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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]

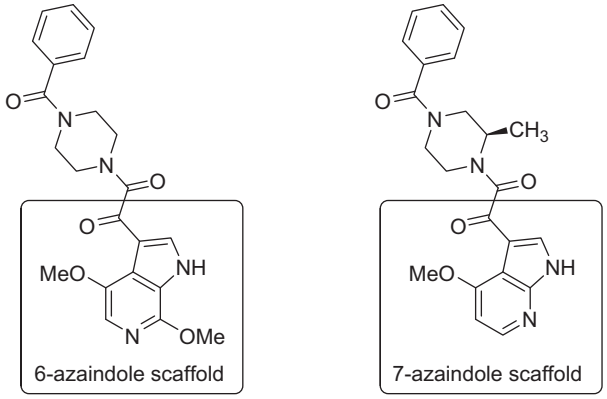

Figure 1. Anti-HIV agents with a 6- and 7-azaindole core.

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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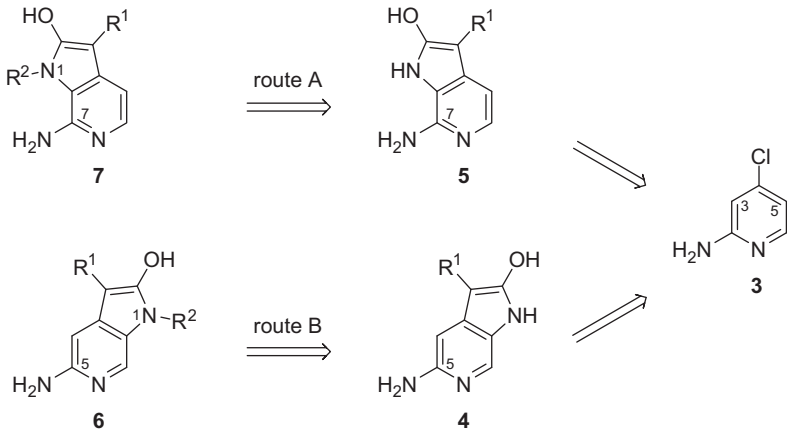


Scheme 1. Retrosynthesis of 5- and 7-amino-6-azaoxindoles.

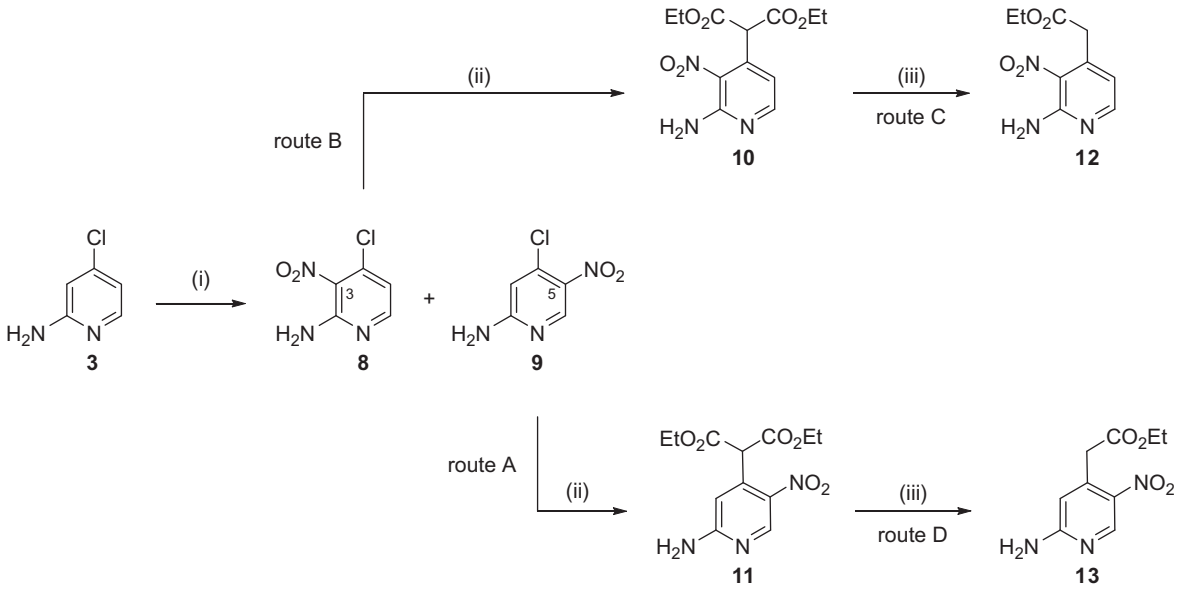
amino-substituted 6-azaindole derivatives is more difficult because of the existence of tautomeric forms, and due to the basicity of the amino function.

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**).