Synthesis of 3-formyl-6-azaindoles *via* Vilsmeier-Haack formylation of 3-amino-4-methyl pyridines

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ABSTRACT: An efficient method for the preparation of 6-azaindoles bearing 3-formyl functionality from commercially available substrates with (*ortho*-methyl)aminopyridine moiety is described. This transformation features a distinct, though broad, substrate scope, and simple experimental procedure and can easily be scaled up to 40 g of the target formyl derivative. The structural characteristics of pyridine substrates that allow them to be successfully used in the reaction were investigated and discussed. Collected observations were mechanistically rationalized and the proposed mechanism was additionally confirmed by spectroscopic studies. Mechanistic studies clearly reveal the crucial role of the methyl group activation by *in situ* protonation of in-ring nitrogen atom. Functional group interconversions employing synthesized 3-formyl-6-azaindoles additionally prove this building block utility for MedChem investigations.

Key words: 6-azaindoles, [4+1]-cyclization, formylation, medicinal chemistry, building blocks

INTRODUCTION

A heterocyclic system of 1*H*-pyrrolo[2,3-c]pyridine, also named 6-azaindole, is a valuable object for medicinal chemistry[1]. The system has brought FDA-approved HIV entry inhibitor ***Fostemsavir***[2] and promising drug **YH4808** against reflux esophagitis, which achieved Phase 2 clinical trials.[3] In addition, the 6-azaindole scaffold is actively exploited in early-stage drug discovery. As an example, a lead biopharmaceutical company Bristol Myers Squibb has recently developed promising compound **III** for treating inflammatory and autoimmune diseases *via* inhibition of signaling through Toll-like receptors 7 or 8, or 9,[4] and Janssen Pharmaceutica company has released an effective menin/MLL protein/protein interaction inhibitors **IV** useful for treating cancer diseases[5] (**Figure 1**). Therefore, the development of effective synthetic pathways toward MedChem-relevant building blocks with 6-azaindole core is still an urgent task, even could be subject to patent.[6] 3-Formyl-6-azaindoles are valuable building blocks that could either be directly used for the preparation of promising bioactive compounds[7,6,8], or be transformed into other derivatives using classical functional group interconversion procedures. However, we were surprised by the fact that in the Reaxys database the parent aldehydes, unsubstituted at pyrrole ring, are presented only by 20 examples, 4 of which are reported in journal articles, and the rest in patents. The published approaches are based on the formylation of 6-azaindoles **VI** by Duff with urotropine[9] or by Rieche with Cl_2CHOMe[7] (**Figure 2**). Recently our group disclosed a scalable and efficient synthesis of 2-trifluoromethyl-3-trifluoroacetyl-6-azaindoles from 3-amino-4-methylpyridines under treatment with TFAA[10,11]. We found that the reaction is critically sensitive to the steric hindrance around the pyridine nitrogen atom. In the course of this work, we found a neglected procedure by Parrick described in 1970 where the simplest 3-formyl-6-azaindole was obtained by Vilsmeier-Haack formylation in 19% yield. We re-checked and optimized the approach and achieved a yield of 62% for the simplest representative. In this work, we present the

study concerning the scope and limitations of 3-formyl-6-azaindoles synthesis *via* Vilsmeier-Haack formylation of corresponding 3-amino-4-methyl pyridines **VII** (**Figure 2**).

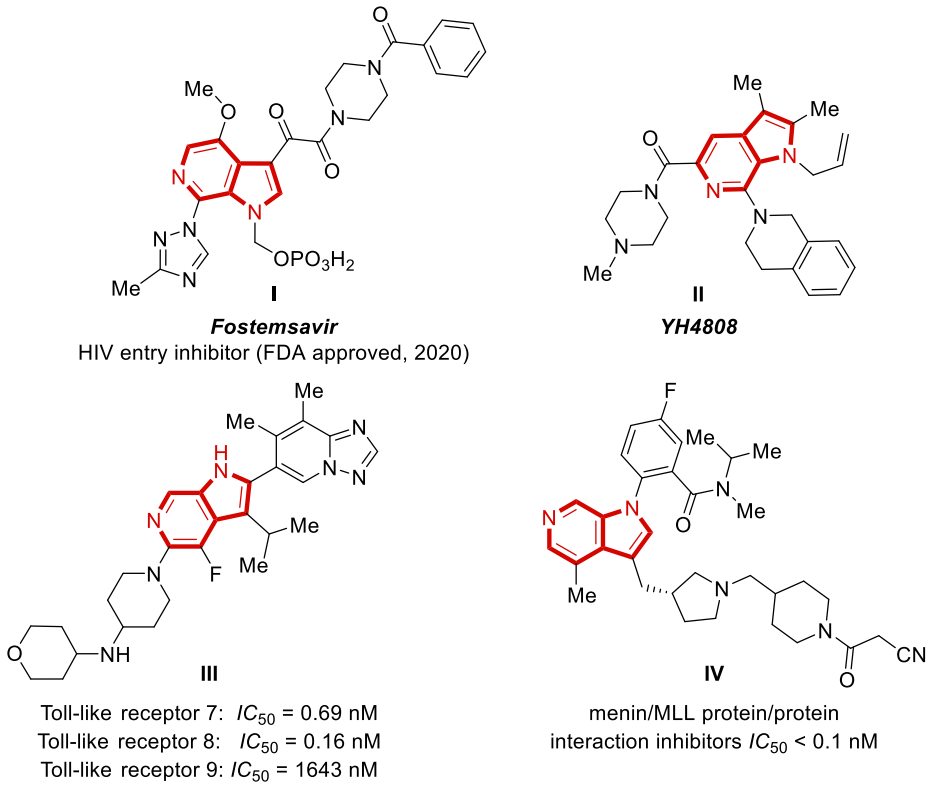


Figure 1. MedChem valuable derivatives of 6-azaindole

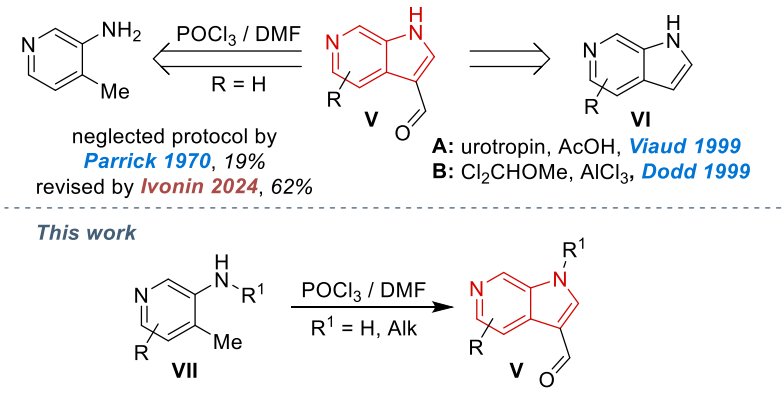


Figure 2. Reported approaches to 3-formyl-6-azaindoles

RESULTS AND DISCUSSION

For these systematic investigations of the reaction, we chose a set of 3-amino-4-methyl pyridine derivatives listed in **Figure 3**. To the set, NHMe derivative **1h** and 3-amino-2-methylpyridine (**2**) were added as well. To test reactivity of the substrates the standard protocol was applied. To DMF (20 mL) $POCl_3$ (3.2 mL, 33 mmol) was added at rt with stirring. After 15 min to the resulting solution pyridine **1** or **2** (10 mmol) was added and the reaction mixture was kept at rt with stirring for 48 hours. Then the precipitate formed was filtered off, washed with MeCN (*ca*. 10 mL) and dissolved in water (*ca*. 30 mL). The solution formed was alkalized by K_2CO_3 to pH 10 and a solid formed was filtered off. In case the precipitate was not formed the alkaline solution was extracted

by EtOAc (3×30 mL), and the organic phase was separated, dried over Na_2SO_4, and the solvent was evaporated *in vacuo*, thus affording a pure reaction product.

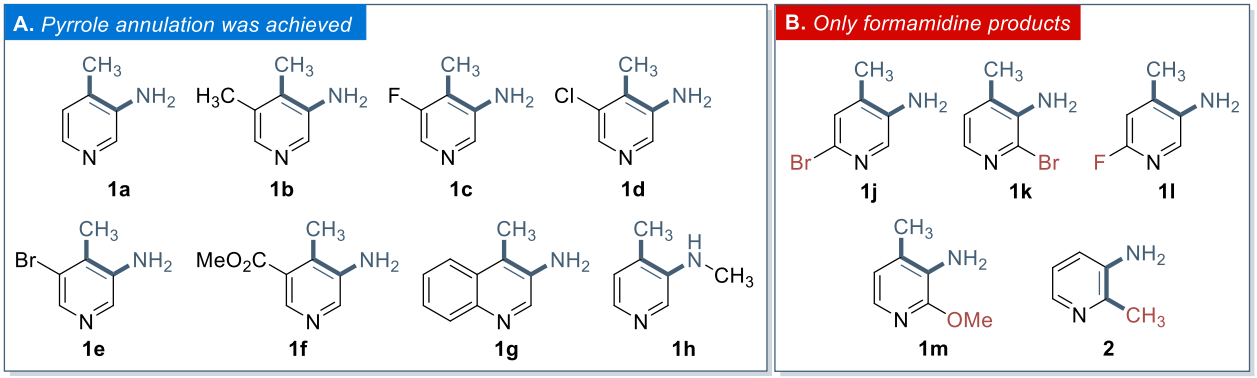
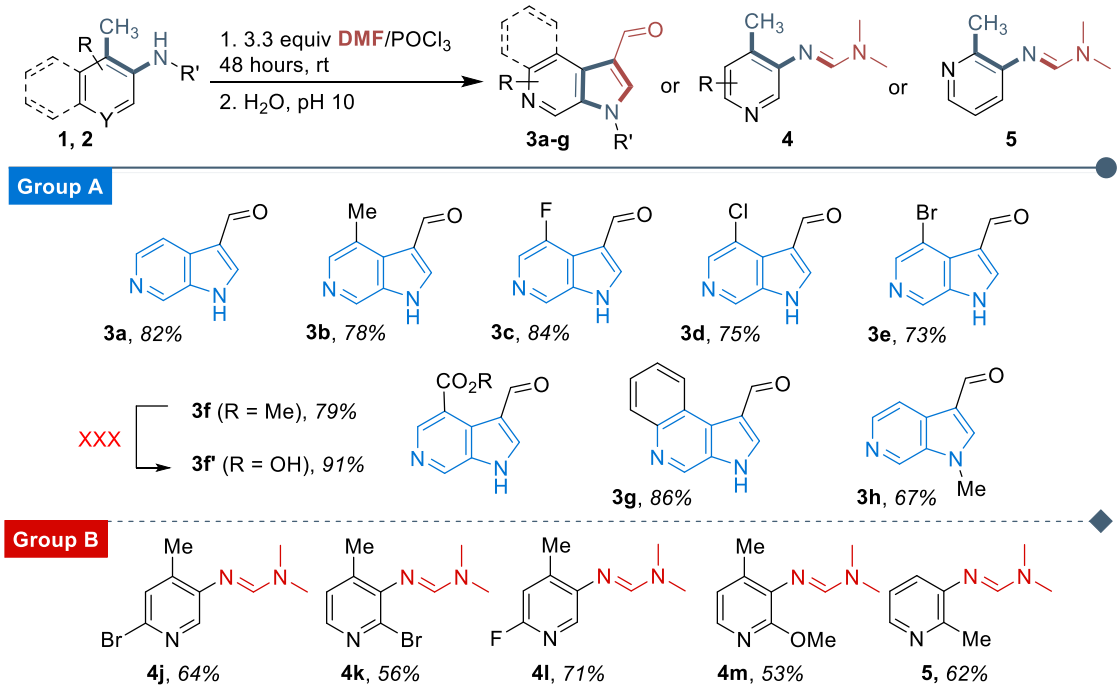


Figure 3. Starting cyclization counterparts used in the research

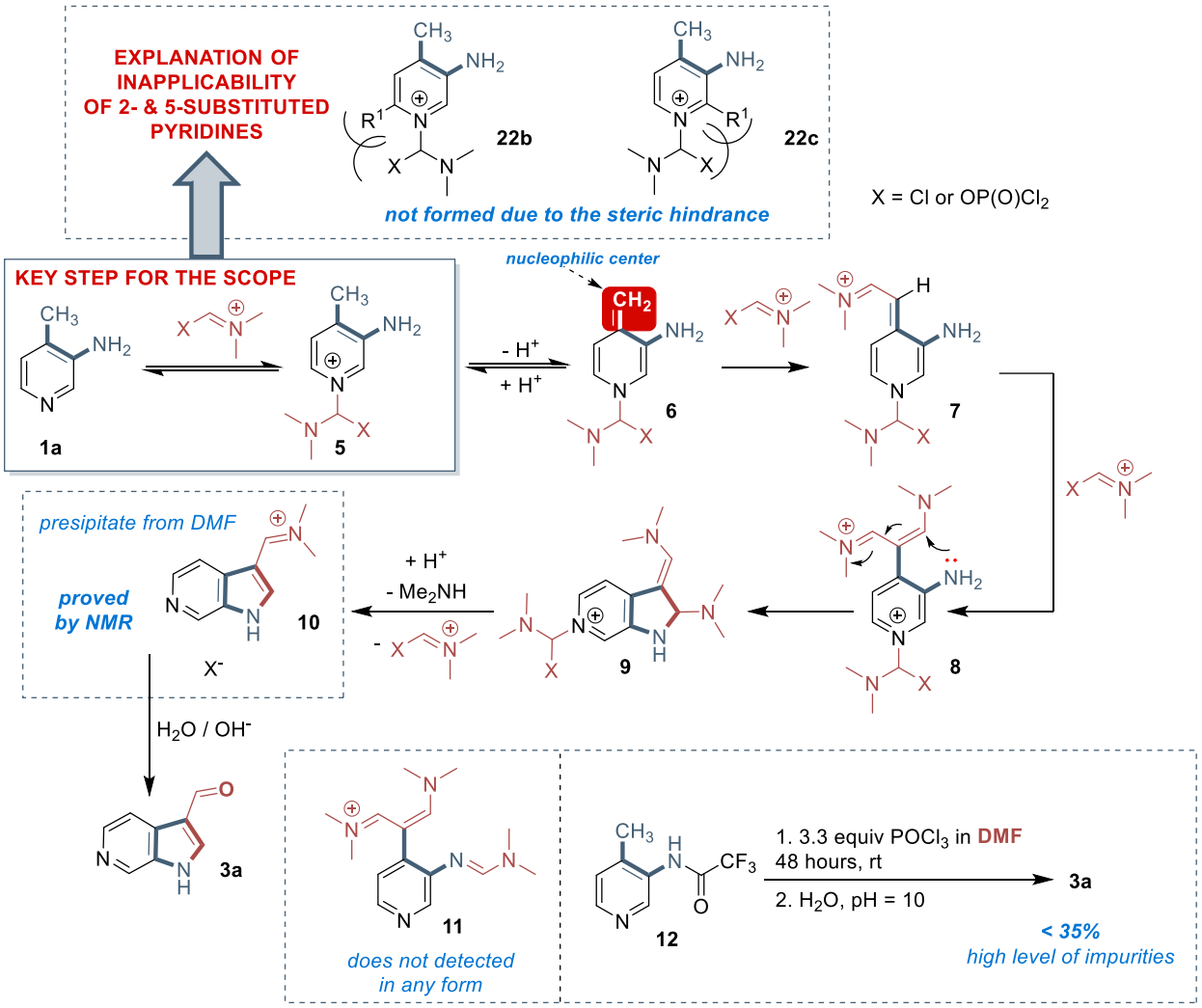
As in the case of trifluoroacylation, formylation divided the set of pyridine counterparts into two groups. For one group of the starting pyridines the corresponding 3-formyl-6-azaindoles **3a-g** were isolated in good preparative yields. Another group provided furnished only corresponding formamidine derivatives **4j-m** and **5** (**Scheme 1**). According to the earlier established regularities, the current cyclization was sensitive to the presence/absence of a group in α-position of the pyridine ring. We hoped that the switch of the reaction conditions from basic (for trifluoroacylation) to acidic (for the Vilsmeier-Haack formylation) could alter the reaction scope due to protonation of the pyridine ring that in turn should have led to the activation of the methyl group. However, all α-substituted pyridine derivatives gave only the product of amino group functionalization.



Scheme 1. Formylation of 3-amino-4-methylpyridines

We assumed, that mechanistically this cyclization proceeds likewise to trifluoroacylation reaction as we described before. A key step of the cyclization is quaternization of the pyridine nitrogen by the Vilsmeier reagent resulting in salt **5** containing an activated methyl group with pronounced CH-acidity. An indirect evidence of this stage is the reaction scope. The introduction of a

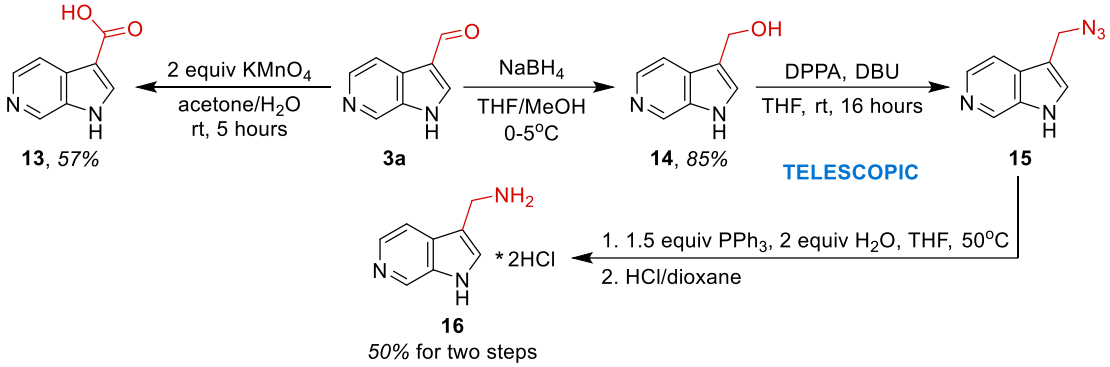
substituent in α-position of the pyridine ring creates steric hindrance, which prevents quaternization and makes activation of the methyl group impossible. The following deprotonation of **5** leads to a highly reactive C-nucleophile **6**, which enters double formylation affording vinamidinium salt **8**. The intramolecular 5-exo-trig cyclization of **8** leads to salt **10**, which precipitates from the reaction media. This salt with an anion of variable composition was isolated and characterized by NMR (*see* SI). Salt **10** was found to be very hygroscopic and easily hydrolyzed. Our attempts to convert it to salt with a single anion (PF_6^-, BF_4^- or ClO_4^-) failed. In all cases, partial hydrolysis occurred. The complete hydrolysis was achieved in alkaline water. Our assumption that the amino group remains intact during the methyl group formylation was proved by the next observations. NMR investigation of the reaction mixtures and precipitates did not detect the structures of type **11**. Moreover, introducing TFA-derived amine **12** to the protocol led to a low yield of the final product with a high level of impurities (**Scheme 2**).



Scheme 2. Mechanistic explanation of the scope and limitation of the reaction

Finally, taking into account that N(1)-H–N(6)-H tautomerism of the 6-azaindoles could bring some "surprises" to aldehyde function reactivity we tested it in in-house protocols for electron-rich aldehydes. The low accessibility of aldehydes **3** has led to only 10 single-step reactions (4 from journal articles) employing **3a** according to the Reaxys database. In our hands aldehyde **3a** was oxidized to acid **13** by $KMnO_4$. As far as we know, this 2-step pathway to simple parent acid **13** is the most efficient among existing ones; it was also scaled up to 40 g of **13** from one run (**Scheme 3**). In previous works acid **13** was obtained *via* multistep synthesis utilizing commercially

unavailable starting materials.[12] Aldehyde **3a** could be easy reduced to alcohol **14** by $NaBH_4$. This alcohol was tested for the direct conversion to azide **15** using DPPA–DBU system[13]. The reaction was used by us to test the stabilization of corresponding "carbocationic" intermediates. Alcohol **14** gave corresponding azide **15** under the mentioned conditions, and the latter was converted to amine **16** by PPh_3 – H_2O treatment in a telescopic fashion.



Scheme 3. Simple FGI of compound **3a**

CONCLUSION

In summary, herein we report a new, one-pot, scalable and metal-free synthesis of 3-formyl-6-azaindoles starting from 3-amino-4-methylpyridines under Vilsmeier-Haak reaction conditions. The reaction is regioselective, requires no catalysts, scalable to more than 50 g from one synthetic run and easy to perform. The reaction scope covers β-substituted 3-amino-4-methylpyridines. Meanwhile α-substituted counterparts do not give cyclized products and the reaction stops at the corresponding formamidine step. Such a difference was rationalized by the reaction mechanism involving the formation of pyridinium salt as a key step of the methyl group activation.

EXPERIMENTAL PART

General procedure for the synthesis of 1*H*-pyrrolo[2,3-*c*]pyridine-3-carbaldehydes 3

$POCl_3$ (3.3 equiv) was added dropwise to DMF (10 mL) and the mixture was stirred for 15 min at room temperature. Then, the corresponding aminomethylpyridine **1** (1 mmol) was added to the resulting solution and continued to stir for 48 hours at room temperature. The formed precipitate was filtered off, washed with CH_3CN, dissolved in water and neutralized with a K_2CO_3 solution to pH 10. The solid was filtered off, washed with water and dried to give a title product.

General procedure for the synthesis of formamidines 4 and 5

$POCl_3$ (3.3 equiv) was added dropwise to 10 mL of DMF and the mixture was stirred for 15 min at room temperature. Then, the corresponding aminomethylpyridine **1** (1 mmol) was added to the resulting solution and continued to stir for 48 hours at room temperature. The formed precipitate was filtered, washed with CH_3CN, dissolved in water and neutralized with K_2CO_3 solution to pH 10. The mixture was extracted with ethyl acetate (2×10 mL), the organic layer was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* furnishing the title product.

Procedure for the preparation of (1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)methanol (14)

A solution of aldehyde **3a** (0.15 g, 1 mmol) in 15 mL of THF-methanol (2:1) mixture was cooled to 0-5°C followed by addition of $NaBH_4$ (0.06 g, 1.5 mmol). The mixture was stirred at room temperature for 16 hours. After that, the mixture was evaporated to dryness, diluted with 10 mL

of water, the precipitate was collected by filtration, washed with water and dried. Yield – 127 mg (85%), white powder.

Procedure for the preparation of 3-(azidomethyl)-1*H*-pyrrolo[2,3-*c*]pyridine (15)

Diphenylphosphorylazide (0.33 g, 1.2 mmol) was added to a mixture of alcohol **14** (0.148 g, 1 mmol) and DBU (0.18 mL, 1.2 mmol) in THF (10 mL) and the mixture was stirred for 16 h at room temperature. The lower organic layer was separated from the reaction mixture and used in the next step without additional purification. Yield – 173 mg (100%), brown oil.

Procedure for the preparation of (1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)methanamine dihydrochloride (16)

To a solution of azide **15** (0.173 g, 1 mmol) in THF (15 mL) obtained in previous step was added water (0.036 mL, 2 mmol) and triphenylphosphine (0.39 g, 1.5 mmol). The reaction mixture was heated at 50°C for 16 hours and cooled to room temperature. Then HCl/dioxane solution was added to reach pH 2. The formed precipitate was filtered off, washed with THF and dried. The resulting solid was purified by recrystallization from methanol. Yield – 110 mg (50%), dihydrochloride, white powder.

Procedure for the preparation of 1*H*-pyrrolo[2,3-*c*]pyridine-3-carboxylic acid (13)

To a solution of aldehyde **3a** (0.05 g, 0.33 mmol) in acetone (1.25 mL) was added solution of $KMnO_4$ (0.1 g, 0.66 mmol) in water (0.62 mL) and the resulting mixture was stirred for 5 hours at room temperature. Acetone was evaporated, the residue was filtered, and the filtrate was acidified to pH 2. The resulting solution was evaporated to dryness giving the target product. Yield – 32 mg (57.6%) of hydrochloride, yellow-brown powder.

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