

Article

Synthesis of Pyridoxine-Derived Dimethylpyridinols Fused with Aminooxazole, Aminoimidazole, and Aminopyrrole

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Abstract: Described in this paper are studies on the preparation of three classes of dimethylpyridinols derived from pyridoxine fused with aminooxazole, aminoimidazole, and aminopyrrole. The key feature of this synthetic strategy is the manipulation of hydroxymethyl moiety of C(5)-position of the pyridoxine starting material along with the installation of an amino group at C(6)-position. Efficient and practical synthesis for the oxazole- and imidazole-fused targets was accomplished, while the instability of the pyrrole-fused one was observed.

Keywords: aminobicyclic pyridinols; pyridoxine; oxazole; imidazole; pyrrole



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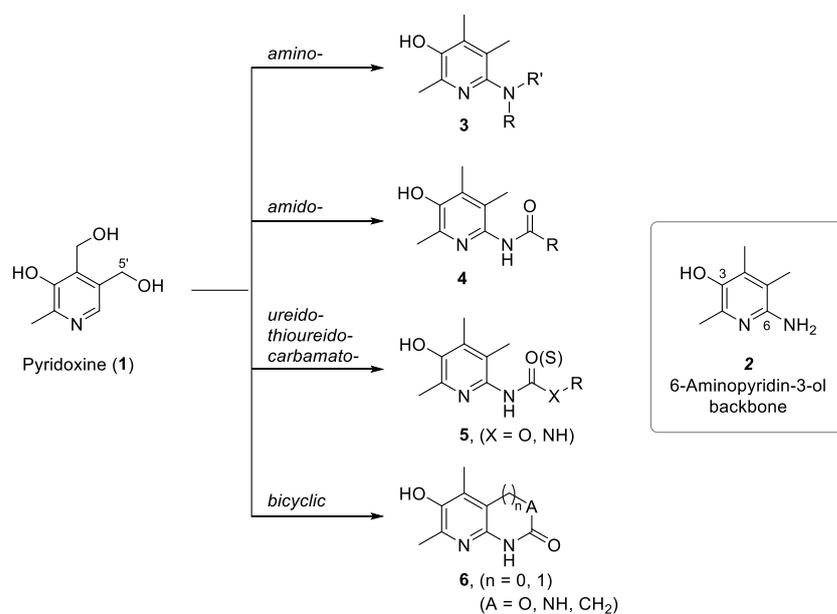
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1. Introduction

Phenotypic screening campaigns have long been crucial to the identification of biologically active small molecules in conjunction with target-based approaches [1,2]. Because of their biological relevancy and favorable physicochemical properties, novel scaffolds from nature are frequently used to inspire the preparation of compound collections for phenotypic screening [3–6]. Pyridoxine (**1**) is a form of vitamin B₆ that scavenges reactive oxygen species and regulates diverse cellular metabolisms, including amino acid biosynthesis and fatty acid biosynthesis (Figure 1) [7–11]. Inspired by pyridoxin (**1**), our group has pursued derivative syntheses along with biological investigations to explore the pharmacological potential of the 6-aminopyridin-3-ol scaffold (**2**). The class of aminopyridinols (**3**) was found to have anti-angiogenic activity, which is linked to cancer and age-related diseases, as well as anti-inflammatory activity against ulcerative colitis. [12,13]. Notably, remarkable anticancer activity was observed in novel structures where the 6-aminopyridin-3-ol core was hybridized with biologically active agents such as α -tocopherol and sunitinib. An α -tocopherol-hybridized compound **10** suppressed lung tumor growth by dual inhibition of NADPH oxidase 2 and receptor tyrosine kinases. A sunitinib-hybridized compound **11** was also discovered as an apoptosis-inducing anticancer agent by controlling the p53 level, with a safer cytotoxicity profile than sunitinib [14]. Therefore, these results showcase that the 6-amino-pyridin-3-ol scaffolds indeed have the potential to provide favorable biological activities and demand further studies to expand the scope of the scaffolds.

Our previous synthetic strategies for lead compound discovery are summarized and illustrated in Figure 1 [12,13,15–22]. Using an amine group of **2** at C(6)-position as a synthetic handle, amidopyridinols **3** and ureido-/thioureido-/carbamate-pyridinols **4** have been synthesized to generate a diverse set of compound collections [23–27]. In addition, heteroatom-containing bicyclic pyridinols **6** were designed and constructed, providing more constrained structures [14,28–33]. As an ongoing project to increase the compound diversity of 6-amino-pyridin-3-ol collections, here we present synthetic studies towards the preparation of three bicyclic pyridinol backbones **12–14** fused with five-membered heteroaromatic ring systems (Scheme 1). Our strategy for the synthesis of pyrrolo- (**12**), imidazo- (**13**), and oxazo- (**14**) features divergent synthesis starting from

pyridoxine, in line with the previous syntheses of pyridinol derivatives [31]. We also envision the introduction of an additional amino functional group on a five-membered ring, which would allow for appendage derivatization in the future. In this work, the hydroxy group at C(5')-position in pyridoxine (**1**) serves as a synthetic tool for the installation of various functionalities, including nitrile, amide, phenolic OH, and anilinic NH₂ in synthetic intermediates.



representative examples:

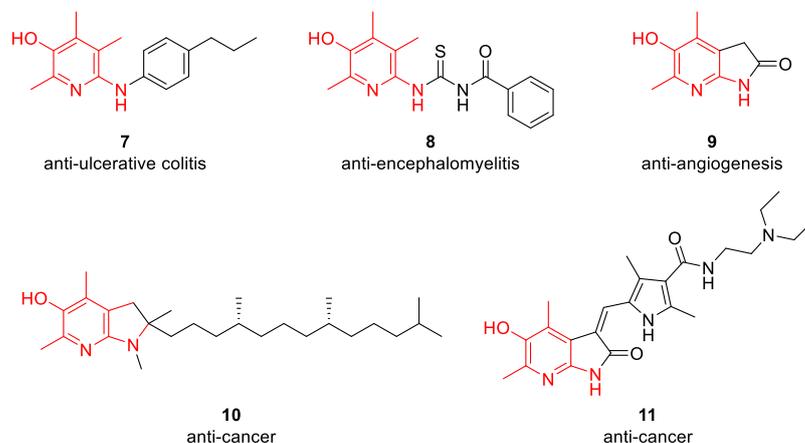
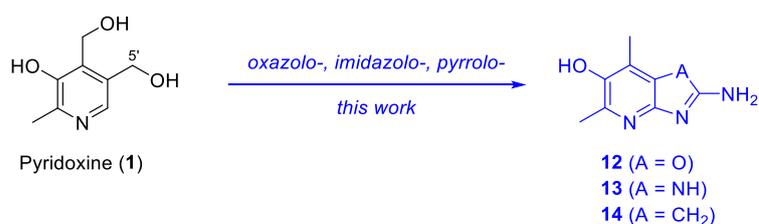


Figure 1. Pyridoxine-derived compounds.

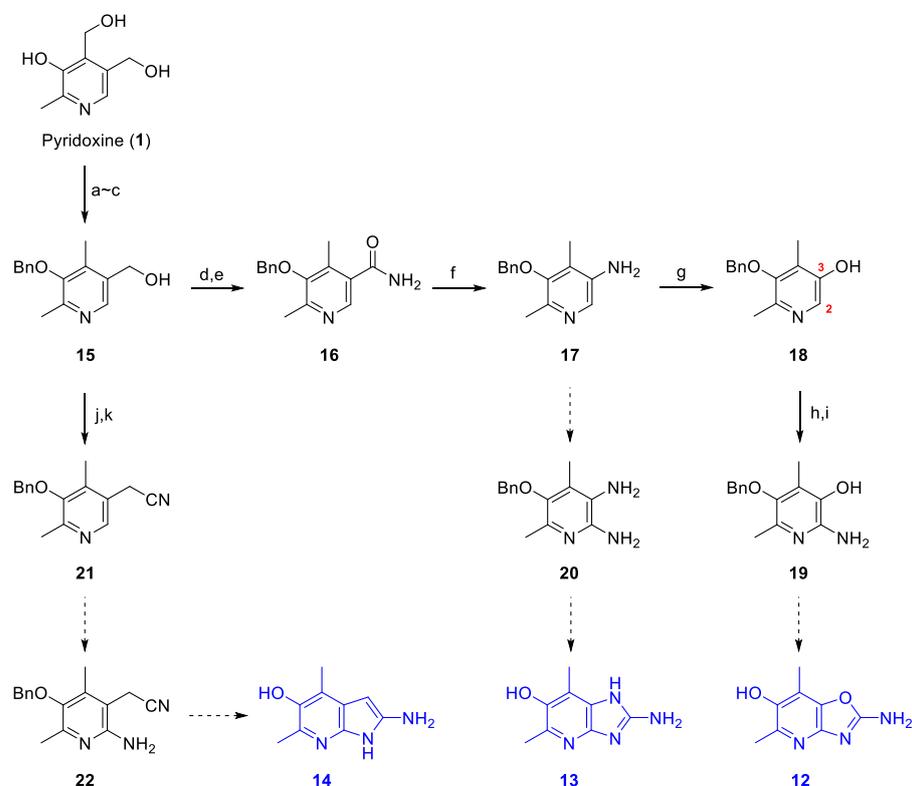


Scheme 1. Pyridoxine-derived five-membered heterocycle-fused pyridinols.

2. Results and Discussion

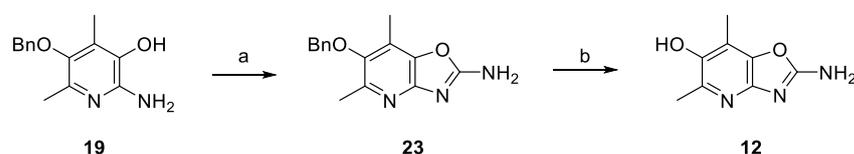
A general outline of the synthetic strategy for the preparation of dimethylpyridinols fused with aminooxazole (**12**), aminoimidazole (**13**), and aminopyrrole (**14**) is shown in

Scheme 2. This began with the preparation of known primary alcohol **15**, which was used as a common intermediate for the syntheses of three final products, according to the three-step sequence starting from pyridoxine (**1**) established by us [10,31].



Scheme 2. A strategy for the divergent synthesis of dimethylpyridinols fused with aminooxazole (**12**), aminoimidazole (**13**), and aminopyrrole (**14**) starting from pyridoxine (**1**). Solid arrows: known methods established by us. Dotted arrow: methods developed in this study. (a) Zn, AcOH, reflux, 12 h, 81%; (b) PhCH₂Br, K₂CO₃, DMF, r.t., 12 h, 91%; (c) K₂CO₃, MeOH, r.t., 0.5 h, 98%; (d) NaOCl, TEMPO, NaHCO₃, CH₂Cl₂-H₂O, r.t., 1 h, 88%; (e) (i) I₂, NH₄OH, THF-H₂O, r.t., 1 h; (ii) H₂O₂, NH₄OH, THF-H₂O, 91%; (f) NaOCl, NaOH, THF-H₂O, r.t., 1 h, 93%; (g) NaNO₂, H₂SO₄, THF-H₂O, 0 °C, 1 h, r.t. 2 h, 86%; (h) PhNH₂, NaNO₂, 6 M HCl, 2.5 M NaOH, THF-H₂O, 0 °C, 1 h then r.t., 2 h, 95%; (i) Zn, AcOH, MeOH, reflux, 1 h, 80%; (j) SOCl₂, DMF, ClCH₂CH₂Cl, reflux, 12 h, 94%; (k) KCN, DMF, 40 °C, 2 d, 82%.

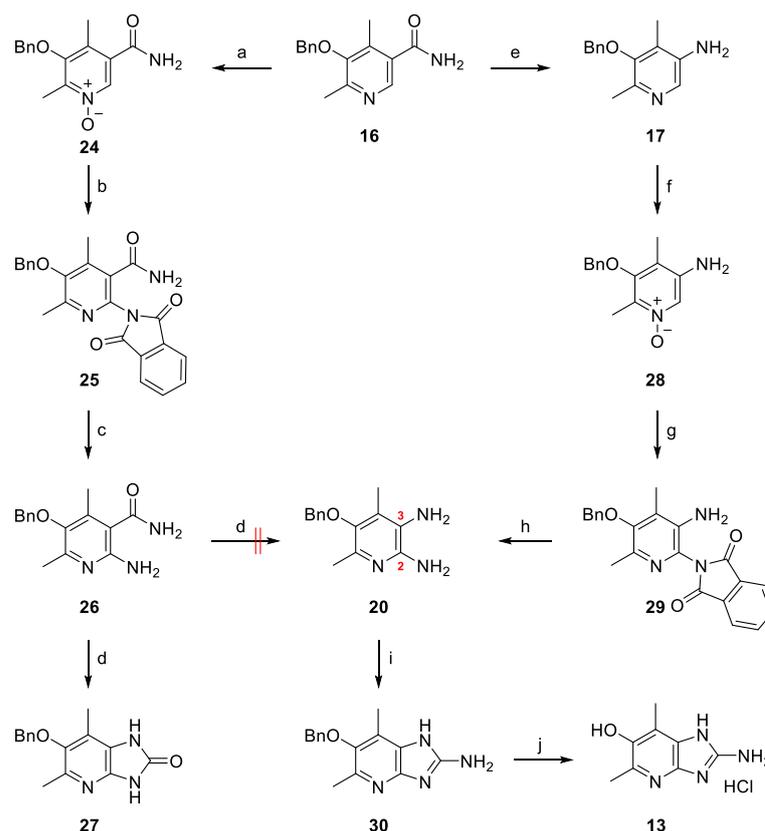
First, for the synthesis of the aminooxazole-containing analogue **12**, the hydroxymethyl moiety of **15** was converted to amine **17** in three steps [31]. The amino group of **17** was replaced by hydroxy group to afford **18** as we previously reported [31]. Then, an amine group was successfully introduced at the C(2)-position of **18** in the presence of free alcohol at the C(3)-position, without additional protection/deprotection steps [31]. The resulting 2-amino-3-hydroxy pyridinol **19** was nicely constructed to test the formation of the aminooxazole moiety. Gratefully, the formation of the aminooxazole ring was accomplished by using cyanogen bromide in almost quantitative yield (compound **23**) [34], which was followed by debenzoylation to afford the first target compound **12** (Scheme 3).



Scheme 3. Synthesis of 2-amino-5,7-dimethyloxazolo[4,5-*b*]pyridine-6-ol (**12**). Reagents and Conditions: (a) BrCN, H₂O, reflux, 15 min, 99%; (b) H₂, Pd/C, MeOH, r.t., 6 h, 99%.

Having observed the successful aminooxazole formation, we applied a similar approach to achieve analogue synthesis, which is the installation of corresponding functional groups followed by cyclization as outlined in Scheme 2. Since aminopyridinol intermediates (15~17) with diverse functionalities were generated during the preparation of aminooxazolopyridinol 12, we envisaged that these intermediates could serve as great branching points for the synthesis of aminoimidazole 13 and aminopyrrole 14.

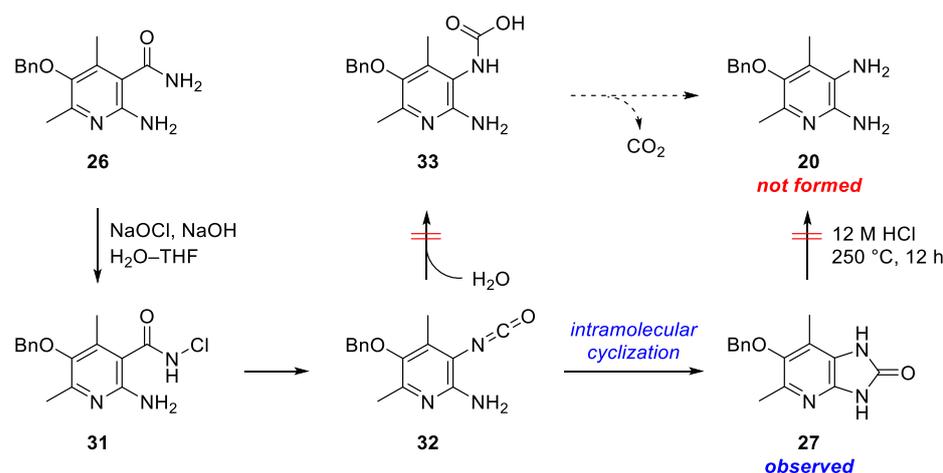
The synthesis of aminoimidazolopyridinol 13 initiated with the preparation of the diamine compound 20 (Scheme 4). We first attempted to introduce an amino group at 2-position of the pyridine ring in the primary amide compound 16 via phthalimidation and subsequent Hofmann rearrangement (the left side of Scheme 4). After *m*-CPBA oxidation of 16 to pyridine *N*-oxide 24, the nucleophilic addition of phthalimide to the *O*-*p*-toluenesulfonylated pyridinium intermediate followed by the elimination of *p*-toluenesulfonic acid afforded 25. Removal of the *N*-phthalyl group in 25 was smoothly proceeded by the treatment of hydrazine to give free amine 26 [31]. The trial for Hofmann rearrangement of the primary amide compound 26 to obtain the diamine compound 20 was performed in a mixed solvent with alkaline water and tetrahydrofuran, employing hypochlorite for activation of the primary amide. However, contrary to our expectations, the desired diamine compound 20 was not produced under the reaction conditions. A cyclic urea compound 27 was instead obtained in a moderate yield (40%).



Scheme 4. Synthesis of 2-amino-5,7-dimethyl-1H-imidazo[4,5-*b*]pyridin-6-ol (13). Reagents and Conditions: (a) *m*-CPBA, CH₂Cl₂, r.t., 1 h, 83%; (b) *p*-TsCl, phthalimide, *i*-Pr₂NEt, r.t., 1 h, 75%; (c) H₂NNH₂·H₂O, THF–EtOH, r.t., 12 h, 84%; (d) NaOCl, NaOH, THF–H₂O, r.t., 1 h, 90 °C, 2 h, 40% (for 27); (e) NaOCl, NaOH, THF–H₂O, r.t., 1 h, 70%; (f) *m*-CPBA, CH₂Cl₂, r.t., 1 h, 65%; (g) *p*-TsCl, phthalimide, *i*-Pr₂NEt, r.t., 1 h, 72%; (h) H₂NNH₂·H₂O, THF–EtOH, r.t., 12 h, 73%; (i) BrCN, H₂O, reflux, 15 min, 85%; (j) BCl₃, CH₂Cl₂, r.t., 12 h, 87%.

A possible route of the formation of imidazolidinone compound 27 is shown in Scheme 5. Once reactive isocyanate intermediate 32 was formed via the rearrangement of *N*-chloroamide intermediate 31, and the amine at 2-position might attack the isocyanate

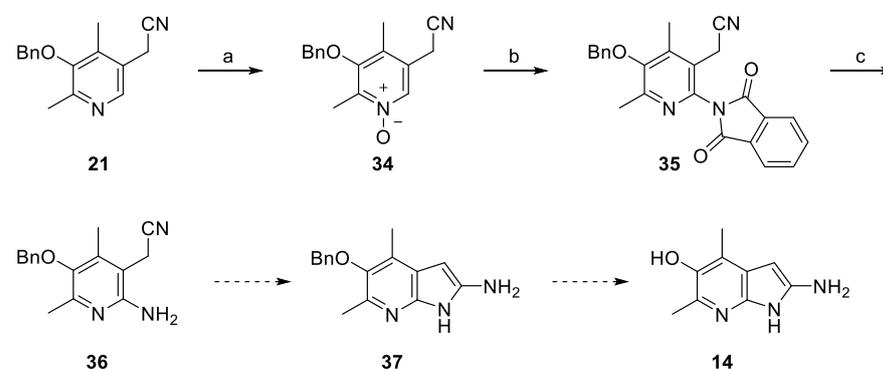
to form a five-membered cyclic urea **27**. Since we experienced such a fact in this trial, we expected that using water as a solvent would increase the probability of transformation of isocyanate intermediate **32** to carbamic acid **33**, which then spontaneously decomposed to the desired diamine **20** with the liberation of carbon dioxide. However, based on the results we observed, the intramolecular cyclization outcompeted the hydroxide (or water) addition to the isocyanate **32**. Several attempts to cleave the urea of compound **27** to obtain the diamine **20** under acidic conditions with high temperatures only gave a debenzylated compound quantitatively instead of the desired product.



Scheme 5. Plausible mechanism for the formation of cyclic urea compound **27**.

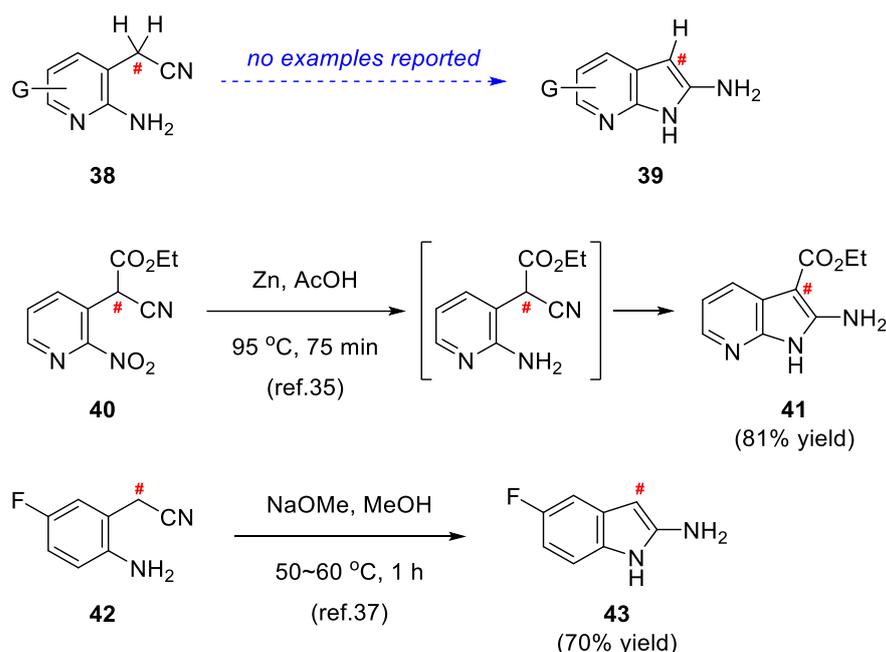
To avoid such a troublesome intramolecular cyclization issue, we decided to change the synthetic sequence. The conversion of the primary amide group at C(3)-position to a free amino group was performed prior to the installation of another free amino group at C(2)-position as depicted on the right side of Scheme 4. Hofmann rearrangement of **16** followed by *N*-oxide formation (**28**) and phthalimide substitution proceeded smoothly to afford **29**, which was then treated with hydrazine to produce the diamine compound **20**. The aminoimidazole backbone of compound **30** was successfully constructed by the treatment of **20** with cyanogen bromide. Finally, the aminoimidazole-fused pyridinol **13** was obtained by debenylation.

Next, we investigated the synthesis of aminopyrrole-containing analog **14** (Scheme 6). The initial attempt includes the substitution of primary alcohol of the common intermediate **15** with nitrile functionality (**21**) [31] and phthalimide of *N*-oxide compound **34**. Reactions proceeded smoothly, generating compound **35**, and phthalimide cleavage using hydrazine successfully furnished the requisite substrate **36** for aminopyrrole formation.



Scheme 6. Synthesis of the substrate **36** for 2-amino-4,6-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-ol (**14**). Reagents and Conditions: (a) *m*-CPBA, CH₂Cl₂, r.t., 1 h, 92%; (b) *p*-TsCl, phthalimide, *i*-Pr₂NEt, r.t., 1 h, 63%; (c) H₂NNH₂·H₂O, THF, EtOH, r.t., 12 h, 67%.

Having installed the 2-amino group together with the nitrile group in **36**, trials were made for the cyclization to form a 2-amino-7-azaindole framework. According to a database search result using the SciFinderⁿ on the transformation of reactants **38** to products **39**, no example has been known in the case of an unsubstituted compound at C(#)-position (Scheme 7). Even if the search range was expanded to cases where there was a substituent other than hydrogen at the C(#)-position, only a couple of examples were found including the synthesis of compound **41** [35,36]. Formation of 2-aminoindoles, such as compound **43**, from C(#)-unsubstituted-2-(2-aminopyridin-3-yl)acetonitrile compounds, such as **42**, was also found to be rare [37,38].

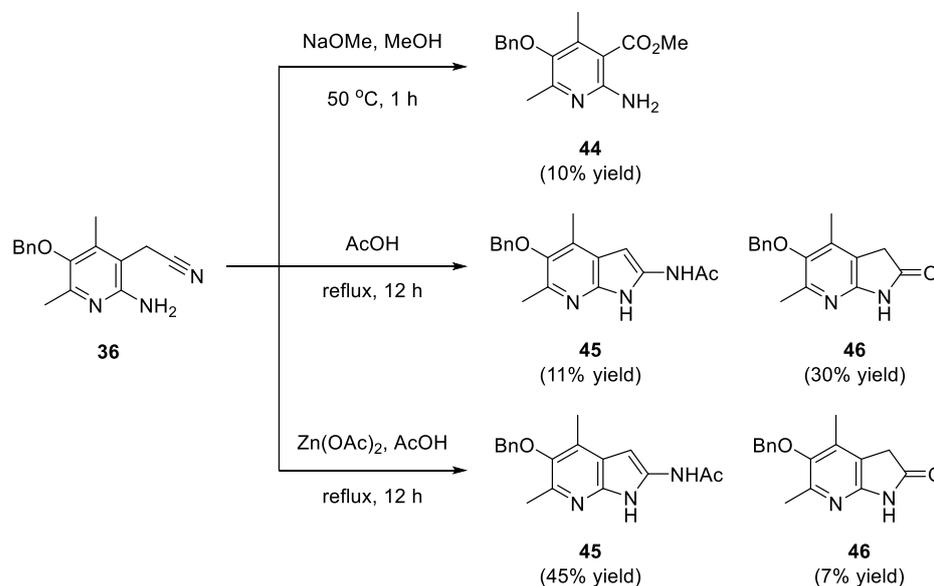


Scheme 7. Database search results using SciFinderⁿ on the formation of aminopyrrole-fused benzenes/pyridines and representative examples. The α -position to nitrile is indicated with “#” sign.

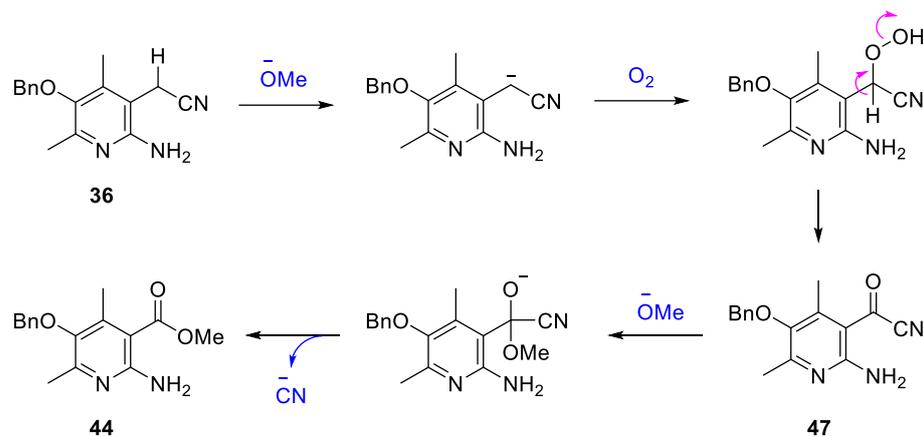
The first trial was done under basic conditions using sodium methoxide, which has been successfully applied in the preparation of 2-aminoindole ring formation (Scheme 8) [37]. Contrary to the literature in which the 2-aminoindole **43** was obtained in 70% yield from **42** (Scheme 7), the reaction of compound **36** under the same reaction conditions was messy, and the desired product **37** was not obtained. It can be presumed that the difference in nucleophilicity between the amine attached to benzene in compound **42** and the amine attached to pyridine in compound **36** might be one of the main reasons for the success or failure of the 2-aminopyrrole cyclization reaction under similar reaction conditions. Interestingly, the formation of a very small amount of a by-product **44** was observed instead. We speculate that this side reaction may have proceeded as follows (Scheme 9). Formation of α -ketonitrile intermediate **47** might have been facilitated by the deprotonation with methoxide at the site adjacent to the nitrile group in **36**, which is also a benzylic position. After the successive aerobic oxidation, the cyano group of **47** might be replaced by methoxide anion affording compound **44**.

To avoid such a deprotonation/oxidation problem, we exposed compound **36** to hot acetic acid. However, the desired 2-amino-7-azaindole compound **37** was not obtained under the acidic conditions either. Instead, its *N*-acetyl compound **44** was obtained, albeit in small quantities, and the formation of a lactam **46** was also observed. Use of an additive like zinc acetate to activate the cyclization improved the formation of compound **44** to some extent. Unlike the other two targets, aminooxazolopyridinol and aminoimidazolopyridinol, which were readily prepared, an aminopyrrolopyridine-containing compound like **37** might be presumed to have quite poor chemical stability. The free amino compound **37**

was not obtained under both basic and acidic reaction conditions, and even the isolated pure *N*-acetylated compound **44** was observed to gradually decompose in solution over time. Naturally, all efforts made for *N*-deacetylation were not fruitful.

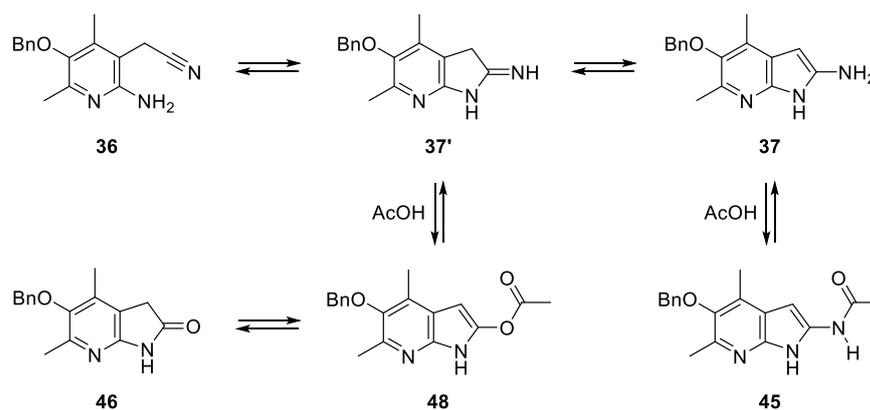


Scheme 8. Attempts on the cyclization towards 2-aminopyrrole.



Scheme 9. Possible mechanism for the formation of compound **44**.

Based on our observations, a possible mechanism for the generation of **45** and **46** was proposed in Scheme 10. The reaction is initiated by intramolecular cyclization of **36** to form a 1,3-dihydro-2*H*-pyrrole-2-imine **37'**, which undergoes tautomerization to yield a 2-aminopyrrole **37**. Under the reflux condition, the electron-rich amino group in **37** further reacts with acetic acid to generate *N*-acetyl adduct **45**. Another pathway involves the nucleophilic addition of acetic acid to the electrophilic imine-carbon in **37'** and the subsequent elimination of ammonia to afford **48**. Acidolysis of the resulting acetate **48** followed by tautomerization provides a lactam **46**. Since high temperature and long reaction time are necessary to make the intramolecular cyclization of **36** happen, the reversible reactions illustrated in Scheme 10 might occur and generate the mixture of **45** and **46**. Unlike our system, compound **40** contains an additional ester group at the C(#)-position (Scheme 7) [35]. This carbonyl functional group may accelerate cyclization/tautomerization events and make the resulting amine of **41** less nucleophilic, preventing the formation of an *N*-acetyl adduct of **41**.



Scheme 10. Possible mechanism for the formation of compounds 45 and 46.

3. Materials and Methods

3.1. General

Unless otherwise specified, all the materials obtained from Merck (Kenilworth, NJ, USA), TCI (Tokyo, Japan), and Alfa Aesar (Ward Hill, MA, USA) were used without further purification. Inert gas conditions were applied to the sensitive reactions towards air and moisture. The progress of the reactions was traced by TLC analysis using silica gel 60 F₂₅₄ plates (Merck, Kenilworth, NJ, USA). Visualization of the TLC spots was done using a UV lamp (254 nm, Spectroline Corp., Westbury, NY, USA) and staining solutions (Anisaldehyde solution and KMnO₄ solution) prepared by us using commercially available reagents. Products were purified by flash column chromatography using silica gel 60 (70–230 mesh, Merck, Kenilworth, NJ, USA) or by using the Biotage ‘Isolera One’ (Biotage, Uppsala, Sweden) system with indicated solvents. Melting points were determined using a Büchi melting point B-540 apparatus (Büchi Labortechnik, Flawil, Switzerland) and were unchanged. ¹H and ¹³C NMR spectra were obtained using a Bruker-250 spectrometer (¹H and ¹³C frequencies were 250 and 63 MHz, respectively, Bruker Corp., Billerica, MA, USA), and a Bruker Avance Neo 400 spectrometer (¹H and ¹³C frequencies were 400 and 100 MHz, respectively, Bruker Corp., Billerica, MA, USA). ¹H and ¹³C NMR spectra of all synthesized molecules are available in the Supplementary Materials (Figures S1–S26). Chemical shifts (δ) were expressed in ppm calibrated to residual solvent signals and the coupling constant (J) in hertz. HR-ESIMS was performed using a Thermo Scientific Q Exactive hybrid Quadrupole-Orbitrap mass spectrometer (Waltham, MA, USA) coupled to a Thermo Scientific Vanquish UHPLC system (Waltham, MA, USA) at the Core Research Support Center for Natural Products and Medical Materials (CRCNM).

3.2. 6-(Benzyloxy)-5,7-dimethyloxazolo[4,5-b]pyridin-2-amine (23)

To a solution of cyanogen bromide (30 mg, 0.12 mmol) in H₂O (2 mL), we added Compound 19 (13 mg, 0.13 mmol). The resulting mixture was refluxed for 15 min. On completion of reaction, the reaction mixture was cooled to room temperature and neutralized using NaHCO₃. The solids precipitated out were filtered and washed using CHCl₃. The organic phase was dried over MgSO₄, filtered, and concentrated to give 23 (33 mg, 99%) as a white solid. R_f 0.36 (CHCl₃:MeOH = 15:1); m.p. 153 °C; ¹H NMR (DMSO-*d*₆) δ 7.69 (s, 2H), 7.51–7.32 (m, 6H), 4.81 (s, 2H), 2.37 (s, 3H), 2.27 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ 164.6, 152.7, 145.6, 145.0, 138.2, 137.1, 128.4 (2C), 128.2 (2C), 128.1, 120.5, 74.7, 19.2, 9.5; HRMS (ESI) *m/z* [M+H]⁺ calculated for C₁₅H₁₆N₃O₂ 270.1237, found 270.1235.

3.3. 2-Amino-5,7-dimethyloxazolo[4,5-b]pyridin-6-ol (12)

To a solution of compound 23 (28 mg, 0.10 mmol) in MeOH (3 mL), we added 10% palladium on activated carbon (5 mg). The mixture was stirred under hydrogen atmosphere at room temperature for 6 h. The mixture was filtered through celite pad and the filtrate was concentrated to give 12 (18 mg, 99%) as a white solid. R_f 0.32 (CHCl₃:MeOH = 7:1);

m.p. 282 °C; ^1H NMR (DMSO- d_6) δ 8.25 (br s, 1H), 7.43 (s, 2H), 2.32 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 163.4, 149.5, 143.6, 139.8, 138.4, 115.8, 19.6, 9.5; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calculated for $\text{C}_8\text{H}_{10}\text{N}_3\text{O}_2$ 180.0768, found 180.0767.

3.4. 6-Benzoyloxy-5,7-dimethyl-1H-imidazo[4,5-b]pyridin-2(3H)-one (27)

To a solution of NaOH (100 mg, 0.37 mmol) in THF–H₂O (1:1, 8 mL), we added 4% aqueous NaOCl (2 mL) and **26** (45 mg, 1.10 mmol). The mixture was stirred at room temperature for 1 h and then at 90 °C for 2 h. The mixture was cooled to room temperature and diluted with CH₂Cl₂. The organic layer was neutralized with saturated aqueous NH₄Cl solution, and the aqueous layer was extracted with CH₂Cl₂. The combined organic solution was washed with brine, dried over MgSO₄, and concentrated to give **27** (39 mg, 40%) as a white solid. R_f 0.40 (CHCl₃:MeOH = 10:1); m.p. 295 °C; ^1H NMR (DMSO- d_6) δ 11.0 (br s, 1H), 7.50–7.36 (m, 4H), 4.77 (s, 2H), 2.33 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (DMSO- d_6) δ 155.3, 146.5, 140.9, 139.8, 137.3, 128.4 (2C), 128.2 (2C), 128.1, 121.9, 120.3, 74.5, 18.8, 10.6; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_2$ 270.1237, found 270.1243.

3.5. 5-Amino-3-(benzyloxy)-2,4-dimethylpyridine 1-oxide (28)

To a solution of compound **17** (100 mg, 0.44 mmol) in CH₂Cl₂ (3 mL), we added *m*-CPBA (84 mg, 0.49 mmol). The mixture was stirred at room temperature for 1 h and was diluted with CH₂Cl₂. The organic layer was successively washed with saturated aqueous NaHCO₃ solution and brine. The resulting organic solution was then dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂:MeOH = 15:1) to give **28** (66 mg, 62%) as a white solid. R_f 0.25 (CHCl₃:MeOH = 15:1); m.p. 164 °C; MS m/z 245 $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl₃) δ 7.80 (s, 1H), 7.51–7.35 (m, 5H), 4.75 (s, 2H), 4.06 (br s, 2H), 2.36 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (CDCl₃) δ 153.2, 141.7, 136.1, 134.6, 128.8 (2C), 128.6, 128.2 (2C), 123.2, 117.9, 75.8, 11.3, 9.9; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_2$ 245.1285, found 245.1282.

3.6. 2-(3-Amino-5-(benzyloxy)-4,6-dimethylpyridin-2-yl)isoindoline-1,3-dione (29)

To a solution of compound **28** (66 mg, 0.27 mmol) in anhydrous CH₂Cl₂ (15 mL), we added phthalimide (40 mg, 0.27 mmol), *N,N*-diisopropylethylamine (0.15 mL, 0.81 mmol), and *p*-tosyl chloride (77 mg, 0.41 mmol). The mixture was stirred under argon atmosphere at room temperature for 1 h. The mixture was diluted with CH₂Cl₂, and the organic phase was washed with H₂O. The organic solution was dried over MgSO₄, filtered, and concentrated. The residual solid was filtered and washed with Et₂O to give **29** (73 mg, 72%) as a white solid. R_f 0.41 (CHCl₃:MeOH = 20:1); m.p. 156 °C; ^1H NMR (CDCl₃) δ 7.93 (dd, J = 5.2, 2.9 Hz, 2H), 7.85–7.69 (m, 2H), 7.56–7.33 (m, 5H), 4.84 (s, 2H), 3.60 (br s, 2H), 2.46 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (CDCl₃) δ 167.4 (2C), 153.0, 142.3, 138.2, 136.9, 134.6 (2C), 132.3 (2C), 128.8 (2C), 128.4, 128.0 (2C), 127.5, 126.7, 124.0 (2C), 75.1, 19.0, 10.8; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_3$ 374.1499, found 374.1494.

3.7. 5-(Benzyloxy)-4,6-dimethylpyridine-2,3-diamine (20)

To a solution of compound **29** (143 mg, 0.38 mmol) in THF–EtOH (1:1, 4 mL) we added hydrazine (1.0 mL). The mixture was stirred at room temperature for 12 h, and the solvent was evaporated. The residue was diluted with Et₂O, and the insoluble solids were filtered off. The filtrate was diluted with CH₂Cl₂ and washed with H₂O. The organic solution was dried over MgSO₄, filtered, and concentrated to give **20** (68 mg, 73%) as a brown solid. R_f 0.22 (CHCl₃:MeOH = 20:1); m.p. 129 °C; ^1H NMR (CDCl₃) δ 7.50–7.30 (m, 5H), 4.72 (s, 2H), 4.08 (br s, 2H), 3.26 (br s, 2H), 2.33 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (CDCl₃) δ 145.8, 144.0, 138.7, 137.4, 128.7 (2C), 128.2, 128.1 (2C), 126.3, 125.6, 75.4, 18.5, 10.4; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}$ 244.1444, found 244.1442.

3.8. 6-(Benzyloxy)-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-2-amine (30)

To a solution of cyanogen bromide (57 mg, 0.53 mmol) in H₂O (2 mL) we added compound **20** (130 mg, 0.53 mmol) in H₂O (4 mL). The reaction mixture was refluxed for 12 h. The mixture was cooled to room temperature, and the solids precipitated out were filtered and recovered using CHCl₃. The organic solution was dried over MgSO₄ and concentrated to give **30** (129 mg, 85%) as a beige solid. R_f 0.24 (CHCl₃:MeOH = 9:1); ¹H NMR (DMSO-*d*₆) δ 7.53–7.47 (m, 2H), 7.45–7.33 (m, 3H), 6.31 (s, 2H), 4.77 (s, 2H), 2.37 (s, 3H), 2.29 (s, 3H); ¹³C NMR (DMSO-*d*₆) δ 156.1, 145.9, 140.0, 137.6, 128.4 (2C), 128.1 (2C), 127.9, 74.5, 19.1, 10.6; HRMS (ESI) *m/z* [M+H]⁺ calculated for C₁₅H₁₇N₄O 269.1397, found 269.1393.

3.9. 2-Amino-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-6-ol hydrochloride (13)

To a suspension of compound **30** (20 mg, 0.075 mmol) in CH₂Cl₂ (3 mL), we added 1 M BCl₃ in CH₂Cl₂ (0.75 mL) at 0 °C. After the mixture was stirred overnight, a mixed solvent of CHCl₃:MeOH (9:1) was added. The resulting solution was concentrated to give **13** (14 mg, 87%) as a white solid. R_f 0.20 (CHCl₃:MeOH = 5:1); ¹H NMR (CD₃OD) δ 2.60 (s, 3H), 2.53 (s, 3H); ¹³C NMR (CD₃OD) δ 155.3, 148.2, 136.4, 134.8, 128.9, 127.4, 15.6, 12.0; HRMS (ESI) *m/z* [M+H–Cl]⁺ calculated for C₈H₁₁N₄O 179.0927, found 179.0927.

3.10. 3-(Benzyloxy)-5-(cyanomethyl)-2,4-dimethylpyridine 1-oxide (34)

To a solution of compound **21** (100 mg, 0.40 mmol) in CH₂Cl₂ (5 mL), we added *m*-CPBA (75 mg, 0.44 mmol), and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ solution and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (CH₂Cl₂:MeOH = 25:1) to give **34** (98 mg, 92%) as a white solid. R_f 0.28 (CHCl₃:EtOAc = 20:1); m.p. 144 °C; ¹H NMR (CDCl₃) δ 8.21 (s, 1H), 7.45–7.35 (m, 5H), 4.83 (s, 2H), 3.60 (s, 2H), 2.47 (s, 4H), 2.21 (s, 3H); ¹³C NMR (CDCl₃) δ 153.8, 145.3, 135.5, 135.3, 129.9, 129.0, 128.9 (2C), 128.3 (2C), 125.2, 115.6, 76.2, 19.6, 12.1, 12.1; HRMS (ESI) *m/z* [M+H]⁺ calculated for C₁₆H₁₇N₂O₂ 269.1285, found 269.1282.

3.11. 2-(5-(Benzyloxy)-2-(1,3-dioxoisindolin-2-yl)-4,6-dimethylpyridin-3-yl)acetonitrile (35)

To a solution of compound **34** (72 mg, 0.27 mmol) in anhydrous CH₂Cl₂ (5 mL), we added phthalimide (42 mg, 0.29 mmol) and *p*-tosyl chloride (82 mg, 0.43 mmol). After the reaction mixture became a clear solution, *N,N*-diisopropylethylamine (0.15 mL, 0.85 mmol) was added and the resulting mixture was stirred under argon atmosphere at room temperature for 1 h. The mixture was diluted with CH₂Cl₂ and washed with H₂O. The organic solution was dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel column chromatography (Hexanes:EtOAc = 5:1) to give **35** (67 mg, 63%) as a white solid. R_f 0.25 (Hexanes:EtOAc = 1:1); m.p. 171 °C; ¹H NMR (CDCl₃) δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.51–7.37 (m, 5H), 4.88 (s, 2H), 3.61 (s, 2H), 2.55 (s, 3H), 2.41 (s, 3H); ¹³C NMR (CDCl₃) δ 167.0 (2C), 153.6, 152.9, 142.0, 139.3, 136.2, 134.8 (2C), 132.0 (2C), 128.8 (2C), 128.6, 128.0 (2C), 124.2 (2C), 123.3, 115.8, 75.2, 19.7, 17.5, 13.2; HRMS (ESI) *m/z* [M+H]⁺ calculated for C₂₄H₂₀N₃O₃ 398.1499, found 398.1497.

3.12. 2-(2-Amino-5-(benzyloxy)-4,6-dimethylpyridin-3-yl)acetonitrile (36)

To a solution of compound **35** (265 mg, 0.67 mmol) in THF–EtOH (1:1, 2 mL), we added 60% hydrazine hydrate (2 mL). The reaction mixture was stirred at room temperature for 12 h and concentrated. The residue was diluted with Et₂O, and the insoluble solids were filtered off. The filtrate was diluted with CH₂Cl₂ and was washed with H₂O. The organic solution was dried over MgSO₄, filtered, and concentrated to give **36** (119 mg, 67%) as a white solid. R_f 0.25 (CHCl₃:MeOH = 15:1); m.p. 189 °C; ¹H NMR (CDCl₃) δ 7.45–7.36 (m, 5H), 4.73 (s, 2H), 4.36 (br s, 2H), 3.52 (s, 2H), 2.39 (s, 3H), 2.24 (s, 3H); ¹³C NMR (CDCl₃)

δ 152.1, 150.4, 145.8, 140.9, 136.9, 128.8 (2C), 128.4, 128.1 (2C), 116.6, 107.0, 75.5, 19.3, 16.4, 12.9; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{16}H_{18}N_3O$ 268.1444, found 268.1440.

3.13. Methyl 2-amino-5-(benzyloxy)-4,6-dimethylnicotinate (44)

To a solution of compound **36** (30 mg, 0.11 mmol) in MeOH (3 mL), we added 25% NaOMe in MeOH (0.25 mL, 1.1 mmol). The mixture was stirred at 50 °C for 1 h under argon atmosphere and cooled to room temperature. The mixture was poured into water and extracted with EtOAc. The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (Hexanes:EtOAc = 1:1) to give **44** (3 mg, 10%) as a white solid. R_f 0.30 ($CHCl_3$:MeOH = 15:1); 1H NMR ($CDCl_3$) δ 7.49–7.32 (m, 5H), 5.85 (s, 2H), 4.71 (s, 2H), 3.89 (s, 3H), 2.42 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.8, 155.6, 155.5, 144.6, 143.8, 137.1, 128.8, 128.4, 128.1, 106.4, 75.3, 51.8, 20.0, 15.3; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{16}H_{19}N_2O_3$ 287.1390, found 287.1355.

3.14. N-(5-(benzyloxy)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridin-2-yl)acetamide (45)

To a solution of compound **36** (13 mg, 0.048 mmol) in glacial acetic acid, we added zinc acetate (45 mg, 0.24 mmol). The mixture was refluxed under argon atmosphere for 12 h. The mixture was concentrated, and the residue was diluted with H_2O . The aqueous layer was extracted with CH_2Cl_2 , and the combined organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel preparative thin layer chromatography to give **45** (7 mg, 45%) as a brown solid. R_f 0.29 (Hexanes:EtOAc:MeOH = 10:10:1); 1H NMR ($CDCl_3$) δ 10.55 (br s, 1H), 7.83 (br s, 1H), 7.55–7.47 (m, 2H), 7.46–7.33 (m, 3H), 5.75 (s, 1H), 4.83 (s, 2H), 2.58 (s, 3H), 2.41 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.3, 147.1, 145.1, 141.0, 137.6, 134.7, 130.6, 128.7 (2C), 128.3, 128.1 (2C), 118.9, 82.6, 75.5, 24.1, 19.7, 12.8; HRMS (ESI) m/z $[M+H]^+$ calculated for $C_{18}H_{20}N_3O_2$ 310.1550, found 310.1545.

4. Conclusions

In this study, the aminooxazole-, aminoimidazole-, and aminopyrrole-containing pyridinols were divergently synthesized starting from pyridoxine. The synthetic strategy relied on the conversion of hydroxymethyl functionality in the common intermediate **15** into phenol, aniline, and cyanomethyl structures, respectively. The installation of nitrogen-containing functional group at α -position in pyridine was achieved via either diazotization or phthalimidation. These synthetic routes enable the rapid construction of the three different aminobicyclic pyridinol derivatives in an efficient and divergent way. With the two chemical handles including the 5'-hydroxy group and arylamino group, these backbones may serve as a valuable starting point for the generation of diverse sets of compound libraries through appendage diversification.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules27072075/s1>, Copies of 1H and ^{13}C NMR spectra for all new compounds. Figure S1: 1H -NMR Spectrum of compound **23**, Figure S2: ^{13}C -NMR Spectrum of compound **23**, Figure S3: 1H -NMR Spectrum of compound **12**, Figure S4: ^{13}C -NMR Spectrum of compound **12**, Figure S5: 1H -NMR Spectrum of compound **27**, Figure S6: ^{13}C -NMR Spectrum of compound **27**, Figure S7: 1H -NMR Spectrum of compound **28**, Figure S8: ^{13}C -NMR Spectrum of compound **28**, Figure S9: 1H -NMR Spectrum of compound **29**, Figure S10: ^{13}C -NMR Spectrum of compound **29**, Figure S11: 1H -NMR Spectrum of compound **20**, Figure S12: ^{13}C -NMR Spectrum of compound **20**, Figure S13: 1H -NMR Spectrum of compound **30**, Figure S14: ^{13}C -NMR Spectrum of compound **30**, Figure S15: 1H -NMR Spectrum of compound **13**, Figure S16: ^{13}C -NMR Spectrum of compound **13**, Figure S17: 1H -NMR Spectrum of compound **34**, Figure S18: ^{13}C -NMR Spectrum of compound **34**, Figure S19: 1H -NMR Spectrum of compound **35**, Figure S20: ^{13}C -NMR Spectrum of compound **35**, Figure S21: 1H -NMR Spectrum of compound **36**, Figure S22: ^{13}C -NMR Spectrum of compound **36**, Figure S23: 1H -NMR Spectrum of compound **44**, Figure S24: ^{13}C -NMR Spectrum of compound **44**, Figure S25: 1H -NMR Spectrum of compound **45**, Figure S26: ^{13}C -NMR Spectrum of compound **45**.

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