Synthesis of Ferrocenyl-Substituted 3-Cyano-2-methylpyridines

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Synopsis. Ferrocenyl-substituted 3-cyano-2-methylpyridines were easily prepared by the sonication of α,β-unsaturated carbonyl compounds substituted by ferrocenes in acetonitrile in the presence of potassium *t*-butoxide.

Though many methods to synthesize pyridines have been reported, those of ferrocenylpyridines are unknown.[1] Recently, we have reported synthesis of 3-cyano-2-methylpyridines under ultrasound irradiation.[2]

Since 3-cyanopyridines can be easily converted into the corresponding nicotinic acids[3] and nicotinamides,[4] which are known to be important vitamines,[5] the ferrocenyl-substituted 3-cyanopyridines might be precursors of the nicotinic acids and nicotinamides with a ferrocenyl group. In this report, synthesis of ferrocenyl-substituted 3-cyano-2-methylpyridines have been examined.

Results and Discussion

An acetonitrile suspension containing potassium *t*-butoxide was sonicated and α,β-unsaturated carbonyl compounds substituted by a ferrocenyl group **1** were added to the suspension, followed by sonication. After the reaction is over, the suspension was poured into brine and extracted with ether. After evaporation of the ether, resultant residue was recrystallized from ethanol. The ferrocenyl-substituted 3-cyano-2-methylpyridines **2** obtained are shown in Table 1. The yields of 3-cyano-2-methylferrocenyl-pyridines **2** were fair to good.

As previously proposed,[2] the mechanism for the formation of ferrocenyl-substituted pyridines seems to involves the Michael additions of the acetonitrile dimers to the chalcones containing ferrocenyl groups, followed by dehydration and dehydrogenation.

In conclusion, the ultrasound irradiation of α,β-unsaturated carbonyl compounds in acetonitrile in the presence of potassium *t*-butoxide offers a convenient and effective method to prepare ferrocenyl-substituted 3-cyano-2-methylpyridines.

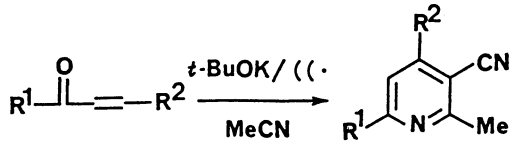
Experimental

Instruments. Sonication was carried out by using a Branson ultrasonic cleaner (150 W, 47 kHz). Melting points were measured with a Yanagimoto micro melting point apparatus and uncorrected. NMR and mass spectra were recorded with JEOL GX-270 and Shimadzu QP-1000 spectrometers, respectively.

Synthesis of α,β-Unsaturated Carbonyl Compounds. A General Procedure: To an ethanol solution (15 ml) containing a methyl ketone (0.02 mol) and 10% aqueous potassium hydroxide (15 ml) was added an aldehyde (0.02 mol) and the mixture was stirred at room temperature for 2 h. After the reaction is over, the precipitate was filtered and recrystallized from methanol. Physical and spectral data of the resulting enones are shown below:

1-Ferrocenyl-3-phenyl-2-propen-1-one (**1a**). Yield: 95%; mp 141—142 °C (lit,[6] mp 141—142 °C).

Table 1. Synthesis of Ferrocenyl-Substituted 3-Cyano-2-methylpyridines **2**



1 **2**

Run	Compd	R^1	R^2	Isolated yield of **2**/%
1	**a**	Ferrocenyl	Phenyl	82
2	**b**	Ferrocenyl	2-Furyl	55
3	**c**	Ferrocenyl	2-Thienyl	63
4	**d**	Ferrocenyl	2-Pyridyl	89
5	**e**	Ferrocenyl	4-Chlorophenyl	80
6	**f**	Ferrocenyl	4-Methoxyphenyl	85
7	**g**	Ferrocenyl	1-Naphthyl	60
8	**h**	Ferrocenyl	Ferrocenyl	80
9	**i**	*t*-Butyl	Ferrocenyl	74
10	**j**	Phenyl	Ferrocenyl	82
11	**k**	2-Furyl	Ferrocenyl	85
12	**l**	2-Thienyl	Ferrocenyl	88
13	**m**	2-Pyridyl	Ferrocenyl	68
14	**n**	4-Chlorophenyl	Ferrocenyl	63
15	**o**	4-Methoxyphenyl	Ferrocenyl	76

1-Ferrocenyl-3-(2-furyl)-2-propen-1-one (**1b**). Yield 46%; mp 155—157 °C (lit,[6] mp 158 °C).

1-Ferrocenyl-3-(2-thienyl)-2-propen-1-one (**1c**). Yield 56%; mp 145—147 °C (lit,[6] mp 149 °C).

1-Ferrocenyl-3-(2-pyridyl)-2-propen-1-one (**1d**). Yield 44%; mp 152—153 °C (lit,[6] mp 153 °C).

3-(4-Chlorophenyl)-1-ferrocenyl-2-propen-1-one (**1e**). Yield 57%; mp 160—161 °C (lit,[6] 160 °C).

1-Ferrocenyl-3-(4-methoxyphenyl)-2-propen-1-one (**1f**). Yield 58%; mp 153—154 °C (lit,[6] mp 150 °C).

1-Ferrocenyl-3-(1-naphthyl)-2-propen-1-one (**1g**). Yield 60%; mp 137—139 °C; ^{1}H NMR ($CDCl_3$) δ=4.25 (s, 5H),4.62 (t, J=1.7 Hz, 2H), 4.95 (t, J=1.7 Hz, 2H), 7.21 (d, J=15.4 Hz, 1H), 7.51—8.33 (m, 7H), and 8.63 (d, J=1.5 Hz, 1H); MS (20 eV) m/z (rel intensity) 366 (M^+, 100). Found: C, 75.57; H, 4.78%. Calcd for $C_{23}H_{18}OFe$: C, 75.43; H, 4.95%.

1,3-Diferrocenyl-2-propen-1-one (**1h**). Yield 57%; mp 211—213 °C (lit,[6] 210 °C).

1-(*t*-Butyl)-3-ferrocenyl-2-propen-1-one (**1i**). Yield 27%; mp 108—109 °C; ^{1}H NMR ($CDCl_3$) δ=1.19 (3, 9H), 4.14 (s, 5H), 4.42 (t, J=1.7 Hz, 2H), 4.52 (t, J=1.7 Hz, 2H), 7.21 (d, J=15.4 Hz, 1H), and 7.57 (d, J=15.4 Hz, 1H); MS (20 eV) m/z (rel intensity) 296 (M^+, 73) and 239 (100). Found: C, 69.02; H, 6.65%. Calcd for $C_{17}H_{20}OFe$: C, 68.94; H, 6.81%.

3-Ferrocenyl-1-phenyl-2-propen-1-one (**1j**). Yield 95%; mp 134—135 °C (lit,[6] mp 140 °C).

3-Ferrocenyl-1-(2-furyl)-2-propen-1-one (**1k**). Yield 73%; mp 120—121 °C; ^{1}H NMR ($CDCl_3$) δ=4.18 (s, 5H), 4.49 (t, J=1.7 Hz, 2H), 4.61 (t, J=1.7 Hz, 2H), 6.58 (dd, J=3.4 and 1.7 Hz, 1H), 7.04 (d, J=15.8 Hz, 1H), 7.28 (d, J=3.4 Hz, 1H), 7.64 (d, J=1.7 Hz, 1H), and 7.83 (d, J=15.8 Hz, 1H); MS (20 eV) m/z (rel intensity) 306 (M^+, 100). Found: C, 66.81; N, 4.42%. Calcd for $C_{17}H_{14}O_2Fe$: C, 66.70; H, 4.61%.

3-Ferrocenyl-1-(2-thienyl)-2-propen-1-one (**1l**). Yield 75%; mp 129—130 °C (lit,[6] mp 136 °C).

3-Ferrocenyl-1-(2-pyridyl)-2-propen-1-one (**1m**). Yield 82%; mp 164—165 °C (lit,[6] 158 °C).

1-(4-Chlorophenyl)-3-ferrocenyl-2-propen-1-one (**1n**) Yield 76%; mp 166—167 °C; ^{1}H NMR ($CDCl_3$) δ=4.19 (s, 5H), 4.51 (t, J=1.7 Hz, 2H), 4.60 (t, J=1.7 Hz, 2H), 7.08 (d, J=15.4 Hz, 1H), 7.47 (d, J=8.6 Hz, 2H), 7.77 (d, J=15.4 Hz, 1H), and 7.93 (d, J=8.6 Hz, 2H); MS (20 eV) m/z (rel intensity) 350 (M^+, 100). Found: C, 65.18; H, 4.19%. Calcd for $C_{19}H_{15}OClFe$: C, 65.09; H, 4.31%.

3-Ferrocenyl-1-(4-methoxyphenyl)-2-propen-1-one (**1o**). Yield 90%; mp 152—153 °C; ^{1}H NMR ($CDCl_3$) δ=3.89 (s, 3H), 4.18 (s, 5H), 4,47 (s, 2H), 4.59 (s, 2H), 6.98 (d, J=8.8 Hz, 2H), 7.14 (d, J=15.0 Hz, 1H), 7.74 (d, J=15.0 Hz, 1H), and 8.01 (d, J=8.8 Hz, 2H); MS (20 eV) m/z (rel intensity) 346 (M^+, 99) and 281 (100). Found: C, 69.27; H, 5.09%. Calcd for $C_{20}H_{18}O_2Fe$: C, 69.39; H, 5.24%.

Synthesis of 3-Cyano-2-methylpyridines. A General Procedure: A suspension of potassium *t*-butoxide (110 mg) in acetonitrile (20 ml) was sonicated at 35 °C for 15 min. α,β-Unsaturated carbonyl compound **1** (10 mmol) was added to the suspension and sonicated for additional 2 h. After the reaction is over, the suspension was poured into brine (50 ml) and extracted with ether (30 ml×2). The extract was dried with sodium sulfate. The solvent was evaporated and the residue was recrystallized from ethanol. Physical and spectral data of the resulting pyridines are shown below:

3-Cyano-6-ferrocenyl-2-methyl-4-phenylpyridine (**2a**). Mp 190—192 °C; ^{1}H NMR ($CDCl_3$) δ=2.83 (s, 3H), 4.07 (s, 5H), 4.50 (t, J=1.7 Hz, 2H), 4.99 (t, J=1.7 Hz, 2H), 7.28 (s, 1H), and 7.52—7.64 (m, 5H); MS (20 eV) m/z (rel intensity) 378 (M^+, 100) and 313 (19). Found: C, 72.89; N, 4.96; N, 7.57%. Calcd for $C_{23}H_{18}N_2Fe$: C, 73.03; H, 4.80; N, 7.41%.

3-Cyano-6-ferrocenyl-4-(2-furyl)-2-methylpyridine (**2b**). Mp 175—176 °C; ^{1}H NMR ($CDCl_3$) δ=2.78 (s, 3H), 4.07 (s, 5H), 4.50 (t, J=1.8 Hz, 2H), 5.01 (t, J=1.8 Hz, 2H), 6.62 (dd,J=3.7 and 1.8 Hz, 1H), 7.57 (d, J=3.7 Hz, 1H), 7.64 (d, J=1.8 Hz, 1H), and 7.64 (s, 1H); MS (20 eV) m/z (rel intensity) 368 (M^+, 100). Found: C, 68.74; H, 4.59; N, 7.81%. Calcd for $C_{21}H_{16}N_2OFe$: C, 68.84; H, 4.38; N, 7.60%.

3-Cyano-6-ferrocenyl-2-methyl-4-(2-thienyl)pyridine (**2c**). Mp 141—142 °C; ^{1}H NMR ($CDCl_3$) δ=2.80 (s, 3H), 4.07 (s, 5H), 4.50 (t, J=1.8 Hz, 2H), 4.98 (t, J=1.8 Hz, 2H), 7.21 (dd, J=5.1 and 4.0 Hz, 1H), 7.37 (s, 1H), 7.52 (dd, J=5.1 and 1.1 Hz, 1H), and 7.86 (dd, J=4.0 and 1.1 Hz, 1H); (20 eV) m/z (rel intensity) 384 (M^+, 100). Found: C, 65.35; N, 3.95; N, 7.32%. Calcd for $C_{21}H_{16}N_2SFe$: C, 65.63; H, 4.20; N, 7.29%.

3-Cyano-6-ferrocenyl-2-methyl-4-(2-pyridyl)pyridine (**2d**). Mp 182—183 °C; ^{1}H NMR ($CDCl_3$) δ=2.85 (s, 3H), 4.07 (s, 5H), 4.51 (t, J=1.8 Hz, 2H), 5.03 (t, J=1.8 Hz, 2H), 7.40—7.45 (m, 1H), 7.60 (s, 1H), 7.84—7.89 (m, 2H), and 8.81—8.83 (m, 1H); MS (20 eV) m/z (rel intensity) 379 (M^+, 100). Found: C, 69.87; N, 4.42; N, 10.93%. Calcd for $C_{22}H_{17}N_3Fe$: C, 69.67; N, 4.52; N, 11.08%.

4-(4-Chlorophenyl)-3-cyano-6-ferrocenyl-2-methylpyridine (**2e**). Mp 170—171 °C; ^{1}H NMR ($CDCl_3$) δ=2.82 (s, 3H), 4.08 (s, 5H), 4.52 (t, J=1.7 Hz, 2H), 4.99 (t, J=1.7 Hz, 2H), 7.23 (s, 1H), 7.51 (d, J=9.0 Hz, 2H), and 7.56 (d, J=9.0 Hz, 2H); MS (20 eV) m/z (rel intensity) 412 (M^+, 100). Found: C, 66.79; H, 3.92; N, 6.905. Calcd for $C_{23}H_{17}N_2ClFe$: C, 66.94; H 4.15; N, 6.79%.

3-Cyano-6-ferrocenyl-4-(4-methoxyphenyl)-2-methylpyridine (**2f**). Mp 129—130 °C; ^{1}H NMR ($CDCl_3$) δ=2.81 (s, 3H), 3.88 (s, 3H), 4.07 Is, 5H), 4.49 (t, J=1.7 Hz, 2H), 4.99 (t, J=1.7 Hz, 2H), 7.06 (d, J=8.8 Hz, 2H), 7.26 (s, 1H), and 7.59 (d, J=8.8 Hz, 2H); MS (20 eV) m/z (rel intensity) 408 (M^+, 100). Found: C, 70.75; H, 4.67; N, 6.97%. Calcd for $C_{24}N_{20}N_2OFe$: C, 70.61; H, 4.94; N, 6.86%.

3-Cyano-6-ferrocenyl-2-methyl-4-(1-naphthyl)pyridine (**2g**). Mp 207—209 °C ^{1}H NMR ($CDCl_3$) δ=2.86 (s, 3H), 4.10 (s, 5H), 4.49 (t, J=1.7 Hz, 2H), 4.98 (t, J=1.7 Hz, 2H), 7.35 (s, 1H), and 7.50—8.01 (m, 7H); MS (20 eV) m/z (rel intensity) 428 (M^+, 100). Found: C, 75.59; H, 4.66; N, 6.70. Calcd for $C_{27}H_{20}N_2Fe$: C, 75.71; H, 4.71; N, 6.54%.

3-Cyano-4,6-diferrocenyl-2-methylpyridine (**2h**). Mp 167—168 °C; ^{1}H NMR ($CDCl_3$) δ=2.78 (s, 3H) , 4.07 (s, 5H), 4.19 (s, 5H), 4.49 (t, J=1.8 Hz, 2H), 4.53 (t, J=1.8 Hz, 2H), 4.98 (t, J=1.8 Hz, 2H), 5.05 (t, J=1.8 Hz, 2H), and 7.34 (s, 1H); MS (20 eV) m/z (rel intensity) 486 (M^+, 100) and 421 (34). Found: C, 66.52; H, 4.46; N, 5.88 %. Calcd for $C_{27}H_{22}N_2Fe_2$: C, 66.70; H, 4.56; N, 5.76%.

6-(*t*-Butyl)-3-cyano-4-ferrocenyl-2-methylpyridine (**2i**). Mp 130—131 °C; ^{1}H NMR ($CDCl_3$) δ=1.37 (s, 9H), 2.76 (s, 3H), 4.15 (s, 5H), 4.49 (t, J=1.7 Hz, 2H), 4.98 (t, J=1.7 Hz, 2H), and 7.30 (s, 1H); MS (20 eV) m/z (rel intensity) 358 (M^+, 100). Found: C, 70.18; H, 6.37; N, 7.82%. Calcd for $C_{21}H_{22}N_2Fe$: C, 70.40; H, 6.19; N, 7.81%.

3-Cyano-4-ferrocenyl-2-methyl-6-phenylpyridine (**2j**). Mp 159—160 °C; ^{1}H NMR ($CDCl_3$) δ=2.86 (s, 3H), 4.19 (s, 5H), 4.55 (t, J=1.7 Hz, 2H), 5.09 (t, J=1.7 Hz, 2H), 7.49—7.52 (m, 3H), 7.68 (s, 1H), and 8.02—8.06 (m, 2H); MS (20 eV) m/z (rel intensity) 378 (M^+, 100) and 313 (51). Found: C, 73.27; H, 5.03; N, 7.23%. Calcd for $C_{23}H_{18}N_2Fe$: C, 73.03; H, 4.80; N, 7.41%.

3-Cyano-4-ferrocenyl-6-(2-furyl)-2-methylpyridine (**2k**). Mp 200—201 °C; ^{1}H NMR ($CDCl_3$) δ=2.80 (s, 3H), 4.18 (s, 5H), 4.55 (t, J=1.7 Hz, 2H), 5.10 (t. J=1.7 Hz, 2H), 6.59 (dd, J=3.4 and 1.7 Hz, 1H), 7.22 (d, J=3.4 Hz, 1H), 7.60 (d, J=1.7 Hz, 1H), and 7.56 (s, 1H); MS (20 eV) m/z (rel intensity) 368 (M^+, 100) and 303 (61). Found: C, 68.76; H, 4.51; N, 7.87%. Calcd for $C_{21}H_{16}N_2OFe$: C, 68.84; H, 4.38; N, 7.60%.

3-Cyano-4-ferrocenyl-2-methyl-6-(2-thienyl)pyridine (**2l**). Mp 156—157 °C; ^{1}H NMR ($CDCl_3$) δ=2.80 (s, 3H), 4.20

(s, 5H), 4.55 (s, 2H), 5.07 (s, 2H), 7.16 (dd, J=5.1 and 3.9 Hz, 1H), 7.56 (dd, J=5.1 and 0.9 Hz, 1H), 7.58 (s, 1H), and 7.71 (dd, J=3.9 and 0.9 Hz, 1H); MS (20 eV) m/z (rel intensity) 384 (M^+, 100) and 319 (55). Found: C, 65.44; H, 4.32; N, 7.51%. Calcd for $C_{21}H_{16}N_2SFe$: C, 65.63; K, 4.20; N, 7.29%.

3-Cyano-4-ferrocenyl-2-methyl-6-(2-pyridyl)pyridine (**2m**). Mp 201—202 °C; ^{1}H NMR ($CDCl_3$) δ=2.86 (s, 3H), 4.19 (s, 5H), 4.55 (t, J=1.7 Hz, 2H), 5.18 (t, J=1.7 Hz, 2H), 7.34—7.39 (m, 1H), 7.82—7.89 (m, 1H), 8.44 (d, J=7.7 Hz, 1H), and 8.72 (dd, J=4.7 and 0.9 Hz, 1H); MS (20 eV) m/z (rel intensity) 379 (M^+, 100) and 314 (38). Found: C, 69.50; H, 4.69; N, 11.02%. Calcd for $C_{22}H_{17}N_3Fe$: C, 69.67; H, 4.52; N, 11.08%.

6-(4-Chlorophenyl)-3-cyano-4-ferrocenyl-2-methylpyridine (**2n**). Mp 252—254 °C; ^{1}H NMR ($CDCl_3$) δ=2.85 (s, 3H), 4.19 (s, 5H), 4.56 (t, J=1.7 Hz, 2H), 5.08 (d, J=1.7 Hz, 2H), 7.48 (d, J=8.6 Hz, 2H), 7.64 (s, 1H), and 8.00 (d, J=8.6 Hz, 2H); MS (20 eV) m/z (rel intensity) 412 (M^+, 100), 411 (82), 347 (67), and 346 (64). Found: C, 66.71; H, 4.34; N, 6.95%. Calcd for $C_{23}H_{17}N_2ClFe$: C, 66.94; H, 4.15; N, 6.79%.

3-Cyano-4-ferrocenyl-6-(4-methoxyphenyl)-2-methylpyridine (**2o**). Mp 141—142 °C; ^{1}H NMR ($CDCl_3$) δ=2.84 (s, 3H), 3.89 (s, 3H), 4.19 (s, 5H), 4.54 (t, J=1.7 Hz, 2H), 5.08 (t, J=1.7 Hz, 2H), 7.03 (d, J=8.8 Hz, 2H), 7.63 (s, 1H), and 8.03 (d, J=8.8 Hz, 2H); MS (20 eV) m/z (rel intensity) 408 (M^+, 100), 407 (82), 343 (45), and 342 (41). Found: C, 70.76; H, 4.97; N, 6.83%. Calcd for $C_{24}H_{20}N_2OFe$: C, 70.61; H, 4.94; N, 6.86%.

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