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Facile synthesis of 5-amino- and 7-amino-6-azaoxindole derivatives

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ABSTRACT

An efficient approach for the formation of 5-amino- and 7-amino-6-azaoxindole derivatives was developed. 2-Amino-4-chloro-3-nitropyridine (**8**), and its 5-nitro-substituted regioisomer (**9**), respectively, were obtained by reaction with ethyl malonate. The resulting 2-amino-3/5-nitropyridine derivatives substituted in the 4-position with malonic acid diethyl ester (**10**, **11**) were subjected to reductive cyclization yielding 3-ethoxycarbonyl-6-azaoxindole derivatives **4a** and **5a**. Protection of the amino function was not required. Intermediates **10** and **11** could also be converted to the corresponding 4-acetic acid ethyl esters **12** and **13** by dealkoxycarbonylation with LiCl, and subsequently cyclized under reductive conditions yielding 3-unsubstituted 5-/7-aminooxazindoles.

Indoles are present in numerous natural products as well as in synthetic compounds with biological activity. In contrast, azaindoles, which represent bioisosteres of indoles and purines, are rarely found in nature.[1,2] There has been an increasing interest in azaindoles as versatile scaffolds, so-called 'privileged structures', in drug development.[3] For example, 3-oxoacetyl-4-benzoylpiperazino-substituted 6- and 7-azaindoles, such as BMS-488043 (**1**) and BMS-378806 (**2**), have been identified as promising antiviral agents active against HIV-1 (Fig. 1).[3a,b] The efficacy of **1** as a virus attachment inhibitor was demonstrated in vivo in HIV-1-infected patients.[4] The azaindole scaffold shows better water-solubility than the indole structure due to the pyridine fragment by featuring an additional site for protonation and salt formation.[5] Consequently, several synthetic methods for the construction of differently substituted azaindole derivatives involving a variety of heterocyclizations[6–12] and palladium-catalyzed heteroannulations[9e,13] have been developed. The most common methods have been inspired by various synthetic strategies applied for indole ring formation.[6,7] The majority of synthetic procedures was developed for the preparation of 7-azaindoles, while relatively a few have been applied to the synthesis of substituted 6-azaindole derivatives.[8,9a,b,10b,11,13b,c] This fact could be explained by the unfavorable electron-deficient character of the pyridine ring conditioned by an alteration of the π-electron system during the heterocyclization step.[6b,13d] Thus, many classical indole synthesis methods are not useful for the formation of 6-azaindole scaffold.[13d] Formally, 6-azaindoles can be considered as compounds formed by condensation of the π-electron-deficient pyridine ring and the π-electron-abundant pyrrole ring resulting in pyrrolo[2,3-*c*]pyridine.[14]

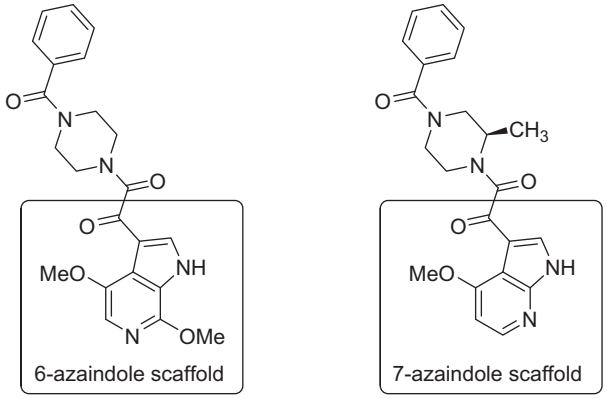

Figure 1. Anti-HIV agents with a 6- and 7-azaindole core.

In the present study we were interested in the preparation of 6-azaindole derivative substituted with an amino group in the 5- or 7-position, respectively. The desired structure consisting of a hydrogen bond acceptor (pyridine N) and an adjacent hydrogen bond donor (NH_2 function) in a bi-heterocyclic ring system would imitate the nucleobase adenine. Such compounds may interact with adenine nucleoside- and/or nucleotide-binding proteins, such as adenosine receptors,[15] P2 purinergic (ATP/ADP) receptors,[16] protein kinases,[17] nucleoside/nucleotide kinases,[18] and *ecto*-nucleotidases,[19] some of which are considered as important new drug targets. In contrast to unsubstituted 6-azaindole the synthesis of

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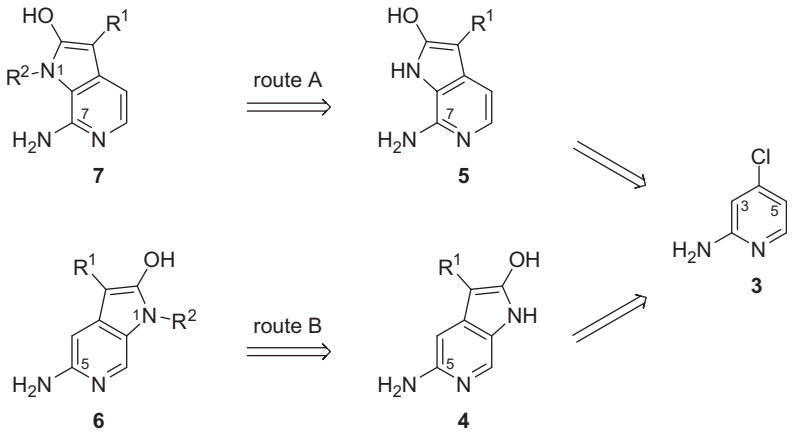


Scheme 1. Retrosynthesis of 5- and 7-amino-6-azaoxindoles.

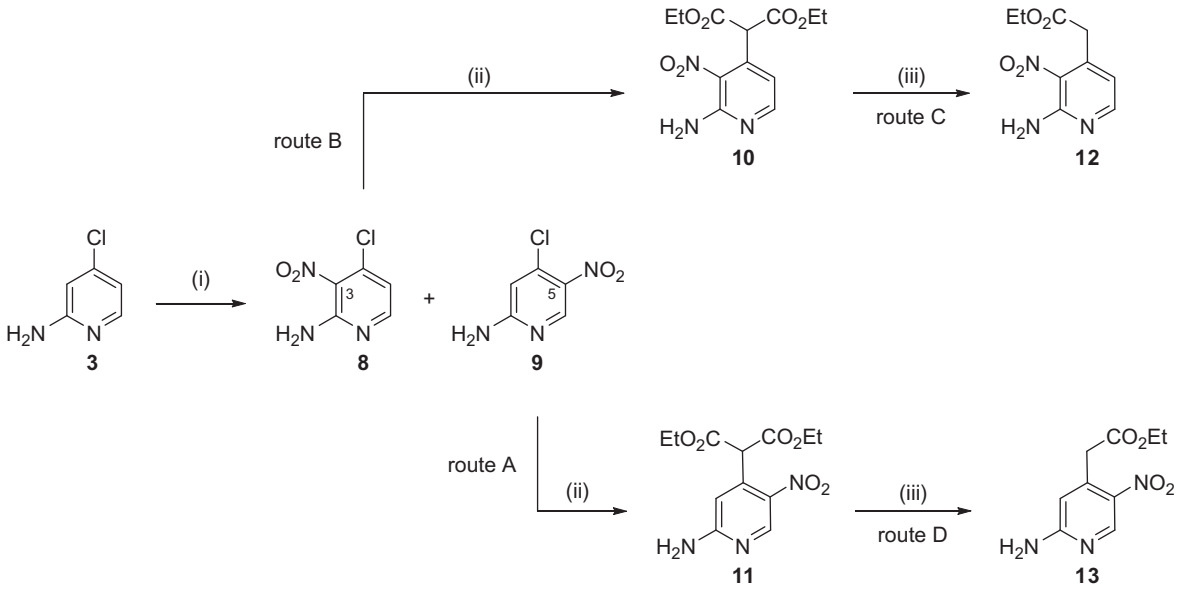
amino-substituted 6-azaindole derivatives is more difficult because of the existence of tautomeric forms, and due to the basicity of the amino function.

Herein we describe a synthetic access to 5-amino- and 7-amino-6-azaindole derivatives which allows a broad variation of the substitution pattern.

Our synthetic concept is illustrated in Scheme 1. Starting from 2-amino-4-chloropyridine (**3**) both, 5-amino- and 7-amino-2-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine (**4** and **5**) should be accessible. In either case the nitrogen atom N1 may be substituted with a variety of residues (R^2) in the very last step leading to compounds **6** and **7**, respectively.

5- and 7-aminosubstituted 6-azaoxindoles **4a**/**5a** and **4b**/**5b** were synthesized adapting a reaction procedure described for 6-azaindoles without the amino group.[20] We found that the reaction sequence did not require protection of the amino function (see Scheme 2). 2-Amino-4-chloro-3-nitropyridine (**8**) and 2-amino-4-chloro-5-nitropyridine (**9**) were prepared from **3** as previously described.[21]

Nitration of **3** yielded a mixture of 3- and 5-nitro-substituted regioisomers (**8**:**9** = 1.3:1) by 2-nitraminopyridine rearrangement.[22] The regioisomers were separated and isolated as described with some modifications and improvements.[23] Condensation of **8** and **9** with diethyl malonate using sodium hydride as a base in DMF[20a] afforded **10** (route A) and **11** (route B) in 82 and 73% yield, respectively. We observed that reaction times for the conversion of 3-substituted pyridines were shorter (40 min for **8** to **10** cf. 4 h for **9** to **11**) than for the 5-substituted regioisomer probably due to the faster mesomeric destabilization of the reactive intermediate **8** under basic conditions. This may be explained by the *para*-position of the amino group with respect to the nitro function in compound **9**, which is more favorable for mesomeric stabilization. Reduction of the nitro group in **10** and **11** followed by in situ heterocyclization led to the formation of 5-amino- and 7-amino-6-azaoxindoles **4a** and **5a** in 96% and 78% yields, respectively. Reductive cyclization was performed under two different conditions: (i) using a large excess of zinc dust in an acetic acid–water mixture (3:1) followed by heterocyclization with 25% aqueous ammonia solution at room



Scheme 2. Synthesis of ethyl 2-(2-amino-3/5-nitropyridin-4-yl)acetates **12** and **13**. Reagents and conditions: (i) (1) (c) H_2SO_4/c. HNO_3, 0–5 °C, 2–3 days, (2) H_2SO_4 (92%), 0 °C to rt, 3 h;[21–23] Yield 41% (**8**) and 30% (**9**); (ii) NaH (3.6 equiv), malonic acid diethyl ester (3.6 equiv), DMF, 40–50 °C, 50 min (for **10**) and 4 h (for **11**);[20] Yield 82% (**10**) and 73% (**11**); (iii) LiCl (3.0 equiv), DMSO, reflux, 28 h (for **12**) and 41 h (for **13**);[22] Yield 91% (**12**) and 75% (**13**).

Table 1
Yields and reaction conditions of the reductive cyclization step

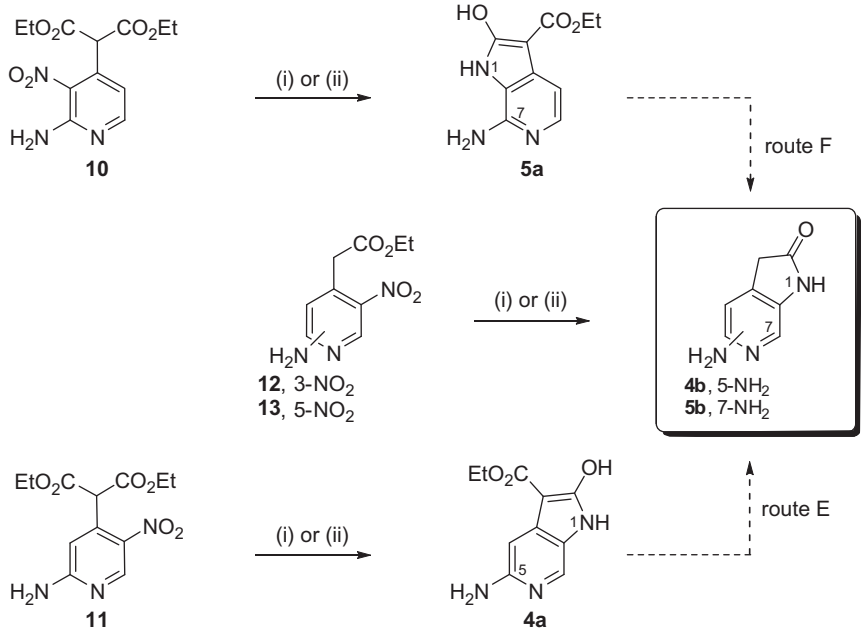
Starting compd.	Conditions[a]	Method	Solvent	Time (min)	Product	Yield (%)
10	(1) Zn (5.0 equiv), NH_4Cl	1	MeOH–THF (1:1)	120	**5a**	40[c]
	(2) NH_4OAc		H_2O	30		
10	(1) Zn (5.0 equiv)	1	AcOH–H_2O (3:1)	120	**5a**	65[d]
	(2) NH_4OH (25%)		H_2O	15		
10	(1) Zn (10.0 equiv)	1	AcOH–H_2O (3:1)	40	**5a**	74[d]
	(2) NH_4OH (25%)		H_2O	10		
10	(1) Zn (20.0 equiv)	1	AcOH–H_2O (3:1)	15	**5a**	78[d]
	(2) NH_4OH (25%)		H_2O	5		
10	(1) Pd/C (10%), 40 psi[b]	2	EtOH	120	**5a**	20[c]
	(2) HCl (18%)		EtOH	300		
11	(1) Zn (20.0 equiv.)	1	AcOH–H_2O (3:1)	30	**4a**	96[d]
	(2) NH_4OH (25%)		H_2O	10		
11	(1) Pd/C (10%), 40 psi[b]	2	EtOH	180	**4a**	94[d]
	(2) HCl (18%)		EtOH	720		
12	(1) Zn (20.0 equiv.)	1	AcOH–H_2O (3:1)	5	**5b**	78[d]
	(2) NH_4OH (25%)		H_2O	10		
13	(1) Zn (20.0 equiv)	1	AcOH–H_2O (3:1)	5	**4b**	65[c]
	(2) NH_4OH (25%)		H_2O	10		
13	(1) Pd/C (10%), 40 psi[b]	2	EtOH	90	**4b**	32[c]
	(2) HCl (18%)		EtOH	720		

[a] Reactions were carried out at room temperature.
[b] Hydrogenation was carried out in a Parr apparatus.[28]
[c] Product yields were determined by quantitative LC/ESI-MS of the free amines.
[d] Isolated yields.

temperature; (ii) in the presence of palladium as a catalyst in ethanol in a Parr hydrogenation apparatus and subsequent ring closure with 18% aqueous hydrochloric acid at room temperature (for more details, see Table 1). Pure products **4a** and **5a** were isolated and characterized by NMR and LC/ESI-MS analyses. Both products may exist as a mixture of their oxo and hydroxy tautomers. However, based on NMR analysis in DMSO we found that only the enol form was present, which can be explained by a stabilizing effect of the ester group at the 3-position of **4a** and **5a**.

In an attempt to apply this methodology for the preparation of 3-unsubstituted 5-amino- and 7-amino-6-azaoxindoles **4b** and **5b**, the malonic acid diethylester derivatives **10** and **11** were converted into the corresponding dealkoxycarbonylated compounds in analogy to a method described by Krapcho[25] using lithium chloride (3.0 equiv) in refluxing water:DMSO (1:1). The products **12** (route C) and **13** (route D) were isolated after purification by column chromatography in 91% and 75% yield, respectively (Scheme 2). In a subsequent step the acetic acid ethyl esters **12** and **13** were reductively cyclized yielding 5-amino- and 7-amino-6-azaoxindoles, **4b** and **5b** (Scheme 3). The same conditions could be successfully applied for the cyclization of **12** and **13** as for **10** and **11**. Alternatively, 3-unsubstituted amino-substituted 6-azaoxindoles may also be obtained by saponification and subsequent decarboxylation[27] of **4a** (route E) and **5b** (route F) (Scheme 3).[26] However, this procedure would require prior protection of the amino function to avoid side-reactions.

Different experiments were performed in order to improve the product yields of the key step of the synthesis of amino-substituted



Scheme 3. Synthesis of 5- and 7-amino-6-azaoxindole derivatives **4a,b** and **5a,b**. Reagents and conditions: (i) method 1;[23,24] (ii) method 2.[25]

6-azaindole derivatives, the reductive cyclization. Thus, solvent, reaction time, and the amount of reagents were varied (Table 1). In general, fast reactions and highest yields of **4a** (96%), **5a** (78%), and **4b** (65%) were obtained when the reduction was performed in AcOH:water (3:1) in the presence of a large excess of zinc dust (20.0 equiv) followed by ring closure in 25% aqueous ammonia at room temperature (method 1).[23,24] A similarly high yield of **4a** (94%) was obtained when the reduction was performed with palladium as a catalyst in ethanol in a Parr hydrogenation apparatus at 40 psi and subsequent treatment of the diamino intermediate with 18% aqueous hydrochloric acid (method 2).[25] However, the reductive cyclization took longer requiring a reaction time of up to 18 h. No significant improvement was observed for the preparation of **4b** and **5a** (32% and 20% determined yields) when using method 2.

In conclusion, the preparation of drug-like 5-amino- and 7-amino-6-azaoxindole derivatives, substituted at the 1- and 3-position, has been efficiently achieved. For this purpose, we applied a convergent synthetic concept starting from the commercially available 2-amino-4-chloropyridine (**3**) without the necessity for protection of the amino group. The reaction sequence involves reductive cyclization as a key step affording the 6-azaoxindoles **4a**/**5a** and **4b**/**5b** in a regioselective manner. The synthetic procedure was optimized for several steps. Our results demonstrate that the described procedures are suitable for the preparation of compound libraries that can be used for drug screening and drug development.

Acknowledgments

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Supplementary data

Supplementary data (all synthetic procedures and analytical data of compounds **4a**, **5a**, and **10–13**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.140.

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22. Optimization of the 2-nitraminopyridine rearrangement was achieved by stirring of the nitramine intermediate over night at −5 °C followed by neutralization of the reaction mixture with 25% aqueous ammonia solution.
23. The product ratio of the regioisomeric mixture **8**:**9** was determined by LC/ESI-MS analysis. The 3- and 5-nitro isomers **8** and **9** were separated by column chromatogryphy on silica gel following by recrystallization from dichloromethane:petroleum ether (1:1, 100 mL per 1.0 g of product), giving 41% and 30% yield, respectively.
24. Representative procedure for reductive cyclization of **8** and **9** (Table 1, method 1):
(a) *Ethyl 5-amino-2-hydroxy-1H-pyrrolo[2,3-c]pyridine-3-carboxylate* (***4a***): To a stirred solution of diethyl 2-(2-amino-5-nitropyridin-4-yl)malonate (**11**, 180 mg, 0.61 mmol) in AcOH:water (36 mL, 3:1) was added to zinc dust in small portions (800 mg, 12.2 mmol). The mixture was stirred at rt for 30 min and filtered under reduced pressure to remove the zinc dust. The residue was diluted with water (2 mL) and treated with 25% aqueous ammonia (10 mL). The resulting mixture was stirred at rt for 10 min and extracted with *n*-butanol (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was re-crystallized from ethyl acetate:petroleum ether and/or methanol (3:1, 15 mL) to yield 129 mg (96%) of the product as a white solid. Mp 328–330 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm]: 1.27 (t, J = 7.25 Hz, 3H, OCH_2CH_3), 4.10 (q, J = 7.25 Hz, 2H, OCH_2CH_3), 4.65 (s-broad, 2H, NH_2), 6.43 (s, 1H), 7.23 (s, 1H), 7.30 (d, J = 6.30 Hz, 1H), 9.13 (s, 1H, OH), 11.1 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ [ppm]: 15.2 (OCH_2CH_3), 56.9 (OCH_2CH_3), 95.9, 112.9, 114.1, 123.9, 137.1, 152.8, 159.7, 166.9 (O=COEt); LC/ESI-MS *m/z*: negative mode 220 ($[M-H]^-$), positive mode 222 ($[M+H]^+$). Purity (HPLC-UV 328 nm): 97.6%.
(b) *Ethyl 7-amino-2-hydroxy-1H-pyrrolo[2,3-c]pyridine-3-carboxylate* (***5a***): To a stirred solution of diethyl 2-(2-amino-3-nitropyridin-4-yl)malonate (**10**, 300 mg, 1.01 mmol) in AcOH: water (60 mL, 3:1) was added to zinc dust in small portions (1.32 g, 20.2 mmol). The mixture was stirred at rt for 15 min and filtered under reduced pressure to remove the zinc dust. The residue was diluted with water (3 mL) and treated with 25% aqueous ammonia (14 mL). The resulting mixture was stirred at rt for 5 min and extracted with *n*-butanol (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was re-crystallized from petroleum ether:dichloromethane:methanol (10:5:1, 16 mL) to yield 174 mg (78%) of the product as a white solid. Mp 302–303 °C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6) δ [ppm]: 1.25 (t, J = 6.94 Hz, 3H, OCH_2CH_3), 4.13 (q, J = 6.63 Hz, 2H, OCH_2CH_3), 6.84 (s-broad, 2H, NH_2), 7.01 (d, J = 8.10 Hz, 1H), 7.05 (d, J = 5.99 Hz, 1H), 7.30 (d, J = 6.30 Hz, 1H), 10.2 (s, 1H, OH), 11.6 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ [ppm]: 14.9 (OCH_2CH_3), 57.5 (OCH_2CH_3), 87.7, 104.5, 110.0, 126.0, 135.7, 137.9, 164.9, 166.5 (O=COEt); LC/ESI-MS *m/z*: negative mode 220 ($[M-H]^-$), positive mode 222 ($[M+H]^+$). Purity (HPLC-UV 342 nm): 98.6%.
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26. Ester cleavage of **5a** was achieved with lithium hydroxide in a methanol–THF solution (1:1) at room temperature. The yield was determined by quantitative LC/ESI-MS analysis. Initial experiments for decarboxylation under different conditions (e.g., 18% aqueous HCl solution, or LiCl in water–DMSO) showed a formation of by-products when the amino group remained unprotected.
27. Protection of the amino group in **8** and **9** was performed with *N*,*N*-dimethylformamide dimethyl acetal (DMA) in methanol at 75 °C for 16 h to yield the amino-protected pyridines in good yields (85% on average).
28. Hydrogenation was performed in a Hogen GC hydrogen generator (Proton Energy Systems, Inc.).