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Synthesis of Trifluoromethylpyrroles and Related Heterocycles from 4-Ethyloxy-1,1,1-trifluorobut-3-ene-2-one

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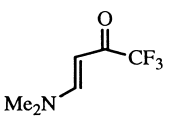
Abstract—Syntheses of intermediate 4-dialkylamino-1,1,1-trifluorobut-3-ene-2-ones are described from 4-ethyloxy-1,1,1-trifluorobut-3-ene-2-one and α-aminoacids. In subsequent cyclisations pyrroles and other bicyclic heteroaromatics having trifluoromethyl substitution are obtained either by simple dehydration or with concomitant decarboxylation.

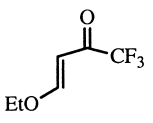
Introduction

The synthesis of trifluoromethyl substituted heterocycles has become an important objective. The use of trifluoromethyl substituted heterocycles as herbicides and as compounds of pharmaceutical interest illustrates the need for efficient syntheses of these heterocycles. The synthesis of the following skeletons having trifluoromethyl substitution has recently been reported: pyridines[1] including dihydropyridines,[2] furans,[3] pyrroles,[4–6] pyrazoles,[7,8] isoxazolidines,[9] imidazoles,[10] thiazoles,[11] oxazoles,[11] oxadiazoles,[12] purines,[13] pyrimidines,[14] pyrazolines,[15] pyridazines,[16] triazines,[17] indoles,[18] quinolines,[19] thiazines,[20] benzodiazepines,[21] piperidines,[22] and indolizidinone derivatives.[23] Most of these syntheses depend upon a cyclisation of an acyclic building block incorporating a trifluoromethyl group. In the accompanying papers[24,25] we describe the use of 4-dimethylamino-1,1,1-trifluorobut-3-ene-2-one (**1**) and of 4-ethyloxy-1,1,1-trifluoro-3-buten-2-one (**2**) in the synthesis of alicyclic compounds having trifluoromethyl substitution and in the synthesis of unsaturated trifluoromethyl ketones. In this paper we report the use of 4-ethyloxy-1,1,1-trifluoro-3-buten-2-one (**2**) in the synthesis of trifluoromethylpyrroles.

There is a recent report[5] of the use of 4-substituted-1,1,1-trifluoro-3-buten-2-ones in the synthesis of pyrroles. In this French study the key substrates for cyclisations were prepared by reaction of 4-chloro-1,1,1-trifluoro-3-buten-2-ones with esters of α-aminoacids. Five examples of subsequent cyclisations afforded trifluoromethylated pyrroles. In our study we have chosen 4-ethyloxy-1,1,1-trifluoro-3-buten-2-one (**2**) as our readily available substrate. Using the procedure of Hojo et al.[26] we find that the ketone (**2**) is easily prepared from trifluoroacetic anhydride and ethylvinyl ether. We have used the ketone (**2**) in preparation of 4-dimethylamino-1,1,1-trifluorobut-3-ene-2-one (**1**) in other studies[24] and find preparation of diverse 4-dialkylamino-1,1,1-trifluoro-3-buten-2-ones can readily be extended by using α-aminoacids directly. We now report that their subsequent cyclisation provides an efficient route both to trifluoromethylpyrroles and related trifluoromethylated heterocyclic skeletons.



(**1**)



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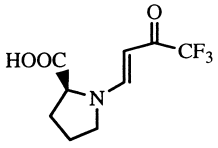

(**3**)

Results and Discussion

The viability of a reaction sequence based on reaction of an α-aminoacid with the alkoxy unsaturated ketone (**2**) followed by a cyclisation was established with three aminoacids with isolation of the intermediate β-dialkylamino unsaturated ketones. Reaction of proline with freshly prepared 4-ethoxy-1,1,1-trifluoro-3-buten-2-one (**2**) gave aminoacid (**3**) in 73% yield. Similarly racemic *N*-methylalanine and *N*-benzylglycine gave the amino acids (**4**) and (**5**) in 35 and 41% yields, respectively. The NMR spectra of the product (**3**) were somewhat complex. At room temperature in $CDCl_3$ the two conformers (**3a**) and (**3b**) were observed in a ratio of 85:15. In DMSO at 403 K the rotational equilibrium was established and signal coalescence occurred. In a similar manner the aminoacid (**4**) was observed at room temperature in $CDCl_3$ to give two sets of signals, again corresponding to the conformers (**4a**) and (**4b**). At 358 K complete coalescence of the signals of the two conformers was observed. Observation of a *trans*

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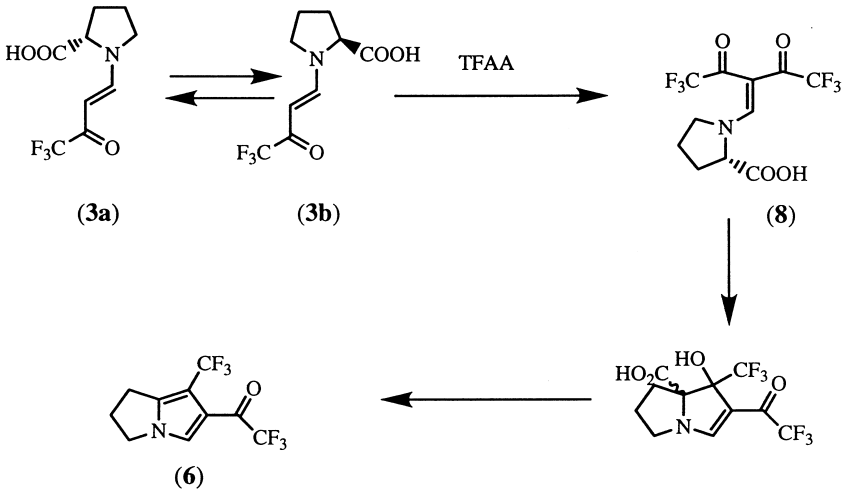
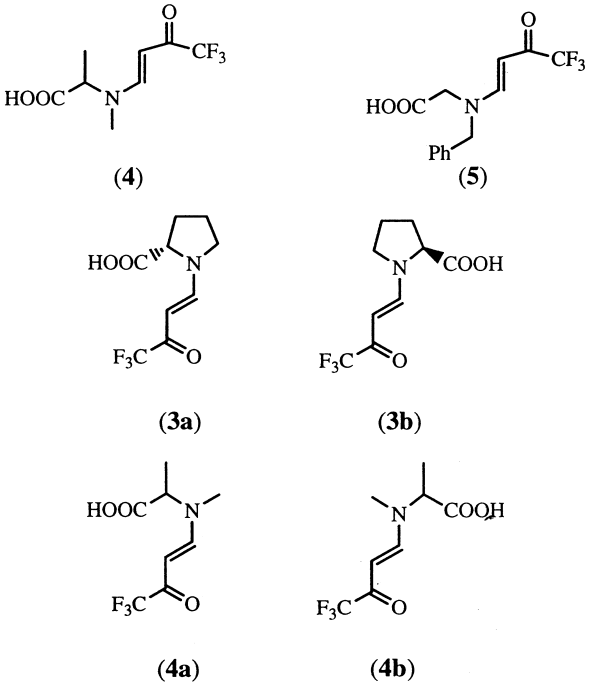
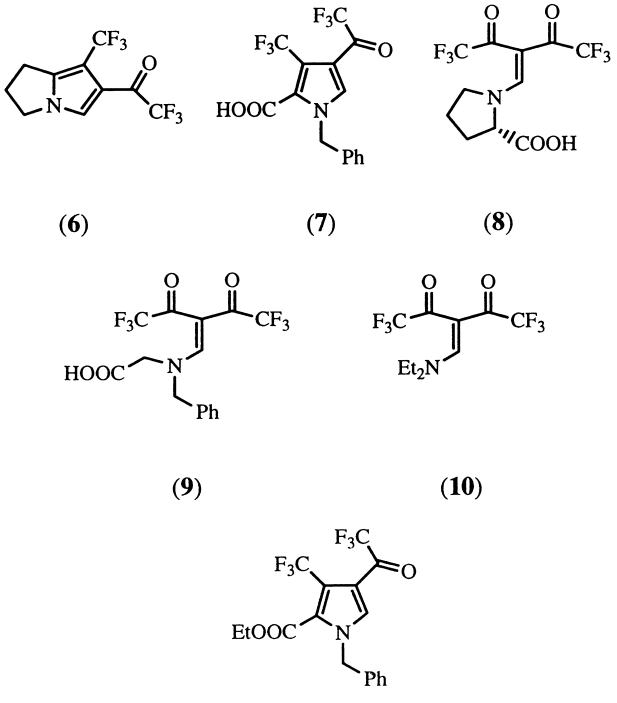


Scheme 1.

coupling constant (J=12 Hz) in both the major conformer at 8.05 ppm and in the minor conformer at 7.99 ppm indicated that the origin of the conformational equilibria were rotations about the carbon–nitrogen bonds rather than rotations about the carbon–carbon double bonds. The major conformer (**4a**) gave rise to a resonance at 4.71 ppm and the minor conformer (**4b**) to an equivalent resonance at 4.66 ppm. Wojcik et al.[27] have associated lower field signals with the *Z* configuration about the carbon–nitrogen bonds and our tentative assignment is based on their findings. The product (**5**) from *N*-benzylglcine again showed two conformers in an approximate ratio of 55:45. However no variable temperature studies were made in this case.

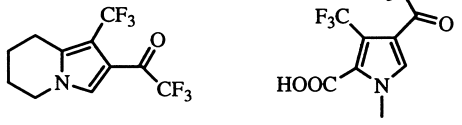


Reaction of the aminoacid (**3**) with trifluoroacetic anhydride gave the fluorinated pyrrole (**6**) in 70% yield. In contrast under similar conditions the aminoacid (**5**) gave the fluorinated pyrrole carboxylic acid (**7**) in 43% yield. The formation of the pyrroles can be rationalised by a sequence involving trifluoroacetylation of the enamines (**3**) and (**4**). Cyclisation in the proline series of the resulting dione (**8**) is followed by loss of water and carbon dioxide to give the aromatic product (**6**) (see Scheme 1). In contrast in the case of *N*-benzylglycine loss of water alone from the dione intermediate (**9**) leads to the aromatic carboxylic acid (**7**). Support for this reaction scheme can be found in the work of Levy et al.,[28] who reported the reaction of the dione (**10**) with an ester of *N*-benzylglycine to give a pyrrole (**11**). The formation of the bicyclic (**6**) through a final decarboxylation provides a contrasting and novel extension of the chemistry of enamines derived from the vinyl ether (**2**).



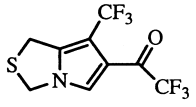
An obvious simplification of this pyrrole synthesis might be a one-pot procedure involving the sequence of Friedel–Crafts trifluoroacetylation of ethyl vinyl ether, enamine

formation and final cyclisation of the intermediate enamine. This three step sequence was applied to pipecolic acid, *N*-methylglycine and thiaproline. Pipecolic acid and *N*-methylglycine gave the pyrroles (**12**) and (**13**) in 24 and 33% overall yields, respectively. Hence pipecolic acid and proline behave in analogous manner and again the outcome with *N*-methylglycine is analogous to that with *N*-benzylglycine. In the case of thiaproline two products (**14**) and (**15**) are obtained. The former product (**14**) is clearly analogous to the product (**6**) isolated from proline. The origin of the second product (**15**) could be through one of two routes. Either the pyrrole (**15**) could be a product formed by detrifluoroacetylation of the trifluoroacetylated pyrrole (**14**), or it might arise via cyclisation of the intermediate monoketone (**16**). A cyclisation of a related ketone has been reported[29] earlier and we consider reaction via the latter pathway is the more probable. In contrast to these successful cyclisations, no product was obtained from the attempted cyclisation of the intermediate (**4**) from *N*-methylalanine, or the intermediate (**17**) from *N*-benzylalanine.

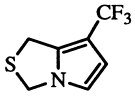


(**12**)

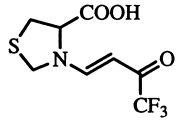
(**13**)



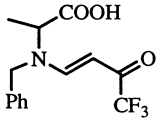
(**14**)



(**15**)



(**16**)



(**17**)

These cyclisations based on enamines derived from aminoacids provide a one-pot direct synthesis of a variety of pyrroles. Although no such routes have been reported from aminoacids, there are two related studies based on esters of aminoacids. In the work of Levy et al.[28] the esters of the aminoacids are reacted with the unstable diketone (**10**), which itself is only obtained in 25% yield by reaction of trifluoroacetic anhydride with triethylamine. Clearly in this instance the pyrrole synthesis based on the aminoacids is preferable. The formation of pyrrole carboxylic acids is closely related to the study of Laurent et al.[5] leading to the esters of pyrrole carboxylic acids. However, not only do our results extend to a different range of compounds, but more importantly they illustrate a different reaction pathway with proline, thiaproline and pipecolic acid involving decarboxylation. These decarboxylations afford fluorinated derivatives of heterocyclic skeletons known to exhibit interesting biological activity. Overall our results provide a rapid entry to an interesting range of fluorinated pyrroles.

Experimental

General experimental methods are described in the previous paper.[25]

(2*S*)-1-[(*E*)-4,4,4-Trifluoro-3-oxo-1-butenyl]tetrahydro-1*H*-2-pyrrolecarboxylic acid (3). To a stirred solution of 4-dimethylaminopyridine (4 mg) and trifluoroacetic anhydride (1.16 g) in dichloromethane (6 ml), ethyl vinyl ether (0.36 g) was added dropwise at −10°C. After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent was removed in vacuo. To the stirred resulting oil acetonitrile (10 ml) and L-(−)-proline (0.75 g) were added at room temperature. After stirring for 4 h, the solvent was removed in vacuo and the resulting yellow semi-solid was purified by flash chromatography (silica gel; light petroleum 50%, ethyl acetate 50%) and recrystallised (ethyl acetate/light petroleum) to give the title compound (**3**) as pale yellow crystals (0.86 g, 73%) mp 109–110°C (lit.[30] mp 103°C); δ_H (room temperature) 8.22 (0.85H, d, J=12 Hz, H-1′), 8.08 (0.15H, d, J=10 Hz, H-1′), 7.33 (1H, br s, OH), 5.42 (0.85H, d, J=12.5 Hz, H-2′), 5.22 (0.15H, d, J=13 Hz, H-2′), 4.45 (0.85H, t, J=5.7 Hz, H-2), 4.23 (0.15H, dd, J=8.8, 3.7 Hz, H-2), 3.76 (0.30H, m, H-5), 3.48 (1.70H, m, H-5) and 2.23 (4H, m, H-3 Hz, H-4); δ_C 177.40 (q, J_{CF}=33 Hz, C-3′), 173.05 (COOH), 155.54 and 154.10 (C-1′), 117.94 (q, J_{CF}=197 Hz, C-4′), 90.25 and 89.66 (C-2′), 65.01 and 60.53 (C-2), 54.02 and 48.67 (C-5), 30.69 and 29.60 (C-4) and 23.71 and 23.53 (C-3); δ_F −84.98 (CF_3); ν_{max} 3448 (OH), 2956, 2884, 1727 (CO), 1649 (CO), 1555 (C=C), 1257, 1187, 1137 and 1098 cm^{-1}; *m/z* 236 (M^-−H, 100%) and 192 (M^-−COOH, 17).

2-{(Methyl)[(*E*)-4,4,4-trifluoro-3-oxo-1-butenyl]amino}-propanoic acid (4). In a similar manner ethyl vinyl ether (0.23 g) was reacted with trifluoroacetic anhydride (0.73 g) in the presence of DMAP (2 mg) and the product was heated under reflux for 12 h in acetonitrile (6 ml) with D,L-*N*-methylalanine (0.66 g). The mixture was allowed to cool to room temperature and the solvent was removed in vacuo. Diethyl ether (6 ml) and water (6 ml) were added and the two phases separated. The aqueous phase was further extracted with diethyl ether (5×6 ml), the combined ether extracts dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting orange solid was purified by flash chromatography (silica gel; light petroleum 50%, ethyl acetate 50%) and recrystallised (diethyl ether/*n*-pentane) to give the title compound (**4**) as white crystals (0.25 g, 35%) mp 129–130°C; δ_H (room temperature) 8.05 (0.83H, d, J=12 Hz, H-1′), 7.99 (0.17H, d, J=12.5 Hz, H-1′), 5.50 (0.17H, d, J=12.5 Hz, H-2′), 5.41 (0.83H, d, J=12 Hz, H-2′), 4.71 (0.83H, q, J=7 Hz, H-2), 4.66 (0.17H, q, J=7 Hz, H-2), 2.90 (3H, s, NCH_3), 1.45 (2.49H, d,

J=7.4 Hz, H-3) and 1.40 (0.51H, d, J=7 Hz, H-3); δ_H (358 K) 8.08 (1H, d, J=12 Hz, H-1′), 5.48 (1H, d, J=12 Hz, H-2′), 4.66 (1H, q, J=7 Hz, H-2), 3.01 (3H, s, NCH_3) and 1.56 (3H, d, J=7 Hz, H-3); δ_C (room temperature) 175.02 (q, J_{CF}=31 Hz, C-3′), 171.83 and 170.94 (C-1), 157.93 and 157.02 (C-1′), 117.61 (q, J_{CF}=292 Hz, C-4′), 86.76 (C-2′), 63.36 and 55.87 (C-2), 33.62 (NCH_3) and 15.26 and13.70 (C-3); δ_C (366 K) 174.72 (q, J_{CF}=31 Hz, C-3′), 170.95 (C-1), 155.91 (C-1′), 117.19 (q, J_{CF}=292 Hz, C-4′), 86.85 (C-2′), 62.99 (C-2), 33.49 (NCH_3), 14.91 (C-3); ν_{max} 1736 (CO), 1658 (CO), 1572 (C=C), 1186, 1139 and 1103 cm^{-1} Found M^+ 225.0614 $C_8H_{10}F_3NO_3$ requires M^+ 225.0613; m/z 224 (M^-−H, 62%) and 180 (M^-−COOH, 100); Found: C, 42.6; H, 4.6; N, 6.0 $C_8H_{10}F_3NO_3$ requires C, 42.7; H, 4.5; N, 6.2%.

2-{(Phenylmethyl)[(*E*)-4,4,4-trifluoro-3-oxo-1-butenyl]-amino}ethanoic acid (5). In a similar manner ethyl vinyl ether (0.22 g) was reacted with trifluoroacetic anhydride (0.69 g) and the product was stirred for 3 h at room temperature with *N*-benzylglycine hydrochloride (0.6 g) in 2.5 M sodium hydroxide solution (3.0 ml). The solution was acidified to pH 3 and extracted with diethyl ether (4×3 ml). The combined organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The resulting yellow oil was purified by flash chromatography (silica gel, ethyl acetate) and recrystallised (diethyl ether/*n*-pentane) to give the title compound (**5**) as orange crystals (0.36 g, 41%) mp 113–114°C; δ_H 8.74 (1H, br s, OH), 8.19 (0.55H, d, J=13 Hz, H-1′), 8.15 (0.45H, d, J=13 Hz, H-1′), 7.39 (3H, m, Ar–H), 7.22 (2H, m, Ar–H), 5.69 (0.45H, d, J=12 Hz, H-2′), 5.37 (0.55H, d, J=12.5 Hz, H-2′), 4.62 (1.10H, s, NCH_2Ph), 4.54 (0.90H, s, NCH_2Ph), 4.07 (0.90H, s, H-2) and 3.91 (1.1H, s, H-2); δ_C 178.68 (q, J_{CF}=33 Hz, C-3′), 171.28 and 170.49 (C-1), 159.33 and 157.54 (C-1′), 133.64 and 132.97 (Ar), 129.46, 129.27, 128.96, 128.47 and 127.94 (Ar), 117.61 (q, J_{CF}=290 Hz, C-4′), 89.92 and 89.05 (C-2′), 61.46 and 55.49 (NCH_2Ph) and 53.64 and 48.59 (C-2); δ_F −84.73 (CF_3); ν_{max} 3029, 2937, 1718 (CO), 1673 (CO), 1568 (C=C), 1258, 1089, 925, 778 and 705 cm^{-1}; Found M^+ 287.0769 $C_{13}H_{12}F_3NO_3$ requires M^+ 287.0769; m/z 286 (M^-−H, 67%) and 242 (M^-−COOH, 100).

2,2,2-Trifluoro-1-[7-(trifluoromethyl)-2,3-dihydro-1*H*-6-pyrrolizinyl]-1-ethanone (6). To a stirred solution of (2*S*)-1-[(*E*)-4,4,4-trifluoro-3-oxo-1-butenyl] tetrahydro-1*H*-2-pyrrolecarboxylic acid (**3**) (0.10 g) in anhydrous dichloromethane (4 ml) was added dropwise at room temperature under nitrogen trifluoroacetic anhydride (0.12 g). After stirring for 4 h at room temperature, the solvent was removed in vacuo and the resulting brown solid was purified by flash column chromatography (silica gel; petroleum ether/diethyl ether 7:3). Recrystallisation (ethanol/water) gave the title compound (**6**) as white crystals (0.08 g, 70%) mp 38–39°C; δ_H 7.33 (1H, s, H-5′), 4.40 (2H, t, J=7.4 Hz, H-3′), 3.04 (2H, t, J=7.5 Hz, H-1′), 2.65 (2H, quin, J=7.5 Hz, H-2′); δ_C 170.17 (q, J_{C-F}=36 Hz, C-1), 147.93 (C-7a′), 122.96 (q, J_{C-F}=267 Hz, C-7′–CF_3), 122.94 (quin, J_{C-F}=3 Hz, C-5′), 121.41 (C-6′), 116.85 (q, J_{C-F}=290 Hz, C-2), 109.87 (q, J_{C-F}=39 Hz, C-7′), 49.34 (C-3′), 26.64 and 24.44 (C-1′ and C-2′); δ_F −92.40 (C-7′–CF_3), 89.22 (C-2–F_3); ν_{max} (cm^{-1}) 3151, 2976, 2932, 2866, 1680 (CO), 1568 (C=C), 1499, 1245, 1165, 1116, 1052, 945; found M^+ 271.0452 $C_{10}H_7F_6NO$ requires 271.0432, m/z 272 (M^++H, 100%), 202 (76).

1-(Phenylmethyl)-4-(2,2,2-trifluoroacetyl)-3-(trifluoromethyl)-1*H*-2-pyrrolecarboxylic acid (7). To a stirred solution of 2-{(phenylmethyl)[(*E*)-4,4,4-trifluoro-3-oxo-1-butenyl]amino}ethanoic acid (**5**) (0.11 g) in anhydrous dichloromethane (4 ml) under nitrogen was added dropwise at room temperature trifluoroacetic anhydride (0.17 g). After stirring for 6 h at room temperature, the solvent was removed in vacuo and the resulting brown oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 9:1) to give the title compound (**7**) as impure orange crystals (0.06 g, 43%) mp 37–41°C δ_H 9.78 (1H, s, OH), 7.54 (1H, br d, J=1.5 Hz, H-5), 7.29 (5H, m, Ar–H) 5.54 (2H, s, NCH_2); δ_C 178.98 (COOH), 169.44 (q, J_{C-F}=39 Hz, $COCF_3$), 159.46 (C-2), 134.52 (q, J_{C-F}=4 Hz, C-5), 134.29 (C-1′), 129.39, 129.03 and 127.66 (C-2′, C-3′, C-4′, C-5′, C-6′), 116.26 and 116.02 (q, J_{C-F}=288 Hz, C-3–CF_3 and $COCF_3$), 112.46 and 104.96 (C-3 and C-4), 55.59 (NCH_2); δ_F −87.32 (C-3–CF_3), 85.40 ($COCF_3$); ν_{max} (cm^{-1}) 3546 (OH), 1659 (CO), 1585 (C=C), 1514 (C=C), 1210 and 1153; Found M^+ 365.0487 $C_{15}H_9F_6NO_3$ requires 365.0485 m/z 364 (M^-−H, 100) (APCI mode).

2,2,2-Trifluoro-1-[1-(trifluoromethyl)-5,6,7,8-tetrahydro-2-indolizinyl]-1-ethanone (12). To a stirred solution of 4-dimethylaminopyridine (2 mg) and trifluoroacetic anhydride (0.73 g) in anhydrous dichloromethane (4 ml) was added dropwise at −10°C ethyl vinyl ether (0.23 g). After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent removed in vacuo. To the stirred resulting oil was added dropwise at room temperature D,L-pipecolic acid (0.83 g) in acetonitrile (6 ml). After heating under reflux for 6 h, the mixture was allowed to cool to room temperature and the solvents were removed in vacuo. Diethyl ether (10 ml) and water (10 ml) were added and the two phases separated. The aqueous phase was further extracted with diethyl ether (9×10 ml) and the combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo. To the resulting orange solid at room temperature under nitrogen was added trifluoroacetic anhydride (1.34 g) in anhydrous dichloromethane (30 ml). After stirring at room temperature for 24 h, the solvent was removed in vacuo. The resulting brown oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 4:1) and then by recrystallisation (ethanol/water) to give the title compound (**12**) as colourless needles (0.22 g, 24%) mp 61–62°C; Found: C, 46.1; H, 3.2; N, 4.9. $C_{11}H_9F_6NO$ requires C, 46.3; H, 3.2; N, 4.9%; δ_H 7.36 (1H, s, H-3′), 4.40 (2H, t, J=6.1 Hz, H-5′), 2.98 (2H, t, J=6.3 Hz, H-8′), 2.03 (2H, dquin, J=3.3, 5.9 Hz, H-6′ or H-7′), 1.91 (2H, dquin, J=3.3, 6.0 Hz, H-6′ or H-7′); δ_C 169.91 (q, J_{C-F}=35 Hz, C-1), 141.46 (C-8a′), 123.22 (C-2′), 123.14 (q, J_{C-F}=267 Hz, C-1′–CF_3), 121.21 (quin, J_{C-F}=3 Hz, C-3′), 117.00 (q, J_{C-F}=291 Hz, C-2), 113.47 (quin, J_{C-F}=37 Hz, C-1′), 47.13 (C-5′), 22.87 (C-8′), 22.62 and 18.60 (C-6′ and C-7′); δ_F −92.46 (C-1′–CF_3), 90.17 (C-2–F_3); ν_{max} (cm^{-1}) 2940, 1679 (CO), 1556 (C=C), 1507, 1171, 1134, 1099; Found M^+ 285.0584 $C_{11}H_9F_6NO$ requires M^+ 285.0588, m/z 285 (M^+, 60%), 266 (10), 216 (100), 188 (9).

1-Methyl-4-(2,2,2-trifluoroacetyl)-3-(trifluoromethyl)-1*H*-2-pyrrolecarboxylic acid (13). To a stirred solution of 4-dimethylaminopyridine (2 mg) and trifluoroacetic anhydride (0.73 g) in dichloromethane (4 ml) was added dropwise at −10°C ethyl vinyl ether (0.23 g). After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent removed in vacuo. To the stirred resulting oil was added dropwise at room temperature *N*-methylgylcine (0.57 g) in acetonitrile (6 ml). After stirring at room temperature for 23 h, the solvents were removed in vacuo. Diethyl ether (6 ml) and water (6 ml) were added and the two phases separated. The aqueous phase was further extracted with diethyl ether (7×6 ml) and the combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo. To the resulting yellow solid was added at room temperature with stirring under nitrogen trifluoroacetic anhydride (1.34 g) in anhydrous dichloromethane (30 ml) and after stirring at room temperature for 24 h, the solvents were removed in vacuo. The resulting brown solid was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 4:1). Recrystallisation (ethanol/water) afforded the title compound (**13**) as off white crystals (0.30 g, 33%) mp 79–80°C; Found: C, 37.2; H, 1.6; N, 4.8 $C_9H_5F_6NO_3$ requires C, 37.4; H, 1.7; N, 4.8%; δ_H 9.75 (1H, s, OH), 7.48 (1H, br q, J=0.7 Hz, H-5), 4.00 (3H, s, NCH_3); δ_C 178.78 and 178.27 (COOH), 169.79 (q, J_{C-F}=39 Hz, $COCF_3$), 159.12 (C-2), 134.98 (d, J_{C-F}=4 Hz, C-5), 116.32 and 116.07 (both q, J_{C-F}=288 Hz, C-3–CF_3, $COCF_3$), 113.02 and 104.56 (C-3 and C-4), 40.65 (NCH_3); δ_F −87.21 (C-3–CF_3), 85.23 ($COCF_3$); ν_{max} (cm^{-1}) 3435 (OH), 1649 (CO), 1582 (C=C), 1462, 1206, 1161, 1122; found M^+ 289.0171 $C_9H_5F_6NO_3$ requires 289.0174 *m/z* 288 (M^-−H, 100) (APCI mode).

2,2,2-Trifluoro-1-[7-(trifluoromethyl)-1*H*-pyrrolo[1.2-*c*]-[1,3]thiazol-6-yl]-1-ethanone (14) and 7-(trifluoromethyl)-1*H*-pyrrolo[1,2-*c*][1,3]thiazole (15). To a stirred solution of 4-dimethylaminopyridine (2 mg) and trifluoroacetic anhydride (0.73 g) in dichloromethane (4 ml) was added dropwise at −10°C ethyl vinyl ether (0.23 g). After stirring for 19 h at 0°C the mixture was allowed to warm to room temperature and the solvent removed in vacuo. To the stirred resulting oil was added dropwise at room temperature thiaproline (0.85 g) in acetonitrile (6 ml). After stirring at room temperature for 24 h, the solvents were removed in vacuo. Diethyl ether (10 ml) and water (10 ml) were added and the two phases separated. The aqueous phase was further extracted with diethyl ether (5×10 ml) and the combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo. To the resulting yellow solid was added at room temperature with stirring under nitrogen trifluoroacetic anhydride (0.88 g) in anhydrous dichloromethane (30 ml) and after stirring at room temperature for 6 h, the solvents were removed in vacuo. The resulting brown oil was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 9:1). Recrystallisation (ethanol/water) of the first fraction afforded the title compound, 2,2,2-trifluoro-1-[7-(trifluoromethyl)-1*H*-pyrrolo[1.2-*c*][1,3]thiazol-6-yl]-1-ethanone (**14**) as colourless crystals (0.13 g, 14%) mp 63–64°C δ_H 7.42 (1H, s, H-5′), 5.44 (2H, t, J=2.0 Hz, H-3′), 4.22 (2H, s, H-1′); δ_C 170.94 (q, J_{C-F}=37 Hz, C-1), 144.93 (C-7a′), 123.48 (C-5′), 122.42 (q, J_{C-F}=267 Hz, C-7′–CF_3), 122.01 (C-6′), 116.61 (q, J_{C-F}=289 Hz, C-2), 110.30 (q, J_{C-F}=39 Hz, C-7′), 51.13 (C-3′), 27.98 (C-1′); δ_F −92.58 (C-7′–CF_3), −89.25 (C-2–F_3); ν_{max} (cm^{-1}) 3152, 2924, 1676 (CO), 1564 (C=C), 1501, 1213, 1166, 1147, 1117 and 955; Found M^+ 289.0001 $C_9H_5F_6NOS$ requires 288.9996, *m/z* 289 (M^+100%), 270 (13), 256 (42), 244 (13), 220 (37). Recrystallisation (ethanol–water) of the second fraction afforded the title compound, 7-(trifluoromethyl)-1H-pyrrolo[1.2-*c*][1.3]thiazole (**15**) as yellow crystals (0.32 g, 52%) mp 38–39°C Found: C, 43.3; H, 2.9; N, 7.0. $C_7H_6F_3NS$ requires C, 43.5; H, 3.1; N, 7.3%; δ_H 6.64 (1H, d, J=3.0 Hz, H-5), 6.45 (1H, d, J=3.0 Hz, H-6), 5.03 (2H, s, H-3), 4.15 (2H, q, J=1.3 Hz, H-1); δ_C 134.48 (d, J_{C-F}=4 Hz, C-7a), 124.01 (q, J_{C-F}=266 Hz, CF_3), 115.92 (C-5), 111.55 (d, J_{C-F}=3 Hz, C-6), 106.69 (q, J_{C-F}=38 Hz, C-7), 48.83 (C-3), 28.36 (C-1); δ_F −91.21 (CF_3); ν_{max} (cm^{-1}) 3109, 2942, 2900, 2863, 1584 (C=C), 1500, 1436, 1374, 1268, 1177, 1125, 975; found M^+ 193.0170 $C_7H_6F_3NS$ requires 193.0173, *m/z* 193 (M^+100%), 148 (75), 124 (19).

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