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**Graphical** **Abstract**

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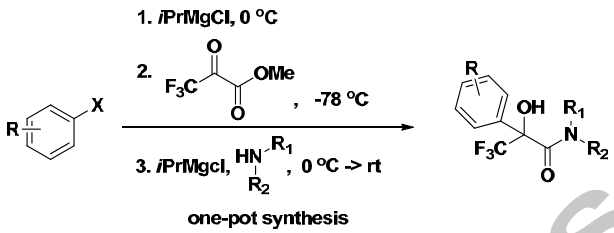

# Development of one-pot synthesis of α-hydroxy α-trifluoromethyl amides

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**Abstract**—

An efficient one-pot-three-step method has been developed to assemble readily available aryl or heteroaryl halides, methyl trifluoropyruvate and amines into biologically important α-hydroxy α-trifluoromethyl amides without isolation of any intermediates.


Keywords:

One-pot
α-Hydroxy α-trifluoromethyl amides
Halogen-magnesium exchange reaction
Bodroux reaction

Although rarely found in nature,[1] organofluorine compounds account for approximately 20% of pharmaceuticals on the markets, including some of the top selling drugs.[2] Selective installation of fluorine atom(s) or fluorinated group(s) into drug candidates often results in remarkable changes in pharmacokinetic and physicochemical properties as well as biological activities.[3]

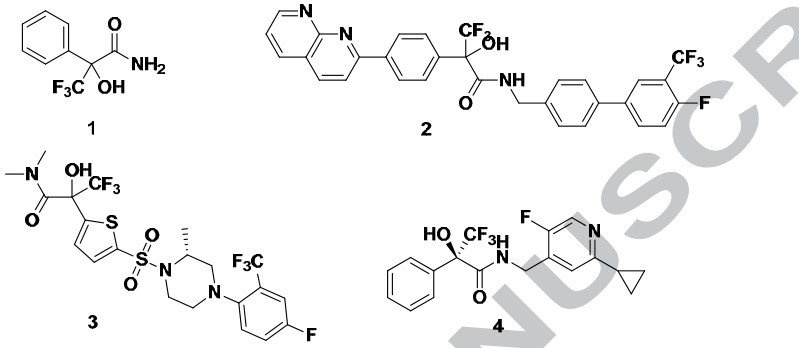
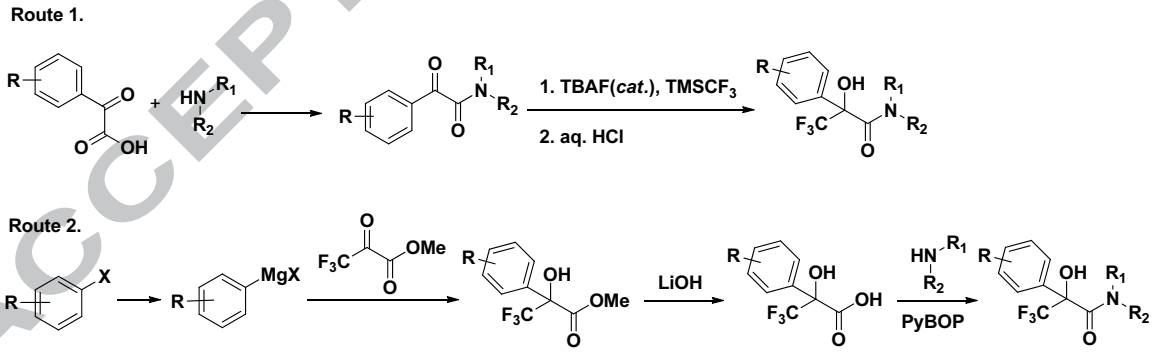



**Figure 1.** Examples of biologically active α-hydroxy α-trifluoromethyl amides

α-Hydroxy α-trifluoromethyl amides constitute an interesting sub-class of organofluorine containing compounds and have been widely studied as potential pharmaceutical agents (Figure 1); for example, anesthetic **1**,[4] hGPR91 antagonist **2**,[5] 11β-HSD1 inhibitor **3**,[6] and androgen receptor modulator **4**.[7]




**Scheme 1.** Known synthetic routes of α-hydroxy α-trifluoromethyl amides

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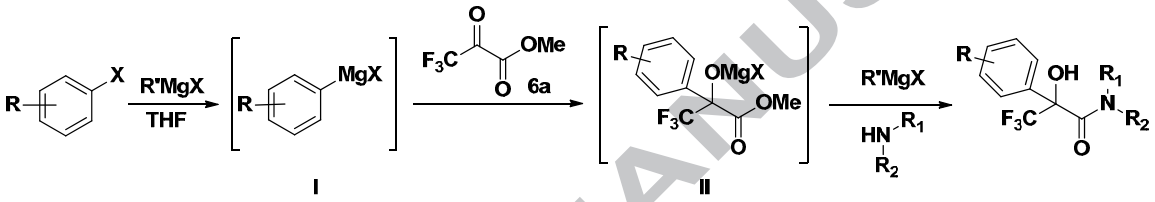
Therefore, several methods have been developed for the preparation of this class of compounds (Scheme 1). One route involves the TBAF-catalyzed nucleophilic trifluoromethylation of α-keto amides with TMS-$CF_3$ followed by acidic hydrolysis of the resultant silyl ether.[8] However, this procedure is limited by the availability of α-keto acids. α-Hydroxy α-trifluoromethyl amides can also be made by a four-step sequence from substituted halides: Grignard reagent preparation, addition to methyl trifluoropyruvate, ester saponification, and PyBOP-mediated amide bond formation.[9] Although the second approach is more general because of the readily available halides, it requires a number of tedious work-up steps and purification of intermediates.

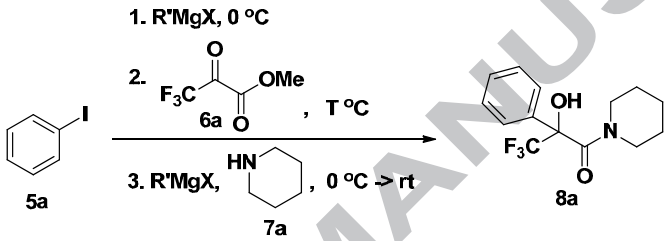



**Scheme 2.** Rationale of one-pot-three-step synthesis

These factors prompted us to search for a more general and efficient methodology to overcome these limitations. One-pot, multi-step reactions allows the construction of several bonds in one-pot manner without the need for any intermediate isolations and is a valuable tool to improve synthetic efficiency.[10] As shown in Scheme 2, the selective halogen-magnesium exchange reaction promoted by an alkyl Grignard reagent such as *i*PrMgCl is a widely utilized method for the generation of highly functionalized organomagnesium reagents.[11] Reaction of the *in situ* formed arylmagnesium reagent **I** with the highly electrophilic methyl trifluoropyruvate **6a** results in a rapid and regioselective addition to the α-keto functional group. We envisioned that without purification, subsequent reaction of the methyl ester intermediate **II** with an appropriate amine in the presence of a Grignard reagent would afford directly the desired amide (the Bodroux reaction).[12] Herein, we present the discovery and development of this one-pot-three-step reaction towards the α-hydroxy α-trifluoromethyl amide scaffold, its scope and limitations.

Initially, as shown in Table 1, we carried out a model study using iodobenzene **5a**, methyl trifluoropyruvate **6a** and piperidine **7a** as substrates. Thus, treatment of a solution of iodide **5a** in THF with *i*PrMgCl at 0 °C for 1 hour was followed by cooling to -78 °C and pyruvate **6a** was added to trap the newly formed Grignard reagent. Once the transformation was completed, the α-hydroxy α-trifluoromethyl ester intermediate was not isolated but immediately reacted with amine **7a** and excess *i*PrMgCl at 0 °C. The reaction mixture was then warmed to room temperature and stirred overnight to provide the desired amide **8a** in 78% isolated yield.

**Table 1** Optimization of the one-pot reaction




| Entry | R'MgX | T°C | Yield[a] of **8a** (%) |
|---|---|---|---|
| 1 | *i*PrMgCl | -78 °C | 78 |
| 2 | *i*PrMgBr | -78 °C | 64 |
| 3 | *i*PrMgCl.LiCl | -78 °C | 75 |
| 4 | *i*PrMgCl | 0 °C | 26 |

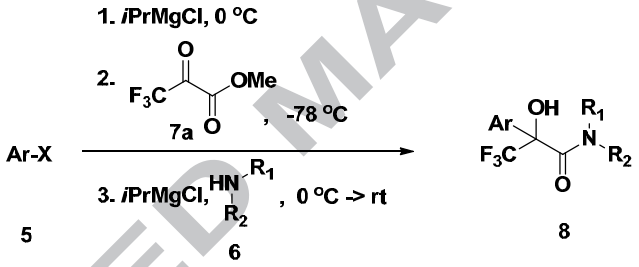
[a] Isolated yield.

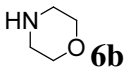
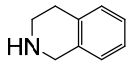
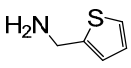
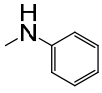
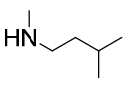
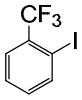
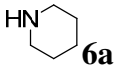
Next, the alkyl Grignard reagent was optimized and *i*PrMgCl was found to give the best yield (Table 1). A temperature survey then revealed that a higher yield was obtained when addition of the Grignard trapping reagent, methyl trifluoropyruvate, was carried out at lower temperature (-78 °C, entry 1). Possibly due to its reactive electrophile nature, addition of methyl trifluoropyruvate at higher temperature (0 °C, entry 4) didn't improve the yield and the crude material contained extensive impurities.

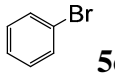
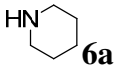
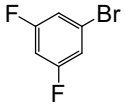
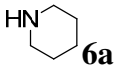
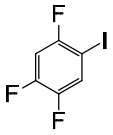
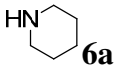
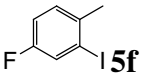
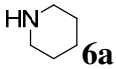
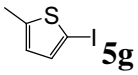
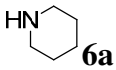
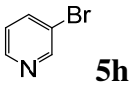
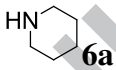
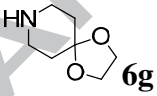
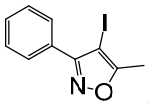
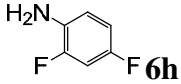
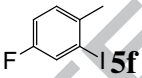
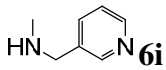
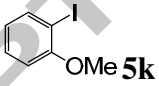
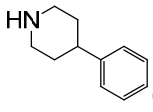
With optimal reaction conditions established, we then studied the scope and limitations of this one-pot-three-step transformation with respect to the halides and amines employed in the process, and the results are summarized in Table 2. The

generality of this method was first tested using various primary and secondary, aliphatic and aromatic amines (entries 1-5) and all cases provided moderate to good yield. Next, instead of using phenyl iodide **5a**, a range of functionalized aryl and heteroaryl halides were selected for evaluation. Clearly, this one-pot process's overall yield is highly dependent on the halide-magnesium exchange rate at the first step. Arylbromides are known to undergo exchange more slowly than the corresponding iodides[11] and a reaction starting from phenyl bromide **5c** gave no desired product (entry 7). However, electron-poor aryl bromides, such as 1-bromo-3, 5-difluorobenzene **5d** (entry 8), did provide the amide in 46% yield. It is noteworthy that from heteroaryl halides containing pyridine, thiophene, and isoxazole, the corresponding amides were also obtained (entries 11, 12 and 14).

**Table 2** One-pot synthesis of α-hydroxy α-trifluoromethyl amides



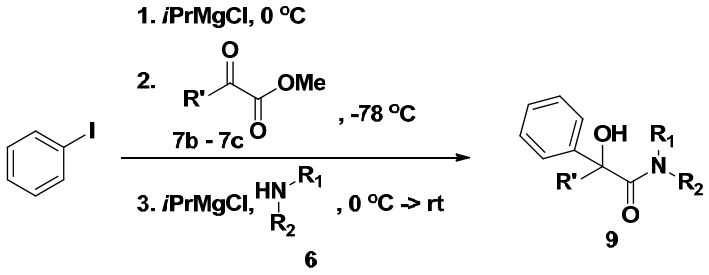

| Entry | Halides **5** | Amines **6** | Yield[a] of **8** (%) |
|---|---|---|---|
| 1 |  **5a** |  **6b** | 74 (**8b**) |
| 2 |  **5a** |  **6c** | 65 (**8c**) |
| 3 |  **5a** |  **6d** | 72 (**8d**) |
| 4 |  **5a** |  **6e** | 71 (**8e**) |
| 5 |  **5a** |  **6f** | 70 (**8f**) |
| 6 |  **5b** |  **6a** | 56 (**8g**) |

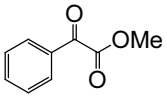
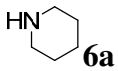
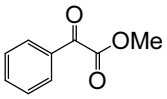
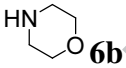
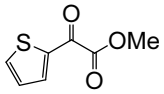
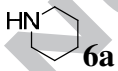
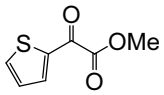
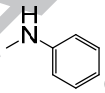
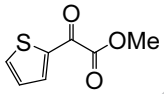
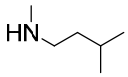
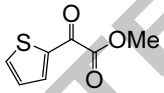
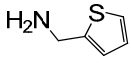
| | | | |
|---|---|---|---|
| 7 |  **5c** |  **6a** | 0 |
| 8 |  **5d** |  **6a** | 46 (**8h**) |
| 9 |  **5e** |  **6a** | 52 (**8i**) |
| 10 |  **5f** |  **6a** | 56 (**8j**) |
| 11 |  **5g** |  **6a** | 59 (**8k**) |
| 12 |  **5h** |  **6a** | 27 (**8l**) |
| 13 |  **5i** |  **6g** | 63 (**8m**) |
| 14 |  **5j** |  **6h** | 53 (**8n**) |
| 15 |  **5f** |  **6i** | 47 (**8o**) |
| 16 |  **5k** |  **6j** | 41 (**8p**) |

[a] Isolated yield.

Furthermore, as shown in Table 3, besides methyl trifluoropyruvate, this one-pot-three-step protocol could also be successfully applied to other types of α-keto esters, such as **7b** and **7c** (Table 3).

**Table 3** One-pot synthesis of α-hydroxy α-non-trifluoromethyl amides




| Entry | α-Keto ester **7** | Amines **6** | Yield[a] of **9** (%) |
|---|---|---|---|
| 1 |  **7b** |  **6a** | 48 (**9a**) |
| 2 |  **7b** |  **6b** | 72 (**9b**) |
| 3 |  **7c** |  **6a** | 53 (**9c**) |
| 4 |  **7c** |  **6e** | 46 (**9d**) |
| 5 |  **7c** |  **6f** | 50 (**9e**) |
| 6 |  **7c** |  **6d** | 66 (**9f**) |

[a] Isolated yield.

In conclusion, we have developed a general and efficient one-pot-three-step approach to assemble readily available aryl or heteroaryl halides, methyl trifluoropyruvate and amines into biologically important α-hydroxy α-trifluoromethyl amides without isolation of any intermediates. Moreover, this methodology has been successfully extended to use non-$CF_3$ containing keto esters as trapping reagents.

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13. Representative procedure for the synthesis of α-hydroxy α-trifluoromethyl amides **8**: preparation of 3,3,3-trifluoro-2-hydroxy-1-morpholino-2-phenylpropan-1-one **8b** (Table 2, entry 1). To a solution of phenyl iodide **5a** (300 uL, 2.68 mmol) in THF (4 mL) at 0 $^{o}$C, isopropylmagnesium chloride in THF (1338 µL, 2.68 mmol, 2M) was added dropwise. After stirring at 0 $^{o}$C for 1h, a solution of methyl trifluoropyruvate **7a** (273 uL, 2.68 mmol) in THF (3 mL) was added dropwise at -78 $^{o}$C. The mixture was stirred at -78 $^{o}$C for 1h and then warmed to 0 $^{o}$C, morpholine **6b** (350 µL, 4.01 mmol) and isopropylmagnesium chloride (2.0 mL, 4.01 mmol, 2 M) were added dropwise. At the end of the addition, the external cooling was removed, and the reaction was aged at room temperature overnight. At 0 $^{o}$C, the reaction mixture was quenched with slow addition of sat. $NH_4Cl$ and extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (0-60% EtOAc/hexane) provided the desired amide **8b** (479.9 mg, 62%). $^{1}$H-NMR (DMSO-$d_6$) δ: (ppm) 7.46-7.41 (m, 5H), 5.39 (s, 1H), 4-2.9 (m, 8H). HRMS calcd for [M+H]: 290.0999. Found: 290.0999.

14. Representative procedure for the synthesis of α-hydroxy α-non-trifluoromethyl amides **9**: preparation of 2-hydroxy-1-morpholino-2,2-diphenylethanone **9a** (Table 3, entry 1). To a solution of phenyl iodide **5a** (300 uL, 2.68 mmol) in THF (4 mL) at 0 $^{o}$C, isopropylmagnesium chloride in THF (1338 µL, 2.68 mmol, 2M) was added dropwise. After stirring at 0 $^{o}$C for 1h, a solution of ethyl 2-oxo-2-phenylacetate **7b** (477 mg, 2.68 mmol) in THF (3 mL) was added dropwise at -78 $^{o}$C. The mixture was stirred at -78 $^{o}$C for 1h and then warmed to 0 $^{o}$C, morpholine **6b** (350 µL, 4.01 mmol) and then isopropylmagnesium chloride (2007 µL, 4.01 mmol, 2 M) were added dropwise. At the end of the addition, the external cooling was removed, and the reaction was aged at room temperature overnight. At 0 $^{o}$C, the reaction mixture was quenched with slow addition of sat. $NH_4Cl$ and extracted with EtOAc. The combined organic layers were dried over

anhydrous $Na_2SO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (0-60% EtOAc/hexane) provided the desired amide **9a** (570 mg, 72%). $^1$H-NMR (DMSO-$d_6$) δ: (ppm) 7.44-7.30 (m, 10H), 5.76 (s, 1H), 3.72-3.08 (m, 8H). HRMS calcd for [M+H]: 298.1438. Found: 298.1431.