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Direct Racemic Mixture Synthesis of Fluorinated Amino Acids by Perfluoroalkyl Radical Addition to Dehydroamino Acids Terminated by Asymmetric Protonation

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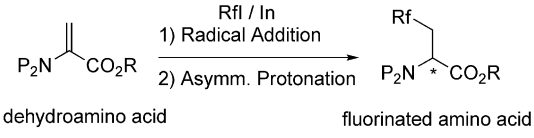
The development of efficient methods for the synthesis and purification of chiral organic compounds is a challenge in modern science and technology. Pharmaceutically and agrochemically important compounds are especially required in optically pure form. We report the racemic mixture synthesis of β-perfluoroalkyl α-amino acids, which is based on the In-mediated addition of perfluoroalkyl radicals to dehydroamino acids followed by asymmetric protonation. All the enantiomers can be separated by using a single chiral HPLC column, without orthogonal use of a fluorous column.

Introduction

Fluorinated amino acids are one of the most promising non-proteinogenic amino acids and have gained increased attention not only in pharmaceuticals but also in supramolecular science.[1] Specifically, β-perfluoroalkyl α-amino acids are highly expected to provide new functional compounds such as Teflon proteins,[2] because of their chemical/thermal stability and unique natures: Their hydrophobicity, bulkiness, and electronegativity are adjustable by introduction of a variety of perfluoroalkyl groups. However, efficient synthetic methods for chiral fluorinated amino acids are quite limited.[1] We reported the synthesis of chiral β-perfluoroalkyl α-iodo amides by a chiral auxiliary method[3] and the racemic mixture synthesis (RMS)[4] of fluorinated α-iodo esters that could be enantioseparated[5] as precursors for α-amino acids.

Here we report direct access to chiral β-perfluoroalkyl α-amino acids and the procedure is based on the indium-mediated addition of perfluoroalkyl radicals to dehydroamino acids; the reaction sequence is terminated by asymmetric protonation (Scheme 1). The present approach to chiral β-perfluoroalkyl α-amino acids features: (1) The indium-mediated radical addition of perfluoroalkyl iodide to dehydroamino acids to directly provide fluorinated amino esters by captodative synergistic stabilization[6] of the resultant α-amino ester radicals, although highly electrophilic perfluoroalkyl radicals are recognized to be less favorable to add to electron-deficient acrylates.[3] (2) The radical addition reaction can be terminated by asymmetric protonation[7] of the resultant α-amino ester enolates generated by single-electron transfer. (3) In RMS,[4] simultaneous demix, enantioseparation, and identification of amino esters having perfluoroalkyl substituents rather than fluorous tags solve the problems in solution-phase[8] combinatorial[9] synthesis by using only one single chiral HPLC column[10] and no orthogonal use of a fluorous column.[4,11]



Scheme 1. Direct synthesis of fluorinated α-amino acids.

Results and Discussion

The perfluoroalkyl radical addition[12] was first investigated on *N*-benzyloxycarbonyl dehydroamino acid methyl ester[13] (**1a**). Radical initiators such as Et_3B, Bu_3SnH, and AIBN were totally ineffective. Reductively induced radical conditions were then investigated (Table 1). To a solution of dehydroamino ester **1a** and *n*-C_4F_9I (5 equiv.) was added a reductant (4 equiv.), and the reaction mixture was then stirred at 20 °C. When the reaction was performed with $Pd(PPh_3)_4$,[14] $RhCl(PPh_3)_3$,[15] or $RuCl_2(PPh_3)_3$[16] a complex mixture of products was obtained (Table 1, Entries 1–3). The reaction with zinc[17] gave the desired perfluoroalkylated product in 11% (Table 1, Entry 4). The use of in-

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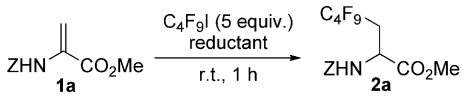
dium[18] instead of Zn increased the yield up to 48% (Table 1, Entry 5), although there has been no report on the Michael addition of RfI (Rf = perfluoroalkyl) mediated by In.

Table 1. Reductively induced radical addition of C_4F_9I.

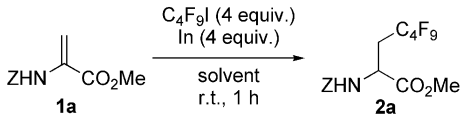


Entry	Reductant	Solvent	% Yield
1	$Pd(PPh_3)_4$	MeOH	–[a]
2	$RhCl(PPh_3)_3$	MeOH	–[a]
3	$RuCl_2(PPh_3)_3$	MeOH	–[a]
4	Zn	CH_2Cl_2	11
5	In	MeOH	48

[a] Complex mixture of products.

The reaction conditions were then optimized by using In as a radical initiator (Table 2). When the reaction was performed with the use of protic polar solvents such as *i*PrOH or MeOH the desired products were obtained (Table 2, Entries 1, 2, and 9). However, the reaction did not take place in the presence of water[19] (Table 2, Entries 7 and 8). In aprotic (Table 2, Entries 3 and 4) or less polar (Table 2, Entries 5 and 6) solvents, the reaction did not proceed. The best result was obtained in MeOH at 50 °C when *n*-C_4F_9I (8 equiv.) and In (7 equiv.) were used to generate the perfluorobutyl radical through single-electron transfer[18] (Table 2, Entry 11). Indeed, in the presence of TEMPO as a radical scavenger, the reaction did not proceed at all (vide infra; Table 2, Entry 12).

Table 2. In-mediated radical addition of C_4F_9I.

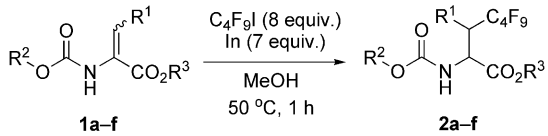


Entry	Solvent	% Yield
1	*i*PrOH	12
2	THF	24
3	MeCN	14
4	DMF	0
5	CH_2Cl_2	0
6	toluene	0
7	H_2O	trace
8	CH_2Cl_2 + H_2O (δ =100 ppm)	0
9	MeOH	48
10[a]	MeOH	50
11[a]	MeOH (50 °C)	54
12	MeOH + TEMPO	0

[a] C_4F_9I (8 equiv.) and In (7 equiv.) were used.

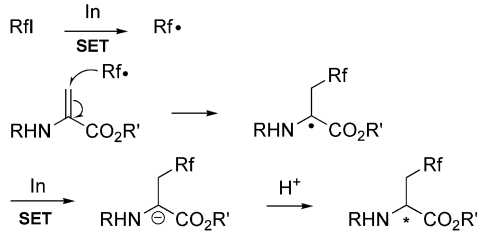
The reaction of *n*-C_4F_9I with various dehydroamino esters (**1**) was further investigated under the best reaction conditions (Table 3). Cbz-protected dehydroamino esters (**1a** and **1b**) gave good yields. Boc and Teoc protection (**1c** and **1d**) gave lower yields. Free carboxylic acid **1e** also underwent the reaction but in low yield. No reaction took place with β-substituted dehydroamino ester **1f**. The reactivity of various perfluoroalkyl radicals was then investigated with Cbz-protected dehydroamino ester **1a**. Various lengths of perfluoroalkyl radicals can be directly introduced into the dehydroamino ester, with the trifluoromethyl radical in particular (CF_3 59%, *n*-C_3F_7 45%, *n*-C_4F_9 54%).

Table 3. Radical addition of C_4F_9I to various dehydroamino esters.



Entry	Substrate	R^1	R^2	R^3	% Yield
1	**1a**	H	Bn	Me	54
2	**1b**	H	Bn	Bn	41
3	**1c**	H	*t*Bu	Me	22
4	**1d**	H	Et	Me	28
5	**1e**	H	Bn	H	16
6	**1f**	Bn	Et	Bn	–

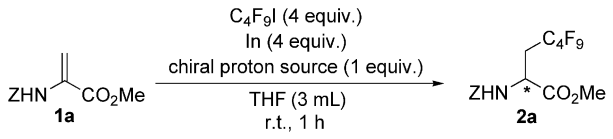
The reaction can be recognized by a single-electron transfer radical mechanism (Scheme 2). Indium[18] generates a perfluoroalkyl radical by single-electron transfer. Indeed, TEMPO as a radical scavenger, totally retarded the addition (vide supra) (Table 2, Entry 12). The perfluoroalkyl radical adds to the dehydroamino acid to give the captodatively stabilized[6] α-amino ester radical intermediate. Indium further reduces the perfluoroalkylated α-amino ester radical intermediate through single-electron transfer to give an ester enolate and final protonation gives the desired hydroperfluorinated product. Indeed, when the reaction was performed in [D_4]MeOH as a solvent, the corresponding α-deuterated product was produced.



Scheme 2. Indium-mediated single-electron transfer mechanism.

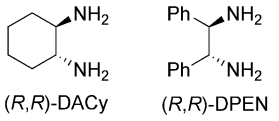
Therefore, the asymmetric protonation[7,20] was executed in the presence of a chiral proton source (Table 4). THF was used as an aprotic solvent instead of protic MeOH to prevent proton transfer from the achiral protic solvent. The use of chiral alcohol proton sources such as binaphthol (BINOL) gave the α-amino acid in 32% yield with 8%*ee* (Table 4, Entry 2). The enantioenriched amino acid was actually obtained with chiral amino acids, diamines, and their hydrochloride salts (Table 4, Entries 3–7). The hydrochloride salt of the cyclic diamine 1,2-diaminocyclohexane (DACy) gave the amino ester product with 28%*ee* in 16% yield (Table 4, Entry 4). Acyclic diamine derivatives, the hydrochloride salt of diphenylethylenediamine (DPEN), DPEN·2HCl, in particular gave the highest enantioselectivity (58%*ee*; Table 4, Entry 7).

Table 4. Asymmetric protonation with chiral proton sources.



Entry	Chiral proton source	% Yield	% *ee*[a]
1	none	24	–
2	(*R*)-BINOL	32	8
3	(L)-proline	34	13
4	(*R*,*R*)-DACy·2HCl	16	28
5	(*R*,*R*)-DPENTf	19	0
6	(*R*,*R*)-DPEN	19	30
7	(*R*,*R*)-DPEN·2HCl	21	58

[a] Determined by chiral HPLC (DAICEL AD-H) analysis.



The RMS of fluorinated amino acids can thus be terminated by asymmetric protonation[7,19] (Figure 1). The mixture of three perfluoroalkyl iodides [RfI = CF_3I (large excess because of volatility), *n*-C_3F_7I, and *n*-C_4F_9I] was treated with dehydroamino ester **1a** and then DPEN·2HCl in the same pot to give a mixture of perfluoroalkylated alanine derivatives in 43% combined yield. The separation of the mixture into six pure enantiomers was then established. All six enantiomers were baseline separated just by using a single chiral column (DAICEL AD-H), without orthogonal use of a fluorous column. Each amino ester was separated and identified respectively as shown in the order of decreasing lengths of the perfluoroalkyl substituents (Retention times: *n*-C_4F_9 < *n*-C_3F_7 < CF_3). The absolute configuration of the enantiomers could be determined by CD or OR detectors.[21] The one-pot radical addition/asymmetric protonation reaction and simultaneous demix/enantioseparation/identification thus solves the problems in solution-phase combinatorial synthesis just by using a single chiral column and six pure enantiomers were obtained, depending on the lengths of the fluorinated amino acids.

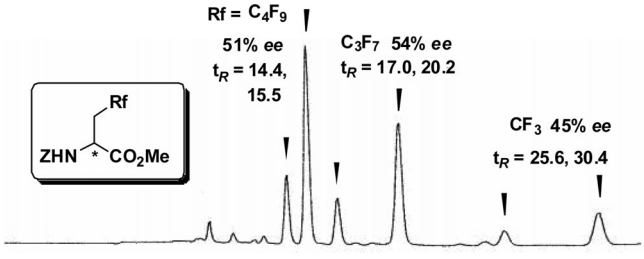


Figure 1. RMS terminated by asymmetric protonation. Column: AD-H, flow: 0.5 mL/min, solvent: Hex/*i*PrOH = 90:10, UV: 210 nm, temperature: 25 °C.

Conclusions

In conclusion, we have developed direct access to β-perfluoroalkyl α-amino acids through the In-mediated reductive radical addition of perfluoroalkyl iodides to dehydroamino acids terminated by asymmetric protonation to give products in up to 58% *ee*. The reaction can be further extended to the direct racemic mixture synthesis by using a single chiral HPLC column for simultaneous demix/enantioseparation/identification to give the enantiopure pairs of different lengths of β-perfluoroalkyl α-amino acids.

Experimental Section

Typical Experimental Procedure for the *Direct* "Racemic" Mixture Synthesis (RMS) Terminated by Asymmetric Protonation: To a solution of dehydroamino ester **1a** (94 mg, 0.4 mmol) in THF (6 mL) was added In (powder, 184 mg, 1.6 mmol, 4 equiv.) and three kinds of perfluoroalkyl iodides [CF_3I (1.6 g, 8 mmol, 20 equiv.), *n*-C_3F_7I (0.12 mL, 0.8 mmol, 2 equiv.), and *n*-C_4F_9I (0.14 mL 0.8 mmol, 2 equiv.)] at room temperature, and the reaction mixture was heated at 50 °C. After stirring for 1 h at that temperature, the reaction mixture was treated with the hydrochloride salt of diphenylethylenediamine (DPEN·2HCl; 114 mg, 0.4 mmol, 1 equiv.) at room temperature for 1 h. The mixture was extracted with CH_2Cl_2, and the extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography to afford pure products in 43% combined yield. Yield was determined by ^1H NMR spectroscopy by using $(CHCl_2)_2$ as an internal standard. The mixture thus obtained was separated into three enantiomer pairs of β-perfluoroalkyl α-amino esters by using a single chiral (DAICEL AD-H) HPLC column as follows: HPLC analysis was performed with a JASCO HPLC system (pump: PU-1580, gradient unit: LG-1580-04, degasser: DG-1580-54, column oven: CO-1560, UV and CD detector: CD-1595, auto sampler: AS-1555) by using a polysaccharide-based chiral column (DAICEL CHIRALPAK® AD-H, 25 cm × 4.6 mm i.d.) with a GL cart (0.5 cm × 4.6 mm i.d.) as a guard column and a JASCO HPLC system [pump: PU-1580, gradient unit: LG-1580-04, degasser: DG-1580-54, column oven: CO-1560, UV and CD detector: CD-995 (1595), auto sampler: AS-1555]. Peak areas were calculated by JASCO-BORWIN as an automatic integrator.

Acknowledgments

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