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One-Step Synthesis of 1-Hydroxymethyl-6-aryl-2*H*-anthra[9,1-*bc*]furans, 6-Benzyl-2-hydroxymethylbenzonitriles, and 3-Arylmethyl-4-methylphthalimides

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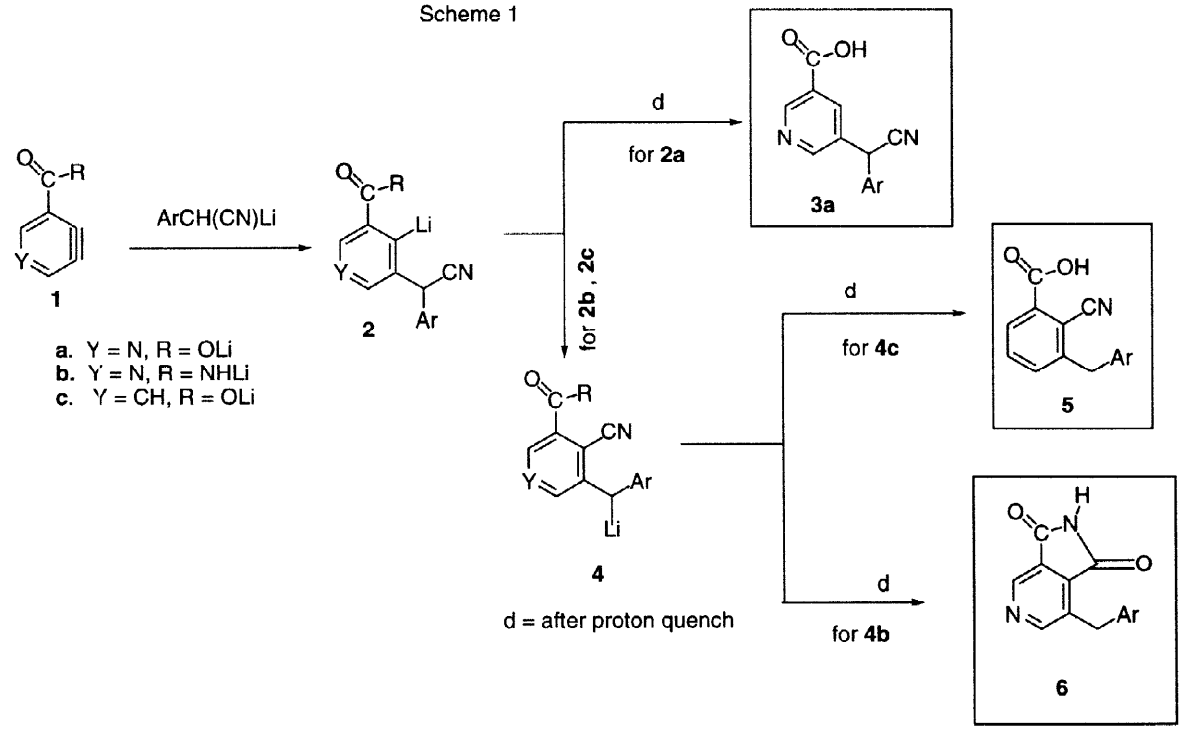
Abstract: Titled compounds were prepared by the reaction of 2-chlorobenzyl alcohol or 2-bromobenzamide with arylacetonitriles in the presence of LDA. A mechanism in terms of an initial tandem rearrangement pathway followed by appropriate cyclization processes is proposed.

During the course of our study on the effect of substituents on the orientation of addition and reactivity of arynes, we turned our attention to substituents which contain a negatively charge β heteroatom and are located next to the triple bond of the aryne. Arynes studied previously to this report include: 3,4-pyridyne-5-carboxylate (**1a**),[1] 3,4-pyridyne-5-carboxamidate (**1b**),[2] and benzyne-3-carboxylate (**1c**).[3] Scheme 1 summarizes the salient features of these arynes. First, the addition of

Scheme 1



arylacetonitrile anions occurs regioselectively at the remote position of the "triple bond;" presumably

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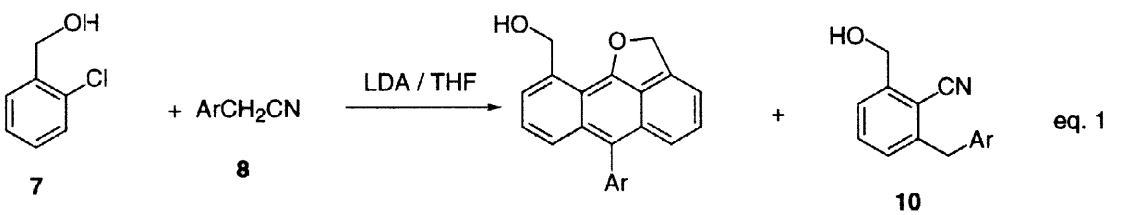
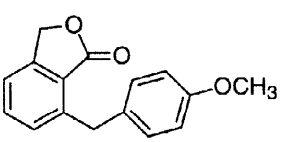
addition to the inductively favored carbon adjacent to the charged substituent[4] is impeded by unfavorable electrostatic interactions between the charged substituent and arylacetonitrile anion. The initially formed aryne-nitrile anion adducts (**2a-c**) can proceed to products by three different pathways. First, the pyridyne-3-carboxylate-arylacetonitrile adduct (**2a**) simply awaits proton quench to give typical aryne arylated products (**3**).[5] The other two adducts (**2b** and **2c**) however rearrange[6] to the respective dilithiated pyridine carboxamidate (**4b**) and benzenecarboxylate (**4c**) intermediates in which the nitrile and charged substituents are suitably situation for further cyclization. Of these, only **4b** cyclizes and gives 7-arylmethyl-*1H*- pyrrolo[3,4-*c*]pyridine-1,3-(2H)-diones (**6**).[1] However, due to the lower nucleophilicity of carboxylate as compared to carboxamidate, **4c** resists cyclization and supplies 2-cyano-3-(arylmethyl)benzoic acids (**5**) after proton quench.

To obtain more information on the influence of negatively charge β substituents on the fate of initially-formed aryne-nitrile adducts, LDA-mediated reactions of 2-chlorobenzyl alcohol (**7**) and the 2-bromobenzamide (**12**) with arylacetonitriles (**8**) were carried out. As shown in eq. 1, the reaction of the chloro alcohol (**7**) with **8a-e** gave 6-aryl-*2H*-anthra[9,1-*bc*]furans (**9a-e**) as major products (46-32%) along with smaller amounts (32-15%) of the rearranged products, 6-arylmethyl-2-hydroxymethyl-benzonitriles (**10a-e**). In addition, the lactone, 4-(4-methoxyphenyl-methyl)-(1, 3*H*-)-benzo[*c*]-furan-3-one (**11**) was obtained in 26% yield from the reaction of **7** with 4-methoxyphenylacetonitrile (**8e**).



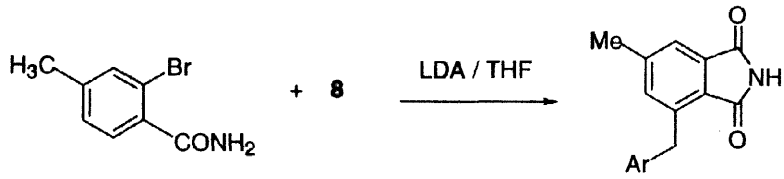
7 **8** **9** **10**

a. Ar = C_6H_5	41%	21%
b. Ar = 2-$MeOC_6H_4$	46%	32%
c. Ar = 3,4-di$MeOC_6H_3$	32%	15%
d. Ar = 1-naphthyl	33%	18%
e. Ar = 4-$MeOC_6H_4$	37%	16%



11 (26%)

In addition, the reaction of 2-bromo-4-methybenzamide (**12**) with arylacetonitriles (**8a-d**) and LDA gave the phthalimides (**13a-d**) along with intractable tars (eq. 2) . Attempts to extend this reaction to 2-bromobenzamide with other arylacetonitriles gave complex mixtures which could not be separated by the usual chromatographic methods. The products **9-11**, and **13** were isolated in pure form by column chromatography. The structures of all products were consistent with their ^{1}H NMR, IR spectra and elemental analysis. For example, the furans (**9a-e**) exhibit signals at *ca.* δ 5.3 ppm and 6.1 ppm which correspond to the methylene hydrogens of the 10-hydroxymethyl and the methylene hydrogens in the furan ring, respectively. Additionally, the IR spectra of the rearranged nitriles (**10**) revealed bands around

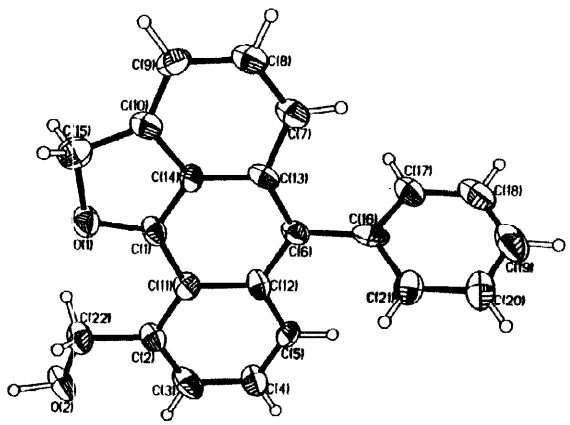


12

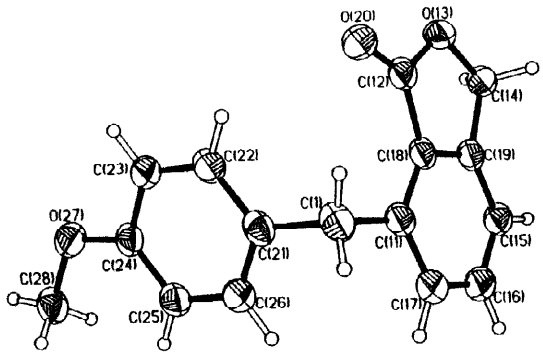
13

a. Ar = C_6H_5 46%
b. Ar = 4-MeO-C_6H_4 51%
c. Ar = 2-MeO-C_6H_4 30%
d. Ar = 1-Naphthyl-C_6H_4 37%

2225 cm^{-1} which is indicative of a nitrile group bonded to an aromatic ring, whereas the characteristic ester carbonyl stretch was observed at 1745 cm^{-1} for the lactone (**11**). The structures of **9a** and **11**were further confirmed by single crystal x-ray crystallographic analysis; their ORTEP drawings are shown below.



ORTEP Drawing of **9a**



ORTEP Drawing of **11**

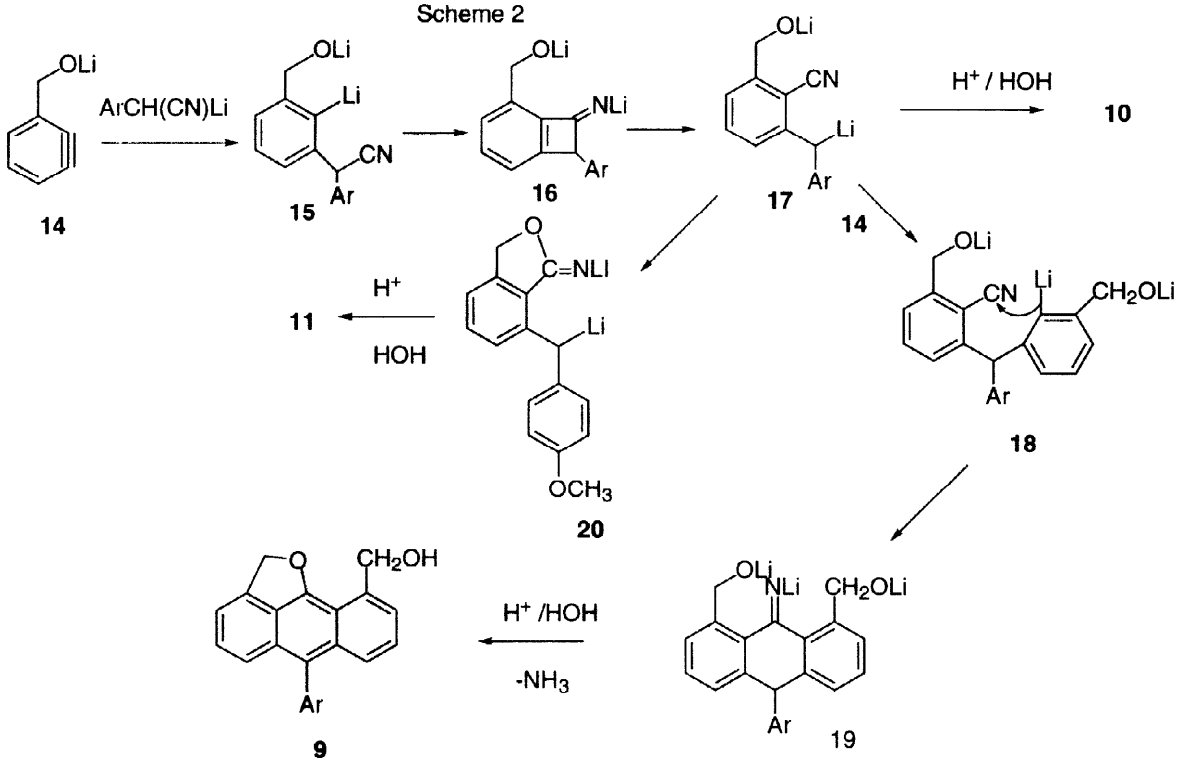
A possible mechanism for the formation of the products (**9-11**) *via* 2,3-dehydrobenzyl oxide (**14**) is shown in Scheme 2. Accordingly, 2,3-dehydrobenzyl oxide (**14**) reacts with lithiated arylacetonitriles to give an initial adduct (**15**) which cyclizes to a benzocyclobutenium intermediate (**16**). The latter step has been proposed as the key step in the tandem addition-rearrangement mechanism.[6]

That the regioselectivity of nucleophilic addition occurred at the remote 3-position rather than the 2-position of **14** (which would be favored on the basis of the +I inductive effect of CH_2OLi)[4] indicates that although the OLi group is smaller than carboxylate, unfavorable electrostatic interactions still prevent addition to the adjacent site in **14**. Ring opening of **16** then affords the dilithiated adduct (**17**) which can be converted to products **9-11** in the following ways.

First, it may react with another molecule of aryne **14** to give the trilithiated intermediate (**18**), which undergoes two successive ring closures to give furan product **9.** The first cyclization involves addition of the aryl lithium to the nitrile group to yield the tricyclic ring (**19**), which to our knowledge

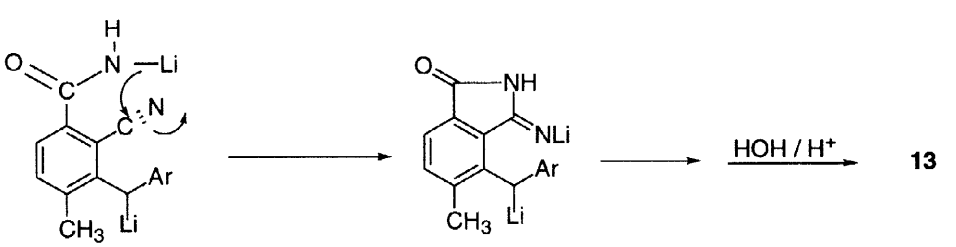
is unprecedented in LDA-mediated tandem addition-rearrangement aryne reactions. The second ring closure probably occurs during the aqueous acid workup in which either one of the CH_2OH groups cycloadds to the C=O formed by the hydrolysis of the cyclic imine intermediate. Alternatively, adduct **17** may either await acidic-aqueous quenching to give the rearranged nitriles (**10**) or undergo cyclization via addition of the CH_2 OLi group on the adjacent nitrile group to give intermediate **20** which is converted to the lactone (**11**) after proton quench.

Scheme 2



The phthalimides (**13**) most likely are formed by a mechanism shown in Scheme 3 in which the dilithiated intermediate (**21**) undergoes a similar cylization as that proposed for the cyclization of **17** to **20**

Scheme 3



21 **22**

above to give the phthalimide precursor (**22**); proton quench of **22** then provides **13.**

This study demonstrates that the increased nucleophilicity of the CH_2OLi and CONLi as compared to the carboxylate group facilitates intramolecular ring annulations of the initially formed adducts **17** and **22**, to

yield 6-aryl-2*H*-anthra[9,1-*bc*]furans (**9**), (1, 3*H*-)-benzo[*c*]-furan-3-ones (**11**) and phthalimides (**13**). These compounds should prove to be valuable precursors to biologically active compounds.[7]

Experimental Section

The amines were dried over calcium hydride and distilled prior to use; n-butyllithium was used as received. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrophotometer and chemical shifts were related to TMS as an internal standard. IR spectra were obtained on a FTIR instrument. Elemental analyses were carried out by E+R Microanalytical Laboratory, Inc, Parsippany, NJ. High resolution mass spectra were performed by the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant Np. P41RR0954). All benzyne reactions were done under an atmosphere of dry O_2-free N_2.

X-ray Single Crystal Analyses. All data were collected on a Nicolet R3m/V diffractometer using the $\theta-2\theta$ scan technique, Mo-Kα radiation ($\lambda = 0.71073$), scan speed 3.0-15 deg min^{-1}, scan range 3.5-50.0^0 and a graphite monochromator. Data were corrected for Lorentz, absorption, and polarization effects. The structures were solved by direct methods using SHELXS-86,[8] and the model was refined by using full-matrix least-squares techniques. Pertinent data are given in the Table 2.

Table 2

	Compound **9a**	Compound **11**
formula	$C_{22}H_{16}O_4$	$C_{16}H_{14}O_3$
crystal dmns, cm^{-3}	0.40 X 0.40 X 0.30	0.35 X 0.30
Space Group	$P2_1$	$P2_1/c$
a (Å)	8.040(1)	17.996 (2)
b (Å)	21.299(1)	8.240(1)
c (Å)	18.369(1)	8.63(1)
β (°)	99.16(1)	93.847(7)
V (Å^3)	3195.5(14)	1278.0(3)
Z-value	8	4
D calc (g-cm^3)	1.336	
abs coeff, mm^{-1}	0.084	0.091
T (K)	228	228
decay, %	0.051	0.054
Data collected	4236	2422
Unique reflections	3712	1406
R_{int}	0.064	0.062
Parameters	865	173
R, R_w	0.064, 0.178	0.062, 0.089
$(\Delta/\sigma)_{max}$	<0.01	<0.01
$\rho_{max};\rho_{min}$ (eÅ^{-3})	0.28; -.0.25	0.28,-0.25
GOF	1.03	2.03

General Procedure for the Reaction of 2-Chlorobenzyl Alcohol (7), with Arylacetonitriles (8) and LDA. In a flame-dried flask flushed with nitrogen, fresh LDA (15 mmol) was prepared by adding *n*-BuLi (15 mmol, 2.5 M in hexane) to a solution of diisopropylamine (15 mmol) in THF (30 mL) at -70 °C. After stirring for 10 min, the 2-chlorobenzyl alcohol (**7**) (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 (**8**) was then added (5 mmol) during which the solution developed a deep red color. The resulting solution was stirred for an additional 30 min, allowed to warm to room temperature, stirred overnight, and quenched with sat. aq. NH_4Cl (30 mL). The THF was evaporated under reduced pressure, and the remaining residue was extracted with methylene chloride (3 X 20 mL). The combined extracts were washed with dilute HCl (1 X 20 mL), brine (2 X 20 mL), dried (Na_2SO_4), and concentrated (rotary evaporator) to provide 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, which was recrystallized from EtOAc. The mp, elemental analyses and IR and NMR spectral data of isolated compounds **9-11, 13** are given below.

10-Hydroxymethyl-6-phenyl-*2H*-anthra[9,1-*bc*]furan (9a): yellow solid, mp 151-153 °C. ^{1}H NMR (acetone-d_6) δ 5.35 (s, 2 H), 6.11 (s, 2 H), 7.30-7.34 (m, 3 H), 7.42-7.46 (m, 2 H), 7.50-7.43 (m, 3 H), 7.60-7.62 (m, 3 H). ^{13}C NMR ($CDCl_3$) δ 65.9, 77.9, 113.6, 113.8, 122.2, 124.0, 124.2, 125.5, 125.9, 126.9, 127.3, 127.5, 128.4, 128.6, 131.7, 134.2, 135.9, 138.5, 139.6, 157.2. Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.75; H, 5.08.

10-Hydroxymethyl-6-(2-methoxyphenyl)-*2H*-anthra[9,1-*bc*]furan (9b): yellow solid, mp 161-163 °C. IR (Nujol) 3473 cm^{-1} (OH). ^{1}H NMR (acetone-d_6) δ 3.63 (s, 3 H), 5.34 (s, 2 H), 6.11 (s, 2 H), 7.18-7.29 (m, 6 H), 7.43-7.50 (m, 4 H). ^{13}C NMR ($CDCl_3$) δ 48.2, 55.7, 77.9, 111.5, 113.4, 114.0, 120.9, 122.5, 123.3, 124.2, 124.3, 125.3, 127.0, 127.6, 128.4, 128.7, 129.3, 133.3, 134.4, 135.9, 129.1, 157.3, 158.3. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.89; H, 5.41.

10-Hydroxymethyl-6-(3,4-dimethoxyphenyl)-*2H*-anthra[9,1-*bc*]furan (9c): yellow solid, mp 157-159 °C. ^{1}H NMR (acetone-d_6) δ 3.84 (s, 3 H), 3.95 (s, 3 H), 5.33 (s, 2 H), 6.10 (s, 2 H), 6.92 (d, J = 8.0 Hz, 1 H), 6.99 (s, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 7.28-7.30 (m, 5 H), 7.67 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 56.1, 60.4, 65.9, 77.9, 111.4, 113.5, 113.8, 114.8, 122.2, 123.9, 124.2, 124.0, 125.4, 126.7, 127.6, 128.4, 128.7, 130.9, 134.5, 135.9, 139.1, 148.4, 149.1, 157.1. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.59; H, 5.54.

10-Hydroxymethyl-6-(1-naphthyl)-*2H*-anthra[9,1-*bc*]furan (9d): yellow solid, mp 196-198 °C. ^{1}H NMR (acetone-d_6) δ 5.41 (s, 2 H), 6.18 (s, 2 H), 7.21 (d, J = 6.8 Hz, 1 H), 7.21 (d, J = 8.8 Hz, 1 H), 7.26-7.28 (m, 4 H), 7.29-7.32 (m, 1 H), 7.52-7.55 (m, 3 H), 7.75 (m, 1 H), 8.07-8.11 (m, 2 H). ^{13}C NMR δ 65.3, 78.1, 113.6, 113.9, 122.3, 124.3, 124.6, 125.6, 125.7, 126.0, 126.2, 126.5, 127.8, 128.1, 128.3, 128.5, 129.3, 129.5, 132.2, 133.7, 133.9, 135.1, 136.0, 136.2, 139.1, 157.6. Calcd for $C_{26}H_{18}O_2$: C, 86.17; H, 5.01. Found: 87.26; H, 5.15.

10-Hydroxymethyl-6-(4-methoxyphenyl)-*2H*-anthra[9,1-*bc*]furan (9e): yellow solid, mp 191-192 °C. ^{1}H NMR (acetone-d_6) δ 3.94 (s, 3 H), 5.35 (s, 2 H), 6.10 (s, 2 H), 7.17 (d, J = 8.8 Hz, 2 H),

7.29 (d, J = 8.8 Hz, 2 H), 7.28-7.32 (m, 3 H), 7.32-7.35 (m, 2 H), 7.49 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 55.4, 65.9, 77.9, 113.5, 113.9, 114.1, 122.2, 124.2, 125.3, 126.0, 126.7, 127.6, 128.3, 123.8, 130.5, 132.7, 134.5, 135.9, 139.1, 157.0, 159.0. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: 80.83; H, 5.46.

2-Benzyl-6-hydroxymethylbenzonitrile (10a): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 4.23 (s, 2 H), 4.85 (s, 2 H), 7.30-7.34 (m, 6 H), 7.60 (m, 2 H). HRMS: Calcd for $C_{15}H_{13}NO$ 223.0997. Found: 223.0993. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; 6.27. Found: C, 80.85; H, 5.98; N, 6.33.

2-Hydroxymethyl-6-(2-methoxyphenylmethyl)benzonitrile (10b): colorless solid, mp 95 °C. IR (Nujol) 3313 cm^{-1} (OH), 2226 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3 H), 4.19 (s, 2 H), 4.85 (s, 2 H), 6.86-6.99 (m, 2 H), 7.15-7.26 (m, 3 H), 7.56 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 55.4, 62.3, 110.7, 110.9, 116.7, 120.7, 125.3, 127.4, 128.3, 128.9, 130.6, 132.6, 144.7, 145.5, 157.5. HRMS: Calcd for 253.1103. Found: 253.1110. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; 5.97; N, 5.53. Found: C, 76.59 ; H, 5.90; N, 5.60.

2-Hydroxymethyl-6-(3,4-dimethoxyphenyl)methylbenzonitrile (10c): viscous oil. ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.81 (s, 3 H), 4.15 (s, 2 H), 4.86 (s, 2 H), 6.79-6.83 (m, 1 H), 6.86-6.87 (m, 1 H), 8.70 (s, 1 H), 7.33-7.34 (m, 1 H), 6.79-6.83 (m, 2 H). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07, 6.05, 4.94. Found: C, 72.15; H, 6.13; N, 5.09.

2-Hydroxymethyl-6-(1-naphthyl)methylbenzonitrile (10d): green solid mp 140-141 °C. IR (Nujol) 3511 cm^{-1} (OH), 2221 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$) δ 4.72 (s, 2 H), 4.91 (s, 2 H), 7.03 (d, J = 7.2 Hz, 1 H), 7.30 (d, J = 7.2 Hz, 1 H), 7.47-7.62 (m, 5 H), 7.88 (d, J = 8.0 Hz, 1 H), 7.96-7.98 (m, 1 H), 8.03-8.06 (m, 1 H). HRMS: Calcd for $C_{19}H_{15}NO$: 273.1154. Found: 273.1159. Anal. Calcd for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.67; H, 5.70; N, 5.25.

2-Hydroxymethyl-6-(4-methoxyphenyl)methylbenzonitrile (10e): viscous liquid; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3 H), 4.12 (s, 2 H), 4.85 (s, 2 H), 6.82 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 7.17-7.20 (m, 2 H), 7.45-7.47 (m, 1 H). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; 5.97; N, 5.53. Found: C, 75.98; H, 6.07, N, 5.45.

4-(4-methoxyphenylmethyl)-(1*H*,3*H*)-benzo[*c*]furan-3-one (11): yellow solid, mp 110-111 °C. IR (Nujol) 1746 cm^{-1} (CO_2CH_2). NMR ($CDCl_3$) δ 3.76 (s, 3 H), 4.27 (s, 2 H), 5.34 (s, 2 H), 6.85 (d, J = 8.0 Hz, 2 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.36 (d, J = 7.2 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.64 (t, J = 7.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$), δ 34.6, 54.6, 68.8, 113.9, 122.6, 129.9, 130.0, 132.8, 134.0 142.9, 148.1, 158.3, 170.6. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.91; H, 5.29.

3-Benzyl-4-methylphthalimide (13a): ^{1}H NMR (acetone-d_6) δ 2.32 (s, 3 H), 4.89 (s, 2 H), 7.16-7.25 (m, 5 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.62 (d, J = 7.6 Hz, 1 H), 8.64 (s, 1 H). HRMS: Calcd for $C_{16}H_{13}NO_2$: 251.0946 Found: 251.0947. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.54; H, 5.30; N, 5.70.

3-(*p*-Methoxyphenyl)methyl-4-methylphthalimide (13b): ^{1}H NMR (acetone-d_6) 2.33 (s, 3 H), 3.73 (s, 3 H), 4.80 (s, 2 H), 6.80 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 7.6 Hz, 1 H), 7.60 (d, J= 7.6 Hz, 1 H), 8.64 (s, 1 H). HRMS: Calcd for $C_{17}H_{15}NO_3$: 281.1052. Found: 281.1056. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.60; H, 5.46; N, 4.79.

3-(*o*-Methoxyphenyl)methyl-4-methylphthalimide (13c): ^{1}H NMR (acetone-d_6) δ 2.28 (s, 3 H), 3.91 (s, 3 H), 4.58 (s, 2 H), 6.59 (d, J = 7.6 Hz, 1 H), 6.76 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1 H), 7.17 (t, J = 7.6 Hz, 1 H), 7.64 (d, J = 7.6 Hz, 1 H), 7.64 (d, J = 7.6 Hz, 1 H), 7.67 (d, J = 7.6 Hz, 1 H), 8.65 (s, 1 H). HRMS: Calcd for $C_{17}H_{15}NO_3$: 281.1052. Found: 281.1055. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.30; H, 5.36; N, 4.98.

4-Methyl-3-(1-naphthyl)methylphthalimide (13d): ^{1}H NMR (acetone-d_6) δ 2.27 (s, 3 H), 5.32 (s, 2 H), 6.65 (d, J = 7.2 Hz, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 7.54-7.75 (m, 5 H), 7.95 (d, J = 7.6 Hz, 1 H), 8.38 (d, J = 7.6 Hz, 1 H), 8.47 (s, 1 H). Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.89; H, 5.10; N, 4. 42.

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