Synthesis of α-trifluoromethyl α-amino acids with aromatic, heteroaromatic and ferrocenyl subunits in the side chain

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Summary. 5-Benzyloxy-4-trifluoromethyl-1,3-oxazoles, obtained from 5-fluoro-4-trifluoromethyloxazoles and benzyl alcohols, are capable for rearrangements. A 1,3 shift of a benzyl group is the key step of a new general route toward α-trifluoromethyl substituted aromatic and heteroaromatic amino acids, demonstrating that 5-fluoro-4-trifluoromethyl-1,3-oxazole is a synthetic Tfm-Gly equivalent. On reaction with benzpinacol partially fluorinated oxazoles are transformed into bis(trifluoromethyl) substituted 2,5-diamino adipic acid and N-benzoyl-2-benzhydryl-3,3,3-trifluoroalanine.

Keywords: 5-Fluoro-4-trifluoromethyl-1,3-oxazoles – Nucleophilic heteroaromatic substitution – 1,3-Benzyl group migration versus Claisen rearrangement – α-Trifluoromethylamino acids – Synthetic Tfm-Gly equivalent

Abbreviations: TfmAmino Acids, trifluoromethylamino acids; TfmGly equivalent, trifluoromethylglycine equivalent

Introduction

Recently it was disclosed that hydrophobic interactions are far more essential in ligand/receptor interactions than assumed, while the influence of hydrogen bonding was overestimated (Shimohigashi, 1997). The mechanism of hydrophobic interactions, however, has not been elucidated in detail yet (Fujita et al., 2000). When aromatic systems react with the side-chain of Leu, Ile, Val and Ala they serve as hydrogen bond acceptor. These interactions are denoted as CH/π interactions, a concept which has been established by Nishio (Nishio et al., 1995, 1998).

Furthermore, it is well documented that non-covalent aromatic–aromatic interactions are important in determining molecular conformation, stability and activity of biologically relevant molecules (Burley and Petsko, 1985; Desiraju and Steiner, 2001; Meyer et al., 2003). Phe, Tyr and Trp often are incorporated into strategic positions of hydrophobic pockets to bind aromatic substrates (Hangauer et al., 1984; Obst et al., 1997; Breje et al., 2001). The weak acidic C–H group of the benzene ring acts as a hydrogen-bond donor and the π-system of the benzene ring as an acceptor. Thus, the benzene ring can serve as a pocket for accepting cationic species through cation/π-interactions (Meyer et al., 2003; Quinonero et al., 2002; In et al., 2003). Recent quantum-chemical calculations suggest the possibility of anion binding to uncharged π receptors (Mascal et al., 2002; Alkorta et al., 2002; Garau et al., 2003; Kim, 2004). Noncovalent interactions of anions have become one of the most actively explored areas of supramolecular chemistry (Rosokha et al., 2004). Therefore, aromatic and heteroaromatic amino acids are of actual interest as they can undergo different types of molecular interactions depending whether they are electron rich or electron deficient.

Modulation of pharmacokinetic properties by fluorine substitution has become a well-established strategy for lead compound optimization (Welch, 1987; O'Hagan and Rzepa, 1997; Smart, 2001) and resulted in a large number of clinically used fluoro-containing drugs. Substitution of hydrogen by fluorine causes minimal steric effects (Welch, 1991), while on the other hand a number of properties, such as lipophilicity, pk_a-values and metabolic stability can be considerably affected (Tang et al., 2001; Yoder and Kumar, 2002). Multiple fluorination changes the quadrupol moment of aromatic rings and

profoundly influences aromatic-aromatic interaction (Meyer et al., 2003).

Likewise, the introduction of a trifluoromethyl group into α-position of an amino acid improves proteolytic stability, lipophilicity, transport rates and permeability through certain body barriers. Because of the high electron density, the trifluoromethyl group is capable to participate in hydrogen bonding (Howard et al., 1996) and may act as coordinative site in metal complexes. Furthermore, the trifluoromethyl group can serve as powerful NMR label for spectroscopic studies of metabolism and conformation. Therefore, trifluoromethyl substituted amino acids with aromatic and heteroaromatic subunits in the side chain are interesting monomers for peptide modification and secondary structure design.

Several routes to α-trifluoromethyl substituted amino acids have been described (Kukhar and Soloshonok, 1995). The most general approach is the amidoalkylation of carbon nucleophiles with 2-(alkoxycarbonylimino)-3,3,3-trifluoropropionates (Sewald and Burger, 1995). Herein we introduce a concise route to trifluoromethyl substituted amino acids with aromatic, heteroaromatic and metal-containing groups in the side-chain. The syntheses start from 5-fluoro-4-trifluoromethyl-1,3-oxazoles that are readily available from N-acylimines of hexafluoroacetone on treatment with tin(II)-chloride (Ottlinger et al., 1978; Burger et al., 1982).

Materials and methods

Melting points were determined on a Boetius heating table. IR spectra were recorded with a FTIR spectrometer (Genesis ATI Mattson/Unicam). ^{1}H 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

A solution of oxazole **1** (2.31 g, 10 mmol), KOH (1.12 g, 20 mmol) and the corresponding alcohol (10 mmol) in dry dioxane (50 mL) was stirred at room temperature for 24–48 h. Then water (10 ml) was added and the mixture was stirred for another 12 h until the reaction was complete (^{19}F NMR and TLC control). The mixture was brought to pH = 1–2 with diluted HCl and evaporated to dryness in vacuo. The residue was extracted with ether (5 × 20 ml), then the solvent was removed under reduced pressure. Finally, the crude product was purified by column chromatography (eluent: CHCl$_3$/methanol).

N-Benzoyl-2-benzyl-3,3,3-trifluoroalanine (**7a**)

Yield: 2.93 g (87%) **7a**, mp >145 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 3.64$ (1H, d, $J = 13.7$ Hz), 4.15 (1H, d, $J = 13.7$ Hz), 7.22–7.24 (3H, m), 7.32–7.34 (2H, m), 7.48–7.57 (3H, m), 7.78–7.80 ppm (2H, m). ^{13}C NMR (d$_6$-acetone): $\delta = 35.3$, 67.5 (q, $J = 28.0$ Hz), 125.6 (q, $J = 288.0$ Hz), 128.0, 128.1, 129.0, 129.5, 131.4, 132.7, 135.0, 135.6, 167.3, 167.8 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 5.8$ ppm (s, 3F). IR (KBr): $\nu = 3380$, 3260–2700, 1749, 1647, 1519 cm^{-1}. MS (EI): m/z = 337 [M]$^+$, 293 [M − CO$_2$]$^+$, 292 [M − CO$_2$H]$^+$, 217 [M − C$_7$H$_6$NO]$^+$, 172 [M − C$_7$H$_6$NO. − CO$_2$H]$^+$, 105 [C$_7$H$_5$O]$^+$, 91 [C$_7$H$_7$]$^+$, 77 [C$_6$H$_5$]$^+$. Anal cald for C$_{17}$H$_{14}$F$_3$NO$_3$ (337.31): C, 60.53; H, 4.18; N, 4.15. Found: C, 60.75; 4.43; N, 4.38%.

N-Benzoyl-2-(4-tert.butylbenzyl)-3,3,3-trifluoroalanine (**7b**)

Yield: 0.95 g (24%) **7b**, mp 162 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 1.25$ (s, 9H), 3.61 (d, $J = 14.0$ Hz, 1H), 4.09 (d, $J = 14.0$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.49 (m, 2H), 7.57 (m, 1H), 7.71 (s br, 1H), 7.81 ppm (m, 2H). ^{13}C NMR (d$_6$-acetone): $\delta = 31.6$, 34.9, 35.2, 67.3 (q, $J = 28.0$ Hz), 125.5 (q, $J = 288.0$ Hz), 125.9, 128.1, 129.5, 131.0, 131.7, 132.7, 135.4, 150.9, 167.4, 167.6 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 6.0$ ppm (s, 3F). IR (KBr): $\nu = 3380$, 1745, 1660, 1520 cm^{-1}. MS (EI): m/z = 393 [M]$^+$, 272 [M − C$_7$H$_7$NO]$^+$, 257 [M − C$_7$H$_7$NO, −CH$_3$]$^+$, 147 [C$_{11}$H$_{15}$]$^+$, 105 [C$_7$H$_5$O]$^+$, 77 [C$_6$H$_5$]$^+$. Anal calcd for C$_{21}$H$_{22}$F$_3$NO$_3$ (393.41): C, 64.11, H, 5.64, N, 3.56. Found: C, 64.08, H, 5.65, N, 3.42%.

N-Benzoyl-2-(fluoren-9-yl)-3,3,3-trifluoroalanine (**7c**)

Yield: 1.48 g (36%) **7c**, mp 112 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 5.56$ (s, 1H), 7.31–7.38 (m, 2H), 7.46–7.52 (m, 2H), 7.56–7.62 (m, 2H), 7.65–7.72 (m, 2H), 7.85–7.98 ppm (m, 5H). ^{13}C NMR (CDCl$_3$): $\delta = 50.0$, 69.8, 119.7, 121.2 (q, $J = 285.0$ Hz), 121.9, 124.0, 125.1, 140.5, 144.3, 163.2, 167.0 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 12.9$ ppm (s, 3F). MS (EI): m/z = 412 [M + H]$^+$, 434 [M + Na]$^+$. Anal calcd for C$_{23}$H$_{16}$F$_3$NO$_3$ (411.39): C, 67.15, H, 3.92, N, 3.40. Found: C, 66.98, H, 3.76, N, 3.54%.

N-Benzoyl-2-(9-anthrylmethyl)-3,3,3-trifluoroalanine (**7d**)

Yield: 1.84 g (42%) **7d**, mp 190 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 3.12$ (m, 2H), 7.58–7.90 ppm (m, 14H). ^{13}C NMR (d$_6$-acetone): $\delta = 35.9$, 67.5, 125.2 (q, $J = 245$ Hz), 126.8 (m), 172.0, 174.5 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 10.7$ ppm (s, 3F). MS (EI): m/z = 437 [M + H]$^+$, 459 [M + Na]$^+$. Anal calcd for C$_{25}$H$_{18}$F$_3$NO$_3$ (437.43): C, 68.65, H, 4.15, N, 3.20. Found: C, 68.32, H, 4.26, N, 3.45%.

N-Benzoyl-2-(xanthen-9-yl)-3,3,3-trifluoroalanine (**7e**)

Yield: 1.32 g (31%) **7e**, mp 150 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 5.45$ (m, 1H), 7.25–7.80 ppm (m, 13H). ^{13}C NMR (d$_6$-acetone): $\delta = 40.9$, 66.4, 117.8, 119.2, 120.1, 122.4, 124.0, 122.6, 125.3 (q, $J = 274.0$ Hz), 125.5, 127.5, 128.1, 133.1,153.1, 165.9, 168.5 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 12.1$ ppm (s, 3F). MS (EI): m/z = 428 [M + H]$^+$, 466 [M + K]$^+$. Anal calcd for C$_{23}$H$_{16}$F$_3$NO$_4$ (427.39): C, 64.64, H, 3.78, N, 3.27. Found: C, 64.35, H, 4.03, N, 2.98%.

N-Benzoyl-2-(1-methylnaphth-2-yl)-3,3,3-trifluoroalanine (**9**)

A mixture of **1** (2.31 g, 10 mmol) in dry dioxane (30 ml), 1-hydroxymethyl-naphthaline (1.58 g, 10 mmol) and KOH (1.12 g, 10 mmol) was heated up to 70 °C in an oil bath. When the reaction was complete water (10 ml) was added (^{19}F NMR analysis). Work-up see general procedure.

Yield: 2.13 g (55%) **9**, mp 78 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 2.68$ (3H, s), 6.95–7.62 (6H, m), 7.81–8.18 ppm (5H, m). ^{13}C NMR (d$_6$-acetone): $\delta = 15.7$, 69.6 (q, $J = 27.0$ Hz), 125.1, 125.6 (q, $J = 290.0$ Hz), 126.7, 126.9, 127,1, 127.2, 127.6, 128.0, 129.0, 129.6, 132.5, 132.9, 133.4,, 133.9, 134.1, 165.3, 169.2 ppm. ^{1}F NMR (d$_6$-acetone): $\delta = 9.8$ ppm (s, 3F). IR (KBr): $\nu = 3410$, 1745, 1695–1670, 1515, 1490 cm^{-1}. MS (EI): m/z = 387 [M]$^+$. 343 [M − CO$_2$]$^+$, 323 [M − CO$_2$, −HF]$^+$, 141 [C$_{11}$H$_9$]$^+$, 105

$[C_7H_5O]^+$, 77 $[C_6H_5]^+$. Anal calcd for $C_{21}H_{16}F_3NO_3$ (387.37): C, 65.12; H, 4.16; N, 3.62. Found: C, 65.12; H, 4.80; N, 3.59%.

N-Benzoyl-2-(2-methyl-3-furyl)-3,3,3-trifluoroalanine (12a)

Yield: 1.54 g (47%) 12a, mp 89 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 2.43$ (s, 3H), 6.77 (s br, 1H), 7.54 (m, 4H), 8.09 ppm (m, 3H). ^{13}C NMR (d$_6$-acetone): $\delta = 13.9$, 64.4 (q, $J = 29.0\,Hz$), 112.1, 113.7, 125.6 (q, $J = 286.0\,Hz$), 128.8, 129.5, 133.0, 134.7, 141.2, 152.0, 166.7, 167.6 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 5.6$ ppm (s, 3F). IR (KBr): $\nu = 3380$, 3100–2700, 1780, 1690, 1650, 1515 cm^{-1}. MS (EI): m/z = 327 [M]$^+$, 309 [M − H$_2$O]$^+$, 283 [M − CO$_2$]$^+$, 105 [C$_7$H$_8$O]$^+$, 77 [C$_6$H$_5$]$^+$. Anal calcd for $C_{15}H_{12}F_3NO_4$ (327.26): C, 55.05, H, 3.70, N, 4.28. Found: C, 55.36, H, 3.96, N, 4.45%.

N-Benzoyl-2-(2-methyl-3-thienyl)-3,3,3-trifluoroalanine (12b)

Yield: 1.03 g (30%) 12b, mp. 188 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 2.54$ (s, 3H), 7.27–7.95 ppm (m, 7H). ^{13}C NMR (d$_6$- acetone): $\delta = 14.5$, 66.3 (q, $J = 29.0\,Hz$), 122.3, 125.3 (q, $J = 287.0\,Hz$), 128.0, 128.5, 129.4, 132.9, 134.5, 139.3, 166.9 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 6.5$ ppm (s, 3F). IR (KBr): $\nu = 3380$, 1740, 1645, 1510 cm^{-1}. MS (EI): m/z = 299 [M − CO$_2$]$^+$, 279 [M − CO$_2$, −HF]$^+$, 105 [C$_7$H$_8$O]$^+$, 97 [C$_5$H$_5$S]$^+$, 77 [C$_6$H$_5$]$^+$. Anal calcd for $C_{15}H_{12}F_3NO_3S$ (343.33): C, 52.48, H, 3.52, N, 4.08. Found: C, 52.78, H, 3.78, N, 4.06%.

N-Benzoyl-3-(2,2′:5′,2″-terthien-5-yl)-3,3,3-trifluoroalanine (13)

Yield: 1.98 g (39%) 13a, mp 65 °C (decomp.). ^{1}H NMR (d$_6$-acetone): $\delta = 3.93$ (1H, d, $J = 15.0\,Hz$), 4.55 (1H, d, $J = 15.0\,Hz$), 6.95 (1H, m), 7.07 (3H, m), 7.14 (1H, m), 7.25 (1H, m), 7.40 (1H, m), 7.50 (3H, m), 7.58 (1H, m), 7.88 ppm (1H, m). ^{13}C NMR (d$_6$-acetone): $\delta = 30.1$, 67.7 (q, $J = 28.0\,Hz$), 125.1 (q, $J = 288.0\,Hz$), 124.2, 124.8, 125.2, 125.3, 125.9, 128.1, 129.00, 129.5, 130.5, 132.9, 135.5, 135.6, 136.6, 136.9, 137.4, 137.6, 167.5, 167.8 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 5.37$ ppm (3F, s). IR (KBr): $\nu = 3400$, 1750, 1650, 1515 cm^{-1}. MS (EI): m/z = 507 [M]$^+$, 489 [M − H$_2$O]$^+$, 463 [M − CO$_2$]$^+$, 443 [M − CO$_2$, −HF]$^+$, 342 [M − CO$_2$, −C$_7$H$_7$NO]$^+$, 261 [C$_{13}$H$_9$S$_3$]$^+$, 105 [C$_7$H$_5$O]$^+$, 77 [C$_6$H$_5$]$^+$. Anal calcd for $C_{23}H_{16}F_3NO_3S_3$ (507.39): C, 54.45; H, 3.18; N, 2.76. Found: C, 55.13; H, 3.80; N, 3.14%.

N-Benzoyl-3-ferrocenyl-3,3,3-trifluoroalanine (14)

Yield: 2.50 g (56%) 14, mp 97 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 3.35$ (1H, d, $J = 14.0\,Hz$), 4.15 (10H, m), 7.14 (1H, s br.), 7.47 (3H, m), 7.68 (2H, m), 9.54 ppm (1H, s br.). ^{13}C NMR (d$_6$-acetone): $\delta = 29.5$, 67.0 (q, $J = 28.0\,Hz$), 69.6, 68.6–70.8, 123.2 (q, $J = 288.0\,Hz$), 127.1, 128.8, 132.2, 134.1, 167.9, 168.8 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 6.62$ ppm (3F, s). IR (KBr): $\nu = 3385$, 1730, 1675, 1505 cm^{-1}. MS (EI): m/z = 445 [M]$^+$, 427 [M − H$_2$O]$^+$, 401 [M − CO$_2$]$^+$, 382 [M − H$_2$O, −CO$_2$H]$^+$, 280 [M − CO$_2$, −C$_7$H$_7$NO]$^+$, 199 [C$_{11}$H$_{11}$Fe]$^+$, 121 [C$_7$H$_7$NO]$^+$, 105 [C$_7$H$_5$O]$^+$, 77 [C$_6$H$_5$]$^+$. Anal calcd for $C_{21}H_{18}F_3FeNO_3$ (445.22): C, 56.65, H, 4.08, N, 3.15. Found: C, 56.32, H, 4.62, N, 3.19%.

1,4-Bis[2-phenyl-4-trifluoromethyl-oxazol-5-yl(oxymethyl)]benzol (15)

See general procedure; the product crystallizes directly from the reaction mixture and is separated by filtration. Purification by chromatography (eluent: petroleum ether/ethyl acetate).

Yield: 3.92 g (70%) 15, mp 135 °C. ^{1}H NMR (CDCl$_3$): $\delta = 5.38$ (m, 4H), 7.42–7.50 (m, 10 H), 7.90–7.93 ppm (m, 4H). ^{13}C NMR (CDCl$_3$): $\delta = 75.6$, 108.6 (q, $J = 40.1\,Hz$), 121.2 (q, $J = 264.9\,Hz$), 126.1, 126.4, 128.3, 128.6, 128.9, 129.1, 131.0, 135.4, 153.1, 155.8 ppm. ^{19}F NMR (CDCl$_3$): $\delta = 15.8$ ppm (s, 6F). IR (KBr): $\nu = 1650$, 1605, 1485, 1440 cm^{-1}. MS (EI): m/z = 561 [M + H]$^+$, 583 [M + Na]$^+$. Anal calcd

for $C_{28}H_{18}F_6N_2O_4$ (560.47): C, 60.00, H, 3.24, N, 5.00. Found: C, 60.35, H, 3.45, N, 5.23%.

1,4-Bis[N-benzoyl-2-trifluoromethyl-3-alanyl]benzol (16)

Yield: 2.20 g (37%) 16, mp 187 °C. ^{1}H NMR (CDCl$_3$): $\delta = 3.21$ (m, 2H), 3.34 (m, 2H), 7.35 (m, 4H), 7.85 ppm (m, 10H). ^{13}C NMR (CDCl$_3$): $\delta = 32.0$, 67.8 (m), 126.0, 127.5, 128.7, 128.9, 129.0, 129.2 (q, $J = 250.9\,Hz$), 132.4, 134.6, 163.0, 166.2 ppm. ^{19}F NMR (CDCl$_3$): $\delta = 14.5$ ppm (s, 6F). MS (EI): m/z = 619 [M + H]$^+$, 636 [M + H + K]$^+$. Anal calcd for $C_{28}H_{22}F_6N_2O_6$ (596.50): C, 56.38, H, 3.72, N, 4.70. Found: C, 56.17, H, 3.78, H, 5.02%.

A solution of oxazole 1 (2.31 g, 10 mmol), KOH (1.12 g, 20 mmol) and benzpinacol (3.66 g, 10 mmol) in dry dioxane (50 ml) was treated due to the general protocol. Compounds 17/18 were separated by column chromatography (eluant: CHCl$_3$/CH$_3$OH).

2,5-Bis-(N-benzoylamino)-3,3,4,4-tetraphenyl-2,5-bis(trifluoromethyl)adipic acid (17)

Yield: 2.23 g (27%) 17, mp 165 °C. ^{1}H NMR (d$_6$-acetone): $\delta = 7.59$–7.70 (m, 20H), 7.81–7.85 ppm (m, 10H). ^{13}C NMR (CDCl$_3$): $\delta = 66.0$ (m), 68.5 (m), 128.1, 128.4, 128.6, 128.8, 129.2, 129.6 (q, $J = 255.4\,Hz$), 130.1, 130.4, 133.7, 137.1, 165.8, 169.2 ppm. ^{19}F NMR (d$_6$-acetone): $\delta = 12.0$ ppm (s, 6F). MS (EI) m/z = 824 [M]$^+$. Anal calcd for $C_{46}H_{34}F_6N_2O_6$ (824.80): C, 66.99, H, 4.16, N, 3.40. Found: C, 66.65, H, 3.97, N, 3.27%.

N-Benzylamino-2-benzhydryl-3,3,3-trifluoroalanine (18)

Yield: 0.83 g (20%) 18, mp 110 °C. ^{1}H NMR (acetone-d$_6$): $\delta = 5.31$ (1H, s), 7.40 (m, 15 H). ^{13}C NMR (acetone-d$_6$): $\delta = 54.5$, 68.3 (m, $J = 13.0\,Hz$), 127.3, 127.6, 128.6, 128.8, 128.9 (q, $J = 287.2\,Hz$), 130.5, 130.8, 132.1, 138.6, 165.7, 166.1 ppm. ^{19}F NMR (CDCl$_3$): $\delta = 14.3$ ppm (s, 3F). MS (EI): m/z = 414 [M + H]$^+$, 827 [2 M + H]$^+$. Anal calcd for $C_{23}H_{18}F_3NO_3$ (413.40): C, 66.82; H, 4.39, N, 3.39. Found: C, 67.02; H, 4.51, N, 3.17%.

Results and discussion

The single fluorine atom adjacent to the trifluoromethyl group of the oxazole system 1 can be readily replaced by various nucleophiles to give libraries of trifluoromethyl substituted heterocycles of biological relevance (Burger et al., 1988). When allyl alcohols are used as nucleophiles in the presence of a base (KOH powder or NaH) after a short induction period a slightly exothermic reaction starts. Under the reaction conditions applied the substitution products 2 could not be isolated. Instead, we got 5(4H)oxazolones, the products of a consecutive Claisen rearrangement (2 → 3) (Burger et al., 1989, 2005), which can be transformed into the N-protected amino acid (4) on stirring with 1N HCl at 50 °C. Now, we report on the reaction of 1 with allyl systems where the CC double bond is part of an aromatic or heteroaromatic system. Under those conditions the Claisen route should become energetically unfavorable such that alternative rearrangements will compete or dominate.
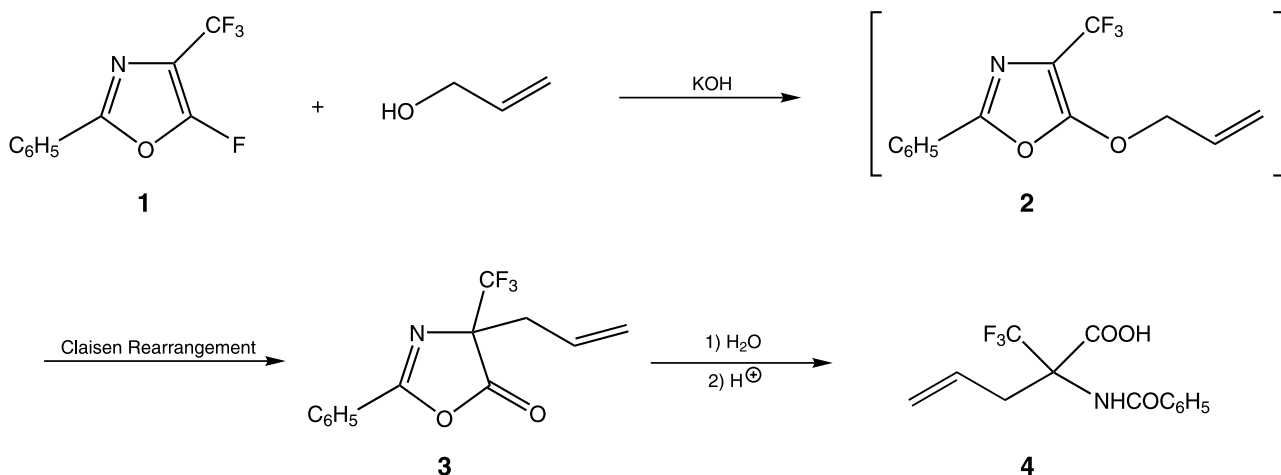
Tfm phenylalanines

Hydroxymethyl substituted aromatic compounds like benzyl alcohol react with 5-fluoro-4-trifluoromethyl-1,3-oxazoles **1** in the presence of a base exothermally to give benzylether **5**. In the ^{19}F NMR spectrum the doublet for the CF$_3$ group at $\delta = 15.5$ ppm ($^4J_{FF} = 11.5$ Hz) disappears and a singlet emerges around $\delta = 16.6$ ppm. Compounds **5** are stable at room temperature. However, on heating they rearrange to give lactones [5(4H)oxazolone: $\nu = 1830$ cm^{-1}]. A thermally induced [3 + 2] cyclo-elimination of CO$_2$ (Burger et al., 1989) and a readily occurring aminolytic ring opening is typical for a lactone moiety. Consequently, the carboxy-activated species can be used directly for
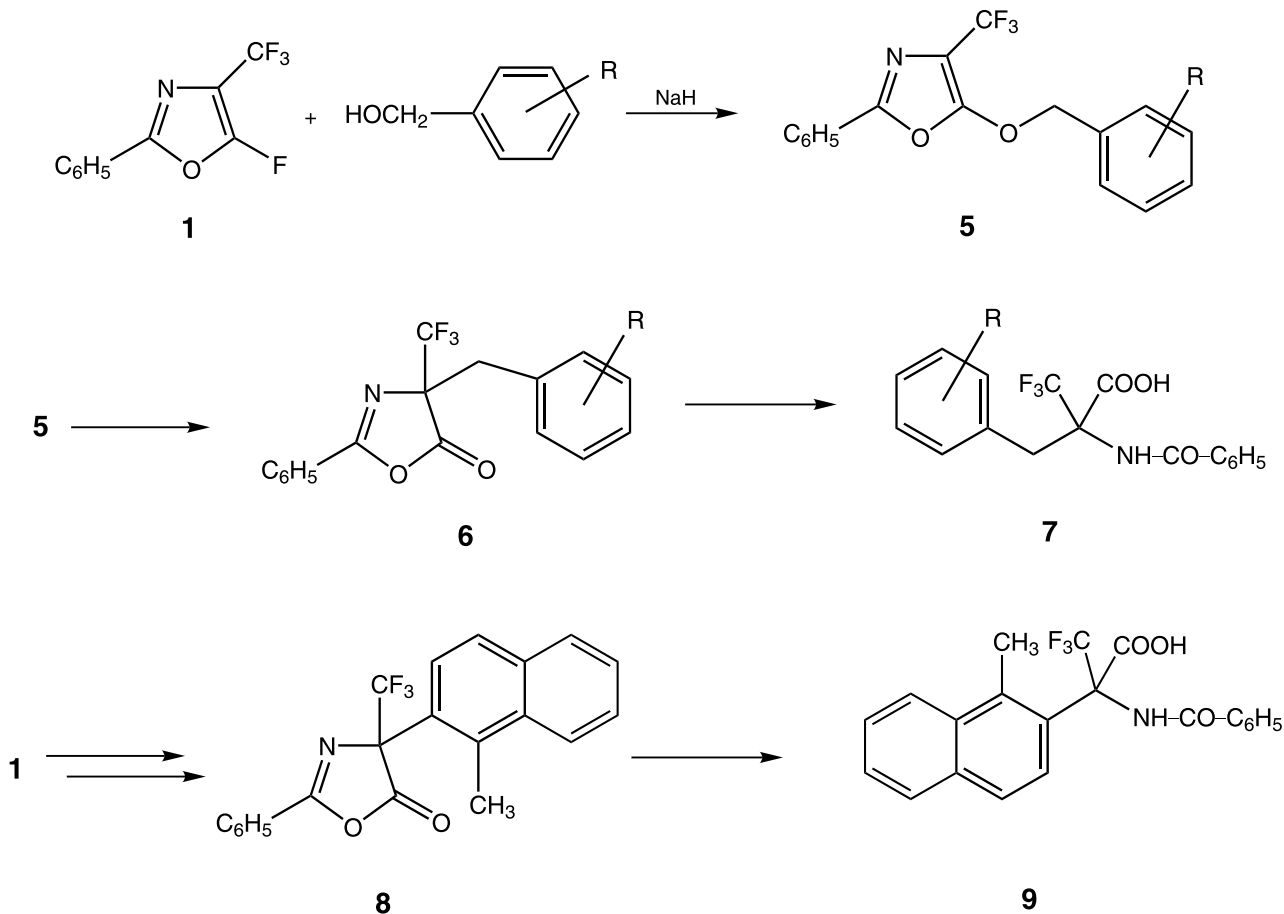
peptide synthesis. The ^{19}F NMR spectrum shows a singlet at 3.80 ppm indicating that the trifluoromethyl group is bound to a sp^3 hybridized carbon atom.

Compounds **7** formed by a 1,3-benzyl group migration are characterized by the presence of a methylene group which resonates at $\delta = 33$–35 ppm in the ^{13}C NMR spectrum. From the ^{1}H NMR spectrum two diastereotopic protons around $\delta = 3.60$ and 4.15 ppm can be detected. All benzylethers studied so far follow route **5 → 7**. From intercrossing experiments it was shown that the process is non-concerted (Burger et al., 1989). Surprisingly, the rearranged product obtained from 1-hydroxymethylnaphthaline and **1** shows signals for a methyl group (^{1}H NMR: $\delta = 2.68$ ppm, ^{13}C NMR: $\delta = 15.7$ ppm) that is typical for a Claisen rearrangement, while 9-hydroxymethylanthrazene rearranges *via* [1,3] shift. Thus, the reaction pathway depends considerably on structural properties and on the degree of aromaticity of the aromatic subunit that is present in the allyl system. Deprotection can be achieved on heating with diluted HCl.

The reaction sequence consisting of nucleophilic substitution and rearrangement can be readily monitored by ^{19}F NMR spectroscopy. The oxazol → oxazolin-5-one rearrangement was first described by Steglich et al. for unfluorinated species (Kübel et al., 1975; Engel et al., 1977; Fischer et al., 1986). Since benzylalcohols with highly variable substituent pattern are commercially available the above described route can be used for the generation of libraries of α-trifluoromethyl substituted phenylalanines.

Fluorescence spectroscopy has become a valuable technique for conformational studies of biopolymers. Incorporation of a fluorescence probe into a peptide chain may be achieved by site-selective reaction with side-chain functional groups or by direct use of amino acids where fluorophores are already present. In this context, fluorescent amino acids like antAib (I) and antAla (II) designed by Wakselman (Wakselman et al., 2005) may represent useful reporter groups. Compound **7d**, readily available from **1**, represents the Tfm-analogue of antAla (II).

antAib (I)   antAla (II)
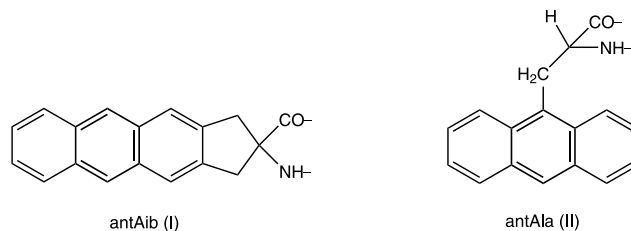
Heteroaromatic Tfm amino acids

Likewise, the above disclosed strategy provides ready access to heterocyclic Tfm amino acids of high structural diversity. Surprisingly, we observed a completely different reaction behavior for 2-hydroxymethylthiophene and hydroxymethylfuran compared to (2,2′,5′,2″terthien-5-yl)methanol. Nucleophilic substitution products **10a/b** obtained from **1** and 2-hydroxymethylthiophene and hydroxymethylfuran undergo a Claisen rearrangement (**10 → 11 → 12**). From

1   X = O, S   10

Claisen Rearrangement

11   12

a) X = O
b) X = S
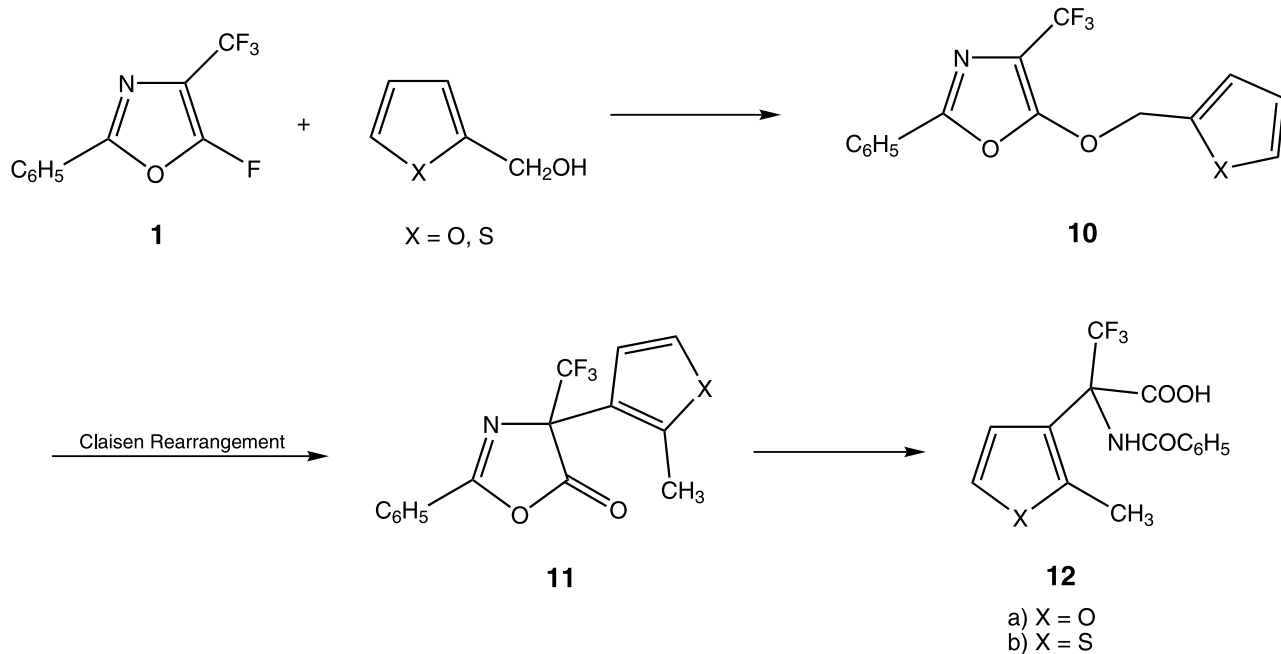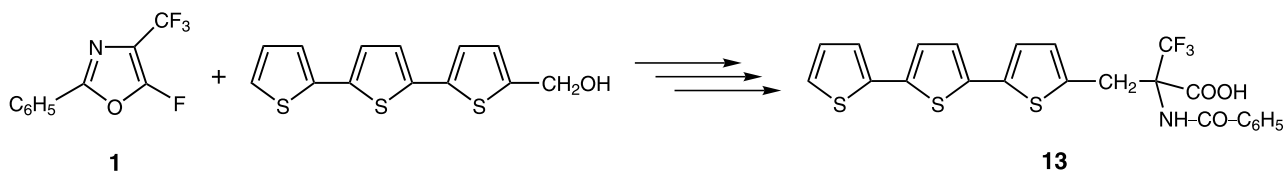
the ^{1}H NMR spectrum a methyl group can be identified ($\delta = 2.54/2.43$ ppm) which was confirmed by a ^{13}C NMR resonance signal at $\delta = 14.5/13.9$ ppm.

In contrast, the ^{1}H NMR spectrum of the terthienyl derivative **13** shows signals for two magnetically non equivalent protons of a methylene group [$\delta = 3.93$ ppm (d, $J = 15.0$ Hz); $\delta = 4.55$ ppm (d, $J = 15.0$ Hz)] and in the ^{13}C NMR spectrum a signal at $\delta = 30.1$ ppm that is typical for a methylene carbon atom.

Metal-containing TFM amino acids

The preparatively simple access of N-benzoyl-2-ferrocenyl-3,3,3-trifluoroalanine **14** starting from hydroxymethyl ferrocene is interesting for medicinal chemistry. Since *cis*-platin was introduced as antitumor agent (Rosenberg et al., 1969; Wong and Giandomenico, 1999; Kelland and Farrell, 2000) there has been a steadily growing interest in the synthesis of metal-containing amino aids (Severin et al., 1998). Cancer activity of several metallocene derivatives has been reported. A new interesting class of compounds with special biological properties can be obtained on linking metallocenes to biomolecules like peptides, depsipeptides and glycopeptides *via* metal-containing Tfm amino acids.

### Tfm diamino dicarboxylic acids

The design and synthesis of aromatic bis(amino acid) derivatives has attracted considerable interest (Hiebl et al., 1999) mainly due to their presence as subunits in many peptide antibiotics (Williams and Hendrix, 1992; Rao et al., 1995). One of the requirements for the action of these antibiotics is most likely the restricted conformational freedom imposed by the cyclic peptide backbone. Moreover, the incorporation of aromatic bis(amino acid) derivatives into peptide loops may mimic the peptide structures derived from non-covalent aryl/aryl interactions that are found in oligopeptides and proteins (Burley and Petsko, 1986, 1989; Burley et al., 1987; Singh and Thornton, 1985).

In principle, every aromatic and heteroaromatic system with two HOCH$_2$-groups should be capable to react with two equivalents of the Tfm Gly synthon, providing tailormade side chains that can be used to study the influence of noncovalent aromatic/aromatic interactions on the conformation of peptides.

It is our aim to provide methodology for generating an arsenal of building blocks that reliably induce a desired conformation of a peptide. Consequently, numerous efforts have been undertaken to develop new strategies for the construction of scaffolds that induce well-defined secondary structure motifs or allow to switch between different secondary sructures. New types of scaffolds like **16** and **17** become accessible e.g. from commercially available starting materials like 1,4-di(hydroxymethyl)benzene and benzpinacol *via* the above disclosed strategy. The formation of the bis(trifluoromethyl) substituted 2,5-diamino adipic acid (**17**) is accompanied by 20% of a byproduct which we ascribed structure **18** (Tsouker, 2003).

Advantageously, the new approach to αTfm amino acids is performed as "one-pot" procedure. The moderate overall yields (not optimized) are compensated by the versatility and the simplicity of the procedure.
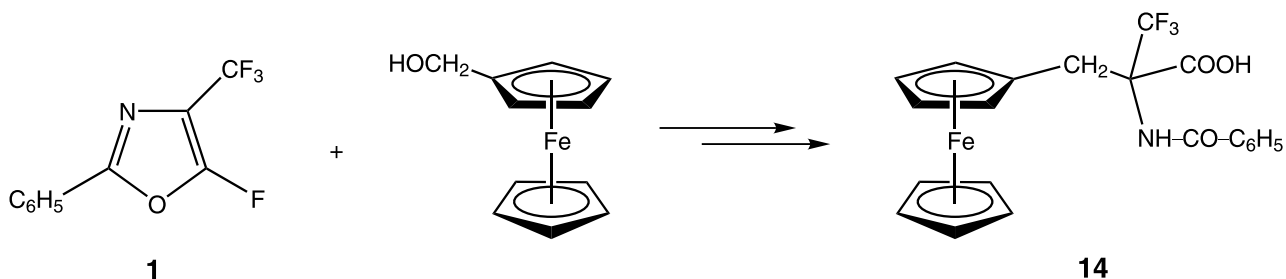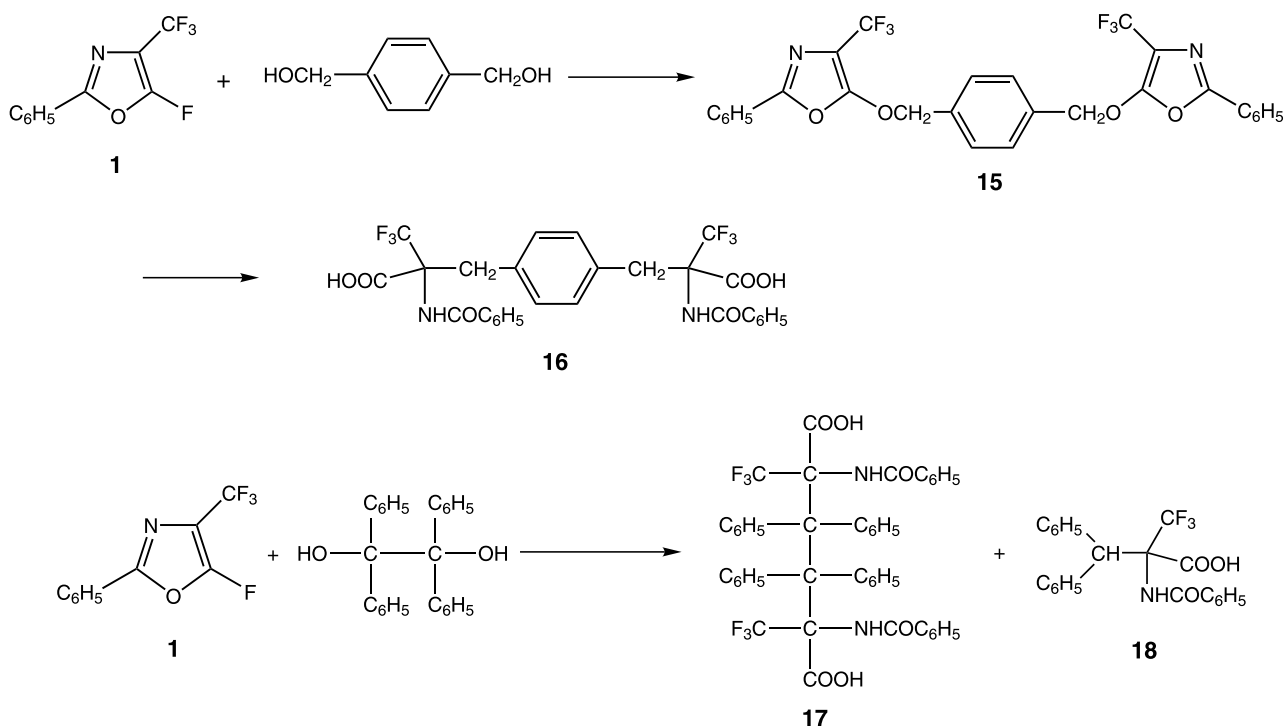
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