

Catalyzed reaction of enaminonitrile with primary amines by SbF₃: synthesis of new 2-aminosubstituted-pyridine-fused δ-lactones

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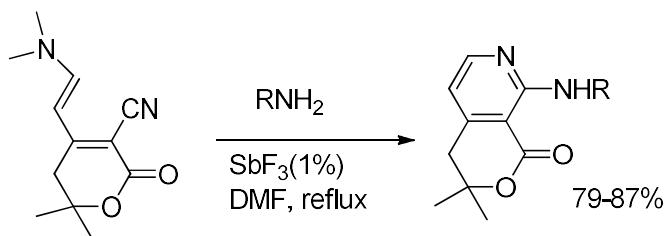
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Abstract

A novel methodology for the synthesis of substituted 2-aminopyridine δ-lactones is reported. It involves the reactions of enaminonitrile, 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile, with amines which is catalyzed by antimony trifluoride SbF₃. The structures of the new compounds obtained were characterized by various spectroscopic methods (IR, ¹H NMR, ¹³C NMR and MS).



Keywords: 2-Aminopyridine, enaminolactone nitrile, 2-aminopyridine δ-lactones, catalysis

Introduction

Among nitrogen containing heterocycles, 2-aminopyridines have gained considerable interest for synthetic research groups due to their high impact applications into biological and material science fields.¹⁻⁷ Specifically, the 2-aminopyridine moiety is present in many pharmacologically and biologically important compounds, including nitric oxide synthases (NOS),^{2,8} CXCR1/2,⁹ and renin¹⁰ inhibitors, displaying antifungal,¹¹⁻¹³ anti-inflammatory,¹¹⁻¹⁴ analgesic,^{11,14} antiparasitic,¹⁵ antiviral,¹⁶ antipyretic,¹⁷ and antimicrobial¹⁷ properties.

Recently, we focused on the preparation of bioactive nitrogen-containing heterocycles and we have shown that the synthesis of 2-aminopyridines from enaminolactone nitriles and primary aliphatic and aromatic amines was promising and constituted a valuable strategy.¹⁸ Thus, we have reported a new method for the synthesis of 2-aminopyridines fused with a five-membered lactone (γ -lactone). A novel synthesis of 3-cyano-2-aminopyridine derivatives then, from enaminonitrile and various primary amines have been also studied.¹⁹ δ -lactones, as γ -lactones, are widely found in natural products and often display many biological properties. In this paper we focus on extending our preliminary results concerning butenolide aminopyridines to new 2-aminopyridines fused with a six-membered lactone (Figure 1). It should point out that the δ -lactone nitrile **1** used, was previously studied by Lukevics *et al.*^{20,21}

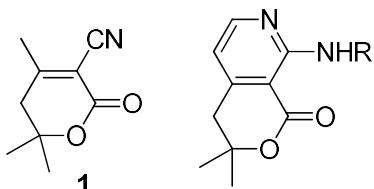
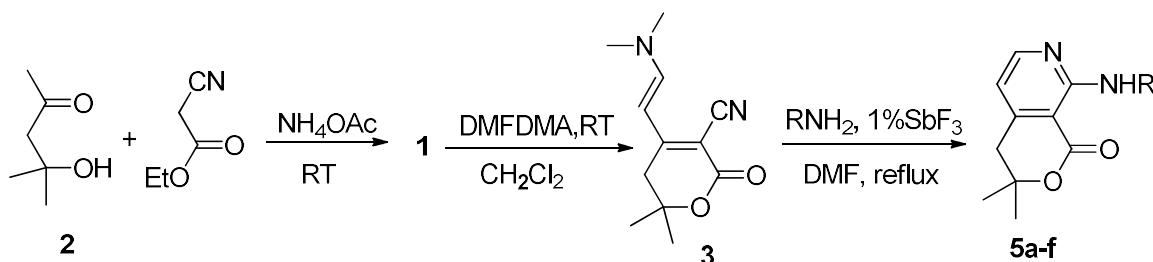


Figure 1. Structure of δ -lactone nitrile, 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile **1** and general structure of 2-aminopyridine δ -lactones.

Results and Discussion

We are reporting herein the synthesis 2-aminosubstituted-pyridine-fused δ -lactones by the reaction of amines with enaminonitrile, 4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile (Scheme 1).



Scheme 1. Synthesis of 2-aminopyridine δ -lactone derivatives.

Synthesis of δ -lactone nitrile

The δ -lactone nitrile **1** (4,6,6-trimethyl-2-oxo-5,6-dihydro-2H-pyran-3-carbonitrile) was prepared by the condensation of β -hydroxyketone (4-hydroxy-4-methylpentan-2-one) **2** with an equimolar amount of ethyl

cynoacetate, in a basic medium of ammonium acetate in excess, according to the protocol of Lukevics et al.^{16,17}

Synthesis of δ -lactone enaminonitrile

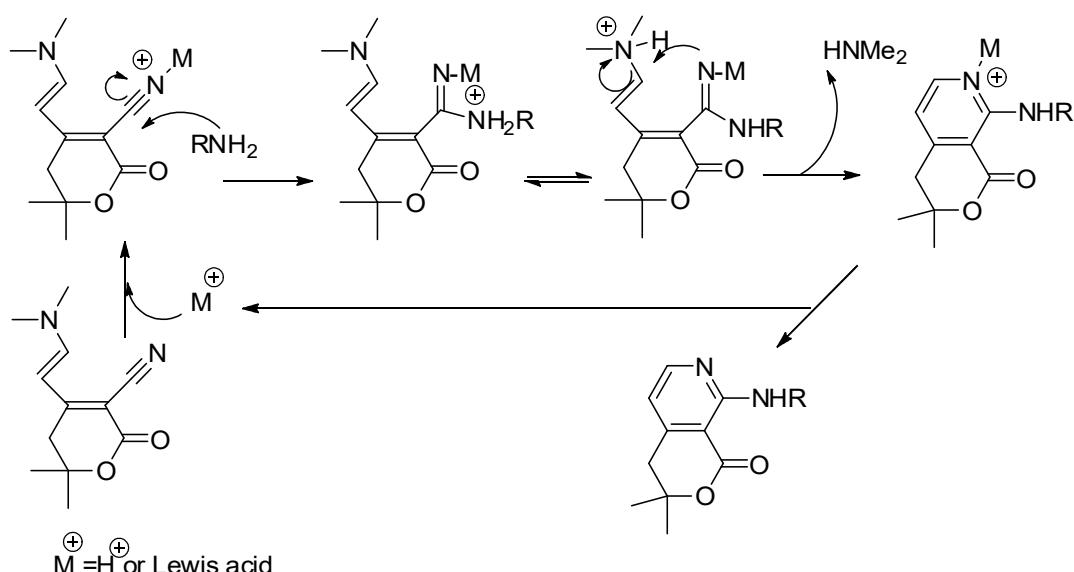
The δ -lactone nitrile **1** was converted efficiently into the condensation product δ -lactone enaminonitrile **3** via dimethylformamide dimethylacetal DMFDMA used in stoichiometric amounts. The attempts to avoid the use of solvent were unsuccessful and the reaction proceeded too slowly. However, the addition of dichloromethane rendered the reaction to completion at room temperature. Finally, the reaction was performed during 24 h furnishing the δ -lactone enaminonitrile **3** in a good overall yield (72%) (Scheme 1).

The structure of the δ -lactone enaminonitrile **3** was confirmed by spectral analysis. The ^1H NMR spectrum showed two doublets at $\delta = 7.23$ and $\delta = 5.59$ ppm with a large coupling constant value of 12.4 Hz characteristic of a conjugated double bond C=C with a 'E' configuration. The mass spectrum displayed molecular ion peak in agreement with the expected structure.

Synthesis of 2-aminopyridine δ -lactone derivatives

We report the synthesis of a series of new substituted 2-aminopyridine δ -lactones **5a-f** via condensation between δ -lactone enaminonitrile **3** and primary amines **4a-f**.

Initially, we have investigated the reaction conditions of the δ -lactone enaminonitrile **3** with benzylamine **4a**. In the absence of acid, the reaction proceeded very slowly and the yield obtained was very poor (<10%) contrary to the results obtained with γ -lactones.¹⁸ Thus, we have tested protic and Lewis catalysts. As protic acids, pentafluoroanilinium triflate (PFAT) was found the more efficient among β -alanine, APTS, oxalic, camphosulfonic and sulfamic acids. As Lewis acids, zinc chloride ZnCl_2 was inefficient, bismuth trichloride BiCl_3 or indium trichloride InCl_3 gave many by-products and antimony trifluoride SbF_3 has proven to be very efficient affording clean 2-aminopyridine δ -lactones. SbF_3 was known as fluorinating agent²² and it was not widely used as Lewis acid catalyst²³ in the literature. A plausible acid catalyzed mechanism of the synthesis of 2-aminopyridine δ -lactones according to the following scheme 2 is proposed.



Scheme 2. Plausible acid catalyzed mechanism of the synthesis of 2-aminopyridine δ -lactones.

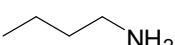
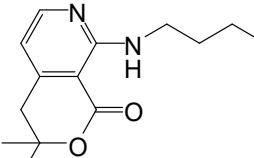
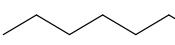
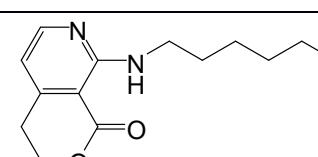
The choice of various amines, including aliphatic, aromatic, and heterocyclic was expressly large to investigate the versatility of the reaction. The 2-aminopyridine δ -lactones **5a-f** were obtained by heating an equimolar mixture of δ -lactone enaminonitrile **3** and different primary amines (benzylamine **4a**, (S)-(-)- α -methylbenzylamine **4b**, histamine **4c**, furfurylamine **4d**, butylamine **4e** and hexylamine **4f** for 6 h in the presence of dimethylformamide, in the yields of 86–95% (Table 1).

All these compounds **5a-f** were characterized by standard spectroscopic methods (^1H , ^{13}C NMR, IR, MS data), which have confirmed their structures. The IR spectrum revealed in each case the disappearance of the band of CN nitrile at 2195 cm^{-1} of the δ -lactone enaminonitrile and the appearance of new bands of medium intensity in the region $1675\text{-}1577\text{ cm}^{-1}$ for $\text{v}(\text{C}=\text{N})$, with concomitant appearance of bands corresponding to NH function at a range of $3332\text{-}3398\text{ cm}^{-1}$. Also, ^1H NMR spectra of the compounds **5a-f** showed characteristic signals due to NH proton of 2-aminopyridine (typically at a range of δ $8.22\text{-}8.71\text{ ppm}$) which come from the nucleophilic attack of NH function of primary amine on nitrile group of δ -lactone enaminonitrile **3**.

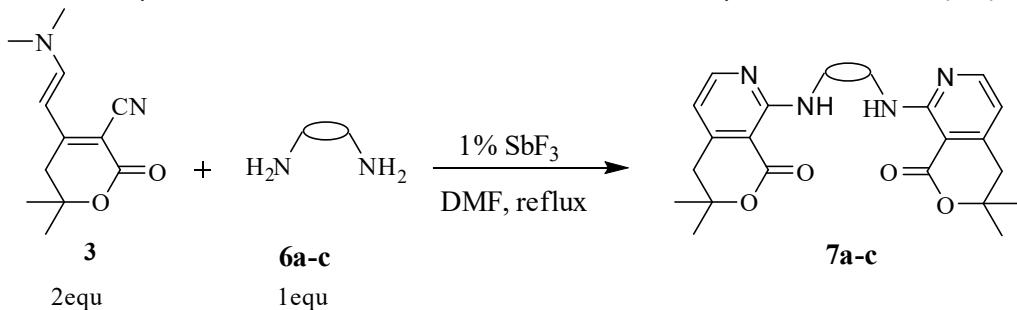
Table 1. Preparation of substituted 2-aminopyridine δ -lactones **5a-f** by reaction of one equivalent of δ -lactone enaminonitrile **3** and one equivalent of primary amines **4a-f**, in the presence of SbF_3 (1%), in DMF

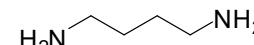
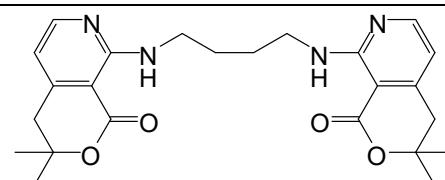
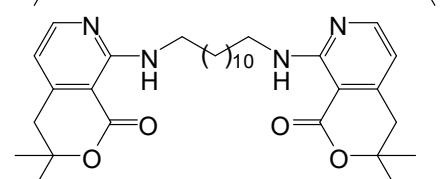
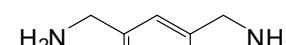
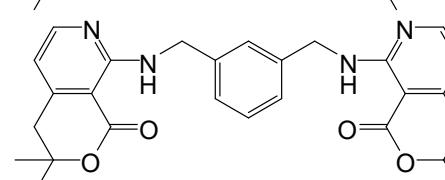
Entry	Enaminolactone 3	RNH ₂ 4a-f	Product 5a-f	Yield (%)
1				82
2				86
3				81
4				79

Table 1 (continued)

Entry	Enaminolactone	RNH ₂	Product	Yield (%)
5	3	 4e		5e 85
6	3	 4f		5f 87

Encouraged by these results, we have chosen to extend the scope of such reactions with several diamines under similar reaction conditions mentioned above, affording new original polycyclic compounds: bis(2-aminopyridine δ-lactones) **7a-c**.

Table 2. Preparation of substituted bis-aminopyridine δ-lactones **7a-c** from reaction of one equivalent of diamines **6a-c** with two equivalents of δ-lactone enaminonitrile **3** in the presence of SbF₃ (1%), in DMF

Entry	Enamino lactone	RNH ₂	Product	Yield (%)
1	3	 6a		7a 57
2	3	 6b		7b 60
3	3	 6c		7c 89

The reactions between one equivalent of diamines **6a-c** with two equivalents of δ -lactone enaminonitrile **3** were refluxed in DMF during 6 h. After removing the solvent, the purification by column chromatography afforded the new original bis-(2-aminopyridine) δ -lactones **7a-c** in moderate to good yields (Table 2). The structures of the compounds **7a-c** were confirmed by spectral data (IR, ^1H NMR and ^{13}C NMR).

Conclusions

In this study, a novel easy synthesis of new original 2-aminopyridine δ -lactones is developed. We have found that antimony trifluoride (SbF_3) is an efficient catalyst of this reaction. The wide variety of aliphatic, aromatic, and heterocyclic amines used indicates that this methodology can be suitable for a large range of synthetic applications. Further investigations of the biological properties of these molecules are currently in progress.

Experimental Section

General. Melting points were measured on a Kofler apparatus and are reported uncorrected. IR spectra were obtained with solids or neat liquids with a Fourier transform Perkin-Elmer Spectrum One with ATR accessory. The frequencies of absorption are given in cm^{-1} . Only significant absorptions are listed. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded while using CDCl_3 with TMS as an internal standard on a Bruker DPX 400 NMR spectrometer. Chemical shifts are reported in ppm. Mass spectra were recorded on a Xevo G2-XS QToF WATERS, mass range (50-1000 m/z), source temperature 120 °C, desolvatation temperature 500°C. Pentafluoroanilinium triflate PFAT was obtained according to the literature.²⁴

Preparation of δ -enaminolactone 4-(2 (dimethylamino)vinyl)-6,6-dimethyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carbonitrile (3). DMFDMA (2.38 g, 20 mmol) was added to the 4,6,6-trimethyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carbonitrile **1** (3.30 g, 20 mmol). The mixture was stirred at room temperature in the presence of dichloromethane (10 mL) during 24 h and a solid was formed. The solid was washed with ethyl acetate, and then purified by column chromatography over silica gel using a mixture of CH_2Cl_2 -MeOH (95:5) as eluent. The eluent was evaporated in vacuo to give **3** as a yellow solid. Yield (3.16 g, 72%) yellow solid, *mp* 268°C. IR ν_{max} (neat/ cm^{-1}): 2978, 2195, 1676, 1618, 1535, 1264. ^1H NMR (CDCl_3) δ 7.23 (1H, d, 3J 12.4 Hz, $\text{CH}=\text{CHN}$), 5.59 (1H, d, 3J 12.4 Hz, $\text{CH}=\text{CHN}$), 3.22 (3H, s, $\text{N}-\text{CH}_3$), 2.99 (3H, s, $\text{N}-\text{CH}_3$), 2.60 (2H, s, CH_2), 1.40 (6H, s, 2 \times CH_3). ^{13}C NMR (CDCl_3) δ 163.7, 162.9, 154.8, 117.6, 94.5, 80.7, 77.5, 45.1, 37.1, 26.7. HRMS (ESI-QTOF) calcd for $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) 221.1290. Found 221.1300.

Synthesis of 2-aminopyridine δ -lactones

In search of better catalysts for the 2-aminopyridine δ -lactone (5a) synthesis. Pentafluoroanilinium triflate (PFAT),²² β -alanine, APTS, oxalic, camphosulfonic, sulfamic acids, ZnCl_2 , BiCl_3 , InCl_3 , SbF_3 were tested as catalysts.

A stock solution of reactives was prepared by dissolving 2 g (9 mmol) of enamo- δ -lactone nitrile **3** and 0.96 g (9 mmol) of benzylamine **4a** in DMF (20 mL). In a tube of a Carousel Radley 12, 2 mL of stock solution was added to the catalyst (1%) then stirred and refluxed under argon during 3h. After reaction the mixture of all tubes were analysed by TLC (ethyl acetate/cyclohexane). The product **5a** displayed a fluorescent spot and can be quantified by spot image analysis. The product **5a** was separated with a Acquity UPLC H-Class Waters, on a column Waters Acquity UPLC CSH C18 1.7 μm , with a gradient water, 0.1% formic acid/acetonitrile 0.1% formic

acid, debit 0.5 mL/min, at 35°C. The products were analyzed by coupled mass spectrometer Xevo C2-XS QT of Waters, ESI positive (50-1000 m/z, source 120°C; desolvatation 500°C; capillary 0.3kV; cone: 40V). Elution: 2.35 min; compound **5a**: C₁₇H₁₉N₂O₂ (M+H): calcd for 283.1447. Found 283.1448

General procedure 1 for the synthesis of 2-aminopyridines δ-lactones (5a-f). A mixture of 4-(2-(dimethylamino)vinyl)-6,6-dimethyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carbonitrile **3** (0.5 g, 2.27 mmol), primary amine **4a-f** (2.27 mmol) and antimony trifluoride (1%) was refluxed for 6 h in the presence of DMF (5 mL). Volatile components were evaporated in vacuo to give oil, which was purified by column chromatography (silica gel, ethyl acetate/cyclohexane (70:30)) to give 2-aminopyridine δ-lactone **5a-f**. The 2-aminopyridine δ-lactones correspond to the fluorescent spot under UV in TLC.

8-(Benzylamino)-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-c]pyridin-1-one (5a). The general procedure **1** (0.243 g, 2.27 mmol) of benzylamine **4a**, gave (0.588 g, 92%) **5a** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3346, 2979, 1673, 1589, 1521, 1376, 1176. ¹H NMR (CDCl₃) δ 8.63 (1H, s large, NH), 8.10 (1H, d, ³J 5.2 Hz, CH-N), 7.28-7.12 (5H, m, Harom), 6.24 (1H, d, ³J 5.2 Hz, CH=CH-N), 4.68 (2H, d, ³J 4.0 Hz, NH-CH₂), 2.73 (2H, s, CH₂ cyc), 1.33 (6H, s, 2×CH₃). ¹³C NMR (CDCl₃) δ 166.1 (C=O), 158.4 (N-C-NH), 154.1 (Cqpyr), 149.3 (CH-N), 139.2 (Cqarom), 128.5 (Carom), 127.4 (Carom), 127.0 (Carom), 111.2 (CH=CH-N), 101.0 (C-C=O), 79.8 (C(CH₃)₂), 44.7 (CH₂NH), 39.2 (CH₂ cyc), 27.3 (CH₃). HRMS (ESI-QTOF) calcd for C₁₇H₁₉N₂O₂ (M+H) 283.1447; Found 283.1447.

(S)-3,3-Dimethyl-8-(1-phenylethylamino)-3,4-dihydro-1*H*-pyrano[3,4-c]pyridin-1-one (5b). The general procedure **1** (0.275 g, 2.27 mmol) (S)-(−)-α-methylbenzylamine **4b**, gave (0.645 g, 96%) **5b** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3332, 2978, 1675, 1580, 1516, 1380, 1176. ¹H NMR (CDCl₃) δ 8.71 (1H, d, ³J 8.0 Hz, NH), 8.09 (1H, d, ³J 4.0 Hz, CH-N), 7.34-7.17 (5H, m, Harom), 6.24 (1H, d, ³J 4.0 Hz, CH=CH-N), 5.41 (1H, m, NH-CH-CH₃), 2.81 (2H, s, CH₂ cyc), 1.53 (6H, s, 2×CH₃), 1.39 (3H, d, ³J 8.0 Hz, CH₃). ¹³C NMR (CDCl₃) δ 166.2 (C=O), 157.7 (N-C-NH), 154.1 (Cqpyr), 149.2 (CH-N), 144.8 (Cqarom), 128.4 (Carom), 127.0 (Carom), 126.8 (Carom), 110.9 (CH=CH-N), 100.9 (C-C=O), 79.8 (C(CH₃)₂), 49.9 (CH-NH), 39.4 (CH₂ cyc), 29.7 (CH₃), 23.4 (CH₃). HRMS (ESI-QTOF) calcd for C₁₈H₂₁N₂O₂ (M+H) 297.1603; Found 297.1606.

8-(2-1*H*-Imidazol-4-yl)ethylamino)-3,3-dimethyl-3,4-dichloro-1*H*-pyrano(3,4-c)pyridin-1-one (5c). The general procedure **1** using (0.252 g, 2.27 mmol) histamine **4c**, gave (0.616 g, 95%) **5c** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3398, 2976, 2934, 1661, 1603, 1530, 1375, 1177. ¹H NMR (CDCl₃) δ 8.45 (1H, s, NH), 8.18 (1H, d, ³J 4.8 Hz, CH-N), 7.59 (1H, d, ³J 4.0 Hz, NH-CH=N), 6.86 (1H, d, ³J 5.6 Hz, C=CH-NH), 6.31 (1H, d, ³J 4.8 Hz, CH=CHN), 3.78 (2H, q, ³J_{CH2NH} = ³J_{CH2CH2} 6.4 Hz, NH-CH₂-CH₂), 3.58 (2H, t, ³J 6.4 Hz, CH₂-CH₂-C), 3.22 (2H, s, CH₂ cyc), 1.38 (6H, s, 2×CH₃). ¹³C NMR (CDCl₃) δ 166.2 (C=O), 161.5 (N-C-NH), 154.0 (Cqpyr), 149.5 (CH-N), 136.3 (Cimid), 132.6 (Cimid), 111.0 (CH=CH-N), 101.1 (C-C=O), 96.1 (Cimid), 79.9 (C(CH₃)₂), 45.9 (CH₂-NH), 40.4 (CH₂ cyc), 29.7 (CH₂-CH₂-NH), 28.2 (CH₃). HRMS (ESI-QTOF) calcd for C₁₅H₁₉N₄O₂ (M+H) 287.1508. Found 287.1516.

8-(Furan-2-ylmethylamino)-3,3-dimethyl-3,4-dihydro-1*H*-pyrano(3,4-c)pyridin-1-one (5d). The general procedure **1** using (0.22 g, 2.27 mmol) of furfurylamine **4d**, gave (0.592 g, 96%) **5d** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3348, 3055, 1680, 1610, 1523, 1377, 1105. ¹H NMR (CDCl₃) δ 8.48 (1H, t, ³J 5.5 Hz, NH), 8.23 (1H, d, ³J 4.9 Hz, CH-N), 7.58 (1H, d, ³J 1.9 Hz, CH=CH-O), 6.55 (1H, d, ³J 4.9 Hz, CH=CH-N), 6.39 (1H, dd, ³J 3.1 and 1.9 Hz, CH-CH=CH-O), 6.27 (1H, d, ³J 3.1 Hz, C=CH-CH=), 4.68 (2H, d, ³J 5.5 Hz, CH₂NH), 2.97 (2H, s, CH₂ cyc), 1.35 (6H, s, 2×CH₃). ¹³C NMR (CDCl₃) δ 165.4 (C=O), 157.3 (N-C-NH), 153.8 (Cqpyr), 152.6 (Cqfur), 150.1 (CH-N),

142.2 (**Cfur**), 111.9 (**CH=CH-N**), 110.5 (**Cfur**), 106.9 (**Cfur**), 100.8 (**C-C=O**), 80.1 (**C(CH₃)₂**), 38.0 (**CH₂ cyc**), 37.2 (**CH₂-NH**), 26.8 (**CH₃**). HRMS (ESI-QTOF) calcd for C₁₅H₁₇N₂O₃ M+H 273.1239. Found 273.1244.

8-(Butylamino)-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one (5e). The general procedure **1** using (0.166 g, 2.27 mmol) of butylamine **4e**, gave (0.534 g, 95%) **5e** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3346, 2931, 1671, 1577, 1524, 1371, 1176. ¹H NMR (CDCl₃) δ 8.22 (1H, s large, NH), 8.08 (1H, d, ³J 4.0 Hz, CH-N), 6.19 (1H, d, ³J 4.0 Hz, CH=C-N), 3.37 (2H, q, ³J_{CH2NH} = ³J_{CH2CH2} 8.0 Hz, NH-CH₂), 2.73 (2H, s, CH₂ cyc), 1.52 (2H, m, CH₂-CH₂-CH₂), 1.31 (6H, s, 2CH₃), 1.13 (2H, m, CH₂-CH₂-CH₃), 0.83 (3H, t, ³J 8.0 Hz, CH₃). ¹³C NMR (CDCl₃) δ 165.9 (**C=O**), 158.3 (**N-C-NH**), 153.8 (**Cqpyr**), 149.0 (**CH-N**), 110.3 (**CH=CH-N**), 100.4 (**C-C=O**), 79.4 (**C(CH₃)₂**), 40.5 (**CH₂-NH**), 39.1 (**CH₂ cyc**), 31.3 (**CH₂**), 27.0 (**CH₃**), 20.0 (**CH₂**), 13.6 (**CH₃**). HRMS (ESI-QTOF) calcd for C₁₄H₂₁N₂O₂ (M+H) 249.1603; Found 249.1602.

8-(Hexylamino)-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one (5f). The general procedure **1** using (0.229 g, 2.27 mmol) of hexylamine **4f**, gave (0.545 g, 87%) **5f** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3348, 2955, 2929, 2858, 1703, 1675, 1520, 1371, 1314. ¹H NMR (CDCl₃) δ 8.31 (1H, s large, NH), 8.27 (1H, d, ³J 5.2 Hz, CH-N), 6.28 (1H, d, ³J 5.2 Hz, CH=CH-N), 3.46 (2H, q, ³J 5.2 Hz, CH₂-NH), 2.83 (2H, s, CH₂ cyc), 1.63 (2H, m, CH₂-CH₂), 1.45 (6H, s, 2×CH₃), 1.31 (2H, m, CH₂-CH₃), 1.18 (4H, m, 2×CH₂), 0.88 (3H, t, ³J 6.0 Hz, CH₃). ¹³C NMR (CDCl₃) δ 166.8 (**C=O**), 158.5 (**N-C-NH**), 154.1 (**Cqpyr**), 149.3 (**CH-N**), 110.5 (**CH=CH-N**), 102.0 (**C-C=O**), 79.8 (**C(CH₃)₂**), 41.1 (**CH₂ cyc**), 40.7 (**CH₂-NH**), 31.7 (**CH₂**), 27.5 (**CH₂**), 27.3 (**CH₃**), 26.7 (**CH₂**), 22.5 (**CH₂**), 14.1 (**CH₃**). HRMS (ESI-QTOF) calcd for C₁₆H₂₅N₂O₂ (M+H) 277.1916; Found 277.1926.

General procedure 2 for the synthesis of bis(2-aminopyridine δ-lactones) (7a-c). The mixture of 4-(2-(dimethylamino)vinyl)-6,6-dimethyl-2-oxo-5,6-dihydro-2*H*-pyran-3-carbonitrile **3** (1 g, 4.54 mmol), diamine **6a-c** (2.27 mmol) and antimony trifluoride (1%) was refluxed for 6 h in the presence of DMF (10 mL). The solvent was evaporated and the residue obtained was purified by column chromatography (silica gel, ethyl acetate/cyclohexane (70:30) to give bis (2-aminopyridine δ-lactones) **7a-c**.

8,8'-(Butane-1,4-diylbis(azanediyl))bis(3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one) 7a. The general procedure **2** using (0.2 g, 2.27 mmol) of 1,4-diaminobutane **6a**, gave (0.566 g, 57%) **7a** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3348, 2933, 1678, 1580, 1526, 1320, 1178. ¹H NMR (CDCl₃) δ 8.41 (2H, s large, 2×NH), 8.19 (2H, d, ³J 5.2 Hz, 2×CH=CH-N), 6.32 (2H, d, ³J 5.2 Hz, 2×CH=CH-N), 3.71 (4H, q, ³J_{CH2NH} = ³J_{CH2CH2} 7.2 Hz, 2×NH-CH₂-CH₂), 2.86 (4H, s, 2×CH₂ cyc), 1.45 (12H, s, 4×CH₃), 1.26-1.16 (4H, m, 2×CH₂-CH₂-CH₂). ¹³C NMR (CDCl₃) δ 163.8 (**C=O**), 158.4 (**N-C-NH**), 152.6 (**Cqpyr**), 117.9 (**CH=CH-N**), 114.1 (**C-C=O**), 85.3 (**C(CH₃)₂**), 48.3 (**CH₂-NH**), 41.1 (**CH₂ cyc**), 26.4 (**CH₂-CH₂-NH**), 24.2 (**CH₃**). HRMS (ESI-QTOF) calcd for C₂₄H₃₁N₄O₄ (M+H) 439.2345; Found 439.2343.

8,8'-(Dodecane-1,12-diylbis(azanediyl))bis(3,3-dimethyl-3,4-dihydro-1*H* pyrano [3,4-*c*] pyridin-1-one) 7b. The general procedure **2** using (0.45 g, 2.27 mmol) of 1,12-dodecanediamine **6b**, gave (0.749 g, 60%) **7b** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3347, 2925, 1675, 1579, 1528, 1373, 1199, 1177. ¹H NMR (CDCl₃) δ 8.42 (2H, s large, 2×NH), 8.22 (2H, d, ³J 4.8 Hz, 2×CH=CH-N), 6.32 (2H, d, ³J 4.8 Hz, 2×CH=CH-N), 3.51 (4H, q, ³J_{CH2NH} = ³J_{CH2CH2} 7.2 Hz, 2×NH-CH₂-CH₂), 2.86 (4H, s, 2×CH₂ cyc), 1.65 (4H, m, 2×CH₂-CH₂-CH₂), 1.45 (12H, s, 4×CH₃), 1.33-1.16 (16H, m, 2×CH₂-(CH₂)₄CH₂). ¹³C NMR (CDCl₃) δ 166.1 (**C=O**), 158.2 (**N-C-NH**), 153.6 (**Cqpyr**), 149.7 (**CH-N**), 110.5 (**CH=CH-N**), 101.0 (**C-C=O**), 79.8 (**C(CH₃)₂**), 41.3 (**CH₂-NH**), 39.4 (**CH₂ cyc**), 29.6 (**CH₂**), 29.6 (**CH₂**), 29.4 (**CH₂**), 29.4 (**CH₂**), 27.3 (**CH₃**), 27.1 (**CH₂**). HRMS (ESI-QTOF) calcd for C₃₂H₄₇N₄O₄ (M+H) 551.3597; Found 551.3596.

8,8'-(1,3-Phenylenebis(methylene))bis(azanediyl)bis(3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-1-one) 7c. The general procedure **2** using (0.309 g, 2.27 mmol) of m-xylylenediamine **6c**, gave (0.981 g, 89%) **7c** as viscous oil. IR ν_{max} (neat/cm⁻¹): 3346, 2978, 1673, 1580, 1521, 1259, 1176. ¹H NMR (CDCl_3) δ 8.85 (2H, s large, 2× NH), 8.19 (2H, d, ³J 4.0 Hz, 2× CH-N), 7.35-7.23 (4H, m, Harom), 6.37 (2H, d, ³J 4.0 Hz, 2× CH=CH-N), 4.78 (4H, d, ³J 8.0 Hz, 2× CH₂-NH), 2.88 (4H, s, 2× CH₂ cyc), 1.44 (12H, s, 4×CH₃). ¹³C NMR (CDCl_3) δ 166.1 (**C**=O), 158.4 (N-C-NH), 154.1 (**C**qpyr), 149.3 (**CH**-N), 139.5 (**C**qarom), 128.8 (**Carom**), 126.7 (**Carom**), 126.1 (**Carom**), 111.2 (**CH**=CH-N), 101.1 (**C**-C=O), 79.8 (**C**(CH₃)₂), 44.7 (**CH**₂-NH), 39.3 (**CH**₂ cyc), 27.4 (**CH**₃). HRMS (ESI-QTOF) calcd for C₂₈H₃₁N₄O₄ (M+H) 487.2345; Found 487.2344.

Supplementary Material

Supplementary material contains NMR spectra.

References

- Yale, H. L.; Coutts, R. T.; Casy, A. F. In *Pyridine and Its Derivatives Supplement IV*; Abramovitch, R. A., Ed.; Wiley: New York, 1975; p 445.
<http://onlinelibrary.wiley.com/doi/10.1002/9780470186633.fmatter/pdf>.
- Hagmann, W. K.; Caldwell, C. G.; Chen, P.; Durette, P. L.; Esser, C. K.; Lanza, T. J.; Kopka, I. E.; Guthikonda, R.; Shah, S. K.; MacCoss, M.; Chabin, R. M.; Fletcher, D.; Grant, S. K.; Green, B. G.; Humes, J. L.; Kelly, T. M.; Luell, S.; Meurer, R.; Moore, V.; Pacholok, S. G.; Pavia, T.; Williams, H. R.; Wong, K. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1975–8.
<http://dx.doi.org/10.1016/j.bmcl.2010>.
<https://www.ncbi.nlm.nih.gov/pubmed/10987430>.
- Adib, M.; Mahdavi, M.; Noghani, M. A.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 7263–5.
<http://dx.doi.org/10.1016/j.tetlet.2007.08.049>.
- Matschke, M.; Blumhoff, J.; Beckert, R. *Tetrahedron* **2008**, *64*, 7815–21.
<http://dx.doi.org/10.1016/j.tet.2008.05.117>.
- Vardanyan, R.; Hruby, V. *Synthesis of Essential Drugs*; Elsevier: Amsterdam, 2006; p 51.
ISBN: 9780444521668.
- Ma, H. R.; Wang, Y. Y.; Liu, P.; Li, D. S.; Shi, Q. Z.; Lee, G. H.; Peng, S. M. *Polyhedron* **2005**, *24*, 215–20.
<http://dx.doi.org/10.1016/j.poly.2004.11.013>.
- Kempe, R. *Eur. J. Inorg. Chem.* **2003**, 791–803.
<http://dx.doi.org/10.1002/ejic.200390108>.
- Kang, S.; Li, H.; Tang, W.; Martasek, P.; Roman, L. J.; Poulos, T. L.; Silverman, R. B. *J. Med. Chem.* **2015**, *58*(14): 5548–60.
<http://dx.doi.org/10.1021/acs.jmedchem.5b00573>.
- Schuler, A. D.; Engles, C. A.; Maeda, D. Y.; Quinn, M. T.; Kirpotina, L. N.; Wicomb, W.N.; Mason, S. N.; Auten, R. L.; Zebala, J. A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3793–7.
<http://dx.doi.org/10.1016/j.bmcl.2015.07.090>.
- Imaeda, Y.; Tawada, M.; Suzuki, S.; Tomimoto, M.; Kondo, M.; Tarui, N.; Sanada, T.; Kanagawa, R.; Snell, G.; Behnke, C. A.; Kubo, K.; Kuroita, T. *Bioorg. Med. Chem.* **2016**, *24*, 5771–80.
<http://dx.doi.org/10.1016/j.bmc.2016.09.030>.

11. Gholap, A. R.; Toti, K. S.; Shirazi, F.; Kumari, R.; Bhat, M. K.; Deshpande, M. V.; Srinivasan, K. V. *Bioorg. Med. Chem.* **2007**, *15*, 6705–15.
<http://dx.doi.org/10.1016/j.bmc.2007.08.009>.
12. Manna, F.; Chimenti, F.; Bolasco, A.; Bizzarri, B.; Filippelli, W.; Filippelli, A.; Gagliardi, L. G. *Eur. J. Med. Chem.* **1999**, *34*, 245–54.
13. Altundas, A.; Ayvaz, S.; Logoglu, E. *Med. Chem. Res.* **2011**, *20*, 1–8.
<http://dx.doi.org/10.1007/s00044-009-9273-x>.
14. Ann, J.; Ki, Y.; Yoon, S.; Kim, M. S.; Lee, J.-U.; Kim, C.; Lee, S.; Jung, A.; Baek, J.; Hong, S.; Choi, S.; Pearce, L. V.; Esch, T. E.; Turcios, N. A.; Lewin, N. E.; Ogunjirin, A. E.; Herold, B. K. A.; McCall A. K.; Blumberg, P. M.; Lee, J., *Bioorg. Med. Chem.* **2016**, *24*, 1231-40.
<http://dx.doi.org/10.1016/j.bmc.2016.01.051>.
15. Valenciano, A. L.; Ramsey, A. C.; Santos, W. L.; Mackey, Z. B. *Bioorg. Med. Chem.* **2016**, *24*, 4647-51.
<http://dx.doi.org/10.1016/j.bmc.2016.07.069>.
16. Kolodziej, K.; Romanowska, J.; Stawinski, J.; Boryski, J.; Dabrowska, A.; Lipniacki, A.; Piasek, A.; Kraszewski, A.; Sobkowski M., *Eur. J. Med. Chem.* **2015**, *100*, 77- 88.
<http://dx.doi.org/10.1016/j.ejmecm.2015.06.004>.
17. Abdel-Aziz, A. A.-M.; El-Subbagh, H. I.; Kunieda, T., *Bioorg. & Med. Chem.* **2005**, *13*, 4929-35.
<http://dx.doi.org/10.1016/j.bmc.2005.05.027>.
18. Cheikh, N.; Villemin, D.; Bar, N.; Lohier, J. F.; Choukchou-Braham, N.; Mostefa-Kara, B.; Sopkova J. *Tetrahedron*. **2013**, *69*, 1234-47.
<http://dx.doi.org/10.1016/j.tet.2012.10.108>.
19. Villemin, D.; Belhadj, Z.; Cheikh, N.; Choukchou-Braham, N.; Bar, N.; Lohier, J. F. *Tetrahedron Lett.* **2013**, *54*, 1664–68.
<http://dx.doi.org/10.1016/j.tetlet.2013.01.021>.
20. Jansone, D.; Fleisher, M. ; Andreeva, G.; Leite, L.; Lukevics, E. *Chem. Heterocycl. Comp.* **2005**, *41*(12), 1863-64.
<http://dx.doi.org/10.1007/s10593-006-0034-1>.
21. Lukevics, E.; Jansone, D.; Leite, L.; Popelis, J.; Andreeva, G.; Shestakova, I.; Domracheva, I.; Bridane, V.; Kanepe, I. *Chem Heterocycl. Comp.* **2009**, *45*(10), 1529-38.
<http://dx.doi.org/10.1007/s10593-010-0411-7>.
22. Gerstenberger, M. R. C. ; Haas, A. *Angew. Chem. Int. Ed.* **1981**, *20*, 8, 647–667.
<http://dx.doi.org/10.1002/anie.198106471>
23. Benjamin, S. L.; Burt, J.; Levason, W.; Reid G.; Webster, M. J. *Fluorine Chem.* **2012**, *135*, 108–117.
<http://dx.doi.org/10.1016/j.jfluchem.2011.09.007>.
24. Funatomi, T.; Wakasugi, K.; Misaki, T.; Tanabe, Y., *Green Chem.* **2006**, *8*(12), 1022-27.
<http://dx.doi.org/10.1039/B609181B>.