Electrophilic Cyanations Using 1-Cyanobenzotriazole: sp^2 and sp Carbanions

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Received September 22, 1998

Introduction

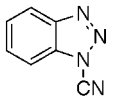
The introduction of a cyano group via carbon−carbon bond forming reactions is a fundamental process in organic synthesis. While this transformation is usually accomplished through the nucleophilic attack of a cyanide ion (CN^-) at an electrophilic carbon, a few reagents react as a cyano cation (CN^+) equivalent upon treatment with a carbanion. These include tosyl cyanide,[1−3] 2-chlorobenzylthiocyanate,[4] and cyanogen chloride.[5] Recently, we described a new and convenient synthesis of 1-cyanobenzotriazole[6] (**1**) and preliminary results showing its utility as an electrophilic C-cyanating reagent by the conversion of arylacetonitrile anions to the corresponding aryl malononitriles (Scheme 1). To expand the utility of **1** as a reagent for electrophilic cyanations, we reacted **1** with a variety of carbon nucleophiles. Thus the cyanations of the anions of arenes, heteroarenes, and alkynes are described.

Results and Discussion

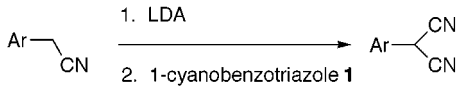
The order of addition was found to influence the yields of the cyanation reactions with *inverse additions* giving higher yields. For example, Table 1, entry 1a, shows a 40% yield for the normal addition of the bithiophene anion to the electrophile **1**. However, the same heteroarenyl anion gave a 68% yield (Table 1, entry 1b) for the inverse addition of the electrophile to the anion. One explanation for this is that the heteroarenyl anion can react with the electrophile **1** or the heteroarenenitrile formed during the reaction to give a bisheteroarene imine. Therefore, through inverse addition, the concentration of **1** is high relative to the heteroarenenitrile formed during the reaction and the desired cyanation is observed in better yield.

Overall, the cyanation reactions worked in poor to good yields depending on the nucleophile used. Good yields, 61−83%, were obtained for the cyanations of the thiophene ring system (Table 1, entries 1, 3, and 7) where the heteroarene anion was generated either by direct lithiation or lithium/halogen exchange and for the cyanation of phenylacetylene (Table 1, entry 4). The latter example may be especially useful as an addition to the current methodology for the cyanations of acetylenes.[7] A poor yield, however, was obtained for the cyanation of a novel thiophene (Table 1, entry 8). The simple arenyl anions generated from 2-bromonaphthalene and 9-bromoanthracene gave good yields, 61−75%, of the cyanation products (Table 1, entries 9 and 10).

Scheme 1



1



Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were obtained at 360 MHz, and chemical shifts are reported in ppm relative to internal $CHCl_3$ (7.26 ppm). ^{13}C NMR spectra were obtained at 90 MHz and chemical shifts are reported in ppm relative to internal $CHCl_3$ (77 ppm). All moisture- or air-sensitive reactions were carried out under an atmosphere of nitrogen in oven-dried glassware. All reagents were used as obtained from commercial suppliers except for the following: THF was freshly distilled from sodium-benzophenone ketyl. 1-Cyanobenzotriazole,[6] 5,5′-dibromo-2,2′-bithiophene,[8] 1-(*p*-toluenesulfonyl)indole,[9] 1-(*p*-toluenesulfonyl)pyrrole,[10] *N*-dodecyl-2,5-bis(2-thienyl)pyrrole,[11] and 1,3-di(2-thienyl)isothianaphthene[12] were prepared according to published methods.

General Cyanation Procedure A (Normal Addition). 5-Cyano-2,2′-bithiophene (2a) {Table 1, entry 1a}. A solution of 2,2′-bithiophene (1.06 g, 6.38 mmol) in THF (45 mL) was cooled to −78 °C, and 2.5 M BuLi (3.0 mL, 7.5 mmol) was added. The solution was then stirred at 0 °C for 30 min and cooled to −78 °C, and a solution of 1-cyanobenzotriazole (1.07 g, 7.4 mmol) in THF (15 mL) was added via a syringe. The solution was stirred at −78 °C for 1 h, warmed to room temperature, and stirred for 1 h. The solution was then poured into 10% HCl (300 mL) in ice and extracted with CH_2Cl_2 (2 × 100 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The residue was purified via column chromatography (SiO_2) (hexanes/CH_2Cl_2) to give **2a** (0.49 g, 40%) as a pale yellow solid: mp 72−74 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1H, J = 3.91 Hz), 7.35 (d, 1H, J = 5.07 Hz), 7.28 (d, 1H, J = 3.80 Hz), 7.13 (d, 1H, J = 3.91 Hz), 7.07 (dd, 1H, J = 5.14, 1.17 Hz); ^{13}C NMR ($CDCl_3$) δ 144.61, 138.19, 134.78, 128.27, 126.89, 125.99, 123.40, 114.11, 107.42; IR ($CHCl_3$) 3028, 2224, 1454, 1223 cm^{-1}. Anal. Calcd for $C_9H_5NS_2$: C, 56.51; H, 2.63; N, 7.32; S, 33.53. Found: C, 56.57; H, 2.62; N, 7.23; S, 33.54.

General Cyanation Procedure B (Inverse Addition). 5-Cyano-2,2′-bithiophene (2a) {Table 1, entry 1b}. A solution of 2,2′-bithiophene (1.01 g, 6.07 mmol) in THF (45 mL) was cooled to −78 °C, and 2.5 M BuLi (3.0 mL, 7.5 mmol) was added. The solution was then stirred at 0 °C for 30 min and cooled to −78 °C. This solution was added via cannula to a cooled (−78

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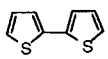
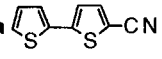
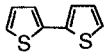
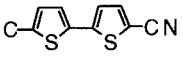
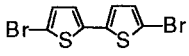
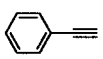
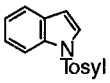
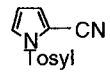
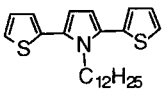
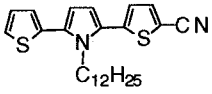
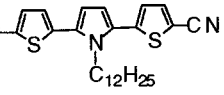
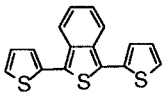
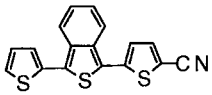
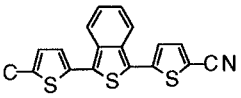
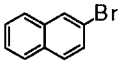
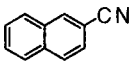
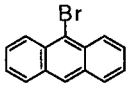
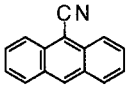
10.1021/jo981924w CCC: $18.00
Published on Web 12/16/1998

Table 1. Reaction of the Substrate Anion with 1-Cyanobenzotriazole (1)

Entry	Substrate	eq. of BuLi = eq. of **1**	Products	Yield[a]
1.		1.1	**2a** 	40[b], 68[c]
2.		2.2	**2a** , **2b** 	16, 37[b,d] 45, 16[c,d]
3.		1.1	**2a** , **2b**	10, 71[c,e]
4.		1.1	**3** 	83[c,e,f]
5.		1.1	**4** 	43[b,d,e] 40[c,d,e]
6.		1.1	**5** 	55[c,d,e]
7.		1.2	**6a**  **6b** 	61, 20[c]
8.		2.2	**7a**  **7b** 	24, 33[c,d]
9.		1.1	**8** 	75[c,e]
10.		1.1	**9** 	61[c,e]

[a] Yields for isolated compounds. [b] Normal addition. [c] Inverse addition. [d] TMEDA used; no. of equivalents used = no. of equivalents of BuLi used. [e] Reaction temperature was maintained at −78 °C until the reaction was quenched with **1**. [f] Et_2O used as solvent.

°C) solution of 1-cyanobenzotriazole (1.09 g, 7.57 mmol) in THF (15 mL). The solution was stirred at − 78 °C for 1 h, warmed to room temperature, and stirred for 1 h. The solution was poured into 10% HCl (300 mL) in ice and extracted with CH_2Cl_2 (2 × 80 mL), dried over Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The residue was purified via column chromatography (SiO_2) (hexanes/CH_2Cl_2) to give **2a** (0.79 g, 68%).

5,5′-Dicyano-2,2′-bithiophene (2b): pale yellow solid, mp 260−262 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 2H, J = 3.92 Hz), 7.26 (d, 2H, J = 3.00 Hz); ^{13}C NMR ($CDCl_3$) δ 141.38, 138.29, 125.67, 113.32, 110.30; IR ($CHCl_3$) 3027, 1224 cm^{-1}. Anal. Calcd for $C_{10}H_4N_2S_2$: C, 55.53; H, 1.86; N, 12.95; S, 29.65. Found: C, 55.52; H, 1.85; N, 12.71; S, 29.85.

3-Phenyl-2-propynenitrile (3): white crystalline solid with a strong mint odor, mp 35−37 °C (mp lit[13] 37−39 °C); ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 2H, J = 7.46 Hz), 7.54 (t, 1H, J = 7.34 Hz), 7.42 (t, 2H, J = 7.49 Hz); ^{13}C NMR ($CDCl_3$) δ 133.39, 131.82, 128.79, 117.38, 105.36, 82.92, 62.97; IR (KBr) 2975, 2271, 2145 cm^{-1}.

1-(*p*-Toluenesulfonyl)-2-cyanoindole (4): white solid, mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (d, 1H, J = 8.17 Hz), 7.90 (d, 2H, J = 8.39 Hz), 7.58 (d, 1H, J = 8.08 Hz), 7.54 (t, 1H, J = 7.34 Hz), 7.36 (s, 1H), 7.34 (d, 1H, J = 5.61 Hz), 7.27 (d, 2H, J = 8.57 Hz), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.10, 136.63, 134.38, 130.19, 128.58, 127.58, 127.48, 127.11, 124.68, 122.98, 122.48, 114.59, 112.16, 108.99, 21.60; IR (KBr) 3140, 2975, 2224 cm^{-1}; MS m/z (M^+) 296. Anal. Calcd for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.82. Found: C, 64.56; H, 4.13; N, 9.48; S, 10.70.

1-(*p*-Toluenesulfonyl)-2-cyanopyrrole (5): white crystals, mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 2H, J = 8.38 Hz), 7.47 (dd, 1H, 3.24, 1.63 Hz), 7.37 (d, 2H, J = 8.31 Hz), 6.95 (dd, 1H, J = 3.70, 1.57 Hz), 6.32 (t, 1H, J = 3.41 Hz), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.52, 134.12, 130.36, 127.85, 126.57, 126.57, 126.51, 112.30, 111.63, 103.74, 21.69; IR (KBr) 3148, 2975, 2226, 1594 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37; S, 13.02. Found: C, 58.49; H, 4.11; N, 11.36; S, 13.02.

1-Dodecyl-2-(5-cyanothienyl)-5-thienylpyrrole (6a): thick green oil; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1H, J = 3.92 Hz), 7.35 (dd, 1H, J = 4.67, 1.20 Hz), 7.11−7.08 (m, 2H), 7.03(d, 1H, J = 3.91 Hz), 6.45 (d, 1H, J = 3.70 Hz), 6.33 (d, 1H, J = 3.65 Hz), 4.14 (t, 2H, J = 7.81 Hz), 1.24−1.14 (m, 20H), 0.88 (t, 3H, J = 6.65 Hz); ^{13}C NMR ($CDCl_3$) δ 142.78, 137.75, 133.96, 130.51, 127.37, 126.60, 126.13, 125.93, 124.44, 114.29, 112.63, 111.53, 107.64, 45.44, 31.87, 31.12, 29.57, 29.43, 29.30, 28.87, 26.29, 22.67, 14.09; IR (NaCl) neat 3103, 2926, 2853, 2215, 1544 cm^{-1}; HRMS calcd for $C_{25}H_{32}N_2S_2$ 424.2007, found 424.2022.

1-Dodecyl-2,5-di(5-cyanothienyl)pyrrole (6b): thick oil which solidified on standing to give a yellow solid, mp 60−61 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 2H, J = 3.88 Hz), 7.06 (d, 2H, J = 3.89 Hz), 6.46 (s, 2H), 4.16 (t, 2H, J = 7.61 Hz), 1.24−1.15 (m, 20H), 0.88 (t, 3H, J = 7.46 Hz); ^{13}C NMR ($CDCl_3$) δ 141.60, 137.75, 127.99, 125.45, 113.92, 113.21, 108.76, 45.73, 31.84, 31.14, 29.54, 29.40, 29.27, 28.85, 26.24, 22.63, 14.07; IR (KBr)

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3121, 2920, 2850, 2214, 1556 cm^{-1}. Anal. Calcd for $C_{26}H_{31}N_3S_2$: C, 69.45; H, 6.95; N, 9.34; S, 14.26. Found: C, 69.46; H, 7.06; N, 9.41; S, 14.13.

1-(5-cyanothienyl)-2-thienylbenzo[*c*]thiophene (7a): red solid: mp 153−155 °C; ^1H NMR ($CDCl_3$) δ 7.99 (d, 1H, J = 8.78 Hz), 7.91 (d, 1H, J = 8.83 Hz), 7.63 (d, 1H, J = 3.95 Hz), 745 (dd, 1H, J = 5.02, 0.88 Hz), 7.40 (dd, 1H, J = 3.74, 0.96 Hz), 7.31 (d, 1H, J = 3.99 Hz), 7.24−7.17 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 143.14, 137.97, 136.26, 135.38, 134.67, 129.92, 128.09, 126.57, 126.46, 126.44, 125.13, 124.40, 123.11, 121.96, 120.76, 114.28, 107.73; IR (KBr) 2973, 2209, 1435, 1053 cm^{-1}; HRMS calcd for $C_{17}H_9NS_3$ 322.9897, found 322.9923. Anal. Calcd for $C_{17}H_9NS_3 \cdot 1/2\ H_2O$: C, 61.41; H, 3.03; N, 4.21; S, 28.93. Found: C, 61.11; H, 3.14; N, 4.13; S, 28.69.

1,3-Di(2-thienyl)benzo[*c*]thiophene-5,5′-dicarbonitrile (7b): red crystals, mp 226−228 °C; ^1H NMR ($CDCl_3$) δ 7.95 (d, 1H, J = 2.96 Hz), 7.93 (d, 1H, J = 3.14 Hz), 7.66 (d, 2H, J = 3.96 Hz), 7.35 (d, 2H, J = 3.95 Hz), 7.32 (d, 1H, J = 2.92 Hz), 7.30 (d, 1H, J = 2.97 Hz); ^{13}C NMR ($CDCl_3$) δ 142.01, 138.08, 136.41, 126.75, 126.18, 125.57, 121.20, 113.91, 109.19; IR (KBr) 2958, 2925, 2199, 1432 cm^{-1}. Anal. Calcd for $C_{18}H_8N_2S_3$: C, 62.04; H, 2.31; N, 8.04; S, 27.60. Found: C, 61.88; H, 2.41; N, 7.92; S, 27.65.

2-Cyanonaphthalene (8): white solid, mp 64−66 °C (mp lit.[14] 66 °C); ^1H NMR ($CDCl_3$) δ 8.22 (s, 1H), 7.91−7.87 (m, 3H), 7.65−7.57 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 134.56, 134.04, 132.15, 129.10, 128.96, 128.31, 127.96, 127.57, 126.23, 119.17, 109.30; IR (KBr) 3057, 2930, 2226 cm^{-1}.

9-Cyanoanthracene (9): yellow solid, mp 167.5−169 °C (mp lit.[15] 170−172 °C); ^1H NMR ($CDCl_3$) δ 8.69 (s, 1H), 8.43 (d, 2H, J = 8.59 Hz), 8.09 (d, 2H, J = 8.49 Hz), 7.73 (t, 2H, J = 7.99 Hz), 7.60 (t, 2H, J = 6.75 Hz); ^{13}C NMR ($CDCl_3$) δ 133.21, 132.66, 130.53, 128.88, 128.26, 126.28, 125.19, 117.20, 105.32; IR (KBr) 3059, 2210, 735 cm^{-1}.

Acknowledgment. The authors thank the National Science Foundation for a grant (CHE-9612350) in partial support of this work.

JO981924W

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