Photocatalyzed [2 + 2 + 2]-Cycloaddition of Nitriles with Acetylene: An Effective Method for the Synthesis of 2-Pyridines under Mild Conditions

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The photocatalyzed [2 + 2 + 2]-cycloaddition of nitriles with 2 equiv of acetylene to 2-pyridines can be carried out under mild conditions and represents a valuable extension to common synthetical methods. For the ideal wavelength range (350−500 nm), lamps as well as sunlight can be used. Working at room temperature and in organic solvents such as toluene or hexane as well as in water gives satisfying results in many cases. However, it is also possible to vary the solvent and the reaction temperature of the photocatalyzed synthesis and to choose, with respect to the specific substrate, specific requirements for this particular reaction and general requirements of the method. This simple and selective method derives its potential mainly from the large variety of applicable nitriles. Suitable substrates include (functionalized) aliphatic and aromatic nitriles as well as cyanamides derived from secondary amines.

Introduction

Pyridines as basic modules are of persistent importance for academic research as well as for the chemical industry and pharmaceutical drug research. Therefore, a simple, selective, flexible, and waste-free synthetic access to pyridine derivatives is desired.

The unsubstituted 2-pyridyl moiety, although often presumed to be rather exotic, can actually be found in a range of pharmacologically active compounds (Scheme 1).

This can be exemplified with both approved drugs and investigational compounds, e.g., the muscarinic antagonist vamicamide **1**,[1] the partial μ-opioid agonist propiram **2**,[2,3] the selective κ-opioid agonist HZ-2 **3**,[4] several histamine H_1-antagonists (pheniramine **4**,[3,5] doxylamine **5**,[3,6] and carbinoxamine **6**[3,7−8]), nonsteroidal antiinflammatory drugs of the oxicame class (COX-inhibitors; e.g. piroxicam **7**[3,9]), or the histamine H_1-agonist betahistine **8**.[3,10−11]

In synthetic approaches toward these compounds, the 2-pyridyl moiety is usually introduced through 2-pyridyl building blocks such as 2-picoline, 2-chloro- or 2-bromopyridine, pyridine-2-carbaldehyde, or pyridin-2-ylamine. Once introduced, the pyridine ring substantially influences the physicochemical properties of the molecule and thus can be a limitation for further derivatization.

In this respect, the photocycloaddition of nitriles with 2 equiv of acetylene presented here is an attractive alternative. Through the creation of three new bonds within one reaction, this [2 + 2 + 2]-cycloaddition (Scheme 2) is an atom-economical,[12,13] versatile, safe, and extraordinarily effective method for the synthesis of 2-pyridines.

Suitable substrates include (functionalized) aliphatic and aromatic nitriles as well as cyanamides derived from secondary amines. The scope of this reaction is usually limited only by the conversion of the substrate, a problem that in many cases can be overcome by a repeated addition of the catalyst, or by substrates incorporating chromophores prone to photochemical side reactions upon irradiation.

Results and Discussion

The Co(I)-catalyzed pyridine synthesis can conveniently be carried out at room temperature and atmospheric pressure, as long as energy is supplied to the system in the form of visible light.[14] Thus, the drastic reaction conditions described for the thermally initiated variant of this reaction can be avoided.[5,15] This is

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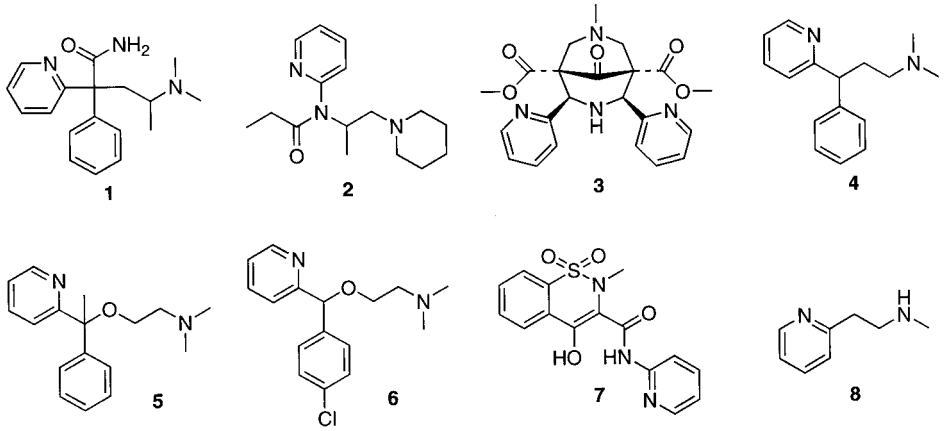
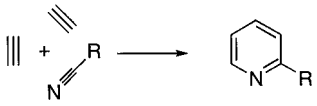
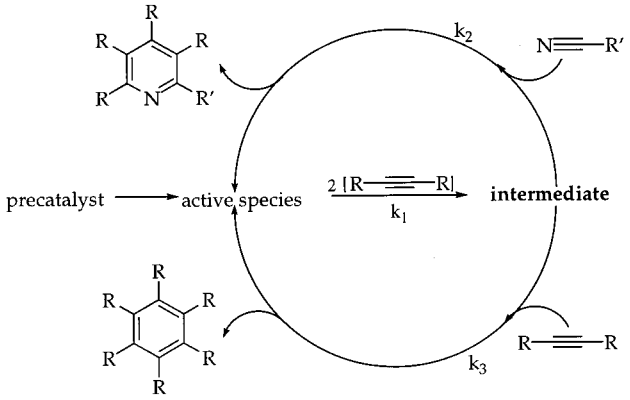
Scheme 1. Pharmacologically Active Compounds with a 2-Pyridyl Moiety



Scheme 2. [2 + 2 + 2]-Cycloaddition



Scheme 3. Postulated Mechanism of the [2+ 2 + 2]-Cycloaddition



important since gaseous acetylene must be handled, so a protocol requiring only mild conditions is advantageous.[16]

For the ideal wavelength range (350−500 nm), lamps as well as sunlight[17] can be used. The use of light seems to favor the conversion of the precatalyst, e.g., η^5-cyclopentadienyl-η^4-cycloocta-1,5-diene-cobalt(I) (cpCo(cod))[18] into an active species through the creation of free coordination places and most likely promotes the formation of the central catalytic intermediate through the addition of two acetylene molecules (Scheme 3).[19] At this stage, the addition of a third acetylene molecule leads to the formation of benzene as a common byproduct. Here, another major advantage of the photochemical reaction over the thermally induced cycloaddition becomes obvious: with a low acetylene concentration (a diminished acetylene partial pressure and/or suitable solvents with low acetylene solubility, e.g. water and/or an excess of nitrile), the homotrimerization of acetylene can be almost completely avoided.[20,21]

Suitable Nitriles. The scope of this photocatalyzed [2 + 2 + 2]-cycloaddition with acetylene depends on the nature of the nitriles employed. With simple aliphatic and aromatic nitriles as well as nitriles containing ether or carbonyl groups usually yields of 70−90% are obtained (Table 1). Yields are lower (50−60%) for nitriles containing primary or secondary amines but better for tertiary amines (>70%). Nitriles incorporating carbon−carbon double bonds tend to give low yields, probably due to partial complexation and/or inactivation of the catalyst. Working in high dilution and using more catalyst is advantageous in these cases. Carbon−carbon triple bonds in the nitrile may compete with acetylene in the [2 + 2 + 2]-cycloaddition and thus can lead to a formation of complex reaction mixtures.

As a rule of thumb, functional groups in the nitrile are reasonably well tolerated if they do not directly interact with the Co(I) catalyst.[22] For example, the functionalized acetonitrile derivative **10**, derived from piperidine-2-carboxylic acid **9** through BOC-protection, amidation with *n*-propylamine, deprotection, and alkylation with bromoacetonitrile, can be converted into the corresponding 2-pyridine **11** in high yield (78%) (Scheme 4).

Experiments with optically active nitriles have led to promising preliminary results in an effort to extend this methodology to the synthesis of optically active pyridines.[23]

Temperature Range and Reaction Medium. As shown in Table 1, many nitriles can be converted into the corresponding pyridine derivatives by photochemical cyclocotrimerization with acetylene at room temperature in organic solvents such as toluene, hexane, or pentane with satisfactory results. Reaction conditions can be

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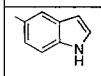
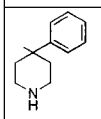
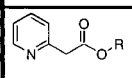
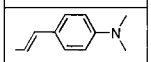
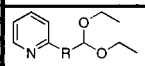
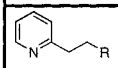
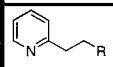
(21) In contrast to the thermally initiated reaction, the mild conditions of the photocatalyzed synthesis convert the nitrile to the desired pyridine only. Byproducts besides benzene have not been observed.

(22) Deactivation of the catalyst would be conceivable through, e.g., a conjugated double bond resulting in the formation of stable π-complexes and, thus, stoichiometric catalyst deactivation.

(23) First experiments using mono- and disubstituted alkynes are currently being carried out; see Experimental Section. Further investigations into the use of mono- and disubstituted alkynes are in progress.

Table 1. [2 + 2 + 2]-Cycloaddition of Acetylene with Different Nitriles[a]

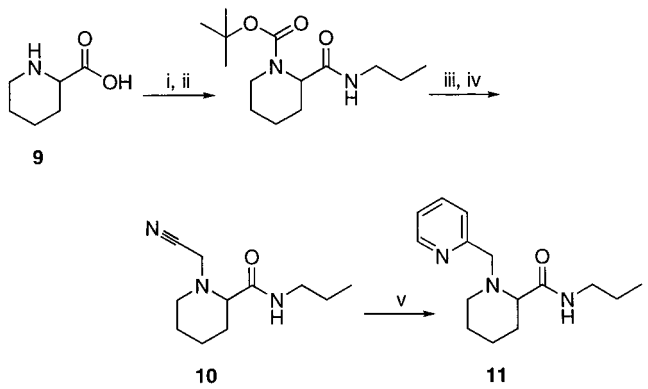
$2C_2H_2$ + R'CN** → pyridine	R	solvent	yield	$2C_2H_2$ + R'CN** → pyridine	R	solvent	yield
		toluene	75 %		-NH-$(CH_2)_3$-CH_3	toluene	55 %
			68 %				79 %
			62 %				69 %
			49%		-$(CH_2)_6$-CH_3		88 %
					-$(CH_2)_9$-CH_3		89 %
			81 %			hexane	81 %
			10 %				
		hexane	90 %		-CH_2-	water +	85 %
					-$(CH_2)_2$-	2 vol% toluene	81 %
		hexane	70 %			toluene	75 %
	-O-$(CH_2)_2$-CH_3	toluene	77 %				75 %
	-O-$(CH_2)_3$-CH_3		75 %		-$N(CH_3)_2$		58 %
	-O-$(CH_2)_6$-CH_3		77 %				79 %
	-O-$(CH_2)_7$-CH_3		80 %		-NH-$(CH_2)_7$-CH_3		50 %
	-O-$(CH_2)_8$-CH_3		78 %		-NH-$(CH_2)_9$-CH_3		51 %

[a] Reaction conditions (see Experimental Section): temp, 25 °C; reaction time, 3−4 h; catalyst, [cpCo(cod)]. [b] R′ corresponds to the substituent in the 2-position of the produced pyridine.

modified if, e.g., solubility problems occur. For example, the yield of the cyclocotrimerization of 4-dimethylaminocinnamic acid nitrile with acetylene can be increased from 10 on 19% by a raising the reaction temperature from 25 to 50 °C.

To investigate the ideal temperature range of our photocatalyzed reaction, we studied the reaction of 1 mmol of benzonitrile with acetylene in 10 mL of toluene at −40 °C and at 60 °C with a catalytic amount (0.01 mmol) [cpCo(cod)]. At 60 °C, the obtained yield on 2-phenylpyridine was 95% within 60 min. At −40 °C, a similar result is achieved (70 min: 90% yield), but benzene is formed to a great extent. This byproduct arises from the [2 + 2 + 2]-homocycloaddition of three acetylene molecules. This is in accordance with the highly temperature-dependent solubility (or concentration) of acetylene. Thus, while reactions below 0 °C are possible in principle, we have encountered no practical need for this until today. With respect to suitable solvents, it is important to recognize the usefulness of water as a reaction medium. In comparison to common organic solvents such as cyclohexane or toluene, acetylene solubility is much

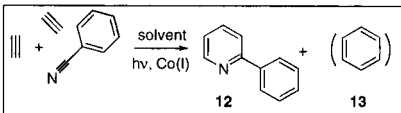
Scheme 4. Preparation of 1-Pyridin-2-yl-methyl-piperidine-2-carboxylic Acid Propylamid Starting from Piperidine-2-carboxylic Acid[a]



9 10 11

[a] Reaction Conditions: (i) BOC_2O, NEt_3, dioxane/water; (ii) BOC_2O, pyridine, DMAP (catalytic), THF, and then *n*-$PrNH_2$; (iii) HCl, EtOH; (iv) NEt_3 MeOH, and then $BrCH_2CN$; (v) HC≡CH, [cpCo(cod)] (catalist), *hν*.

Table 2. [2 + 2 + 2]-Cycloaddition in Different Reaction Media in a Solar Facility[a]

	Yield**	molar ratio: **12 / 13**
toluene	81%	1.9
cyclohexan	79%	20
water (with 5vol% toluene)	89%	38

[a] Reaction conditions: 1000 mL of solvent, 50 mmol of benzonitrile, 0.5 mmol of [cpCo(cod)] as the catalyst, 30 °C, 4h. [b] Detected by GLC.

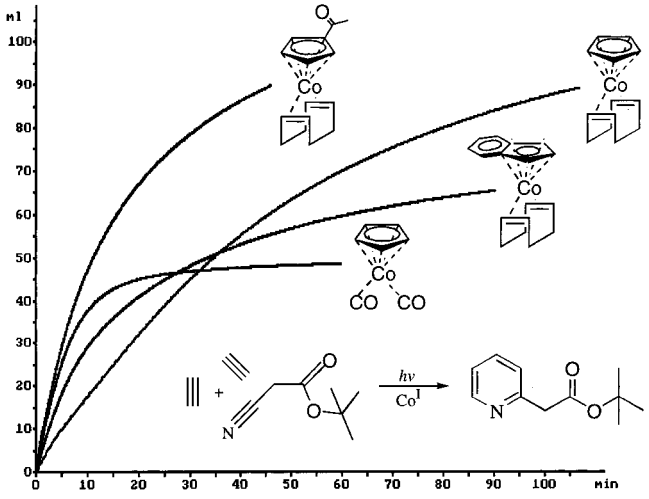


Figure 1. Acetylene consumption with different Co(I) catalysts.

lower in water, so the competing homotrimerization of acetylene to benzene can be suppressed (Table 2).

While the cycloaddition exclusively works with non-watersoluble nitriles in pure water, watersoluble nitriles (e.g., methoxypropionitrile) can be converted to pyridines when a cosolvent, e.g., toluene, is added, but yields are poor (30%). Working in an aqueous medium is not recommended for basic nitriles, especially primary or secondary amines because yields are substantially lower than in organic solvents.

Liquid nitriles can be converted to pyridines without additional solvent. Usually only small amounts of benzene are formed but often yields of pyridine are low. This is due to diffussion problems caused by a low acetylene concentration relative to the nitrile resulting in a fast deactivation of the catalyst.

Cobalt(I) Precatalysts. Several cobalt(I) complexes are suitable catalysts for the photocatalyzed [2 + 2 + 2]-cycloaddition. The reaction of cyanoacetic acid *tert*-butyl ester with acetylene using different precatalysts was followed employing an apparatus measuring gas consumption.[19] Figure 1 shows the consumption of acetylene recorded online. All investigated cobalt(I) complexes adequately catalyze the [2 + 2 + 2]-cycloaddition under photochemical conditions. The different catalytic activities observed seem to be correlated to the Co(I) ligands. This is currently being investigated in detail in several organic solvents and at different reaction temperatures.

Recently, we have demonstrated that several different Co(I) precatalysts also effectively catalyze photochemical [2 + 2 + 2]-cycloadditions in water.[20,24] While [cpCo(CO)$_2$] is often used because of its commercial availability, our results suggest a relatively low activity for this particular precatalyst. Accordingly, the synthesis of pyridine-containing macrocycles recently reported by Maryanoff et al.[25] could probably be improved and carried out under milder reaction conditions if [cpCo(cod)] was used instead of [cpCo(CO)$_2$].

Summary

The photocatalyzed synthesis of 2-pyridines described here derives its potential mainly from the large variety of applicable nitriles. This simple, atom-economical, effective, and selective method can be carried out under mild conditions and represents a valuable extension to common synthetic methods.

Experimental Section

Analytical Measurements: Analytical Measurements were carried out with standard equipment and protocols except that GLC analyses were performed with HP1 coated fused silica capillaries 12 m in length (temperature program: 10 min at 35 °C, and then heating 10 °C per minute up to 200 °C); argon was used as a carrier gas, 1 mL/min.

Mass Spectra. Mass spectra were measured on an HP1 column 25 m in length or an HP5 column 25 m in length.

Chemicals. All operations were performed under an atmosphere of argon and strict exclusion of air. Acetylene of 99.5% purity was used without further purification. Commercially available nitriles and organic solvents were rigorously dried and distilled. The precatalysts [cpCo(cod)] (η^5-cyclopentadienyl-η^4-cycloocta-1,5-diene-cobalt(I)), [cp^{ac}Co(cod)] acetylcyclopentadienyl-cycloocta-1,5-diene-cobalt(I), and [IndCo(cod)] indenyl-cycloocta-1,5-diene-cobalt(I) were prepared according to literature procedures.[18] [cpCo(CO)$_2$] [η^5-cyclopentadienyl-dicarbonyl-cobalt(I)] is commercially available.

General Procedure for [2 + 2 + 2]-Cycloadditions ("Standard Conditions"): 2-(2,2-Diethoxy-ethyl)-pyridine. A thermostated (25 °C) reaction vessel, equipped with a very effective quill spin bar, was loaded with 7.3 mL (50 mmol) of 3,3-diethoxypropionitrile and 58 mg (0.25 mmol) of [cpCo(cod)]. To the mixture was added 45 mL of toluene, and the vessel was connected to an acetylene measuring and delivering device providing a constant pressure of acetylene.

(24) Using a water soluble Co(I) catalyst, Eaton and coworker have successfully trimerized but-1-yne-1,4-diol to the hexasubstitued benzene derivative in water: Sigman, M. S.; Fatland, A. W.; Eaton, B. E. *J. Am. Chem. Soc.* **1998**, *120*, 5130−5131.

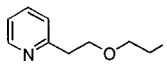
(25) Moretto, A. F.; Zhang, H.-C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2001**, *123*, 3157−3158.

Alternatively, acetylene may simply be bubbled through the solution. The mixture was irradiated by two 460 W lamps (~420 nm) for 4 h. The reaction was quenched by switching off the lamps and simultaneously introducing air. The obtained reaction mixture was filtered; the solvent was removed, and the residue was either distilled under vacuum (boiling point of the desired pyridine: 60−62 °C at 10^{-2} mbar) or chromatographed on silica gel (5:1 toluene/ethyl acetate) to give 8.6 g (44.5 mmol) of pure 2-(2,2-diethoxy-ethyl)-pyridine (yield 87%; GLC result from crude product, 89%).

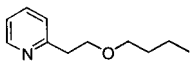
Reaction with Solid Nitrile and Alkyne Compounds. The same procedure was employed using solid nitriles and/or alkynes. The nitrile (and/or alkyne) was dissolved in 10 mL of an organic solvent like toluene or hexane.

Reaction in Liquid Nitrile (Without Additional Solvent). The same procedure was employed working without additional solvent.

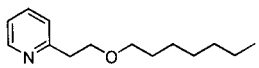
Examples.



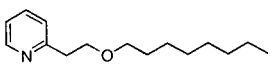
2-(2-Propoxy-ethyl)-pyridine: yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, 3H, J = 7.4 Hz, CH_3), 1.36 (m, 2H, CH_2), 2.87 (t, 2H, J = 6.8 Hz, CH_2), 3.19 (t, 2H, J = 6.6 Hz, CH_2O), 3.60 (t, 2H, J = 6.8 Hz, CH_2O), PY 6.89 (t, 1H, J = 6.2 Hz), 7.00 (d, 1H, J = 7.7 Hz), 7.36 (t, 1H, J = 7.6 Hz), 8.32 (d, 1H, J = 5.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.1, 22.5, 38.4, 69.6, 72.2, PY 120.8, 123.1, 135.7, 148.8, 159.0; MS m/z 164 (M^+ − H, 1), 150 (1), 136 (2), 122 (100), 106 (27), 93 (41). Anal. Calcd for $C_{10}H_{15}NO$ (165.23): C, 72.69; H, 9.15, N, 8.48. Found: C, 72.67; H, 9.10; N, 8.47.



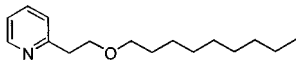
2-(2-Butoxy-ethyl)-pyridine: yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, 3H, J = 7.4 Hz, CH_3), 1.21 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 2.95 (s, 2H, J = 6.8 Hz, CH_2), 3.33 (t, 2H, J = 6.5 Hz, CH_2O), 3.68 (t, 2H, J = 6.9 Hz, CH_2O), PY 6.99 (t, 1H, J = 6.2 Hz), 7.10 (d, 1H, J = 8.0 Hz), 7.46 (t, 1H, J = 7.7 Hz), 8.42 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.7, 19.1, 31.5, 38.5, 69.8, 70.5, PY 121.0, 123.3, 135.9, 149.0, 159.2; MS m/z 180 (M^+ + H, 1), 164 (2), 150 (1), 136 (2), 122 (100), 106 (21), 93 (22). Anal. Calcd for $C_{11}H_{17}NO$ (179.26): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.71; H, 9.50; N, 7.83.



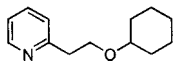
2-(2-Heptyloxy-ethyl)-pyridine: yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 6.9 Hz, CH_3), 1.21 (m, 8H, 4 × CH_2), 1.49 (m, 2H, CH_2), 3.01 (t, 2H, J = 6.9 Hz, CH_2), 3.38 (t, 2H, J = 6.6 Hz, CH_2O), 3.74 (t, 2H, J = 6.8 Hz, CH_2O), PY 7.06 (t, 1H, J = 6.1 Hz), 7.16 (d, 1H, J = 7.9 Hz), 7.53 (t, 1H, J = 7.6 Hz), 8.48 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 22.5, 26.0, 29.0, 29.5, 31.7, 38.7, 69.9, 71.0, PY 121.1, 123.5, 136.1, 149.1, 159.3; MS m/z 221 (M^+, 2), 206 (2), 164 (2), 136 (3), 122 (100), 106 (35), 93 (36). Anal. Calcd for $C_{14}H_{23}NO$ (221.34): C, 75.97; H, 10.47; N, 6.33. Found: C, 76.01; H, 10.62; N, 6.47.



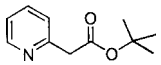
2-(2-Octyloxy-ethyl)-pyridine: yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (t, 3H, J = 6.8 Hz, CH_3), 1.03 (m, 10H, 5 × CH_2), 1.31 (m, 2H, CH_2), 2.83 (t, 2H, J = 6.8 Hz, CH_2), 3.19 (t, 2H, J = 6.6 Hz, CH_2O), 3.56 (t, 2H, J = 6.8 Hz, CH_2O), PY 6.84 (t, 1H, J = 6.2 Hz), 6.97 (d, 1H, J = 7.9 Hz), 7.32 (t, 1H, J = 7.6 Hz), 8.28 (d, 1H, J = 4.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.6, 22.2, 25.7, 28.8, 28.9, 29.2, 31.4, 38.3, 69.5, 70.5, PY 120.7, 123.0, 135.5, 148.7, 158.9; MS m/z 234 (M^+ − H, 1), 178 (2), 164 (2), 136 (2), 122 (100), 106 (21), 93 (22). Anal. Calcd for $C_{15}H_{25}NO$ (235.37): C, 76.55; H, 10.71; N, 5.95. Found: C, 76.53; H, 11.00; N, 5.96.



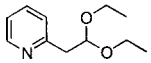
2-(2-Nonyloxy-ethyl)-pyridine: yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, 3H, J = 6.9 Hz, CH_3), 1.17 (m, 12H, 6 × CH_2), 1.46 (m, 2H, CH_2), 2.98 (t, 2H, J = 6.8 Hz, CH_2), 3.35 (t, 2H, J = 6.6 Hz, CH_2O), 3.71 (t, 2H, J = 6.9 Hz, CH_2O), PY 7.02 (t, 1H, J = 6.2 Hz), 7.12 (d, 1H, J = 7.9 Hz), 7.45 (t, 1H, J = 7.7 Hz), 8.45 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9, 22.5, 26.0, 29.1, 29.3, 29.4, 29.5, 31.7, 38.6, 69.9, 70.9, PY 121.0, 123.4, 136.0, 149.1, 159.2; MS m/z 250 (M^+ + H, 4), 248 (7), 136 (2), 122 (100), 106 (26), 93 (18). Anal. Calcd for $C_{16}H_{27}NO$ (249.39): C, 77.06; H, 10.91; N, 5.62. Found: C, 77.06; H, 10.92; N, 5.61.



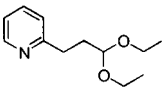
2-(2-Cyclohexyloxy-ethyl)-pyridine: yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05−1.25 (m, 5H, 5 × CH_2 a), 1.44 (m, 1H, CH_2 e), 1.61 (m, 2H, 2 × CH_2 e), 1.78 (m, 2H, 2 × CH_2 e), 2.98 (t, 2H, J = 6.9 Hz, CH_2), 3.17 (m, 1H, CHO), 3.75 (t, 2H, J = 6.9 Hz, CH_2O), PY 7.03 (t, 1H, J = 6.1 Hz), 7.15 (d, 1H, J = 7.7 Hz), 7.51 (t, 1H, J = 7.6 Hz), 8.45 (d, 1H, J = 4.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.9 (2C), 25.7, 32.1 (2C), 39.1, 67.1, 77.4, PY 121.0, 123,5, 136.0, 149.0, 159.4; MS m/z 204 (M^+ − H, 1), 122 (100), 106 (39), 93 (34). Anal. Calcd for $C_{13}H_{19}NO$ (205.30): C, 76.06; H, 9.33; N, 6.82. Found: C, 76.07; H, 9.39; N, 6.88.



***tert*-Butyl-(pyridin-2-yl)-acetate:** yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H, 3 × CH_3), 3.74 (s, 2H, CH_2-C=O), PY 7.15 (t, 1H, J = 7.2 Hz), 7.25 (d, 1H, J = 7.7 Hz), 7.62 (t, 1H, J = 7.7 Hz), 8.53 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 28.0 (3C), 45.1, 81.1, 169.9, PY 121.8, 123.7, 136.4, 149.4, 154.9; MS m/z 193 (2), 138 (4), 120 (17), 92 (22), 57 (100). Anal. Calcd for $C_{11}H_{15}NO_2$ (193.24): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.10; H, 7.95; N, 7.26.

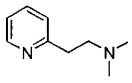


2-(2,2-Diethoxy-ethyl)-pyridine: yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 6H, J = 7.1 Hz, 2 × CH_3), 2.82 (d, 2H, J = 5.8 Hz, CH_2), 3.14−3.25 (m, 2H, CH_2O), 3.36−3.46 (m, 2H, CH_2O), 4.64 (t, 1H, J = 5.8 Hz, CH), PY 6.82 (t, 1H, J = 6.2 Hz), 6.94 (d, 1H, J = 7.8 Hz), 7.29 (t, 1H, J = 7.7 Hz), 8.25 (d, 1H, J = 4.4 Hz); ^{13}C NMR 14.9 (2C), 43.1, 61.7 (2C), 102.6, PY 121.1, 124.0, 135.8, 148.8, 157.4; MS m/z 195 (M^+, 1), 166 (14), 150 (40), 122 (46), 103 (100). Anal. Calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17. Found: C, 67.81; H, 8.99; N, 6.81.

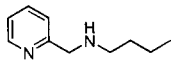


2-(3,3-Diethoxy-propyl)-pyridine: yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, 6H, J = 7.1 Hz, 2 × CH_3), 1.96−2.01 (m, 2H, CH_2), 2.78 (t, 2H, J = 7.9 Hz, CH_2), 3.37−3.61 (m, 4H, 2 × CH_2O), 4.44 (t, 1H, J = 5.7 Hz, CH), PY 7.00 (t, J = 6.1 Hz), 7.06 (d, J = 7.7 Hz), 7.48 (t, J = 7.7 Hz), 8.43 (d, J = 4.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.2 (2C), 33.2, 33.3, 61.0 (2C), 102.2, PY 120.8, 122.6, 136.1, 149.1, 161.4; MS m/z 209 (M^+, 1), 180 (16), 164 (74), 136 (37), 118 (57), 103 (100),

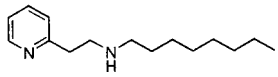
93 (46). Anal. Calcd for $C_{12}H_{19}NO_2$ (209.28): C, 68.87; H, 9.15; N, 6.69. Found: C, 68.78; H, 9.07; N, 6.66.



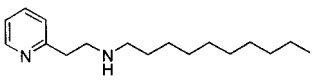
Dimethyl-(2-pyridin-2-yl-ethyl)-amine: yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 6H, 2 × NCH_3), 2.53−2.59 (m, 2H, NCH_2), 2.79−2.86 (m, 2H, CH_2), PY 6.96 (t, 1H, J = 6.2 Hz), 7.04 (d, 1H, J = 7.8 Hz), 7.44 (t, 1H, J = 7.7 Hz), 8.38 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 36.3, 45.2 (2C), 59.2, PY 120.9, 122.8, 136.0, 149.0, 160.1; MS m/z 150 (M^+, 4), 133 (2), 106 (8), 94 (3), 78 (4), 58 (100). Anal. Calcd for $C_9H_{14}N_2$ (150.22): C, 71.96; H, 9.39; N, 18.65. Found: C, 71.66; H, 9.42; N, 18.41.



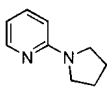
Butyl-pyridin-2-yl-methyl-amine: yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, J = 7.3 Hz, CH_3), 1.23−1.32 (m, 2H, CH_2), 1.38−1.47 (m, 2H, CH_2), 1.77 (br, 1H, NH), 2.57 (t, 2H, J = 7.2 Hz, CH_2N), 3.82 (s, 2H, CH_2N), PY 7.06 (t, 1H, J = 6.2 Hz), 7.22 (d, 1H, J = 7.9 Hz), 7.54 (t, 1H, J = 7.7 Hz), 8.46 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.8, 20.3, 32.1, 49.2, 55.2, PY 121.6, 122.1, 136.2, 149.1, 159.9; MS m/z 164 (M^+, 1), 146 (3), 131 (4), 121 (26), 93 (100). Anal. Calcd for $C_{10}H_{16}N_2$ (164.25): C, 73.13; H, 9.82; N, 17.06. Found: C, 72.95; H, 9.51; N, 17.29.



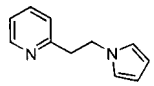
Octyl-(2-pyridin-2-yl-ethyl)amine: yield 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 6.8 Hz, CH_3), 1.20 (m, 10H, 5 × CH_2), 1.41 (m, 2H, CH_2), 1.78 (br, 1H, CH_2), 2.56 (t, 2H, J = 7.3 Hz, CH_2), 2.93 (m, 4H, 2 × CH_2N), PY 7.05 (t, 1H, J = 6.1 Hz), 7.10 (d, 1H, J = 7.7 Hz), 7.52 (t, 1H, J = 7.6 Hz), 8.47 (d, 1H, J = 4.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 22.5, 27.2, 29.1, 29.4, 30.0, 31.7, 38.5, 49.4, 49.8, PY 121.0, 123.1, 136.2, 149.2, 160.3; MS m/z 234 (M^+, 4), 205 (2), 135 (47), 121 (11), 106 (37), 93 (100). Anal. Calcd for $C_{15}H_{26}N_2$ (234.38): C, 76.87; H, 11.18; N, 11.95. Found: C, 76.57; H, 10.83; N, 11.72.



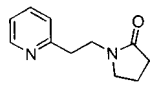
Decyl-(2-pyridin-2-yl-ethyl)amine: yield 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 6.9 Hz, CH_3), 1.19 (m, 14H, 7 × CH_2), 1.41 (m, 2H, CH_2), 1.67 (br, 1H, NH), 2.57 (t, 2H, J = 7.3 Hz, CH_2), 2.94 (m, 4H, 2 × CH_2N), PY 7.05 (t, 1H, J = 6.2 Hz), 7.11 (d, 1H, J = 7.8 Hz), 7.52 (t, 1H, J = 7.7 Hz), 8.47 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 22.6, 27.2, 29.2, 29.43, 29.46, 29.49, 29.9, 31.8, 38.4, 49.3, 49.8, PY 121.1, 123.2, 136.2, 149.2, 160.3; MS m/z 262 (M^+, 2), 170 (11), 135 (40), 121 (9), 106 (29), 93 (100). Anal. Calcd for $C_{17}H_{30}N_2$ (262.43): C, 77.80; H, 11.52; N, 10.67. Found: C, 77.59; H, 11.70; N, 10.81.



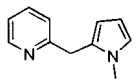
2-Pyrrolidin-1-yl-pyridine: yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (m, 4H, 2 × CH_2), 3.40 (m, 4H, 2 × CH_2N), PY 6.30 (d, 1H, J = 8.5 Hz), 6.46 (t, 1H, J = 6.0 Hz), 7.37 (t, 1H, J = 7.8 Hz), 8.12 (d, 1H, J = 5.1 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 25.4 (2C), 46.5 (2C), PY 106.3, 110.9, 136.7, 148.1, 157.2; MS m/z 148 (M^+, 43), 132 (4), 119 (100), 106 (13), 93 (17), 78 (35). Anal. Calcd for $C_9H_{12}N_2$ (148.21): C, 72.94; H, 8.16; N, 18.90. Found: C, 72.84; H, 8.10; N, 19.20.



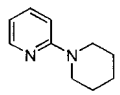
2-(2-Pyrrol-1-yl-ethyl)-pyridine: yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 (t, 2H, J = 7.2 Hz, CH_2), 4.21 (t, 2H, J = 7.3 Hz, CH_2N), 6.09 (m, 2H, 2 × −CH═), 6.59 (m, 2H, 2 × NCH═), PY 6.97 (d, 1H, J = 7.7 Hz), 7.13 (t, 1H, J = 6.2 Hz), 7.54 (t, 1H, J = 7.7 Hz), 8.57 (d, 1H, J = 4.3 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 40.4, 49.1, 107.9 (2C), 120.3 (2C), PY 121.6, 123.4, 136.4, 149.4, 158.2; MS m/z 172 (M^+, 63), 130 (25), 106 (54), 93 (63), 80 (100). Anal. Calcd for $C_{11}H_{12}N_2$ (172.23): C, 76.71; H, 7.02; N, 16.27. Found: C, 76.51; H, 6.98; N, 16.43.



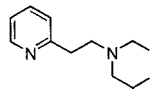
1-(2-Pyridin-2-yl-ethyl)-pyrrolidin-2-one: yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 2H, CH_2), 2.29 (t, 2H, J = 8.1 Hz, CH_2C═O), 2.98 (t, 2H, J = 7.3 Hz, CH_2 + Py), 3.26 (t, 2H, J = 7.0 Hz, CH_2N), 3.64 (t, 2H, J = 7.3 Hz, CH_2N), PY 7.09 (t, 1H, J = 6.1 Hz), 7.18 (d, 1H, J = 7.7 Hz), 7.57 (t, 1H, J = 7.7 Hz), 8.49 (d, 1H, J = 4.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.9, 30.9, 36.0, 42.4, 47.0, 174.9, PY 121.5, 123.2, 136.4, 149.2, 158.8; MS m/z 190 (M^+, 54), 162 (20), 106 (100), 98 (66), 70 (74). Anal. Calcd for $C_{11}H_{14}N_2O$ (190.24): C, 69.45; H, 7.42; N, 14.73. Found: C, 69.21; H, 7.32; N, 14.93.



1-Methyl-2-(pyridin-2-yl-methyl)-pyrrol: yield 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H, NCH_3), 4.14 (s, 2H, CH_2), 5.99 (m, 1H, −CH═), 6.08 (m, 1H, −CH═), 6.57 (m, 1H, NCH═), PY 7.08 (d, 1H, J = 7.6 Hz), 7.10 (t, 1H, J = 6.2 Hz), 7.56 (d, 1H, J = 7.7 Hz), 8.51 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 33.8, 35.6, 106.7, 107.9, 121.9, 129.8, PY 121.2, 122.5, 136.5, 149.0, 159.6; MS m/z 172 (M^+, 98), 156 (15), 130 (11), 117 (8), 94 (100). Anal. Calcd for $C_{11}H_{12}N_2$ (172.23): C, 76.71; H, 7.02; N, 16.27. Found: C, 76.53; H, 7.02; N, 16.00.

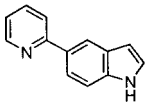


3,4,5,6-Tetrahydro-2*H*-[1,2′]bipyridinyl: yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 6H, 3 × CH_2), 3.46 (m, 4H, CH_2N), PY 6.49 (t, 1H, J = 6.0 Hz), 6.57 (d, 1H, J = 8.6 Hz), 7.37 (t, 1H, J = 7.9 Hz), 8.12 (d, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.5, 25.3 (2C), 46.1 (2C), PY 106.9, 112.1, 137.1, 147.6, 159.5; MS m/z 162 (M^+, 83), 147 (14), 133 (100), 119 (56), 107 (40), 94 (28), 79 (94). Anal. Calcd for $C_{10}H_{14}N_2$ (162.23): C, 74.03; H, 8.70; N, 17.27. Found: C, 73.85; H, 8.82; N, 17.25.

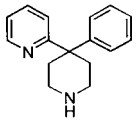


2-(2-Piperidin-1-yl-ethyl)-pyridine: yield 79%; ^{1}H NMR (400 MHz $CDCl_3$) δ 1.21 (m, 2H, CH_2), 1.31−1.47 (m, 4H, 2 × CH_2), 2.23 (m, 4H, 2 × CH_2N), 2.44−2.54 (m, 2H, CH_2), 2.75 (m, 2H, CH_2N), PY 6.84 (t, 1H, J = 6.2 Hz), 6.92 (d, 1H, J = 7.8 Hz), 7.31 (t, 1H, J = 7.7 Hz), 8.27 (d, 1H, J = 4.2 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.9, 25.6 (2C), 35.4, 54.0 (2C), 58.8, PY 120.5, 122.7, 135.7, 148.7, 160.2; MS m/z 189 (M^+ − H, 1), 131 (3), 118 (4), 106 (14), 98 (100), 93(13). Anal. Calcd for

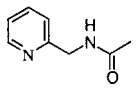
$C_{12}H_{18}N_2$ (190.28): C, 75.74; H, 9.53; N, 14.72. Found: C, 75.71; H, 9.60; N, 14.62.



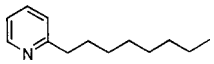
5-(2-Pyridyl)-indole: yield 62%; ^{1}H NMR (400 MHz $CDCl_3$) δ 6.63 (m, 1H, CH ar), 7.24 (t, 1H, J = 2.8 Hz, NCH═), 7.77 (d, 1H, J = 8.0 Hz, CH ar), 7.88 (d, 1H, J = 8.6 Hz, CH ar), 8.27 (s, 1H, CH ar), 8.29 (br, 1H, NH), PY 7.17 (t, 1H, J = 6.0 Hz), 7.47 (d, 1H, J = 8.6 Hz), 7.72 (t, 1H, J = 7.6 Hz), 8.68 (d, 1H, J = 4.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 103.3, 111.3, 119.5, 121.1, 125.1, 128.3, 131.4, 136.4, PY 120.5, 121.3, 136.7, 149.3, 158.8; MS *m*/*z* 194 (M^+, 100), 167 (12), 139 (7), 97 (9), 83 (14). Anal. Calcd for $C_{13}H_{10}N_2$ (194.23): C, 80.39; H, 5.19; N, 14.42. Found: C, 80.13; H, 5.44; N, 14.13.



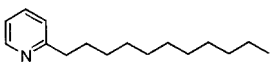
4-Pyridin-2-yl-4-phenylpiperidine: yield 49%; ^{1}H NMR (400 MHz, MeOH) δ 2.13 (br, 1H, NH), 2.26 (m, 2H, CH_2 a), 2.62 (m, 2H, CH_2 e), 2.77−2.95 (m, 4H, 2 × CH_2), 7.07−7.14 (m, 1H, Ph), 7.20−7.29 (m, 4H, Ph), PY 7.02 (t, 1H, J = 6.1 Hz), 7.07 (d, 1H, J = 8.1 Hz), 7.50 (t, 1H, J = 7.8 Hz), 8.51 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 36.4 (2C), 43.1 (2C), 47.3, Ph 126.0 (2C), 126.6, 128.4 (2C), 146.8, PY 120.9, 122.1, 136.5, 148.7, 165.5; MS *m*/*z* 238 (M^+, 8), 209 (4), 194 (6), 182 (100), 167 (43), 117 (2). Anal. Calcd for $C_{16}H_{18}N_2$ (238.33): C, 80.63; H, 7.61; N, 11.75. Found: C, 80.35; H, 7.45; N, 12.00.



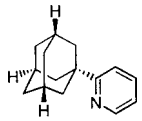
N-Pyridin-2-yl-methyl-acetamide: yield 79.5%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H, CH_3), 4.54 (d, 2H, J = 4.9 Hz, CH_2), 6.76 (br, 1H, NH), PY 7.19 (t, 1H, J = 6.3 Hz), 7.24 (d, 1H, J = 7.2 Hz), 7.65 (t, 1H, J = 7.6 Hz), 8.52 (d, 1H, J = 4.5 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.7, 44.5, 170.1, PY 122.1, 122.4, 136.8, 149.0, 156.2; MS *m*/*z* 150 (M^+, 24), 135 (13), 107 (100), 92 (28). Anal. Calcd for $C_8H_{10}N_2O$ (150.18): C, 63.98; H, 6.71; N, 18.65. Found: C, 63.90; H, 6.80; N, 18.50.



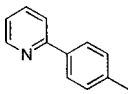
2-Octyl-pyridine: yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, 3H, J = 7.4 Hz, CH_3), 1.13−1.29 (m, 10H, 5 × CH_2), 1.66 (m, 2H, CH_2), 2.71 (t, 2H, J = 7.8 Hz, CH_2), PY 7.00 (t, 1H, J = 6.2 Hz), 7.06 (d, 1H, J = 7.7 Hz), 7.49 (t, 1H, J = 7.6 Hz), 8.45 (d, 1H, J = 4.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 22.5, 29.1, 29.3, 29.4, 29.8, 31.7, 38.4, PY 120.6, 122.5, 136.0, 149.1, 162.4; MS *m*/*z* 191 (M^+, 1), 162 (2), 148 (3), 120 (4), 106 (7), 93 (26), 28 (100). Anal. Calcd for $C_{13}H_{21}N$ (191.31): C, 81.61; H, 11.06; N, 7.32. Found: C, 81.69; H, 11.17; N, 7.38.



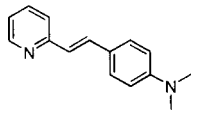
2-Undecyl-pyridine: yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, 3H, J = 6.8 Hz, CH_3), 1.16−1.36 (m, 16H, 8 × CH_2), 1.68 (m, 2H, CH_2), 2.74 (t, 2H, J = 7.8 Hz, CH_2), PY 7.03 (t, 1H, J = 6.2 Hz), 7.09 (d, 1H, J = 7.8 Hz), 7.52 (t, 1H, J = 7.6 Hz), 8.48 (d, 1H, J = 4.7 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.0, 22.6, 29.27, 29.34, 29.43, 29.49, 29.55, 29.57, 29.86, 31.8, 38.4, PY 120.7, 122.6, 136.1, 149.1, 162.5; MS *m*/*z* 233 (M^+, 2), 162 (4), 148 (4), 120 (15), 106 (27), 93 (100). Anal. Calcd for $C_{16}H_{27}N$ (233.39): C, 82.34; H, 11.66; N, 6.00. Found: C, 82.15; H, 11.55; N, 6.08.



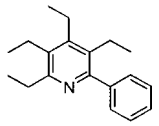
2-Adamantan-1-yl-pyridine: yield 90%; ^{1}H NMR (400 MHz, C_6D_6) δ 1.70−1.76 (m, 6H, 3 × CH_2), 2.01−2.06 (m, 3H, 3 × CH), 2.09−2.14 (m, 6H, 3 × CH_2), PY 6.64 (t, 1H, J = 6.1 Hz), 6.99 (d, 1H, J = 8.1 Hz), 7.16 (m, 1H), 8.58 (d, 1H, J = 4.8 Hz); ^{13}C NMR (400 MHz, C_6D_6) δ 29.2 (3C), 37.1 (3C), 39.4, 42.2 (3C), PY 118.6, 120.7, 135.8, 149.3, 169.3; MS *m*/*z* 213 (M^+, 100), 198 (9), 184 (3), 170 (17), 156 (37), 144 (10). Anal. Calcd for $C_{15}H_{19}N$ (213.32): C, 84.46; H, 8.98; N, 6.57. Found: C, 84.27; H, 9.13; N, 6.62.



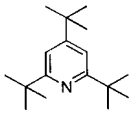
2-*p*-Tolyl-pyridine: yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H, CH_3), 7.24 (d, 2H, J = 8.5 Hz, 2 × Ph), 7.88 (d, 2H, J = 8.3 Hz, 2 × Ph), PY 7.19−7.22 (m, 1H), 7.64 (m, 2H), 8.65 (d, 1H, J = 4.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.0, 126.5 (2C), 129.3 (2C), 136.36, 138.7, PY 120.0, 121.6, 136.43, 149.3, 157.2; MS *m*/*z* 169 (M^+, 100), 154 (10), 141 (5), 115 (5). Anal. Calcd for $C_{12}H_{11}N$ (169.22): C, 85.17; H, 6.55; N, 8.28. Found: C, 84.98; H, 6.60; N, 8.10.



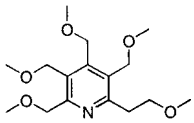
N,N-Dimethyl-4-(2-pyridin-2-yl-vinyl)-aniline: yield 10%; purity 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (s, 6H, 2 × NCH_3), 6.71 (d, 2H, J = 8.9 Hz, 2 × Ph), 6.97 (d, 1H, J = 16.0 Hz, −CH═), 7.48 (d, 2H, J = 8.8 Hz, 2 × Ph), 7.55 (d, 1H, J = 16.1 Hz, −CH═) PY 7.06 (t, 1H, J = 6.1 Hz), 7.33 (d, 1H, J = 7.9 Hz), 7.60 (t, 1H, J = 6.7 Hz), 8.55 (d, 1H, J = 4.6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 40.3, 112.2, 121.1, 121.4, 121.5 123.5, 124.8, 128.3, 132.9, 135.7, 136.3, 149.5, 150.5, 156.5; MS *m*/*z* 224 (M^+, 72), 223 (100), 207 (31), 180 (12) 167 (8), 144 (7), 111 (10). Anal. Calcd for $C_{15}H_{16}N_2$ (224.30): C, 80.32; H, 7.19; N, 12.49. Found: C, 80.11; H, 7.15; N, 12.19.



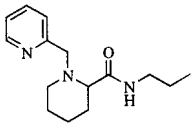
2-Phenyl-3,4,5,6-tetraethyl-pyridine: yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.5 Hz, CH_3), 1.22 (t, 3H, J = 7.4 Hz, CH_3), 1.25 (t, 3H, J = 7.4 Hz, CH_3), 1.29 (t, 3H, J = 7.5 Hz, CH_3), 2.57 (q, 2H, J = 7.5 Hz, CH_2), 2.72 (q, 4H, J = 7.2 Hz, 2 × CH_2), 2.83 (q, 2H, J = 7.5 Hz, CH_2), 7.32−7.44 (m, 5H, Ph), ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.7, 15.3, 15.4, 15.5, 21.4, 21.7, 21.9, 28.3, 127.1, 127.9 (2C), 128.8 (2C), 156.6, PY 132.3, 133.3, 142.3, 149.2 158.2, 158.0; MS *m*/*z* 267 (M^+, 26), 266 (100), 238 (8), 208 (4), 165 (3), 152 (3). Anal. Calcd for $C_{19}H_{25}N$ (267.41): C, 85.34; H, 9.42; N, 5.24. Found: C, 85.13; H, 9.41; N, 5.24.



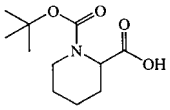
2,4,6-Tri-tert-butyl-pyridine: yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H, 3 × CH_3), 1.34 (s, 18H, 6 × CH_3), 7.07 (s, 2H, PY); ^{13}C NMR (400 MHz, $CDCl_3$) δ 30.3 (6C), 30.9 (3C), 34.9, 37.7 (2C), PY 112.1 (2C), 159.4, 167.2 (2C); MS *m*/*z* 247 (M^+, 41), 246 (50), 232 (96), 205 (100), 191 (32). Anal. Calcd for $C_{17}H_{29}N$ (247.42): C, 82.52; H, 11.81; N, 5.66. Found: C, 82.62; H, 11.53; N, 5.70.



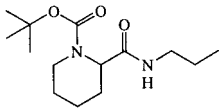
2-(2-Methoxy-ethyl)-3,4,5,6-(tetramethoxy-methyl)-pyridine: yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (t, 2H, J = 7.2 Hz, CH_2), 3.24 (s, 3H, CH_3O), 3.29 (s, 3H, CH_3O), 3.31 (s, 3H, CH_3O), 3.33 (s, 6H, 2 × CH_3O), 3.66 (t, 2H, J = 7.2 Hz, CH_2O), 4.48 (s, 2H, CH_2O), 4.49 (s, 2H, CH_2O), 4.52 (s, 2H, CH_2O), 4.56 (s, 2H, CH_2O); ^{13}C NMR (400 MHz, $CDCl_3$) δ 35.1, 58.0, 58.1, 58.2, 58.3, 58.4, 66.7, 66.8, 67.2, 72.0, 74.3, PY 129.2, 130.3, 145.7, 155.7, 158.0; MS *m*/*z* 313 (M^+, 7), 298 (100), 268 (56), 253 (37), 238 (49), 204 (77), 174 (54), 146 (27). Anal. Calcd for $C_{16}H_{27}NO_5$ (313.39): C, 61.32; H, 8.68; N, 4.47. Found: C, 61.21; H, 8.87; N, 4.55.



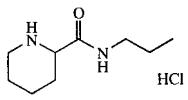
1-Pyridin-2-yl-methyl-piperidine-2-carboxylic Acid Propylamid (11): yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 7.4 Hz, CH_3), 1.24−1.73 (m, 7H, CH_2), 2.03−2.09 (m, 1H, CH_2 e), 2.05 (td, 1H, J_t = 11.9 Hz, J_d = 2.8 Hz, CHN), 2.86 (dt, 1H, J_d = 11.7 Hz, J_t = 3.2 Hz, CH_2N), 2.91 (dd, 1H, J_{d1} = 10.8 Hz, J_{d2} = 3.5 Hz, CH_2N), 3.23 (m, 2H, CH_2-NH), 3.29 (d, 1H, J = 14.0 Hz, PYCH_2N), 3.91 (d, 1H, J = 14.0 Hz, PYCH_2N), 7.57 (br, 1H, NH), PY 7.17 (t, 1H, J = 6.2 Hz), 7.24 (d, 1H, J = 6.5 Hz), 7.63 (t, 1H, J = 7.6 Hz), 8.58 (d, 1H, J = 4.9 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.5, 22.8, 23.5, 24.9, 30.8, 40.8, 52.3, 62.4, 67.6, 174.5, PY 122.2, 122.7, 136.3, 149.6, 158.5; MS *m*/*z* 261 (M^+, 2), 202 (1), 176 (89), 169 (59), 158 (10), 147 (14), 130 (8), 119 (8), 93 (100). Anal. Calcd for $C_{15}H_{23}N_3O$ (261.36): C, 68.93; H, 8.87; N, 16.08. Found: C, 68.73; H, 8.90; N, 16.00.



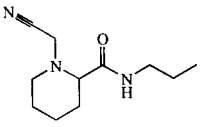
Synthesis of 1-Cyanomethyl-piperidine-2-carboxylic Acid Propylamide (10): (a) Piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester. Pipecolinic acid (9, 100 mmol, 12.92 g) and triethylamine (100 mmol, 13.9 mL) were dissolved in 80 mL of 1,4-dioxane and 15 mL of water. Di-*tert*-butyl carbonate (110 mmol, 24 g) was added, and the solution was stirred for 18 h. The solvent was evaporated, and the residue was dissolved in 500 mL of ethyl acetate. The solution was washed with 200 mL of HCl (5%) and 200 mL of brine (three times). After the last washing procedure, the pH of the aqueous layer has to be >5. The organic layer was dried over Na_2SO_4, filtered, and evaporated to obtain colorless crystals: yield 20.67 g (90%); mp 130−131 °C; IR 3448 (OH), 2937 (CH), 1738 (C═O acid), 1686 (C═O urethane) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.23−1.66 (m, 14H, CH_2 + CH_3), 2.20 (s, 1H, CH_2 e), 2.94−2.96 (m, 1H, CH_2N), 3.92−3.98 (m, 1H, CH_2N), 4.74, 4.92 (2s, 1H, CHN), 10.93 (s, 1H, COOH); ^{13}C NMR ($CDCl_3$) 20.7, 24.6, 26.5, 28.2, 41.0, 42.0 (CH_2N), 53.5, 54.6 (CHN), 80.2, 155.5, 156.1 (C═O urethane), 177.0 (C═O acid). Anal. Calcd for $C_{11}H_{19}NO_4$ (229.27): C, 57.62; H, 8.35; N, 6.11. Found: C, 57.10; H, 8.25; N, 6.06.



(b) 2-Propylcarbamoyl-piperidine-1-carboxylic Acid *tert*-Butyl Ester. Piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (90.0 mmol, 20.20 g) was dissolved in 250 mL of dry THF and di-*tert*-butyl carbonate (94.5 mmol, 20.62 g); dry pyridine (99.0 mmol, 8.0 mL) and 100 mg of 4-(dimethylamino)pyridine were added under an argon atmosphere. The solution was stirred for 30 min before *n*-propylamine (99.0 mmol, 7.4 mL) was added. The reaction was monitored by TLC (silica gel, eluent EtOAc) for 48 h. The solvent was evaporated, and the residue was dissolved in 300 mL of diethyl ether. The organic layer was washed with 100 mL of 1 M HCl, 100 mL of saturated $NaHCO_3$, and 100 mL of brine. The organic layer was dried and evaporated, and the residue was recrystallized from pentane (4 °C) to achieve a colorless solid: yield 15.87 g (65%); mp 128 °C; TLC (SiO_2/EtOAc), R_f 0.76; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J = 7.6 Hz, CH_3), 1.23−1.59 (m, 16H, CH_2 + CH_3−*t*-Bu), 2.28 (br, 1H, CH_2CH$_3$), 2.73 (t, 1H, J = 12.6 Hz, CH_2N), 3.16−3.27 (m, 2H, CH_2NH), 3.99 (br, 1H, CH_2N), 4.67 (s, 1H, CHN), 6.08 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) 11.2, 20.4, 22.8, 24.8, 25.4, 28.3, 41.0, 41.9, 54.7, 80.5, 155.6 (C═O urethane), 170.8 (C═O amide). Anal. Calcd for $C_{14}H_{26}N_2O_3$ (270.37): C, 62.19; H, 9.69; N, 10.36. Found: C, 62.36; H, 9.70; N, 10.18.



(c) Piperidine-2-carboxylic Acid Propylamide Hydrochloride. 2-Propylcarbamoyl-piperidine-1-carboxylic acid *tert*-butyl ester (9.0 mmol, 2.42 g) was dissolved in 50 mL of EtOH and 10 mL of Et_2O. Concentrated HCl (5 mL) was added, and the solution was stirred for 24 h and monitored by TLC (silica gel, eluent EtOAc). The solvent was evaporated, and the residue was dried in vacuo to get a pale yellow solid: yield 1.81 g (98%); ^{1}H NMR (DMSO-d_6) 0.89 (t, 3H, J = 7.7 Hz, CH_3), 1.34−1.76 (m, 6H, CH_2), 2.11−2.21 (m, 1H, CH_2CH a), 2.80−3.30 (m, 4H, CH_2CH e + CH_2NH a + C$H_2NH_2^+$), 3.45 (br, 1H, CH), 3.78 (br, 1 H, CH_2NH e), 8,75 (br, 2H, NH_2^+), 9.55 (br, 1H, NH);^{13}C NMR (d^{6}DMSO): 12.1, 22.0, 22.4, 23.0, 27.9, 41.2, 44.1, 57.6, 169.1.



(d) 1-Cyanomethyl-piperidine-2-carboxylic Acid Propylamide (10). Piperidine-2-carboxylic acid propylamide hydrochloride (59.9 mmol, 12.38 g) was dissolved in 80 mL of MeOH and diluted with 43 mL of triethylamine. The solution was stirred for 5 min before bromoacetonitrile (329 mmol, 23.0 mL) was added. The mixture was stirred for 24 h at 25 °C, and the solvent was evaporated. The residue was diluted with 150 mL of saturated $NaHCO_3$ and 150 mL of dichloromethane. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The pale yellow solid was recrystallized from cyclohexane to achieve a colorless solid: yield 12.0 g (96%); mp 82 °C; TLC (SiO_2/EtOAc), R_f 0.52; IR 3290 (NH), 2950, 2900, 2860 (C−H), 1660 (C═O−amide), 1520 (NH−def.) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7.3 Hz, CH_3), 1.23−1.78 (m, 7H, CH_2CH a + CH_2), 1.94 (d, 1H, J = 13.4 Hz, CH_2CH e), 2.44 (td, 1H, J_t = 11.9 Hz, J_d = 2.8 Hz, CH), 2.84 (dd, 1H, J_{d1} =

11.0 Hz, $J_{d2} = 3.0$ Hz, CH_2N a), 2.91 (d, 1H, $J = 11.0$ Hz, CH_2N e), 3.17−3.26 (m, 2H, CH_2NH), 3.45 (d, 1H, $J = 17.3$ Hz, CH_2-CN), 3.57 (d, 1H, $J = 17.3$ Hz, CH_2CN), 6.26 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) 11.2, 22.7, 24.7, 30.3, 40.7, 41.2, 52.3, 56.1, 66.0, 114.4, 171.7. Anal. Calcd for $C_{11}H_{19}N_3O$ (209.29): C, 63.13; H, 9.15; N, 20.08. Found: C, 63.37; H, 8.88; N, 19.94.

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