Synthesis of 4,4-Disubstituted 2,3-Dicyano-5-imino-2-pyrrolines. Reaction of Alkylidenemalononitriles with Trimethylsilyl Cyanide

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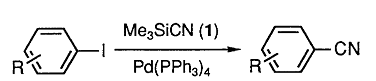
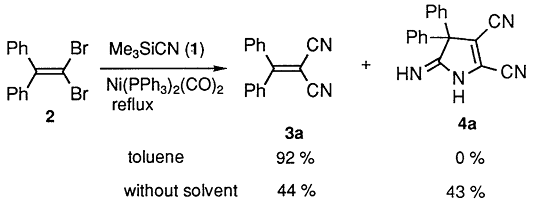
Synopsis. The reaction of alkylidenemalononitriles with trimethylsilyl cyanide in the presence of KCN/18-crown-6 gave 4,4-disubstituted 2,3-dicyano-5-imino-2-pyrrolines in high yields.

In a series of transition metal-catalyzed reaction of trimethylsiyl cyanide (**1**),[1] we have already reported that **1** reacted with aryl iodides in the presence of $Pd(PPh_3)_4$ to give aryl cyanides in good yields (Eq. 1).[2]



(1)

During the examination of scope and limitations of the cyanation reaction, we found that 1,1-dibromo-2,2-diphenylethylene (**2**) reacted with **1** in refluxing toluene in the presence of $Ni(PPh_3)_2(CO)_2$ gave (diphenylmethylene)malononitrile (**3a**) in 92% yield (Eq.2). However, 2,3-dicyano-4,4-diphenyl-5-imino-2-pyrroline (**4a**) was obtained along with **3a** when the reaction was carried out without solvent. It was expected that **4a** would be produced by a further reaction of the primary product **3a** with **1**. Actually, **4a** was obtained in a high yield from the Ni-catalyzed reaction of **3a** with 1. As a result of optimization of the reaction conditions, we have found that the nickel catalyst was not neccessary to proceed the construction of pyrroline ring from **3**. We now wish to report that the reaction of alkylidenemalononitriles **3** with **1** gave 4,4-disubstituted 2,3-dicyano-5-imino-2-pyrrolines (**4**) in high yields (Eq. 3).[3]

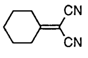
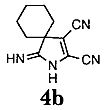
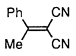
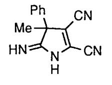
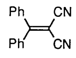
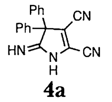


(2)

(3)

The results are summarized in Table 1. Cyclohexylidenemalononitrile (**3b**) was used as substrate for optimization of the reaction conditions. Higher temperatures gave higher yields (Entries 1—3). Formation of **4b** proceeded even the reaction temperature was 25 °C and even no catalyst was present (Entry 3). Although the presence of KCN did not affect the yield of the **4b** (Entry 4), we have found that a small

Table 1. Reaction of Alkylidenemalononitriles with Me_3SiCN (**1**)[a)]

Entry	Substrate	Temp/°C	Catalyst	Product	Yield/%[b)]
1	 **3b**	Reflux	—	 **4b**	92
2	**3b**	80	—	**4b**	82
3	**3b**	25	—	**4b**	52
4	**3b**	25	KCN	**4b**	60
5	**3b**	25	KCN/18-crown-6	**4b**	98
6	 **3c**	25	KCN/18-crown-6	 **4b**	50
7	 **3a**	25	KCN/18-crown-6	 **4a**	26
8	**3a**	50	KCN/18-crown-6	**4a**	86

a) Reaction conditions: alkylidenemalononitrile (2.5 mmol), Me_3SiCN (15 mmol, 2.0 ml), KCN (0.1 mmol), 18-crown-6 (0.1 mmol) for 20 h. b) Isolated yields based on the substrate.

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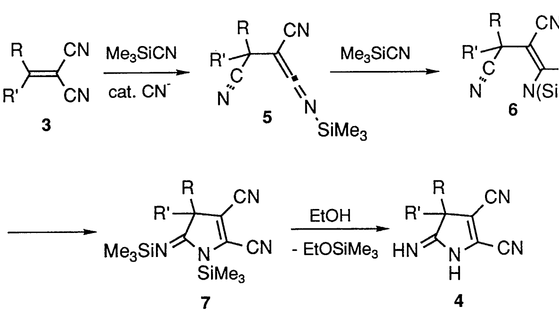
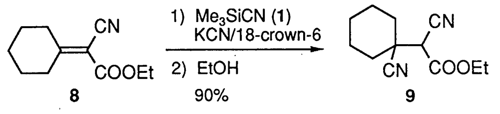


Scheme 1.

amount of KCN/18-crown-6 are exceptionally mild and efficient catalyst for the formation of **4b** (Entry 5).[4] Phenyl-substituted alkylidenemalononitriles **3a** and **3c** gave the corresponding 2,3-dicyano-5-imino-2-pyrrolines **4a** and **4c**, respectively (Entries 6—8). The reaction of benzylidenemalononitrile (**3d**), which has a hydrogen at the vinylic position, with **1** gave a complex mixture.

A plausible reaction path is shown in Scheme 1. Michael addition of **1** to alkylidenemalononitrile **3** catalyzed by CN$^-$[5] gave a ketenimine **5** to which **1** added to give intermediate **6**. Ring closure of **6** by an intramolecular nucleophilic attack of the silylamino group at the cyano group led silyl-protected 2,3-dicyano-5-imino-2-pyrroline derivative **7**. Desilylation of **7** by EtOH gave a pyrroline **4**.

The reaction of cyclohexylidenecyanoacetate (**8**) did not give an expected product but hydrocyanation product **9** was obtained as a sole product (Eq. 4).



(4)

In summary, we found that alkylidenemalononitriles are the presursor for the preparation of 4,4-disubstituted 2,3-dicyano-5-imino-2-pyrrolines,[6] which would be useful intermediates for organic synthesis because of their multi-functionalities.[7]

Experimental

General. Melting points (mp) were determined on a Yanagimoto micro melting point apparatus and uncorrected. Infrared spectra were obtained on a Hitachi 260-10 spectrometer. Peaks are reported in units of cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM 360 spectrometer and are reported in ppm from tetramethylsilane or chloroform as an internal standard on the δ scale. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br=broad), coupling constant, integration, and interpretation. Mass spectra were obtained on a JMS-DX 300 with ionization voltages of 70 eV. Elemental analyses were performed on a Perkin-Elmer 240C by the ISIR Material Analysis Center in Osaka University.

Materials. 1,1-Dibromo-2,2-diphenylethylene (**2**) was prepared by the literature method.[8] Alkylidenemalononitriles (**3**) were prepared from the Knoevenagel reaction[9] of corresponding ketones with malononitrile according to the method reported previously by our group.[10] Trimethylsilyl cyanide was obtained from Tokyo Kasei Co., and distilled from CaH$_2$. 18-Crown-6 was purchased from Aldrich Co., and recrystallized from CH$_3$CN.

General Procedure for the Reaction of Alkylidenemalononitriles with Trimethylsilyl Cyanide. To a solution of alkylidenemalononitrile (2.5 mmol) and Me$_3$SiCN (15 mmol, 2.0 ml) was added KCN/18-crown-6 (0.1 mmol/0.1 mmol). The solution was stirred at 25 °C for 20 h and exess Me$_3$SiCN was distilled in vacuo. To the residue was added EtOH (20 ml) and the mixture was stirred at 25 °C for 1 h. Recrystallization of the residue from acetone/hexane gave 4,4-disubstituted 2,3-dicyano-5-imino-2-pyrrolines. Spectral samples were obtained by recrystallization from EtOH.

2,3-Dicyano-5-imino-4,4-pentamethylene-2-pyrroline (4a). White solid, mp 220 °C (decomp); IR (Nujol) 3360, 3330, 2230, 2205, 1675, 1650, 1550 cm^{-1}; ^{1}H NMR (acetone-d_6) δ=1.74—1.96 (c, 10 H, CH$_2$), 7.63 (br, 1 H, NH), 8.04 (br, 1 H, NH); ^{13}C NMR (acetone-d_6) δ=22.58, 25.24, 34.12, 58.54, 112.2, 114.3, 116.7, 142.0, 185.6; MS m/z 200 (M$^+$). Found: C, 66.01; H, 5.85; N, 27.77%. Calcd for $C_{11}H_{12}N_4$: C, 65.98; H. 6.04; N, 27.98%.

2,3-Dicyano-5-imino-4-methyl-4-phenyl-2-pyrroline (4b). White solid; mp 218 °C (decomp); IR (Nujol)2420, 2230, 2200, 1655, 1570; ^{1}H NMR (acetone-d_6) δ=1.84 (s, 3H, CH$_3$), 7.43 (d, J=7.0 Hz, 2 H, Ph), 7.44—7.46 (m, 3 , Ph), 7.65(br, 1 H, NH), 8.14 (br, 1 H, NH); ^{13}C NMR (acetone-d_6) δ=20.52, 61.58, 113.7, 114.1, 116.2, 127.0, 129.5, 130.2, 136.7, 140.2, 185.5. MS m/z 222 (M$^+$); Found: C, 69.96; H, 4.16; N, 24.55%. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21%.

2,3-Dicyano-4,4-diphenyl-5-imino-2-pyrroline (4c). White solid; mp 280 °C (decomp); IR (Nujol) 3400, 2210, 1670, 1560; ^{1}H NMR (acetone-d_6) δ=7.29—7.51 (m, 10 H, Ph), 8.69(br, 2 H, NH); MS m/z 284 (M$^+$). Found: C, 76.25; H, 4.13; N, 19.29%. Calcd for $C_{18}H_{12}N_4$: C, 76.04; H, 4.25; N, 19.71%.

Ethyl Cyano(1-cyanocyclohexyl)acetate (11). Colorless oil; IR (neat) 2250, 2240, 1745; ^{1}H NMR (CDCl$_3$) δ=4.33 (q, J=7.2 Hz, 2 H, CH$_2$O), 3.65 (s, 1 H, CH), 2.24 (m, 1 H, CH$_2$), 2.08 (m, 1 H, CH), 1.53—1.88 (m, 8 H, CH$_2$), 1.37 (t, J=7.2 Hz, 3 H, CH$_3$); MS, m/z 220 (M$^+$).

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