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Domino reactions with fluorinated five-membered heterocycles. α-Trifluoromethyl α-amino acids with unsaturated side-chains

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Summary. α-Trifluoromethyl α-amino acids with unsaturated side-chains have been prepared from 5-fluoro-4-trifluoromethyloxazole and allyl, propargyl as well as terpene alcohols in a one-pot procedure.

Keywords: 5-Fluoro-4-trifluoromethyloxazoles – Allyl alcohols – Propargyl alcohols – Geraniol – Farnesol – Nucleophilic aromatic substitution – Claisen rearrangement – α-Trifluoromethyl α-amino acids – Secondary structure

Abbreviations: Tfm Gly, Trifluoromethylglycine; Mag, Methylallylglycine; Tfmag, Trifluoromethylallyl-glycine

Introduction

Turn and helix motifs are fundamental constituents of many biologically active peptides (Gellman, 1998). These folding motifs often are critical for their biological activity. The relevance of stable secondary structure elements in peptides and proteins stimulated the development of new methodology for the construction of rigid domains. A general and widely used strategy for the generation of rigidified peptides is the incorporation of $C^{\alpha\alpha}$-dialkylated α-amino acids. The decrease of the conformational freedom gives rise to an increase in the tendency to fold into β-turn and 3_{10}-helical structures (Spatola, 1983; Aubry et al., 1988; Hruby et al., 1990; Karle and Balaran, 1990; Toniolo et al., 1993; Polese et al., 1996; Peggion et al., 2000).

During the last few years allyl C^{α}-substituted α-amino acids and C^{α}-methyl C^{α}-allylglycines attracted growing interest, that arises from the wide versatility of the CC double bond functionality. Therefore, several synthetic approaches to this new class of amino acids have been developed (for relevant literature see Peggion et al., 2000). Peptides have been prepared containing a pendant unsaturation site as a handle for cross-linking reactions (Poché et al., 1997; Guinn et al., 1995). C^{α}-Allyl amino acid derivatives have been used as intermediates in the synthesis of conformationally restricted peptidomimetics (Semple et al., 1997; Badorrey et al., 1997) *via* metathesis (Blackwell and Grubbs, 1998). Another useful application of allyl amino acids is the addition of radical species (Burger et al., 1991; Broxterman et al., 1992). C^{α}-methyl C^{α}-allylglycine (Mag) represents another interesting monomer with functionalizable side-chain (Peggion et al., 2000). In the last few years a variety of routes toward Mag have been published (van der Werf and Kellogg, 1988; Kaptein et al., 1992, 1993; Schoemaker et al., 1992; Rutjes et al., 1999; Williams, 1999). The remarkable bias of C^{α}-methyl C^{α}-allylglycine (Mag) to stabilize secondary structure elements like β-turns and 3_{10}-helix (Peggion et al., 2000) should be even more pronounced in the case of their fluoroanalogues while the reactivity of the allylic CC double bonds should remain unchanged. Therefore, C^{α}-trifluoromethyl C^{α}-allyl amino acids should be useful candidates for the rational design of rigidified peptidomimetics.

Syntheses of C^{α}-fluoroalkyl substituted amino acids and their incorporation into strategic positions of peptides attract growing interest, because the modified peptides exhibit *i.a.* increased metabolic (Koksch et al., 1997) and conformational stability (Burger et al., 1994; Koksch et al., 1999). Furthermore, the trifluoromethyl group has a positive effect on lipophilicity, on transport rates, on

in vivo absorption and improves permeability through certain body barriers. Due to the high electron density, the trifluoromethyl group is capable for participating in hydrogen bonding (Howard et al., 1996) and may act as coordinative site in metal complexes (Carrell et al., 1987). Another attractive feature of the trifluoromethyl group is its high stability and relative low toxicity (Welch and Eswarakrishnan, 1991). Furthermore, the ^{19}F atom can serve as powerful NMR label for spectroscopic studies on metabolism and conformation (Gerig, 1994).

The often postulated quasi-isosterism between CH_3 and CF_3 groups is still a controversial issue (Nagai et al., 1992). The Van der Waals radii are quite similar (2.0 and 2.7 Å), whereas the Van der Waals volumes differ significantly (16.8 and 42.6 $Å^3$). The steric bulk of a trifluoromethyl group seems to be close to an isopropyl group (Seebach, 1990; Jaeckel and Koksch, 2005).

Lipid-modified proteins are often attached to cell membranes, with the lipidic moiety anchoring the protein to membranes, mediating protein–protein interactions. In many cases these lipid-linked proteins are involved in the transduction of extracellular signals across the plasma membrane and into the nucleus (Waldmann, 2003). In order to study these roles on a molecular level, methodology for the synthesis of differently lipidated peptides and amino acids has to be developed.

Materials and methods

Melting points were determined on a Boetius heating table. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^1H NMR spectra were recorded with VARIAN Gemini 2000 spectrometers at 200 and 300 MHz. Chemical shifts were reported in part per million relative to tetramethylsilane (TMS) in $CDCl_3$; *J* values given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 50 and 75 MHz. ^{19}F NMR spectra were recorded at 188 MHz with trifluoroacetic acid (TFA) as external standard. Mass spectra were recorded on a VG 12–250 and a MAT 212 (Masslab) electron ionization spectrometer (EI-MS, EI = 70 eV). Elemental analyses were performed with a CHNO-S Rapid apparatus (Fa. Heraeus). Organic solvents were dried and distilled prior to use.

General procedure: synthesis of trifluoromethyl substituted amino acids from 5-fluoro-4-trifluoromethyloxazoles via Claisen rearrangement

To a stirred solution of 1.16 g (5 mmol) **1** in dry dioxane (15 ml) the corresponding allyl alcohol (or propargyl alcohol) (5 mmol) and solid KOH (0.56 g, 10 mmol) were added. After a short induction period an exothermal reaction starts. When the conversion was complete (^{19}F NMR analysis) water (5 ml) was added. As soon as the lactone ring was cleaved (^{19}F NMR analysis) the solvents were removed *in vacuo*. The residue was taken up in a biphase system ether/water (20 ml, 1:1). The organic phase was extracted twice with 5n NaOH (5 ml). The combined water phase was acidified (pH 1–2) with dil. HCl and extracted with ether (3 × 10 ml). After drying with $MgSO_4$ the organic solvent was distilled off *in vacuo*. The remaining solid was recrystallized from ether/pentane.

2-(N-Benzoylamino)-2-trifluoromethyl-pent-4-enoic acid (**5a**)

Yield: 0.86 g (60%) **5a**, mp 141 °C. ^1H NMR (d_6-acetone): δ = 3.07 (1H, dd, *J* = 14.2 Hz, 7.4 Hz), 3.38 (1H, dd, *J* = 14.2 Hz, 7.1 Hz), 5.18 (1H, dd, *J* = 11.0 Hz, 1.8 Hz), 5.28 (1H, dd, *J* = 17.1 Hz, 1.8 Hz), 5.84 (1H, dddd, *J* = 17.1 Hz, 11.0 Hz, 7.4 Hz, 7.1 Hz), 7.46–7.59 (3H, m), 7.86–7.88 ppm (2H, m). ^{13}C NMR (d_6-acetone): δ = 29.8, 65.7 (q, *J* = 28.0 Hz), 120.6, 125.4 (q, *J* = 286.0 Hz), 128.0, 129.3, 131.2, 132.6, 134.8, 167.0, 167.2 ppm. ^{19}F NMR (d_6-acetone): δ = 5.0 ppm (3F, s). IR (KBr): ν = 3380, 1740, 1730, 1631, 1518 cm^{-1}. MS (EI): m/z = 287 $[M]^+$ 270 $[M - OH]^+$, 243 $[M - CO_2]^+$, 242 $[M - CO_2H]^+$, 223 $[M - CO_2, - HF]^+$, 174 $[M - CO_{2,} - CF_3]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$. Anal calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.56; H, 4.24; N. 5.03%.

2-(N-Benzoylamino)-3-methyl-2-trifluoromethyl-pent-4-enoic acid (**5b**)

Yield: 1.04 g (69%) **5b**, mp 168 °C. ^1H NMR (d_6-acetone): δ = 1.34 (3H, d, *J* = 7.0 Hz), 3.33 (1H, quint., *J* = 7.0 Hz), 5.24 (1H, d, *J* = 10.0 Hz), 5.32 (1H, d, *J* = 16.0 Hz), 5.97 (1H, m), 7.53 (3H, m), 7.84 (2H, m), 8.00 ppm (1H, s br.). ^{13}C NMR (d_6-acetone): δ = 16.4, 43.5, 67.0 (q, *J* = 26.0 Hz), 118.7, 125.9 (q, *J* = 288.0 Hz), 128.1, 129.4, 132.7, 135.1, 138.4, 166.5, 166.6 ppm. ^{19}F NMR (d_6-acetone): δ = 10.11 ppm (3F, s). IR (KBr): ν = 3410, 1760, 1650, 1520 cm^{-1}. MS (EI): m/z = 301 $[M]^+$, 286 $[M - CH_3]^+$, 257 $[M - CO_2]^+$, 256 $[M - CO_2H]^+$, 237 $[M - CO_2, - HF]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$, 55 $[C_5H_7]^+$. Anal calcd for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 55.75; H, 4.68; N, 4.55%.

2-(N-Benzoylamino)-3-ethyl-2-trifluoromethyl-pent-4-enoic acid (**5c**)

Yield: 0.66 g (42%) **5c**, mp 122 °C. ^1H NMR (d_6-acetone): δ = 0.90 (3H, t, *J* = 7.0 Hz), 1.53 (1H, m), 1.90 (1H, m), 2.98 (1H, t, *J* = 11.0 Hz), 5.41 (2H, m), 5.80 (1H, m), 7.43 (1H, s br.), 7.49 (3H, m), 7.84 (2H, m), 10.79 ppm (1H, s br.). ^1H NMR (d_6-acetone): δ = 12.8, 22.5, 52.0, 66.7 (q, *J* = 26.0 Hz), 121.3, 125.8 (q, *J* = 288.0 Hz), 128.0, 129.4, 132.8, 134.8, 136.5, 166.4, 166.7 ppm. ^{19}F NMR (d_6-acetone): δ = 10.50 ppm (3F, s). IR (KBr): ν = 3420, 1760, 1730, 1685 cm^{-1}. MS (EI): m/z = 315 $[M]^+$, 286 $[M - CH_3CH_2]^+$, 270 $[M - CO_2H]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$. Anal calcd for $C_{15}H_{16}F_3NO_3$: C, 57.15; H, 5.12; N, 4.44. Found: C, 57.20; H, 5.13; N, 4.44%.

2-(N-Benzoylamino)-3,3-dimethyl-2-trifluoromethyl-pent-4-enoic acid (**5d**)

Yield: 0.73 g (46%) **5d**, mp 165 °C. ^1H NMR (d_6-acetone): δ = 1.41 (3H, s), 1.49 (3H, s), 5.27 (1H, d, *J* = 11.0 Hz), 5.39 (1H, d, *J* = 17.0 Hz), 6.36 (1H, *J* = 17.0 Hz, *J* = 11.0 Hz), 7.15 (1H, s br.), 7.51 (3H, m), 7.80 (2H, m), 10.10 ppm (1H, s br.). ^{13}C NMR (d_6-acetone): δ = 23.2, 25.6, 43.8, 69.2 (q, *J* = 26.0 Hz), 115.2, 126.4 (q, *J* = 289.0 Hz), 128.0, 129.5, 132.7, 135.4, 144.0, 166.2, 166.6 ppm. ^{19}F NMR (d_6-acetone): δ = 13.67 ppm (3F, s). IR (KBr): ν = 3390, 3140, 1760, 1660, 1530 cm^{-1}. MS (EI): m/z = 315 $[M]^+$, 300 $[M - CH_3]^+$, 271 $[M - CO_2]^+$, 251 $[M - CO_2, - HF]^+$, 236 $[M - CH_3, - CO_2, - HF]^+$, 105 $[C_6H_5]^+$, 77 $[C_6H_5]^+$, 69 $[C_5H_9]^+$. Anal calcd for $C_{15}H_{16}F_3NO_3$: C, 57.15; H, 5.12; N, 4.44. Found: C, 56.37; H, 5.08; N, 4.42%.

2-(N-Benzoylamino)-3-phenyl-2-trifluoromethyl-pent-4-enoic acid (**5e**)

Yield: 0.73 g (40%) 5e, mp 184 °C. ^1H NMR (d_6-acetone): δ = 4.85 (1H, d, *J* = 10.0 Hz), 5.33 (1H, d, *J* = 11.0 Hz), 5.37 (1H, d, *J* = 17.0 Hz), 6.67 (1H, m), 7.12 (1H, s br.), 7.22–8.01 ppm (10H, m). ^{13}C NMR (d_6-acetone): δ = 52.4, 68.3 (q, *J* = 26.0 Hz), 120.0, 125.5 (q, *J* = 288.0 Hz), 127.7, 128.7, 129.4, 129.5, 130.3, 132.8, 135.2, 136.4, 138.7, 166.4, 166.8 ppm. ^{19}F NMR (d_6-acetone): δ = 9.98 ppm (3F, s). IR (KBr):

$\nu = 3350$, 1720, 1620, 1510 cm^{-1}. MS (EI): m/z = 363 $[M]^+$, 319 $[M - CO_2]^+$, 318 $[M - CO_2H]^+$, 299 $[M - CO_2, - HF]^+$, 294 $[M - CF_3]^+$, 122 $[M - C_7H_8NO]^+$, 117 $[C_9H_9]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$. Anal calcd for $C_{19}H_{16}F_3NO_3$: C, 62.81; H, 4.44; N, 3.86. Found: C, 61.86; H, 4.54; N, 3.88%.

2-(N-Benzoylamino)-2-trifluoromethylhepta-4,6-dienoic acid (**6**)

Yield: 1.40 g (89%) **6**, mp 137 °C. ^{1}H NMR (d_6-acetone): δ = 3.10 (1H, dd, J = 14.0 Hz, 8.0 Hz), 3.42 (1H, dd, J = 14.0 Hz, 7.0 Hz), 5.02 (1H, dd, J = 10.0 Hz, 2.0 Hz), 5.16 (1H, dd, J = 17.0 Hz, 2.0 Hz), 5.70 (1H, m), 6.32 (2H, m), 6.85 (1H, s br.), 7.53 (3H, m), 7.86 ppm (2H, m). ^{13}C NMR (d_6-acetone): δ = 34.6, 65.8 (J = 28.0 Hz), 117.4, 125.5 (J = 287.0 Hz), 126.7, 128.2, 129.3, 132.6, 135.1, 136.8, 137.5, 166.9, 167.3 ppm. ^{19}F NMR (d_6-acetone): δ = 4.84 ppm (3F, s). IR (KBr): $\nu = 3380$, 1740, 1640, 1520 cm^{-1}. MS (EI): m/z = 313 $[M]^+$, 295 $[M - H_2O]^+$, 269 $[M - CO_2]^+$, 249 $[M - CO_2, - HF]^+$, 132 $[C_7H_8NO]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$. Anal calcd for $C_{15}H_{14}F_3NO_3$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.37; H, 4.85; N, 4.39%.

2-(N-Benzoylamino)-3,7-dimethyl-2-trifluoromethyl-3-vinyl-6-octenoic acid (**7a**)

Yield: 0.96 g (45%) **7a**, oil. ^{1}H NMR (d_6-acetone): δ = 1.38 (s, CH_3), 1.46 (s, CH_3), 1.57 (s, CH_3), 1.90 (4H, m, CH_2CH_2), 5.25 (1H, m, =CH), 5.40 (1H, m, =CH), 5.56 (1H, m, =CH), 5.47 (1H, m), 6.20 (1H, m, =CH), 7.64 ppm (5H, m, Harom). ^{13}C NMR (d_6-acetone): δ = 18.0, 23.1, 26.3, 28.2, 31.9, 47.2 (m), 61.1 (m), 123.9, 124.0, 129.8 (q, J = 264.7 Hz), 130.7, 132.2, 133.1, 135.1, 140.4, 141.1, 165.3, 170.3 ppm. ^{19}F NMR ($CDCl_3$): δ = 14.39 ppm (3F, s). MS (EI): m/z = 384 $[M + H]^+$, 406 $[M + Na]^+$, 767 $[2M + H]^+$, 789 $[2M + Na]^+$.

2-(N-Benzoylamino)-3,7,11-trimethyl-2-trifluoromethyl-3-vinyl-6,10-dodecadienoic acid (**7b**)

Yield: 1.17 g (52%) **7b**, oil. ^{1}H NMR (d_6-acetone): δ = 1.49 (s, CH_3), 1.62 (s, CH_3), 1.69 (s, CH_3), 1.77 (s, CH_3), 2.10 (8H, m, 2 × CH_2CH_2), 4.79 (1H, m, =CH), 4.81 (1H, m, =CH), 5.14 (1H, m, =CH), 5.47 (1H, m, =CH), 6.30 (1H, m, =CH), 7.75 ppm (5H, m, Harom). ^{13}C NMR (d_6-acetone): δ = 14.3, 26.8, 29.6, 30.0, 35.1, 36.6, 36.7, 58.4 (m), 63.1 (m), 121.3, 123.5, 125.3 (q, J = 273.6 Hz), 124.4, 126.3, 126.9, 128.8, 132.2, 131.4, 135.3, 140.5, 170.8, 173.4 ppm. ^{19}F NMR ($CDCl_3$): δ = 14.74 ppm (3F, s). MS (EI): m/z = 452 $[M + H]^+$, 903 $[2M + H]^+$.

2-(N-Benzoylamino)-2-trifluoromethyl-penta-3,4-dienoic acid (**8a**)

Yield: 0.91 g (64%) **8a**, mp 113–116 °C. ^{1}H NMR (d_6-acetone): δ = 5.18 (2H, dd, J = 6.7 Hz, J = 3.3 Hz), 5.84 (1H, t, J = 6.7 Hz) 7.44–7.57 (3H, m), 7.88–7.90 (2H, m), 8.19 ppm (1H, s br.). ^{13}C NMR (d_6-acetone): δ = 64.5 (q, J = 28.0 Hz), 81.2, 87.9, 124.9 (q, J = 285.0 Hz), 128.4, 129.2, 132.7, 134.5, 165.9, 167.2, 209.2 ppm. ^{19}F NMR (d_6-acetone): δ = 4.4 ppm (3F, s). IR (KBr): $\nu = 3290$, 1982, 1762, 1650, 1533 cm^{-1}. MS (EI): m/z = 285 $[M]^+$, 241 $[M - CO_2]^+$, 240 $[M - CO_2H]^+$, 221 $[M - CO_2, - HF]^+$, 172 $[M - CO_2, - CF_3]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$, 39 $[C_3H_3]^+$. Anal calcd for $C_{13}H_{10}F_3NO_3$: C, 54.74; H, 3.53; N, 4.91. Found: C, 53.83; H, 4.10; N, 4.91%.

2-(N-Benzoylamino)-2-trifluoromethyl-hepta-3,4-dienoic acid (**8b**)

Yield: 1.02 g (64%) **8b**, mp 98 °C, mixture of diasteromers. ^{1}H NMR (d_6-acetone): δ = 0.96/1.02 (3H, t, J = 7.0 Hz), 2.06 (2H, m), 5.70 (1H, m), 5.80 (1H, m), 7.52 (3H, m), 7.88 (2H, m), 8.09 (1H, s br.), 10.75 ppm (1H, s br.). ^{13}C NMR (d_6-acetone): δ = 13.2, 22.0, 64.7 (q, J = 31.0 Hz), 88.89/89.02, 99.93/100.19, 125.1 (q, J = 285.0 Hz), 128.03/128.06, 129.35/129.47, 132.56/132.68, 135.21/135.37, 146.77/147.19, 149.89/150.10, 166.12/166.32, 166.94/167.30, 204.5 ppm. ^{19}F NMR (d_6-acetone): δ = 4.28/4.42 ppm (3F, s). IR (KBr): $\nu = 3320$, 1736, 1660, 1525 cm^{-1}. MS (EI): m/z = 313 $[M]^+$, 298 $[M - CH_3]^+$, 269 $[M - CO_2]^+$, 268 $[M - CO_2H]^+$, 249 $[M - CO_2, - HF]^+$, 244 $[M - CF_3]^+$, 234 $[M - CH_3, - CO_2, - HF]^+$, 200 $[M - CF_3, - CO_2]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$. Anal calcd for $C_{15}H_{14}F_3NO_3$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.75; H, 4.68; N, 4.55%.

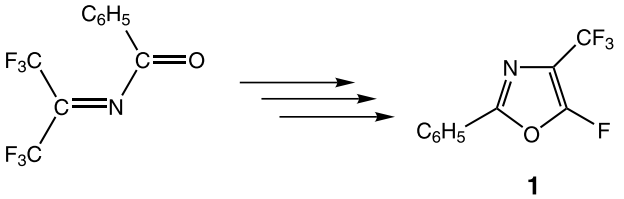
2-(N-Benzoylamino)-5-methyl-2-trifluoromethyl-hepta-3,4-dienoic acid (**8c**)

Yield: 1.00 g (62%) **8c**, mp 112 °C, mixture of diastereomers. ^{1}H NMR (d_6-acetone): δ = 0.98/1.01 (3H, t, J = 7.0 Hz), 1.68/1.77 (3H, d, J = 3.0 Hz), 2.05 (2H, m), 5.71 (1H, m), 7.46–7.88 ppm (5H, m). ^{13}C NMR (d_6-acetone): δ = 12.07/12.12, 18.38/18.39, 27.19/27.31, 65.0 (q, J = 20.0 Hz), 88.3, 109.72/109.89, 125.0 (q, J = 285.0 Hz), 128.29/129.29, 132.65/132.68, 134.71/134.77, 166.28/126.31, 166.80/166.96, 202.16/202.29 ppm. ^{19}F NMR (d_6-acetone): δ = 4.20/4.30 ppm (3F, s), IR (KBr): $\nu = 3410$, 3100, 2980, 1965, 1775, 1765, 1515 cm^{-1}. MS: m/z = 327 $[M]^+$, $[M - CO_2]^+$, 282 $[M - CO_2H]^+$, 263 $[M - CO_2, - HF]^+$, 122 $[C_7H_8NO]^+$, 105 $[C_7H_5O]^+$, 77 $[C_6H_5]^+$. Anal calcd for $C_{16}H_{16}F_3NO_3$: C, 58.72; H, 4.93; N, 4.28. Found: C, 58.85; H, 5.38; N, 4.59%.

Results and discussion

Different synthetic strategies for α-trifluoromethyl substituted amino acids (αTfm amino acids) have been developed (Kukhar and Soloshonok, 1995). The most general approach is the amidoalkylation of carbon nucleophiles with alkyl 2-(alkoxycarbonylimino)-3,3,3-trifluoropropionates (Burger et al., 1990), where the side-chain is directly linked to an αTfm Gly synthon. The stereoselective version of this synthesis proceeds via amidoalkylation of carbon nucleophiles with in situ formed homochiral cyclic acyl imines (Burger et al., 1990) which represents a modified Schöllkopf reaction (Groth and Schöllkopf, 1983). The dioxopiperazines (DOP) obtained with good stereoselectivity can be transformed into homochiral dipeptide esters on site selective acidolysis in methanol.

Herein, we disclose an alternative approach to αTfm amino acids of high structural diversity by linking the side-chain directly to a heterocyclic αTfmGly synthon (Scheme 1). 5-Fluoro-4-trifluoromethyloxazoles (**1**) are available from *N*-acylimines of hexafluoroacetone on treatment with tin(II)-chloride (Burger et al., 1982, 1988, 1990).

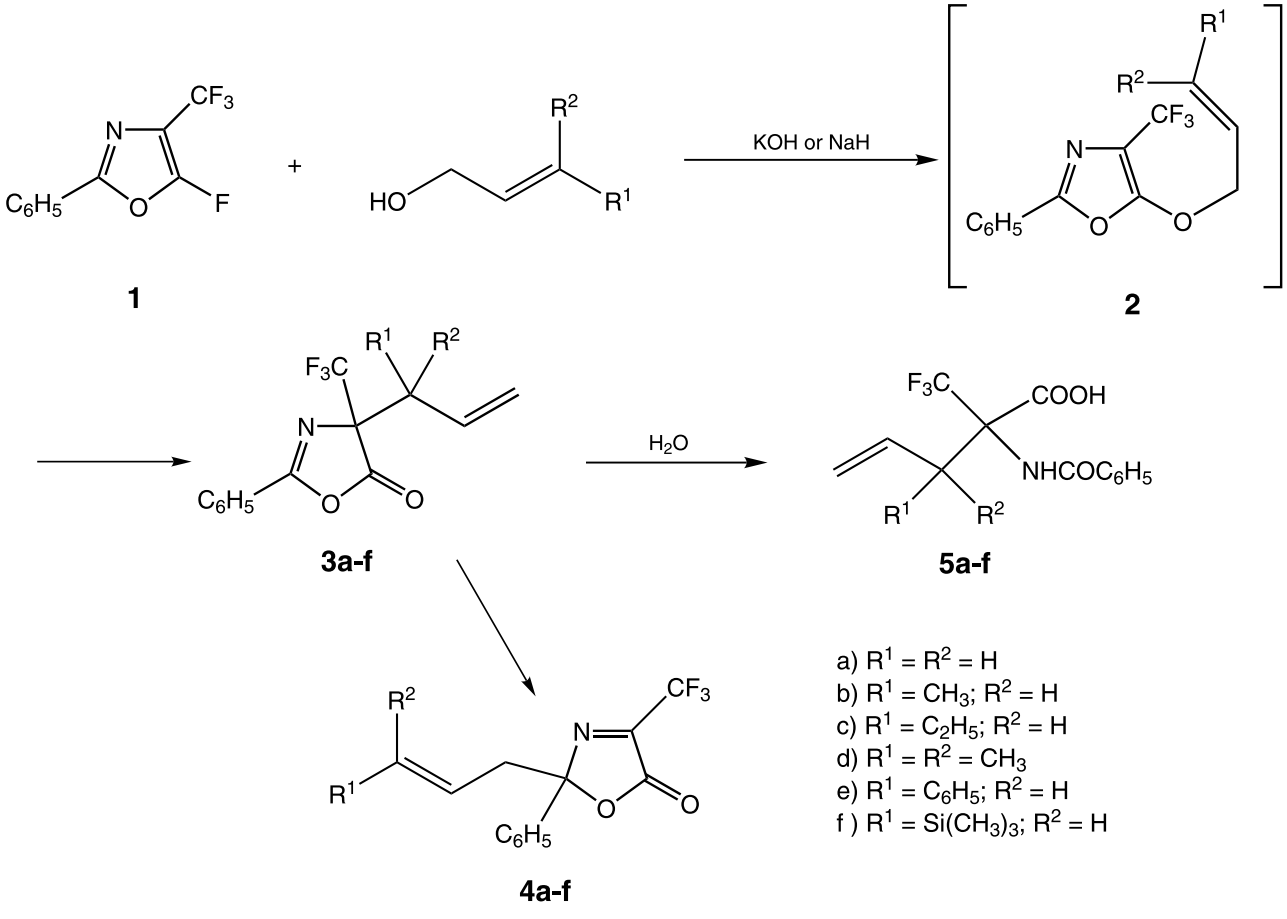


Scheme 1

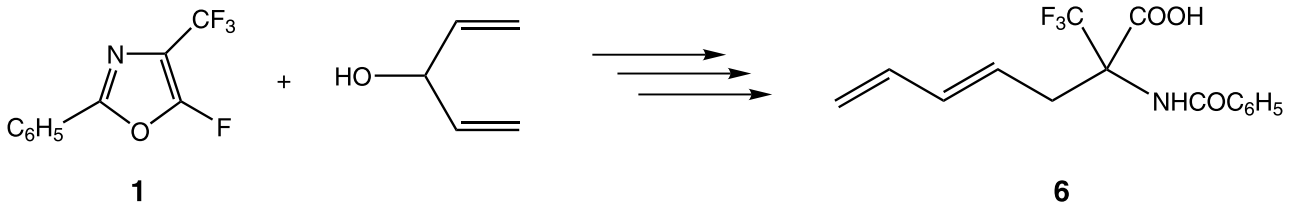
The single fluorine atom at C-5 of the oxazole system **1** is activated by the adjacent trifluoromethyl group and therefore readily susceptible to nucleophilic displacement reactions (Burger et al., 1988). When allyl alcohols are used as nucleophiles in the presence of KOH (powder) or NaH, after a short induction period, a slightly exothermic reaction starts. However, the expected nucleophilic substitution products **2** cannot be isolated. Under the reaction conditions applied, spontaneously a Claisen rearrangement resulting in the formation of 5(4H)-oxazolones (**3**) takes place (Burger et al., 2001, 2005). The lactone moiety shows a characteristic IR-absorption in the region of 1830 cm^{-1}. However, when a sterically demanding allyl alcohol $(CH_3)_3Si–CH=CH–CH_2OH$ is used as nucleophil, the rate of consecutive Claisen reaction is decreased and the substitution product **2f** is now stable enough to be characterized spectroscopically. On prolonged standing at room temperature **2f** rearranges to give the corresponding 5(4H)-oxazolone (**3f**).

A second [3,3] sigmatropic rearrangement transfering the allyl moiety from position 4 into position 2 of the oxazolone ring could not be detected. For 5(2H)-oxazolones **4** we would expect a characteristic IR-absorption below 1800 cm^{-1} for a conjugated lactone group. In the case of unfluorinated 4-alkyl- and 4-aryl-5(4H)oxazolones a Cope rearrangement occurs readily (Kübel et al., 1975; Engel et al., 1977; Fischer et al., 1986). The presence of the trifluoromethyl group seems to influence the rate of the Cope rearrangement considerably (Gajewski, 1997).

Compounds **3** are *N*-protected, carboxy activated amino acid derivatives and therefore suitable for direct use in peptide synthesis. Ring cleavage to give the *N*-protected αTfm allyl amino acids **5** can be achieved by addition of water. Deprotection of the amino group occurs on boiling with conc. HCl. Structural diversification can be achieved by variation of the substituent pattern of the allyl alcohol. A broad selection of allyl alcohols is commercially available. Furthermore, a 1,3-diene substructure can be introduced on reaction of **1** with α-vinyl allyl alcohol (**1→6**) (Burger et al., 1991). Therefore, the new approach offers a general, preparatively simple access to 2-trifluoromethyl

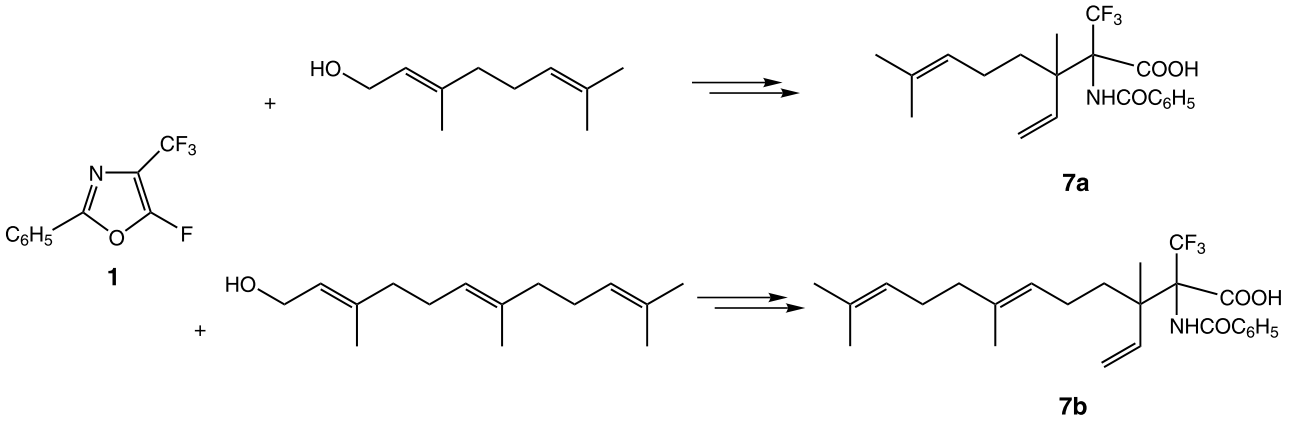


Scheme 2



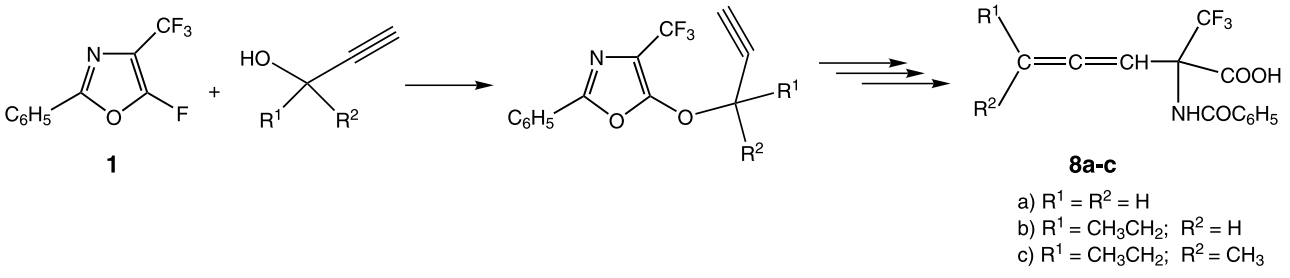
1 **6**

Scheme 3



7a **1** **7b**

Scheme 4



1 **8a-c**

a) $R^1 = R^2 = H$
b) $R^1 = CH_3CH_2$; $R^2 = H$
c) $R^1 = CH_3CH_2$; $R^2 = CH_3$

Scheme 5

amino acids with unsaturated side-chains. The presence of a 1,3-diene unit allows a decoration of peptide and depsipeptide chains with carbo- and heterocycles *via* Diels Alder reactions.

In this context, terpene alcohols, like geraniol, nerol, farnesol, phytol etc. are interesting building blocks for an efficient construction of new types of αTfm amino acids with lipid-modified side-chains **7** (C-10–C-20). The three-step sequence, consisting of nucleophilic substitution, Claisen rearrangment and hydrolytic cleavage of the oxazolone ring, can be run as a one-pot procedure.

When propargyl alcohols are used as nucleophiles, αTfm amino acids with a 1,2-diene subunit (**8**) in the side-chain are formed (Burger and Gaa, 1990).

We have demonstrated that 5-fluoro-4-trifluoromethyloxazole (**1**) exhibits the synthetic potential of a (Tfm)Gly synthon providing ready access to C^{α}-trifluoromethyl amino acids with CC double bonds in the side-chain, which can be functionalized or cross-linked after incorporation into a peptide chain to generate highly rigid domains. With terpene alcohols trifluoromethyl substituted α-amino acids with lipid-modified side-chains are obtained.

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