The synthesis of 2-arylmethyl-6-hydroxybenzenecarbonitriles from the base-mediated aryne reaction of bromophenols with arylacetonitriles

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A facile one-step synthesis of 2-arylmethyl-6-hydroxybenzenecarbonitriles from readily available arylacetonitriles is described. The substitution pattern was verified by X-ray diffractometric analysis of 2-benzyl-6-hydroxybenzonitrile. An explanation of the addition to and reactivity of the 2,3-didehydrophenoxide intermediate, which is supported by DFT calculations, is presented.

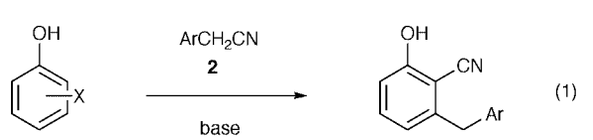
Introduction

Halophenols form aryne intermediates when treated with sodium or potassium amide in liquid ammonia only with difficulty.[1] We have recently shown that the arynes 4-nitro-2,3-didehydrophenoxide[2] and 3,4-didehydropyridine 5-oxide[3] can be readily generated in the presence of α-lithiated arylacetonitriles from the reaction of 2-bromo-4-nitrophenol and 5-chloropyridin-3-ol, respectively, with LDA or LiTMP (lithium 2,2,6,6-tetramethylpiperidinide) in THF.

These reactive intermediates display different reactivities towards the α-lithiated arylacetonitriles. For example, nitrile anion addition occurs regioselectively at the 3-position of 3,4-didehydropyridine 5-oxide to give, after proton quench, simple aryne addition products, *i.e.* α-aryl-α-(3-hydroxy-5-pyridyl)-acetonitriles.[4] However, nitrile anion addition occurs non-regioselectively to both positions of 4-nitro-2,3-didehydrophenoxide. The adduct from 2-addition undergoes intramolecular cyclization to supply benzofurans, whereas the adduct from 3-addition gives benzyl-4-nitro-2-cyanophenols presumably by the tandem addition rearrangement pathway.[5]

Results and discussion

To see if the replacement of the pyridine ring with a benzene might lead to an increase in the rate of the rearrangement pathway, we investigated the reaction of 3-bromo- **1a** and 2-bromophenol **1b** with various arylacetonitriles **2a**–**f** under aryne-forming conditions. In all cases, a 2-arylmethyl-6-hydroxybenzenecarbonitrile **3a**–**f** was obtained as the major product. As shown in eqn. 1, the carbonitriles **3a**–**f** were



(1)

1a X = 3-bromo
1b X = 2-bromo

base = LiTMP or LDA

3a Ar = C_6H_5
3b Ar = 4-$MeOC_6H_4$
3c Ar = pyridin-3-yl
3d Ar = 2-MeC_6H_4
3e Ar = naphthalen-1-yl
3f Ar = 3,4-$(MeO)_2C_6H_3$

obtained in highest yields (48–63%) when **1** was allowed to react with **2a**–**f** in the presence of 2,2,6,6-tetramethylpiperidinide (LiTMP). A minor amount of phenol (5–10%) was also obtained. Monitoring the reaction by GC-MS showed that aryne generation commenced very slowly around −40 °C. However, by allowing the system to warm to room temperature, the reactions were essentially over in 6 h. These reaction temperatures and times, which are significantly higher than those observed for 2-bromo-4-nitrophenol and 5-chloropyridin-3-ol, reflect the lower acidity of the benzenoid hydrogen atoms in **1a**,**b** as compared with the those in the nitrogen-containing aryne analogs.

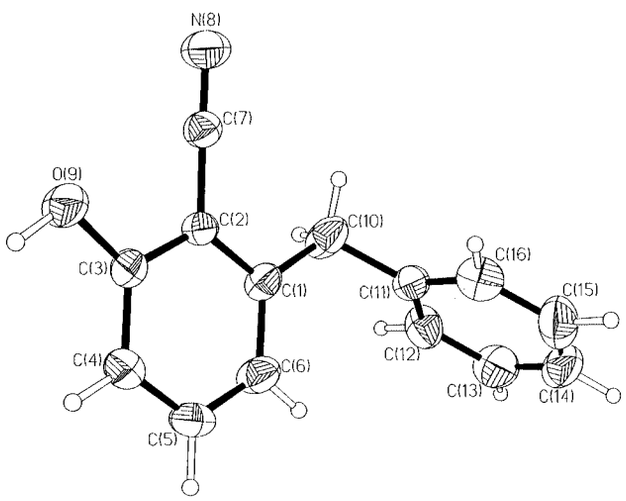
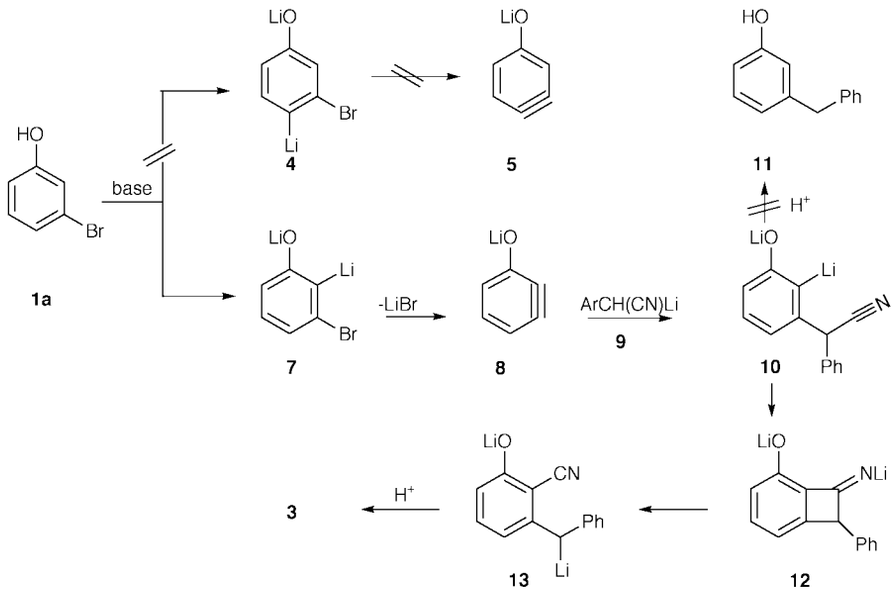


Fig. 1 ORTEP plot of compound **3a**.

The use of LDA, which is less expensive but less sterically demanding than LiTMP, gave lower yields of **3a**–**f** (35–45%) and greater amounts of phenol (10–18%) as compared with the LiTMP-mediated reactions. Also, a 2:3 ratio of 2- and 3-diisopropylaminophenol, respectively, was obtained in 15–25% yields.

The identities of products **3a**–**f** were determined by ^{1}H NMR, ^{13}C NMR and elemental analyses. The regiochemistry of nitrile addition was ascertained by X-ray crystallographic analysis of 2-benzyl-6-hydroxybenzenecarbonitrile **3a**, which is shown in the ORTEP[6] drawing in Fig. 1.

An explanation of these findings is shown in Scheme 1 using the synthesis of **3a** from **1a** as a typical example. As shown, treatment of **1a** with base can, in principle, generate two arynes: 3,4-didehydrophenoxide **5** *via* the 4-lithio derivative **4**, and 2,3-didehydrophenoxide **8**, *via* the 2-lithio derivative **7**. However,



Scheme 1

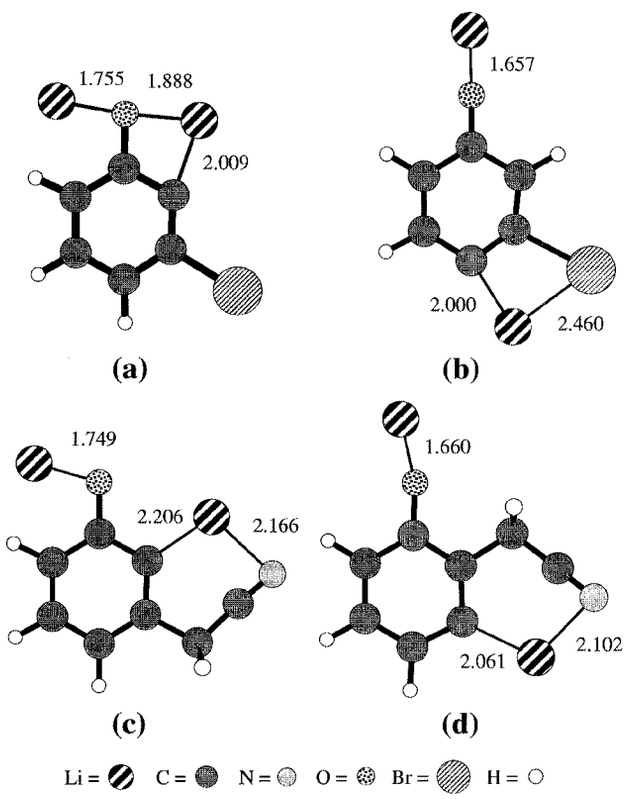


Fig. 2 Computed DFT geometries in Å. Total energies in Hartrees, (a) −2895.35147, (b) −2895.34610, (c) −453.05672, (d) −453.0401. Full structural details can be obtained from the authors on request.

the substitution pattern in the nitrile products **3a**–**f** clearly shows that nitrile addition occurs regioselectively to the 3-position of **8**. DFT calculations suggest that 2-lithiation of **1a**, which yields **7**, the precursor to **8**, is energetically more favored than 4-lithiation, which yields **4**, the precursor to **5**. The optimized structures of **7** and **4** are shown in Figs. 2a and 2b, respectively. The former was computed to be more stable by 14.1 kJ mol^{-1}. This difference seems to be associated with the location of the anionic center in the favorable electrostatic environment between the heteroatoms and is not a consequence of the interesting lithium bridging evident in the computed structure. Thus, the energy difference increased to 49.8 kJ mol^{-1} when the Li^+ ions were excluded, *i.e.* when the calculations were carried out on the carbanions corresponding to the C2 and C4 deprotonated phenols. The nitrile anion **9a**, prepared *in situ* by reaction of the base and **1a**, then adds to the 3-position of **8** affording the aryne-nitrile adduct **10**.

The regioselective 3-addition appears to be due to a similar stabilization of the carbanionic centre adjacent to the OLi group observed in **7**. DFT calculations on the analogous acetonitrile adducts suggest this pathway to be 38.8 kJ mol^{-1} more stable than addition to the 2-position. The computed structures of the dilithium salts are shown in Figs. 2c and 2d. Again, the energy difference was computed to be even greater in the absence of the Li^+ ions (59.3 kJ mol^{-1}), *i.e.* for the analogous structures resulting from addition of the acetonitrile anion to the 2- and 3-positions of 2,3-didehydrophenol.

That no simple nitrile products **11** were observed indicates that adduct **10** preferentially cyclizes to intermediate **12**. This is consistent with previous studies which show that electron-releasing groups (OLi in this case) enhance the cyclization step by increasing the nucleophilicity of the lithiated site in **10**. Ring opening of **12** and proton quenching of the rearranged lithio derivative **13** gives the observed product **3a**.

In addition to introducing two biologically important functional groups concomitantly and regioselectively, the 1,2,3-substitution pattern contained in **3** is difficult to assemble by traditional methods. Indeed, no method is presently available that allows one-step synthesis of **3** from readily available starting materials.

Experimental

General data

Melting points were taken on a Mel-Temp II capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IR™ 550 FTIR spectrometer, and the ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard. Elemental analyses were obtained from E + R Microanalytical Laboratories, Inc., Corona, NY. Bromophenols, arylacetonitriles, 2,2,6,6-tetramethylpiperidine, and *n*-BuLi were purchased from Aldrich Chemical Company. Both the diisopropylamine and the 2,2,6,6-tetramethylpiperidine were refluxed over and distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from Na–benzophenone

Table 1 Analytical data for the benzenecarbonitriles **3a–f**

Compound (Formula)	Yield (%)	Mp/°C[a]	Found (%) (Required %) C	H	N
3a ($C_{14}H_{11}NO$)	48	155–157	80.2 (80.4)	5.2 (5.3)	6.6 (6.7)
3b ($C_{15}H_{13}NO_2$)	54	122–123	75.1 (75.3)	5.4 (5.5)	5.8 (5.85)
3c ($C_{13}H_{10}N_2O$)	46	220–221	74.0 (74.3)	4.7 (4.8)	13.3 (13.3)
3d ($C_{18}H_{13}NO$)	61	125–127	80.1 (80.7)	6.2 (5.9)	6.3 (6.3)
3e ($C_{18}H_{13}NO$)	60	208–209	83.4 (83.4)	5.1 (5.05)	5.4 (5.4)
3f ($C_{16}H_{13}NO_3$)	63	144–145	71.4 (71.6)	5.6 (5.7)	5.2 (5.4)

[a] All products were recrystallized from hexane–ethyl acetate (4:1).

immediately prior to use. The glassware was heated at 125 °C in an oven overnight prior to use. All benzyne reactions were done under an atmosphere of dry oxygen-free N_2 *via* balloon.

General procedure for aryne reactions

In a flame-dried flask flushed with nitrogen, fresh LiTMP or LDA (40 mmol) was prepared by adding *n*-BuLi (40 mmol, 2.5 M in hexane) to a solution of 2,2,6,6-tetramethylpiperidine (6.6 g, 40 mmol) or diisopropylamine (4.0 g, 40 mmol) in THF (50 mL) at −70 °C. After stirring for 10 min, the appropriate arylacetonitrile (20 mmol) was added, and the stirring continued for 20 min to ensure complete anion formation. The bromophenol (0.174 g, 10 mmol) was added and the resulting solution was allowed to warm to room temperature over 6 h. The typical red-colored reaction solution (indicative of a successful base-mediated benzyne reaction) was not achieved until the solution was warmed to room temperature. The reaction was quenched with saturated NH_4Cl solution (30 mL) and then extracted with methylene dichloride. The combined extracts were washed with dilute HCl, then dried (Na_2SO_4) and concentrated (rotary evaporator) to give a crude oily material. Chromatography of this material on silica gel (hexane–ethyl acetate, 4:1) gave the pure product **3a–f**. The yields, mp and elemental analyses for **3a–f** are shown in Table 1 and the spectral data of **3a–f** are given below.

2-Hydroxy-6-(phenylmethyl)benzenecarbonitrile 3a. δ_H(400 MHz; $CDCl_3$) 4.12 (s, 2 H), 6.77 (d, 1 H), 6.82 (d, 1 H), 7.21–7.32 (m, 5 H); δ_C(400 MHz; $CDCl_3$) 39.8 , 100.5, 114.5, 116.2, 122.5, 126.3, 127.9, 130.2, 134.3, 138.5, 138.8, 146.6, 159.6.

2-Hydroxy-6-[(4-methoxyphenyl)methy]benzenecarbonitrile 3b. δ_H(400 MHz; $CDCl_3$) 3.86 (s, 3 H), 4.14 (s, 2 H), 6.87 (t, J = 8.7 Hz, 2 H), 6.92 (d, J = 8.6 Hz, 2 H), 7.21 (d, J = 8.6 Hz, 2 H), 7.40 (t, J = 8.0 Hz, 1 H); δ_C(400 MHz, $CDCl_3$) 39.9, 55.7, 100.4, 114.4, 114.5, 116.2, 122, 130.4, 131.3, 134.6, 147.1, 158.7, 159.8.

2-Hydroxy-6-[(pyridin-3-yl)methyl]benzenecarbonitrile 3c. δ_H(400 MHz; $CDCl_3$) 4.01 (s, 2 H), 6.59 (d, J = 7.6 Hz, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 7.13–7.21 (m, 2 H), 7.48 (d, J = 7.6 Hz, 1 H), 8.36 (d, J = 4.8 Hz, 1 H), 8.41 (s, 1 H); δ_C(400 MHz; $CDCl_3$) 42.5, 105, 119.6, 120.5, 125.5, 128.7, 139.1, 139.9, 141.5, 149.5, 152.9, 155.1, 166.4.

2-Hydroxy-6-[(2′-methylphenyl)methyl]benzenecarbonitrile 3d. δ_H(400 MHz; $CDCl_3$) 2.41 (s, 3 H), 4.19 (s, 2 H), 6.87 (d, J = 7.6 Hz, 1 H), 6.94 (d, J = 8.3 Hz, 1 H), 7.14 (s, 3 H), 7.28 (t, J = 7.8 Hz, 1 H), 7.44 (t, J = 8.1 Hz, 1 H); δ_C(400 MHz; $CDCl_3$) 21.8, 40.7, 100.5, 114.5, 116.1, 122.3, 126.3, 126.4, 127.9, 128.9, 130.1, 134.6, 138.7, 138.9, 146.6, 159.6. Anal. calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.87; H, 6.18; N, 6.25%.

2-Hydroxy-6-[(naphthalen-1-yl)methyl]benzenecarbonitrile 3e. δ_H(400 MHz; $CDCl_3$) 4.69 (s, 2 H), 6.62 (d, J = 7.6 Hz, 1 H), 6.91 (d, J = 8.2 Hz, 1 H), 7.38 (m, 2 H), 7.58 (m, 3 H), 7.90 (d, J = 8.2 Hz, 1 H), 7.97 (m, 2 H); δ_C(400 MHz; $CDCl_3$) 39.5, 100.4, 114.5, 116.1, 122.1, 123.0, 123.5, 126.4, 126.7, 126.8, 127.0, 126.8, 127.2, 128.1, 133.0, 134.0, 147.2, 158.5.

2-Hydroxy-3-[(3′,4′-dimethoxyphenyl)methyl]benzenecarbonitrile 3f. δ_H(400 MHz; $CDCl_3$) 3.86 (s, 3 H), 3.87 (s, 3 H), 4.10 (s, 2 H), 6.80–6.86 (m, 5 H), 7.35 (t, J = 8.0 Hz, 1 H).

X-Ray analysis of 3a

X-Ray analysis of crystals of **3a**† ($C_{14}H_{11}NO$, M 209.02) was carried out on a Bruker AXS P4 diffractometer at 228 K. The crystal was monoclinic space group $P2_1/n$ with unit cell a = 10.496(1), b = 11.407(1), c = 19.715(1) Å, β = 91.53(1)°, V = 2239.9(3) Å^3, Z = 8, D_x = 1.241 g cm^{-3}, μ = 0.079 mm^{-1}. Mo-Kα radiation (λ = 0.71073 Å). 4414 reflections measured, 3944 unique, 2409 with $F \geq 2\sigma(F)$ gave R_1 = 0.047 in a full-matrix, least-squares refinement[7] with 289 parameters.

DFT calculations

DFT calculations were carried out using Density Functional Theory (DFT) as implemented in the Spartan package.[8] Geometries were fully optimized within the constraints of C_S symmetry. Exchange and correlation functions of Becke[9] and Perdew[10] were used with the DN* numerical basis developed by Wavefunction, Inc.[11] The latter is a polarized split-valence basis set designed to mimic the analytical Gaussian basis set 6-31G(d).[12] For computational efficiency non-local corrections to the exchange and correlation functions are added "perturbatively" following convergence of the local density model.[13]

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† CCDC reference number 207/389. See http://www.rsc.org/suppdata/p1/a9/a907980g for crystallographic files in .cif format.

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