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One-Pot Synthesis of Substituted Trifluoromethylated 2,3-Dihydro-1*H*-imidazoles

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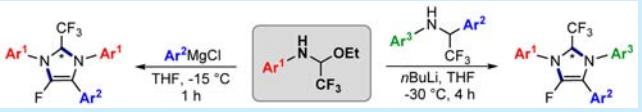
Supporting Information

ABSTRACT: An operationally simple one-pot reaction for the preparation of a novel class of racemic trifluoromethylated 2,3-dihydro-1*H*-imidazoles derived from electron-poor *N*,*O*-acetals and aryl Grignard reagents is described. In addition, access to highly functionalized 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles was accomplished by reaction of *N*-aryl hemiaminal ethers and *N*-aryl trifluoroethylamines in the presence of an excess of *n*-butyllithium.



Owing to their ability to modify important biological and physicochemical properties, fluorinated substructures are widely employed in the synthesis of agrochemicals and pharmaceuticals.[1] The rationale for the incorporation of fluorine substituents mostly relies on their positive effects on metabolic stability, bioavailability, lipophilicity, and binding selectivity/affinity of the parent compound.[1a] Driven by these potential rewards, research on innovative methods for the preparation of specifically fluorinated molecules is of considerable interest. In particular, improved strategies for efficient and controlled incorporation of CF_3 groups are highly desired.[2] Beyond the growing number of approaches toward late stage fluorinations,[3] the use of fluorinated building blocks for quick and flexible scaffold assembly is still a vital strategy pursued in medicinal chemistry.[4]

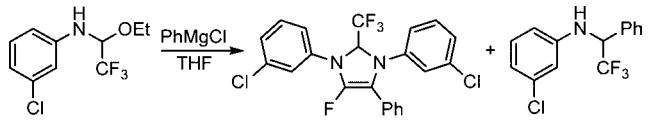
Despite a large and diverse set of known biologically active compounds possessing imidazole ring structures,[5] the number of pharmaceuticals and agrochemicals comprising fluorinated imidazole and benzimidazole analogs is yet surprisingly limited.[6] This is most presumably due to difficulties in quickly accessing a large number of diverse fluorinated imidazole derivatives during drug discovery. Similarly, pharmacophores containing fluorinated or trifluoromethylated imidazolone derivatives have remained scarce, although 2-imidazolones are present in numerous biologically active compounds with intriguing pharmacological activities.[7]

Recently, we reported the usage of shelf-stable trifluoroacetaldehyde-derived hemiaminal ether building blocks to efficiently access functionalized di- and trifluoromethylated *N*-aryl amine derivatives.[8] In the course of these studies, we also observed formation of unprecedented pentasubstituted 2,3-dihydro-1*H*-imidazoles, bearing a CF_3 group at C-2 and an additional fluorine substituent at C-4 (Figure 1). We now present a straightforward one-pot protocol to access various racemic and highly substituted 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles, which may be regarded as novel versatile CF_3-isosteres of 2-imidazolones for potential pharmaceutical applications.

Figure 1. 2-Imidazolone and trifluoromethylated 2,3-dihydro-1*H*-imidazole.

In our initial study, we found that treating 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** with an excess of phenylmagnesium chloride (PhMgCl, 3 equiv) in tetrahydrofuran (THF) provided trifluoromethylated imidazole derivate **2a** as the main product instead of targeted trifluoroethylamine **3a**, which was only formed in minor amounts (Scheme 1).

Scheme 1. Conversion of Hemiaminal Ether 1a with PhMgCl



1a **2a**, 70% **3a**, 16%

Moreover, by applying the same reaction conditions to hemiaminal ether **1b**, 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole **2b** was obtained as the sole reaction product and no traces of the corresponding trifluoromethylated amine were observed. Interestingly, this transformation required 2.5 equiv of PhMgCl to proceed with full conversion, whereas reduced amounts of

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the Grignard reagent afforded mixtures of hemiaminal ether **1b** and 1*H*-imidazole **2b**. Increasing the reaction temperature of up to 0 °C failed to improve the yield by promoting formation of significant amounts of byproducts, again.

However, the rapid and clean formation of product **2b** at −15 °C in THF encouraged us to explore the scope and generality of this transformation (Figure 2). To our delight,

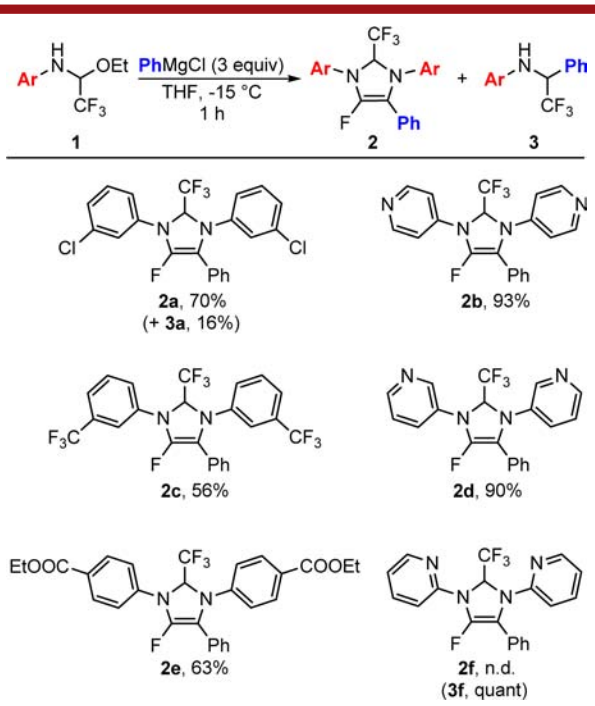


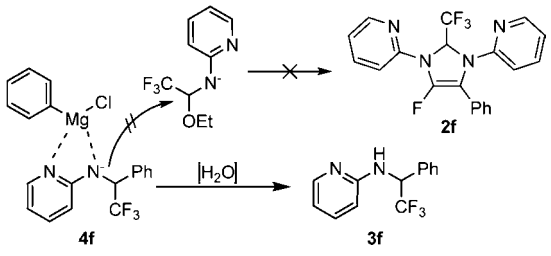
Figure 2. Scope of the reaction of hemiaminal ether **1** with PhMgCl.

diverse *N*-aryl hemiaminal ethers were readily converted into 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles in moderate to high yields. Thereby, even labile functionalities, such as halides and ethyl esters, proved compatible with the reaction conditions.

N,*O*-Acetals derived from electron-poor aminopyridines are a notable exception, where the substitution pattern strongly influences the reaction outcome. Thus, complete conversion to the desired CF_3-imidazole derivatives was only observed for 4-aminopyridyl hemiaminal ether **1b** and 3-aminopyridyl hemiaminal ether **1d**. Contrarily, 2-aminopyridyl derivative **1f** provided the corresponding trifluoroethylamine **3f** exclusively, most presumably due to a stabilizing metal chelate of the deprotonated aminopyridine unit **4f**,[9] which prevents further attack to a second *N*,*O*-acetal molecule, as shown in Scheme 2.

After investigating the scope of *N*,*O*-acetals, we turned our attention to the applicability of functionalized aromatic Grignard reagents for this transformation (Figure 3). Thus, 1-

Scheme 2. Presumed Chelation of Metalated Intermediate 4f



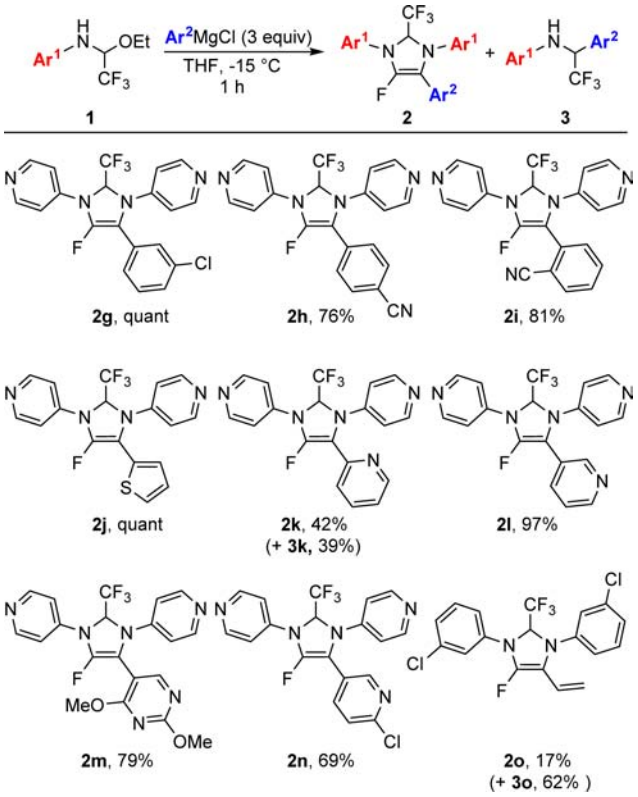


Figure 3. Scope of the reaction of hemiaminal ether **1** with aryl Grignard reagents.

bromo-2-chlorobenzene was converted into the corresponding Grignard reagent by treatment with *i*PrMgCl·LiCl in THF. The latter was then added to a THF solution of the hemiaminal ether **1b** at −15 °C to provide the desired 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole **2g** in quantitative yield. Similarly, Grignard reagents prepared from 4- and 2-bromobenzonitrile afforded the functionalized imidazole derivatives **2h** and **2i** in high yields. As summarized in Figure 3, the reaction is general for Grignard reagents having electron-deficient aryl and heteroaryl groups. It should be noted, however, that reaction of pyrid-2-ylmagnesium chloride with *N*,*O*-acetal **1b** again provided significant amounts of trifluoroethylamine **3k** as a byproduct, most presumably again due to complexation phenomena. Finally, also vinylmagnesium chloride was less effective as a substrate by furnishing increased amounts of trifluoroethylamine **3o**, whereas simple alkyl Grignard reagents failed in this reaction.

A plausible reaction mechanism for the 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole formation is proposed in Scheme 3. Thereby the reaction is initiated by deprotonation of the *N*,*O*-acetal **1b**. The resulting anionic species **5b** then undergoes a nucleophilic substitution reaction with PhMgCl to form the deprotonated trifluoroethylamine **4b**. Subsequent nucleophilic attack at a second *N*,*O*-acetal **5b** affords intermediate **6b**, which after transformation into difluoroenamine **7b** cyclizes under fluoride elimination to the desired reaction product **2b**.

To verify the proposed reaction mechanism, we initially performed low temperature NMR studies, which unfortunately did not disclose any intermediates owing to the high reaction rate. We therefore decided to examine the reaction in a stepwise manner and subjected hemiaminal ether **1b** to deprotonation with 1 equiv of *n*BuLi. Recorded NMR spectra

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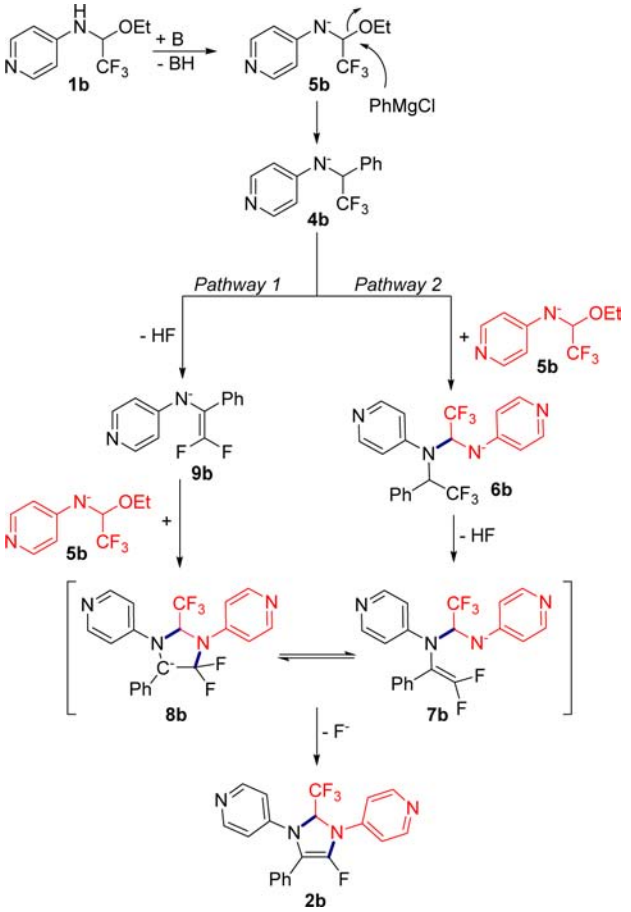
Scheme 3. Proposed Mechanisms for the Formation of Trifluoromethylated 2,3-Dihydro-1*H*-imidazole 2b



of the reaction mixture proved formation of two deprotonated species, which after treatment with iodomethane yielded the corresponding *N*-methylated products. Alternatively, formation of a transient imine species could be postulated, which however was not observed under these conditions.[10] In principle, the reaction could then proceed further, either via substitution product **6b** (*pathway 2*) or involvement of an enamine species **9b** (*pathway 1*), resulting from **4b** by HF elimination. To distinguish between these two possible routes, we aimed at preparation of *gem*-difluoroenamine **9b**, which however was not feasible by treatment of *N*-(2,2,2-trifluoro-1-phenylethyl)-pyridine-4-amine **3b** with PhMgCl. In contrast, using more basic *n*BuLi and **3b** furnished **9b**, which was proven by characteristic resonance signals at −100/−107 ppm in the corresponding ^{19}F NMR spectra (see Supporting Information (SI)).[11] Interestingly, upon increasing the temperature above −30 °C, compound **9b** undergoes exchange of one of the vinylic fluorine atoms by a butyl group (see SI). Since this transformation was not observed under the reaction conditions leading to formation of 1*H*-imidazoles (i.e., in the presence of Grignard reagents), the direct nucleophilic attack of **4b** at *N*,*O*-acetal **5b** to generate **6b** was considered more likely, although formation of intermediate **9b** cannot be fully excluded. Next, generation of intermediate **6b** was attempted by combining a solution of hemiaminal ether **1b** and 1 equiv of *n*BuLi with a solution of trifluoroethylamine **3b** and 1 equiv of PhMgCl at −60 °C. Aqueous workup then provided both substrates and the desired trifluoromethylated 1*H*-imidazole **2b** in a 1:1:1.7 ratio as determined by ^{19}F NMR spectroscopy (see SI).

The possibility of conducting the initial deprotonation step separately led us to investigate the synthesis of 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole derivatives bearing two different *N*-aryl substitution patterns (Figure 4). Therefore,

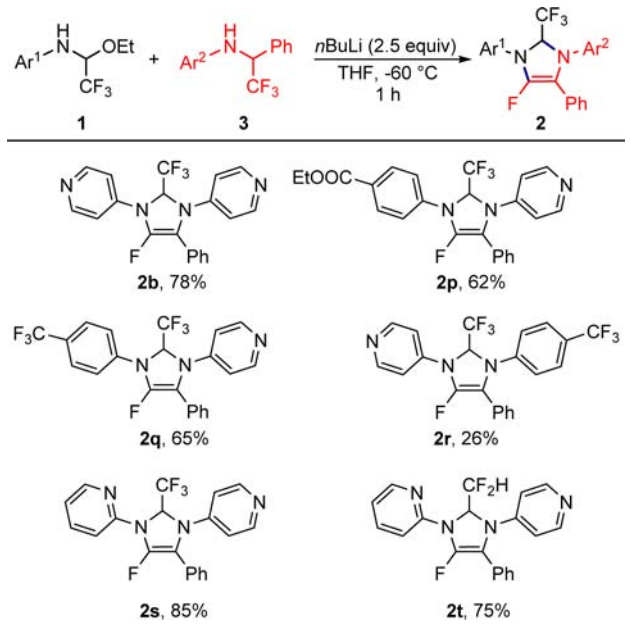


Figure 4. Synthesis of further functionalized 2-CF_3-2,3-dihydro-1*H*-imidazole derivatives.

equimolar amounts of ethyl 4-((1-ethoxy-2,2,2-trifluoroethyl)-amino)benzoate **1e** and trifluoroethylamine **3b** were deprotonated separately with *n*BuLi/PhMgCl and merged, to furnish the desired imidazole derivative **2p** in 62% isolated yield. To our delight, a comparable yield of **2p** was also obtained by a one-pot protocol, in which a solution of both substrates in THF was treated with 2.5 equiv of *n*BuLi. For instance, subjecting trifluoroethylamine **3b** and *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1q** to these conditions provided the corresponding trifluoromethylated imidazole **2q** in 65% isolated yield. Interestingly, reversal of the substitution pattern reaction, i.e., by reaction of *N*,*O*-acetal **1b** and *N*-(2,2,2-trifluoro-1-phenylethyl)-4-(trifluoromethyl)aniline **3r**, resulted in a diminished isolated yield of 26% of the desired product **2r** and large amounts of unreacted substrate. Moreover, the protocol allows preparation of 1*H*-imidazole derivatives bearing *N*-2-pyridyl substituents, which were previously difficult to access. However, this transformation is limited to reactions of 2-pyridyl-substituted hemiaminal ethers such as **1f**, whereas trifluoroethylamines bearing the 2-pyridyl substituent are not compatible. Finally, the product portfolio was also extended toward hitherto unknown 2-difluoromethyl-2,3-dihydro-1*H*-imidazole derivatives, e.g. **2t**, which was efficiently prepared from *N*-(1-ethoxy-2,2-difluoroethyl)pyridin-2-amine **1t** and **3b**.

In summary, we have devised a rapid and practical method for the synthesis of racemic 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles. The latter belong to a novel class of fluorinated imidazole derivatives of high pharmaceutical potential, which are accessible by condensation of *N*-aryl hemiaminal ethers with aryl Grignard reagents or *N*-aryl trifluoroethylamines. Crossover and control experiments have provided the first

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insights into the reaction mechanism. The operational simplicity of the protocol and the ready availability of the starting materials make this a very convenient approach for the synthesis of novel structurally diverse imidazole building blocks. With regard to their complex substitution patterns, the synthesis of reported 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles might be of particular interest for future pharmacological applications. Hence, their use for targeted synthesis is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01672.

Experimental procedures and data for all new compounds, and NMR studies (PDF)

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Notes

The authors declare no competing financial interest.

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