DOI 10.1515/hc-2012-0158 — Heterocycl. Commun. 2012; 18(5-6): 233–237

Aleksandr Piroyan* and Gagik Melikyan*

Convenient synthetic route to 3-cyanopyridine-2(1*H*)-one derivatives with aromatic substituents

Abstract: A new efficient method of synthesizing 3-cyanopyridine-2(1*H*)-ones containing variable substituents at position 4 and various aromatic substituents at position 1 of the pyridinone ring has been developed. The method is based on the reaction of ylidenecyanoacetic acid ethyl esters with dimethylformamide dimethyl acetal, the reamination of obtained derivatives with several aromatic amines in glacial acetic acid and the final cyclization of the intermediate products to targeted *N*-aryl-3-cyano-pyridine-2(1*H*)-ones. The condensation reactions of some of the synthesized compounds with several aldehydes have been investigated.

Keywords: alkaloids; 3-cyano-pyridine-2(1*H*)-one; milrinone; ricinine.

Corresponding authors: Aleksandr Piroyan and Gagik Melikyan, Department of Organic Chemistry, Yerevan State University, Alex Manoogian 1, Yerevan, 0025, Armenia,
e-mail: aleksandrpiroyan@gmail.com; gold@ysu.am

Introduction

The development of new routes to substituted pyridines with a wide variety of substituents continues to attract considerable attention for application in heterocyclic chemistry, natural product synthesis and medicinal chemistry. Compounds have been associated with antitumor, antifungal, antibacterial, antiviral, antithrombotic, psychotherapeutic and anti-HIV properties (Cox and O'Hagan, 1991; Curran and Liu, 1992; Kozikowski et al., 1996; Williams et al., 1997; Fraley et al., 2003). They are the structural basis of some natural alkaloids, e.g., ricinine and nudiflorine (Mukherjee and Chaterjee, 1966; Yuldashev, 2001; Leite et al., 2005). Substituted 3-cyanopyridine-2(1*H*)-ones are also effective cardiotonic (e.g., milrinone) agents (Hopkins, 1990; Kulnevich et al., 1990; Shiao et al., 1990; Litvinov et al., 1999; Saad et al., 2002; El-Sayed et al., 2011). Some authors consider that biological activity of 3-cyanopyridine-2(1*H*)-ones depends on the substituent at a nitrogen atom of the pyridinone ring (Kulnevich et al., 1990). Serious changes in biological activity by replacing one alkyl group with another have been reported.

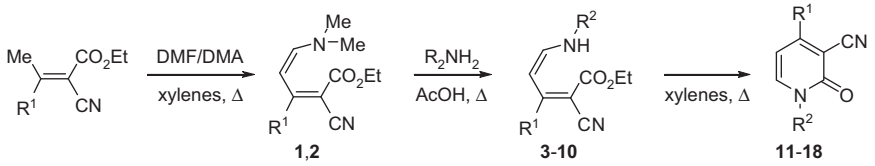
The routine method for the synthesis of 3-cyanopyridine-2(1*H*)-ones is the condensation of β-enamino derivatives of carbonyl compounds with cyanoacetic acid amides or malononitrile (Ratemi et al., 1993; Litvinov et al., 1999). However, these approaches do not allow obtaining the variety of substituents at the pyridinone ring which could be a tempting idea for the application in combinatorial chemistry and drug design. Other methods allow obtaining 4,5,6-substituted 3-cyanopyridinones with a large variety of substituents, but they are not convenient for introducing substituents at the nitrogen atom of the pyridinone ring (Nalage et al., 2010; Elassar, 2011).

Some pyridinone derivatives containing aromatic substituents have valuable properties and display a variety of biological activities (Litvinov et al., 1999). In our previous report, we described the synthesis of some substituted 3-cyanopyridine-2(1*H*)-ones with various aliphatic substituents at positions 1 and 4 of the pyridinone ring (Melikyan and Piroyan, 2006). Taking this into account, we report herein a new and simple path for synthesizing *N*-substituted 3-cyanopyridine-2(1*H*)-ones with aromatic substituents.

Results and discussion

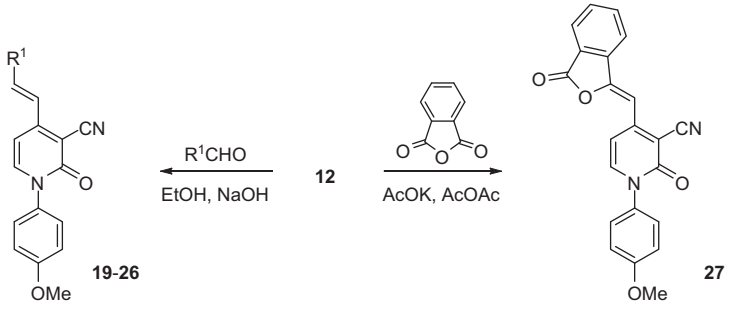
We started from various ethyl ylidenecyanoacetates obtained by the condensation of methyl ketones with ethyl cyanoacetate. These ylidene derivatives were condensed with dimethylformamide dimethyl acetal to yield the new dimethylaminovinyl derivatives **1** and **2** in good yields. The reaction was carried out in anhydrous xylenes under reflux for 3 h (Scheme 1).

The key point of our investigation was the reaction of dimethylaminovinyl derivatives **1** and **2** with aromatic amines in glacial acetic acid at 90°C to give new arylaminovinyl derivatives **3–10**. Compounds **3–10** are brightly colored (yellow, orange, red), which can be explained by the presence of a chromophorous moiety (the arylamino group) conjugated through the system of double bonds with the cyano group.



1: R^1=Me
2: R^1=Ph
3: R^1=Me, R^2=4-Br-Ph
4: R^1=Me, R^2=4-MeO-Ph
5: R^1=Ph,R^2=4-MeO-Ph
6: R^1=Ph, R^2=4-Me-C(O)-Ph
7: R^1=Ph, R^2=4-EtO(O)C-Ph
8: R^1=Ph, R^2=4-HO-Ph
9: R^1=R^2=Ph
10: R^1=Me, R^2=Ph
11: R^1=Me, R^2=4-Br-Ph
12: R^1=Me, R^2=4-MeO-Ph
13: R^1=Ph, R^2=4-MeO-Ph
14: R^1=Ph, R^2=4-Me-C(O)-Ph
15: R^1=Ph, R^2=4-EtO_2C-Ph
16: R^1=Ph, R^2=4-HO-Ph
17: R^1=R^2=Ph
18: R^1=Me, R^2=Ph

Scheme 1



19: R^1=2-thienyl
20: R^1=2-pyridyl
21: R^1=Ph
22: R^1=1-Me-2-pyrrolyl
23: R^1=4-F-Ph
24: R^1=2-furyl
25: R^1=4-Me_2N-Ph
26: R^1=4-piperonyl

Scheme 2

Compounds **3–10** undergo intramolecular cyclization in refluxing xylenes. The products obtained in high yields are new derivatives of substituted 3-cyanopyridine-2(1*H*)-ones **11–18** containing variable substituents at position 4 of the pyridinone ring and several aromatic substituents at the nitrogen atom of the ring.

It is important to note that refluxing compounds **1**, **2** in acetic acid, as reported for the synthesis of condensed pyridazinones (Abu-Shanab et al., 1995), did not result in ring closure and the desired 3-cyanopyridine-2(1*H*)-ones **11–18** were not obtained. Instead, impure compounds **3–10** with low yields were obtained.

It has been previously shown that some vinyl-substituted heterocycles are of practical interest (Melikyan et al., 1993; Leite et al., 1999). Considering this, we carried out condensation of 4-methyl-2-oxo-1,2-dihydropyridine **12** with a number of aromatic and heterocyclic aldehydes in dry ethyl alcohol media in the presence of catalytic amount of sodium hydroxide. The resulting 3-cyano-4-(substituted vinyl)pyridin-2(1*H*)-ones **19–26** were obtained in high yields. It was estimated by the analysis of coupling constants in the ^{1}H NMR spectra that these products are trans-isomers (Scheme 2).

Taking into account a wide spectrum of the applications of phthalic acid derivatives, we extended the condensation reactions on phthalic acid anhydride. Condensation of **12** with phthalic anhydride was carried out at 120–130°C for 2 h in acetic anhydride in the presence of potassium acetate catalytic amounts to give the expected product **27**.

Conclusions

A new convenient synthesis of 3-cyano-pyridine-2(1*H*)-ones with aromatic substituents was developed. Easy variability of substituents allows using this method to be used in combinatorial chemistry and drug design. The availability of the substrates, efficient work-up and high yields make this route an attractive methodology.

Experimental section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained in DMSO-d_6 or a mixture of DMSO-d_6 and CCl_4 on a Varian Mercury 300 spectrometer at 303 K.

Synthesis of compounds 1 and 2

The starting ethyl ylideneacetate (0.01 mol) in anhydrous xylenes (20 mL) was treated with dimethylformamide dimethyl acetal (0.011

mol). The mixture was heated under reflux for 3 h, and then allowed to cool to room temperature. Light petroleum (10 mL, bp 60–80°C) was added to the mixture and the resultant solid product was collected by filtration and crystallized from light petroleum.

Ethyl 2-cyano-5-(dimethylamino)-3-methylpenta-2,4-dienoate (1) Yield 55%; mp 98–101°C; mixture of two stereoisomers **a** and **b**. Isomer **a**: yield 66%; ^{1}H NMR: δ 1.30 (t, *J* = 7 Hz, 3H), 2.25 (s, 3H), 3.00 (s, 3H), 3.22 (s, 3H), 4.12 (q, *J* = 7 Hz, 2H), 6.99 (d, *J* = 13 Hz, 1H), 7.58 (d, *J* = 13 Hz, 1H). Isomer **b**: yield 34%; ^{1}H NMR: δ 1.29 (t, *J* = 7 Hz, 3H), 2.41 (s, 3H), 3.00 (s, 3H), 3.22 (s, 3H),4.11 (q, *J* = 7 Hz, 2H), 5.60 (d, *J* = 13 Hz, 1H), 7.58 (d, *J*=13 Hz, 1H). Anal. for mixture of isomers. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.21; H, 7.56; N, 14.11.

Ethyl 2-cyano-5-dimethylamino-3-phenylpenta-2,4-dienoate (2) Yield 85%; mp 141–142°C; mixture of two stereoisomers **a** and **b**. Isomer **a**: yield 75%; ^{1}H NMR: δ 1.34 (t, *J* = 7 Hz, 3H), 3.04 (s, 6H), 4.19 (q, *J* = 7 Hz, 2H), 6.50 (d, *J* = 13 Hz, 1H), 7.14 (d, *J* = 13 Hz, 1H), 7.15–7.25 (m, 2H), 7.50–7.39 (m, 3H). Isomer **b**: yield 25%; ^{1}H NMR: δ 1.03 (t, *J* = 7 Hz, 3H), 3.03 (s, 6H), 3.86 (q, *J* = 7 Hz, 2H), 5.79 (d, *J* = 12 Hz, 1H), 6.40 (d, *J* = 12 Hz, 1H), 7.10–7.00 (m, 2H), 7.38–7.30 (m, 3H). Anal. for mixture of isomers. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.95; H, 6.63; N, 10.68.

General procedure for synthesis of compounds 3–10

A mixture of dimethylamino derivative **1** or **2** (0.005 mol) and an amine (0.0055 mol) in glacial acetic acid (10 mL) was heated at 90°C for 4–5 h, then cooled to room temperature and treated with water (10 mL). The resultant solid product was filtered, washed with water (20 mL), dried and crystallized from light petroleum (bp 60–80°C). In the case of compounds **6–10**, the crude products were used in the next step without further purification.

Ethyl 5-(4-bromophenylamino)-2-cyano-3-methylpenta-2,4-dienoate (3) Yield 95%; mp 185–190°C; mixture of two stereoisomers **a** and **b**. Isomer **a**: yield 47%; ^{1}H NMR: δ 1.31 (t, *J* = 7 Hz, 3H), 2.51 (s, 3H), 4.16 (q, *J* = 7 Hz, 2H), 6.36 (d, *J* = 13 Hz, 1H), 7.09–7.14 (m, 2H), 7.30–7.40 (m, 2H), 7.90 (t, *J* = 13 Hz, 1H), 10.32 (s, 1H). Isomer **b**: yield 53%; ^{1}H NMR: δ 1.32 (t, *J* = 7 Hz, 3H), 2.38 (s, 3H), 4.19 (q, *J* = 7 Hz, 2H), 7.10–7.19 (m, 2H), 7.29–7.40 (m, 2H), 7.54 (d, *J* = 13 Hz, 1H), 7.91 (t, *J* = 13 Hz, 1H), 10.28 (s, 1H). Anal. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.41; H, 4.30; N, 8.11.

Ethyl 2-cyano-5-(4-methoxyphenylamino)-3-methylpenta-2,4-dienoate (4) Yield 94%; mp 172–173°C; mixture of two stereoisomers **a** and **b**. Isomer **a**: yield 46%; ^{1}H NMR: δ 1.30 (t, *J* = 7 Hz, 3H), 2.48 (s, 3H), 3.74 (s, 3H), 4.14 (q, *J* = 7 Hz, 2H), 6.31 (d, *J* = 13 Hz, 1H), 6.73–6.81 (m, 2H), 7.01–7.09 (m, 2H), 7.77 (d, *J* = 13 Hz, 1H), 10.11 (br s, 1H). Isomer **b**: yield 54%; ^{1}H NMR: δ 1.30 (t, *J* = 7 Hz, 3H), 2.34 (s, 3H), 3.74 (s, 3H), 4.15 (q, *J* = 7 Hz, 2H), 6.73–6.81 (m, 2H), 6.98–7.05 (m, 2H), 7.51 (d, *J* = 13 Hz, 1H), 7.72 (d, *J* = 13 Hz, 1H), 10.15 (br s, 1H). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.32; H, 6.21; N, 10.08.

Ethyl 2-cyano-5-(4-methoxyphenylamino)-3-phenylpenta-2,4-dienoate (5) Yield 90%; mp 137–139°C; mixture of two stereoisomers **a** and **b**. Isomer **a**: yield 24%; ^{1}H NMR: δ 1.03 (t, *J* = 7 Hz, 3H), 3.69 (s, 3H), 3.88 (q, *J* = 7 Hz, 2H), 6.45 (d, *J* = 12 Hz, 1H), 6.59–6.93 (m, 5H), 7.06–7.14 (m, 2H), 7.32–7.40 (m, 3H), 10.44 (br s, 1H). Isomer **b**: yield 76%; ^{1}H NMR: δ 1.33 (t, *J* = 7 Hz, 3H), 3.69 (s, 3H), 4.21 (q, *J* = 7 Hz, 2H), 6.57–6.95 (m, 5H), 7.21–7.32 (m, 2H), 7.40–7.51 (m, 3H), 7.63 (d, *J* = 13 Hz, 1H), 10.49 (br s, 1H). Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.24; H, 5.61; N, 8.11.

General procedure for synthesis of compounds 11–18

A solution of an arylamino derivative **3–10** (0.01 mol) in anhydrous xylenes (20 mL) was heated under reflux for 5–6 h and then allowed to cool to room temperature. Light petroleum (10 mL, bp 60–80°C) was added to the mixture and the resultant precipitate of **11–18** was filtered and crystallized from xylenes.

1-(4-Bromophenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (11) Yield 65%; mp 220–225°C; ^{1}H NMR: δ 2.48 (s, 3H), 6.37 (d, *J* = 7 Hz, 1H), 7.40–7.32 (m, 2H), 7.68–7.62 (m, 2H), 7.76 (d, *J* = 7 Hz, 1H); ^{13}C NMR: δ 20.5, 104.0, 107.9, 114.2, 121.7, 128.0, 131.7, 138.2, 141.2, 158.2, 159.8. Anal. Calcd for $C_{13}H_9BrN_2O$: C, 54.00; H, 3.14; N, 9.69. Found: C, 53.86; H, 3.51; N, 9.84.

1-(4-Methoxyphenyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (12) Yield 60%; mp 189–190°C; ^{1}H NMR: δ 2.46 (s, 3H), 3.83 (s, 3H),6.25 (d, *J* = 7 Hz, 1H), 7.06–6.88 (m, 2H), 7.32–7.15 (m, 2H), 7.60 (d, *J* = 7 Hz, 1H); ^{13}C NMR: δ 20.4, 54.8, 104.3, 107.2, 113.8, 114.2, 126.9, 131.8, 141.2, 158.5, 159.0, 159.1. Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.28; H, 4.95; N, 11.12.

1-(4-Methoxyphenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (13) Yield 65%; mp 195–196°C; ^{1}H NMR: δ 3.82 (s, 3H), 6.58 (d, *J* = 7 Hz, 1H), 7.12–7.05 (m, 2H), 7.46–7.39 (m, 2H), 7.63–7.56 (m, 3H), 7.73–7.66 (m, 2H), 8.05 (d, *J* = 7 Hz, 1H); ^{13}C NMR: δ 55.5, 101.1, 107.0, 114.4, 116.3, 127.8, 128.1, 129.0, 130.7, 132.3, 135.5, 144.0, 159.4, 159.9. Anal. Calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.24; H, 4.61; N, 9.01.

1-(4-Acetylphenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (14) Yield 61%; mp 203–205°C; ^{1}H NMR: δ 2.65 (s, 3H), 6.66 (d, *J* = 7 Hz, 1H), 7.54–7.78 (m, 7H), 8.05–8.19 (m, 3H); ^{13}C NMR: δ 26.9, 39.5, 101.4, 107.4, 116.1, 127.1, 128.1, 129.0, 129.2, 130.9, 135.4, 137.0, 143.1, 159.6, 160.3, 197.4. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.44; H, 4.59; N, 8.72.

Ethyl 4-(3-cyano-2-oxo-4-phenylpyridin-1(2H)-yl)benzoate (15) Yield 60%, mp 221–223°C; ^{1}H NMR: δ 1.35 (t, *J* = 7 Hz, 3H), 4.36 (q, *J* = 7 Hz, 2H), 6.66 (d, *J* = 7 Hz, 1H), 7.56–7.77 (m, 7H), 8.07–8.19 (m, 3H); ^{13}C NMR: δ 14.2, 61.2, 101.4, 107.4, 116.0, 127.2, 128.1, 129.0, 130.1, 130.3, 130.9, 135.3, 143.1, 143.2, 159.5, 160.3, 165.0. Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.59; H, 4.61; N, 7.93.

1-(4-Hydroxyphenyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (16) Yield 63%; mp >250°C; ^{1}H NMR: δ 6.55 (d, *J* = 7 Hz, 1H), 6.90 (m, 2H), 7.28 (m, 2H), 7.63–7.50 (m, 3H), 7.75–7.63 (m, 2H), 8.02 (d, *J* = 7 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR: δ 101.0, 106.9, 115.6, 116.3, 127.7, 128.1, 129.0, 130.7, 130.9, 135.5, 144.1, 157.7, 159.8, 159.9.

Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.89; H, 4.51; N, 9.54.

1,4-Diphenyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (17) Yield 70%; mp 190–192°C; ^{1}H NMR: δ 6.61 (d, *J* = 7 Hz, 1H), 7.55 (m, 8H), 7.71 (m, 2H), 8.09 (d, *J* = 7 Hz, 1H); ^{13}C NMR: δ 101.3, 107.1, 116.2, 126.7, 128.1, 129.0, 129.0, 129.3, 130.8, 135.4, 139.5, 143.7, 159.7, 160.1. Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.07; H, 4.32; N, 9.98.

4-Methyl-2-oxo-1-phenyl-1,2-dihydropyridine-3-carbonitrile (18) Yield 55.5%; mp = 197–199°C; ^{1}H NMR: δ 2.48 (s, 3H), 6.37 (d, *J* = 7 Hz, 1H), 7.59–7.31 (m, 5H), 7.77 (d, *J* = 7 Hz, 1H); ^{13}C NMR: δ 19.7, 102.8, 107.2, 109.67, 124.1, 128.1, 129.5, 137.3, 140.8, 149.5, 163.3. Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.08; H, 4.76; N, 13.21.

General procedure for synthesis of compounds 19–26

A mixture of compound **12** (0.005 mol), an aldehyde (0.006 mol) and a catalytic amount of sodium hydroxide in anhydrous ethanol (10 mL) was heated under reflux for 5–6 h. Then the mixture was cooled slowly to room temperature which caused crystallization of product **19–26**. The product was filtered, washed with water (20 mL) and crystallized from ethanol.

1-(4-Methoxyphenyl)-2-oxo-4-(2-(thiophen-2-yl)vinyl)-1,2-dihydropyridine-3-carbonitrile (19) Yield 77%; mp 248–252°C; ^{1}H NMR: δ 3.86 (s, 3H), 6.86 (d, *J* = 7 Hz, 1H), 7.01 (d, *J* = 15 Hz, 1H), 6.94–7.07 (m, 2H), 7.12 (dd, *J* = 5 Hz and 4 Hz, 1H), 7.26–7.37 (m, 2H), 7.43 (d, *J* = 4 Hz, 1H), 7.56 (d, *J* = 5 Hz, 1H), 7.74 (d, *J* = 7 Hz, 1H), 7.93 (d, *J* = 15 Hz, 1H); ^{13}C NMR: δ 55.5, 96.0, 103.5, 111.0, 116.9, 119.0, 126.8, 126.9, 127.4, 128.3, 130.7, 132.8, 135.3, 143.2, 147.6, 159.2, 160.1. Anal. Calcd for $C_{19}H_{14}N_2O_2S$: C, 68.24; H, 4.22; N, 8.38. Found: C, 68.02; H, 4.56; N, 8.10.

1-(4-Methoxyphenyl)-2-oxo-4-(2-(pyridin-3-yl)vinyl)-1,2-dihydropyridine-3-carbonitrile (20) Yield 57%; mp >255°C; ^{1}H NMR: δ 3.86 (s, 3H), 6.96 (d, *J* = 7 Hz, 1H), 7.00–7.10 (m, 2H), 7.28–7.40 (m, 3H), 7.45 (dd, *J* = 8 Hz and 5 Hz, 1H), 7.79–7.91 (m, 2H), 8.08–8.17 (m, 1H), 8.56 (dd, *J* = 5 Hz and 2 Hz, 1H), 8.81 (d, *J* = 2 Hz, 1H); ^{13}C NMR: δ 56.1, 98.9, 105.5, 112.4, 114.9, 124.0, 124.9, 126.9, 131.1, 132.8, 133.2, 134.8, 137.6, 146.8, 149.8, 151.3, 158.8, 162.3. Anal. Calcd for $C_{20}H_{15}N_3O_2$: C, 72.94; H, 4.59; N, 12.76. Found: C, 72.74; H, 4.95; N, 12.91.

1-(4-Methoxyphenyl)-2-oxo-4-styryl-1,2-dihydropyridine-3-carbonitrile (21) Yield 65%; mp 239–241°C; ^{1}H NMR: δ 3.86 (s, 3H), 6.83 (d, *J* = 7 Hz, 1H), 7.00–7.06 (m, 2H), 7.52–7.29 (m, 6H), 7.81 (d, *J* = 7 Hz, 1H), 7.84–7.95 (m, 2H); ^{13}C NMR: δ 56.1, 100.2, 104.4, 111.3, 114.6, 122.7, 127.0, 128.1, 128.6, 128.8, 132.8, 135.3, 136.1, 138.1, 145.8, 157.6, 162.3. Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.58; H, 4.83; N, 8.39.

1-(4-Methoxyphenyl)-4-[2-(1-methyl-1*H*-pyrrol-2-yl)vinyl]-2-oxo-1,2-dihydropyridine-3-carbonitrile (22) Yield 81%; mp 233–236°C; ^{1}H NMR: δ 3.78 (s, 3H), 3.81 (s, 3H), 6.19 (dd, *J* = 4 Hz and 2 Hz, 1H), 6.81 (dd, *J* = 4.0 Hz and 2 Hz, 1H), 6.88 (d, *J* = 16 Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 7.03–7.09 (m, 3H), 7.31–7.41 (m, 2H), 7.73 (d, *J* = 16 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H); ^{13}C NMR: δ 34.0, 55.5, 97.9, 101.8, 109.8, 111.8, 114.3, 116.0, 125.9, 127.9, 128.5, 129.3, 130.2, 132.5, 142.0, 155.5, 159.2, 160.0. Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.31; H, 5.21; N, 12.46.

4-(4-Fluorostyryl)-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (23) Yield 55%; mp 247–249°C; ^{1}H NMR: δ 3.82 (s, 3H), 6.96 (d, *J* = 7 Hz, 1H), 7.03–7.12 (m, 2H), 7.19 (d, *J* = 16 Hz, 1H), 7.24–7.46 (m, 4H), 7.73–7.83 (m, 2H), 7.87 (d, *J* = 16 Hz, 1H), 7.96 (d, *J* = 7 Hz, 1H); ^{13}C NMR: δ 55.5, 100.5, 102.1, 114.3, 116.1, 116.4, 121.5, 127.8, 130.3, 130.4, 131.7, 132.3, 139.3, 143.0, 154.7, 159.3, 159.8. Anal. Calcd for $C_{21}H_{15}FN_2O_2$: C, 72.82; H, 4.37; N, 8.09. Found: C, 72.77; H, 4.26; N, 8.24.

4-[2-(2-Furyl)vinyl]-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (24) Yield 62%; mp 249–252°C; ^{1}H NMR: δ 3.81 (s, 3H), 6.68 (dd, *J* = 4 Hz and 2 Hz, 1H), 6.92 (d, *J* = 8 Hz, 1H), 6.92 (d, *J* = 4 Hz, 1H), 7.03 (d, *J* = 16 Hz, 1H), 7.03–7.13 (m, 2H) 7.32–7.44 (m, 2H), 7.74 (d, *J* = 16 Hz, 1H), 7.91 (d, *J* = 8 Hz, 1H), 7.91 (d, *J* = 2 Hz, 1H); ^{13}C NMR: δ 55.5, 99.9, 101.6, 113.1, 114.3, 115.7, 116.1, 118.7, 127.4, 127.8, 132.4, 142.9, 146.3, 151.1, 154.4, 158.3, 159.2. Anal. Calcd for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.71; H, 4.33; N, 8.59.

4-[4-(Dimethylamino)styryl]-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (25) Yield 76%; mp 238–241°C; ^{1}H NMR: δ 3.01 (s, 6H), 3.81 (s, 3H), 6.74–6.82 (m, 2H), 6.92 (d, *J* = 7 Hz, 1H), 6.96 (d, *J* = 16 Hz, 1H), 7.02–7.10 (m, 2H), 7.33–7.40 (m, 2H), 7.52–7.60 (m, 2H), 7.76 (d, *J* = 16 Hz, 1H), 7.83 (d, *J* = 7 Hz, 1H): ^{13}C NMR: δ 55.5, 67.2, 101.7, 105.1, 108.8, 112.0, 114.3, 115.5, 116.1, 122.3, 127.8, 129.9, 134.8, 141.6, 142.1, 151.9, 155.5, 159.1. Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.61; H, 5.54; N, 11.28.

4-[2-(Benzo[*d*][1,3]dioxol-5-yl)vinyl]-1-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (26) Yield 62%; mp >250°C; ^{1}H NMR: δ 3.81 (s, 3H), 6.10 (s, 2H), 6.86–6.96 (m, 1H), 6.97–7.14 (m, 4H), 7.24 (dd, *J* = 8 Hz and 1.7 Hz, 1H), 7.31–7.42 (m, 3H), 7.78 (d, *J* = 16 Hz, 1H), 7.92 (d, *J* = 7 Hz, 1H); ^{13}C NMR: δ 55.5, 67.2, 101.8, 102.0, 106.5, 108.8, 108.9, 114.3, 119.7, 124.5, 127.8, 127.8, 129.5, 132.4, 140.5, 142.8, 148.2, 149.4, 155.0, 159.2. Anal. Calcd for $C_{22}H_{16}N_2O_4$: C, 70.96; H, 4.33; N, 7.52. Found: C, 71.02; H, 4.11; N, 7.27.

1-(4-Methoxyphenyl)-2-oxo-4-[(3-oxoisobenzofuran-1(3*H*)-ylidene)methyl]-1,2-dihydropyridine-3-carbonitrile (27) A mixture of compound **12** (0.003 mol), phthalic anhydride (0.006 mol), acetic anhydride (0.45 mL) and a catalytic amount of potassium acetate was stirred at 130–135°C for 2 h. Then the mixture was cooled to room temperature. The solid product **27** was filtered, washed with ethanol and aqueous sodium hydrocarbonate, dried and crystallized from xylenes. Yield 76%; mp >250°C; ^{1}H NMR: δ 3.82 (s, 3H), 6.79 (s, 1H), 7.01–7.16 (m, 3H), 7.36–7.47 (m, 2H), 7.82 (t, *J* = 8 Hz, 1H), 7.96 (t, *J* = 8 Hz, 1H), 8.05 (d, *J* = 8 Hz, 2H), 8.29 (d, *J* = 8 Hz, 1H); ^{13}C NMR: δ 55.6, 99.5, 101.6, 105.8, 114.4, 115.6, 117.0, 122.4, 123.6, 125.8, 127.8, 132.3, 132.7, 135.8, 138.5, 143.7, 151.5, 151.7, 159.4, 165.2. Anal. Calcd for $C_{22}H_{14}N_2O_4$: C, 71.35; H, 3.81; N, 7.56. Found: C, 70.98; H, 4.02; N, 7.37.

Received October 26, 2012; accepted November 3, 2012

References

Abu-Shanab, F. A.; Wakefield, B.; Al-Omran, F.; Khalek, M. M. A.; Elnagdi, H. Alkyl(oxy)pyridazinecarbonitriles as building blocks in heterocyclic synthesis: novel syntheses of pyrido[3,4-*c*] pyridazines, pyrido[3,4-*d*]pyridazines, thiopyrano[3,4-*c*] pyridazines and 1,3,4-thiadiazaacenaphthylenes. *Chem. Res.* **1995**, *12*, (S) 488–489, (M) 2224.

Cox, R. J.; O'Hagan, D. Synthesis of isotopically labelled 3-amino-2-phenylpropionic acid and its role as a precursor in the biosynthesis of tenellin and tropic acid. *J. Chem. Soc., Perkin Trans.* **1991**, *1,* 2537–2540.

Curran, D. P.; Liu, H. New 4 + 1 radical annulations. A formal total synthesis of (.+-.)-camptothecin. *J. Am. Chem. Soc.* **1992**, *114*, 5863–5864.

Elassar, A. Z. A. Synthesis and reactions of 3-cyano-4,6-dimethyl-2-pyridone. *J. Heterocycl. Chem.* **2011**, *48*, 272–278.

El-Sayed, H. A.; Moustafa, A. H.; Haikal, A.-F. Z.; Abu-El-Halawa, R.; El Ashry, S. H. Synthesis, antitumor and antimicrobial activities of 4-(4-chlorophenyl)-3-cyano-2-(β-O-glycosyloxy)-6-(thien-2-yl)-nicotinonitrile. *Eur. J. Med. Chem*. **2011**, *46*, 2948–2954.

Fraley, A. W.; Chen, D.; Johnson, K.; McLaughlin, L. W. An HIV reverse transcriptase-selective nucleoside chain terminator. *J. Am. Chem. Soc*. **2003**, *125*, 616–617.

Hopkins, S. J. Milrinone lactate. *Drugs Today* **1990**, *26*, 295–298.

Kozikowski, A. P.; Campiani, G.; Sun, L.-Q.; Wang, S.; Saxena, A.; Doctor, B. P. Identification of a more potent analogue of the naturally occurring alkaloid huperzine A. Predictive molecular modeling of its interaction with AChE. *J. Am. Chem. Soc*. **1996**, *118*, 11357–11362.

Kulnevich, V. G.; Kaigorodova, E. A.; Arustamova, I. S.; Korobchenko, L. V.; Vladyko, G. V.; Boreko, E. I. Synthesis and anti-viral activity of N-alkyl-3-cyano-2-pyridones and 3-cyano-2-alkoxypyridines. *Pharm. Chem. J*. **1990**, *24*, 132–135.

Leite, A. C.; Cabral, E. C.; Dos Santos, D. A. P.; Fernandes, J. B.; Viera, P. C.; Da Silva, M. F. D. G. F. Isolation of the alkaloid ricinine from the leaves of *Ricinus communis* (Euphorbiaceae) through counter-current chromatography. *Qim. Nova* **2005**, *28*, 983–985.

Leite, L.; Jansone, D.; Veveris, M.; Cirule, H.; Popelis, Y.; Melikyan, G.; Avetisyan, A. Vasodilating and antiarrhythmic activity of heteryllactones. *Eur. J. Med. Chem*. **1999**, *34*, 859–865.

Litvinov, V. P.; Krivokolisko, S. G.; Dyachenko, V. D. Synthesis and properties of 3-cyanopyridine-2(1H)-chalcogenones. *Chem. Het. Comp*. **1999**, *35*, 509–540.

Melikyan, G. S.; Lakova, M.; Kralova, K.; El-Shaaer, H. M.; Henselova, M.; Avetisyan, A. A. Reactions of methyl-derivatives of 2-penten-5-olide, 2-buten-4-olide, and coumarin with dicarboxylic anhydrides and with 3-formylchromones under the Perkin synthesis conditions. *Chem. Papers* **1993**, *47*, 388–392.

Melikyan, G.; Piroyan, A. Facile approach to prepare 3-cyanopyridin-2(1H)-one derivatives. *Arkivoc* **2006**, *iv*, 234–239.

Mukherjee, R.; Chaterjee, A. Structure and synthesis of nudiflorine: a new pyridone alkaloid. *Tetrahedron* **1966**, *22*, 1461–1466.

Nalage, S. V.; Ajay, P. N.; Mohan, B. K.; Vijay, S. P.; Umesh, D. P.; Kamlesh, R. D.; Shamkant, L. P.; Sidhanath, V. B. One-pot four component synthesis of 4,6-disubstituted 3-cyano-2-pyridones in polyethylene glycol. *Lett. Org. Chem*. **2010**, *7*, 406–410.

Ratemi, E. S.; Namdev, N.; Gibson, M. S. Pyridine and pyrimidine ring syntheses from 4-(4-morpholino)-3-pentenone and from ethyl 3-(4-morpholino)-2-butenoate. *J. Heterocycl. Chem*. **1993**, *30*, 1513–1516.

Saad, H. A.; Mokbil, M. N.; El-Gendy, A. M.; Haikal, A. Z. Synthesis of some glycosides of pyridinone derivatives. *Synth. Commun*. **2002**, *32*, 1189–1195.

Shiao, M.-J.; Shyu, L.-M.; Chen, C.-F. Synthesis of milrinone, a cardiotonic agent. *Heterocycles* **1990**, *31*, 523–527.

Williams, D. R.; Lowder, P. D.; Gu, Y.-G. Studies toward funiculosin. Intramolecular carbonyl condensations using carboxamidimidazolide intermediates. *Tetrahedron Lett*. **1997**, *38*, 327–330.

Yuldashev, P. Kh. Ricinine and its transformations. *Chem. Nat. Comp*. **2001**, *37*, 274–275.