5.72.

7-Methoxyquinoline (1a).[3] The procedure above was used to prepare **1a** from 7-quinolinol (500 mg, 3.45 mmol), NaH (207 mg, 8.62 mmol), and iodomethane (515 μL, 6.90 mmol). The yield of **1a**, a low melting solid, R_f 0.40 (EtOAc), was 482 mg (3.03 mmol, 73%). IR 3003, 2939, 2834, 1620, 1508, 1323, 1267, 1017, 833 cm^{-1}; ^1H NMR δ 3.86 (3H, s), 7.10-7.18 (2H, m), 7.36 (1H, d, J = 3.0 Hz), 7.59 (1H, d, J = 9.0 Hz), 7.96 (1H, d, J = 9.0 Hz), 8.76 (1H, d, J = 3.0 Hz); ^{13}C NMR δ 55.2, 107.0, 118.8, 119.6, 123.3, 128.6, 135.4, 149.7, 150.3, 160.4; mass spectrum (EI, 70 eV) *m/z* (relative intensity) 159 (100), 129 (47), 116 (83), 89 (42), 63 (30), 39 (22). These spectral data are in agreement with the reported data.[3]

7-Ethoxyquinoline (1b).[2] The procedure above was used to prepare **1b** from 7-quinolinol (500 mg, 3.45 mmol), NaH (207 mg, 8.62 mmol) and iodoethane

(550 μL, 6.90 mmol). The yield of **1b**, a low melting solid, R_f 0.45 (EtOAc), was 588 mg (3.40 mmol, 99%). IR 3059, 2971, 2882, 1620, 1508, 1395, 1267, 1042, 825 cm^{-1}; ^1H NMR δ 1.34-1.39 (3H, m), 4.02-4.09 (2H, m), 7.06-7.11 (2H, m), 7.31 (1H, s), 7.54 (1H, d, J = 9.0 Hz), 7.90 (1H, d, J = 9.0 Hz), 8.71 (1H, d, J = 3.0 Hz); ^{13}C NMR δ 14.4, 63.4, 107.6, 118.6, 119.7, 123.1, 128.4, 135.3, 149.7, 150.2, 159.6; mass spectrum (EI, 70 eV) *m/z* (relative intensity) 173 (54), 145 (100), 117 (27), 89 (24), 63 (16), 39 (14). These spectral data are in agreement with the reported data.[2]

7-Propoxyquinoline (1c).[2] The procedure above was used to prepare **1c** from 7-quinolinol (500 mg, 3.45 mmol), NaH (207 mg, 8.62 mmol) and 1-iodopropane (672 μL, 6.90 mmol). The yield of **1c**, a low melting solid, R_f 0.50 (EtOAc), was 619 mg (3.31 mmol, 96%). IR 3059, 2955, 2930, 2874, 1620, 1493, 1443, 1323, 1267, 985, 833 cm^{-1}; ^1H NMR δ 1.03 (3H, t, J = 7.8 Hz), 1.80-1.87 (2H, m), 4.02 (2H, t, J = 7.0 Hz), 7.13-7.20 (2H, m), 7.37 (1H, d, J = 3.0 Hz),7.62 (1H, dd, J = 9.0, 3.0 Hz), 7.99 (1H, d, J = 9.0 Hz), 8.77 (1H, d, J = 3.0 Hz); ^{13}C NMR δ 10.4, 22.2, 69.5, 107.7, 118.7, 119.9, 123.2, 128.6, 135.5, 149.8, 150.3, 160.0; mass spectrum (EI, 70 eV) *m/z* (relative intensity) 187 (23), 145 (100), 117 (21), 89 (16), 63 (13), 41 (14), 39 (12). These spectral data are in agreement with the reported data.[2]

7-Butoxyquinoline (1d).[2] The procedure above was used to prepare **1d** from 7-quinolinol (500 mg, 3.45 mmol), NaH (207 mg, 8.62 mmol) and 1-iodobutane (784 μL, 6.90 mmol). The yield of **1d**, a low melting solid, R_f 0.55 (EtOAc), was 675 mg (3.36 mmol, 96%). IR 3051, 2955, 2939, 2874, 1620, 1500, 1323, 1259, 1170, 1011, 833 cm^{-1}; ^1H NMR δ 0.92 (3H, t, J = 7.4 Hz), 1.41-1.49 (2H, m), 1.73-1.78 (2H, m), 4.02 (2H, t, J = 7.5 Hz), 7.1-7.34 (2H, m), 7.34 (1H, s),

7.55 (1H, d, J = 9.0 Hz), 7.93 (1H, d, J = 9.0 Hz), 8.74 (1H, d, J = 3.0 Hz); ^{13}C NMR δ 13.6, 19.1, 30.8, 67.6, 107.6, 118.6, 119.8, 123.1, 128.5, 135.4, 149.7, 150.2, 159.9; mass spectrum (EI, 70 eV) *m/z* (relative intensity) 201 (16), 145 (100), 117 (18), 89 (14), 63 (8), 41 (16), 39 (10). These spectral data are in agreement with the reported data.[2]

7-Pentoxyquinoline (1e).[2] The procedure above was used to prepare **1e** from 7-quinolinol (500 mg, 3.45 mmol), NaH (207 mg, 8.62 mmol) and 1-iodopentane (900 μL, 6.90 mmol). The yield of **1e**, a low melting solid, R_f 0.60 (EtOAc), was 713 mg (3.32 mmol, 96%). IR 3059, 2939, 2866, 1620, 1500, 1443, 1315, 1170, 1017, 833 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J = 7.0 Hz), 1.30-1.42 (4H, m), 1.75-1.79 (2H, m), 4.02 (2H, t, J = 7.5 Hz), 7.09-7.14 (2H, m), 7.34 (1H, s), 7.57 (1H, dd, J = 9.0, 3.0 Hz), 7.93 (1H, d, J = 8.1 Hz), 8.74 (1H, d, J = 1.8 Hz); ^{13}C NMR δ 13.8, 22.2, 28.0, 28.5, 67.9, 107.6, 118.6, 119.8, 123.1, 128.4, 135.3, 149.7, 150.2, 159.9; mass spectrum (EI, 70 eV) *m/z* (relative intensity) 215 (11), 145 (100), 117 (11), 89 (10), 63 (8), 43 (26), 41 (18), 39 (12), 29 (11). These spectral data are in agreement with the reported data.[2]

7-Hexoxyquinoline (1f).[2] The procedure above was used to prepare **1f** from 7-quinolinol (500 mg, 3.45 mmol), NaH (207 mg, 8.62 mmol) and 1-iodohexane (1.02 mL, 6.90 mmol). The yield of **1f**, a low melting solid, R_f 0.65 (EtOAc), was 765 mg (3.34 mmol, 97%). IR 3051, 2939, 2858, 1620, 1500, 1323, 1267, 1170, 825 cm^{-1}; ^1H NMR δ 0.91 (3H, t, J = 6.9 Hz), 1.32-1.38 (4H, m), 1.47-1.52 (2H, m), 1.81-1.88 (2H, m), 4.11 (2H, t, J = 6.9 Hz), 7.19-7.28 (2H, m), 7.43 (1H, s), 7.69 (1H, d, J = 9.0 Hz), 8.10 (1H, d, J = 9.0 Hz), 8.82 (1H, d, J = 3.0 Hz); ^{13}C NMR δ 14.0, 22.6, 25.7, 29.0, 31.6, 68.3, 107.4, 118.8, 120.4, 123.4, 128.7, 136.1, 149.5, 150.0, 160.4; mass spectrum (EI, 70 eV) *m/z*

(relative intensity) 229 (9), 145 (100), 117 (12), 89 (8), 43 (24), 41 (16). These spectral data are in agreement with the reported data.[2]

7-Heptoxycoumarin (2). To a slurry of NaH (148 mg, 6.16 mmol) in dry DMF (10 mL) at 0 °C was added 7-hydroxycoumarin (500 mg, 3.08 mmol) in dry DMF (20 mL). The mixture was stirred for 1 hour and then allowed to warm to room temperature. 1-Iodoheptane (758 μL, 4.62 mmol) was added and the mixture was stirred for 24 hours while progress of the reaction was monitored by TLC (50% EtOAc/hexanes). The reaction mixture was then poured into ice water and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (25 mL), brine (25 mL), dried ($MgSO_4$), and concentrated. The residue was subjected to column chromatography on silica gel 60 (70-230 mesh) eluted with 20% EtOAc/hexanes to yield **2** as a white solid, mp 38-39 °C, R_f 0.80 (50% EtOAc/hexanes). The yield was 633 mg (2.43 mmol, 79%). IR 3083, 2922, 2850, 1709, 1612, 1395, 1275, 1122, 1009, 841 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J = 6.9 Hz), 1.29-1.46 (8H, m), 1.76-1.81 (2H, m), 3.97 (2H, t, J = 6.6 Hz), 6.20 (1H, d, J = 9.3 Hz), 6.75 (1H, s), 6.80 (1H, dd, J = 8.7, 2.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.60 (1H, d, J = 9.6 Hz); ^{13}C NMR δ 13.8, 22.3, 25.6, 28.7, 28.7, 31.4, 68.4, 101.0, 112.0, 112.5, 112.6, 128.4, 143.2, 155.6, 161.0, 162.1; mass spectrum (EI, 70 eV) *m/z* (relative intensity) 260 (12), 162 (100), 134 (54), 57 (36), 43 (31), 41 (43), 29 (30).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.14; H, 7.63.

7-Heptoxyresorufin (3). To a solution of resorufin sodium salt (500 mg, 2.13 mmol) in dry DMF (30 mL) was added 1-iodoheptane (380 μL, 2.34 mmol). The reaction mixture was stirred for 4 days while progress of the reaction was

monitored by TLC (50% EtOAc/hexanes). The reaction mixture was then poured into ice water and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (25 mL), brine (25 mL), dried ($MgSO_4$), and concentrated. The residue was subjected to column chromatography on silica gel 60 (70-230 mesh) eluted with 30% EtOAc/hexanes to yield **3** as an orange solid, mp 137-138 °C, lit.[5] mp 136 °C, R_f 0.70 (50% EtOAc/hexanes). The yield was 432 mg (1.39 mmol, 66%). IR 3051, 2914, 2858, 1620, 1556, 1508, 1335, 1259, 1098, 857 cm^{-1}; ^1H NMR δ 0.89 (3H, t, J = 6.9 Hz), 1.31-1.49 (8H, m), 1.80-1.85 (2H, m), 4.05 (2H, t, J = 6.6 Hz), 6.32 (1H, d, J = 1.8 Hz), 6.78 (1H, d, J = 2.7 Hz), 6.83 (1H, dd, J = 9.6, 1.5 Hz), 6.93 (1H, dd, J = 8.7, 2.4 Hz), 7.42 (1H, d, J = 9.9 Hz), 7.68 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 14.0, 22.5, 25.8, 28.9, 28.9, 31.7, 69.1, 100.3, 106.6, 114.2, 128.2, 131.5, 134.0, 134.6, 145.2, 145.7, 149.8, 163.3, 186.2; mass spectrum (EI, 70 eV) *m/z* (relative intensity) 311 (14), 213 (76), 185 (41), 78 (38), 63 (100), 57 (68), 43 (66), 41 (78), 29 (58), 28 (40).

Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.42; H, 7.03; N, 4.46.

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