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An efficient route to 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones as potential nAChRs ligands

Nicolas Leflemme, Patrick Dallemagne* and Sylvain Rault

Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, 1 rue Vaubénard, 14032 Caen Cedex, France

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Abstract—A new efficient pathway to synthesise 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones is described. This reaction sequence involved, as a key step, a Suzuki cross-coupling reaction between various boronic acids and an 6-iodo-2,3-dihydropyridin-4-one. A final deprotecting step furnished the attempted products.

1. Introduction

Recently, numerous studies have focused on the synthesis of ligands for neuronal nicotinic acetylcholine receptors (nAChRs).[1,2] Because, structures analogues of well established nAChRs ligands have been suggested as potential therapeutic agents for several neurological disorders, including attention deficit, hyperactivity disorder, Tourette's syndrome, schizophrenia, Alzheimer's and Parkinson's diseases.[3]

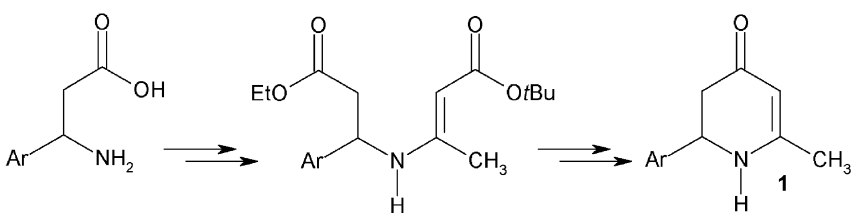
Moreover, most of the nAChRs ligands with high affinity contain pyridine and cyclic amine pharmacophoric moieties, and comprehensive reviews, which summarized the structure–activity relationships of ligands for nAChRs, have emphasized the importance in the ligand structure of a π-system, such as a heteroaromatic ring or carbonyl group as a hydrogen bond acceptor moiety, and a basic cyclic amine group.[4]

Dihydropyridinones are interesting building blocks for a large variety of heterocycles because their aminoenone moiety can be used in various reactions leading to key intermediates particularly useful in the synthesis of alkaloids and pharmacologically active agents.[5] In peculiar, we have pointed out the interest of the dihydropyridinones of type **1** (Scheme 1) as memory enhancers in relation to their nicotinic acetylcholine receptor activity.[6] Recently, we have developed a new versatile and efficient four steps procedure for the preparation of 6-alkyl-2-(het)aryl-2,3-dihydro-1*H*-pyridin-4-ones **1**,[7] starting from available β-(het)aryl-β-amino acids[8] (Scheme 1).

With the aim to determine the influence of the double bond position on the pharmacological properties we have turned our attention to synthesise the isomers compounds 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones **2**.[9]

2. Results and discussion

In connection with our previous works, we have studied the



Scheme 1.

Keywords: Cross-coupling; Suzuki reaction; Boronic acids; Heterocycles; Dihydropyridinone.
* Corresponding author. Tel.: +33-2-31-56-59-10; fax: +33-2-31-93-11-88; e-mail address: dallemagne@pharmacie.unicaen.fr

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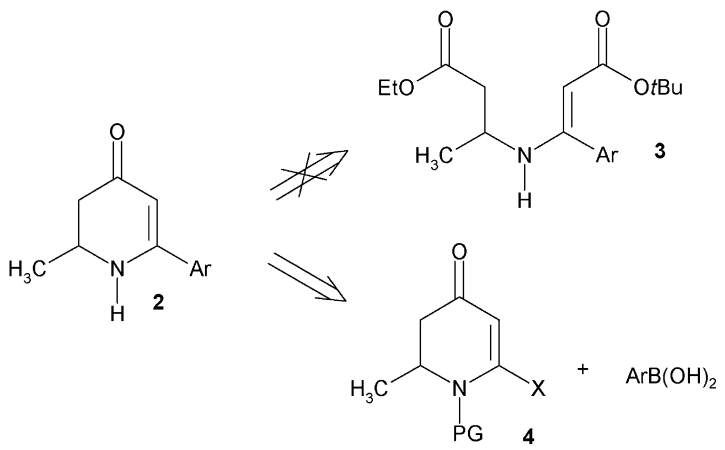
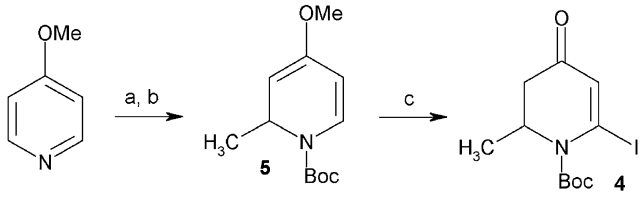


Scheme 2. Retrosynthetic approach.

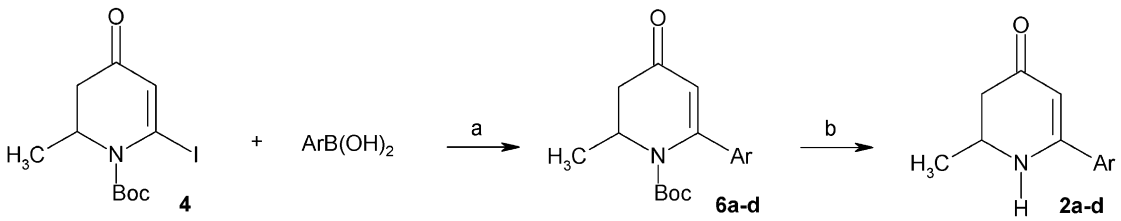


Scheme 3. Reagents and conditions: (a) (i) PhOCOCl (1.01 equiv.), THF, −25 °C; (ii) MeMgBr (1.05 equiv.), THF, −25 °C to room temperature; (b) *t*-BuOK (4 equiv.), THF, −60 °C (91% in 2 steps); (c) (i) *n*-BuLi (1.2 equiv.), THF, −60 °C; (ii) I_2 (1.1 equiv.), THF, −60 °C to room temperature; (iii) HCl 1 N (76%).

enaminone formation by the use of the acetate salt of ethyl 3-aminobutyrate and *tert*-butyl β-aryl-β-ketoester but this method failed to produce the expected enaminone intermediate **3** and instead led to degradation products (Scheme 2).

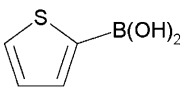
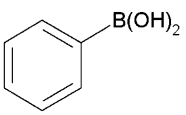
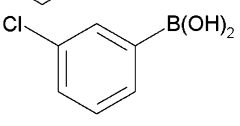
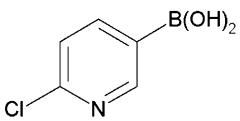
We have therefore envisaged a second synthetic procedure which consisted in a Suzuki cross-coupling reaction between a protected 6-halo-2,3-dihydroprydin-4-one **4** and various boronic acids (Scheme 2).

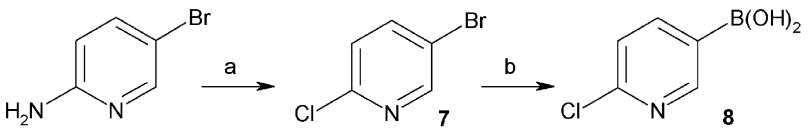
As illustrated in Scheme 3, the intermediate **4** was prepared by applying Comins's methodology.[10] 1-Acylpyridinium



Scheme 4. Reagents and conditions: (a) $NaHCO_3$ (2.5 equiv.), 5 mol% $Pd(PPh_3)_4$, DME/H_2O (v/v), reflux; (b) TFA (10 equiv.), CH_2Cl_2, room temperature.

Table 1. Suzuki cross-coupling reaction of 6-iodo-2,3-dihydropyridin-4-one with arylboronic acids and clivage of Boc protecting group in acidic conditions

Entry	$ArB(OH)_2$	Cross-coupled product (isolated yield)	Deprotected product (isolated yield)
1		**6a** (87%)	**2a** (91%)
2		**6b** (78%)	**2b** (92%)
3		**6c** (78%)	**2c** (91%)
4		**6d** (80%)	**2d** (76%)



Scheme 5. Reagents and conditions: (a) (i) $NaNO_2$ (2 equiv.), HCl 6 N, 0 °C; (ii) CuCl (1.25 equiv.), 0 °C to room temperature (56%); (b) (i) *n*-BuLi (1.2 equiv.), Et_2O, −78 °C; (ii) $B(OiPr)_3$ (1.2 equiv.), Et_2O, −78 °C to room temperature (78%).

salt was formed in situ by addition of phenyl chloroformate to 4-methoxypyridine in THF at −25 °C, and subsequent treatment with methylmagnesium bromide afforded the crude 1-phenoxycarbonyl-1,2-dihydropyridine.[11] The latter was converted to the *N*-Boc derivative **5** using *t*-BuOK at −60 °C in 91% overall yield for the two steps. Due to its low stability **5** was engaged without purification in a α-lithiation–iodation sequence[12] using *n*-BuLi and iodine to obtain, after an acidic workup, 6-iodo-2,3-dihydropyridin-4-one **4** in 76% yield.

Intermediate **4** was then involved in a Suzuki-type cross-coupling reaction[13] with various commercial boronic acids (Scheme 4). The use of aqueous condition[14] to improve the reactivity of the partners afforded derivatives **6** in good yields after standard flash chromatography performed on silica gel (Table 1).

The 6-chloro-3-pyridinyl moiety confers high potency to several types of compounds, like epibatidine[15] and synthetic analogues,[2] acting at the nAChRs. In order to incorporate this moiety on our dihydropyridinone structure, we have turned our attention to synthesise the requisite boronic acid.

Intermediate 5-bromo-2-chloropyridine **7**, easily obtained by a current Sandmeyer[16] procedure from 2-amino-5-bromopyridine, was engaged in a lithium–halogen exchange reaction, carried out in Et_2O at −78 °C using *n*-BuLi, followed by the reaction with $B(OiPr)_3$.[13] The desired boronic acid **8** is thus obtained with 78% yield after an appropriate mild acido-basic work up and an easy purification by recrystallisation (Scheme 5).[17]

Finally, protecting groups *t*-butoxycarbonyl were cleaved in acid conditions using trifluoroacetic acid to give the title 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones **2a–d** in high yields (Table 1).

In conclusion, we have developed an efficient new method for the synthesis of various substituted 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones, based on a fast and clean Suzuki cross-coupling reaction. The biological evaluation of these new compounds is now under investigation.

3. Experimental

3.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer Spectrum BX FT-IR System spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in ppm downfield from the residual deuterated solvent or the internal standard tetramethylsilane. Thin layer chromatographies (TLC) were performed on 0.2 mm precoated plates of silica gel 60F-254 (Merck). Visualization was made with ultraviolet light (254 nm). Column chromatographies were carried out using silica gel 60 (0.063–0.2 mm) (Merck). Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

3.1.1. *tert*-Butyl 6-iodo-2-methyl-1,2,3,4-tetrahydropyridine-1-carboxylate (4).[12a] To a stirred solution of 4-methoxypyridine (2.03 mL, 20.0 mmol) in dried THF, cooled to −25 °C, was added phenyl chloroformate (2.53 mL, 20.2 mmol, 1.01 equiv.). The resulting reaction mixture containing a white precipitate of pyridinium salts was allowed to react at this temperature over 1 h, at which point a solution of 3 M methylmagnesium bromide (7.0 mL, 21.0 mmol, 1.05 equiv.) was added dropwise. The reaction mixture was abandoned at −25 °C for 1 h, and then allowed to warm to room temperature under stirring for an additional hour. The mixture was quenched with water (50 mL) and extracted with diethyl ether (2×75 mL). The combined organic layers were then dried ($MgSO_4$) and the solvents removed in vacuo. The oily residue was dissolved in dry THF, cooled to −40 °C, and *t*-BuOK (8.98 g, 80.0 mmol, 4 equiv.) was added. The mixture was then abandoned at −40 °C for 2 h, and then allowed to warm to room temperature under stirring for an additional hour. Diethyl ether and water were then added to the mixture. The organic layer was separated, dried over $MgSO_4$ and concentrated to dryness to yield **5** (4.10 g, 91%) as a yellow oil. The residue was used without further purification in the next step. To a solution of **5** (4.06 g, 18.0 mmol) in freshly distilled THF, cooled to −60 °C, was added dropwise a solution of 2.5 M *n*-BuLi (8.64 mL, 21.6 mmol, 1.2 equiv.). The resulting mixture was allowed to react at this temperature over 30 min. A solution of iodine (5.03 g, 19.8 mmol, 1.1 equiv.) in THF was then added. The reaction mixture was abandoned at −60 °C for 2 h, and then allowed to warm to room temperature under stirring for an additional hour. The mixture was quenched by addition of 1 N HCl, extracted with diethyl ether, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using diethyl ether/petroleum ether (4/6) as eluent to give **4** (4.61 g, 76%) as a yellow oil. IR (KBr): 2978, 2932, 1722, 1668, 1549, 1369, 1324, 1158, 1121 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.36 (s, 1H), 4.94 (m, 1H), 2.83 (dd, J=17.5, 5.9 Hz, 1H), 2.34 (d, J=17.5 Hz, 1H), 1.59 (s, 9H), 1.36 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 191.0, 151.4, 128.2, 109.8, 84.5, 53.2, 43.4, 28.1, 16.2. MS (EI) *m/z* (relative intensity) 337 ([$M^{+\cdot}$], 25), 280 (20), 263

(25), 237 (33), 236 (100), 221 (69), 193 (17), 165 (12), 110 (48), 84 (10).

3.1.2. 6-Chloropyridin-3-ylboronic acid (8). White solid (78%). Spectroscopic data corresponds to that reported in the literature.[17]

3.2. General procedure for the synthesis of *tert*-butyl 6-aryl-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-1-carboxylates (6a–d)

To a solution of **4** (500 mg, 1.48 mmol) in DME (10 mL) was added successively arylboronic acid (1.78 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (86 mg, 5 mol%) and a solution of $NaHCO_3$ (312 mg, 3.71 mmol, 2.5 equiv.) in water (5 mL). The reaction mixture was heated at reflux, TLC indicated complete conversion of the substrate (6 h). After cooling to room temperature, the mixture was extracted with $CHCl_3$ (2×15 mL), then the combined organic layers were dried over $CaCl_2$ and the solvents were removed in vacuo to leave the crude product which was purified by column chromatography on silica gel. Elution with diethyl ether–petroleum ether furnished **6a–d**.

3.2.1. *tert*-Butyl 2-methyl-4-oxo-6-(thien-2-yl)-1,2,3,4-tetrahydropyridine-1-carboxylate (6a). Yellow solid (87%), mp 90–91 °C. IR (KBr): 3087, 2973, 2933, 1718, 1659, 1584, 1424, 1389, 1308, 1227, 1160, 703 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.43 (d, J=4.9 Hz, 1H), 7.21 (d, J=3.3 Hz, 1H), 7.07 (dd, J=4.9, 3.3 Hz, 1H), 5.79 (s, 1H), 5.02 (m, 1H), 2.92 (dd, J=17.4, 5.8 Hz, 1H), 2.35 (d, J=17.4 Hz, 1H), 1.41 (d, J=7.0 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 194.0, 152.9, 148.3, 141.5, 127.7, 127.5, 126.7, 112.5, 82.6, 51.3, 43.7, 27.5, 16.8. Anal. calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.34; H, 6.71; N, 4.86.

3.2.2. *tert*-Butyl 2-methyl-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridine-1-carboxylate (6b). Beige solid (78%), mp 99 °C. IR (KBr): 3057, 3033, 2981, 2967, 2929, 1709, 1655, 1569, 1326, 1231, 1161, 768 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41–7.33 (m, 5H), 5.63 (s, 1H), 5.04 (m, 1H), 2.98 (dd, J=17.3, 5.9 Hz, 1H), 2.40 (d, J=17.3 Hz, 1H), 1.44 (d, J=7.0 Hz, 3H, CH_3), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 194.1, 155.0, 152.6, 138.9, 129.7, 128.4, 126.1, 112.8, 82.5, 51.3, 43.6, 27.4, 16.7. Anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.92; H, 7.51; N, 4.71.

3.2.3. *tert*-Butyl 6-(3-chlorophenyl)-2-methyl-4-oxo-1,2,3,4-tetra-hydropyridine-1-carboxylate (6c). Beige solid (78%), mp 101 °C. IR (KBr): 3022, 2968, 2931, 2876, 1714, 1674, 1582, 1562, 1478, 1396, 1368, 1311, 1153, 799 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41–7.23 (m, 4H), 5.61 (s, 1H), 5.05 (m, 1H), 2.96 (dd, J=17.3, 5.8 Hz, 1H), 2.37 (d, J=17.3 Hz, 1H), 1.44 (d, J=6.8 Hz, 3H, CH_3), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 193.9, 153.3, 152.2, 140.6, 134.4, 129.8, 129.5, 126.2, 124.3, 113.1, 82.8, 51.3, 43.5, 27.5, 16.7. Anal. calcd for $C_{17}H_{20}NO_3Cl$: C, 63.45; H, 6.26; N, 4.35. Found: C, 63.39; H, 6.36; N, 4.21.

3.2.4. *tert*-Butyl 6-(6-chloropyridin-3-yl)-2-methyl-4-oxo-1,2,3,4-tetra-hydropyridine-1-carboxylate (6d). Beige solid (80%), mp 115 °C. IR (KBr): 3038, 3003, 2969, 2932, 1711, 1660, 1592, 1455, 1406, 1369, 1317, 1235, 1154, 1087, 816 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.32 (d, J=2.4 Hz, 1H), 7.55 (dd, J=8.0, 2.4 Hz, 1H), 7.35 (d, J=8.0 Hz, 1H), 5.57 (s, 1H), 5.03 (m, 1H), 2.93 (dd, J=17.2, 5.8 Hz, 1H), 2.36 (d, J=17.2 Hz, 1H), 1.49 (d, J=6.7 Hz, 3H, CH_3), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 193.3, 152.1, 151.7, 150.4, 146.9, 136.0, 133.6, 123.9, 113.8, 83.4, 51.3, 43.3, 27.6, 16.7. Anal. calcd for $C_{16}H_{19}N_2O_3Cl$: C, 59.54; H, 5.93; N, 8.68. Found: C, 59.75; H, 5.88; N, 8.42.

3.3. General procedure for the synthesis of 6-aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones (2a–d)

To a solution of *tert*-butyl 6-aryl-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-1-carboxylate (0.85 mmol) in CH_2Cl_2 (5 mL), cooled to 0 °C, was added dropwise TFA (830 μL, 8.52 mmol, 10 equiv.). This mixture was stirred at room temperature until complete by TLC analysis (Et_2O/petroleum ether). Once complete (4 h) the reaction mixture was quenched with aqueous saturated K_2CO_3 solution, extracted with CH_2Cl_2, dried over $CaCl_2$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc as eluent to give **2a–d.**

3.3.1. 2-Methyl-6-(thien-2-yl)-2,3-dihydro-1*H*-pyridin-4-one (2a). Yellow solid (91%), mp 155–156 °C. IR (KBr): 3288, 3071, 2963, 2926, 1605, 1572, 1505, 1449, 1339, 1275, 1248, 1166, 769, 708 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45 (dd, J=5.1, 0.8 Hz, 1H), 7.43 (dd, J=3.7, 0.8 Hz, 1H), 7.11 (dd, J=5.1, 3.7 Hz, 1H), 5.50 (s, 1H), 5.24 (s, 1H), 3.94 (m, 1H), 2.46 (dd, J=16.1, 5.1 Hz, 1H), 2.37 (dd, J=17.4, 13.0 Hz, 1H), 1.41 (d, J=6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 193.0, 154.3, 137.9, 128.5, 128.1, 126.6, 97.8, 49.1, 43.5, 20.3. Anal. calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.24. Found: C, 62.34; H, 5.62; N, 7.02.

3.3.2. 2-Methyl-6-(phenyl)-2,3-dihydro-1*H*-pyridin-4-one (2b). Beige solid (92%), mp 161 °C. IR (KBr): 3268, 2971, 2934, 1605, 1580, 1511, 1449, 1387, 1348, 1271, 1167, 769, 694 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.54–7.52 (m, 5H), 5.39 (s, 1H), 5.04 (s, 1H), 3.94 (m, 1H), 2.46 (dd, J=16.2, 5.3 Hz, 1H), 2.38 (dd, J=16.2, 13.1 Hz, 1H), 1.41 (d, J=6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 193.2, 161.5, 135.7, 130.8, 128.9, 126.1, 98.5, 49.2, 43.3, 20.4. Anal. calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.21; H, 7.06; N, 7.22.

3.3.3. 6-(3-Chlorophenyl)-2-methyl-2,3-dihydro-1*H*-pyridin-4-one (2c). Beige solid (91%), mp 133 °C. IR (KBr): 3255, 3080, 2973, 2932, 2887, 1605, 1574, 1514, 1447, 1339, 1275, 1165, 782, 492 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.51–7.37 (m, 4H), 5.33 (s, 1H), 5.10 (s, 1H), 3.93 (m, 1H), 2.45 (dd, J=16.1, 4.8 Hz, 1H), 2.37 (dd, J=16.1, 13.1 Hz, 1H), 1.41 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 193.3, 160.0, 137.5, 134.9, 130.7, 130.3, 126.3, 124.2, 98.9, 49.3, 43.2, 20.3. Anal. calcd for $C_{12}H_{12}NOCl$: C, 65.02; H, 5.46; N, 6.32. Found: C, 65.15; H, 5.79; N, 6.13.

3.3.4. 6-(6-Chloropyridin-3-yl)-2-methyl-2,3-dihydro-1*H*-pyridin-4-one (2d). Beige solid (76%), mp 216 °C. IR (KBr): 3256, 3104, 2968, 2927, 2891, 1613, 1591, 1567, 1513, 1459, 1332, 1275, 1109, 796, 486 cm^{-1}. ^1H NMR (d6-DMSO) δ 8.65 (d, J=2.0 Hz, 1H), 8.07 (dd, J=8.3,

2.0 Hz, 1H), 7.69 (s, 1H), 7.61 (d, J=8.3 Hz, 1H), 5.15 (s, 1H), 3.78 (s, 1H), 2.28 (dd, J=15.9, 4.3 Hz, 1H), 2.16 (dd, J=15.9, 13.0 Hz, 1H), 1.29 (d, J=6.0 Hz, 3H). ^{13}C NMR (d_6-DMSO) δ 191.2, 157.0, 151.8, 147.9, 137.9, 130.3, 124.2, 97.0, 48.5, 42.9, 19.4. Anal. calcd for $C_{11}H_{11}N_2OCl$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.19; H, 5.08; N, 12.39.

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