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Zreigh, M.M., Adams, H., Jackson, R.F.W. et al. (1 more author) (2019) The first crystal structure of the pyrrolo[1,2-c]oxazole ring system. Acta Crystallographica Section E: Crystallographic Communications, 75 (9). pp. 1336-1338. ISSN 2056-9890

https://doi.org/10.1107/s2056989019011095

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Acta Cryst. (2019). E75, 1336–1338

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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-1H-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 (2S,4R)-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 (2S,4R)-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 ($^\circ$)]. 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)$^\circ$]. 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$^\circ$ groups and $\pi$–$\pi$ stacked ring systems (Fig. 4). The shortest $\pi$–$\pi$ stacking interaction between centroymmetrically 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$^\circ$.

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-

![Figure 3](image)

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

![Figure 4](image)

View along the $b$ axis of the crystal packing for 5, showing the alternating layers of interdigitated CF$^\circ$ groups and bicyclic ring systems. Hydrogen bonds are shown as dashed lines; hydrogen atoms not involved in forming these bonds are omitted for clarity.
120.3 (CF₃, q, J = 283.0), 121.7, 156.7. Analysis calculated for C₇H₃NO₂F₃: C, 43.9; H, 2.1; N, 7.10. m/z (ES⁻) 190 (M − H)⁻, 100%. Found: [M − H]⁻ 190.0115 C₇H₃NO₂F₃ 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 sp² aromatic and 0.98 Å for sp³ methine CH atoms) and refined as riding atoms with relative isotropic displacement parameters Uiso(H) = 1.2 Ueq of the parent atoms.

Acknowledgements
We thank Zawia University for support (MMZ).

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Table 2
Experimental details.

| Crystal data      | Chemical formula     | C₇H₃NO₂F₃ |
|-------------------|----------------------|-----------|
| Mᵣ               | 191.11               |           |
| Crystal system, space group | Monoclinic, P 2₁/c |           |
| Temperature (K)   | 100                  |           |
| a, b, c (Å)       | 8.2767 (5), 8.5106 (5), 10.5500 (7) |           |
| β (°)             | 99.443 (3)           |           |
| V (Å³)            | 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_max, T_min      | 0.700, 0.746         |           |
| No. of measured, independent and observed [I > 2σ(I)] reflections | 13286, 1681, 1595 |           |
| Rint              | 0.033                |           |
| (sin θ/λ)max (Å⁻¹) | 0.650               |           |

| Refinement        | R[F² > 2σ(F²)], wR(F²), S | 0.030, 0.078, 1.08 |
|--------------------|---------------------------|--------------------|
| No. of reflections | 1681                      |                    |
| No. of parameters  | 118                       |                    |
| H-atom treatment  | H-atom parameters constrained |                |
| Δρ(+) max, Δρ(min) (e Å⁻³) | 0.39, −0.30 |                |

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

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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-1H-pyrrolo[1,2-c]oxazol-1-one

Crystal data

C₇H₄F₃NO₂  
M_r = 191.11  
Monoclinic, P2₁/c  
a = 8.2767 (5) Å  
b = 8.5106 (5) Å  
c = 10.5500 (7) Å  
β = 99.443 (3)°  
V = 733.07 (8) Å³  
Z = 4

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 > 2σ(I)  
R(int) = 0.033  
θ_max = 27.5°, θ_min = 2.5°  
h = −10→10  
k = −11→11  
l = −13→13

Refinement

Refinement on F²  
Least-squares matrix: full  
R[F² > 2σ(F²)] = 0.030  
wR(F²) = 0.078  
S = 1.08  
1681 reflections  
118 parameters  
0 restraints

Hydrogen site location: inferred from neighbouring sites  
H-atom parameters constrained  
w = 1/[σ²(Fo²) + (0.0348P)² + 0.3122P]  
where P = (Fo² + 2Fc²)/3  
(Δ/σ)max < 0.001  
Δρ_max = 0.39 e Å⁻³  
Δρ_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 (Å²)

|     | x          | y          | z          | Uiso*/Ueq |     |
|-----|------------|------------|------------|-----------|-----|
| 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 (Å²)

|     | U¹¹       | U¹²       | U¹³       | U²²       | U²³       | U³³       |     |
|-----|-----------|-----------|-----------|-----------|-----------|-----------|-----|
| 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, °)

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| 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)  1.4108 (15)
O1—C1 1.4262 (12)  C5—H5 0.9300  0.9300
O1—C2 1.4036 (13)  C4—C5 1.3846 (16)  1.3846 (16)
O2—C2 1.2000 (13)  C5—C6 1.3846 (16)  1.3846 (16)
C1—H1 0.9800  C7—F1 1.3374 (13)  1.3374 (13)
C1—C7 1.5265 (15)  C7—F2 1.3339 (13)  1.3339 (13)
C2—C3 1.4456 (14)  C7—F3 1.3363 (13)  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)  106.00 (9)
C6—N1—C3 110.01 (9)  C5—C4—H4 125.6
C2—O1—C1 110.98 (8)  C4—C5—H5 125.6
N1—C1—H1 111.1  C6—C5—H5 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—C7 108.73 (8)  N1—C6—H6 126.7
C1—C7—C1 111.1  N1—C6—H6 126.7
F1—C7—C1 110.80 (9)  C1—O1—C2—O2 179.38 (9)
O1—C2—C3 106.55 (8)  C1—O1—C2—C3 −0.12 (11)
O2—C2—O1 120.33 (9)  C2—O1—C1—N1 −0.25 (11)
O2—C2—C3 133.12 (10)  C2—O1—C1—C7 117.77 (9)
N1—C3—C2 107.54 (9)  C2—C3—C4—C5 −178.20 (14)
N1—C3—C4 108.48 (9)  C3—C4—C5—C6 0.20 (13)
C4—C3—C2 143.96 (10)

Hydrogen-bond geometry (Å, °)

| D—H—A | D—H | H—A | D···A | D—H···A |
|-------|-----|-----|-------|---------|
| C1—H1···O2' | 0.98 | 2.46 | 3.2683 (13) | 140 |
| C6—H6···F1' | 0.93 | 2.53 | 3.4065 (13) | 156 |

Symmetry code: (i) x, −y+1/2, z−1/2.