Stereoselective Synthesis of 2-[1-Methylpyridin-2(1*H*)-ylidene]malononitrile Derivatives

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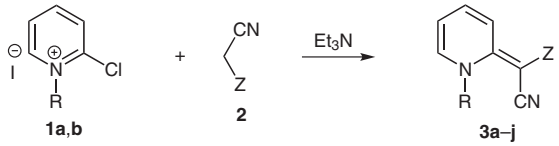
Abstract: An efficient synthesis of 2-[1-methylpyridin-2(1*H*)-ylidene]malononitrile derivatives have been identified, the reactions have been proved to be stereoselective; the spatial location of substituents has been determined.

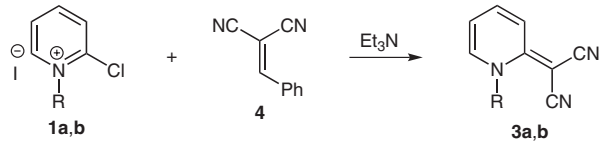
Key words: 1-alkyl-2-chloropyridinium iodide, CH-acids, nitrile group, hydrogen bond, stereoselectivity

2-(Dicyanomethylene)-1-methyl-1,2-dihydropyridines have specific synthetic abilities, for example, they can react with maleic acid derivatives (Diels–Alder reaction) and form the isoquinuclidine skeleton in comparatively high yield.[1]

During our investigations of the reactions and synthetic abilities of 2-chloropyridinium salts,[2,3] we have studied the nucleophilic substitution of chlorine in N-alkyl derivatives salts **1a**,**b** by various CH-acids, such as malononitrile derivatives. We have shown that 1-alkyl-2-chloropyridinium iodides **1a**,**b** react with various malononitrile derivatives **2** in the presence of two equivalents of a tertiary base to give 1-alkyl-1,2-dihydropyridines **3a**–**j** (Scheme 1, Table 1); the reactions occur under mild conditions.



Scheme 1



Scheme 2

The structure of **3a** was first synthesized and characterized by Kröhnke and Pauls.[4] According to the literature the first synthesis of **3c** was performed by Boyd and Ezekiel,[5a] however, this report involves the presence of a strong nucleophilic reagent, such as the hydroxide ion, and it lacks physicochemical data. The method reported by Zagulyaeva and co-workers[5b] is more realistic.

The synthesis of compounds **3a**,**b** was also carried out by synthesis using 1-alkyl-2-chloropyridinium salts and 2-(phenylmethylene)malononitrile (**4**) (Scheme 2).

The compounds **3a**–**j** have similar stretching vibrations for the cyano groups (2160–2172 cm^{-1}), which is evidence for these compounds having the cyano group in identical positions.

In ^1H NMR spectrum of compounds **3a**–**j** the most characteristic peaks are the doublets of H3 and H6 in the pyridine ring (by CSSI); ^3J = 8.4–9.2 Hz is typical for H3, while J = 5.8–7.2 Hz is typical for H6: compound **3a** has H3 ^3J = 8.5 Hz and H6 ^3J = 7 Hz.[4]

It is well known[6] that if there is a possibility to form a hydrogen bond between H3 in a pyridine ring and an electron-withdrawing atom (O, N) of the Z substituent then H3 shifts to lower field. The degree of shift depends on the strength of the hydrogen bond. In compounds **3a**,**b**, where there is no possibility to form a hydrogen bond, the doublets of H3 appear in the range δ = 7.16 and δ = 7.20–7.25, respectively. In compounds **3d**,**e**, where the amides of the sp^2 hybrid carbon atom can take part in forming a hydrogen bond, H3 appears in the range δ = 7.56–7.62. In compound **3c**, where the oxygen atom of the ester group functions as an electron-donor component for hydrogen bond formation, the shift is more intensive: H3 appears in the range of δ = 8.01–8.05. The most intensive shifts occur in the compounds that contain a thiazole ring, where a nitrogen atom of the heterocycle functions as an electron-donor component for hydrogen bond formation: H3 for **3f**–**j** appears in range δ = 8.33–8.76. Thus, we can conclude that the compounds **3c**–**j** are formed with high stereoselectivity. The spatial location of substituents is shown for the compounds **3c**,**d**,**f** (Figure 1).

Thus, a convenient 2-[1-methylpyridin-2(1*H*)-ylidene]malononitrile derivatives as been found, furthermore the reactions proved to be stereoselective. The spatial location of substituents has been determined.

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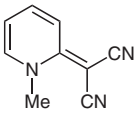
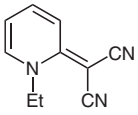
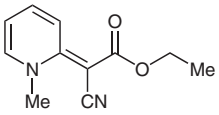
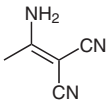
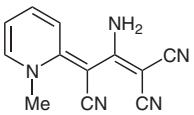
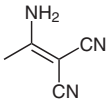
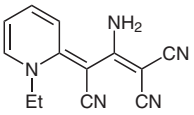
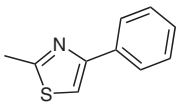
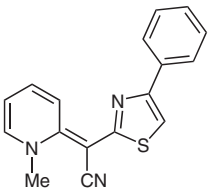
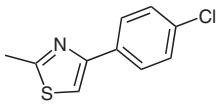
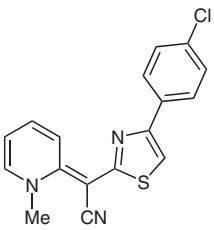
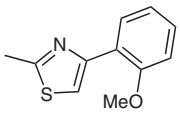
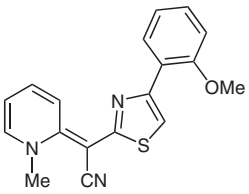
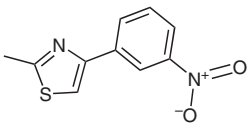
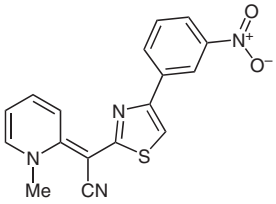
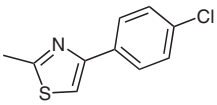
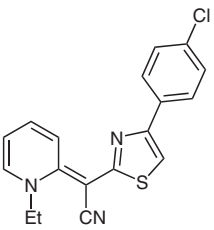
Table 1 Substituents, Melting Points, Solvent of Crystallization, and Yields for **3a–j**

Compd	R	Z	Product	Mp (°C) [Lit.]	Solvent for crystallization	Yield[a] (%)
3a	Me	CN		204 [205[4]]	EtOH	65 (67)
3b	Et	CN		120–121	EtOH	24 (52)
3c	Me	CO_2Et		124–125 [127–128[5a]]	MeOH	25[b]
3d	Me			256–266	EtOH	59
3e	Et			232–234	EtOH	57
3f	Me			129–130	EtOH–H_2O (1:1)	61
3g	Me			133	EtOH–H_2O (1:1)	56
3h	Me			148–149	EtOH	75
3i	Me			207–210	EtOH–AcOH (4:1)	68
3j	Et			193–195	EtOH	60

[a] Yield from method B given in parentheses.
[b] Yield in ref 5a = 24.5%.

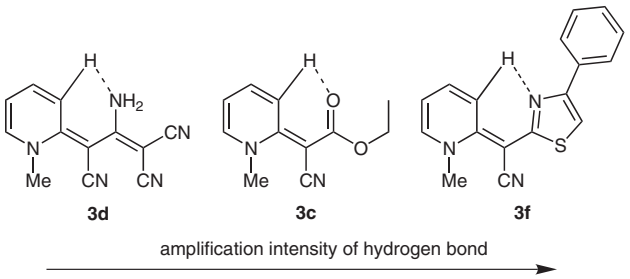


Figure 1 Intramolecular hydrogen bonding

The structures of compounds have been confirmed by IR and ^{1}H NMR spectroscopy, and elemental analysis. IR spectra were measured with an IKS-40 spectrophotometer (mineral oil mull). ^{1}H NMR spectra were recorded with a Varian VRX-200 (199.9969 MHz, internal standard TMS). Commercial DMSO-d_6 was used as solvent without further purification. The purity of the products was monitored by TLC performed on Silufol UV-254 plates (acetone–hexane, 3:5). Elemental analysis was carried out on a Perkin-Elmer CHN analyzer. Melting points were determined on a Kofler hot stage.

2-Chloro-1-methylpyridinium Iodide (1a)
A mixture of 2-chloropyridine (1.7 g, 15 mmol) and MeI (6.39 g, 45 mmol) was heated on a water bath for 2 h and then it was left to stand at r.t. overnight. Then acetone (15 mL) was added and the mixture was allowed to stand at r.t. After 3 d the sediment was filtered off and washed (acetone); yield: 1.4 g (37%).

Anal. Calcd for C_6H_7NClI: C, 28.21; H, 2.76; N, 5.48. Found: C, 28.27; H, 2.86; N, 5.39.

2-Chloro-1-ethylpyridinium Iodide (1b)
A mixture of 2-chloropyridine (4.97 g, 43.75 mmol) and EtI (20.75 g, 131.25 mmol) was heated on a water bath for 2.5 h. When the reaction was complete, the mixture was allowed to cool to r.t., acetone (20 mL) was added and the mixture was allowed to stand overnight at 25 °C. Then residue was filtered off and washed (acetone); yield: 8.3 g (70%).

Anal. Calcd for C_7H_9NClI: C, 31.20; H, 3.37; N, 5.20. Found: C, 31.12; H, 3.43; N, 5.29.

2-[1-Alkylpyridin-2(1*H*)-ylidene]acetonitriles 3a–j; General Procedures
Method A: To a stirred mixture of **1a**,**b** (2.5 mmol) and CH-acid (2.5 mmol) in EtOH (10–15 mL) was added Et_3N (2 equiv). When the reagents had dissolved, the mixture was filtered (fold filter) and allowed to stand overnight at 25 °C. The residue was filtered off, washed (EtOH and hexane), and crystallized (solvent, see Table 1)

Method B: To a stirred mixture of **1a**,**b** (2.5 mmol) and (phenylmethylene)malononitrile (2.5 mmol) was added Et_3N (2 equiv). The mixture was then treated as for Method A.

2-[1-Methylpyridin-2(1*H*)-ylidene]malononitrile (3a)
IR: 2166, 2194 cm^{-1}.

^{1}H NMR: δ = 7.93 (d, J = 7.0 Hz, 1 H, H6), 7.62 (dd, $J_1 = J_2$ = 7.0 Hz, 1 H, H4), 7.16 (d, J = 8.5 Hz, 1 H, H3), 6.79 (dd, $J_1 = J_2$ = 7.0 Hz, 1 H, H5), 3.98 (s, 3 H, Me).

Anal. Calcd for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.72; H, 4.51; N, 26.78.

2-[1-Ethylpyridin-2(1*H*)-ylidene]malononitrile (3b)
IR: 2160, 2192 cm^{-1}.

^{1}H NMR: δ = 8.31 (d, J = 7.2 Hz, 1 H, H6), 7.66 (t, J = 9.2 Hz, 1 H, H4), 7.22 (d, J = 9.2 Hz, 1 H, H3), 6.86 (t, J = 7.2 Hz, 1 H, H5), 4.39 (dd, $J_1 = J_2$ = 7.3 Hz, 2 H, CH_2), 1.38 (t, J = 7.3 Hz, 3 H, Me).

Anal. Calcd for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.15; H, 5.34; N, 24.51.

Ethyl (*E*)-2-Cyano-2-[1-methylpyridin-2(1*H*)-ylidene]acetate (3c)
IR: 2172, 1652 cm^{-1}.

^{1}H NMR: δ = 8.19 (d, J = 6.6 Hz, 1 H, H6), 8.03 (d, J = 9.0 Hz, 1 H, H3), 7.78 (t, J = 9.0 Hz, 1 H, H4), 7.47 (t, J = 6.6 Hz, 1 H, H5), 4.05 (dd, $J_1 = J_2$ = 7.2 Hz, 2 H, CH_2), 3.89 (s, 3 H, NMe), 1.18 (t, J = 7.2 Hz, 3 H, Me).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.64; H, 5.96; N, 13.70.

(*Z*)-2-{1-Amino-2-cyano-2-[1-methylpyridin-2(1*H*)-ylidene]ethylidene}malononitrile (3d)
IR: 3406, 3324, 3164, 2202, 2183, 2162 cm^{-1}.

^{1}H NMR: δ = 8.38 (d, J = 6.4 Hz, 1 H, H6), 7.91 (t, J = 8.4 Hz, 1 H, H4), 7.58 (d, J = 8.4 Hz, 1 H, H3), 7.30 (s, 2 H, NH_2), 7.22 (t, J = 6.4 Hz, 1 H, H5), 3.82 (s, 3 H, Me).

Anal. Calcd for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.37. Found: C, 64.49; H, 4.11; N, 31.35.

(*Z*)-2-{1-Amino-2-cyano-2-[1-ethylpyridin-2(1*H*)-ylidene]ethylidene}malononitrile (3e)
IR: 3386, 3308, 3192, 2204, 2194, 2166 cm^{-1}.

^{1}H NMR: δ = 8.43 (d, J = 6.4 Hz, 1 H, H6), 7.92 (t, J = 8.6 Hz, 1 H, H4), 7.59 (d, J = 8.6 Hz, 1 H, H3), 7.29 (t, J = 6.4 Hz, 1 H, H5), 7.22 (s, 2 H, NH_2), 4.34 (dd, $J_1 = J_2$ = 7.0 Hz, 2 H, CH_2), 1.42 (t, J = 7.0 Hz, 3 H, Me).

Anal. Calcd for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.83; H, 4.72; N, 29.49.

(*E*)-2-[1-Methylpyridin-2(1*H*)-ylidene]-2-(4-phenylthiazol-2-yl)acetonitrile (3f)
IR: 2164 cm^{-1}.

^{1}H NMR: δ = 8.57 (d, J = 9.2 Hz, 1 H, H3), 8.01 (d, J = 6.0 Hz, 1 H, H6), 7.89 (d, J = 6.8 Hz, 2 H, Ar), 7.65 (s, 1 H, $H_{thiazolyl}$), 7.63 (t, J = 8.1 Hz, 1 H, H4), 7.34 (m, 3 H, Ar), 6.80 (dt, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1 H, H5), 3.92 (s, 3 H, Me).

Anal. Calcd for $C_{17}H_{13}N_3S$: C, 70.08; H, 4.50; N, 14.42. Found: C, 70.15; H, 4.46; N, 14.47.

(*E*)-2-[4-(4-Chlorophenyl)thiazol-2-yl-2-[1-methylpyridin-2(1*H*)-ylidene]acetonitrile (3g)
IR: 2162 cm^{-1}.

^{1}H NMR: δ = 8.57 (d, J = 9.0 Hz, 1 H, H3), 8.02 (d, J = 6.6 Hz, 1 H, H6), 7.91 (d, J = 8.4 Hz, 2 H, Ar), 7.71 (s, 1 H, $H_{thiazolyl}$), 7.64 (t, J = 8.8 Hz, 1 H, H4), 7.45 (d, J = 8.4 Hz, 2 H, Ar), 6.81 (t, J = 6.7 Hz, 1 H, H5), 3.92 (s, 3 H, Me).

Anal. Calcd for $C_{17}H_{12}N_3ClS$: C, 62.67; H, 3.71; N, 12.90. Found: C, 62.73; H, 3.69; N, 12.93.

(*E*)-2-[4-(2-Methoxyphenyl)thiazol-2-yl-2-[1-methylpyridin-2(1*H*)-ylidene]acetonitrile (3h)
IR: 2160 cm^{-1}.

^{1}H NMR: δ = 8.56 (d, J = 9.2 Hz, 1 H, H3), 8.02 (dd, J_1 = 6.9 Hz, J_2 = 14.2 Hz, 2 H), 7.69 (s, 1 H, $H_{thiazolyl}$), 7.61 (t, J = 8.0 Hz, 1 H, H4), 7.29 (t, J = 7.5 Hz, 1 H, Ar), 7.1 (d, J = 7.4 Hz, 1 H), 7.0 (t, J = 7.4 Hz, 1 H), 6.77 (t, J = 6.6 Hz, 1 H, H5), 3.90 (s, 6 H, OMe, Me).

Anal. Calcd for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.24; H, 4.75; N, 13.02.

(*E*)-2-[1-Methylpyridin-2(1*H*)-ylidene]-2-[4-(3-nitrophenyl)thiazol-2-yl]acetonitrile (3i)
IR: 2168 cm^{-1}.

^1H NMR: δ = 8.66 (s, 1 H, Ar), 8.57 (d, *J* = 8.7 Hz, 1 H, H3), 8.35 (d, *J* = 7.8 Hz, 1 H, H6), 8.18–8.03 (m, 2 H, Ar), 7.97 (s, 1 H, $H_{thiazolyl}$), 7.76–7.61 (m, 2 H, H4, Ar), 6.85 (dt, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1 H, H5), 3.94 (s, 3 H, Me).

Anal. Calcd for $C_{17}H_{12}N_4O_2S$: C, 60.70; H, 3.60; N, 16.66. Found: C, 60.78; H, 3.65; N, 16.61.

(*E*)-2-[4-(4-Chlorophenyl)thiazol-2-yl-2-[1-ethylpyridin-2(1*H*)-ylidene]acetonitrile (3j)
IR: 2162 cm^{-1}.

^1H NMR: δ = 8.74 (d, *J* = 9.2 Hz, 1 H, H3), 8.03 (d, *J* = 6.7 Hz, 1 H, H6), 7.92 (d, *J* = 8.4 Hz, 2 H, Ar), 7.72 (s, 1 H, $H_{thiazolyl}$), 7.61 (t, *J* = 8.6 Hz, 1 H, H4), 7.45 (d, *J* = 8.5 Hz, 2 H, Ar), 6.82 (dt, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1 H, H5), 4.45 (dd, $J_1 = J_2$ = 7.1 Hz, 2 H, CH_2), 1.43 (t, *J* = 7.1 Hz, 3 H, Me).

Anal. Calcd for $C_{18}H_{14}N_3ClS$: C, 63.62; H, 4.15; N, 12.36. Found: C, 63.69; H, 4.20; N, 12.31.

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