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Synthesis of α-fluoro-β-amino acids via the Reformatsky reaction of chiral *N-tert*-butylsulfinylimines with ethyl bromofluoroacetate

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Abstract

Treatment of chiral *N-tert*-butyl sulfinylimines with ethyl bromofluoroacetate in the presence of activated Zn dust in THF afforded the α-fluoro-β-amino acid derivatives in good yields (70–86%) and moderate diastereoselectivity (66:34–92:8).

Keywords: Fluorinated amino acids; Reformatsky reaction; *N-tert*-Butyl sulfinylimine

1. Introduction

The (R)- and (S)-isomers of *N-tert*-butylsulfinylamide reported by Ellman *et al*. [1,2] are versatile reagents for the asymmetric synthesis of various classes of substituted amines, amino acids, amino alcohols, and diamines. Staas *et al*. reported the diasteroselective synthesis of α,α-difluoro-β-amino acids via the Reformatsky reaction between ethyl bromodifluoroacetate and *N-tert*-butylsulfinylimines derived from the Ellman's *N-tert*-butylsulfinamide [3]. The Reformatsky reaction between Davis' *N*-sulfinylimines (optically active *N-p*-toluenesulfinylimines) and ethyl bromodifluoroacetate was also applied for the asymmetric synthesis of β-substituted α,α-difluoro-β-amino acids [4,5]. Most recently, the asymmetric synthesis of fluorine-containing amino acids mediated by chiral sulfinyl group has been reviewed [6]. However, the asymmetric Reformatsky reaction between ethyl bromofluoroacetate and chiral sulfinylimines has not been investigated and the resulting α-fluoro-β-amino acids may have potential medical applications. In this paper we found that the diastereoselective preparation of α-fluoro-β-amino acids can be readily achieved by the Reformatsky reaction of Ellman's *N-tert*-butyl sulfinylimines with ethyl bromofluoroacetate.

N-tert-Butylsulfinimines **1** were prepared in good yields through $Ti(OEt)_4$ mediated condensation of *N-tert*-butyl sulfinylamide with aldehydes and ketones according to the reported procedures [7,8]. The Reformatsky reaction was performed by the drop wise addition of a solution of **1** (1 equiv) and ethyl bromofluoroacetate (2 equiv) to a suspension of activated Zn dust in THF at reflux. The addition reaction underwent smoothly and completed within 2 h as monitored by thin layer chromatography (TLC). Four diastereomers were formed in the diastereoselective Reformatsky reaction and could be separated from each other in two diastereomer set (**I** and **II**) by careful silica gel

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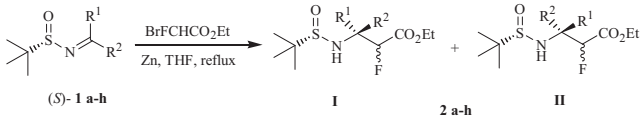
Table 1
The Reformatsky reactions of ethyl bromofluoroacetate with *N-tert*-butylsulfinimine[a].



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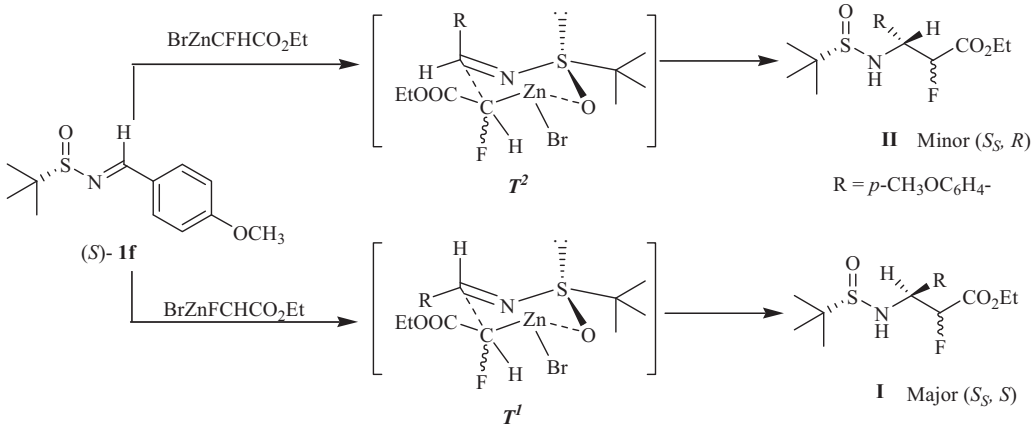
Entry	Substrate	R^1	R^2	Product	Yield[b] (%)	**I**:**II**[c]
1	**1a**	H	C_6H_5	**2a**	74	73:27
2	**1b**	H	2-Br-C_6H_4	**2b**	86	92:8
3	**1c**	H	4-Br-C_6H_4	**2c**	80	80:20
4	**1d**	H	4-F-C_6H_4	**2d**	77	69:31
5	**1e**	H	4-CH_3-C_6H_4	**2e**	84	73:27
6	**1f**	H	4-CH_3O-C_6H_4	**2f**	70	66:34
7	**1g**	H	*i*-Pr	**2g**	85	80:20
8	**1h**	Me	C_6H_5	**2h**	82	71:29
9	**1f**	H	4-CH_3O-C_6H_4	**2f**	77	64:36[d]

[a] **1** (1 equiv), ethyl bromofluoroacetate (2 equiv), Zn (2 equiv), THF, reflux, 2 h.
[b] Total yields of isolated products.
[c] The ratios of **I** and **II** were determined by ^{1}H NMR and ^{19}F NMR analyses of the crude products.
[d] Toluene was used as solvent.

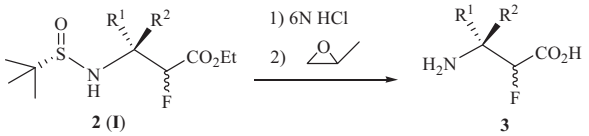
chromatography except for **2g** due to their close polarities. As listed in Table 1, the ratios of the two set of diastereomers (**I** and **II**) were determined by ^{1}H NMR and ^{19}F NMR analyses of the crude products and were in the range from 66:34 for electron donating group substituted aryl side chains such as *p*-methoxylphenyl (entries 6 and 9) to 92:8 for sterically hindered aryl side chains such as *o*-bromophenyl (entry 2). The reactions were efficient to achieve α-fluoro-β-amino acid derivatives with good yields (70–86%) though the diastereoselectivities (from 66:34 to 92:8) were not good enough as expected. The diastereomeric ratios were slightly lower than Staas' results that the reaction of *N-tert*-butylsulfinylimines with ethyl bromodifluoroacetate in the presence of zinc dust afforded α,α-difluoro-β-amino acid derivatives in diastereomeric ratios ranging from 81:19 to 95:5 [3].

Single crystals of **2f** were obtained from methanol solution of its diastereomers **I**. The absolute configuration of the (S_S,*S*,*S*)-**2f** was determined by single crystal X-ray diffraction analysis based on the chiral center of sulfur atom [10]. A possible mechanism was proposed based on the stereochemical outcome of the addition reactions and previous reports [3,7–9]. The addition of metal reagent to *N-tert*-butylsulfinylimines appears to proceed via six-membered chair-like transition states $\boldsymbol{T^1}$ and $\boldsymbol{T^2}$ (Scheme 1), and $\boldsymbol{T^2}$ is the favored transition state to give the major product because both of the bulky *tert*-butyl group and substituent in sulfinylimine could occupy equatorial positions. No diastereoselectivity



Scheme 1. Possible transition states in the Reformatsky reaction.

Table 2
Acidic cleavage of amides to free amino acids.



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Entry	Substrate (**I**)	R^1	R^2	Product	Yield (%)[a]
1	**2a**	H	C_6H_5	**3a**	70
2	**2b**	H	2-Br-C_6H_4	**3b**	92[b]
3	**2c**	H	4-Br-C_6H_4	**3c**	80
5	**2d**	H	4-F-C_6H_4	**3d**	87
6	**2e**	H	4-CH_3-C_6H_4	**3e**	70
7	**2f**	H	4-CH_3O-C_6H_4	**3f**	70
8	**2h**	Me	C_6H_5	**3h**	93[b]

[a] Isolated yields.
[b] Isolated yields of α-fluoro-β-amino acids hydrochloride salt.

on the alpha carbon bearing a fluorine atom would be expected due to small steric difference between fluorine and hydrogen atoms and freely rotation of carbon–carbon single bond in the Reformatsky reagents.

Finally, the protecting groups in the major products (**I**) of **2a–f**, **h** were removed with 6N HCl at reflux and followed by treatment with propylene oxide to afford the corresponding free α-fluoro-β-amino acids **3a–f**, **h** in 70–93% yields (Table 2).

In summary, we have developed a practical method for the asymmetric syntheses of α-fluoro-β-amino acids *via* Reformatsky-type addition reaction between *N-tert*-butylsulfinylimine and ethyl bromofluoroacetate in good yields (70–86%) and diastereoselectivities (66:34–92:8).

2. Experimental

2.1. General procedure for the Reformatsky reactions between sulfinylimines and ethyl bromofluoroacetate

A round-bottomed flask was flame dried, purged with argon, and charged with freshly activated zinc dust (4.8 mmol) and dry THF (10 mL). Then a solution of sulfinylimine (2.4 mmol) and ethyl bromofluoroacetate (4.8 mmol) in THF (6 mL) was added drop wise under reflux. The mixture was allowed to stir at reflux until the color of zinc was changed from gray to brownish, typically, it takes 2 h, then the reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl, and diluted with ethyl acetate. The aqueous layer was separated and extracted twice with ethyl acetate (30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography to give the desired product. **2a** [isomer **I**]: white solid; mp 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.35 (m, 5 H), 5.28 (dd, 1 H, J = 48.4, 4.4 Hz), 4.88 (dddd, 1 H, J = 28, 21.6, 6.4, 4.0 Hz), 4.27 (d, 1 H, J = 6.4 Hz), 4.10–4.19 (m, 2 H), 1.22 (s, 9 H), 1.14–1.17 (t, 3 H, J = 7.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ –200.64 (dd, 1 F, J = 48.0, 21.1 Hz).

2.2. General procedure for the cleavage of protecting group to afford free α-fluoro-β-amino acids

A solution of amide (0.3 mmol) in 6 mol/L HCl (10 mL) was refluxed for 4 h with stirring. The aqueous phase was washed with ether (30 mL) and the aqueous solution was concentrated under reduced pressure to dryness. The resulting solid was treated with *i*-PrOH (5 mL) and propylene oxide (2 mmol), and the reaction mixture was stirred for 5 h. Precipitate was collected by filtration and washed with ether to provide free amino acid. **3a**: ^{1}H NMR (400 MHz, D_2O): δ 7.38–7.42 (m, 5H), 5.34 (dd, 1H, J = 50.8, 2.8 Hz), 4.85 (dd, 1H, J = 28.4, 3.2 Hz). ^{19}F NMR (376 MHz, D_2O) δ –197.21 (dd, 1 F, J = 48.5, 27.4 Hz).

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