Master of Science HES-SO in Life Sciences

Cyclopropanation of imine-protected heterocyclic benzylamines

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CHEMICAL DEVELOPMENT & PRODUCTION

HEIA-FR

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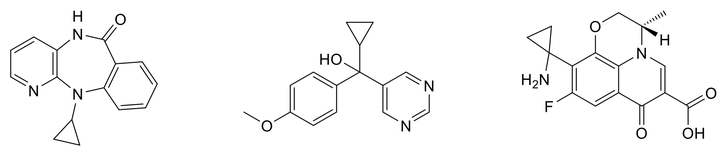
DESCRIPTION

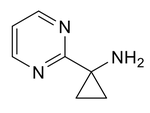
The importance of heterocyclic compounds and especially cyclopropanated heterocyclic compounds is increasing year after year in the pharmaceutical and agrochemical field (e.g. Nevirapine - HIV-1 treatment; Ancymidol – plant growth regulator; Pazufloxacin – anti-bacterial). Due to its unique electronic, steric, and conformational properties, the cyclopropane moiety can change drastically the biological and physicochemical properties of organic compounds (e.g. solubility, metabolic stability improvement) and is of great interest in drug discovery.



Nevirapine Ancymidol Pazufloxacin

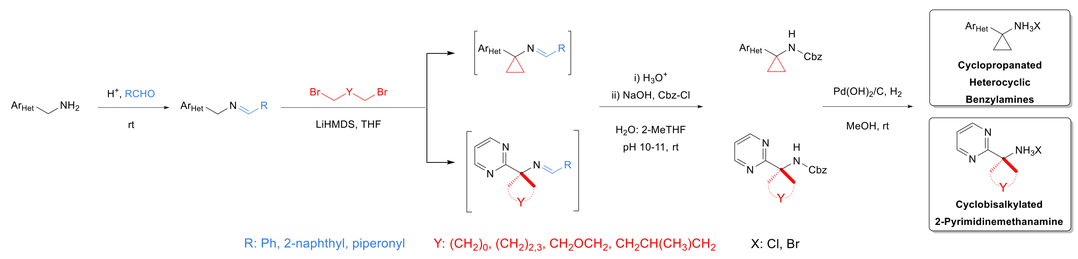
Example of cyclopropanated active molecules

Idorsia Pharmaceuticals Ltd. interest was to develop a robust and scalable route to 1-(pyrimidin-2-yl)cyclopropan-1-amine **(1)** which is commercially available only in small quantities for ca. 1'000 $/g.



(1)

The difficulty to synthesize cyclopropanated heterocyclic compound such as **(1)** is often challenging due to its high polarity and the lack of clean and short process for kg-scale. For these reasons, direct cyclopropanation using imine-protected heterocyclic benzylamines has been investigated with different various imine protecting groups. The application of the process was tested with different heterocycles and dihaloalkanes.



Synthetic route to cyclobisalkylated heterocyclic benzylamines

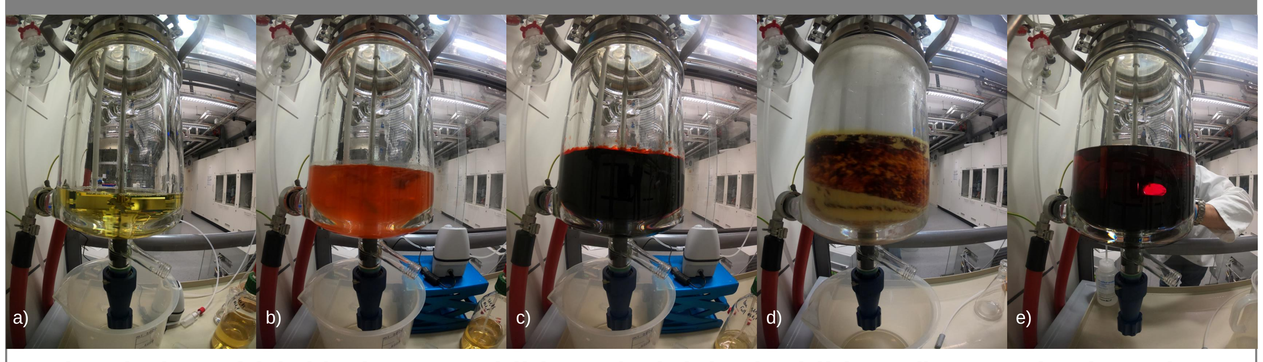
OBJECTIFS

The aim of this Master Thesis was to access relevant and cheaper building blocks via the cyclopropanation of imine-protected heterocyclic benzylamines.

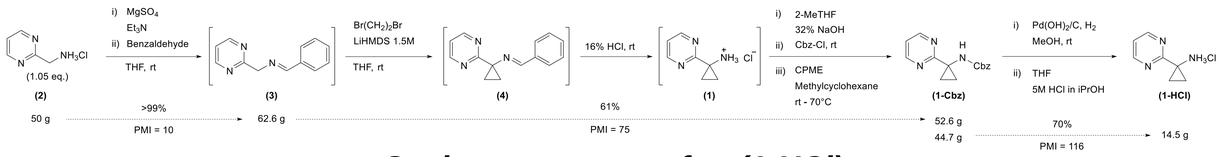
The following objectives were initially defined:

- Synthesis and characterization of solid of 2-pyrimidinemethanamine Schiff bases for a scale-up approach (thermally stable and easily isolated)
- Optimization of relevant Schiff bases and their cyclopropanation
- Scale-up of optimized route to 1-(pyrimidin-2-yl)cyclopropan-1-amine **(1)**
- Test of generalized α,α-cyclobisalkylation (cyclobutane, -pentane, -hexane, etc.)
- Substrate scope of cyclopropanation reaction with regards to heterocyclic benzylamine and 1,2-dibromoethane

RESULTS

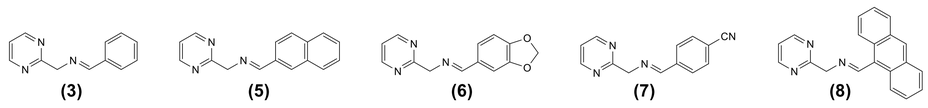


a) Solution of (3), b) LiHMDS addition, c) Finished addition, d) Quench, e) Work-up



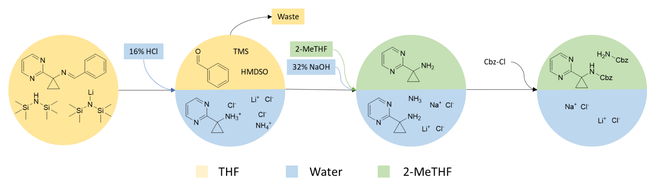
Scale-up process of to (1-HCl)

Solid and thermally stable imines **(5)**, **(6)**, **(7)** and **(8)** were successfully isolated (31-76%). Although their cyclopropanation performed well, the work-up procedure was cumbersome with dark sticking residue formed in the reactor, making the process less suitable for larger scale.



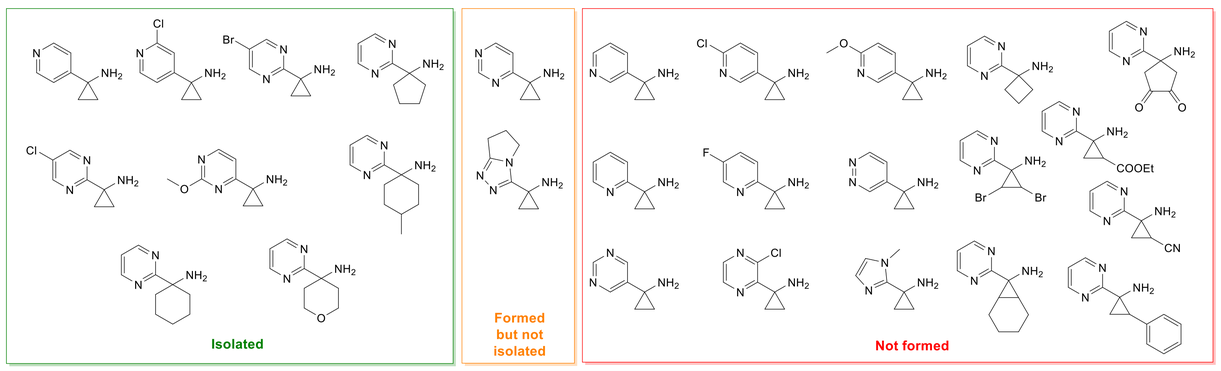
(3) **(5)** **(6)** **(7)** **(8)**

(3) was found to be the intermediate of choice with high yield for its synthesis and the near absence of residue in the cyclopropanation step. The liquid-liquid extraction of **(1)** being a challenge due to its high polarity, **(1)** was derivatized to **(1-Cbz)** during the work-up with benzyl chloroformate. This telescoped work-up had the negative effect to also produce benzyl carbamate from the ammonia generated LiHMDS hydrolysis. **(1-Cbz)** was crystallized as a stable solid and then hydrogenated to give **(1)** or **(1-HCl)**.



Benzyl carbamate origin

The application of the developed procedure enabled the synthesis and characterization of 9 new compounds out of 27 experiment with low to moderate overall yield (5-76%).



CONCLUSION

The process developed during this project allowed the production of **(1-HCl)** with an overall yield of 43% on a 50g-scale. The improvement was observed with the use of different aldehydes to protect **(2)** which all produced **(1)** as a reddish-brown oil. The introduction of the derivatisation and hydrogenation steps allowed the production of **(1-HCl)** as pure off-white powder with a raw material cost of 42'419 CHF/kg.

Although many different imine-protected heterocyclic benzylamine have been synthesized and cyclobisalkylated with great success, the developed procedure was not suitable with other heterocyclic benzylamine and dihaloalkanes. The influence of the heterocycle and its substituents was noted to disfavour the deprotonation and/or the cyclization of the imine. Regarding the use of dihaloalkanes, the presence of functional groups was noticed to either not react or to degrade the imine.

The cyclopropanation of imine-protected heterocyclic benzylamine should be further tested with differents heterocycles containing oxygen, nitrogen and sulphur atomes, and dialkylating reagents (cyclic sulfates and dihaloalkane containing different halogens) to better understand the effects encountered.

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