Preparation of 2-Cyanobenzoic Acids from the Reaction of Bromobenzoic Acids with Arylacetonitriles and LDA

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The reaction of various bromobenzoic acids **1** with arylacetonitriles **3** in the presence of LDA at −70 °C gave predominantly 2-cyanobenzoic acids **4** plus minor amounts of 3-(arylcyanomethyl)-benzoic acids **5** and debrominated benzoic acids **6**. The reaction is thought to proceed through a benzyne-3-carboxylate intermediate **2**, which is formed at −70 °C upon the addition of the arylacetonitrile **3** to a solution of the appropriate lithium halobenzoate and excess LDA. The base-initiated generation of an aryne intermediate from a haloarene at such low temperatures is unprecedented. To confirm the orientation of the cyano and carboxylic acid groups, 4-methoxy-2-cyanobenzoic acid (**4f**) was converted to the corresponding anhydride (**8**) via phthalic acid (**7**) and to 3,3-dimethyl- and 3,3-di-*n*-butyl-2,3-dihydro-5-methoxy-4-(4-methoxyphenyl)-methyl-1H-isoindol-1-ones (**9**).

Introduction

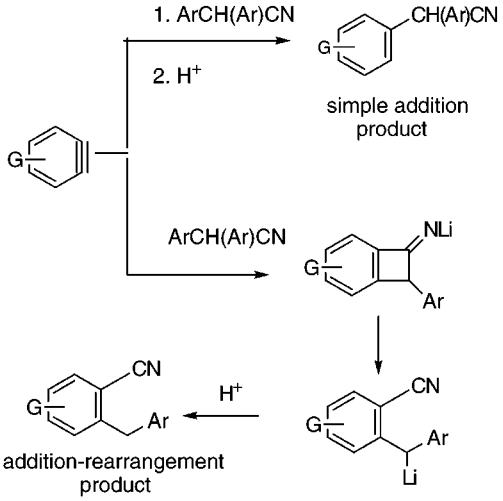
We[1] have shown that arynes, generated by the reaction of haloarenes and LDA, react with preformed α-lithio-arylacetonitriles to give either simple addition products, such as α-arylated arylacetonitriles or rearranged *o*-(arylmethyl)benzonitriles. The product distributions from these reactions were thought to arise from competing tandem addition−rearrangement[2] and simple aryne addition pathways,[3] as shown in Scheme 1. Further studies on arynes containing neutral substituents showed that the preferred reaction pathway was highly dependent upon the nature of the substituent on the haloarene, with electron-releasing groups favoring rearranged nitriles and electron-withdrawing substituents favoring simple addition nitriles.[4,5]

To obtain information on the role of negatively charged substituents on the regioselectivity of aryne addition, the reactions of 2-bromobenzoic acid (**1a**) and 3-bromo-4-methoxy- (**1b**), 3-bromo-4-methyl- (**1c**), and 3-bromo-4,5-dimethoxybenzoic acids (**1d**) with different arylacetonitriles **3a**−**d** and LDA in THF were carried out (Table 1). These studies should provide information on the role of negatively charged substituents in directing the orientation pathway of intramolecular nucleophilic addition to arynes. Such systems have been little studied.[6]

Results and Discussion

When the reactions were carried out by adding the bromobenzoic acids (**1**) to THF solutions containing the preformed α-lithiated arylacetonitriles and excess LDA at −40 °C, the major products were the corresponding 3-(diisopropylamino)benzoic acids. However, when the arylnitrile (**3**) was added to a solution of the bromo acid **1a**−**d** in excess LDA at −70 °C and then warmed to room temperature and quenched, moderate yields (40−70%) of the rearranged nitriles **4a**−**d** were obtained along with minor amounts of α-aryl-α-cyanomethylbenzoic acids **5** and debrominated benzoic acids **6**. These reactions are summarized in Scheme 2. The yields of **5** and **6** were estimated by an ^{1}H NMR analysis of the reaction mixtures, with pure samples of **5a**,**c**,**d** being isolated and characterized. The structures of all isolated products were confirmed by IR, MS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

Scheme 1



When the nitrile **3** was added to the light pink solution containing the lithiated acid **1** and LDA at −70 °C, the reaction solution immediately developed a bright red color, which we have found to be indicative of a product formed from an aryne.[7] The red color gradually intensified as the solution was warmed to room temperature and was discharged upon quenching with aqueous acid.

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Scheme 2

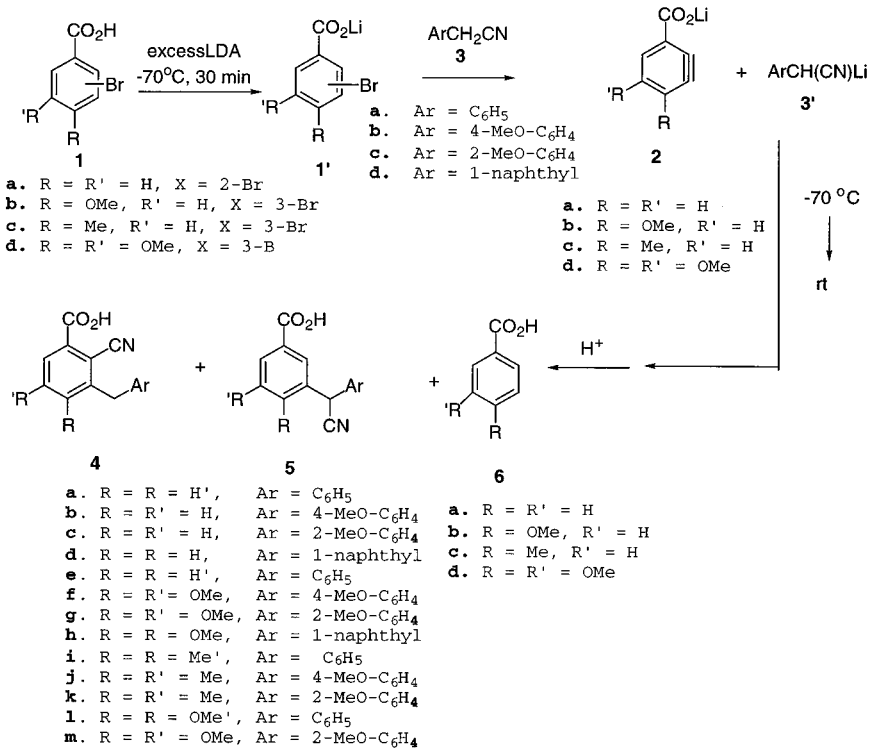


Table 1. Reaction of Halobenzoic Acids with Various Arylacetonitriles

entry	bromo acid **1**	aryl nitrile **3**	cyano acid **4**	yield, %	arylated nitrile **5**	yield, %	debromo acid **6**	yield, %
1	**a**	**a**	**a**	40	**a**	7	**a**	11
2	**a**	**b**	**b**	42	**b**	6	**a**	9
3	**a**	**c**	**c**	44	**c**	<2	**a**	8
4	**a**	**d**	**d**	50	**d**	<2	**a**	12
5	**b**	**a**	**e**	56	**e**	9	**b**	11
6	**b**	**b**	**f**	70	**f**	8	**b**	12
7	**b**	**c**	**g**	44	**g**	5	**b**	10
8	**b**	**d**	**h**	48	**h**	5	**b**	8
9	**c**	**a**	**i**	53	**i**	<2	**c**	7
10	**c**	**b**	**j**	43	**j**	<2	**c**	8
11	**c**	**a**	**k**	53	**k**	<2	**c**	12
12	**d**	**a**	**l**	55	**l**	<2	**d**	9
13	**d**	**b**	**m**	58	**m**	<2	**d**	9

Table 2. Distribution of 3-[(4-Methoxyphenyl)methyl]-2-cyanobenzoic Acids 4b,f,g vs Bromobenzoic Acids 1a−c as a Function of Time and Temperature

		distribution **4**:**1**[a]		
acid (**1**)	nitrile (**4**)	−70 °C, 1 h[b]	−55 °C, 3.5 h	−45 °C, 5 g
a	**b**	31:69	73:27	100:0
b	**f**	60:40	100:0	
c	**j**	3:97	10:90	15:85

[a] Distribution of **4**:**1** = the molar ratio of **4**:**1** as determined from a comparison of the peak areas of ^{1}H NMR signals of the 3-methylene proton in **4** and the least shielded proton in **1**. [b] An aliquot was taken at the appropriate time and added immediately to a cooled solution of methanol, and the resulting solution was evaporated. The resulting oil was then analyzed by NMR analysis. In all cases, material balances were >90%.

Since this LDA-initiated aryne formation at −70 °C is unprecedented, the reactions of the 2-bromobenzoic acid (**1a**) and its 3-bromo-4-methoxy (**1b**) and 3-bromo-4-methyl (**1c**) analogues with 4-methoxyphenylacetonitrile (**3b**) were carried out, and the relative amounts of the corresponding 3-[(4-methoxyphenyl)methyl]-2-cyanobenzoic acid (**4**) products and starting bromobenzoic acids (**1**) were determined at various temperatures and reaction times (see Table 2). The distributions after 1 h at −70 °C show that the rearranged nitriles (**4**) were formed by all three bromobenzoic acids (**1**), but at different rates, with the relative amount of **4** decreasing along the series **1b** (4-MeO) > **1a** ≫ **1c** (4-Me). The data also show that the reactions of **1b** and **1a** with **3b** are well on their way to completion after 3.5 h at −55 °C and 5.5 h at −45 °C, respectively. On the other hand, **1c** required warming to room temperature and additional stirring for 6 h for complete reaction. These observations are consistent with the inductive effect of the 4-substituents on the acidity of the hydrogen ortho to bromine; the removal of this hydrogen has been shown to be rate determining in base-initiated aryne reactions.[3]

The preponderance of rearranged nitriles (**4**) in these reactions is consistent with the electron-releasing ability of the carboxylate group.[8] Furthermore, the 5−7% yields of the aryne arylated benzoic acids **5a**−**d** (R = H) and 4-methoxy substituted acids (**5e**−**h**) are greater than those found for the 4-methyl- (**5i**−**k**) and 4,5-dimethoxybenzoic acids (**5l**−**m**) (<2%). This may be a reflection of the greater ability of the 4-methyl and 5-methoxy groups to increase the nucleophilicity at a 2-lithiated site.

Currently, it is not clear what specific function these lithiated nitriles play in enhancing aryne formation under the present experimental conditions. Acetonitrile

(7) The red color associated with successful base-initiated aryne reactions involving nitriles is presumably due to delocalized α-lithiated monoarylated and/or diarylated nitrile intermediates. These isolated products do form red solutions when put back in strongly basic solutions.

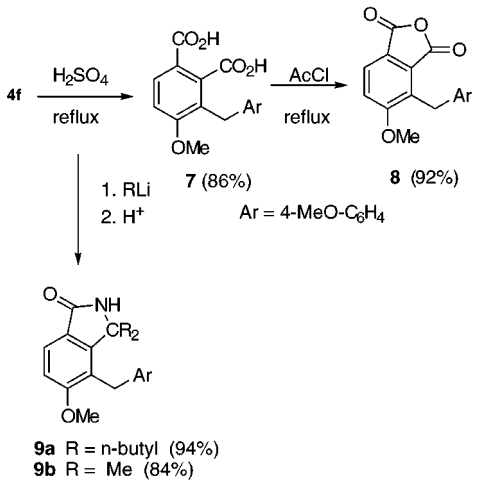
(8) The reported σ_m and σ_p for the carboxylate group range from −0.30 to 0.02 and from −0.25 to 0.00, respectively, which are similar to those reported for the methyl group. Exner, O. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Ed.; Plenum: New York, 1978; Chapter 10, pp 439−540.

anions have been known to dramatically increase the rate of certain sodium amide-initiated aryne reactions,[9] and it was suggested that the nitrile anions exerted their catalytic effect by increasing the basicity of the amide ion. In addition, there is much evidence that benzoic acids can undergo dilithiation. For example, it was found that benzoic acid could be dilithiated by treatment with *s*-BuLi/TMEDA complex at −90 °C; however, the reaction failed when *n*-BuLi/TMEDA was used at −70 °C.[10] In addition, certain heteroaromatic carboxylic acids can be dilithiated with LDA,[11] but benzoic acid resists such treatment.[12] In separate experiments, treatment of 3-bromo-4-methoxybenzoic acid (**1b**) with either excess LDA at −70 °C or excess α-lithiated arylacetonitriles alone for 2 h gave only starting materials. These results indicate that both LDA and the arylacetonitriles (presumably α-lithiated arylacetonitriles) must be present at −70 °C for the benzyne-3-carboxylate to be generated from bromobenzoic acids.

We also attempted to carry out similar reverse addition aryne reactions using 2-chlorobenzoic acid. However, these reactions proved unsuccessful. The addition of phenylacetonitrile to a solution of lithium 3-chlorobenzenecarboxylate and excess LDA at −70 °C did not give the red color characteristic of aryne generation solutions but instead produced a light green solution that gradually darkened when heated to −50 °C and turned black upon warming to room temperature. The usual workup gave mainly an intractable polymeric mixture, with the desired nitriles **4** being obtained in low yields (<10%). Parham has observed[13] that ortho -lithiated lithium benzoates, which were formed by halogen-exchange using excess *n*-butyllithium at −70 °C, underwent decomposition at temperatures >−50 °C to give polymeric materials. The higher temperature required to generate the lithium 2-lithio-3-chlorobenzenecarboxylate aryne precursor as compared to its 3-bromo counterparts probably reflects the poorer leaving group ability of chloride ion vs bromide ion.[14]

The above results show that lithiated arylacetonitrile nucleophilic addition occurs regioselectively at the 1-position of benzyne-3-carboxylate (**2a**), its 6-methyl derivative (**2c**), and 6-methoxybenzyne-3-carboxylate (**2b**). These results indicate that nucleophilic orientation to these arynes is determined predominantly by the electrostatic effect of the carboxylate group and not by the usual inductive effect of the carboxylate,[8] methoxy,[15] or methyl groups.[15] For example, the strong electron-withdrawing inductive effect of the 4-methoxy group would have directed nucleophilic addition exclusively to the 2-position and the weakly electron-releasing carboxylate and methyl groups would have directed addition to both the 2- and 3-positions of benzyne-3-carboxylate.

Scheme 3



The synthetic utility of the reactions outlined in Scheme 2 was demonstrated by the further reaction of one of the nitrile products, 2-cyano-4-methoxy-3-[(4-methoxyphenyl)methyl]phthalic acid (**4f**), which was readily hydrolyzed in 6 N sulfuric acid to give the phthalic acid **7** and then cyclized to the phthalic anhydride **8** in 86 and 92% yields, respectively (see Scheme 3). In addition, when **4f** was treated with BuLi or MeLi, the corresponding 3,3-di-*n*-butyl-2,3-dihydro-4-methoxy- (**9a**) or 2,3-dihydro-4-methoxy-3,3-dimethyl-*1H*-isoindol-1-ones (**9b**) were obtained in yields of 94% and 84%, respectively. These latter syntheses are particularly impressive in that the construction of the amide group occurs at low temperatures and in very high yields.

To demonstrate the synthetic interaction between the carboxylic and arylmethyl groups, phthalic acid (**7**) was smoothly converted to 4,7-dimethoxy-9-anthrone-1-carboxylic acid by treatment with concd sulfuric acid in 74% yield.

In conclusion, we have shown that 2-cyano-3-(arylmethyl)benzoic acids with specific substitution patterns can be readily obtained from the one-step aryne reactions involving halobenzoic acids and arylacetonitriles in the presence of LDA. Our method complements Meyer's two-step syntheses of 3-cyano-2-alkylbenzoic acids, which involve nitrile addition to the 2-position of oxazolinobenzyne followed by the hydrolysis of the resulting cyanooxazoline derivatives. When Meyer's method was applied to arylacetonitriles, the 2-(arylmethyl)-3-cyanobenzoic acids were obtained in poor yields (~20%).[2] Furthermore, the aryne methodology reported herein is a safer alternative to those involving the copper cyanide displacement of bromine in *o*-bromobenzoic acids.[16] It also gives 2-cyano acids in yields comparable with those obtained from the electrosynthesis of 2-chlorobenzonitrile.[17] The selective hydrolysis of the phthalonitriles to 2-cyanobenzoic acids can be achieved, but the yields are generally low.[18]

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Experimental Section

General Data/ Melting points were taken on an electrochemical apparatus and are uncorrected. IR spectra were obtained from a FTIR spectrometer, and the ^{1}H and ^{13}C NMR spectra were recorded on a 200 or 400 MHz spectrometer; chemical shifts were related to TMS as internal standard. Elemental analyses were obtained from E + R Microanalytical Laboratories, Inc., Corona, NY. High-resolution mass spectra were performed by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant No. P41RR0954). Chemicals were purchased from Aldrich Chemical Co. Diisopropylamine was refluxed over and distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from Na/benzophenone immediately prior to use. *n*-Butyllithium (*n*-BuLi) was purchased from Aldrich Chemical Co. as a solution in hexanes. The glassware was heated at 125 °C in an oven overnight prior to use. All the benzyne reactions were done under an atmosphere of dry O_2−free N_2 contained in a balloon.

General Procedure for Aryne Reactions. In a flame-dried flask flushed with nitrogen, fresh LDA (15 mmol) was prepared by adding *n*-butyllithium (15 mmol, 2.5 M in hexane) to a solution of diisopropylamine (15 mmol) in THF (30 mL) at −70 °C. After the mixture was stirred for 10 min, the appropriate bromobenzoic acid (5 mmol) in THF (30 mL) was added dropwise over 20 min, and the stirring was continued for 10 min at −70 °C. The appropriate arylacetonitrile then was added, during which time the solution developed a deep red color. The resulting solution was stirred for an additional 30 min and then was allowed to warm to room temperature and immediately quenched with 30 mL of saturated NH_4Cl in the case of **1a**,**b**,**d** or stirred overnight in the case of **1c** before quenching. The THF was evaporated under reduced pressure, and the remaining residue was extracted with methylene chloride (3 × 20 mL). The combined extracts were washed with dilute HCl (1 × 20 mL) and NaCl brine (2 × 20 mL), dried (Na_2SO_4), and concentrated (rotary evaporator) to provide a crude solid material. The mixture was subjected to flash column chromatography (silica gel) using a mixture of hexane/acetone (6:4) as the eluent to give a solid product that was recrystallized from EtOAc. The mp, elemental analyses, and NMR spectral data of isolated compounds are given below.

2-Cyano-3-benzylbenzoic acid (4a): mp 189−191 °C; ^{1}H NMR (acetone-d_6) δ 4.34 (s, 2 H), 7.24 (m, 1 H), 7.32 (m, 4 H), 7.74 (m, 2H), 8.05 (m, 1 H); ^{13}C NMR δ 40.5, 116.8, 126.8, 127.5, 129.5, 130.0, 133.3, 134.7, 140.0, 148.0, 165.8; IR 3412 (OH), 2235 (CN) cm^{-1}; HRMS exact mass calcd for $C_{15}H_{11}NO_2$ 237.0790, found 237.0791. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.02; H, 4.75; N, 5.99.

2-Cyano-3-[4-methoxyphenyl)methyl]benzoic acid (4b): mp 295−297 °C; ^{1}H NMR (DMSO-d_6) δ 3.70 (s, 3 H), 4.10 (s, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 7.17 (d, J = 8.6 Hz, 2 H), 7.37 (d, J = 7.2 Hz, 1 H), 7.48 (t, J = 7.2 Hz, 1 H), 7.80 (d, J = 7.2 Hz, 1 H); ^{13}C NMR δ 31.2, 56.4, 112.3, 115.3, 119.3, 129.0, 129.4, 131.0, 131.6, 132.8, 144.9, 146.9, 159.2, 170.2; IR 3412 (OH), 2235. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.85; H, 4.97; N, 5.17.

2-Cyano-3-[(2-methoxyphenyl)methyl]benzoic acid (4c): mp 190−192 °C; ^{1}H NMR (acetone-d_6) δ 3.82 (s, 3 H), 4.28 (s, 2 H), 6.92 (t, J = 7.6 Hz, 1 H), 7.02 (d, J = 8.0 Hz, 1 H), 7.21 (d, J = 7.6 Hz, 1 H), 7.27 (t, J = 7.6 Hz, 1 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.67 (t, J = 8.0 Hz, 1 H), 8.03 (d, J = 7.6 Hz, 1 H); ^{13}C NMR δ 33.7, 54.3, 110.2, 115.3, 120.0, 126.5, 127.8, 128.2, 129.8, 131.4, 133.1, 146.4, 157.0, 158.4, 164.5, 175.0; IR (CN) cm^{-1}; HRMS exact mass calcd for $C_{16}H_{13}NO_3$ 267.0895, found 267.0894. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.99; H, 4.82; N, 5.20.

2-Cyano-3-(1-naphthylmethyl)benzoic acid (4d): mp 205−207 °C; ^{1}H NMR (acetone-d_6) δ 4.81 (s, 2 H), 7.31 (d, J = 6.8 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 7.47−7.55 (m, 3 H), 7.65 (t, J = 8.0 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.97 (m, 1 H), 8.01−8.08 (m, 2 H); ^{13}C NMR δ 36.0, 105.5, 115.2, 123.2, 125.1, 125.3, 125.9, 126.9, 127.2, 128.3, 128.5, 131.7, 133.0, 133.5, 134.0, 145.2, 146.0, 164.4, 175.0; IR 2238 (CN) cm^{-1}; HRMS exact mass calcd for $C_{19}H_{13}NO_2$ 287.0946, found 287.0945. Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.87. Found: C, 79.55; H, 4.63; N, 4.98.

3-Benzyl-2-cyano-4-methoxybenzoic acid (4e): mp 185−186 °C; ^{1}H NMR (acetone-d_6) δ 3.65 (s, 3 H), 4.10 (s, 2 H), 6.90 (d, J = 8.4 Hz, 1 H), 7.08−7.20 (m, 5 H), 8.20 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 34.5, 56.3, 118.6, 126.9, 129.0, 129.4, 133.3, 134.5, 140.3, 146.7, 160.1, 176.4; IR 3412 (OH), 2235 (CN) cm^{-1}; HRMS exact mass calcd for $C_{16}H_{13}NO_3$ 267.0895, found 267.0891. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24.

2-Cyano-4-methoxy-3-[(4-methoxyphenyl)methyl]benzoic acid (4f): mp 190−192 °C; ^{1}H NMR (DMSO-d_6) δ 3.73 (s, 3 H), 4.01 (s, 2 H), 4.22 (s, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H), 7.41 (d, J = 8.8 Hz, 1 H), 8.11 (d, J = 8.8 Hz, 1 H); ^{13}C NMR δ 33.7, 55.4, 56.8, 114.6, 115.0, 117.0, 125.5, 129.4, 130.4, 131.8, 132.5, 137.1, 138.1, 159.3, 161.8, 165.5; IR 3412 (OH), 2266 (CN) cm^{-1}; HRMS exact mass calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.1003. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.28; H, 5.09; N, 4.71. Found: C, 68.53; H, 5.23; N, 4.52.

2-Cyano-4-methoxy-3-[(2-methoxyphenyl)methyl]benzoic acid (4g): mp 202−204 °C; ^{1}H NMR (acetone-d_6) δ 3.87 (s, 3 H), 3.90 (s, 3 H), 4.25 (s, 2 H), 6.59 (d, J = 7.2 Hz, 1 H), 6.76 (t, J = 7.2 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 7.35 (*d*, J = 8.8 Hz, 1 H), 8.15 (d, J = 8.8 Hz, 1 H); ^{13}C NMR δ 39.3, 54.3, 55.3, 105.5, 108.8, 109.7, 113.2, 119.5, 126.7, 127.3, 131.0, 133.1, 138.6, 153.2, 158.5, 163.4, 174.2; IR 3454 (OH), 2224 (CN) cm^{-1}; HRMS exact mass calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.1001. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09, N, 4.71. Found: C, 68.87; H, 5.17; N, 4.84.

2-Cyano-3-(1-naphthylmethyl)-4-methoxybenzoic acid (4h): mp 235−237 °C; ^{1}H NMR (acetone-d_6) δ 3.89 (s, 3 H), 4.79 (s, 2 H), 6.68 (d, J = 7.2 Hz, 1 H), 7.32 (m, 1 H), 7.51 (d, J = 8.8 Hz, 1 H), 7.57 (t, J = 8.0 Hz, 1 H), 7.65 (t, J = 8.0 Hz, 1 H), 7.78 (d, J = 8.8 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 8.8 Hz, 1 H), 8.37 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 30.1, 55.4, 55.3, 113.6, 115.0, 122.8, 123.0, 124.3, 124.9, 125.2, 125.6, 126.3, 127.7, 128.1, 131.5, 133.3, 133.8, 134.1, 161.0, 164.1, 175.0; IR 3398 (OH), 2266 (CN) cm^{-1}; HRMS exact mass calcd for $C_{20}H_{15}NO_3$ 317.1052, found 317.1049. Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.79; H, 4.85; N, 4.32.

3-Benzyl-2-cyano-4-methylbenzoic acid (4i): mp 128−130 °C; ^{1}H NMR (acetone-d_6) δ 2.37 (s, 3 H), 4.43 (s, 2 H), 7.15 (d, J = 7.6 Hz, 1 H), 7.28 (m, 2 H), 7.63 (d, J = 8.0 Hz, 1 H), 8.20 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 20.3, 37.8, 115.0, 117.0, 127.2, 129.0, 129.4, 130.5, 135.0, 139.4, 143.0, 144.0, 145.5, 175.5; IR 3412 (OH), 2235 (CN) cm^{-1}; HRMS calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0948. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.50; H, 5.23; N, 5.67.

2-Cyano-3-[(4-methoxyphenyl)methyl]-4-methylbenzoic acid (4j): mp 146−137 °C; ^{1}H NMR (acetone-d_6) δ 2.47 (s, 3 H), 3.88 (s, 2 H), 4.21 (s, 2 H), 6.74 (d, J = 6.4 Hz, 2 H), 6.94 (d, J = 6.4 Hz, 2 H), 7.21 (d, J = 8.4 Hz, 1 H), 8.11 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 17.9, 27.4, 50.3, 109.1, 109.5, 113.5, 124.8, 126.0, 126.6, 128.7, 133.0, 138.2, 140.7, 154.0, 167.0; IR 3412 (OH), 2235 (CN) cm^{-1}; HRMS exact mass calcd for $C_{17}H_{15}NO_3$ 281.1052, found 281.1053. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.51; H, 5.33; N, 5.02.

2-Cyano-4-methoxy-3-[(2-methoxyphenyl)methyl]benzoic acid (4k): mp 202−204 °C; ^{1}H NMR (acetone-d_6) δ 3.87 (s, 3 H), 3.90 (s, 3 H), 4.25 (s, 2 H), 6.59 (d, J = 7.2 Hz, 1 H), 6.76 (t, J = 7.2 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 7.35 (*d*, J = 8.8 Hz, 1 H), 8.15 (d, J = 8.8 Hz, 1 H); ^{13}C NMR δ 39.3, 54.3, 55.3, 105.5, 108.8, 109.7, 113.2, 119.5, 126.7, 127.3, 131.0, 133.1, 138.6, 153.2, 158.5, 163.4, 174.2; IR 3454 (OH), 2224 (CN) cm^{-1}; HRMS exact mass calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.1001. Anal. Calcd for $C_{17}H_{15}NO_4$: 68.68; H, 5.09; 4.71. Found: C, 68.69; H, 5.14; N, 4.64.

3-Benzyl-2-cyano-4,5-dimethoxybenzoic acid (4l): mp 230−231 °C dec; ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 3 H), 3.86 (s, 3

H), 4.13 (s, 2 H), 7.17 (d, J = 7.0 Hz, 2 H), 7.25 (t, J = 7.0 Hz, 1 H), 7.53 (s, 1 H); ^{13}C NMR δ 35.1, 57.2, 61.5, 105.5, 107.0, 110.5, 114.1, 127.4, 129.6, 130.5, 138.5, 139.5, 143.0, 140.9, 156.0, 168.0, 177.1; IR 3412 (OH), 2235 (CN) cm^{-1}; HRMS exact mass calcd for $C_{17}H_{15}NO_4$ 297.1001, found 297.1002. Anal. Calcd for $C_{17}H_{15}NO_4$: 68.68; H, 5.09; 4.71. Found: C, 68.63; H, 5.10; N, 4.74.

3-(α-Phenylcyanomethyl)benzoic acid (5a): mp 147−149 °C; ^{1}H NMR ($CDCl_3$) δ 5.21 (s, 1 H), 7.40 (m, 5 H),7.51 (m, 1 H), 7.62 (m, 1 H), 8.09 (m, 2 H); ^{13}C NMR δ 42.3, 120.5, 128.6, 129.1, 129.5, 130.1, 130.2, 132.7, 132.9, 137.4, 138.4, 143.3, 167.2; IR (acetone) 3413 (OH), 2259 (CN) cm^{-1}; HRMS exact mass calcd for $C_{15}H_{11}NO_2$ 237.0790, found 237.0791. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.85; H 4.65; N, 5.87.

4-Methoxy-3-(α-phenylcyanomethyl)benzoic acid (5e): mp 199−201 °C; ^{1}H NMR (acetone-d_6) δ 3.96 (s, 3 H), 5.75 (s, 1 H), 7.17 (d, J = 6.4 Hz, 1 H), 7.32−7.45 (m, 5 H), 8.07 (m, 2 H); ^{13}C NMR δ 37.2, 56.6, 112.2, 120.0, 124.0, 125.8, 128.6, 128.9, 129.9, 131.5, 134.0, 136.7, 160.9, 176.0; IR (acetone) 3421 (OH), 2269 (CN) cm^{-1}; HRMS exact mass calcd for $C_{16}H_{13}NO_3$ 267.0895, found, 267.0897. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.93; H, 4.97; N, 5.19.

4-Methyl-3-(α-phenylcyanomethyl)benzoic acid (5i): mp 184−186 °C; ^{1}H NMR (acetone-d_6) δ 2.39 (s, 3 H), 5.84 (s, 1 H), 7.36−7.49 (m, 6 H), 7.95 (d, J = 8.0 Hz, 1 H), 8.16 (s, 1 H); ^{13}C NMR δ 19.8, 40.1, 120.2, 128.7, 129.1, 130.1, 130.4, 130.5, 132.4, 135.8, 136.3, 142.7, 146.6, 167.0; IR (acetone) cm^{-1}; HRMS exact mass calcd for $C_{16}H_{13}NO_2$ 251.0946, found 251.0949. Anal. Calcd for $C_{16}H_{13}NO_2$: 76.48; H, 5.09; N, 4.71. Found: C, 76.41; H, 5.14; N, 4.77.

Preparation of 4-Methoxy-3-[(4-methoxyphenyl)methyl]phthalic Acid (7). A 100 mg (0.37 mmol) sample of 2-cyano-4-methoxy-3-[(4-methoxyphenyl)methyl]phthalic acid (**4f**) was refluxed in 10 mL of 6 N H_2SO_4 for 8−10 h. After the mixture was cooled to room temperature, the solid phthalic acid **6** was filtered, washed with water, and dried: 92 mg (86%); mp 171−173 °C; ^{1}H NMR (acetone-d_6) δ 3.72 (s, 3 H), 3.96 (s, 3 H), 4.01 (s, 2 H), 6.77 (d, J = 8.8 Hz, 2 H), 7.11 (d, J = 8.8 Hz, 1 H), 7.20 (d, J = 8.8 Hz, 2 H), 8.00 (d, J = 8.8 Hz, 1 H); ^{13}C NMR δ 31.5, 539, 54.9, 109.0, 112.7, 119.1, 126.4, 129.1, 130.2, 131.4, 137.5, 157.4, 160.8, 168.4, 175.0; IR (acetone) cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.01. Found: C, 76.41; H, 5.14; N, 4.77.

Preparation of 4-Methoxy-3-[(4-methoxyphenyl)methyl]phthalic Anhydride (8). A mixture containing 60 mg (0.21 mmol) of phthalic acid **6** and acetyl chloride (1.5 mL) was heated at reflux for 6 h. After the mixture was cooled to room temperature, most of the liquid was removed under vacuum. The resulting suspension was filtered to yield 52 mg (92%) of the solid anhydride **7**: mp 122−124 °C; ^{1}H NMR (acetone-d_6) δ 3.71 (s, 3 H), 4.05 (s, 3 H), 4.35 (s, 2 H), 6.77 (d, J = 8.8 Hz, 2 H), 7.251 (d, J = 8.8 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 2 H), 8.00 (d, J = 8.8 Hz, 1 H), 7.93 (d, J = 8.4 Hz, 1 H); ^{13}C NMR δ 30.0, 55.4, 57.4, 114.5, 118.5, 123.5, 126.5, 126.8, 130.6, 130.7, 132.0, 132.5, 159.2, 163.4, 164.5, 164.8. Anal. Calcd for $C_{17}H_{14}O_5$: 68.45; H, 4.73. Found: C, 76.41; H, 5.14; N, 4.77.

Preparation of 3,3-Di-*n*-butyl-2,3-dihydro-5-methoxy-4-[(4-methoxyphenyl)methyl]-1*H*-isoindol-1-one (9a). To a 33 mg (0.12 mmol) sample of 2-cyano-4-methoxy-3-[(4-methoxyphenyl)methyl]phthalic acid (**4f**) in 15 mL of THF was added 30 mmol of *n*-BuLi (20 mL of 1.5M soln) at −70 °C. The resulting solution was allowed to warm to room temperature. After being quenched with brine (10 mL), the mixture was worked up in the usual way to give 37 mg (94%) of **9a**: colorless solid: mp 138−140 °C: ^{1}H NMR ($CDCl_3$) δ 0.55 (m, 2 H), 0.64 (t, J = 9.0 Hz, 6H), 0.97 (m, 2 H), 1.00 (m, 4 H), 1.79 (m, 2 H), 1.93 (m, 2 H), 3.73 (s, 3 H), 3.90 (s, 3 H), 4.13 (s, 2 H), 6.80 (d, J = 8.4 Hz, 2 H), 6.98 (d, J = 8.4 Hz, 2 H), 7.10 (s, 1 H), 7.19 (d, J = 8.4 Hz, 1 H), 7.61 (d, J = 8.4, 1 H); ^{13}C NMR δ 13.3, 22.3, 25.5, 30.1, 38.4, 54.7, 55.6, 65.6, 110.6, 113.6, 122.7, 123.5, 127.5, 128.7, 131.5, 148.0, 161.2, 169.0. Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 76.41; H, 5.14; N, 4.77. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.92; H, 8.41; N, 3.54. Found: C, 76.11; H, 8.33; N, 3.47.

Preparation of 2,3-Dihydro-5-methoxy-4-[(4-methoxyphenyl)methyl]-3,3-dimethyl-1*H*-isoindol-1-one (9b). A 33 mg (0.12 mmol) sample of 2-cyano-4-methoxy-3-[(4-methoxyphenyl)methyl]phthalic acid (**4f**) in 15 mL of THF was added 30 mmol of MeLi (20 mL of 1.5 M solution) at −70 °C. The resulting solution was treated in manner similar to as that described above for **9a** to give 26 g (84%) of compound **9b**: colorless solid: mp 194−195 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 6 H), 3.71 (s, 3 H), 3.79 (s, 1 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.93 (d, J = 8.4 Hz, 2 H), 7.14 (d, J = 8.4 Hz, 2 H), 7.40 (s, 1 H), 7.61 (d, J = 8.4 Hz, 1 H). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.21; H, 6.89; N, 4.45.

Preparation of 4,7-Dimethoxy-9-anthrone-1-carboxylic Acid (10). A mixture containing 63 mg (20 mmol) of 4-methoxy-3-[(4-methoxyphenyl)methyl]phthalic acid (**7**) and 10 mL of concd H_2SO_4 was refluxed for 4 h. Upon neutralization, a colorless solid was obtained that was recrystallized from EtOAc: mp 113−115 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3 H), 4.01 (s, 3 H), 7.01 (d, J = 8.4 Hz, 1 H), 7.47 (d, J = 8.4 Hz, 1 H), 7.59 (d, J = 8.4 Hz, 1 H), 7.86 (s, 1 H), 7.96 (d, J = 8.4 Hz, 1 H). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.90; H, 5.80.

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Supporting Information Available: Copies of NMR spectra of **4a**−**m, 5a,e,i, 7,** and **8** (23 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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