

Synthesis of functionalized α -trifluoroethyl amine scaffolds via Grignard addition to *N*-aryl hemiaminal ethers†

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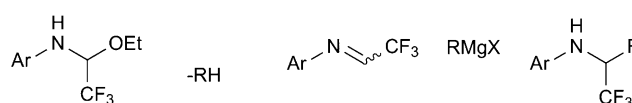
The synthesis of a variety of α -branched trifluoroethyl amines was achieved by reaction of *N*-aryl hemiaminal ethers with organo-magnesium reagents.

The design of compounds suitable for drug development is a multi-dimensional process that requires the fine tuning of molecular properties beyond potency. For instance, physical-chemical properties that directly affect hydrolytic stability and bioavailability of the compound must be addressed to avoid side effects *in vivo*. Due to the excellent pharmacological profile of fluorinated drugs, the strategic incorporation of fluorine atoms has nowadays become routine in medicinal chemistry development programs.¹ For instance, incorporation of a trifluoromethyl substituent adjacent to an amine is a means to improve the metabolic stability and to attenuate the basicity of the compound by shifting its pK_a value more towards those of amides.² Furthermore the C–CF₃ bond is substantially isopolar with the C=O bond and the trifluoroethyl amine moiety has a structural similarity to the tetrahedral proteolytic transition state.³ As a consequence, trifluoroethyl amines can be used as versatile hydrolysis-resistant bioisosteres of amides⁴ which retain the geometry of the amide bond and, in contrast to other mimetics⁵, also preserve the donating properties of the N–H bond. An illustrative example for the successful replacement of the amide functionality by a trifluoroethyl amine is given by Odanacatib, a highly potent drug candidate for the inhibition of Cathepsin K.⁶

Various methods for the synthesis of α -trifluoromethylated amines have been described so far,⁷ including hydrogenation⁸ and aromatic substitution⁹ of activated imines, as well as base-

catalyzed asymmetric isomerization reactions of ketoimines.¹⁰ Furthermore, nucleophilic addition reactions of various organo-metallics to trifluoromethylated imines¹¹ and hydrazones¹² have been reported. In this context, Lauzon and Charette have shown that trifluoromethyl amine derivatives can be prepared by copper-catalyzed nucleophilic addition of diorganozinc reagents to *N*-phosphinoylimines, using an excess of organozinc reagent.¹³ Similarly, trifluoromethylated α,α -dibranched carbinamines can be obtained from *N*-*tert*-butylsulfinyl hemiaminals with organo-magnesium or organolithium reagents.¹⁴ However, most of these approaches are either hampered by the high tendency of α,α,α -trifluoroethylamines to form hydrates or by the need of additional deprotection steps for further functionalization of the nitrogen atom. In a seminal paper, Mikami and coworkers showed that an excess of Grignard reagents can be used to prepare α -trifluoromethylated amines from stable *N*,*O*-acetals of trifluoroacetaldehyd.^{15,16} This work was recently extended to the use of arylboroxines for palladium(II)-catalyzed synthesis of α -(trifluoromethyl)arylmethyl amines.¹⁷

Herein, we report a systematic study on the synthesis of functionalized α -substituted trifluoromethyl amines using Grignard reagents and readily available trifluoromethylated hemiaminal ethers.¹⁸ The latter are shelf-stable compounds derived from 1-ethoxy-2,2,2-trifluoroethanol and aromatic amines and can be converted into trifluoromethylated aldimines *in situ*. Thus, upon treatment with Grignard reagent deprotonation should provide the corresponding imine which would then undergo nucleophilic attack by excess Grignard reagent to furnish the desired trifluoromethyl amine (Scheme 1). Formation of the transient imine species was confirmed by observing the corresponding imine hydrate *via* HPLC-MS after addition of MeMgBr to the reaction mixture.



Scheme 1

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Table 1 Optimization studies

| Entry | Ar | Eq. [MeMgBr] | T [°C] | Yield (%) ^a | Product |
|-------|-----------------------------------|--------------|--------|------------------------|-----------|
| 1 | 3-ClC ₆ H ₄ | 2 | 40 | 65 | 2a |
| 2 | 3-ClC ₆ H ₄ | 2 | 25 | 70 | 2a |
| 3 | 3-ClC ₆ H ₄ | 2 | 0 | 84 | 2a |
| 4 | 3-ClC ₆ H ₄ | 2 | -15 | 87 | 2a |
| 5 | 3-ClC ₆ H ₄ | 2 | -78 | 74 | 2a |
| 6 | 3-ClC ₆ H ₄ | 3 | -15 | 75 | 2a |
| 7 | C ₆ H ₅ | 1 | -15 | 34 ^b | 2b |
| 8 | C ₆ H ₅ | 2 | -15 | 63 | 2b |
| 9 | C ₆ H ₅ | 3 | -15 | 65 | 2b |

^a Yield of isolated product after flash chromatography. ^b Reaction time of 2 h.

Table 2 Addition of MeMgBr to (hetero)aromatic N,O-acetals^a

| Entry | Ar | Yield (%) ^b | Product |
|-------|--------------------------------------|------------------------|-----------|
| 1 | 3-ClC ₆ H ₄ | 87 | 2a |
| 2 | C ₆ H ₅ | 63 | 2b |
| 3 | 4-pyridyl | 81 | 2c |
| 4 | 4-OMeC ₆ H ₄ | 40 | 2d |
| 5 | 4-COOEtC ₆ H ₄ | 94 ^c | 2e |
| 6 | | 57 | 2f |
| 7 | | 69 | 2g |
| 8 | | 96 ^d | 2h |
| 9 | | 80 | 2i |
| 10 | | 74 | 2j |

^a All reactions were performed according to the optimized procedure. ^b After flash chromatography. ^c Use of 3 eq. MeMgBr. ^d Without further purification.

To determine the optimal conditions, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** was treated with MeMgBr in dry THF under argon at different reaction temperatures (Table 1). Thus, the addition proceeded smoothly at -78 °C furnishing the desired trifluoroethyl amine **2a** in 74% yield after one hour. Whereas higher temperatures above 0 °C led to significant formation of side and decomposition products, best yields were obtained at a temperature of -15 °C (Table 1, entries 1–5). For complete conversion of the trifluoromethyl N,O-acetals at least 2 eq. MeMgBr are required. However, larger excess of the nucleophile did not improve the yield significantly. Similar results were obtained with *N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1b** bearing a neutral aryl ring (Table 1, entries 7–9).

With the optimized reaction conditions in hands, the substrate scope of the nucleophilic addition was tested using various functionalized aryl N,O-acetals **1** and MeMgBr (Table 2). We were pleased to find that besides halides also ester, triazole, trifluoromethyl groups and morpholino substituents are well tolerated to provide the desired trifluoroethyl amines **2** in fair to excellent yields (Table 2, entries 1, 5, 6 and 8). However, electron-rich aniline derivatives proceeded more sluggishly and led to formation of the desired product with only diminished yields (Table 2, entry 4). In contrast, both electron-deficient and moderately electron-rich heteroaromatic N,O-acetals **1c** and **1g–j** were readily converted to the corresponding amines **2c**, **2g–j** (Table 2, entries 3, 7–10), thus giving access to compounds with potential applications in drug design.

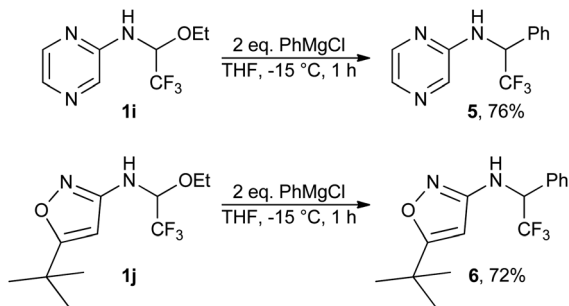
Next, we turned our attention to other Grignard reagents for nucleophilic addition to trifluoromethylated N,O-acetals. Thus,

Table 3 Addition of Grignard reagents to 3-chlorophenyl N,O-acetal^a

| Entry | RMgX | Yield of 3 (%) ^b | Yield of 4 (%) ^b |
|-------|-------------------------|------------------------------------|------------------------------------|
| 1 | <i>i</i> -PrMgCl | 3a , 70 | 16 |
| 2 | <i>i</i> -PrMgCl · LiCl | 3a , 67 | 30 |
| 3 | <i>n</i> -BuMgBr | 3b , 94 | nd ^c |
| 4 | <i>t</i> -BuMgCl | 3c , 57 | nd |
| 5 | | 3d , 78 | nd |
| 6 | | 3e , 26 | 19 |
| 7 | | 3f , 62 | nd |
| 8 | | 3g , 84 | nd |
| 9 | | 3h , 85 | nd |

^a All reactions were performed according to the optimized procedure. ^b After flash chromatography. ^c nd = not detected.





upon treatment of 3-chlorophenyl hemiaminal **1a** with several alkyl Grignard reagents, various α -branched trifluoromethyl *N*-arylamines **3a–e** were obtained in moderate to good yields (Table 3, entries 1–6). Notably, even highly sterically hindered nucleophiles like *t*-BuMgCl or cyclohexylmagnesium bromide can be successfully employed in this reaction (Table 3, entries 4 and 5). Interestingly, by using *i*-PrMgCl, *i*-PrMgCl·LiCl and cyclohexylmethylmagnesium chloride as nucleophiles, also generation of the formal reduction product 3-chloro-*N*-(2,2,2-trifluoroethyl)aniline **4** was observed. It is worth mentioning that the yield of this side-product was substantially higher with *i*-PrMgCl·LiCl (up to 30%) than with *i*-PrMgCl and cyclohexylmethylmagnesium chloride (Table 3, entries 1, 2 and 6). This is presumably due to the higher degree of complexation in the presence of LiCl, which facilitates hydride transfer to the substrate. Furthermore, nucleophilic addition of alkenyl Grignard reagents proceeded smoothly and provided the desired unsaturated trifluoromethyl *N*-arylamines **3f**, **3g** and **3h** in moderate to good yields (Table 3, entries 7–9).

Finally, PhMgCl can be used for conversion of trifluoromethyl *N,O*-acetals into trifluoromethylated benzylamine derivatives. For instance, treatment of the pyrazine derivative **1i** and the isoxazolyl hemiaminal ether **1j** with 2 eq. PhMgCl afforded amines **5** and **6** in good yields (Scheme 2).

In summary, an efficient procedure for the synthesis of α -branched trifluoromethylated amines has been developed starting from stable *N*-aryl trifluoromethyl hemiaminal ethers. Whereas alkyl amines were incompatible with *N,O*-acetal formation, a broad range of aromatic and heteroaromatic substrates can be applied successfully to allow for rapid generation of functionalized amine scaffolds for medicinal chemistry purposes after addition of alkyl, alkenyl and aryl Grignard reagents. Moreover and in contrast to other known protocols, protecting group manipulations are not required if the resulting trifluoromethylated amines are to be used as amide bio-isosteres for use in lead optimization. Further investigations in this direction and on the use of functionalized organometallic reagents are ongoing and will be reported in due course.

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