Highly substituted, trifluoromethylated imidazoles as potential scaffolds in medicinal chemistry

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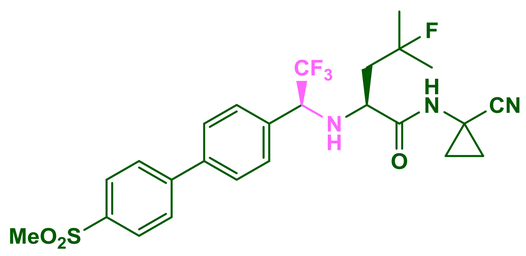
Introduction

Imidazole and its derivatives have attracted considerable interest for their versatile properties in medicinal chemistry research. Next to the optimization of solubility and bioavailability parameters in active lead structures, imidazole derivatives themselves posses a broad spectrum of biological activities including anticancer and antibacterial activity.[1] Due to the excellent pharmacological profile of fluorinated drugs, we are interested in the strategic incorporation of fluorine in trifluoromethylated amine and imidazole structures for future application in medicinal chemistry.



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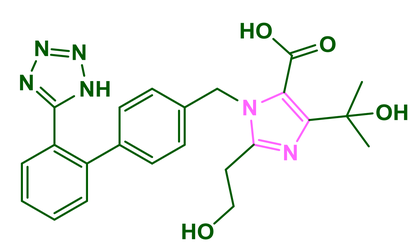
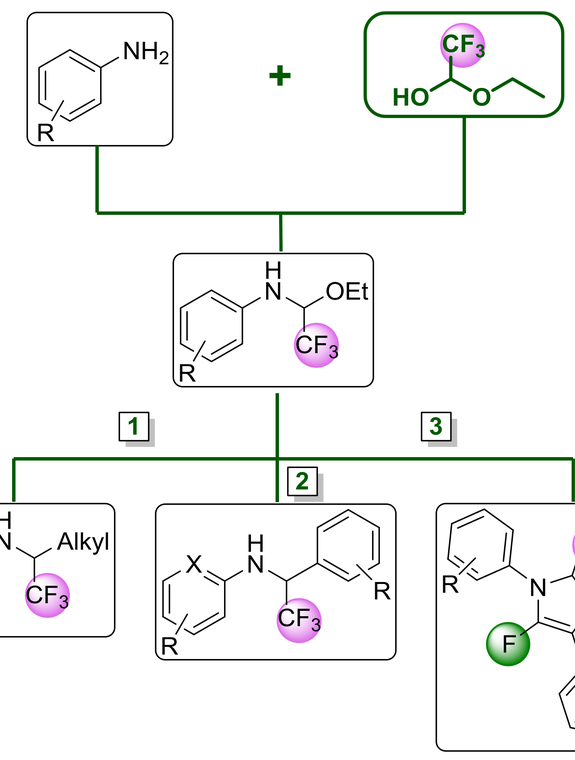
J. Y. Gauthier *et al*., *Bioorg. Med. Chem. Lett.* **2008,** 18, 923.

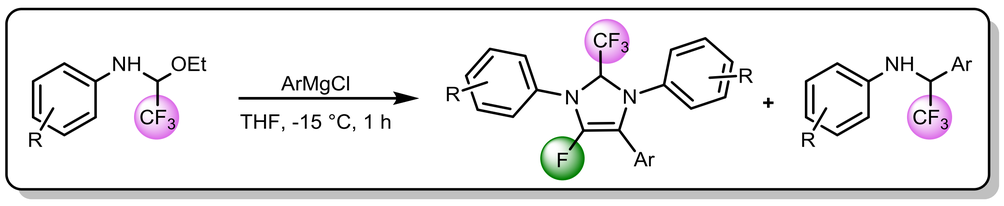


Olmesartan

US5616599 A1, 1997.

General Method





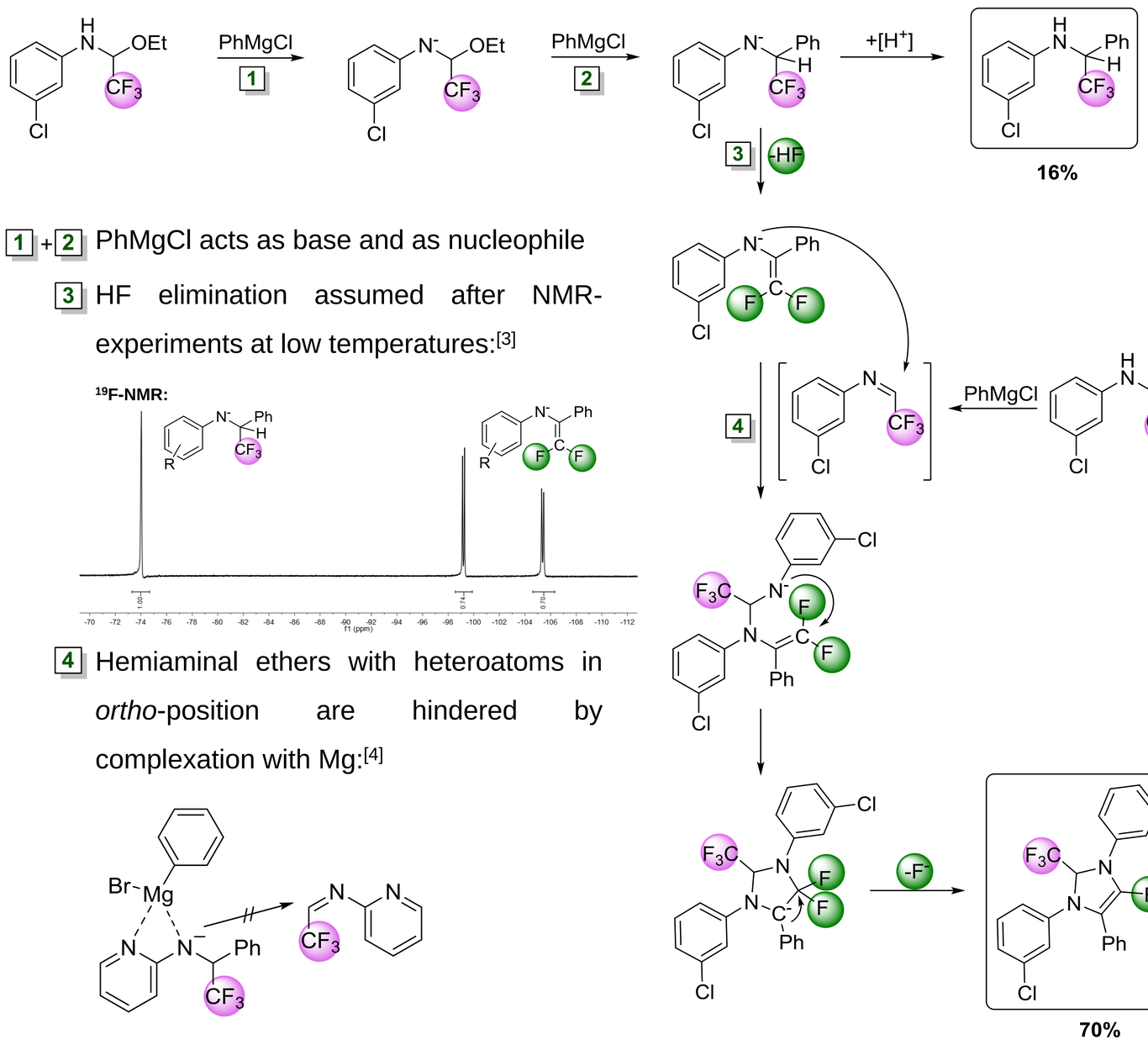
Trifluoromethylated imidazoles and trifluoroethyl amines are accessible from hemiaminal ethers, which are synthesized starting from the corresponding amines and trifluoroacetaldehyde ethyl hemiacetal (TFAE). The resulting hemiaminal ethers can then be converted into trifluoromethylated imidazoles or trifluoroethyl amines[2] *via* addition of Grignard reagents depending on the substrates and the Grignard reagents.

1 Conversion of any hemiaminal ether with alkyl magnesium reagents

2 Conversion of electron rich and neutral substrates or hemiaminal ethers with heteroatoms in *ortho*-position with aryl magnesium reagents

3 Conversion of electron poor hemiaminal ethers with aryl magnesium reagents

Proposed Mechanism



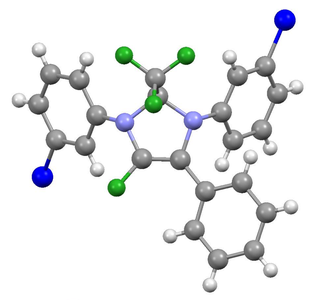
1 + 2 PhMgCl acts as base and as nucleophile

3 HF elimination assumed after NMR-experiments at low temperatures:[3]

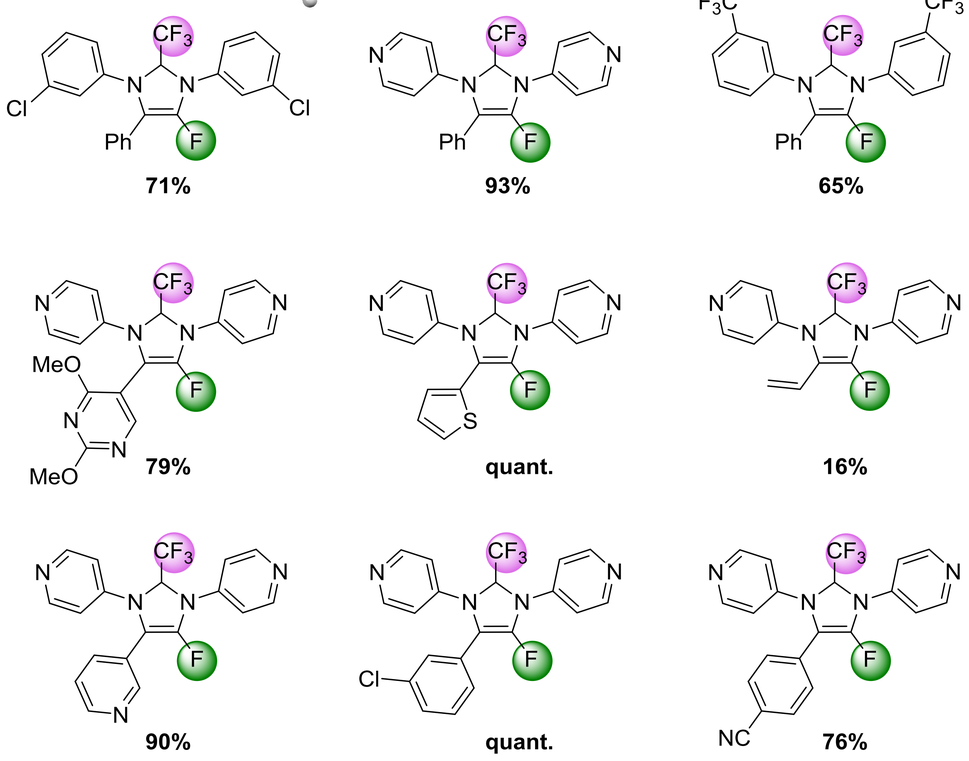
^{19}F-NMR:

4 Hemiaminal ethers with heteroatoms in *ortho*-position are hindered by complexation with Mg:[4]

Synthesized Structures



- ✓ highly substituted
- ✓ new functionalization patterns



Future directions:

- Further NMR studies to elucidate the mechanism
- Application of CF_3-imidazole derivatives for lead optimization studies

References: [1] Zhang *et al*., *Med. Chem. Rev.* **2014**, *34*, 2, 340. [2] Deutsch *et al*., *RSC Advances* **2014**, *4*, 9288−9291. [3] Kirij *et al*., *J. Fluorine Chem.* **2008**, *129*, 14. [4] Ortu *et al*., *Inorg. Chem.* **2013**, *52 (21), 12429.*