

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

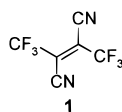
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Introduction

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 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

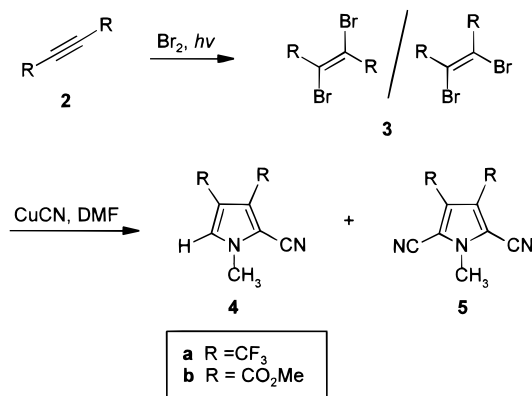
As shown in Scheme 1, the addition of 1 equiv of bromine to **2a** gave the expected product, 1,2-bis(trifluoromethyl)-1,2-dibromoethylene, **3a**, (approximately equal amounts cis and trans isomers) in 95% yield. Treatment of this vinylic dibromide with 2 equiv of copper(I) cyanide in DMF did not produce **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

(1) Miller, J. S.; Epstein, A. J. *J. Chem. Soc., Chem. Commun.* **1998**, 1319–1325 and references therein.

(2) Proskow, S.; Simmons, H. E.; Cairns, T. L. *J. Am. Chem. Soc.* **1963**, *85*, 2341. Proskow, S.; Simmons, H. E.; Cairns, T. L. *J. Am. Chem. Soc.* **1966**, *88*, 5254–5266.

(3) Fitzgerald, J.; Taylor, W.; Owens, H. *Synthesis* **1991**, 686–688.

Scheme 1



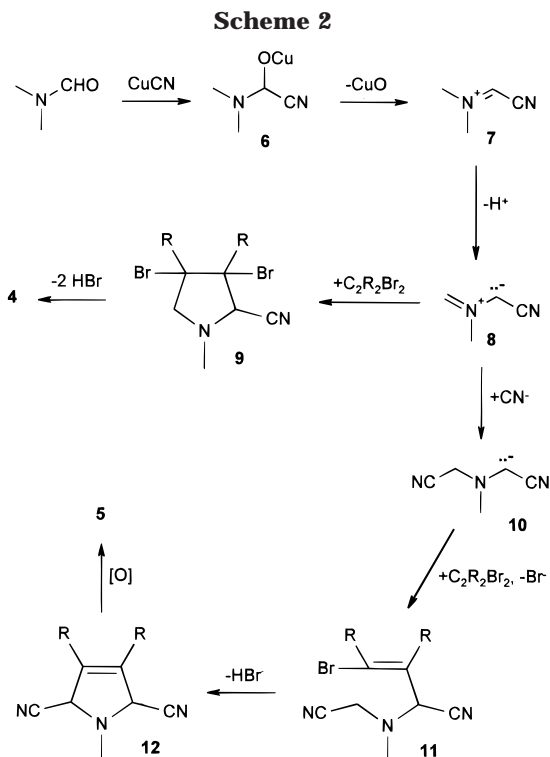
Our initial hypothesis was that the observed products were the result of isomerization of the expected *trans*-dinitrile to its *cis* stereoisomer, which then cyclized to the pyrrole via a Paal–Knorr-like reaction.⁵ Accordingly, the reaction temperature and time were reduced in an effort to produce the 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 α 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 α 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 copper(I) bromide or potassium cyanide. The ratio of products **4a** to **5a** were found to depend on the reactant stoichiometry. Reducing the amount of copper(I) cyanide to 1 equiv based on dibromide, **3a**, resulted in almost exclusive production of **4a**, still in approximately 70%

(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.

(5) Davies, D. T. *Aromatic Heterocyclic Chemistry*; Oxford University: Oxford, 1992; pp 11–12.

(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 vinylic 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,⁷ **3b** (approximately equal amounts of *cis* and *trans* isomers) gave an analogous mixture of *N*-methylpyrroles; 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 vinylic dihalides bearing electron-withdrawing groups.

These results are most consistent with a 3 + 2 cycloaddition between the alkene and an azomethine ylide⁸ 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.⁹ 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 dibromoalkene. 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*-diethylformamide 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 product. 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 vinylic dihalides, CuCN and DMF. A copper-mediated substitution reaction to give dinitriles occurs for vinylic dihalides bearing alkyl and aryl groups³ while those bearing electron-withdrawing groups give 3,4-disubstituted 1-methyl-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 reaction¹⁰ while reducing it for the latter.¹¹

3,4-Bis(trifluoromethyl)pyrroles have been prepared by Diels–Alder addition of hexafluoro-2-butyne to pyrroles followed by a retro Diels–Alder elimination of acetylene.¹² However, the initial Diels–Alder reaction fails for pyrroles bearing electron-withdrawing groups at the α -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-butyne, 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-CuCN⁶ and dimethyl 2,3-dibromo-2-butenedioate⁷ 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 manometer while the other sidearm was connected to a liquid nitrogen-cooled trap and then a mechanical vacuum pump. The

(7) Produced from dimethylacetylenedicarboxylate by the method of Kloster-Jensen, E. *Acta Chem. Scand.* **1963**, *17*, 1866–1874. Identical to dimethyl 2,3-dibromo-2-butenedioate reported by Lutz, R. *J. Am. Chem. Soc.* **1930**, *52*, 3405–3422.

(8) Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231–349.

(9) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602–604.

(10) Carey, F.; Sundberg, R. *Advanced Organic Chemistry*; Plenum: New York, 1977; pp 601–603.

(11) Carey, F.; Sundberg, R. *Advanced Organic Chemistry*; Plenum: New York, 1977; pp 300–307.

(12) Kaesler, R. W.; LeGoff, E. *J. Org. Chem.* **1982**, *47*, 4779–4780.

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 allowed into the flask. 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 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 ^{19}F NMR confirmed the presence of two isomers in a 3:4 ratio: ^{19}F NMR (CDCl_3) δ = 56.3 (s, 3F), 52.8 (s, 4F) vs $\text{C}_6\text{H}_5\text{F}$; ^{13}C NMR (^1H decoupled, CDCl_3) δ = 127.0–125.3 (m), 119.7 (q, J_{CF} = 276 Hz) 119.4 (q, J_{CF} = 276 Hz), 116.9 (q of q, J_{CF} = 39 Hz, $J_{\text{CF}''}$ = 1.5 Hz); IR (neat): $1/\lambda$ = 1596, 1245, 1190, 1162 cm^{-1} ; MS (EI) m/z = 320, 322, 324 (M^+).

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-bis(trifluoromethyl)ethylene or dimethyl 2,3-dibromo-2-butenedioate (approximately equal amounts of cis and trans isomers) were 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 (SiO_2 , 2/1 hexanes/ CH_2Cl_2 eluent). The major products were isolated by flash chromatography on silica gel (solvent gradient of hexanes \rightarrow 1/1 hexanes/ CH_2Cl_2 for **4a** and **5a** while a solvent gradient of hexanes \rightarrow 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 (CDCl_3): δ = 7.22 (s, 1H), 3.89 (s, 3H); ^{19}F NMR (CDCl_3): δ = 55.5 (s, 1F), 56.0 (s, 1F) vs $\text{C}_6\text{H}_5\text{F}$; ^{13}C NMR (^1H decoupled, CDCl_3): δ = 127.7 (s), 121.0 (q, J_{CF} = 267.3 Hz), 120.4 (q, J_{CF} = 269.8 Hz) 120.1 (q of q, J_{CF} = 39.1 Hz, $J_{\text{CF}''}$ = 2.5 Hz), 113.7 (q of q, J_{CF} = 38.3 Hz, $J_{\text{CF}''}$ = 2.5 Hz) 109.3 (s), 106.9 (q, $J_{\text{CF}''}$ = 3.0 Hz), 36.1 (s); IR (neat): $1/\lambda$ = 2240, 1315, 1245, 1150 cm^{-1} ; MS (EI) m/z = 242 (M^+). Anal. Calcd for $\text{C}_8\text{H}_4\text{N}_2\text{F}_6$: 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 (CDCl_3): δ = 4.06 (s); ^{19}F NMR (CDCl_3): δ = 56.0 (s) vs $\text{C}_6\text{H}_5\text{F}$; ^{13}C NMR (^1H decoupled, CDCl_3): δ = 120.6 (q of q, J_{CF} = 41 Hz, $J_{\text{CF}''}$ = 2.2 Hz), 119.4 (q, J_{CF} = 271 Hz), 110.4 (br s), 107.9 (s), 36.0 (s); IR (KBr): $1/\lambda$ = 2234, 1322, 1251, 1157 cm^{-1} ; MS (EI) m/z = 267 (M^+). Anal. Calcd for $\text{C}_9\text{H}_3\text{N}_3\text{F}_6$: 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 (CDCl_3): δ = 7.34 (s, 1H), 3.92 (s, 3H), 3.83 (s, 6H); ^{13}C NMR (^1H decoupled, CDCl_3): δ = 162.2, 161.5, 131.6, 116.7, 111.0, 52.5, 52.0, 36.2; IR (KBr): $1/\lambda$ = 3120, 2240, 1725, 1300 cm^{-1} ; MS (EI) m/z = 222 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_4$: 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 (CDCl_3): δ = 3.99 (s, 3H), 3.94 (s, 6H); ^{13}C NMR (^1H decoupled, CDCl_3): δ = 176.2, 159.5, 123.7, 108.9, 52.6, 35.2; IR (KBr): $1/\lambda$ = 2220, 1735, 1300 cm^{-1} ; MS (EI) m/z = 247 (M^+). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_4 \cdot 1/2\text{C}_2\text{H}_6\text{O}$: 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>.

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