The Synthesis of Poly-Nitrile Aromatic and Oligopyridine Ligands Via Palladium-Catalyzed Cyanation of Aryl Halides

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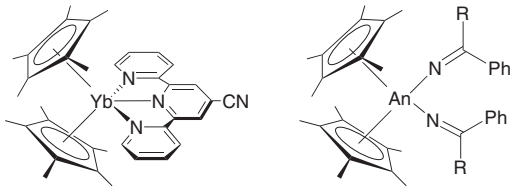
Abstract: Modification of Beller's palladium-catalyzed cyanation procedure for simple aromatic halides leads to a versatile and rapid route to complex multi-nitrile aryl and oligopyridyl ligands that improves on known literature methods. By heating the reagents in the high boiling solvent mesitylene to reflux temperatures at ambient pressure, we have observed the conversion of halogenated precursors to the corresponding nitrile compounds. The resulting compounds can be precipitated from CH_2Cl_2 solutions of the reaction mixtures and isolated as pure compounds in moderate to high yields. The current approach offers a safer alternative to the pressure tube method, as it does not involve the use of KCN at high pressures.

Key words: palladium-catalyzed cyanation, aryl halide, bipyridine, terpyridine, nitrile

The nitrile group is used frequently by organic chemists as a means to access a diverse range of functionalities (i.e., carboxylic acids/esters, aldehydes, amines and amidines).[1] Compounds containing cyano substituents are also utilized in a variety of commercial applications including herbicides,[2] drug intermediates,[3] and materials where the electronic nature of the nitrile group is critical to the intrinsic properties of these materials, such as nonlinear optical (NLO) response.[4] Our primary interest in nitrile compounds stems from their direct application in the synthesis of the novel ytterbium mixed-valence 4′-cyanoterpyridine adducts[5] and in formation of actinide ketimido complexes[6] that can be prepared by reaction of aromatic nitrile ligands with actinide bisalkyl or bisaryl precursors (Figure 1).



(**A**) (**B**) An = U, Th; R = Me, Ph, CH_2Ph

Figure 1 Lanthanide (**A**) and actinide (**B**) complexes employing aryl-nitrile functionalities.

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During the course of our research in this field, we became interested in aromatic and oligopyridyl ligands that contain multiple nitrile groups (Figure 2, complexes **1**–**5**). Examination of known literature procedures indicates that Potts condensation methods have been used to prepare 4′-cyano-2,2′:6′,2″-terpyridine (**1**)[7] (overall yield; 4% in five steps) and Ochiai's[8] *N*-oxide addition/elimination protocols have been used to access 6,6″-dicyano-2,2′:6′,2″-terpyridine (**4**)[9] (overall yield; 46% in 2 steps). Not surprisingly, the more difficult substitution patterns of 5-cyano-2,2′-bipyridine (**2**)[10], 5,5′-dicyano-2,2′-bipyridine (**3**)[11] and 1,3,5-tricyanobenzene (**5**)[12] (overall yields; 46% in two steps for **2**, 23–54% in two steps for **3**, 40% in two steps for **5**) have necessitated the use of harsh amide dehydration procedures to obtain the desired nitrile group. Deterred by the complexity of the many different synthetic methods required for preparation of these nitrile ligands, we investigated whether a common simplified procedure would be feasible.

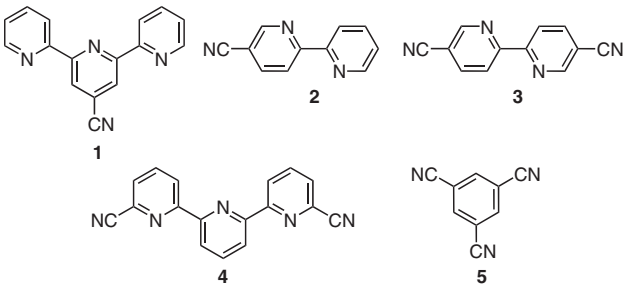


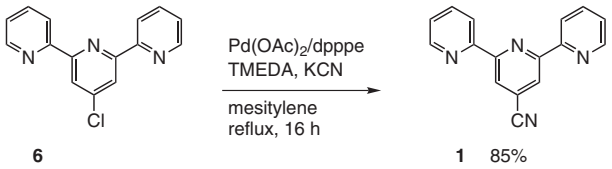
Figure 2 Target poly-nitrile ligands synthesized in this work.

Since Rosenmund–Von Braun[13] first discovered that aryl bromides/iodides could be transformed into aryl nitriles, albeit with stoichiometric copper(I) cyanide, progress in this area has been directed at investigating metal catalyzed systems. Palladium-mediated cyanations[14,15] have received the most attention as this metal allows access to a wide range of conditions and also tolerates many functional groups. Of these reports, there is one example where a 4-chloro-2,2′:6′,2″-terpyridine ruthenium complex is converted to the 4-cyano-2,2′:6′,2″-terpyridine ruthenium derivative using palladium with $Zn(CN)_2$ as the nitrile source.[16] Here, the terpyridine ligand is not available for further binding. Unfortunately, there are no reported conditions for halide cyanation of non-coordinated complex heterocyclic ligands. Furthermore, we have foreseen that certain coupling reaction conditions {e.g.

CuCN,[13c] $Zn(CN)_2$,[16,17] and $K_4[Fe(CN)_6]$[15]} may not be appropriate for heterocyclic precursors given that these ligands (**1**–**5**) will be applied in magnetic materials. Thus we developed a simple and convenient approach for the synthesis of poly-nitrile complex ligands using palladium-mediated catalysis.

Initially, we chose Beller's palladium-catalyzed procedure[14] to convert simple aryl chlorides to aryl nitriles because the method tolerated a variety of functionalized aromatic and heteroaromatic species. The reaction of commercially available 4′-chloro-2,2′:6′,2″-terpyridine (**6**) (using Beller's protocol[14]) with $Pd(OAc)_2$/dppe as the active catalyst in the presence of TMEDA in a pressure tube containing toluene heated to 160 °C gave discouraging results. Analysis of the crude reaction mixture by GC–MS indicated that 4′-cyano-2,2′:6′,2″-terpyridine (**1**) formed in less than 10% yield, while the majority of the material was unreacted 4′-chloroterpyridine (**6**).

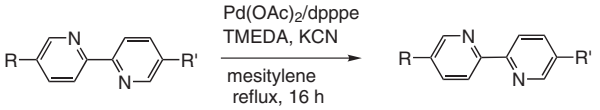
We considered that the solubility of the ligand might be a factor in the poor conversion of the chloride to the nitrile goup,[18] and decided to use conventional reflux conditions with the high boiling solvent mesitylene, thereby eliminating the need for pressure tube conditions. Accordingly, using the same amounts of reagents as before, the reaction was conducted at ambient pressures and reflux temperatures under an inert atmosphere (Scheme 1). The organic precursor appeared to be completely soluble at reflux temperature. GC–MS analysis of the reaction mixture after 16 hours revealed that 4′-chloroterpyridine (**6**) had been completely consumed and the reaction was clean, affording 4′-cyanoterpyridine (**1**) as the main product. The pure product **1** was precipitated as a white powder from a CH_2Cl_2 solution of the reaction mixture in 85% yield. No further purification is necessary.



6 **1** 85%

Scheme 1

This method was used to provide **4** and **5** in moderate to high yields (Table 1). Bipyridine derivatives **2** and **3** were prepared starting from 5-bromo-2,2′-bipyridine (**7**) and 5,5′-dibromo-2,2′-bipyridine (**8**) respectively, which are both accessed in two steps from commercially available materials.[19] The cyanation of **7** and **8** (Scheme 2) gave **2** and **3** directly in 72% and 67% yield respectively. The overall yields for **2** and **3** from synthesized precursors are 56% and 64%, respectively, which is a moderate improvement form previous methods (Table 1).



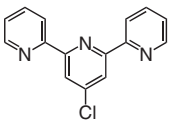
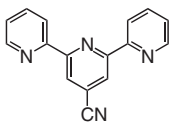
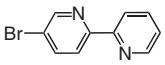
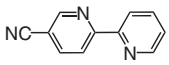
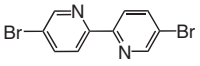
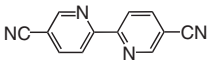
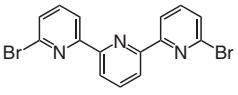
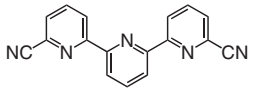
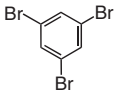
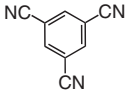
7 R = H; R' = Br
8 R, R' = Br

2 R = H; R' = CN 72%
3 R, R' = CN 67%

Scheme 2

In conclusion, a simple modification of the palladium-mediated cyanation protocol developed by Beller and coworkers[15] provides a convenient and safe synthetic route to mono-, di-, and tri-substituted aryl nitriles in moderate to high yields. The method appears to tolerate a wide variety of precursors and works well for pyridyl ligands halogenated at the *ortho*-, *meta*- and *para*-positions. This

Table 1 Summary of Cyanations of *N*-Heterocyclic/Aryl Halides as Compared to Previously Reported, Multi-Step Literature Preparations

Entry	Precursor	Product	Yield[a] (%)	Previously reported yield[b] (%)
1			85 (1)	4 (5)[7]
2			56 (2)[b]	46 (2)[10]
3			64 (2)[b]	23–54 (2)[11]
4			70 (1)	46 (2)[9]
5			50 (1)	40 (2)[12]

[a] Yields reported are from this work.
[b] Yields reported are overall yields based on the availability of commercial starting materials. Value in parentheses refers to the total number of synthetic steps required to obtain the final product.

modified procedure uses the identical catalytic system reported by Beller with the exception that toluene (in a sealed tube at 160 °C) is substituted with mesitylene at ambient pressure and reflux temperatures. This is a notable safety advance since it does not require the heating of a sealed system containing KCN.

All reactions were carried out at atmospheric pressures unless noted otherwise (600 mTorr at Los Alamos, NM, elevation 7200 ft). 4′-Chloro-2,2′:6′,2″-terpyridine [TPY-Cl] (Acros), 6,6″-dibromo-2,2′:6′,2″-terpyridine [TPY-(Br)$_2$] (Aldrich), 1,3,5-tribromobenzene (Aldrich), KCN and NaCN (Fisher), palladium(II) acetate [Pd(OAc)$_2$] (Strem), 1,5-bis(diphenylphosphino)pentane [dpppe] (Aldrich), mesitylene (Acros), CH_2Cl_2 (Acros), CD_2Cl_2 (Cambridge Isotopes), HPLC grade water (Aldrich), and pentane (Acros) were used as received. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine [TMEDA] (Acros) was passed through an activated column of alumina prior to use. 5-Bromo-2,2′-bipyridine and 5,5′-dibromo-2,2′-bipyridine were prepared according to the literature procedure.[19] Caution: Cyanide salts are extremely toxic. All reactions should be quenched with water and the aqueous wash made basic before disposal.

NMR spectra were recorded at ambient temperature (25 °C) on a Bruker Avance 400 MHz spectrometer. IR Spectra were recorded on a Thermo-Nicolet FT-IR module instrument Magna 760 spectrometer at 4 cm^{-1} resolution as mineral oil mulls. GC–MS data were obtained with a Hewlett Packard 6890 gas chromatograph configured with a DB-5 column (0.32 mm ID, 30 m) in series with an HP 5973 quadrupole mass detector. The column was operated at a flow rate of 0.6 mL/min and ramped between 70–230 °C at a rate of 20 °C/min.

4′-Cyano-2,2′:6′,2″-Terpyridine (1)

TPY-Cl (0.535 g, 2.00 mmol), KCN (0.130 g, 2.00 mmol), Pd(OAc)$_2$ (0.009 g, 0.04 mmol), dpppe (0.035 g, 0.080 mmol), TMEDA (0.06 mL, 0.4 mmol) and mesitylene (5 mL) were loaded into a 25 mL round bottom flask equipped with a stir bar. The flask was fitted with a reflux condenser and the whole apparatus was purged under Ar for 10 min before initiating reflux. The contents were heated to reflux temperatures under Ar for 16 h during which time the color of the reaction became dark brown. The reaction was allowed to cool yielding a gray-colored gel. HPLC grade water (10 mL) was added to the reaction flask and the slurry was stirred for 10 min. The slurry was filtered through a medium sintered glass frit providing a gray solid, which was then dissolved in CH_2Cl_2 (30 mL) and the solution was filtered through a medium sintered glass frit. The solvent was removed under vacuum using a rotatory evaporator and the powder was rinsed with pentane (3 × 20 mL) on a sintered glass frit and dried under vacuum for 12 h (at 50 mTorr) to yield **1** as a white powder. Yield: 0.439 g (1.70 mmol, 85%); mp 168–169 °C (Lit.[7] 168.5–169 °C).

IR (mineral oil): 2238 (C≡N) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_2Cl_2, 25 °C): δ = 8.72 (overlapping s, dd, 4 H, H6, H3′, H5′, H6″), 8.62 (dd, *J* = 8.0 Hz, 2 H, H3, H3″), 7.91 (dt, 2 H, H4, H4″ or H5, H5″), 7.42 (ddd, 2 H, H4, H4″ or H5, H5″).

^{13}C{^{1}H} NMR (100.61 MHz, CD_2Cl_2, 25 °C): δ = 157.3, 154.8, 150.0, 137.7, 125.4, 123.0, 122.9 (C≡N), 121.6, 117.6.

5-Cyano-2,2′-bipyridine (2)

5-Cyano-2,2′-bipyridine was prepared according to the same method as for TPY-CN from 5-bromo-2,2′-bipyridine (0.305 g, 1.30 mmol), NaCN (0.064 g, 1.3 mmol), Pd(OAc)$_2$ (0.013 g, 0.058 mmol), dpppe (0.053 g, 0.12 mmol), TMEDA (0.08 mL, 0.5 mmol) and mesitylene (5 mL). Product isolation varied slightly from that of TPY-CN due to the partial solubility of the product in mesitylene. The aqueous slurry from the first filtration step was extracted with CH_2Cl_2 (2 × 15 mL) and this was combined with the undissolved portion. The product **2** was isolated as an off-white powder. Yield: 0.170 g (0.940 mmol, 72%); mp 147–148.5 °C (Lit.[10] 148–150 °C).

IR (mineral oil): 2233 (C≡N) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_2Cl_2, 25 °C): δ = 8.92 (br d, *J* = 2.0 Hz, 1 H, H6), 8.70 (br dt, *J* = 4.5, 1.0 Hz, 1 H, H6′), 8.59 (d, *J* = 8.3 Hz, 1 H, H3), 8.47 (d, *J* = 8.0 Hz, 1 H, H3′), 8.09 (dd, *J* = 8.3, 2.0 Hz, 1 H, H4), 7.87 (td, *J* = 8.0, 7.6, 1.7 Hz, 1 H, H4′), 7.39 (ddd, *J* = 7.4, 4.5, 1.0 Hz, 1 H, H5′).

^{13}C{^{1}H} NMR (100.61 MHz, CD_2Cl_2, 25 °C): δ = 159.6, 154.7, 152.5, 150.1, 140.7, 137.7, 125.5, 122.3, 121.1, 117.6 (C≡N), 110.0.

5,5′-Dicyano-2,2′-bipyridine (3)

5,5′-Dicyano-2,2′-bipyridine was prepared according to the same method as for TPY-CN from 5,5′-dibromo-2,2′-bipyridine (0.400 g, 1.28 mmol), NaCN (0.124 g, 2.54 mmol), Pd(OAc)$_2$ (0.036 g, 0.16 mmol), dpppe (0.15 g, 0.34 mmol), TMEDA (0.13 mL, 0.86 mmol) and mesitylene (5 mL). Product isolation varied slightly from that of TPY-CN due to the partial solubility of the product in mesitylene. The aqueous slurry from the first filtration step was extracted with CH_2Cl_2 (2 × 15 mL) and this was combined with the undissolved portion. The product **3** was isolated as an off-white powder. Yield: 0.176 g (0.859 mmol, 67%); mp 268–269 °C (Lit. 275.4–276.2 °C,[11a] 284–285 °C,[11b] 269–271 °C[11c]).

IR (mineral oil): 2231 (C≡N) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_2Cl_2, 25 °C): δ = 8.97 (d, *J* = 2.0, 0.8 Hz, 2 H, H6, H6′), 8.63 (d, *J* = 8.0, 0.8 Hz, 2 H, H3, H3′), 8.15 (dd, *J* = 8.0, 2.0 Hz, 2 H, H4, H4′).

^{13}C{^{1}H} NMR (100.61 MHz, CD_2Cl_2, 25 °C): δ = 157.5, 152.7, 141.2, 122.1, 117.1 (C≡N), 111.2.

6,6″-Dicyano-2,2′:6′,2″-terpyridine (4)

Dicyanoterpyridine was prepared according to the same method as for TPY-CN from 6,6″-dibromo-2,2′:6′,2″-terpyridine (0.782 g, 2.00 mmol), KCN (0.260 g, 4.00 mmol), Pd(OAc)$_2$ (0.018 g, 0.080 mmol), dpppe (0.070 g, 0.16 mmol), TMEDA (0.12 mL, 0.80 mmol) and mesitylene (5 mL). Product isolation varied slightly from that of TPY-CN due to the partial solubility of the product in mesitylene. The aqueous slurry from the first filtration step was extracted with CH_2Cl_2 (2 × 15 mL) and this was combined with the undissolved portion. The product **4** was isolated as an off-white powder. Yield: 0.394 g (1.39 mmol, 70%); mp 239–241 °C (Lit.[9b] 230–232 °C).

IR (mineral oil): 2237 (C≡N) cm^{-1}.

^{1}H NMR (400.13 MHz, CD_2Cl_2, 25 °C): δ = 8.84 (dd, *J* = 8.0, 1.0 Hz, 2 H, H3, H3″ or H5, H5″), 8.55 (d, *J* = 8.0 Hz, 2 H, H3′, H5′), 8.00–8.10 (overlapping m, 3 H, H4, H4′, H4″), 7.77 (dd, *J* = 8.0, 1.0 Hz, 2 H, H3, H3″ or H5, H5″).

^{13}C{^{1}H} NMR (100.61 MHz, CD_2Cl_2, 25 °C): δ = 157.3, 153.6, 138.6, 138.1, 133.2, 128.5, 124.2, 122.3, 117.4 (C≡N).

1,3,5-Tricyanobenzene (5)

Tricyanobenzene was prepared according to the same method as for TPY-CN from 1,3,5-tribromobenzene (0.631 g, 2.00 mmol), KCN (0.390 g, 6.00 mmol), Pd(OAc)$_2$ (0.027 g, 0.12 mmol), dpppe (0.105 g, 0.240 mmol), TMEDA (0.18 mL, 1.2 mmol) and mesitylene (5 mL). Product isolation varied slightly from that of TPY-CN due to the partial solubility of the product in mesitylene. The aqueous slurry from the first filtration step was extracted with CH_2Cl_2 (2 × 15 mL) and this was combined with the undissolved portion. The product was isolated as a tan powder. Yield: 0.151 g (0.990 mmol, 50%); compound **5** decomposed above 240 °C (no mp data reported in the literature).

IR (mineral oil): 2240 (C≡N) cm^{-1}.

^1H NMR (400.13 MHz, CD_2Cl_2, 25 °C): δ = 8.16 (s, 3 H, aromatic).

$^{13}C\{^1H\}$ NMR (100.61 MHz, CD_2Cl_2, 25 °C): δ = 138.9 (CH), 116.1 (*C*C≡N), 114.8 (*C*C≡N).

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