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An asymmetric synthesis of both enantiomers of 2,2,2-trifluoro-1-furan-2-yl-ethylamine and 3,3,3-trifluoroalanine from 2,2,2-trifluoro-1-furan-2-yl-ethanone

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Abstract—The selective conversion of 2,2,2-trifluoro-1-furan-2-yl-ethanone into (*E*)- and (*Z*)-oximes and oxime ethers and subsequent oxazaborolidine-catalyzed enantioselective reduction using different amino alcohols furnished both enantiomers of the important chiral building block 2,2,2-trifluoro-1-furan-2-yl-ethylamine with e.e. of up to 88%. Oxidation of the furan ring afforded both enantiomers of 3,3,3-trifluoroalanine in 91–93% yields.

1. Introduction

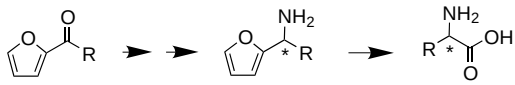
The polyhalogenated alanine analogue 3,3,3-trifluoroalanine is known to be a potent inhibitor of PLP-containing enzymes.[1] Several methods have been published for the synthesis of 3,3,3-trifluoroalanine and its derivatives but few examples have been reported for the asymmetric synthesis of these compounds.[2] Uneyama described the synthesis of enantiomerically enriched 3,3,3-trifluoroalanine (up to 62% e.e.) by the asymmetric reduction of 2-(*N*-arylimino)-3,3,3-trifluoropropanoic acid esters with a chiral oxazaborolidine catalyst followed by oxidative removal of the *N*-aromatic moiety with retention of configuration.[3] The asymmetric reduction of imino esters using (*S*)-reductants afforded the (*S*)-configured amino esters together with the (*R*)-configured amino alcohol. It was found that the use of the oxazaborolidine in combination with catecholborane completely suppressed the formation of amino alcohol and the amino ester was obtained in 63% e.e. Bravo et al. have developed several synthetic routes using chiral sulfoxides as stereocontrolling elements for the synthesis of fluorinated alanines. Forming the chiral fluoroalkyl(sulfinyl)methyl imines and then reducing these compounds stereoselectively gave the corresponding amines with diastereomeric ratios (d.r.) of up to 93:7. The amines were then transformed into fluoroalanines in good yield.[4]

As we reported earlier, furyl alkyl ketones can be used as starting materials for the enantioselective synthesis of both enantiomers of α-amino acids. Oxime ether formation and oxazaborolidine-catalyzed enantioselective reduction followed by oxidation of the furan ring furnished the α-amino acids in good yields and high enantiomeric purities (Scheme 1).[5]

In connection with our reported preliminary results, we describe herein the enantioselective synthesis of 2,2,2-trifluoro-1-furan-2-yl-ethylamine and 3,3,3-trifluoroalanine starting from 2,2,2-trifluoro-1-furan-2-yl-ethanone.

2. Results and discussion

2,2,2-Trifluoro-1-furan-2-yl-ethanone **1** was synthesized using the literature procedure.[6] As illustrated in Scheme 2, the ketone **1** was converted to oxime **2** using $H_2NOH.HCl/NaOAc$ in EtOH. Oxime **2** was obtained in 92% yield as a mixture of diastereomers ((*E*)/(*Z*) ratio: 28:72) (mp 104–106°C). The chromatographic separation of isomers gave pure (*E*)-isomer (mp 100–102°C, 24%) and (*Z*)-isomer (mp 110–111°C, 70%) as colorless solids which had intense fresh bread-like odor. The reaction of **2** ((*E*)/(*Z*) mixture) with hydrogen



Scheme 1.

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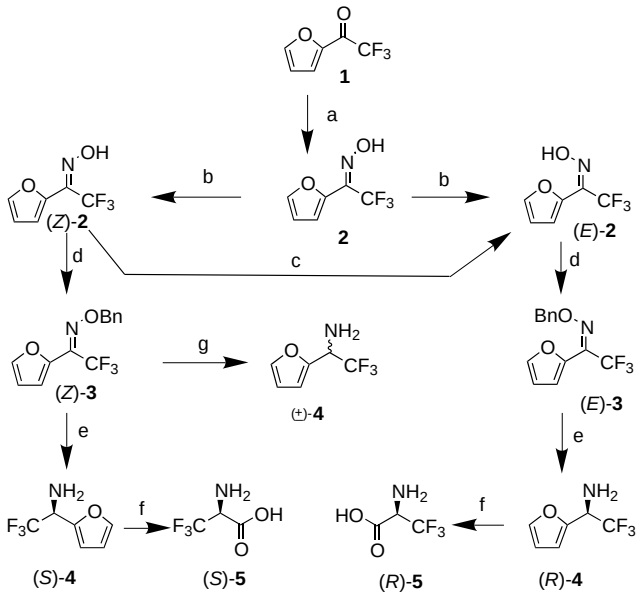

Scheme 2. (a) $H_2NOHHCl$, NaOAc, EtOH; (b) separation; (c) HCl(g), MeOH; (d) NaH, BnBr, DMF; (e) BH_3·THF, cat.; (f) O_3, MeOH, −78°C.

chloride in ether furnished oxime **2** with an (*E*)/(*Z*) ratio of 4:1, which was purified by recrystallization. The (*E*)- and (*Z*)-isomers were identified by their ^1H and ^{13}C NMR spectra (the (*Z*)-isomer displays a multiplet for the C(3) proton of the furan ring at 6.84 ppm and the (*E*)-isomer displays the multiplet for the same proton at 7.58 ppm. Additionally, the ^{13}C NMR shift for carbon C(3) of the (*Z*)-isomer is 114.9 ppm, whereas for the (*E*)-isomer the shift is 121.4 ppm). The purity of the ((*E*)- and (*Z*)-isomers was confirmed by glc analysis of the corresponding *O*-benzyl ether derivatives of the oximes.

The oximes were converted to the *O*-benzyl oximes (*E*)-**3** and (*Z*)-**3** using NaH and benzyl bromide in 94–96% yields. No isomerization was observed during this conversion. The *O*-benzyl oximes were purified by flash column chromatography and isolated as viscous oils. Compounds **3** were also synthesized from ketones and *O*-benzyl hydroxylamine hydrochloride. This procedure gave a mixture of isomers which were separated by flash column chromatography to afford the (*E*)- and (*Z*)-oxime ethers in 28 and 36% yields, respectively.

Oxime ethers are a class of readily available compounds for the conversion of carbonyl groups to amines. One of the most important works in this area was reported by Itsuno et al.[7] who showed that acetophenone oxime ethers can be converted into amines with high e.e.s using BH_3–oxazaborolidine complexes. The enantioselective reduction of (*Z*)-**3** and (*E*)-**3** was carried out with BH_3 in the presence of oxazaborolidine complexes[8] prepared from different chiral amino alcohols using the following procedure: A solution of borane (20 mmol) in THF (20 mL) was added under argon dropwise to a solution of (−)-(1*R*,2*S*)-norephedrine (10 mmol) in THF (10 mL) at −20°C. The resulting mixture was allowed to warm to −5°C and stirred at this temperature for 16 h before the oxime ether (*Z*)-**3** (8 mmol) in THF (10 mL) was added dropwise. The resulting solution was stirred at 30°C for 48 h (monitored by TLC) and was decomposed by slow addition of 2 M aqueous HCl. The product amine (*S*)-**4** was obtained in 80% yield and 76% e.e. after purification of the crude product by bulb-to-bulb distillation and converted to its hydrochloride salt using methanolic hydrogen chloride. Under similar conditions using the (*E*)-oxime ether, (*E*)-**3** furnished amine (*R*)-**4** in 74% yield and 73% e.e. Different amino alcohols were used in the reduction reaction and as shown in Table 1 the (*R*)- and (*S*)-amine are obtained in 73–80% yields and 73–88% e.e. The highest e.e. was found with amino alcohol **8**.

The best enantiomeric purity was obtained when the ratio of borane:amino alcohol:oxime ether was ca. 2.5:1.25:1.0. An excess of borane relative to the amino alcohol led to product with low enantiomeric purities.

Table 1. Enantioselective synthesis of (*S*)-**4** and (*R*)-**4** using different amino alcohols

O-benzyloxime **3**	Amino alcohols: (1*R*,2*S*)- **6**		(*S*)-**7**		(*S*)-**8**	
	4[a]					
	Yield(%)	E.e.(%)	Yield(%)	E.e.(%)	Yield(%)	E.e.(%)
Z	80	76 (*S*)	73	80(*S*)	73	88(*S*)
E	74	73 (*R*)	77	82(*R*)	74	86(*R*)

a) E.e. values were determined from ^{19}F NMR of corresponding (*S*)-MTPA derivative and by HPLC analysis of *N*-acetyl derivative (Chiralcel OB, eluent Hexane/propan-2-ol 95:5, retention time 7.12 min. (*S*), 8.36 min. (*R*).

The amines were characterized by NMR and IR. The enantiomeric purity of the products was determined via preparation of the Mosher amide and analysis by ^{19}F NMR, or via analysis of the *N*-acetyl derivative by HPLC on a chiral stationary phase column compared to racemic product, which was synthesized from (*Z*)-**3** using $BH_3{\cdot}SMe_2$. The absolute configuration of (*S*)-**4** and (*R*)-**4** was found by comparison of the specific rotation values with known data.[9] The amino alcohols used for the preparation of the oxazaborolidines were recovered in 93–95% yields during the work up procedure as their HCl salts.

The reduction of oxime ether (*Z*)-**3** under similar condition with catalytic amount of oxazaborolidine complexes prepared with amino alcohol (*S*)-**8** (0.1–0.2 equiv.) afforded products with e.e. of 15–22%.

The effect of the *O*-protecting group on the reduction of oxime ethers **3** was investigated. The reduction was carried out on a (*Z*)-*O*-methyl oxime and determination of the e.e.s of the product amines showed low selectivity (32% e.e.). As shown in Scheme 2, the amines (*S*)- and (*R*)-**4** are converted into 3,3,3-trifluoroalanine by oxidation of the furan ring with ozone in 91–93% yields.

3. Conclusion

2,2,2-Trifluoro-1-furan-2-yl-ethanone **1** was converted into its (*E*)- and (*Z*)-oxime selectively in good yield and oxazaborolidine-catalyzed enantioselective reduction of the corresponding *O*-benzyl oxime ethers afforded both enantiomers of 2,2,2-trifluro-1-furan-2-yl-ethylamine in good yield with e.e. of up to 88%. Both enantiomers of 3,3,3-trifluoroalanine were then obtained in high yield by oxidation of the furan ring with ozone. The chirality of the amine products is controlled by appropriate choice of geometrical isomer of the *O*-benzyloxime.

4. Experimental

4.1. General methods

NMR spectra were recorded on a Bruker DPX 400. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) GC–LC–MS equipped with an appropriate optically active column, as described in the footnotes of the corresponding Tables. Optical rotations were measured with Bellingham & Stanley P20 polarimeter or with Perkin–Elmer 241 polarimeter. Elemental analyses were performed at the Middle East Technical University Analysis Center.

4.2. 2,2,2-Trifluoro-1-furan-2-yl-ethanone oxime 2

2,2,2-Trifluoro-1-furan-2-yl-ethanone **1** (8.20 g, 50 mmol), $NH_2OH{\cdot}HCl$ (4.16 g, 60 mmol) and CH_3CO_2-Na (4.92 g, 60 mmol) were mixed in absolute ethanol (70 mL) and stirred under reflux for 12 h. The reaction was monitored by TLC. After 12 h the hot solution was filtered and ethanol was evaporated. The remaining solid was dissolved in water and extracted with diethyl ether. The ether layer was washed with water and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 8.2 g (92%) of **2** as an isomeric mixture. Mp 104–106°C. IR(KBr): 3650, 2980–2990, 1550 cm^{-1}. ^1H NMR ($CDCl_3$): δ ppm 6.50–6.71 (m, *E*- and *Z*-oxime of C-4 H, furan), 6.80–7.61 (m, *Z*-oxime C-3 H, furan), 7.5–7.6 (m, *Z*- and *E*-oxime C-5 H and *E*-oxime C-3 H, furan).

Purification of 8.0 g of the crude product by flash column chromatography (flash silica, EtOAc/*n*-hexane, 1:4) gave (*Z*)-**2** (5.60 g, 70%) as a colorless solid, mp 110–111°C, ^1H NMR ($CDCl_3$): δ 6.49 (m, 1H), 6.84 (m, 1H), 7.54 (m, 1H), 10.54 (br.s, 1H). ^{13}C NMR ($CDCl_3$): δ 112.2, 114.9 118.3 (q, $J=280$ Hz), 138.6 (q, $J=32$ Hz), 143.7, 145.4. Anal. calcd for $C_6H_4F_3NO_2$ (179.1): C, 40.24; H, 2.25; N, 7.82. Found: C, 40.39; H, 2.38; N, 7.68%. The purification also afforded (*E*)-**2** (1.92 g, 24%) as the minor product, colorless solid, mp 100–102°C, ^1H NMR ($CDCl_3$): δ 6.59 (m, 1H), 7.55 (m, 1H), 7.58(m, 1H), 9.74 (br. S, 1H). ^{13}C NMR ($CDCl_3$): δ 112.5, 120.5 (q, $J=273$ Hz), 121.4, 137.9 (q, $J=33$ Hz), 140.7, 144.5. Anal. calcd for $C_6H_4F_3NO_2$ (179.1): C, 40.24; H, 2.25; N, 7.82. Found: C, 40.44; H, 2.47; N, 7.61%.

4.3. Isomerization of oxime

Oxime **2** (1.79 g, 10 mmol) ((*E*)/(*Z*) mixture) was suspended in dry ether (50 mL) and HCl gas was bubbled through the solution at 0°C The reaction was monitored by TLC. Initially a clear solution was seen and then a white precipitate formed. Evaporation of solvent gave oxime **2** with an (*E*)/(*Z*) ratio of 4:1. Separation of the isomers by flash column chromatography (silica gel, EtOAc/hexane 1:4) furnished *E*-**2** (1.33 g) and *Z*-**2** (0.32 g).

4.4. 2,2,2-Trifluoro-1-furan-2-yl-ethanone-*O*-benzyl oxime 3

To a suspension of NaH (mineral oil removed by washing with hexane, 35 mmol) in DMF (100 mL) under argon atmosphere at 0°C was slowly added oxime **2** (25 mmol) over 30 min. Benzyl bromide (26 mmol) was added and the mixture stirred for 10 h at rt (the reaction was monitored by TLC). After addition of water (50 mL) the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over $MgSO_4$. The crude product was purified by flash column chromatography (flash silica, EtOAc/*n*-hexane, 1:4).

4.5. (*Z*)-2,2,2-Trifluoro-1-furan-2-yl-ethanone-*O*-benzyl oxime (*Z*)-3

Yellow oil, (6.07 g, 96%), IR (neat): 3010–2820, 1590 cm^{-1}, ^1H NMR($CDCl_3$): δ 5.41 (s, 2H, benzyl CH_2), 6.45 (dd, 1H, C-4 H, furan, $J=1.5$ Hz and 3 Hz), 6.75

(dd, 1H, C-3 H, furan, $J=0.7$ Hz and 2.6 Hz), 7.21–7.42 (m, 5H, phenyl), 7.50–7.61 (m, 1H, C-5 H furan). Anal. calcd for $C_{13}H_{10}F_3NO_2$ (269.07): C, 58.00; H, 3.74; N, 5.20. Found: C, 58.23; H, 3.97; N, 5.11%.

4.6. (*E*)-2,2,2-Trifluoro-1-furan-2-yl-ethanone-*O*-benzyl oxime (*E*)-3

Yellow oil, (5.94 g, 94%), IR (neat): 3010–2800, 1590 cm^{-1}, ^1H NMR ($CDCl_3$): δ ppm 5.40 (s, 2H, benzyl CH_2), 6.45 (dd, 1H, C-4 H, furan, $J=1.5$ Hz and 3 Hz), 7.31–7.52 (m, 7H, C-3, C-5 H furan, phenyl H). Anal. calcd for $C_{13}H_{10}F_3NO_2$ (269.07): C, 58.00; H, 3.74; N, 5.20. Found: C, 58.16; H, 3.86; N, 5.31%.

4.7. 2,2,2-Trifluoro-1-furan-2-yl-ethylamine 4

A solution of borane (20 mmol) in THF (20 mL) was added under argon dropwise to a solution of amine (10 mmol) in THF (10 mL) at −20°C. The resulting mixture was allowed to warm to −5°C and stirring continued at this temperature for 16 h. A solution of the oxime ether (8 mmol) in THF (10 mL) was added dropwise. The resulting solution was stirred at 30°C for 48 h (monitored by TLC) and was decomposed by slow addition of aqueous 2 M HCl. The product amine was separated from the residue of amines by bulb-to-bulb distillation and converted to its HCl salts using HCl(g)/MeOH.

4.8. (*S*)-2,2,2-Trifluoro-1-furan-2-yl-ethylamine (*S*)-4

^1H NMR ($CDCl_3$): δ ppm 1.82 (s, 2H), 4.2–4.7 (m, 1H), 6.21–6.48 (m, 2H), 7.22–7.51 (m, 1H).

4.9. (*S*)-2,2,2-Trifluoro-1-furan-2-yl-ethylamine hydrochloride (*S*)-4·HCl

$[\alpha]_D^{25}=+5.5$ (c 2, MeOH) for 88% e.e., (lit.[9] $[\alpha]_D^{25}=+6.60$ (c 2, MeOH) for >99% e.e.), ^1H NMR (400 MHz, CD_3OD): δ 5.63 (q, $J=7$ Hz, 1H), 6.56 (m, 1H), 6.84 (d, $J=3.4$ Hz, 1H), 7.72 (s, 1H), ^{13}C NMR (100 MHz, CD_3OD): δ 50.8 (q, $J=36$ Hz), 112.2, 114.9, 123.6 (q, $J=278$ Hz), 141.9, 146.6.

4.10. (*R*)-2,2,2-Trifluoro-1-furan-2-yl-ethylamine hydrochloride (*R*)-4·HCl

$[\alpha]_D^{25}=-5.35$ (c 2, MeOH) for 86% e.e.

4.11. Ozonolysis of 2,2,2-trifluoro-1-furan-2-yl-ethylamine

Ozone gas was passed through a solution of amine **4** (0.83 g, 5 mmol) in methanol (50 mL) at −78°C. After 30 min the reaction was stopped and N_2 was passed through the mixture to remove the excess ozone. Evaporation of the solvent gave the product as a white powder. (*S*)-**5**: yield (0.65 g, 91%); mp >206 decomp., (lit.[4b] mp 205–207°C (sublimate)), $[\alpha]_D^{25}=-13.65$ (c 1, MeOH) for 88% e.e., (lit.[4b] $[\alpha]_D^{20}=+15.4$ (c 0.78, MeOH) for (*R*)-enantiomer with >99% e.e.; lit.[3] $[\alpha]_D^{20}=+6.8$ (c 0.76, MeOH) for (*R*)-enantiomer with 62% e.e.), (*R*)-**5**: yield (0.66 g, 93%); $[\alpha]_D^{25}=+13.3$ (c 1, MeOH) for (*R*)-enantiomer with 86% e.e., (lit.[4b] $[\alpha]_D^{20}=+15.4$ (c 0.78, MeOH) for (*R*)-enantiomer with >99% e.e.; lit.[3] $[\alpha]_D^{20}=+6.8$ (c 0.76, MeOH) for (*R*)-enantiomer with 62% e.e.), ^1H NMR (400 MHz, D_2O): 4.34 (q, $J=10$ Hz, 1H) data of the products are in agreement with the published data.[3,4b]

4.12. Synthesis of (±)-2,2,2-trifluoro-1-furan-2-yl-ethylamine (±)-4

To a solution of (*Z*)-**3** (1.35 g, 5 mmol) in abs. THF (25 mL) was added $BH_3{\cdot}SMe_2$ (12 mmol) drop wise during 1 h. Then the mixture was stirred for 36 h at rt and hydrolyzed with 2N aqueous HCl and extracted with ether. The water layer was separated basified with ammonium hydroxide solution and extracted with ether. The organic layer was separated, washed with water and dried over anhydrous $MgSO_4$. The crude product was purified by bulb-to-bulb distillation to afford the product (±)-**4** (0.73 g, 88%).

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