Nitrile-Stabilized Carbanions. Nucleophilic Substitution Reactions on Bromopyridines

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A series of bis(2-heteroaryl)acetonitriles were synthesized, characterized, and transformed into the corresponding bis(2-heteroaryl)methanes, which can be readily oxidized with SeO_2 in glacial acetic acid to the respective ketones. These disubstituted acetonitriles are ideal precursors to heterocalixarenes. The configuration in the solid state of *meso*-cyano compound **16** was ascertained by an X-ray crystal structure.

Introduction

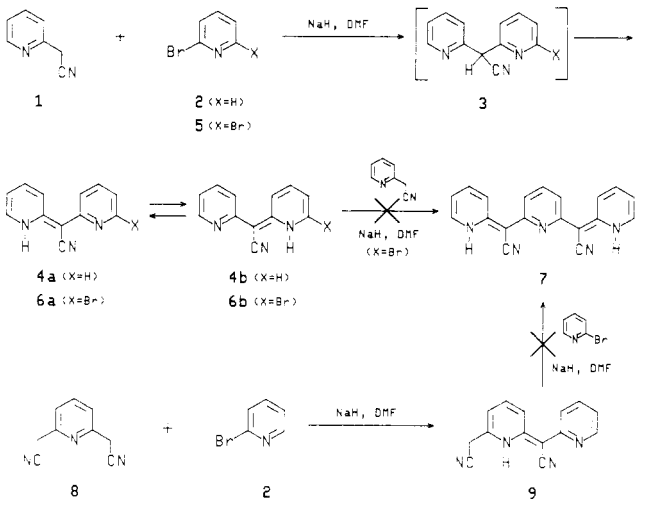
For nearly half a century, Scheibe et al.[2] made significant synthetic and structural contributions to the field of "quinolylmethanes",[3] which have been shown to be fundamental building blocks of many cyanine dyestuffs and possess interesting tautomeric properties. The simplest example of these heteroarylmethanes is di(2-pyridyl)methane, which was generated by the acid hydrolysis of di(2-pyridyl)acetonitrile (**4**), prepared (12%) by heating 2-chloropyridine with $NaNH_2$ and CH_3CN in dry toluene.[3j] In general, the symmetrical di[2(or 4)-heteroaryl]methanes were prepared from the respective 2(or 4)-halogen derivatives with $NaNH_2$ and CH_3CN under similar conditions.

Borr and Haeberer[4] reported an alternate preparation of the related 2(1*H*)-quinolylidenes, in which the sodium salt of cyanoacetamide was reacted with 2-chloroquinoline in DMF to give the high-melting 2-quinolyl-2(1*H*)-quinolylideneacetonitrile in 34% yield. The characteristic IR absorption at 2200 cm^{-1} for the presence of a conjugated nitrile supported the structural assignment. Similarly, the reaction between the sodium salt of cyanoacetamide and 6,6′-dibromo-2,2′-bipyridine[5] gave (20%) a deeply colored tetraaza macrocycle, exhibiting the appropriate nitrile absorption[6] at 2180 cm^{-1}.

Since inclusion of typical electron-withdrawing groups will enhance the acidity of the α-hydrogens of acetonitrile, 2-pyridylacetonitrile has been reported[7] to readily generate the corresponding carbanion. Thus, when 2-pyridylacetonitrile was heated with ethanolic ethoxide, dimer formation was realized; whereas with acetaldehyde and a base, the expected Knoevenagel reaction was demonstrated.

As part of a program directed to the syntheses of new heterocalixarenes,[8] these *meso*-cyano compounds were studied for insight into their physical and chemical properties as well as evaluated as suitable precursors.

Scheme I



Results and Discussion

Syntheses of Pyridylmethanes. Heating 2-pyridylacetonitrile (**1**) with NaH and 2-bromopyridine (**2**) in dry DMF gave (73%) di(2-pyridyl)acetonitrile (**4**) as yellow fibers (Scheme I). The ^1H NMR spectrum of **4** showed a broad singlet at δ 16.3, indicative of a strong N–H··N interaction;[2] interestingly, this proton was not readily exchanged with D_2O at 25 °C. In the aromatic region only the triplet of doublets at δ 6.61 and 7.91 for 5-py*H* and 6-py*H*, respectively, could be assigned; the remainder appeared as a multiplet in the olefinic region. Support for the facile tautomerization in **4** was shown in the ^{13}C NMR data in that six signals for the pyridine and nitrile carbons appeared at the expected positions and the methine carbon uniquely appeared at δ 67.5. The IR spectrum of **4** further supported a conjugated nitrile by the intense absorption at 2190 cm^{-1}.

Under identical reaction conditions, 2-pyridylacetonitrile (**1**) and 2,6-dibromopyridine (**5**) were expected to generate the desired tripyridine **7**; surprisingly, however, **6** was isolated (81%) as yellow fibers along with unchanged starting materials. The ^1H NMR spectrum of **6** exhibited a characteristic broad singlet at δ 15.1 indicative of the N–H··N interaction, and ^{13}C NMR data showed 12 signals

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(2) (a) Scheibe, G.; Rossner, E. *Chem. Ber.* **1920**, *53*, 2064. (b) Scheibe, G. *Chem. Ber.* **1921**, *54*, 786. (c) Scheibe, G.; Schmidt, G. *Chem. Ber.* **1922**, *55*, 3157. (d) Scheibe, G. *Chem. Ber.* **1923**, *56*, 137. (e) Scheibe, G.; Fischer, W. *Chem. Ber.* **1926**, *59*, 502. (f) Scheibe, G.; Reiss, W. *Chem. Ber.* **1959**, *92*, 2189. (g) Scheibe, G.; Friedrich, H. J. *Chem. Ber.* **1961**, *94*, 1336. (h) Scheibe, G.; Friedrich, H. J.; Guckel, W.; Credner, H. H. *Angew. Chem.* **1961**, *73*, 273. (i) Scheibe, G.; Friedrich, H. J.; Hohlneicher, G. *Angew. Chem.* **1961**, *73*, 383. (j) Friedrich, H. J.; Guckel, W.; Scheibe, G. *Chem. Ber.* **1962**, *95*, 1378.

(3) Scheibe, G.; Daltrozzo, E. *Adv. Heterocycl. Chem.* **1966**, *7*, 153.

(4) Borr, A. L.; Haeberer, A. F. *J. Org. Chem.* **1965**, *30*, 243.

(5) Newkome, G. R.; Nayak, A.; Fronczek, F. R.; Kawato, T.; Taylor, H. C. R.; Meade, L.; Mattice, W. *J. Am. Chem. Soc.* **1979**, *101*, 4472.

(6) Ogawa, S.; Narushima, R.; Arai, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5760.

(7) Gutsche, C. D.; Voges, H. W. *J. Org. Chem.* **1967**, *32*, 2685.

(8) (a) Newkome, G. R.; Joo, Y. J.; Theriot, K. J.; Fronczek, F. R. *J. Am. Chem. Soc.* **1986**, *108*, 6074. (b) Newkome, G. R.; Joo, Y. J.; Fronczek, F. R. *J. Chem. Soc., Chem. Commun.* **1987**, 854.

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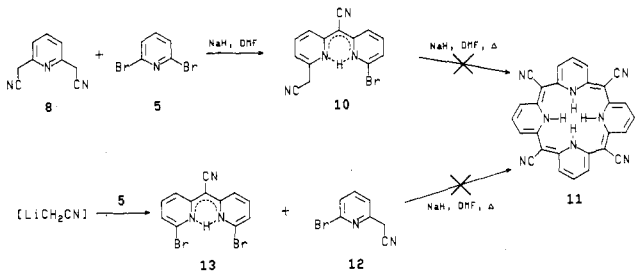
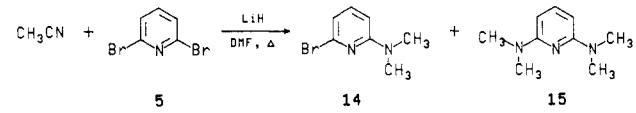
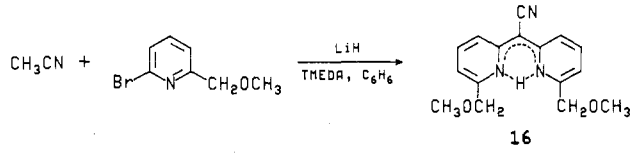
Scheme II



Scheme III



Scheme IV



including the signal at δ 68.4 for the methine bridge carbon. The absorption (IR) at 2185 cm^{-1} was again characteristic of a conjugated nitrile. The MS data for **6** were dominated by two peaks at *m/e* 275 and 273 with the ratio 4:5 of the relative intensities, corresponding to the isotopically different molecular ions.

The reaction conditions were modified (reaction time, solvent/temperature, base–catalyst) in an attempt to prepare **7**, all to no avail. At this juncture, a different approach was attempted, in which the sodium salt of 2,6-bis(cyanomethyl)pyridine (**8**), prepared from the corresponding bis(chloromethyl)pyridine with cyanide, and 2-bromopyridine (**2**) were warmed in DMF. *Only* 2-pyridyl[6′-(cyanomethyl)-2′-pyridyl]acetonitrile (**9**) could be isolated (36%). This structural assignment of **9** was confirmed by (^{1}H NMR) the singlet at δ 4.00 for CH_2CN and a characteristic broad singlet at δ 15.8 for the N*H* proton. Further supportive ^{13}C NMR data showed 14 signals including the methine bridge carbon at δ 75.5. The IR spectrum displayed *both* conjugated and nonconjugated nitrile peaks at 2180 and 2250 cm^{-1}, respectively.

Application of this nucleophilic substitution of α-pyridyl carbanions to prepare heteromacrocycle **11** was attempted (Scheme II). The general procedure required careful control of the temperature (120 °C) in DMF to prevent unwanted side reactions as well as to prevent the decomposition of DMF. Macrocycle **11** was not detected (<3%), but instead, **10** was isolated (75%) as yellow fibers. The ^{1}H NMR spectrum of **10** exhibited a singlet at δ 5.41 assigned to the α-methylene protons and a broad singlet at δ 15.6, typical of the bridging hydrogen. The MS data for **10** were again dominated by two peaks at *m/e* 314 and 312, corresponding to the relative intensities of the isotopically different molecular ions.

Abstraction of an α-hydrogen from CH_3CN in liquid ammonia by means of $NaNH_2$ generates the desired sodioacetonitrile, as demonstrated by subsequent alkylation[9] and benzoylation.[10] Successful monoalkylations of primary nitriles have generally employed strong bases, such as alkali metal hydrides, amides, dialkyl amides, bis(trimethylsilyl) amides, or alkyl(aryl)lithium reagents[11] to generate high concentrations of the requisite nitrile carbanions, which were subsequently trapped with primary or secondary alkyl halides.

Sodium and lithium hydrides react slowly with active methylene compounds bearing only one electron-withdrawing group; thus their use has been limited to the alkylation of (hetero)arylacetonitriles. The convenience in handling these hydride reagents, relative to $NaNH_2$, offset the diminished yields[12] of alkylated products occasionally encountered with the use of NaH rather than $NaNH_2$.

Generally, the use of LiH (NaH) for the alkylation of aliphatic acetonitriles leads to extensive polymerization[13] under the usual heterogeneous conditions.

In hopes of ultimately synthesizing bis(6-bromo-2-pyridyl)acetonitrile (**13**), we used *n*-BuLi in *n*-hexane in the generation of $LiCH_2CN$ at −70 °C. Lithioacetonitrile with 2,6-dibromopyridine (**5**) gave, along with unchanged starting **5** and 6-bromo-2-pyridylacetonitrile (**12**, 27%), only traces of the desired **13**. The ^{1}H NMR spectrum of **12** exhibited a singlet at δ 3.93 for CH_2CN, while the ^{13}C NMR spectrum showed seven signals. The MS data were again dominated by two peaks at *m/e* 198 and 196 with the appropriate relative intensities. When **12** was treated with NaH in DMF, macrocyclization to give **11** did not occur but rather **12** was recovered unchanged.

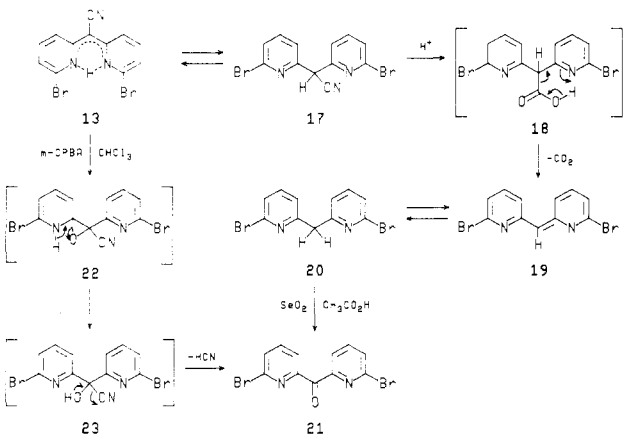
Contrary to results with alkyllithiums, LiH (NaH) reacted too slowly with CH_3CN in dry DMF at 25 °C to generate lithio- or sodioacetonitrile within a reasonable time frame, whereas at elevated (100 °C) temperatures, the solvent (DMF) decomposed with hydride to give the amide ion, which subsequently reacted with 2,6-dibromopyridine (**5**) to give (*N,N*-dimethylamino)pyridines (**14** and **15**), as well as traces of **13** (Scheme III). The ^{1}H NMR spectrum of **14** exhibited a singlet at δ 3.05 for two *N*-methyl groups, two doublets at δ 6.35 and 6.65 for 3- and 5-py*H*, respectively, and a doublet of doublets at δ 7.23 for 4-py*H*. The MS data showed two peaks at *m/e* 202 and 200 for the molecular ions possessing one residual bromine. Disubstituted **15** was confirmed (^{1}H NMR) by a singlet at δ 3.02 for the *N*-methyls, a doublet at δ 5.80 for the 3,5-py*H*, and a triplet at δ 7.27 assigned to the 4-py*H*.

The use of refluxing *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)/benzene as cosolvents retarded this side reaction; thus, $LiCH_2CN$ with 2,6-dibromopyridine gave 47% of the desired **13**, which was identified by its characteristic ^{1}H NMR spectrum consisting of a complex olefinic–aromatic region as well as the broad singlet at δ 16.0 for the bridging hydrogen. The ^{13}C NMR spectrum of **13** appeared as the typical seven signals including the methine carbon at δ 64.5. The IR spectrum showed a conjugated nitrile absorption at 2200 cm^{-1}. The MS data were dominated by three peaks at *m/e* 355, 353, and 351 in a 1:2:1 ratio corresponding to the isotopically different molecular ions.

The reaction between CH_3CN and 2-(methoxymethyl)-6-bromopyridine[14] with LiH in 5% TMEDA/benzene gave bis[6-(methoxymethyl)-2-pyridyl]acetonitrile (**16**), as yellow needles (Scheme IV). The ^{1}H NMR spectrum of **16** showed a characteristic broad singlet at δ 16.4 indicative of the N–H interaction and two singlets at δ 3.49 and 4.52 for CH_3O and CH_2O, respectively; a triplet

(9) Bergstrom, F. W.; Agostinho, R. *J. Am. Chem. Soc.* **1945**, *67*, 2152.
(10) Hauser, C. R.; Eby, L. J. *J. Am. Chem. Soc.* **1957**, *79*, 728.
(11) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React. (N.Y.)* **1984**, *31*, 1 and references therein.
(12) Goermer, G. L.; Holzschuh, A. A. *J. Org. Chem.* **1958**, *23*, 1346.
(13) Kaiser, E. M.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402.
(14) Pappalardo, S., unpublished results.

Scheme V



of doublets at δ 6.60 for 5-py*H*; a doublet at δ 7.34 for 3-py*H*; and a triplet at δ 7.56 for 4-py*H*. The MS data were dominated by the parent peaks at *m/e* 284 and 283 possessing the appropriate intensity ratio. Spectroscopic evidence agreed with tautomeric equilibrium in solution via N–H forming a bifurcated hydrogen bond.

The characteristic spectral features of these *meso*-cyano compounds are the conjugated nitrile absorption (IR) in the range of 2160–2200 cm^{-1}, a broad singlet (^1H NMR) at δ 15.7 ± 0.8 ($CDCl_3$) for the N–H··N bond, and the signals (^{13}C NMR) in the region of δ 70 ± 6 for the methine-bridge sp^2-carbon atoms. Other physical features are typically high melting points, compared to structural counterparts, and low solubility in common organic solvents, which frequently poses purification and characterization problems.

In order to generate the appropriate heteroaryl connecting groups possessing limited functionality, we attempted conversion of the R_2CHCN moiety to $R_2C{=}O$ (Scheme V). The nitrile group of **13** was easily removed by means of acidic conditions to afford (81%) **20** as colorless needles. The process was monitored by the appearance (^1H NMR) of a singlet at δ 4.27 for the free methylene; the 3-py*H* appeared as a multiplet at δ 7.19, and there were two doublets of doublets at δ 7.37 and 7.58 for 5- and 4-py*H*, respectively. A possible reaction pathway for the loss of the nitrile can be envisioned to proceed through intermediate **18** from tautomer **17** via a six-center transition state[15] to generate **19**. The oxidation[16] of the CH_2 to desired ketone **21** was accomplished with SeO_2 in glacial acetic acid to give (72%) the known bis(6-bromo-2-pyridyl) ketone (**21**).[17]

An alternate procedure to directly convert R_2CHCN to $R_2C{=}O$ (**13** to **21**) circumvented the acidic conditions. The first step involved a facile epoxidation[18] of the exocyclic double bond in **13** with *m*-chloroperbenzoic acid to afford intermediate **22**, which underwent a facile rearrangement to give the cyanohydrin **23**, which smoothly eliminated cyanide to afford (>90%) **21**.

Finally, it was deemed necessary to obtain firm bond data and insight into the structural orientations of the rings so necessary for subsequent macrocyclization. The crystal structure[19] of **16** is presented in Figure 1, which confirms the desired configuration in the solid state; C8 (methine) is planar, and only one of the pyridyl units is protonated. The NH [bond length 0.931 (12) Å] hydrogen forms a bifurcated hydrogen bond with H(N1)–N3 [1.876 (12) Å] and H(N1)–O1 [2.219 (11) Å]. The major features of its solid-state conformation are described by several key torsion angles (Table I). Torsion angles O1–C2–C3–N1 and N3–C14–C15–O2 are 6.7° and 175.7°, respectively, because of hydrogen bonding H(N1)–O1 and non-hydrogen bonding H(N1)--O2. An average torsion angle of N1–C7–C8–C9 and N3–C10–C8–C9 is 179.1°, indicating that the dipyridylmethine unit is nearly planar. The N1 pyridine forms dihedral angles of 4.9° and 1.6° with N2 pyridine and the best plane containing the nitrile, respectively, which form a dihedral angle of 3.4° with each other. Bond angles of C7–C8–C9, C7–C8–C10, and C9–C8–C10 are 116.8 (1)°, 125.9 (1)°, and 117.2 (1)°, respectively. The bond length of C7–C8 [1.410 (1) Å, methine to a protonated pyridine] is shorter than that of C8–C10 [1.452 (1) Å, methine to an unprotonated pyridine]; however, both bond lengths are longer than double bonds (ca. 1.32 Å), but shorter than single bonds [C2–C3 and C14–C15 are 1.498 (2) and 1.496 (1) Å, respectively]. These bond-length data afford a rationale as to why the methine carbon resonances (^{13}C NMR) appear at δ 70 ± 6 instead of in the double-bond region. The protonated pyridine ring is more distorted than the unprotonated pyridine ring [C3–C4, 1.357 (1) Å; C13–C14, 1.385 (1) Å]. However, C4–C5 [1.400 (2) Å] and C6–C7 [1.418 (1) Å] are longer than C12–C13 [1.385

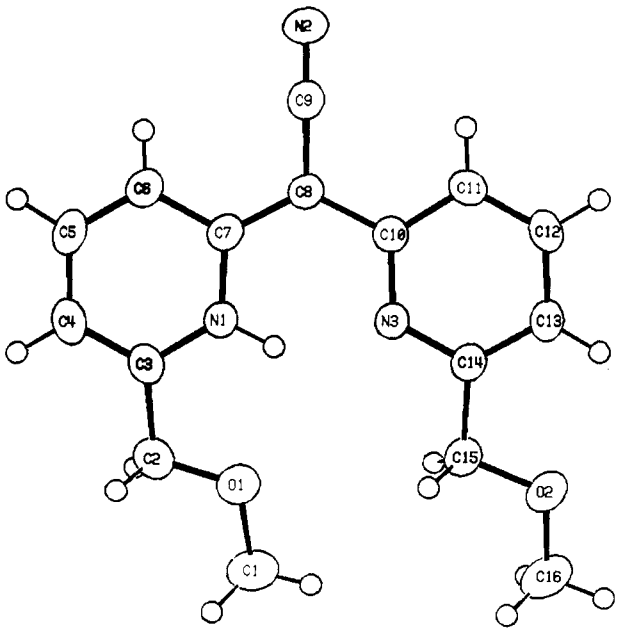


Figure 1. **16**, illustrating molecular conformation and numbering scheme.

Table I. Important Torsion Angles (Degrees) for 16

atoms	angle (deg)	atoms	angle (deg)
C1–O1–C2–C3	-175.3	N3–C10–C8–C9	179.3
O1–C2–C3–N1	6.7	N3–C14–C15–O2	175.7
N1–C7–C8–C9	-178.8	C14–C15–O2–C16	-172.8

(15) (a) Swain, C. G.; Bader, R. F. W.; Esteve, R. M.; Griffin, R. N. *J. Am. Chem. Soc.* **1961**, *83*, 1951. (b) House, H. O. *Modern Synthetic Reactions*; Benjamin: California, 1972; pp 510–512.

(16) (a) Rabjohn, N. *Org. React. (N.Y.)* **1968**, *5*, 331. (b) Lee, H. W. Ph.D. Dissertation, Louisiana State University, 1983. (c) Newkome, G. R.; Lee, H. Y. *J. Am. Chem. Soc.* **1983**, *105*, 5958.

(17) (a) Parks, J. E.; Wagner, B. E.; Holm, R. H. *J. Organomet. Chem.* **1973**, *56*, 53. (b) Newkome, G. R.; Taylor, H. C. R.; Fronczek, F. R.; Delord, T. J. *J. Org. Chem.* **1984**, *49*, 2961.

(18) Newkome, G. R.; Joo, Y. J.; Evans, D. W.; Fronczek, F. R., to be submitted for publication in *J. Org. Chem.*

(19) Crystal data for **16**: $C_{16}H_{17}N_3O_2$, M_r 283.3, triclinic space group $P\bar{1}$, a = 7.5310 (6) Å, b = 9.9577 (12) Å, c = 11.0301 (12) Å, α = 65.957 (10)°, β = 73.652 (8)°, γ = 85.889 (8)°, Z = 2, D_{calcd} = 1.300 g cm^{-3}, μ(Mo Kα) = 0.82 cm^{-1}, R = 0.046 for 2137 observations (of 3171 unique data), 1° < θ < 27°, 235 variables. All H atoms except CH_3 were refined.

(1) Å] and C10–C11 [1.401 (1) Å], respectively. These bond-length data corroborate the fact that the three shorter bond lengths (C3–C4, C5–C6, and C7–C8) have more double-bond character than C4–C5, C6–C7, and C8–C10; C7–C8 and C8–C10 are 1.410 (1) and 1.452 (1) Å, respectively.

Experimental Section

General Comments. Uncorrected melting points were measured in capillary tubes with either a Thomas-Hoover Unimelt or Laboratory Devices Mel-Temp apparatus for samples melting below or above 260 °C, respectively. Infrared (IR) spectra were recorded with a Perkin-Elmer 621 grating spectrophotometer. ^{1}H NMR spectra were measured with a Bruker WP-80, AC-100, WP-200, or AM-400 spectrometer in $CDCl_3$, unless otherwise noted, containing Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on a Bruker WP-80 spectrometer operating at 20 MHz or a Bruker WP-200 spectrometer operating at 50 MHz; the middle peak of the $CDCl_3$ triplet was used as reference.

Mass spectral (MS) data were obtained by H. M. Land (L.S.U.) on a Hewlett-Packard Model 5985 GC/MS spectrometer and are recorded herein as (assignment, relative intensity). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The X-ray data were collected on an Enraf-Nonius CAD4 diffractometer equipped with Mo Kα (λ = 0.71073 Å) radiation and a graphite monochromator. Crystallographic calculations were conducted with the programs MULTAN and the Enraf-Nonius Structure Determination Package on a digital PDP 11/34 computer.

The recorded R_f values were determined by a standard thin-layer-chromatography (TLC) procedure using Baker-flex silica gel IB2-F or alumina IB2-F without activation eluted with the stipulated solvent system. Preparative thick-layer chromatography (ThLC) was performed on 20 × 40 cm glass plates coated with a 2-mm layer of Brinkmann silica gel P/UV-254-366 or Brinkmann EM-aluminum oxide PF-254 type T activated at 115 °C for a minimum of 4 h before use, using the stimulated solvent. Column chromatography was performed by using either silica gel (Baker, 60–200 mesh) or aluminum oxide (Brinkmann EM, neutral, activity I, 70–230 mesh).

Unless otherwise indicated, all of the chemicals used were reagent grade, and no additional purification was necessary. Benzene and toluene were distilled over sodium and stored over molecular sieves (Linde type 4A). Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately before use. Acetonitrile was distilled[20] over P_2O_5 (0.5–1.0%, w/v) after drying over molecular sieves (Linde type 4A) and stored under N_2. *N,N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled[21] from CaH_2 at reduced pressure and stored over molecular sieves (Linde type 4A) under an argon atmosphere. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was dried over molecular sieves (Linde type 4A), distilled from *n*-butyllithium (2.5 N, *n*-hexane, 5% v/v), and stored under N_2.[22]

Bis(2-pyridyl)acetonitrile (4). Oil-free NaH (980 mg, 41 mmol) was added to a stirred solution of 2-(cyanomethyl)pyridine (1; 1.21 g, 10.3 mmol) in dry DMF (100 mL) at 25 °C under a N_2 atmosphere. Upon addition of NaH, the pale yellow solution changed to an orange mixture. When a sample (1 mL) of the orange mixture was quenched with D_2O, the ^{1}H NMR spectrum showed the absence of the methylene hydrogens (δ 3.91) for **1**. After 30 min, 2-bromopyridine (**2**) (0.98 mL; 1.62 g, 10.3 mmol) was added at 25 °C. The resultant dark brown mixture was heated to 90 °C for 6 h, and then the reaction mixture was cooled to 25 °C and quenched with water. The mixture was concentrated in vacuo, made acidic with 0.1 N HCl, and extracted with $CHCl_3$ (2 × 100 mL). The combined organic extract was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting yellow solid was column chromatographed (silica gel, DCM) and recrystallized from $CHCl_3$/benzene to afford (73%) **4**, as yellow fibers: 1.45 g; mp 129–130 °C (lit.[2i] mp 129 °C); R_f 0.34; ^{1}H NMR δ 6.61 (td, 5-py*H*, *J* = 5.9, 2.1 Hz, 2 H), 7.44 (m, 3,4-py*H*, 4 H), 7.91 (dt, 6-py*H*, *J* = 5.7, 1.3 Hz, 2 H), 16.3 (br s, N*H*); ^{13}C NMR δ 67.5 (*C*CN), 112.5 (*C*5), 119.3 (*C*3), 122.0 (*C*≡N), 136.2 (*C*4), 139.1 (*C*6), 155.1 (*C*2); IR (KBr) 2190 cm^{-1} (C≡N); MS, *m/e* 196 (M$^+$ + 1, 8), 195 (M$^+$, 75), 194 (M$^+$ – H, 100), 169 (M$^+$ – CN, 64).

2-Pyridyl(6'-bromo-2'-pyridyl)acetonitrile (6). A mixture of 2-(cyanomethyl)pyridine (**1**; 490 mg, 4.2 mmol), oil-free NaH (400 mg, 16.6 mmol), 2,6-dibromopyridine (**5**; 490 mg, 2.1 mmol), and dry DMF (100 mL) was heated to 120 °C for 16 h under a N_2 atmosphere. After cooling to 25 °C, the mixture was quenched with water, concentrated in vacuo, and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give a yellow solid, which was chromatographed (silica gel, DCM) and recrystallized from $CHCl_3$/hexane to afford (81% from **5**) **6**, as yellow fibers: 460 mg; mp 157–158 °C; R_f 0.39; ^{1}H NMR δ 6.49 (m, 5-py*H*, 1 H), 6.97 (dd, 5'-py*H*, *J* = 5.0, 2.2 Hz, 1 H), 7.37 (m, 3,4,3',4'-py*H*, 4 H), 7.6 (m, 6-py*H*, 1 H), 15.1 (br s, N*H*); ^{13}C NMR δ 68.4 (*C*CN), 110.5 (*C*5), 117.3 (*C*5'), 119.1 (*C*3), 121.3 (*C*≡N), 133.4 (*C*3'), 137.4 and 137.6 (*C*4,4'), 138.4 (*C*6), 138.6 (*C*6'), 152.7 (*C*2'), 158.5 (*C*2); IR (KBr) 2185 cm^{-1} (C≡N); MS, *m/e* 275 [M$^+$(^{81}Br), 80], 274 [M$^+$(^{81}Br) – H, 76], 273 [M$^+$(^{79}Br), 100], 272 [M$^+$(^{79}Br) – H, 72], 249 [M$^+$(^{81}Br) – CN, 63], 247 [M$^+$(^{79}Br) – CN, 66], 194 (M$^+$ – Br, 37), 193 (M$^+$ – HBr, 42), 167 (M$^+$ – CHNBr, 26). Anal. Calcd for $C_{12}H_8BrN_3$: C, 52.58; H, 2.94; N, 15.33. Found: C, 52.65; H, 3.11; N, 15.66.

2-Pyridyl[6'-(cyanomethyl)-2'-pyridyl]acetonitrile (9). Oil-free NaH (570 mg, 24 mmol) was added to a solution of 2,6-bis(cyanomethyl)pyridine[23] (**8**; 470 mg, 3.0 mmol) in dry DMF (100 mL) under a N_2 atmosphere at 25 °C. Upon addition of NaH, the color changed from pale yellow to bright brown. 2-Bromopyridine (**2**; 950 mg, 6.0 mmol) was added to this brown suspension, and then the mixture was heated to 90 ± 5 °C for 7 h. After cooling, the mixture was quenched with water, concentrated in vacuo, and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give a yellow solid, which was chromatographed (silica gel, DCM) and recrystallized from DCM/hexane to afford (36%) **9**, as yellow needles: 250 mg; mp 246–248 °C; R_f 0.25; ^{1}H NMR δ 4.00 (s, CH_2CN, 2 H), 6.73 (m, 5-py*H*, 1 H), 7.60 (m, 3,4,3',4',5'-py*H*, 5 H), 8.63 (d, 6-py*H*, *J* = 4.0 Hz, 1 H), 15.8 (br s, N*H*); ^{13}C NMR δ 27.2 (*C*H$_2$), 75.5 (*C*CN), 111.1 (*C*5'), 114.2 (*C*5), 118.6 (*C*3'), 121.6 (*C*3), 122.7 and 123.3 (*C*≡N), 134.9 (*C*4'), 137.9 and 138.1 (*C*4,6), 146.7 (*C*6'), 153.7 and 154.3 (*C*2,2'); IR (KBr) 2250, 2180 cm^{-1} (C≡N); MS, *m/e* 235 (M$^+$ + 1, 17), 234 (M$^+$, 100), 233 (M$^+$ – H, 80), 208 (M$^+$ – CN, 58), 207 (M$^+$ – CHN, 21). Anal. Calcd for $C_{14}H_{10}N_4 \cdot H_2O$: C, 69.65; H, 4.80; N, 22.21. Found: C, 69.80; H, 4.75; N, 22.57.

(6-Bromo-2-pyridyl)[6'-(cyanomethyl)-2'-pyridyl]acetonitrile (10). A mixture of LiH (250 mg), 2,6-bis(cyanomethyl)pyridine (**8**; 420 mg, 2.7 mmol), and 2,6-dibromopyridine (**5**; 630 mg, 2.7 mmol) in dry TMEDA (5 mL) and dry benzene (95 mL) was refluxed for 2 days under a N_2 atmosphere. The resulting yellow mixture was quenched with water and concentrated in vacuo. The yellow solid was dissolved in DCM, which was washed with aqueous saturated $NaHCO_3$, and dried over anhydrous $MgSO_4$. Evaporation of the extract in vacuo gave a yellow solid, which was chromatographed (silica gel, DCM) and recrystallized from DCM/hexane to give (75%) pure **10**, as yellow fibers: 640 mg; mp 255–257 °C; R_f 0.76 (10% EtOH/DCM); ^{1}H NMR δ 5.41 (d, CH_2, *J* = 2.0 Hz, 2 H), 6.72 (dt, 5'-py*H*, *J* = 6.3, 2.0 Hz, 2 H), 6.96 (dd, 3'-py*H*, *J* = 6.1, 2.3 Hz, 2 H), 7.26–7.73 (m, 3,4,5,4'-py*H*, 4 H), 15.6 (br s, N*H*, 1 H); IR (KBr) 2245, 2190 cm^{-1} (C≡N); MS, *m/e* 314 [M$^+$(^{81}Br), 95], 313 [M$^+$(^{81}Br) – H, 55], 312 [M$^+$(^{79}Br), 100], 288 [M$^+$(^{81}Br) – CN, 89], 286 [M$^+$(^{79}Br) – CN, 90], 274 [M$^+$(^{81}Br) – C_2H_2N, 27], 272 [M$^+$(^{79}Br) – C_2H_2N, 28], 232 (M$^+$ – HBr, 20). Anal. Calcd for $C_{14}H_9BrN_4 \cdot H_2O$: C, 50.77; H, 3.34; N, 13.92. Found: C, 50.91; H, 2.90; N, 14.03.

(6-Bromo-2-pyridyl)acetonitrile (12). To a stirred solution of *n*-BuLi (1.6 N/hexane; 4.3 mL, 6.9 mmol) at –70 °C under a N_2 atmosphere was rapidly added dry THF (50 mL), followed

(20) Coetzee, J. F. *Pure Appl. Chem.* **1966**, *13*, 429.
(21) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: New York, 1980; 2/e.
(22) Hay, J. N.; McCabe, J. F.; Robb, J. C. *J. Chem. Soc., Faraday Trans. 1* **1972**, *68*, 1.
(23) Baker, W.; Buggle, K. M.; McOmie, J. F. W.; Watkins, D. A. M. *J. Chem. Soc.* **1958**, 3594.

immediately by a solution of dry MeCN (400 μL; 320 mg, 7.7 mmol) in dry THF (20 mL) added over a 5-min period. After 1 h below −70 °C, the resulting white suspension was treated with 2,6-dibromopyridine (**5**; 540 mg, 2.3 mmol). The pale yellow solution was stirred for 1 h at −70 °C and then warmed to 25 °C before quenching with water. The organic solvent was evaporated in vacuo to give a yellowish residual solid, which was dissolved in DCM. The organic layer was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$ to give the crude product, which was recrystallized from hexane to afford (27%) **12**, as white needles: 120 mg; mp 43.0–43.5 °C; R_f 0.46; ^{1}H NMR δ 3.93 (s, CH_2, 2 H), 7.42 (m, 3,5-py$H$, 2 H), 7.63 (t, 4-py$H$, J = 7.0 Hz, 1 H); ^{13}C NMR δ 22.6 (CH_2), 121.0 (C3), 122.8 (C≡N), 127.6 (C5), 130.9 (C2), 139.6 (C4), 142.2 (C6); MS, m/e 198 [M^+(^{81}Br), 52], 196 [M^+(^{79}Br), 48], 117 (M^+ − Br, 100), 90 (M^+ − CNBr, 64). Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.47; H, 2.54; N, 13.74.

Bis(6-bromo-2-pyridyl)acetonitrile (13). To a stirred mixture of LiH (1.0 g, 125 mmol) in dry TMEDA (10 mL) and dry toluene (250 mL) at 25 °C under a N_2 atmosphere was added dry MeCN (1.1 mL; 860 mg, 21 mmol). The resulting white suspension was treated with 2,6-dibromopyridine (**5**; 5.04 g, 21 mmol), and the pale yellow suspension was refluxed for 2 days and then poured onto ice–water/HCl. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with aqueous saturated NaCl and dried over anhydrous $MgSO_4$. The organic solvent was then evaporated in vacuo to give a yellow solid, which was column chromatographed (alumina, DCM) and recrystallized from DCM/cyclohexane to give (47%) **13**, as yellow fibers: 1.77 g; mp 163–164 °C; R_f 0.40 (DCM); ^{1}H NMR δ 6.61 (m, 5-py$H$, 2 H), 7.51 (m, 3,4-py$H$, 4 H), 16.0 (br s, NH); ^{13}C NMR δ 64.5 (CCN), 116.2 (C5), 118.5 (C3), 121.8 (C≡N), 128.2 (C4), 138.2 (C6), 141.6 (C2); IR (KBr) 2200 cm^{-1} (C≡N); MS, m/e 355 [M^+(^{2}^{81}Br), 45], 354 [M^+(^{2}^{81}Br) − H, 35], 353 [M^+(^{81}Br^{79}Br), 100], 352 [M^+(^{81}Br^{79}Br) − H, 53], 351 [M^+(^{2}^{79}Br), 54], 329 [M^+(^{2}^{81}Br) − CN, 40], 327 [M^+(^{81}Br^{79}Br) − CN, 85], 325 [M^+(^{2}^{79}Br) − CN, 40]. Anal. Calcd for $C_{12}H_7Br_2N_3$: C, 40.83; H, 2.00; N, 11.90. Found: C, 41.16; H, 2.11; N, 11.92.

6-Bromo-2-(dimethylamino)pyridine (14) and 2,6-Bis(dimethylamino)pyridine (15). A mixture of **5** (3.44 g, 14.5 mmol), oil-free LiH (610 mg, 76 mmol), MeCN (310 mg, 7.6 mmol), and dry DMF (50 mL) was heated to 120 °C for 24 h under a N_2 atmosphere. After cooling to 25 °C, the mixture was quenched with water, concentrated in vacuo, and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a dark brown oil, which was chromatographed (silica gel, DCM) to afford two major products.

Fraction A was recrystallized from C_6H_{12} to give (35%) 6-bromo-2-(dimethylamino)pyridine (**14**), as colorless microcrystals: 1.02 g; mp 56–57 °C; R_f 0.71; ^{1}H NMR δ 3.05 (s, CH_3, 6 H), 6.35 (dd, 3-py$H$, J = 8.4, 0.5 Hz, 1 H), 6.65 (dd, 5-py$H$, J = 7.0, 0.5 Hz, 1 H), 7.23 (dd, 4-py$H$, J = 8.4, 7.5 Hz, 1 H); MS, m/e 202 [M^+(^{81}Br), 58], 200 [M^+(^{79}Br), 59], 187 [M^+(^{81}Br) − CH_3, 48], 185 [M^+(^{79}Br) − CH_3, 43], 173 [M^+(^{81}Br) − C_2H_5, 93], 171 [M^+(^{79}Br) − C_2H_5, 100]. Anal. Calcd for $C_7H_9BrN_2 \cdot {}^1/_4C_6H_{12}$: C, 45.96; H, 5.45; N, 10.62. Found: C, 46.49; H, 5.17; N, 10.87.

Fraction B was recrystallized from C_6H_{12} to afford 2,6-bis(dimethylamino)pyridine (**15**), as a colorless solid: 360 mg; mp 31–32 °C (lit.[24] mp 33–34 °C); R_f 0.33; ^{1}H NMR δ 3.02 (s, CH_3, 12 H), 5.80 (d, 3-py$H$, J = 8.0 Hz, 2 H), 7.27 (t, J = 8.0 Hz, 1 H); MS, m/e 166 (M^+ + 1, 26), 165 (M^+, 100), 150 (M^+ − CH_3, 46), 136 (M^+ − C_2H_5, 69), 121 (M^+ − C_3H_8, 31).

Bis[6-(methoxymethyl)-2-pyridyl]acetonitrile (16) was prepared from 2-bromo-6-(methoxymethyl)pyridine [^{1}H NMR δ 3.47 (s, OCH_3, 3 H), 4.55 (s, py$H$, 2 H), 7.2–7.7 (m, py$H$, 3 H)] by the same procedure used for **13**: ^{1}H NMR δ 3.49 (s, OCH_3, 6 H), 4.52 (s, pyCH_2, 4 H), 6.60 (td, 5-py$H$, J = 6.5, 0.8 Hz, 2 H), 7.34 (dd, 3-py$H$, J = 8.0, 0.5 Hz, 2 H), 7.56 (t, 4-py$H$, J = 8.3 Hz, 2 H), 16.4 (br s, NH, 1 H); MS, m/e 284 (M^+ + 1, 14), 283 (M^+, 86), 253 (M^+ − C_2H_6, 27), 223 (M^+ − $C_2H_4O_2$, 100); X-ray details in supplementary data.

Bis(6-bromo-2-pyridyl)methane (20). A mixture of **13** (740 mg, 2.1 mmol) in concentrated HCl (50 mL) and EtOH (50 mL) was refluxed for 8 h. The resulting colorless solution was carefully neutralized with NaOH (15 g) and extracted with $CHCl_3$. The combined organic layer was washed with aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated in vacuo to afford (81%) **20**, as colorless needles after recrystallization from DCM/EtOH: 560 mg; R_f 0.20 (DCM); ^{1}H NMR δ 4.27 (s, CH_2, 2 H), 7.19 (m, 3-py$H$, 2 H), 7.37 (dd, 5-py$H$, J = 9.0, 3.2 Hz, 2 H), 7.58 (t, 4-py$H$, J = 7.7 Hz, 2 H). Anal. Calcd for $C_{11}H_8Br_2N_2$: C, 40.28; H, 2.46; N, 8.54. Found: C, 40.36; H, 2.50; N, 8.33.

Bis(6-bromo-2-pyridyl) Ketone (21). Method A. A mixture of **20** (240 mg, 0.73 mmol) and SeO_2 (280 mg) in glacial AcOH (20 mL) was refluxed for 22 h. The mixture was filtered through a Celite pad and concentrated in vacuo to dryness, and then the residue was dissolved in $CHCl_3$. The organic layer was washed with aqueous saturated $NaHCO_3$ and aqueous saturated NaCl and dried over anhydrous $MgSO_4$ to yield (72%) **21**:[17] 180 mg.

Method B. A stirred mixture of *m*-chloroperbenzoic acid (240 mg, 85%, 1.2 mmol) and **13** (380 mg, 1.1 mmol) in $CHCl_3$ (50 mL) was maintained at 0 °C for 5 h. The colorless solution was washed with aqueous saturated $NaHCO_3$, then aqueous saturated NaCl, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give **21**, which was recrystallized (90%) from $CHCl_3$/EtOH: 330 mg.

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Supplementary Material Available: Tables of atomic coordinates, bond distances, bond angles, and anisotropic thermal parameters for **16** ($C_{16}H_{17}N_3O_2$) (4 pages). Ordering information is given on any current masthead page.

(24) Gompper, R.; Heinemann, U. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 297.