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A convenient one-pot synthesis of (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives

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ABSTRACT

A convenient one-pot synthesis of enantiopure (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives has been developed. The key step in this synthetic methodology turned out to be the amide formation in which (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid hydrochloride was simultaneously protected and activated by Vilsmeier reagent.

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Introduction

Comparing to natural amino acids, α-trifluoromethyl-α-amino acids exhibit a number of unique properties such as high electronegativity, high lipophilicity, high electron density, and high steric hindrance that are imparted by the trifluoromethyl group, which endows them significant potentials with practical applications.[1] Therefore, α-trifluoromethyl-α-amino acids are of great attraction in the design of biologically active molecules, particularly peptides.[2] (*R*)-3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-phenylpropanamide (Fig. 1) derivatives were originally reported as potent antiandrogen agents.[3,4] It was also found that some derivatives possessed undesirable hypotensive activity, which is most likely due to the activation of ATP-sensitive K^+ channels (K_{ATP} channels).[5–7] Moreover, these compounds can also act as inhibitors of Pyruvate Dehydrogenase Kinase (PDK), which is much more potent than the anti-cancer agent dichloroacetate[8] in primary enzymatic assay and is orally bioavailable.[9] Hence, we envisioned that the structurally similar (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide (Fig. 1) derivatives that contain a α-trifluoromethyl-α-amino acid fragment might have some special properties, particularly the anti-cancer activities. To the best of our knowledge, (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives have not yet been explored. Herein we report the one-pot synthesis of (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives from (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid via the intermediate of a *N*,*N*-dimethylformamidine protected acid chloride.

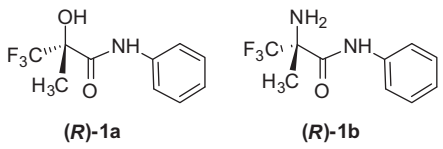

Figure 1. Structure of (*R*)-3,3,3-trifluoro-2-hydroxy-2-methyl-*N*-phenylpropanamide (**1a**) and (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide (**1b**).

Results and discussion

(*R*)-2-Amino-3,3,3-trifluoro-2-methylpropanoic acid hydrochloride was prepared according to the literature procedures.[10,11] In short, a solution of 1,1,1-trifluoropropan-2-one and (*R*)-phenylglycinol in toluene was refluxed in the presence of pyridinium 4-toluenesulfonate, furnishing oxazolidine **2** as the product. Afterward the oxazolidine **2** reacted with trimethylsilyl cyanide (TMSCN) to afford the amino nitriles **3** and **4**, which were further conveniently converted into 2-amino-3,3,3-trifluoro-2-methylpropanoic acids hydrochloride 5 and **6** by treating with concentrated HCl (Scheme 1).

For synthesizing (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives, we initially envisaged that the target molecule could be achieved by protecting the NH_2 group of (*R*)-5 with amino protecting reagents and subsequently coupling with anilines or transforming into acyl chloride followed by aniline treatment (Table 1). However, our preliminary experiments

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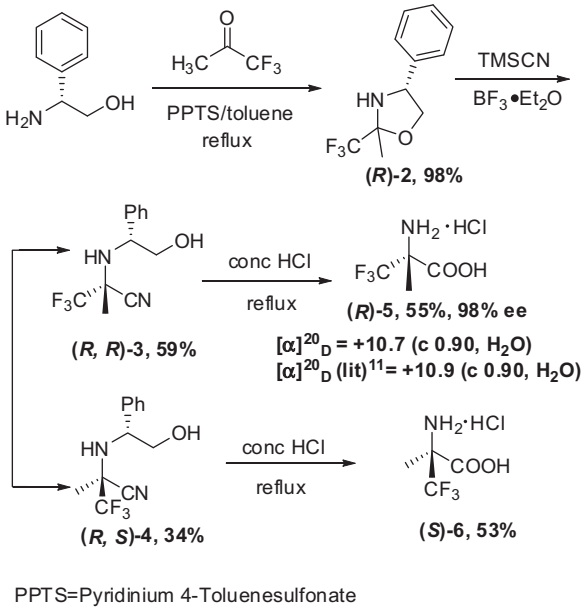
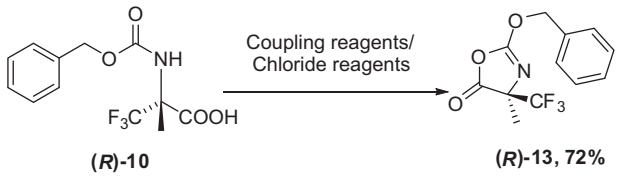


Scheme 1. Synthesis of (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid hydrochloride using (*R*)-phenylglycinol as a chiral auxiliary. PPTS = pyridinium 4-toluenesulfonate



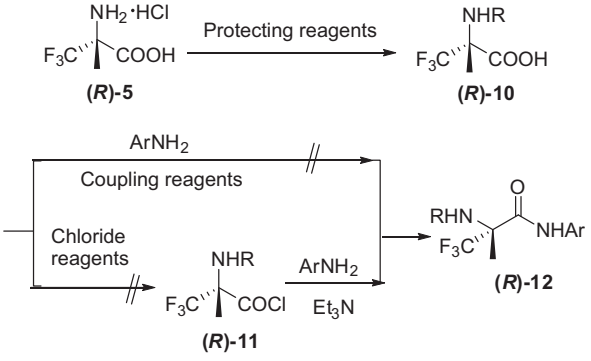
Scheme 2. (*R*)-*N*-Cbz-2-amino-3,3,3-trifluoro-2-methylpropanoic acid undergoes an intramolecular dehydration in the presence of coupling reagents or chloride reagents.

showed that the reaction of (*R*)-5 with Boc_2O failed to give any desired product, which may because of the poor basicity of the amino group in (*R*)-5 (Table 1).[12]

Then we turned to a more active reagent CbzCl for protecting the NH_2 group, which led to the formation of (*R*)-*N*-Cbz-α-trifluoromethylalanine. To our surprise, the subsequent treatment with aniline in the presence of various coupling reagents resulted in no formation of the desired product but something else; similar results were also observed with different chloride reagents (Table 1). We isolated the product from the above reactions and it was assigned as (*R*)-2-(benzyloxy)-4-methyl-4-(trifluoromethyl)oxazol-5(4*H*)-one (**13**). The result is consistent with Burger's report that (*R*)-*N*-Cbz-α-trifluoromethylalanine would transform into compound **13** under the mediation of coupling reagents such as DCC or chloride reagents such as $SOCl_2$ (Scheme 2).[13] Aliphatic amides of (*R*)-**5** could be prepared from **13** and aliphatic amines. However, the formation of aromatic amides from **13** and anilines was problematic, which may due to the much lower reactivity of anilines than aliphatic amines. Other types of amino protecting reagents such as TsCl, CH_3COCl, and PhCHO had also been employed (Table 1). The reaction of (*R*)-5 with TsCl or PhCHO only gives a very low yield of amino protected product (*R*)-10, while CH_3COCl gives a good yield of (*R*)-*N*-Ac-α-trifluoromethylalanine. However they all failed to give our desired products (*R*)-12 after subsequent treatment with aniline.

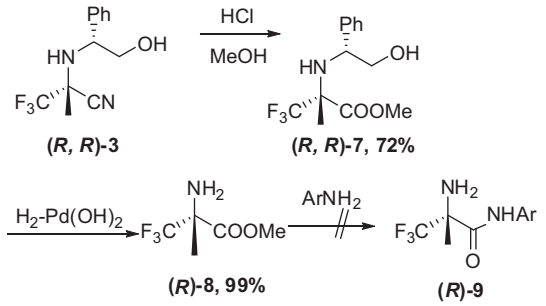
Considering the poor basicity of the amino group of (*R*)-5, we next turned our attention to a new working scenario, in which anilines reacted with ester of (*R*)-5 to give our desired products (Scheme 3). However, our experiments with (*R*)-methyl-2-amino-3,3,3-trifluoro-2-methylpropanoate (**8**) and aniline completely failed, probably owing to the poor reactivity of the aromatic amine moiety of anilines.

Table 1
Amide formation using various amino protecting reagents to protect the amino groups of (*R*)-5



Protecting reagents	R	Coupling reagents	Chloride reagents	10, % yield [a]	12, % yield
Boc_2O	Boc	—	—	—	—
CbzCl	Cbz	DCC	—	60	—
CbzCl	Cbz	EDC·HCl	—	60	—
CbzCl	Cbz	—	$(COCl)_2$	60	—
CbzCl	Cbz	—	$SOCl_2$	60	—
CbzCl	Cbz	—	PCl_3	60	—
CbzCl	Cbz	—	$POCl_3$	60	—
TsCl	Ts	DCC	—	11	—
TsCl	Ts	—	$SOCl_2$	11	—
CH_3COCl	CH_3CO	DCC	—	66	—
CH_3COCl	CH_3CO	—	$SOCl_2$	66	—
PhCHO	PhCH=N	DCC	—	8	—
PhCHO	PhCH=N	—	$SOCl_2$	8	—

[a] Yield of pure, isolated yield.

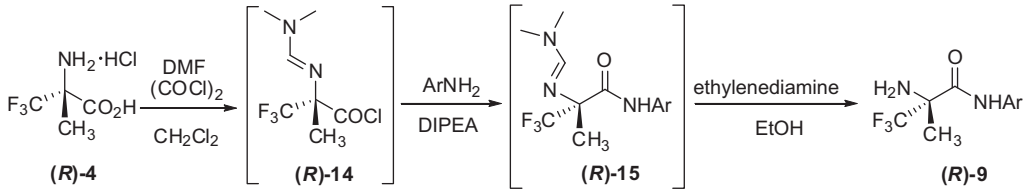


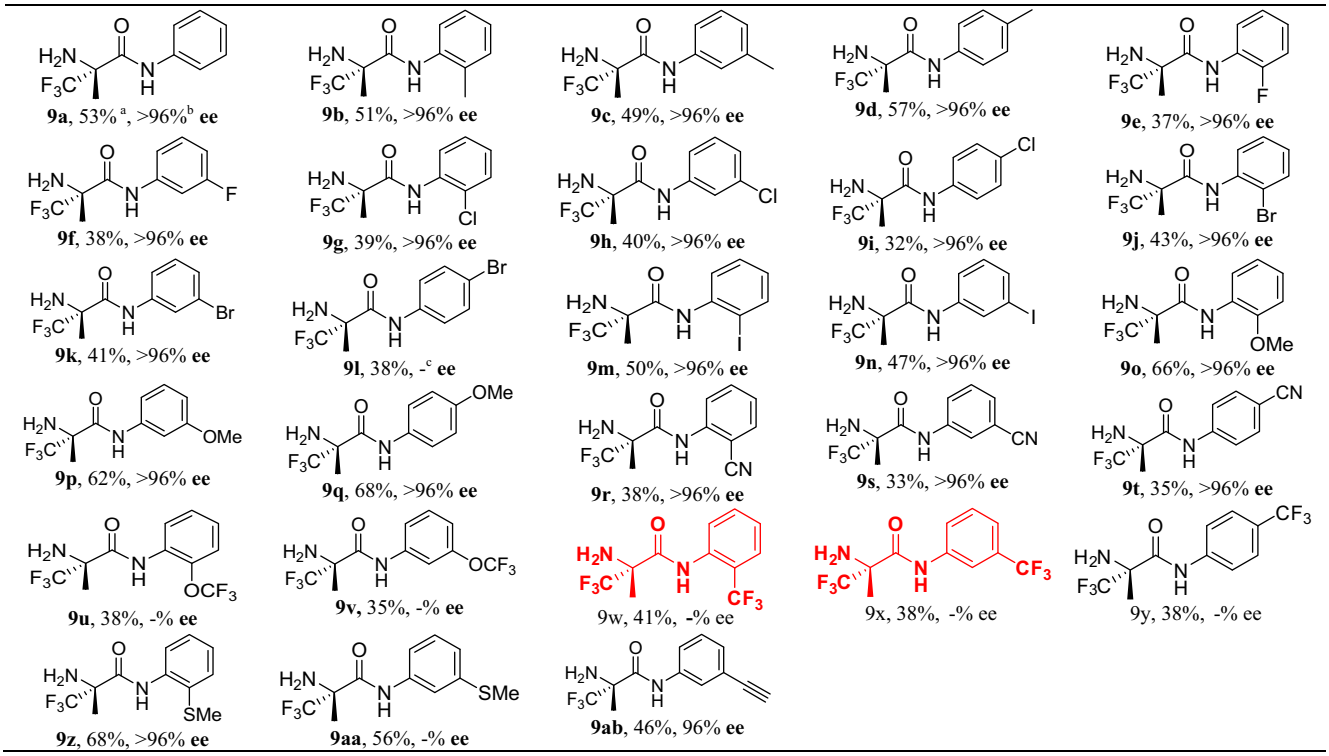
Scheme 3. Amide formation using aniline and ester of (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid.

The unsuccessful amidation of (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid with aniline under standard or modified peptide synthesis conditions prompted us to seek an alternative synthetic route for (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives. The low reactivity of the starting materials was attributed to the poor basicity of the amino groups in (*R*)-5 and aniline. Actually, we did notice that the basicity of the amino group in (*R*)-5 is significantly reduced, while the acidity of (*R*)-5 is increased, comparing to the corresponding non-fluorinated counterparts.[12] A similar situation also exists in amino-benzoic acids comparing to the aliphatic amino acids. Recently, Zhichkin et al developed a successful one-pot amidation of amino-benzoic acid which was simultaneously protected and activated with Vilsmeier reagent.[14] Therefore, we wondered that Vilsmeier reagent could be applied in our case for the synthesis of the desired compounds.

Thus, (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid hydrochloride was added to a suspension of 2 equivalents of the in situ prepared Vilsmeier reagent from DMF and oxalyl chloride in CH_2Cl_2 at room temperature, directly furnishing the unstable acid chloride **14**. Then a further treatment with anilines and *N*,*N*-diisopropylethylamine (DIPEA) afforded the protected amide **15**. Afterward **15** underwent a deprotection in the presence of ethylenediamine in ethanol under reflux to give the desired products.[15] By utilizing this methodology, a variety of (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives were synthesized in moderate yields (Table 2).

Table 2
Synthesis of (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives using Vilsmeier reagent for simultaneous protection and activation of (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid hydrochloride





[a] Yield of pure, isolated yield.
[b] Determined by HPLC equipped with a chiral Crownpak Cr(+) column (operated isocratically at 1 mL/min with 100% perchloric acid (pH = 1.0)).
[c] Means enantiopurity could not be determined owing to the poor solubility in water.

Conclusion

In conclusion, a convenient one-pot method for the simultaneous protection and activation of (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid for amide formation has been developed. The transformation was effected by the reaction of (*R*)-2-amino-3,3,3-trifluoro-2-methylpropanoic acid with Vilsmeier reagent, affording *N*,*N*-dimethylformamidine protected acid chlorides. These acid chlorides were used in situ for direct coupling reactions with weakly nucleophilic anilines to form the corresponding anilides. The pharmacological evaluations of these (*R*)-2-amino-3,3,3-trifluoro-2-methyl-*N*-phenylpropanamide derivatives, such as PDK inhibitory and anti-cancer activities, are in progress.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.086.

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15. *Typical procedure*: The Vilsmeier reagent was prepared by adding oxalyl chloride (2.52 g, 19.8 mmol) dropwise to a solution of anhyd. DMF (1.50 g, 20.5 mmol) in CH_2Cl_2 (20 mL) at 0–5 °C (CAUTION: Foaming!) and stirring at rt for 30 min. Compound 5 (1.57 g, 10.0 mmol) was added at 0 °C to Vilsmeier reagent (20.0 mmol) in CH_2Cl_2 (20 mL) prepared as described above, and the mixture was stirred at rt for 1 h. At 0 °C, a solution of substituted aniline (0.93 g, 10.0 mmol) in CH_2Cl_2 (10 mL) was added, followed by DIPEA (5.16 g, 31.0 mmol), and the mixture was stirred for 1 h at rt. It was then concentrated to dryness, and the residue was heated at reflux in ethanol (25 mL) with ethylenediamine (2.70 g, 45.0 mmol) for 3 h. The resulting mixture was evaporated to dryness, stirred with water (50 mL), and partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (petroleum ether/ethyl acetate) to afford compound 9a (53%, 1.23 g). *(R)-2-amino-3,3,3-trifluoro-2-methyl-N-phenylpropanamide (**9a**)*:Brown oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.0 Hz, 1H), 1.96 (s, 2H), 1.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 137.2, 129.4, 125.8 (q, J = 284.7 Hz), 124.9, 119.8, 118.6, 115.3, 61.4 (q, J = 27.5 Hz), 21.3. ESI-MS:m/z = 233.1 $[M+H]^+$, 255.0 $[M+Na]^+$.