Electrophilic [4+1]-cyclization of picolines – efficient avenue towards 6-azaindole and 6-azabenzofuranes

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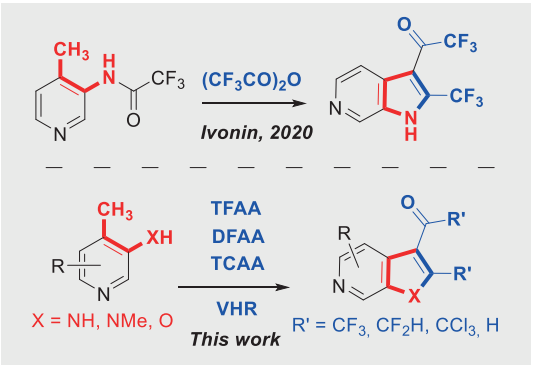
Introduction and Aim

Heterocyclic system of 6-azaindole is a valuable object for medicinal chemistry. Nevertheless this system itself is not known to occur in nature, its benzofused analogue, β-carboline scaffold is a part of ca. 800 natural products including antiplasmodial alkaloid *Aplidiopsamine A* and antifungal *Pyonitrin* family. FDA approved HIV entry inhibitor *Fostemsavir* contains 6-azaindole core.

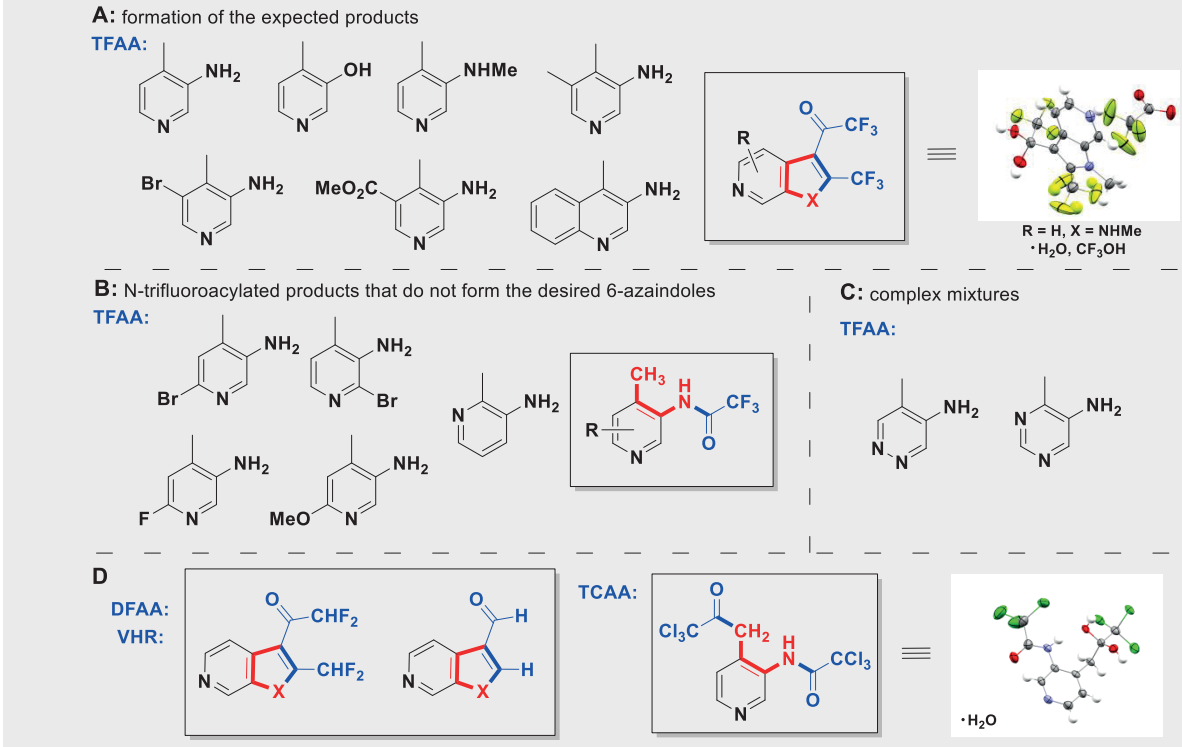
Recently we elaborated a catalyst free, simple and scalable synthesis[1] of 2-trifluoromethyl-6-azaindole from available 3-amino-4-methylpyridine and trifluoroacetic anhydride (TFAA). In contrast to the previously reported methods[2] preliminary methyl group activation by strong organolithium base was not required. Therefore, the range of tolerant functional groups is widely enlarged.

Hereby, we expand the scope the reaction for variously substituted pyridine scaffolds. Vilsmeier-Haack reagent (VHR), difluoroacetic (DFAA) and trichloroacetic (TCAA) anhydrides were tested as electrophilic agents.

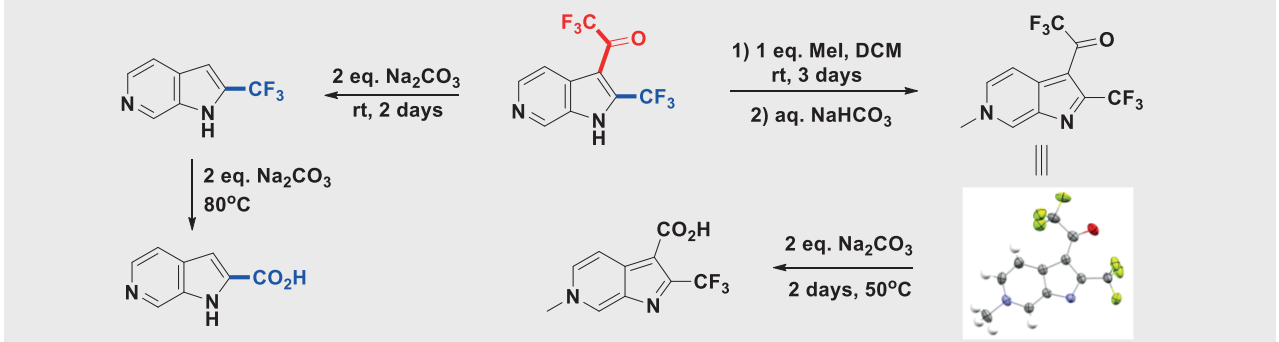
Limitations of the reaction were established and explained.



Scope and Limitations



Representative Transformations of the Obtained Products



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References

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2a) Hands D. et al. Synthesis 1996, 1996, 877; (2b) Song J. J. et al. J. Org. Chem. 2005, 70, 6512; 2c) Kurhade S. et al., Tet Lett. 2014, 55, 2415.