Synthesis of N-Substituted 6-Trifluoromethyl-1,3-oxazinanes


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Este trabalho apresenta a síntese de duas novas séries de 6-trifluormetil-1,3-oxazinanas N-substituídas e 6-trifluormetil-1,3-oxazinan-2-onas N-substituídas, a partir da ciclização de 4-ilamino-1,1,1-trifluor-butan-2-óis com formaldeído e trifosgênio, respectivamente. Os 4-ilamino-1,1,1-trifluor-butan-2-óis foram obtidos através da reação de redução dos precursores 4-ilamino-1,1,1-trifluor-but-3-en-2-onas, utilizando hidrogênio e 10% Pd/C, com bons rendimentos.

This work reports the synthesis of two new series of N-substituted 6-trifluoromethyl-1,3-oxazinanes and N-substituted 6-trifluoromethyl-1,3-oxazinan-2-ones from the cyclization of 4-ylamino-1,1,1-trifluoro-butan-2-ols with formaldehyde and triphosgene, respectively. The 4-ylamino-1,1,1-trifluoro-butan-2-ols were obtained in good yields from the reduction of the parent 4-ylamino-1,1,1-trifluoro-but-3-en-2-ones with hydrogen and 10% Pd/C.

Keywords: γ-amino alcohols, β-enamino ketones, 1,3-oxazinanes, 1,3-oxazinan-2-ones, 1,3-oxazines

Introduction

1,3-Oxazines belong to a class of compounds that have been largely studied due to their wide range of biological activities and easy synthetic accessibility. Special attention has been given to these compounds since the development of Efavirenz, a trifluoromethyl-1,3-oxazin-2-one, which is a non-nucleoside reverse transcriptase inhibitor that shows high activity against a variety of HIV-1 mutant strains.1

Although, 1,3-oxazinanes have not been used as extensively as the parent 1,3-oxazines, probably due to the difficulties to synthesize the saturated 1,3-oxazine ring with a wide range of substituents, 1,3-oxazinanes exhibit a variety of biological activities. Just to mention a few, they are being explored as anti-inflammatory and agents for treating ulcers, allergies, asthma, arthritis, and diabetes.2

1,3-Oxazinanes have been used as key intermediates in the synthesis of thrombolytic agents,3 liquid crystal devices,4 chiral auxiliaries in organic synthesis,5,6 and 1,3-amino alcohols,7-10 and β-carbolines.11

The synthesis of 1,3-oxazinanes, is much less developed than the parent 1,3-oxazines and there are not many available synthesis for 1,3-oxazinanes described in the literature. One of the first methods reported to synthesize 5-nitro-5-alkyl-1,3-oxazinanes, from the reaction of a primary nitroalkane with formaldehyde and ammonia or primary amines, was explored in the fifties and sixties.12 Another method to synthesize 1,3-oxazinanes is by peracid-induced ring opening of isoxazolidines derived from the reaction of nitrones and alkenes.13 A chiral approach to the synthesis of 1,3-oxazinan-2-ones utilizes aspartic acid as the starting material in a multistep procedure that includes the formation of an epoxide containing a Cbz-protected arylamine as the key intermediate. The synthesis continues with the epoxide ring opening by sodium azide followed by an intramolecular cyclization of the hydroxy group with the benzylcarbamate group to give the desired 1,3-oxazinan-2-one.14 1,3-Oxazinan-2-ones were also obtained by halocyclization of homoallylic benzylcarbamates promoted by iodine.7 Recently, Ella-Menye et al.15 reported a multistep synthesis of chiral 1,3-oxazinan-2-ones from carbohydrate derivatives. An alternative method to obtain 1,3-oxazinanes is by cyclization of 1,3-amino alcohols with phosgene and aldehydes.16,17 The access to 1,3-amino alcohols is usually done by the reduction of the respective β-enaminones or β-enamino esters, which are obtained from the reaction of amine with the corresponding 1,3-
dicarbonyl compounds\textsuperscript{18-22} or \(\beta\)-alkoxyvinyl ketones\textsuperscript{23-30}.

It has been reported that the introduction of a trifluoromethyl group in heterocycles frequently results in much more potent activity than that of the parent compounds, a fact that is probably related to the high lipophilicity of the trifluoromethyl group.\textsuperscript{31-32} There was not found in the literature 1,3-oxazinanes containing trifluoromethyl group and also there is no methods reported that utilizes 4-alkoxy-1,1,1-trifluoro-alk-3-en-2-ones to approach the synthesis of 1,3-oxazinanes. Thus, the aim of this work is to report a new application of 4-alkoxyvinyl-1,1,1-trifluoro-alk-3-en-2-one to synthesize series of new \(N\)-substituted-6-trifluoromethyl-1,3-oxazinanes and their corresponding \(N\)-substituted-6-trifluoromethyl-1,3-oxazinan-2-ones.

Results and Discussion

The Scheme outlines the synthetic strategy developed to obtain the 1,3-oxazinanes 4a-e and 5a-e. This strategy starts with the reaction of the readily available 4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (1)\textsuperscript{33} with methylamine and amino acids to give the series of 4-ylamino-1,1,1-trifluoro-but-3-en-2-ones 2a-e. Although, the synthesis of \(\beta\)-enaminones 2a and 2e were already reported\textsuperscript{28-30} in this work the synthesis of 2a-e was done in a modified procedure that takes much shorter time than the related method from the literature. Compounds 2a-e were synthesized using the procedure reported in reference 23, which is more efficient than previous methods reported for the preparation of 2a and 2e.\textsuperscript{28-30}

A key step for the synthesis was the reduction of the \(\beta\)-enaminones 2a-e to the corresponding 1,3-amino alcohols 3a-e. Two methods have been reported for the reduction of normal \(\beta\)-enamin ketones to 1,3-amino alcohols. Initially we tried to reduce the \(\beta\)-enamin ketones 2a-e using the two procedures described in the literature: Use of lithium aluminum hydride in THF or ethyl ether proposed by Barluenga et al.\textsuperscript{34} and sodium/isopropanol in THF reported by Bartoli et al.\textsuperscript{35} Both methods furnished mixture of products which included unreacted material, non identified compounds, and those resulting from reduction of the carbonyl group, simultaneous reduction of the carbonyl and the carbon-carbon double bond. Sodium borohydride in ethanol and hydrogenation in methanol under 5\% Pd/C catalysis were also used without success. The only method that efficiently reduced the enaminones 2 was hydrogenation in methanol under 10\% Pd/C catalysis. This method has normally been used to reduce carbon-carbon double bonds.\textsuperscript{36}

The further reduction of the carbonyl, in compounds 2b-e, is probably due to the presence of the trifluoromethyl group in \(\alpha\)-position that increases the reactivity of the carbonyl toward the nucleophilic addition of hydride, after the reduction of the carbon-carbon double bond. The \(\gamma\)-amino alcohols 3a-e were obtained as brown oils after column chromatography. Although, the enaminones 2c-e bear amino acid residues with a defined stereochemistry (\(L\)-amino acid derivatives) the reductions furnished amino alcohols 3c-e as diastereomeric mixtures that could not be separated by column chromatography. The structures of \(\gamma\)-amino alcohols 3 were confirmed by IR, GC/MS, \(^1\)H and \(^13\)C NMR spectroscopy. The Figure 1 shows the atom numbering used for the NMR assignment of compounds 3, 4, and 5. The major evidence for the reduction of the \(\beta\)-enamino ketones to the \(\gamma\)-amino alcohols comes from the chemical shifts changes observed for the C-2, C-3, and C-4.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme1.png}
\caption{Scheme 1.}
\end{figure}
C-4. For example, the chemical shift of the C-2 (C=O) shifted from the range of 174 – 178 ppm, on the enaminoketones, to 65 – 75 ppm on the amino alcohols. The chemical shift of the carbons of the carbon-carbon double bond (C-3 and C-4) shifted from the range of 85 – 88 and 156 – 160 ppm, respectively on the enaminones, to 30 – 40 and 40 – 50 ppm respectively, on the amino alcohols. Also the reduction can be confirmed from the 1H NMR spectra by observing the disappearance of the doublet and the doublet of doublets of the vinylic hydrogens H-3 and H-4 on the range of 5.4 and 7.0 ppm, respectively on the enaminones to appear as complex multiplets on the range of 1.7 – 2.0 and 2.7 – 3.3 ppm respectively, on the amino alcohols. The amino alcohols also showed a multiplet at about 4 ppm relative to the H-2, absent in the enaminones.

The reaction of 1,3-amino alcohols 3a-e with formaldehyde in refluxing ethanol, furnished the 3-substituted 6-trifluoromethyl-1,3-oxazinanes 4a-e, as brown oils in 41 to 75% yield. Compound 3a failed to react with aldehydes such as acetaldehyde, benzaldehyde, and 4-nitrobenzaldehyde. Compounds 4a-e were obtained as brown oils after purification by column chromatography. The oxazinanes 4a-e showed both 1H and 13C NMR spectra very similar to the corresponding amino alcohol precursors. The observation of two doublets in the region of 4-5 ppm due to the diastereotopic methylene hydrogens coming from the formaldehyde and the appearance of a resonance at about 82 ppm of the same methylene carbon are the main indications that the cyclization took place. Also, the molecular ion on the mass spectra showed that the oxazinanes 4a-e have 12 mass units more than the corresponding γ-amino alcohols 3a-e.

The reaction of γ-amino alcohols 3a-e with triphosgene in 1,2-dichloroethane and pyridine under reflux for 16 hours furnished the corresponding 3-substituted 4-trifluoromethyl-1,3-oxazinan-2-ones 5a-e in 50 – 73% yield (Scheme 1). Cyclization of 1,3-amino alcohols to construct 1,3-oxazine-2-ones have been done using phosgene or from a intramolecular cyclization of a 1,3-hydroxy carbamate under in the presence of a strong base. In this work the inconvenience of handling the highly dangerous phosgene gas was avoided by using a crystalline stable solid triphosgene. The main evidence of the formation of compounds 5a-e is the appearance of the carbamate carbonyl on the range of 150-151 ppm. Also, it was observed that the resonances of H-6 and H-7 of oxazinones 5a-e moved downfield, in average, 0.37 and 1.02 ppm, respectively in relation to the respective (H-2 and H-6) of the γ-amino alcohols 3a-e (see Figure 1). In addition, the molecular ion on the mass spectra showed that the oxazinanes 5a-e have 26 mass units more than the corresponding γ-amino alcohols 3a-e.

Compounds 4a-b and 5a-b were obtained as racemic mixtures while compounds 4c-e and 5c-e were obtained as inseparable mixture of diastereoisomers, in a 1:1 ratio. The mixture of diastereoisomers can be confirmed by the duplication of signals observed in the 1H- and 13C NMR spectra and GC/MS showing two peaks in the chromatogram with identical fragmentation pattern.

Conclusions

In summary, this work described the first, mild, and efficient method for the reduction of 4-ylamino-1,1,1-trifluoro-but-3-en-2-ones (2a-e) to the corresponding 4-ylamino-1,1,1-trifluoro-butan-2-ols (3a-e), using hydrogen in 10% Pd/C, in good yields. In addition, the usefulness of 1,3-amino alcohols (3a-e) for the preparation of two new series of N-substituted 6-trifluoromethyl-1,3-oxazinanes and N-substituted-6-trifluoromethyl-1,3-oxazinan-2-ones, was demonstrated.

Experimental

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. The 4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (1) were prepared according to reference 33. Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. 1H and 13C NMR spectra and

Figure 1. Atom numbering used for the NMR assignment of compounds 3, 4, and 5.
2D NMR experiments were acquired on a Bruker DPX 400 spectrometer (1H at 400.13 MHz and 13C at 100.62 MHz) or on a Bruker DPX 200 spectrometer (1H at 200.13 MHz and 13C at 50.32 MHz) in DMSO-d6 or CDCl3 using TMS as the internal reference. IR spectra were recorded on a Bruker IFS 28 FT-IR spectrometer in film. Elemental analysis were performed on a Vario EL Elementar Analysensysteme. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC interfaced by a pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30m, 0.32mm of internal diameter), and helium was used as the carrier gas.

General procedure for the synthesis of g-amino alcohols, 3a-e

To a solution of enamino ketones 2a-e (10 mmol) in anhydrous methanol (30 mL), contained in a hydrogenator vessel (H. Jurgens & Co., Bremen, Germany), catalytic amount of 10% Pd/C (~30 mg) was slowly added under hydrogen pressure (3.0 atm) for 4h at room temperature. The mixture was stirred under positive nitrogen atmosphere. The mixture was stirred under positive hydrogen pressure (3.0 atm) for 4h at room temperature. The Palladium catalyst was recovered by filtration and the filtrate was concentrated. The evolved gases were collected in a gas burette. The reactant was then heated at 65°C for 30 min. After the reaction was complete, a considerable amount of 10% Pd/C (~30 mg) was slowly added under hydrogen pressure (3.0 atm) for 4h at room temperature. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel 60A (230-400 Mesh) using 2% methanol in dichloromethane as the eluant.

Data for 1,1,1-trifluoro-4-methylamino-butan-2-ol, (3a).

Brown oil, 80% yield. 1H NMR (200 MHz, CDCl3): δ 1.74 - 1.92 (m, 2H, H-3), 2.43 (s, 3H, N-CH3), 2.77 - 3.05 (m, 2H, H-4), 4.08 - 4.17 (m, 1H, H-2), 5.00 (br s, 2H, OH, NH). 13C NMR (50 MHz, CDCl3): δ 26.8 (C3), 35.2 (N-CH3), 42.0, 42.3 (C8), 44.8, 45.7 (C4), 51.9 (-OCH3), 59.0, 59.7 (C6), 71.0, 71.1 (2q, JCF 31.0, 31.3 Hz, C2), 125.0, 125.1 (2q, JCF 281.0, 282.0 Hz, -CF3), 174.9 (C=O). GC-MS (EI, 70 ev): m/z (%) 305 (M+, 2), 246 (58), 214 (100), 212 (100), 154 (62), 127 (62), 70 (65). IR (film) νmax/cm⁻¹: 3398, 1733, 1265. Anal. Calc. for C14H18F3NO3 (305.29): C, 55.08; H, 5.94; N, 4.59 %. Found: C, 54.82; H, 5.83; N, 4.72 %.

Data for 3-methyl-2-(4,4,4-trifluoro-3-hydroxybutylamino)-pentanoic acid methyl ester, (3d, 3d').

Brown oil, 90% yield. 1H NMR (200 MHz, CDCl3): δ 0.86 - 0.99 (m, 12H, H-9, H-10), 1.07 - 1.54 (m, 4H, H-8, H-11), 1.71 - 1.87 (m, 6H, H-7, H-3), 2.51 - 3.03 (m, 4H, H-4, H-7), 3.14 (d, 1H, 3JH,H6' 5.6 Hz, H-6'), 3.21 (d, 1H, 3JH,H6' 5.6 Hz, H-6'), 3.74 (s, 6H, -OCH3), 4.22 (br s, 6H, H-2, -OH, -NH). 13C NMR (200 MHz, CDCl3): δ 11.2 (C9), 15.5, 15.7 (C10), 25.2 (C8), 27.5 (C3), 38.1 (C7), 46.7 (C4), 51.7 (-OCH3), 66.3 (C6), 71.9 (q, JCF 31.1 Hz, C2), 124.7, (q, JCF 281.0 Hz, -CF3), 173.2, 174.2 (C=O). GC-MS (EI, 70 ev): m/z (%) 271 (M+, 2), 213 (58), 212 (100), 154 (62), 127 (62), 70 (65). IR (film) νmax/cm⁻¹: 3398, 1733, 1265. Anal. Calc. for C14H20F4NO3 (271.27): C, 48.70; H, 7.43; N, 5.16 %. Found: C, 48.40; H, 7.12; N, 5.00 %.

Data for 4-methyl-2-(4,4,4-trifluoro-3-hydroxybutylamino)-pentanoic acid methyl ester, (3c, 3c').

Brown oil, 88% yield. 1H NMR (200 MHz, CDCl3): δ 0.92 (d, 12H, JHF 6.4 Hz, H-9, H-10), 1.45 - 1.53 (m, 2H, H-8, H-6), 1.64 - 1.85 (m, 8H, H-3, H-7), 2.51 - 3.25 (m, 4H, H-4), 3.33 - 3.39 (m, 2H, H-6), 3.74 (s, 6H, -OCH3), 4.14 - 4.24 (m, 2H, H-2), 4.33 (br s, 4H, -OH, -NH). 13C NMR (50 MHz, CDCl3): δ 21.7, 21.8 (C9), 22.5, 22.6 (C10), 24.7 (C7), 26.8, 27.5 (C3), 42.0, 42.3 (C8), 44.8, 45.7 (C4), 51.9 (-OCH3), 59.0, 59.7 (C6), 71.0, 71.1 (2q, JCF 31.0, 31.3 Hz, C2), 125.0, 125.1 (2q, JCF 281.0, 282.0 Hz, -CF3), 174.9 (C=O). GC-MS (EI, 70 ev): m/z (%) 305 (M+, 2), 246 (194), 212 (100), 154 (62), 127 (62), 70 (65). IR (film) νmax/cm⁻¹: 3398, 1733, 1265. Anal. Calc. for C14H20F4NO3 (305.29): C, 55.08; H, 5.94; N, 4.59 %. Found: C, 54.82; H, 5.83; N, 4.72 %.

General procedure for the synthesis 1,3-oxazinanes, (4a-e)

To a solution of γ-amino alcohols 3a-e (3mmol) in anhydrous ethanol (20 mL), p-formaldehyde (0.18 g, 6 mmol), and 4-toluenesulfonic acid (catalytic amount) was added at room temperature. The reaction mixture was stirred for 2h. The reaction mixture was diluted with water (10 mL) and then extracted with ethyl acetate (3x10 mL). The organic layers were dried over MgSO4, filtered, and concentrated. The residue was purified by column chromatography on silica gel 60A (230-400 Mesh) using 2% methanol in dichloromethane as the eluant.
added under stirring at room temperature. The mixture was refluxed for 24 hours and allowed to cool to room temperature. The solid formed during the course of the reaction was filtered off and discarded. The pH of the filtrate was adjusted to 9 by the addition of 1 mol L⁻¹ sodium hydroxide solution and extracted with dichloromethane (3×15 mL). The organic layer was dried under anhydrous MgSO₄, and the solvent removed by rotary evaporator. The products 4a-e were obtained as brown oils and purified by column chromatography on silica-gel Aldrich 60A (230—400 Mesh) using 2% of methanol in dichloromethane as the eluant.

**Data for 3-methyl-6-trifluoromethyl-1,3-oxazinan-5-one (4a).** Brown oil, 41% yield. ¹H NMR (200 MHz, CDCl₃): δ 1.65 - 1.77 (m, 1H, H-5), 1.96 - 2.04 (m, 1H, H-5'), 2.57 (s, 3H, H-7), 2.89 - 3.00 (m, 1H, H-4), 3.14 - 3.38 (m, 1H, H-4), 3.84 - 3.90 (m, 1H, H-6), 4.28 (s, 1H, ³J_H,H= 9.6 Hz, H-2), 4.61 (d, 1H, ³J_H,H= 9.6 Hz, H-2'), 13C NMR (50 MHz, CDCl₃): δ 19.6 (C7), 38.7 (CS), 49.7 (C4), 74.3 (q, ²J_CF= 52.3 Hz, C6), 85.4 (C2), 123.6 (q, ²J_CF= 279.0 Hz, -CF₃). GC-MS (EI, 70eV): m/z (%) 169 (M⁺, 40), 154 (100).

**Data for 6-trifluoromethyl-1,3-oxazinan-5-yl-acetic acid methyl ester (4b).** Brown oil, 67% yield. ¹H NMR (200 MHz, CDCl₃): δ 1.45 - 1.53 (m, 1H, H-5), 1.90 - 2.07 (m, 1H, H-5'), 3.15 - 3.20 (m, 2H, H-4), 3.52 (d, 1H, ³J_H,H= 17.1 Hz, H-7), 3.70 (d, 1H, ³J_H,H= 17.1 Hz, H-7'), 3.73 (s, 3H, -OCH₃), 3.90 - 4.01 (m, 1H, H-6), 4.48 (d, 1H, ³J_H,H= 10.5 Hz, H-2), 4.62 (d, 1H, ³J_H,H= 10.5 Hz, H-2'). ¹³C NMR (100 MHz, CDCl₃): δ 19.4 (C5), 48.0 (C4), 51.7 (-OCH₃), 52.2 (C7), 74.4 (q, ²J_CF= 32.4 Hz, C6), 84.2 (C2), 123.4 (q, ²J_CF= 279.0 Hz, -CF₃), 170.2 (C=O). GC-MS (EI, 70eV): m/z (%) 227 (M⁺, 43), 168 (100), 154 (54), 138 (43), 116 (45), 74 (57). IR (film) ν_{max}/cm⁻¹: 1748, 1266. Anal. Calc. for C₇H₆FNO₂ (225.17): C, 50.88; H, 7.12; N, 4.39 %. Found: C, 50.88; H, 7.12; N, 4.39 %.

**Data for 3-phenyl-2-(6-trifluoromethyl-1,3-oxazinan-3-yl)-propionic acid methyl ester (4c).** Brown oil, 75% yield. ¹H NMR (200 MHz, CDCl₃): δ 1.55 - 1.59, 1.93 - 2.00 (m, 4H, H-5), 2.89 - 3.01 (m, 6H, H-4, H-8), 3.10 - 3.28, 3.63 - 3.71 (m, 2H, H-4), 3.55, 3.59 (s, 6H, -OCH₃), 3.62 - 3.71 (m, 2H, H-7), 3.80 - 3.90 (m, 2H, H-6), 4.28 (d, 1H, ³J_H,H= 9.8 Hz, H-2), 4.35 (d, 1H, ³J_H,H= 10.3 Hz, H-2), 4.73 (d, 1H, ³J_H,H= 9.8 Hz, H-2'), 4.80 (d, 1H, ³J_H,H= 10.3 Hz, H-2'), 7.14 - 7.30 (m, 10H, Ph). ¹³C NMR (50 MHz, CDCl₃): δ 21.3, 22.2 (C5), 36.4, 36.8 (C8), 46.0, 46.1 (C4), 51.3, 51.4 (-OCH₃), 65.3, 65.6 (C7), 74.0, 74.5 (2q, ²J_CF= 32.0 Hz, C6), 82.0, 82.4 (C2), 123.2, 123.6 (2q, ²J_CF= 286.5 Hz, -CF₃), 126.5, 126.6, 128.0, 128.3, 128.9, 129.0, 137.0, 137.2 (Ph), 172.1, 172.6 (C=O). GC-MS (EI, 70eV): m/z (%) 317 (M⁺, 1), 258 (72), 226 (100), 91 (41). IR (film) ν_{max}/cm⁻¹: 1733, 1265. Anal. Calc. for C₁₅H₁₃FNO₂ (317.30): C, 56.78; H, 5.72; N, 4.41 %. Found: C, 56.53; H, 5.47; N, 4.54 %.

**General procedure for the synthesis of 1,3-oxazinan-2-ones (5a-e).**

To a solution of γ-amino alcohols 3a-e (3 mmol), anhydrous 1,2-dichloroethane (15 mL) and anhydrous triethylamine (0.42 mL, 3 mmol) was added triphosgene
(0.89 g, 3 mmol) under argon atmosphere. The mixture was refluxed for 24 hours and allowed to cool to room temperature. Then the mixture was cooled in refrigerator until the triethylammonium hydrochloride precipitates (about 12 hours). The salt was filtered off and the organic layer was washed with water (3 × 15 mL) and dried under MgSO4. The solvent was removed by rotary evaporator and the products 5a-e were obtained as brown oils. Compounds 5a-e were purified by column chromatography on silica-gel Aldrich 60A (230–400 Mesh) using 2% of methanol in dichloromethane as the eluant.

Data for 3-methyl-6-trifluoromethyl-1,3-oxazinan-2-one (5a). Brown oil, 50% yield. 1H NMR (400 MHz, CDCl3): δ 2.04 - 2.10, 2.23 - 2.27 (m, 2H, H-5), 2.96 (s, 3H, H-7), 3.35 (ddd, 1H, 3JH,H-7 11.6 Hz, 3JH,H-1' 6.4 Hz, H-7), 3.72 (d, 1H, 3JH,H-1' 6.4 Hz, H-7), 3.74 (s, 3H, -OCH3), 3.87–4.16 (m, 1H, H-6). 13C NMR (100 MHz, CDCl3): δ 20.5, 20.9, 20.7 (C5), 34.0, 34.2 (C8), 41.8, 42.0 (C4), 51.9, 52.0, 52.2, 52.4 (-OCH3), 61.2, 61.3 (C6), 73.3, 73.5 (2q, 1JCF 34.5 Hz, C6), 123.0 (q, 1JCF 279.5 Hz, -CF3), 150.8 (C2). IR (film) νmax/cm-1: 1750, 1719, 1266. Anal. Calc. for C12H18F3NO4 (297.27): C, 48.48; H, 6.10; N, 4.71 %. Found: C, 48.89; H, 6.49; N, 5.07 %.

Data for 3-methyl-2-(2-oxo-6-trifluoromethyl-1,3-oxazinan-3-yl)-pentanoic acid methyl ester (5d, 5d'). Brown oil, 70% yield. 1H NMR (200 MHz, CDCl3): δ 0.86 - 0.98 (m, 12H, H-10, H-11), 1.49 - 1.56 (m, 2H, H-9), 1.73 - 1.76 (m, 4H, H-8), 2.11 - 2.37 (m, 4H, H-5), 3.32 - 3.54 (m, 4H, H-4), 3.73 (s, 3H, -OCH3), 4.64 - 4.74 (m, 2H, H-6), 5.03 - 5.07 (m, 2H, H-7). 13C NMR (100 MHz, CDCl3): δ 20.9 (C5), 21.0, 21.1, 23.1, 23.2 (C10, C11), 24.8, 25.1 (C9), 36.8, 37.0 (C8), 38.8, 39.9 (C4), 52.3 (-OCH3), 57.0, 57.2 (C7), 73.4 (q, 1JCF 34.3 Hz, C6), 123.0 (q, 1JCF 280.0 Hz, -CF3), 151.4 (C2), 171.7 (C=O). GC-MS (EI, 70ev): νmax/%, 297 (M+ 1), 238 (100), 196 (31), 182 (39), 69 (49). IR (film) νmax/cm-1: 1739, 1716, 1265. Anal. Calc. for C12H18F3NO4 (297.27): C, 48.48; H, 6.10; N, 4.71 %. Found: C, 48.89; H, 6.49; N, 5.07 %.

Data for 3-methyl-2-(2-oxo-6-trifluoromethyl-1,3-oxazinan-3-yl)-pentanoic acid methyl ester (5d, 5d'). Brown oil, 70% yield. 1H NMR (200 MHz, CDCl3): δ 0.86 - 0.98 (m, 12H, H-10, H-11), 1.49 - 1.56 (m, 2H, H-9), 1.73 - 1.76 (m, 4H, H-8), 2.11 - 2.37 (m, 4H, H-5), 3.32 - 3.54 (m, 4H, H-4), 3.73 (s, 3H, -OCH3), 4.64 - 4.74 (m, 2H, H-6), 5.03 - 5.07 (m, 2H, H-7). 13C NMR (100 MHz, CDCl3): δ 20.9 (C5), 21.0, 21.1, 23.1, 23.2 (C10, C11), 24.8, 25.1 (C9), 36.8, 37.0 (C8), 38.8, 39.9 (C4), 52.3 (-OCH3), 57.0, 57.2 (C7), 73.4 (q, 1JCF 34.3 Hz, C6), 123.0 (q, 1JCF 280.0 Hz, -CF3), 151.4 (C2), 171.7 (C=O). GC-MS (EI, 70ev): νmax/%, 297 (M+ 1), 238 (100), 196 (31), 182 (39), 69 (49). IR (film) νmax/cm-1: 1739, 1716, 1265. Anal. Calc. for C12H18F3NO4 (297.27): C, 48.48; H, 6.10; N, 4.71 %. Found: C, 48.89; H, 6.49; N, 5.07 %.

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