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Synthesis of 2-substituted-7-azaindoles from 2-amino-3-picolin

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Abstract

An easy route to the synthesis of 2-substituted-7-azaindole derivatives has been developed. The carbinol intermediate dissolved in DMF undergoes cyclization upon treatment with sodium hydride, trifluoroacetic anhydride, and trifluoroacetic acid at 120 °C in a straightforward and one-pot step. An alternative methodology using $(CF_3SO_2)_2O$ in acetonitrile in basic media followed by the addition of CF_3COOH affords the expected 2-substituted azaindole in best yields.

1. Introduction

The introduction of a basic nitrogen atom in the aromatic ring of the indole leads to the azaindole derivatives, which are bioisosters of the indole-based compounds.[1] Because of their interesting biological activity in diverse therapeutic areas, the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) scaffold was the objective of several synthetic studies. Recently, several efficient methods have been reported for the syntheses of 7-azaindoles.[2] Classical approaches generally focus on the cyclization process under drastic conditions. Less traditional methods for the preparation of these compounds use transition metals (palladium,[3a–c] copper,[3d] or ruthenium catalyst[3e]) and microwave technique[1f] for the five-membered ring formation. Herein we report a simple sequence that employs 2-amino-3-picolin as starting compound.

2. Results and discussion

Azaindole compounds were prepared according to the standard indole synthesis procedures using the Fischer, Madelung, or Reissert methods, which involve an intramolecular cyclization.[4a] Most recent procedures include the Leimbruger–Batcho reaction and the Lorenz-type cyclization.[4b] However, these methods suffer from harsh reaction conditions and modest yield, primarily because the low reactivity of the π-deficient pyridine ring or the drastic basic conditions with high reaction temperatures limit both the degree of substitution and type of functionality that can be incorporated into the azaindole core.[1e,4c,d] Zhang et al.[4b] published a procedure for the preparation of 4- and 6-azaindole involving the treatment of nitro pyridines with an excess of vinyl Grignard reagents. Recently, O'Shea and Cottineau[2k] reported a convenient process to prepare 7-azaindole based on a carbolithiation of 2-amino-3-vinylpyridines.

Other authors have simply started with commercially available 7-azaindole or derivatives.[5a–f] The direct *ortho*-lithiation with butyllithium or lithium diisopropylamide requires a removable directing metalation group to protect the nitrogen at C-1 position.[4c,5b] In relation to this procedure Desarbre et al.[4c] have suggested alternative metallic derivatives other than lithium species (Zn, B, and Sn) via the Heck, Stille, or Suzuki coupling reactions for the introduction of different substituents at C-2 position of 7-azaindole.[4d,e,5c,f]

We focused our strategy on the formation of the azaindole ring from 2-amino-3-picolin. Several transition metal-mediated synthetic methods have been developed to overcome the disadvantages of the classical methods. Most of these are palladium-mediated coupling reactions with internal alkynes and functionalized pyridines.[4d,5b–d] Another alternative was

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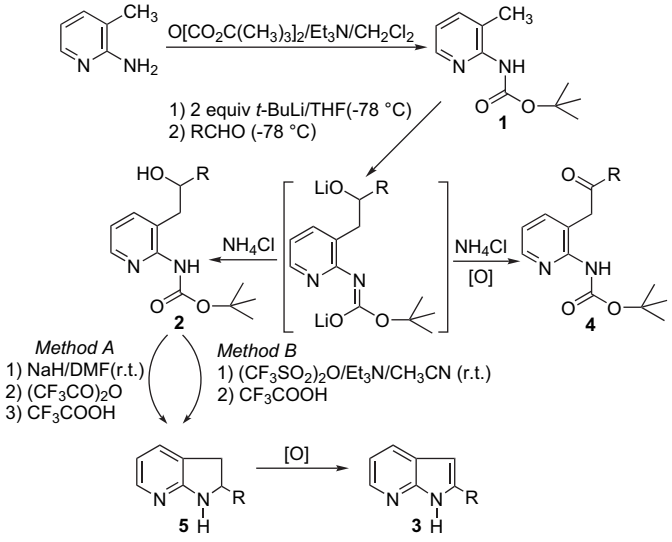
first developed by Herbert and Wibberley,[6a] who explored different routes to the synthesis of 2-substitued-7-azaindoles by the nucleophilic attack of an internal carbanion to the carbonyl position of 2-(*N*-*tert*-butoxycarbonylamine)-3-methylpyridine derivatives.

The work of Hands et al.[6b] is notable for the way in which the dilithio intermediate obtained from 2-*tert*-butylcarbonylamino-3-methylpyridine was condensed with DMF, followed by hydrolysis, cyclization, and dehydration to give the 7-azaindole.

According to this strategy, which has been applied by other workers to the synthesis of azaindoles[6c–e] and indoles[6f,g] and looking into the possibility of using 2-(*N*-*tert*-butoxycarbonylamine)-3-methylpyridine **1** as a starting product, we envisaged that the direct condensation of **1**[7] with an aldehyde would lead to the adduct **2** (Scheme 1). This resulting alcohol could cyclize into the corresponding 2-substituted-7-azaindole derivative **3**. We performed the addition of various aldehydes to the intermediate dilithio species at −78 °C (Table 1) to prepare a number of adducts **2a–f**, and the best results were obtained with compounds **2a**, **2b**, and **2f**. Regarding compound **2d**, we detected the oxidized adduct with a carbonyl at the benzylic position **4d** (12%), and in a minor proportion the corresponding ketone **4f** (4%) was isolated in the preparation of **2f** after aqueous workup. In the case of 3,4,5-trimethoxybenzaldehyde the formed carbinol is rapidly transformed to a mixture of the ketone **4g** and the olefin **7g** (Table 1).

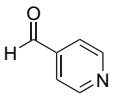
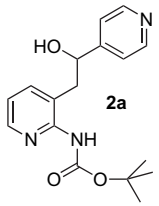
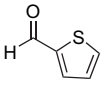
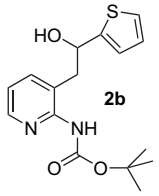
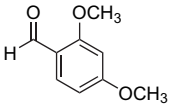
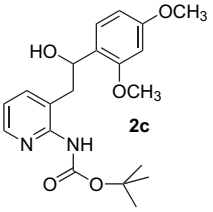
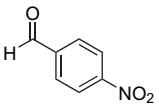
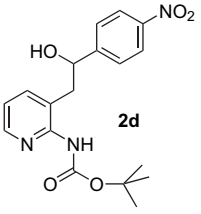
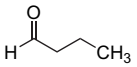
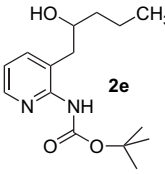
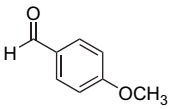
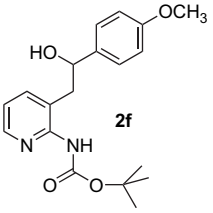
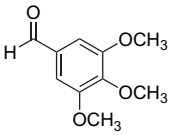
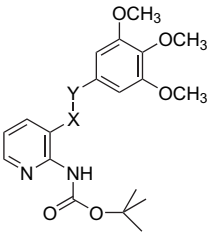


Scheme 1. Proposed synthesis of 2-substituted-7-azaindoles.

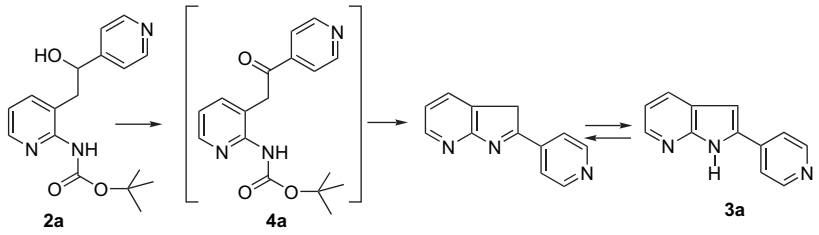
We envisaged that the oxidation of the benzylic position of compound **2** using mild conditions,[8] thus giving the ketone **4** (Scheme 2), followed by a hydrolysis cyclization and dehydration, would lead to compound **3**.[6b,6f] With such conditions, we tested the oxidation followed by cyclization of **2a**, thus expecting to obtain compound **3a**. After several attempts, the ketone **4** was achieved using MnO_2 in dry $CHCl_3$. The intramolecular ring closure of **4** was performed in acidic media (HCl/THF)[6b] to give **3a** in low yield.

Starting from compound **2**, we designed two different procedures for the preparation of 2-substituted 7-azaindoles **3**.

Table 1
Electrophilic addition of the lithiated **1**[a]

Entry	Electrophile	Compound	Yield[b] %
1		 **2a**	87
2		 **2b**	82
3		 **2c**	78
4		 **2d**	75
5		 **2e**	62
6		 **2f**	82
7		 **4g** X-Y = -CH_2-CO-	23
		7g X-Y = -CH=CH-	19

[a] Conditions: see Section 4.
[b] Isolated yield of chromatographically pure material.



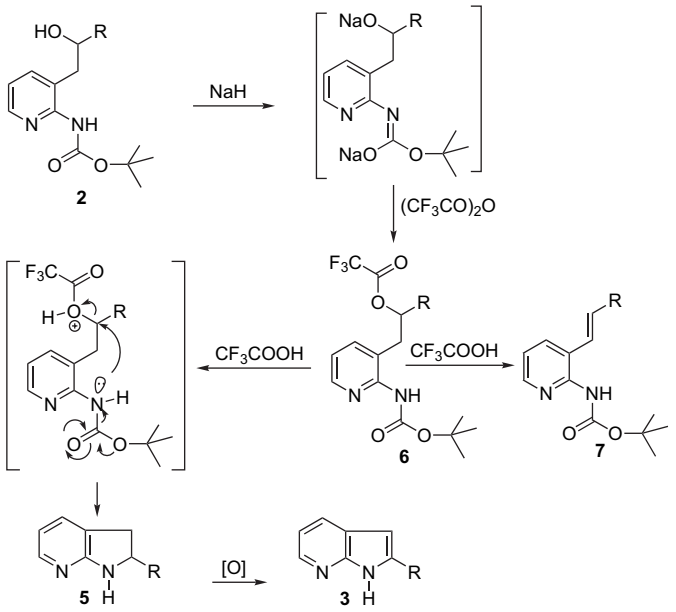
Scheme 2. Alternative synthesis of 2-substituted-7-azaindoles.

Following *method A*, the alcohol was treated with sodium hydride (Scheme 3) and trifluoroacetic anhydride at 120 °C overnight.

The addition of trifluoroacetic acid and the continuous heating for several hours (see conditions in Section 4) gave the cyclized product. This three-step procedure was performed in the same flask in a one-pot reaction. Although Hands et al.[6b] had carried out a similar cyclization procedure by refluxing the mixture with 5.5 M hydrogen chloride, we were more inclined to use milder conditions; and through these we overcame the appearance of intermediate reaction products. Thus, several trifluoroacetate esters **6** were isolated and their structure identified (**6g**). Moreover, azaindolines such as **5** can be characterized by MS and ^{1}H NMR. Clark et al.[9] have reported that long reaction time and continuous heating of trifluoroacetic acid in dichloromethane removes the protecting group. A related intramolecular cyclization was reported by Yates and Schwartz.[10]

Muchowski and Venuti[11] have described the *ortho*-lithiation of 2-(*N*-*tert*-butylcarbonylamine)pyridine, however, the *tert*-butoxycarbonyl moiety offers more advantages than the *tert*-butylcarbonyl one as a protecting group. Instead of dichloromethane, we attempted the reaction with dimethylformamide (DMF) that offered more advantages.

The tentative mechanism of the procedure (Scheme 3), after acylation of the alkoxy adduct and continuous heating with acidic conditions, involves the intramolecular nucleophilic attack of the amido group on the trifluoroacyloxy one and the subsequent elimination of the trifluoroacyloxy and *tert*-butoxycarbonyl moieties,[6b,9] affording the cyclized adduct **5** and this compound after instantaneous oxidation gives the corresponding 2-substituted-7-azaindole compound **3**. In the synthesis of **3**, traces of intermediate trifluoroacetate esters **6** and 7-azaindolines **5** were detected.

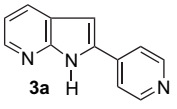
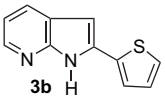
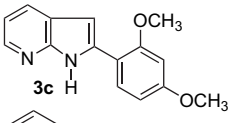
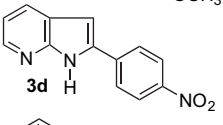
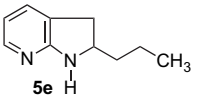
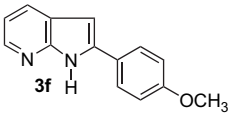


Scheme 3. Tentative mechanism for the cyclization (method A).

These intermediates allowed us to propose a possible mechanism for the synthesis of 2-substituted-7-azaindoles. Moreover, the detection of 7-azaindole *N*-protected indicates that the cyclization of **6** does not require the removal of the protecting group.

Under our conditions, we obtained the best yield with compounds **3f** and **3a** (Table 2, entries 1 and 6). Herbert and Wibberley[6a] had reported previously the preparation of compound **3a** in an 18% yield. According to our results it seems that the

Table 2
Synthesis of 2-substituted-7-azaindoles (**3a–d**, **5e**, and **3f**) from **2a–f**[a]

Entry	Compound	Product	A yield[b] %	B yield[b] %
1	**2a**	 **3a**	32	56
2	**2b**	 **3b**	26	64
3	**2c**	 **3c**	16	68
4	**2d**	 **3d**	Trac.[c]	Trac.
5	**2e**	 **5e**	Trac.	Trac.
6	**2f**	 **3f**	34	84

[a] Conditions: see Section 4.
[b] Isolated yield of chromatographically pure material.
[c] Traces. A: method A; B: method B.

presence of π-deficient or π-excessive aryl moieties does not influence the first step of pyridine alkylation, but the cyclization of the intermediate amido-ester proved far more difficult than expected. In spite of that, once formed, azaindole proved reasonably robust without special handling. Yet, we achieved different results for the cyclization of compounds **2d** and **2e** (Table 2, entries 4 and 5). At this step the nitro moiety contributes to the low yield of the procedure.[4a] Moreover the presence of nitro substituents in the aryl ring is problematic when basic conditions are used.[1c] Herbert and Wibberley reported the same problem on the cyclization of 3-methyl-2-(4-nitrophenyl)amidopyridine.[6a] Sherman et al. pointed out the low yield of the cyclization when *meta*-nitrosulfonamides were used.[12] The presence of electron-withdrawing groups on the phenyl interferes with the cyclization.

The cyclization of compound **2d** into **3d** (Table 2, entry 5), after column chromatography, provided trace amounts of a yellow substance. Mass spectral data (*m/z* (%)=239 (3)) showed that the crude of the reaction, among other compounds, contained 2-(4-nitrophenyl)-7-azaindole adduct (**3d**).

We also detected the olefin **7d** obtained from **6d** by elimination of the trifluoroacetoxy group. Attempts to obtain good conditions for cyclizing **2e** into the corresponding 2-propyl-7-azaindole **3e** were unsuccessful. After column chromatography we isolated a colorless substance that contained several compounds, one of which was the 2-propyl-2*H*-7-azaindole adduct **5e** (*m/z* (5)=162 (14) [M^+], 119 (100) [M^+-43]). Attempts of dehydrogenation of **5e** using MnO_2 or Pd–C in decalin were unsuccessful and only degradation of starting material was detected. This result shows that the alkyl substituent difficult the formation of azaindole system under these conditions.

The alternative *method B* consists in the treatment of the intermediate alcohol **2** with trifluoromethanesulfonic anhydride in acetonitrile in the presence of triethylamine, followed by the addition of trifluoroacetic acid. This method gave the 7-azaindoles **3** in the best yields. The alcohols **2**, possessing a rich electronically aromatic group, gave the azaindoles **3** in good yields (Table 2, entries 2, 3, and 6).

3. Conclusion

Starting from commercially available products, we have reached the synthesis of 2-substituted-7-azaindole compounds in two steps. Although several reports have been published on the 2-substituted azaindole derivatives, our method opens a new synthetic strategy leading to the preparation of such compounds and their derivatives. However, the method might not be suitable for the synthesis of compounds bearing a nitroaryl moiety or an alkyl at the C-2 position.

4. Experimental

4.1. General

Melting points were obtained on an MFB-595010 M Gallenkamp apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a FTIR Perkin–Elmer 1600 Infrared Spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 and 50.3 MHz, respectively) or Varian Gemini-300 (300 and 75.5 MHz) Instrument using $CDCl_3$ as solvent with tetramethylsilane as internal standard or $(CD_3)_2CO$. Other ^1H NMR spectra and heterocorrelation $^1H-^{13}C$ (HMQC and HMBC) experiments were recorded on a Varian VXR-500 (500 MHz). Mass spectra were recorded on a Hewlett–Packard 5988-A. Column chromatography was performed with silica gel (E. Merck, 70–230 mesh). Reactions were monitored by TLC using 0.25 mm silica gel F_{254} (E. Merck). Microanalysis was determined on a Carlo Erba-1106 analyzer. All reagents were of commercial quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures. Commercial products were obtained from Sigma–Aldrich.

4.2. 2-tert-Butoxycarbonylamino-3-methylpyridine (*1*)

3-Methyl-2-aminopyridine (1 g, 9.2 mmol) and 2.4 g (11 mmol) of di-*tert*-butyl dicarbonate, each dissolved in 20 mL of dichloromethane, were poured into a 100 mL round bottomed flask. Afterward 1.16 g (11.4 mmol) of triethylamine was added. The mixture was stirred for 16 h at room temperature and washed with 3×20 mL of distilled water. The organic layer was dried over anhydrous sodium sulfate, filtered off, and the solvent was removed under vacuum. The reaction crude (1.9 g) was dissolved in 5 mL of dichloromethane and loaded into a 2.5×30 cm column of chromatography packed with silica gel (70–230 mesh). An increasing polarity elution gradient of hexane/ethyl acetate 70:30 gave 1.61 g (7.70 mmol, 83%) of **1** as a white solid. Mp 134–135 °C (ethyl acetate) (lit.[6b] mp 134–136 °C). IR (KBr) ν cm^{-1}: 3196 (NH), 1719 (C=O), 1281 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.53 (s, 9H, CH_3–), 2.29 (s, 3H, CH_3–), 6.79 (br s, 1H, NH), 7.02 (m, 1H), 7.51 (d, J=7.4 Hz, 1H), 8.25 (dd, J_1=3.2 Hz, J_2=1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 27.9 (CH_3), 80.4 (C, *t*-bu), 120.5, 126.3, 139.6, 145.6, 149.9, 152.7.

4.3. General procedure for the synthesis of alcohols *2*

2-*tert*-Butoxycarbonyl-3-methylpyridine (0.3 g, 1.44 mmol) dissolved in 5 mL of dry tetrahydrofuran (THF), kept under argon atmosphere, was transferred into a 50 mL three-neck round bottomed flask (provided with argon inlet and outlet and a stirring bar). The solution was cooled down to −78 °C with solid-CO_2–acetone bath. Afterward 2.1 mL of a solution of *tert*-butyllitium in pentane (1.7 M) was added dropwise by syringe. The reaction mixture was maintained at −78 °C for 3 h. Afterward 2.1 mmol of the corresponding aldehyde was added by syringe. The reaction mixture was stirred for 16 h to let it warm up to room temperature. The reaction mixture was quenched by addition of 5 mL of a saturated solution of ammonium chloride in water and then stirred for 0.5 h at room temperature. Then 5 mL of a solution of sodium hydroxide (1.0 M) was added dropwise followed by 5 mL of distilled

water. The mixture was extracted with 3×20 mL of ether. The organic layer was washed with 2×20 mL of distilled water, dried over anhydrous sodium sulfate, and filtered off. The solvent was removed by evaporation under vacuum. The crude of reaction was dissolved in 5 mL of CH_2Cl_2 and loaded into a 3×30 cm column of chromatography packed with silica gel. An increasing polarity elution gradient of ethyl acetate/methanol was used.

*4.3.1. 2-tert-Butoxycarbonylamino-3-(2-hydroxy-2-(4-pyridyl)ethyl)pyridine (**2a**)*

The general procedure was followed using 0.23 g (2.1 mmol) of 4-pyridinecarbaldehyde to give 0.392 g (1.24 mmol, 87%) of pure 3-(2-hydroxy-2-(4-pyridyl)ethyl)-2-[*N*-(*tert*-butoxy carbonyl)]aminopyridine **2a** as a white solid. Mp 45–47 °C (hexane/ethyl acetate). IR (KBr) ν cm^{-1}: 3220 (OH), 1726 (C=O), 1504 (C=C), 1238 (Ar–O), 1156 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.49 (s, 9H, CH_3–), 2.98 (m, 2H, CH_2), 3.05 (m, 1H, –OH), 5.02 (m, 1H, CH–OH), 7.08 (m, 1H), 7.91 (d, J=9.20 Hz, 2H), 7.42 (d, J=9.20 Hz, 1H), 8.25 (m, J=3.8 Hz, 1H), 8.40 (d, J=9.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.3 (CH_3), 40.8 (CH_2), 73.1 (CH, CH–O–), 80.6 (C, *t*-bu), 119.9, 120.8, 125.7, 139.8, 146.6, 149.1, 131.2, 152.9, 153.7. Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32%. Found: C, 64.67; H, 6.43; N, 13.71%.

*4.3.2. 3-(2-Hydroxy-2-(thiophen-2-yl)ethyl)-2-[N-(tert-butoxycarbonyl)]aminopyridine (**2b**)*

The general procedure was followed using 0.245 g (2.19 mmol) of freshly distilled 2-thiophenecarboxaldehyde to give 0.376 g (1.17 mmol, 82%) of **2b** as a yellow solid (hexane/ethyl acetate 30:70, v/v). Mp 112–113 °C (ethyl acetate). IR (KBr) ν (cm^{-1}): 3209 (OH), 1730 (C=O), 1159 (C–O–). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.48 (s, 9H, CH_3–), 3.07 (d, J=6.2 Hz, CH_2–), 4.36 (br s, 1H, OH), 5.22 (t, J=6.2 Hz, 1H, CH–OH), 6.92 (m, 3H), 7.20 (m, 1H), 7.40 (d, J=7.4 Hz, 1H), 8.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.3 (CH_3), 41.4 (CH_2), 70.7 (CH, CH–OH), 80.6 (C, *t*-bu), 120.2, 123.3, 124.3, 126.2, 126.6, 139.8, 146.6, 148.2, 150.4, 153.2. Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74%. Found: C, 59.67; H, 6.12; N, 8.43%.

*4.3.3. 3-(2-Hydroxy-2-(2,4-dimethoxyphenyl)ethyl)-2-[N-(tert-butoxycarbonyl)]aminopyridine (**2c**)*

The general procedure was followed using 0.287 g (1.7 mmol) of 2,4-dimethoxybenzaldehyde to give 0.43 g (1.09 mmol, 78%) of **2c** as a white solid powder. IR (KBr) ν (cm^{-1}): 3381 (O–H), 2970 (NH), 1734 (C=O), 1256 (Ar–O–), 1253 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.39 (s, 9H, CH_3–), 2.68 (m, 2H, CH_2–), 3.64 (s, 3H, CH_3–O–), 3.69 (s, 3H, CH_3O–), 5.01 (m, 1H, CH–OH), 6.27 (s, 1H), 6.31 (m, 1H), 6.78 (m, 1H), 7.11 (m, 1H), 7.16 (m, 1H), 8.10 (m, 1H), 8.38 (s, 1H, N–H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.3 (CH_3), 31.0 (CH_3), 39.4 (CH_3), 55.2 (CH_2), 69.5, 80.2, 98.1, 103.9, 119.3, 124.6, 125.9, 126.6, 136.7, 146.2, 150.4, 152.5, 156.4, 159.7. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48%. Found: C, 64.43; H, 7.34; N, 7.20%.

*4.3.4. 3-(2-Hydroxy-2-(4-nitrophenyl)ethyl)-2-[N-(tert-butoxycarbonyl)]aminopyridine (**2d**)*

The general procedure was followed using 0.175 g (1.2 mmol) of 4-nitrobenzaldehyde to give 0.515 g (1.46 mmol, 75%) of pure 3-(2-hydroxy-2-(4-nitrophenyl)ethyl)-2-[*N*-(*tert*-butoxycarbonyl)]aminopyridine. Mp 94–95 °C (ethyl acetate). IR (NaCl) ν (cm^{-1}): 3276 (OH), 2975 (NH), 1728 (C=O), 1454, 1247 (C–O), 1157 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.33 (s, 9H, CH_3), 2.92 (m, 2H, CH_2–), 4.92 (br s, 1H, OH), 5.02 (m, 1H, CH–O–), 6.99 (m, 1H), 7.23 (m, 1H), 7.45 (d, J=7.0 Hz, 2H), 8.02 (d, J=7.0 Hz, 2H), 8.20 (m, 1H), 8.21 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.0 (CH_3), 40.9 (CH_2), 73.3 (CH, CH–O–), 80.1 (C, *t*-bu), 120.2, 123.3, 126.3, 130.1, 140.2, 146.3, 148.0, 149.9, 151.8, 153.4. Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.70%. Found: C, 60.52; H, 5.52; N, 11.54%.

*4.3.5. 3-(2-Hydroxypentyl)-2-[N-(tert-butoxycarbonyl)]aminopyridine (**2e**)*

The general procedure was followed using 0.16 g (2.22 mmol) of butyraldehyde to give 0.249 g (0.9 mmol, 62%) of colorless oil. IR (KBr) ν (cm^{-1}): 3275 (O–H), 2958 (NH), 1736 (C=O), 1246 (Ar–O–), 1163 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 0.95 (m, 3H, CH_3–), 0.98 (m, 2H, CH_2–CH_3), 1.48 (s, 9H, *t*-bu), 1.52 (m, 2H), 2.20 (br s, 1H, OH), 2.72 (m, 2H), 3.96 (m, 1H, CH–OH), 7.01 (dd, J_1=7.4 Hz, J_2=4.6 Hz, 1H), 7.45 (dd, J_1=7.4 Hz, J_2=1.4 Hz, 1H), 8.15 (s, 1H, N–H), 8.29 (dd, J_1=4.6 Hz, J_2=1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 14.0 (CH_3), 18.8 (CH_2), 28.3 (CH_3, *t*-bu), 38.8 (CH_2), 39.7 (CH_2), 72.4 (CH, CH–O), 80.2 (C, *t*-bu), 119.8, 126.9, 139.5, 146.2, 150.5, 152.9. Anal. Calcd for $C_{15}H_{24}N_2O_3$: C, 64.26; H, 8.63; N, 9.99%. Found: C, 64.58; H, 8.91; N, 9.68%.

*4.3.6. 3-[2-Hydroxy-2-(4-methoxyphenyl)]ethyl-2-[N-(tert-butoxycarbonyl)]aminopyridine (**2f**)*

Starting from 0.3 g (1.44 mmol) of 2-*tert*-butoxycarbonyl-3-methylpyridine **1** dissolved in 5 mL of dry THF and following the above reported method was obtained the carbinol **2f** as a yellow solid (82% yield). Mp 110–111 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3282 (O–H), 3055 (NH), 1723 (C=O), 1244 (Ar–O–), 1158 (C–O). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.64 (s, 9H, CH_3–), 3.12 (d, J=6 Hz, 2H, CH_2–), 3.96 (s, 3H, CH_3O–), 5.13 (t, J=6 Hz, 1H, CH–O), 7.02 (d, J=8 Hz, 2H), 7.10 (t, J=6 Hz, 1H), 7.40 (d, J=8 Hz, 2H), 7.45 (d, J=8 Hz, 1H, H-4), 8.25 (s, 1H), 8.42 (s, 2H, NH, OH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.2 (CH_3), 41.2 (CH_2), 55.2 (CH_3), 74.6 (CH, CH–O), 80.4 (C, *t*-bu), 114.0, 119.9, 127.3, 135.9, 139.5, 139.7, 146.7, 148.2, 152.0, 158.2. Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13%. Found: C, 66.13; H, 7.38; N, 7.89%.

4.4. Preparation of 2-aryl-7-azaindoles

General procedure A. A solution of **2** (0.95 mmol) in 10 mL of freshly distilled DMF was poured into a 50 mL round bottomed flask followed by the addition of 32 mg of sodium hydride (60%, w/w). The mixture was stirred at room temperature for 10 min. Then 0.70 mmol of trifluoroacetic anhydride (99%) was added. The mixture was heated at 120 °C overnight. Then 0.2 mL of trifluoroacetic acid was added and the mixture was maintained under these conditions for 3 h. After cooling the mixture to room temperature, 5 mL of a solution of sodium hydroxide (1.0 M) was added. The mixture was extracted with 3×20 mL of ethyl ether. The organic layer was dried over anhydrous sodium sulfate and filtered off. The solvent was removed under vacuum. The resulting crude was purified by column chromatography on silica gel. *General procedure B*. A solution of **2** (1 mmol) in acetonitrile (12 mL) was cooled to 0 °C, triethylamine (1.2 mmol) and trifluoromethanesulfonic anhydride (1.1 mmol) were added over 5 min. The mixture was stirred at room temperature for 2 h. Then trifluoroacetic acid was added (1.5 mmol) and the mixture was heated under reflux for 1 h. The crude of reaction was allowed to cool to room temperature and 2 N NaOH was added until neutralization. The aqueous layer was extracted with ethyl ether (3×25 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuum. The crude product was purified by column chromatography on silica gel to afford the expected 7-azaindoles (**3**). The yields are indicated on Table 2.

4.4.1. 2-(4-Pyridyl)-7-azaindole (*3a*)

According to the general procedure A described for the cyclization of hydroxyaminopyridines, the resulting crude was purified by column chromatography using hexane/ethyl acetate 2:8 as eluent on silica gel to afford 32% of **3a** as a pure white powder. According to the general procedure B, the azaindole **3b** was obtained in 64% yield. Mp 274–276 °C (lit.[6a] mp 273–275 °C). ^{1}H NMR ($CDCl_3$+CD_3OD, 300 MHz) δ (ppm): 6.99 (s, 1H, C3-H), 7.13 (dd, J_1=3.4 Hz, J_2=5.3 Hz, 1H), 7.72 (dd, J_1=1.0 Hz, J_2=3.1 Hz, 2H), 8.00 (dd, J_1=1.0 Hz, J_2=5.3 Hz, 1H), 8.29 (dd, J_1=1.0 Hz, J_2=3.4 Hz, 1H), 8.62 (dd, J_1=1.0 Hz, J_2=3.1 Hz, 2H). ^{13}C NMR ($CDCl_3$+CD_3OD, 50.3 MHz) δ (ppm): 100.3, 116.6, 119.6, 122.1, 129.9, 135.9, 139.8, 143.6, 149.0, 149.9. Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52%. Found: C, 74.11; H, 4.34; N, 21.21%.

4.4.2. 2-(Thiophen-2-yl)-7-azaindole (*3b*)

This compound was obtained according to the general procedure A described for the cyclization of hydroxyaminopyridines, the resulting crude was loaded into a 1.5×30 cm column of chromatography packed with silica gel. An increasing polarity elution gradient of hexane/ethyl acetate 70:30 gave 0.024 g (0.1 mmol, 26%) of **3b** as a yellow paste. IR (NaCl) ν (cm^{-1}): 3381 (NH), 1606, 1448, 1185. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.59 (br s, 1H, NH), 6.72 (dd, J=3.4, 1.2 Hz, 1H), 6.82 (s, 1H), 6.96 (dd, J_1=1.0 Hz, J_2=3.6 Hz, 1H), 7.14 (dd, J=6.6, 0.4 Hz, 1H), 7.23 (d, J=4.0 Hz, 1H), 7.60 (dd, J_1=5.0 Hz, J_2=0.8 Hz, 1H, C4–H), 8.15 (dd, J_1=0.4 Hz, J_2=6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 114.0, 115.1, 118.7, 119.1, 124.7, 126.5, 127.1, 128.9, 134.5, 148.2, 154.1. Anal. Calcd for $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99%. Found: C, 66.23; H, 4.43; N, 14.34%. According to the general procedure B, the azaindole **3b** was obtained in 64% yield.

4.4.3. 2-(2,4-Dimethoxyphenyl)-7-azaindole (*3c*)

According to the general procedure A described for the cyclization of hydroxyaminopyridines, the crude of the reaction was loaded into a 1.5×30 cm column of chromatography packed with silica gel. An increasing polarity elution gradient of hexane/ethyl acetate gave 0.0263 g (0.1 mmol, 16%) of **3c** as a white solid powder). IR (NaCl) ν (cm^{-1}): 2924 (NH), 1608, 1209 (Ar–O), 1159 (C–O). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.75 (m, 3H, CH_3–O–), 3.84 (m, 3H, CH_3–O–), 6.49 (m, 2H), 6.70 (dd, J_1=3.4 Hz, J_2=4.8 Hz, 1H), 6.86 (s, 1H), 7.06 (dt, J_1=5.0 Hz, J_2=3.4 Hz, J_3=1.0 Hz, 1H), 7.86 (dd, J_1=3.4 Hz, J_2=5.2 Hz, 1H), 8.23 (dd, J_1=3.4 Hz, J_2=0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 55.4 (CH_3), 55.5 (CH_3), 98.4, 104.9, 114.7, 119.2, 120.8, 127.6, 128.2, 129.3, 134.5, 145.6, 148.9, 158.2, 159.2. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02%. Found: C, 70.65; H, 5.78; N, 11.42%. According to the general procedure B, the azaindole **3c** was obtained in 68% yield.

4.4.4. 2-(4-Methoxyphenyl)-7-azaindole (*3f*)

Starting from 0.3 g of **2f** and following the method described for **3a**, the desired compound **3f** was obtained as a white solid (84% yield). Mp 70–71 °C. IR (NaCl) ν (cm^{-1}): 3383 (NH), 1715 (C=N), 1252 (Ar–O), 1178 (C–O). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.62 (s, 1H), 6.92 (m, 1H), 7.02 (d, J=8.8 Hz, 2H), 7.73 (d, J_1=8.8 Hz, 2H), 7.92 (d, J=8.8 Hz, 1H), 8.22 (m, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 55.2 (CH_3), 98.6 (CH, C-3), 114.4, 118.5, 127.9, 128.1, 128.7, 131.5, 134.7, 146.2, 149.0, 157.1. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49%. Found: C, 74.61; H, 5.05; N, 12.65%. According to the general procedure B, the azaindole **3f** was obtained in 84% yield.

4.4.5. 3-(2-Oxo-2-(4-nitrophenyl)ethyl)-2-[N-(tert-butoxy carbonyl)]aminopyridine (*4d*)

Colorless oil (12%). IR (NaCl) ν (cm^{-1}): 3370 (NH), 1734 (C=O), 1720 (C=O), 1513, 1158 (C–O–). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.49 (s, 9H, CH_3), 4.47 (s, 2H, CH_2O), 7.02 (m, 1H), 7.19 (m, 1H), 7.56 (d, J=6.0 Hz, 2H), 8.21 (m, 3H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.2 (CH_3), 63.6 (CH_2), 80.8 (C, *t*-bu), 120.7, 123.3, 126.8, 139.7, 140.2, 145.4, 146.1, 148.7, 149.5, 153.1, 184.0.

4.4.6. 3-(2-Oxo-2-(4-methoxyphenyl)ethyl)-2-[N-(tert-butoxycarbonyl)]aminopyridine (*4f*)

Yellow oil (4%). IR (NaCl) ν (cm^{-1}): 3354 (NH), 1723 (C=O), 1712 (C=O), 1504, 1109 (C–O–). ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.62 (s, 9H, CH_3), 4.02 (s, 3H,

CH_3O), 4.43 (s, 2H, CH_2Ar), 7.02 (d, J=8 Hz, 2H), 7.23 (m, 1H), 7.64 (d, J=8.8 Hz, 1H), 7.83 (br s, 1H, NH), 8.19 (d, J=8 Hz, 2H), 8.60 (d, J=8.8 Hz, 1H).

*4.4.7. 3-(2-(3,4,5-Trimethoxyphenyl)-2-oxo)ethyl-2-(tert-butoxycarbonyl)aminopyridine (**4g**)*

Yellow solid (23%). Mp 75–76 °C (hexane/ethyl acetate). IR (NaCl) ν (cm^{-1}): 3055 (NH), 1727 (N–C=O), 1715 (C=O), 1505 (C=C), 1232 (Ar–O), 1127 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.32 (s, 9H, CH_3), 3.02 (m, 2H), 3.80 (s, 3H, CH_3–O), 3.82 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 6.49 (s, 2H), 7.00 (m, 1H), 7.40 (m, 1H), 7.82 (br s, 1H, NH), 8.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.3 (CH_3), 40.0 (CH_2), 56.1 (2×CH_3–O), 60.8 (CH_3–O), 74.2 (C, *t*-bu), 102.5, 118.0, 126.7, 139.4, 146.2, 153.1, 162.4, 194.1. Anal. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96%. Found: C, 62.98; H, 6.41; N, 6.59%.

*4.5. 2-Propyl-2,3-dihydro-7-azaindole (**5e**)*

White solid (2% yield). Mp 146–148 °C (hexane/ethylacetate). IR (NaCl) ν (cm^{-1}): 3360 (NH), 1671 (C=N), 1508 (C=C). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.98 (m, 3H, CH_3), 1.5 (m, 4H, CH_2), 2.58 (d, J=5.6 Hz, 2H, C3–H), 3.95 (t, J=5.8 Hz, 1H, C2–H), 5.06 (br s, 1H, NH), 6.48 (m, 1H), 7.18 (d, J=8.6 Hz, 1H), 7.89 (d, J=6.5 Hz, 1H). MS (EI) (*m*/*z*, %): 162 (M^+, 14), 119 (100), 92 (11).

*4.6. 2-(4-Methoxyphenyl)-2,3-dihydro-7-azaindole (**5f**)*

Colorless solid (7% yield). Mp 122–123 °C (hexane/ethyl acetate). IR (NaCl) ν (cm^{-1}): 3328 (NH), 1668 (C=N), 1513 (C=C), 1248 (Ar–O), 1174 (C–O). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.99 (m, 2H, C3–H), 3.75 (s, 3H, CH_3O), 5.62 (dd, J_1=8.2 Hz, J_2=1.4 Hz, 1H, C2–H), 6.78 (d, J_1=8.8 Hz, 2H), 6.98 (m, 1H), 7.15 (d, J=8.8 Hz, 2H), 7.42 (d, J=6.6 Hz, 1H), 8.19 (d, J_1=6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 34.7 (CH_2, C-3), 55.2 (CH, C-2), 59.6 (CH_3, CH_3–O), 113.9, 118.2, 124.5, 126.4, 133.4, 134.0, 146.4, 158.6, 169.4.

*4.7. 3-[2-Trifluoroacetoxy-2-(4-methoxyphenyl)]ethyl-2-[N-(tert-butoxycarbonyl)]aminopyridine (**6g**)*

Only traces of an oil compound. IR (KBr) ν (cm^{-1}): 3058 (NH), 1712 (C=O), 1223 (Ar–O–), 1109 (C–O). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.26 (s, 9H, CH_3–), 2.98 (dd, J= 5.8, 8.0 Hz, 1H), 3.41 (dd, J=5.8, 8.0 Hz, 1H), 3.81 (s, 3H), 4.99 (m, 1H, CH–O), 6.89 (t, J=8.0 Hz, 1H), 6.92 (d, J= 8.8 Hz, 2H), 7.28 (m, 1H), 7.29 (d, J=8.8 Hz, 2H, C2′-H, C6′-H), 7.98 (d, J=8.0 Hz, 1H).

*4.8. 3-[2-(4-Nitrophenyl)-1-ethenyl]-2-(tert-butoxy carbonyl)aminopyridine (**7d**)*

Yellow oil (32% yield). IR (NaCl) ν (cm^{-1}): 3276 (NH), 1728 (N–C=O), 1596 (C=N), 1512 (C=C), 1247 (Ar–O), 1157 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.31 (s, 9H, CH_3), 4.96 (d, J=7.2 Hz, 1H, CH=CH), 5.98 (d, J=7.2 Hz, 1H, CH=CH), 6.78 (m, 1H), 7.00 (d, J=5.8 Hz, 2H), 7.18 (d, J=8.4 Hz, 1H), 7.56 (d, J=6.0 Hz, 2H), 8.05 (d, J=8.4 Hz, 1H). MS (EI) (*m*/*z*, %): 341 (M^+, 24), 134 (55), 57 (100).

*4.9. 3-[2-(3,4,5-Trimethoxyphenyl)-1-ethenyl]-2-(tert-butoxycarbonyl)aminopyridine (**7g**)*

Yellow solid (19%). Mp 73–75 °C (hexane/ethyl acetate). IR (NaCl) ν (cm^{-1}): 3063 (NH), 1727 (N–C=O), 1587 (C=N), 1505 (C=C), 1236 (Ar–O), 1127 (C–O). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.33 (s, 9H, CH_3), 3.84 (s, 3H, CH_3–O), 3.87 (s, 3H, CH_3O), 3.92 (s, 3H, CH_3O), 4.81 (d, J=7.4 Hz, 1H, CH=CH), 5.67 (d, J=7.4 Hz, 1H, CH=CH), 6.45 (s, 2H), 6.98 (m, 1H), 7.27 (d, J=8.8 Hz, 1H), 8.40 (d, J= 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 28.0 (CH_3), 56.3 (2×CH_3–O), 56.5 (CH_3–O), 80.1 (C, *t*-bu), 102.5, 106.9, 117.6, 130.2, 132.1, 138.4, 147.2, 152.2, 153.2 (3×C), 162.8. Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25%. Found: C, 65.58; H, 6.66; N, 6.08%.

*4.10. Oxidation of alcohol (**2a**)*

A 50 mL, one-necked flask, provided with a septum an argon inlet and outlet, and a stirrer was charged with a solution of the alcohol (0.315 g, 1 mmol) in dry $CHCl_3$ (15 mL). The solution was stirred, and then, activated MnO_2 (0.435 mg, 5 mmol) and glacial acetic acid (0.2 mL) were added. Stirring was continued for 12 h and then H_2O was added (10 mL). The reaction mixture was filtered and the solution obtained was further diluted with H_2O (5 mL) and $CHCl_3$ (15 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude of the reaction was purified by column chromatography (Silica gel, 70–230 mesh) using hexane/ethyl acetate as eluant. The ketone **4a** was obtained in 67% yield as yellow oil. IR (KBr) ν (cm^{-1}): 3167 (NH), 1732 (N–C=O), 1735 (C=O), 1721 (C=O), 1102 (C–O–). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.35 (s, 9H, CH_3), 4.02 (s, 2H, CH_2O), 6.95 (br s, 1H, NH), 7.18 (m, 1H), 7.35 (d, J=9.0 Hz, 1H), 7.67 (d, J=9.0 Hz, 2H), 8.25 (m, J=4 Hz, 1H), 8.56 (d, J=9.0 Hz, 2H).

The ketone **4a** (80 mg, 0.25 mmol) was dissolved in THF (10 mL) and treated with 5.5 M HCl (0.5 mL).[6b] The mixture was stirred at 50 °C for 24 h. Then, the mixture was cooled, basified with 5 M NaOH, and extracted with ether (3×15 mL). The combined organic fractions were dried and concentrated to give **3a** in 12%.

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References and notes

1. (a) Chi, S.; Choi, J.; Yum, E.; Chi, D. *Tetrahedron Lett.* **2000**, *41*, 919–922; (b) Marminon, C.; Pierre, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 679–687; (c) Mahboobi, S.; Pongratz, H.; Hufsky, H.; Hockemeyer, J.; Frieser, M.; Lyssenko, A.; Paper, D.; Burgermeister, J.; Bohmer, F.; Fiebig, H.; Burger, A.; Baasner, S.; Beckers, T. *J. Med. Chem.* **2001**, *44*, 4535–4553; (d) Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Golsteyn, R.; Prudhomme, M. *Tetrahedron Lett.* **2004**, *45*, 4643–4647; (e) Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 4607–4611; (f) Schirok, H. *J. Org. Chem.* **2006**, *71*, 5538–5545; (g) Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 7304–7316; (h) O'Neil, D. J.; Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Zhang, H.-C.; Maryanoff, B. E.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *Bioorg. Med. Chem.* **2004**, *12*, 3167–3185.
2. (a) Popowycz, F.; Routier, S.; Joseph, B.; Mérour, J.-Y. *Tetrahedron* **2007**, *63*, 1031–1064; (b) Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471–506; (c) Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428–444; (d) Gluszok, S.; Goossens, L.; Depreux, P.; Barbry, D.; Hénichart, J.-P. *Synth. Commun.* **2006**, *36*, 2797–2805; (e) Wang, X.; Zhi, B.; Baum, J.; Chen, Y.; Crockett, R.; Huang, L.; Eisenberg, S.; Ng, J.; Larsen, R.; Martinelli, M.; Reider, P. *J. Org. Chem.* **2006**, *71*, 4021–4023; (f) Guillard, J.; Decrop, M.; Gallay, N.; Espanel, C.; Boissier, E.; Herault, O.; Viaud-Massuard, M. C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1934–1937; (g) Bignan, G. C.; Battista, K.; Connolly, P. J.; Orsini, J. J.; Liu, J.; Middleton, S. A.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3524–3528; (h) Elokdah, H.; Li, D.; McFarlane, G.; Bernotas, R. C.; Robichaud, A. J.; Magolda, R. L.; Zhang, G. M.; Smith, D.; Schechter, L. E. *Bioorg. Med. Chem.* **2007**, *15*, 6208–6226; (i) Hugon, B.; Anizon, F.; Bailly, C.; Golsteyn, R. M.; Pierré, A.; Léonce, S.; Hickman, J.; Pfeiffer, B.; Prudhomme, M. *Bioorg. Med. Chem.* **2007**, *15*, 5965–5980; (j) Huang, S.; Li, R.; Connolly, P. J.; Emanuel, S.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4818–4821; (k) Cottineau, B.; O'Shea, F. D. *Tetrahedron* **2007**, *63*, 10354–10362; (l) Potashman, M. H.; Bready, J.; Coxon, A.; DeMelfi, T. M.; DiPrietro, L.; Doerr, N.; Elbaum, D.; Estrada, J.; Gallant, P.; Germain, J.; Gu, Y.; Harmange, J.-C.; Kaufman, S. A.; Kendall, R.; Kim, J. L.; Kumar, G. N.; Long, A. M.; Neervannan, S.; Patel, V. F.; Polverino, A.; Rose, P.; van der Plas, S.; Whittington, D.; Zanon, R.; Zhao, H. *J. Med. Chem.* **2007**, *50*, 4351–4373.
3. (a) Nazaré, M.; Scheneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526–4528; (b) Lachance, N.; April, M.; Joly, M.-A. *Synthesis* **2005**, 2571–2577; (c) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152–5160; (d) Pearson, S. E.; Nandan, S. *Synthesis* **2005**, 2503–2506; (e) Tsuji, Y.; Kotachi, S.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 580–584.
4. (a) Kelly, A.; Parrick, J. *Can. J. Chem.* **1966**, *44*, 2455–2459; (b) Zhang, Z.; Yang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2002**, *67*, 2345–2347; (c) Desarbre, E.; Coudret, S.; Meheust, C.; Mérour, J.-Y. *Tetrahedron* **1997**, *53*, 3637–3648; (d) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355–5358; (e) Zheng, X.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 3777–3779 and references cited therein.
5. (a) Robison, M. M.; Robison, B. L. *J. Am. Chem. Soc.* **1955**, *77*, 457–460; (b) Curtis, N.; Kulagowski, J.; Leeson, P.; Ridgill, M.; Emms, F.; Freedman, S. B.; Patel, S.; Patel, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 585–588; (c) Ujjainwalla, F.; Walsh, T. *Tetrahedron Lett.* **2001**, *42*, 6441–6445; (d) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *J. Comb. Chem.* **2005**, *7*, 510–512; (e) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; (f) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897–2900.
6. (a) Herbert, R.; Wibberley, D. *J. Chem. Soc. C* **1969**, *11*, 1505–1514; (b) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J.; Cottrell, I.; Wright, S. *Synthesis* **1996**, 877–882; (c) Houlihan, W.; Parrino, V.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511–4515; (d) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401–3408; (e) Fuhrer, W. *J. Org. Chem.* **1979**, *44*, 1133–1136; (f) Dillard, R. D.; Bach, N. J.; Draheim, S. E.; Berry, D. R.; Carlson, D. G.; Chirgadze, N. Y.; Clawson, D. K.; Hartley, L. W.; Johnson, L. M.; Jones, N. D.; McKinney, E. R.; Mihelich, E. D.; Olkowski, J. L.; Schevits, R. W.; Smith, A. C.; Snyder, D. W.; Sommers, C. D.; Wery, J.-P. *J. Med. Chem.* **1996**, *39*, 5119–5136; (g) Mattsson, C.; Sonesson, C.; Sandahl, A.; Greiner, H. E.; Gassen, M.; Plashke, J.; Leibrock, J.; Böttcher, H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4230–4234.
7. For the preparation of 3-methyl-2-(*N*-*tert*-butoxy carbonyl)aminopyridine see experimental procedures in Section 4.
8. (a) Naidu, M.; Rao, G. *Synthesis* **1979**, 144–145; (b) Kim, S.; Borisova, G. *Synth. Commun.* **2003**, *33*, 3961–3967.
9. Clark, R.; Muchowski, J.; Fisher, L.; Flippin, F.; Repke, D.; Souchet, M. *Synthesis* **1991**, 871–878.
10. Schwartz, D. A.; Yates, P. *Can. J. Chem.* **1983**, *61*, 1126–1131.
11. Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798–4801.
12. Sherman, E.; Chemler, S.; Tan, T.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573–1575.