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A convenient synthetic route to substituted pyrrolo[2,3-*b*]pyridines via a novel ethylene-bridged compound

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ABSTRACT

A convenient synthetic route to 4-substituted pyrrolo[2,3-*b*]pyridines is presented. The novel ethylene bridged compound 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene was prepared and further derivatized. The novel synthesis was applied in the preparation of 3-cyano-4-hydroxypyrrolo[2,3-*b*]pyridine.

Pyrrolo[2,3-*b*]pyridines (7-azaindoles) are widely investigated for their promising biological activities as indole and purine bioisosteres. The pyrrolo[2,3-*b*]pyridine scaffold has been reported in various kinase inhibitors, as the ring heteroatoms are known to form hinge interactions in the kinase ATP binding site.[1] Several pyrrolo[2,3-*b*]pyridines have been reported as selective inhibitors of different isoforms of Janus kinase (JAK).[2] The complex pyrrolo[2,3-*b*]pyridine BMS-911543 is currently undergoing clinical trials as selective JAK-2 inhibitor.[3]

In contrast to indoles, the pyrrolo[2,3-*b*]pyridine scaffold is found in only few natural products, for example, the variolins. Variolins, alkaloids isolated from the Antarctic marine sponge *Kirkpatrick varialosa*, are potent cyclin-dependent kinase (CDK) inhibitors. Variolin B is an efficient activator of apoptosis, showing potent cytotoxic activity against a variety of human cancer cell lines, including those overexpressing P-glycoprotein, a cell efflux pump responsible for the resistance of cancerous cells to many chemotherapy agents.[4,5]

We have been interested in the biocatalytic synthesis and transformation of nitriles since several years.[6] Recently, we have investigated nitrile reductase queF,[7] an unprecedented enzyme catalyzing the reduction of a nitrile group to the corresponding amine.[8] 3-Cyano-4-hydroxypyrrolo[2,3-*b*]pyridine is a close structural analogue of the natural substrate, 2-amino-5-cyanopyrrolo[2,3-*d*]pyrimidin-4-one, of nitrile reductase queF and was thus synthesized for the investigation of the substrate scope of nitrile reductase queF.

Pyrrolo[2,3-*b*]pyridines are mostly synthesized starting from substituted pyridine precursors,[9–11] although syntheses starting from pyrrole precursors have also been reported.[12] Various routes known from indole synthesis, such as the Fischer, Madelung, or Reissert syntheses, are limited by their narrow scope, drastic reaction conditions, and poor yields.[5] Palladium catalyzed reactions have proven an invaluable tool in the synthesis of pyrrolo[2,3-*b*]pyridines.[10] Most notably, a number of pyrrolo[2,3-*b*]pyridines have been prepared by Sonogashira coupling of a 3-halosubstituted 2-aminopyridine. The resulting alkynylpyridines were then reacted under a variety of conditions to give the desired pyrrolo[2,3-*b*]pyridines.[11]

Here, we report a novel synthetic route for the preparation of 4-substituted pyrrolo[2,3-*b*]pyridines. 1,2-Bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (Schemes 1 and 2) was serendipitously discovered as product of the condensation reaction of 2-amino-4-azidopyridine with chloroacetaldehyde. 1,2-Bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**) was then used as a starting point for the subsequent synthesis of 3,4-disubstituted pyrrolo[2,3-*b*]pyridines, including the desired 3-cyano-4-hydroxypyrrolo[2,3-*b*]pyridine.

We have previously used the condensation reactions of chloroacetaldehyde with an appropriately substituted pyrimidine precursor for the synthesis of pyrrolo-[7b] and thieno[2,3-*d*]pyrimidines[13] (see Electronic supplementary information) and intended to apply this reaction for the synthesis of pyrrolo[2,3-*b*]pyridines. The reaction of chloroacetaldehyde with 2-amino-4-hydroxypyridine did

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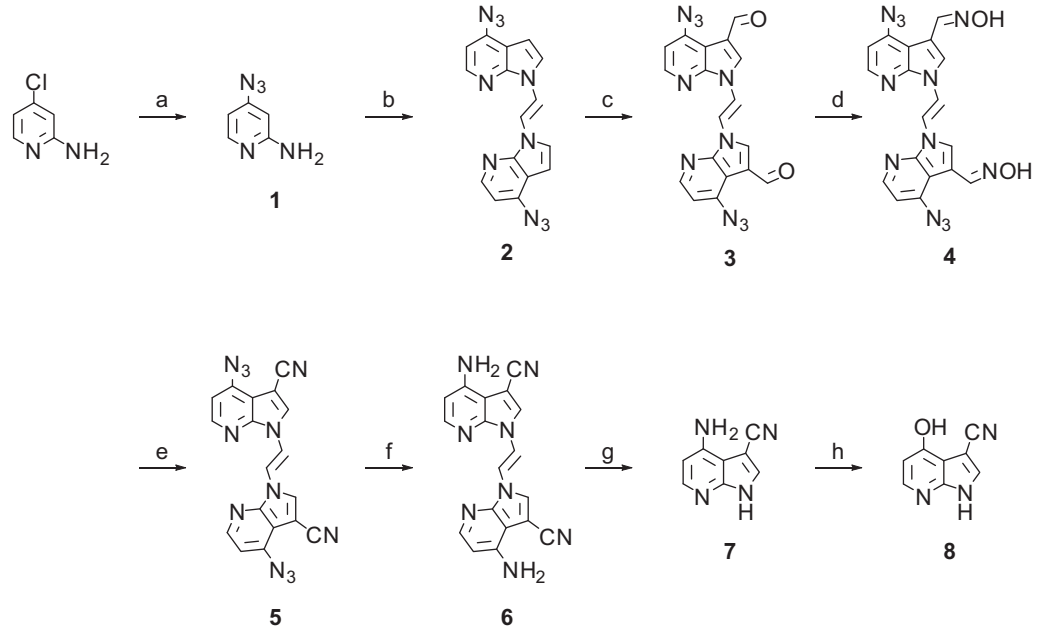
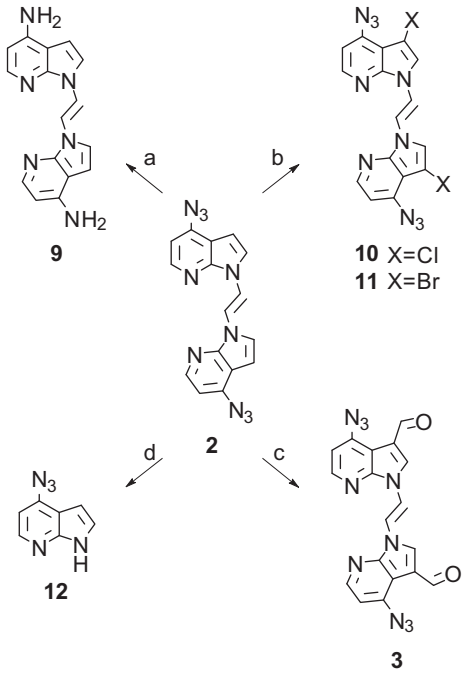


Scheme 1. Synthesis of 5-cyano-4-hydroxypyrrolo[2,3-*b*]pyrimidine. Reagents and conditions: (a) sodium azide, DMF, ammonium formate, 120 °C, yield 53%; (b) chloroacetaldehyde, sodium acetate trihydrate, water, 60 °C, yield 78%; (c) $POCl_3$, DMF, yield 54%; (d) hydroxylamine hydrochloride, ethanol, aq NaOH, yield 82%; (e) (1) acetic anhydride, (2) acetic acid, reflux, yield 17%; (f) Pd/C, THF, hydrogen, yield 87%; (g) $NaIO_4$, $NaClO_2$, OsO_4, acetonitrile, water, yield 57%; (h) $NaNO_2$, acetic acid, water, 100 °C, yield 87%.



Scheme 2. Reactions starting from 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**). Reagents and conditions: (a) Pd/C, ethanol, 25 bar hydrogen, steel autoclave, yield 88%; (b) NBS, THF, rt, yield 49% or NCS, THF, rt, yield 78%; (c) $POCl_3$, DMF, yield 54%; (d) $NaIO_4$, $NaClO_2$, OsO_4, acetonitrile, water, yield 54%.

not give the expected 4-hydroxypyrrolo[2,3-*b*]pyridine as product, but 1-(2-chloroethenyl)-4-hydroxypyrrolo[2,3-*b*]pyridine. Protection of the hydroxyl group as methoxy group gave a complex mixture of undesired products in the condensation reaction.

The reaction of chloroacetaldehyde with 2,4-diaminopyridine gave the desired product 4-aminopyrrolo[2,3-*b*]pyridine in 15% yield and a byproduct resulting from the condensation of a second molecule of chloroacetaldehyde to the desired product. With increasing reaction time, only the amount of byproduct increased to up to 50% conversion after four hour reaction time, while the amount of the desired product 4-aminopyrrolo[2,3-*b*]pyridine could not be increased.

We then investigated 2-amino-4-azidopyridine (**1**) as the starting material for the condensation reaction with chloroacetaldehyde. Unexpectedly, 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**) was formed as the only product and was initially isolated in 54% yield. The yield was further improved by a brief optimization of the reaction conditions to 78% (Scheme 1). The preparation of an ethylene-bridged pyrrolo[2,3-*b*]pyridine has so far not been reported in the literature. The ethylene bridge acts as an atom efficient protecting group of the pyrrole nitrogen, thereby offering advantages over the unprotected pyrrolo[2,3-*b*]pyridine.

1,2-Bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**) was a useful starting material for a number of subsequent reactions (Scheme 2). The azide group was reduced to give 1,2-bis(4-aminopyrrolo[2,3-*b*]pyridinyl)ethene (**9**) in 88% yield. Compound **9** could be interesting for further derivatization, for example, in amide couplings, Buchwald–Hartwig type cross-couplings, or reductive aminations. Chlorination and bromination in position 5 of 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**) was readily achieved to give compounds **10** and **11**. These halide substituted compounds are particularly interesting as starting materials in palladium catalyzed reactions. The ethylene bridge of 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**) was cleaved by dihydroxylation and periodate cleavage in a one pot procedure using sodium chlorite for the re-oxidation of the osmium tetraoxide. Dihydroxylation and periodate cleavage of the ethylene bridge of compound **2** results in a formyl group on the pyrrole nitrogen. The use of basic work up conditions with isopropanol/sodium hydroxide[14] quantitatively cleaved the formyl group, giving 4-azidopyrrolo[2,3-*b*]pyridine (**12**) as the only product in one step from the bridged compound **2**.

Formylation of pyrrolo[2,3-*b*]pyridines in position 5 is most commonly achieved using the Duff,[15] or Vilsmeier–Haack[16]

reaction. The Duff reaction was originally reported for the preparation of 3- and 5-formylsalicylic acids.[17] The reaction proceeds in a series of equilibrium reactions. A secondary amine is formed with hexamethylenetetramine, which is then dehydrogenated to Schiff bases by heating in acetic acid. The Schiff bases can then be hydrolyzed to give aldehydes. 4-Azidopyrrolo[2,3-*b*]pyridine (**12**) was used as the starting material for Duff and Vilsmeier–Haack formylation reactions. 4-Azido-3-formylpyrrolo[2,3-*d*]pyridine was obtained using both formylation conditions. Yields and product purity were relatively low, in particular for the Duff reaction. In contrast, the Vilsmeier–Haack formylation of 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**) gave the formylated product **3** in 54% and high purity.

The ethylene bridged pyrrolo[2,3-*b*]pyridine system was beneficial in the formylation reaction, consequently we decided to proceed with the bridged pyrrolo[2,3-*b*]pyridine **3**. The subsequent step to give the oxime 1,2-bis(4-azido-3-(hydroxyiminomethyl) pyrrolo[2,3-*b*]pyridin-1-yl)ethene proceeded in excellent yield of 82% and gave the (*E*)/(*Z*)-isomers in a ratio of 1.6:1. Dehydration of the oxime to the corresponding nitrile (**5**) was carried out with acetic anhydride. The (*Z*)-oxime was quantitatively converted into the nitrile, as observed by NMR, however the (*E*)-oxime was *O*-acetylated under the reaction conditions. The *O*-acetylated (*E*)-oxime was then converted into the nitrile (**5**) by reflux in acetic acid.

Cyano groups in position 3 of pyrrolo[2,3-*b*]pyridines have been introduced by dehydration of the oxime,[18] or palladium catalyzed C–H cyanation.[19,20] Direct cyanation with chloro-sulfonylisocyanate has been reported for a number of heterocycles including indoles.[21] Direct cyanation of 1,2-bis (4-azidopyrrolo[2,3-*b*]pyridinyl)ethene (**2**) was not successful in our hands, while formylation proceeded in good yield and purity.

The azide group in 1,2-bis(4-azido-3-cyanopyrrolo[2,3-*b*] pyridin-1-yl)ethene (**5**) was reduced to the corresponding amino-group in a hydrogenation reaction with platinum or palladium on charcoal as the catalyst. Higher yields were obtained using palladium on charcoal. Cleavage of the ethylene bridge was carried out analogously as for 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridin-1-yl) ethene (**2**) and similar yields of 57% were observed. In the final step, the 4-amino substituent was converted into a hydroxyl group in a diazotization reaction. The desired product 3-cyanopyrrolo [2,3-*b*]pyridine was obtained in 87% yield.

We have presented a novel synthetic route for the preparation of 4-substituted pyrrolo[2,3-*b*]pyridines, via the novel ethylene-bridged compound 1,2-bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene. 1,2-Bis(4-azidopyrrolo[2,3-*b*]pyridinyl)ethene was shown to be a useful starting material for a number of subsequent reactions. 3-Cyano-4-hydroxypyrrolo[2,3-*b*]pyridine was successfully prepared using this novel synthetic route.

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Supplementary data

Supplementary data (synthetic procedures and characterization data, including graphical NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.031.

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