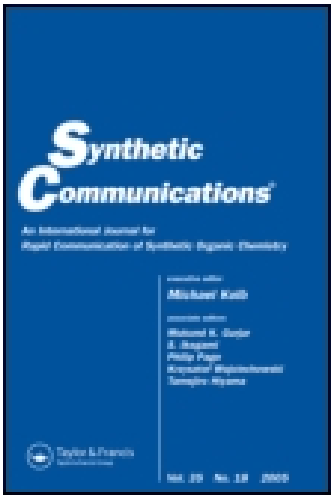

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Facile Synthesis of 3,3-Dialkyl-6-phenyl-imidazopyridinones

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Facile Synthesis of 3,3-Dialkyl-6-phenyl-imidazopyridinones

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Abstract: A series of novel 3,3-dialkylated imidazopyridinones bearing 6-aryl groups were designed as mimetics of active progesterone antagonists, 3,3-disubstituted-5-aryloxindoles. The four-step synthetic route is described. The key steps are base-catalyzed cyclization, base-catalyzed alkylation, and Suzuki coupling reaction.

Keywords: cyclization reaction, imidazopyridinone, Suzuki coupling reaction

INTRODUCTION

A number of novel classes of nonsteroidal antiprogestins[1] have emerged during the past several years, aimed at improving the side-effect profile inherent with steroidal antiprogestins and exploring therapeutic opportunities other than abortifacients, such as the treatment of breast cancer, endometriosis, uterine fibroids and, contraceptive agents.

Nonsteroidal progesterone receptor antagonists, 3,3-disubstituted-5-aryloxindoles **1**, were reported to be active in blocking progesterone-induced alkaline phosphatase in the human breast-cancer cell line T47D.[2] The structure–activity study showed that small alkyl and spiroalkyl groups R are required to achieve better progesterone receptor (PR) antagonist activity. We now report the syntheses of a series of imidazopyridinone analogs **2** to mimic compound **1** (Fig. 1).

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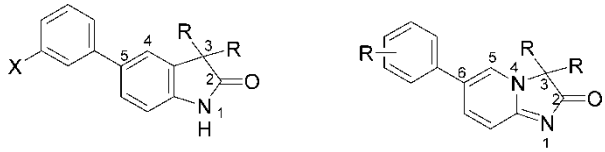


1. X = Cl, R: -$(CH_2)_4$-
3,3-disubstituted-5-arylindoles

2. Imidazopyridinone

Figure 1. Structure of arylindoles and imidazopyridinones.

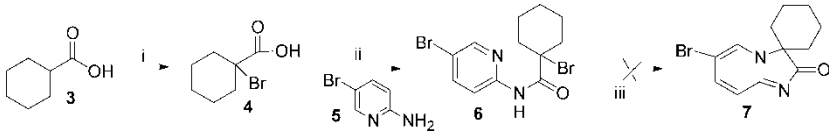
To the best of our knowledge, imidazopyridinones, bearing dialkyl groups at 3-position and an aromatic ring at 6-position, were never synthesized before.[3] In the course of our ongoing program related to the synthesis and the biological evaluation of progesterone receptor modulators, an efficient and straightforward route has been developed for the synthesis of compound **2**.

CHEMISTRY

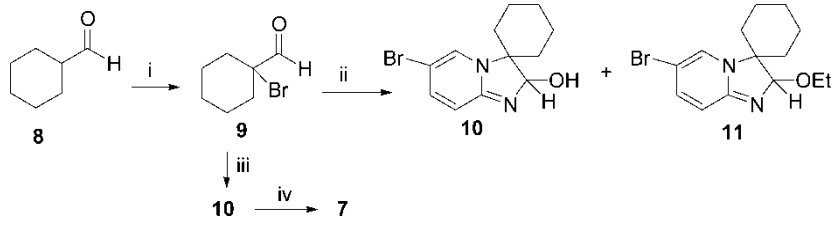
The method reported by Argade[4] was first tried, where the key cyclization step is the S_N2 reaction of pyridine nitrogen to bromide adjacent to an amide carbonyl group. However, although it works for the secondary bromide in Argade's report, because of the steric hindrance in tertiary bromide **6**, the cyclization step leading to desired product **7** failed, as shown in Scheme 1.

Because the formation of the desired product involves the tertiary bromide **6**, we adopted a reaction condition reported by Helissey et al.[5] to take advantage of the tertiary cation as a reaction intermediate. As shown in Scheme 2, despite of the contamination of a significant amount of **11**, the desired product **10** was isolated. According to the mechanism in Scheme 3, the formation of the side product **11** occurred because of the use of the solvent ethanol. By changing the solvent from ethanol to a mixture of water and dioxane, the undesired side product **11** was eliminated and the desired product **10** was isolated in 47% yield.

Several attempts were taken to convert alcohol **10** to ketone **7**. Compound **10** was first subjected to Swern oxidation conditions [$Me_2S(O)$, $(COCl)_2$], but the desired oxidized product **7** was not detected. When compound **10** was



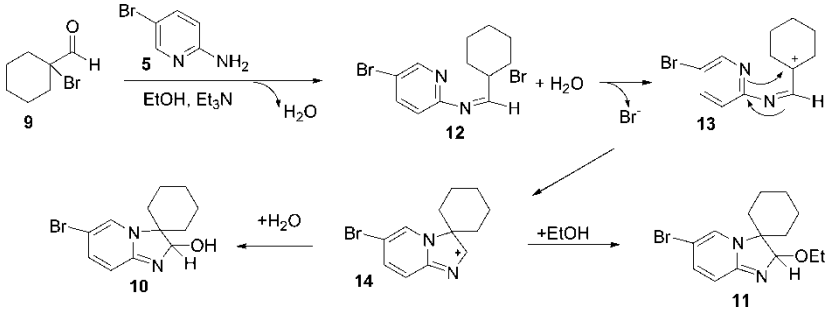
Scheme 1. (i) PBr_3, Br_2, 70°C, 17 h, 75%; (ii) $(COCl)_2$, then 5-bromo-pyridin-2-ylamine **5**; 40%; and (iii) a) MeLi or b) nBuLi.



Scheme 2. (i) Br_2, $NaHCO_3$, quantitative; (ii) 5-bromo-pyridin-2-ylamine **5**, EtOH, Et_3N; (iii) 5-bromo-pyridin-2-ylamine **5**, H_2O, 1,4-dioxane, Et_3N, 47%; and (iv) Dess–Martin oxidation, 22%.

subjected to Dess–Martin oxidation conditions, the desired product **7** was isolated in 22% with a significant contamination of some side products, as shown in Scheme 2.

Finally, the third route turned out to be feasible to preparing the target compound **2**. As shown in Fig. 2, compound **15** was prepared via quaternization of pyridine nitrogen.[6] Because of the electron-deficiency caused by the pyridine ring and the electron-withdrawing substituent Br, *N*-alkylation of aminopyridine **5** is comparatively difficult. Thus, as shown in Scheme 4, refluxing for an extended period of time (16 h) is required to generate compound **18** with excellent purity in large quantities. Condensations between a keto or aldehyde group and an active amino group in many pyridinium salts under basic conditions have been established,[7] but the similar participation of an ester group instead of the keto or aldehyde group is less well-known. Cyclization of compound **18** via intramolecular aminolysis under basic conditions (NaOMe) generated pyridine imidazole **19**. An alternate basic condition (KOH/EtOH)[8] provided the product **19** in a lower yield. For the structure of **16** in Fig. 2, an aromatic enol structure, such as **17,** is possible. However, the aromatic imidazopyridinol structure **20**, in Fig. 2, was excluded by comparison of the ^1H NMR spectral data of **19** with those of known 3-methylene-2,3-dihydroindolizin-2-ones and indolizin-2-ol



Scheme 3.

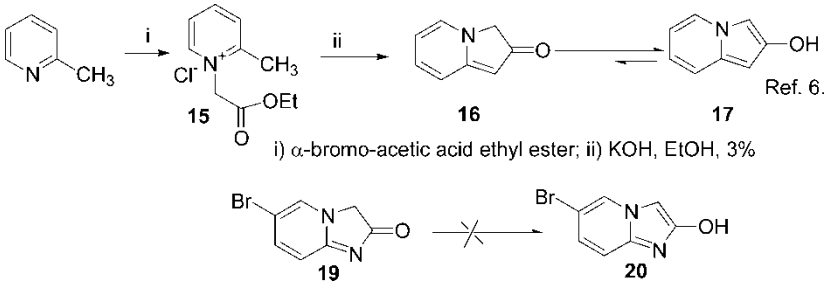
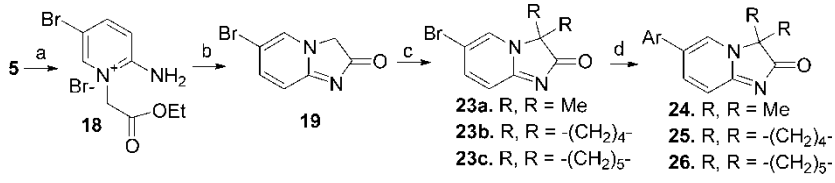


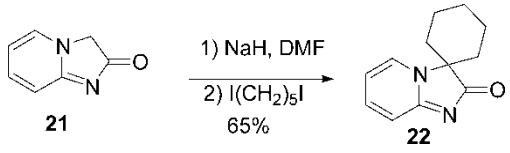
Figure 2. Structures of pyridine imidazoles and their tautomeric enol forms.

derivatives.[8] For example, the ^{1}H NMR spectra exhibited a two-proton singlet at δ 4.52, due to an active methylene in **19**. The chemical shift (δ 4.52) of the unsaturated ring proton in **19** was obviously higher than those (less than δ 6.50) of indolizin-2-ol derivatives.[8]

However, the synthesis of compound **19** on a large scale results in a low yield. This is consistent with the literature-reported yield (3%) for simple 2,3-dihydroindolizin-2-one **16** systems.[8] It was also found that compound **19** was unstable under basic conditions for an extended period of time because of the deprotonation of hydrogens adjacent to the carbonyl group. This is also consistent with the literature report that compound **16** is stable in the cold or in ethanol but decomposes rapidly in chloroform or on standing at room temperature. We found that the reaction time of the cyclization step is crucial for an acceptable yield. Installation of a gem-dimethyl, cyclopentane, or cyclohexane group was realized by treating compound **19** with NaOMe and alkyl iodide.[2b] We developed a protocol to combine the cyclization and alkylation steps; thus compound **23** could be generated from compound **18** in one pot (**18** → **23**). Compared to the two-step sequences (**18** → **19** → **23**), the yield decreased slightly, and the reaction is more difficult to monitor by thin-layer chromatography (TLC). The instability of compound **18** under basic conditions might also contribute to the low yield for the alkylation step (**18** → **23**). In addition, as shown in Scheme 5, it was discovered that alkylation on a simpler system, imidazo[1,2-a]pyridin-2-one **21**, proceeded



Scheme 4. Reagents and conditions: (a) α-bromo-acetic acid ethyl ester, 64%; (b) NaOMe, 15%; (c) NaOMe, 2 eq. RI, 25–50%; (d) $Pd(PPh_3)_4$, $ArB(OH)_2$, K_2CO_3. 58%–80%.



Scheme 5.

with higher yield (65%) to generate compound **22**. This indicates that the chemical property of bromide **19** is similar to that of vinyl bromide, which is less stable than aromatic bromide under basic conditions.

Finally, a Suzuki coupling reaction provided the target compounds **24**, **25**, and **26** (see Table 1 for yield). In the literature, there are only limited examples of Suzuki coupling reactions involving bromoenamines.[9] It is well established that oxidative addition is often the rate-determining step in the catalytic cycle of a Suzuki reaction.[10] Aryl and 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with electron-donating groups. The reported enamine is connected with an electron-withdrawing CF_3,[9] which should activate the halide. Consistent with the chemical property of bromide **19**, because of the sp^3 configuration of the nitrogen atom in the six-membered ring, compound **23** is chemically eqivalent to a bromoenamine connected with an acetamide via a carbon–carbon double bond. So, the reactivity of **23** should be similar as the reported bromoenamine.[9] As a result, both deactivated boronic acids (precursors for **24c**, **26c**) bearing electron-donating groups and activated boronic acids (precursors for **24a**, **24b**, **24d**, **24e**, **24f**,

Table 1. Synthesis of 6-aryl 3,3-gem-dimethyl or spiral imidazopyridinones **30**, **31**, and **32**

Comp	R, R	Ar	Yield (%)
24a	Dimethyl	3-Cl-phenyl	67
24b	Dimethyl	3-CF_3-phenyl	73
24c	Dimethyl	3-MeO-phenyl	54
24d	Dimethyl	3-F-phenyl	72
24e	Dimethyl	2,4-di-F-phenyl	65
24f	Dimethyl	3,5-di-CF_3-phenyl	75
24g	Dimethyl	3,5-di-F-phenyl	73
25a	Spirocyclopentane	3-Cl-phenyl	60
25b	Spirocyclopentane	3-F-phenyl	58
25c	Spirocyclopentane	3, 4-di-Cl-phenyl	58
25d	Spirocyclopentane	3,5-di-CF_3-phenyl	80
26a	Spirocyclohexane	3-Cl-phenyl	71
26b	Spirocyclohexane	3-CF_3-phenyl	65
26c	Spirocyclohexane	3-MeO-phenyl	67

24g, etc.) bearing electron-withdrawing groups gave good yields of coupling products in the Suzuki reaction within a similar amount of reaction time. It is known that a very wide range of palladium(0) catalysts, such as $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2/PPh_3$, can be used for Suzuki reactions. $Pd(PPh_3)_4$ is chosen because of its stability to air and ease of handling. Inorganic bases, such as K_2CO_3, K_3PO_4, KOH, or NaO*t*Bu, are necessary for the Suzuki reaction, in order to accelerate the transmetalation of aryl group from boron to palladium by quaternizing the boron with negatively charged anion from bases. The most commonly used base, K_2CO_3, was employed here. In Table 1, the yields for the Suzuki coupling reaction are slightly lower than what was reported by the literature [89–96%, $Pd(PPh_3)_4$, NaOH/benzene].[9]

In summary, a novel series of dialkylated imidazopyridinone compounds were prepared by cyclization reaction under basic conditions, followed by anionic alkylation to provide the C3 substitution, and then by Suzuki coupling reaction to install the C6 aromatic ring. These compounds only showed weak activities as progesterone receptor antagonists. Future work to utilize this methodology to access other substituted imidazopyridinones, aiming at improving the biological activities, is in progress.

EXPERIMENTAL

General Information for Chemistry

NMR spectra were obtained at 400 MHz and 300 MHz on Brucker Avance 300 and Avance 400 spectrometers. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Thin-layer chromatography (TLC) was carried out using 2.5 × 7.5-cm silica gel 60 (250-μM-layer) plates with UV detection. Magnesium sulfate was employed to dry organic extracts prior to concentration by rotary evaporation. Flash chromatography was done using EM science silical gel 60 (230–400 mesh). Standard solvents from J. T. Baker were used as received. Anhydrous solvents from J. T. Baker or Aldrich and all other commercially available reagents were used without further purification. Mass spectra were obtained on a Hewlett-Packard 5989A quadrupole mass spectrometer. Silica gel (E. Merck, 230–400 mesh) was used for all flash chromatography. TLC was performed on Analtech silica-gel GF prescored plates (250 μm). High pressure liquid chromatograph (HPLC) analysis was carried out on Agilent 1100 Series LC/MSD equipment.

2-Amino-5-bromo-1-ethoxycarbonylmethyl-pyridinium Bromide (18)

2-Amino-5-bromopyridine (10.88 g, 62.9 mmol) was dissolved in acetone (65 mL). Ethyl bromoacetate (7.7 mL, 69.2 mmol) to this solution was added. The solution was heated to reflux overnight under nitrogen. The

reaction mixture was cooled, and an off-white solid was obtained by filtration. The solid was washed with acetone, then dried to provide the title compound as an off-white solid (13.74 g, 64%). ^{1}H NMR (DMSO-d_6) δ 8.91 (s, 2H), 8.42 (d, $J = 2.2$ Hz, 1H), 8.09 (dd, $J = 2.2$ and 9.5 Hz, 1H), 7.10 (d, $J = 9.5$ Hz, 1H), 5.11 (s, 2H), 4.21 (q, $J = 7.1$ and 14.2, 2H), 1.26 (t, $J = 7.1$, 3H); MS (m/e): 259 (MH^+).

6-Bromo-imidazo[1,2-a]pyridin-2-one (19)

To a solution of 2-amino-5-bromo-1-ethoxycarbonylmethyl-pyridinium bromide **18** (0.11 g, 0.323 mmol) in methanol (2 mL), sodium methoxide (25 wt%, 0.090 g, 0.417 mmol) was added. The reaction mixture was stirred at room temperature under nitrogen. The process was closely monitored by HPLC-MS. As soon as HPLC showed no more product was formed, the reaction mixture was immediately quenched with water and then extracted three times with ethyl acetate. The organic extracts were washed with brine, dried, filtered, and evaporated to yield a tan solid. The crude material was purified by column chromatography, eluting with 3–10% methanol/dichloromethane, to afford the product as a brown solid (12 mg, 15%). ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.67 (dd, $J = 1.6$, 9.5 Hz, 1H), 7.07 (d, $J = 9.5$ Hz, 1H), 4.52 (s, 2H); MS (m/e): 215 (MH^+); HRMS: calcd. MH^+ for $C_7H_5BrN_2O$ 212.9672; found 212.9664.

6-Bromo-3,3-dimethyl-imidazo[1,2-a]pyridin-2-one (23a)

A solution of 2-amino-5-bromo-1-ethoxycarbonylmethyl-pyridinium bromide **18** (6.11 g, 17.97 mmol) in 100 mL of ethanol was prepared, followed by the addition of sodium ethoxide (21 wt%, 20.5 mL, 54.9 mmol). After 1 h, iodomethane was added (2.3 mL, 37.7 mmol), and the reaction was stirred at room temperature overnight. The solvent was evaporated, and the residue was taken up in dichloromethane. The mixture was filtered, and the filtrate was concentrated and purified by column chromatography, eluting with 5% methanol/dichloromethane. The product was obtained as a tan solid (1.07 g, 25%). ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.67 (dd, $J = 1.8$ and 9.4 Hz, 1H), 7.13 (d, $J = 9.4$ Hz, 1H), 1.59 (s, 6H); MS (m/e): 241 (MH^+); HRMS: calcd. MH^+ for $C_9H_9BrN_2O$ 240.9976; found 240.9979.

6-Bromo-3,3-spiro[cyclopentane]-imidazo[1,2-a]pyridin-2-one (23b)

6-Bromo-imidazo[1,2-a]pyridin-2-one **19** (0.211 g, 1.0 mmol), NaOMe (25% in MeOH, 0.26 g, 1.2 mmol), was stirred in MeOH (5.0 mL). 1,4-Diiodobutane (0.310 g, 1.0 mmol) was added slowly. This was stirred at ambient

temperature for 16 h. The reaction mixture was diluted with water and then extracted three times with ethyl acetate. The organic extracts were washed with brine, dried, filtered, and evaporated to yield a tan solid. The crude material was purified by column chromatography, eluting with 5% methanol/dichloromethane, to afford a white solid (20 mg, 20%). Several runs with different scales were carried out, and the best yield was 50%. Mp 192.0–193.0°C (decomp.); ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.62 (d, $J = 12.0$ Hz, 1H), 7.04 (d, $J = 12.0$ Hz, 1H), 2.52–1.83 (m, 8H); MS (m/e): 267(MH^+); HRMS: calcd. MH^+ for $C_{11}H_{11}BrN_2O$ 267.0133; found 267.0125.

6-Bromo-3,3-spiro[cyclohexane]-imidazo[1,2-a]pyridin-2-one (23c)

A solution of 2-amino-5-bromo-1-ethoxycarbonylmethyl-pyridinium bromide **18** (4.66 g, 13.70 mmol) in 80 mL of ethanol was prepared followed by sodium ethoxide (21 wt%, 15.4 mL, 41.11 mmol). After 1 h, 1,5-diiodopentane was added (2.2 mL, 15.07 mmol), and the reaction was allowed to proceed overnight. The reaction mixture was diluted with water and then extracted three times with ethyl acetate. The organic extracts were washed with brine, dried, filtered, and evaporated to yield a tan solid. The crude material was purified by column chromatography, eluting with 5% methanol/dichloromethane, to afford an orange solid (1.15 g, 30%). ^{1}H NMR ($CDCl_3$) δ 7.73 (d, $J = 1.8$ Hz, 1H), 7.63 (dd, $J = 2.2$ and 9.4 Hz, 1H), 7.07 (d, $J = 9.0$ Hz, 1H), 2.35–2.24 (m, 2H), 2.01–1.96 (m, 2H), 1.88–1.81 (m, 1H), 1.75–1.64 (m, 4H), 1.46–1.37 (s, 1H); MS (m/e): 281(MH^+); HRMS: calcd. MH^+ for $C_{12}H_{13}BrN_2O$ 281.0289; found 281.0292.

6-(3-Chloro-phenyl)-3,3-dimethyl-imidazo[1,2-*a*]pyridin-2-one (24a)

To a round-bottom flask, 6-bromo-3,3-dimethyl-imidazo[1,2-*a*]pyridin-2-one **23a** (60 mg, 0.25 mmol), 3-chlorophenylboronic acid (39 mg, 0.25 mmol), potassium carbonate (69 mg, 0.25 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), dioxane (5 mL), and water (1 mL) were added. The mixture was heated at reflux until the starting material was consumed. The solution was cooled, and water was added. The reaction mixture was extracted twice with ethyl acetate, and the combined organic layers were dried, filtered, and concentrated. The residue was purified by column chromatography, eluting with 5% methanol/dichloromethane, to provide the desired product as an off-white solid (43 mg, 63%). Mp 191.0–192.0°C; ^{1}H NMR ($CDCl_3$) δ7.84 (dd, $J = 1.8$ and 9.1 Hz, 1H), 7.74 (s, 1H), 7.46–7.27 (m, 5H), 1.64 (s, 6H); MS (m/e): 273 (MH^+); HRMS: calcd. MH^+ for $C_{15}H_{13}ClN_2O$ 273.0794; found 273.0800.

3,3-Dimethyl-6-(3-trifluoromethyl-phenyl)-imidazo[1,2-*a*]pyridin-2-one (24b)

The title product was prepared in 73% yield as an off-white solid according to the procedure described for compound **24a**, using 6-bromo-3,3-dimethyl-imidazo[1,2-a]pyridin-2-one **23a** and 3-trifluoromethylphenyl boronic acid as starting material. ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.76 (s, $J = 1.5$ Hz, 1H), 7.70–7.61 (m, 4H), 7.30 (d, $J = 9.2$, 1H), 1.65 (s, 6H); MS (m/e): 307 (MH^+); HRMS: calcd. MH^+ for $C_{16}H_{13}F_3N_2O$ 307.1058; found 307.1052.

6-(3-Methoxy-phenyl)-3,3-dimethyl-imidazo[1,2-a]pyridin-2-one (24c)

The title compound was prepared in 54% yield according to the procedure described for compound **24a**, starting from **23a** and 3-methoxyphenyl boronic acid. ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.73 (d, $J = 1.5$ Hz, 1H), 7.43–7.39 (m, 1H), 7.28–7.25 (m, 1H), 7.05 (m, 1H), 6.97–6.94 (m, 2H), 3.88 (s, 3H), 1.63 (s, 6H); MS (m/e): 269 (MH^+); HRMS: calcd. MH^+ for $C_{16}H_{16}N_2O_2$ 269.1290; found 269.1296.

6-(3-Fluoro-phenyl)-3,3-dimethyl-imidazo[1,2-a]pyridin-2-one (24d)

The title compound was prepared in 72% yield according to the procedure described for compound **24a**, starting from **23a** and 3-fluorophenyl boronic acid. Mp 183.0–184.0°C; ^{1}H NMR ($CDCl_3$) δ 7.84 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.75 (d, $J = 1.6$ Hz, 1H), 7.49–7.43 (m, 1H), 7.29–7.24 (m, 2H), 7.19–7.10 (m, 2H), 1.64 (m, 6H); MS (m/e): 257 (MH^+); HRMS: calcd. MH^+ for $C_{15}H_{13}FN_2O$ 257.1090; found 257.1084.

6-(2,4-Difluoro-phenyl)-3,3-dimethyl-imidazo[1,2-*a*]pyridin-2-one (24e)

The title product was prepared in 65% yield as a white solid according to the procedure described for compound **24a**, using **23a** and 2,4-di-fluorophenyl boronic acid as starting material. Mp 200.0–201.0°C; ^{1}H NMR ($CDCl_3$) δ 7.78–7.74 (m, 2H), 7.37 (m, 1H), 7.28–7.26 (m, 1H), 7.05–6.95 (m, 2H), 1.62 (s, 6H); MS (m/e): 275 (MH^+); HRMS: calcd. MH^+ for $C_{15}H_{12}FN_2O$ 275.0996; found 275.1008.

6-(3,5-Bis-trifluoromethyl-phenyl)-3,3-dimethyl-imidazo[1,2-a]pyridin-2-one (24f)

The title compound was prepared in 75% yield according to the procedure described for compound **24a**, starting from **23a** and 3,5-di-trifluoromethylphenyl boronic acid. Mp 229.0–230.0°C; ^{1}H NMR ($CDCl_3$) δ 7.93–7.91 (m, 3H), 7.88–7.86 (m, 2H), 7.33 (dd, $J = 1.8$ and 8.4 Hz, 1H), 1.67 (s, 6H); MS (m/e): 375 (MH^+); HRMS: calcd. MH^+ for $C_{17}H_{12}F_6N_2O$ 375.0932; found 375.0933.

6-(3,5-Difluoro-phenyl)-3,3-dimethyl-imidazo[1,2-*a*]pyridin-2-one (24g)

The title product was prepared in 73% yield as a yellow solid according to the procedure described for compound **24a**, using **23a** and 3,5-difluorophenyl boronic acid as starting material. Mp 182.0–183.0°C; ^{1}H NMR ($CDCl_3$) δ 7.81 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.77 (d, $J = 1.4$ Hz, 1H), 7.29 (d, $J = 0.6$ Hz, 1H), 7.02–6.98 (m, 2H), 6.90–6.84 (m, 1H), 1.64 (s, 6H); MS (m/e): 275(MH^+); HRMS: calcd. MH^+ for $C_{15}H_{12}FN_2O$ 275.0996; found 275.1009.

6-(3-Chloro-phenyl)-3,3-spiro[pentane]-imidazo[1,2-a]pyridin-2-one (25a)

The title compound was prepared in 60% yield according to the procedure described for compound **24a**, starting from 6-bromo-3,3-spiro[cyclopenane]-imidazo[1,2-a]pyridin-2-one **23b** and 3-chlorophenyl boronic acid. Mp 201.0–202.0°C; ^{1}H NMR ($CDCl_3$) δ 7.80 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.73 (d, $J = 1.6$ Hz, 1H), 7.45–7.39 (m, 3H), 7.34–7.31 (m, 1H), 7.25–7.23 (m, 1H), 2.53–2.48 (m, 2H), 2.20–2.16 (m, 2H), 2.05–1.94 (m, 4H); MS (m/e): 299 (MH^+); HRMS: calcd. MH^+ for $C_{17}H_{15}ClN_2O$ 299.0951; found 299.0945.

6-(3-Fluoro-phenyl)-3,3-spiro[pentane]-imidazo[1,2-a]pyridin-2-one (25b)

The title compound was prepared in 58% yield according to the procedure described for compound **24a**, starting from **23b** and 3-fluorophenyl boronic acid. Mp 193.0–194.0°C; ^{1}H NMR ($CDCl_3$) δ 7.81 (dd, $J = 2.0$ and 9.1 Hz, 1H), 7.74 (d, $J = 1.8$ Hz, 1H), 7.49–7.43 (m, 1H), 7.27–7.22 (m, 2H), 7.17–7.10 (m, 2H), 2.54–2.48 (m, 2H), 2.21–2.14 (m, 2H), 2.08–1.94 (m, 4H); MS (m/e): 283 (MH^+); HRMS: calcd. MH^+ for $C_{17}H_{15}FN_2O$ 283.1246; found 283.1242.

6-(3,4-Dichloro-phenyl)-3,3-spiro[pentane]-imidazo[1,2-a]pyridin-2-one (25c)

The title compound was prepared in 58% yield according to the procedure described for compound **24a**, starting from 6-bromo-3,3- spiro[cyclopenane]-imidazo[1,2-a]pyridin-2-one **23b** and 3, 4-dichloro-phenyl boronic acid. Mp 263.0–264.0°C; ^{1}H NMR ($CDCl_3$) δ 7.77 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.72 (m, 1H), 7.57–7.53 (m, 2H), 7.30–7.23 (m, 2H), 2.53–2.47 (m, 2H), 2.21–2.14 (m, 2H), 2.08–1.94 (m, 4H); MS (m/e): 331 (MH^-); HRMS: calcd. MH^+ for $C_{17}H_{14}Cl_2N_2O$ 333.0561; found 333.0569.

6-(3,5-Bis-trifluoromethyl-phenyl)-3,3-spiro[pentane]-imidazo[1,2-a]pyridin-2-one (25d)

The title compound was prepared in 80% yield according to the procedure described for compound **24a**, starting from **23b** and 3,5-bis-trifluoromethyl-phenyl boronic acid. ^{1}H NMR ($CDCl_3$) δ 7.93 (s, 1H), 7.88 (s, 2H), 7.84–7.79 (m, 2H), 7.30–7.28 (m, 1H), 2.54–2.48 (m, 2H), 2.23–2.16 (m, 2H), 2.09–1.97 (m, 4H); MS (m/e): 401 (MH^+); HRMS: calcd. MH^+ for $C_{19}H_{14}F_6N_2O$ 401.1088; found 401.1094.

6-(3-Chloro-phenyl)-3,3-spiro[cyclohexane]-imidazo[1,2-a]pyridin-2-one (26a)

The title compound was prepared in 71% yield according to the procedure described for compound **24a**, starting from 6-bromo-3,3- spiro[cyclohepane]-imidazo[1,2-a]pyridin-2-one **23c** and 3-chloro-phenyl boronic acid. ^{1}H NMR ($CDCl_3$) δ 7.81 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.76 (d, $J = 1.4$, 1H), 7.45–7.33 (m, 3H), 7.25–7.23 (m, 2H), 2.40–2.30 (m, 2H), 2.05–2.00 (m, 2H), 1.91–1.86 (m, 1H), 1.78–1.71 (m, 4H), 1.49–1.42 (m, 1H); MS (m/e): 313 (MH^+); HRMS: calcd. MH^+ for $C_{18}H_{17}ClN_2O$ 313.1108; found 313.1109.

6-(3-Trifluoromethyl-phenyl)-3,3-spiro[cyclohexane]-imidazo[1,2-a]pyridin-2-one (26b)

The title compound was prepared in 65% yield according to the procedure described for compound **24a,** starting from **23c** and 3-trifluoromethyl–phenyl boronic acid. ^{1}H NMR ($CDCl_3$) δ 7.84 (dd, $J = 2.2$ and 9.2 Hz, 1H), 7.78 (d, $J = 1.4$ Hz, 1H), 7.69–7.62 (m, 4H), 7.28–7.25 (m, 1H), 2.39–2.32 (m, 2H), 2.05–2.00 (m, 2H), 1.91–1.86 (m, 1H), 1.80–1.71 (m, 4H), 1.47–1.43 (m, 1H); MS (m/e): 347 (MH^+); HRMS: calcd. MH^+ for $C_{19}H_{17}F_3N_2O$ 347.1371; found 347.1365.

6-(3-Methoxy-phenyl)-3,3-spiro[cyclohexane]-imidazo[1,2-a]pyridin-2-one (26c)

The title compound was prepared in 67% yield according to the procedure described for compound **24a**, starting from **23c** and 3-methoxy-phenyl boronic acid. Mp 187.0–188.0°C; ^{1}H NMR ($CDCl_3$) δ 7.83 (dd, $J = 2.1$ and 9.2 Hz, 1H), 7.77 (d, $J = 1.4$ Hz, 1H), 7.40–7.38 (m, 1H), 7.24–7.22 (m, 1H), 7.04–7.02 (m, 1H), 6.97–6.95 (m, 2H), 3.88 (s, 3H), 2.40–2.30 (m, 2H), 2.05–2.00 (m, 2H), 1.92–1.80 (s, 1H), 1.77–1.68 (m, 4H), 1.50–1.38 (m, 1H); MS (m/e): 309 (MH^+); HRMS: calcd. MH^+ for $C_{19}H_{20}N_2O_2$ 309.1603; found 309.1606.

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