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Benzotriazole Mediated Syntheses of α-Fluoro-β-amino Esters

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Abstract: Mono- and difluoro-β-amino esters were synthesized *via* Reformatsky reaction of fluorinated ethyl bromoacetates with *N*-(α-aminoalkyl)benzotriazoles. Secondary and tertiary amines are easily formed, but primary amines can only be made in the difluorinated case. This approach has led to the first synthesis of di- and tetrafluorinated bis(β-amino esters).

Replacement of hydrogen with fluorine frequently confers bioactivity to organic molecules. In particular, fluorinated amino acids are important in medicinal chemistry.[1] Previous syntheses of difluorinated β-lactams from Reformatsky reaction with imines,[2,1c] ketene-imine condensations[3] or enolate-imine condensations[3a,4] in most cases are apparently not easily modified to allow the isolation of the corresponding fluorinated β-amino esters. A single example of the synthesis of a difluorinated β-amino ester by Reformatsky reaction with an iminium cation precusor was described.[2] Moreover, syntheses of monofluorinated β-lactams[5] are rare and no synthesis of a monofluorinated β-amino ester or a fluorinated bis(β-amino ester) was found. We now demonstrate that Reformatsky reaction of mono- and difluorobromoacetates with iminium salts provide a general and efficient route to mono- and difluoro-β-amino esters and -bis(β-amino esters).

N-(α-Aminoalkyl)benzotriazoles, easily prepared from an amine, an aldehyde and benzotriazole, were used as the iminium salt precursors[6] and provided α-fluorinated-β-amino esters **3** *via* a high yielding Reformatsky reaction with ethyl bromofluoroacetates **2** (Scheme 1, Table).[7] The three substituents of compound **3**, R^1, R^2 and R^3, can be H, alkyl or aryl. The synthesis of **3g,i** demonstrated that the benzotriazole derivatives **1** need not be purified before reaction with the Reformatsky reagent; thus, β-amino esters **3** can be made in a high yielding, one-pot reaction from an amine. The conversion of **3g** into **3h** shows that this method allows for the synthesis of primary difluoro-β-amino esters **3** from the corresponding tertiary amine, without the use of ammonia, by reductive debenzylation. However, attempts to make the

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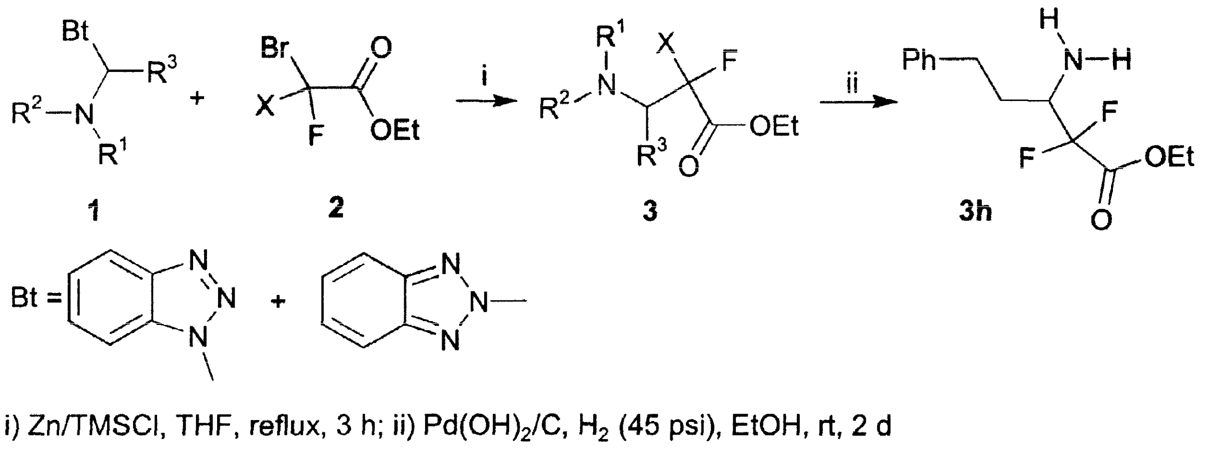


Scheme 1

primary monofluoro-β-amino ester from **3i** resulted in conversion to unidentified products. Excepting primary amines, the monofluoro compounds **3** are made just as easily as their difluoro analogs.

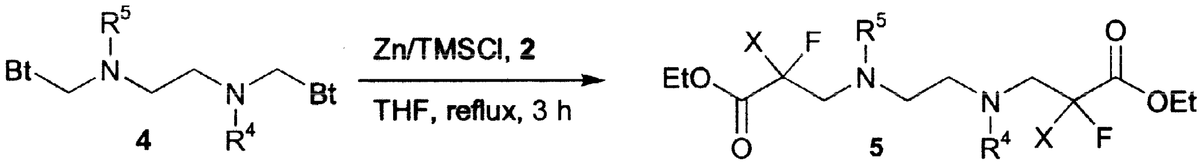
Table. α-Fluoro-β-amino Esters **3** Derived from *N*-(α-Aminoalkyl)benzotriazoles **1**.

Product	X	R^1	R^2	R^3	Yield (%)
3a	F	Ph	Me	H	90
3b	H	Ph	Me	H	91
3c	F	Ph	Ph	H	87
3d	F	Ph	H	H	92
3e	H	Ph	H	H	77
3f	F	Ph	Me	*i*-Pr	89
3g	F	Bn	Bn	$PhCH_2CH_2$	80[a]
3h	F	H	H	$PhCH_2CH_2$	88[b]
3i	H	Bn	Bn	$PhCH_2CH_2$	78[a]

a) Two step yield. b) Yield from reductive debenzylation of **3g**.

The present method was extended to the synthesis of fluorinated bis(β-amino esters) **5** (Scheme 2). The substituents R^4 and R^5 can be aryl or alkyl, in which case they can be part of a cyclic structure. Both mono- and difluoro esters **5** are easily synthesized.[7]

All of the β-amino esters **3, 5** gave satisfactory ^{1}H and ^{13}C NMR spectra and microanalysis (C, H, N: ±0.4%).[8] The ^{13}C NMR spectra showed the splitting expected due to the coupling between carbon and fluorine.



5	X	R^4	R^5	Yield(%)
a	F	$-CH_2CH_2-$		82
b	H	$-CH_2CH_2-$		86
c	F	Ph	Ph	79
d	H	Ph	Ph	85

Scheme 2

In conclusion we have developed the Reformatsky reaction of bromofluoroacetates with *N*-(α-aminoalkyl)benzotriazoles, and shown its utility in the synthesis of mono- and difluoro β-amino esters **3**. In addition to supplementing other methods for such compounds, this approach has led to the first synthesis of fluorinated bis(β-amino esters) **5**.

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7. A typical procedure for the synthesis of β-amino esters **3** and **5** is as follows: To a nitrogen protected schlenk flask with stirrer was added Zn (2 equiv.), THF (25 mL) and chlorotrimethylsilane (0.8 equiv.). After 10 min **2** (1.5 equiv.) was added, followed by **1** or **4** (5 mmol) after 10 min more. After 3 h of refluxing, the solution was allowed to cool before being quenched with 10 mL of saturated $NaHCO_3$(aq) and filtered through Celite 545®. The layers were separated, and the aqueous phase was extracted with ether (3 x 10 mL). The combined

organics were washed with 10 mL of brine, and dried over sodium sulphate. After the solvent was removed under reduced pressure, compounds **3**, **5** were isolated by flash column chromatography (10:1 hexanes:ethyl acetate) of the crude product.

8. For example: Ethyl 2-fluoro-3-(*N*-phenyl-*N*-methylamino)propanoate (**3b**): yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.03 (t, J = 7.8 Hz, 2H), 6.55 (d, J = 8.3 Hz, 3H), 4.86 (dm, $^2J_{H-F}$ = 49.5 Hz, 1H), 4.01-3.90 (m, 2H), 3.73-3.39 (m, 2H), 2.76 (s, 3H), 1.04 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.9 (d, J =23.0 Hz), 148.0, 128.7, 116.8, 112.1, 88.7 (d, J = 186.4 Hz), 61.1, 54.0 (d, J = 21.2 Hz), 38.6, 13.5. Anal. Calcd. for $C_{12}H_{16}FNO_2$: C, 63.98 %; H, 7.16 %; N, 6.22 %. Found: C, 63.65 %; H, 7.36 %; N, 6.21 %. Ethyl 2-fluoro-3-(*N*-phenylamino)propanoate (**3e**): yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.18 (t, J = 7.7 Hz, 2H), 6.75 (t, J = 7.1 Hz, 1H), 6.65 (d, J = 8.0 Hz, 2H), 5.07 (dm, $^2J_{H-F}$ = 48.8 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 4.04 (br/s, 1H), 3.74-3.52 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.3 (d, J = 23.2 Hz), 146.8, 129.2, 118.3, 113.3, 87.5 (d, J = 185.6 Hz), 61.7, 45.6 (d, J = 21.5 Hz), 14.0. Anal. Calcd. for $C_{11}H_{14}FNO_2$: C, 62.55 %; H, 6.68 %; N, 6.63 %. Found: C, 62.22 %; H, 6.73 %; N, 6.76 %. Ethyl 3-amino-2,2-difluoro-5-phenylpentanoate (**3h**): white solid (ethyl acetate), decomposes 122°C. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.27-7.15 (m, 5H), 4.23 (q, J = 7.1 Hz, 2H), 3.20-3.17 (m, 1H), 2.91-2.83 (m, 1H), 2.72-2.62 (m, 1H), 1.98-1.86 (m, 1H), 1.66-1.54 (m, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 163.6 (t, J = 32.5 Hz), 140.9, 128.2, 128.1, 125.8, 115.9 (t, J = 253.4 Hz), 62.4, 53.4 (t, J = 24.1 Hz), 31.5, 31.2, 13.5. Anal. Calcd. for $C_{13}H_{17}F_2NO_2$: C, 60.69 %; H, 6.66 %; N, 5.44 %. Found: C, 60.93 %; H, 6.30 %; N, 5.28 %. 1,4-Di(2-fluoro-3-ethoxy-3-oxopropyl)piperazine (**5b**): colorless rods (ethyl acetate), mp = 83-85°C. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.14-5.12 (m, 1H), 4.98-4.95 (m, 1H), 4.31-4.23 (m, 4H), 2.93-2.81 (m, 4H), 2.64-2.53 (m, 8H), 1.31 (t, J = 7.0 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.7 (d, J = 23.6 Hz), 88.9 (d, J = 186.9 Hz), 61.4, 59.2 (d, J = 19.9 Hz), 53.6, 14.2. Anal. Calcd. for $C_{14}H_{24}F_2N_2O_4$: C, 52.16 %; H, 7.50 %; N, 8.69 %. Found: C, 52.26 %; H, 7.73 %; N, 8.66 %. *N,N'*-Diphenyl-*N,N'*-di(2-fluoro-3-ethoxy-3-oxopropyl)-1,2-ethylenediamine (**5c**): yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.28-7.22 (m, 4H), 6.85-6.79 (m, 6H), 4.16 (q, J = 7.1 Hz, 4H), 3.91 (t, J = 13.6 Hz, 4H), 3.61 (s, 4H), 1.21 (t, J = 7.1 Hz, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): 163.7 (t, J = 31.8 Hz), 147.3, 129.3, 118.8, 114.8 (t, J = 254.7 Hz), 114.0, 63.1, 54.8 (t, J = 26.5 Hz), 48.4, 13.7. Anal. Calcd. for $C_{24}H_{28}F_4N_2O_4$: C, 59.50 %; H, 5.83 %; N, 5.78 %. Found: C, 59.50 %; H, 6.00 %; N, 5.80 %. *N,N'*-Diphenyl-*N,N'*-di(2,2-difluoro-3-ethoxy-3-oxopropyl)-1,2-ethylenediamine (**5d**): white prisms (ethyl acetate), mp = 73-75°C. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.28-7.23 (m, 4H), 6.80-6.77 (m, 6H), 5.07 (dm, $^2J_{H-F}$ = 49.5 Hz, 2H) 4.24-4.22 (m, 4H), 4.02-3.84 (m, 2H), 3.76-3.57 (m, 6H), 1.30-1.20 (m, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.3 (d, J = 23.3 Hz), 146.7, 146.6, 129.5, 117.5, 112.5, 87.9 (d, J = 186.3 Hz), 87.8 (d, J = 186.3 Hz), 61.7, 53.9 (d, J = 21.1 Hz), 53.8 (d, J = 21.2 Hz), 48.9, 48.8, 14.0. Anal. Calcd. for $C_{24}H_{30}F_2N_2O_4$: C, 64.27 %; H, 6.74 %; N, 6.25 %. Found: C, 64.03 %; H, 6.97 %; N, 6.21 %.