A Very Facile S_NAr Reaction with Elimination of Methoxide

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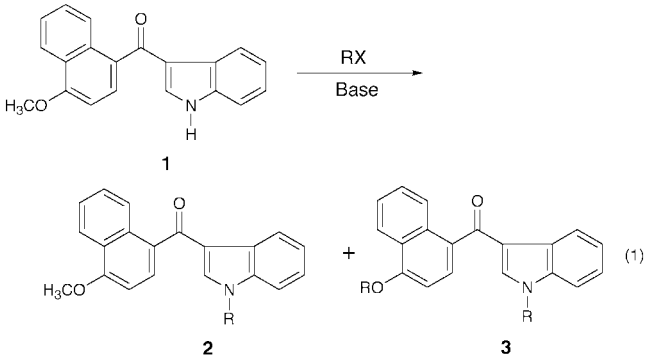
It has been found that 1-alkyl-3-(1-naphthoyl)indoles are potent agonists for the cannabinoid brain receptor and the 1-propyl-2-methyl analogue shows selectivity for the peripheral (spleen) cannabinoid receptor.[1,2] In the course of preparing a series of 3-(4-methoxy-1-naphthoyl)-indole derivatives designed to be selective agonists for the peripheral receptor, the reaction of 3-(4-methoxy-1-naphthoyl)indole (**1**) with a series of primary alkyl halides in the presence of KOH in DMSO was carried out (eq 1). This is an established procedure for the



N-alkylation of 3-aroylindoles and usually provides the *N*-alkylindoles in fair to good yield.[1,3] However, in contrast to expectations, the reaction products were a mixture of the desired 1-alkyl-3-(4-methoxy-1-naphthoyl)-indole (**2**) and a 1-alkyl-3-(4-alkoxy-1-naphthoyl)indole (**3**).

As shown in Table 1 (method A) when the alkylation was carried out at 80 °C with *n*-alkyl halides from ethyl through hexyl, mixtures of products were obtained in yields of 41−90%. In addition to the expected N-alkylation product, a substantial fraction of the product was formed by additional replacement of the methoxyl group by an alkoxyl group. The reaction is very temperature dependent, since a decrease of only 5 °C (method B) completely suppresses the formation of the O-alkylation products with the ethyl or propyl halide. However, *n*-hexyl bromide provided a 75% yield of hexyl ether **3f** under these conditions. At 55 °C (method C) alkylation with *n*-hexyl bromide gave only the N-alkylation product (**2f**).

Table 1. Alkylation of Indole 1

			product and yield (%)	
compd	R[a]	method[b]	**2**	**3**
a	CH_3	A	90	NA
b	CH_3CH_2	A	45	16
b	CH_3CH_2	B	95	0
c	$CH_3(CH_2)_2$	A	31	14
c	$CH_3(CH_2)_2$	B	95	0
d	$CH_3(CH_2)_3$	A	40	23
e	$CH_3(CH_2)_4$	A	20	24
f	$CH_3(CH_2)_5$	A	14	27
f	$CH_3(CH_2)_5$	B	13	75
f	$CH_3(CH_2)_5$	C	88	0
f	$CH_3(CH_2)_5$	D	78	0

[a] Methyl and ethyl iodide were used for alkylation; all others were bromides. [b] Method A: KOH, DMSO, 80 °C, 18 h. Method B: KOH, DMSO, 75 °C, 18 h. Method C: KOH, DMSO, 55 °C, 18 h. Method D: KH, DMSO, 80 °C, 1 h.

Two mechanistic rationalizations for the formation of ethers **3** appeared plausible. The first was nucleophilic ether cleavage by hydroxide to provide a phenoxide which is subsequently alkylated to provide the ether (**3**). A second possible reaction path was an S_NAr reaction with hydroxide as nucleophile, to provide a phenol, which would exist as the conjugate base in the presence of KOH in DMSO. Alkylation of the phenoxide by the alkyl halide present in the reaction mixture then provides the corresponding ether (**3**).

It is generally considered that S_NAr reactions which proceed via apparent direct nucleophilic displacement of a substituent from the aromatic ring require the presence of at least one strongly electron withdrawing group; however, alkoxide is not favored as a leaving group, nor is hydroxide a particularly effective nucleophile.[4] Recently, it has been found that the S_NAr displacement of *o*-methoxy groups in the naphthalene series by a variety of nucleophiles, and with several activating groups, is of considerable synthetic utility.[5] Many of these reactions employ Grignard or organolithium reagents as nucleophiles, and simultaneous complexation of the organometallic with the methoxy and the activating group facilitates the S_NAr reaction. There are also several examples in which the *o*-methoxy group was displaced by an alkoxide.[5b] There has been one study of the displacement of methoxide by alkoxide in DMF using methyl 1-methoxy-2-naphthoate and methyl 2-methoxybenzoate as substrates.[6] This displacement proceeds in good yield with isopropoxide, benzyloxide, and *n*-butoxide but failed with *tert*-butoxide and phenoxide. The reaction was extended to the methyl esters of 3- and 4-methoxybenzoic acids. Only the *p*-methoxy was displaced, and then in a meager 22% overall yield. These results were rational

(1) Huffman, J. W.; Dai, D.; Martin, B. R.; Compton, D. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 563.

(2) Showalter, V. M.; Compton, D. R.; Martin, B. R.; Abood, M. E. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 989.

(3) D'Ambra, T. E.; Estep, K. G.; Bell, M. R.; Eissenstat, M. A.; Josef, K. A.; Ward, S. J.; Haycock, D. A.; Baizman, E. R.; Casiano, F. M.; Beglin, N. C.; Chippari, S. M.; Grego, J. D.; Kullnig, R. K.; Daley, G. T. *J. Med. Chem.* **1992**, *35*, 124.

(4) (a) Paradisi, C. Arene Substitution via Nucleophilic Addition to Electron Deficient Arenes. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 4, pp 423−450. (b) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. (c) Peishoff, C. E.; Jorgenson, W. L. *J. Org. Chem.* **1985**, *50*, 1056.

(5) (a) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (b) Hattori, T.; Sakamoto, J.; Hayashizaka, N.; Miyano, S. *Synthesis* **1994**, 199. (c) Hattori, T.; Tanaka, H.; Okaishi, Y.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 235. (d) Hattori, T.; Suzuki, M.; Komuro, Y.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1473.

(6) Hattori, T.; Satoh, S.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3840.

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ized in terms of stabilization of the intermediate in the *ortho*-substitution reaction as a complex with sodium ion. These authors also note, without explanation, that naphthyl systems are more effective substrates for S_NAr reactions than simple benzenoid systems.[6] A similar S_N-Ar reaction of a methoxyfluorenone with hydrazine in ethanol was described recently by Gould et al.[7]

Although published data indicated that methoxynaphthoylindoles **1** and **2**, which are activated only by a single carbonyl group para to the site of nucleophilic attack, should not be particularly favorable substrates for S_NAr reactions, studies were undertaken to explore this possibility. Indole **2f** (R = 1-hexyl) was treated under the conditions employed for alkylation, using 1-hexanol rather than an alkyl halide, and gave a mixture of recovered **2f**, ether **3f** (R, R′ = 1-hexyl), and the corresponding phenol (**3**, *N*-hexyl, OR = OH). Similarly, reaction of **2a** (R = methyl) with potassium pentoxide in DMSO afforded the S_NAr product, (**3**, *N*-methyl, *O*-*n*-pentyl) in 43% yield. With potassium ethoxide in DMSO indole **2b** (R = ethyl) gave a mixture of ether **3b** (53%) and the corresponding phenol (18%). Reaction of **1** with 1-bromohexane using potassium hydride in DMSO, conditions which had been employed earlier for the alkylation of 3-(1-naphthoyl)pyrrole,[8] gave as the only isolable product the N-alkylation product, 1-hexyl-3-(4-methoxy-1-naphthoyl)indole (**2f**), in 78% yield. Although these experiments indicate that the carbonyl group para to the methoxy is sufficiently electron withdrawing to permit an S_NAr reaction under very mild conditions, the formation of phenols in these experiments is consistent either with nucleophilic ether cleavage or an S_NAr reaction with adventitious water.

To further explore the course of these reactions, a less complex model system, 1-benzoyl-4-methoxynaphthalene, was employed. Reaction of this substrate with KOH in DMSO under the conditions employed for the alkylation of **1** provided 4-benzoyl-1-naphthol in 53% yield. When the reaction was repeated using KOH prepared in situ from potassium hydride and water enriched in ^{18}O (approximately 10%), mass spectrometry indicated that *the reaction product contained approximately 10% ^{18}O.* These results are clearly consistent only with an S_NAr reaction with hydroxide as the nucleophile and methoxide as the nucleofuge. Reaction of 1-benzoyl-4-methoxynaphthalene with potassium ethoxide prepared in situ from anhydrous ethanol in DMSO gave 1-benzoyl-4-ethoxynaphthalene as the only isolable product in 74% yield. Sodium ethoxide gave the same product, but in 48% yield. However, reaction of 1-benzoyl-4-methoxynaphthalene with potassium phenoxide in DMSO gave only recovered starting material. Similar S_NAr reactions were also carried out in the benzophenone series; 4-methoxybenzophenone with KOH in DMSO gives 4-benzoylphenol, and with potassium ethoxide in ethanol 4-ethoxybenzophenone is obtained. The yields in this series were only 42% and 11%, respectively; however, no effort was made to optimize them.

In agreement with the results of Hattori et al., reaction of 4-methoxybenzophenone did not appear to be as efficient as that of naphthyl ketones.[6] To determine whether the S_NAr reaction of 4-methoxybenzophenone was actually slower than that of indoles **1** and **2a**−**g**, and 4-methoxy-1-benzoylnaphthalene, competition experiments were carried out in order to determine the relative rates of these reactions. Reaction of an equimolar mixture of 4-methoxybenzophenone and 1-benzoyl-4-methoxynaphthalene in DMSO, in the presence of less than 1 equiv of potassium ethoxide, gave a 1:1.4 mixture of 4-ethoxybenzophenone and 1-benzoyl-4-ethoxynaphthalene, verifying the suggestion that a naphthalene substrate undergoes the S_NAr reaction faster than a monocyclic aromatic. A similar competition reaction was carried out employing 1-benzoyl-4-methoxynaphthalene and 1-ethyl-3-(4-methoxy-1-naphthoyl)indole (**2b**). The ratio of 1-benzoyl-4-ethoxynaphthalene to 1-ethyl-3-(4-ethoxy-1-naphthoyl)indole (**3b**) was 20:1, indicating that the indolyl ketone reacted considerably more slowly than the benzoyl analogue.

The enhanced S_NAr reactivity of 1-benzoyl-4-methoxynaphthalene relative to that of 4-methoxybenzophenone is not surprising. Assuming the usually accepted value of 61 kcal/mol for the delocalization energy of naphthalene, and 36 kcal/mol for benzene, this corresponds to an approximate loss of 25 kcal/mol in the formation of the intermediate from 4-methoxy-1-benzoylnaphthalene and 36 kcal/mol from 4-methoxybenzophenone. These differences in energy would be reflected in the transition state energies leading to the intermediates, which would in turn be reflected in the relative reaction rates. The decrease in rate for indolyl ketone **2b** may be attributed to stabilization of the carbonyl by electron delocalization involving the indole nitrogen. 3-Acylindoles have the properties of vinylogous amides, and this stabilization would be lost in the formation of the S_NAr intermediate.

The facile carbonyl activated displacement of a *p*-methoxy in the S_NAr reactions of indoles **1** and **2a**−**g**, and 4-methoxy-1-benzoylnaphthalene with hydroxy as nucleophile, and methoxy the leaving group, is quite unusual. Methoxy is a poor leaving group, hydroxy is a mediocre nucleophile, and the displacement of a *para*-substituent in even modest yield with only a ketonic carbonyl as an activating substituent is apparently unprecedented. It is, however, known that the use of polar aprotic solvents such as DMSO favors these reactions.[9]

On the basis of the results obtained with indoles **1** and **2**, 1-benzoyl-4-methoxynaphthalene, and 4-methoxybenzophenone, it would appear that S_NAr reactions involving activation by *p*-carbonyl are more facile than conventional wisdom dictates. The use of a naphthyl ketone as substrate and DMSO as solvent certainly facilitate the reaction.

Experimental Section

Melting points are uncorrected. Low-resolution mass spectra were determined at an ionizing voltage of 70 eV. Ether and THF were distilled from Na−benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Universal silica gel (32−63 μm) using the indicated solvents as eluents. HRMS data were provided by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois.

(7) Gould, S. J.; Chen, J.; Cone, M. C.; Gore, M. P.; Melville, C. R.; Tamayo, N. *J. Org. Chem.* **1996**, *61*, 5720.

(8) Lainton, J. A. H.; Huffman, J. W.; Martin, B. R.; Compton, D. R. *Tetrahedron Lett.* **1995**, *36*, 1401.

(9) Zoltawicz, J. A. *Top. Curr. Chem.* **1975**, *59*, 33.

3-(4-Methoxy-1-naphthoyl)indole (1). To a solution of 7.2 mL of 2.7 M methylmagnesium bromide in THF (19.3 mmol) at 0 °C was added 1.88 g (16.1 mmol) of indole in 7 mL of dry ether. The reaction mixture was allowed to warm to room temperature, and a solution of 4-methoxy-1-naphthoyl chloride (prepared from 3.26 g, 16.1 mmol, of 4-methoxy-1-naphthalenecarboxylic acid in 6 mL of THF) was added cautiously. The reaction mixture was heated at reflux with stirring for 1.5 h. After the solution was cooled to room temperature, saturated aqueous NH_4Cl was added cautiously, and the ether was distilled off. The solid was collected by filtration and suspended in 30 mL of CH_3OH, and 5 mL of 20% aqueous NaOH was added. The suspension was stirred at reflux for 4 h and cooled to room temperature, and the solid was collected by filtration. After being dried in vacuo, there was obtained 2.81 g (58%) of 3-(4-methoxy-1-naphthoyl)-indole (**1**) as a pale-yellow solid. Recrystallization from ethyl acetate/DMSO gave material with the following: mp 270−275 °C: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.03 (s, 3H), 7.02 (d, J = 8.0 Hz, 1H), 7.25−7.30 (m, 2H), 7.52−7.57 (m, 3H), 7.70−7.73 (m, 2H), 8.15−8.18 (m, 1H), 8.20−8.28 (m, 1H), 8.30−8.35 (m, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 55.9, 103.1, 112.4, 117.4, 121.6, 121.8, 122.1, 123.2, 125.1, 125.5, 125.7, 126.2, 127.3, 128.0, 131.6, 131.9, 156.2, 191.1. Anal. Calcd for $C_{20}H_{15}NO_2 \cdot {}^1/_4H_2O$: C, 78.54; H, 5.11; N, 4.58. Found: C, 78.63; H, 5.12, N; 4.60. Several separate samples of this compound gave consistent analytical data.

General Procedures for the Alkylation of 3-(4-Methoxy-1-naphthoyl)indole. Methods A, B, and C. To a stirred solution of 0.390 g (1.3 mmol) of indole **1** and 0.50 g of powdered KOH in 5 mL of DMSO was added 3 equiv of the appropriate alkyl halide. The resulting solution was heated to 80 °C (method A), 75 °C (method B), or 55 °C (method C) and stirred at this temperature overnight. After the solution was cooled to room temperature, water was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixtures for elution.

Method D. To a stirred solution of 0.400 g (3 mmol, 30 wt %) of KH in 2 mL of DMSO at ambient temperature was added a solution of 0.300 g (1 mmol) of indole **1** in 2 mL of DMSO, followed by 3 mmol of the appropriate alkyl halide. The resulting solution was heated to 80 °C and stirred at this temperature for 1 h. After the solution was cooled to room temperature, water was added, and the reaction mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), and the solvents were evaporated in vacuo. The residue was purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate mixtures for elution.

1-Methyl-3-(4-methoxy-1-naphthoyl)indole (2a): mp 194−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H), 4.01 (s, 3H), 6.76 (d, J = 7.9 Hz, 1H), 7.32−7.35 (m, 4H), 7.46−7.49 (m, 2H), 7.60 (d, J = 7.9 Hz, 1H), 8.26−8.33 (m, 2H), 8.44−8.48 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.3, 55.6, 102.1, 109.6, 117.2, 122.0, 122.6, 123.5, 125.5, 125.6, 127.1, 127.3, 131.3, 132.1, 137.6, 138.4, 156.9, 191.7. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.42; N, 4.44. Found: C, 79.90; H, 5.50; N, 4.44.

1-Ethyl-3-(4-methoxy-1-naphthoyl)indole (2b): mp 170−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J = 7.3 Hz, 3H), 3.96 (s, 3H), 4.03 (q, J = 7.3 Hz, 2H), 6.73 (d, J = 8.0 Hz, 1H), 7.29−7.33 (m, 3H), 7.38 (s, 1H), 7.43−747 (m, 2H), 7.59 (d, J = 8.0 Hz, 1H), 8.29−8.32 (m, 2H), 8.46−8.50 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.9, 41.5, 55.5, 102.0, 109.7, 117.6, 121.9, 122.5, 122.7, 123.3, 125.5, 125.6, 127.1, 127.2, 127.7, 131.2, 132.0, 136.7, 156.8, 191.6. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.29; H, 5.75; N, 4.23.

1-Ethyl-3-(4-ethoxy-1-naphthoyl)indole (3b): viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 1.57 (t, J = 7.0 Hz, 3H), 4.11 (q, J = 7.2 Hz, 2H), 4.24 (q, J = 7.0 Hz, 2H), 6.78 (d, J = 7.9 Hz, 1H), 7.31−7.37 (m, 3H), 7.42 (s, 1H), 7.47−7.50 (m, 2H), 7.62 (d, J = 7.9 Hz, 1H), 8.28−8.31 (m, 1H), 8.35−8.39 (m, 1H), 8.44−8.48 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7, 15.1, 41.6, 63.9, 102.8, 109.7, 117.8, 122.1, 122.6, 122.8, 123.4, 125.5, 125.7, 127.2, 127.8, 131.1, 132.1, 136.7, 156.3, 191.8; MS (EI) m/z (rel intensity) 343 (91), 326 (47), 314 (48), 286 (35), 172 (100); HRMS calcd for $C_{25}H_{21}NO_2$ 343.1572, found 343.1573.

1-Propyl-3-(4-methoxy-1-naphthoyl)indole (2c): mp 146−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 1.82 (sextet, J = 7.2 Hz, 2H), 4.02 (t, J = 7.2 Hz, 2H), 4.4 (s, 3H), 6.80 (d, J = 7.9 Hz, 1H), 7.31−7.37 (m, 3H), 7.40 (s, 1H), 7.48−7.51 (m, 2H), 7.64 (d, J = 7.9 Hz, 1H), 8.29−8.34 (m, 2H), 8.46−8.49 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.3, 23.6, 48.6, 55.6, 102.1, 109.9, 117.6, 122.0, 122.6, 122.8, 123.4, 125.6, 125.8, 127.2, 127.3, 127.8, 131.4, 132.1, 136.9, 137.5, 157.0, 191.7. Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.42; H, 6.20; N, 3.98.

1-Propyl-3-(4-propoxy-1-naphthoyl)indole (3c): viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.54 (t, J = 7.3 Hz, 3H), 1.82 (sextet, J = 7.3 Hz, 2H), 1.98 (sextet, J = 7.3 Hz, 2H), 4.02 (t, J = 7.1 Hz, 2H), 4.14 (t, J = 6.4 Hz, 2H), 6.79 (d, J = 7.9 Hz, 1H), 7.31−7.37 (m, 3H), 7.40 (s, 1H), 7.47−7.50 (m, 2H), 7.63 (d, J = 7.9 Hz, 1H), 8.29−8.33 (m, 1H), 8.36−8.39 (m, 1H), 8.46−8.49 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.7, 11.3, 22.5, 23.0, 48.6, 69.7, 102.8, 109.9, 117.6, 122.1, 122.5, 122.8, 123.3, 125.4, 125.7, 127.2, 127.9, 131.1, 132.1, 136.9, 137.5, 156.5, 191.8; MS (EI) m/z (rel intensity) 371 (100), 328 (60), 312 (25), 300 (66); HRMS calcd for $C_{25}H_{25}NO_2$ 371.1885, found 371.1884.

1-Butyl-3-(4-methoxy-1-naphthoyl)indole (2d): mp 143−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3H), 1.23−1.33 (m, 2H), 1.72−1.81 (m, 2H), 4.04 (s, 3H), 4.06 (t, J = 7.2 Hz, 2H), 6.81 (d, J = 7.9 Hz, 1H), 7.32−7.39 (m, 3H), 7.40 (s, 1H), 7.48−7.51 (m, 2H), 7.64 (d, J = 7.9 Hz, 1H), 8.29−8.35 (m, 2H), 8.45−8.48 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5, 20.0, 31.8, 46.8, 55.6, 102.1, 109.9, 117.6, 122.0, 122.6, 122.8, 123.4, 125.6, 125.8, 127.3, 127.8, 131.3, 132.1, 136.9, 137.4, 157.0, 191.7. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.52; H, 6.45; N, 3.88.

1-Butyl-3-(4-butoxy-1-naphthoyl)indole (3d): viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H), 1.21−1.33 (m, 2H), 1.40−1.68 (m, 2H), 1.71−1.80 (m, 2H), 1.88−1.98 (m, 2H), 4.04 (t, J = 7.1 Hz, 2H), 4.18 (t, J = 6.3 Hz, 2H), 6.78 (d, J = 7.9 Hz, 1H), 7.30−7.36 (m, 3H), 7.39 (s, 1H), 7.47−7.50 (m, 2H), 7.62 (d, J = 7.9 Hz, 1H), 8.29−8.32 (m, 1H), 8.35−8.38 (m, 1H), 8.45−8.48 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5, 13.9, 19.4, 20.0, 31.2, 31.8, 46.8, 68.0, 102.8, 109.9, 117.7, 122.1, 122.5, 122.8, 123.3, 125.4, 125.8, 127.2, 127.9, 131.1, 132.2, 136.9, 137.4, 156.5, 191.7; MS (EI) m/z (rel intensity) 399 (100), 342 (53), 326 (50), 300 (48), 200 (67); HRMS calcd for $C_{27}H_{29}NO_2$ 399.2198, found 399.2188.

1-Pentyl-3-(4-methoxy-1-naphthoyl)indole (2e): mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 6.8 Hz, 3H), 1.21−1.28 (m, 4H), 1.76 (pentet, J = 7.2 Hz, 2H), 4.00 (s, 3H), 4.01 (t, J = 6.8 Hz, 2H), 6.77 (d, J = 7.9 Hz, 1H), 7.30−7.36 (m, 3H), 7.38 (s, 1H), 7.46−7.49 (m, 2H), 7.62 (d, J = 7.9 Hz, 1H), 8.29−8.34 (m, 2H), 8.46−8.49 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 22.1, 28.8, 29.4, 47.0, 55.6, 102.1, 109.9, 117.6, 122.0, 122.5, 122.7, 123.3, 125.5, 125.6, 125.7, 127.1, 127.2, 127.8, 131.3, 132.1, 136.9, 137.4, 156.9, 191.7. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.94; H, 6.80; N, 3.71.

1-Pentyl-3-(4-pentoxy-1-naphthoyl)indole (3e): viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H), 1.21−1.31 (m, 4H), 1.41−1.59 (m, 4H), 1.74−1.81 (m, 2H), 1.90−1.97 (m, 2H), 4.02 (t, J = 7.1 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 6.77 (d, J = 7.9 Hz, 1H), 7.30−7.36 (m, 3H), 7.38 (s, 1H), 7.47−7.50 (m, 2H), 7.62 (d, J = 7.9 Hz, 1H), 8.30−8.33 (m, 1H), 8.35−8.38 (m, 1H), 8.46−8.49 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 14.0, 22.1, 22.4, 28.4, 28.8, 29.4, 47.0, 68.2, 102.7, 109.8, 117.6, 122.1, 122.5, 122.8, 123.3, 125.4, 125.7, 127.2, 127.9, 131.0, 132.1, 136.9, 137.4, 156.5, 191.7; MS (EI) m/z (rel intensity) 427 (100), 356 (44), 340 (38), 300 (57); HRMS calcd for $C_{29}H_{33}NO_2$ 427.2511, found 427.2512.

1-Hexyl-3-(4-methoxy-1-naphthoyl)indole (2f): viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 6.7 Hz, 3H), 1.20−1.30 (m, 6H), 1.73−1.82 (m, 2H), 4.03 (s, 3H), 4.04 (t, J = 7.2 Hz, 2H), 6.79 (d, J = 7.9 Hz, 1H), 7.31−7.37 (m, 3H), 7.39 (s, 1H), 7.47−7.50 (m, 2H), 7.63 (d, J = 7.9 Hz, 1H), 8.29−8.34 (m, 2H), 8.46−8.49 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.4, 26.4, 29.7, 31.1, 47.0, 55.6, 102.1, 109.9, 117.6, 122.0, 122.5, 122.8, 123.3, 125.6, 125.7, 127.1, 127.3, 127.8, 131.3, 132.1, 136.9,

137.5, 157.0, 191.8; MS (EI) *m*/*z* (rel intensity) 385 (100), 368 (44), 314 (59), 228 (59); HRMS calcd for $C_{26}H_{27}NO_2$ 385.2043, found 385.2040.

1-Hexyl-3-(4-hexoxy-1-naphthoyl)indole (3f): viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 6.7 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H), 1.23 (br s, 6H), 1.37−1.42 (m, 4H), 1.50−1.62 (m, 2H), 1.70−1.80 (m, 2H), 1.89−1.98 (m, 2H), 4.02 (t, J = 7.2 Hz, 2H), 4.15 (t, J = 6.3 Hz, 2H), 6.76 (d, J = 7.9 Hz, 1H), 7.30−7.35 (m, 3H), 7.38 (s, 1H), 7.45−7.51 (m, 2H), 7.61 (d, J = 7.9 Hz, 1H), 8.30−8.38 (m, 2H), 8.46−8.49 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 13.9, 22.3, 22.5, 25.9, 26.4, 29.1, 29.6, 31.1, 31.5, 47.0, 68.2, 102.7, 109.8, 117.6, 122.1, 112.5, 122.7, 123.3, 125.4, 125.7, 127.2, 127.9, 131.0, 132.1, 136.9, 137.4, 156.4, 191.7; MS (EI) *m*/*z* (rel intensity) 455 (100), 438 (18), 370 (36), 300 (54); HRMS calcd for $C_{31}H_{37}NO_2$ 455.2824, found 455.2823.

1-Hexyl-3-(4-hexoxy-1-naphthoyl)indole (3f) and 1-Hexyl-3-(4-hydroxy-1-naphthoyl)indole. To a stirred solution of 0.068 g (0.18 mmol) of 1-hexyl-3-(4-methoxy-1-naphthoyl)indole (**2f**) in 2 mL of DMSO was added 0.037 g (0.036 mmol) of 1-hexanol, followed by 0.1 g of powdered KOH. The resulting solution was heated to 80 °C and stirred at this temperature for 20 h. After the solution was cooled to room temperature, water was added, and the reaction mixture was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by flash chromatography (hexanes/ethyl acetate 95:5) to give 0.012 g (15%) of 1-hexyl-3-(4-hexoxy-1-naphthoyl)indole (**3f**), 0.026 g (38%) of recovered **2f**, and 0.025 g (37%) of 1-hexyl-3-(4-hydroxy-1-naphthoyl)indole as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 6.7 Hz, 3H), 1.18−1.29 (m, 6H), 1.75−1.85 (m, 2H), 4.08 (t, J = 7.3 Hz, 2H), 6.72 (d, J = 7.7 Hz, 1H), 7.31−7.49 (m, 7H), 7.86 (br s, 1H), 8.17−8.27 (m, 2H), 8.43−8.50 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.4, 29.7, 31.2, 47.2, 107.5, 110.0, 117.6, 122.1, 122.8, 123.5, 124.9, 125.3, 125.7, 127.1, 127.8, 130.9, 132.4, 137.1, 138.3, 154.2, 193.0; MS (EI) *m*/*z* (rel intensity) 371 (100), 300 (63), 228 (65), 171 (88); HRMS calcd for $C_{25}H_{25}NO_2$ 371.1885, found 371.1886.

1-Methyl-3-(4-pentoxy-1-naphthoyl)indole. To 0.20 g (1.5 mmol, 30 wt %) KH in 6 mL of dry DMSO at ambient temperature was added 0.40 g (4.6 mmol) of 1-pentanol, followed by 0.20 g (0.63 mmol) of 1-methyl-3-(4-methoxy-1-naphthoyl)-indole (**2a**). The resulting solution was heated at 80 °C for 6 h. After the solution was cooled to room temperature, water was added, and the reaction mixture was extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), and the solvents were evaporated in vacuo. The solid residue was recrystallized from ethyl acetate/petroleum ether to give 0.10 g (43%) of 1-methyl-3-(4-pentoxy-1-naphthoyl)indole: mp 147−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 3H), 1.40−1.62 (m, 4H), 1.98 (pentet, J = 7.9 Hz, 2H), 3.77 (s, 3H), 4.19 (t, J = 6.4 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 7.33−7.39 (m, 4H), 7.46−7.53 (m, 2H), 7.63 (d, J = 7.9 Hz, 1H), 8.25−8.31 (m, 1H), 8.32−8.39 (m, 1H), 8.42−8.50 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 22.5, 28.4, 28.9, 33.5, 68.3, 102.8, 109.6, 117.6, 122.1, 122.7, 122.8, 123.5, 125.5, 127.0, 127.3, 130.8, 132.0, 137.5, 138.3, 156.5, 191.6. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.72; H, 6.76; N, 3.74.

1-Ethyl-3-(4-ethoxy-1-naphthoyl)indole and 1-Ethyl-3-(4-hydroxy-1-naphthoyl)indole. Reaction of 0.10 g (0.30 mmol) of 1-ethyl-3-(4-methoxy-1-naphthoyl)indole with KH and ethanol in DMSO as described above gave 0.033 g (53%) of 1-ethyl-3-(4-ethoxy-1-naphthoyl)indole, identical to that described above, and 0.017 g (18%) of 1-ethyl-3-(4-hydroxy-1-naphthoyl)indole, mp 180−181 °C, after chromatography (hexanes/ethyl acetate 95:5) and recrystallization from ethyl acetate/petroleum ether: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 4.13 (q, J = 7.2 Hz, 2H), 6.63 (d, J = 7.7 Hz, 1H), 7.30−7.48 (m, 7H), 8.05 (br s, 1H), 8.15−8.25 (m, 2H), 8.44−8.51 (m, 1H). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.76; H, 5.44; N, 4.35.

4-Benzoyl-1-naphthol. A. Reaction of 0.30 g (1.2 mmol) of 1-benzoyl-4-methoxynaphthalene[10] under the conditions of method A for the alkylation of indole **1**, employing 0.63 g of KOH in 6 mL of DMSO at 90 °C for 20 h, provided 0.15 g (53%) of 4-benzoyl-1-naphthol, mp 166−167 °C (lit.[11] mp 166−167 °C), after chromatography (petroleum ether/ethyl acetate 4:1) and recrystallization from hexanes/ethyl acetate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (d, J = 7.8 Hz, 1H), 6.90 (s, 1H), 7.43−7.58 (m, 6H), 7.83 (dd, J = 7.0, 1.4 Hz, 2H), 8.30 (m, 1H), 8.38 (dd, J = 6.5, 2.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 106.8, 112.1, 124.6, 125.8, 128.1, 128.3, 130.4, 131.5, 132.6, 133.0, 139.3, 155.3, 197.9; IR (KBr) 1659, 1591 cm^{-1}; MS (EI) *m*/*z* 248 (67), 247 (20), 171 (100), 115 (44).

B. Reaction of 0.15 g (0.57 mmol) of 1-benzoyl-4-methoxynaphthalene with 0.11 g of KH and 0.055 mL of water in 2.5 mL of DMSO at 95 °C for 20 h, under the conditions described above, provided 0.13 g (89%) of 4-benzoyl-1-naphthol, mp 166−167 °C, after chromatography and recrystallization from hexanes/ethyl acetate. This material was identical to that described in part A. When the reaction was carried out under these conditions, using 0.114 g of 1-benzoyl-4-methoxynaphthalene and 0.051 mL of water containing approximately 10% ^{18}O for 15 h, the product was identical in all respects except for the MS (EI) data: *m*/*z* 250 (7), 248 (62), 249 (14), 247 (20), 171 (100), 173 (11).

1-Benzoyl-4-ethoxynaphthalene. To a mixture of 0.15 g of KH (3.75 mmol) in 2.5 mL of dry ethanol was added 0.15 g (0.57 mmol) of 1-benzoyl-4-methoxynaphthalene. The reaction mixture was stirred at reflux for 15 h, cooled, poured into 50 mL of water, and extracted with three portions of ethyl acetate. The combined extracts were washed with 5% aqueous HCl and dried ($MgSO_4$), and the solvent was removed in vacuo to give an oil. Chromatography (petroleum ether/ethyl acetate 25:1) gave 0.11 g (74%) of product as a yellow oil which failed to crystallize:[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (t, J = 6.9 Hz, 3H), 4.27 (q, J = 6.9 Hz, 2H), 6.77 (d, J = 8.2 Hz, 1H), 7.43−7.60 (m, 6H), 7.83 (d, J = 6.9 Hz, 2H), 8.38 (dd, J = 7.4, 2.5 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.9, 64.9, 102.6, 122.3, 125.7, 127.8, 127.9, 128.2, 130.2, 131.6, 132.4, 132.6, 139.5, 157.7, 197.3; MS (EI) *m*/*z* 276 (100), 247 (33), 199 (37). When the reaction was repeated with 0.25 g of 1-benzoyl-4-methoxynaphthalene, using NaH, there was obtained 0.12 g (42%) of product, identical in all respect to that described above.

4-Benzoylphenol. Reaction of 0.15 g (0.71 mmol) of 4-methoxybenzophenone with KH and water in DMSO under the conditions described above gave 0.059 g (48%) of 4-benzoylphenol, mp 136−137 °C (lit.[13] mp 132−133.5 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93−6.97 (m, 2H), 7.44−7.48 (m, 2H), 7.50−7.61 (m, 2H), 7.74−7.80 (m, 4H). The ^{13}C NMR was identical to that reported.[14]

4-Ethoxybenzophenone. Reaction of 0.40 g (1.9 mmol) of 4-methoxybenzophenone with KH in ethanol under the conditions described above gave 0.045 g (11%) of 4-ethoxybenzophenone[15] as a yellow oil after chromatography (petroleum ether/ethyl acetate 20:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (t, J = 7.0 Hz, 3H), 4.11 (q, J = 7.0 Hz, 2H), 6.95 (dd, J = 8.8, 2.6 Hz, 2H), 7.46 (t, J = 7.8 Hz, 2H), 7.54 (m, 1H), 7.75 (dd, J = 7.1, 1.3 Hz, 2H), 7.82 (7.0, J = 1.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6, 63.7, 114.0, 128.1, 129.6, 129.9, 131.8, 132.5, 138.3, 162.6, 195.5; IR (KBr) 1665, 1608 cm^{-1}; MS (EI) *m*/*z* 226 (88), 197 (15), 149 (100). The ^{13}C NMR data were consistent with those reported by Frahm and Hambloch.[16]

Competition Experiments. A. Reaction of a mixture of 0.10 g (0.47 mmol) of 4-methoxybenzophenone and 0.12 g (0.47 mmol) of 1-benzoyl-4-methoxynaphthalene with KH and ethanol under the conditions described above for 0.5 h, followed by analysis of the crude reaction mixture by GC/MS, indicated that 0.35 equiv of 4-methoxybenzophenone and 0.47 equiv of 1-benzoyl-4-methoxynaphthalene had been converted to the corresponding ethyl ethers.

(10) Fierz-David, H. E.; Jaccard, G. *Helv. Chim. Acta* **1928**, *11*, 1042.

(11) Domanska, U. *Ind. Eng. Chem. Res.* **1990**, *29*, 470.

(12) Lapkin (Lapkin, I. I. *Zh. Obshch. Khim.* **1953**, *23*, 780; *Chem. Abstr.* **1954**, *48*, 3940*i*) report this compound as a solid, mp 81−82 °C.

(13) Norell, J. R. *J. Org. Chem.* **1973**, *38*, 1924.

(14) Shapiro, M. J. *Tetrahedron* **1977**, *33*, 1091.

(15) Mndzhoyan (Mndzhoyan, O. L.; Morozova, N. M. *Izv. Akad. Nauk. SSR, Khim. Nauki* **1962**, *15*, 553; *Chem. Abstr.* **1962**, *59*, 6287*b*) report mp 47−48 °C.

(16) Frahm, A. W.; Hambloch, H. F. *Org. Magnet. Reson.* **1980**, *14*, 444.

B. Reaction of a mixture of 0.11 g (0.47 mmol) of 1-benzoyl-4-methoxynaphthalene and 0.14 g (0.42 mmol) of indole **2b** with KH as described above indicated that 0.79 equiv of 1-benzoyl-4-methoxynaphthalene and 0.04 equiv of **2b** had been converted to the corresponding ethyl ethers.

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Supporting Information Available: ^{13}C NMR spectra of **2f**, **3b**, **3c**, **3d**, **3e**, **3f**, and **3**, *N*-hexyl, OH (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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