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단 신

N-메틸-2-피리딜 시안아미드 및 2-피리딜 치오시아네이트와 Grignard 시약의 반응. 니트릴 및 설파이드의 합성

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Reaction of *N*-Methyl-2-pyridyl Cyanamide and 2-Pyridyl Thiocyanate with Grignard Reagents. Formation of Nitriles and Sulfides

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The reaction of cyanate, cyanamide, and thiocyanate reagents with organometallics has been known to produce nitriles. The procedures for preparing nitriles using cyanate reagents involve the reaction of cyanogen,[1] cyanogen chloride,[2] and cyanogen bromide[3] which are highly volatile and toxic with appropriate organometallics. The reaction of alkyl[4] and aryl cyanates[4,5] with Grignard or RLi (R=vinyl, alkynyl) reagents affords nitriles, but the separation of the corresponding alcohol is often tedious. Although the reaction of 2-pyridyl cyanate[6] with Grignard reagents can circumvent this limitation, this reagent begin to decompose slowly after *ca.* 2 weeks in a refrigerator. *p*-Toluenesulfonyl cyanide[7] has been also utilized for converting functionalized organozinc halides into polyfunctional nitriles.

However, only few examples of the reaction of cyanamide and thiocyanate reagents with organometallics have been reported. The treatment of *N*-methylphenyl cyanamide[8] with Grignard reagents affords nitriles, but the yields are low. Furthermore, reactions between thiocyanate reagents[9] and Grignard reagents have received very little attention because they result in concomitant substitution of the CN group and the thioalkyl group to give a mixture of the sulfides and the nitriles. Although the reaction of 1-alkynyl thiocyanate[10] with methyl lithium produces the corresponding sulfide, the scope of the reaction is not fully investigated. Herein, we report that nitriles and sulfides can be selectively prepared by the treatment of *N*-methyl-2-pyridyl cyanamide **1** and 2-pyridyl thiocyanate **3** with Grignard reagents, respectively.

EXPERIMENTAL

Preparation of *N*-methyl-2-pyridyl cyanamide (1). To a 2-(methylamino)pyridine (540.7 mg, 5.0 mmol) in THF (10 mL) was slowly added *tert*-butylmagnesium chloride (1 M in THF, 5.0 mL, 5.0 mmol) at 0 °C. After being stirred for 0.5 h, the resulting solution was added to 2-pyridyl cyanate (572 mg, 4.76 mmol) in THF (5.0 mL) at 0 °C. After 0.5 h, the reaction mixture was quenched with sat. NH_4Cl (2.0 mL) and THF was evaporated under vacuum. The reaction mixture was extracted with dichloromethane (3×25 mL) and washed with sat. NH_4Cl (30 mL). The organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness under vacuum. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/1) to give reagent **1** (570.4 mg, 90%). M.p. 41 °C; FT-IR (KBr) 3077, 3027, 2957,

2220, 1590, 1471, 1439, 1340, 1300, 775, 732 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.34(d, *J*=5 Hz, 1H), 7.74~7.68(m, 1H), 7.20(d, *J*=8 Hz, 1H), 7.03~6.99 (m, 1H), 3.44(s, 3H); Ms *m/z*(%) 133(M^+, 57), 107(27), 93(8), 79(100), 78(43), 51(25).

Preparation of *p*-methylbenzonitrile (2f) <typical procedure>. To a reagent **1** (266.3 mg, 2.0 mmol) in THF (2.0 mL) was added *p*-methylphenylmagnesium bromide (0.32 M in THF, 6.25 mL, 2.0 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 1.5 h between 0 °C and room temperature, the reaction mixture was quenched with 0.025 M oxalic acid (40 mL), extracted with dichloromethane (3×15 mL), dried with anhydrous $MgSO_4$, filtered, and evaporated to dryness under vacuum. The crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/4) to give compound **2f** (196.8 mg, 84%). FT-IR(film) 3038, 2925, 2229, 1609, 1514, 817 cm^{-1}; ^1H NMR($CDCl_3$) δ 7.46(d, *J*=8 Hz, 2H), 7.17(d, *J*=8 Hz, 2H), 2.40(s, 3H). Spectral data, **2a**: IR(film) 2965, 2240 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.37 (t, *J*=6 Hz, 2H), 2.20~1.12(m, 12H), 0.99(t, *J*= 6 Hz, 3H). **2b**: IR (film) 3040, 2920, 2240 cm^{-1}; ^1H NMR($CDCl_3$) δ 7.40~7.00(m, 5H), 2.65(t, *J*=7 Hz, 2H), 2.50~1.81(m, 4H). **2c**: IR(film) 2930, 2230 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.65(m, 1H), 1.75~ 1.05(m, 10H). **2d**: IR(film) 3030, 2227 cm^{-1}; ^1H NMR($CDCl_3$) δ 7.40~6.40(m, 4H), 2.25(s, 3H). **2e**: IR(film) 3050, 2960, 2220 cm^{-1}; ^1H NMR($CDCl_3$) δ 7.58(d, *J*=8 Hz, 2H), 6.95(d, *J*=8 Hz, 2H), 3.85 (s, 3H). **2g**: IR(film) 3060, 2240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05~7.27(m, 4H). **2h**: IR(film) 3065, 2235 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.24~7.50(m, 4H), 7.50~7.18(m, 3H). **2i**: IR(film) 3020, 2930, 2230 cm^{-1}; ^1H NMR($CDCl_3$) δ 6.90(s, 2H), 2.50(s, 6H), 2.40(s, 3H).

Preparation of 2-pyridyl thiocyanate (3). To a cyanogen bromide (3 M in CH_2Cl_2, 3.0 mL, 9.0 mmol) in THF (12.0 mL) was slowly added an equimolar solution of 2-mercaptopyridine (1.0005 g, 9.0 mmol) and pyridine (728 μL, 9.0 mmol) in THF (15.0 mL) at 0 °C. After 0.5 h, pyridinium hydrobromide was filtered off. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (EtOAc/*n*-hexane=1/4) to give reagent **3** (1.1398 g, 93%). FT-IR(film) 3053, 2162, 1573, 1450, 1421, 1120, 761 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.34(d, *J*=5 Hz, 1H), 7.50~7.46(m, 2H), 6.99(dd, *J*=5, 8 Hz, 1H); Ms *m/z*(%) 138(M^++2, 3), 136(M^+, 59), 110(1), 78(100), 51(27).

Preparation of ethyl 2-pyridyl sulfide (4a) <typical procedure>. To a reagent **3** (272.3 mg, 2.0 mmol) in THF (2.0 mL) was added ethylmagnesium bromide (0.37 M in THF, 5.4 mL, 2.0 mmol) at 0 °C under nitrogen atmosphere. After 15 min, the reaction mixture was quenched with sat. NH_4Cl (20 mL), extracted with dichloromethane (3×15 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under vacuum. The crude product was purified by silica gel column chromatography (EtOAc/ *n*-hexane=1/4) to give compound **4a** (253.4 mg, 91%). FT-IR(film) 3045, 2969, 2927, 1579, 1556, 1454, 1414, 1127, 757, 723 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 8.43(d, *J*=5 Hz, 1H), 7.51~7.45(m, 1H), 7.17(d, *J*=8 Hz, 1H), 6.99~6.95(m, 1H), 3.17(q, *J*=7 Hz, 2H), 1.38(t, *J*=7 Hz, 3H); Ms *m/z*(%) 141(M^++2, 2.5), 139(M^+, 51), 124(48), 111(27), 106(100), 79(48), 67(40). Spectral data, **4b**: IR(film) 3045, 2920 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.20(d, *J*=4 Hz, 1H), 7.54~6.41(m, 4H), 6.41~5.56(m, 1H), 1.71(d, *J*=6 Hz, 3H). **4c**: IR(film) 3040, 2926 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.22(d, *J*=4 Hz, 1H), 7.54~6. 70(m, 3H), 3.50~2.90(m, 1H), 2.04~1.12(m, 10H). **4d**: IR(film) 3050 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.21(d, *J*=4 Hz, 1H), 7.80~7.07(m, 7H), 6.94~6.55(m, 1H). **4e**: IR(film) 3040, 2970 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.21(d, *J*=4 Hz, 1H), 7.82~6.99(m, 5H), 6.99~ 6.41(m, 2H), 2.35(s, 3H). **4f**: IR(film) 3050, 2970 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.15 (d, *J*=5 Hz, 1H), 7.30(d, *J*=8 Hz, 2H), 6.72(d, *J*=8 Hz, 2H), 7.35~ 6.50(m, 3H), 3.62(s, 3H). **4g**: IR(film) 3043, 2987 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.40(d, *J*=5 Hz, 1H), 7.97~6.76(m, 7H), 2.49(s, 3H). **4h**: IR(film) 3040 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.43(d, *J*=5 Hz, 1H), 7.55~7.41(m, 1H), 7.53(d, *J*=9 Hz, 2H), 7.39(d, *J*=9 Hz, 2H), 7.06~7.02(m, 1H), 6.94(d, *J*=8 Hz, 1H). **4i**: IR(film) 3040, 2919 cm^{-1}; ^1H NMR($CDCl_3$) δ 8.19 (d, *J*=4 Hz, 1H), 7.40~6.48(m, 3H), 6.77(s, 2H), 2.21(s, 6H), 2.16(s, 3H).

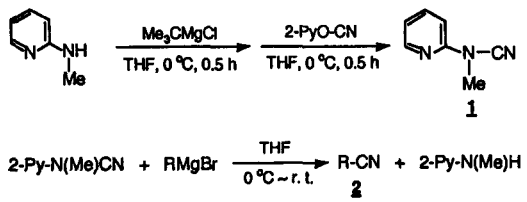
RESULTS AND DISCUSSION

Reaction of *N*-methyl-2-pyridyl cyanamide with Grignard reagents. Initial attempt to prepare reagent **1** by addition of an equimolar solution of 2-(methylamino)pyridine and pyridine in THF to a cyanogen bromide was fruitless. The procedure by the von Braun reaction[11] of 2-dimethylaminopyridine and cyanogen bromide was not also successful. Finally, we prepared **1** by addition of 2-(methylamino)pyridylmagnesium chloride, generated from 2-(methylamino)pyridine and *tert*-butylmagnesium chloride, to an equimolar solution of 2-pyridyl cyanate in THF at 0 °C in 90% yield (*Scheme* 1). The reagent **1** was very stable crystalline compound and showed no sign of decomposition in a refrigerator for several months.

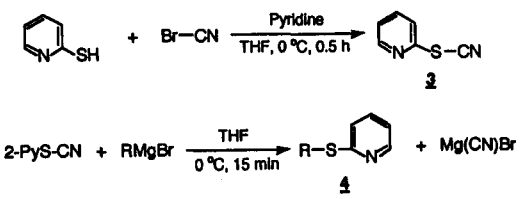
The success of nitriles synthesis using **1** depends largely on selective substitution of the 2-(methylamino)pyridyl group without concomitant addition of the cyano group. The treatment of **1** with 1 equiv of *p*-methylphenylmagnesium bromide gave the *p*-methylbenzonitrile **2f** within 1.5 h between 0 °C and room temperature and there was no observable by-product such as the corresponding ketone. The preferential formation of nitrile may be ascribed to the formation of six-membered chelate, coordinated between two nitrogen atoms of **1** and magnesium atom of Grignard reagent.

The result of nitriles synthesis was summarized in *Table* 1. In general, nitriles **2a~i** were obtained in satisfactory yields. The reaction worked well with both aliphatic (**2a~2c**) and aromatic Grignard reagents (**2d~2i**), but the cyanation of hindered 2,4,6-trimethylphenylmagnesium bromide (**2i**) proceeded slowly. The cyanation of *p*-methoxy (**2e**), *p*-methyl (**2f**), and *p*-chlorophenylmagnesium bromide (**2g**, 1.5 equiv) with **1** required 1 h, 1.5 h, and 5 h, respectively, for the completion of the reaction, reflecting a nucleophilic order of the corresponding Grignard reagents.

Reaction of 2-pyridyl thiocyanate with Grignard reagents. The reagent **3** was prepared by addition of an equimolar solution of 2-mercaptopyridine and pyridine in THF to a cyanogen bromide at 0 °C (*Scheme* 2). The use of triethylamine as a base for the preparation of **3** led to competing von Braun degradation which produced by-product diethylcyanamide (~10%). The reagent **3** was se-



Scheme 1.



Scheme 2.

Table 1. Preparation of Nitriles from *N*-Methyl-2-pyridyl cyanamide and Grignard reagents

Entry **2**	RMgBr R	Reaction time, h	Product R-CN	Isolated yield, %
a	$CH_3(CH_2)_7$	1	$CH_3(CH_2)_7CN$	82
b	$C_6H_5(CH_2)_3$	4	$C_6H_5(CH_2)_3CN$	81
c	*c*-C_6H_{11}[a,b]	3	*c*-$C_6H_{11}CN$	84
d	*o*-CH_3-C_6H_4	4	*o*-CH_3-C_6H_4CN	90
e	*p*-CH_3O-C_6H_4	1	*p*-CH_3O-C_6H_4CN	97
f	*p*-CH_3-C_6H_4	1.5	*p*-CH_3-C_6H_4CN	84
g	*p*-Cl-C_6H_4[b]	5	*p*-Cl-C_6H_4CN	81
h	α-Naphtyl	6	α-Naphtyl-CN	74
i	2,4,6-$(CH_3)_3$-C_6H_2	7	2,4,6-$(CH_3)_3$-C_6H_2CN	82

[a]The corresponding magnesium chloride was used. [b]1.5 equiv was used.

Table 2. Preparation of Alkyl 2-pyridyl sulfides from 2-Pyridyl thiocyanate and Grignard reagents[a]

Entry 4	RMgBr R	Product R-S-2-Py	Isolated yield, %
a	CH_3CH_2	CH_3CH_2-S-2-Py	91
b	CH_3CH=CH	CH_3CH=CH-S-2-Py	90
c	*c*-C_6H_{11}[b]	*c*-C_6H_{11}-S-2-Py	80
d	C_6H_5	C_6H_5-S-2-Py	93
e	*o*-CH_3-C_6H_4	*o*-CH_3-C_6H_4-S-2-Py	95
f	*p*-CH_3O-C_6H_4	*p*-CH_3O-C_6H_4-S-2-Py	88
g	*p*-CH_3-C_6H_4	*p*-CH_3-C_6H_4-S-2-Py	90
h	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4-S-2-Py	93
i	2,4,6-$(CH_3)_3$-C_6H_2	2,4,6-$(CH_3)_3$-C_6H_2-S-2-Py	92

[a]The reaction was carried out for 15 min at 0 °C. [b]The corresponding magnesium chloride was used.

parated by filtering off pyridinium hydrobromide and obtained in 93% yield after silica gel column chromatography.

In contrast with reagent **1**, nucleophilic displacement on the **3** by Grignard reagent took place on the sulfur atom, resulting in the formation of the corresponding alkyl 2-pyridyl sulfide. Thus, the treatment of **3** with 1 equiv of *p*-chlorophenylmagnesium bromide gave the *p*-chlorophenyl 2-pyridyl sulfide **4h** without the formation of *p*-chlorobenzonitrile. The preferential attack on the sulfur atom seems to result from the ability of sulfur to stabilize negative charge by vacant 3d orbital.

The reaction of **3** with Grignard reagents was completed within 15 min at 0 °C and the result was summarized in *Table* 2. The reaction worked well with both aliphatic (**4a~4c**) and aromatic Grignard reagents (**4d~4i**), including 1-propenylmagnesium bromide (**4b**) and hindered 2,4,6-trimethylphenylmagnesium bromide (**4i**). The presence of electron-donating or electron-withdrawing group in *p*-substituted phenylmagnesium bromide didn't affect the efficiency of the reaction under the present reaction conditions.

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