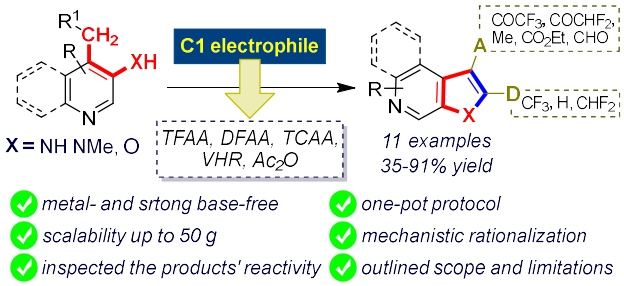
Synthesis of 6-azaindoles via electrophilic [4+1]-cyclization of 3-amino-4-methyl pyridines: scope and limitations

Sergey P. Ivonin,[a] Volodymyr V. Voloshchuk,[a,b] Eduard B. Rusanov,[a] Sergey Suikov,[a] Serhiy V. Ryabukhin,*[a,b,c] and Dmytro M. Volochnyuk*[a,b,c]

[a]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Academik Kukhar str., Kyiv, Ukraine*
[b]*Enamine Ltd, 78 Winston Churchill str., Kyiv, Ukraine*
[c]*Taras Shevchenko National University of Kyiv, 60 Volodymyrska str., Kyiv, Ukraine*

Abstract: A scalable and efficient synthesis of the 2-trifluoromethyl-3-trifluoroacetyl-6-azaindoles from 3-amino-4-methylpyridines under treatment with TFAA was disclosed. The reaction scope and limitation towards the pyridine and electrophilic components were investigated. Examining the pyridine components using trifluoroacetic anhydride (TFAA) as a model electrophile allowed us to divide them into three groups with different impacts on the reaction outcome. Among electrophilic components difluoroacetic anhydride (DFAA), trichloroacetic anhydride (TCAA) and Vilsmeier-Haack reagent (VHR) were inspected. The results superposition led to a cyclization mechanism rationalizing our observations.

Key words: 6-azaindoles, [4+1]-cyclization, medicinal chemistry, building blocks, 3-aminopyridines.



Introduction

A heterocyclic system of 1*H*-pyrrolo[2,3-*c*]pyridine, which is also named 6-azaindole, is a valuable object for medicinal chemistry. This core is not represented in nature as is. Still, its benzofused analogue β-carboline is a well-known scaffold for the plenty of natural compounds (787 structures are presented in the Reaxys database). Recently representatives of another benzofused system, 3*H*-pyrrolo[2,3-*c*]quinoline have been found in natural objects, e.g. antiplasmodial alkaloid ***Aplidiopsamine A*** [1] and antifungal ***Pyonitrin*** family [2] (**Figure 1, A**). However, 6-azaindole heterocyclic system has brought an FDA approved HIV entry inhibitor ***Fostemsavir*** [3]. In 2009 this system was also found by GSK scientists as a template for the construction of potassium competitive acid blockers (pCABs) [4], which led to the developing by Yuhan Research Institute [5] a promising drug candidate **YH4808** against reflux esophagitis having achieved Phase 2 of clinical trials [6]. Furthermore, Bristol Myers Squibb has recently developed a promising compound incorporating a 6-azaindole scaffold for treating inflammatory and autoimmune diseases via inhibition of signaling pathways through Toll-like receptors 7, 8, or 9 [7] (**Figure 2, B**). All the mentioned indicate a growing need for efficient synthetic approaches to MedChem relevant building blocks comprising the 6-azaindole core.

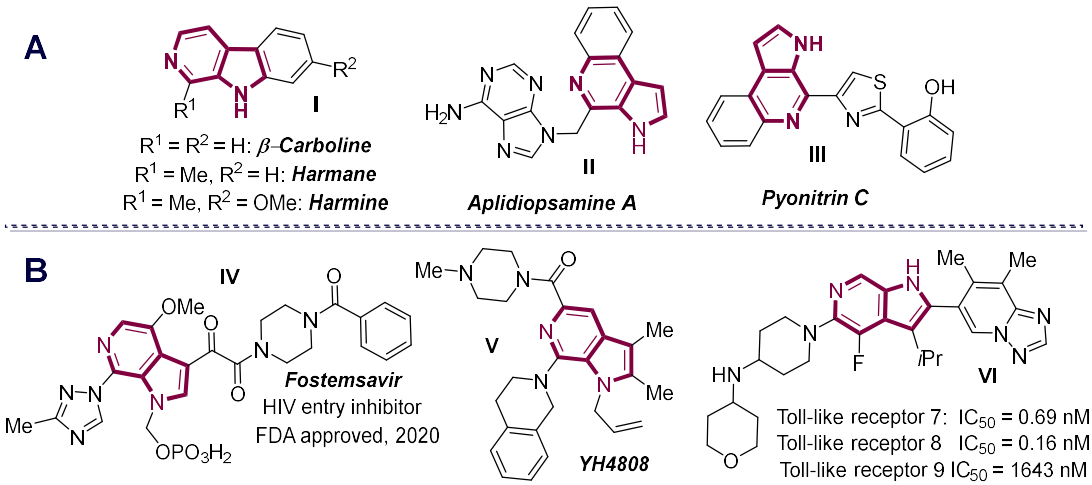


Figure 1. Naturally occurring (**A**) and MedChem valuable (**B**) derivatives of 6-azaindoles

Recently, our group has elaborated a scalable and efficient synthesis of 2-trifluoromethyl-6-azaindole from 3-trifluoroacetylamino-4-methylpyridine [8], recognized by the scientific community [9]. The method was based on a formal [4+1] cyclization, where TFAA plays the role of C1-bielectrophile and additionally acts as a trifluoroacetylating agent (**Figure 2, A**). Such [4+1] cyclizations based on 3-amino-4-methyl pyridines and carboxylic acid derivatives are plenty rare and require preliminary methyl group activation by a strong organolithium base, which is intolerant to the majority of functional groups [10, 11, 12] (**Figure 2, B**). As far as we know, there is only one example, besides our work, describing 3-amino-4-methylpyridine [4+1] cyclization without prior organolithium activation. In this case, the product was achieved with the use of the Vilsmeier-Haack reagent (VHR) as C1-bielectrophile [13] and the reaction was accompanied by an additional electrophilic functionalization at the pyrrole ring (formylation). Keeping in mind the importance of the scope and limitation issues of rare and unusual reactions, we decided to investigate comprehensively the [4+1] base-less cyclization and eventually to outline the applicable substrate range.

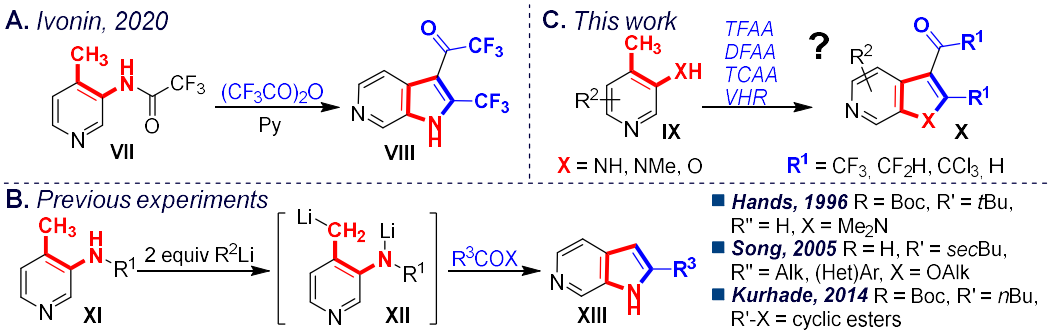


Figure 2. Electrophilic [4+1]-cyclization of 3-amino-4-methylpyridines to 6-azaindoles

Results and discussion

For the systematic investigations of the [4+1]-cyclization we chose a set of 3-amino-4-methylpyridine derivatives (**Figure 3**). Besides diverse ring-substituted 3-amino-4-methylpyridines **1d-f,j-m**, 3-hydroxy-4-methylpyridine (**1b**), 3-methylamino-4-methylpyridine (**1c**), 3-amino-4-methylquinoline (**1g**) were added to the list as well. For a deeper understanding of the reaction scope 4-ethyl and 4-CH_2CO_2Et substituted pyridines **1h** and **1i** with active methylene group were also tested. Additionally, isomeric 3-amino-2-methyl pyridine (**2**) as well as two diazine derivatives **3** and **4** were added to the group. First, we modified a procedure of the pyrrole ring fusion using an earlier published one as a starting point [8]. Based on parent 3-amino-

4-methylpyridine (**1a**) the procedure was updated to the one-pot protocol avoiding isolation of N-trifluoroacylated derivative **6a**. A 0.2 M solution of the starting aminopyridine **1a** in dry pyridine was treated with 3.3 equiv of TFAA at 0 ºC (**Scheme 1**). Then the stirred reaction mixture was allowed to warm to rt and left to stand for 48 h. Next, the reaction mixture was diluted with water, extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4 and evaporated to dryness affording crude **5a**. Pure compound **5a** was obtained after flash chromatography over SiO_2 using EtOAc-hexane as eluent in 82% preparative yield. The protocol is easy to scale up and implemented on more than 50 g scale with the same efficiency.

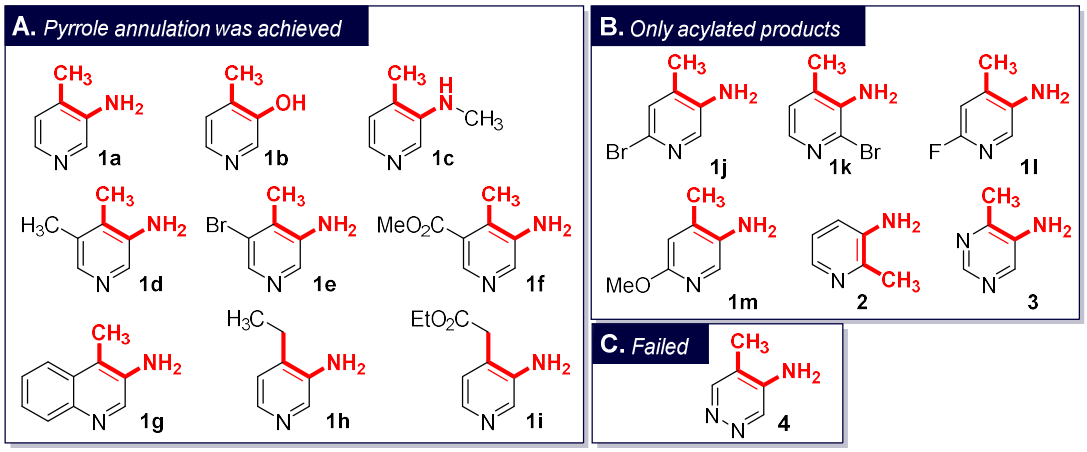
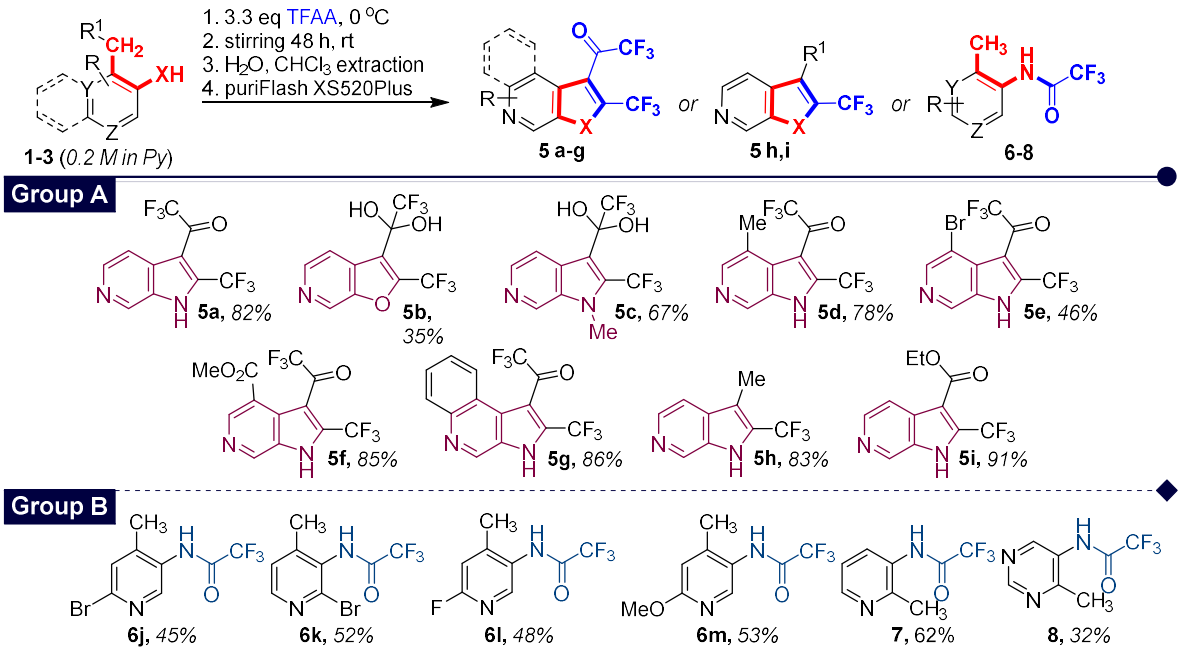


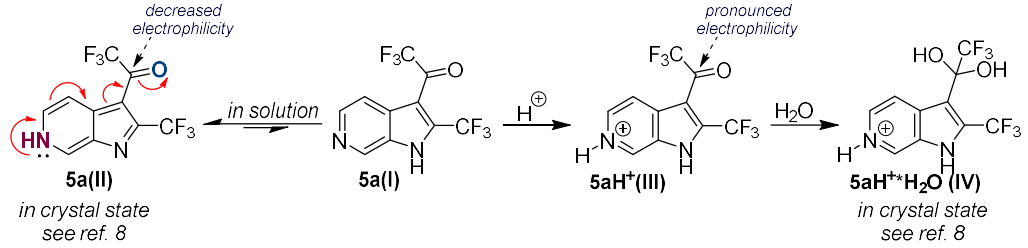
Figure 3. Starting cyclization counterparts used in the research.

Application of the above-mentioned protocol and TFAA as a model electrophile enabled us to classify the pyridine-based counterparts into three groups (**A**, **B** and **C** respectively, *see* **Figure 3**). Thus, in the case of pyrazine derivative **4** the protocol led to a hardly separable mixture of undefined products (group **C**). When 3-amino-4-methyl pyridines bearing an α-substituent were subjected to the reaction conditions (including 3-amino-2-methylpyridine (**2**) and 5-amino-4-methylpyrimidine (**3**)), we observed N-trifluoroacylated derivatives **6** to be the sole isolable products (group **B**). Finally, substrates from group **A**, after applying the protocol, gave expected 6-azaindoles **5** in 46-86% yields. It is noteworthy that 3-amino-4-methylquinoline (**1g**) falls into this set too. Ethyl-substituted pyridine **1h** and 4-CH_2CO_2Et substituted pyridine **1i** also entered heterocyclization reaction affording 6-azaindole ring system with methyl (**5h**) or CO_2Et (**5i**) groups installed instead of $COCF_3$ moiety. It was noticed that in the typical protocol all substrates give "free" trifluoroacetyl derivatives except for 3-hydroxy-4-methylpyridine (**1b**) and 3-methylamino-4-methylpyridine (**1c**). In these two cases, the corresponding hydrates **5b** and **5c** were isolated in 35% and 67% preparative yields (**Scheme 1**).



Scheme 1. Results for the reaction employing the model set of aminopyridines

Such a difference in the behavior of the cyclization products type **5** could be explained by the possible tautomerism of 6-azaindole heterocyclic system. For the parent compound, this phenomenon is illustrated in **Scheme 2**. Although we described the tautomeric transformation in our previous paper, we did not pay much attention to it. The "usual" N(1)-H tautomer **5a(I)** exists in equilibrium with N(6)-H tautomer **5a(II)**. According to crystallographic data (*see* CCDC 1976871 [8]) one can assume that with such a substitution pattern the equilibrium is shifted to tautomer **II** as it is the only form of the compound in crystalline state. Conjugation of $COCF_3$ group with the lone pair of N(6), existing in tautomer **II**, diminishes electrophilic properties of the former. Protonation of the system interrupts such a type of conjugation, thus increasing $COCF_3$ electrophilicity and facilitating hydrate **IV** formation (*see* CCDC 1976873 [8]) (**Scheme 2**).

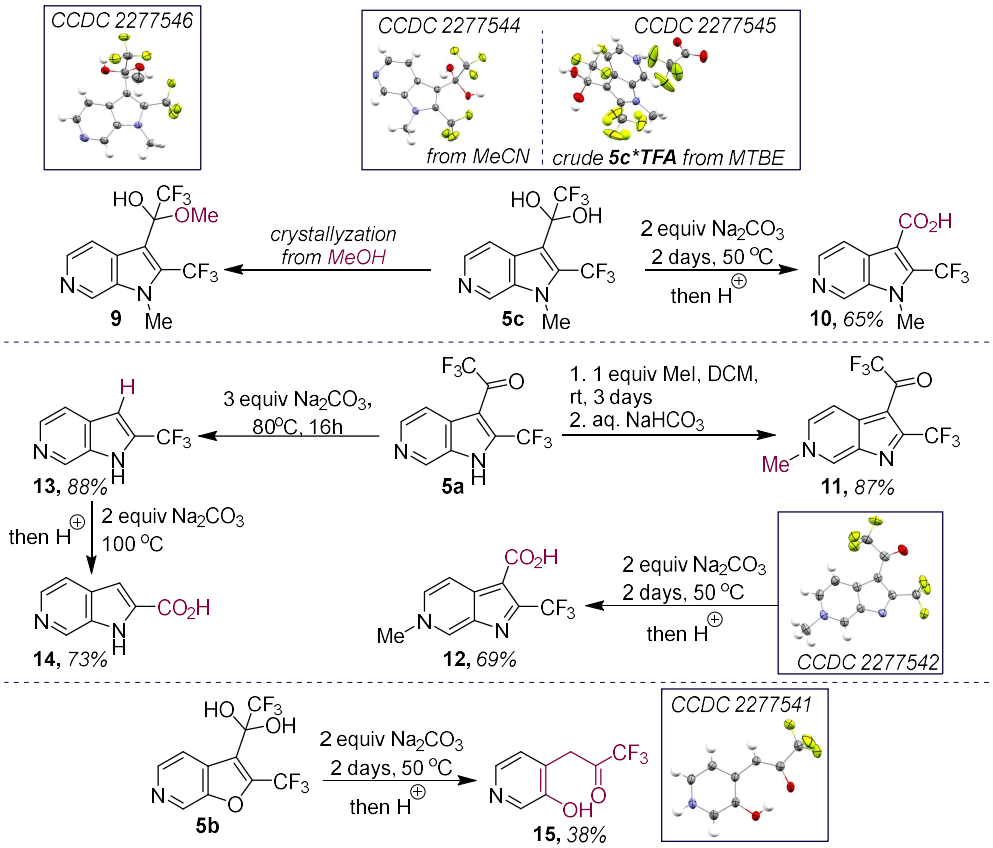


Scheme 2. Tautomeric behavior of compound **5a**

In the case of oxygen analogue **5b** and N(1)-methylated derivative **5c** the tautomerism is impossible. Therefore, the compounds were expected to display pronounced electrophilicity of $COCF_3$ group as compared with the parent compound and easily give corresponding hydrates. This suggestion was confirmed by NMR and X-ray crystallographic studies of the hydrates obtained. Suitable for the investigation crystals were obtained after crystallization of the crude product **5c** from MTBE. In this case the structure turned out to be a TFA salt of the corresponding hydrate (analogously to CCDC 1976873 [8]) (**5c*TFA**, CCDC 2277545, **Scheme 3**). Subsequently, after chromatographic purification, compound **5c** was crystallized from MeCN in acid-free conditions and its crystal structure was resolved as free-base hydrate form (**5c**, CCDC 2277544, **Scheme 3**). Recrystallization of **5c** from MeOH provided semi-acetal **9** (CCDC 2277546, **Scheme 3**). Additionally, it has shown that utilization of NH-alkyl substituted 3-amino-4-methyl pyridines in

the heterocyclization is crucial for the preparation of 1-alkyl-6-azaindoles as an alkyl substituent installation into the "parent" compound occurs exclusively at N(6) [14]. The structure of the corresponding N(6) methylated product **11** was unambiguously proved by X-ray (CCDC 2277542, **Scheme 3**). Noteworthy, this product does not form corresponding hydrate in the presence of water.

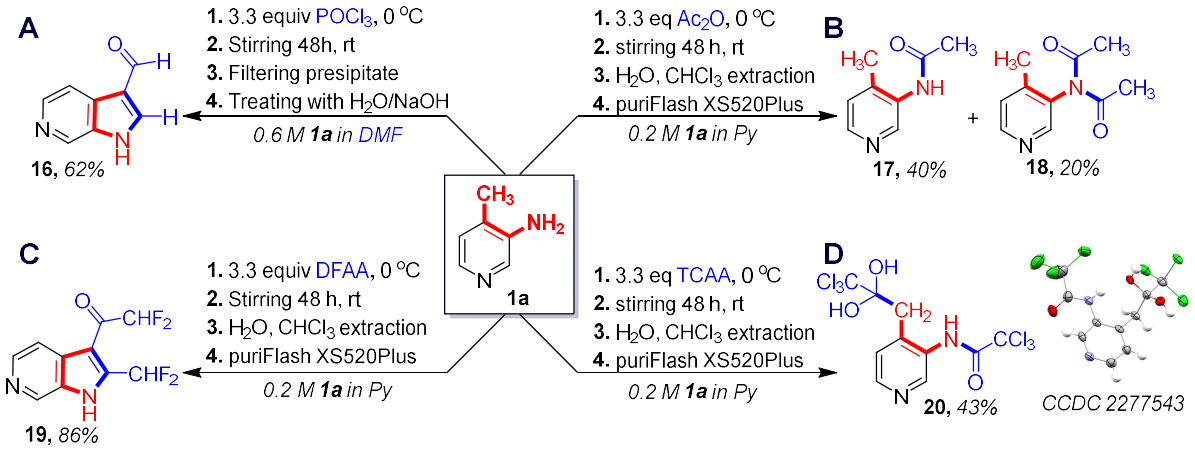
Also it was observed, that non-methylated and N(1)/N(6)-methylated 6-azaindoles possess different reactivity towards mild basic hydrolysis (aq. Na_2CO_3). In a case of non-methylated compound hydrolysis leads to formal de-trifluoroacylation affording 2-CF_3-6-azaindole (**13**). In harsher conditions (~80 ºC) deeper hydrolysis occurs giving 6-azaindole-2-carboxylic acid (**14**). At the same time, mild hydrolysis of the N-methylated compounds stopped on CF_3 acid step affording derivatives **10** and **12**. Hydrolysis of the oxygen analogue **5b** led to cleavage of the furan ring providing hydroxyketone **15** as the only isolable product (**Scheme 3**).



Scheme 3. Comparison of chemical behavior of compounds **5a**, **5b** and **5c**

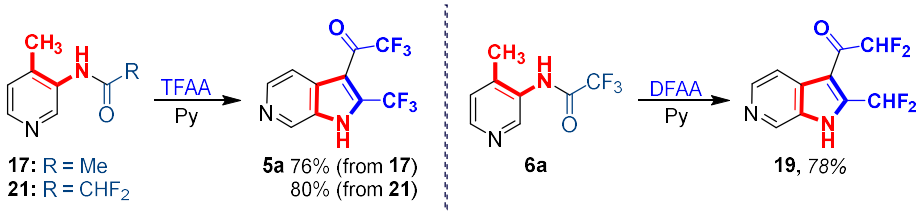
After substrate screening for the reactivity towards TFAA, we tested other C1 electrophiles using parent 3-amino-4-methyl pyridine (**1a**). Thus, in the case of Vilsmeier-Haack reagent (VHR) 3-formyl-6-azaindole (**16**) was isolated. However, unlike the seminal paper [13], where product **16** was isolated in 19% yield, optimized in this work procedure (*see* SI file) gave significantly higher yield 62% (**Scheme 4**, A). In a case of Ac_2O, the standard protocol did not lead to the azaindole ring formation. At the same time, the formation of a mixture containing mono- and di-acetylated aminopyridines **17** and **18** respectively was observed in *ca.* 2:1 ratio (**Scheme 4,** B). When more electrophilic DFAA was subjected to the standard protocol the expected difluoromethyl substituted 6-azaindol **19** was isolated in 86% preparative yield. The difluoromethylated compound appeared to be stable against mild basic hydrolysis unlike compound **5a** (**Scheme 4**, C). In the case of TCAA used in the protocol a product of double trichloroacetylation at both NH_2 and Me-groups **20** was formed without fusion of the pyrrole ring. The structure of a product was proved by the single

crystal X-ray diffraction study. Probably the expected cyclization does not occur here due to increased steric hindrance resulting from CCl_3 groups compared to CF_3 ones (**Scheme 5**, D).



Scheme 4. Reaction of parent compound **1a** with a set of model C1 electrophiles

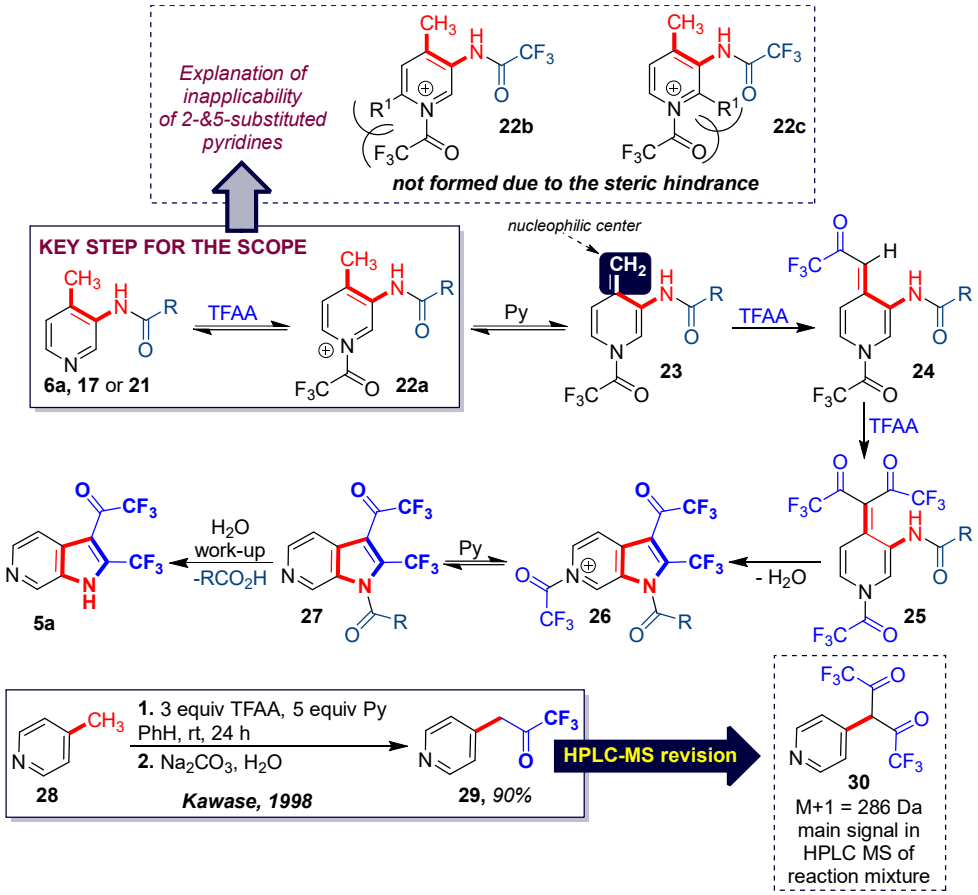
For a deeper understanding of the mechanistic aspects of cyclization, we performed the "cross" experiments involving the interaction of preliminary obtained 3-acylamino-4-methylpyridine with a different acyl-donating agent – TFAA or DFAA (**Scheme 5**). The experiments indicate that substituents in 2 and 3 positions of 6-azaindole core come from an "external" acyl donor.



Scheme 5. The "cross" cyclization of acylated 3-amino-4-methylpyridines

The superposition of all the obtained experimental results is not in accordance with the cyclization mechanism we proposed previously and implies compounds type **13** being intermediates in the cyclization [8]. In this regard, we checked the possibility of trifluoroacetylation of compound **13** in the cyclization conditions and found out that compound **13** is tolerant towards TFAA. Therefore, the installation of the $COCF_3$ group occurs in earlier steps before cyclization. Hence, we proposed the following plausible mechanism (**Scheme 6**). A key step of the reaction, which could explain the limitation to only α-substituted pyridines, is the formation of trifluoroacetylated pyridinium salt type **22a**. In basic pyridine medium salt **22a** is in equilibrium with C-nucleophilic methylidene derivative **23**. In contrast to α-unsubstituted substrates, substituted ones could not form pyridinium salts type **22b** or **22c** due to the existing steric hindrance created by an α-substituent. Further, methylidene derivative **23** is easily mono, and then bis-trifluoroacetylated by TFAA affording intermediate **25**, which undergoes cyclization into the azaindole ring system. The further water workup leads to the hydrolysis of acylated fragments at both N(1) and N(6) atoms giving the final product. This sequence of steps also explains the above-mentioned "cross" experiments dealing with different acyl groups. The additional proof of the mechanism including the key step of methyl group activation *via* generation of trifluoroacylated pyridinium salt was previously published by *Kawase et al.* wprocedure of trifluoroacetylation of 4-methylpyridine (**28**) giving compound **29** in a high preparative yield [[15]]. The best results were reported for 3 equiv of TFAA and 5 equiv of pyridine. The authors explained the need of 3 equiv of TFAA to achieve high reaction efficiency with by the formation of the **25**-like intermediate. We reproduced the procedure but with the

monitoring of the reaction mixture by HPLC-MS and found in the pre-workup mixture an ion $[M+H]^+$ = 286 Da, which corresponds to the expected protonated intermediate **30**.



Scheme 6. Mechanistic explanation of the scope and limitation of the reaction

Conclusion

In summary, herein we report a new, one-pot, scalable and metal-free synthesis of 2-trifluoromethyl-3-trifluoroacetyl-6-azaindoles starting from 3-amino-4-methylpyridines and trifluoroacetic anhydride. The reaction is regioselective, requires no catalysts, scalable to more than 50 g from 1 synthetic run and easy to perform. 3-Methylamino-4-methylpyridine and 3-hydroxy-4-methylpyridine also preparatively enter into the reaction giving corresponding fused pyrrolo-/furano-derivatives, though in hydrated form. 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 trifluoroacetamide step. Such a difference was rationalized by the reaction mechanism involving the formation of trifluoroacylated pyridinium salt as a key step of the methyl group activation. Among other C1 electrophilic components – Ac_2O, DFAA, TCAA and Vilsmeier-Haack reagent (VHR) – only DFAA and VHR afford similar to TFAA assembling of 6-azaindole system.

ASSOCIATED CONTENT

The Supporting Information including experimental procedures, characterization data and copies of ^1H, ^{13}C NMR and HPLC-MS spectra (PDF).

Accession Codes

CCDC 2277541-2277546 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data

request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Dmitriy M. Volochnyuk; orcid.org/0000-0001-6519-1467; E-mail: d.volochnyuk@gmail.com. Phone: +380967139494.

Sergey V. Ryabukhin; orcid.org/0000-0003-4281-8268; E-mail: s.v.ryabukhin@gmail.com. Phone: +380506424763.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The work was funded by Enamine Ltd, National Academy of Sciences of Ukraine (Grant No. 0119U102718). The authors thank Dr. Dmitry A. Lega for his help with preparation of the manuscript.

REFERENCES

[1] Carroll, A. R.; Duffy, S.; Avery, V. M. Aplidiopsamine A, an Antiplasmodial Alkaloid from the Temperate Australian Ascidian, Aplidiopsis confluata. *J. Org. Chem.* **2010,** *75* (23), 8291-8294.

[2] Mevers, E.; Saurí, J.; Helfrich, E. J. N.; Henke, M.; Barns, K. J.; Bugni, T. S.; Andes, D.; Currie, C. R.; Clardy, J. Pyonitrins A–D: Chimeric Natural Products Produced by Pseudomonas protegens. *J. Am. Chem. Soc.* **2019,** *141* (43), 17098-17101.

[3] Seval, N.; Frank, C.; Kozal, M. Fostemsavir for the treatment of HIV. *Expert Review of Anti-infective Therapy* **2021,** *19* (8), 961-966.

[4] Panchal, T.; Bailey, N.; Bamford, M.; Demont, E.; Elliott, R.; Farre-Gutierrez, I.; Garton, N.; Hayhow, T.; Hutley, G.; Naylor, A. Evaluation of basic, heterocyclic ring systems as templates for use as potassium competitive acid blockers (pCABs). *Bioorg. Med. Chem. Lett.* **2009,** *19* (23), 6813-6817.

[5] Yoon, Y. A.; Kim, D. H.; Lee, B. M.; Kim, T. K.; Cha, M. H.; Sim, J. Y.; Kim, J. G. Novel 1H-pyrrolo[2,3-c]pyridines as acid pump antagonists (APAs). *Bioorg. Med. Chem. Lett.* **2010,** *20* (17), 5237-5240.

[6] Yi, S.; Lee, H.; Jang, S. B.; Byun, H. M.; Yoon, S. H.; Cho, J.-Y.; Jang, I.-J.; Yu, K.-S. A novel K+ competitive acid blocker, YH4808, sustains inhibition of gastric acid secretion with a faster onset than esomeprazole: randomised clinical study in healthy volunteers. *Alimentary Pharmacology & Therapeutics* **2017,** *46* (3), 337-346.

[7] Dyckman, A.; Dodd, D.; Kumar, S. R.; Barre, D. B. R.; Duraisamy, S. K. WO2019126082A1, 2019.

[8] Ivonin, S. P.; Yurchenko, A. A.; Voloshchuk, V. V.; Yurchenko, S. A.; Rusanov, E. B.; Pirozhenko, V. V.; Volochnyuk, D. M.; Kostyuk, A. N. A convenient approach to 3-trifluoromethyl-6-azaindoles. *J. Fluorine Chem.* **2020,** *233*, 109509.

[9] Snieckus, V.; Lee, C. F.; Reed, M. A. One-Pot Synthesis of 2-Trifluoromethyl-6-azaindoles. *Synfacts* **2020,** *16* (07), 0778.

[10] Hands, D.; Bishop, B.; Cameron, M.; Edwards, J. S.; Cottrell, I. F.; Wright, S. H. B. A Convenient Method for the Preparation of 5-, 6- and 7-Azaindoles and Their Derivatives. *Synthesis* **1996,** *1996* (07), 877-882.

[11] Song, J. J.; Tan, Z.; Gallou, F.; Xu, J.; Yee, N. K.; Senanayake, C. H. A Novel One-Step Synthesis of 2-Substituted 6-Azaindoles from 3-Amino-4-picoline and Carboxylic Esters. *J. Org. Chem.* **2005,** *70* (16), 6512-6514.

[12] Kurhade, S.; Rajopadhyay, V.; Avaragolla, S. V.; Koul, S.; Ramaiah, P. A.; Bhuniya, D. Synthesis of l-azaisotryptophan and its analogs: a general access to new 2-substituted azaindoles. *Tetrahedron Lett.* **2014,** *55* (15), 2415-2419.

[13] Clark, B. A. J.; Parrick, J.; West, P. J.; Kelly, A. H. Diazaindenes (azaindoles). Part III. Reactions of Vilsmeier reagents leading to 3-formyl-1,6-diazaindene and -1,4-diazabenz[f]indene. *Journal of the Chemical Society C: Organic* **1970,** 3, 498-501.

[14] Mahadevan, I.; Rasmussen, M. Ambident heterocyclic reactivity: the alkylation of pyrrolopyridines (azaindoles, diazaindenes). *Tetrahedron* **1993,** *49* (33), 7337-7352.

[15] Kawase, M.; Teshima, M; Saito, S.; Tani, S. Trifluoroacetylation of Methylpyridines and Other Methylazines: A Convenient Access to Trifluoroacetonylazines. Heterocycles 1998, *48* (10), 2103-2109.