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The first crystal structure of the pyrrolo[1,2-*c*]oxazole ring system

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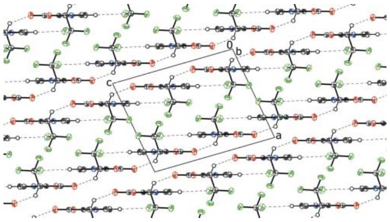
The title compound, $C_7H_4F_3NO_2$, 3-trifluoromethyl-1*H*-pyrrolo[1,2-*c*]oxazol-1-one, is the first crystal structure of the pyrrolo[1,2-*c*]oxazole ring system: the fused ring system is almost planar (r.m.s. deviation = 0.006 Å). In the crystal, weak C—H⋯O and C—H⋯F hydrogen bonds link the molecules into [001] chains and π–π stacking interactions consolidate the structure.



1. Chemical context

In the context of an approach to the synthesis of proline-derived ketones **3** by the proposed palladium-catalyzed Negishi coupling of organozinc reagent **1** with protected 4-hydroxyproline-derived acid chloride **2**, we needed access to a suitably *N*,*O*-diprotected 4-hydroxyproline derivative (Fig. 1). Our initial choice was to use TFA protection, since related cross-coupling reactions with the TFA-protected proline acid chloride had been successful (Deboves *et al.* 2001), and so the preparation of *N*,*O*-bis-trifluoroacetyl-4-hydroxy-L-proline **4** was attempted. The preparation of this compound had been reported, but without a detailed procedure (Mori *et al.*, 1986).

Treatment of (2*S*,4*R*)-4-hydroxyproline with trifluoroacetic anhydride TFAA (3 eq.) in dichloromethane at 273 K, followed by heating at reflux, gave a mixture of two compounds, which could be separated by column chromatography (Fig. 2). The more polar compound was the desired *bis*-TFA protected (2*S*,4*R*)-4-hydroxyproline **4** (47%), and the less polar material was an unknown by-product **5** (52%). This

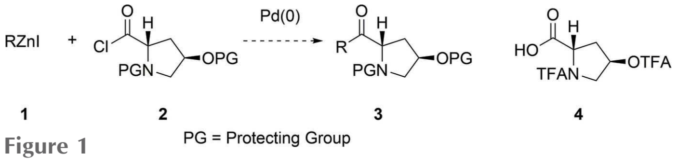


Figure 1
Proposed reaction scheme to access proline-derived ketones **3** from the Negishi coupling of organozinc reagents **1** with 4-hydroxyproline-derived acid chlorides **2**, specifically towards the formation of compound **3**

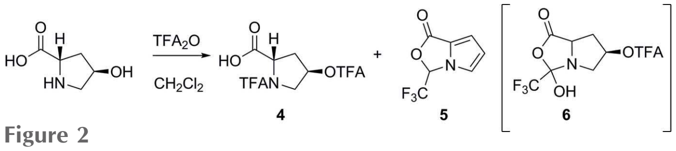


Figure 2
Reaction scheme for the synthesis of **5** along with the desired product **4**.

latter unknown compound exhibited signals in the aromatic region of the ^{1}H NMR spectrum, suggesting that the hydroxy group had been eliminated and a pyrrole derivative had been formed. The mass spectrum obtained for **5** showed a base peak at *m*/*z* 190 (100%), and the IR spectrum exhibited a stretching frequency in the carbonyl region at 1781 cm^{-1}. A crystal structure was obtained (see below), which confirmed that the compound was a new bicycle, a rare representative of the pyrrolo[1,2-*c*]oxazole ring system as first described by Katritzky *et al.* (2004).

When the reaction was repeated under milder conditions, omitting the period of heating under reflux, the desired *bis*-TFA protected 4-hydroxy-L-proline **4** was obtained in near quantitative yield, suggesting that it was partially converted into the novel pyrrolo[1,2-*c*]oxazole **5** under reflux conditions, presumably by elimination from an intermediate of structure **6**.

2. Structural commentary

Compound **5** crystallizes in the monoclinic space group $P2_1/c$: its asymmetric unit comprises of a single molecule (Fig. 3). The fused bicyclic aromatic system is almost planar [r.m.s. deviation = 0.006 Å; dihedral angle between the five-membered rings = 0.86 (6)°]. Atom C7, which bears the fluorine atoms, is displaced from the ring plane by 1.282 (1) Å and F3 lies *anti* to O1 [O1—C1—C7—F3 = −176.33 (8)°]. In the arbitrarily chosen asymmetric molecule, the stereogenic centre C1 has an *R* configuration but crystal symmetry generates a racemic mixture.

3. Supramolecular features

In the crystal, two weak hydrogen bonds (Table 1) are observed between **5** and the adjacent molecule related by the symmetry operation ($x, -y+\frac{1}{2}, z-\frac{1}{2}$). These form between the sp^3 hydrogen atom H1 and the carbonyl oxygen atom O2 and the aromatic proton H6 and F1 of the triflomethyl group: together, they generate an [001] chain. The molecules pack in sheets parallel to the (010) plane with alternating layers of interdigitated CF$_3$ groups and π–π stacked ring systems (Fig. 4). The shortest π–π stacking interaction between centrosymmetrically related N1/C3–C6 rings has a centroid–centroid separation of 3.5785 (7) Å with a vertical distance of 3.4196 (5) Å and a shift of 1.017 Å with an inter-planar angle of 0°.

Table 1
Hydrogen-bond geometry (Å, °).

D—H$\cdots$$A$	D—H	H$\cdots$$A$	$D\cdots A$	D—H$\cdots$$A$
C1—H1$\cdots$O2^{i}	0.98	2.46	3.2683 (13)	140
C6—H6$\cdots$F1^{i}	0.93	2.53	3.4065 (13)	156

Symmetry code: (i) $x, -y+\frac{1}{2}, z-\frac{1}{2}$.

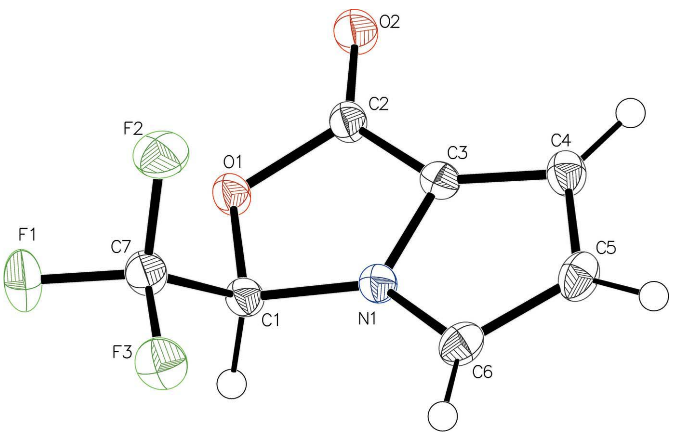


Figure 3
The molecular structure of **5**, showing displacement ellipsoids drawn at the 50% probability level.

4. Database survey

A search in the Cambridge Structural Database (CSD, V5.40, update February 2019; Groom *et al.*, 2016) was performed to confirm that there have been no previous crystal structures of the pyrrolo[1,2-*c*]oxazole ring system.

5. Synthesis and crystallization

Trifluoroacetic anhydride (0.33 ml, 2.31 mmol, 2.1 eq) was added dropwise to a stirred solution of *trans*-4-hydroxy-L-proline (144 mg, 1.1 mmol) in CH$_2$Cl$_2$ (2 ml) at 273 K. The reaction mixture was warmed to room temperature, and then heated under reflux for 1.5 h. The excess of CH$_2$Cl$_2$ was removed under reduced pressure to give a crude product that was purified by column chromatography (petrol:ethyl acetate, 80:20%) to give 3-trifluoromethyl-1*H*-pyrrolo[1,2-*c*]oxazol-1-one (0.11 g, 52%) as a white powder, m.p. 338–340 K; R_f 0.27 (petrol:ethyl acetate, 80:20%); $\nu_{\max}$(film)/cm^{-1} 3150, 2977, 2918, 1781, 1548, 1318, 1276; δ_H (400 MHz; CDCl$_3$) 6.20 (1H, *q*, *J* = 3.5), 6.62 (1H, *dd*, *J* = 2.5, 4.0), 6.91 (1H, *dd*, *J* = 1.0, 4.0), 7.12–7.15 (1H, m); δ_C (100 MHz; CDCl$_3$) 111.2, 118.7, 119.2,

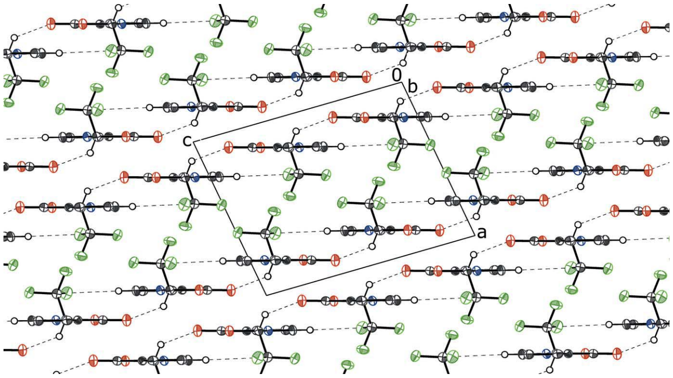


Figure 4
View along the *b* axis of the crystal packing for **5**, showing the alternating layers of interdigitated CF$_3$ groups and bicyclic ring systems. Hydrogen bonds are shown as dashed lines; hydrogen atoms not involved in forming these bonds are omitted for clarity.

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120.3 (CF_3, *q*, $J = 283.0$), 121.7, 156.7. Analysis calculated for $C_7H_3NO_2F_3$: C, 43.9; H, 2.1; N, 7.3. Found: C, 43.92; H, 2.16; N, 7.10. *m*/*z* (ES^-) 190 $(M - H)^-$, 100%). Found: $[M - H]^-$ 190.0115 $C_7H_3NO_2F_3$ requires 190.0116. Recrystallization from petroleum ether:ethyl acetate 80:20% solution led to colourless blocks of **5**.

The mass balance (47%) was the known *bis*-TFA-4-hydroxy-L-proline **4** (Mori *et al.*, 1986).

6. Refinement

Crystal data, data collection and structure refinement details are summarized in Table 2. The H atoms were positioned geometrically (C—H = 0.93 Å for sp^2 aromatic and 0.98 Å for sp^3 methine CH atoms) and refined as riding atoms with relative isotropic displacement parameters $U_{iso}(H) = 1.2U_{eq}$ of the parent atoms.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_7H_4F_3NO_2$
M_r	191.11
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	100
a, *b*, *c* (Å)	8.2767 (5), 8.5106 (5), 10.5500 (7)
β (°)	99.443 (3)
V (Å^3)	733.07 (8)
Z	4
Radiation type	Mo *Kα*
μ (mm^{-1})	0.18
Crystal size (mm)	0.43 × 0.32 × 0.32
Data collection	
Diffractometer	Bruker APEXII CCD
Absorption correction	Multi-scan (*SADABS*; Bruker, 2009)
T_{min}, T_{max}	0.700, 0.746
No. of measured, independent and observed $[I > 2\sigma(I)]$ reflections	13286, 1681, 1595
R_{int}	0.033
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.650
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.030, 0.078, 1.08
No. of reflections	1681
No. of parameters	118
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.39, −0.30

Computer programs: *APEX2* and *SAINT* (Bruker, 2009), *SHELXT* (Sheldrick, 2015*a*), *SHELXL* (Sheldrick, 2015*b*) and *OLEX2* (Dolomanov *et al.*, 2009).

Acknowledgements

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supporting information

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Computing details

Data collection: *APEX2* (Bruker, 2009); cell refinement: *SAINT* (Bruker, 2009); data reduction: *SAINT* (Bruker, 2009); program(s) used to solve structure: SHELXT (Sheldrick, 2015a); program(s) used to refine structure: *SHELXL* (Sheldrick, 2015b); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *OLEX2* (Dolomanov *et al.*, 2009).

3-Trifluoromethyl-1*H*-pyrrolo[1,2-*c*]oxazol-1-one

Crystal data

$C_7H_4F_3NO_2$
$M_r = 191.11$
Monoclinic, $P2_1/c$
$a = 8.2767\ (5)$ Å
$b = 8.5106\ (5)$ Å
$c = 10.5500\ (7)$ Å
$\beta = 99.443\ (3)°$
$V = 733.07\ (8)$ Å^3
$Z = 4$

$F(000) = 384$
$D_x = 1.732$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 9927 reflections
$\theta = 3.1–27.6°$
$\mu = 0.18$ mm^{-1}
$T = 100$ K
Block, colourless
0.43 × 0.32 × 0.32 mm

Data collection

Bruker APEXII CCD diffractometer
φ and ω scans
Absorption correction: multi-scan (SADABS; Bruker, 2009)
$T_{min} = 0.700$, $T_{max} = 0.746$
13286 measured reflections

1681 independent reflections
1595 reflections with $I > 2\sigma(I)$
$R_{int} = 0.033$
$\theta_{max} = 27.5°$, $\theta_{min} = 2.5°$
$h = -10 \rightarrow 10$
$k = -11 \rightarrow 11$
$l = -13 \rightarrow 13$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.030$
$wR(F^2) = 0.078$
$S = 1.08$
1681 reflections
118 parameters
0 restraints

Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0348P)^2 + 0.3122P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.39$ e Å^{-3}
$\Delta\rho_{min} = -0.30$ e Å^{-3}

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	$U_{\rm iso}$*/$U_{\rm eq}$
N1	0.20468 (11)	0.42629 (11)	0.56351 (8)	0.0174 (2)
O1	0.14217 (9)	0.27976 (9)	0.72729 (7)	0.01878 (18)
O2	0.08840 (11)	0.47329 (9)	0.86114 (7)	0.02351 (19)
C1	0.19006 (13)	0.26514 (12)	0.60398 (10)	0.0173 (2)
H1	0.107086	0.208458	0.544158	0.021*
C2	0.12893 (12)	0.43833 (12)	0.76072 (10)	0.0176 (2)
C3	0.17020 (12)	0.52963 (12)	0.65500 (9)	0.0168 (2)
C4	0.18460 (13)	0.68045 (13)	0.61032 (10)	0.0197 (2)
H4	0.167818	0.773574	0.652411	0.024*
C5	0.22998 (13)	0.66468 (14)	0.48775 (11)	0.0221 (2)
H5	0.248941	0.747088	0.434193	0.027*
C6	0.24167 (14)	0.50640 (14)	0.46028 (10)	0.0215 (2)
H6	0.269396	0.463188	0.385775	0.026*
C7	0.35527 (14)	0.18148 (13)	0.61947 (11)	0.0211 (2)
F1	0.34284 (9)	0.03455 (8)	0.66179 (7)	0.03022 (19)
F2	0.46888 (8)	0.25554 (9)	0.70256 (7)	0.03067 (19)
F3	0.40810 (8)	0.17430 (9)	0.50653 (7)	0.02723 (18)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0210 (4)	0.0154 (4)	0.0160 (4)	−0.0006 (3)	0.0032 (3)	0.0002 (3)
O1	0.0248 (4)	0.0147 (4)	0.0178 (4)	−0.0008 (3)	0.0064 (3)	0.0003 (3)
O2	0.0321 (4)	0.0207 (4)	0.0193 (4)	0.0014 (3)	0.0089 (3)	−0.0002 (3)
C1	0.0204 (5)	0.0153 (5)	0.0163 (5)	−0.0018 (4)	0.0034 (4)	−0.0002 (4)
C2	0.0179 (5)	0.0149 (5)	0.0195 (5)	−0.0003 (4)	0.0019 (4)	0.0002 (4)
C3	0.0168 (5)	0.0167 (5)	0.0169 (5)	−0.0008 (4)	0.0023 (4)	−0.0014 (4)
C4	0.0180 (5)	0.0166 (5)	0.0243 (5)	−0.0009 (4)	0.0024 (4)	0.0014 (4)
C5	0.0201 (5)	0.0217 (5)	0.0243 (5)	−0.0020 (4)	0.0028 (4)	0.0071 (4)
C6	0.0242 (5)	0.0241 (5)	0.0168 (5)	−0.0007 (4)	0.0049 (4)	0.0039 (4)
C7	0.0229 (5)	0.0185 (5)	0.0221 (5)	0.0003 (4)	0.0044 (4)	0.0000 (4)
F1	0.0360 (4)	0.0185 (4)	0.0383 (4)	0.0071 (3)	0.0122 (3)	0.0059 (3)
F2	0.0220 (3)	0.0351 (4)	0.0319 (4)	0.0010 (3)	−0.0045 (3)	−0.0043 (3)
F3	0.0265 (4)	0.0300 (4)	0.0275 (4)	0.0021 (3)	0.0113 (3)	−0.0018 (3)

Geometric parameters (Å, º)

N1—C1	1.4474 (13)	C3—C4	1.3792 (15)
N1—C3	1.3700 (13)	C4—H4	0.9300

N1—C6	1.3617 (14)	C4—C5	1.4108 (15)
O1—C1	1.4262 (12)	C5—H5	0.9300
O1—C2	1.4036 (13)	C5—C6	1.3846 (16)
O2—C2	1.2000 (13)	C6—H6	0.9300
C1—H1	0.9800	C7—F1	1.3374 (13)
C1—C7	1.5265 (15)	C7—F2	1.3339 (13)
C2—C3	1.4456 (14)	C7—F3	1.3363 (13)

C3—N1—C1	111.31 (8)	C3—C4—H4	127.0
C6—N1—C1	138.68 (9)	C3—C4—C5	106.00 (9)
C6—N1—C3	110.01 (9)	C5—C4—H4	127.0
C2—O1—C1	110.98 (8)	C4—C5—H5	125.6
N1—C1—H1	111.1	C6—C5—C4	108.82 (10)
N1—C1—C7	110.90 (9)	C6—C5—H5	125.6
O1—C1—N1	103.62 (8)	N1—C6—C5	106.68 (10)
O1—C1—H1	111.1	N1—C6—H6	126.7
O1—C1—C7	108.73 (8)	C5—C6—H6	126.7
C7—C1—H1	111.1	F1—C7—C1	110.80 (9)
O1—C2—C3	106.55 (8)	F2—C7—C1	111.87 (9)
O2—C2—O1	120.33 (9)	F2—C7—F1	107.88 (9)
O2—C2—C3	133.12 (10)	F2—C7—F3	108.00 (9)
N1—C3—C2	107.54 (9)	F3—C7—C1	110.14 (9)
N1—C3—C4	108.48 (9)	F3—C7—F1	108.01 (9)
C4—C3—C2	143.96 (10)		

N1—C1—C7—F1	177.53 (8)	C1—O1—C2—O2	179.38 (9)
N1—C1—C7—F2	57.11 (12)	C1—O1—C2—C3	−0.12 (11)
N1—C1—C7—F3	−63.02 (11)	C2—O1—C1—N1	−0.25 (11)
N1—C3—C4—C5	−0.21 (12)	C2—O1—C1—C7	117.77 (9)
O1—C1—C7—F1	64.22 (11)	C2—C3—C4—C5	−178.20 (14)
O1—C1—C7—F2	−56.21 (11)	C3—N1—C1—O1	0.55 (11)
O1—C1—C7—F3	−176.33 (8)	C3—N1—C1—C7	−115.95 (9)
O1—C2—C3—N1	0.46 (11)	C3—N1—C6—C5	−0.03 (12)
O1—C2—C3—C4	178.46 (14)	C3—C4—C5—C6	0.20 (13)
O2—C2—C3—N1	−178.94 (11)	C4—C5—C6—N1	−0.11 (13)
O2—C2—C3—C4	−0.9 (2)	C6—N1—C1—O1	−178.81 (12)
C1—N1—C3—C2	−0.64 (11)	C6—N1—C1—C7	64.69 (16)
C1—N1—C3—C4	−179.40 (8)	C6—N1—C3—C2	178.91 (9)
C1—N1—C6—C5	179.34 (11)	C6—N1—C3—C4	0.15 (12)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C1—H1···O2^{i}	0.98	2.46	3.2683 (13)	140
C6—H6···F1^{i}	0.93	2.53	3.4065 (13)	156

Symmetry code: (i) *x*, −*y*+1/2, *z*−1/2.