Facile approach to prepare 3-cyanopyridin-2(1*H*)-one derivatives

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Dedicated to Professor Armand Lattes on 50th anniversary of his educational and scientific activity

Abstract
A new and efficient high yielding synthesis of N-substituted 3-cyanopyridin-2-ones has been developed. The reaction of ylidencyanoacetic acid ethyl esters and dimethylformamide dimethyl acetal has been investigated. Intermediate dimethylamino derivatives so formed were treated with various primary amines in xylene. The targeted 3-cyanopyridin-2-ones were obtained in good yields.

Keywords: 3-Cyanopyridin-2-ones, cardiotonic agent, milrinone, alkaloid, ricinine

Introduction

The pharmacological and physiological activity of 3-cyanopyridin-2-ones has attracted much attention in recent years with the synthesis and the study of the non-glycosidic cardiotonic agent milrinone,[1,2] as well as with a number of 3-cyanopyridin-2-one derivatives which proved to be active against the herpes virus and the human immunodeficiency virus.[3,4] The 3-cyanopyridin-2-one nucleus is also the structural basis of the alkaloid ricinine – the first known alkaloid containing a cyano-group (Figure 1).

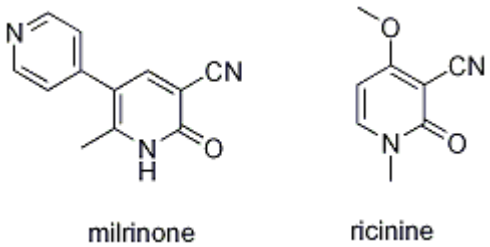
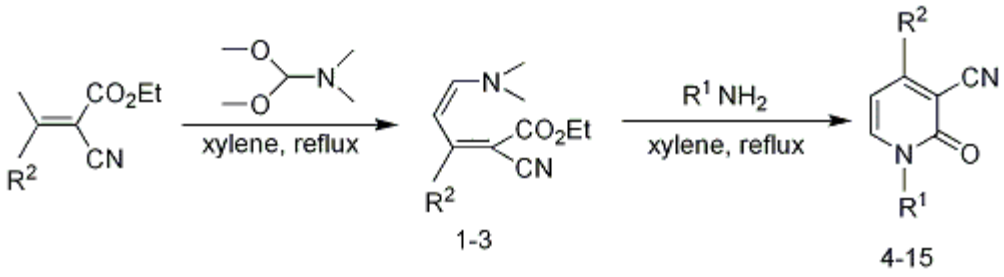


Figure 1

Results and Discussion

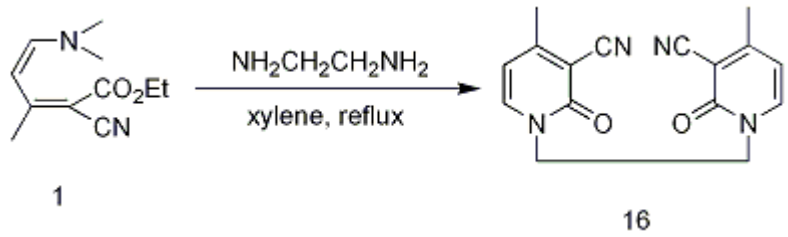
There are many reported methods for the formation of 3-cyanopyridin-2-ones. The main strategy involves the condensation of β-enaminoderivatives of carbonyl compounds with cyanoacetic acid amides or malononitrile.[5,6]

We report herein a new, efficient and convenient synthetic approach to 3-cyanopyridin-2-ones utilizing various ylidenecyanoacetic acid ethyl esters and dimethylformamide dimethyl acetal as starting materials. The reaction was carried out in anhydrous xylene under reflux for 3 hours. The intermediate dimethylamino derivatives **1-3** so formed were treated with primary amines in xylene under reflux for 13-15 hours to yield the targeted 3-cyanopyridin-2-ones **4-15** in good yields. The course of the reaction was monitored by the evolution of gaseous dimethylamine (Scheme 1).



Scheme 1

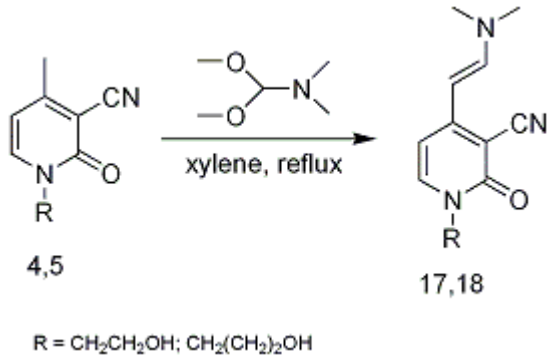
It is known that bis lactams are the structural component of some natural compounds.[7] Considering this fact we have prepared the corresponding bis-pyridinone **16** using ethylene diamine as the primary amine (Scheme 2).



Scheme 2

Taking into account that pyridinones with functionalized substituents, in particular containing unsaturated bonds are an interesting class of compounds, we also carried out the condensation of 1-oxyethyl- and 1-oxypropyl-3-cyano-4-methylpyridin-2-ones with

dimethylformamide dimethyl acetal in xylene under reflux. The targeted products **17, 18** were isolated in 70-75% yields (Scheme 3).



Scheme 3

In conclusion, we have developed a new and efficient high yielding synthesis of N-substituted 3-cyanopyridin-2-ones.

Experimental Section

General Procedures. All melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a "Varian Mercury 300" spectrometer at 300 and 75 MHz with tetramethylsilane (TMS) as internal reference in DMSO-d_6, DMSO-d_6 : CCl_4 (1:3) and DMSO-d_6 : CCl_4 (3:1) solutions at 303K. IR spectra were recorded on a NEXUS FT-IR. Elemental analysis satisfactory obtained: C $\pm$ 0.32, H $\pm$ 0.20, N $\pm$ 0.27.

Compounds 1-3 and 17, 18

A solution of each initial compound (0,01 mol) in anhydrous xylene (20 ml) was treated with dimethylformamide dimethyl acetal (0,011 mol). The reaction mixture was refluxed for 3 hours, then allowed to cool. Light petroleum (10 ml, b.p. 60-80 ^{o}C) was added to the reaction mixture at room temperature. The solid products so formed were collected by filtration and crystallized from light petroleum. Data of the compounds are shown below.

Ethyl 2-cyano-5-(dimethylamino)-3-methylpenta-2,4-dienoate (1). Yellow crystals, yield 55%, m.p. 98–101°C; mixture of two stereoisomers : A and B.

A (~66%) :

^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.30 (t, 3H, *J*=7.1Hz), 2.25 (s, 3H), 3.00 (s, 3H), 3.22 (s, 3H), 4.12 (q, 2H, *J*=7.1Hz), 6.99 (d, 1H, *J*=13.1Hz), 7.58 (d, 1H, *J*=13.1Hz).

B (~34%) :

^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.29 (t, 3H, *J*=7.1Hz), 2.41 (s, 3H), 3.00 (s, 3H), 3.22 (s, 3H), 4.11 (q, 2H, *J*=7.1Hz), 5.60 (d, 1H, *J*=12.7Hz), 7.58 (d, 1H, *J*=12.7Hz).

Ethyl 2-cyano-5-(dimethylamino)-3-isopropylpenta-2,4-dienoate (2). Yellow crystals, yield 56%, m.p. 128–130°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.31 (t, 3H, *J*=7.1Hz), 1.36 (d, 6H, *J*=7.2Hz), 3.10 (s, 6H), 3.30 (sept., 1H, *J*=7.2Hz), 4.12 (q, 2H, *J*=7.1Hz), 6.92 (d, 1H, *J*=13.3Hz), 7.69 (d, 1H, *J*=13.3Hz);

Ethyl 2-cyano-3-cyclopropyl-5-(dimethylamino)penta-2,4-dienoate (3). Dark-yellow crystals, yield 59%, m.p. 93–95°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.69 (q, 2H, *J*=5.8Hz), 1.07 (m, 2H), 1.30 (t, 3H, *J*=7.1Hz), 1.69 (m, 1H), 3.01 (s, 3H), 3.22 (s, 3H), 4.12 (q, 2H, *J*=7.1Hz), 6.87 (d, 1H, *J*=13.0Hz), 7.86 (d, 1H, *J*=12.9Hz);

3-Cyano-4-[2-(dimethylamino)vinyl]-1-(2-hydroxyethyl)pyridin-2(1*H*)-one (17): Green crystals, yield 80%, m.p. 170-172 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 3.06 (s, 6H), 3.62 (t, 2H, *J*=5.2Hz), 3.83 (t, 2H, *J*=5.3Hz), 4.61 (br., 1H), 5.15 (d, 1H, *J*=13.1Hz), 6.34 (d, 1H, *J*=7.5Hz), 7.33 (d, 1H, *J*=7.5Hz), 7.58 (d, 1H, *J*=13.1Hz);

3-Cyano-4-[2-(dimethylamino)vinyl]-1-(3-hydroxypropyl)pyridin-2(1*H*)-one (18). Dark-green crystals, yield 76%, m.p. 165-167 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.78 (p, 2H, *J*=6.4Hz), 3.06 (s, 6H), 3.42 (br. t, 2H, *J*=5.7Hz), 3.86 (t, 2H, *J*=6.7Hz), 4.28 (br., 1H), 5.15 (d, 1H, *J*=13.1Hz), 6.38 (d, 1H, *J*=7.5Hz), 7.36 (d, 1H, *J*=7.5Hz), 7.59 (d, 1H, *J*=13.1Hz);

Compounds 4-16

A mixture of each dimethylamino derivatives (1-3) (0,005 mol) and the corresponding amine (0,015 mol) (in case of ethylenediamine – 0,0075 mol) in xylene (10 ml) was refluxed for 13-15 hours. The progress of the reaction was monitored by the evolution of gaseous dimethylamine. After completion of the reaction, the mixture was cooled to room temperature. Then, light petroleum (10 ml, b.p. 60-80 °C) was added to the reaction mixture. The solid products were filtered off and washed with light petroleum (20 ml) and the crude products isolated. The crude products were purified by recrystallization from xylene. Data of the compounds are shown below:

3-Cyano-1-(2-hydroxyethyl)-4-methylpyridin-2(1*H*)-one (4). Beige crystals, yield 55%, m.p. 128-130 °C; IR (vaseline, cm^{-1}) 3412, 2223, 1649, 1598; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.40 (s, 3H), 3.66 (t, 2H, *J*=5.2Hz), 3.98 (t, 2H, *J*=5.2Hz), 4.64 (br., 1H), 6.19 (d, 1H, *J*=6.9Hz), 7.74 (d, 1H, *J*=6.9Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 1:3) δ 20.26, 51.55, 58.15, 102.66, 106.38, 114.79, 143.13, 158.51, 158.95.

3-Cyano-1-(3-hydroxypropyl)-4-methylpyridin-2(1*H*)-one (5). White crystals, yield 60%, m.p. 136-138 °C; IR (vaseline, cm^{-1}) 3410, 2225, 1651, 1601; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.83 (p, 2H, *J*=6.4Hz), 2.40 (s, 3H), 3.44 (q, 2H, *J*=5.4Hz), 4.01 (t, 2H, *J*=6.9Hz), 4.32 (br. t, 1H, *J*=5.0Hz), 6.21 (d, 1H, *J*=6.9Hz), 7.81 (d, 1H, *J*=6.8Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 1:3) δ 20.22, 30.92, 46.51, 57.01, 102.97, 106.88, 114.66, 142.36, 158.39, 158.90.

3-cyano-1-cyclopropyl-4-methylpyridin-2(1*H*)-one (6). White crystals, yield 52%, m.p. 93-94 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.89 (m, 2H), 1.08 (m, 2H), 2.25 (s, 1H), 3.34 (m, 1H), 6.17 (d, 1H, *J*=7.1Hz), 7.65 (d, 1H, *J*=7.1Hz).

3-Cyano-1-cyclopentyl-4-methylpyridin-2(1*H*)-one (7). Beige crystals, yield 57%, m.p. 133-134 °C; IR (vaseline, cm^{-1}) 2226, 1651, 1600; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.63-2.19 (m,

8H), 2.40 (s, 3H), 5.06 (p, 1H, *J*=7.9Hz), 6.23 (d, 1H, *J*=7.1Hz), 7.76 (d, 1H, *J*=7.1Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 1:3) δ 20.09, 23.63, 31.08, 56.82, 102.85, 107.37, 114.66, 138.42, 157.54, 158.92.

3-Cyano-1-cyclohexyl-4-methylpyridin-2(1*H*)-one (8). White needles, yield 62%, m.p. 136-138 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.17-1.98 (m, 10H), 2.39 (s, 3H), 4.65 (tt, 1H, *J*=3.6Hz, *J*=11.7Hz), 6.23 (d, 1H, *J*=7.1Hz), 7.78 (d, 1H, *J*=7.1Hz);

3-Cyano-1-cycloheptyl-4-methylpyridin-2(1*H*)-one (9). White crystals, yield 60%, m.p. 111-113 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.54-1.91 (m, 12H), 2.39 (s, 3H), 4.70-4.83 (m, 1H), 6.23 (d, 1H, *J*=7.1Hz), 7.76 (d, 1H, *J*=7.1Hz);

3-Cyano-1-cyclopentyl-4-isopropylpyridin-2(1*H*)-one (10). Grey crystals, yield 55%, m.p. 119-120 °C; IR (vaseline, cm^{-1}) 2231, 1649, 1600; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.27 (d, 6H, *J*=6.9Hz), 1.63-2.18 (m, 8H), 3.17 (sept., 1H, *J*=6.8Hz), 5.06 (p, 1H, *J*=7.9Hz), 6.27 (d, 1H, *J*=7.3Hz), 7.82 (d, 1H, *J*=7.3Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 1:3) δ 21.11, 23.62, 31.01, 32.16, 56.90, 101.27, 102.76, 114.36, 139.27, 159.10, 166.72.

3-Cyano-1-cyclohexyl-4-isopropylpyridin-2(1*H*)-one (11). Beige crystals, yield 68%, m.p. 171-172 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.27 (d, 6H, *J*=6.8Hz), 1.44-1.94 (m, 10H), 3.17 (sept., 1H, *J*=6.7Hz), 4.66 (tt, 1H, *J*=3.6Hz, *J*=11.5Hz), 6.27 (d, 1H, *J*=7.2Hz) ppm 7.83 (d, 1H, *J*=7.2Hz);

3-Cyano-4-cyclopropyl-1-[2-(dimethylamino)ethyl]pyridin-2(1*H*)-one (12). White crystals, yield 55%, m.p. 71-74 °C; IR (vaseline, cm^{-1}) 2235, 1653, 1599; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.97 (m, 2H), 1.26 (m, 2H), 2.17 (td, 1H, *J*=4.7Hz, *J*=8.8Hz), 2.22 (s, 6H), 2.52 (t, 2H, *J*=6.2Hz), 3.95 (t, 2H, *J*=6.1Hz),5.65 (d, 1H, *J*=7.2Hz), 7.67 (d, 1H, *J*=7.2Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 1:3) δ 10.36, 14.21, 44.89, 46.06, 56.87, 99.09, 101.66, 115.00, 142.85, 158.55, 164.44.

3-Cyano-4-cyclopropyl-1-(2,2-dimethoxyethyl)pyridin-2(1*H*)-one (13). White crystals, yield 54%, m.p. 86-87 °C; IR (vaseline, cm^{-1}) 2230, 1649, 1600; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.99 (m, 2H), 1.28 (m, 2H), 2.19 (m, 1H), 3.36 (s, 6H), 3.95 (d, 2H, *J*=5.3Hz), 4.55 (t, 1H, *J*=5.3Hz), 5.68 (d, 1H, *J*=7.3Hz), 7.64 (d, 1H, *J*=7.3Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 1:3) δ 10.52, 14.33, 50.10, 53.97, 99.42, 100.69, 101.62, 114.82, 143.31, 158.70, 165.02.

3-Cyano-1,4-dicyclopropylpyridin-2(1*H*)-one (14). White crystals, yield 56%, m.p. 154-156 °C; IR (vaseline, cm^{-1}) 2222, 1655, 1604; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.86 (m, 2H), 0.95 (td, 2H, *J*=4.6Hz, *J*=7.2Hz), 1.07 (m, 2H), 1.26 (m, 2H), 2.18 (tt, 1H, *J*=4.8Hz, *J*=8.2Hz), 3.31 (tt, 1H, *J*=4.2Hz, *J*=7.5Hz), 5.65 (d, 1H, *J*=7.4Hz), 7.58 (d, 1H, *J*=7.3Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 1:3) δ 6.07, 10.35, 14.20, 31.65, 99.46, 101.70, 114.92, 141.10, 159.65, 164.21.

3-Cyano-1-cyclohexyl-4-cyclopropylpyridin-2(1*H*)-one (15). Grey crystals, yield 71%, m.p. 176-178 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 0.96 (m, 2H), 1.26 (td, 2H, *J*=4.6Hz, *J*=6.9Hz), 1.40-1.95 (m, 10H), 2.18 (tt, 1H, *J*=4.8Hz, *J*=8.3Hz), 4.63 (tt, 1H, *J*=3.3Hz, *J*=11.7Hz), 5.71 (d, 1H, *J*=7.4Hz), 7.70 (d, 1H, *J*=7.4Hz);

3-Cyano-1-[2-(3-cyano-4-methyl-2-oxopyridin-1(2*H*)-yl)ethyl]-4-methylpyridin-2(1*H*)-one (16). Beige crystals, yield 78%, m.p. >250 ^{o}C; IR (vaseline, cm^{-1}) 2235, 1650, 1600; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 6H), 4.23 (s, 4H), 6.29 (d, 2H, *J*=6.9Hz), 7.72 (d, 2H, *J*=6.9Hz); ^{13}C-NMR (75 MHz, DMSO-d_6 : CCl_4 / 3:1) δ 20.47, 47.69, 102.40, 107.71, 115.27, 142.69, 159.32, 159.95.

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