Synthesis of Substituted 1-Methyl-2-cyanopyrroles via Unprecedented Addition of N,N-Dimethylformamide to Electron-Deficient Alkenes in the Presence of Copper(I) Cyanide

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Introduction

Unsaturated molecules bearing strongly electron-withdrawing groups, such as tetracyanoethylene (TCNE), dichlorodicyanoquinone (DDQ), etc., have been used recently as electron acceptors in charge-transfer salts that show unusual magnetic properties.1 Our interest in these materials led us to consider 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene, 1, as a potential electron acceptor. While trying to develop a convenient synthesis of 1, we discovered, and are reporting here, an unprecedented reaction in which electron-deficient alkenes react with withdrawing groups, such as tetracyanoethylene (TCNE), dichlorodicyanoquinone (DDQ), etc., have been used with DMF in the presence of CuCN to form substituted 1-methyl-2-cyanopyrroles.

The published three-step synthesis of 1, which includes steps involving liquid HCN and a pyrolysis in molten sulfur, produces an equimolar mixture of cis and trans stereoisomers.2 While we were able to produce 1 by this method, its difficulty and scale limitations prompted us to seek an alternate synthesis. One possibility was bromination of commercially available hexafluoro-2-butyne, 2a, followed by copper-mediated substitution of bromide by cyanide.3

Results and Discussion

As shown in Scheme 1, the addition of 1 equiv of bromine to 2a gave the expected product, 1,2-bis(trifluoromethyl)-1,2-dibromoethylene, 3a, (approximately equal amounts cis and trans isomers) in 95% yield. Treatment of this vinylic dibromide with 2 equiv of copper(I) cyanide in DMF did not produce 1 but instead provided a 6:1 mixture of 1-methyl-2-cyano-3,4-bis(trifluoromethyl)pyrrole, 4a, and 1-methyl-2,5-dicyano-3,4-bis(trifluoromethyl)pyrrole, 5a, in a combined yield of 74%.4

Our initial hypothesis was that the observed products were the result of isomerization of the expected trans-dinitrile to its cis stereoisomer, which then cyclized to the pyrrole via a Paal-Knorr-like reaction.5 Accordingly, the reaction temperature and time were reduced in an effort to produce the putative fumaronitrile or maleonitrile under conditions at which it would be stable, all to no avail. In an effort to better understand the formation of these products, 3a was allowed to react with 13C-labeled CuCN6 under identical conditions. Surprisingly, the 13C label appeared only in the cyano groups of 4a and 5a; neither carbon atom of 4a or 5a was isotopically labeled. Thus, the pyrrole ring is not formed by cyclization of a dicyanoethylene intermediate but instead results from reaction of the alkene, 3a, with the solvent, DMF (or intermediates derived therefrom). This conclusion has been confirmed by reaction of 3a with CuCN in 13C-labeled DMF (isotopically labeled at the carbonyl carbon atom). In this reaction, product 4a is shown by mass spectrometry and NMR to be labeled only at C2; the other carbon, C5, was unlabeled. Also 5a is formed exclusively with only one of its α-carbon atoms isotopically labeled. Thus the two pyrrolic α-carbon atoms are derived from the formyl group and one of the N-methyl groups of DMF. Activation of the alkyl group on a substituted amide under these conditions is unprecedented.

The generality of this reaction was explored by varying the reactants, the stoichiometry, and the solvent. Substitution of DMF with N,N-diethylformamide or N,N-dimethylacetamide resulted in formation of intractable products. Similarly, no identifiable products were obtained when copper(I) cyanide was replaced by either 13C-labeled CuCN6 or 13C-labeled DMF (isotopically labeled at the carbonyl carbon atom) (product 4a was shown by mass spectrometry and NMR to be labeled only at C2; the other carbon, C5, was unlabeled). Also 5a is formed exclusively with only one of its α-carbon atoms isotopically labeled. Thus the two pyrrolic α-carbon atoms are derived from the formyl group and one of the N-methyl groups of DMF. Activation of the alkyl group on a substituted amide under these conditions is unprecedented.

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(4) In addition to the spectroscopic characterization of 4 and 5 given in the Experimental Section, the atom connectivity for 4a has also been unambiguously characterized by a single-crystal diffraction study that was of low quality due to extensive decomposition in the X-ray beam. Yap, G. P. A.; Rheingold, A. L., The University of Delaware, unpublished results, 1994.
(6) 13C-labeled copper(I) cyanide was prepared from 13C-labeled potassium cyanide by the procedure of Barber, H. J. Chem. Soc. 1943, 79.
yield. When the reaction was conducted with a 4:1 initial ratio of CuCN to 3a, products 4a and 5a were obtained in essentially equal amounts. Interestingly, replacement of the vinlylic dibromide starting material, 3a, with 4a, under the usual reaction conditions, did not produce any dicyanopyrrole, 5a, indicating that 4a is not an intermediate in the production of 5a.

Substitution of 3a with dimethyl 2,3-dibromo-2-butenedioate, 3b (approximately equal amounts of cis and trans isomers) gave an analogous mixture of N-methylene pyrroles; dimethyl 1-methyl-2-cyano-3,4-pyrroledicarboxylate, 4b, and dimethyl 1-methyl-2,5-dicyano-3,4-pyrroledicarboxylate, 5b, were produced in a 10:1 ratio in an overall yield of 35%. Thus, this pyrrole-forming reaction appears to be general for vinlylic dihalides bearing electron-withdrawing groups.

These results are most consistent with a 3 + 2 cycloaddition between the alkene and an azomethine ylide generated by reaction of DMF and CuCN as outlined in Scheme 2. Formation of a cyanohydrin-like intermediate, 6, is followed by nitrogen-assisted loss of oxygen to give an iminium ion, 7. Loss of a proton from the activated N-alkyl group forms a resonance-stabilized azomethine ylide, 8. Grigg has reported N-alkyl group activation in similar iminium ions prepared by condensations of secondary amines and carbonyl groups bearing a conjugated moiety. Addition of 8 to the alkene followed by elimination of 2 equiv of HBr from intermediate 9 would give products 4. Products 5 could arise from cyanide attack on 8, followed by nucleophilic attack on the dibromoaalkene. Loss of another proton from 11 followed by displacement of the second bromide, by an addition–elimination process, completes the ring, which is then oxidized to 5 on workup.

The above mechanism is consistent with the facts that 1) the observed ratio of 4 to 5 depends on the relative amount of CuCN to 3 and 2) that 4 is not an intermediate in the formation of 5. One can rationalize the lack of similar products when N,N-dimethylacetamide or N,N-dimethylformamide were used as solvents on steric grounds. The role of the copper(I) ion is not obvious; it may activate the carbonyl group of DMF for addition of cyanide and/or it may act as a Lewis acid, facilitating the loss of the oxide or bromide ions.

Preliminary attempts to trap the proposed azomethine ylide, 8, with reactive dipolarophiles have been unsuccessful. Substitution of 3 with either fumaronitrile or maleic anhydride under the usual reaction conditions gave no evidence for a 3 + 2 cycloaddition. While the maleic anhydride was likely hydrolyzed in the reaction, all of the fumaronitrile was recovered unreacted.

**Conclusion**

Two reaction manifolds are possible for mixtures of vinlylic dihalides, CuCN and DMF. A copper-mediated substitution reaction to give dinitriles occurs for vinlylic dihalides bearing alkyl and aryl groups while those bearing electron-withdrawing groups give 3,4-disubstituted 1-methy1-2-cyanopyrroles possibly via cycloadditions with an azomethine ylide generated in situ from DMF. It is reasonable to expect that electron-withdrawing groups on the alkene raise the activation energy for the former reaction while reducing it for the latter.

3,4-Bis(trifluoromethyl)pyrroles have been prepared by Diels–Alder addition of hexafluoro-2-butene to pyrroles followed by a retro Diels–Alder elimination of acetylene. However, the initial Diels–Alder reaction fails for pyrroles bearing electron-withdrawing groups at the a-positions. Thus, the reaction reported here is the only method, of which we are aware, for preparing 2-cyanopyrroles bearing additional electron-withdrawing groups in the 3 and 4 positions.

**Experimental Section**

All reagents were purchased from Aldrich Chemical Co. except for hexafluoro-2-butene, which was purchased from PCR, Inc., Gainesville, FL, and 13C-potassium cyanide and 13C-DMF, both of which were purchased from Cambridge Isotope Laboratories. 13C-CuCN and dimethyl 2,3-dibromo-2-butenediode were prepared by modifications of literature procedures. All reagents were of commercial quality. Samples were submitted to Galbraith Laboratories or Desert Analytics Laboratory for elemental analyses.

1,2-Dibromo-1,2-bis(trifluoromethyl)ethylene (3a). A 2 L three-neck round-bottom flask was used as a gas-phase reactor. To one neck of the reactor was connected a small round-bottom flask containing a few milliliters of liquid bromine. To another neck was connected a cylinder of hexafluoro-2-butyne, and the third neck was connected to the sidearm of a T-shaped stopcock. The central arm of the stopcock was connected to a nitrogen-cooled trap and then a mechanical vacuum pump. The


entire system was evacuated, and the T-shaped stopcock was used to isolate the reactor and manometer from the vacuum. The stopcock to the bromine solution was opened, and bromine vapor was allowed into the reactor until the pressure had increased by 50 Torr. When the pressure had stabilized an equimolar amount of hexafluoro-2-butyne, as measured by the pressure changes on the manometer, was added. The mixture quickly turned a deep brick-red color. After stirring for 4 h at 95 °C under an inert atmosphere, the solution was cooled to room temperature and the gas mixture was irradiated with a heat lamp. Within 1 min of irradiation the reddish color of the bromine vapor had disappeared and the pressure had dropped to one-half the pressure of the gas mixture. The entire system was evacuated and the product collected in the trap. This process was repeated 10 times within 1 h. The trap containing the frozen product, as well as some unreacted starting materials, was allowed to warm well as some unreacted starting materials, was allowed to warm to room temperature where unreacted hexafluoro-2-butyne evaporated. The crude product was purified by vacuum distillation using a water aspirator (bp 38 °C). Yield = 16.65 g (95%). GC and 19F NMR confirmed the presence of two isomers in a 3:4 ratio: 19F NMR (CDCl3) δ = 56.3 (s, 3F), 52.8 (s, 4F) vs C6H5F; 13C NMR (1H decoupled, CDC13) δ = 127.0–125.3 (m), 119.7 (q, JCF = 276 Hz) 119.4 (q, JCF = 276 Hz), 116.9 (q of q, JCF = 39 Hz, JCF′ = 1.5 Hz); IR (neat): 1/2 = 1596, 1245, 1150 cm−1; MS (EI) m/z = 242 (M+). Anal. Calcd for C9H3N3F6: C, 40.47; H, 1.13; N, 15.72. Found: C, 39.95; H, 1.87; N, 15.10. 

1-Methyl-2-cyanopyrroles (4a–5b). A 25 mL round-bottom flask, charged with 1.00 g (11.2 mmol) of CuCN and 10 mL of DMF, was fitted with a magnetic stir bar and a condenser. This mixture was heated with stirring at 95 °C under an inert atmosphere for 1 h after which 5 mmol of either 1,2-dibromo-1,2-dicyanoethene (2a), trifluoro-1,2-dibromo-1,2-dicyanoethene (2b), 1,2-bis(trifluoromethyl)ethylene or dimethyl 2,3-dibromo-2,3-dicyanoethene (2c), or a combination of these reagents was added. The mixture quickly turned a deep brick-red color. After stirring for 4 h at 95 °C under an inert atmosphere, the solution was cooled to room temperature and poured into 100 mL of water. This mixture was extracted three times with 50 mL of ether, and the combined ether layers were washed once with 50 mL of water and once with 50 mL of saturated aqueous NaCl, dried over sodium sulfate, filtered, and reduced to a viscous red oil on a rotary evaporator. The crude product was analyzed on capillary GC (100 °C, 1 min, 4 °C/min, 140 °C, 5 min) and by TLC (SiO2, 2/1 hexanes/CH2Cl2 eluent). The major products were isolated by flash chromatography on silica gel (solvent gradient of hexanes → 1/1 hexanes/CH2Cl2 for 4a and 5a while a solvent gradient of hexanes → 1/1 hexanes/ether for 4b and 5b). Removal of solvent gave either white solids or clear oils which solidified on standing.

1-Methyl-2-cyano-3,4-bis(trifluoromethyl)pyrrole (4a). Yield = 0.77 g (64%); mp 37 °C; 1H NMR (CDCl3): δ = 7.22 (s, 1H), 3.89 (s, 3H); 19F NMR (CDCl3): δ = 55.5 (s, 1F), 56.0 (s, 1F) vs C6H5F; 13C NMR (1H decoupled, CDCl3): δ = 127.7 (s), 121.0 (q, JCF′ = 267.3 Hz), 120.4 (q, JCF′ = 269.8 Hz) 120.1 (q of q, JCF = 39.1 Hz, JCF′ = 2.5 Hz), 113.7 (q of q, JCF = 38.3 Hz, JCF′ = 2.5 Hz) 109.3 (s), 106.9 (q, JCF = 3.0 Hz), 36.1 (s); IR (neat): 1/2 = 2420, 1315, 1245, 1150 cm−1; MS (EI) m/z = 242 (M+). Anal. Calcd for C9H4F2N3: C, 39.69; H, 1.67; N, 11.56. Found: C, 39.95; H, 1.87; N, 11.60. 

1-Methyl-2,5-dicyano-3,4-bis(trifluoromethyl)pyrrole (5a). Yield = 0.14 g (10%); mp 135 °C; 1H NMR (CDCl3): δ = 4.06 (s); 19F NMR (CDCl3): δ = 56.0 (s) vs C6H5F; 13C NMR (1H decoupled, CDCl3): δ = 120.6 (q of q, JCF = 41 Hz, JCF′ = 2.2 Hz), 119.4 (q, JCF = 271 Hz), 110.4 (br s), 107.9 (s), 36.0 (s); IR (KBr): 1/2 = 2234, 1322, 1251, 1157 cm−1; MS (EI) m/z = 267 (M+). Anal. Calcd for C9H4F2N2: C, 40.47; H, 1.13; N, 15.72. Found: C, 40.81; H, 1.32; N, 15.81. 

Dimethyl 1-Methyl-2-cyano-3,4-pyrroledicarboxylate (4b). Yield = 0.35 g (31.5%); mp 84 °C; 1H NMR (CDCl3): δ = 7.34 (s, 1H), 3.92 (s, 3H), 3.83 (s, 6H); 13C NMR (1H decoupled, CDCl3): δ = 162.2, 161.5, 131.6, 116.7, 111.0, 52.5, 52.0, 36.2; IR (KBr): 1/2 = 1094, 1040, 995, 903, 852, 840, 744 cm−1; MS (EI) m/z = 224 (M+). Anal. Calcd for C10H11O2N: C, 54.06; H, 4.54; N, 12.60. Found: C, 53.87; H, 3.80; N, 12.93. 

Dimethyl 1-Methyl-2,5-dicyano-3,4-pyrroledicarboxylate (5b). Yield = 0.039 g (3.2%); mp 199 °C; 1H NMR (CDCl3): δ = 7.18 (s, 3H), 3.94 (s, 6H); 13C NMR (1H decoupled, CDCl3): δ = 176.2, 159.5, 123.7, 108.9, 52.6, 35.2; IR (KBr): 1/2 = 2220, 1735, 1300 cm−1; MS (EI) m/z = 247 (M+). Anal. Calcd for C13H12O2N2: C, 53.33; H, 4.44; N, 15.55. Found: C, 53.88; H, 3.96; N, 15.89. 

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Supporting Information Available: Mass, NMR, and IR spectra available for 3a, 4a, 5a, 4b, and 5b. This material is available free of charge via the Internet at http://pubs.acs.org. J O991440F