SHORT COMMUNICATION

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Flow Synthesis of Fluorinated α-Amino Acids

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Fluorinated α-amino acids are versatile compounds that are used for many purposes in medicinal and biochemistry. However, their synthesis remains a significant hurdle, often requiring multiple steps, multiple protecting groups, and/or the use of highly toxic reagents. These challenges have limited the application of fluorinated α-amino acids. A convenient, protecting-group-free and semi-continuous process for the synthesis of racemic fluorinated α-amino acids from fluorinated amines is described. Following a singlet-oxygen-driven photooxidative cyanation, an acid-mediated hydrolysis of the intermediate α-amino nitrile yields the desired α-amino acid. Aliphatic, benzylic, and homobenzylic residues with different fluorination degrees are tolerated, providing good overall yields (50–67 %). This semi-continuous process is particularly advantageous for an aliphatic amine, the intermediate α-amino nitrile of which decomposes upon isolation.

Introduction

Despite the existence of only one naturally occurring fluorinated amino acid (4-fluoro-threonine),[1] their synthetic variants have found a wide range of applications, for example as mechanistic probes and enzyme inhibitors.[2,3] Fluorinated amino acids have also been utilized for peptide[4] and protein[5] modification, affecting the kinetics of β-sheet formation,[6] as well as the thermal stability,[7] binding,[8] and folding[9] of α-helical coiled coil systems. While these synthetic compounds continue to exhibit great potential for the manipulation and control of complex biological processes, their use in research is limited due to the lack of facile access to the appropriate fluorinated amino acids.[10] Currently, there are three major synthetic pathways for the synthesis of the canonical fluorinated α-amino acids (Figure 1).[3,10,11] Disconnect A represents the introduction of a fluorinated group to a protected glycine,[12] requiring several protection/deprotection steps and a limited pool of available coupling agents. The second strategy (Disconnect B) introduces the fluorinated side chain and amine equivalent sequentially, however, multiple synthetic steps are required to procure the starting materials.[13] The Strecker synthesis[14] (Disconnect C) is the most common method for α-amino acid synthesis, and involves nucleophilic addition of cyanide to an imine, followed by acid-mediated hydrolysis.[15,16]

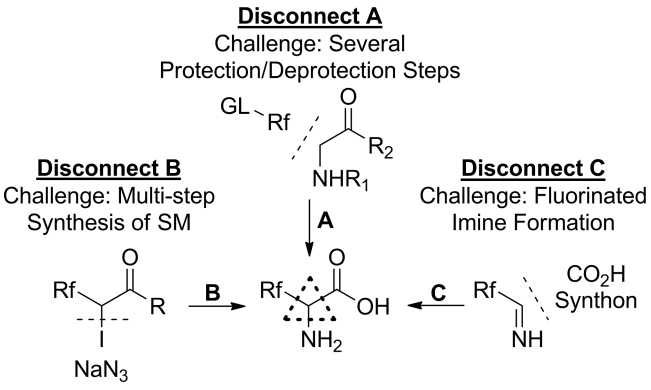

Figure 1. Three strategies for the synthesis of fluorinated α-amino acids. R_f = fluorinated alkyl or aromatic group.

The Strecker synthesis represents a concise, protecting-group-free route, but suffers from drawbacks related to the preparation of primary imines,[17] such as the need to remove water and the reactivity of aldehydes. Aldimines themselves are unstable, resulting in nitrile and enamine formation as well as polymerization. Recently, we developed a fast and clean method for the direct oxidation of primary amines to imines in a flow photoreactor.[18,19] These valuable intermediates can be trapped in situ to yield α-cyanoepoxides[20] and α-amino nitriles.[18] We hypothesized that a wide range of fluorinated α-amino acids could be quickly accessed by coupling the photooxidative cyanation of fluorinated amines with an acid-mediated hydrolysis (Scheme 1).

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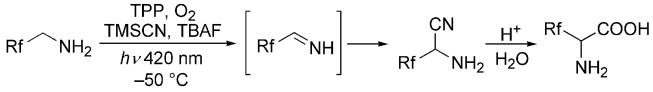
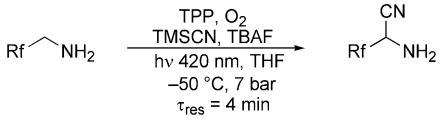


Scheme 1. Proposed coupling of photooxidation with acid-mediated hydrolysis for the synthesis of fluorinated α-amino acids in flow.

Results and Discussion

Utilizing the previously optimized conditions for primary amine oxidation,[18] a 0.1 M solution of 4-fluorobenzylamine with trimethylsilyl cyanide (TMSCN; 2.5 equiv.), tetrabutylammonium fluoride (TBAF; 10 mol-%), and tetraphenylporphyrin (TPP; 0.02 mol-%) in THF (1 mL min^{-1}) was mixed with oxygen gas[21] (2 mL min^{-1}) via a T-mixer prior to entering the 7.5 mL photooxidation module at –50 °C.[22,23] After a residence time of four minutes, the desired α-amino nitrile was obtained in 76% yield.[24] By adding 3.5 equiv. of TMSCN, the yield was improved to 94% (Table 1, entry 1) with complete consumption of starting material.

Table 1. Synthesis of fluorinated α-amino nitriles from fluorinated amines.[a]



Entry	R_f	Yield [%][b]
1	4-FC_6H_4	70 (94)[c]
2	3-FC_6H_4	88
3	2-FC_6H_4	61
4[d]	4-$CF_3C_6H_4$	27
5[d]	3-$CF_3C_6H_4$	52
6[d]	2-$CF_3C_6H_4$	36
7	3,4-$F_2C_6H_3$	55
8	3,5-$F_2C_6H_3$	40
9	4-$CF_2HOC_6H_4$	55
10	4-$FC_6H_4CH_2$	89
11	3-$FC_6H_4CH_2$	79
12	2-$FC_6H_4CH_2$	75
13	$CF_3(CH_2)_2$	decomposition

[a] Amine (0.1 M in THF), TMSCN (3.5 equiv.), TBAF (0.14 equiv.), TPP (0.02 mol-%), O_2 (3–5 mL min^{-1}), LED 420 nm, –50 °C, τ_{res} = 5 min, 7 bar BPR. For full reaction details, see supporting information. [b] Isolated yield. [c] Yield determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard. [d] Reaction was run at –60 °C.

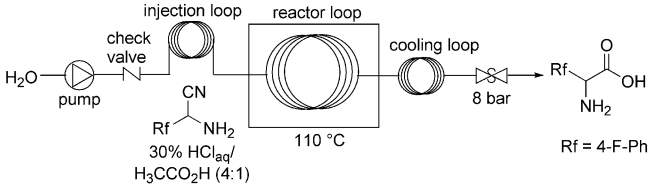
These optimized conditions were applied to a series of benzyl and homobenzyl primary amines bearing varying degrees of fluorination. Monofluorinated benzylamines (Table 1, entries 1–3) gave good to high yields with the exception of the *ortho* derivative (entry 3), presumably due to the slower rate of oxidation for this derivative.[25] Yields of 75–89% were observed for the homobenzyl species (entries 10–12). However, multiple fluorine atoms (entries 7 and 8) or trifluoromethyl groups (entries 4–6) on the aromatic ring resulted in poor to moderate yields of the corresponding α-amino nitriles, even at decreased temperatures.[18]

An alkyl substrate, 4,4,4-trifluorobutylamine, was also tested in these reaction conditions (Table 1, entry 13). While full conversion was observed with a 94% yield based on ^{19}F NMR spectroscopy, the product could not be isolated due to decomposition. As such, we sought a means of performing the subsequent hydrolysis step directly from the crude α-amino nitrile.

With a series of fluorinated α-amino nitriles in hand, hydrolysis of the nitrile under acidic conditions[26] was attempted in flow. One advantage of flow chemistry over traditional batch procedures is the ability to use solvents, such as the required 30% HCl_{aq}, well above their boiling point.[27] However, upon evaporation of the THF from the previous step,[28] the α-amino nitriles were found to be only partially soluble in this acidic solution. While alcohol co-solvents, such as 2-propanol or *n*-butanol, gave homogeneous solutions, the corresponding α-amino esters were obtained, as well as the desired amino acid.[29] After a short screen of solvent mixtures, acetic acid in 30% HCl_{aq} [1:4 (*v*/*v*)] was found to be optimal.

A 0.1 M solution of 4-fluorobenzyl amino nitrile was placed in an injection loop and passed through a 22 mL reactor (70 °C) at 8 bar pressure.[22] With a residence time of 37 min, nearly full conversion of the α-amino nitrile was observed. However, amide formation was observed, resulting from incomplete hydrolysis (Table 2, entry 1). Increasing the temperature to 110 °C gave full conversion to the desired α-amino acid with no intermediate amide (entry 3). Decreasing the residence time resulted in incomplete conversion (entries 4 and 5).

Table 2. Effects of residence time (τ_{res}) and temperature on amino acid formation from pure α-amino nitrile.[a]



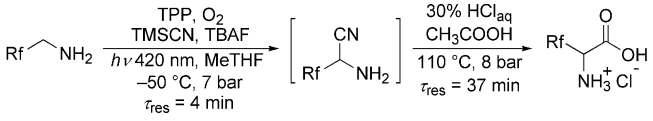
Entry	Temperature [°C]	τ_{res} [min]	Ratio of products[b] Amino acid	Amide	Amine salt
1	70	37	1.00	2.70	0.10
2	90	37	1.00	0.10	0.00
3	110	37	1.00	0.00	0.00
4	110	18	1.00	0.15	0.00
5	110	9	1.00	0.54	0.00

[a] Amino nitrile [0.1 M in CH_3COOH/30% HCl_{aq} (1:4 *v*/*v*)]. For full reaction details, see the Supporting Information. [b] Determined by ^{19}F NMR spectroscopy.

Finally, a fully semi-continuous process was developed. To facilitate the transition between the two processes, the solvent for the photooxidative cyanation was changed from THF to 2-MeTHF to allow for the extraction of water-soluble byproducts from the first step.[30] Upon subsequent sol-

vent removal, the crude material was dissolved in a 4:1 mixture of 30% HCl_{aq}/acetic acid to provide a 0.1 M solution with small amounts of precipitate, which were easily filtered.[31] Good yields were observed for the two-step process, providing benzylic (Table 3, entries 2 and 4) and homobenzylic (entry 1) fluorinated α-amino acids in 60–67%. The lower yield observed for the *meta*-CF_3 derivative (entry 3) presumably is due to its inefficient photooxidative cyanation (Table 1, entry 5). The true advantage of the described process is shown in entry 5. An aliphatic derivative, the intermediate of which decomposes upon purification (vide supra), can efficiently be transformed to the isolatable α-amino acid in comparable yields to the aromatic containing species. This rapid semi-continuous procedure requires no chromatography.

Table 3. Two-step synthesis of α-amino acids from fluorinated amines.[a]



Entry	R_f	Yield [%]
1	4-$FC_6H_4CH_2$	64
2	4-FC_6H_4	67
3	3-$CF_3C_6H_4$	50
4	3,4-$F_2C_6H_3$	60
5	$CF_3CH_2CH_2$	63[b]

[a] For full experimental details, see the Supporting Information. [b] Average yield of two runs.

Conclusions

In conclusion, a convenient, protecting-group-free method for the synthesis of racemic fluorinated α-amino acids from fluorinated amines is described. This semi-continuous process links a photooxidative cyanation, providing synthetically valuable fluorinated α-amino nitriles,[32] to an acid-mediated nitrile hydrolysis to yield aliphatic, benzylic, and homobenzylic racemic α-amino acids with varied fluorination patterns. The extension of this methodology towards optically pure amino acids is currently underway.

Experimental Section

General Procedure for Synthesis of Fluorinated Amino Nitriles: TMSCN (3.5 equiv.) was added to the solution of amine (1 mM) and TPP (1 mg per 5 mL) in THF, followed by addition of a 1 M solution of TBAF in THF (4 mol-% based on TMSCN). The resulting solution was mixed with oxygen gas (solution flow rate 1.0 mL min^{-1}) and pumped through a photoreactor. Gas flow rate was adjusted such that the residence time was four minutes. The solvent was removed in vacuo and the residue was purified by column chromatography. In the case of CF_3 substituted aromatics, work-up with saturated aqueous $Na_2S_2O_3$ was done prior to removing the solvent in vacuo.

General Procedure for Synthesis of Fluorinated Amino Acids from Fluorinated Amines: 2-MeTHF was used as a solvent for the synthesis of fluorinated amino nitriles by using the set-up described above. The reaction mixture, collected after the photoreactor, was washed with water (3 × 20 mL) and solvent was removed in vacuo. The reaction mixture was dissolved in acetic acid (1.2 mL); 30% aqueous HCl (3.5 mL) was added followed by sonication for 2 min and filtration. The precipitate was washed with 30% HCl (2.5 mL). An injection loop was then filled with the filtrate and the solution was passed through a 22 mL reactor heated to 110 °C at 0.6 mL min^{-1}. The solvent was removed in vacuo and the residue was purified, if necessary, by column chromatography to afford the desired amino acid salt as a white solid.

Acknowledgments

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[21] Dry compressed air (20.5 ± 0.5% O_2 in N_2) can also be used and gives similar yields of α-amino nitriles. See the Supporting Information for details.

[22] See the Supporting Information for full experimental details.

[23] For data describing the relationship of photooxidation yield and lamp power, see Figures S1 and S2 in the Supporting Information.

[24] Yield determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard.

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[29] The observed ratio of amino acid to ester was approximately 5:1.

[30] Aqueous work up was used to quench an excess of TMSCN and to remove TBAF. The yields of α-amino nitriles in 2-MeTHF were similar to those in THF.

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