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Steric Factors in Amide-Directed Metalations of *N,N*-Dialkyl-6-methoxynaphthalene-2-carboxamides: Synthesis of a Sterically Perturbed Acylnaphthol

Rajeshwar D. Bindal and John A. Katzenellenbogen*

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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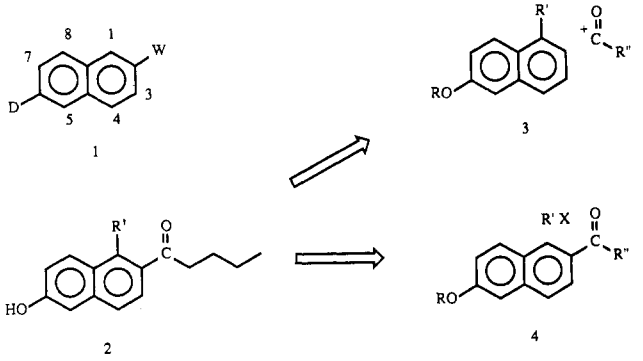
The powerful ortho-metalating directive effect of the *N,N*-dialkylcarboxamide group can be used for the preparation of C-1 alkyl-substituted 2,6-acylnaphthols. The alternative reaction pathways of C-1 metalation vs. acylation (carbonyl addition) in the reaction of alkyllithium reagents with *N,N*-dialkyl-6-methoxynaphthalenecarboxamides depends upon the cumulative steric nature of the *N*-alkyl and lithium alkyl groups: The *N,N*-dimethylamide **7** undergoes carbonyl addition with *n*-BuLi and *t*-BuLi; the *N,N*-diethylamide **8**, carbonyl addition with *n*-BuLi, but metalation with *t*-BuLi; and the *N,N*-diisopropylamide **9** only C-1 metalation with *n*-BuLi. Subsequent reaction of the *N,N*-diethyl-1-ethyl-6-methoxynaphthalene-2-carboxamide (**13**) with *n*-BuLi gives the desired 2,6-acylnaphthyl methyl ether, whereas the corresponding ethylated diisopropylamide **14** undergoes additional metalation on the ethyl group. These 1-ethyl-2-carboxamidonaphthalenes are very sterically crowded and show evidence in the proton NMR of hindered rotation about both the amide bond and the ethyl group. The UV and fluorescence spectra of the acylnaphthols **17** and **18** show the consequences of this steric crowding through reduced conjugation between the acyl group and the naphthalene group. The more hindered 1-ethylated acylnaphthol **18** shows lower molar absorptivity, and it fluoresces only in basic solution.

2,6-Disubstituted naphthalenes **1**, wherein one substituent is electron withdrawing and the other is electron donating, are environmentally sensitive fluorescent probes of wide biochemical applicability.[1] In a continuation of



our previous studies,[2] we thought that the incorporation of an ethyl substituent at C-1 of 2-pentanoyl-6-hydroxynaphthalene (**2**) might impart a certain "thickness" that appears to be required for high-affinity binding to the estrogen receptor. The synthesis of such an alkylated acylnaphthol could be achieved either by acylation of the alkylnaphthol **3** or by alkylation of an appropriately functionalized naphthol **4**, which could later be transformed to the required ketone.

While 2-acyl-6-methoxynaphthalenes have been routinely prepared by Friedel–Crafts acylation of 2-naphthyl methyl ether,[3] all of our attempts to acylate at C-2 of 1-ethyl-6-methoxynaphthalene provided either a mixture of isomers or acylation at C-4 or C-5.

Recently, it has been shown that carboxamides have ortho-metalation-directing activity in benzene and naphthalene systems that is superior to many other substituents, including methoxy groups.[4] Ketones can be subsequently prepared from the amides by the addition of organolithium reagents.[5] In this paper we report that by the proper adjustment of the steric bulk of the alkyl groups on the amide and the lithium alkyl, one can develop a general synthetic approach to 1-alkyl-2-acyl-6-naphthols.

Results and Discussion

N,N-Dimethyl-, *N,N*-diethyl-, and *N,N*-diisopropyl-6-methoxynaphthalene-2-carboxamides (**7**–**9**) (Scheme I)

(1) Weber, G.; Farris, F. J. *Biochemistry* **1979**, *18*, 3075.
(2) Bindal, R. D.; Katzenellenbogen, J. A. *J. Steroid Biochem.* **1985**, *23*, 929.
(3) Buu Hoi, N. P. *Recl. Trav. Chim. Pays-Bas* **1949**, *68*, 759.
(4) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (b) Beak, P.; Tse, A.; Hawkins, J.; Chen, C.-W.; Mills, S. *Tetrahedron* **1983**, *39*, 1983.
(5) Scilly, N. F. *Synthesis* **1973**, 160.

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Scheme I

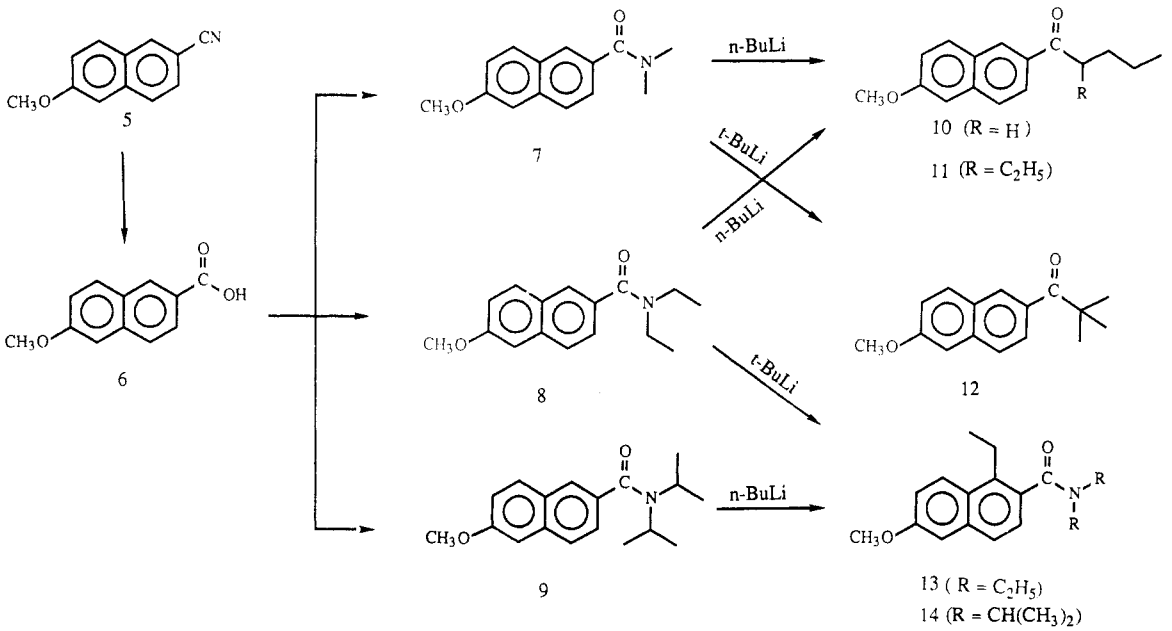


Table I. Product Distribution for Metalation vs. Carbonyl Addition in the Reaction of Naphthalenecarboxamides 7–9 with Alkyllithium Reagents[a]

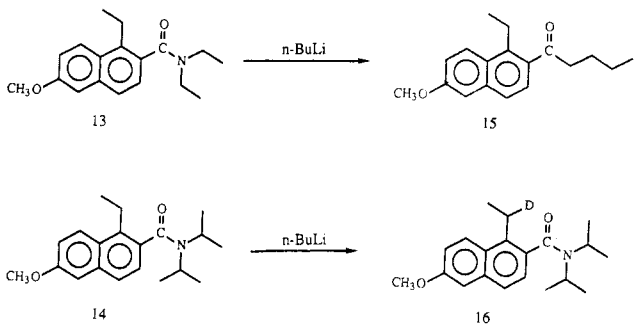
amide	RLi	acylation yield, % (product)	metalation–ethylation yield, % (product)
Me (7)	*n*-BuLi	40 (**10**), 30 (**11**)	0
	t-BuLi	73 (**12**)	0
Et (8)	*n*-BuLi	34 (**10**), 38 (**11**)	0
	t-BuLi	0	68 (**13**)
i-Pr (9)	*n*-BuLi	0	95 (**14**)

[a] The amides **7–9** were treated in THF with 1.2 equiv of the alkyllithium reagent at −78 °C for 20 min and then quenched with a five-fold excess of ethyl iodide. The ratio of products was determined by product isolation.

were prepared by reacting 6-methoxy-2-naphthoic acid (**6**) with thionyl chloride and quenching the acid chloride thus formed with the corresponding dialkylamine.[6] The naphthoic acid **6** was prepared by alkaline hydrogen peroxide hydrolysis of 6-methoxy-2-naphthonitrile (**5**).

The treatment of naphthalenecarboxamides **7–9** with *n*-BuLi or *t*-BuLi in tetrahydrofuran at −78 °C,[6] followed by quenching with ethyl iodide (−78 to +40 °C), furnished either the ketones **10–12** or C-1-ethylated naphthalenecarboxamides **13** and **14** (Table I). The relative proportion of naphthalenecarboxamide carbonyl addition (**10–12**) vs. metalation (**13, 14**) products can be understood by considering the steric bulk of the amide alkyl groups and the size of the alkyllithium reagents, a trend that has been noted previously in the benzamide series.[7b] The reaction of the least hindered *N,N*-dimethylnaphthalenecarboxamide **7** with either *n*-BuLi or *t*-BuLi resulted exclusively in amide carbonyl addition, furnishing ketones **10** and **11** with *n*-BuLi and **12** with *t*-BuLi (Table I). Compound **11** is presumably formed by the ethyl iodide quench of the enolate generated by deprotonation of **10** by *n*-BuLi. This enolization must compete with carbonyl addition, since about 30% of the starting amide **7** is recovered when a stoichiometric amount of *n*-BuLi is used (Table I).

Scheme II



The more sterically encumbered *N,N*-diethyl-6-methoxynaphthalene-2-carboxamide (**8**) underwent a similar reaction with *n*-BuLi to provide the acylated products **10** and **11** by alkyllithium addition to the amide. However, with the more hindered reagent, *t*-BuLi, the diethylcarboxamide **8** undergoes ring metalation at C-1, forming the C-1 ethylation product **13** after the ethyl iodide quench. Metalation does not take place at the other available ortho positions, C-3, C-5 and C-7.[7]

While *N,N*-diethylamide **8** requires the more hindered alkyllithium (*t*-BuLi) for ring metalation, the most hindered *N,N*-diisopropylamide **9** undergoes exclusive metalation at C-1 with the less hindered *n*-BuLi, producing **14** after the ethyl iodide quench. Thus, carbonyl addition is the exclusive fate of the dimethylamide **7** and ring metalation the exclusive fate of the diisopropylamide **9**, while with the diethylamide **8** the course of the reaction is dictated by the bulk of the lithium alkyl.[7b]

Steric factors also affect the course of reaction of *n*-BuLi with ethyl-substituted amides **13** and **14** (Scheme II). While the isopropylamide **14** underwent further metalation at the methylene position of the C-1 ethyl group to afford deuteriated amide **16** after a D_2O quench,[4b] reaction with amide **13** gave carbonyl addition and furnished the desired ketone **15** in almost quantitative yield (Scheme II). Demethylation of ketones **10** and **15** in dichloromethane with $BF_3/(CH_3)_2S$ furnished the corresponding naphthols **17** and **18**, respectively.[8]

(6) (a) Harvey, R. G.; Cortez, C.; Jacobs.; S. A. *J. Org. Chem.* **1982**, *47*, 2120. (b) Harvey, R. G.; Cortez, C. *J. Org. Chem.* **1987**, *52*, 283.
(7) (a) Watanabe , B.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457. (b) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.
(8) Williard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731.

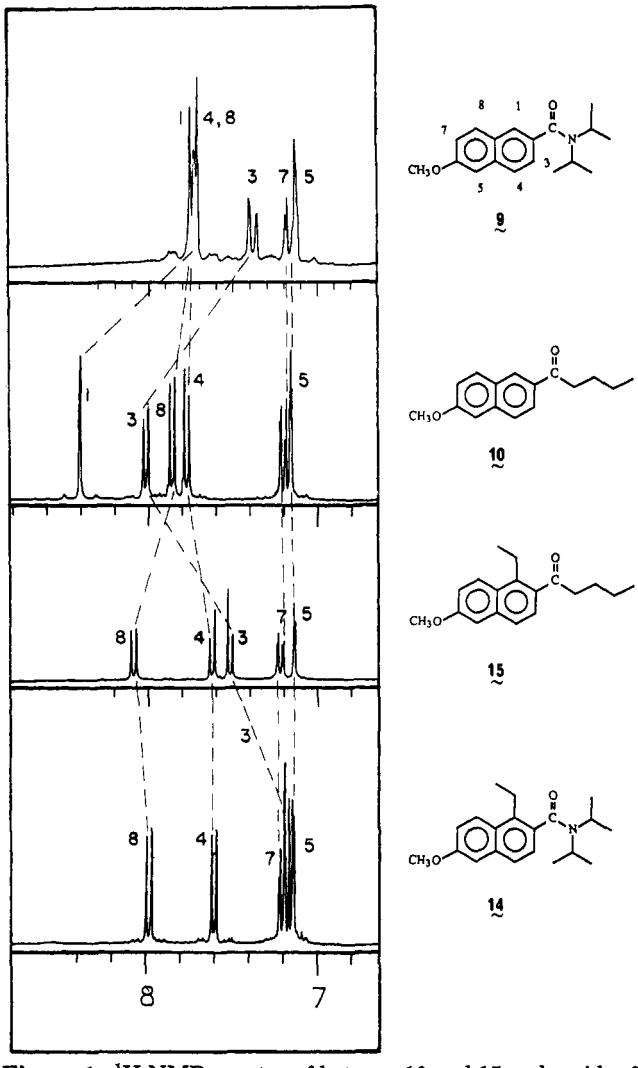


Figure 1. ^1H NMR spectra of ketones **10** and **15** and amides **9** and **14** obtained at 300 MHz in $CDCl_3$ solution. Assignments were made on the basis of structural chemical shift correlations, structural comparisons, and shift reagent studies, as described in the text.

Proton NMR of Naphthalenecarboxamides and Ketones. The assignment of C-1 as the site of ethylation in the amide **10** and ketone **15** follows clearly from the proton NMR. The aromatic region of the proton NMR of compounds **9**, **10**, **14**, and **15** is shown in Figure 1.

The clearest evidence of C-1 ethylation comes from a comparison of ketone **10** with ethylated ketone **15**. The assignments are made on the basis of coupling constant comparison and the known effect of substituents on the resonance of aromatic protons.[9] The most upfield proton in **10** (H-5, ortho to methoxy) shows a meta coupling of 2.6 Hz with H-7, which in turn is ortho coupled (J = 8.7 Hz) to H-8 at δ 7.89. The signal at δ 8.02 is assigned to H-3, since it shows a meta coupling of 2.6 Hz with H-1 at δ 8.4 and an ortho coupling of 8.7 Hz with H-4 at δ 7.78. Ethylation of **10** to give **15** results in the disappearance of the most downfield signal, assigned to H-1, and an upfield shift of the signal for H-3 by δ 0.5. The latter effect is presumed to arise from steric crowding in the ethylated ketone **15** that twists the valeroyl group out of planarity, reducing its conjugation with the naphthalene ring and shifting the deshielding region away from this hydrogen.

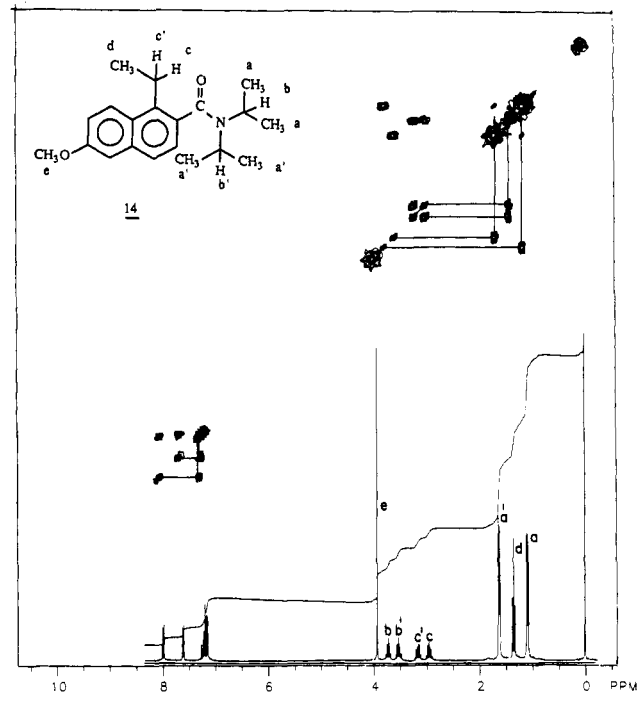


Figure 2. Homonuclear J-correlated two-dimensional ^1H NMR spectrum of the ethylated diisopropylamide **14**. The spectrum was obtained at 300 MHz in $CDCl_3$ solution.

The assignments of H-3 and H-4 in ethylated ketone **15** were made by the serial additon of shift reagent Resolve-Al EuFOD. The proton ortho to the ketone (H-3 at δ 7.52) shows a threefold greater downfield shift compared with H-4.

The aromatic NMR region for the corresponding diisopropylamides **9** and **14** are also shown (Figure 1). The spectra match those of the corresponding ketones **10** and **15** quite well, the most notable difference being that the signals for the hydrogens in H-1 and 3, and to a lesser extent H-8, are less strongly deshielded.

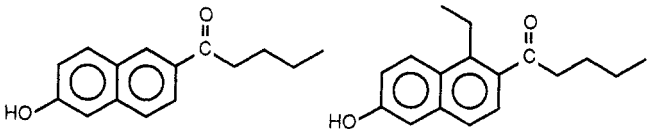
Aliphatic region of the NMR of the ethylated diisopropylamide **14** shows clear features of hindered rotation due to steric crowding (Figure 2).[9] Two distinct sets of isopropyl signals [δ 1.09 ("doublet" a) with δ 3.71 ("septet" b), and δ 1.62 ("doublet" a′) with δ 3.52 ("septet" b′)—assigned by cross-correlations in 2D J-correlated spectrum] indicate that rotation about the amide bond is slow on the NMR time scale. In addition, the "doublet" signals at δ 1.09 and 1.62 are actually each a set of two closely spaced doublets ($\Delta\delta$ = 0.022 ppm), indicating that rotation about each N–C_{iso} bond is also hindered. It is of note that the unsubstituted diisopropylamide **9**, as well as both the unsubstituted and substituted diethylamides **8** and **13**, shows partial coalescence of the amide alkyl resonances. Similar rotational barriers in hindered benzamides have been noted by others.[4b,10]

The other notable feature in the NMR of amide **14** is that the signals for the methylene hydrogens of the ethyl group appear as an AB quartet (c and c′, showing additional quartet splitting by the methyl group). Thus, rotation of the ethyl group is also hindered. Since the unsubstituted diisopropylamide **9** shows near coalescence of amide resonances at room temperature, whereas in **14** all of the diisopropyl resonances are distinct and nonequiv-

(9) Pretsch, E.; Clerc. T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, Heidelberg, New York, Tokyo, 1983; pp H245, H260.

(10) Oki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Deerfield Beach, FL, 1983; pp 43, 181, 224, and references therein.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(12) Adcock, W.; Wells, P. R. *Aust. J. Chem.* **1965**, *18*, 1351.

Table II. Ultraviolet Spectroscopic Properties of Phenolic Ketones 17 and 18[a]



17

18

	ethanol		ethanol + 0.1 N KOH	
compd	λ_{max}, nm	$\epsilon \times 10^4$	λ_{max}, nm	$\epsilon \times 10^4$
17	262	3.27	248	2.46
	318	1.51	284	1.69
			376	2.25
18	260	2.63	254	2.15
	316	0.58	278	1.58
			372	1.00

[a] Ultraviolet spectra were obtained in the solvents indicated with a Hewlett-Packard 8451 diode array spectrophotometer; suitable, known concentrations were used to keep the absorbance maxima in the range 0.1–0.5 absorbance unit.

alent, ethylation at C-1 slows the rotation about the C_{ar}–C_{co} bond as well.[10]

Because of the great hindrance to rotation about the naphthalene bonds to both the ethyl and carboxamide groups in **14**, it is possible for this molecule to exist in two atropisomeric forms. However, only one set of methyl signals from the ethyl group is seen, suggesting that a single atropisomer is formed with high selectivity during the ethylation reaction. On the basis of the examination of space-filling (CPK) models and molecular mechanics (MMPMI), it appears that the isomer with the methyl group of the ethyl substituent and the oxygen of the diisopropylcarboxamide group twisted toward the same side of the naphthalene ring is the sterically less congested isomer.

Fluorescence and UV Properties of Ketones 17 and 18. Comparisons of the UV and fluorescence properties of ketones **17** and **18** (Table II) highlight the consequences of the conformational constraints enforced by ethyl substitution at C-1 in **18**. As suggested by the NMR studies on **16**, the ketone function in the corresponding free phenol **18** is twisted out of the plane of the naphthalene ring, with the result that the molar absorptivities of the longest wavelength bands in the UV spectrum of the ethylated ketone **18** in either neutral or basic conditions are less than half those of the corresponding bands in the parent ketone **17**.

The effect of C-1 ethylation in **18** is also apparent in the fluorescence spectra. The unsubstituted phenolic ketone **17** is fluorescent in both neutral (excitation 318 nm, emission 421 nm) and basic ethanol (excitation 376 nm, emission 495 nm); by contrast, the ethylated phenolic ketone **18** fluoresces only in basic ethanol (excitation 373 nm, emission 495 nm) and not under neutral conditions.

Conclusion

In our work on fluorescent estrogens, we have undertaken an investigation of the structural features required for a molecule to be both highly fluorescent and a high-affinity binder for the estrogen receptor.[2] Because of their desirable fluorescence properties, the 2,6-acylnaphthols were selected as a potential point for the development of suitable receptor ligands.[1]

The reports documenting that the tertiary amides are more effective ortho ring metalation directing groups than others, such as methoxy,[4a,b] led us to investigate this route of synthesis.[13] A systematic study of the bulk requirements of the alkyl groups on the amide nitrogen and the lithium alkyl for metalation vs. acylation (Table I) led us to an interesting observation of general synthetic utility: While *n*-BuLi with the dimethyl- and diethylamides and *t*-BuLi with the dimethylamide always result in amide carbonyl addition, *t*-BuLi with the diethylamide or *n*-BuLi with the diisopropylamide results in metalation ortho to the amide. It is fortuitous that the diethylamide **8** can be ethylated at C-1, since subsequent reaction with a primary alkyllithium results in acylation, giving the desired ketone **18**. The ethylated diisopropylamide **9**, in contrast, undergoes side-chain metalation upon further treatment with *n*-BuLi. Thus, the diethylamide **8** possesses the appropriate level of steric hindrance to give ring metalation with *t*-BuLi, but acylation upon treatment of the C-1 ethyl-substituted product with *n*-BuLi. This finding paves the way for the convenient and efficient synthesis of a number of variously substituted acylnaphthols.

Experimental Section

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on General Electric QE-300 (300-MHz) and Varian XL-200 (200-MHz) spectrometers. The spectra were recorded with an internal lock on the deuterium resonance of the solvent, using tetramethylsilane (Me_4Si) as the internal standard. Data are reported on the δ scale (downfield from Me_4Si). Mass spectra were run on a Varian-MAT CH-5 spectrometer by electron impact at 10–70 eV or a Varian MAT 731 spectrometer by chemical ionization mode. Exact-mass determinations by high-resolution mass spectrometry were also obtained on a Varian MAT 731 spectrometer. Data are presented in the form *m/z* (intensity relative to base peak). Ultraviolet spectra were taken on a Hewlett-Packard 8451 diode array spectrophotometer. Fluorescence spectra were recorded by photon counting on Spex Fluorolog 2 spectrophotometer (Model 111C) with a Datamate microprocessor controller. Melting points were determined on a Thomas Hoover capillary melting point apparatus, and temperatures reported are uncorrected. Elemental analyses were provided by the Microanalytical Laboratory of the University of Illinois. Flash chromatography was performed as described by Still,[11] on Woelm 32–63-μm silica gel supplied by Universal Scientific, Atlanta, GA. Analytical thin-layer chromatography (TLC) was conducted on E. Merck plastic plates precoated with 0.2 mm of silica gel 60 F_{254}. Thin-layer chromatograms were visualized with 5% ethanolic phosphomolybdic acid reagent and by UV light.

All reactions were carried out in a dry nitrogen atmosphere, unless water was used in the reaction, by using standard techniques for the exclusion of moisture. Tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl just prior to use. General reaction workup procedure involves extraction with ethyl acetate, washing the combined organic layer with water or brine, drying over anhydrous sodium sulfate, filtration, and concentration of the organic phase in vacuo.

6-Methoxy-2-naphthoic Acid (6). A solution of 6-methoxy-2-naphthonitrile (**5**; 1.8 g, 10.0 mmol) in 10 mL of ethanol was diluted with 20% potassium hydroxide solution (50 mL) and 3 mL of 36% hydrogen peroxide. The solution was heated to reflux for 18 h, cooled in an ice bath, and acidified by the dropwise addition of 30% hydrochloric acid. General reaction workup afforded **6**: 98%, 1.7 g; mp 202–204 °C (methanol) (lit.[12] mp 203–204.5 °C).

***N*,*N*-Dialkyl-6-methoxynaphthalene-2-carboxamides (7–9).** To a solution of 6-methoxy-2-naphthoic acid (**6**; 1.0 g, 5 mmol) in ether (50 mL) and tetrahydrofuran (5 mL) was added dropwise freshly distilled thionyl chloride (0.73 mL, 10.0 mmol)

(13) Oxazolines, which are effective in directing metalations in benzenes systems, are inconsistent in naphthalene systems, promoting ring-addition reactions, in some cases. See: (a) Meyers, A. I.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881. (b) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865.

at room temperature. After the completion of addition, the mixture was stirred at 40–45 °C for another 40 min. The solvent and unreacted thionyl chloride were removed under aspirator vacuum and then high vacuum. The acid chloride, thus obtained as a light brown oil, was redissolved in 50 mL of anhydrous ether and the resultant mixture cooled to 0 °C in an ice bath prior to the dropwise addition of the appropriate dialkylamine (3 mol equiv). After the resultant mixture was stirred for 30 min at 25 °C, the solvent was removed under reduced pressure, and the liquid thus obtained was chromatographed over silica gel (200 g), eluting with ether to furnish the corresponding dialkylnaphthamides, isolated as pale yellow oils.

***N,N*-Dimethyl-6-methoxynaphthalene-2-carboxamide (7)**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.05 and 3.15 (vbr s, 6 H, CH_3), 3.91 (s, 3 H, OCH_3), 7.12 (d, 1 H, C-5 H, J = 3 Hz), 7.17 (dd, 1 H, C-7 H, J = 3, 6 Hz), 7.44 (d, 1 H, C-4 H, J = 6.4 Hz), 7.75 (d, 2 H, C-3 and C-8 H, J = 6.4 Hz), 7.85 (s, 1 H, C-1 H); MS (CI), m/z $(M + 1)^+$ 230 (100); high-resolution MS calcd for $C_{14}H_{16}NO_2$ (M + 1) 230.1181, found 230.1186.

***N,N*-Diethyl-6-methoxynaphthalene-2-carboxamide (8)**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15 and 1.25 (vbr s, 6 H, CH_3), 3.33 and 3.58 (vbr s, 4 H, CH_2), 3.88 (s, 3 H, OCH_3), 7.13 (d, 1 H, C-5 H, J = 3.2 Hz), 7.18 (dd, 1 H, C-7 H, J = 3, 6.4 Hz), 7.44 (d, 1 H, C-4 H, J = 6.2 Hz), 7.75 (d, 2 H, C-3 and C-8 H, J = 6 Hz), 7.80 (s, 1 H, C-1 H); MS (10 eV), m/z M^+ 257 (49.6), 185 (100), 157 (22.8); high-resolution MS calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1414.

***N,N*-Diisopropyl-6-methoxynaphthalene-2-carboxamide (9)**: ^{1}H NMR (200 MHz, $CH(CH_3)$ δ 1.38 (vbr s, 12 H, $CH(CH_3)_2$), 3.75 (vbr s, 2 H, $CH(CH_3)_2$), 3.92 (s, 3 H, OCH_3), 7.13 (d, 1 H, C-5 H), 7.16 (dd, 1 H, C-7 H), 7.38 (dd, 1 H, C-3 H), 7.72 (m, 3 H, C-1, C-4, and C-8 H); MS (10 eV), m/z M^+ 285 (51), 163 (10); high-resolution MS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1730.

General Procedure for Metalation or Acylation (10–16). About 100 mg of dialkylnaphthalenecarboxamides **7–9**, **13**, and **14** was dissolved in about 10 mL of freshly distilled tetrahydrofuran. The solution was cooled in an acetone–dry ice bath to −78 °C, and then 1.2 mol equiv of *n*-BuLi or *t*-BuLi was added dropwise by a syringe. The solution was stirred for an additional 20 min, and then a fivefold excess of ethyl iodide or deuterium oxide in 10% deuterium chloride (for **15**) was added. The reaction was allowed to warm to room temperature and then heated to 40 °C for 30 min. After being cooled to 0 °C, it was quenched with 2% aqueous hydrochloric acid. General reaction workup and flash chromatography furnished the products **10–16** isolated as colorless oils.

2-Valeryl-6-methoxynaphthalene (10): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3 H, CH_3), 1.47 (sextet, 2 H, CH_2CH_3), 1.78 (quintet, 2 H, $COCH_2CH_2$), 3.09 (t, 2 H, $COCH_2$), 3.98 (s, 3 H, OCH_3), 7.19 (d, 1 H, C-5 H), 7.20 (dd, 1 H, C-7 H), 7.79 (d, 1 H, C-4 H), 7.87 (d, 1 H, C-8 H), 8.03 (dd, 1 H, C-3 H), 8.42 (d, 1 H, C-1 H); MS (70 eV), m/z M^+ 242 (23.5), 200 (55.3), 185 (100), 157 (19.4); high-resolution MS calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1319.

2-(2-Ethylpentanoyl)-6-methoxynaphthalene (11): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (dt, 6 H, CH_2CH_3), 1.32 (sextet, 2 H, $CH_2CH_2CH_3$), 1.58 (m, 2 H, $CHCH_2CH_3$), 1.82 (m, 2 H, $CHCH_2CH_2$), 3.52 (m, 1 H, COCH), 3.97 (s, 3 H, OCH_3), 7.19 (d, 1 H, C-5 H), 7.20 (dd, 1 H, C-4 H), 7.79 (d, 1 H, C-4 H), 7.87 (d, 1 H, C-8 H), 8.03 (dd, 1 H, C-3 H), 8.42 (d, 1 H, C-1 H); MS (70 eV), m/z M^+ 270 (8.3), 228 (8.2), 175 (100), 157 (19.8), 86 (40), 84 (62.3); high-resolution MS calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1618.

2-Pivaloyl-6-methoxynaphthalene (12): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H, $C(CH_3)_3$), 3.98 (s, 3 H, OCH_3), 7.15 (d, 1 H, C-5 H), 7.20 (dd, 1 H, C-7 H), 7.55 (d, 1 H, C-4 H), 7.82 (d, 1 H, C-8 H), 7.85 (dd, 1 H, C-3 H), 8.26 (d, 1 H, C-1 H); MS (70 eV), m/z M^+ 242 (26), 185 (42), 157 (100); high-resolution MS calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1311.

***N,N*-Diethyl-1-ethyl-6-methoxynaphthalene-2-carboxamide (13)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 and 1.28 (vbr s, 6 H, NCH_2CH_3), 1.20 (t, 3 H, CH_2CH_3), 3.35 and 3.58 (vbr s, 4 H, NCH_2), 3.48 (q, 2 H, CH_2CH_3), 3.96 (s, 3 H, OCH_3), 7.14 (d, 1 H, C-5 H), 7.17 (dd, 1 H, C-7 H), 7.44 (dd, 1 H, C-3 H), 7.75 (d, 1 H, C-4 H), 7.78 (d, 1 H, C-8 H); MS (70 eV), m/z M^+ 285 (20.8), 256 (24.2), 213 (100); high-resolution MS calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1718.

***N,N*-Diisopropyl-1-ethyl-6-methoxynaphthalene-2-carboxamide (14)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (dd, 6 H, $CH(CH_3)_2$), 1.35 (t, 3 H, CH_2CH_3, J = 7.5 Hz), 1.62 (dd, 6 H, $CH(CH_3)_2$), 2.94 (dq, 1 H, $CHCH_3$, ABM_3 J_{AB} = 7.4, J_{AM} = 14.8 Hz), 3.15 (dq, 1 H, $CHCH_3$, ABM_3 J_{AB} = 7.4, J_{AM} = 14.8 Hz), 3.52 (m, 1 H, $CH(CH_3)_2$, J = 6.9 Hz), 3.71 (m, 1 H, $CH(CH_3)_2$, J = 6.9 Hz), 3.92 (s, 3 H, OCH_3), 7.14 (d, 1 H, C-5 H, J = 2.6 Hz), C-3 H, J = 8.4 Hz), 7.98 (d, 1 H, C-8 H, J = 9.3 Hz); MS (CI, CH_4), $(M + 1)^+$ 314 (100), 284 (14), 213 (27), 128 (17); high-resolution MS calcd for $C_{20}H_{28}NO_2$ 314.2120, found 314.2124.

1-Ethyl-2-pentanoyl-6-methoxynaphthalene (15): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3 H, $CH_3CH_2CH_3$), 1.36 (t, 3 H, CH_2CH_3), 1.40 (m, 2 H, $CH_2CH_2CH_3$), 1.72 (q, 2 H, $COCH_2CH_2$), 2.93 (t, 2 H, $COCH_2$), 3.15 (q, 2 H, CH_2CH_3), 3.94 (s, 3 H, OCH_3), 7.13 (d, 1 H, C-5 H), 7.22 (dd,1 H, C-7 H), 7.52 (d, 1 H, C-3 H), 7.62 (d, 1 H, C-4 H), 8.09 (d, 1 H, C-8 H); MS (CI, CH_4, $(M + 1)^+$ 257 (100), 199 (45); high-resolution MS calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1544.

***N,N*-Diisopropyl-1-(1-[$^2H_1$]ethyl)-6-methoxynaphthalene-2-carboxamide (16)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (q, 6 H, $NCH(CH_3)_2$), 1.35 (d, 3 H, $CHDCH_3$), 1.62 (q, 6 H, $NCH(CH_3)_2$), 2.94 and 3.15 (quintet, 1 H, $CDHCH_3$), 3.52 (septet, 1 H, $CH(CH_3)_2$), 3.71 (septet, 1 H, $CH(CH_3)_2$), 3.92 (s, 3 H, OCH_3), 7.14 (d, 1 H, C-5 H), 7.18 (d, 1 H, C-3 H), 7.20 (dd, 1 H, C-7 H), 7.60 (d, 1 H, C-4 H), 7.98 (d, 1 H, C-8 H); MS (CI, CH_4, $(M + 1)^+$ 315 (100), 214 (27); high-resolution MS calcd for $C_{20}H_{27}NO_2D$ 315.2183, found 315.2186.

General Procedure for the Deprotection of Ketones 10 and 15. Ketones **10** and **15** were demethylated to the corresponding phenols by the method of Williard and Fryhle.[8] The phenols were obtained in almost quantitative yields and were purified by flash chromatography through a small amount of silica (1:1, hexane/ether).

2-Pentanoyl-6-hydroxynaphthalene (17): white crystalline powder; mp 150–153 °C (ether/hexane); ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.96 (t, 3 H, CH_3), 1.47 (sextet, 2 H), CH_2CH_3), 1.78 (quintet, 2 H, $COCH_2CH_2$), 3.09 (t, 2 H, $COCH_2$), 7.08 (d, 1 H, C-5 H), 7.09 (dd, 1 H, C-7 H), 7.68 (d, 1 H, C-4 H), 7.72 (d, 1 H, C-8 H), 7.94 (dd, 1 H, C-3 H), 8.36 (, 1 H, C-1 H); MS (CI, CH_4), $(M + 1)^+$ 229 (100), 200 (12), 185 (20), 171 (27); high-resolution MS calcd for $C_{15}H_{17}O_2$ (M + 1) 229.1229, found 229.1238.

1-Ethyl-2-pentanoyl-6-hydroxynaphthalene (18): white crystalline powder (ether, hexanes); mp 121–123 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, $CH_2CH_2CH_3$), 1.29 (t, 3 H, CH_2CH_3), 1.31 (m, 2 H, $CH_2CH_2CH_3$), 1.65 (m, 2 H, $CH_2CH_2CH_2$), 2.85 (t, 2 H, $COCH_2$), 3.07 (q, CH_2CH_3), 7.09 (d, 1 H, C-5 H), 7.10 (dd, 1 H, C-7 H), 7.42 (d, 1 H, C-3 H), 7.49 (d, 1 H, C-4 H), 8.03 (d, 1 H, C-8 H); MS (CI, CH_4), $(M + 1)^+$ 257 (100), 199 (45); high-resolution MS calcd for $C_{17}H_{21}O_2$ (M + 1) 257.1542, found 257.1544.

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