Rearrangements of fluorinated cyclopropylamines as a novel approach toward fluoroalkene-based peptidomimetics

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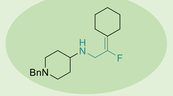
Actuality

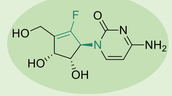
Fluoroalkene-based peptidomimetics:

- Increased lipophilicity
- Strict conformation
- More metabolically stable

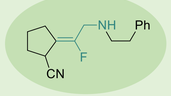
→ **Higher biological activity**



DPP II inhibitor

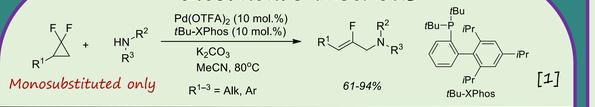


[F]-Neplanocin A

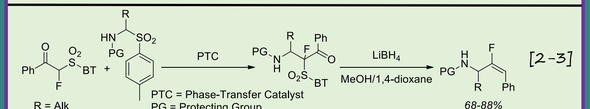


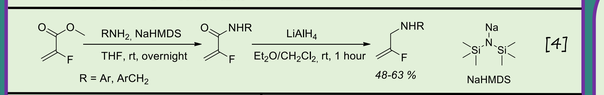
DPP IV inhibitor

Literature methods



Monosubstituted only





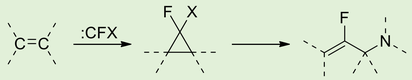
Disadvantages:

- High price
- Low substrate scope
- Inability to make cyclic structure

Bibliography:

1. J. Xu, E.-A. Ahmed, B. Xiao, Q.-Q. Lu, Y.-L. Wang, C.-G. Yu, Y. Fu, *Angew. Chem.* **127** (2015) 8349 –8353.
2. C. Calata, E. Pfund, T. Lequeux, *Tetrahedron* **67** (2011) 1398–1405.
3. C. B. Jacobsen, M. Nielsen, D. Worgull, T. Zweifel, E. Fisker, Jorgensen, *J. Am. Chem. Soc.* **133** (2011) 7398–7404.
4. Y. Li, K. Li, Y. Wu, Q. Ma, X. Lei, *Tetrahedron* **72** (2016) 4845–4853.

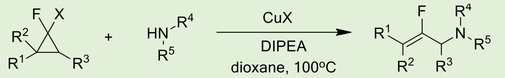
gem-Fluorohalocyclopropane based methodology



Comparing to literature:

- Ability to synthesize cyclic fluoroalkenes
- Short synthesis from readily available substrates

Earlier in our laboratory



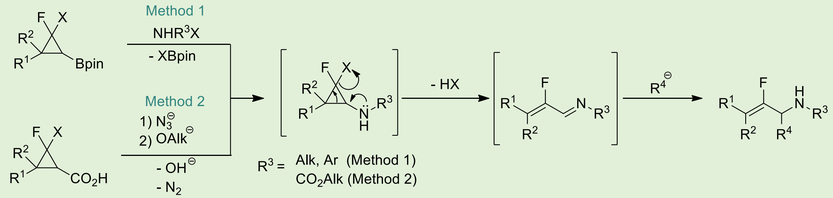
R = Alk, Ar, H
X = Cl, Br

Comparing to literature:

- Up to 2 substituents in cyclopropane
- Less steps

M. A. Novikov, Y. A. Ibatov, N. V. Volchkov, M. B. Lipkind, S. E. Semenov, O. M. Nefedov, *J. Fluorine Chem.* **194** (2017) 58–72

New idea

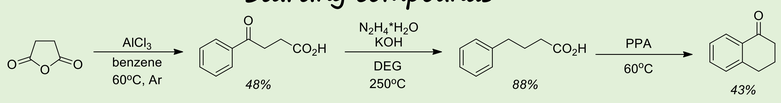


R³ = Alk, Ar (Method 1)
CO_2Alk (Method 2)

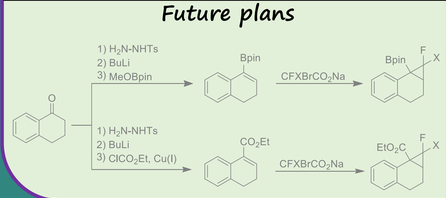
Advantages:

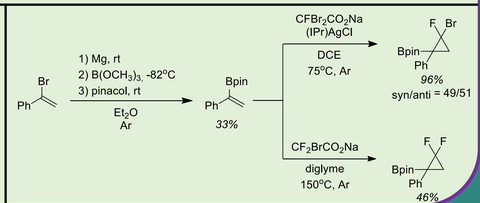
- Rearrangement occurs without heating (functional groups tolerance)
- Possibility to synthesize R^4 separately (convergent synthesis)

Starting compounds

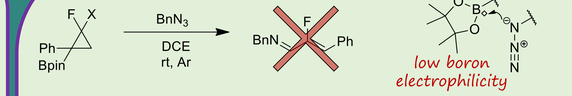


Future plans

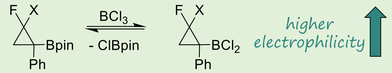




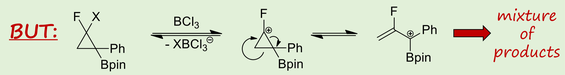
Method 1



Standard method to increase electrophilicity



BUT:

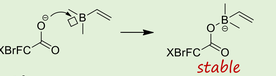


Future plans

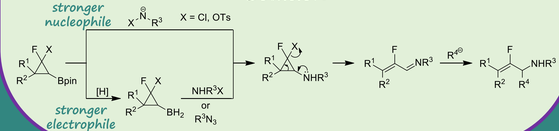
conjugation decreases electrophilicity

no conjugation nothing decreases electrophilicity

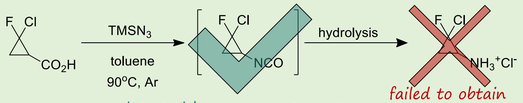
Problem: too high electrophilicity, hard to cyclopropanate



Solution

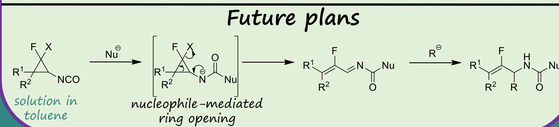


Method 2



detected by mass spectrometry and gas chromatography

Future plans



Results

- We suggested new way to the synthesis of fluoroalkene-based peptidomimetics
- We revealed that electrophilicity of Bpin group is not big enough to react with azide
- We detected the formation of isocyanate in the reaction of acid with $TMSN_3$

What we learned

- To use NMR and mass-spectrometry methods to identify compounds and their structure
- To purify obtained products by distillation, column chromatography, extraction and evaporation
- To perform reactions under an inert atmosphere and work with vacuum

Acknowledgements

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