Modern Organic Chemistry Research, Vol. 2, No. 1, February 2017
https://dx.doi.org/10.22606/mocr.2017.21004

Efficient Synthesis of Long-Chain *N'*-hydroxy-*N*-alkyl- and -*N,N*-dialkylpyridinecarboximidamides

Przemysław Aksamitowski[1], Karolina Wieszczycka[1], Aleksandra Wojciechowska[1], Irmina Wojciechowska[1], Grzegorz Framski[2]

[1]Institute of Chemical Technology and Engineering, Poznan University of Technology, Berdychowo St. 4, 60-965 Poznan, Poland

[2]Institute of Bioorganic Chemistry, Polish Academy of Science, Noskowskiego St. 12/14, 61-704 Poznan, Poland
Email: karolina.wieszczycka@put.poznan.pl

Abstract. *N'*-hydroxy-*N*-alkylpyridinecarboximidamides are new class of *N*-substituted imidamide derivatives, with diverse potential applications. In this study, the synthesis of novel long-chain *N*-substituted pyridinecarboximidamides: *N'*-hydroxy-*N*-alkylpyridinecar-boximidamides and *N'*-hydroxy-*N,N*-dialkylpyridinecarboximidamides is reported. The two methods were proposed and compared: (I) the two-step procedure (synthesis of *N*-alkylpyri-dinecarboximidamide and next *N'*-hydroxy-*N*-alkylpyridinecarboximidamide) and (II) the three-step procedure (synthesis from pyridineamidoxime by pyridinehydroximoyl chloride and finally preparation of *N'*-hydroxy-*N*-alkyl- or -*N,N*-dialkylpyridinecarboximidamide). It was indicated that only the three-step procedure enabled the efficient synthesis of the *N'*-hydroxy-*N,N*-dialkylpyridinecarboximi-damide with the substituent at position 3 and 4 of the pyridine ring.

Keywords: *N'*-hydroxy-*N*-alkylpyridinecarboximidamides; synthesis; substitution

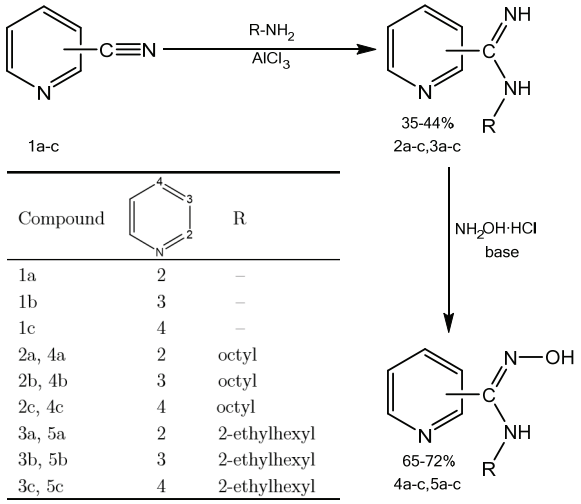
1 Introduction

N- and *N'*-substituted imidamides, similar to well known simple amidoximes [1-3], possess very important biological activities [4]. They have already been used as antimicrobial [5,6] bactericidal [7] or fungidal agents [8]. *N'*-substituted pyridinecarboximidamides have been also studied as antihypertensive drugs [9] and in porcine isolated coronary artery [10]. The most important key issues for the preparation of such compounds are their complexing nature mainly towards divalent metals ions [11,12]. *N*-substituted imidamides especially containing both *N*-hydroxy and *N*-alkyl groups are amphoteric substances and show tautomeric properties with domination of the oxime form. These properties allow to suppose that the long-chain *N'*-hydroxy-*N*-alkylpyridinecarboximidamides and *N'*-hydroxy-*N,N*-dialkylpyridinecarboximidamid-es may also demonstrate biological as well as complexing properties. Therefore, the goal of the research was to synthesize *N'*-hydroxy-*N*-alkyl- (4a-c – 6a-c) and -*N,N*-dialkylpyridine-2-, -3-, and -4-carboximidamides (7a-c) with hexyl, octyl and 2-ethylhexyl chain. In this work, two methods were proposed and compared, however, only the three-step procedure enabled the synthesis of *N'*-hydroxy-*N*-alkylpyridinecarboximidamides and *N'*-hydroxy-*N,N*-dialkylpyridine-carboximidamides containing substituent at position 3 and 4 of the pyridine ring.

2 Results and Discussion

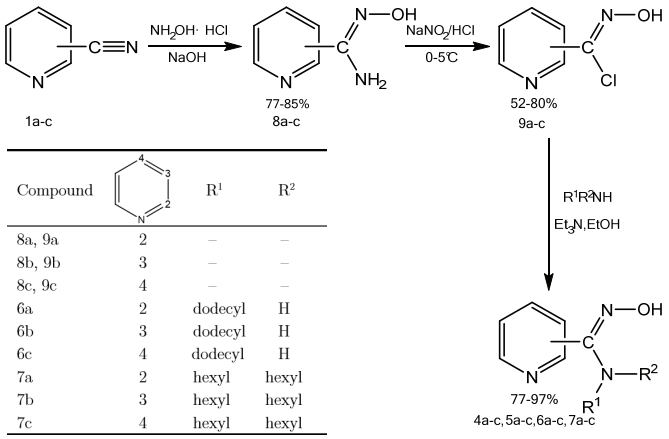
The *N'*-hydroxy-*N*-alkylpyridinecarboximidamides (4a-c, 5a-c) and *N'*-hydroxy-*N,N*-dialkylpyridinecar-boximidamide (7a-c) were prepared according to a modified procedure of Khalifa et al. [13] (Scheme 1) and Karatas and Tuzun [14] (Scheme 2). However, starting from pyridine-2-, -3- or 4-carbonitrile (1a-c) only *N*-alkylpyridinecarboximidamides (2a, 3a) were synthesised (Scheme 1) with a yield of 34 and 44%, respectively. 2a and 3a were then converted to the final *N'*-hydroxy-*N*-alkylpyridinecarboximidamides (4a, 5a) via nucleophilic substitution by using hydroxylamine hydrochloride at pH = 7 in an ethanol-water mixture (3:1, v/v). All the synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and

FT-IR, and their spectral data were summarized in Table 1 and 2.



Compound		R
1a	2	–
1b	3	–
1c	4	–
2a, 4a	2	octyl
2b, 4b	3	octyl
2c, 4c	4	octyl
3a, 5a	2	2-ethylhexyl
3b, 5b	3	2-ethylhexyl
3c, 5c	4	2-ethylhexyl

Scheme 1. Two-step synthesis of *N'*-hydroxy-*N*-alkylpyridinecarboximidamides (4a-c, 5a-c).



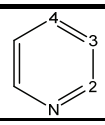
Compound		R^1	R^2
8a, 9a	2	–	–
8b, 9b	3	–	–
8c, 9c	4	–	–
6a	2	dodecyl	H
6b	3	dodecyl	H
6c	4	dodecyl	H
7a	2	hexyl	hexyl
7b	3	hexyl	hexyl
7c	4	hexyl	hexyl

Scheme 2. Three-step synthesis of *N'*-hydroxy-*N*-alkyl- (4a-c – 6a-c) and *N,N*-dialkylpyridinecarboximi-damides (7a-c).

Table 1. Yields and spectral data of synthesized *N*-alkylpyridinecarboximidamides (2a-c, 3a-c).

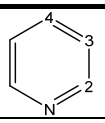
Compound		R	Yield[%]	Form	^{1}H-NMR[ppm]	^{13}C-NMR[ppm]	FT-IR[cm^{-1}]
2a	2	octyl	34	Viscous oil	10.39 (s, N-H)	157.44	1643 C=N
					10.82 (s, N-H)	(C=N)	3332 N-H
							3454 N-H
3a	2	2-ethylhexyl	44	Viscous oil	10.16 (s, N-H)	157.45	1652 C=N
					10.61 (s, N-H)	(C=N)	3357 N-H
							3496 N-H
2b	3	octyl	No reaction occurred or yield was below 1%				
3b	3	2-ethylhexyl					
2c	4	octyl	No reaction occurred or yield was below 1%				
3c	4	2-ethylhexyl					

Table 2. Yields and characteristic spectral data of synthesized *N'*-hydroxy-*N*-octylpyridine-2-carboximidamides (4a, 5a).

Compound		R	Yield[%]	Form	^{1}H-NMR[ppm]	^{13}C-NMR[ppm]	FT-IR[cm^{-1}]
4a	2	octyl	65	Viscous oil	5,81 (s, N-H) 9,92 (s, N-OH)	149,99 (C=N)	932 N-O 1631 C=N 3224 O-H 3340 N-H
5a	2	2-ethylhexyl	72	Viscous oil	5,83 (s, N-H) 9,40 (s, N-OH)	163,72 (C=N)	955 N-O 1625 C=N 3181 O-H 3415 N-H

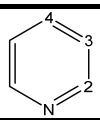
The three-step procedure (Scheme 2) enabled the synthesis of both *N'*-hydroxy-*N*-alkylpyridinecarboximidamides (4a-c, 5a-c) and *N'*-hydroxy-*N,N*-dialkylpyridinecarboximida-mide (7a-c). The provided methods involve a first step in which the appropriate pyridinecar-bonitrile (1a-c) was reacted with hydroxylamine to form the corresponding *N'*-hydroxypyridinecarboximidamides (8a-c). Yield of *N'*-hydroxypyridine-2-carboximidamide (1a) was 85% (m.p. 120-122°C), *N'*-hydroxypyridine-3-carboximidamide (1b) 77% (m.p. 132-134°C) and *N'*-hydroxypyridine-4-carboximidamide was 83% (1c) (m.p. 205-207°C). The melting points found are in accordance with the literature values [15]. The second step of the procedure is the reaction of the corresponding *N'*-hydroxypyridinecarboximidamides (1a-c) with sodium nitrite in HCl solution at 0°C [16]. The products of this step were pyridinehydroximoyl chlorides (8a-c). Spectral data and yields of the synthesized pyridinehydroximoyl chlorides were summarized in Table 3. The presented H^{1}-NMR and FT-IR data are in accordance with the literature values [15].

Table 3. Yields and melting points of synthesized pyridinehydroximoyl chlorides (8a-c).

Compound		Yield [%]	H^{1}-NMR [ppm]	FT-IR [cm^{-1}]	M.p. [°C]
8a	2	73	12.71 (s, OH) 8.69 (m, C_6-H) 7.92 (m, C_3-H,C_4-H) 7.50 (C_5-H)	954 N-O 1666 C=N 1745 C=N 3361 O-H	123-126
8b	3	52	12.79 (s, OH) 8.99 (m, C_2-H) 8.72 (m, C_6-H) 8.18 (m, C_4-H) 7.57 (m,C_5-H)	945 N-O 1689 C=N 1770 C=N 3363 O-H	141-144
8c	4	80	12.99 (s, OH) 8.76 (m, C_2-H,C_6-H) 7.86 (m, C_3-H,C_5-H)	948 N-O 1687 C=N 1782 C=N 3363 O-H	147-149

N'-hydroxy-*N*-alkylpyridinecarboximidamides (4a-c – 6a-c) and *N'*-hydroxy-*N,N*-dialkyl-pyridinecarboximidamides (7a-c) were obtained from the reactions of octylamine, 2-ethylhexylamine, dodecylamine and dihexylamine with the appropriate synthesised pyridinehydroximoyl chloride (8a-c) in the presence of triethylamine as a catalyst [14] (Scheme 2). 4a-c, 6a-c and 7a-c were isolated as the major products with yields in a range of 77-97% (Table 4).

Table 4. Results of synthesis of *N'*-hydroxy-*N*-alkylpyridinecarboximidamides (4a-c – 6a-c) and *N'*-hydroxy-*N,N*-dialkylpyridinecarboximidamides (7a-c).

Compound		R^1	R^2	Yield [%]	Form
4a	2	octyl	H	85	Viscous oil
5a	2	2-ethylhexyl	H	89	Viscous oil
6a	2	Dodecyl	H	87	Viscous oil
7a	2	hexyl	hexyl	95	Viscous oil
4b	3	octyl	H	87	Viscous oil
5b	3	2-ethylhexyl	H	91	Viscous oil
6b	3	dodecyl	H	92	Wax
7b	3	hexyl	hexyl	97	Wax
4c	4	octyl	H	83	Viscous oil
5c	4	2-ethylhexyl	H	86	Viscous oil
6c	4	dodecyl	H	77	m.p. 71-74°C
7c	4	hexyl	hexyl	90	Viscous oil

3 Conclusion

In conclusion, the three-step procedure is an efficient and general synthetic procedure affording *N'*-hydroxy-*N*-alkylpyridinecarboximidamides and *N'*-hydroxy-*N,N*-dialkylpyridinecarboximida-mides in good overall yields. It is especially appropriate for the synthesis of *N'*-hydroxy-*N*-alkylpyridine-3- and-4-carboximidamides and *N'*-hydroxy-*N,N*-dialkylpyridine-2-, -3- and -4-carboximidamides, that are not readily available by the procedure from pyridinecarbonitrile by a *N*-alkylpyridinecarboximidamide.

4 Experimental

4.1 Material and Methods

Melting-point values were determined on a Kofler hot-stage apparatus (Boetius). Infrared (FT-IR) spectra were recorded with a Vertex 70, Bruker Optics spectrophotometer for solutions in chloroform, by attenuated total reflection (ATR) or for solid as KBr pellets. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Avance II 400 MHz UltraShield Plus spectrometer (402.6 and 101.2 MHz, respectively) operating in the Fourier transform mode using solutions in deuterochloroform. Chemical shifts (δ) are expressed in parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard. High-resolution electrospray ionization–mass spectrometry (ESI–MS) was performed on an API 4000 QTRAP, AB Sciex (Foster City, CA, USA) spectrometer. Reaction progress and purity of the compounds were monitored by thin-layer chromatography (TLC) using precoated aluminum-backed silica plates (E. Merck, DC-60F_{254}) and monitored by UV lamp (UV 254 nm) and iodine chamber. Silica gel 60 (E. Merck 70–230 mesh) was used for column chromatography. Reagents and solvents were of commercial grade (Aldrich Chemical Co.).

4.2 Synthesis of *N'*-hydroxy-*N*-alkyl Pyridinecarboximidamides - Method I

4.2.1 Synthesis of *N*-alkylpyridinecarboximidamide (2a-c, 3a-c)

The appropriate amine (0.1 mol) was added to a solution of 100 mmol pyridine-2-, -3- or -4-carbonitrile and 100 mmol (13.34 g) of anhydrous aluminium chloride in 100 ml dichloromethane or dimethyl sulphoxide. The mixture was then stirred under reflux for 1 hour. Next, the solution was neutralized by adding stoichiometric amount of aqueous solution of sodium hydroxide (20%). The

resulting aqueous solution was then extracted using chloroform, washed with brine and dried with anhydrous $MgSO_4$. The crude product was chromatographed on silica gel (100 g) with chloroform-acetone (5:1, v/v) as an eluent.

N-octylpyridine-2-carboximidamide (2a) Rf=0.53 (acetone-chloroform 1:1)

N-(2-ethylhexyl)pyridine-2-carboximidamide (3a) Rf=0.51 (acetone-chloroform 1:1)

4.2.2 Synthesis of *N'*-hydroxy-*N*-alkylpyridinecarboximidamides (4a-c, 5a-c)

In round bottom flask, 25 mmol of hydroxylamine hydrochloride (2.1 g) and 25 mmol sodium bicarbonate (1.74 g) were dissolved in 100 ml of an ethanol-water mixture 4:1 (v/v) and warmed up to 50°C, after that appropriate *N*-alkylpyridine-2-carboximidamide (2a, 3a) was added to the reaction mixture and heated under reflux by 3 h. The mixture was then filtered and concentrated under reduced pressure using a rotary evaporator. The crude product was chromatographed on silica gel (250 g) with a toluene-chloroform mixture (4:1, v/v) as an eluent.

N'-hydroxy-*N*-octylpyridine-2-carboximidamide (**4a**) Rf=0.57 (acetone-chloroform 1:1, v/v)

N'-hydroxy-*N*-(2-ethylhexyl)pyridine-2-carboximidamide (**5a**) Rf=0.56 (acetone-chloroform 1:1, v/v)

4.3 Synthesis of *N'*-hydroxy-*N*-alkyl-pyridinecarboximidamides and *N'*-hydroxy-*N,N*-dialkylpyridinecarboximidamides - Method II

4.3.1 Synthesis of *N'*-hydroxypyridinecarboximidamides (8a-c)

A mixture of hydroxylamine hydrochloride (250 mmol, 21 g) and 250 mmol (17.37 g) of sodium bicarbonate was dissolved in 250 ml of an ethanol-water mixture (4:1, v/v) and was allowed to warm up to 50°C for two hours. Then, 250 mmol (26.03 g) of pyridine-2-, -3- or -4-carbonitrile (1a-c) was slowly added and heated under reflux with stirring for 3 hours. After the reaction is completed, the mixture was filtered, concentrated on a rotary evaporator and left to crystallization, yielding the desired compound (8a-c).

4.3.2 Synthesis of pyridinehydroximoyl chlorides (9a-c)

50 mmol (6.56 g) of the corresponding *N'*-hydoxypyridinecarboximidamide (8a-c) was dissolved in 220 ml 10% solution of hydrochloric acid, and the mixture was submerged in a salt-ice bath (0°C). To the mixture was then added sodium nitrite (62 mmol, 4.28 g) dissolved in 24 ml of water. After stirring at 0

C for 1.5 h, the resulting reaction mixture was allowed to warm up to room temperature, neutralised (pH≈3) and filtered through celite. The fine precipitate was filtered off, washed with water and dried in a vacuum. Recrystallization from a hot ethanol-water mixture (2:1, v/v) yielded yellow crystals of the desired 2-, 3- or 4-pyridinehydroximoyl chloride (9a-c).

4.3.3 Synthesis of *N'*-hydroxy-*N*-alkylpyridinecarboximidamides and *N'*-hydroxy-*N,N*-dialkylpyridicarboximidamides (4a-c – 7a-c)

A mixture of the corresponding pyridinehydroximoyl chloride (9a-c) (25 mmol, 3.91 g), 25 mmol (2.53 g) of triethylamine and 25 mmol of the corresponding amine (primary or secondary amine) in ethanol (150 ml) was stirred at 0°C for 24 h. After evaporation of the solvent *in vacuo*, the residue was purified by extraction with chloroform, washed with water and dried over anhydrous magnesium sulfate. The crude product was chromatographed on silica gel (100 g) with. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (toluene-chloroform (5:2, v/v), affording the desired imidamides (4a-c – 7a-c).

N'-hydroxy-N-octylpyridine-2-carboximidamide **(4a) FT-IR [cm^{-1}]:** 3340 (N-H), 3224 (O-H), 3059, 2926 (C-H), 1631 (C=N), 1589, 1566, 1525 (C=C, C=N), 1434 (C-H), 932 (N-O), 792 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.61 (d, 1H, 4.65 Hz, Hpy(6)), 7.72 (d, 1H, 3.67 Hz, Hpy(3)), 7.32 (m, 2H, Hpy(4,5)), 5.68 (s, 1H, N-H), 3.39 (t, 2H, NH-CH), 1.53 (m, 2H), 1.24 (m, 10H), 0.85 (t,3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 152.58 (C=N), 150.06 (Hpy(2)), 148.15 (Hpy(6)), 138.25 (Hpy(3)), 128.58 (Hpy(5)), 122.37 (Hpy(4)), 43.52 (NH-C), 31.28, 30.86, 28.73, 28.66, 26.11, 22.12, 13.57; (ESI-MS) m/z: 249.18 $(M+H)^+$. Rf=0.57 (acetone-chloroform 1:1)

N'-hydroxy-N-octylpyridine-3-carboximidamide **(4b) FT-IR [cm^{-1}]:** 3375 (N-H), 3190 (O-H), 3058, 2928 (C-H), 1628 (C=N), 1596, 1566, (C=C, C=N), 1466 (C-H), 812 (N-O), 756 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.70 (s, 1H, Hpy(1)), 8.64 (dd, 1H, 6.36 Hz, 3.4 Hz, Hpy(6), 7.95 (dt, 1H, 11.5 Hz, 4.16 Hz, Hpy(5)), 7.32 (dd, 1H, 12.7 Hz, 4.7 Hz, Hpy(4), 5.38 (s, 1H, N-H), 3.97 (m, 2H, NH-CH), 1.42 (m, 2H), 1.20 (m,10H), 0.85 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 153.66 (C=N), 149.91

(Hpy(2)), 148.73 (Hpy(6)),135.67 (Hpy(3)), 127.30 (Hpy(5)), 122.02 (Hpy(4)), 43.35 (NH-C), 31.22, 30.77, 28.65, 28.59, 25.96, 20.08, 13.55; (ESI-MS) m/z: 249.18 $(M+H)^+$. Rf=0.54 (acetone-ethyl acetate-chloroform 1:1:1)

N'-hydroxy-N-octylpyridine-4-carboximidamide **(4c) FT-IR [cm^{-1}]:** 3429 (N-H), 3267 (O-H), 3043, 2927 (C-H), 1651 (C=N), 1601, 1548, (C=C, C=N), 1464 (C-H), 933 (N-O), 796 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.66 (d, 2H, 5.87 Hz, Hpy(2,6), 7.63 (d, 2H, 5.87 Hz, Hpy(3,5), 5.47 (s, 1H, N-H), 3.41 (t, 2H, NH-CH), 1.60 (m, 2H), 1.24 (m, 10H), 0.84 (t, 3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 165.10 (C=N), 149.75 (Hpy(2,6)), 141.56 (Hpy(4)), 120.57 (Hpy(3,5)), 39.79 (NH-C), 31.24, 28.94, 28.72, 28.66, 26.46, 22.08, 13.53 (ESI-MS) m/z: 249.18 $(M+H)^+$. Rf=0.57 (acetone-ethyl acetate-chloroform 1:1:1)

N'-hydroxy-N-(2-ethylhexyl)pyridine-2-carboximidamide **(5a) FT-IR [cm^{-1}]:** 3415 (N-H), 3181 (O-H), 2956, 2915 (C-H), 1625 (C=N), 1589, 1567, 1508 (C=C, C=N), 1467, 1439 (C-H), 955 (N-O), 792 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.62 (d, 1H, 4.40 Hz, Hpy(6)), 7.75 (d, 1H, 7.82 Hz, Hpy(3)), 7.69 (t, 1H, Hpy(5)),7.31 (t, 1H, Hpy(4)), 5.66 (s, 1H, N-H), 3.18 (d, 2H, NH-CH), 1.53 (m, 1H), 1.32-1.1 (m, 10H), 0.85 (t,3H, CH_3), 0.77 (t,3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 153.13 (C=N), 150.17 (Hpy(2)), 148.15 (Hpy(6)), 136.28 (Hpy(3)), 123.53 (Hpy(5)), 122.61 (Hpy(4)), 46.10 (NH-C), 40.38, 30.13, 29.43, 28.26, 23.36, 22.42, 13.52, 10.28; (ESI-MS) m/z: 249.18 $(M+H)^+$, Rf=0.56 (acetone-chloroform 1:1)

N'-hydroxy-N-(2-ethylhexyl)pyridine-3-carboximidamide **(5b) FT-IR [cm^{-1}]:** 3394 (N-H), 3194 (O-H), 2956, 2928 (C-H), 1628 (C=N), 1596, 1562 (C=C, C=N), 1464, 1423 (C-H), 926 (N-O), 812 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.70 (s, 1H, Hpy(2)), 8.62 (dd, 1H, 6.11 Hz, 3.42 Hz, Hpy(6)), 7.76 (dt, 1H, 7.83 Hz, 4.11 Hz, Hpy(5)),7.31 (dd, 1H, 12.72 Hz, 2.93 Hz Hpy(4)), 5.38 (s, 1H, N-H), 2.89 (d, 2H, NH-CH), 1.27 (m, 1H),1.21 (q, 2H) 1.1 (m, 10H), 0.82 (t,3H, CH_3), 0.74 (t,3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 153.71 (C=N), 149.66 (Hpy(2)), 148.82 (Hpy(6)), 135.71 (Hpy(3)), 128.68 (Hpy(5)), 122.69 (Hpy(4)), 46.08 (NH-C), 40.38, 29.99, 28.21, 23.20, 22.36, 13.47, 10.23; (ESI-MS) m/z: 249.18 $(M+H)^+$, Rf=0.58 (acetone-ethyl acetate-chloroform 1:1:1)

N'-hydroxy-N-(2-ethylhexyl)pyridine-4-carboximidamide **(5c) FT-IR [cm^{-1}]:** 3407 (N-H), 3193 (O-H), 2958, 2927, 2859 (C-H), 1624 (C=N), 1603, 1546, (C=C, C=N), 1462, 1408 (C-H), 936 (N-O), 828 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.62 (d, 2H,4.89 Hz Hpy(2,6)), 7.38 (d, 2H, 5.87 Hz, Hpy(3,5)), 7.31 (s, 1H, Hpy(4)), 5.33 (s, 1H, N-H), 2.89 (d, 2H, NH-CH), 1.26 (m, 1H),1.19 (q, 2H) 1.1 (m, 10H), 0.81 (t,3H, CH_3), 0.74 (t,3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 154.32 (C=N), 149.19 (Hpy(2,6)), 139.67 (Hpy(3,5)), 122.65 (Hpy(4)), 46.11 (NH-C), 40.38, 29.96, 28.28, 23.19, 22.35, 13.46, 10.23; (ESI-MS) m/z: 249.18 $(M+H)^+$ Rf=0.59 (acetone-ethyl acetate-chloroform 1:1:1)

N'-hydroxy-N-dodecylpyridine-2-carboximidamide **(6a) FT-IR [cm^{-1}]:** 3340 (N-H), 3240 (O-H), 3058, 2923, 2854 (C-H), 1631 (C=N), 1589, 1566, 1527 (C=C, C=N), 1465, 1434 (C-H), 933 (N-O), 790 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.62 (d, 1H, 4.16 Hz, Hpy(6)), 8.82 (d, 1H, 7.83 Hz, Hpy(3)), 7.70 (t, 1H, Hpy(5)), 7.30 (t, 1H, Hpy(4)), 5.60 (s, 1H, N-H), 3.36 (q, 2H, NH-CH), 1.51 (m, 2H), 1.25 (m, 18H), 0.88 (t,3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 150.38 (C=N), 148.16 (Hpy(2)), 136.20 (Hpy(6)), 125.51 (Hpy(3)), 123.47 (Hpy(5)), 122.31 (Hpy(4)), 43.53 (NH-C), 31.40, 30.92, 29.13, 29.12, 29.10, 29.07, 28.98, 28.83, 28.45, 22.16, 13.60; (ESI-MS) m/z: 277.22 $(M+H)^+$, Rf=0.57 (acetone-chloroform 1:1)

N'-hydroxy-N-dodecylpyridine-3-carboximidamide **(6b) FT-IR [cm^{-1}]:** 3336 (N-H), 3240 (O-H), 3026, 2916, 2850(C-H), 1654 (C=N), 1612, 1521, 1510 (C=C, C=N), 1469, 1400 (C-H), 919 (N-O), 817 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.72 (s, 1H, Hpy(2)), 8.65 (d, 1H, 4.65 Hz, Hpy(6)), 7.81 (d, 1H, 7.82 Hz Hpy(4)), 7.35 (t, 1H, Hpy(5)), 5.41 (s, 1H, N-H), 2.91 (q, 2H, NH-CH), 1.70 (m, 2H), 1.24 (m, 18H), 0.87 (t,3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 153.74 (C=N), 149.99 (Hpy(2)), 148.78 (Hpy(6)), 135.66 (Hpy(3)), 127.40 (Hpy(5)), 122.85 (Hpy(4)), 43.33 (NH-C), 39.51, 31.40, 29.13, 29.08, 28.97, 28.70, 28.55, 27.26, 26.11, 22.16, 13.59; (ESI-MS) m/z: 277.22 $(M+H)^+$ Rf=0.59 (acetone-chloroform 1:2)

N'-hydroxy-N-dodecylpyridine-4-carboximidamide **(6c) FT-IR [cm^{-1}]:** 3307 (N-H), 3244 (O-H), 2954, 2918 (C-H), 1635 (C=N), 1600, 1539 (C=C, C=N), 1490, 1471 (C-H), 929 (N-O), 830 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.74 (d, 1H, 5.62 Hz, Hpy(2)), 8.68 (d, 1H, 5.87 Hz, Hpy(6)), 7.61 (d, 1H, 6.11 Hz, Hpy(3)), 7.39 (d, 1H, 5.87 Hz Hpy(5)), 5.41 (s, 1H, N-H), 3.00 (q, 2H, NH-CH), 1.62 (m, 2H), 1.45 (m, 2H), 1.24 (m, 14H), 0.87 (t,3H, CH_3); ^{13}C-NMR ($CDCl_3$) δ in ppm: 149.95 (C=N), 149.47

(Hpy(2,6)), 122.46 (Hpy(3,5)), 122.31 (Hpy(4)), 43.42 (NH-C), 31.40, 30.74, 29.11, 29.02, 28.89, 28.75, 28.69, 26.46, 25.95, 22.18, 13.61; (ESI-MS) m/z: 277.22 $(M+H)^+$ Rf=0.62 (acetone-chloroform 1:2)

***N'-hydroxy-N,N-dihexylpyridine-2-carboximidamide* (7a) FT-IR [cm^{-1}]:** 3253 (O-H), 2954, 2929, 2856 (C-H), 1681 (C=N), 1608, 1585, 1568 (C=C, C=N), 1465, 1434 (C-H), 925 (N-O), 794 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.70 (d, 1H, 4.65 Hz, Hpy(6)), 7.78 (t,1H, Hpy(5)), 7.42 (d, 1H, 7.83 Hz, Hpy(3)), 7.30 (t, 1H, Hpy(4)), 3.20 (t, 2H, N-CH), 3.12 (t, 2H, N-CH'), 2.99 (m, 2H), 2.89 (m, 2H), 1.87 (m, 2H), 1.52 (m, 2H), 1.40 (m, 2H), 1.28 (m, 2H), 1.25 (m, 2H), 1.18 (m, 2H), 0.84 (t,3H, CH_3, CH_3'); ^{13}C-NMR ($CDCl_3$) δ in ppm: 158.33 (C=N), 151.12 (Hpy(2)), 148.85 (Hpy(6)), 135.79 (Hpy(3)), 124.03 (Hpy(5)), 122.99 (Hpy(4)), 51.27 (N-C), 48.13 (N-C'), 47.30, 45.38, 31.00, 30.69, 26.89, 26.11, 25.30, 21.94, 13.48, 8.13; (ESI-MS) m/z: 305.25 $(M+H)^+$ Rf=0.61 (acetone-chloroform 1:1)

***N'-hydroxy-N,N-dihexylpyridine-3-carboximidamide* (7b) FT-IR [cm^{-1}]:** 3240 (O-H), 2954, 2927, 2856 (C-H), 1674 (C=N), 1608, 1585, 1539 (C=C, C=N), 1460, 1415 (C-H), 950 (N-O), 742 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.62 (s, 1H, Hpy(2)), 8.42 (d, 1H, 4.40 Hz, Hpy(6)), 7.71 (d, 1H, 7.83 Hz, Hpy(6)), 7.36 (t, 1H, Hpy(4)), 3.14 (t, 2H, N-CH'), 2.99 (t, 2H, N-CH), 2.89 (m, 2H), 1.87 (m, 2H), 1.39- 1.18 (m, 8H), 0.86 (t,6H, CH_3, CH_3'); ^{13}C-NMR ($CDCl_3$) δ in ppm: 157.99 (C=N), 149.00 (Hpy(2)), 136.20 (Hpy(6)), 127.38 (Hpy(3)), 123.12 (Hpy(5)), 122.55 (Hpy(4)), 47.93 (N-C), 47.30 (N-C'), 31.01, 30.69, 26.89, 26.79, 26.01, 25.56, 25.31, 25.01, 21.94, 13.40, 8.13; (ESI-MS) m/z: 305.25 $(M+H)^+$, Rf=0.66 (acetone-chloroform 1:3)

***N'-hydroxy-N,N-dihexylpyridine-4-carboximidamide* (7c) FT-IR [cm^{-1}]:** 3218 (O-H), 2954, 2925, 2854 (C-H), 1652 (C=N) 1595, 1548, 1496 (C=C, C=N), 1460, 1407 (C-H), 962 (N-O), 827 (C-H); ^{1}H-NMR ($CDCl_3$, D_2O) δ in ppm: 8.67 (d, 1H, 4.89 Hz, Hpy(2)), 8.58 (d, 1H, 4.40 Hz, Hpy(6)), 7.49 (d, 1H,5.38 Hz, Hpy(3)), 7.39 (d, 1H, 5.38 Hz, Hpy(5)), 3.19 (t, 2H, N-CH'), 2.96 (t, 2H, N-CH), 1.48 (m, 4H), 1.33- 1.18 (m, 12H), 0.84 (t,6H, CH_3, CH_3'); ^{13}C-NMR ($CDCl_3$) δ in ppm: 157.15 (C=N), 149.82 (Hpy(2)), 149.21 (Hpy(6)), 140.03 (Hpy(3)), 123.11 (Hpy(5)), 121.51 (Hpy(4)), 47.86 (N-C), 47.19 (N-C'), 35.30, 31.01, 28.37, 26.82, 26.04, 25.51, 24.23, 22.02, 13.46, 7.56; (ESI-MS) m/z: 305.25 $(M+H)^+$, Rf=0.67 (acetone-chloroform 1:3)

Acknowledgments: This research was financial supported with grant 03/32/DSPB/0600. We acknowledge the support of the Ministry of Science and Higher Education and European Fund for Regional Development under grant UDA-POIG.02.01.00-30-182/09 (^{1}H and ^{13}C NMR analysis).

References

1. E. Abele, R. Abele and E. Lukevics, "Pyridine oxime: synthesis, reactions and biological activity. Review", *Chemistry* of *Heterocyclic Compounds,* vol. 39, no. 7, pp. 825–865, 2003.
2. E. F. V. Scriven, R. Murugan, "Pyridine and Pyridine Derivatives", Kirk-Othmer Encyclopedia of Chemical Technology, 2005.
3. S. Shimizu, N. Watanabe, T. Kataoka, T. Shoji, N. Abe, S. Morishita, H. Ichimura, „Pyridine and Pyridine Derivatives", Ullmann's Encyclopedia of Industrial Chemistry, 2000.
4. K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litinas, E. Varella and D. N. Nicolaides, "Recent developments in the chemistry and in the biological applications of amidoximes", *Current Pharmaceutical Design,* vol.14, pp.1001–1047, 2008.
5. J. E. Hall, J. E. Kerrigan, K. Ramachandran, B. C. Bender, J. P. Stanko, S. K. Jones, D.A. Patrick and R. R. Tidwell, "Anti-pneumocystis Activities of aromatic diamidoxime prodrugs", *Antimicrobial Agents and Chemotherapy*, vol. 42, pp. 666–674, 1998.
6. L. Keurulainen, M. Heiskari, S. Nenonen, A. Nasereddin, D. Kopelyanskiy, T. O. Leino, J. Yli-Kauhaluoma, C. L. Jaffe and P. Kiuru, "Synthesis of carboxyimidamide-substituted benzo[c][1,2,5]oxadiazoles and their analogs, and evaluation of biological activity against", *Leishmania donovani*, *Medical Chemical Communications*, vol. 6, pp. 1673-1678, 2015.
7. D. W. Boykin, A. Kumar, B. C. Bender, J. E. Hall and R. R. Tidwell, "Anti-pneumocystis activity of bis-amidoximes and bis-*O*-alkylamidoximes prodrugs", *Bioorganic and Medicinal Chemistry Letters,* vol. 6, pp. 3017–3020, 1996.

8. P. Desbordes, S. Gary, M.C. Grosjean-Cournoyer, B. Hartmann, P. Rinolfi and J.P. Vors, "Fungicidal N-cycloalkyl-benzyl-thiocarbox amides or N-cycloalkyl-benzyl-N'-sunstituted-amidine derivatives" US Patent 8410157, 2013
9. T. Izawa, T. Kashiwabara, S. Nakajima and N. Ogawa, "Pyridyl carboximidamide compounds useful in treating blood pressure", US Patent 5223508, 1993.
10. T. Yokoyama, Y. Okada, N. Ogawa, T. Izawa and H. Fukushima "Vasodilating mechanisms of Ki1769, Ki3315 and KRN2391, pyridinecarboximidamide derivatives, in isolated porcine coronary artery", *Japanese Journal of Pharmacology,* vol. 64, pp. 241-241, 1994.
11. M. Salonen, H. Saarinen and I. Mutikainen, "Equilibrium and structural studies of copper(II) and nickel(II) complexes with pyridine-2,6-diamidoxime in aqueous solution", *Journal of Coordination Chemistry,* vol. 61, no. 9, pp. 1462-1474, 2008.
12. M. Salonen, "Formation of zinc(II) and cadmium(II) complexes with pyridine-2-carboxamidoxime and pyridine-2-acetamidoxime in aqueous solution", *Journal of Coordination Chemistry,* vol. 63, no. 17, pp. 3127-3136, 2010.
13. M. M. Khalifa, M. J. Bodner, J. A. Berglund and M. M. Haley Synthesis of *N*-substituted aryl amidines by strong base activation of amines", *Tetrahedron Letters*, vol. 56, no. 27, pp. 4109-4111, 2015.
14. I. Karatas and C. Tuzun "Synthesis of some terephtalo-N,N'-di and tetra substituted amidoximes", C*ommunications Faculty of Science of University Ankara, Series B: Chemistry, Chemical Engineering*, vol. 37, pp. 31-35, 1991.
15. E. Bernasek, "Pyridineamidoximes", *Journal of Organic Chemistry*, vol. 22, pp. 1263–1263, 1957.
16. M. Kočevar, S. Polanc, M. Sollner, M. Tišler and B. Verček, "Simple procedure for the synthesis of pyridinecarbohydroximoyl chlorides and bromides", *Synthetic Communications: An international journal for rapid communication of synthetic organic chemistry*, vol. 18, no. 12, pp. 1427-1432, 1988.

